

Enhancing the use of network meta-analysis to synthesize information on benefits and harms
of drugs to support regulatory and reimbursement decisions in Canada

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ABSTRACT

BACKGROUND AND OBJECTIVES: Standard meta-analysis compares two treatments whereas network meta-analysis compares multiple treatments. In light of the increasing number of treatments available, we have seen a shift from using standard meta-analysis towards using network meta-analyses to support regulatory and reimbursement decisions. This thesis (composed of nine separate papers) applied network meta-analysis to a series of real world problems which simultaneously addressed many of these methodological issues while also supporting healthcare decision making.

METHODS: In the first chapter, background information on network meta-analysis and outline the rationale for each of the subsequent chapters is provided. In Chapter 2, an applied example is presented where we use FDA Public Summary documents to populate a network meta-analysis of antithrombotic therapies for atrial fibrillation. In Chapter 3, the advantages and disadvantages of rapid network meta-analysis using ClinicalTrials.gov are investigated by re-doing Chapter 3 but only using data available in ClinicalTrials.gov and examining concordance. In Chapter 4, the application of network meta-analysis when events are rare are investigated using an illustrative example investigating the risk of serious infection in biologics. In Chapter 5, the application of network meta-analysis to a complex network – triptans for migraine – are presented where there are a large number of studies and treatments. In Chapter 6 a network meta-analysis which assesses both a benefit and harm and integrates findings using a benefit harm methodology is presented. In Chapter 7, methods to incorporate non-randomized studies into network meta-analysis are investigated using data on risk

of myocardial infarction derived from the Mini-Sentinel distributed data network.

FINDINGS AND CONCLUSION: Pragmatic research around methodological areas in network meta-analysis were conducted to address real world problems for decision makers. It is my hope that this thesis and the approaches used in this thesis for the application of network meta-analysis will be disseminated to enhance research capacity in conducting network meta-analysis in Canada.

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LIST OF ABBREVIATIONS AND SYMBOLS

ADDIS	Aggregate Data Drug Information System
AF	Atrial fibrillation
AMI	Acute myocardial infarction
ASA	acetylsalicylic acid
CADTH	Canadian Agency for Drugs and Technologies in Health
CDEC	Canadian Drug Expert Committee
CI	Confidence interval
CIHR	Canadian Institutes for Health Research
CDR	Common Drug Review
CEA	cost-effectiveness analysis
CNODES	Canadian Network for Observational Drug Effect Studies
CrI	Credible interval
CVD	cardiovascular disease
DIC	Deviance information criterion
DMARDs	disease-modifying anti-rheumatic drugs
DRS	Disease risk scores
DPP-5	dipeptidyl peptidase-4
DSEN	Drug Safety and Effectiveness Network
FDA	Food and Drug Administration
FE	fixed effects
HTA	health technology assessment
HR	Hazard ratio
ICHD	International Classification of Headache Disorders
INR	international normalised ratio
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITT	intention to treat
ISTH	International Society on Thrombosis and Haemostasis
MCMC	Markov Chain Monte Carlo (MCMC)
Mg	milligram
MSDD	Mini-Sentinel Distributed Database
MTX	methotrexate
NICE	National Institute for Health and Care Excellence
NNTB(H)	number needed to treat to benefit (harm)
NMA	network meta-analysis
NSAIDS	non-steroidal anti-inflammatory drugs
ODPRN	Ontario Drug Policy Research Network
ODT	Oral dissolvable tablet
OR	Odds ratio
PICO	population, intervention, comparator, and outcome (PICO)
PICOS	population, intervention, comparator, outcome, study design
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
PSM	Propensity score matching

QoL	quality of life
RA	Rheumatoid arthritis
RE	random effects
RR	relative risks
RCT	Randomized controlled trial
RE-LY	Randomized Evaluation of Long-Term Anti-coagulation Therapy
SAE	Serious adverse events
SD	Standard dose
SE	Systemic embolism
SU	Sulfonylurea
SUCRA	surface under the cumulative ranking
TTR	time in therapeutic range
UK	United Kingdom
USA	United States of America
VKA	vitamin K antagonists
WDAE	withdrawals due to adverse events

PREFACE / DECLARATION OF ACADEMIC ACHIEVEMENT

This thesis takes the form of a series of articles, each prepared for publication in a peer-reviewed journal. The first paper, entitled “*Systematic Review and Network Meta-analysis comparing Antithrombotic Agents for the Prevention of Stroke and Major Bleeding in Patients with Atrial Fibrillation*” was written in 2012/2013. This paper was published in *BMJ Open*. The second paper, written in 2014, is entitled “*Rapid Network meta-analysis using ClinicalTrials.gov: An application using antithrombotics for atrial fibrillation.*” and was submitted to *Systematic Reviews* in 2015. The third paper in this thesis was written in 2014 and is entitled “*Triptans in the acute treatment of migraine: A systematic review and network meta-analysis.*” and was published in *Headache* in 2015. The fourth paper in this thesis was written in 2013/14 and is entitled “*The risk of serious infection with biologics in treating patients with rheumatoid arthritis.*” and was published in *Lancet* in 2015. The fifth paper is entitled “*Clinical and Safety Outcomes Associated with Treatment of Acute Venous Thromboembolism: A Systematic Review and Meta-analysis*” and was published in *JAMA*. The sixth paper entitled “*Benefit-harm assessment of treatments for Acute Venous Thromboembolism*” and will be submitted to *Value in Health* in 2015. The seventh paper is entitled “*Network meta-analysis incorporating non-randomized studies for assessing medical product safety: pitfalls and opportunities*” and was written in 2014 and was submitted to *Systematic Reviews* in 2015. The eighth paper is entitled “*Network meta-analysis using observational data from distributed health data networks: An application using acute myocardial infarction in association with use of anti-diabetic agents*” and will be submitted to the *Journal of Clinical Epidemiology* in 2015. The ninth paper is entitled “*A Microsoft-Excel- based tool for running and critically appraising network meta-analyses –*

an overview and application of NetMetaXL” was written in 2014 and published in *Systematic Reviews* in late 2014.

I’m the first author on six papers in this thesis. For each of these six papers, I was responsible for writing all the papers, with guidance from supervisors and other co-authors. I’m listed as the co-first author on three other papers included in this thesis. For two of the three papers, I shared co-first authorship with the lead systematic reviewer. For one of these papers, I wrote the initial draft and for the second paper, I drafted the methods and results sections. For both papers where I’m listed as co first author, I conducted all network meta-analyses, and generated all tables and figures related to findings from the network meta-analysis. I also responded to all feedback on the network meta-analysis that was provided during the peer review process for both of these papers. For the remaining paper, I drafted the paper but shared first authorship with the programmer of the software. I submitted the manuscript for publication, and I’m listed as corresponding author, and was responsible for addressing all feedback received during the peer-review process.

CHAPTER 1: INTRODUCTION AND BACKGROUND

Traditional meta-analysis is a statistical technique of combining data from studies comparing two treatments.^{1,2} Meta-analyses may pool data from pre-market clinical trials, post-market clinical trials or observational studies, although the majority of meta-analyses to date have focused largely on pooling data from clinical trials.³ Although the use of traditional meta-analysis is widespread, there are several notable limitations with the use of traditional meta-analysis for synthesizing information on benefits and harms of drugs. First, traditional meta-analyses have been traditionally based largely on clinical studies, and the sample size of clinical studies is often too small or duration too short to rule out important harms.^{4,5} Second, traditional meta-analyses also often yield incomplete or disparate information because only two treatments of interest are considered simultaneously, one of which is often placebo.⁶ The aforementioned limitations reduce the applicability of traditional meta-analysis to support drug regulatory and reimbursement decisions. Decision makers are often interested in how a drug compares to all available treatments, not necessarily how a drug compares with the one other drug or placebo compared in a clinical trial.

Consequently, new meta-analytic methods have emerged which enable simultaneous comparison of more than two drugs, and increase the overall sample size of the evidence network.⁶⁻⁸ These methods are often referred to as network meta-analysis (Figure 1).

Network meta-analyses can generate estimates of comparative benefits and harms among multiple drugs simultaneously, including some that may have not been compared in clinical trials.⁶ Further, by including more studies, network meta-analysis may increase the sample size and ability to detect potential harms. These two improvements over traditional meta-

analysis are particularly advantageous when evaluating a drug when it is launched to the market and comparative data or observational data are either limited or not available.

Consequently, we have seen a shift from using standard meta-analysis towards using network meta-analyses to support regulatory and reimbursement decisions. Indeed, the Drug Safety and Effectiveness Network (DSEN), which is funded by the Canadian Institutes for Health Research (CIHR), developed a Collaborative Centre for Network Meta-Analysis in 2011 to coordinate the conduct of network meta-analyses to support regulatory and reimbursement decisions in Canada.⁹ The DSEN Collaborating Centre for Network Meta-Analysis awarded funding to three teams to conduct research related to network-meta-analysis. One team – officially called the Canadian Collaboration for Drug Safety, Effectiveness, and Network Meta-Analysis – is primarily responsible for methods applications and capacity development, while the other teams are responsible for innovative knowledge synthesis methods and developing tools for drug safety and effectiveness. In Collaboration with the Canadian Collaboration for Drug Safety, Effectiveness, and Network Meta-Analysis I helped identify several areas for methodological research and capacity development for network meta-analysis in Canada:

1. Incorporating information on variability in benefits and harms into network meta-analysis using information available in FDA public summary documents
2. Conducting rapid network meta-analysis using ClinicalTrials.gov
3. Network meta-analysis of complex evidence networks including large numbers of treatments and/or studies
4. Network meta-analysis of harms data when events are rare

5. Integrating information derived from a network meta-analysis using benefit-harm assessment methodologies
6. Integrating information from non-randomized studies into network meta-analysis

The central aim of my thesis will be to conduct pragmatic research around the aforementioned methodological areas using real-world illustrative examples, with the hope of disseminating these approaches across the country to enhance research capacity in conducting network meta-analysis in Canada.

BACKGROUND

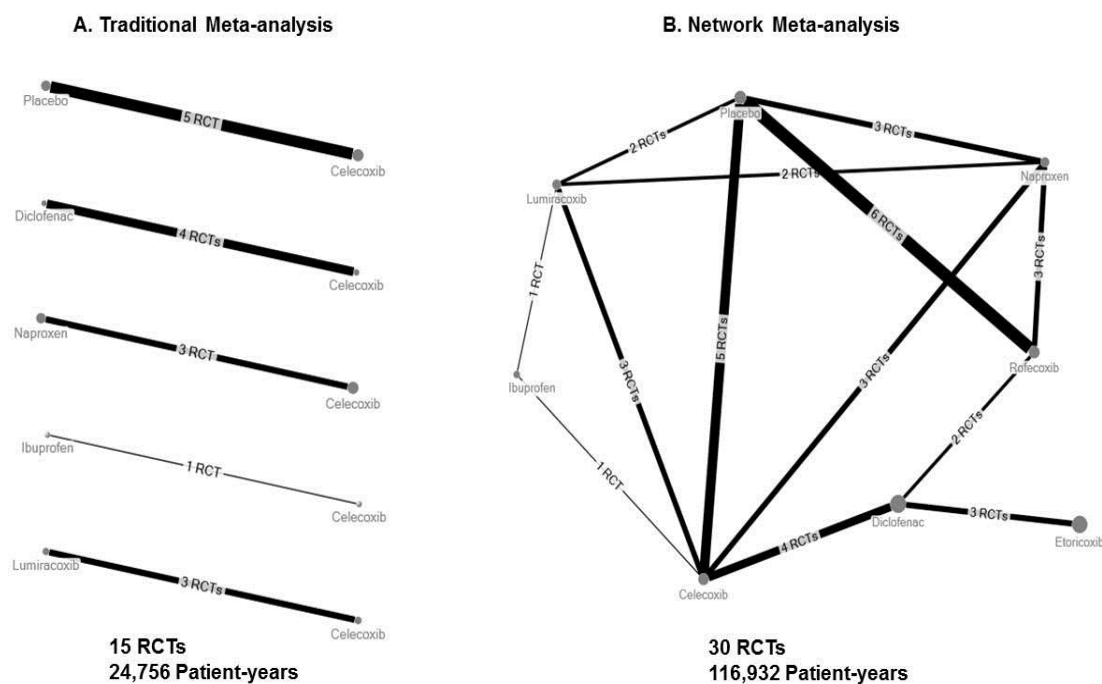
In this section, I introduce network meta-analysis and describe the advantages and disadvantages of conducting a network meta-analysis compared with traditional meta-analysis in evaluating the benefits and harms of drugs using an illustrative example. As discussed previously, traditional meta-analysis is a statistical technique of combining data from studies comparing two treatments.^{1,2} By contrast, network meta-analyses simultaneously combines data from studies on multiple treatments.⁶ For the illustrative example, I will evaluate the risk of myocardial infarction of celecoxib versus other alternative non-steroidal anti-inflammatory drugs (NSAIDs) using traditional meta-analysis and network meta-analysis. I begin by describing the data set used for the illustrative example, and then explain how the body of information available for assessing the risk of myocardial infarction for celecoxib differs for traditional meta-analysis and network meta-analysis. I will then discuss other advantages and disadvantages that network meta-analysis offers compared traditional meta-analysis, and opportunities for improving the use of network meta-analysis for assessing the benefits and harms of drugs moving forward.

ILLUSTRATIVE EXAMPLE – RISK OF MYOCARDIAL INFARCTION WITH NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

Figure 1 shows the illustrative dataset used to evaluate the risk of myocardial infarction in patients using non-steroidal anti-inflammatory drugs for A.) traditional meta-analysis and B.) network meta-analysis. The methods used to identify studies included in the evidence network, and the criteria for inclusion and exclusion in the data set have been described elsewhere.¹⁰ Briefly, a systematic search of the literature was undertaken to identify large scale randomized controlled trials comparing any non-steroidal anti-inflammatory drug with other non-steroidal anti-inflammatory drugs, paracetamol (acetaminophen), or placebo. To be included in this review, trials required at least two arms with at least 100 patient years of follow-up. The indications for use of NSAIDs included prevention of Alzheimer's disease, prevention of cancer degeneration of adenomatous polyps, osteoarthritis and rheumatoid arthritis. The search was last updated in July 2009.¹⁰ Individual patient data were not available. Available data are reported in Appendix A and a summary of study characteristics reported in Trelle et al¹⁰ are provided in Appendix B.

For traditional meta-analysis, there are 15 RCTs with 24,756 years of patient data comparing celecoxib with either placebo, naproxen, diclofenac, ibuprofen, or lumiracoxib (Figure 1). Traditional meta-analysis only compares two treatments at a time; therefore, pair-wise comparisons of celecoxib versus other NSAIDs are considered separately (Figure 1) unless the analyst decides to merge drugs within a class (e.g., combine naproxen, diclofenac, ibuprofen into one node), an approach taken by others who have conducted traditional meta-

Figure 1: Body of information available to evaluate risk of myocardial infarction in patients using Celecoxib versus other non-steroidal anti-inflammatory drugs or placebo for A.) Traditional meta-analysis and B.) Network Meta-analysis. The width of the lines is proportional to the number of randomized controlled trials (RCTs) comparing each pair of treatments, and the size of each treatment node is proportional to patient-years of follow-up available for each treatment.



analyses on this topic.^{11,12} However, merging nodes may introduce heterogeneity if there are differences between treatments combined into the same node. Further, it often doesn't make sense from a clinical or funding perspective to merge nodes because drugs are often considered one versus another and not necessarily as a class. By contrast, when the information is considered within a network meta-analysis, multiple treatments are considered simultaneously and individual NSAIDs can be treated as separate nodes. For example, all pair-wise comparisons (i.e., comparison of two treatments) for NSAIDs versus celecoxib are integrated but kept as separate nodes, and combined with information available for other non-selective non-steroidal anti-inflammatory drugs provided this information can be

connected to the network via a common comparator. As such, the body of information available to evaluate risk of myocardial infarction for celecoxib increases to 30 trials comparing eight treatments including placebo and 116,932 patient-years of follow-up in the network meta-analysis. There are 28 possible pair-wise contrasts between the eight treatments in the evidence network, and the data set provides direct evidence on 13 of them.

There are different statistical approaches to combine the data depending on the outcome of interest and these statistical methods have been described in detail elsewhere.^{7,13} For this example, the data in the publication was reported as events and person-years so a Poisson likelihood model^{7,13} was used to combine data. To facilitate comparison between analyses, a Bayesian random effects model for both traditional and network meta-analysis was used, which fully preserved randomized treatment comparisons within trials.^{6,13} All analyses were conducted using Markov chain Monte Carlo methods with vague prior distributions. Markov Chain Monte Carlo methods are a class of algorithms for sampling from a probability distribution,^{13,14} whereas prior distribution of a parameter represents the uncertainty about the parameter before the current data are examined.^{6,13} A ‘vague’ prior is thought to ‘let the data drive the analysis.’^{6,13} Multiplying the prior and the likelihood function together leads to the posterior distribution of the parameter. The posterior distribution is used to carry out all inferences. Three chains were fit for each analysis, each employing at 50,000 iterations, with a burn-in of 50,000 iterations.^{13,14} Hazard ratios were calculated as well as corresponding 95% credibility intervals, and for simplicity it was assumed that in each arm of each trial the hazard is constant over the follow-up period.

The results for traditional and network meta-analyses are provided in Figure 2. As you can see in Figure 2, network meta-analysis provides much more information on risk of myocardial infarction of celecoxib versus other alternative non-steroidal anti-inflammatory drugs compared with traditional meta-analysis. The network meta-analysis provides estimates of effect for celecoxib versus all NSAIDs whereas traditional meta-analysis only provides estimates of effect for celecoxib with either placebo, naproxen, diclofenac, ibuprofen, or lumiracoxib (Figure 2). This can be very advantageous when conducting cost-effectiveness analyses^{15,16} where many treatments have to be compared simultaneously due to differences in costs and effects among treatments. The effect estimates for network meta-analysis incorporate information from all pair-wise contrasts while the traditional meta-analysis only incorporate information for the pair-wise contrast considered.^{6,13} This can be seen when observing the effect estimates for celecoxib versus naproxen. The traditional meta-analyses based solely using data from trials comparing celecoxib versus naproxen reported a hazard ratio of 0.92. By contrast, the network meta-analysis reported a hazard ratio of 1.65 using all information in the network. The estimate from the network meta-analysis aligns more closely with what has been stated in FDA reviews of NSAIDs, where it has been suggested that naproxen has a more favorable cardiovascular risk profile than other NSAIDs such as ibuprofen, diclofenac, and COX-2 inhibitors. Further, the network meta-analysis borrows strength from the indirect comparisons,^{6,7,13} thereby improving the precision of effect estimates and reducing the width of the credible intervals. For example, the credible interval (0.23, 10.63) for the hazard ratio for celecoxib versus placebo from the traditional meta-analysis is much wider than the credible interval (0.72, 2.75) from the network meta-analysis.

Figure 2: Hazard ratios from network meta-analyses for myocardial infarction. Hazard ratios available from network meta-analysis are below the diagonal in blue (row-defining treatment versus column-defining treatment) and those for traditional pair-wise meta-analyses are above the diagonal and in white (column-defining treatment versus row-defining treatment).

Placebo	NA	NA	NA	1.51(0.23,10.63)	NA	NA	NA
0.83(0.38,1.67)	Naproxen	NA	NA	0.92(0.03,62.82)	NA	NA	NA
0.82(0.29,2.28)	0.99(0.33,3.1)	Diclofenac	NA	3.36(0.34,428.8)	NA	NA	NA
1.67(0.5,5.85)	2.03(0.61,7.52)	2.03(0.53,8.35)	Ibuprofen	2314000(1.6,269300000000000000000)	NA	NA	NA
1.36(0.72,2.75)	1.65(0.79,3.93)	1.66(0.74,4.08)	0.82(0.27,2.38)	Celecoxib	NA	0.95(0.36,2.51)	NA
2.1(1.24,3.63)	2.52(1.26,5.66)	2.55(0.89,7.6)	1.23(0.34,4.42)	1.53(0.69,3.28)	Rofecoxib	NA	NA
2.01(0.74,6.4)	2.45(0.95,7.38)	2.47(0.67,9.83)	1.22(0.37,3.99)	1.47(0.53,4.36)	0.96(0.33,3.2)	Lumiracoxib	NA
0.74(0.22,2.54)	0.91(0.27,3.42)	0.91(0.5,1.72)	0.45(0.1,2)	0.55(0.19,1.54)	0.36(0.1,1.24)	0.37(0.08,1.53)	Etoricoxib

Figure 2 also illustrates another advantage of network meta-analysis versus traditional pair-wise meta-analysis. In some instances, the network meta-analysis can handle zero events better than traditional meta-analysis.¹³ In the illustrative example above, the comparison of celecoxib versus lumiracoxib yielded an extremely high and uncertain hazard ratio in the traditional meta-analysis (upper diagonal) because there were no events in the celecoxib arm in both studies comparing celecoxib with lumiracoxib. Consequently, the Bayesian pair-wise meta-analysis ends up churning out very high values due to the zero cells (i.e., essentially dividing by a value close to zero). This finding would have been less pronounced for frequentist pair-wise meta-analysis although a continuity correction factor^{17,18} would have to have to be applied. By contrast, the effect estimate for celecoxib versus lumiracoxib in the network meta-analysis is estimated to be much lower (and more certain) because the network

meta-analysis harnessed information from other studies in the network, including those where there were non-zero events in the celecoxib arm. The enhanced ability to handle zeroes in the network meta-analysis may permit estimates of risk of harm without adding a continuity correction factors in some instances,^{17,18} a practice routinely performed in traditional meta-analysis software packages.

Bayesian network meta-analysis also allows the analyst to estimate the probability that a treatment is best, second best, and so on for a particular outcome (Table 1). A simple numerical summary of these probabilities – the surface under the cumulative ranking (SUCRA)¹⁹ – for each treatment can also be calculated. The SUCRA¹⁹ would be 100% when a treatment is certain to be the best and 0% when a treatment is certain to be the worst. For each treatment j out of the a competing treatments, SUCRA is calculated by calculating a vector of cumulative probabilities $\text{cum}_{j,b}$ to be among the b best treatments, $b=1,.., a$. SUCRA values enable the ranking of treatments overall for a particular outcome.¹⁹ For the illustrative example above, the SUCRA value for celecoxib is 39%, which is better than rofecoxib, lumiracoxib and ibuprofen but worse than naproxen, etoricoxib and placebo. Rofecoxib is the worst (15%), while Etoricoxib (79%) and naproxen (77%) are the best and second best for myocardial infarction. It is reassuring that rofecoxib had the lowest SUCRA for myocardial infarction given it was pulled from the market due to cardiovascular toxicity. Although these probabilities based measures are intuitive and attractive from a decision making perspective, they can be unstable and exaggerate small differences in relative effects. As such, these measures should always be presented alongside effect estimates, particularly absolute effect measures if available, and only presented when they has been significant efforts to adjust for heterogeneity and assess inconsistency within the network.

Table 1: Probability that each treatment is best, second best, etc. and the surface under the cumulative ranking (SUCRA) values for myocardial infarction. Higher SUCRA values indicate more attractive treatments with respect to the outcome of interest. The SUCRA would be 100% when a treatment is certain to be the best and 0% when a treatment is certain to be the worst.

	Treatment							
Rank	Placebo	Naproxen	Diclofenac	Ibuprofen	Celecoxib	Rofecoxib	Lumiracoxib	Etoricoxib
Best	9%	30%	15%	4%	0%	0%	1%	39%
Second	16%	18%	36%	4%	1%	0%	2%	23%
Third	22%	26%	20%	7%	6%	1%	3%	14%
Fourth	30%	16%	14%	8%	14%	2%	5%	10%
Fifth	14%	7%	8%	12%	38%	7%	9%	6%
Sixth	6%	3%	4%	22%	25%	20%	16%	4%
Seventh	2%	0%	2%	23%	12%	30%	28%	2%
Eighth	0%	0%	0%	21%	2%	40%	35%	1%
SUCRA	64%	77%	74%	32%	39%	15%	20%	79%

Network meta-analysis also offers other benefits over traditional meta-analysis beyond calculation of effect estimates and probabilities. The exercise of constructing an evidence network²⁰ itself provides the decision maker with a better sense of information available to address a research question. For example, it becomes fairly obvious when looking at the evidence network in Figure 1 that there is more data available for assessing the risk of myocardial infarction for celecoxib than ibuprofen. Similarly, it can be seen that more large scale RCTs for celecoxib were compared with diclofenac than ibuprofen – i.e., the connections to ibuprofen are narrower in comparison than those to diclofenac.

Finally, and probably the most important advantage, network meta-analyses offers more insight around heterogeneity and its impact on effect estimates. Heterogeneity within the context of network meta-analysis is viewed as between-trial variation within treatment contrasts. A critical step of any meta-analysis is to collect information about the clinical

trials, and carefully consider whether trials across the entire dataset are similar enough to be compared. By collecting and comparing information across the entire set of trials versus a subset of trials, more insight gained be gained around how the study and patient characteristics may vary across treatments. If there is minor heterogeneity, the analysis may be able to use relaxed version of the exchangeability assumption., e.g., random-effects model versus fixed effects model or adjust for heterogeneity using statistical methods (e.g., meta-regression, sub-group analysis). There are various statistical methods available to adjust for heterogeneity at the aggregate level,^{21–23} and also using both patient and aggregate level data.²⁴ If there is substantial heterogeneity, it may be inappropriate to calculate an overall summary of effect size using current body of evidence, and a more homogeneous set of trials may have to be considered. In addition to adjusting for heterogeneity, network meta-analysis allows one to formally examine whether findings are consistent across comparisons. Inconsistency can be thought of as a conflict between ‘direct’ and ‘indirect’ evidence. Similar to heterogeneity, inconsistency is caused by heterogeneity, specifically by an imbalance in the distribution of effect modifiers in the direct and indirect evidence. Decisions should be based on consistent models that fit the data. Traditional meta-analyses fail to capture this important consideration.

The use of network meta-analysis also offers advantages over traditional meta-analysis when integrating with health economic evaluations. In health economic evaluation, decisions are based on the mean net health benefits irrespective of whether differences are statistically significant. Consequently, health economic evaluations are particularly concerned with reflecting uncertainty around parameter estimates, particularly those for effect estimates. Network meta-analyses reflect uncertainty around effect estimates to a greater degree.

Firstly, network meta-analysis considers multiple treatments simultaneously, and includes information from both active and placebo controlled comparisons. Secondly, between study variance is treated as a distribution in Bayesian meta-analysis versus constant in frequentist meta-analysis, and network meta-analysis are typically Bayesian in nature. There are also analytical advantages beyond parameter estimation. There are opportunities for harnessing information derived from network meta-analysis to more accurately estimate other parameters in the health economic model;^{25–27} seamless integrate findings between network meta-analysis and health economic evaluations itself using WinBUGS/R and Excel;^{28,29} and integrate data from network meta-analysis with value of information analysis.^{15,30}

The main disadvantages of conducting a network meta-analysis relate to time, resources and complexity. More time and resources are required to conduct a systematic review including all treatments compared with conducting a traditional meta-analysis of all comparisons versus one treatment (e.g., celecoxib). For example, in the illustrative example above, reviewers would have to sift through many more studies in the systematic review involving all treatments, and also extract data from more studies (30 studies versus 15 studies). Further, more time and effort is required to collect information about the clinical trials, and carefully consider whether trials across the entire dataset are similar enough to be compared. The systematic review, data extraction and data cleaning steps are the most time and resource intensive steps of a systematic review and meta-analysis.

The analysis phase of a network meta-analysis is more complex than traditional meta-analyses. More time and effort is required to collect information about the clinical trials, and carefully consider whether trials across the entire dataset are similar enough to be compared.

Further, although the assumptions for network meta-analysis are remarkably similar to those for traditional meta-analysis, one additional assumption must be validated – similarity of the relative effects across the entire set of trials.⁶ In addition, formal assessments of inconsistency must be performed when possible, which may further add time and complexity to the analysis. Finally, the computation phase for network meta-analyses is also slightly more time consuming when compared with traditional frequentist meta-analyses because network meta-analyses have typically been performed using Bayesian statistics and these require one to specify the model, compile the model, run the sampler, choose priors, assess convergence, etc., which may take a few extra minutes to complete and time to learn. Despite the added complexity and time to perform network meta-analyses, I would argue that these are not substantive enough to justify doing a traditional meta-analysis instead of a network meta-analysis in most instances, particularly when a systematic review of all treatments has already been undertaken. For example, had the systematic review for the above illustrative example included all NSAIDs (versus focused on comparisons solely with celecoxib), it would be difficult to justify why results are presented as disparate pair-wise meta-analyses instead of an integrated network meta-analysis when the most time and resource intensive components (i.e., systematic review and data extraction) of a review had already been undertaken. Under the revised scenario, it is obvious that a network meta-analysis is a superior methodological approach compared with traditional meta-analysis. The majority of NSAID treatments have multiple comparators and traditional meta-analysis cannot account for this. Network meta-analysis also provides the opportunity to adjust for heterogeneity within and between pair-wise contrasts allows the analyst to assess inconsistency of evidence whereas traditional meta-analysis does not. Five years ago, one might be able to argue that they conducted a traditional meta-analysis as opposed to a network meta-analysis because

they felt that the methods for network meta-analysis are not well refined. However, these methods have undergone substantial development^{7,13,21–23} in recent years and there are various diagnostic tools available to assess validity of findings.^{7,13,21–23} Although the use of network meta-analysis requires the use of more sophisticated software packages such as WinBUGS and R, readily accessible code is now available,¹³ and stand-alone statistical packages⁷ to conduct network meta-analysis are also in development. Further, the capacity of researchers to conduct these types of analyses have increased dramatically through research programs such as the CIHR DSEN Collaborative Center for Network Meta-Analysis in Canada and The Centre for Research Synthesis and Decision-Making in the United Kingdom.

Based on the above, it would be difficult to justify conducting a traditional meta-analysis as opposed to a network meta-analysis in most instances moving forward (Box 1). A well conducted network meta-analysis using transparent and accepted methodologies is much better than the alternative – conducting disparate pair-wise meta-analyses and making informal comparisons between pair-wise comparisons and not formally considering differences in study and patient characteristics, consistency of evidence, and so on. Nonetheless, similar to traditional meta-analysis, particular care must be taken when conducting a network meta-analysis. As eloquently stated by John Ioannidis,³¹ *“Transition from a single patient to a study of many patients is a leap of faith in generalizability. A further leap is needed for the transition from a single study to meta-analysis and from a traditional meta-analysis to a treatment network and multiple treatments meta-analysis, let alone wider domains. With this caveat, zooming out toward larger scales of evidence may help us to understand the strengths and limitations of the data guiding the medical care of*

individual patients.” data guiding the medical care of individual patients.”

Box 1 – Key advantages and disadvantages of network meta-analysis over traditional meta-analysis

Advantages

- considers multiple treatments simultaneously
- includes active and placebo-controlled comparisons for a treatment
- combines direct and indirect evidence
- generate estimates of comparative benefits and harms among drugs that have not been compared
- enhanced ability to account for zero cells in some instances
- enables one to estimate the probability that a treatment is best, second best, and so on for a particular outcome
- provides more holistic picture of the evidence – drawing evidence diagram itself gives a better sense of the body of information available for an outcome
- enhanced ability to explore heterogeneity among studies either qualitatively or quantitatively
- ability to formally assess whether findings are consistent across comparisons
- can be seamlessly integrated into cost-effectiveness and value of information analysis
- information is better suited to informing health economic evaluations

Disadvantages

- often requires a larger systematic reviews to identify relevant studies
- more time and effort required to conduct larger systematic review and extract data from studies
- more time and effort required to collect information about the clinical trials, and carefully consider whether trials across the entire dataset are similar enough to be compared
- requires use of more sophisticated software such as WinBUGS and R, although code to conduct such analyses is becoming more accessible and more user-friendly software is in development
- analyses are more complex due to the need for analyzing inconsistency, adjusting for heterogeneity, specifying the model, choosing priors, assessing convergence, etc
- limited capacity to conduct network meta-analyses compared with traditional meta-analysis in Canada and abroad

MOVING FORWARD – EXTENSIONS TO NETWORK META-ANALYSIS TO ENHANCE DECISION MAKING

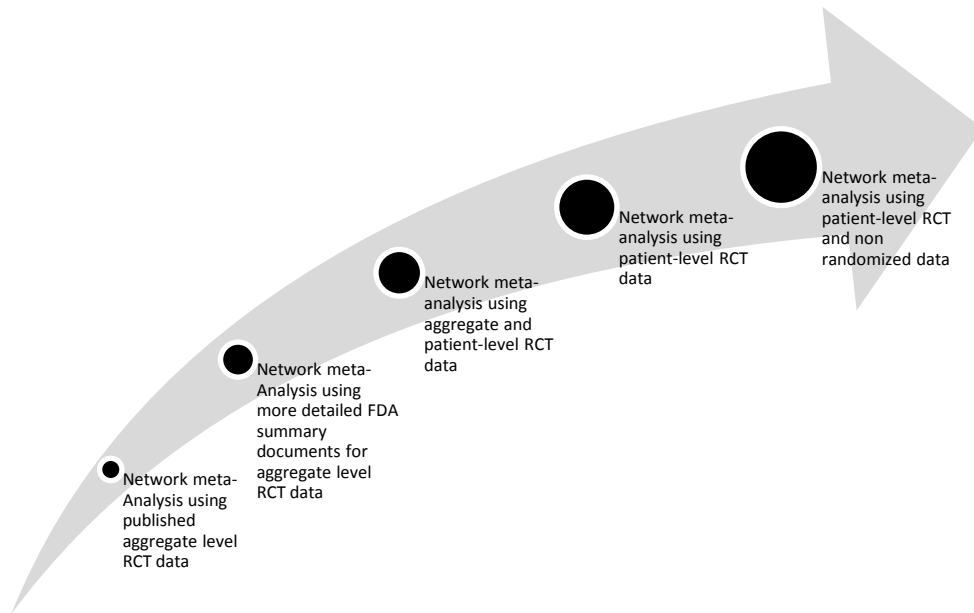
Despite the advantages of network meta-analysis over traditional meta-analysis in summarizing the benefits and harms of treatments, there is significant room for improving the use and applicability of this methodology to support decision making. The following section discusses some potential areas for improving the use of network meta-analysis using the illustrative example discussed above. Some of these methodological issues, along with a few others, will be examined in greater detail in the next section where I present six central chapters of my thesis.

Gathering more information on heterogeneity

There are differences across individuals in the benefits and harms associated with using drugs. It is often possible to explain some of this variation on the basis of patient characteristics. For example, patients who are aged ≥ 60 years have a two to three fold increase in in major vascular events versus those aged < 60 years.³² However, this valuable information is neglected when network meta-analyses are based solely on aggregate level RCT information and only considered in relative terms. Information on heterogeneity could potentially be used to help guide decision makers towards diverting the use of treatments (and funds) to patient populations who are most likely to benefit, and using the funds that would have been spent on patients with a lower benefit to harm ratio elsewhere, ultimately increasing population health in the long run. Further research is needed in this area in light of ongoing economic uncertainty/restraint in Canada and abroad. Indeed, there has have been recent attempts to gather more detailed information on heterogeneity (see Figure 3) using FDA Public Summary Documents,^{33,34} and using patient-level data.³² There has also been a surge in the development of research methodologies to explore heterogeneity within network

meta-analysis. Methods have been developed to adjust for heterogeneity when reported at aggregate level,^{21–23} and also analyze both patient and aggregate level data.²⁴

Figure 3: Changing landscape on level of information incorporated into network meta-analysis



Rapid network meta-analyses

To date, network meta-analyses have been largely underpinned by a primary systematic review. Indeed, that was the case for the illustrative example.¹⁰ However, the primary systematic review stage of a network meta-analysis takes considerable time and resources to complete and timelines may not be adequate^{35,36} to meet the needs of decision makers where decisions are made in days not months or years. In many instances, a primary systematic review may also represent a duplication of effort/resources as existing meta-analyses are sometimes available and could have been pieced together to construct the evidence network and conduct the analysis more quickly. For example, if a decision maker needed findings on

potential risk of myocardial infarction associated with celecoxib more quickly and couldn't wait for a primary systematic review to be conducted, Trelle et al¹⁰ could have potentially used existing published pair-wise meta-analyses^{11,12} to construct the network meta-analyses as opposed to conducting a primary systematic review to identify available studies and subsequently conduct the analyses. Alternatively, if a repository of data from NSAID trials were readily available, one could link the data and run and update network meta-analyses more quickly. By contrast, a rapid search may not capture all relevant trials. Further research is needed evaluating the advantages and disadvantages of approaches to conduct network meta-analyses more rapidly to support decision making, especially using data repositories such as ClinicalTrials.gov.

Considering both benefits and harms

If a potential harm is identified, it is imperative that the risk of harm is considered in light of the chance of benefit of a drug, and vice versa. However, several recently conducted meta-analyses and network meta-analyses have focused solely on the harm side of the equation. For example, a recent review of biologics focused solely on harms,³⁷ and a meta-analysis of varenicline³⁸ focused on serious adverse cardiovascular events. Indeed, the illustrative example¹⁰ above focused solely on cardiovascular risks of non-steroidal anti-inflammatory drugs. While focusing solely on harms may reduce the scope of a review and result in publications in high profile journals if a potential signal is identified, it is imperative that a well-balanced picture is presented, i.e., risk of harm information is presented alongside benefits, and presented in absolute terms. As a society, we don't want individuals who would greatly benefit from taking a smoking cessation therapy for example to stop using varenacline because they read an article³⁸ on varenacline which only considered harms, and

risks were presented largely in relative terms. As such, more research is needed evaluating methods for integrating information on the balance of absolute harms and benefits derived from network meta-analysis. There has been limited research around integrating network meta-analysis with benefit-harm assessments in Canada, although some research has been done internationally.³⁹ For example, information from the above illustrative example would ideally be coupled with a follow-up benefit-harm assessment^{40,41} where information on absolute risks of myocardial infarction (and other cardiovascular risks) are formally integrated with information data on absolute risk of gastrointestinal events; uncertainty around gastrointestinal benefits and cardiovascular harms; differences in preferences for gastrointestinal benefits/cardiovascular harms; investigate how benefit/harm profiles vary across different patient profiles, and integrated with network meta-analysis, cost-effectiveness analysis and value of information analyses methodologies. Formally combining information on both absolute benefits and harms in a systematic framework will provide a more holistic picture of the evidence.

Considering non-randomized information

Despite inclusion of randomized evidence of all available treatments and across multiple indications (e.g., Alzheimer's disease, prevention of cancer degeneration of adenomatous polyps, osteoarthritis and rheumatoid arthritis) in the illustrative example above, the number overall events was low (554 cases in 116 932 person-years), especially for some treatments such as lumiracoxib where there were only two studies and one of the studies had a zero cell. This makes it difficult to draw firm conclusions around the comparative risk of myocardial infarction among treatments using the network meta-analysis. Incorporation of non-randomized information⁴² into evidence networks could provide more data to assess the

potential risk of myocardial infarction among treatments. Indeed, traditional meta-analysis has investigated method for combining non-randomized data.⁴² The majority of network meta-analyses conducted to date have focused primarily on pooling data from randomized studies.³ However, the use of network meta-analyses which incorporates non-randomized evidence will likely increase in the future with proposed progressive licensing frameworks and increased use of product listing agreements.⁴³ Further research is needed investigating the advantages and disadvantages of incorporating non-randomized evidence into evidence networks using novel statistical approaches.^{44,45} In particular, which type of non-randomized evidence (e.g., propensity matched studies⁴⁴) should be incorporated with randomized evidence, and whether new methods where multiple groups are propensity matched (versus two treatments)⁴⁶ will provide more robust estimates.

OVERVIEW OF RESEARCH CHAPTERS

There are six central chapters, and an introduction/background and a discussion chapter. In the introduction chapter, I provide a general introduction to my thesis, overview of each of the research chapters. In this chapter I also provide a general overview of network meta-analysis, the advantages and disadvantages of conducting a network meta-analysis compared with traditional meta-analysis using an illustrative example. In the discussion chapter, I present my own integrated view on how six central chapters relate, discuss general findings, provide my overall conclusion, and research implications. In the six central chapters (and the background chapter), I provide real-world illustrative examples to show approaches to address the aforementioned methodological issues, some of which were presented in the illustrative example in the general introduction section. A more detailed description of each of the central chapters that form the basis of my thesis is provided below, and a summary is

presented in Figure 4.

Chapter 2 – Incorporating information on variability in benefits and harms into network meta-analysis using information available in FDA public summary documents

The second chapter concerns embracing information on variability in benefits and harms across patient populations to support decision making at the regulatory and reimbursement level.⁴⁷ In this chapter, I explore the strengths and limitations of using network meta-analysis to identify sub-populations of patients who are more or less likely to appreciably benefit from using a drug. In particular, I harness information available in FDA public summary documents³⁴ to compare newer oral anti-coagulants versus warfarin for the management of atrial fibrillation in different sub-populations (e.g., elderly patients, well controlled on warfarin, low risk of stroke). FDA public summary documents may also provide more detailed information on study design issues (e.g., intention to treat analysis versus per protocol). Traditionally, meta-analyses and network meta-analyses have largely considered published clinical studies in their analyses,³ which limit the ability to conduct detailed subgroup analysis. FDA public summary documents contain much more information than publications and this information will be particularly valuable for decision making moving forward, especially if the prices of drugs continue to increase. Information on sub-groups of patients who are more or less likely to appreciably benefit is particularly valuable at the time of product launch when real-world data is not available. It gives decision makers the ability to restrict use (and enhance effectiveness and cost-effectiveness)⁴⁷ initially to sub-populations with a more favorable benefit-harm profile until they gather more real-world data to support use in other populations, or provide wider access initially but monitor certain patient populations with less favorable balance of benefits and harms more closely.

Chapter 3 – Conducting rapid network meta-analysis using ClinicalTrials.gov

The third chapter explores the advantages and disadvantages of conducting rapid network meta-analysis using ClinicalTrials.gov. It is commonplace^{10,48,49} for systematic reviews and meta-analyses to perform primary systematic reviews (i.e, de novo start from scratch).⁵⁰ This is problematic for many reasons. First, primary systematic reviews require a large amount of resources to complete. The systematic review and data extraction stage (when conducted from scratch) requires many people to complete and may utilize upwards to 80% of the resources on a health technology assessment project (Personal Communication – CADTH). Second, it takes considerable time to conduct a primary systematic review. The average time to conduct a Cochrane systematic review was 1139 hours (~6 months), but ranged from 216 to 2518 hours.^{35,36} In many instances, these long timelines are impractical^{35,36} and not adequate to meet the needs of decision makers where decisions are made in days not months or years. Finally, conducting primary reviews is costly and in many instances may be an inefficient use of research dollars and tax payer money. A primary review may cost upwards to \$250,000 to complete whereas a rapid review using ClinicalTrials.gov should cost much less. There are so many research questions that need to be answered and limited capacity to conduct the research in Canada and abroad. There is an opportunity cost to devoting unnecessary time and resources to conducting redundant systematic review when you can utilize the information from ClinicalTrials.gov– these resources could have been dedicated to conducting novel research and society doesn't yield the health benefits that may be obtained from such research.

To tackle this important issue, I evaluate the strengths and limitations of conducting a rapid

network meta-analysis based solely on existing information in ClinicalTrials.gov I use the publication from Chapter 2 as the starting point, but then re-perform the review using only data reported in ClinicalTrials.gov to examine simultaneously the advantages and disadvantages of these two approaches.

Chapter 4 – Conveying information derived from network meta-analyses of complex networks

The fourth chapter applies network meta-analysis methods to complex networks, where there are a large number of studies and nodes. This approach is increasingly becoming an important tool for conducting network meta-analyses in light of the number of therapies being used and broad disease areas being considered. We will conduct a network meta-analysis of triptan monotherapies and combination therapies for treatment of migraine. In this clinical area, there are over 130 studies and 30 different monotherapy and combination therapies treatments. The proposed analysis was requested by the Ontario Drug Policy Research Network (ODPRN). Approaches for presenting data for large numbers of treatments and studies more succinctly are investigated. In particular, methods for reporting absolute probabilities of events which may assist in more succinctly reporting findings compared with approaches of presenting league tables are explored.

Chapter 5 – Network meta-analysis of harms data when events are rare

The fifth chapter investigates methods for incorporating zeroes into network meta-analysis when events are rare. Typically, special precautions do not have to be taken when conducting a network meta-analysis when there are occasional trials with a zero count within an evidence network. However, in cases where events are rare, they may be several trials with zero cells in an evidence network and this may make the network meta-analysis numerically

unstable.¹³ Traditionally, network meta-analyses have excluded studies which have zeroes in both (or all arms), whereas studies with one zero have been adjusted for using a constant (e.g., 0.5).^{13,17,18} There have been several methodological papers that have addressed the issue around handling zeroes in pair-wise meta-analysis,^{17,18} but limited research has examined how to handle zeroes when conducting a network meta-analysis. This methodological issue is addressed by evaluating the risk of serious lung infection among patients using biologics. This illustrative example is well suited for evaluating this methodological issue because there are many trials evaluating biologics which contain one or more zeroes,³⁷ and inclusion or exclusion of such trials may impact effect estimates.

Chapter 6 – Integrating information derived from a network meta-analysis using benefit-harm assessment methodologies

The seventh chapter deals with approaches for integrating information on benefits and harms of drugs into a single framework. Alternative benefit-harm assessment methodologies are evaluated,^{40,51} to consider information on benefits and harms derived from network meta-analysis. Despite the increased use of network meta-analysis in health technology assessment,⁶ there has been limited research around integrating network meta-analysis with benefit-harm assessments in Canada, although some research has been done internationally.³⁹ To evaluate specific alternative benefit-harm assessment methodologies, findings from a network meta-analysis of new oral anticoagulants for treatment of acute venous thromboembolism are integrated using several of these methods. Part 1 of this chapter consists of a network meta-analysis itself, while Part 2 integrates data from the network meta-analysis conducted in Part 1. This is a timely topic in light of Health Canada's proposed progressive licensing framework.^{43,52} The role of benefit-harm assessment could

dramatically increase in Canada in the future if progressive licensing^{43,52} becomes reality. This research could serve as an example to illustrate how network meta-analysis can be integrated with benefit harm assessment, and the capacity of different benefit-harm methodologies to incorporate various data sources; multiple benefits and harms; uncertainty around benefits and harms; differences in preferences for benefits/harms; different patient profiles; seamlessly integrated cost-effectiveness analysis and value of information analysis methodologies; and easily updated over time as new information evolves.^{40,51,53–55}

Chapter 7 – Integrating information from non-randomized studies in network meta-analysis

The seventh chapter examines the role of integrating information from non-randomized studies into network meta-analysis. As discussed previously, the use of network meta-analysis is particularly advantageous over traditional meta-analysis when evaluating a drug when it is launched to the market and comparative data or observational data are either limited or not available. Further, randomized controlled trials are often done in patients who may not be reflective of the real world. Alternatively, network meta-analysis can be undertaken after the drug has been introduced in the real-world. Incorporation of ‘real-world’ or non-randomized information into evidence networks after adoption could aid in assessing real world benefits and harms of drugs, albeit more methodologically complex. To date, the majority of network meta-analyses have focused primarily on pooling data from randomized studies.³

However, the use of network meta-analyses which incorporates non-randomized evidence will likely increase in the future with proposed progressive licensing frameworks and

increased use of product listing agreements.⁴³ Further, use may become more widespread with the development of improved and more sophisticated research methodologies.^{44,45} As such, the feasibility of integrating non-randomized evidence into existing evidence networks are investigated, using an applied example examining the risk of myocardial infarction in patients with diabetes. This Chapter was conducted within Mini-Sentinel, a distributed health data network which includes records for over 150 million patients in the United States. As part of my PhD, I was awarded a Michael Smith Foreign Study Supplement to travel and study for 3 months at the Harvard University Department of Population Medicine/Harvard Pilgrim Health Care, which is home to the FDA Mini-Sentinel distributed health network. While in Boston, I drafted two manuscripts related to integrating non-randomized studies into network meta-analyses. These two manuscripts form the basis of this chapter.

A summary of the six central chapters, and introduction, background and a discussion chapter, are presented in Figure 4.

Chapter 8 – Excel-based Tools for network meta-analysis

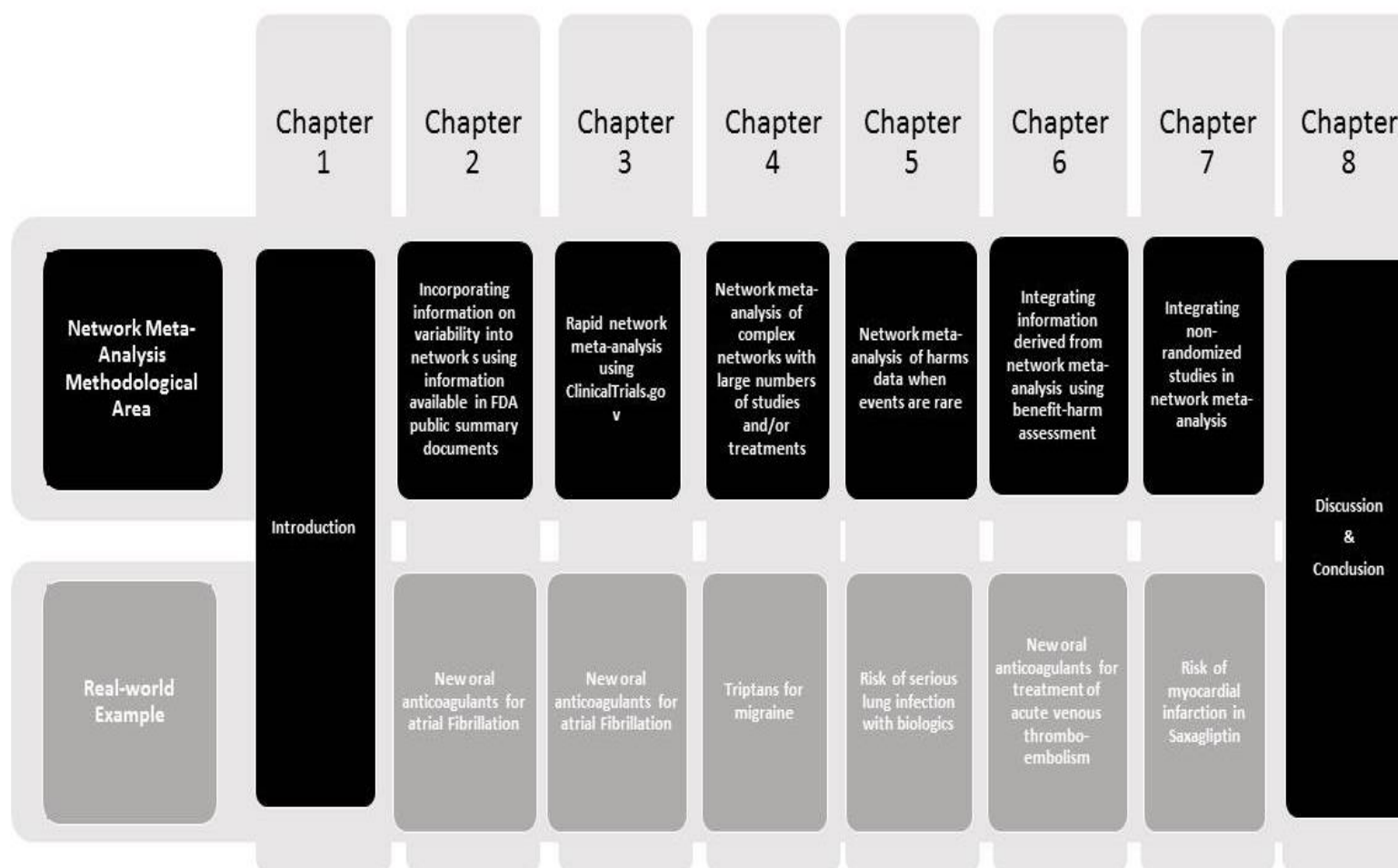
Throughout this thesis, I have developed practical approaches to link findings from a network meta-analyses conducted in WinBUGS with Microsoft Excel either directly using macros developed in Visual Basic or indirectly linking through other software packages.²⁸ Microsoft Excel is one of the most widely used and accessible software packages available. Further, Microsoft Excel is often regarded as user-friendly compared with WinBUGS. In this Chapter, a Microsoft Excel-based Tool that was developed in collaboration with a programmer over the course of my thesis is presented. Limited research has been conducted in this area. The majority of research around making network meta-analyses more accessible

have focused largely on developing stand-alone software packages that are easier to use.^{7,56}

Summary

Collectively, these Chapters demonstrate the application of pragmatic research around a number of methodological areas in network meta-analysis to address real world problems for decision makers. Ideally, the Chapters in this thesis and the approaches used for the application of network meta-analysis will be disseminated to enhance research capacity in conducting network meta-analysis in Canada.

Figure 4: Overview of chapters in thesis



CHAPTER 2: NETWORK META-ANALYSIS USING SUB-GROUP DATA FROM FDA PUBLIC SUMMARY REPORTS: AN APPLICATION COMPARING ANTITHROMBOTICS FOR ATRIAL FIBRILLATION

Systematic Review and Network Meta-analysis comparing Antithrombotic Agents for the Prevention of Stroke and Major Bleeding in Patients with Atrial Fibrillation

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CHAPTER 2: NETWORK META-ANALYSIS USING SUB-GROUP DATA FROM FDA PUBLIC SUMMARY REPORTS: AN APPLICATION COMPARING ANTITHROMBOTICS FOR ATRIAL FIBRILLATION

Systematic Review and Network Meta-analysis comparing Antithrombotic Agents for the Prevention of Stroke and Major Bleeding in Patients with Atrial Fibrillation

SUMMARY:

In this chapter, the comparative efficacy and safety of antithrombotic treatments (apixaban, dabigatran, edoxaban, rivaroxaban, apixaban, edoxaban, and vitamin K antagonists (VKA) at a standard adjusted dose (target international normalised ratio 2.0-3.0), acetylsalicylic acid, acetylsalicylic acid and clopidogrel) for non-valvular atrial fibrillation and among sub-populations is examined. Our systematic review considered information reported in FDA Public Summary Documents. In doing so, we were able to obtain information not available in published papers such as sub-group data for rivaroxaban on the intention-to-treat population.

LINKS:

This article was published in BMJ Open following peer review and can also be viewed on the journal's website at: <http://bmjopen.bmj.com/content/4/6/e004301.full.pdf+html>

The online appendices are available online:

<http://bmjopen.bmj.com/content/suppl/2014/06/02/bmjopen-2013-004301.DC1/bmjopen-2013-004301supp.pdf>

A pdf of the final publication is presented in Appendix C

CONTRIBUTION:

I was responsible for writing the paper, with guidance from supervisors and other co-authors. I conducted all network meta-analyses, and generated all tables and figures related to findings from the network meta-analysis. I also responded to all feedback on the network meta-analysis that was provided during the peer review process with guidance from supervisors and other co-authors.

ABSTRACT

Objective: To examine the comparative efficacy and safety of antithrombotic treatments (apixaban, dabigatran, edoxaban, rivaroxaban, apixaban, edoxaban, and vitamin K antagonists (VKA) at a standard adjusted dose (target international normalised ratio 2.0-3.0), acetylsalicylic acid, acetylsalicylic acid and clopidogrel) for non-valvular atrial fibrillation and among sub-populations.

Design: Systematic review and network meta-analysis.

Data sources: A systematic literature search strategy was designed and carried out using MEDLINE, EMBASE, Cochrane Register of Controlled Trials, and grey literature including the websites of regulatory agencies and health technology assessment organizations for trials published in English from 1988 to January 2014.

Eligibility criteria for selecting studies: Randomized controlled trials were selected for inclusion if they were published in English, included at least one antithrombotic treatment and involved patients with non-valvular atrial fibrillation eligible to receive anticoagulant therapy.

Results: For stroke or systemic embolism, apixaban and dabigatran 150 mg and apixaban twice daily were associated with reductions relative to standard adjusted dose VKA whereas low-dose ASA and the combination of clopidogrel plus low-dose ASA were

associated with increases. Absolute risk reductions ranged from 6 fewer events per 1,000 patients treated for dabigatran 150 mg twice daily to 15 more events for clopidogrel plus ASA. For major bleeding, edoxaban 30 mg daily, apixaban, edoxaban 60 mg daily, and dabigatran 110 mg twice daily, edoxaban 30 mg daily, and edoxaban 60 mg daily were associated with reductions compared to standard adjusted dose VKA. Absolute risk reductions with these agents ranged from 18 fewer per 1,000 patients treated each year for edoxaban 30 mg daily to 24 more for medium dose ASA.

Conclusions: Compared with standard adjusted dose VKA, new oral anticoagulants were associated with modest reductions in the absolute risk of stroke and major bleeding. People on antiplatelet drugs experienced more strokes compared with anticoagulant drugs without any reduction in bleeding risk. To fully elucidate the comparative benefits and harms of antithrombotic agents across the various sub-populations, rigorously conducted comparative studies or network meta-regression analyses of patient-level data are required.

(PROSPERO registry - CRD42012002721)

ARTICLE SUMMARY

Strengths and limitations of this study:

- This network meta-analysis includes data on edoxaban from the recently published ENGAGE AF-TIMI 48 trial
- We report detailed a priori sub-group analyses for stroke or systemic embolism and major bleeding using data derived from FDA Public Summary Documents. This allowed us to compare treatments using ITT population
- The studies pooled in this meta-analysis include antiplatelet agents in addition to newer oral anticoagulants and standard adjusted dose vitamin K antagonists
- We present findings on both the relative and absolute scale, and graphically illustrate absolute risks using icon arrays
- Comparisons between antithrombotic treatments were largely comprised of single studies, albeit large studies
- There is notable heterogeneity and the small number of studies limits the analyses that can be conducted to account for heterogeneity in the absence of patient-level data
- Icon arrays only consider the primary efficacy and safety endpoints of underlying studies and do not for different clinical consequences associated with each of the outcomes

INTRODUCTION

Atrial fibrillation (AF) is a common cardiac arrhythmia associated with increased morbidity and mortality.^{1,2} Patients with AF sustain an increased risk of arterial thromboembolism and stroke, associated with high recurrence and substantial debilitating impact. Therefore, antithrombotic strategies using anticoagulant drugs and antiplatelet agents are recommended for AF patients presenting with risk factors for stroke. Antithrombotic therapy is also associated with a risk of bleeding; therefore, the beneficial effects on stroke prevention should always be compared against a patient's risk of major bleeding.^{1,2}

Existing guidelines recommend anticoagulant therapy for patients at intermediate or high risk of stroke.^{1,2} Although standard adjusted dose vitamin K antagonists (VKA) (e.g., warfarin) has been the cornerstone treatment for reducing the risk of stroke or systemic embolism (SE) in this population, it is associated with several drawbacks.² which have prompted the development of newer oral anticoagulants such as direct thrombin (dabigatran) and Xa (e.g. apixaban, edoxaban rivaroxaban) inhibitors.^{1,2} While some of these newer treatment options have been demonstrated to be efficacious in preventing stroke or SE compared to standard adjusted dose VKA, the relative efficacy and risk of bleeding of newer oral anticoagulants, both among themselves and in comparison to antiplatelet agents, is not clear, especially in certain sub-populations of patients, e.g., CHADS₂ score <2 or ≥2; time in therapeutic range (TTR) < 66% or ≥ 66%; Age <75 or ≥ 75 years. Therefore, the objective of this paper was to compare antithrombotic agents for the prevention of stroke and major bleeding in patients

with non-valvular AF and among sub-populations.

METHODS

Published literature was identified by searching MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, BIOSIS Previews, PubMed and the Cochrane Central Register of Controlled Trials were searched through the Ovid interface to identify English-language clinical articles published from 1988 to January 23, 2014. Regular alerts were also established. Websites of regulatory agencies, Canadian and major international health technology assessment agencies, clinical practice guidelines as well as The Cochrane Library (2012, Issue 6) and University of York Centre for Reviews and Dissemination databases were searched. Complete details of the electronic search strategy, including any limits used, are reported in Appendix 1. The protocol was published online and was registered in the PROSPERO International Prospective Register of Systematic Reviews (PROSPERO registry - CRD42012002721).

The population of interest was individuals with non-valvular AF requiring anticoagulation (including all risk levels and regardless of any comorbidities). The following treatments were included in the review: apixaban, dabigatran, edoxaban, rivaroxaban, standard adjusted dose VKA, acetylsalicylic acid (ASA), ASA and clopidogrel. Numerous outcomes were considered and results are reported elsewhere;³ however, the focus of this publication is the outcomes of all-cause stroke or SE and major bleeding as defined by the International Society on Thrombosis and Haemostasis [ISTH] definition),⁴ which were the primary

efficacy and safety outcomes used in the newer oral anticoagulant studies.

Active and placebo-controlled randomized controlled trials (RCTs) were selected for inclusion if they were published in English, included at least one antithrombotic treatment under review (using pre-specified doses), reported data for stroke/SE or major bleeding, and involved patients with non-valvular AF eligible to receive anticoagulant therapy, regardless the level of stroke risk. Trials that included patients with contraindication to anticoagulant treatment were excluded. VKA trials were included if the dose was adjusted to a target international normalised ratio (INR) 2.0-3.0. Any dose of ASA was considered for inclusion, but ASA dose was stratified in the analysis as low (≤ 100 mg daily), medium (>100 mg to ≤ 300 mg daily), or high (>300 mg daily). We only included new oral anticoagulants which had at least one large phase III study. Three reviewers independently extracted the data on baseline characteristics, intervention(s) evaluated, including dose, duration, and relevant co-medication and results for each included article, using a standardized template. All extracted data was checked for accuracy by three independent reviewers. Any disagreements in the assessment of these data were resolved through discussion until consensus was reached. Quality assessment of RCTs was also performed independently by two reviewers using a standardized table based on major items from the SIGN 50 instrument for internal validity.⁵ The trial selection process is presented in a flowchart based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)⁶ statement (Appendix 2).

Bayesian network meta-analyses were conducted using WinBUGS software (MRC Biostatistics Unit, Cambridge, UK). A binomial likelihood model⁷ which accounts for the use of multi-arm trials was used for the analyses given the datasets provided were

dichotomous outcomes and included multi-arm trials. Trials with zero cells in both arms or nodes where there were no events were excluded from the evidence networks because they do not contribute information or allow interpretable information.⁷ Both fixed and random-effects network meta-analyses were conducted, although the fixed-effects model was chosen for the reference case analysis, as the evidence network was largely comprised of single study connections. We modeled point estimates and 95% credible intervals for odds ratios (OR) using Markov Chain Monte Carlo methods. The absolute risk difference per 1000 patients treated each year for each outcome was also calculated, based on the standard adjusted dose VKA arm of the Randomized Evaluation of Long-Term Anti-coagulation Therapy (RE-LY) trial.⁸ The RE-LY trial⁸ was selected because it contained data for both CHADS₂<2 and CHADS₂≥2 and had detailed data available from the Food and Drug Administration (FDA) Public Summary Report.⁹ We also assessed the probability that each treatment was the most efficacious regimen, the second best, the third best, and so on.¹⁰ Vague or flat priors, such as N(0, 100²) were assigned for basic parameters throughout, although informative priors were considered.¹¹ Assessment of model fit was based on deviance information criterion (DIC) and comparison of residual deviance to number of unconstrained data points.^{7,12} To ensure convergence was reached, trace plots and the Brooks-Gelman-Rubin statistic were assessed.¹³ Three chains were fit in WinBUGS for each analysis, with at least 40,000 iterations, and a burn-in of at least 40,000 iterations. We also qualitatively compared the results from our network meta-analysis with direct pair-wise estimates. Frequentist pair-wise meta-analyses were conducted using R (R Language and Environment for Statistical Computing, Vienna, Austria) and package meta.¹⁴

A key assumption behind network meta-analysis is that the analysed network is consistent,

i.e., there is no conflict between direct and indirect evidence.¹⁵ To assess inconsistency, we compared deviance and DIC statistics in fitted consistency and inconsistency models.¹⁵ We also plotted the posterior mean deviance of the individual data points in the inconsistency model against their posterior mean deviance in the consistency model to identify any loops in where inconsistency is present (Appendix 10).¹⁵ Additionally, the results from our network meta-analysis were qualitatively compared with direct frequentist pair-wise estimates.

Network meta-analysis also requires that studies are sufficiently similar in order to pool their results.¹⁶ Available study and patient characteristics were assessed to ensure similarity and to investigate the potential impact of heterogeneity on effect estimates. Clinical and methodological heterogeneity was identified in a number of areas. The issues identified were similar to those reported in previous systematic reviews of anticoagulant drugs (e.g., differences in TTR, CHADS₂ score).¹⁷ Heterogeneity was assessed by conducting network meta-analysis with the following pre-specified subgroup data reported in the individual RCTs: TTR < 66% or $\geq$ 66%; CHADS₂ score <2 or $\geq$ 2; Age <75 or $\geq$ 75 years.¹⁷ The data to conduct these sub-group analyses were derived from FDA Public Summary Documents when not available in the publications.^{9,18,19} Secondary evidence networks were constructed for each of the sub-group analyses. The WinBUGS code⁷ and data needed to replicate all analyses are available online.

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RESULTS

Study Characteristics of included studies

The systematic review included 16 individual RCTs (reported in 32 publications and FDA reports); all evaluated the efficacy and safety of antithrombotic agents: apixaban (5 mg twice daily), dabigatran (150 or 110 mg twice daily), edoxaban (30 or 60 mg daily), rivaroxaban (20 mg daily), standard adjusted dose VKA, ASA (low dose (< 100 mg daily); medium dose (100-300 mg daily), or low dose-ASA plus clopidogrel (75 mg daily) in patients with non-valvular AF. None of the included studies directly compared one new oral anticoagulant drug with another (Appendix 4). Of the 82,396 randomized patients included in the primary analysis, five large multicentre trials account for 78,296 patients (96%): ENGAGE AF-TIMI 48 (n=21,105),²⁰ ARISTOTLE (n=18,201),²¹ RE-LY (n=18,113),⁸ ROCKET-AF (n=14,264)²² and ACTIVE-W (n=6706).²³ Most trials included stroke and SE as a primary efficacy outcome, while bleeding events were a frequent safety outcome. Follow-up ranged from 12 weeks to 3.5 years. All trials published results between 1989 and 2013. Mean CHADS₂ score was reported in eight trials, encompassing the vast majority of patients included in the systematic review. Reported CHADS₂ scores were consistent with a high-risk population (CHADS₂ ≥ 2), with patients from ROCKET-AF²² showing the highest risk for stroke (mean CHADS₂ = 3.5).

Mean age across the included trials ranged from 62 years to 83 years (Appendix 3). All trials included patients of both gender and had a higher proportion of male participants in most studies. However, the proportions of patients with a prior stroke or TIA varied substantially across the included trials, ranging from 3% in JAST to 55% in ROCKET-AF.²² The same

observation can be made regarding the proportions of patients with other concomitant conditions, i.e. congestive heart failure, hypertension, diabetes, myocardial infarction, and prior vitamin K antagonist experience. TTR was reported in all but one trial that included a standard adjusted dose VKA treatment arm. Patient baseline characteristics are summarized in Appendix 3.

The studies were individually critically appraised and the details are reported elsewhere.³ Overall, there was substantial variation in study quality. However, large multicentre trials comparing newer anticoagulants with standard adjusted dose VKA such as ENGAGE AF-TIMI 48 (n=21,105), ARISTOTLE (n = 18,201), RE-LY (n = 18,113), and ROCKET-AF (n = 14,264), which account for the vast majority of patients included in the systematic review, appear to be methodologically rigorous.

Stroke or Systemic Embolism

The evidence network (Figure 1) for the primary analysis was comprised of twelve RCTs representing eight treatments in addition to placebo/observation (N =82,396). Four RCTs (Chung et al,²⁶ PETRO,²⁴ WASPO²⁵, and Yamashita et al²⁷) were not included in the analysis because they did not report data for this outcome or had zeroes in both arms.

Dabigatran (150 mg twice daily) and apixaban were associated with reductions in stroke or SE relative to standard adjusted dose VKA (Figure 2). The use of these two agents led to absolute risk reductions ranging from 4 to 6 fewer events per 1,000 patients treated each year. By contrast, low-dose ASA and the combination of clopidogrel plus low-dose ASA appeared to have a higher risk of stroke or SE than standard adjusted dose VKA, leading to

an increase in the number of stroke or SE ranging from 14 to 15 more events per 1,000 patients treated each year (Figure 4 and Appendix 6). No differences were detected between standard adjusted dose VKA and each of the following interventions: dabigatran (110 mg twice daily), edoxaban (30 mg or 60 mg daily), rivaroxaban, and medium-dose ASA (Figure 3).

The estimates of effect derived from the direct pair-wise comparisons aligned well with those obtained from the network meta-analysis in both direction and magnitude (Appendix 6).

Furthermore, the posterior mean residual deviance (29.41) is close to the number of unconstrained data points (27), which is an indication of reasonable model fit. A number of sub-group analyses and alternative modeling strategies were conducted on the primary analysis, including adjusting for CHADS₂, TTR, and age (Table 1). We also conducted a sensitivity analysis where we included the AVERROES²⁸ and ACTIVE A²⁹ trials (Appendix 11). These studies were excluded from the main analysis because we required patients to be eligible for anticoagulant therapy, including treatment with a VKA. The results differed slightly from the reference case (Appendix 11). The primary analysis was conducted using a fixed-effects model because the network was comprised of single study connections; these results were also compared against those obtained using a random-effects model with informative and vague priors on the standard deviation, and found to be similar in magnitude although wider credible intervals were observed (Appendix 9).

Major bleeding

The evidence network for the primary analysis for major bleeding was comprised of 15 RCTs representing eight treatments in addition to placebo/observation (N =83,015). The evidence network for major bleeding is similar to the evidence network for stroke or SE

(Figure 1) but includes one extra RCT (WASPO²⁵) comparing medium dose ASA with standard adjusted dose VKA, and two extra RCTs (Chung et al,²⁶ and Yamashita et al²⁷) comparing edoxaban with standard adjusted dose VKA (Appendix 5).

Edoxaban 30 mg daily, apixaban, edoxaban 60 mg daily, and dabigatran 110 mg twice daily were associated with reductions in the risk of major bleeding compared with standard adjusted dose VKA (Figure 2). No differences for major bleeding were detected between standard adjusted dose VKA and each of the remaining interventions: dabigatran 150 mg twice daily, rivaroxaban, clopidogrel plus low-dose ASA, and all ASA dosages (Figure 2). The absolute risk difference of major bleeding relative to standard adjusted dose VKA ranged from 18 fewer to 24 more events per 1000 patients treated per year (Figure 4 and Appendix 7). A summary of the results for the Bayesian and direct pair-wise meta-analyses is shown in Appendix 7, and Bayesian network meta-analysis results are represented graphically in Figure 2. Complete results from the Bayesian network meta-analysis for all possible comparisons are presented in Figure 3.

The estimates of effect derived from the direct pair-wise comparisons aligned well with those obtained from the network meta-analysis in both direction and magnitude (Appendix 7). Furthermore, the posterior mean residual deviance (38.0) is close to the number of unconstrained data points (35), which is an indication of reasonable model fit. A number of sub-group analyses and alternative modeling strategies were conducted on the primary analysis (Table 1). We also conducted a sensitivity analysis where we included the AVERROES²⁸ and ACTIVE A²⁹ trial (Appendix 11), as well as analyses using a random-effects model with vague and informative priors (Appendix 9).

Benefit-Harm Assessment – Stroke or systemic embolism versus major bleeding

Figure 3 summarises the results for all pair-wise comparisons derived from the Bayesian fixed-effects network meta-analysis (Appendix 9). Results relative to standard adjusted dose VKA have been discussed above. For pair-wise comparisons among newer oral anticoagulants for stroke or SE, dabigatran 150 mg twice daily was associated fewer events versus dabigatran 110 mg twice daily, edoxaban 30mg daily, edoxaban 60 mg daily, and rivaroxaban. Apixaban and rivaroxaban were also associated with fewer events compared to edoxaban 30mg daily. There were no differences among low-dose ASA, medium-dose ASA, and clopidogrel plus low-dose ASA. However, low-dose ASA and the combination of clopidogrel plus low-dose ASA were associated with increases in stroke or systemic embolism compared to all newer oral anticoagulants. For major bleeding, apixaban, dabigatran 110 mg twice daily were associated with fewer events versus dabigatran 150 mg twice daily and rivaroxaban. Edoxaban 30 mg daily was associated with fewer events than other new oral anticoagulants, while edoxaban 60 mg daily was associated with fewer events compared with rivaroxaban and clopidogrel plus low-dose ASA. The risk of major bleeding for apixaban was lower compared to clopidogrel plus low-dose ASA. There were no differences associated with the ASA treatments, both for comparisons among themselves and compared to the anticoagulant treatments.

Figure 4 plots the absolute risk for stroke or SE and major bleeding per 1000 treated for the 10 treatments analyzed. Data in Figure 4 were obtained from the results presented in Appendix 6 and 7. Examination of the data in Figure 4 suggests that the balance of benefits and harms of the new oral anticoagulants for stroke or systemic embolism and major

bleeding is positive compared to standard adjusted dose VKA (decrease in stroke or systemic embolism and/or major bleeding) and largely similar among one another. Comparison of all anticoagulant treatment (including standard adjusted dose VKA) to ASA, or ASA in combination with clopidogrel indicates that whereas the new oral anticoagulants decrease the risk of both stroke or systemic embolism and major bleeding, ASA has a less favorable balance of benefits and harms, i.e., fails to minimize the risk of stroke or systemic embolism and/or major bleeding.

DISCUSSION

We identified 16 RCTs comparing antithrombotic agents for the prevention of all cause stroke or systemic embolism and major bleeding in patients with AF. To the best of our knowledge, this is the most up-to-date systematic review and network meta-analysis^{30–34} to synthesize the available benefits and harms on newer oral anticoagulants, standard adjusted dose VKA, and antiplatelet agents for the prevention of stroke and major bleeding in patients with non-valvular AF (Appendix 12). Harenberg et al³⁰ recently summarized the published indirect comparisons and network meta-analyses evaluating newer oral anticoagulants for AF and an earlier unpublished version of our analysis¹⁷ was considered among the most comprehensive analyses at that time.³⁰ This network meta-analysis expands upon that unpublished report.¹⁷ Overall, our findings align with those reported in previously published network meta-analyses;^{30,31,33} however, unlike previous analyses,³⁰ we include recently published edoxaban data,²⁰ and also include antiplatelet agents. We also present detailed evidence networks³⁵ to illustrate the body of evidence for each outcome; report analysis using multiple statistical models (Appendix 9); report detailed *a priori* sub-group analyses

for each outcome using data derived from FDA Public Summary Documents;^{9,18} present findings on both the relative and absolute scale,^{36,37} and graphically illustrate results using icon arrays. Our network meta-analysis was registered in PROSPERO, and also adheres to PRISMA reporting standards. It also differs from a recently published traditional meta-analysis by Ruff et al³² given we report comparison of newer oral anticoagulants versus each other, and also include comparisons with antiplatelet agents.

For stroke or systemic embolism, dabigatran 150 mg and apixaban twice daily were associated with reductions in stroke or systemic embolism relative to standard adjusted dose VKA. By contrast, low-dose ASA and the combination of clopidogrel plus low-dose ASA appeared were associated with increases in stroke or systemic embolism relative to standard adjusted dose VKA. No differences were detected between standard adjusted dose VKA and each of the following interventions: dabigatran 110 mg twice daily, edoxaban 30 and 60 mg daily, rivaroxaban, medium-dose ASA, and no treatment/placebo. The absolute risk reduction of stroke or systemic embolism relative to standard adjusted dose VKA ranged from 6 fewer to 15 more events per 1000 patients treated per year, with dabigatran 150 mg twice daily yielding the largest absolute risk reduction and clopidogrel plus low-dose ASA the largest absolute risk increase.

For major bleeding, edoxaban 30 mg daily, apixaban, edoxaban 60 mg daily, and dabigatran 110 mg twice daily were associated with a decreased risk of major bleeding relative to standard adjusted dose VKA. No differences for major bleeding were detected between standard adjusted dose VKA and each of the remaining interventions: dabigatran 150 mg twice daily, rivaroxaban, clopidogrel plus low-dose ASA, and all ASA dosages. The absolute risk difference of major bleeding relative to standard adjusted dose VKA ranged from 18

fewer to 24 more events per 1000 patients treated, with edoxaban 30 mg daily yielding the largest absolute risk reduction and medium dose ASA the largest absolute risk increase. Results of network meta-analyses reflect the relative efficacy and safety profile of antiplatelet and anticoagulant drugs as documented by large clinical trials. Thus, international guidelines^{1,2} for prevention of stroke in patients with AF also recommended oral anticoagulation over antiplatelet therapy as the latter had only modest protective effects. With respect to the new oral anticoagulants none of the guidelines has given a recommendation to prefer one of the new oral anticoagulants over another.^{1,2}

Network meta-analysis involves pooling of trials. We observed variability across studies included in the evidence network in terms of CHADS₂, age and TTR (Appendix 3 and 4). For example, patients using rivaroxaban had a higher risk of stroke because ROCKET-AF²² included patients with CHADS₂ ≥ 2 . We used publicly available information in FDA Public Summary documents to adjust for heterogeneity. FDA Public Summary documents^{9,18,19} enhanced our ability to account for variability across studies, and allowed us to use intention to treat (ITT) population for rivaroxaban versus per-protocol as-treated population reported in publication²². Results from these sub-group analyses differed slightly from those reported in the primary analysis, indicating that there may be differences in the benefits and harms across sub-groups. This becomes more apparent when sub-group analyses are reported on the absolute scale.³ It is unclear whether the absolute risk reductions associated with these differences translate into clinically meaningful benefits in practice, especially in sub-populations of patients with a lower baseline risk of stroke or systemic embolism. To fully elucidate the comparative benefits and harms of antithrombotic agents across the various sub-populations, rigorously conducted comparative studies,^{38,39} or network meta-regression

analyses of patient-level data⁴⁰ are required.

There are several limitations with the analysis we employed. First, there is notable heterogeneity in patients and study characteristics (Appendix 3 and 4). However, the small number of studies limits the analyses that can be conducted to account for heterogeneity in the absence of patient-level data. Second, there is insufficient sub-group data available for other outcomes reported in the RCTs included. As a consequence, detailed analysis was limited to two outcomes – stroke and SE and major bleeding. Third, we reported the results from the fixed-effects model in the main text. We felt that this was appropriate as the nodes in evidence networks are connected largely by single studies. Effect estimates derived from the fixed-effects model aligned more closely with the direct estimates. Reporting results from the fixed-effects model in the main text likely biases results in favour of the new oral anticoagulants, as treatments that achieved statistically significant results in the primary RCTs retained statistically significant findings when using the fixed-effects model, but not always when using the random-effects model due to the prior¹¹ on the between study variance. Nevertheless, the results from the random-effects model have also been reported in Appendix 9, along with detailed discussion around the limitations in using the fixed-effects model. Fourth, the absolute risk reduction for the network meta-analysis was calculated using the event rate in the standard adjusted dose VKA arm of the RE-LY study. The RE-LY trial was selected because it contained data for both $\text{CHADS}_2 < 2$ and $\text{CHADS}_2 \geq 2$ and had detailed data made publicly available following an FDA review of dabigatran. Use of a different study (e.g., ARISTOTLE) for baseline event rate data is unlikely to change the results substantially given that the event rates in standard adjusted dose VKA arms were similar across studies. Fifth, we present findings using graphics that have been largely

applied in the network meta-analysis literature,⁴¹ such as a table with odds ratios for all pairwise comparisons. This method of presenting findings on the relative scale is problematic when you are conducting assessments to compare the balance of benefits and harms, which need to be standardized. As such, we also provided results in absolute terms. We report our findings using icon arrays, although it should be noted that these results do not account for the utility values based upon patient preferences for each of the outcomes,^{42,43} nor do they reflect uncertainty although we report absolute reductions on the risk benefit plane reflecting uncertainty in Appendix 8. There are other methods available that can incorporate patient preferences for outcomes.^{42,43} Further, estimates of benefit and harm with several of the therapies (e.g., rivaroxaban) come from one trial and thus such data are not particularly robust. Further research is needed comparing the balance of benefit and harms using other research methodologies, incorporating other relevant outcomes, patient preferences for each of the outcomes,^{42,43} and additional studies when they become available. Finally, haemorrhagic stroke is also considered a major bleed in underlying studies. Accordingly, we may have double counted haemorrhage stroke in this analysis. Unfortunately, we are not able to account for this issue in all included studies. Nonetheless, it is important to note this limitation and highlight that this potentially biases results in favor of newer oral anticoagulants given these agents were associated with reductions in these events.

CONCLUSIONS

Compared with standard adjusted dose VKA, dabigatran 150 mg and apixaban twice daily were associated with reductions in the incidence of stroke or systemic embolism in patients with AF, whereas, low-dose ASA and the combination of clopidogrel plus low-dose ASA increased the risk relative to standard adjusted dose VKA at preventing stroke or systemic

embolism. Edoxaban 30 mg daily, apixaban, edoxaban 60 mg daily, and dabigatran 110 mg twice daily and was associated with a reduced risk in major bleeding compared with standard adjusted dose VKA. Although the results of the current review revealed that there were differences in stroke or systemic embolism and major bleeding among antithrombotic agents in the management of patients with AF in relative terms, it is unclear whether the absolute risk reductions associated with these differences translate into clinically meaningful benefits in practice, especially in sub-populations of patients with a lower baseline risk of stroke or systemic embolism. Rigorously conducted comparative studies or network meta-regression analyses of patient-level data are required to fully elucidate the comparative benefits and harms of antithrombotic agents across the various sub-populations.

TABLES AND FIGURES

Table 1: Sub-group and sensitivity analyses for stroke or systemic embolism and major bleeding relative to standard adjusted dose VKA, Odds ratios $\pm$ 95% Credible Intervals versus standard adjusted dose VKA

Treatment	Reference Case – Fixed Effect NMA	Subgroup analysis by CHADS ₂ Score		Subgroup analysis by Age		Subgroup analysis by TTR	
		CHADS ₂ < 2	CHADS ₂ ≥ 2	Age < 75 years	Age ≥ 75 years	TTR < 66%	TTR ≥ 66%
Stroke or Systemic Embolism							
Dabigatran 150 mg twice daily	0.66 (0.53,0.82)	0.61 (0.37,1)	0.66 (0.52,0.85)	0.63 (0.46,0.87)	0.66 (0.48,0.9)	0.54 (0.39,0.73)	0.81 (0.58,1.11)
Apixaban 5 mg twice daily	0.78 (0.65,0.94)	0.86 (0.57,1.28)	0.78 (0.63,0.95)	0.85 (0.67,1.07)	0.71 (0.53,0.95)	0.79 (0.62,1.003)	0.79 (0.60,1.05)
Edoxaban 60 mg daily	0.87 (0.74,1.02)	NA	0.87 (0.74,1.01)	0.91 (0.73,1.14)	0.83 (0.66,1.04)	0.83 (0.65,1.07) [†]	0.91 (0.73,1.13) [†]
Rivaroxaban 20 mg daily	0.88 (0.74,1.04)	NA	0.88 (0.74,1.04)	0.95 (0.75,1.2)	0.8 (0.63,1.03)	0.81 (0.65,1.01)	0.72 (0.47,1.1)
Dabigatran 110 mg twice daily	0.91 (0.74,1.12)	1 (0.64,1.55)	0.89 (0.71,1.12)	0.93 (0.7,1.24)	0.88 (0.66,1.19)	0.91 (0.69,1.19)	0.9 (0.66,1.24)
Edoxaban 30 mg daily	1.14 (0.98,1.32)	NA	1.14 (0.98,1.32)	1.16 (0.94,1.44)	1.13 (0.91,1.4)	1.01 (0.80,1.28) [†]	1.24 (1.01,1.24) [†]
Medium Dose ASA (> 100 mg and ≤ 300 mg daily)	1.35 (0.74,2.47)	1.97 (0.63,6.73) **	NA	NA	NA	NA	NA
Low Dose ASA (≤ 100 mg daily)	1.87 (1.26,2.8)	2.2 (1.18,4.25)	2.1 (0.91,5.15) *	NA	2.04 (1.33,3.20)	NA	NA
Clopidogrel 75 mg daily & Low dose Aspirin (≤ 100 mg daily)	1.93 (1.42,2.64)	3.16 (1.39,8.22)	1.15 (0.84,1.57)	NA	NA	1.52 (0.96,2.45)	2.4 (1.59,3.71)
Major Bleeding							
Edoxaban 30 mg daily	0.46 (0.4,0.54)	NA	0.46 (0.4,0.54)	0.50 (0.41,0.61) ‡	0.51 (0.41-0.62) ‡	0.45 (0.35,0.58) ‡ [†]	0.51 (0.43,0.61) ‡ [†]
Apixaban 5 mg twice daily	0.69 (0.6,0.8)	0.59 (0.44,0.78)	0.73 (0.62,0.87)	0.73 (0.6,0.89)	0.65 (0.52,0.80)	0.57 (0.45,0.71)	0.81 (0.67,0.98)
Edoxaban 60 mg daily	0.79 (0.69,0.9)	NA	0.79 (0.69,0.9)	0.74 (0.62-0.90) ‡	0.82 (0.68-0.98) ‡	0.69 (0.55,0.87) ‡ [†]	0.83 (0.70,0.97) ‡ [†]

Treatment	Reference Case – Fixed Effect NMA	Subgroup analysis by CHADS ₂ Score		Subgroup analysis by Age		Subgroup analysis by TTR	
		CHADS ₂ < 2	CHADS ₂ ≥ 2	Age < 75 years	Age ≥ 75 years	TTR < 66%	TTR ≥ 66%
Dabigatran 110 mg twice daily	0.8 (0.69,0.93)	0.65 (0.47,0.89)	0.86 (0.73,1.02)	0.62 (0.49,0.77)	1.02 (0.84,1.25)	0.74 (0.61,0.91)	0.86 (0.69,1.06)
Dabigatran 150 mg twice daily	0.93 (0.81,1.08)	0.77 (0.57,1.04)	1.01 (0.86,1.19)	0.7 (0.56,0.86)	1.19 (0.98,1.45)	0.76 (0.62,0.94)	1.15 (0.94,1.4)
Rivaroxaban 20 mg daily	1.03 (0.89,1.19)	NA	1.03 (0.89,1.19)	0.93 (0.76,1.13)	1.15 (0.93,1.41)	0.92 (0.77,1.1)	1.3 (1.01,1.69)
Low Dose ASA (≤ 100 mg daily)	1.05 (0.6,1.87)	0.83 (0.42,1.64)	1.6 (0.55,5.02) *	NA	1.01 (0.57,1.78)	NA	NA
Clopidogrel 75 mg daily & Low dose Aspirin (≤ 100 mg daily)	1.1 (0.83,1.47)	1.51 (0.89,2.61)	0.97 (0.69,1.36) †	NA	NA	0.66 (0.42,1.02)	1.66 (1.12,2.47)
Medium Dose ASA (> 100 mg and ≤ 300 mg daily)	1.79 (0.63,5.67)	1.48 (0.11,19.07)**	NA	NA	NA	NA	NA

ASA= acetylsalicylic acid; mg= milligram; NA=not available; NMA= network meta-analysis; OR=odds ratio; TTR= time in therapeutic range; VKA=vitamin K antagonist

* Results may be slightly biased against LDASA. Derived from BAFTA study where CHADS₂ subgroup data stratified by CHADS₂ 1-2 (vs. 0-1) and CHADS₂ 3-6 (vs. 2-6).

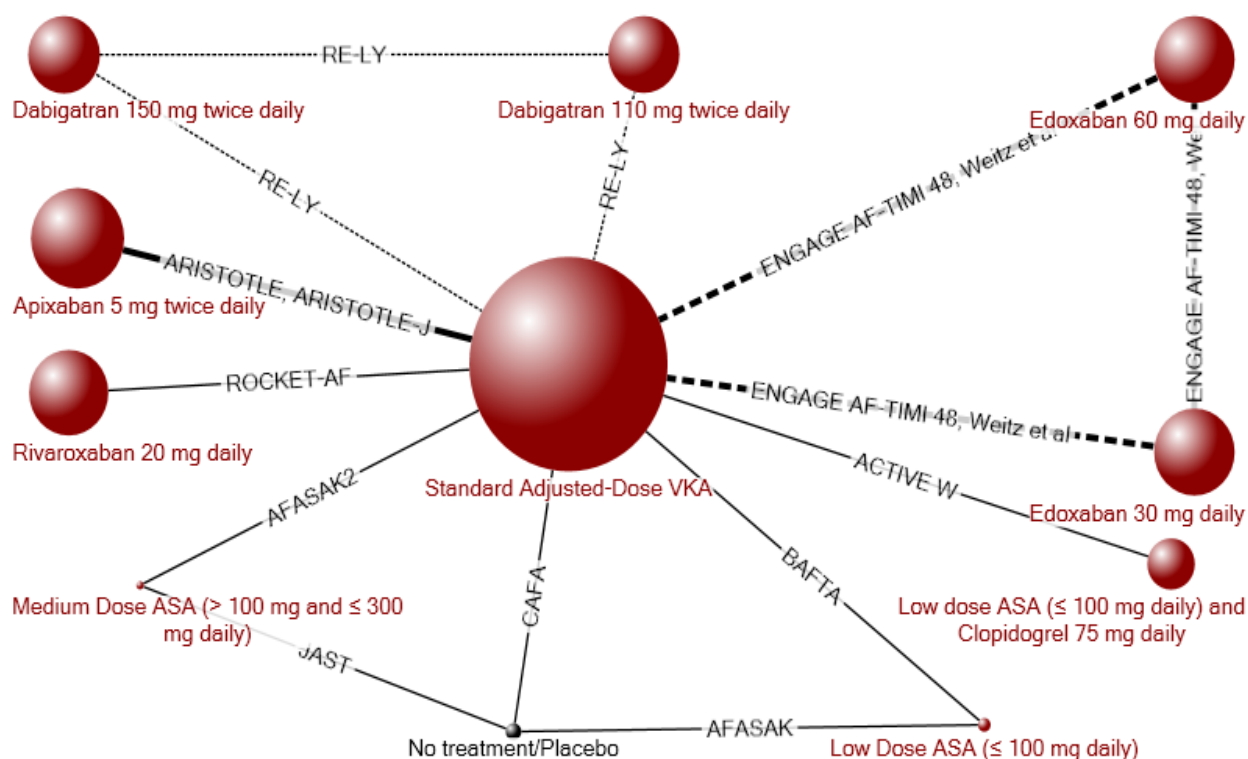
** Results may be slightly biased against medium-dose ASA. Based on study level results from CAFA and JAST studies. Although these studies consisted primarily of low-risk populations, some patients may have CHADS₂ scores greater than 2.

† Estimated from subgroup study by Healey et al 2008

¶ Data provided from ENGAGE AF-TIMI 48²⁰ uses TTR greater than 60%

‡ Based on overall time period where overall time period was defined as first dose to the last dose plus 3 days.

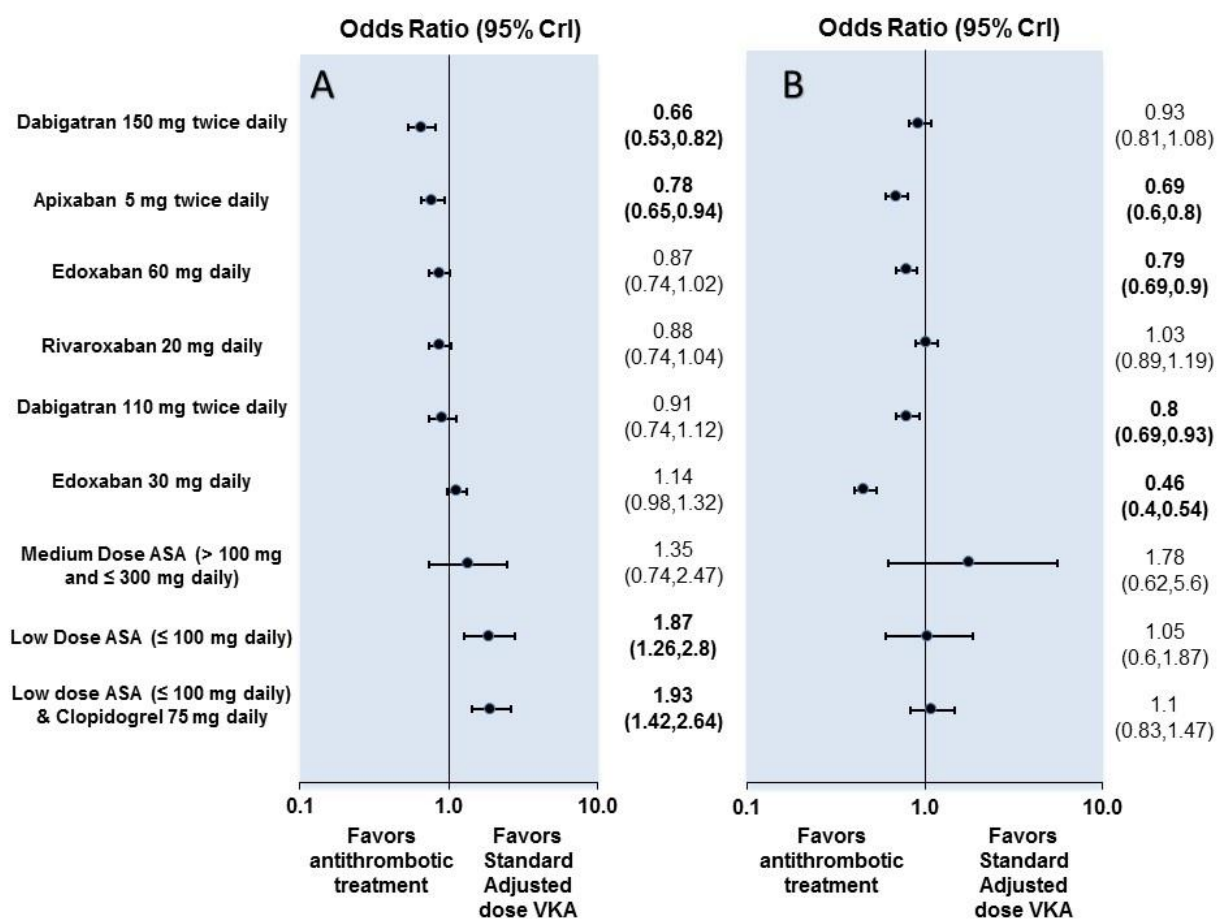
Figure 1: Evidence network for all cause stroke or systemic embolism.* The width of the lines is proportional to the number of randomized controlled trials comparing each pair of treatments, and the size of each treatment node is proportional to the number of randomised participants (sample size). A dotted line indicates a three-arm randomized controlled trial and a black node indicates a node included in the analysis but not reported in the main text.



ASA= acetylsalicylic acid; mg= milligram; RCT= RCT = randomized controlled trial; VKA= vitamin K antagonist

*Four RCTs (PETRO,²⁴ WASPO²⁵, Chung et al,²⁶ and Yamashita et al²⁷) were not included in the analysis because they did not report data for this outcome or had zeroes in both arms

Figure 2: Odds ratio for all cause stroke or systemic embolism (A) and major bleeding (B) in Bayesian network meta-analysis versus standard adjusted dose VKA.



CrI= credible interval; mg= milligram; VKA= vitamin K antagonist

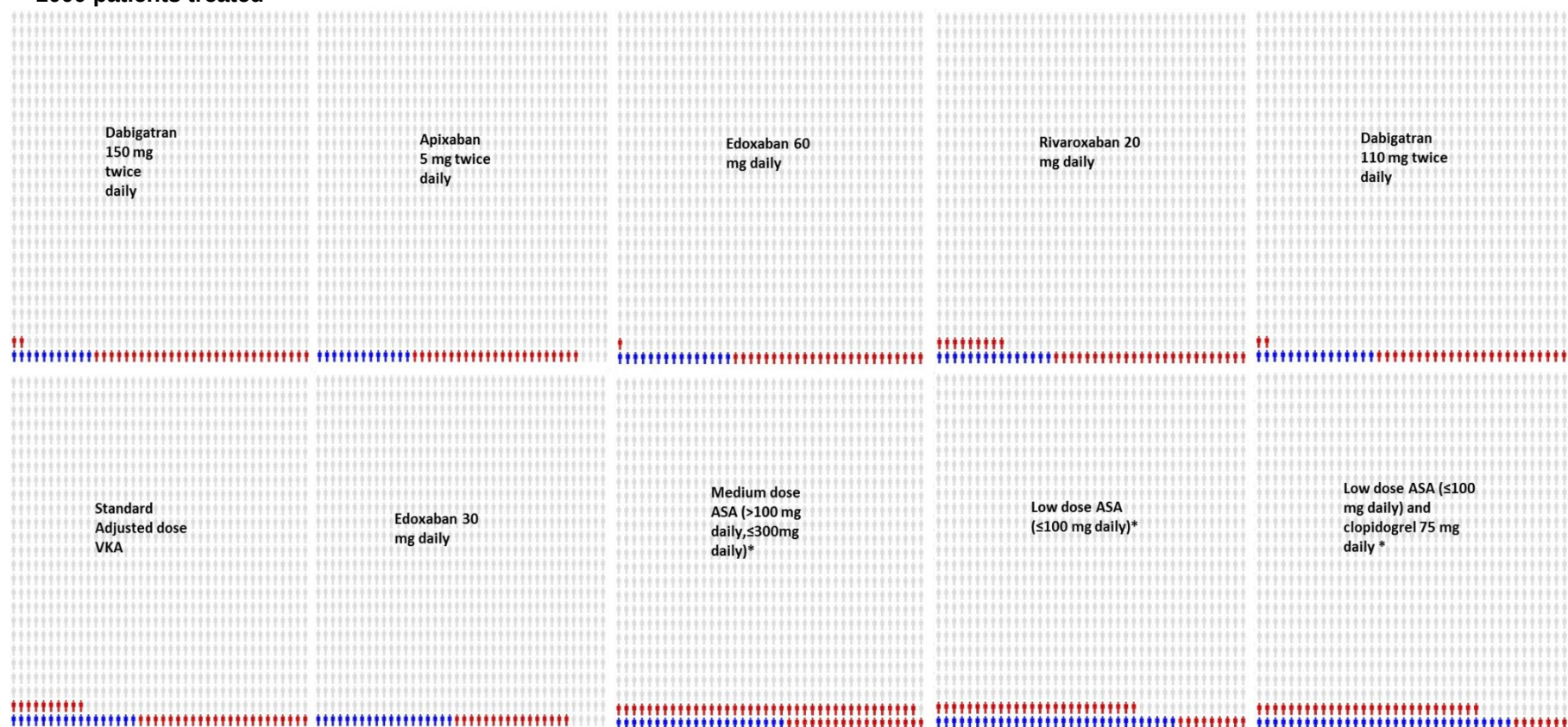
Figure 3: Odds Ratios (OR) from network meta-analyses for stroke or systemic embolism and major bleeding for all pair-wise comparisons.* ORs for recurrence of stroke or systemic embolism are below the diagonal (row-defining treatment versus column-defining treatment) and those for major bleeding are above the diagonal and in blue (column-defining treatment versus row-defining treatment). To obtain ORs for comparisons in the opposite direction, reciprocals should be taken (e.g., the OR for standard dose warfarin compared with apixaban 5 mg twice daily for stroke or systemic embolism is 1/0.78=1.28). Significant results are in bold and underscored (and in larger font).

Standard Adjusted-Dose VKA	0.93 (0.81,1.08)	0.69 (0.6,0.8)	0.79 (0.69,0.9)	1.03 (0.89,1.19)	0.8 (0.69,0.93)	0.46 (0.4,0.54)	1.78 (0.62,5.6)	1.05 (0.6,1.87)	1.1 (0.83,1.47)
0.66 (0.53,0.82)	Dabigatran 150 mg twice daily	0.74 (0.6,0.91)	0.84 (0.69,1.03)	1.1 (0.9,1.35)	0.86 (0.74,1.003)	0.5 (0.4,0.61)	1.91 (0.66,6.08)	1.13 (0.63,2.04)	1.18 (0.85,1.63)
0.78 (0.65,0.94)	1.19 (0.89,1.58)	Apixaban 5 mg twice daily	1.14 (0.93,1.38)	1.49 (1.21,1.82)	1.16 (0.94,1.43)	0.67 (0.54,0.83)	2.57 (0.89,8.18)	1.52 (0.85,2.75)	1.59 (1.16,2.2)
0.87 (0.74,1.02)	1.31 (1.002,1.73)	1.11 (0.87,1.41)	Edoxaban 60 mg daily	1.31 (1.08,1.59)	1.02 (0.83,1.25)	0.59 (0.5,0.69)	2.27 (0.78,7.17)	1.34 (0.75,2.41)	1.4 (1.02,1.92)
0.88 (0.74,1.04)	1.33 (1.01,1.76)	1.12 (0.87,1.43)	1.01 (0.8,1.28)	Rivaroxaban 20 mg daily	0.78 (0.63,0.96)	0.45 (0.37,0.56)	1.74 (0.6,5.48)	1.02 (0.57,1.85)	1.07 (0.78,1.48)
0.91 (0.74,1.12)	1.38 (1.11,1.74)	1.17 (0.88,1.53)	1.05 (0.81,1.37)	1.04 (0.8,1.36)	Dabigatran 110 mg twice daily	0.58 (0.47,0.72)	2.22 (0.77,7.03)	1.31 (0.73,2.37)	1.37 (0.99,1.9)
1.14 (0.98,1.32)	1.73 (1.32,2.26)	1.45 (1.15,1.84)	1.31 (1.13,1.54)	1.3 (1.04,1.63)	1.25 (0.97,1.61)	Edoxaban 30 mg daily	3.85 (1.32,12.18)	2.27 (1.26,4.1)	2.38 (1.72,3.3)
1.35 (0.74,2.47)	2.04 (1.08,3.9)	1.72 (0.92,3.24)	1.56 (0.84,2.91)	1.54 (0.83,2.88)	1.48 (0.79,2.8)	1.18 (0.64,2.21)	Medium Dose ASA (> 100 mg and ≤ 300 mg daily)	0.59 (0.17,1.94)	0.62 (0.19,1.84)
1.87 (1.26,2.8)	2.84 (1.81,4.5)	2.39 (1.55,3.72)	2.16 (1.42,3.34)	2.14 (1.4,3.31)	2.05 (1.32,3.23)	1.64 (1.08,2.53)	1.39 (0.74,2.61)	Low Dose ASA (≤ 100 mg daily)	1.05 (0.55,1.97)
1.93 (1.42,2.64)	2.93 (2.01,4.3)	2.46 (1.73,3.54)	2.23 (1.58,3.17)	2.2 (1.55,3.14)	2.11 (1.46,3.07)	1.69 (1.21,2.4)	1.43 (0.73,2.81)	1.03 (0.62,1.7)	Low dose ASA (≤ 100 mg daily) & Clopidogrel 75 mg daily

mg= milligram; VKA= vitamin K antagonist

* Results between individual treatments, especially newer oral anticoagulants, should be interpreted with caution given the limitations associated with using a fixed-effects model. See Appendix 9 for additional details.

Figure 4: Icon array illustrating the absolute risks of Stroke or systemic embolism (blue) and major bleeding episodes (red) per 1000 patients treated*



* Figures do not reflect uncertainty around effect estimates and there is more uncertainty (i.e., wider credible intervals) for low dose ASA, medium dose ASA, and clopidogrel plus low dose ASA (See Online Appendix 8). Underlying studies may also double count haemorrhage stroke.

REFERENCES

1. Kirchhof, P. *et al.* Atrial fibrillation guidelines across the Atlantic: a comparison of the current recommendations of the European Society of Cardiology/European Heart Rhythm Association/European Association of Cardiothoracic Surgeons, the American College of Cardiology Fou. *Eur. Heart J.* **34**, 1471–1474 (2013).
2. Skanes, A. C. *et al.* Focused 2012 update of the Canadian Cardiovascular Society atrial fibrillation guidelines: recommendations for stroke prevention and rate/rhythm control. *Can. J. Cardiol.* **28**, 125–36 (2012).
3. *Antithrombotic agents for the prevention of stroke and systemic embolism in patients with atrial fibrillation.* (2013). at http://www.cadth.ca/media/pdf/TR0003_AntithromboticAgents-AF_ScienceReport-e.pdf
4. Schulman, S. & Kearon, C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J. Thromb. Haemost.* **3**, 692–4 (2005).
5. NHS Quality Improvement Scotland (NHS QIS). *SIGN 50. A guideline developer's handbook.* (2008). at <http://www.sign.ac.uk/pdf/sign50.pdf>
6. Moher, D., Liberati, A., Tetzlaff, J. & Altman, D. G. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* **6**, e1000097 (2009).
7. Dias, S., Welton, N. J., Sutton, A. J. & Ades, A. *NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials.* *Trop. Med.* 1–96 (2011). at www.nicedsu.org.uk
8. Connolly, S. & Ezekowitz, M. Dabigatran versus warfarin in patients with atrial fibrillation. *N. Engl. J. Med.* **361**, 1139–1151 (2009).
9. Ingelheim, B. *Advisory committee briefing document: dabigatran etexilate [Internet].* 1–168 (2010). at <http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/cardiovas>
10. Cipriani, A. *et al.* Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. *Lancet* **373**, 746–58 (2009).
11. Turner, R. M., Davey, J., Clarke, M. J., Thompson, S. G. & Higgins, J. P. Predicting the extent of heterogeneity in meta-analysis, using empirical data from the Cochrane Database of Systematic Reviews. *Int. J. Epidemiol.* **41**, 818–27 (2012).
12. Spiegelhalter, D. J., Best, N. G., Carlin, B. P. & van der Linde, A. Bayesian measures of model complexity and fit. *J. R. Stat. Soc. Ser. B (Statistical Methodol.* **64**, 583–639 (2002).

13. Spiegelhalter, D., Thomas, A. & Best, N. WinBUGS user manual. *MRC Biostat. Unit* **2**, (2004).
14. meta: Meta-Analysis with R. at <<http://cran.r-project.org/web/packages/meta/index.html>>
15. Dias, S., Welton, N.J., Sutton, A.J., Caldwell, D.M., Guobing, L. & Ades, A. E. *NICE Technical Support Document 4: Inconsistency in Networks of Evidence Based on Randomised Controlled Trials*. 1–39 (2011). at <www.nicedsu.org.uk>
16. Salanti, G., Marinho, V. & Higgins, J. P. T. A case study of multiple-treatments meta-analysis demonstrates that covariates should be considered. *J. Clin. Epidemiol.* **62**, 857–64 (2009).
17. Wells, G., Coyle, D., Cameron, C., Steiner, S. & Kelly, S. *Safety, effectiveness, and costeffectiveness of new oral anticoagulants compared with warfarin in preventing stroke and other cardiovascular events in patients with atrial fibrillation*. (2012). at <http://www.cadth.ca/media/pdf/NOAC_Therapeutic_Review_final_report.pdf>
18. Johnson & Johnson Pharmaceutical Research & Development. *Rivaroxaban for the Prevention of Stroke and Non-Central Nervous System (CNS) Systemic Embolism in Patients With Atrial Fibrillation*. **7939**, 222 (2011).
19. McDonagh, M. S., Peterson, K., Balshem, H. & Helfand, M. US Food and Drug Administration documents can provide unpublished evidence relevant to systematic reviews. *J. Clin. Epidemiol.* (2013). doi:10.1016/j.jclinepi.2013.05.006
20. Giugliano, R. P. *et al.* Edoxaban versus warfarin in patients with atrial fibrillation. *N. Engl. J. Med.* **369**, 2093–104 (2013).
21. Granger, C. & Alexander, J. Apixaban versus warfarin in patients with atrial fibrillation. *N. Engl. J. Med.* 981–992 (2011).
22. Patel, M., Mahaffey, K. & Garg, J. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N. Engl. J. Med.* 883–891 (2011).
23. Connolly, S. *et al.* Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. *Lancet* **367**, 1903–12 (2006).
24. Ezekowitz, M. D. *et al.* Dabigatran with or without concomitant aspirin compared with warfarin alone in patients with nonvalvular atrial fibrillation (PETRO Study). *Am. J. Cardiol.* **100**, 1419–26 (2007).
25. Rash, A. *et al.* A randomised controlled trial of warfarin versus aspirin for stroke prevention in octogenarians with atrial fibrillation (WASPO). *Age Ageing* **36**, 151–6 (2007).

26. Chung, N. *et al.* Safety of edoxaban, an oral factor Xa inhibitor, in Asian patients with non-valvular atrial fibrillation. *Thromb. Haemost.* **105**, 535–44 (2011).
27. Yamashita, T. *et al.* Randomized, Multicenter, Warfarin-Controlled Phase II Study of Edoxaban in Japanese Patients With Non-Valvular Atrial Fibrillation. *Circ. J.* **76**, 1840–1847 (2012).
28. Connolly, S. & Eikelboom, J. Apixaban in patients with atrial fibrillation. *N. Engl. J. Med.* **364**, 806–817 (2011).
29. Connolly, S. J. *et al.* Effect of clopidogrel added to aspirin in patients with atrial fibrillation. *N. Engl. J. Med.* **360**, 2066–78 (2009).
30. Harenberg, J. & Weiss, C. Clinical trials with new oral anticoagulants. Additive value of indirect comparisons also named network meta-analyses. *Hamostaseologie* **33**, 62–70 (2013).
31. Dogliotti, A., Paolasso, E. & Giugliano, R. P. Current and new oral antithrombotics in non-valvular atrial fibrillation: a network meta-analysis of 79 808 patients. *Heart* (2013). doi:10.1136/heartjnl-2013-304347
32. Ruff, C. T. *et al.* Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fi brillation : a meta-analysis of randomised trials. *Lancet* **6736**, 1–8 (2013).
33. Assiri, A., Al-Majzoub, O., Kanaan, A. O., Donovan, J. L. & Silva, M. Mixed treatment comparison meta-analysis of aspirin, warfarin, and new anticoagulants for stroke prevention in patients with nonvalvular atrial fibrillation. *Clin. Ther.* **35**, 967–984.e2 (2013).
34. Slot, K. & Berge, E. Factor Xa inhibitors versus vitamin K antagonists for preventing cerebral or systemic embolism in patients with atrial fibrillation. *Stroke* (2013). at <<http://stroke.ahajournals.org/content/44/12/e165.short>>
35. Salanti, Georgia, Kavvoura, F, Ioannidis, J. Exploring the geometry of treatment networks. *Ann. Intern. Med.* **148**, 544–553 (2008).
36. Barratt, A. *et al.* Tips for learners of evidence-based medicine: 1. Relative risk reduction, absolute risk reduction and number needed to treat. *Can. Med. Assoc. J.* **171**, 353–8 (2004).
37. Schechtman, E. Odds ratio, relative risk, absolute risk reduction, and the number needed to treat--which of these should we use? *Value Health* **5**, 431–6 (2002).
38. Berger, M. L., Mamdani, M., Atkins, D. & Johnson, M. L. Good research practices for comparative effectiveness research: defining, reporting and interpreting nonrandomized studies of treatment effects using secondary data sources: the ISPOR Good Research Practices for Retrospective Database Analysis Task Force . *Value Health* **12**, 1044–52 (2009).

39. Berger, M. L. *et al.* Prospective observational studies to assess comparative effectiveness: the ISPOR good research practices task force report. *Value Health* **15**, 217–30 (2012).
40. Jansen, J. P. Network meta-analysis of individual and aggregate level data. *Res. Synth. Methods* **3**, 177–190 (2012).
41. Salanti, G., Ades, A. & Ioannidis, J. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *J. Clin. Epidemiol.* **64**, 163–71 (2011).
42. Guo, J. J. *et al.* A review of quantitative risk-benefit methodologies for assessing drug safety and efficacy-report of the ISPOR risk-benefit management working group. *Value Health* **13**, 657–66 (2010).
43. Boyd, C. *et al.* *Methods Research Report Methods for Benefit and Harm Assessment in Systematic Reviews*. 52 (2012). at <www.ncbi.nlm.nih.gov/books/NBK115750/>
44. Thorlund, K., Thabane, L. & Mills, E. J. Modelling heterogeneity variances in multiple treatment comparison meta-analysis – Are informative priors the better solution? *BMC Med. Res. Methodol.* **13**, 1 (2013).

APPENDICES

Appendix 1: Search Strategy

OVERVIEW		
Interface:	Ovid	
Databases:	EBM Reviews - Cochrane Central Register of Controlled Trials <May 2012> Ovid Embase 1974 to June 6, 2012 Ovid MEDLINE 1946 to June 7, 2012 Ovid MEDLINE Daily Ovid MEDLINE In-Process & Other Non-Indexed Citations Note: Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.	
Date of Search:	June 7, 2012; updated January 23, 2014	
Alerts:	Monthly search updates began June 11, 2012 and ran until project completion	
Study Types:	Randomized Controlled Trials	
Limits:	Publication years 1988-present Humans Conference abstracts omitted	
SYNTAX GUIDE		
/	At the end of a phrase, searches the phrase as a subject heading	
.sh	At the end of a phrase, searches the phrase as a subject heading	
MeSH	Medical Subject Heading	
exp	Explode a subject heading	
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings	
#	Truncation symbol for one character	
ADJ	Requires words are adjacent to each other (in any order)	
ADJ#	Adjacency within # number of words (in any order)	
.ti	Title	
.ab	Abstract	
.hw	Heading Word; usually includes subject headings and controlled vocabulary	
.nm.	Name of substance word	
.ot	Original title	
.pt	Publication type	
.rn	CAS registry number	
use cctr	Select results from Cochrane database of Clinical Trials	
use oomezd	Select results from Embase database	
use pmez	Select results from Medline database	
Clinical Multi-database Strategy		
Line #	Search	
	1	(211 bibr
	2	(BM 3.rn,
3	(riva	

	597939).ti,ot,ab,sh,rn,hw,nm. or 366789-02-8.rn,nm.
4	(90055-48-4 or 113665-84-2).rn,nm. or (clopidogrel* or clopilet or grepid or iscover or plavix or zopya or zylagren or zyllt or duocover or duoplavin).ti,ot,ab,sh,rn,hw,nm.
5	Aspirin/ or 50-78-2.rn,nm. or (acetylsalicylic acid* or ASA* or acenterine or acesal or acetan or acetard or aceticil or aceticyl or acetilum or acetonyl or acetilum or acetonyl or acetophen or acetosal or acetosalicylic acid or acetosalin or acetosalum or acetyl salicylate or acetyl salicylic acid or acetylin or acetylo or acetylon or acetylosalicylic acid or acetylsal or acetysal or acetylsalicyclic acid or acetylsalicyl or acetylsalicylate or acetylsalicyc acid or acetylsalicyclic acid or oracidulatum or actorin or Acylpyrin or acylpyrine or acytosal or adiro or alabunkun or alasil or albyl-e or alka seltzer or alkASA or Aloxiprimum or anacin or anasprin or anopyrin or ansin or anthrom or aptor or arthralgyl or asaflow or ascription or orasaphen or asapor or asatard or asawin or aspec or aspent or aspergum or aspep or aspilets or aspirem or aspirgran or ASAA or ASAE or ASAlne or aspirisucro or aspisol or aspo cid or aspro or asrina or asrivo or asta or asteric or astrix or bebesan or biprin or bokey or boxazin or breoprin or bufferin or cafenol or caprin or cASA or catalgine or catalgix or cemerit or cemirit or claradin or claragine or Colfarit or comoprin or contrheuma or daga or darosal or Dispril or dispirin or dolean or dusil or Easprin or ecasil or Ecotrin or egalgc or emocin or empirin or encaprin or encine em or Endosprin or entaprin or entercin or enteroprin or enterosarine or enterospirine or entrophen or eskotrin or eutermine or extren or genasprin or globentyl or godamed or gotosan or helicon or idotyl or infatabs a or istopirin or istopyrine or ivepirine or juvepirine or keypo or kilios or kinderASA or Magnecyl or measurin or mejoral or melabon or Micristin or micropyrin or mikristin or miniasal or mycristin or naspro or novasen or nu seal or nu seals or ortho acetoxybenzoate or ortho acetoxybenzoic acid or ortho acetyloxybenzoate or ortho acetyloxybenzoic acid or ostoprin or pancemol or paracin or paynocil or pengo or plewin or Polopirin or polopiryna or premaspin or primaspan or proprin or pyronoval or reumyl or rhodine or rhonal or ronol or salacetin or salisalido or sargepirine or soldral or solpyron or Solprin or solucetyl or solupsa or Solupsan or spren or super tru or tapal or temagin or tevapirin or th 2152 or thrombo-aspilets or treupahlin or treuphalin or tromalyt or tromcor or turiital or verin or vitalink or xaxa or Zorprin).ti,ot,ab,sh,rn,hw,nm.
6	Warfarin/ or 81-81-2.rn,nm. or (adoisine or aldocumar or athrombin* or befarin or brumolin or carfin or circuvit or compound 42 or coumadan or coumadin or coumadine or coumafen or coumafene or coumefene or coumaphene or coumarins or dagonal or farin or jantoven or kumatox or maforan or marevan or orfarin or panwarfarin or panwarfin or prothromadin or simarc 2 or sofarin or tedicumar or tintorane or waran or warfant or warfar or warfarin or warfarine or warfil or warfilone or warnerin).ti,ot,ab,sh,rn,hw,nm.
7	Acenocoumarol/ or 152-72-7.rn,nm. or (acenocoumarol* or nicoumalone or acenocoumarin or acenocoumarine or acenocoumarole or acenocoumarolum or acenocumarol or acenocumarolo or acenocumerol or acenkumarin or acitrom or ascumar or neo sintrom or neosintrom or neositron or nicoumalone or nicumalon or nitrovarfarian or nitrowarfarin or sincoumar or sincumar or sinkumar or sinthrom or sinthrome or sintrom or sintroma or sintron or syncoumar or syncumar or synthrom or syntrom or syntroma or sintron or syncoumar or syncumar or syncumar or syntrom or trombostop or zotil or sinthrome or synthrom or syncoumar or syncumar or sinkumar or sintrom or minisintrom or trombostop or zotil).ti,ot,ab,sh,rn,hw,nm.
8	or/1-7
9	Atrial fibrillation/
10	((atrial or atrium or auricular or heart) adj1 fibrillation*).ti,ab.
11	(a-fib or afib).ti,ab.
12	9 or 10 or 11
13	8 and 12
14	13 use pmez
15	13 use cctr
16	14 or 15
17	*dabigatran/ or (dabigatran* or Pradaxa or Pradax or Prazaxa or praxada or bibr 1048 or bibr1048 or bibr953 or bibr 953 or rendix).ti,ab.
18	*apixaban/ or (BMS 562247 or BMS562247 or apixaban* or Eliquis or Eliques).ti,ab.
19	*rivaroxaban/ or (rivaroxaban* or Xarelto or BAY 59-7939 or BAY59-7939 or BAY597939 or BAY 597939).ti,ab.
20	*clopidogrel/ or *acetylsalicylic acid plus clopidogrel/ or (clopidogrel* or clopilet or grepid or iscover or plavix or zopya or zylagren or zyllt or duocover or duoplavin).ti,ab.
21	*warfarin/ or (adoisine or aldocumar or athrombin* or befarin or brumolin or carfin or circuvit or compound 42 or coumadan or coumadin or coumadine or coumafen or coumafene or coumefene or

	coumaphene or coumarins or dagonal or farin or jantoven or kumatox or maforan or marevan or orfarin or panwarfarin or panwarfin or prothromadin or simarc 2 or sofarin or tedicumar or tintorane or waran or warfant or warfar or warfarin* or warfarine or warfil or warfilone or warnerin).ti,ab.
22	*acetylsalicylic acid/ or (acetylsalicylic acid* or ASA* or acenterine or acesal or acetan or acetard or acetil or aceticyl or acetilum or acetonyl or acetilum or acetonyl or acetophen or acetosal or acetosalicylic acid or acetosalin or acetosalum or acetyl salicylate or acetyl salicylic acid or acetylin or acetylo or acetylon or acetylosalicylic acid or acetylsal or acetysal or acetylsalicyclic acid or acetylsalicyl or acetylsalicylate or acetylsalicyc acid or acetylsalicyclic acid or oracidulatum or actorin or Acylpyrin or acylpyrine or acytosal or adiro or alabunkun or alasil or albyl-e or alka seltzer or alkASA or Aloxiprimum or anasprin or anopyrin or ansin or anthrom or aptor or arthralgyl or asaflow or orasaphen or asapor or asatard or asawin or aspec or aspent or aspergum or aspex or aspilets or aspirem or aspirgran or ASAA or ASAE or ASAine or aspirisucure or aspisol or aspo cid or aspro or asrina or asrivo or asta or asteric or astrix or bebesan or biprin or bokey or boxazin or breoprin or bufferin or cafenol or caprin or cASA or catalgine or catalgix or cemerit or cemirit or claradin or claragine or Colfarit or comoprin or contrheuma or daga or darosal or Dispril or dispirin or dolean or dusil or Easprin or ecasil or Ecotrin or egalgc or emocin or empirin or encaprin or encine em or Endosprin or entaprin or entercin or enteroprin or enterosarine or enterospirine or entrophen or eskotrin or euthermine or extren or genasprin or globentyl or godamed or gotosan or helicon or idotyl or infatabs a or istopirin or istopyrine or ivepirine or juvepirine or keypo or kilios or kinderASA or Magnecyl or measurin or mejoral or melabon or Micristin or micropyrin or mikristin or miniasal or mycristin or naspro or novasen or nu seal or nu seals or ortho acetoxybenzoate or ortho acetoxybenzoic acid or ortho acetyloxybenzoate or ortho acetyloxybenzoic acid or ostoprin or pancemol or paracin or paynocil or pengo or plewin or Polopirin or polopiryna or premaspin or primaspan or proprin or pyronoval or reumyl or rhodine or rhonal or ronol or salacatin or salisalido or sargepirine or soldral or solpyron or Solprin or solucetyl or solupsa or Solupsan or spren or super tru or tapal or temagin or tevapirin or th 2152 or thrombo-aspilets or treupahlin or treuphalin or tromalyt or tromcor or turiital or verin or vitalink or xaxa or Zorprin).ti,ab.
23	*Acenocoumarol/ or (acenocoumarol* or nicoumalone or acenocoumarin or acenocoumarine or acenocoumarole or acenocoumarolum or acenocoumarol or acenocoumarolo or acenocumerol or acenkumarin or acitrom or ascumar or neo sintrom or neosintrom or neositron or nicoumalone or nicumalon or nitrovarfarian or nitrowarfarin or sincoumar or sincumar or sinkumar or sinthrom or sinthrome or sintrom or sintroma or sintron or syncoumar or syncumar or synthrom or syntrom or syntroma or sintron or syncoumar or syncumar or syntrom or trombostop or zotil or sinthrome or synthrom or syncoumar or syncumar or sinkumar or sintrom or minisintrom or trombostop or zotil).ti,ab.
24	or/17-23
25	Heart atrium fibrillation/
26	((atrial or atrium or auricular or heart) adj1 fibrillation*).ti,ab.
27	(a-fib or afib).ti,ab.
28	25 or 26 or 27
29	24 and 28
30	29 use oomezd
31	30 not conference abstract.pt.
32	16 or 31
33	32
34	limit 33 to english language [Limit not valid in CCTR; records were retained]
35	(Randomized Controlled Trial or Controlled Clinical Trial).pt.
36	Randomized Controlled Trial/
37	Randomized Controlled Trials as Topic/
38	"Randomized Controlled Trial (topic)"/
39	Controlled Clinical Trial/
40	Controlled Clinical Trials as Topic/
41	"Controlled Clinical Trial (topic)"/
42	Randomization/
43	Random Allocation/
44	Double-Blind Method/
45	Double Blind Procedure/

46	Double-Blind Studies/
47	Single-Blind Method/
48	Single Blind Procedure/
49	Single-Blind Studies/
50	Placebos/
51	Placebo/
52	Control Groups/
53	Control Group/
54	(random* or sham or placebo*).ti,ab,hw.
55	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
56	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
57	(control* adj3 (study or studies or trial*)).ti,ab.
58	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw.
59	allocated.ti,ab,hw.
60	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw.
61	or/35-60
62	34 and 61
63	limit 62 to yr = "1988 -Current"
64	remove duplicates from 63

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.

Grey Literature

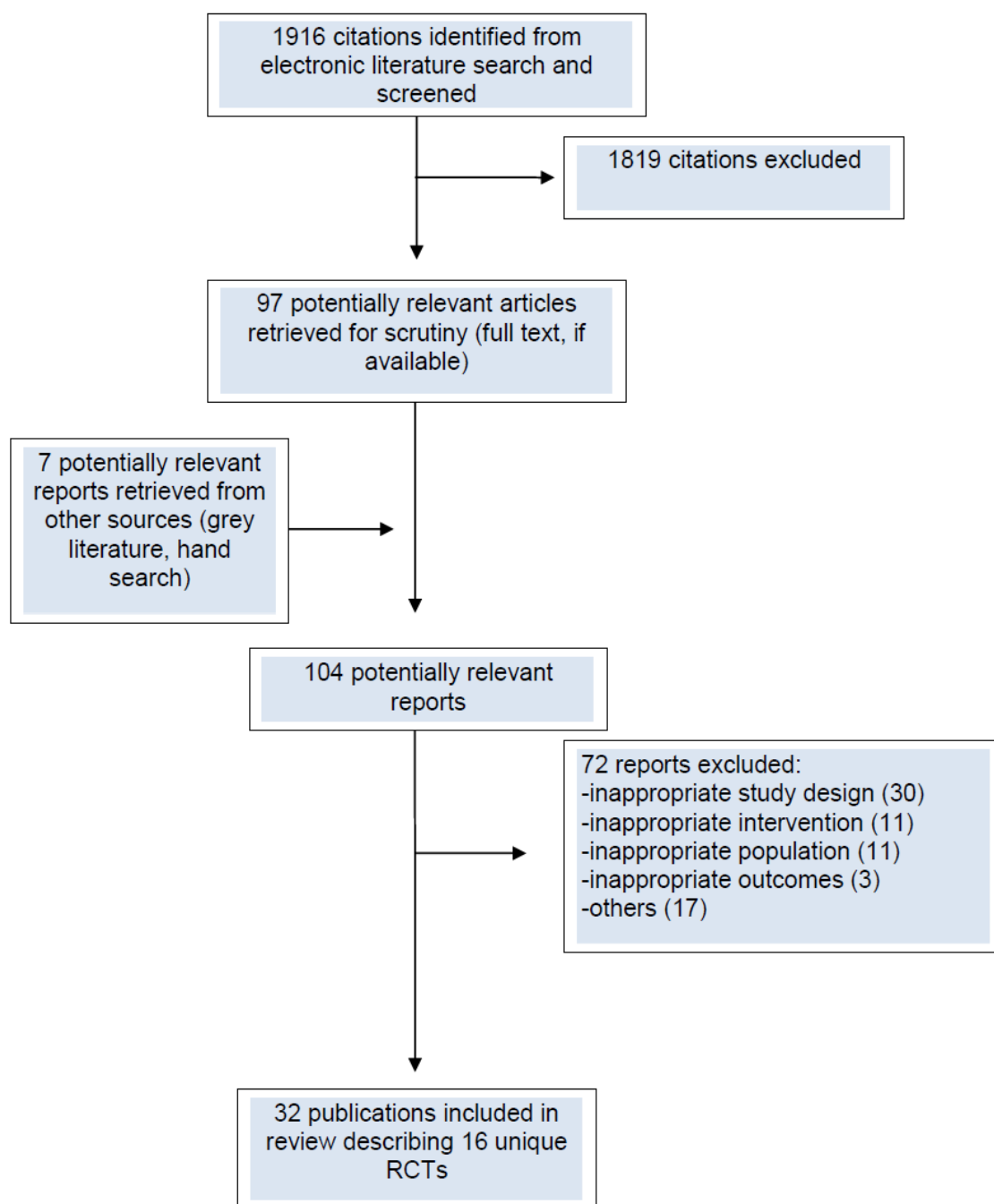
Dates for Search:	June 12, 2012 – July 8, 2012; updated January 2014
Keywords:	dabigatran, Pradax, Pradaxa, apixaban, Eliquis, rivaroxaban, Xarelto, clopidogrel, Plavix, acetylsalicylic acid, Aspirin, warfarin, Coumadin, acenocoumarol, Sintrom, Sinthrome Atrial fibrillation
Limits:	Publication years 1988-present, English

Relevant items from the following sections of the CADTH grey literature checklist, “Grey matters: a practical tool for evidence-based searching” (<http://www.cadth.ca/resources/grey-matters>) were searched:

- Health Technology Assessment Agencies
- Health Economic
- Clinical Practice Guidelines
- Databases (free)

Internet Search

Appendix 2: PRISMA Diagram



Appendix 3: Summary of Patient Baseline Characteristics

Study	Baseline Characteristics															Centre above TTR Throughout follow-up		
	Age, Mean $\pm$ SD (y)	Age Category (%)		Sex (%)		CHADS ₂ , Mean $\pm$ SD	CHADS ₂ Category (%)			Prior Stroke /TIA (%)	DM (%)	Heart Failure (%)	HBP (%)	MI (%)	VKA Naïve (%)	Mean TTR (%)	TTR Category (%)	
		≤ 75 y	> 75 y	M	F		0	1	≥ 2								$\leq 66\%$	$> 66\%$
ACTIVE-W n=6706	70 $\pm$ NR	NR	NR	66	34	2 $\pm$ 1.1	NR	NR	NR	15	21	30	82	17	23	64	48	52
AFASAK n=672	75 $\pm$ NR	NR	NR	54	46	NR $\pm$ NR	NR	NR	NR	6	9	53	32	7	NR	N/A	N/A	N/A
AFASAK-2 n=339	73 $\pm$ NR	NR	NR	61	39	NR $\pm$ NR	NR	NR	NR	8	12	70	45	7	NR	NR	NR	NR
ARISTOTLE n=18201	70 $\pm$ NR	69	31	65	35	2.1 $\pm$ 1.1	0	34	66	19	25	35	87	14	43	62	NR	NR
ARISTOTLE-J n=222	70 $\pm$ NR	69	31	83	17	1.9 $\pm$ NR	1	42	57	28	23	1	83	NR	16	60	NR	NR
BAFTA n=973	82 $\pm$ 4	0	100	55	45	NR $\pm$ NR	NR	NR	NR	13	13	20	54	11	NR	67	NR	NR
CAFA n=378	68 $\pm$ NR	NR	NR	75	25	NR $\pm$ NR	NR	NR	NR	4	12	22	39	13	NR	44	NR	NR
Chung et al 2011 n=234	65 $\pm$ 9	87	13	65	35	1.9 $\pm$ 1.1	0	47	53	24	30	29	71	NR	48	45	NR	NR
ENGAGE AF-TIMI 48 n=21105	72 $\pm$ NR	60	40	62	38	2.8 $\pm$ 1.0	0	0	100	28	36	57	94	12	41	65	52	48
JAST n=871	65 $\pm$ NR	NR	NR	70	30	NR $\pm$ NR	NR	NR	NR	3	14	9	39	NR	92	N/A	N/A	N/A
PETRO n=236	70 $\pm$ NR	70	30	82	18	NR $\pm$ NR	NR	NR	NR	18	25	32	71	NR	0	57	NR	NR
RE-LY n=18113	71 $\pm$ NR	60	40	64	36	2.1 $\pm$ NR	32		68	20	20	23	32	79	17	64	50	50
ROCKET-AF n=14264	73 $\pm$ NR	NR	NR	60	40	3.5 $\pm$ NR	0	0	100	55	40	62	91	17	38	55	NR	NR
WASPO n=75	83 $\pm$ NR	0	100	47	53	NR $\pm$ NR	NR	NR	NR	NR	4	NR	47	NR	NR	69	NR	NR
Weitz et al 2010 n=719	65 $\pm$ 9	NR	NR	62	38	NR $\pm$ NR	0	0	100	NR	NR	NR	NR	NR	66	50	NR	NR

Study	Baseline Characteristics															Centre above TTR Throughout follow-up		
	Age, Mean ± SD (y)	Age Category (%)		Sex (%)		CHADS ₂ , Mean ± SD	CHADS ₂ Category (%)			Prior Stroke /TIA (%)	DM (%)	Heart Failure (%)	HBP (%)	MI (%)	VKA Naïve (%)	Mean TTR (%)	TTR Category (%)	
		≤75y	>75 y	M	F		0	1	≥2								≤66%	>66%
Yamashita et al 2012 n=385	69 ± NR	71	29	83	17	2.1 ± NR	0	100	28	23	27	73	NR	15	73% FOR <70y; 83% FOR ≥70y;	NR	NR	

DM = diabetes mellitus; F = female sex; HBP = high blood pressure; M = male sex; MI = myocardial infarction; N/A = not applicable; NR = not reported; SD = standard deviation; TIA = transient ischemic attack; TTR = time in therapeutic range; VKA = vitamin K antagonist; y = year.

Note: Only data from the included relevant treatment arms have been extracted.

Appendix 4: Summary of Included Trials

Study and Design	Disposition	Population	Interventions	Follow-up	Primary Outcome(s)
ACTIVE-W OL RCT, 2006. Multicenter, 32 countries (including Europe / America).	Randomized: n=6706	AF patients eligible / willing to take anticoagulant therapy, with ≥ 1 pre-specified risk factor for stroke.	Clopidogrel / Low-dose ASA (n=3335) Warfarin – INR 2.0 to 3.0 (n=3371)	1.3 years (stopped early)	First occurrence of stroke, non-CNS SE, MI or vascular death.
AFASAK OL/DB RCT, 1989. Multicenter, Copenhagen.	Randomized: n=1007	AF patients, with no recent anticoagulation or cerebrovascular event, valve replacement or rheumatic heart disease.	OL Warfarin – INR 2.8 to 4.2 * (n=335) Low-dose ASA (n=336) PL (n=336)	2 years	Thromboembolic complication: stroke, TIA or embolic complication to viscera / extremities.
AFASAK-2 OL RCT, 1998. Multicenter, Copenhagen.	Randomized: n=677	AF patients ≥ 60 years (unless with CV or pulmonary disease), without recent TIA or risk factors for bleeding.	Fixed-dose Warfarin * (n=167) Fixed-dose Warfarin / Medium-dose ASA * (n=171) Medium Dose ASA (n=169) Warfarin – INR 2.0 to 3.0 (n=170)	3.5 years	Stroke or SE.
ARISTOTLE DB RCT, 2011. Multicenter, 39 countries (including Europe / America).	Randomized: n=18201	AF patients with ≥ 1 risk factor for stroke, without recent stroke or ASA > 165 mg.	Apixaban 5 mg BID (n=9120) Warfarin – INR 2.0 to 3.0 (n=9081) Concomitant use of ASA (≤ 165 mg daily) or NSAIDs permitted.	NR	Stroke or SE; Major bleeding.
ARISTOTLE-J OL/DB RCT, 2011. Multicenter, Japan.	Randomized: n=222	AF patients with ≥ 1 risk factor for stroke, without recent TIA or ASA > 100 mg.	Apixaban 2.5 mg BID (n=74) Apixaban 5 mg BID (n=74) OL Warfarin – INR 2.0 to 3.0 (n=74) Concomitant use of ASA (≤ 100 mg daily) permitted.	12 weeks	Composite of major bleeding and CRNM bleeding events.
BAFTA OL RCT, 2007. Multicenter, UK.	Randomized: n=973	AF patients ≥ 75 years, with clinical uncertainty around optimal treatment.	Low-dose ASA (n=485) Warfarin – INR 2.0 to 3.0 (n=488)	2.7 years	Disabling stroke, ICH and other clinically significant arterial embolism.
CAFA DB RCT, 1991. Multicenter, Canada.	Randomized: n=378	AF patients without recent stroke, TIA or MI, and who did not require antiplatelet drug therapy.	Warfarin – INR 2.0 to 3.0 (n=187) PL (n=191)	1.2 years (stopped early)	Ischemic stroke, SE, ICH or fatal hemorrhage.

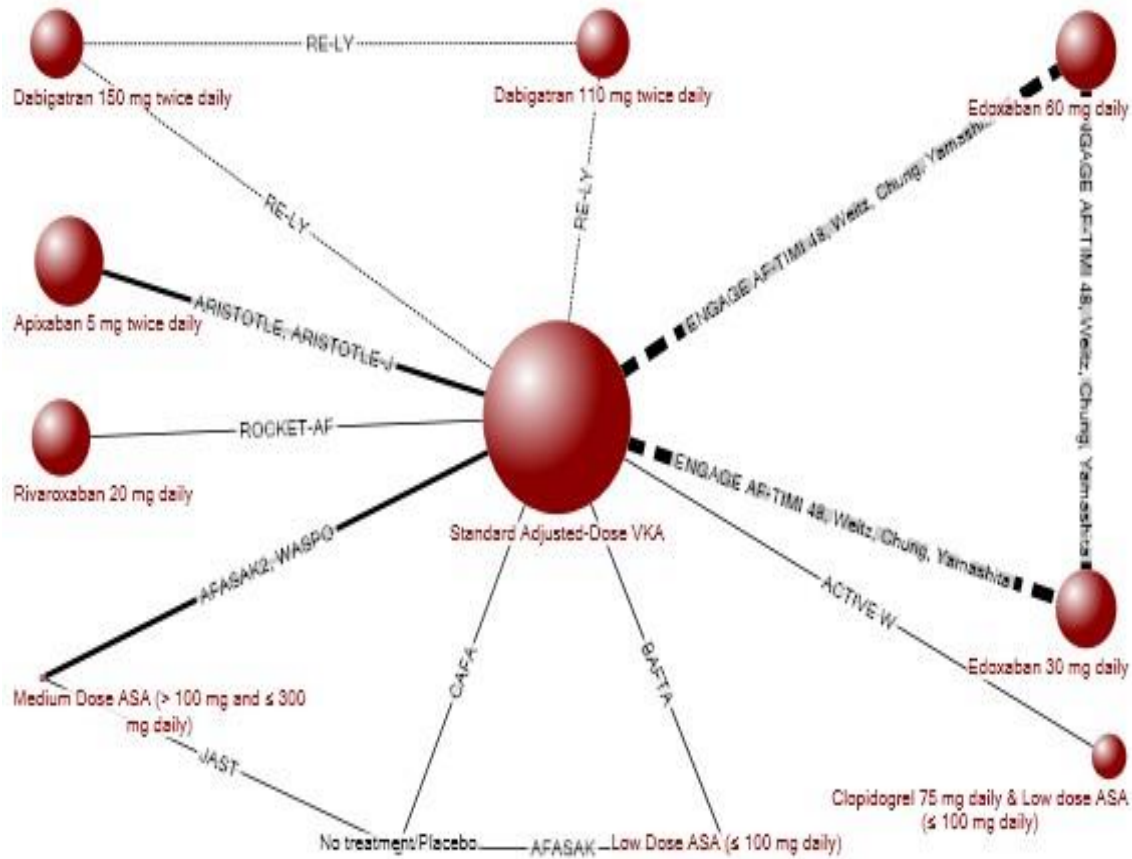
Study and Design	Disposition	Population	Interventions	Follow-up	Primary Outcome(s)
Chung et al 2011 OL RCT, 2011. Multicenter, 4 countries (including Asia).	Randomized: n=234	AF patients at moderate to high risk of stroke (CHADS2 score ≥ 1).	Edoxaban 30 mg OD (n=79) Edoxaban 60 mg OD (n=80) Warfarin – INR 2.0 to 3.0 (n=75)	12 weeks	All bleeding events
ENGAGE AF-TIMI 48 DB RCT, 2013. Multicenter, 46 countries (including Europe / America).	Randomized: n=21105	AF patients at moderate to high risk of stroke (CHADS2 score ≥ 2).	Edoxaban 30 mg OD (n=7034) Edoxaban 60 mg OD (n=7035) Warfarin – INR 2.0 to 3.0 (n=7036) Almost a third of patients in treatment arms took concomitant ASA.	2.8 years	Stroke or SE and major haemorrhage.
JAST OL RCT, 2006. Multicenter, Japan.	Randomized: n=871	AF patients without recent symptomatic thromboembolic disease, ICH or GI bleeding.	Medium-dose ASA (n=426) No treatment (n=445)	2.1 years (stopped early)	CV death, symptomatic brain infarction, or TIA.
PETRO OL/DB RCT, 2007. Multicenter, 4 countries (Europe and USA).	Randomized: n=502	AF patients with ≥ 1 risk factor for stroke and with coronary artery disease (removed halfway to facilitate recruitment). No recent MI, stroke, TIA or major bleed. Warfarin pre-treatment required for ≥ 8 weeks.	Dabigatran 50 mg BID $\pm$ Low-dose or High-dose ASA * (n=105) Dabigatran 300 mg BID $\pm$ Low-dose or High-dose ASA * (n=161) Dabigatran 150 mg BID $\pm$ Low-dose or High-dose ASA [†] (n=166) OL Warfarin – INR 2.0 to 3.0 (n=70)	12 weeks	Thromboembolic events and bleeding events.
RE-LY OL/DB RCT, 2009. Multicenter, 44 countries (including Europe / America).	Randomized: n=18113	AF patients with ≥ 1 risk factor for stroke, without recent stroke or increased risk of bleeding.	Dabigatran 110 mg BID (n=6015) Dabigatran 150 mg BID (n=6076) OL Warfarin – INR 2.0 to 3.0 (n=6022) Concomitant use of ASA (<100 mg daily) or other antiplatelet agents permitted.	2 years	Stroke or SE and major haemorrhage.
ROCKET-AF DB RCT, 2011. Multicenter, 45 countries (including Europe / America).	Randomized: n=14264	AF patients at moderate to high risk of stroke (CHADS2 score ≥ 2).	Rivaroxaban 20 mg OD (n=7131) Warfarin – INR 2.0 to 3.0 (n=7133) Over a third of patients in both arms took concomitant ASA.	1.9 years	Composite of stroke and SE; Composite of major and NMCR bleeding.

Study and Design	Disposition	Population	Interventions	Follow-up	Primary Outcome(s)
WASPO OL RCT, 2007. Multicenter, UK.	Randomized: n=75	Ambulant AF patients > 80 and < 90 years with Folstein score > 25, without previous fall, ICH or GI bleeding. Patients with prior stroke or TIA were excluded.	Warfarin – INR 2.0 to 3.0 (n=36) Medium-dose ASA (n=39)	1 year	Combined endpoints: death; stroke, TIA or SE; serious bleeding; withdrawal.
Weitz et al 2010 DB RCT, 2010. Multicenter, 12 countries (including Eastern Europe / America).	Randomized: n=719	AF patients at moderate to high risk of stroke (CHADS2 score ≥ 2).	Edoxaban 30 mg OD (n=235) Edoxaban 60 mg OD (n=234) Warfarin – INR 2.0 to 3.0 (n=250)	12 weeks	Bleeding and abnormalities of hepatic function
Yamashita et al 2012 DB RCT, 2012. Multicenter, 1 country (Japan).	Randomized: n=385	AF patients at moderate to high risk of stroke (CHADS2 score ≥ 1).	Edoxaban 30 mg OD (n=130) Edoxaban 60 mg OD (n=130) Warfarin – INR 2.0 to 3.0 (n=125)	12 weeks	All bleeding events
AF = atrial fibrillation; ASA = acetylsalicylic acid; CNS = central nervous system; CRNM = clinically relevant non-major bleeding; CV = cardiovascular; DB = double-blind; GI = gastrointestinal; ICH = intracerebral hemorrhage; MI = myocardial infarction; NR = not reported; NSAIDs = non-steroidal anti-inflammatory drugs; OL = open label; PL = placebo; RCT = randomized controlled trial; SE = systemic embolism; TIA = transient ischemic attack; UK = United-Kingdom; VKA = vitamin K antagonist.					

* No data was extracted from these treatment arms since they did not meet the inclusion criteria specified in the protocol. These trials were nevertheless included in the systematic review because they had at least one relevant comparison between two interventions of interest.

† Data was extracted only for dabigatran without ASA (n=100).

Appendix 5: Evidence network for major bleeding. The width of the lines is proportional to the number of randomized controlled trials (RCTs) comparing each pair of treatments, and the size of each treatment node is proportional to the number of randomised participants (sample size). A dotted line indicates a three-arm RCT and a black node indicates a node included in the analysis but not reported in the main text.



mg= milligram; RCT = randomized controlled trial

Appendix 6: Summary of results from Network Meta-analysis for All-cause Stroke or Systemic Embolism

Treatment	Pair-wise Meta-Analysis, OR (95% CI) versus standard adjusted dose VKA	NMA, Odds Ratio (95% CrI) versus standard adjusted dose VKA	NMA, Absolute Risk Difference per 1,000 treated (95% CrI) versus standard adjusted dose VKA	Probability Best (%) for Outcome	Rank for Outcome	SUCRA
Dabigatran 150 mg twice daily	0.66(0.53,0.82)	0.66 (0.53,0.82)	6 fewer (8 fewer-3 fewer)	85.2%	1.2	98.1%
Apixaban 5 mg twice daily	0.79(0.66,0.94)	0.78 (0.65,0.94)	4 fewer (6 fewer-1 fewer)	11.2%	2.5	85.4%
Edoxaban 60 mg daily	0.87(0.71,1.05)	0.87 (0.74,1.01)	3 fewer (5 fewer-1 more)	1.2%	3.7	72.8%
Rivaroxaban 20 mg daily	0.88(0.74,1.05)	0.87 (0.74,1.03)	3 fewer (5 fewer-1 more)	1.0%	3.9	71.2%
Dabigatran 110 mg twice daily	0.91(0.75,1.11)	0.91 (0.74,1.12)	2 fewer (5 fewer-2 more)	0.1%	4.5	64.7%
Standard Adjusted-Dose VKA	NA	NA	NA	0.0%	6.0	50.2%
Edoxaban 30 mg daily	1.14(0.94,1.37)	1.14 (0.98,1.32)	3 more (1 fewer-6 more)	0.0%	7.4	36.5%
Medium Dose Aspirin (> 100 mg and ≤ 300 mg daily)	1.21(0.51,2.87)	1.35 (0.74,2.47)	6 more (5 fewer-24 more)	1.2%	7.8	32.0%
No treatment/Placebo	1.84(0.66,5.1)	1.53 (0.9,2.63)	9 more (2 fewer-26 more)	0.1%	8.9	21.5%
Low Dose Aspirin (≤ 100 mg daily)	2.03(1.32,3.12)	1.87 (1.26,2.8)	14 more (5 more-29 more)	0.0%	10.1	9.4%
Clopidogrel 75 mg OD & Low dose Aspirin (≤ 100 mg daily)	1.93(1.41,2.64)	1.93 (1.42,2.65)	15 more (7 more-26 more)	0.0%	10.2	8.3%

CI = confidence interval; CrI = credible interval; OR= odds ratio

Bayesian network meta-analysis also allows the analyst to estimate the probability that a treatment is best, second best, and so on for a particular outcome. A simple numerical summary of these probabilities – the surface under the cumulative ranking (SUCRA) – for each treatment can also be calculated⁵⁰. The SUCRA would be 100% when a treatment is certain to be the best and 0% when a treatment is certain to be the worst. SUCRA values enable the ranking of treatments overall for a particular outcome. For example, for Dabigatran 150 mg twice daily for stroke/SE the SUCRA value for is 98.1%, which is better than other treatments. By contrast, Clopidogrel 75 mg OD & Low dose Aspirin (≤ 100 mg daily) has a SUCRA of 8.3% for stroke/SE meaning it is certain to be worst for this outcome among active treatments.

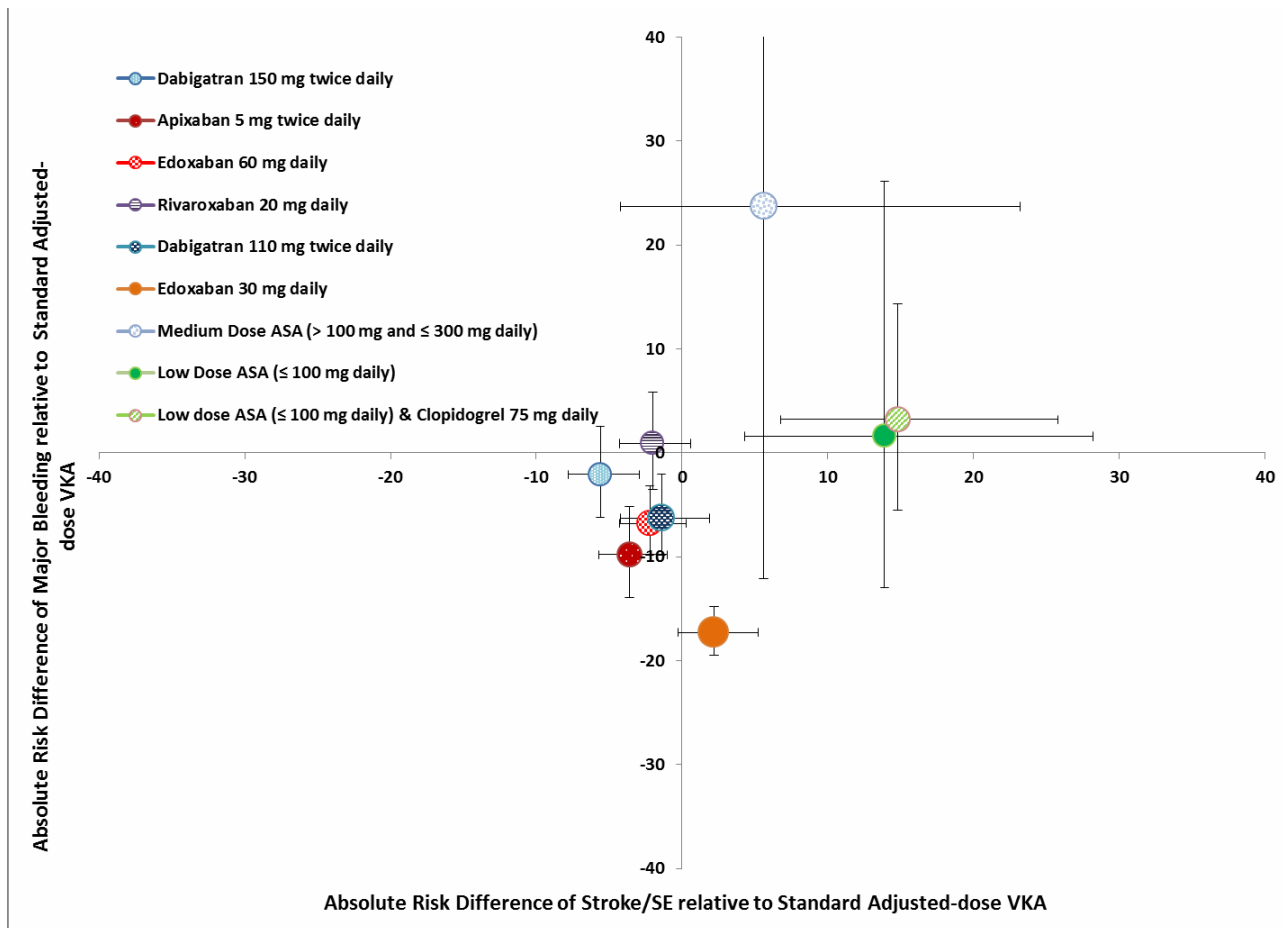
Appendix 7: Summary of results from Network Meta-analysis for Major Bleeding

Treatment	Pair-wise Meta-Analysis, OR (95% CI) versus standard adjusted dose VKA	NMA, Odds Ratio (95% CrI) versus standard adjusted dose VKA	NMA, Absolute Risk Difference per 1,000 treated (95% CrI) versus standard adjusted dose VKA	Probability Best (%) for Outcome	Rank for Outcome	SUCRA
Edoxaban 30 mg daily	0.46(0.39,0.55)	0.46(0.4,0.54)	18 fewer (20 fewer-15 fewer)	29.7%	1.7	92.9%
No treatment/Placebo	0.39(0.08,2.02)	0.33(0.08,1.08)	22 fewer (31 fewer-3 more)	70.2%	1.7	92.6%
Apixaban 5 mg twice daily	0.69(0.60,0.80)	0.69(0.6,0.8)	10 fewer (13 fewer-7 fewer)	0.0%	3.2	78.1%
Edoxaban 60 mg daily	0.78(0.67,0.92)	0.79(0.69,0.9)	7 fewer (10 fewer-4 fewer)	0.0%	4.5	64.6%
Dabigatran 110 mg twice daily	0.8(0.68,0.94)	0.8(0.69,0.93)	7 fewer (10 fewer-3 fewer)	0.0%	4.7	62.7%
Dabigatran 150 mg twice daily	0.93(0.81,1.07)	0.93(0.8,1.08)	3 fewer (7 fewer-3 more)	0.0%	6.8	41.7%
Low Dose Aspirin (≤ 100 mg daily)	1.01(0.57,1.78)	1.05(0.6,1.86)	2 more (13 fewer-26 more)	0.1%	7.9	30.6%
Standard Adjusted-Dose VKA	NA	NA	NA	0.0%	8.0	30.2%
Rivaroxaban 20 mg daily	1.03(0.9,1.18)	1.03(0.89,1.18)	1 more (4 fewer-6 more)	0.0%	8.4	26.3%
Clopidogrel 75 mg OD & Low dose Aspirin (≤ 100 mg daily)	1.1(0.82,1.48)	1.1(0.83,1.47)	4 more (6 fewer-15 more)	0.0%	8.9	20.8%
Medium Dose Aspirin (> 100 mg and ≤ 300 mg daily)	1.68(0.50,5.69)	1.79(0.63,5.67)	24 more (12 fewer-120 more)	0.0%	10.0	9.8%

CI = confidence interval; CrI = credible interval; OR= odds ratio

Bayesian network meta-analysis also allows the analyst to estimate the probability that a treatment is best, second best, and so on for a particular outcome. A simple numerical summary of these probabilities – the surface under the cumulative ranking (SUCRA) – for each treatment can also be calculated⁵⁰. The SUCRA would be 100% when a treatment is certain to be the best and 0% when a treatment is certain to be the worst. SUCRA values enable the ranking of treatments overall for a particular outcome. For example, for major bleeding the SUCRA value for Edoxaban 60 mg is 92.8%, which is better than other treatments. By contrast, Medium Dose Aspirin (> 100 mg and ≤ 300 mg daily) has a SUCRA of 9.9% for major bleeding meaning it is certain to be worst for this outcome.

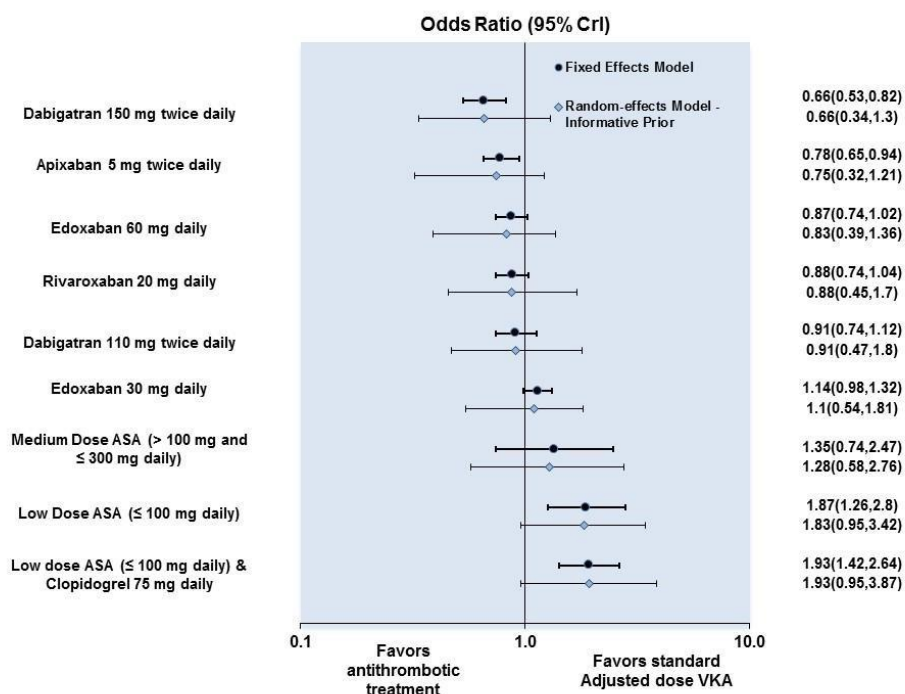
Appendix 8: Benefit-Harm plot for each treatment (absolute harm difference per 1,000 patients treated). The absolute risk difference of recurrence of Stroke or systemic embolism relative to standard adjusted dose VKA is presented on the x-axis, while the absolute risk difference of major bleeding relative to standard adjusted dose VKA is on the y-axis. The dot is representative of the median estimate for each treatment while the 95% credible intervals are presented as error bars.



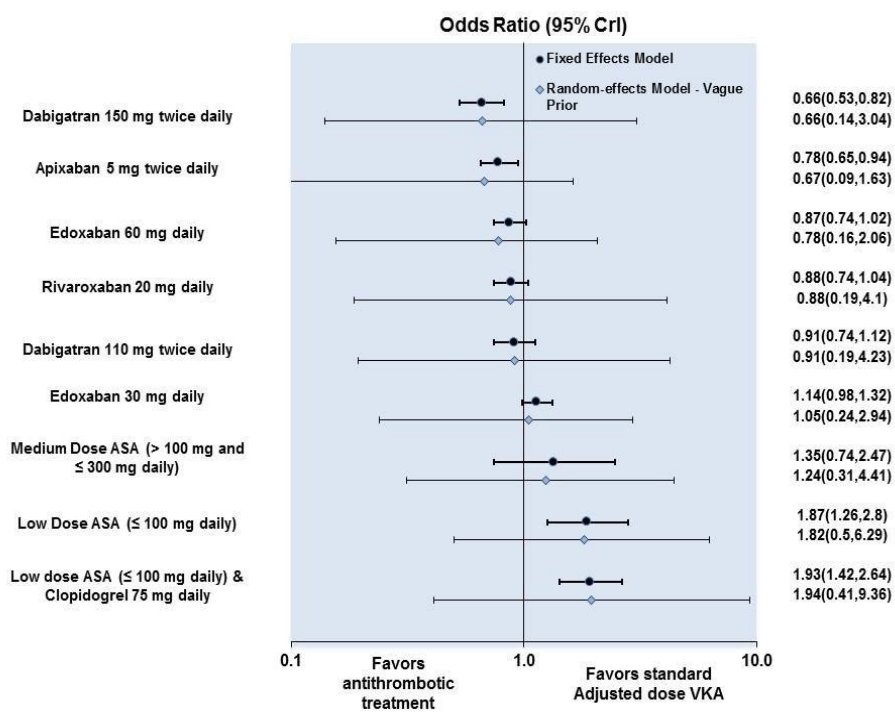
Appendix 9: Rationale of choice of fixed-effects model and limitations

It is challenging to conduct network meta-analyses when evidence structures are comprised of single study connections, especially when there is obvious heterogeneity in the network. The use of a random-effects model with a vague prior on the between study variance exerts a large degree of influence on the credible intervals (CrI's) because there is insufficient studies to reign in the prior and provide an accurate estimate of the between study variance. As a result, results often appear unrealistic (e.g., wide credible intervals for a treatment that was shown to be associated with a statistically significant decrease). Accordingly, we also considered informative priors on the between study variance from the recently published reports.^{11,44} However, even when these priors were applied on the between study variance, they still did not reign in CrI's effect estimates again because the network was comprised of single study connections. The use of the random effects model with either a vague or informative prior was problematic because treatments that were originally associated with statistically significant reductions in stroke or SE relative to standard adjusted dose VKA were no longer associated with significant reductions, limiting external validity of the model (see Figures below on direct estimates in Online Appendix 4 and 5). While we could have opted to use less vague priors (e.g., $\frac{1}{4}$ of prior in Turner et al¹¹), the choice of the prior would have seemed somewhat arbitrary because it was not based on any empirical evidence. As such, we opted to use the fixed-effects model despite the known issues in doing so. By using the fixed-effects model, treatments that were associated with significant reductions in the risk of stroke or SE relative to standard adjusted dose VKA retained significance. We felt that it would have been inappropriate to remove statistical significance by applying vague priors given the large investment involved in developing clinical trials. However, a consequence of retaining statistical significance is seen when comparing newer oral anticoagulants versus one another in Figure 3. Because we assumed the new oral anticoagulants were all associated with reductions in Stroke or SE relative to standard adjusted dose VKA (if that was the case in the underlying trials), significant reductions in the risk of stroke or SE among new oral anticoagulants are observed in Figure 5. This may or may not be the case in clinical practice. As noted in tables 1 and Online Appendix 2, there is considerable heterogeneity across studies. However, the network structure itself (i.e., single study connections), made it difficult to properly adjust for differences in patient and study characteristics using standard approaches. Accordingly, results in Figure 3 should be interpreted with caution. We conducted simple sub-group analyses (breaking randomization) to help adjust for this heterogeneity, which is a very crude way to adjust for heterogeneity. To fully elucidate the comparative benefits and harms of antithrombotic agents, especially across the various sub-populations, rigorously conducted comparative studies, or network meta-regression analyses of patient-level data are required.

Forest Plot – Odds ratio (95% Credible interval) when using informative prior on the sd (i.e, $dlnorm(-3.02, 0.29)$)¹¹



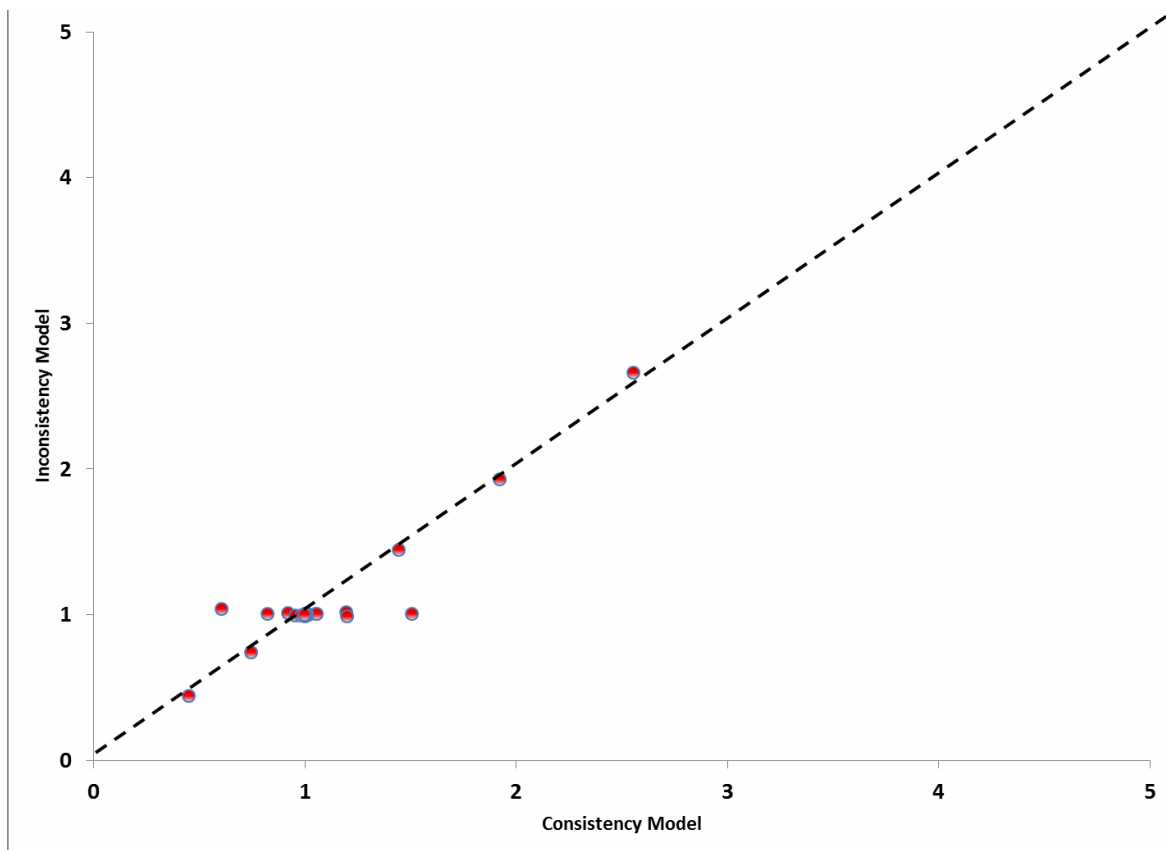
Forest Plot – Odds ratio (95% Credible interval) when using vague prior on the sd (i.e, $duniform(0, 2)$)



Appendix 10: Assessment of Inconsistency

We plotted the posterior mean deviance of the individual data points in the inconsistency model against their posterior mean deviance in the consistency model to help identify loops where inconsistency is present. In our analysis, the posterior mean deviance contributions are very similar and close to 1, for both models. The consistency model has a similar posterior mean of the residual deviance (29.41 vs. 29.37) and DIC (195.00 vs. 196.87) and hence is a similar fit for both models. A few points show a lower value of the posterior mean deviance in the inconsistency model but these values are not too far from 1. Similarly, a few points have higher values of the posterior mean deviance in the consistency model (again with values not too far from 1) suggesting that each model may fit the data points better for certain points. The parameter estimates are also similar for both models and there is considerable overlap in the 95% credible intervals (see table below), suggesting no evidence of inconsistency in the network.

Plot of posterior mean deviance of the individual data points in the inconsistency model against their posterior mean deviance in the consistency model



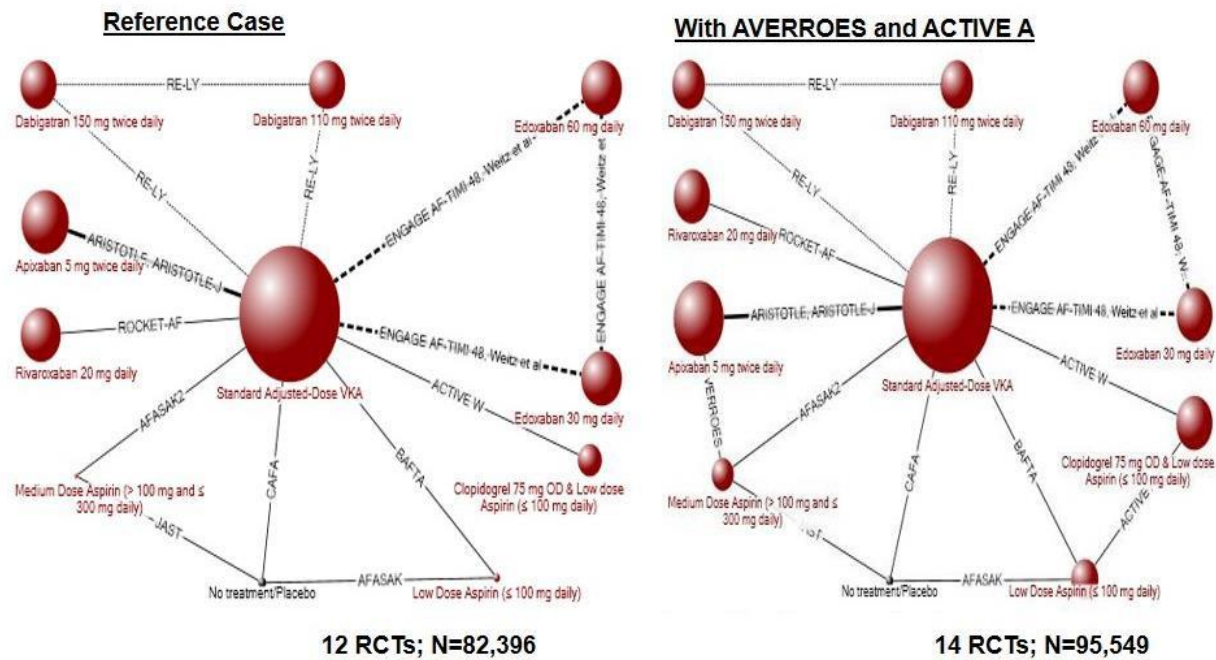
Comparison of effect estimates from consistency and inconsistency models where there is data available for comparison

Comparison	Consistency Model	Inconsistency Model
Dabigatran 150 mg twice daily vs Standard Adjusted-Dose VKA	0.66 (0.53,0.82)	0.66 (0.53,0.82)
Apixaban 5 mg twice daily vs Standard Adjusted-Dose VKA	0.78 (0.65,0.94)	0.78 (0.65,0.94)
Edoxaban 60 mg daily vs Standard Adjusted-Dose VKA	0.87 (0.74,1.01)	0.87 (0.74,1.01)
Rivaroxaban 20 mg daily vs Standard Adjusted-Dose VKA	0.87 (0.74,1.03)	0.88 (0.74,1.03)
Dabigatran 110 mg twice daily vs Apixaban 5 mg twice daily vs Edoxaban 30 mg daily vs Standard Adjusted-Dose VKA	0.91 (0.74,1.12)	0.91 (0.74,1.12)
Medium Dose Aspirin (> 100 mg and ≤ 300 mg daily) vs Standard Adjusted-Dose VKA	1.14 (0.98,1.32)	1.14 (0.98,1.32)
Low Dose Aspirin (≤ 100 mg daily) vs Standard Adjusted-Dose VKA	1.35 (0.74,2.47)	0.82 (0.33,1.98)
Clopidogrel 75 mg OD & Low dose Aspirin (≤ 100 mg daily) vs Standard Adjusted-Dose VKA	1.87 (1.26,2.8)	2.04 (1.33,3.19)
No treatment/Placebo vs Low Dose Aspirin (≤ 100 mg daily)	1.93 (1.42,2.64)	1.93 (1.42,2.65)
Residual deviance	0.82 (0.48,1.38)	1 (0.51,1.98)
DIC	29.41	29.37
	195.00	196.87

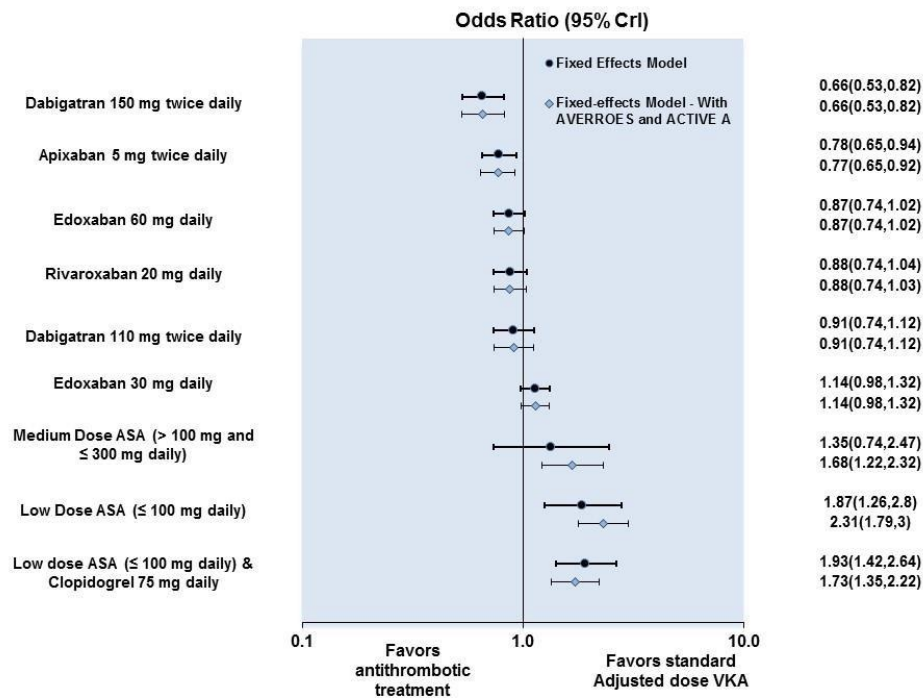
Appendix 11: Sensitivity analysis with AVERROES and ACTIVE A

Stroke or SE

Evidence Networks for Stroke or SE NMA including AVERROES and ACTIVE A studies



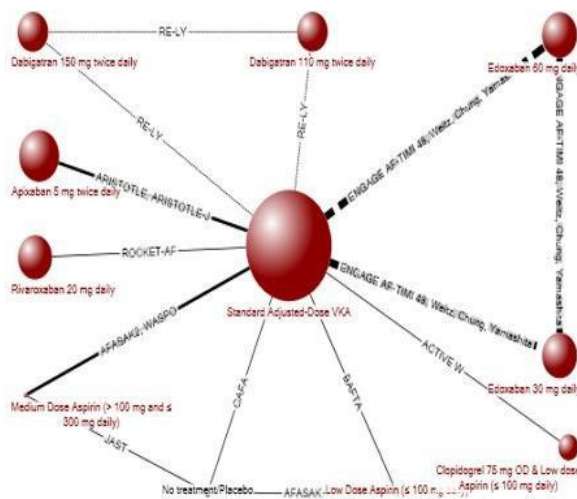
Forest Plot for Stroke or SE NMA including AVERROES and ACTIVE A studies



Major Bleeding

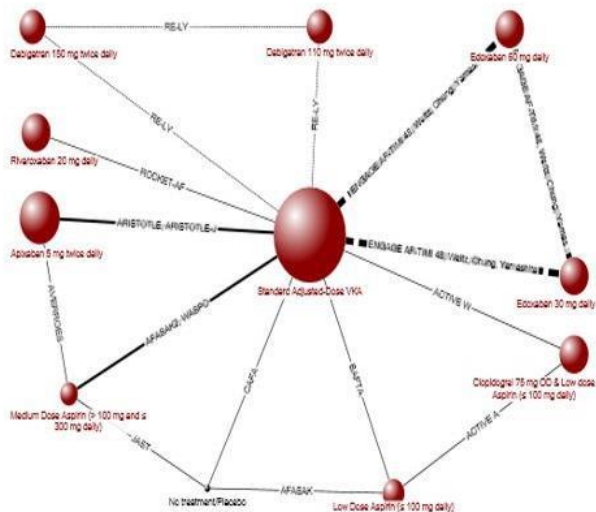
Evidence Networks for Major Bleeding NMA including AVERROES and ACTIVE A studies

Reference Case



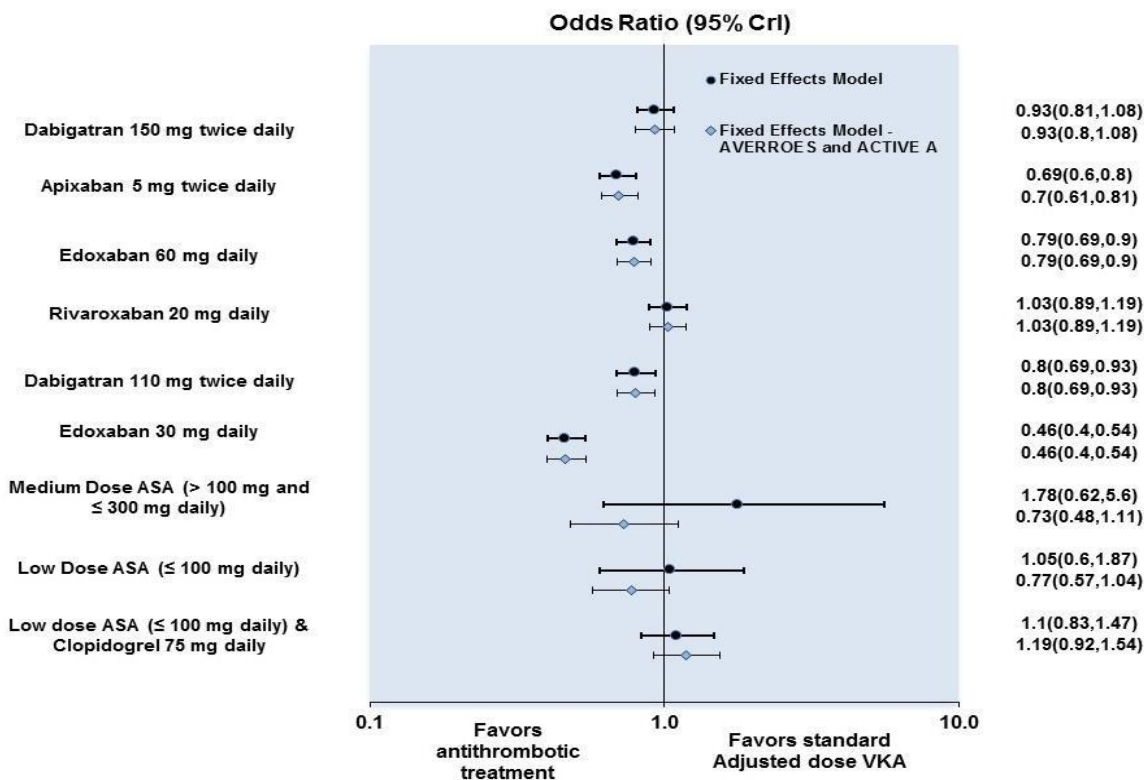
15 RCTs; N=83,015

With AVERROES and ACTIVE A



17 RCTs; N=96,168

Forest Plot for Major Bleeding NMA including AVERROES and ACTIVE A studies



Appendix 12: Comparison with previously published network meta-analyses since Harenberg et al³⁰

Author (Publication Year)	Method	Search Date	Included Treatments	Registered Protocol	Relative Measure(s)	Absolute Measure(s) reported	Subgroup Analyses Reported
Cameron 2014	Bayesian Network Meta- analysis	January 2014	dabigatran, rivaroxaban, apixaban, edoxaban, and vitamin K antagonists (VKA) at a standard adjusted dose (target international normalised ratio 2.0-3.0), acetylsalicylic acid, acetylsalicylic acid and clopidogrel	Yes (PROSPERO registry - CRD42012002721).	OR (95% CrI)	Yes	Yes
Ruff 2013	Traditional Meta- analysis	November 2013	dabigatran, rivaroxaban, apixaban, edoxaban	Not Reported	RR (95%CI)	No	Yes
Dogliotti 2013	Bayesian Network Meta- analysis	May 2012	dabigatran, rivaroxaban, apixaban, vitamin K antagonists (VKA) at a standard adjusted dose, acetylsalicylic acid, acetylsalicylic acid and clopidogrel	Yes (metacardio.org)	OR (95% CrI)	No	No
Assiri 2013	Baysian Network Meta- analysis	August 2012	dabigatran, rivaroxaban, apixaban, vitamin K antagonists (VKA) at a standard adjusted dose, acetylsalicylic acid, acetylsalicylic acid and clopidogrel	Not Reported	RR (95%CrI)	No	No
Bruins 2013	Traditional Meta- analysis	June 2013	antistasin, apixaban, betrixaban, darexaban, DU176b, edoxaban, eribaxaban, fondaparinux, idraparinux, otamixaban, razaxaban, rivaroxaban, yagin, YM150, LY517717, SSR126517E, vitamin K antagonists (warfarin and congeners) with the intensity of anticoagulation dose-adjusted using the International Normalised Ratio (INR)	Yes (Cochrane Library)	OR (95%CI) RR (95%CI) in summary table	Yes	Yes

Appendix 13: Excluded Study List

Inappropriate Study Design

Cardiovasc J S Afr. 2006 Mar;17(2):91. J Fam Pract. 2006;55(9):753. Cardiovasc J Afr. 2009 May;20(3):210. Cardiovasc J Afr. 2009 Sep;20(5):311-2. Australian Journal of Pharmacy. 2009;90(1073):68. Formulary. 2010;45(1):16. Aalbers J. Cardiovasc J Afr. 2010 Nov;21(6):342-3. Alexander W, et al. PT. 2010;35(10):580-1. Belavic JM. Nurse Pract. 2011 Sep;36(9):6-7. Camm AJ. Eur Heart J. 2009 Nov;30(21):2554-5. Chua D, et al. N Engl J Med. 2009;361(13):1312-3. Connolly SJ. Eur J Heart Fail. 2009;11(12):1215. DeSilvey DL. Am J Geriatr Cardiol. 2006 Sep;15(5):326-7. Dunn A. Ann Intern Med. 2011;154(8):JC4-3. Eikelboom JW, et al. J Thromb Haemost. 2012;10(5):9668. Ezekowitz MD, et al. J Interv Card Electrophysiol. 2011 Dec;32(3):173-80. Garcia D, et al. Lancet. 2007 Aug 11;370(9586):460-1. Granger CB. Ann Intern Med. 2012;156(JC1-2):JC1-3. Hart RG, et al. Ann Intern Med. 2007;147(8):590-2. Katona A, et al. Eur Heart J. 2006 Jun;27(11):1382. Kita K, et al. Interventional Cardiology. 2011;3(6):637. Lopes RD, et al. Evid Based Med. 2011;16(6):187-8. Nolan J, et al. Br Heart J. 1992 Dec;68(6):544-7. Paikin JS, et al. Expert Rev Cardiovasc Ther. 2011 Mar;9(3):279-86. Panichpisal K, et al. Future Neurology. 2011;6(2):155-8. Roy B, et al. Am J Cardiol. 2012 Feb 1;109(3):370-7. Sloan MA. Evid Based Med. 2006;11(6):170. Vassiliou VS. N Engl J Med. 2012;366(1):88-90. Veloso HH, et al. Chest. 2005 Jul;128(1):475. Weinberger J. Curr Cardiol Rep. 2010;12(1):1-2.

Inappropriate Intervention

Lancet. 1994 Mar 19;343(8899):687-91. The Stroke Prevention in Atrial Fibrillation Investigators. Arch Intern Med. 1996 Feb 26;156(4):409-16. Archer SL, et al. Am Heart J. 1995 Aug;130(2):287-95. Edvardsson N, et al. J Intern Med. 2003 Jul;254(1):95-101. Hart RG, et al. Cerebrovasc Dis. 2000 Jan;10(1):39-43. Hellemons BS, et al. Control Clin Trials. 1999 Aug;20(4):386-93. Hori M, et al. Circ J. 2012 Jun 5. Miller VT, et al. Neurology. 1996 Jan;46(1):238-40.

Perez-Gomez F, et al. Eur Heart J. 2007;28(8):996-1000
 Singer DE, et al. Am Heart J. 1992 Dec;124(6):1567-73.
 Connolly S, et al. Eur Heart J. 2013 May;34(20):1498-505

Inappropriate Population

ACTIVE Investigators, et al. N Engl J Med 2009;360(20):2066-78.
 Circulation 1991;84(2):527-39.
 Connolly SJ, et al. N Engl J Med 2011;364(9):806-17.
 Dewilde W, et al. Am Heart J. 2009 Nov;158(5):713-8.
 Diener HC, et al. Lancet Neurol. 2012 Mar;11(3):225-31.
 EAFT (European Atrial Fibrillation Trial) Study Group. Lancet. 1993;342(8882):1255-62.
 Eikelboom JW, et al. J Stroke Cerebrovasc Dis. 2012 Aug;21(6):429-35.
 ESPRIT Study Group, et al. Lancet Neurol. 2007 Feb;6(2):115-24.
 Hart RG, et al. Cerebrovasc Dis. 2008;25(4):344-7.
 N Engl J Med 1990;322(12):863-8.
 Wang TH, et al. Eur Heart J. 2007 Sep;28(18):2200-7.

Inappropriate Outcomes

De Caterina R, et al. Eur Heart J. 2010 Sep;31(17):2133-40.
 Ezekowitz MD, et al. Circulation. 1995 Oct 15;92(8):2178-82.
 Lorenzoni R, et al. Am Heart J. 2004 Jul;148(1):e6.

Others

Cardiovasc J Afr. 2011 May;22(3):164.
 Active Steering Committee, et al. Am Heart J. 2006 Jun;151(6):1187-93.
 ROCKET AF Study Investigators. Am Heart J. 2010 Mar;159(3):340-7.
 The Stroke Prevention in Atrial Fibrillation Investigators. Stroke. 1990 Apr;21(4):538-45.
 Boysen G, et al. Stroke. 1990;21(Suppl I):I-92.
 De Schryver EL. Cerebrovasc Dis. 2000 Mar;10(2):147-50.
 Desai A. Clinical Trials Registry - India (CTRI). 2006.
 Eikelboom JW, et al. Am Heart J. 2010 Mar;159(3):348-53.
 Ezekowitz MD, et al. Am Heart J. 2009 May;157(5):805-10, 810.e1-2.
 Flaker G, et al. J Am Coll Cardiol. 2012 Feb 28;59(9):854-5.
 Lopes RD, et al. Lancet. 2012 Oct 2. Epub ahead of print.
 Lopes RD, et al. Am Heart J. 2010 Mar;159(3):331-9.
 Mant J, et al. Cerebrovasc Dis. 2007;23(Suppl 2):10.
 Mant J, et al. Cardiol Rev. 2008;25(7):32-6.
 Mant JW, et al. BMC Cardiovasc Disord. 2003 Aug 26;3:9.
 Posada IS, et al. Am Heart J. 1999 Jul;138(1 Pt 1):137-43.
 Van Latum JC. Ned Tijdschr Geneesk. 1994;138(20):1025-31.
 Yigit Z. Turk Kardiyoloji Dernegi Arsivi. 2000;28(1):8-19+4.

CHAPTER 3: RAPID NETWORK META-ANALYSIS USING CLINICALTRIALS.GOV: AN APPLICATION USING ANTITHROMBOTICS FOR ATRIAL FIBRILLATION

Rapid Network Meta-Analysis using ClinicalTrials.gov: An application using antithrombotics for atrial fibrillation

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CHAPTER 3: RAPID NETWORK META-ANALYSIS USING CLINICALTRIALS.GOV: AN APPLICATION USING ANTITHROMBOTICS FOR ATRIAL FIBRILLATION

Rapid Network Meta-Analysis using ClinicalTrials.gov: An application using antithrombotics for atrial fibrillation

SUMMARY:

In this chapter, we investigate the opportunities and pitfalls of using rapid network meta-analysis of using ClinicalTrials.gov. We conduct a network meta-analysis comparing antithrombotics for atrial fibrillation using data solely derived from ClinicalTrials.gov, and compare findings from Chapter 2 which use traditional systematic review methods, e.g., published literature including the Cochrane Library, MEDLINE and EMBASE.

LINKS:

This manuscript has been submitted for publication in *Systematic Reviews* in May 2015

CONTRIBUTION:

I was responsible for writing the draft manuscript, with guidance from supervisors. I conducted all network meta-analyses, and generated all tables and figures related to findings from the network meta-analysis using ClinicalTrials.gov.

ABSTRACT

Background: Network meta-analysis are typically underpinned by systematic reviews of randomized controlled trials (RCTs). Included RCTs have traditionally been identified by searching published and grey literature. This process can take months and significant resources to complete, especially when large numbers of treatments are considered. Novel methods are needed to reduce the timelines and resources required to conduct systematic reviews and network meta-analysis.

Methods: We conducted a network meta-analysis comparing antithrombotics for atrial fibrillation using data solely derived from ClinicalTrials.gov, and compared findings with those using traditional systematic review methods, e.g., published literature including the Cochrane Library, MEDLINE and EMBASE. Outcome data for stroke or systemic embolism were combined and analyzed using a Bayesian network meta-analysis using both approaches.

Results: We demonstrate the potential application of ClinicalTrials.gov for conducting rapid network meta-analysis using an applied example which compares antithrombotic treatments for atrial fibrillation. Findings were similar for new oral anticoagulants which were recently introduced to the market but ClinicalTrials.gov did not capture data on older treatments and/or studies published prior to 2008.

Interpretation: The application of ClinicalTrials.gov may save time and resources compared to using traditional systematic review methods when performing a network meta-analysis. However, analyses relying on ClinicalTrial.gov will not be as comprehensive as those using traditional systematic review methods – they will likely capture fewer studies and will not include results for studies and/or treatments published before the ClinicalTrials.gov results database was implemented in 2008.

INTRODUCTION

Systematic reviews typically only consider randomized controlled trials (RCTs) and identify these studies by searching published and grey literature. This process is time consuming and typically requires the researcher to sift through thousands of titles and abstracts to identify relevant studies for inclusion in the review, and subsequently complete data extraction from relevant studies. As a result, it often takes considerable time to conduct systematic reviews, especially when multiple treatments are considered simultaneously, which is the case with network meta-analysis. Indeed, the average time for completion of a Cochrane review takes at least six months,¹ and is likely longer for network meta-analyses given they include more treatments. These timelines are not conducive for the decision making paradigm where decisions are often made within days or weeks, not years or months. This has resulted in researchers looking for more efficient ways to conduct systematic reviews and network meta-analyses.²

In this paper, we describe a potential approach to reduce the time and resources for conducting systematic reviews and network meta-analyses. We investigate the advantages and disadvantages of using ClinicalTrials.gov to identify RCTs and data extraction in systematic reviews and network meta-analysis. We compare and contrast the findings from a systematic review and network meta-analysis conducted using ClinicalTrials.gov with traditional systematic review approaches. To illustrate the advantages and disadvantages of the approach, we used an illustrative example comparing antithrombotic agents for

prevention of stroke or systematic embolism in patients with atrial fibrillation.

METHODS

We aimed to investigate the advantages and pitfalls of using ClinicalTrials.gov to conduct network meta-analysis compared with traditional approaches using an applied case study which compared antithrombotics for atrial fibrillation.

Case Study – Antithrombotics for atrial fibrillation

The methods used to identify studies included in the network meta-analysis and to collect trial-level data for our case study have been described in Chapter 2 and published elsewhere.³

A total of 12 randomized studies comparing 8 different treatments in addition to placebo/observation were identified (apixaban, dabigatran, edoxaban, rivaroxaban, apixaban, edoxaban, and vitamin K antagonists (VKA) at a standard adjusted dose (target international normalised ratio 2.0-3.0), acetylsalicylic acid, acetylsalicylic acid and clopidogrel), encompassing a total of 82,396 participants for the stroke or systemic embolism network (Figure 3). We conducted a Bayesian fixed effects network meta-analysis to compare the risk of stroke or systematic embolism or major bleeding among the different treatments. The findings for stroke or systemic embolism, which are the focus of this methods paper, are reported in Figure 4.

Data source

We only included data reported on ClinicalTrials.gov. ClinicalTrials.gov is a Web-based registry and results database that provides the public with easy access to information on

publicly and privately supported clinical studies on a wide range of diseases and conditions. ClinicalTrials.gov was made available to the public in 2000 and expanded in 2008 to include a database for reporting summary results. Since 2000, the number of registered Studies has increased from 5,636 to over 167,456 studies in 2014. The number of registered studies reporting results has grown from 1,835 in 2009 to 11,970 in 2014. The Web site is maintained by the National Library of Medicine (NLM) at the National Institutes of Health (NIH). Information on ClinicalTrials.gov is provided and updated by the sponsor or principal investigator of the clinical study. The International Committee of Medical Journal Editors (ICMJE) requires trial registration in a database such as ClinicalTrials.gov as a condition of the publication of research results.

Study Selection

We searched the website of ClinicalTrials.gov using the advanced search function. We searched the following key words: ‘Apixaban’ OR ‘clopidogrel’ OR ‘Dabigatran’ OR ‘Edoxaban’ OR ‘Rivaroxaban’ OR ‘aspirin’ OR ‘acetylsalicylic acid’ OR ‘warfarin’ AND ‘Atrial Fibrillation’ (Figure 1). To coincide with our previous review of antithrombotic agents for atrial fibrillation, we included clinical trials published from 1988 to January 23, 2014. Citations identified on ClinicalTrials.gov were included if they reported results in the database under the ‘Study Results’ tab or referenced a paper with findings on the “No Study Results Posted” Tab (Figure 2). Searches were exported from ClinicalTrials.gov as comma-separated values and merged in Microsoft Excel. Duplicates from the multiple search strategies were identified by searching on ClinicalTrials.gov ID unique identifier and removed using the Microsoft Excel duplicate function.

The population of interest was identical to our previous review. We included individuals with non valvular AF requiring anticoagulation (including all risk levels and regardless of any comorbidities). The following treatments were included in the review: apixaban, dabigatran, edoxaban, rivaroxaban, standard adjusted dose VKA, acetylsalicylic acid (ASA), ASA and clopidogrel. The outcome considered was stroke or systemic embolism, which was the primary efficacy outcome used in the newer oral anticoagulant studies.

Similar to our previous review, active and placebo-controlled randomized controlled trials (RCTs) were selected for inclusion if they were published in English, included at least one antithrombotic treatment under review (using pre-specified doses), reported data for stroke/systemic embolism(SE), and involved patients with non-valvular AF eligible to receive anticoagulant therapy, regardless the level of stroke risk. Trials that included patients with contraindication to anticoagulant treatment were excluded. VKA trials were included if the dose was adjusted to a target international normalised ratio (INR) 2.0-3.0). Any dose of ASA was considered for inclusion, but ASA dose was stratified in the analysis as low (≤ 100 mg daily), medium (>100 mg to ≤ 300 mg daily), or high (>300 mg daily). We only included new oral anticoagulants which had at least one large phase III study. One reviewer independently extracted the results for each included study, and inserted findings into a NetMetaXL⁴ template. All extracted data was checked for accuracy by one independent reviewer. Any disagreements in the assessment of these data were resolved through discussion until consensus was reached. The trial selection process is presented in a modified flowchart analogous to the flowchart recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)⁵ statement. This was not registered in

PROSPERO given it would not meet the requirements for that registry.

Statistical Analysis

Bayesian network meta-analyses were conducted using NetMetaXL. NetMetaXL is an excel-based WinBUGS software (MRC Biostatistics Unit, Cambridge, UK). A binomial likelihood model⁶ which accounts for the use of multi-arm trials was used for the analyses given the datasets provided were dichotomous outcomes and included multi-arm trials. Trials with zero cells in both arms or nodes where there were no events were excluded from the evidence networks because they do not contribute information or allow interpretable information.⁶ Both fixed and random-effects network meta-analyses were conducted, although the fixed-effects model was chosen for the reference case analysis, as the evidence network was largely comprised of single study connections. We modeled point estimates and 95% credible intervals for odds ratios (OR) using Markov Chain Monte Carlo methods. Vague or flat priors, such as $N(0, 100^2)$ were assigned for basic parameters throughout, although informative priors were considered.⁷ Assessment of model fit was based on deviance information criterion (DIC) and comparison of residual deviance to number of unconstrained data points.^{6,8} To ensure convergence was reached, trace plots and the Brooks-Gelman-Rubin statistic were assessed.⁹ Three chains were fit in WinBUGS for each analysis, with at least 40,000 iterations, and a burn-in of at least 40,000 iterations. We qualitatively compared the results from our network meta-analysis with those reported previously.

Results

The search using the ClinicalTrials.gov database returned 309 database results (**Figure 3**). All 309 database abstracts were imported into Excel. After duplicates were removed, 183 remained to be assessed for inclusion and 90 were excluded because they were not

completed, terminated, or active studies (**Figure 3**). Of the 93 completed, terminated, or active studies, 28 reported results. Of these, 24 were excluded from analysis as they did not meet the PICOS criteria outlined in the original publication,³ or were published after the previous search dates.³ We identified two additional studies by searching the ‘No Study Results Posted’ Tab for previously excluded studies, resulting in a total of 6 included RCTs when deriving data solely from ClinicalTrials.gov.

We provide a list of 12 studies identified in the evidence network for Stroke or SE in our original review (**Table 2**). Using ClinicalTrials.gov, we only identified 6 of these studies – RE-LY, ROCKET-AF, ARISTOTLE, ARISTOTLE-J, ENGAGE AF TIMI 48, and ACTIVE W. As a result, the network included fewer patients (78,444 versus 82,396). The network using data from ClinicalTrials.gov also included fewer treatments – it did not capture studies with data reported for low-dose aspirin, medium dose aspirin or placebo (**Table 1**).

The findings were largely the same for new oral anticoagulants versus warfarin (Figure 4) between analyses. However, there was no data that could be estimated comparing new oral anticoagulants with aspirin or placebo for the analysis which only extracted data using ClinicalTrials.gov (**Figure 4**)

Discussion

We have illustrated an application of ClinicalTrials.gov for identification of studies and data extraction to include in a network meta-analysis. We attempted to replicate findings from a network meta-analysis³ published in the *BMJ Open* comparing antithrombotics for atrial fibrillation. In the future, we plan on investigating the application of ClinicalTrials.gov using additional case studies to better understand situations where use of ClinicalTrials.gov is most appropriate compared with standard systematic review methods.

We found the application of ClinicalTrials.gov saved considerable time and resources compared with traditional systematic review methods. We were able to conduct our search, identify relevant studies, extract data, and conduct our analysis in a matter of weeks using ClinicalTrials.gov versus months which are typically required using traditional systematic review methods. Further, the majority of work was able to be performed by one individual, and we did we also did not require the use of an information specialist. By contrast, our previous review³ relied on several individuals to identify studies, extract data, and run the analysis. We also required the expertise of an information specialist to perform a sophisticated search strategy to capture relevant studies (see [online Appendix 1](#) in original publication).³ We also saved money as there was no need to obtain and pay for as many full text articles.

Despite these advantages, there were several critical disadvantages with relying solely on data using ClinicalTrials.gov to inform our network meta-analysis. We did not capture all relevant studies, in particular those published before the ClinicalTrials.gov results database was launched in September 2008. Indeed, we did not capture AFASAK, AFASAK-2, BAFTA, CAFA, or JAST studies, all of which were identified in our previous review³ using traditional systematic review methods, although the majority of these studies could have been identified via a previous systematic review and meta-analyses.^{10,11}

ClinicalTrials.gov also did not report results for several recently published studies. Indeed, the ENGAGE-TIMI AF¹² trial was not identified under the ClinicalTrials.gov results tab, but rather via a link to the publication listed under the ‘No study results posted’ tab on ClinicalTrials.gov. It is not uncommon for results to not be reported on ClinicalTrials.gov

but there be link to a publication be provided (**Figure 2**). Indeed, the ACTIVE A Trial was also identified using this approach.

Despite this added safeguard, there is still potential that ClinicalTrials.gov will miss relevant studies. Indeed, ClinicalTrials.gov did not report any findings for NCT00504556, or provide a link to the published article despite it being published in 2010.¹³ As noted previously, information on ClinicalTrials.gov is provided and updated by the sponsor or principal investigator of the clinical study, and they may not post results despite initiatives to encourage/mandate such information.

Collectively these shortcomings, particularly the unavailability of studies posted before 2008, resulted in a much smaller evidence network compared to our analysis using traditional systematic review methods³ and lack of comparative data for aspirin. While our findings for new oral anticoagulants versus warfarin were similar using ClinicalTrials.gov, we were not able to generate estimates for new oral anticoagulants versus aspirin for our patient population, a key treatment for our analysis.

However, on the other hand, some may argue that ClinicalTrials.gov not including studies published before 2008 is an added strength for network meta-analysis. There is debate around whether including older studies with newer studies in a network meta-analysis is appropriate given clinical practice has changed substantially over the years. The use of ClinicalTrials.gov may force users to inadvertently restrict their analyses to studies which have been published since 2008.

The use of an information specialist may partially bias our findings against ClinicalTrials.gov. For our previous study,³ we had access to highly trained information specialist to perform our sophisticated search strategy (see [online Appendix 1](#) in original publication), adhering to PRISMA guidance.⁵ Other institutions may not have access to information specialists and perform their search strategy using methods not adhering to best practices. In these instances, the searches performed using traditional systematic review methods may not capture relevant studies and be limited in their own right, i.e., be based on a less rigorous search strategy that used in our previous study.³ Further research is needed comparing ClinicalTrials.gov to searches performed by researchers who used information specialists, and those who did not use information specialists.

There are several other limitations that warrant consideration. We only considered one case study – antithrombotics for atrial fibrillation. Atrial fibrillation is a high profile topic and findings may be more likely to be posted on ClinicalTrials.gov than studies in other disease areas with a lower profile. Further, we only considered one outcome – stroke and systemic embolism –and this outcome was the primary efficacy outcome. It will be interesting to further investigate the application of ClinicalTrials.gov for other disease areas and for secondary outcomes. There may be situations where use of ClinicalTrials.gov yields more studies than using traditional systematic review methods. For example, some secondary outcomes such as health related quality of life may not make it into the main publication, but may be more likely to be reported in ClinicalTrials.gov where there is unlimited room for reporting secondary outcomes. Similarly, there may be instances where findings are reported in the publications but not ClinicalTrials.gov. There may also be instances where the results

from ClinicalTrials.gov may differ from the publication or vice versa. Further research is needed in this area.

We captured a large fraction of total patients (78,444 of 82,396) from the original review. For a traditional meta-analysis, one could argue that capturing greater than 95% of patients might be sufficient and unlikely to alter conclusions. However, for network meta-analysis, this is more complicated given there is potential that patients who were not captured may come largely from a particular treatment option (likely studies published prior to 2008) and this treatment may be a relevant. Further research is needed in this area, and should involve decision makers examining scenarios where are more (or less) likely to be sufficiently informed when using ClinicalTrials.gov.

For NCT00262600, raw data for patients reporting numbers were not posted on ClinicalTrials.gov and we referred to the publication,¹⁴ which added a few additional minutes to the analysis. Also, in both ClinicalTrials.gov and in the traditional systematic review, data for rivaroxaban were reported using a per protocol analysis. Similar to our original review, we incorporated findings using the ITT population derived from FDA Published Summary documents, given ClinicalTrials.gov clearly stated the per protocol population was used *“The per-protocol (PP) population consisted of all randomized unique patients excluding those who had specific pre-defined major protocol deviations that occurred by the time of enrollment into the study or during the trial.”*

In summary, we have demonstrated the application of ClinicalTrials.gov for performing network meta-analyses using an example of a published network meta-analysis comparing

antithrombotics for atrial fibrillation. The use of ClinicalTrials.gov saved time and resources when performing network meta-analyses compared with traditional systematic review methods. However, network meta-analyses relying on ClinicalTrials.gov will not be as comprehensive at this time as those using traditional systematic review methods – we captured fewer studies than traditional systematic review methods and were unable to include studies and/or treatments published before the ClinicalTrials.gov results database was implemented in 2008. Future studies are needed comparing the application of ClinicalTrials.gov for other disease conditions and for secondary outcomes to gain a better understanding of when use of ClinicalTrials.gov is most appropriate and/or inappropriate compared to traditional systematic review methods.

TABLES AND FIGURES

Table 1 Summary of Evidence Network

Characteristic	NMA based on full search strategy	NMA using ClinicalTrials.gov
Number of Interventions	11	8
Number of Studies	12	6
Total Number of Patients in Network	82,396	78,444
Total Number of Events in Network	3,009	2,767
Total Possible Pairwise Comparisons	55	28
Total Number Pairwise Comparisons With Direct Data	14	9
Number of Two-arm Studies	9	4
Number of Multi-Arms Studies	3	2
Number of Studies With No Zero Events	11	5
Number of Studies With At Least One Zero Event	1	1
Number of Studies with All Zero Events	0	0

NMA= network meta-analysis

Table 2 List of Studies included in original evidence network. The asterisk (*) denotes 6 studies captured using ClinicalTrials.gov

Study and Design	Disposition	Population	Interventions	Follow-up
ACTIVE-W* OL RCT, 2006. Multicenter, 32 countries (including Europe / America).	Randomized: n=6706	AF patients eligible / willing to take anticoagulant therapy, with ≥ 1 pre-specified risk factor for stroke.	Clopidogrel / Low-dose ASA (n=3335) Warfarin – INR 2.0 to 3.0 (n=3371)	1.3 years (stopped early)
AFSAK OL/DB RCT, 1989. Multicenter, Copenhagen.	Randomized: n=1007	AF patients, with no recent anticoagulation or cerebrovascular event, valve replacement or rheumatic heart disease.	OL Warfarin – INR 2.8 to 4.2 * (n=335) Low-dose ASA (n=336) PL (n=336)	2 years
AFSAK-2 OL RCT, 1998. Multicenter, Copenhagen.	Randomized: n=677	AF patients ≥ 60 years (unless with CV or pulmonary disease), without recent TIA or risk factors for bleeding.	Fixed-dose Warfarin * (n=167) Fixed-dose Warfarin / Medium-dose ASA * (n=171) Medium Dose ASA (n=169) Warfarin – INR 2.0 to 3.0 (n=170)	3.5 years
ARISTOTLE* DB RCT, 2011. Multicenter, 39 countries (including Europe / America).	Randomized: n=18201	AF patients with ≥ 1 risk factor for stroke, without recent stroke or ASA > 165 mg.	Apixaban 5 mg BID (n=9120) Warfarin – INR 2.0 to 3.0 (n=9081) Concomitant use of ASA (≤ 165 mg daily) or NSAIDs permitted.	NR
ARISTOTLE-J* OL/DB RCT, 2011. Multicenter, Japan.	Randomized: n=222	AF patients with ≥ 1 risk factor for stroke, without recent TIA or ASA > 100 mg.	Apixaban 2.5 mg BID (n=74) Apixaban 5 mg BID (n=74) OL Warfarin – INR 2.0 to 3.0 (n=74) Concomitant use of ASA (≤ 100 mg daily) permitted.	12 weeks
BAFTA OL RCT, 2007. Multicenter, UK.	Randomized: n=973	AF patients ≥ 75 years, with clinical uncertainty around optimal treatment.	Low-dose ASA (n=485) Warfarin – INR 2.0 to 3.0 (n=488)	2.7 years
CAFA DB RCT, 1991. Multicenter, Canada.	Randomized: n=378	AF patients without recent stroke, TIA or MI, and who did not require antiplatelet drug therapy.	Warfarin – INR 2.0 to 3.0 (n=187) PL (n=191)	1.2 years (stopped early)
ENGAGE AF-TIMI 48* DB RCT, 2013. Multicenter, 46 countries (including Europe / America).	Randomized: n=21105	AF patients at moderate to high risk of stroke (CHADS2 score ≥ 2).	Edoxaban 30 mg OD (n=7034) Edoxaban 60 mg OD (n=7035) Warfarin – INR 2.0 to 3.0 (n=7036) Almost a third of patients in treatment arms took concomitant ASA.	2.8 years

Study and Design	Disposition	Population	Interventions	Follow-up
JAST OL RCT, 2006. Multicenter, Japan.	Randomized: n=871	AF patients without recent symptomatic thromboembolic disease, ICH or GI bleeding.	Medium-dose ASA (n=426) No treatment (n=445)	2.1 years (stopped early)
RE-LY* OL/DB RCT, 2009. Multicenter, 44 countries (including Europe / America).	Randomized: n=18113	AF patients with ≥ 1 risk factor for stroke, without recent stroke or increased risk of bleeding.	Dabigatran 110 mg BID (n=6015) Dabigatran 150 mg BID (n=6076) OL Warfarin – INR 2.0 to 3.0 (n=6022) Concomitant use of ASA (<100 mg daily) or other antiplatelet agents permitted.	2 years
ROCKET-AF* DB RCT, 2011. Multicenter, 45 countries (including Europe / America).	Randomized: n=14264	AF patients at moderate to high risk of stroke (CHADS2 score ≥ 2).	Rivaroxaban 20 mg OD (n=7131) Warfarin – INR 2.0 to 3.0 (n=7133) Over a third of patients in both arms took concomitant ASA.	1.9 years
Weitz et al 2010 DB RCT, 2010. Multicenter, 12 countries (including Eastern Europe / America).	Randomized: n=719	AF patients at moderate to high risk of stroke (CHADS2 score ≥ 2).	Edoxaban 30 mg OD (n=235) Edoxaban 60 mg OD (n=234) Warfarin – INR 2.0 to 3.0 (n=250)	12 weeks

Figure 1 Screenshot of search strategy

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

Search for studies: Example: "Heart attack" AND "Los Angeles"
[Advanced Search](#) | [Help](#) | [Studies by Topic](#) | [Glossary](#)

[Find Studies](#) ▾ [About Clinical Studies](#) ▾ [Submit Studies](#) ▾ [Resources](#) ▾ [About This Site](#) ▾

[Home](#) > [Find Studies](#) > [Advanced Search](#) Text Size ▾

Advanced Search

Fill in any or all of the fields below.

Click on a label to the left for further explanation or read the [Help](#).

Search Terms: [Help](#)
Recruitment:
Study Results:
Study Type:

Targeted Search:
Conditions:
Interventions:
Title Acronym/Titles:
Outcome Measures:
Sponsor/Collaborators:
Sponsor (Lead):
Study IDs:

Locations:
State 1:
Country 1:
State 2:
Country 2:
State 3:
Country 3:
Location Terms:

Additional Criteria:
Gender:
☐ Child (birth-17)
Age Group: ☐ Adult (18-85)
☐ Senior (86+)

Figure 2 Screenshot of 'No Study Results Posted' Tab

Trial record 1 of 23 for: edoxaban
Previous Study | Return to List | Next Study >

Global Study to Assess the Safety and Effectiveness of Edoxaban (DU-176b) vs Standard Practice of Dosing With Warfarin in Patients With Atrial Fibrillation (EngageAFTIMI48)

This study has been completed.

Sponsor:
Daiichi Sankyo Inc.

Collaborator:
The TIMI Study Group

Information provided by (Responsible Party):
Daiichi Sankyo Inc.

ClinicalTrials.gov Identifier:
NCT00781391

First received: October 28, 2008
Last updated: September 9, 2014
Last verified: September 2014
History of Changes

Full Text View

Tabular View

No Study Results Posted

Disclaimer

How to Read a Study Record

No Study Results Posted on ClinicalTrials.gov for this Study

About Study Results Reporting on ClinicalTrials.gov

Study Status:	This study has been completed.
Study Completion Date:	May 2013
Primary Completion Date:	April 2013 (Final data collection date for primary outcome measure)

No publications provided by Daiichi Sankyo Inc.

Publications automatically indexed to this study by ClinicalTrials.gov Identifier (NCT Number):
Ruff CT, Giugliano RP, Braunwald E, Mercuri M, Curt V, Betcher J, Grip L, Cange AL, Crompton AE, Murphy SA, Deenadayalu N, Antman EM. Transition of patients from blinded study drug to open-label anticoagulation: the ENGAGE AF-TIMI 48 trial. J Am Coll Cardiol. 2014 Aug 12;64(8):576-84. doi: 10.1016/j.jacc.2014.05.028.
Giugliano RP, Ruff CT, Rost NS, Silverman S, Wiviott SD, Lowe C, Deenadayalu N, Murphy SA, Grip LT, Betcher JM, Duggal A, Dave J, Shi M, Mercuri M, Antman EM, Braunwald E; ENGAGE AF-TIMI 48 Investigators. Cerebrovascular events in 21 105 patients with atrial fibrillation randomized to edoxaban versus warfarin: Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48. Stroke. 2014 Aug;45(8):2372-8. doi: 10.1161/STROKEAHA.114.008025. Epub 2014 Jun 19.

100

Figure 3 Modified PRISMA Flow Diagram using ClinicalTrials.gov

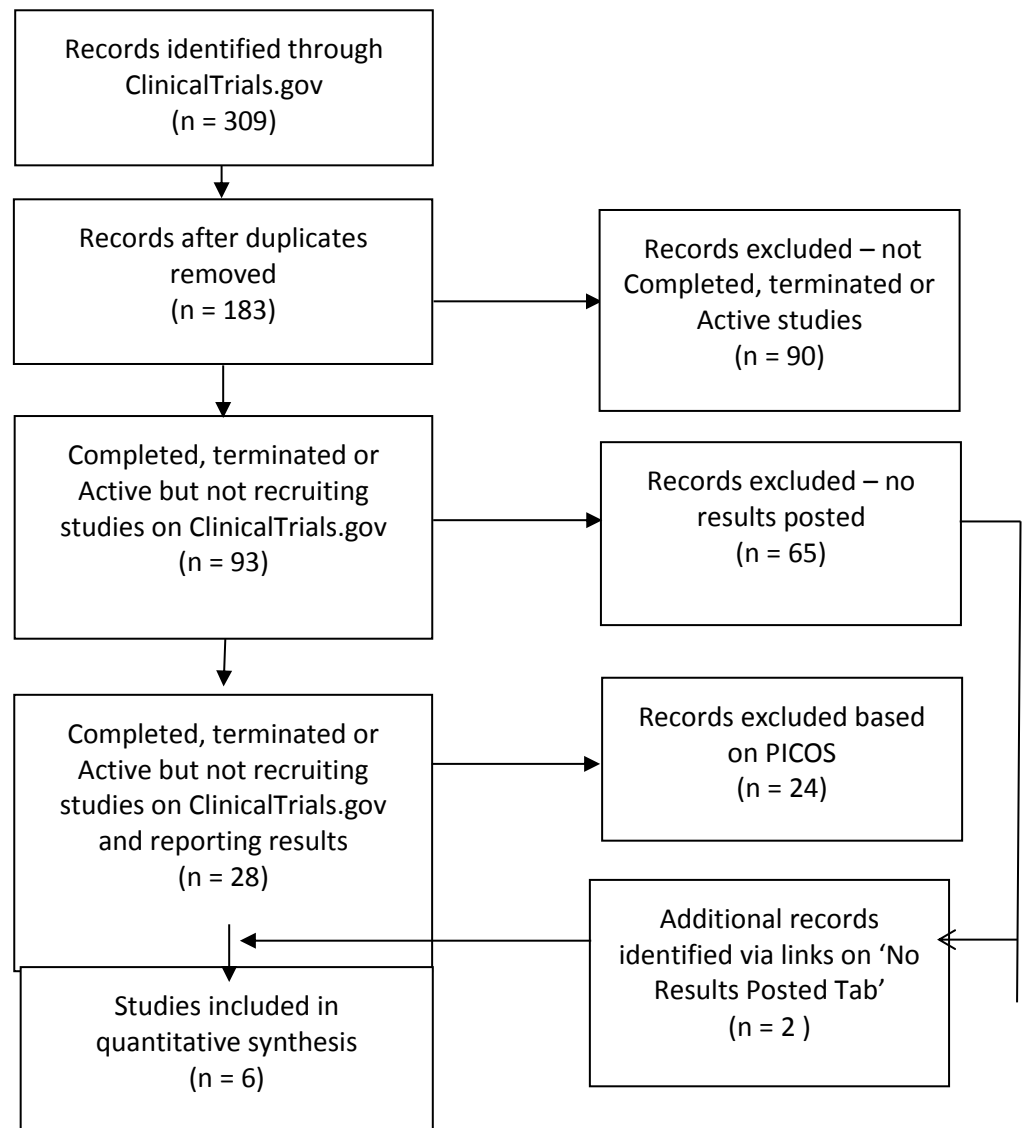


Figure 4 Evidence Diagrams using A) traditional systematic review methods, and B) ClinicalTrials.gov

A)

Dabigatran 150mg twice daily												
0.84 (0.63 – 1.12)	Apixaban 5mg twice daily											
0.76 (0.59 – 1.00)	0.91 (0.71 – 1.14)	Edoxaban 60mg daily										
0.75 (0.58 – 0.98)	0.90 (0.70 – 1.15)	0.99 (0.78 – 1.25)	Rivaroxaban 20mg daily									
0.72 (0.58 – 0.90)	0.86 (0.65 – 1.13)	0.95 (0.73 – 1.22)	0.96 (0.74 – 1.25)	Dabigatran 110mg twice daily								
0.66 (0.53 – 0.81)	0.78 (0.65 – 0.93)	0.86 (0.74 – 1.01)	0.87 (0.74 – 1.03)	0.91 (0.75 – 1.12)	Std Adjusted Dose VKA							
0.58 (0.45 – 0.76)	0.69 (0.55 – 0.87)	0.76 (0.65 – 0.89)	0.77 (0.61 – 0.97)	0.81 (0.62 – 1.04)	0.88 (0.76 – 1.03)	Edoxaban 30mg daily						
0.49 (0.25 – 0.92)	0.58 (0.31 – 1.06)	0.64 (0.33 – 1.16)	0.65 (0.34 – 1.20)	0.68 (0.35 – 1.27)	0.74 (0.40 – 1.34)	0.84 (0.44 – 1.51)	Medium Dose ASA (> 100mg and < 300mg daily)					
0.43 (0.24 – 0.79)	0.52 (0.29 – 0.89)	0.57 (0.32 – 0.98)	0.57 (0.33 – 1.00)	0.60 (0.33 – 1.07)	0.66 (0.38 – 1.12)	0.75 (0.42 – 1.29)	0.89 (0.56 – 1.43)	No Treatment / Placebo				
0.35 (0.22 – 0.55)	0.42 (0.27 – 0.64)	0.46 (0.30 – 0.71)	0.47 (0.30 – 0.71)	0.49 (0.31 – 0.77)	0.53 (0.36 – 0.80)	0.61 (0.39 – 0.93)	0.72 (0.39 – 1.37)	0.81 (0.47 – 1.38)	Low Dose ASA (< 100mg daily)			
0.34 (0.23 – 0.49)	0.40 (0.28 – 0.58)	0.45 (0.31 – 0.64)	0.45 (0.31 – 0.64)	0.47 (0.32 – 0.68)	0.51 (0.37 – 0.70)	0.58 (0.41 – 0.83)	0.69 (0.35 – 1.41)	0.78 (0.42 – 1.49)	0.96 (0.57 – 1.61)	Low Dose ASA (< 100mg daily) & Clopidogrel (75mg daily)		

B)

Dabigatran 150mg twice daily											
0.84 (0.63 – 1.13)	Apixaban 5mg twice daily										
0.75 (0.57 – 1.00)	0.90 (0.70 – 1.14)	Rivaroxaban 20mg daily									
0.75 (0.58 – 0.99)	0.89 (0.70 – 1.14)	1.00 (0.80 – 1.26)	Edoxaban 60mg daily								
0.72 (0.58 – 0.92)	0.86 (0.66 – 1.13)	0.96 (0.74 – 1.25)	0.96 (0.73 – 1.24)	Dabigatran 110mg twice daily							
0.66 (0.53 – 0.83)	0.78 (0.66 – 0.94)	0.88 (0.74 – 1.04)	0.88 (0.75 – 1.02)	0.91 (0.74 – 1.13)	Std Adjusted Dose VKA						
0.57 (0.44 – 0.75)	0.68 (0.54 – 0.86)	0.76 (0.61 – 0.96)	0.76 (0.66 – 0.89)	0.79 (0.62 – 1.02)	0.87 (0.76 – 1.01)	Edoxaban 30mg daily					
0.34 (0.23 – 0.51)	0.41 (0.29 – 0.58)	0.45 (0.32 – 0.64)	0.46 (0.32 – 0.65)	0.47 (0.32 – 0.70)	0.52 (0.38 – 0.70)	0.60 (0.42 – 0.84)	Low Dose ASA (< 100mg daily) & Clopidogrel (75mg daily)				

REFERENCES

1. Allen I OI. Creative nonfiction. *JAMA*. 1999;282(7):634-635. <http://dx.doi.org/10-1001/pubs.JAMA-ISSN-0098-7484-282-7-jbk0818>.
2. Tsafnat G, Glasziou P, Choong MK, Dunn A, Galgani F, Coiera E. Systematic review automation technologies. *Syst Rev*. 2014;3(1):74. doi:10.1186/2046-4053-3-74.
3. Cameron C, Coyle D, Richter T, et al. Systematic review and network meta-analysis comparing antithrombotic agents for the prevention of stroke and major bleeding in patients with atrial fibrillation. *BMJ Open* . 2014;4 (6). doi:10.1136/bmjopen-2013-004301.
4. Brown S, Hutton B, Clifford T, et al. A Microsoft-Excel-based tool for running and critically appraising network meta-analyses--an overview and application of NetMetaXL. *Syst Rev*. 2014;3(1):110. doi:10.1186/2046-4053-3-110.
5. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6(7):e1000097. doi:10.1371/journal.pmed.1000097.
6. Dias S, Welton NJ, Sutton AJ, Ades A. *NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials.*; 2011. www.nicedsu.org.uk. Accessed October 1, 2011.
7. Turner RM, Davey J, Clarke MJ, Thompson SG, Higgins JP. Predicting the extent of heterogeneity in meta-analysis, using empirical data from the Cochrane Database of Systematic Reviews. *Int J Epidemiol*. 2012;41(3):818-827. doi:10.1093/ije/dys041.
8. Spiegelhalter DJ, Best NG, Carlin BP, van der Linde A. Bayesian measures of model complexity and fit. *J R Stat Soc Ser B (Statistical Methodol)*. 2002;64(4):583-639. doi:10.1111/1467-9868.00353.
9. Spiegelhalter D, Thomas A, Best N. WinBUGS user manual. *MRC Biostat Unit*. 2004;2(January). <http://voteview.org/manual14.pdf>. Accessed October 1, 2011.
10. Harenberg J, Weiss C. Clinical trials with new oral anticoagulants. Additive value of indirect comparisons also named network meta-analyses. *Hamostaseologie*. 2013;33(1):62-70. doi:10.5482/HAMO-12-11-0021.
11. Hart R, Pearce L, Aguilar M. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med*. 2007. <http://annals.org/article.aspx?articleid=735042>. Accessed January 29, 2014.

12. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2013;369(22):2093-2104. doi:10.1056/NEJMoa1310907.
13. Weitz JI, Connolly SJ, Patel I, et al. Randomised, parallel-group, multicentre, multinational phase 2 study comparing edoxaban, an oral factor Xa inhibitor, with warfarin for stroke prevention in patients with atrial fibrillation. *Thromb Haemost*. 2010;104(3):633-641. doi:10.1160/TH10-01-0066.
14. Connolly S, Ezekowitz M. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361(12):1139-1151.

CHAPTER 4: NETWORK META-ANALYSIS OF COMPLEX INTERVENTIONS: AN APPLICATION INVESTIGATING TRIPANS FOR ACUTE TREATMENT OF MIGRAINE

Triptans in the acute treatment of migraine: A systematic review and network meta-analysis

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CHAPTER 4: NETWORK META-ANALYSIS OF COMPLEX INTERVENTIONS: AN APPLICATION INVESTIGATING TRIPANS FOR ACUTE TREATMENT OF MIGRAINE

Triptans in the acute treatment of migraine: A systematic review and network meta-analysis

SUMMARY:

In this chapter, we conduct a network meta-analysis of a complex network which has many (>20) treatment nodes. We conduct a network meta-analysis comparing triptans for acute treatment of migraine. We illustrate ways to convey findings when there are a large number of treatments in a network meta-analysis.

LINKS:

This manuscript has been published in Headache:

<http://onlinelibrary.wiley.com/doi/10.1111/head.12601/abstract>

The supplemental appendices are published here:

This findings have also been reported on the Ontario Drug Policy Research Network (ODPRN) website: <http://www.odprn.ca/triptans-for-migraine-therapy/>

CONTRIBUTION:

I was responsible for writing the draft manuscript, with guidance from supervisors. I conducted all network meta-analyses, and generated output populating all tables and figures related to findings from the network meta-analysis.

ABSTRACT

Background: Although triptans are widely used in the acute management of migraine, there is uncertainty around the comparative efficacy of triptans amongst each another and versus non-triptan migraine treatments. We conducted systematic reviews and network meta-analyses to compare the relative efficacy of triptans (alone or in combination with other drugs) for acute treatment of migraines compared to other triptans agents, nonsteroidal anti-inflammatory drugs (NSAIDs), acetylsalicylic acid (ASA), acetaminophen, ergots, opioids, or antiemetics.

Methods: The Cochrane Library, MEDLINE and EMBASE were searched for randomized controlled trials that compared triptans (alone or in combination with other drugs) with placebo-controlled or active migraine treatments. Study selection, data extraction and quality assessment were completed independently by multiple reviewers. Outcome data were combined and analyzed using a Bayesian network meta-analysis. For each outcome, odds ratios, relative risks, and absolute probability of response were calculated.

Results: 133 randomized controlled trials met the inclusion criteria. Standard dose triptans relieved headaches within 2 hours in 42 to 76% of patients, and 2 hour sustained freedom from pain was achieved for 18 to 50% of patients. Standard dose triptans provided sustained headache relief at 24 hours in 29 to 50% of patients, and sustained freedom from pain in 18 to 33% of patients. Use of rescue medications ranged from 20 to 34%. For 2 hour headache relief, standard dose triptan achieved better outcomes (42 to 76% response) than ergots (38%); equal or better outcomes than NSAIDs, ASA, and acetaminophen (46 to 52%), and equal or slightly worse outcomes than combination therapy (62% to 80%). Among individual triptans, sumatriptan subcutaneous injection, rizatriptan ODT, zolmitriptan ODT, and eliptriptan tablets were associated with the most favorable outcomes.

Interpretation: Triptans are effective for migraine relief. Standard dose triptans are associated with better outcomes than ergots, and most triptans are associated with equal or better outcomes compared with NSAIDs, ASA, and acetaminophen. Use of triptans in combination with ASA or acetaminophen, or using alternative modes of administration such as injectables, may be associated with slightly better outcomes than standard dose triptan tablets.

INTRODUCTION

Migraine is a common and potentially disabling neurological condition characterized by recurrent moderate to severe pain generally occurring on one side of the head. Globally, it is estimated that over 10 to 15 percent of people suffer from migraines. (1) The condition causes short and long-term disability, reduces quality of life, and often impacts work productivity, social relationships and family life. (2-4) .

The acute management of migraines includes the use of nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, ergots, opioids and triptans. For many patients with moderate to severe migraine, triptans are considered first-line therapy. There are now seven triptans (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan) available in Canada. The relative efficacy of each triptan amongst each another is uncertain since the majority of triptan studies have been placebo controlled. Further, while other reviews(3-10) have attempted to examine the relative efficacy of triptans amongst each other and versus non-triptan migraine treatments, these studies have not considered multiple routes of administration (tablets, oral disintegrating tablets, injection, nasal spray, rectal suppositories), combination triptan therapy, or dose.

Therefore, as part of a larger initiative by the Ontario Drug Policy Research Network to evaluate triptans for the acute treatment of migraine in adults and provide recommendations for funding changes of these drugs in Ontario (<http://www.odprn.ca/triptans-for-migraine-therapy/>), we conducted a systematic review and network meta-analysis to address the following research

question: What is the evidence for the efficacy, effectiveness and safety of triptans (alone or in combination with other drugs) for acute treatment of migraines compared to: other triptans agents, nonsteroidal anti-inflammatory drugs (NSAIDs), acetylsalicylic acid (ASA), acetaminophen, ergots, opioids, or antiemetics?

METHODS

Data Sources and Searches

Published randomized controlled trials were identified using electronic search strategies developed and tested by an experienced medical information specialist in consultation with the review team. Using the OVID platform, we searched Ovid MEDLINE®, Ovid MEDLINE® In-Process & Other Non-Indexed Citations, and Embase Classic+Embase to identify English-language randomized controlled trials published from inception to October 6, 2013. Using the Cochrane Library on Wiley, the Cochrane Database of Systematic Reviews and CENTRAL were also searched. Strategies utilized a combination of controlled vocabulary (e.g., Migraine Disorders, Triptamines) and keywords (e.g., triptans, rizatriptan, sumatriptan). Vocabulary and syntax were adjusted across databases. Additional references were also sought through hand-searching the bibliographies of relevant articles. Grey literature was searched using Google Scholar and the clinical trial sites listed in CADTH's Grey Matters (<http://cadth.ca/resources/grey-matters>). Complete details of the electronic search strategy, including any limits used, are reported in **Appendix 1**.

Study Selection

The protocol was peer reviewed and published [online](#) prior to the start of the review. Studies were eligible for inclusion in the systematic review if they satisfied the population, intervention,

comparator, and outcome (PICO) statement, including the study designs of interest outlined in our [protocol](#).

The population of interest were adults 18 years and older with migraine specified by the International Headache Society (IHS 1988; IHS 2004, IHS ICDH-2). Studies which included patients with cluster, tension or other headaches, chronic or recurrent migraines who are not experiencing an acute episode were not included. Active and placebo-controlled randomized controlled trials (RCTs) were selected for inclusion if they were published in English and included at least one triptan under review. The following triptans were included in the review: almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan. Triptans were allowed to be used alone or in combination with other drugs. All routes of administration (tablets, oral disintegrating tablets, injection, nasal spray, rectal suppositories) and all doses (any frequency or strength) were included. Doses are classified according to **Table 2**. Allowable comparator groups include: placebo; other triptans used either alone or in combination with other acute migraine therapies; or other acute pharmacologic migraine treatment options (e.g., NSAIDs, ASA, acetaminophen, ergots, opioids, antiemetics). Numerous outcomes were considered and results are reported elsewhere: <http://www.odprn.ca/triptans-for-migraine-therapy/>; however, the focus of this publication are: headache relief at 2 hours (hrs); freedom from pain at 2 hrs; sustained headache response at 24 hrs; sustained freedom from pain at 24 hrs; and use of rescue medication. In general, headache relief was defined as a reduction in headache intensity from moderate or severe to mild or none at 2 or 24 hours, whereas freedom from pain was defined as the percentage of patients pain-free at 2 and 24 hours.

Screening, Data Extraction, and Quality Assessment

In the first phase of screening, the titles and abstracts of all identified citations were screened by two independent reviewers (MM, JP). In the second phase of screening, full manuscripts were retrieved and screened by two independent reviewers on the basis of our predefined patient population, intervention, comparison, outcomes and study design of interest. We only included RCTs/crossovers that reported data for the first attack. Disagreements were resolved through discussion or through adjudication by a third reviewer (SK). For each included study, one of four reviewers independently (MM, JP, SCH, AK) extracted the data on characteristics of trial participants, study characteristics, and details on each study arm/pharmacological intervention, including but not limited to: dose, frequency, route of administration, co-medication/prophylaxis; and results of the clinical safety and efficacy outcomes for the overall study population and the *a priori* subgroups identified. All extracted data was checked for accuracy by another reviewer. Any disagreements in the assessment of these data were resolved through discussion until consensus was reached.

Quality assessment of RCTs was performed independently by four reviewers (MM, JP, SCH, AK) using a standardized table based on major items from the Cochrane Risk of Bias Tool.(11) The trial selection process is presented in a flowchart based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)(12, 13) statement (**Figure 1**).

Data Synthesis and Analysis

We performed a Bayesian network meta-analysis. A Bayesian network meta-analysis requires

two main ingredients: and a likelihood function derived from a model that specifies the relation between the unknown parameters and the observed data, and prior distributions for the unknown parameters.(14) A prior distribution of a parameter represents the uncertainty of parameter before the data are examined.(14,15) The prior chosen may be informative or “vague” where the latter is thought to let the data drive the analysis. Multiplying the prior and the likelihood function leads to the posterior distribution of the parameter, which is used to carry out all inferences in a Bayesian analysis (14,15). Methods for Bayesian network meta-analyses allow analysis of both placebo and active comparison studies simultaneously (14). Both direct and indirect evidence are combined. The results from indirect evidence combined with the direct evidence may strengthen the assessment between treatments evaluated using Bayesian network meta-analysis. Bayesian network meta-analyses were conducted using WinBUGS software version 1.4.3 (MRC Biostatistics Unit, Cambridge, UK). A binomial likelihood model which accounts for the use of multi-arm trials was used for the analyses given the datasets provided were dichotomous outcomes and included multi-arm trials. (14) Bayesian network meta-analysis (MTC) meta-analyses were conducted for the following outcomes: headache relief within 2 hrs; freedom from pain at 2 hrs; sustained headache response at 24 hrs; sustained freedom from pain at 24 hrs; and use of rescue medication. Placebo was chosen as the reference group or index node in the model. Both random-effects network meta-analyses using informative priors and fixed-effects analyses were conducted; (14, 15) assessment of model fit and choice of model was based on assessment of the deviance information criterion (DIC), between study standard deviation, and comparison of residual deviance to number of unconstrained data points. (16, 17).

Point estimates and 95% credible intervals for odds ratios (OR) were derived using Markov

Chain Monte Carlo (MCMC) methods for all nodes in analysis. Risk ratios (RRs) and absolute risk for an outcome of interest were estimated based on the ORs and the mean proportion of patients who experience the outcome in the placebo arms among included studies. Vague priors, such as $N(0, 100^2)$, were assigned for basic parameters throughout (17) and informative priors for the variance parameter based on evidence on the extent of heterogeneity observed in previous meta-analyses, as described in Turner et al. (15). To ensure convergence was reached, trace plots and the Brooks-Gelman-Rubin statistic were assessed.(15, 18) Three chains were fit in WinBUGS for each analysis, with at least 20,000 iterations, and a burn-in of at least 20,000 iterations. (18, 19)

We also qualitatively compared the results from our network meta-analysis with direct pair-wise estimates. We formally assessed inconsistency, by comparing the deviance, between study variance, and DIC statistics in fitted consistency and inconsistency models. (20) We also plotted the posterior mean deviance of the individual data points in the inconsistency model against their posterior mean deviance in the consistency model to identify any loops in where inconsistency is present. (20) We also conducted a sensitivity analysis adjusting for control group response rate to address heterogeneity among included studies, and generated a box plot to illustrate differences among included studies.

RESULTS

Search results

The initial literature search returned 1,694 database abstracts and 78 grey literature documents (**Figure 1**). After duplicates were removed, 1,142 remained to be assessed for inclusion and 730 were excluded. Of the 412 full-text articles reviewed, 202 full-text publications were included

after applying the PICO criteria. Of these, 69 were excluded from analysis as they did not present single migraine attack data. A total of 133 publications reported single migraine attack data in 133 unique RCTs. A complete list of included and excluded studies is available in

Appendix 2.

Characteristics of included studies

A detailed list of included studies, patients and study characteristics are provided in the [Technical Report](#). All included studies were published between 1991 and 2012. Most were large, multicentre studies conducted in a variety of countries worldwide, and often across many different countries. The number of randomized patients was often bigger than the number of participants included in the effect estimates for outcomes in each trial, due to the fact that most trials reported modified intention to treat (ITT) outcome populations, i.e., based on recruited patients who subsequently experienced a migraine event. The trials all recruited migraine sufferers who met the International Classification of Headache Disorders (ICHD) for migraine headaches (21-24), or used inclusion criteria with sufficient comparability to the ICHD criteria. All studies generally included patients affected with migraine with or without aura, and a small number also included some patients with menstrual migraine (25-27). Four RCTs reported solely on menstrual migraine in female participants (28-31). All participants self-administered their study medications. Trial participants were generally between the ages of 18 and 65, with an average age of approximately 40. Very few trials included participants older than 65, and trials of children and adolescents were excluded by the PICO statement. Trial participants were predominantly female. In 133 studies reporting first attack data, the mean percent of females included was over 80%. Patients included in studies were both treatment naïve and experienced. In general, a high proportion of studies included participants with at least one previous treatment

failure with a triptan. The risk of bias assessment for each study is available upon request.

Headache relief at 2 hrs. The evidence network for headache relief at 2 hours included 96 studies and a total of 56,180 participants (**Table 1**). Overall, 45 different treatments were considered, providing for 287 comparisons. There is some evidence of inconsistency in the network (**Appendix 3**). Standard dose (SD) triptans relieved headaches within 2 hours in 42 to 76% of patients, compared to 27% for placebo. Sumatriptan subcutaneous injection (76%), rizatriptan ODT (69%), zolmitriptan ODT (66%) had the largest effect on 2 hour headache relief among monotherapies, whereas ergots (38%), frovatriptan (42%), naratriptan (46%), and ASA (46%) were associated with less favorable outcomes. Standard dose triptans yielded equal or slightly worse outcomes than triptan combination therapies (62% to 80%). Detailed results are reported in **Table 3** including credible intervals around point estimates.

Freedom from Pain at 2 hours

The evidence network for freedom from pain at 2 hours included 88 studies and a total of 50,929 participants. Overall, 41 different treatments were considered, involving 236 comparisons. There was no evidence of inconsistency in the network (**Appendix 3**). With SD triptans, only 18 to 50% of patients had freedom from pain within 2 hours, compared to 11% for placebo. Rizatriptan ODT (50%), eletriptan tablet (39%), rizatriptan tablet (37%), sumatriptan subcutaneous injection (37%), and zolmitriptan ODT (37%) had the largest effect on 2 hour freedom from pain among monotherapies, whereas ergots (16%), naratriptan (18%), NSAIDs (22%), and acetaminophen (22%) were associated with less favorable outcomes. SD triptans yielded equal or slightly worse outcomes than triptan combination therapies (37% to 51%).

Detailed results are reported in **Table 3** including credible intervals around point estimates.

Sustained Headache Relief at 24 Hours

The evidence network for headache relief at 24 hours included 29 studies and a total of 22,963 participants. Overall, 24 different treatments were compared, involving 102 comparisons. There was no evidence of inconsistency in the network (**Appendix 3**). SD triptans provided sustained headache relief at 24 hours ranging from 29% to 50%, compared to 17% for placebo.

Zolmitriptan ODT (50%) and eletriptan tablet (47%) had the largest effect on 24 hour headache relief among monotherapies, whereas ergots (8%), acetaminophen (29%), ASA (29%), and rizatriptan (29%) were associated with less favorable outcomes. SD triptans yielded equal or slightly worse outcomes than triptan combination therapies (46% to 50%). Detailed results are reported in **Table 3** including credible intervals around point estimates.

Sustained Freedom from Pain at 24 Hours

The evidence network for freedom from pain at 24 hours included 42 studies and a total of 27,755 participants. Overall, 20 different treatments were considered, involving, 115 comparisons. There was no evidence of inconsistency in the network (**Appendix 3**). 18 to 33% of patients on SD triptans had sustained freedom from pain at 24 hours, compared to 10% for placebo. Eletriptan tablet (33%) and rizatriptan tablet (24%) had the largest effect on 24-hr freedom from pain among monotherapies, whereas acetaminophen (14%), ASA (16%), and naratriptan (18%) were associated with less favorable outcomes. SD triptans yielded equal or slightly worse outcomes than triptan combination therapies (29% to 33%). Detailed results are reported in **Table 3** including credible intervals around point estimates.

Use of Rescue Medications

The evidence network for the use of rescue medication included 88 studies and a total of 48,363 participants. Overall, 34 different treatments were considered, providing for 222 comparisons. There was some evidence of inconsistency in the network (**Appendix 3**). With SD triptans, the percent of patients using rescue medications ranged from 20 to 34%, compared to 52% for placebo. The NNT in order for one patient to avoid use of rescue medication ranged from 4 to 6 patients. Eletriptan tablet (21%) and zolmitriptan tablet (24%) required the use of the least amount of rescue medications among monotherapies, whereas NSAIDs (37%), sumatriptan tablet (34%), and ASA (33%) used the most. Standard dose triptans yielded equal or slightly worse outcomes than triptan combination therapies (22%). Detailed results are reported in **Table 3** including credible intervals around point estimates.

Comparisons among the standard dose triptans

Figure 2 provides comparisons among the SD triptan tablets. The grey circle indicates that the triptan identified in the ‘row’ is associated with a better outcomes than the ‘column’ triptan; the black circle indicates that the ‘row’ triptan is associated with worse outcome than the ‘column’ triptan; the blank circle indicates that there is no difference between the ‘row’ and ‘column’ triptan; and a missing circle indicates that the outcome was not available for analysis. In general, there were more favorable results observed for eletriptan and rizatriptan (as indicated by the green circles). Results were less favorable for naratriptan and frovatriptan. Use of rescue medications was not significantly different between the triptans except for sumatriptan having a significantly favourable result compared to zolmitriptan. Detailed results are reported in

Appendices 4.

Sensitivity analyses

Figure 3 presents a box plot illustrating control group response rates among treatments included in the network. From Figure 3, it can be seen that some treatments have lower or higher control group response rates than other treatments. We also report findings from a meta-regression analysis adjusting for these differences in control group response rate. Overall, findings for most treatments remained unchanged although those with lower control group response rates (e.g., standard dose eliotriptan tablet) became slightly less favorable, albeit still more favorable than SD triptan tablets (**Appendix 5**).

DISCUSSION

We found that SD triptans relieved headaches within 2 hours in 43 to 76% of patients. Freedom from pain within 2 hours was less common, with about 18 to 50% of patients experiencing freedom from pain within 2 hours. SD triptans provided sustained headache relief at 24 hours in 29 to 50% of patients, and sustained freedom from pain at 24 hours in 18 to 33% of patients. Use of rescue medications among patients using standard dose triptans ranged from 20 to 34%. Our findings align with those reported in other systematic reviews (3-10), although the majority of other reviews only report estimates of relative effect for SD triptans.

SD triptans were associated with more favorable results than ergots for 2 and 24 hour outcomes, and equal or more favorable results than NSAIDs, ASA, and acetaminophen for 2-hour outcomes. These findings align with recommendations from the Canadian Headache Society Guidelines (3) where they gave a strong recommendation for triptans, NSAIDs, ASA, and acetaminophen but

did not recommend ergots for routine use in the acute management of migraine. Similarly, the National Institute for Health and Care Excellence (NICE) in the UK do not recommend ergots for the acute treatment of migraine, but recommend oral triptans, NSAIDs, ASA, and acetaminophen for the acute treatment of migraine in patients who prefer monotherapy (32).

We found that combination therapies such as triptan and ASA or triptan plus acetaminophen, and certain modes of administration such as rizatriptan ODT and sumatriptan subcutaneous injection, were associated with slightly more favorable 2 hour results compared with SD triptans.

However, there is potential that these findings may be due to systematic differences in the patient population and/or study design; that is, studies assessing efficacy of combination therapies or certain modes of administration may have been more extensively studied in a patient populations who are systematically different, i.e., more severe and/or treatment experienced. We attempted to adjust for this possible issue by conducting a meta-regression analysis adjusting for placebo response rate, a proxy that is often helpful in identifying patient populations or study designs that are systematically different (**Figure 3**). We found that findings for combination therapies such as triptan and ASA or triptan plus acetaminophen remained stable after adjustment, whereas those using other modes of administration became slightly less favorable, albeit still more favorable than SD triptan tablets. Recent National Institute for Health and Care Excellence (NICE) guidance recommends combination therapy with an oral triptan and ASA or oral triptan plus acetaminophen, and findings from both our primary analysis and sensitivity analysis seem to support NICE recommendations. (4)

Among individual triptans, our analysis suggests that the majority of triptans, except frovatriptan

and naratriptan, deliver similar pain relief in the acute management of migraines. However, our findings also suggest that eliptriptan and rizatriptan may provide better pain relief than some of the other triptans. This latter finding should be interpreted in light of a number of caveats. Firstly, findings for eliptriptan became slightly less favorable after we adjusted for control groups response rate, albeit still more favorable than other triptans. Second, both eliptriptan and rizatriptan are only available in tablet forms, whereas other triptans such as sumatriptan are available in multiple formulations — which can be advantageous for patients given mixing of triptans is ill advised. Finally, we do not consider costs or cost-effectiveness in this paper. Other triptans such as sumatriptan are available as less expensive generics, whereas eliptriptan is not yet available as a generic. Our companion pharmaceoeconomic report has shown that use of less costly generic triptans could significantly reduce total expenditure on triptans.(32) However, providing more open access to triptans will lead to a significant increase in their use with a high budget impact. NICE in the UK recommends to start with the triptan with the lowest acquisition cost initially, and if this is consistently ineffective, try one or more expensive alternative triptans. (4) Consumer Reports recommends a similar approach, recommending sumatriptan initially because it is available as an inexpensive generic and offers the widest choice for mode of delivery.(2, 33)

Studies were not sufficiently powered or of adequate duration to measure differences in long-term complications or adverse events. Future research is needed assessing the long-term use of triptans in the acute management of recurrent migraines.

As with all analyses, there are several limitations that warrant consideration. First, graphical aids

in the form of network diagrams and forest plots are typically provided for network meta-analyses. However, our analysis consisted of upwards of 45 treatment nodes when the network was stratified by dose, mode of administration and combination therapies . The inclusion of evidence structures with a large number of nodes (>20) makes presentation of network diagrams unwieldy. Similarly, presentation of forest plots or tables with all comparisons becomes challenging given the number of treatments and potential comparisons. As such, we provide tables which concisely report the main findings from them in tabular form compared with placebo (**Table 3**). We also report absolute probability of each comparison.

CONCLUSIONS

Triptans were found to be efficacious for the treatment of acute migraine. Forty-three to 76% of patients experience pain relief at 2 hours when using standard dose triptan tablets. Most triptans were associated with equal or more favourable results than NSAIDs, ASA, acetaminophen and more favorable results than ergots. Use of triptans in combination with aspirin or acetaminophen, or using different modes of administration such as injection, was associated with slightly better results than standard dose triptan tablets.

TABLES AND FIGURES

Table 1: Summary of patient and study characteristics for each evidence network:[†] headache relief at 2 hours, freedom from pain at 2 hours, sustained headache relief at 24 hours, sustained freedom from pain at 24 hours, and use of rescue medications

	2h headache relief	2h freedom from pain	24h sustained headache relief	24h sustained freedom from pain	Use of rescue medications
Number of studies	96	88	29	42	88
Number of Treatment nodes	45	41	24	20	34
Number of participants	56,180	50,929	22,963	27,775	48,363
Number of comparisons	287	236	102	115	222
Number of 2-arm trials	46	47	13	23	50
Number of multi-arm trials	50	41	16	19	38

[†] Evidence networks consisted of a large number of nodes which makes it difficult to illustrate graphically

Table 2: Dose categorization for a migraine attack (and number of RCTs/Number of Patients for 2h relief)*

	Low dose (Half)	Standard dose (Common)	High dose (Double)
Eletriptan	20 mg (3 RCTs /514 Patients)	40 mg (13 RCTs /3143 Patients)	80 mg (10 RCTs /2042 Patients)
Sumatriptan	25 mg (4 RCTs /850 Patients)	50 mg (23 RCTs /5870 Patients)	100 mg (23 RCTs /5210 Patients)
Rizatriptan	5 mg (3 RCTs /752 Patients)	10 mg (11 RCTs /2676 Patients)	20 mg (1 RCTs /82 Patients)
Frovatriptan	--	2.5 mg (5 RCTs /1840 Patients)	5 mg (2 RCTs /338 Patients)
Almotriptan	6.25 mg (2 RCTs /527 Patients)	12.5 mg(7 RCTs /2120 Patients)	25 mg (2 RCTs /352 Patients)
Zolmitriptan	1.25 mg (1 RCTs /52 Patients)	2.5 mg (10 RCTs /3491 Patients)	5 mg (6 RCTs /2084 Patients)
Naratriptan	--	2.5 mg (3 RCTs /512 Patients)	5 mg (No data)

* Numbers for other outcomes are reported in **Appendix 6**

Table 3: Percent of patients (and 95% credible interval) achieving : headache relief at 2 hours, freedom from pain at 2 hours, sustained headache relief at 24 hours, sustained freedom from pain at hours, and use of rescue medications^{†*}

	2h headache relief		2h freedom from pain		24h sustained headache relief		24h sustained freedom from pain		Use of rescue medications	
	% (95%CrI)	OR (95%CrI)	% (95%CrI)	OR (95%CrI)	% (95%CrI)	OR (95%CrI)	% (95%CrI)	OR (95%CrI)	% (95%CrI)	OR (95%CrI)
Placebo	26.70% (25.7%,27.7%)	NA	10.60% (10.0%, 11.3%)	NA	17.00% (15.9%, 18.2)	NA	9.60% (8.9%, 10.3%)	NA	51.60% (50.4%,52.%)	--
TABLET SD										
Almotriptan	48.30% (42.4%,54.2%)	2.56 (2.0,3.3)	24.50% (20.1%,29.6%)	2.73 (2.1,3.6)	35.70% (29.2%,43.0)	2.71 (2.0, 3.7)	20.80% (15.9%,26.8%)	2.48 (1.8,3.5)	32.00% (26.1%,38.5%)	0.44 (0.3,0.6)
Eletriptan	60.40% (56.1%,64.6%)	4.19 (3.5,5.0)	39.20% (34.1%,44.7%)	5.43 (4.3,6.9)	47.30% (43.4%,51.3%)	4.37 (3.7,5.3)	32.90% (27.5%,38.7%)	4.63 (3.5,6.1)	21.10% (17.9%,24.7%)	0.25 (0.2,0.3)
Frovatriptan	42.40% (35.6%,49.5%)	2.02 (1.5,2.7)	34.70% (25.4%,45.9%)	4.48 (2.8,7.3)	-- --	-- --	-- --	-- --	31.00% (16.5%,50.6%)	0.42 (0.2,1.0)
Naratriptan	44.50% (35.6%,53.8%)	2.2 (1.5,3.2)	17.50% (11.8%,25.0%)	1.79 (1.1,2.8)	38.60% (30.7%,46.8%)	3.06 (2.1,4.3)	18.40% (12.0%,26.8%)	2.13 (1.3,3.5)	30.30% (23.0%,38.8%)	0.41 (0.3, 0.6)
Rizatriptan	57.10% (52.4%,61.9%)	3.66 (3.0,4.5)	36.60% (31.7%,42.0%)	4.86 (3.9,6.2)	29.30% (23.7%,35.5%)	2.02 (1.5,2.7)	23.90% (19.0%,29.5%)	2.97 (2.2,4.0)	30.00% (25.6%,34.8%)	0.4 (0.3,0.5)
Sumatriptan	49.70% (46.3%,53.1%)	2.71 (2.4,3.1)	27.70% (24.6%,31.0%)	3.22 (2.7,3.8)	33.10% (30.3%,36.0%)	2.41 (2.1,2.8)	22.80% (2.0%,26.0%)	2.79 (2.3,3.4)	33.80% (30.0%,37.8%)	0.48 (0.4,0.6)
Zolmitriptan	50.00% (45.5%,54.7%)	2.75 (2.3,3.3)	27.10% (22.7%,32.0%)	3.14 (2.5, 4.0)	37.60% (33.4%,42.2%)	2.94 (2.4,3.6)	22.50% (18.0%,27.6%)	2.74 (2.0,3.7)	28.00% (22.8%,33.7%)	0.36 (0.3,0.5)
TABLET LD										
Almotriptan Tablet	43.30% (33.9%,53.3%)	2.1 (1.4,3.1)	18.50% (11.1%,29.4%)	1.92 (1.0,3.5)	31.70% (24.0%,40.4%)	2.26 (1.5,3.3)	-- --	-- --	-- --	-- --
Eletriptan Tablet	52.50%	3.03	28.50%	3.35	37.70%	2.95	24.60%	3.07	24.50%	0.3

	2h headache relief		2h freedom from pain		24h sustained headache relief		24h sustained freedom from pain		Use of rescue medications	
	% (95%CrI)	OR (95%CrI)	% (95%CrI)	OR (95%CrI)	% (95%CrI)	OR (95%CrI)	% (95%CrI)	OR (95%CrI)	% (95%CrI)	OR (95%CrI)
	(44.3%,60.5%)	(2.2, 4.2)	(20.8%,37.6%)	(2.2,5.1)					(18.7%,31.6%)	(0.2,0.4)
Frovatriptan Tablet	27.30%	1.03	12.60%	1.21	(29.8%,46.5%)	--	(18.3%,32.1%)	--	36.70%	0.54
	(18.7%,38.0%)	(0.6, 1.7)	(5.6%,24.4%)	(0.5,2.8)	--	--	--	--	(20.4%,56.7%)	(0.2,1.2)
Naratriptan Tablet	--	--	--	--	--	--	--	--	35.30%	0.51
	--	--	--	--	--	--	--	--	(20.7%,53.4%)	(0.2,1.1)
Rizatriptan Tablet	51.20%	2.88	27.50%	3.19	--	--	--	--	34.30%	0.49
	(43.1%,59.2%)	(2.1, 4.0)	(18.8%,38.2%)	(2.0, 5.2)	--	--	--	--	(24.3%,45.8%)	(0.3, 0.8)
Sumatriptan Tablet	44.20%	2.17	24.90%	2.79	29.80%	2.07	--	--	46.40%	0.81
	(37.1%,51.7%)	(1.6,2.9)	(14.9%,38.0%)	(1.5,5.2)	(23.2%,37.1%)	(1.5,2.9)	--	--	(31.5%,62.0%)	(0.4,1.5)
Zolmitriptan Tablet	44.00%	2.16	21.00%	2.24	29.50%	2.04	--	--	33.10%	0.46
	(27.1%,62.2%)	(1.0,4.5)	(8.5%,41.7%)	(0.8, 6.1)	(17.1%,45.6%)	(1.0,4.1)	--	--	(13.2%,58.8%)	(0.1,1.4)
TABLET HD										
Almotriptan Tablet	50.60%	2.81	32.40%	4.04	--	--	--	--	28.00%	0.36
	(40.4%,60.8%)	(1.9,4.3)	(23.1%,43.2%)	(2.5,6.4)	--	--	--	--	(19.3%,38.6%)	(0.2,0.6)
Eletriptan Tablet	66.20%	5.38	48.00%	7.78	50.50%	4.98	38.90%	6	18.10%	0.21
	(61.6%,70.6%)	(4.4,6.6)	(41.5%,54.7%)	(5.9,10.3)	(45.4%,55.9%)	(4.0,6.3)	(32.0%,46.2%)	(4.4,8.3)	(14.5%,22.3%)	(0.2,0.3)
Frovatriptan Tablet	40.30%	1.85	35.20%	4.58	--	--	--	--	32.30%	0.45
	(30.1%,51.5%)	(1.2, 2.9)	(22.5%,50.7%)	(2.4,8.8)	--	--	--	--	(17.3%,51.8%)	(0.2,1.0)
Rizatriptan Tablet	64.20%	4.92	50.10%	8.44	--	--	--	--	--	--
	(47.9%,77.8%)	(2.5,9.6)	(32.3%,67.9%)	(4.0,17.9)	--	--	--	--	--	--
Sumatriptan Tablet	53.40%	3.14	32.10%	3.99	36.00%	2.75	27.90%	3.65	27.40%	0.35
	(49.8%,56.9%)	(2.7,3.6)	(28.6%,35.8%)	(3.4,4.8)	(32.7%,39.4%)	(2.3,3.2)	(23.8%,32.4%)	(2.9,4.6)	(24.2%,30.8%)	(0.3,0.4)
Zolmitriptan Tablet	51.40%	2.9	31.00%	3.79	38.30%	3.02	23.90%	2.97	33.40%	0.47

	2h headache relief		2h freedom from pain		24h sustained headache relief		24h sustained freedom from pain		Use of rescue medications	
	% (95%CrI)	OR (95%CrI)	% (95%CrI)	OR (95%CrI)	% (95%CrI)	OR (95%CrI)	% (95%CrI)	OR (95%CrI)	% (95%CrI)	OR (95%CrI)
	(45.4%,57.5%)	(2.3,3.7)	(24.8%,38.3%)	(2.8,5.3)	(32.7%,44.3%)	(2.4,3.9)	(17.8%,31.8%)	(2.0,4.5)	(23.9%,44.6%)	(0.3,0.8)
ODT SD										
Rizatriptan	69.00%	6.1	50.20%	8.49	--	--	--	--	19.90%	0.23
	(59.6%,77.0%)	(4.1,9.2)	(34.5%,66.7%)	(4.4,17.0)	--	--	--	--	(6.2%,46.0%)	(0.1 ,0.8)
Zolmitriptan	65.80%	5.28	36.60%	4.87	--	--	--	--	--	--
	(50.6%,78.3%)	(2.8,9.9)	(20.6%,56.8%)	(2.2, 11.1)	--	--	--	--	--	--
ODT LD										
Rizatriptan	57.40%	3.7	37.80%	5.11	--	--	--	--	--	--
	(44.6%,69.3%)	(2.2,6.2)	(23.2%,55.5%)	(2.6,10.6)	--	--	--	--	--	--
ODT HD										
Zolmitriptan	--	--	--	--	50.00%	4.88	--	--	24.40%	0.3
	--	--	--	--	(38.0%,62.6%)	(3.0,8.2)	--	--	(16.0%,35.1%)	(0.2, 0.5)
NASAL SPRAY SD										
Sumatriptan	52.60%	3.04	21.20%	2.26	--	--	--	--	--	--
	(43.6%,61.5%)	(2.1,4.4)	(6.4%,53.4%)	(0.6,9.8)	--	--	--	--	--	--
Zolmitriptan	51.30%	2.89	--	--	--	--	--	--	--	--
	(38.8%,63.9%)	(1.7,4.9)	--	--	--	--	--	--	--	--
NASAL SPRAY LD										
Sumatriptan	41.80%	1.97	--	--	--	--	--	--	--	--
	(32.6%,51.5%)	(1.3,2.9)	--	--	--	--	--	--	--	--
Zolmitriptan	48.20%	2.55	--	--	--	--	--	--	--	--
	(35.6%,61.0%)	(1.5,4.3)	--	--	--	--	--	--	--	--
NASAL SPRAY HD										
Zolmitriptan	62.30%	4.53	33.80%	4.3	41.40%	3.44	27.30%	3.54	22.00%	0.27
	(54.4%,69.7%)	(3.3,6.3)	(24.5%,44.7%)	(2.7,6.8)	(34.6%,48.5%)	(2.6,4.6)	(20.5%,35.5%)	(2.5,5.2)	(14.9%,31.4%)	(0.2, 0.4)
SUBCUTANEOUS INJECTION										

	2h headache relief		2h freedom from pain		24h sustained headache relief		24h sustained freedom from pain		Use of rescue medications	
	% (95%CrI)	OR (95%CrI)	% (95%CrI)	OR (95%CrI)	% (95%CrI)	OR (95%CrI)	% (95%CrI)	OR (95%CrI)	% (95%CrI)	OR (95%CrI)
SD										
Sumatriptan	75.70%	8.54	36.60%	4.87	--	--	23.50%	2.9	23.40%	40.29
	(67.6%,82.5%)	(5.7,12.9)	(25.1%,50.0%)	(2.8,8.5)	--	--	(15.8%,33.6%)	(1.8,4.8)	(17.7%,30.1%)	(0.2,0.4)
Zolmitriptan	--	--	--	--	--	--	--	--	35.00%	0.51
	--	--	--	--	--	--	--	--	(9.1%,74.1%)	(0.1, 2.7)
SUBCUTANEOUS INJECTION										
Sumatriptan	70.10%	6.45	29.10%	3.46	--	--	--	--	25.50%	0.32
	(46.0%,87.2%)	(2.3,18.7)	(11.9%,57.0%)	(1.1,11.3)	--	--	--	--	(10.1%,50.2%)	(0.1,1.0)
PATCH SD										
Sumatriptan	48.30%	2.56	20.60%	2.19	--	--	--	--	26.20%	0.33
	(37.0%,60.0%)	(1.6,4.1)	(12.9%,31.4%)	(1.2,3.9)	--	--	--	--	(12.9%,45.6%)	(0.1,0.8)
SUPPOSITORIES										
Sumatriptan	70.80%	6.64	44.70%	6.8	--	--	--	--	--	--
	(49.4%,86.1%)	(2.7,17.0)	(22.4%,71.1%)	(2.4, 20.8)	--	--	--	--	--	--
NON TRIPTAN SINGLE THERAPIES										
NSAID	48.00%	2.53	21.80%	2.35	29.10%	2	16.40%	1.85	36.90%	0.55
	(42.3%,53.9%)	(2.0,3.2)	(17.6%,26.8%)	(1.8,3.1)	(25.1%,33.5%)	(1.6,2.5)	(12.6%,20.9%)	(1.4,2.5)	(31.0%,43.1%)	(0.4,0.7)
Acetaminophen	51.70%	2.94	22.20%	2.41	29.30%	2.02	14.30%	1.58	--	--
	(30.8%,72.3%)	(1.2,7.2)	(9.2%,43.7%)	(0.9,6.6)	(16.0%,47.5%)	(0.9,4.5)	(5.0%,32.5%)	(0.5,4.6)	--	--
Aspirin	46.10%	2.35	24%	2.66	--	--	--	--	33.40%	0.47
	(32.1%,60.7%)	(1.3,4.2)	(13.7%,38.4%)	(1.3,5.3)	--	--	--	--	(20.2%,50.1%)	(0.2,0.9)
Ergots	38.40%	1.71	15.50%	1.55	7.90%	0.42	--	--	24.00%	0.3
	(29.5%,47.9%)	(1.2,2.5)	(8.2%,27.1%)	(0.8,3.2)	(1.5%,28.2%)	(0.1,1.9)	--	--	(15.8%,34.9%)	(0.2,0.5)
COMBINATION THERAPIES										
Aspirin with antiemetic	50.90%	2.85	19.30%	2.01	--	--	--	--	31.70%	0.44

	2h headache relief		2h freedom from pain		24h sustained headache relief		24h sustained freedom from pain		Use of rescue medications	
	% (95%CrI)	OR (95%CrI)	% (95%CrI)	OR (95%CrI)	% (95%CrI)	OR (95%CrI)	% (95%CrI)	OR (95%CrI)	% (95%CrI)	OR (95%CrI)
	(41.9%,60.0%)	(2.0, 4.1)	(13.0%,27.5%)	(1.3,3.2)	--	--	--	--	(23.0%,41.9%)	(0.3, 0.7)
Triptan with acetaminophen	79.90%	10.9	50.50%	8.61	50.30%	4.93	29.30%	3.92	--	--
	(59.6%,92.7%)	(4.1,35.0)	(29.4%,72.3%)	(3.5, 22.1)	(32.1%,69.0%)	(2.3,11.0)	(14.1%,50.8%)	(1.5,9.9)	--	--
Triptan with NSAID	62.30%	4.53	36.80%	4.91	46.20%	4.2	32.50%	4.55	22.30%	0.27
	(55.3%,68.9%)	(3.4,6.1)	(31.7%,42.1%)	(3.9, 6.2)	(41.3%,51.4%)	(3.4,5.2)	(28.3%,37.0%)	(3.7,5.6)	(18.5%,26.7%)	(0.2,0.3)
OTHER THERAPIES										
SD BI 44370 TA Tablet	57.50%	3.71	25.30%	2.86	47.20%	4.36	28.90%	3.83	26.70%	0.34
	(39.3%,73.7%)	(1.8,7.7)	(12.0%,45.2%)	(1.2,7.0)	(31.4%,62.6%)	(2.2,8.3)	(14.4%,49.0%)	(1.6,9.1)	(17.0%,39.3%)	(0.2,0.6)
HD BI 44370 TA Tablet	63.40%	4.76	32.40%	4.04	54.30%	5.8	30.30%	4.1	20.90%	0.25
	(45.8%,78.2%)	(2.3,9.8)	(17.1%,52.8%)	(1.7,9.5)	(38.8%,69.2%)	(3.0,11.2)	(15.5%,50.6%)	(1.7,9.7)	(12.9%,32.0%)	(0.1,0.4)
LD BI 44370 TA Tablet	38.20%	1.7	9.20%	0.85	20.30%	1.24	7.00%	0.7	48.60%	0.89
	(22.1%,57.1%)	(0.8,3.7)	(2.8%,23.4%)	(0.2,2.6)	(9.9%,35.4%)	(0.5,2.7)	(1.4%,20.1%)	(0.1,2.4)	(34.8%,62.8%)	(0.5,1.6)
SD Tonaberstat	30.20%	1.19	5.90%	0.53	--	--	--	--	--	--
	(18.9%,44.6%)	(0.6,2.2)	(2.0%,14.4%)	(0.2,1.4)	--	--	--	--	--	--
LD Tonaberstat	28.00%	1.07	7.00%	0.64	--	--	--	--	--	--
	(17.9%,42.2%)	(0.6,2.0)	(2.6%,16.3%)	(0.2,1.7)	--	--	--	--	--	--
Acetaminophen, Dichloralphenazone, and Isometheptene	37.70%	1.66	--	--	--	--	--	--	--	--
	(19.1%,60.9%)	(0.7,4.3)	--	--	--	--	--	--	--	--

SD=standard dose, ODT= oral disintegrating tablet

[†]Percent of patients with the outcome are based on the odds ratios from the network meta-analysis and mean proportion of patients who experience the outcome in the placebo group.

* Evidence networks include all treatments in this table although results did not change substantially when low dose or experimental agents were excluded

Figure 1: PRISMA Diagram

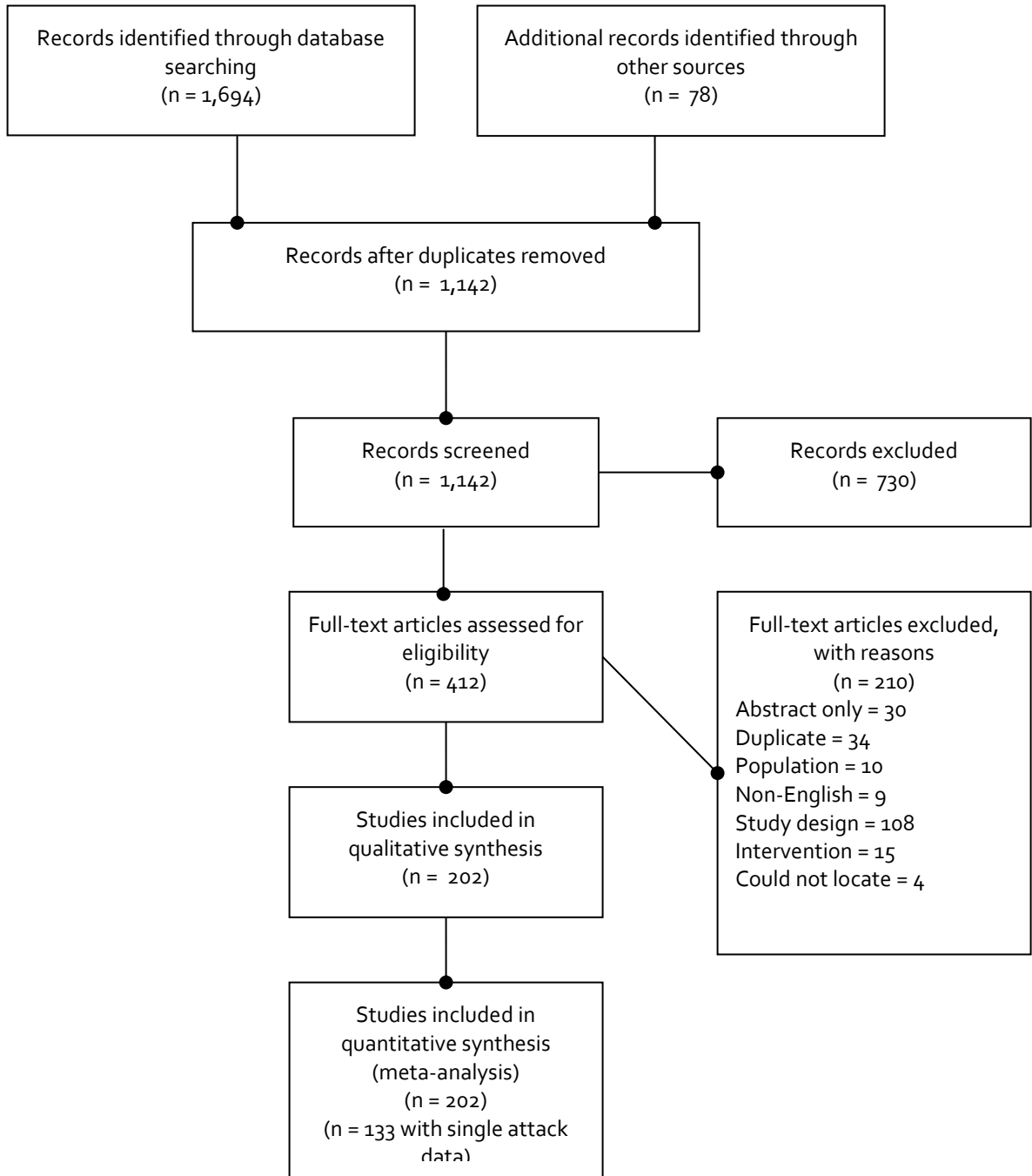
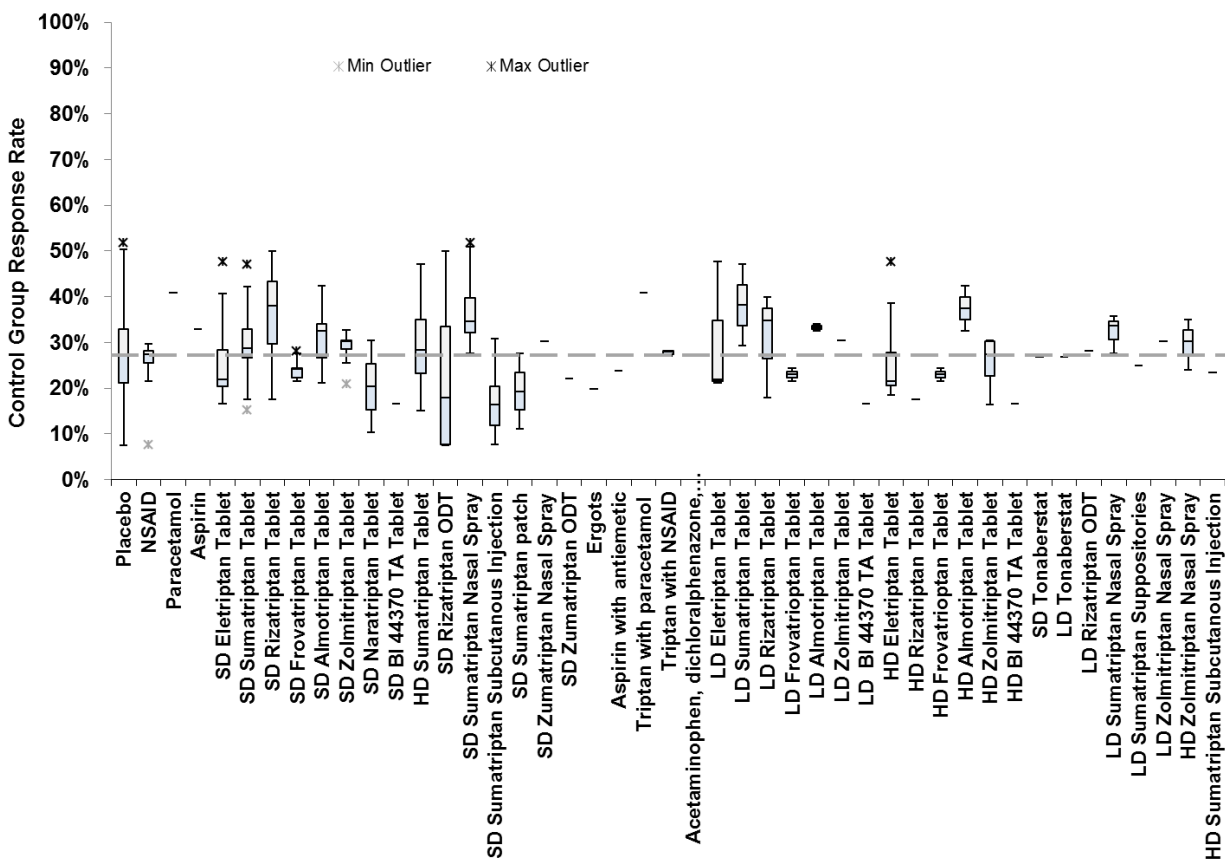


Figure 2: Comparison among the triptans on the 5 efficacy outcomes: headache relief at 2 hours, freedom from pain at 2 hours, sustained headache relief at 24 hours, sustained freedom from pain at hours, and use of rescue medications*

	Almotriptan	Eletriptan	Frovatriptan	Naratriptan	Rizatriptan	Sumatriptan	Zolmitriptan
Almotriptan		●●●●●	○○ ○	○○○○○	●●○○○	○○○○○	○○○○○
Eletriptan	●●●●●		●○ ○	●●●●●	○○●●●	●●●●●	●●●●●
Frovatriptan	○○ ○	●○ ○		○● ○	●○ ○	○○ ○	○○ ○
Naratriptan	○○○○○	●●●●●	○● ○		●●○○○	○●○○○	○●○○○
Rizatriptan	●●○○○	○○●●●	●○ ○	●●○○○		●●○○○	●●●○○
Sumatriptan	○○○○○	●●●●●	○○ ○	○●○○○	●●○○○		○○○○○
Zolmitriptan	○○○○○	●●●●●	○○ ○	○●○○○	●●●○○	○○○○○	

*The 5 contiguous circles correspond, respectively, to the five efficacy outcomes: headache relief at 2 hours, freedom from pain at 2 hours, sustained headache relief at 24 hours, sustained freedom from pain at hours, and use of rescue medications. The grey circle indicates that the 'row' triptan is associated with better outcomes compared with 'column' triptan; The black circle indicates that the 'row' triptan is worse than the 'column' triptan; The white circle indicates that there is no difference between the 'row' and 'column' triptan; A missing circle indicates that the outcome was not available for analysis.

Figure 3: Comparison of control group response rate among studies for 2 hour response



REFERENCES

1. World Health organization Factsheet No 277: Headache Disorders (Available at: <http://www.who.int/mediacentre/factsheets/fs277/en/>). October 2012 (Accessed July 17, 2014).
2. Using the Triptans to Treat: Migraine Headaches. Comparing Effectiveness, Safety, and Price: Consumer Reports Best Buy Drugs 2013 March 2013.
3. Irene Worthington. et al. on behalf of the Canadian Headache Society Acute Migraine Treatment Guideline Development Group. Canadian Headache Society Guideline: Acute Drug Therapy for Migraine Headache. The Canadian Journal of Neurological Sciences. 2013 September 2013; Vol 40, No 5 / Supp 3.
4. NICE. Headaches: Diagnosis and Management of Headaches in Young People and Adults (Clinical guideline 150: Methods, Evidence and Recommendations): National Institute for Health and Clinical Excellence 2012 September 2012.
5. Treating Severe Migraine Headaches in the Emergency Room: A Review of the Research for Adults. 2005.
6. Asseburg C, Peura P, Oksanen T, Turunen J, Purmonen T, Martikainen J. Cost-effectiveness of oral triptans for acute migraine: mixed treatment comparison. *Int J Technol Assess Health Care*. 2012 Oct;28(4):382-9.
7. Ferrari MD, Loder E, McCarroll KA, Lines CR. Meta-analysis of rizatriptan efficacy in randomized controlled clinical trials. *Cephalalgia*. 2001 Mar;21(2):129-36.
8. Ferrari MD, Roon KI, Lipton RB, Goadsby PJ. Oral triptans (serotonin 5-HT_{1B/1D} agonists) in acute migraine treatment: a meta-analysis of 53 trials. *Lancet*. 2001 Nov 17;358(9294):1668-75.
9. Johnston MM, Rapoport AM. Triptans for the management of migraine. *Drugs*. 2010 Aug 20;70(12):1505-18.
10. Thorlund K, Mills EJ, Wu P, Ramos E, Chatterjee A, Druyts E, et al. Comparative efficacy of triptans for the abortive treatment of migraine: A multiple treatment comparison meta-analysis. *Cephalalgia*. 2013 Oct 9.
11. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *Bmj*. 2011;343:d5928.
12. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that

- evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol*. 2009 Oct;62(10):e1-34.
13. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol*. 2009;62(10):1006-12.
 14. Dias S, Sutton AJ, Ades AE, Welton NJ. Evidence synthesis for decision making 2: a generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials. *Med Decis Making*. 2013 Jul;33(5):607-17.
 15. Turner RM, Davey J, Clarke MJ, Thompson SG, Higgins JP. Predicting the extent of heterogeneity in meta-analysis, using empirical data from the Cochrane Database of Systematic Reviews. *Int J Epidemiol*. 2012 Jun;41(3):818-27.
 16. Cooper NJ, Sutton AJ, Morris D, Ades AE, Welton NJ. Addressing between-study heterogeneity and inconsistency in mixed treatment comparisons: Application to stroke prevention treatments in individuals with non-rheumatic atrial fibrillation. *Statistics in Medicine*. 2009;28(14):1861-81.
 17. Dias S, Sutton A, Welton N, Ades A, Golfinopoulos V, Kyrgiou M, et al. NICE DSU Technical Support Document 2: Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials. May 2011 [cited 2012 June 13]: Available from: <http://www.nicedsu.org.uk/TSD6%20Software.final.08.05.12.pdf>.
 18. Spiegelhalter D, Thomas A, Best N, Lunn D. WinBUGS User Manual. Version 1.42003 [cited 2011 June 1]: Available from: <http://www.mrc-bsu.cam.ac.uk/bugs/winbugs/manual114.pdf>.
 19. Ades AE, Welton NJ, Caldwell D, Price M, Goubar A, Lu G. Multiparameter evidence synthesis in epidemiology and medical decision-making. *J Health Serv Res Policy*. 2008 Oct;13 Suppl 3:12-22.
 20. Dias S, Welton NJ, Sutton AJ, Caldwell DM, Lu G, Ades AE. Evidence synthesis for decision making 4: inconsistency in networks of evidence based on randomized controlled trials. *Med Decis Making*. 2013 Jul;33(5):641-56.
 21. The International Classification of Headache Disorders, 3rd edition (beta version). *Cephalalgia*. Jul;33(9):629-808.
 22. Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. Headache Classification Committee of the International Headache Society. *Cephalalgia*. 1988;8 Suppl 7:1-96.
 23. Olesen J. The International Classification of Headache Disorders. *Headache*. 2008 May;48(5):691-3.

24. Olesen J, Steiner TJ. The International classification of headache disorders, 2nd edn (ICDH-II). *J Neurol Neurosurg Psychiatry*. 2004 Jun;75(6):808-11.
25. Goadsby PJ, Massiou H, Pascual J, Diener HC, Dahlof CG, Mateos V, et al. Almotriptan and zolmitriptan in the acute treatment of migraine. *Acta Neurologica Scandinavica*. 2007;115(1):34-40.
26. Gruffyd-Jones K, Kies B, Middleton A, Mulder LJ, Rosjo O, Millson DS. Zolmitriptan versus sumatriptan for the acute oral treatment of migraine: a randomized, double-blind, international study. *European Journal of Neurology*. 2001;8(3):237-45.
27. Sandrini G, Cerbo R, Del BE, Ferrari A, Genco S, Grazioli I, et al. Efficacy of dosing and re-dosing of two oral fixed combinations of indomethacin, prochlorperazine and caffeine compared with oral sumatriptan in the acute treatment of multiple migraine attacks: a double-blind, double-dummy, randomised, parallel group, multicentre study. *International Journal of Clinical Practice*. 2007;61(8):1256-69.
28. Landy S, Savani N, Shackelford S, Loftus J, Jones M. Efficacy and tolerability of sumatriptan tablets administered during the mild-pain phase of menstrually associated migraine. *International Journal of Clinical Practice*. 2004;58(10):913-9.
29. Mannix LK, Loder E, Nett R, Mueller L, Rodgers A, Hustad CM, et al. Rizatriptan for the acute treatment of ICHD-II proposed menstrual migraine: two prospective, randomized, placebo-controlled, double-blind studies. *Cephalalgia*. 2007;27(5):414-21.
30. Mannix LK, Martin VT, Cady RK, Diamond ML, Lener SE, White JD, et al. Combination treatment for menstrual migraine and dysmenorrhea using sumatriptan-naproxen: two randomized controlled trials. *Obstetrics and Gynecology*. 2009;114(1):106-13.
31. Nett R, Landy S, Shackelford S, Richardson MS, Ames M, Lener M. Pain-free efficacy after treatment with sumatriptan in the mild pain phase of menstrually associated migraine. *Obstetrics and Gynecology*. 2003;102(4):835-42.
32. Headaches: Diagnosis and management of headaches in young people and adults. 2012.

APPENDICES

Appendix 1: Search Strategy

Triptans – Acute Migraines – Final Strategies

2013 Oct 6

Database: Embase Classic+Embase <1947 to 2013 October 04>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present> Search Strategy:

-
- 1 exp Migraine Disorders/ (66228)
 - 2 (migrain* or migran*).tw. (89392)
 - 3 (anti-migrain* or antimigrain* or anti-migran* or antimigran*).tw. (2360)
 - 4 sick headache*.tw. (31)
 - 5 or/1-4 (106437)
 - 6 exp Tryptamines/ (86272)
 - 7 (tryptamin* or tryptomin* or triptan* or indolyethylamine* or NSC 73938 or NSC73938).tw. (10838)
 - 8 ("BRN 0125513" or CCRIS 8959 or EINECS 200-510-5 or Indol-3-ethylamine or UNII-422ZU9N5TV).tw. (0)
 - 9 Tryptamines.rn. (4631)
 - 10 (almotriptan* or Almogran or Almotrex or Amignul or Axert or PNU 180638E or PNU-180638E or UNII-PJP312605E).tw. (681)
 - 11 almotriptan.rn. (1149)
 - 12 (eletriptan* or Relpax or Relert or Relepax or "UK 116044" or "UK 116,044" or "UK-116044" or "UK-116,044" or UNII-22QOO9B8KI).tw. (686)
 - 13 eletriptan.rn. (1281)
 - 14 (frovatriptan* or Allegro or Frova or Frovelan or Migard or Miguard or SB 209509 or VML-251 or VML251).tw. (927)
 - 15 frovatriptan.rn. (872)
 - 16 (naratriptan* or Amerge or Colatan or Naragran or Naramig or UNII-QX3KXL1ZA2).tw. (841)
 - 17 naratriptan.rn. (1619)
 - 18 (rizatriptan* or Risatriptan* or "L 705,126" or "L 705126" or "L-705,126" or "L-705126" or Maxalt or "MK 0462" or MK 462 or MK-0462 or MK-462 or rizalief or rizalt or rizaliv or UNII-51086HBW8G).tw. (1299)
 - 19 rizatriptan.rn. (2190)
 - 20 (sumatriptan* or Arcoiran or Alsuma or BRN 6930870 or Diletan or Dolmigran or GR 43175 or GR 43175X or GR-43175 or HSDB 7742 or Imigran* or Imiject or Imitrex or micranil or Migril or Novelian or Sumigrene or Suminat or Sumatran or Sumatriptanum or Sumax or UNII-8R78F6L9VO or Zecuity).tw. (6824)
 - 21 sumatriptan.rn. (8795)
 - 22 (Zolmitriptan* or AscoTop or Flezol or Rapimelt or UNII-2FS66TH3YW or Zolmitriptan or Zomig or Zomig-ZMT or Zomigon or Zomigoro).tw. (1407)
 - 23 Zolmitriptan.rn. (2644)
 - 24 (Treximet or Trexima).tw. (60)

25 or/6-24 (102640)
 26 5 and 25 (11117)
 27 randomized controlled trial.pt. (387867)
 28 exp randomized controlled trials as topic/ (142502)
 29 random allocation/ (145233)
 30 double-blind method/ or single-blind method/ (289667)
 31 Placebos/ (277057)
 32 (random* or RCT\$1 or placebo*).tw. (1760512)
 33 ((singl* or doubl* or trebl* or tripl*) and (mask* or blind* or dumm*)).tw. (332772)
 34 or/27-33 (2166102)
 35 26 and 34 (2796)
 36 adult.mp. (9410610)
 37 middle aged.sh. (4500001)
 38 age\$.tw. (5885873)
 39 or/36-38 (14388970)
 40 35 and 39 (1651)
 41 exp Animals/ not (exp Animals/ and Humans/) (8923948)
 42 40 not 41 (1647)
 43 (comment or editorial or interview or letter or news).pt. (2770847)
 44 42 not 43 (1638)
 45 limit 44 to english language (1599)
 46 45 use prmz (705)
 47 exp migraine/ (66228)
 48 (migrain* or migran*).tw. (89392)
 49 (anti-migrain* or antimigrain* or anti-migran* or antimigran*).tw. (2360)
 50 sick headache*.tw. (31)
 51 or/47-50 (106437)
 52 tryptamine derivative/ (2624)
 53 triptan derivative/ (1999)
 54 (tryptamin* or tryptomin* or triptan* or indolyethylamine* or NSC 73938 or
 NSC73938).tw,tn. (10838)
 55 ("BRN 0125513" or CCRIS 8959 or EINECS 200-510-5 or Indol-3-ethylamine or UNII-
 422ZU9N5TV).tw,tn. (0)
 56 61-54-1.rn. (2370)
 57 almotriptan/ (997)
 58 (almotriptan* or Almogran or Almotrex or Amignul or Axert or PNU 180638E or PNU-
 180638E or UNII-PJP312605E).tw,tn. (681)
 59 154323-57-6.rn. (986)
 60 eletriptan/ (1156)
 61 (eletriptan* or Relpax or Relert or Relepax or "UK 116044" or "UK 116,044" or "UK-
 116044" or "UK-116,044" or UNII-22QOO9B8KI).tw,tn. (686)
 62 143322-58-1.rn. (1135)
 63 frovatriptan/ (792)
 64 (frovatriptan* or Allegro or Frova or Frovelan or Migard or Miguard or SB 209509 or
 VML-251 or VML251).tw,tn. (927)
 65 158747-02-5.rn. (764)

66 naratriptan/ (1470)
67 (naratriptan* or Amerge or Colatan or Naragran or Naramig or UNII-
QX3KXL1ZA2).tw,tn. (841)
68 121679-13-8.rn. (1619)
69 rizatriptan/ (1928)
70 (rizatriptan* or Risatriptan* or "L 705,126" or "L 705126" or "L-705,126" or "L-705126"
or Maxalt or "MK 0462" or MK 462 or MK-0462 or MK-462 or rizalief or rizalt or rizaliv or
UNII-51086HBW8G).tw,tn. (1299)
71 144034-80-0.rn. (1881)
72 sumatriptan/ (8967)
73 (sumatriptan* or Arcoiran or Alsuma or BRN 6930870 or Diletan or Dolmigran or GR
43175 or GR 43175X or GR-43175 or HSDB 7742 or Imigran* or Imiject or Imitrex or micranil
or Migril or Novelian or Sumigrene or Suminat or Sumatran or Sumatriptanum or Sumax or
UNII-8R78F6L9VO or Zecuity).tw,tn. (6824)
74 103628-46-2.rn. (8795)
75 Zolmitriptan/ (2314)
76 (Zolmitriptan* or AscoTop or Flezol or Rapimelt or UNII-2FS66TH3YW or Zolmitriptan
or Zomig or Zomig-ZMT or Zomigon or Zomigoro).tw,tn. (1407)
77 139264-17-8.rn. (2644)
78 naproxen plus sumatriptan succinate/ (23)
79 (Treximet or Trexima).tw,tn. (60)
80 811794-26-0.rn. (0)
81 or/52-80 (25720)
82 51 and 81 (10907)
83 randomized controlled trial/ (747726)
84 "randomized controlled trial (topic)"/ (39581)
85 Randomization/ (145233)
86 double blind procedure/ or single blind procedure/ or placebo/ (330971)
87 (random* or RCT\$1 or placebo*).tw. (1760512)
88 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (301343)
89 or/83-88 (2139152)
90 82 and 89 (2830)
91 exp animals/ or exp animal experimentation/ or exp models animal/ or exp animal
experiment/ or nonhuman/ or exp vertebrate/ (38752497)
92 exp humans/ or exp human experimentation/ or exp human experiment/ (28784180)
93 91 not 92 (9969946)
94 90 not 93 (2826)
95 adult.mp. (9410610)
96 middle aged.sh. (4500001)
97 age\$.tw. (5885873)
98 or/95-97 (14388970)
99 94 and 98 (1648)
100 (letter or editorial).pt. (2467327)
101 99 not 100 (1640)
102 limit 101 to english language (1603)
103 102 use emczd (955)

104 46 or 103 (1660)
 105 remove duplicates from 104 (1054) TOTAL UNIQUE HITS
 106 105 use prmz (644) MEDLINE UNIQUE HITS
 107 105 use emczd (410) EMBASE UNIQUE HITS

Triptans – Network Meta-Analysis Cochrane Strategy

Search Name: Triptans - Network Meta-Analysis
 Date Run: 06/10/13 14:17:26.40
 Description: Ottawa Heart Institute - 2013 Oct 6

ID	Search Hits	
#1	[mh "Migraine Disorders"]	1606
#2	(migrain* or migran*):ti,ab,kw	2899
#3	(anti-migrain* or antimigrain* or anti-migran* or antimigran*):ti,ab,kw	101
#4	(sick next headach*):ti,ab,kw	0
#5	(13-#4)	2907
#6	[mh Tryptamines]	2091
#7	(tryptamin* or tryptomin* or triptan* or indolyethylamine* or "NSC 73938" or NSC73938):ti,ab,kw	415
#8	("BRN 0125513" or "CCRIS 8959" or "EINECS 200-510-5" or "Indol-3-ethylamine" or "UNII-422ZU9N5TV"):ti,ab,kw	0
#9	(almotriptan* or Almogran or Almotrex or Amignul or Axert or "PNU 180638E" or "PNU-180638E" or "UNII-PJP312605E"):ti,ab,kw	63
#10	(eletriptan* or Relpax or Relert or Relepax or "UK 116044" or "UK 116,044" or "UK-116044" or "UK-116,044" or "UNII-22QOO9B8KI"):ti,ab,kw	47
#11	(frovatriptan* or Allegro or Frova or Frovelan or Migard or Miguard or "SB 209509" or "VML-251" or VML251):ti,ab,kw	40
#12	(naratriptan* or Amerge or Colatan or Naragran or Naramig or "UNII-QX3KXL1ZA2"):ti,ab,kw	51
#13	(rizatriptan* or Risatriptan* or "L 705,126" or "L 705126" or "L-705,126" or "L-705126" or Maxalt or "MK 0462" or "MK 462" or "MK-0462" or "MK-462" or rizalief or rizalt or rizaliv or "UNII-51086HBW8G"):ti,ab,kw	118
#14	(sumatriptan* or Arcoiran or Alsuma or "BRN 6930870" or Diletan or Dolmigran or "GR 43175" or "GR 43175X" or "GR-43175" or "HSDB 7742" or Imigran* or Imiject or Imitrex or micranil or Migril or Novelian or Sumigrene or Suminat or Sumatran or Sumatriptanum or Sumax or "UNII-8R78F6L9VO" or Zecuity):ti,ab,kw	523
#15	(Zolmitriptan* or AscoTop or Flezol or Rapimelt or "UNII-2FS66TH3YW" or Zolmitriptan or Zomig or "Zomig-ZMT" or Zomigon or Zomigoro):ti,ab,kw	106
#16	(Treximet or Trexima):ti,ab,kw	1
#17	(151-#16)	2394
#18	#5 and #17	721

DSR - 18
DARE - 20
CENTRAL – 640
Methods – 8
HTA – 6
NHS EED – 29

Only CENTRAL and DSR records were downloaded

Appendix 2: Included Studies

Included Studies (with single attack data) n = 133

1. Ahrens SP, Farmer MV, Williams DL, Willoughby E, Jiang K, Block GA, et al. Efficacy and safety of rizatriptan wafer for the acute treatment of migraine. Rizatriptan Wafer Protocol 049 Study Group. *Cephalalgia*. 1999;19(5):525-30.
2. Allais G, Acuto G, Cabarrocas X, Esbri R, Benedetto C, Bussone G. Efficacy and tolerability of almotriptan versus zolmitriptan for the acute treatment of menstrual migraine. *Neurological Sciences*. 2006;27 Suppl 2:S193-7, 2006 May.:7.
3. Banerjee M, Findley LJ. Sumatriptan in the treatment of acute migraine with aura. *Cephalalgia*. 1992;12(1):39-44.
4. Barbanti P, Carpay JA, Kwong WJ, Ahmad F, Boswell D. Effects of a fast disintegrating/rapid release oral formulation of sumatriptan on functional ability in patients with migraine. *Current Medical Research and Opinion*. 2004;20(12):2021-9.
5. Barbanti P, Fofi L, Dall'Armi V, Aurilia C, Egeo G, Vanacore N, et al. Rizatriptan in migraineurs with unilateral cranial autonomic symptoms: a double-blind trial. *J headache pain*. 2012;13(5):407-14.
6. Bates D, Ashford E, Dawson R, Ensink FB, Gilhus NE, Olesen J, et al. Subcutaneous sumatriptan during the migraine aura. Sumatriptan Aura Study Group. *Neurology*. 1994;44(9):1587-92.
7. Bomhof M, Paz J, Legg N, Allen C, Vandormael K, Patel K. Comparison of rizatriptan 10 mg vs. naratriptan 2.5 mg in migraine. *European Neurology*. 1999;42(3):173-9.
8. Bousser MG, d'Allens H, Richard A. Efficacy of subcutaneous sumatriptan in the acute treatment of early-morning migraine: a placebo-controlled trial. Early-Morning Migraine Sumatriptan Study Group. *Journal of Internal Medicine*. 1993;234(2):211-6.
9. Brandes JL, Kudrow D, Cady R, Tiseo PJ, Sun W, Sikes CR. Eletriptan in the early treatment of acute migraine: influence of pain intensity and time of dosing. *Cephalalgia*. 2005;25(9):735-42.
10. Brandes JL, Kudrow D, Stark SR, O'Carroll CP, Adelman JU, O'Donnell FJ, et al. Sumatriptan-naproxen for acute treatment of migraine: a randomized trial. *JAMA*. 2007;297(13):1443-54.
11. Bussone G, Manzoni GC, Cortelli P, Roncolato M, Fabbri L, Benassuti C. Efficacy and tolerability of sumatriptan in the treatment of multiple migraine attacks. *Neurological Sciences*. 2000;21(5):272-8.
12. Cady R, Crawford G, Ahrens S, Hairwassers D, Getson A, Visser WH, et al. Long-term efficacy and tolerability of rizatriptan wafers in migraine. *Medscape General Medicine*. 2001;3(3):1.
13. Cady R, Martin V, Mauskop A, Rodgers A, Hustad CM, Ramsey KE, et al. Efficacy of Rizatriptan 10 mg administered early in a migraine attack. *Headache*. 2006;46(6):914-24.
14. Cady RC, Ryan R, Jhingran P, O'Quinn S, Pait DG. Sumatriptan injection reduces productivity loss during a migraine attack: results of a double-blind, placebo-controlled trial. *Archives of Internal Medicine*. 1998;158(9):1013-8.
15. Cady RK, Martin VT, Geraud G, Rodgers A, Zhang Y, Ho AP, et al. Rizatriptan 10-mg ODT for early treatment of migraine and impact of migraine education on treatment response. *Headache*. 2009;49(5):687-96.
16. Carpay HA, Matthijsse P, Steinbuch M, Mulder PG. Oral and subcutaneous sumatriptan in the acute treatment of migraine: an open randomized cross-over study. *Cephalalgia*. 1997;17(5):591-5.
17. Carpay J, Schoenen J, Ahmad F, Kinrade F, Boswell D. Efficacy and tolerability of sumatriptan tablets in a fast-disintegrating, rapid-release formulation for the acute treatment of migraine: results of a multicenter, randomized, placebo-controlled study. *Clinical Therapeutics*. 2004;26(2):214-23.

18. Charlesworth BR, Dowson AJ, Purdy A, Becker WJ, Boes-Hansen S, Farkkila M. Speed of onset and efficacy of zolmitriptan nasal spray in the acute treatment of migraine: a randomised, double-blind, placebo-controlled, dose-ranging study versus zolmitriptan tablet. *CNS Drugs*. 2003;17(9):653-67.
19. Colman SS, Brod MI, Krishnamurthy A, Rowland CR, Jirgens KJ, Gomez-Mancilla B. Treatment satisfaction, functional status, and health-related quality of life of migraine patients treated with almotriptan or sumatriptan. *Clinical Therapeutics*. 2001;23(1):127-45.
20. Cull RE, Price WH, Dunbar A. The efficacy of subcutaneous sumatriptan in the treatment of recurrence of migraine headache. *Journal of Neurology Neurosurgery and Psychiatry*. 1997;62(5):490-5.
21. Dahlof C, Diener HC, Goadsby PJ, Massiou H, Olesen J, Schoenen J, et al. Zolmitriptan, a 5-HT(1B/1D) receptor agonist for the acute oral treatment of migraine: a multicentre, dose-range finding study. *European Journal of Neurology*. 1998;5(6):535-43.
22. Dahlof C, Tfelt-Hansen P, Massiou H, Fazekas A, Almotriptan Study G. Dose finding, placebo-controlled study of oral almotriptan in the acute treatment of migraine. *Neurology*. 2001;57(10):1811-7.
23. Dahlof CG, Hauge AW, Olesen J. Efficacy and safety of tonabersat, a gap-junction modulator, in the acute treatment of migraine: a double-blind, parallel-group, randomized study. *Cephalalgia*. 2009;29 Suppl 2:7-16.
24. Dasbach EJ, Carides GW, Gerth WC, Santanello NC, Pigeon JG, Kramer. Work and productivity loss in the rizatriptan multiple attack study. *Cephalalgia*. 2000;20(9):830-4.
25. Di MV, Nicolodi M, Aloisio A, Del BP, Fonzari M, Grazioli I, et al. Efficacy of a fixed combination of indomethacin, prochlorperazine, and caffeine versus sumatriptan in acute treatment of multiple migraine attacks: a multicenter, randomized, crossover trial. *Headache*. 2003;43(8):835-44.
26. Diamond S, Elkind A, Jackson RT, Ryan R, DeBussey S, Asgharnejad M. Multiple-attack efficacy and tolerability of sumatriptan nasal spray in the treatment of migraine. *Archives of Family Medicine*. 1998;7(3):234-40.
27. Diener HC. Efficacy of almotriptan 12.5 mg in achieving migraine-related composite endpoints: a double-blind, randomized, placebo-controlled study in patients controlled study in patients with previous poor response to sumatriptan 50 mg. *Current Medical Research and Opinion*. 2005;21(10):1603-10.
28. Diener HC, Barbanti P, Dahlof C, Reuter U, Habeck J, Podhorna J. BI 44370 TA, an oral CGRP antagonist for the treatment of acute migraine attacks: results from a phase II study. *Cephalalgia*. 2011;31(5):573-84.
29. Diener HC, Eikermann A, Gessner U, Gobel H, Haag G, Lange R, et al. Efficacy of 1,000 mg effervescent acetylsalicylic acid and sumatriptan in treating associated migraine symptoms. *European Neurology*. 2004;52(1):50-6.
30. Diener HC, Gendolla A, Gebert I, Beneke M. Almotriptan in migraine patients who respond poorly to oral sumatriptan: a double-blind, randomized trial. *Headache*. 2005;45(7):874-82.
31. Diener HC, Gendolla A, Gebert I, Beneke M. Almotriptan in migraine patients who respond poorly to oral sumatriptan: a double-blind, randomized trial. *European Neurology*. 2005;53 Suppl 1:41-8.
32. Diener HC, Jansen JP, Reches A, Pascual J, Pitei D, Steiner TJ, et al. Efficacy, tolerability and safety of oral eletriptan and ergotamine plus caffeine (Cafertgot) in the acute treatment of migraine: a multicentre, randomised, double-blind, placebo-controlled comparison. *European Neurology*. 2002;47(2):99-107.

33. Dodick D, Brandes J, Elkind A, Mathew N, Rodichok L. Speed of onset, efficacy and tolerability of zolmitriptan nasal spray in the acute treatment of migraine: a randomised, double-blind, placebo-controlled study. *CNS Drugs*. 2005;19(2):125-36.
34. Dodick DW. Almotriptan increases sustained pain-free outcomes in acute migraine: results from three controlled clinical trials. *Headache*. 2002;42(1):21-7.
35. Dowson AJ, Charlesworth BR. Patients with migraine prefer zolmitriptan orally disintegrating tablet to sumatriptan conventional oral tablet. *International Journal of Clinical Practice*. 2003;57(7):573-6.
36. Dowson AJ, MacGregor EA, Purdy RA, Becker WJ, Green J, Levy SL. Zolmitriptan orally disintegrating tablet is effective in the acute treatment of migraine. *Cephalalgia*. 2002;22(2):101-6.
37. Dowson AJ, Massiou H, Lainez JM, Cabarrocas X. Almotriptan is an effective and well-tolerated treatment for migraine pain: results of a randomized, double-blind, placebo-controlled clinical trial. *Cephalalgia*. 2002;22(6):453-61.
38. Dowson AJ, Massiou H, Lainez JM, Cabarrocas X. Almotriptan improves response rates when treatment is within 1 hour of migraine onset. *Headache*. 2004;44(4):318-22.
39. Eletriptan Steering C. Efficacy and safety of eletriptan 20 mg, 40 mg and 80 mg in Japanese migraineurs. *Cephalalgia*. 2002;22(6):416-23.
40. Farkkila M, Olesen J, Dahlof C, Stovner LJ, ter Brugge JP, Rasmussen S, et al. Eletriptan for the treatment of migraine in patients with previous poor response or tolerance to oral sumatriptan. *Cephalalgia*. 2003;23(6):463-71.
41. Freitag F, Diamond M, Diamond S, Janssen I, Rodgers A, Skobieranda F. Efficacy and tolerability of coadministration of rizatriptan and acetaminophen vs rizatriptan or acetaminophen alone for acute migraine treatment. *Headache*. 2008;48(6):921-30.
42. Freitag F, Taylor FR, Hamid MA, Rodgers A, Hustad CM, Ramsey KE, et al. Elimination of migraine-associated nausea in patients treated with rizatriptan orally disintegrating tablet (ODT): a randomized, double-blind, placebo-controlled study. *Headache*. 2008;48(3):368-77.
43. Freitag FG, Cady R, DiSerio F, Elkind A, Gallagher RM, Goldstein J, et al. Comparative study of a combination of isometheptene mucate, dichloralphenazone with acetaminophen and sumatriptan succinate in the treatment of migraine. *Headache*. 2001;41(4):391-8.
44. Friedman BW, Solorzano C, Esses D, Xia S, Hochberg M, Dua N, et al. Treating headache recurrence after emergency department discharge: a randomized controlled trial of naproxen versus sumatriptan. *Annals of Emergency Medicine*. 2010;56(1):7-17.
45. Gallagher RM, Dennish G, Spierings EL, Chitra R. A comparative trial of zolmitriptan and sumatriptan for the acute oral treatment of migraine. *Headache*. 2000;40(2):119-28.
46. Garcia-Ramos G, MacGregor EA, Hilliard B, Bordini CA, Leston J, Hettiarachchi J. Comparative efficacy of eletriptan vs. naratriptan in the acute treatment of migraine. *Cephalalgia*. 2003;23(9):869-76.
47. Gawel M, Aschoff J, May A, Charlesworth BR, Team RS. Zolmitriptan 5 mg nasal spray: efficacy and onset of action in the acute treatment of migraine--results from phase 1 of the REALIZE Study. *Headache*. 2005;45(1):7-16.
48. Geraud G, Compagnon A, Rossi A, Group CS. Zolmitriptan versus a combination of acetylsalicylic acid and metoclopramide in the acute oral treatment of migraine: a double-blind, randomised, three-attack study. *European Neurology*. 2002;47(2):88-98.
49. Gerth WC, Ruggles KH, Stark SR, Davies GM, Santanello NC. Improvement in health-related quality of life with rizatriptan 10mg compared with standard migraine therapy. *Clinical Drug Investigation*. 2001;21(12):853-60.

50. Gijsman H, Kramer MS, Sargent J, Tuchman M, Matzura-Wolfe D, Polis A, et al. Double-blind, placebo-controlled, dose-finding study of rizatriptan (MK- 462) in the acute treatment of migraine. *Cephalalgia*. 1997;17(6):647-51.
51. Goadsby PJ, Ferrari MD, Olesen J, Stovner LJ, Senard JM, Jackson NC, et al. Eletriptan in acute migraine: a double-blind, placebo-controlled comparison to sumatriptan. Eletriptan Steering Committee. *Neurology*. 2000;54(1):156-63.
52. Goadsby PJ, Massiou H, Pascual J, Diener HC, Dahlof CG, Mateos V, et al. Almotriptan and zolmitriptan in the acute treatment of migraine. *Acta Neurologica Scandinavica*. 2007;115(1):34-40.
53. Goadsby PJ, Zanchin G, Geraud G, De KN, Diaz-Insa S, Gobel H, et al. Early vs. non-early intervention in acute migraine-'Act when Mild (AwM)'. A double-blind, placebo-controlled trial of almotriptan. *Cephalalgia*. 2008;28(4):383-91.
54. Gobel H, Winter P, Boswell D, Crisp A, Becker W, Hauge T, et al. Comparison of naratriptan and sumatriptan in recurrence-prone migraine patients. Naratriptan International Recurrence Study Group. *Clinical Therapeutics*. 2000;22(8):981-9.
55. Goldstein J, Keywood C, Study G. Frovatriptan for the acute treatment of migraine: a dose-finding study. *Headache*. 2002;42(1):41-8.
56. Goldstein J, Smith TR, Pugach N, Griesser J, Sebree T, Pierce M. A sumatriptan iontophoretic transdermal system for the acute treatment of migraine. *Headache*. 2012;52(9):1402-10.
57. Gross ML, Kay J, Turner AM, Hallett K, Cleal AL, Hassani H. Sumatriptan in acute migraine using a novel cartridge system self-injector. United Kingdom Study Group. *Headache*. 1994;34(10):559-63.
58. Gruffyd-Jones K, Kies B, Middleton A, Mulder LJ, Rosjo O, Millson DS. Zolmitriptan versus sumatriptan for the acute oral treatment of migraine: a randomized, double-blind, international study. *European Journal of Neurology*. 2001;8(3):237-45.
59. Henry P, d'Allens H. Subcutaneous sumatriptan in the acute treatment of migraine in patients using dihydroergotamine as prophylaxis. French Migraine Network Bordeaux-Lyon-Grenoble. *Headache*. 1993;33(8):432-5.
60. Ho TW, Ferrari MD, Dodick DW, Galet V, Kost J, Fan X, et al. Efficacy and tolerability of MK-0974 (telcagepant), a new oral antagonist of calcitonin gene-related peptide receptor, compared with zolmitriptan for acute migraine: a randomised, placebo-controlled, parallel-treatment trial. *Lancet*. 2008;372(9656):2115-23.
61. Ho TW, Mannix LK, Fan X, Assaid C, Furtek C, Jones CJ, et al. Randomized controlled trial of an oral CGRP receptor antagonist, MK-0974, in acute treatment of migraine. *Neurology*. 2008;70(16):1304-12.
62. Ishkanian G, Blumenthal H, Webster CJ, Richardson MS, Ames M. Efficacy of sumatriptan tablets in migraineurs self-described or physician-diagnosed as having sinus headache: a randomized, double-blind, placebo-controlled study. *Clinical Therapeutics*. 2007;29(1):99-109.
63. Jelinski SE, Becker WJ, Christie SN, Ahmad FE, Pryse-Phillips W, Simpson SD. Pain free efficacy of sumatriptan in the early treatment of migraine. *Canadian Journal of Neurological Sciences*. 2006;33(1):73-9.
64. Jensen K, Tfelt-Hansen P, Hansen EW, Krois EH, Pedersen OS. Introduction of a novel self-injector for sumatriptan. A controlled clinical trial in general practice. *Cephalalgia*. 1995;15(5):423-9.
65. Kaniecki R, Ruoff G, Smith T, Barrett PS, Ames MH, Byrd S, et al. Prevalence of migraine and response to sumatriptan in patients self-reporting tension/stress headache. *Current Medical Research and Opinion*. 2006;22(8):1535-44.

66. Klapper J, Lucas C, Rosjo O, Charlesworth B, group Zs. Benefits of treating highly disabled migraine patients with zolmitriptan while pain is mild. *Cephalalgia*. 2004;24(11):918-24.
67. Klapper JA, O'Connor S. Rizatriptan wafer--sublingual vs. placebo at the onset of acute migraine. *Cephalalgia*. 2000;20(6):585-7.
68. Klassen A, Elkind A, Asgharnejad M, Webster C, Laurenza A. Naratriptan is effective and well tolerated in the acute treatment of migraine. Results of a double-blind, placebo-controlled, parallel-group study. Naratriptan S2WA3001 Study Group. *Headache*. 1997;37(10):640-5.
69. Kramer MS, Matzura-Wolfe D, Polis A, Getson A, Amaraneni PG, Solbach MP, et al. A placebo-controlled crossover study of rizatriptan in the treatment of multiple migraine attacks. Rizatriptan Multiple Attack Study Group. *Neurology*. 1998;51(3):773-81.
70. Kudrow D, Thomas HM, Ruoff G, Ishkanian G, Sands G, Le VH, et al. Valdecoxib for treatment of a single, acute, moderate to severe migraine headache. *Headache*. 2005;45(9):1151-62.
71. Landy S, Savani N, Shackelford S, Loftus J, Jones M. Efficacy and tolerability of sumatriptan tablets administered during the mild-pain phase of menstrually associated migraine. *International Journal of Clinical Practice*. 2004;58(10):913-9.
72. Lipton RB, Dodick DW, Adelman JU, Kaniecki RG, Lener SE, White JD, et al. Consistency of response to sumatriptan/naproxen sodium in a placebo-controlled, crossover study. *Cephalalgia*. 2009;29(8):826-36.
73. Loder E, Freitag FG, Adelman J, Pearlman S, Abu-Shakra S. Pain-free rates with zolmitriptan 2.5 mg ODT in the acute treatment of migraine: results of a large double-blind placebo-controlled trial. *Current Medical Research and Opinion*. 2005;21(3):381-9.
74. Mannix LK, Loder E, Nett R, Mueller L, Rodgers A, Hustad CM, et al. Rizatriptan for the acute treatment of ICHD-II proposed menstrual migraine: two prospective, randomized, placebo-controlled, double-blind studies. *Cephalalgia*. 2007;27(5):414-21.
75. Mannix LK, Martin VT, Cady RK, Diamond ML, Lener SE, White JD, et al. Combination treatment for menstrual migraine and dysmenorrhea using sumatriptan-naproxen: two randomized controlled trials. *Obstetrics and Gynecology*. 2009;114(1):106-13.
76. Massiou H, Jamin C, Hinzelin G, Bidaut-Mazel C. Efficacy of oral naratriptan in the treatment of menstrually related migraine. *European Journal of Neurology*. 2005;12(10):774-81.
77. Mathew NT, Finlayson G, Smith TR, Cady RK, Adelman J, Mao L, et al. Early intervention with almotriptan: results of the AEGIS trial (AXERT Early Migraine Intervention Study). *Headache*. 2007;47(2):189-98.
78. Mathew NT, Schoenen J, Winner P, Muirhead N, Sikes CR. Comparative efficacy of eletriptan 40 mg versus sumatriptan 100 mg. *Headache*. 2003;43(3):214-22.
79. Misra M, Sharma T, Kalra J, Goel D, Dhasmana DC. Comparative efficacy and tolerability of sumatriptan, ergotamine, naproxen and rizatriptan in moderate to severe acute attack of migraine. *JK Science*. 2010;12(4):175-9.
80. Misra UK, Kalita J, Yadav RK. Rizatriptan vs. ibuprofen in migraine: a randomised placebo-controlled trial. *J headache pain*. 2007;8(3):175-9.
81. Multinational Oral Sumatriptan and Cafergot Comparative Study Group. A randomized, double-blind comparison of sumatriptan and Cafergot in the acute treatment of migraine. The Multinational Oral Sumatriptan and Cafergot Comparative Study Group. *European Neurology*. 1991;31(5):314-22.
82. Myllyla VV, Havanka H, Herrala L, Kangasniemi P, Rautakorpi I, Turkka J, et al. Tolfenamic acid rapid release versus sumatriptan in the acute treatment of migraine: comparable effect in a double-blind, randomized, controlled, parallel-group study. *Headache*. 1998;38(3):201-7.

83. Nappi G, Sicuteri F, Byrne M, Roncolato M, Zerbini O. Oral sumatriptan compared with placebo in the acute treatment of migraine. *Journal of Neurology*. 1994;241(3):138-44.
84. Nett R, Landy S, Shackelford S, Richardson MS, Ames M, Lener M. Pain-free efficacy after treatment with sumatriptan in the mild pain phase of menstrually associated migraine. *Obstetrics and Gynecology*. 2003;102(4):835-42.
85. Olesen J, Diener HC, Schoenen J, Hettiarachchi J. No effect of eletriptan administration during the aura phase of migraine. *European Journal of Neurology*. 2004;11(10):671-7.
86. Oral Sumatriptan and Aspirin plus Metoclopramide Comparative Study Group. A study to compare oral sumatriptan with oral aspirin plus oral metoclopramide in the acute treatment of migraine. The Oral Sumatriptan and Aspirin plus Metoclopramide Comparative Study Group. *European Neurology*. 1992;32(3):177-84.
87. Oral Sumatriptan Dose-Defining Study Group. Sumatriptan--an oral dose-defining study. The Oral Sumatriptan Dose-Defining Study Group. *European Neurology*. 1991;31(5):300-5.
88. Oral Sumatriptan International Multiple-Dose Study Group. Evaluation of a multiple-dose regimen of oral sumatriptan for the acute treatment of migraine. The Oral Sumatriptan International Multiple-Dose Study Group. *European Neurology*. 1991;31(5):306-13.
89. Pascual J, Falk RM, Piessens F, Prusinski A, Docekal P, Robert M, et al. Consistent efficacy and tolerability of almotriptan in the acute treatment of multiple migraine attacks: results of a large, randomized, double-blind, placebo-controlled study. *Cephalalgia*. 2000;20(6):588-96.
90. Pascual J, Vega P, Diener HC, Allen C, Vrijens F, Patel K. Comparison of rizatriptan 10 mg vs. zolmitriptan 2.5 mg in the acute treatment of migraine. Rizatriptan-Zolmitriptan Study Group. *Cephalalgia*. 2000;20(5):455-61.
91. Pfaffenrath V, Cunin G, Sjonell G, Prendergast S. Efficacy and safety of sumatriptan tablets (25 mg, 50 mg, and 100 mg) in the acute treatment of migraine: defining the optimum doses of oral sumatriptan. *Headache*. 1998;38(3):184-90.
92. Pini LA, Fabbri L, Cavazzuti L. Efficacy and safety of sumatriptan 50 mg in patients not responding to standard care, in the treatment of mild to moderate migraine. The Sumatriptan 50 mg Italian Study Group. *International Journal of Clinical Pharmacology Research*. 1999;19(2):57-64.
93. Pini LA, Sternieri E, Fabbri L, Zerbini O, Bamfi F. High efficacy and low frequency of headache recurrence after oral sumatriptan. The Oral Sumatriptan Italian Study Group. *Journal of International Medical Research*. 1995;23(2):96-105.
94. Rapoport A, Ryan R, Goldstein J, Keywood C. Dose range-finding studies with frovatriptan in the acute treatment of migraine. *Headache*. 2002;42 Suppl 2:S74-83, 2002 Apr.:83.
95. Ryan R, Elkind A, Baker CC, Mullican W, DeBussey S, Asgharnejad M. Sumatriptan nasal spray for the acute treatment of migraine. Results of two clinical studies. *Neurology*. 1997;49(5):1225-30.
96. Ryan R, Geraud G, Goldstein J, Cady R, Keywood C. Clinical efficacy of frovatriptan: placebo-controlled studies. *Headache*. 2002;42 Suppl 2:84-92.
97. Sakai F, Iwata M, Tashiro K, Itoyama Y, Tsuji S, Fukuuchi Y, et al. Zolmitriptan is effective and well tolerated in Japanese patients with migraine: a dose-response study. *Cephalalgia*. 2002;22(5):376-83.
98. Sandrini G, Cerbo R, Del BE, Ferrari A, Genco S, Grazioli I, et al. Efficacy of dosing and re-dosing of two oral fixed combinations of indomethacin, prochlorperazine and caffeine compared with oral sumatriptan in the acute treatment of multiple migraine attacks: a double-blind, double-dummy, randomised, parallel group, multicentre study. *International Journal of Clinical Practice*. 2007;61(8):1256-69.

99. Sandrini G, Farkkila M, Burgess G, Forster E, Haughie S, Eletriptan Steering C. Eletriptan vs sumatriptan: a double-blind, placebo-controlled, multiple migraine attack study. *Neurology*. 2002;59(8):1210-7.
100. Savani N, Brautaset NJ, Reunanen M, Szirmai I, Ashford EA, Hassani H, et al. A double-blind placebo-controlled study assessing the efficacy and tolerability of 50 mg sumatriptan tablets in the acute treatment of migraine. Sumatriptan Tablets S2CM07 Study Group. *International Journal of Clinical Practice*, Supplement. 1999;105:7-15.
101. Savani N, Pfaffenrath V, Rice L, Boswell D, Black L, Jones M, et al. Efficacy, tolerability, and patient satisfaction with 50- and 100-mg sumatriptan tablets in those initially dissatisfied with the efficacy of 50-mg sumatriptan tablets. *Clinical Therapeutics*. 2001;23(2):260-71.
102. Schulman EA. Transdermal sumatriptan for acute treatment of migraineurs with baseline nausea. *Headache*. 2012;52(2):204-12.
103. Schulman EA, Cady RK, Henry D, Batenhorst AS, Putnam DG, Watson CB, et al. Effectiveness of sumatriptan in reducing productivity loss due to migraine: results of a randomized, double-blind, placebo-controlled clinical trial. *Mayo Clinic Proceedings*. 2000;75(8):782-9.
104. Scott RJ, Aitchison WR, Barker PR, McLaren GI. Oral sumatriptan in the acute treatment of migraine and migraine recurrence in general practice. *QJM*. 1996;89(8):613-22.
105. Sheftell F, Ryan R, Pitman V, Eletriptan Steering C. Efficacy, safety, and tolerability of oral eletriptan for treatment of acute migraine: a multicenter, double-blind, placebo-controlled study conducted in the United States. *Headache*. 2003;43(3):202-13.
106. Sheftell FD, Dahlof CG, Brandes JL, Agosti R, Jones MW, Barrett PS. Two replicate randomized, double-blind, placebo-controlled trials of the time to onset of pain relief in the acute treatment of migraine with a fast-disintegrating/rapid-release formulation of sumatriptan tablets. *Clinical Therapeutics*. 2005;27(4):407-17.
107. Silberstein SD, Cady RK, Sheftell FD, Almas M, Parsons B, Albert KS. Efficacy of eletriptan in migraine-related functional impairment: functional and work productivity outcomes. *Headache*. 2007;47(5):673-82.
108. Silberstein SD, Mannix LK, Goldstein J, Couch JR, Byrd SC, Ames MH, et al. Multimechanistic (sumatriptan-naproxen) early intervention for the acute treatment of migraine. *Neurology*. 2008;71(2):114-21.
109. Slof J. Cost-effectiveness analysis of early versus non-early intervention in acute migraine based on evidence from the 'Act when mild' study. *Applied Health Economics and Health Policy*. 2012;10(3):201-15.
110. Smith TR, Sunshine A, Stark SR, Littlefield DE, Spruill SE, Alexander WJ. Sumatriptan and naproxen sodium for the acute treatment of migraine. *Headache*. 2005;45(8):983-91.
111. Solomon GD, Cady RK, Klapper JA, Earl NL, Saper JR, Ramadan NM. Clinical efficacy and tolerability of 2.5 mg zolmitriptan for the acute treatment of migraine. The 042 Clinical Trial Study Group. *Neurology*. 1997;49(5):1219-25.
112. Spierings EL, Gomez-Mancilla B, Grosz DE, Rowland CR, Whaley FS, Jirgens KJ. Oral almotriptan vs. oral sumatriptan in the abortive treatment of migraine: a double-blind, randomized, parallel-group, optimum-dose comparison. *Archives of Neurology*. 2001;58(6):944-50.
113. Spierings EL, Rapoport AM, Dodick DW, Charlesworth B. Acute treatment of migraine with zolmitriptan 5 mg orally disintegrating tablet. *CNS Drugs*. 2004;18(15):1133-41.
114. Stark R, Dahlof C, Haughie S, Hettiarachchi J, Eletriptan Steering C. Efficacy, safety and tolerability of oral eletriptan in the acute treatment of migraine: results of a phase III, multicentre, placebo-controlled study across three attacks. *Cephalalgia*. 2002;22(1):23-32.

115. Stark S, Spierings EL, McNeal S, Putnam GP, Bolden-Watson CP, O'Quinn S. Naratriptan efficacy in migraineurs who respond poorly to oral sumatriptan. *Headache*. 2000;40(7):513-20.
116. Steiner TJ, Diener HC, MacGregor EA, Schoenen J, Muirheads N, Sikes CR. Comparative efficacy of eletriptan and zolmitriptan in the acute treatment of migraine. *Cephalalgia*. 2003;23(10):942-52.
117. Sumatriptan Auto-Injector Study Group. Self-treatment of acute migraine with subcutaneous sumatriptan using an auto-injector device. The Sumatriptan Auto-Injector Study Group. *European Neurology*. 1991;31(5):323-31.
118. Sunshine A, Mulhern SA, Olson N, Elkind A, Almas M, Sikes C. Comparative sensitivity of stopwatch methodology and conventional pain assessment measures for detecting early response to triptans in migraine: results of a randomized, open-label pilot study. *Clinical Therapeutics*. 2006;28(8):1107-15.
119. Taylor FR, Heiring JO, Messina E, Braverman-Panza J, Ames MH, Byrd SC, et al. Sumatriptan/naproxen sodium as early intervention for migraine: Effects on functional ability, productivity, and satisfaction in 2 randomized controlled trials. *Journal of Clinical Outcomes Management*. 2007;14(4):195-204.
120. Teall J, Tuchman M, Cutler N, Gross M, Willoughby E, Smith B, et al. Rizatriptan (MAXALT) for the acute treatment of migraine and migraine recurrence. A placebo-controlled, outpatient study. Rizatriptan 022 Study Group. *Headache*. 1998;38(4):281-7.
121. Tepper SJ, Cady R, Dodick D, Freitag FG, Hutchinson SL, Twomey C, et al. Oral sumatriptan for the acute treatment of probable migraine: first randomized, controlled study. *Headache*. 2006;46(1):115-24.
122. Tepper SJ, Cochran A, Hobbs S, Woessner M. Sumatriptan suppositories for the acute treatment of migraine. S2B351 Study Group. *International Journal of Clinical Practice*. 1998;52(1):31-5.
123. Tepper SJ, Donnan GA, Dowson AJ, Bomhof MA, Elkind A, Meloche J, et al. A long-term study to maximise migraine relief with zolmitriptan. *Current Medical Research and Opinion*. 1999;15(4):254-71.
124. Tfelt-Hansen P, Bach FW, Daugaard D, Tsiropoulos I, Riddersholm B. Treatment with sumatriptan 50 mg in the mild phase of migraine attacks in patients with infrequent attacks: a randomised, double-blind, placebo-controlled study. *J headache pain*. 2006;7(6):389-94.
125. Tfelt-Hansen P, Henry P, Mulder LJ, Scheldewaert RG, Schoenen J, Chazot G. The effectiveness of combined oral lysine acetylsalicylate and metoclopramide compared with oral sumatriptan for migraine. *Lancet*. 1995;346(8980):923-6.
126. Tfelt-Hansen P, Teall J, Rodriguez F, Giacobazzo M, Paz J, Malbecq W, et al. Oral rizatriptan versus oral sumatriptan: a direct comparative study in the acute treatment of migraine. Rizatriptan 030 Study Group. *Headache*. 1998;38(10):748-55.
127. Visser WH, Terwindt GM, Reines SA, Jiang K, Lines CR, Ferrari MD. Rizatriptan vs sumatriptan in the acute treatment of migraine. A placebo-controlled, dose-ranging study. Dutch/US Rizatriptan Study Group. *Archives of Neurology*. 1996;53(11):1132-7.
128. Wang SJ, Fuh JL, Wu ZA. Intranasal sumatriptan study with high placebo response in Taiwanese patients with migraine. *Journal of the Chinese Medical Association*. 2007;70(2):39-46.
129. Wells N, Hettiarachchi J, Drummond M, Dphil M, Carter D, Parpia T, et al. A cost-effectiveness analysis of eletriptan 40 and 80 mg versus sumatriptan 50 and 100 mg in the acute treatment of migraine. *Value in Health*. 2003;6(4):438-47.
130. Wells NEJ. Comparison of the effectiveness of eletriptan, sumatriptan and Cafergot in reducing the time loss associated with migraine attacks. *Journal of Medical Economics*. 2001;4(157-166):157-66.

131. White WB, Derosier FJ, Thompson AH, Adams BE, Goodman DK. Evaluation of the migraine treatment sumatriptan/naproxen sodium on blood pressure following long-term administration. *Journal of Clinical Hypertension* (Greenwich, Conn). 2011;13(12):910-6.
132. Winner P, Adelman J, Aurora S, Lener ME, Ames M. Efficacy and tolerability of sumatriptan injection for the treatment of morning migraine: two multicenter, prospective, randomized, double-blind, controlled studies in adults. *Clinical Therapeutics*. 2006;28(10):1582-91.
133. Winner P, Mannix LK, Putnam DG, McNeal S, Kwong J, O'Quinn S, et al. Pain-free results with sumatriptan taken at the first sign of migraine pain: 2 randomized, double-blind, placebo-controlled studies. *Mayo Clinic Proceedings*. 2003;78(10):1214-22.

Included studies (no single attack data) n = 69

1. Allais G, Bussone G, D'Andrea G, Moschiano F, d'Onofrio F, Valguarnera F, et al. Almotriptan 12.5 mg in menstrually related migraine: a randomized, double-blind, placebo-controlled study. *Cephalalgia*. 2011;31(2):144-51.
2. Bartolini M, Giamberardino MA, Lisotto C, Martelletti P, Moscato D, Panascia B, et al. A double-blind, randomized, multicenter, Italian study of frovatriptan versus almotriptan for the acute treatment of migraine. *J headache pain*. 2011;12(3):361-8.
3. Bartolini M, Giamberardino MA, Lisotto C, Martelletti P, Moscato D, Panascia B, et al. Frovatriptan versus almotriptan for acute treatment of menstrual migraine: analysis of a double-blind, randomized, cross-over, multicenter, Italian, comparative study. *J headache pain*. 2012;13(5):401-6.
4. Bigal M, Sheftell F, Tepper S, Tepper D, Ho TW, Rapoport A. A randomized double-blind study comparing rizatriptan, dexamethasone, and the combination of both in the acute treatment of menstrually related migraine: research submission. *Headache*. 2008;48(9):1286-93.
5. Boureau F, Chazot G, Emile J, Bertin L, d'Allens H. Comparison of subcutaneous sumatriptan with usual acute treatments for migraine. French Sumatriptan Study Group. *European Neurology*. 1995;35(5):264-9.
6. Boureau F, Kappos L, Schoenen J, Esperanca P, Ashford E. A clinical comparison of sumatriptan nasal spray and dihydroergotamine nasal spray in the acute treatment of migraine. *International Journal of Clinical Practice*. 2000;54(5):281-6.
7. Cady R, Elkind A, Goldstein J, Keywood C. Randomized, placebo-controlled comparison of early use of frovatriptan in a migraine attack versus dosing after the headache has become moderate or severe. *Current Medical Research and Opinion*. 2004;20(9):1465-72.
8. Cady R, Martin V, Mauskop A, Rodgers A, Hustad C, Ramsey K, et al. Symptoms of cutaneous sensitivity pre-treatment and post-treatment: results from the rizatriptan TAME studies. *Cephalalgia*. 2007;27(9):1055-60.
9. Cady RK, Freitag FG, Mathew NT, Elkind AH, Mao L, Fisher AC, et al. Allodynia-associated symptoms, pain intensity and time to treatment: predicting treatment response in acute migraine intervention. *Headache*. 2009;49(3):350-63.
10. Cady RK, Goldstein J, Silberstein S, Juhasz M, Ramsey K, Rodgers A, et al. Expanding access to triptans: assessment of clinical outcome. *Headache*. 2009;49(10):1402-13.
11. Christie S, Gobel H, Mateos V, Allen C, Vrijens F, Shivaprakash M, et al. Crossover comparison of efficacy and preference for rizatriptan 10 mg versus ergotamine/cafeine in migraine. *European Neurology*. 2003;49(1):20-9.
12. Connor KM, Aurora SK, Loeys T, Ashina M, Jones C, Giezek H, et al. Long-term tolerability of telcagepant for acute treatment of migraine in a randomized trial. *Headache*. 2011;51(1):73-84.

13. Dahlof CG, Lipton RB, McCarroll KA, Kramer MS, Lines CR, Ferrari MD. Within-patient consistency of response of rizatriptan for treating migraine. *Neurology*. 2000;55(10):1511-6.
14. Derosier F, Sheftell F, Silberstein S, Cady R, Ruoff G, Krishen A, et al. Sumatriptan-naproxen and butalbital: a double-blind, placebo-controlled crossover study. *Headache*. 2012;52(4):530-43.
15. Dib M, Massiou H, Weber M, Henry P, Garcia-Acosta S, Bousser MG, et al. Efficacy of oral ketoprofen in acute migraine: a double-blind randomized clinical trial. *Neurology*. 2002;58(11):1660-5.
16. Diclofenac-K/Sumatriptan Migraine Study Group. Acute treatment of migraine attacks: efficacy and safety of a nonsteroidal anti-inflammatory drug, diclofenac-potassium, in comparison to oral sumatriptan and placebo. The Diclofenac-K/Sumatriptan Migraine Study Group. *Cephalalgia*. 1999;19(4):232-40.
17. Diener HC, Bussone G, de LH, Eikermann A, Englert R, Floeter T, et al. Placebo-controlled comparison of effervescent acetylsalicylic acid, sumatriptan and ibuprofen in the treatment of migraine attacks. *Cephalalgia*. 2004;24(11):947-54.
18. Diez FI, Straube A, Zanchin G. Patient preference in migraine therapy. A randomized, open-label, crossover clinical trial of acute treatment of migraine with oral almotriptan and rizatriptan. *Journal of Neurology*. 2007;254(2):242-9.
19. Dowson A. Can oral 311C90, a novel 5-HT_{1D} agonist, prevent migraine headache when taken during an aura? *European Neurology*. 1996;36 Suppl 2:28-31, 1996.:31.
20. Dowson A, Ball K, Haworth D. Comparison of a fixed combination of domperidone and paracetamol (Domperamol) with sumatriptan 50 mg in moderate to severe migraine: a randomised UK primary care study. *Current Medical Research and Opinion*. 2000;16(3):190-7.
21. Dowson A, Bundy M, Salt R, Kilminster S. Patient preference for triptan formulations: a prospective study with zolmitriptan. *Headache*. 2007;47(8):1144-51.
22. Dowson AJ, Charlesworth BR, Purdy A, Becker WJ, Boes-Hansen S, Farkkila M. Tolerability and consistency of effect of zolmitriptan nasal spray in a long-term migraine treatment trial. *CNS Drugs*. 2003;17(11):839-51.
23. Dowson AJ, Massiou H, Aurora SK. Managing migraine headaches experienced by patients who self-report with menstrually related migraine: a prospective, placebo-controlled study with oral sumatriptan. *J headache pain*. 2005;6(2):81-7.
24. Facchinetti F, Allais G, Nappi RE, Gabellari IC, Di Renzo GC, Genazzani AR, et al. Sumatriptan (50 mg tablets vs. 25 mg suppositories) in the acute treatment of menstrually related migraine and oral contraceptive-induced menstrual migraine: a pilot study. *Gynecological Endocrinology*. 2010;26(10):773-9.
25. Facchinetti F, Bonellie G, Kangasniemi P, Pascual J, Shuaib A. The efficacy and safety of subcutaneous sumatriptan in the acute treatment of menstrual migraine. The Sumatriptan Menstrual Migraine Study Group. *Obstetrics and Gynecology*. 1995;86(6):911-6.
26. Geraud G, Olesen J, Pfaffenrath V, Tfelt-Hansen P, Zupping R, Diener HC, et al. Comparison of the efficacy of zolmitriptan and sumatriptan: issues in migraine trial design. *Cephalalgia*. 2000;20(1):30-8.
27. Goadsby PJ, Zagami AS, Donnan GA, Symington G, Anthony M, Bladin PF, et al. Oral sumatriptan in acute migraine. *Lancet*. 1991;338(8770):782-3.
28. Goldstein J, Ryan R, Jiang K, Getson A, Norman B, Block GA, et al. Crossover comparison of rizatriptan 5 mg and 10 mg versus sumatriptan 25 mg and 50 mg in migraine. Rizatriptan Protocol 046 Study Group. *Headache*. 1998;38(10):737-47.
29. Gruffydd-Jones K, Hood CA, Price DB. A within-patient comparison of subcutaneous and oral sumatriptan in the acute treatment of migraine in general practice. *Cephalalgia*. 1997;17(1):31-6.

30. Kolodny A, Polis A, Battisti WP, Johnson-Pratt L, Skobieranda F, Rizatriptan P. Comparison of rizatriptan 5 mg and 10 mg tablets and sumatriptan 25 mg and 50 mg tablets. *Cephalalgia*. 2004;24(7):540-6.
31. Lainez MJ, Evers S, Kinge E, Allais G, Allen C, Rao NA, et al. Preference for rizatriptan 10-mg wafer vs. eletriptan 40-mg tablet for acute treatment of migraine. *Cephalalgia*. 2006;26(3):246-56.
32. Lainez MJ, Galvan J, Heras J, Vila C. Crossover, double-blind clinical trial comparing almotriptan and ergotamine plus caffeine for acute migraine therapy. *European Journal of Neurology*. 2007;14(3):269-75.
33. Lampl C, Huber G, Haas S, Rittberger E, Diener HC. Difference in triptan effect in patients with migraine and early allodynia. *Cephalalgia*. 2008;28(10):1031-8.
34. Landy SH, McGinnis JE, McDonald SA. Pilot study evaluating preference for 3-mg versus 6-mg subcutaneous sumatriptan. *Headache*. 2005;45(4):346-9.
35. Lines CR, Vandormael K, Malbecq W. A comparison of visual analog scale and categorical ratings of headache pain in a randomized controlled clinical trial with migraine patients. *Pain*. 2001;93(2):185-90.
36. Lipton RB, Stewart WF, Cady R, Hall C, O'Quinn S, Kuhn T, et al. 2000 Wolfe Award. Sumatriptan for the range of headaches in migraine sufferers: results of the Spectrum Study. *Headache*. 2000;40(10):783-91.
37. Loder E, Brandes JL, Silberstein S, Skobieranda F, Bohidar N, Wang L, et al. Preference comparison of rizatriptan ODT 10-mg and sumatriptan 50-mg tablet in migraine. *Headache*. 2001;41(8):745-53.
38. Loder E, Silberstein SD, Abu-Shakra S, Mueller L, Smith T. Efficacy and tolerability of oral zolmitriptan in menstrually associated migraine: a randomized, prospective, parallel-group, double-blind, placebo-controlled study. *Headache*. 2004;44(2):120-30.
39. Mathew NT. Almotriptan increases pain-free status in patients with acute migraine treated in placebo-controlled clinical trials. *Headache*. 2002;42 Suppl 1:32-7.
40. Mathew NT, Asgharnejad M, Peykamian M, Laurenza A. Naratriptan is effective and well tolerated in the acute treatment of migraine. Results of a double-blind, placebo-controlled, crossover study. The Naratriptan S2WA3003 Study Group. *Neurology*. 1997;49(6):1485-90.
41. Mathew NT, Kailasam J, Gentry P, Chernyshev O. Treatment of nonresponders to oral sumatriptan with zolmitriptan and rizatriptan: a comparative open trial. *Headache*. 2000;40(6):464-5.
42. Mathew NT, Landy S, Stark S, Tietjen GE, Derosier FJ, White J, et al. Fixed-dose sumatriptan and naproxen in poor responders to triptans with a short half-life. *Headache*. 2009;49(7):971-82.
43. Mauskop A, Farkkila M, Hering-Hanit R, Rapoport A, Warner J. Zolmitriptan is effective for the treatment of persistent and recurrent migraine headache. *Current Medical Research and Opinion*. 1999;15(4):282-9.
44. Mei D, Ferraro D, Zelano G, Capuano A, Vollono C, Gabriele C, et al. Topiramate and triptans revert chronic migraine with medication overuse to episodic migraine. *Clinical Neuropharmacology*. 2006;29(5):269-75.
45. Mitsikostas DD, Vikelis M, Kodounis A, Zaglis D, Xifaras M, Doitsini S, et al. Migraine recurrence is not associated with depressive or anxiety symptoms. Results of a randomized controlled trial. *Cephalalgia*. 2010;30(6):690-5.
46. Padma MV, Jain S, Maheshwari MC, Misra S, Karak B, Singh AK, et al. Efficacy and tolerability of oral Sumatriptan in Indian patients with acute migraine; a multicentre study. *Neurology India*. 1998;46(2):105-8.

47. Pascual J, Bussone G, Hernandez JF, Allen C, Vrijens F, Patel K, et al. Comparison of preference for rizatriptan 10-mg wafer versus sumatriptan 50-mg tablet in migraine. *European Neurology*. 2001;45(4):275-83.
48. Pini LA, Guerzoni S, Cainazzo M, Ciccarese M, Prudeniano MP, Livrea P. Comparison of tolerability and efficacy of a combination of paracetamol + caffeine and sumatriptan in the treatment of migraine attack: a randomized, double-blind, double-dummy, cross-over study. *J headache pain*. 2012;13(8):669-75.
49. Rapoport AM, Ramadan NM, Adelman JU, Mathew NT, Elkind AH, Kudrow DB, et al. Optimizing the dose of zolmitriptan (Zomig, 311C90) for the acute treatment of migraine. A multicenter, double-blind, placebo-controlled, dose range-finding study. The 017 Clinical Trial Study Group. *Neurology*. 1997;49(5):1210-8.
50. Rapoport AM, Visser WH, Cutler NR, Alderton CJ, Paulsgrove LA, Davis RL, et al. Oral sumatriptan in preventing headache recurrence after treatment of migraine attacks with subcutaneous sumatriptan. *Neurology*. 1995;45(8):1505-9.
51. Rederich G, Rapoport A, Cutler N, Hazelrigg R, Jamerson B. Oral sumatriptan for the long-term treatment of migraine: clinical findings. *Neurology*. 1995;45(8 Suppl 7):S15-S20.
52. Russell MB, Holm-Thomsen OE, Rishoj NM, Cleal A, Pilgrim AJ, Olesen J. A randomized double-blind placebo-controlled crossover study of subcutaneous sumatriptan in general practice. *Cephalalgia*. 1994;14(4):291-6.
53. Ryan, Jr., Diamond S, Giammarco RAM, Aurora SK, Reed RC, Fletcher PE. Efficacy of zolmitriptan at early time-points for the acute treatment of migraine and treatment of recurrence: a randomised, placebo-controlled trial. *CNS Drugs*. 2000;13(3):215-26.
54. Ryan RE, Elkind A, Goldstein J. Twenty-four-hour effectiveness of BMS 180048 in the acute treatment of migraine headaches. *Headache*. 1997;37(4):245-8.
55. Salonen R, Ashford EA, Gibbs M, Hassani H. Patient preference for oral sumatriptan 25 mg, 50 mg, or 100 mg in the acute treatment of migraine: a double-blind, randomized, crossover study. Sumatriptan Tablets S2CM11 Study Group. *International Journal of Clinical Practice, Supplement*. 1999;105:16-24.
56. Santanello NC, Polis AB, Hartmaier SL, Kramer MS, Block GA, Silberstein SD. Improvement in migraine-specific quality of life in a clinical trial of rizatriptan. *Cephalalgia*. 1997;17(8):867-72.
57. Savi L, Omboni S, Lisotto C, Sances G, Zanchin G, Ferrari MD. Efficacy of frovatriptan in the acute treatment of menstrually-related migraine: Analysis of a double-blind, Randomized, Multicenter, Comparative study vs. Rizatriptan. *Cephalalgia*. 2011;31 Suppl 1:77-8.
58. Savi L, Omboni S, Lisotto C, Zanchin G, Ferrari MD, Zava D, et al. Efficacy of frovatriptan in the acute treatment of menstrually related migraine: analysis of a double-blind, randomized, cross-over, multicenter, Italian, comparative study versus rizatriptan. *J headache pain*. 2011;12(6):609-15.
59. Savi L, Omboni S, Lisotto C, Zanchin G, Ferrari MD, Zava D, et al. A double-blind, randomized, multicenter, Italian study of frovatriptan versus rizatriptan for the acute treatment of migraine. *J headache pain*. 2011;12(2):219-26.
60. Schoenen J, Pascual J, Rasmussen S, Sun W, Sikes C, Hettiarachchi J. Patient preference for eletriptan 80 mg versus subcutaneous sumatriptan 6 mg: results of a crossover study in patients who have recently used subcutaneous sumatriptan. *European Journal of Neurology*. 2005;12(2):108-17.
61. Seeburger JL, Cady RK, Winner P, MacGregor A, Valade D, Ge Y, et al. Rizatriptan for treatment of acute migraine in patients taking topiramate for migraine prophylaxis. *Headache*. 2012;52(1):57-67.

62. Seeburger JL, Taylor F, Newman L, Friedman D, Ge YJ, Zhang Y, et al. Efficacy and tolerability of rizatriptan for the treatment of acute migraine in sumatriptan non-responders. HeadacheConference: 52nd Annual Scientific Meeting of the American Headache Society Los Angeles, CA United StatesConference Start: 20100624 Conference End: 20100627Conference Publication: (varpagings)50 ()(pp 74), 2010Date of Publication: Augus. 2010.
63. Seeburger JL, Taylor FR, Friedman D, Newman L, Ge Y, Zhang Y, et al. Efficacy and tolerability of rizatriptan for the treatment of acute migraine in sumatriptan non-responders. Cephalalgia. 2011;31(7):786-96.
64. Stronks DL, Tulen JH, Bussmann HB, Mulder LJ, Passchier J. Effects of naratriptan versus naproxen on daily functioning in the acute treatment of migraine: a randomized, double-blind, double-dummy, crossover study. Headache. 2003;43(8):845-52.
65. Touchon J, Bertin L, Pilgrim AJ, Ashford E, Bes A. A comparison of subcutaneous sumatriptan and dihydroergotamine nasal spray in the acute treatment of migraine. Neurology. 1996;47(2):361-5.
66. Tuchman M, Hee A, Emeribe U, Silberstein S. Efficacy and tolerability of zolmitriptan oral tablet in the acute treatment of menstrual migraine. CNS Drugs. 2006;20(12):1019-26.
67. Tullo V, Allais G, Curone M, Ferrari MD, Omboni S, Benedetto C, et al. Frovatriptan versus zolmitriptan for the acute treatment of migraine with aura: a subgroup analysis of a double-blind, randomized, multicenter, Italian study. Neurological Sciences. 2012;33 Suppl 1:S61-S4.
68. Tullo V, Allais G, Ferrari MD, Curone M, Mea E, Omboni S, et al. Frovatriptan versus zolmitriptan for the acute treatment of migraine: a double-blind, randomized, multicenter, Italian study. Neurological Sciences. 2010;31 Suppl 1:S51-S4.
69. Vollono C, Capuano A, Mei D, Ferraro D, Pierguidi L, Evangelista M, et al. Multiple attack study on the available triptans in Italy versus placebo. European Journal of Neurology. 2005;12(7):557-63.

Excluded Studies n = 210

1. A placebo-controlled study of intranasal sumatriptan for the acute treatment of migraine. The Finnish Sumatriptan Group and the Cardiovascular Clinical Research Group. European Neurology. 1991;31(5):332-8.
2. Treatment of acute cluster headache with sumatriptan. The Sumatriptan Cluster Headache Study Group. New England Journal of Medicine. 1991;325(5):322-6.
3. A study comparing the efficiency, safety and tolerability of oral sumatriptan 25, 50 and 100 mg doses in the acute treatment of migraine [abstract]. European Journal of Neurology. 1996;3(Suppl 5):149-50.
4. The long-term tolerability and efficacy of oral zolmitriptan (Zomig, 311C90) in the acute treatment of migraine. An international study. The International 311C90 Long-term Study Group. Headache. 1998;38(3):173-83.
5. Sumatriptan + naproxen: Better than either alone for acute migraine? Journal of Family Practice. 2007;56(7):536.
6. Akpunonu BE, Mutgi AB, Federman DJ, Volinsky FG, Brickman K, Davis RL, et al. Subcutaneous sumatriptan for treatment of acute migraine in patients admitted to the emergency department: a multicenter study. Annals of Emergency Medicine. 1995;25(4):464-9.
7. Allais G, Acuto G, Benedetto C, D'Andrea G, Grazi L, Manzoni GC, et al. Evolution of migraine-associated symptoms in menstrually related migraine following symptomatic treatment with almotriptan. Neurological Sciences. 2010;31 Suppl 1:S115-9, 2010 Jun.:9.

8. Allais G, D'Andrea G, Moschiano F, d'Onofrio F, Valguarnera F, Manzoni G, et al. A randomized, prospective, cross-over, double blind, placebo-controlled multicentre study to assess the efficacy and tolerability of almotriptan 12.5 mg in menstrually-related migraine. *Cephalalgia*. 2009;29:13.
9. Allais G, Tullo V, Benedetto C, Zava D, Omboni S, Bussone G. Efficacy of frovatriptan in the acute treatment of menstrually related migraine: analysis of a double-blind, randomized, multicenter, Italian, comparative study versus zolmitriptan. *Neurological Sciences*. 2011;32 Suppl 1:S99-S104.
10. Allais G, Tullo V, Omboni S, Benedetto C, Sances G, Zava D, et al. Efficacy of frovatriptan versus other triptans in the acute treatment of menstrual migraine: pooled analysis of three double-blind, randomized, crossover, multicenter studies. *Neurological Sciences*. 2012;33 Suppl 1:S65-S9.
11. Anon. Treximet in acute migraine headache: assessing cognitive function. *Clinicaltrials.gov* [www.clinicaltrials.gov]. 2009.
12. Aurora SK, Barrodale PM, McDonald SA, Jakubowski M, Burstein R. Revisiting the efficacy of sumatriptan therapy during the aura phase of migraine. *Headache*. 2009;49(7):1001-4.
13. Azimova I, Tabeeva GR. [Trimigren in stopping migraine attacks: an open prospective multicenter comparative study of rectal suppository and tablet forms of sumatriptan]. *Zhurnal nevrologii i psikiatrii imeni SSKorsakova / Ministerstvo zdravookhraneniia i meditsinsko? promyshlennosti Rossi?sko? Federatsii, Vserossi?skoe obshchestvo nevrologov [i] Vserossi?skoe obshchestvo psikiatrov*. 2009;109(12):71-5.
14. Bakhshayesh B, Seyed Saadat SM, Rezanian K, Hatamian H, Hossieninezhad M. A randomized open-label study of sodium valproate vs sumatriptan and metoclopramide for prolonged migraine headache. *American Journal of Emergency Medicine*. 2013;31(3):540-4.
15. Banks JW, Smith TR, Nicholson RA. A combination of metoclopramide and/or caffeine does not improve the efficacy of frovatriptan in the acute treatment of migraine. *Cephalalgia* Conference: 14th Congress of the International Headache Society Philadelphia, PA United States Conference Start: 20090910 Conference End: 20090913 Conference Publication: (varpagings)29 ()(pp 13-14), 2009 Date of Publication: October 20. 2009.
16. Bell CF, Foley KA, Barlas S, Solomon G, Hu XH. Time to pain freedom and onset of pain relief with rizatriptan 10 mg and prescription usual-care oral medications in the acute treatment of migraine headaches: A multicenter, prospective, open-label, two-attack, crossover study. *Clinical Therapeutics*. 2006;28(6):872-80.
17. Berges A, Walls C, Lener SE, McDonald SA. Pharmacokinetics and tolerability of sumatriptan after single-dose administration of a fixed-dose combination tablet of sumatriptan/naproxen sodium 85/500 mg followed two hours later by subcutaneous sumatriptan 4- or 6-mg injection: a randomized, open-label, three-period crossover study in healthy volunteers. *Clinical Therapeutics*. 2010;32(6):1165-77.
18. Bertin L, Brion N, Farkkila M, Gobel H, Wessely P. A dose-defining study of sumatriptan suppositories in the acute treatment of migraine. *International Journal of Clinical Practice*. 1999;53(8):593-8.
19. Block GA, Goldstein J, Polis A, Reines SA, Smith ME. Efficacy and safety of rizatriptan versus standard care during long-term treatment for migraine. *Rizatriptan Multicenter Study Groups. Headache*. 1998;38(10):764-71.
20. Block GA, Smith M, Jiang K, Reines S, Teall J. Rizatriptan (MK-0462) for the acute treatment of migraine and migraine recurrence [abstract]. *Neurology*. 1997;48(3):A68.
21. Boureau F, Chazot G, Emile J. Sumatriptan vs usual acute treatment of migraine [abstract]. *Canadian Journal of Neurological Sciences*. 1993;20 Suppl 4.

22. Brauneis S, Marzano M, Collini S, Occhigrossi F, Pinto G. [The administration of sumatriptan in the treatment of migraine and cluster headache.]. *Confin Cephalalgica*. 1994;3(4):159-64.
23. Burke R, Pwebster C, Laurenza A, Asgharnejad M. Efficacy of sumatriptan injection for the acute treatment of migraine in a primarily non-caucasian group of patients. *Functional Neurology*. 1998;2(13):182.
24. Burke-Ramirez P, Asgharnejad M, Webster C, Davis R, Laurenza A. Efficacy and tolerability of subcutaneous sumatriptan for acute migraine: a comparison between ethnic groups. *Headache*. 2001;41(9):873-82.
25. Burkiewicz JS, Chan JD, Alldredge BK. Eletriptan: Serotonin 5-HT(1B/1D) receptor agonist for the acute treatment of migraine. *Formulary*. 2000;35(2):129-41.
26. Bussone G, D'Amico D, McCarroll KA, Gerth W, Lines CR. Restoring migraine sufferers' ability to function normally: a comparison of rizatriptan and other triptans in randomized trials. *European Neurology*. 2002;48(3):172-7.
27. Cabanas A, Rodriguez R, Rosado F, Cruz A. Subcutaneous sumatriptan comparative study versus placebo in migraine attacks. *Journal of the Neurological Sciences*. 1997;150 Suppl:S303.
28. Cabarrocas X, Almotriptan Study G. Efficacy and tolerability of subcutaneous almotriptan for the treatment of acute migraine: a randomized, double-blind, parallel-group, dose-finding study. *Clinical Therapeutics*. 2001;23(11):1867-75.
29. Cady R, Sheftell F, Silberstein S, Derosier FJ, Ruoff G, Krishen A, et al. Rescue medication use in a crossover study to evaluate efficacy of a single fixed-dose tablet of sumatriptan and naproxen sodium (sumaRT/Nap) versus butalbital-containing combination medication (BCM) and placebo (PLA) for migraine headache. *HeadacheConference: 52nd Annual Scientific Meeting of the American Headache Society Los Angeles, CA United StatesConference Start: 20100624 Conference End: 20100627Conference Publication: (varpagings)50 ()(pp 10-11), 2010Date of Publication: Au. 2010*.
30. Cady RC, Ryan R, Jhingran P, Pait G, Watson C, Batenhorst A. Sumatriptan injection reduces productivity loss during a migraine attack: results of a double-blind, placebo-controlled trial. *Neurology*. 1997;48(3):A121.
31. Cady RK, Dexter J, Sargent JD, Galer B. Sumatriptan for repeated episodes of migraine. *Annals of Internal Medicine*. 1993;119(Suppl 3):72.
32. Cady RK, Dexter J, Sargent JD, Markley H, Osterhaus JT, Webster CJ. Efficacy of subcutaneous sumatriptan in repeated episodes of migraine. *Neurology*. 1993;43(7):1363-8.
33. Cady RK, Diamond ML, Diamond MP, Ballard JE, Lener ME, Dorner DP, et al. Sumatriptan-naproxen sodium for menstrual migraine and dysmenorrhea: satisfaction, productivity, and functional disability outcomes. *Headache*. 2011;51(5):664-73.
34. Cady RK, Freitag FG, Mathew NT, Elkind AH, Mao L, Fisher AC, et al. Allodynia-associated symptoms, pain intensity and time to treatment: predicting treatment response in acute migraine intervention. *Headache*. 2009;49(3):350-63.
35. Cady RK, Lipton RB, Hall C, Stewart WF, O'Quinn S, Gutterman D. Treatment of mild headache in disabled migraine sufferers: results of the Spectrum Study. *Headache*. 2000;40(10):792-7.
36. Cady RK, Rubino J, Crummett D, Littlejohn TW, III. Oral sumatriptan in the treatment of recurrent headache. *Archives of Family Medicine*. 1994;3(9):766-72.
37. Cady RK, Voirin J, Farmer K, Browning R, Beach ME, Tarrasch J. Two center, randomized pilot study of migraine prophylaxis comparing paradigms using pre-emptive frovatriptan or daily topiramate: research and clinical implications. *Headache*. 2012;52(5):749-64.
38. Cady RK, Wendt JK, Kirchner JR, Sargent JD, Rothrock JF, Skaggs H, Jr. Treatment of acute migraine with subcutaneous sumatriptan. *JAMA*. 1991;265(21):2831-5.

39. Campbell J, Harper S, Hu X. Acute migraine therapy with frovatriptan vs. Sumatriptan: Comparison based on sustained pain-free response with no adverse events. Cephalalgia Conference: 14th Congress of the International Headache Society Philadelphia, PA United States Conference Start: 20090910 Conference End: 20090913 Conference Publication: (varpagings)29 ()(pp 18-19), 2009 Date of Publication: October 20. 2009.
40. Centonze V, Polito MB, Bari M, Fabbri L, Cassiano MA, Bassi A, et al. [Evaluation of the efficacy of oral sumatriptan in the management of migraine attacks. Clinical results]. La Clinica terapeutica. 1995;146(11):721-8.
41. Cerritelli F, Emanuele C, Marcello DV, Luca M, Rina GL, Gabriella M. Is osteopathic manipulative treatment effective in migraine? International Journal of Osteopathic Medicine. 16(1):e15-e6.
42. Chatterjee A, Almas M. Migraine attacks during menses: Efficacy of eletriptan and relationship to recurrence after response. Neurology Conference: 64th American Academy of Neurology Annual Meeting New Orleans, LA United States Conference Start: 20120421 Conference End: 20120428 Conference Publication: (varpagings)78 (1 Meeting Abstract) , 2012 Date of Publication: 22 Apr. 2012(var.pagings).
43. Chen J, Jiang XG, Jiang WM, Gao XL, Mei N. Intranasal absorption of rizatriptan--in vivo pharmacokinetics and bioavailability study in humans. Pharmazie. 2005;60(1):39-41.
44. Conner SJ, Rideout S. What are the best therapies for acute migraine in pregnancy? Journal of Family Practice. 2005;54(11):992+5.
45. Cortelli P, Allais G, Tullo V, Benedetto C, Zava D, Omboni S, et al. Frovatriptan versus other triptans in the acute treatment of migraine: pooled analysis of three double-blind, randomized, cross-over, multicenter, Italian studies. Neurological Sciences. 2011;32 Suppl 1:S95-8, 2011 May.:8.
46. Couch JR, Jr., Saper J, Meloche JP. Treatment of migraine with BMS180048: response at 2 hours. North American BMS180048 Study Group. Headache. 1996;36(9):523-30.
47. Creac'h C, Frappe P, Cancade M, Laurent B, Peyron R, Demarquay G, et al. In-patient versus out-patient withdrawal programmes for medication overuse headache: A 2-year randomized trial. Cephalalgia. 2011;31(11):1189-98.
48. Cutler N, Mushet GR, Davis R, Clements B, Whitcher L. Oral sumatriptan for the acute treatment of migraine: evaluation of three dosage strengths. Neurology. 1995;45(8 Suppl 7):S5-S9.
49. Cutler NR, Claghorn J, Sramek JJ, Block G, Panebianco D, Cheng H, et al. Pilot study of MK-462 in migraine. Cephalalgia. 1996;16(2):113-6.
50. Cutler NR, Hussey EK, Sramek JJ, Clements BD, Paulsgrove LA, Busch MA, et al. Oral sumatriptan in pharmacokinetics in the migrainous state. Cephalalgia. 1991;11(Suppl 11):222-3.
51. Cutler NR, Jhee SS, Majumdar AK, McLaughlin D, Brucker MJ, Carides AD, et al. Pharmacokinetics of rizatriptan tablets during and between migraine attacks. Headache. 1999;39(4):264-9.
52. Cutler NR, Salazar DE, Jhee SS, Fulmor IE, Ford N, Smith RA, et al. Pharmacokinetics and pharmacodynamics of avitriptan in patients with migraine after oral dosing. Headache. 1998;38(6):446-52.
53. Dahlof C, Edwards C, Toth A. Sumatriptan injection is superior to placebo in the acute treatment of migraine--with regard to both efficacy and general well-being. Cephalalgia. 1992;12(4):214-20.
54. Dahlof C, Hogenhuis L, Olesen J, Petit H, Ribbat J, Schoenen J, et al. Early clinical experience with subcutaneous naratriptan in the acute treatment of migraine: a dose-ranging study. European Journal of Neurology. 1998;5(5):469-77.

55. Dahlof C, Winter P, Whitehouse H, Hassani H. Randomized, double-blind, placebo-controlled comparison of oral naratriptan and oral sumatriptan in the acute treatment of migraine [abstract]. *Neurology*. 1997;48(3):A85-A6.
56. Davies GM, Santanello N, Gerth W, Lerner D, Block GA. Validation of a migraine work and productivity loss questionnaire for use in migraine studies. *Cephalalgia*. 1999;19(5):497-502.
57. Davies GM, Santanello N, Lipton R. Determinants of patient satisfaction with migraine therapy. *Cephalalgia*. 2000;20(6):554-60.
58. de Hoon JN, Willigers JM, Troost J, Struijker-Boudier HA, Van Bortel LM. Vascular effects of 5-HT_{1B/1D}-receptor agonists in patients with migraine headaches. *Clinical Pharmacology and Therapeutics*. 2000;68(4):418-26.
59. de Tommaso M, Guido M, Libro G, Scirucchio V, Puca F. Zolmitriptan reverses blink reflex changes induced during the migraine attack in humans. *Neuroscience Letters*. 2000;289(1):57-60.
60. Derosier FJ, Sheftell F, Silberstein S, Cady R, Ruoff G, Krishen A, et al. Crossover study to evaluate the efficacy of a single fixed-dose tablet of sumatriptan and naproxen sodium (SumaRT/Nap) versus butalbital-containing combination medication (BCM) and placebo (PLA) for migraine headache. HeadacheConference: 52nd Annual Scientific Meeting of the American Headache Society Los Angeles, CA United StatesConference Start: 20100624 Conference End: 20100627Conference Publication: (varpagings)50 ()(pp 9-10), 2010Date of Publication: Aug. 2010.
61. Derosier FJ, Thompson AH, Adams BE, Goodman DK. The effect of sumatriptan 85mg formulated with RT technology/naproxen sodium 500mg (sumaRT/Nap), sumatriptan, and naproxen on blood pressure when administered intermittently for six months for the acute treatment of migraine. HeadacheConference: 52nd Annual Scientific Meeting of the American Headache Society Los Angeles, CA United StatesConference Start: 20100624 Conference End: 20100627Conference Publication: (varpagings)50 ()(pp 20), 2010Date of Publication: Augus. 2010.
62. Diamond ML, Cady RK, Mao L, Biondi DM, Finlayson G, Greenberg SJ, et al. Characteristics of migraine attacks and responses to almotriptan treatment: a comparison of menstrually related and nonmenstrually related migraines. *Headache*. 2008;48(2):248-58.
63. Diaz-Insa S, Goadsby PJ, Zanchin G, Fortea J, Falques M, Vila C. The impact of allodynia on the efficacy of almotriptan when given early in migraine: data from the "Act when mild" study. *International Journal of Neuroscience*.121(12):655-61.
64. Diener HC. Efficacy and safety of intravenous acetylsalicylic acid lysinate compared to subcutaneous sumatriptan and parenteral placebo in the acute treatment of migraine. A double-blind, double-dummy, randomized, multicenter, parallel group study. The ASASUMAMIG Study Group. *Cephalalgia*. 1999;19(6):581-8.
65. Diener HC, Tfelt-Hansen P, de BF, Ferrari MD, Olesen J, Dahlof C, et al. The efficacy and safety of sc alniditan vs. sc sumatriptan in the acute treatment of migraine: a randomized, double-blind, placebo-controlled trial. *Cephalalgia*. 2001;21(6):672-9.
66. Diez T, Frank A. Assessment of response consistency to oral sumatriptan in migraine attacks. *Journal of the Neurological Sciences*. 1997;150 Suppl.
67. Djupesland PG, Docekal P, Czech Migraine Investigators G. Intranasal sumatriptan powder delivered by a novel breath-actuated bi-directional device for the acute treatment of migraine: A randomised, placebo-controlled study. *Cephalalgia*. 2010;30(8):933-42.
68. Dodick DW, Kost J, Assaid C, Lines C, Ho TW. Sustained pain freedom and no adverse events as an endpoint in clinical trials of acute migraine treatments: application to patient-level data from a trial of the CGRP receptor antagonist, telcagepant, and zolmitriptan. *Cephalalgia*. 2011;31(3):296-300.

69. Dodick DW, Lipton RB, Goadsby PJ, Tfelt-Hansen P, Ferrari MD, Diener HC, et al. Predictors of migraine headache recurrence: a pooled analysis from the eletriptan database. *Headache*. 2008;48(2):184-93.
70. Duquesnoy C, Mamet JP, Sumner D, Fuseau E. Comparative clinical pharmacokinetics of single doses of sumatriptan following subcutaneous, oral, rectal and intranasal administration. *Eur J Pharm Sci*. 1998;6(2):99-104.
71. Durham PL, Vause CV, Derosier F, McDonald S, Cady R, Martin V. Changes in salivary prostaglandin levels during menstrual migraine with associated dysmenorrhea. *Headache*. 50(5):844-51.
72. Edwards KR, Norton J, Behnke M. Comparison of intravenous valproate versus intramuscular dihydroergotamine and metoclopramide for acute treatment of migraine headache. *Headache*. 2001;41(10):976-80.
73. Elkind A, Laurenza A, Austin R, Asgharnejad M. Efficacy and tolerability of naratriptan tablets in the treatment of migraine: results of a double-blind, placebo-controlled, parallel-group trial [abstract]. *Journal of the Neurological Sciences*. 1997;150(Suppl):S262.
74. Elkind A, McDaris HL, Satin L, Keywood C. The cardiovascular safety of frovatriptan during a migraine attack in patients with known or at high risk of coronary artery disease. *European Journal of Neurology (Abstracts of the 4th Congress of the European Federation of Neurological Sciences, September 7-11, Lisbon, Portugal 1999)*. 1999;6(Suppl 3):141.
75. Elkind AH, Satin LZ, Nila A, Keywood C. Frovatriptan use in migraineurs with or at high risk of coronary artery disease. *Headache*. 2004;44(5):403-10.
76. Ensink FB. Subcutaneous sumatriptan in the acute treatment of migraine. *Journal of Neurology, Supplement*. 1991;238(1):S66-S9.
77. Farmer KU, Cady RK, Derosier FJ, Sheftell FD, Silberstein SD, Ruoff G, et al. Cognitive effects of sumatriptan-naproxen, a butalbital-containing medication, and placebo in a 3-way, double-blind, placebo-controlled crossover study. *HeadacheConference: 54th Annual Scientific Meeting of the American Headache Society Los Angeles, CA United StatesConference Start: 20120621 Conference End: 20120624Conference Publication: (varpagings)52 (5) (pp 874), 2012Date of Publication: 2012(var.pagings):874*.
78. Ferrari MD. Subcutaneous sumatriptan in the acute treatment of migraine. *Can J Neurological Sci*. 1994;20 S:S37.
79. Ferrari MD, Gijsman H, Block GA, Kramer MS, Matzura-Wolfe D, Teall J, et al. Double-blind, placebo-controlled, dose-finding study of rizatriptan (MK-0462) in acute migraine. *Functional Neurology*. 1996;2/3(11):149.
80. Ferrari MD, James MH, Bates D, Pilgrim A, Ashford E, Anderson BA, et al. Oral sumatriptan: effect of a second dose, and incidence and treatment of headache recurrences. *Cephalalgia*. 1994;14(5):330-8.
81. Findley LJ, Abbas A, Bayliss E. The acute treatment of migraine with aura with sumatriptan. *Cephalalgia*. 1991;11(Suppl 11):226-7.
82. Fleishaker JC, McEnroe JD, Azie NE, Francom SF, Carel BJ. Cardiovascular effect of almotriptan in treated hypertensive patients. *Clinical Pharmacology and Therapeutics*. 2002;71(3):169-75.
83. Foldes EG. Comparative treatment study of migraine headache. *Int J Clin Pharmacol*. 1972;6(1):60-6.

84. Francesco C, Emanuele C, Di VM, Gabriella M, Rina GL, Vincenzo C, et al. Is Osteopathic manipulative treatment effective in migraine? European Journal of Integrative MedicineConference: 5th European Congress for Integrative Medicine Florence ItalyConference Start: 20120921 Conference End: 20120922Conference Publication: (varpagings)4 ()(pp 33-34), 2012Date of Publication: Sep. 2012.
85. Freitag F, Smith T, Mathew N, Rupnow M, Greenberg S, Mao L, et al. Effect of early intervention with almotriptan vs placebo on migraine-associated functional disability: results from the AEGIS Trial. *Headache*. 2008;48(3):341-54.
86. Freitag FG, Finlayson G, Rapoport AM, Elkind AH, Diamond ML, Unger JR, et al. Effect of pain intensity and time to administration on responsiveness to almotriptan: results from AXERT 12.5 mg Time Versus Intensity Migraine Study (AIMS). *Headache*. 2007;47(4):519-30.
87. Friedman BW, Solorzano C, Norton J, Adewumni V, Campbell CM, Esses D, et al. A randomized controlled trial of a comprehensive migraine intervention prior to discharge from an emergency department. *Academic Emergency Medicine*. 2012;19(10):1151-7.
88. Furman JM, Marcus DA, Balaban CD. Rizatriptan reduces vestibular-induced motion sickness in migraineurs. *J headache pain*. 2011;12(1):81-8.
89. Fuseau E, Petricoul O, Sabin A, Pereira A, O'Quinn S, Thein S, et al. Effect of encapsulation on absorption of sumatriptan tablets: data from healthy volunteers and patients during a migraine. *Clinical Therapeutics*. 2001;23(2):242-51.
90. Gawel M, Aschoff J, May A, Charlesworth BR, Group RS. Treatment satisfaction with zolmitriptan nasal spray for migraine in a real life setting: results from phase two of the REALIZE study. *J headache pain*. 2005;6(5):405-11.
91. Geraud G, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache*. 2002;42 Suppl 2:S93-S9.
92. Gerth WC, Dasbach EJ, Dahlof C. Extrapolation to europe of the productivity cost benefit of maxalt 10 mg vs. Usual migraine therapy. *European Journal of Neurology (Abstracts of the 4th Congress of the European Federation of Neurological Sciences, September 7 11, Lisbon, Portugal 1999)*. 1999;6(Suppl 3):108.
93. Gerth WC, Ruggles KH, Stark SR, Davies GM, Santanello NC. Improvement in health-related quality of life with rizatriptan 10mg compared with standard migraine therapy. *Clinical Drug Investigation*. 2001;21(12):853-60.
94. Gnechchi-Ruscione T, Bernard X, Pierre P, Anderson D, Legg N, Enahoro H, et al. Effect of naratriptan on myocardial blood flow and coronary vasodilator reserve in migraineurs. *Neurology*. 2000;55(1):95-9.
95. Gobel H, Krapat S, Dworschak M, Heuss D, Ensink FB, Soyka D. Exteroceptive suppression of temporalis muscle activity during migraine attack and migraine interval before and after treatment with sumatriptan. *Cephalalgia*. 1994;14(2):143-8.
96. Gobel H, Krapat S, Soyka D. Effect of sumatriptan on psychological status during migraine attack and migraine interval [abstract]. 1993 Meeting of the European Federation of Neurological Societies (Berlin, Dec 1993). 1993.
97. Goldstein J, Keywood C, Hutchison J. 24-hour migraine recurrence was low during treatment with frovatriptan. *European Journal of Neurology (Abstracts of the 4th Congress of the European Federation of Neurological Sciences, September 7 11, Lisbon, Portugal 1999)*. 1999;6(Suppl 3):139.

98. Goldstein J, Pugach N, Smith T, Nett R, Angelov AS, Pierce MW. Acute anti-migraine efficacy and tolerability of Zelrix, a novel iontophoretic transdermal patch of sumatriptan. CephalalgiaConference: 14th Congress of the International Headache Society Philadelphia, PA United StatesConference Start: 20090910 Conference End: 20090913Conference Publication: (varpagings)29 ()(pp 20), 2009Date of Publication: October 2009. 2009.
99. Gonz lez-Espinosa LE, Gmez-Viera N, Olivera-Leal I, Reyes-Lorente R. [Treatment of acute attack of migraine with sumatriptan]. Revista de Neurologia. 1997;25(147):1672-5.
100. Gross ML, Kay J, Turner AM, Hallett K, Cleal AL, Hassani H. Sumatriptan in acute migraine using a novel cartridge system self-injector. United Kingdom Study Group. Headache. 1994;34(10):559-63.
101. Havanka H, Dahlof C, Pop PHM, Diener HC, Winter P, Whitehouse H, et al. Efficacy of naratriptan tablets in the acute treatment of migraine: A dose-ranging study. Clinical Therapeutics. 2000;22(8):970-80.
102. Ho T, Connor K, Dahlof C, Loeys T, Jones C, Giezek H, et al. Assessment of the long term safety and tolerability of telcagepant for the intermittent treatment of acute migraine: A double-blind, active-controlled study. CephalalgiaConference: 14th Congress of the International Headache Society Philadelphia, PA United StatesConference Start: 20090910 Conference End: 20090913Conference Publication: (varpagings)29 ()(pp 12), 2009Date of Publication: October 2009. 2009.
103. Ho TW. Clinical profile of the novel oral CGRP receptor antagonist telcagepant for the acute treatment of migraine in phase 3 studies. Journal of the Neurological SciencesConference: 19th World Congress of Neurology Bangkok ThailandConference Start: 20091024 Conference End: 20091030Conference Publication: (varpagings)285 ()(pp S149-S150), 2009Date of Publication: October 2009. 2009.
104. Ho TW, Olesen J, Dodick DW, Kost J, Lines C, Ferrari MD. Antimigraine efficacy of telcagepant based on patient's historical triptan response. Headache. 2011;51(1):64-72.
105. Houghton LA, Foster JM, Whorwell PJ, Morris J, Fowler P. Is chest pain after sumatriptan oesophageal in origin? Lancet. 1994;344(8928):985-6.
106. Jackson NC. Clinical measures of efficacy, safety and tolerability for the acute treatment of migraine: a comparison of eletriptan (20-80mg), sumatriptan (100mg) and placebo [abstract]. Neurology. 1998;50(4 Suppl 4):A376.
107. Jakubowski M, Levy D, Goor-Aryeh I, Collins B, Bajwa Z, Burstein R. Terminating migraine with allodynia and ongoing central sensitization using parenteral administration of COX1/COX2 inhibitors. Headache. 2005;45(7):850-61.
108. Jamieson D, Cutrer FM, Goldstein J, Dayno J, Hu XH. Real-world experiences in migraine therapy with rizatriptan. Headache. 2003;43(3):223-30.
109. Jhee SS, Salazar DE, Ford NF, Fulmor IE, Sramek JJ, Cutler NR. A double-blind, randomized, crossover assessment of blood pressure following administration of avatriptan, sumatriptan, or placebo to patients with mild to moderate hypertension. Cephalalgia. 1999;19(2):95-9.
110. Kalita J, Yadav RK, Misra UK. A comparison of migraine patients with and without allodynic symptoms. Clinical Journal of Pain. 2009;25(8):696-8.
111. Kaube H, May A, Pfaffenrath V. Sumatriptan. BMJ (Clinical research ed). 1994;308(6943):1573-4.
112. Klassen A, Webster C, Laurenza A, Austin R, Asgharnejad M. Naratriptan tablets are effective and well-tolerated in the acute treatment of migraine: results of a double-blind placebo-controlled parallel-group trial [abstract]. Neurology. 1997;48(3):A66-A7.

113. Kramer MS, Matzura-Wolf D, Getson A, Polis A, Reines SA. Placebo-controlled double-blind study of Rizatriptan in multiple attacks of acute migraine [abstract]. *Neurology*. 1997;48(3):A68-A9.
114. Krusz JC, Nett R. Naratriptan prevents migraine recurrence after initial relief with sumatriptan. *Jns*. 2001;187(Suppl 1).
115. Krymchantowski AV. Naproxen sodium decreases migraine recurrence when administered with sumatriptan. *Arquivos de Neuro-Psiquiatria*. 2000;58(2B):428-30.
116. Krymchantowski AV, Barbosa JS. Rizatriptan combined with rofecoxib vs. rizatriptan for the acute treatment of migraine: an open label pilot study. *Cephalalgia*. 2002;22(4):309-12.
117. Krymchantowski AV, Bigal ME. Rizatriptan versus rizatriptan plus rofecoxib versus rizatriptan plus tolfenamic acid in the acute treatment of migraine. *BMC Neurol*. 2004;4:10, 2004 Jun 28.
118. Krymchantowski AV, Filho PF, Bigal ME. Rizatriptan vs. rizatriptan plus trimebutine for the acute treatment of migraine: a double-blind, randomized, cross-over, placebo-controlled study. *Cephalalgia*. 2006;26(7):871-4.
119. Laloux P, Vakaet A, Monseu G, Jacquy J, Bourgeois P, van der Linden C. Subcutaneous sumatriptan compared with usual acute treatments for migraine: clinical and pharmacoeconomic evaluation. *Acta Neurologica Belgica*. 1998;98(4):332-41.
120. Landy S, DeRossett SE, Rapoport A, Rothrock J, Ames MH, McDonald SA, et al. Two double-blind, multicenter, randomized, placebo-controlled, single-dose studies of sumatriptan/naproxen sodium in the acute treatment of migraine: function, productivity, and satisfaction outcomes. *Medscape General Medicine*. 2007;9(2):53, 2007.
121. Lener S, Richard N, McDonald S, Thompson A, Wentz A. Prior acute treatment of migraine is not a predictive factor of sumatriptan/naproxen sodium (SumaRT/ Nap) response or superiority over the components. *CephalalgiaConference: 14th Congress of the International Headache Society Philadelphia, PA United StatesConference Start: 20090910 Conference End: 20090913Conference Publication: (varpagings)29 ()(pp 23-24), 2009Date of Publication: October 20, 2009*.
122. Limmroth V, May A, Auerbach P, Wosnitza G, Eppe T, Diener HC. Changes in cerebral blood flow velocity after treatment with sumatriptan or placebo and implications for the pathophysiology of migraine. *Journal of the Neurological Sciences*. 1996;138(1-2):60-5.
123. Linde M, Mellberg A, Dahl" f C. Subcutaneous sumatriptan provides symptomatic relief at any pain intensity or time during the migraine attack. *Cephalalgia*. 2006;26(2):113-21.
124. Lipton RB, McDonald SA, Richard NE, Derosier FJ. Evaluation of consistency of adverse events after treatment of multiple attacks with a fixed-dose single tablet of sumatriptan and naproxen sodium (SumaRT/Nap). *CephalalgiaConference: 14th Congress of the International Headache Society Philadelphia, PA United StatesConference Start: 20090910 Conference End: 20090913Conference Publication: (varpagings)29 ()(pp 25), 2009Date of Publication: October 2009, 2009*.
125. Lipton RB, Stewart WF, Stone AM, Lainez MJ, Sawyer JP, Disability in Strategies of Care Study g. Stratified care vs step care strategies for migraine: the Disability in Strategies of Care (DISC) Study: A randomized trial. *JAMA*. 2000;284(20):2599-605.
126. Lloyd DK, Pilgrim AJ. Sumatriptan and recurrence of migraine. *Lancet*. 1992;340(8827):1110.
127. Loder E, Boyle D, Wang L, Bohidar N, Kolodny A, Santanello N, et al. Comparison of preference for rizatriptan 10 mg or sumatriptan 50 mg tablet for the acute treatment of migraine. *Jns*. 2001;187(Suppl 1).
128. Luthringer R, Djupesland PG, Sheldrake CD, Flint A, Boeijsing P, Danjou P, et al. Rapid absorption of sumatriptan powder and effects on glyceryl trinitrate model of headache following intranasal delivery using a novel bi-directional device. *J Pharm Pharmacol*. 2009;61(9):1219-28.

129. MacGregor EA. Migraine during menstruation and the efficacy of oral eletriptan [abstract]. *Neurology*. 1998;50(4 Suppl 4):A377.
130. MacGregor EA, Pawsey SP, Campbell JC, Hu X. Safety and tolerability of frovatriptan in the acute treatment of migraine and prevention of menstrual migraine: results of a new analysis of data from five previously published studies. *Gender Medicine*. 2010;7(2):88-108.
131. Malmberg I. Evaluation of the cost effectiveness of zolmitriptan for the acute treatment of migraine [abstract]. 15th Annual Meeting of the International Society of Technology Assessment in Health Care; 1999 Jun 20-23. 1999:145.
132. Mannix LK, Adelman JU, Goldfarb SD, Von S, Kozma CM. Almotriptan versus sumatriptan in migraine treatment: direct medical costs of managing adverse chest symptoms. *The American Journal of Managed Care*. 2002;8(3 Suppl):S94-101.
133. Martin V, Cady R, Mauskop A, Seidman LS, Rodgers A, Hustad CM, et al. Efficacy of rizatriptan for menstrual migraine in an early intervention model: a prospective subgroup analysis of the rizatriptan TAME (Treat A Migraine Early) studies. *Headache*. 2008;48(2):226-35.
134. Massiou H. A comparison of sumatriptan nasal spray and intranasal dihydroergotamine (DHE) in the acute treatment of migraine. *Functional Neurology*. 1996;2/3(11):151.
135. Mathew NT, Dexter J, Couch J, Flamenbaum W, Goldstein J, Rapoport A, et al. Dose ranging efficacy and safety of subcutaneous sumatriptan in the acute treatment of migraine. US Sumatriptan Research Group. *Archives of Neurology*. 1992;49(12):1271-6.
136. Mathew NT, Kailasam J, Meadors L. Early treatment of migraine with rizatriptan: a placebo-controlled study. *Headache*. 2004;44(7):669-73.
137. Mathew NT, Peykamian M, Laurenza A, Asgharnejad M. Efficacy and tolerability of naratriptan tablets in the treatment of migraine: Results of a double-blind placebo controlled, crossover trial. *Journal of the Neurological Sciences*. 1997;150 Suppl:S35.
138. McGarvey EL. Biologic measures of a placebo response? 152nd Annual Meeting of the American Psychiatric Association Washington DC, USA 15-20 May, 1999. 1999.
139. Melchart D. Acupuncture versus sumatriptan for early treatment of acute migraine attacks - a randomised controlled clinical trial. *Deutsche Zeitschrift Fur Akupunktur*. 2000;43(1):39.
140. Melchart D, Thormaehlen J, Hager S, Liao J, Linde K, Weidenhammer W. Acupuncture versus placebo versus sumatriptan for early treatment of migraine attacks: a randomized controlled trial. *Journal of Internal Medicine*. 2003;253(2):181-8.
141. Menken M. Efficacy and safety of sumatriptan for migraine. *Annals of Internal Medicine*. 1993;118(Suppl 3):70.
142. Meredith JT, Wait S, Brewer KL. A prospective double-blind study of nasal sumatriptan versus IV ketorolac in migraine. *American Journal of Emergency Medicine*. 2003;21(3):173-5.
143. Midelfart E, Winnem M. [Sumatriptan in the treatment of migraine in general practice]. *Tidsskrift for den Norske L'geforening*. 1994;114(29):3430-2.
144. Milton KA, Kleinermans D, Scott N, Cooper JDH. The bioequivalence of standard sumatriptan tablets and two encapsulated forms of sumatriptan. *International Journal of Pharmaceutical Medicine*. 2001;15(1):21-6.
145. Muller T, Lohse L. Efficacy of parecoxib, sumatriptan, and rizatriptan in the treatment of acute migraine attacks. *Clinical Neuropharmacology*. 2011;34(6):206-9.
146. Mushet GR, Cady RK, Baker CC, Clements B, Gutterman DL, Davis R. Efficacy and tolerability of subcutaneous sumatriptan administered using the IMITREX STATdose System. *Clinical Therapeutics*. 1996;18(4):687-99.

147. Mushet GR, Miller D, Clements B, Pait G, Gutterman DL. Impact of sumatriptan on workplace productivity, nonwork activities, and health-related quality of life among hospital employees with migraine. *Headache*. 1996;36(3):137-43.
148. Nett R, Mannix LK, Mueller L, Rodgers A, Hustad CM, Skobieranda F, et al. Rizatriptan efficacy in ICHD-II pure menstrual migraine and menstrually related migraine. *Headache*. 2008;48(8):1194-201.
149. Neuhauser H, Radtke A, von BM, Lempert T. Zolmitriptan for treatment of migrainous vertigo: a pilot randomized placebo-controlled trial. *Neurology*. 2003;60(5):882-3.
150. Ng-Mak DS, Hu XH, Bigal M. Migraine treatment with rizatriptan and almotriptan: a crossover study. *Headache*. 2009;49(5):655-62.
151. Ng-Mak DS, Hu XH, Chen Y, Ma L, Solomon G. Times to pain relief and pain freedom with rizatriptan 10 mg and other oral triptans. *International Journal of Clinical Practice*. 2007;61(7):1091-111.
152. Norman BA, Block GA, Jiang K, Ahrens S. Two-period crossover comparison of rizatriptan 5 mg and 10 mg to sumatriptan 25 mg and 50 mg for the acute treatment of migraine [abstract]. *Neurology*. 1998;50(4 Suppl 4):A341.
153. Onrat E, Kaya K, Demirkirkan K, Ellidokuz H, Celik A, Melek M. The effect of naratriptan on cardiac autonomic function in patients with migraine: a placebo controlled pilot study. *Ceska a Slovenska Neurologie a Neurochirurgie*. 2004;67(4):246-50.
154. O'Quinn S, DeBussey S, Saiers JA. Sumatriptan injection and nasal spray: onset of efficacy in the acute treatment of migraine [abstract]. *Neurology*. 1998;50(4 Suppl 4):A264-A5.
155. O'Quinn S, Jhingran P, Pait DG, Watson C, Batenhorst A. Relationships between productivity and clinical efficacy measures in a double-blind, placebo-controlled trial of sumatriptan in migraine [abstract]. *Neurology*. 1997;48(3):A236-A7.
156. Pascual J, Diener HC. Use of almotriptan in triptan-experienced and triptan-naive patients. *Current Medical Research and Opinion*. 2007;23(10):2433-40.
157. Payne K, Kozma CM, Lawrence BJ. Comparing dihydroergotamine mesylate and sumatriptan in the management of acute migraine. A retrospective cost-efficacy analysis. *Pharmacoeconomics*. 1996;10(1):59-71.
158. Peikert A, Becker WJ, Ashford EA, Dahlof C, Hassani H, Salonen RJ. Sumatriptan nasal spray: a dose-ranging study in the acute treatment of migraine. *European Journal of Neurology*. 1999;6(1):43-9.
159. Perrotta A. [The importance of early symptomatic treatment of the migraine attack]. *Confinia Cephalalgica*. 2006;15(3):83-7.
160. Pilgrim AJ, Lloyd DK. Migraine. *Lancet*. 1992;340(8810):62.
161. Podhorna J, Diener HC, Dahlof C, Habeck J. BI 44370 TA, An oral cgrp antagonist for the acute treatment of migraine attacks: Results: from a phase II study. *Journal of Headache and Pain*. Conference: 2nd European Headache and Migraine Trust International Congress - EHMTIC Nice France Conference Start: 20101028 Conference End: 20101031 Conference Publication: (varpagings)11 ()(pp S4-S5), 2010 Date of Publ. 2010.
162. Pradel FG, Subedi P, Varghese AA, Mullins CD, Weis KA. Does earlier headache response equate to earlier return to functioning in patients suffering from migraine? *Cephalalgia*. 2006;26(4):428-35.
163. Pryse-Phillips W. Oral eletriptan (40-80 mg) versus oral sumatriptan (50-100 mg) for the treatment of acute migraine in sumatriptan-na'ive patients. *European Journal of Neurology (Abstracts of the 4th Congress of the European Federation of Neurological Sciences, September 7 11, Lisbon, Portugal 1999)*. 1999;6(Suppl 3):21.

164. Rapoport AM, Ryan RE, Jr. Speed and duration of antimigraine effects for zolmitriptan in relation to the time of day. *Headache Quarterly*. 2001;12(1):27-31.
165. Reches A. Comparison of the efficacy, safety and tolerability of oral eletriptan and cafergot(r) in the acute treatment of migraine. *European Journal of Neurology (Abstracts of the 4th Congress of the European Federation of Neurological Sciences, September 7 11, Lisbon, Portugal 1999)*. 1999;6(Suppl 3):57.
166. Ricalde OA. DHE-45 and sumatriptan are similarly effective in migraine. *American Family Physician*. 1994;50(8):1777-8.
167. Roon KI, Olesen J, Diener HC, Ellis P, Hettiarachchi J, Poole PH, et al. No acute antimigraine efficacy of CP-122,288, a highly potent inhibitor of neurogenic inflammation: results of two randomized, double-blind, placebo-controlled clinical trials. *Annals of Neurology*. 2000;47(2):238-41.
168. Rothner A, Edwards K, Kerr L, DeBussey S, Asgharnejad M. Efficacy and safety of naratriptan tablets in adolescent migraine [abstract]. *Journal of the Neurological Sciences*. 1997;150(Suppl):S106.
169. Ruoff G, Derosier FJ, Runken MC, Sheftell F, Cady R, Peykamian MA, et al. Health outcomes endpoints in a crossover study of a single fixed-dose tablet of sumatriptan and naproxen sodium vs butalbital-containing combination medications and placebo for migraine headache. *HeadacheConference: 52nd Annual Scientific Meeting of the American Headache Society Los Angeles, CA United StatesConference Start: 20100624 Conference End: 20100627Conference Publication: (varpagings)50 ()(pp 19-20), 2010Date of Publication: Au. 2010*.
170. Russell MB, Holm-Thomsen OE, Nielsen MR, Cleal A, Pilgrim AJ, Olesen J. [Sumatriptan treatment of migraine in general practice. A randomized, double-blind, placebo-controlled cross-over study]. *Ugeskrift for Laeger*. 1995;157(16):2320-3.
171. Saiers J, Jones M, Kane K, Thaventhiran L, O'Quinn S. Naratriptan tablets 2.5 Mg exhibit prolonged action and are well-tolerated in non-severe migraine attacks: data from a comparator study with sumatriptan. *European Journal of Neurology (Abstracts of the 4th Congress of the European Federation of Neurological Sciences, September 7 11, Lisbon, Portugal 1999)*. 1999;6(Suppl 3):105.
172. Sakai F, Diener HC, Ryan R, Poole P. Eletriptan for the acute treatment of migraine: results of bridging a Japanese study to Western clinical trials. *Current Medical Research and Opinion*. 2004;20(3):269-77.
173. Salonen R. Speed of onset of sumatriptan injection, nasal spray, and tablets in the acute treatment of migraine. *Functional Neurology*. 1998;2(13):179.
174. Salonen R, Ashford E, Dahlof C, Dawson R, Gilhus NE, Luben V, et al. Intranasal sumatriptan for the acute treatment of migraine. *International Intranasal Sumatriptan Study Group. Journal of Neurology*. 1994;241(8):463-9.
175. Salonen R, Ashford E, Dahlof C, Dawson R, Gilhus NE, Luben V, et al. Intranasal sumatriptan for the acute treatment of migraine. *Journal of Neurology*. 1994;241(8):463-9.
176. Sang CN, Ramadan NM, Wallihan RG, Chappell AS, Freitag FG, Smith TR, et al. LY293558, a novel AMPA/GluR5 antagonist, is efficacious and well-tolerated in acute migraine. *Cephalalgia*. 2004;24(7):596-602.
177. Sargent J, Kirchner JR, Davis R, Kirkhart B. Oral sumatriptan is effective and well tolerated for the acute treatment of migraine: results of a multicenter study. *Neurology*. 1995;45(8 Suppl 7):S10-S4.
178. Schoenen J, Bulcke J, Caekebeke J, Dehaene I, Keyser J, Hildebrand G, et al. Self-treatment of acute migraine with subcutaneous sumatriptan using an auto-injector device: comparison with customary treatment in an open, longitudinal study. *Cephalalgia*. 1994;14(1):55-63.

179. Schoenen J, De KN, Giurgea S, Herroelen L, Jacquy J, Louis P, et al. Almotriptan and its combination with aceclofenac for migraine attacks: a study of efficacy and the influence of auto-evaluated brush allodynia. *Cephalalgia*. 2008;28(10):1095-105.
180. Scholpp J, Schellenberg R, Moeckesch B, Banik N. Early treatment of a migraine attack while pain is still mild increases the efficacy of sumatriptan. *Cephalalgia*. 2004;24(11):925-33.
181. Schulman E, O'Neill C, Pierce M, Griesser J, Angelov AS. Efficacy of Zelix, a novel iontophoretic transdermal sumatriptan patch, in the treatment of acute migraine in patients with nausea. *HeadacheConference: 52nd Annual Scientific Meeting of the American Headache Society Los Angeles, CA United States*Conference Start: 20100624 Conference End: 20100627Conference Publication: (varpagings)50 ()(pp 27-28), 2010Date of Publication: Au. 2010.
182. Schulman EA, Dermott KF. Sumatriptan plus metoclopramide in triptan-nonresponsive migraineurs. *Headache*. 2003;43(7):729-33.
183. Seeburger JL, Cady RK, Winner P, MacGregor A, Valade D, Ge Y, et al. Efficacy and tolerability of rizatriptan for the treatment of acute migraine in patients taking topiramate for migraine prophylaxis. *HeadacheConference: 52nd Annual Scientific Meeting of the American Headache Society Los Angeles, CA United States*Conference Start: 20100624 Conference End: 20100627Conference Publication: (varpagings)50 ()(pp 33), 2010Date of Publication: August. 2010.
184. Siegel SJ, O'Neill C, Dube LM, Kaldeway P, Morris R, Jackson D, et al. A unique iontophoretic patch for optimal transdermal delivery of sumatriptan. *Pharmaceutical Research*. 2007;24(10):1919-26.
185. Silberstein S GJ, Mannix LK, Sheftell F, Byrd S., al. AMe. A new migraine therapy: efficacy and tolerability of a fixed single-tablet formulation of sumatriptan RT Technology™ and naproxen sodium in the early intervention paradigm. *Headache* 2006; 46:833 [Abstract]. 2006.
186. Silberstein SD, Massiou H, McCarroll KA, Lines CR. Further evaluation of rizatriptan in menstrual migraine: retrospective analysis of long-term data. *Headache*. 2002;42(9):917-23.
187. Smelt AF, Blom JW, Dekker F, van den Akker ME, Knuistingh NA, Zitman FG, et al. A proactive approach to migraine in primary care: a pragmatic randomized controlled trial. *Canadian Medical Association Journal*. 2012;184(4):E224-E31.
188. Solbach MP, Waymer RS. Treatment of menstruation-associated migraine headache with subcutaneous sumatriptan. *Obstetrics and Gynecology*. 1993;82(5):769-72.
189. Solomon GD, Cady RK, Klapper JA. 2.5 mg 311C90 (zomig, zolmitriptan) is clinically effective in treating migraine: clinical efficacy and improvement in activity [abstract]. *Neurology*. 1997;48(3):A67.
190. Spierings EL, Keywood C. Rapid responders to frovatriptan in acute migraine treatment: results from a long-term, open-label study. *Pain Medicine*. 2009;10(4):633-8.
191. Sramek JJ, Hussey EK, Clements B, Cutler NR. Oral sumatriptan pharmacokinetics in the migraine state. *Clinical Drug Investigation*. 1999;17(2):137-44.
192. Syrett N, Abu-Shakra S, Yates R. Zolmitriptan nasal spray: advances in migraine treatment. *Neurology*. 2003;61(8 Suppl 4):S27-S30.
193. Taylor FR, Seeburger JL, Newman L, Friedman D, Ge Y, Zhang Y, et al. Efficacy of rizatriptan for the treatment of acute migraine in sumatriptan non-responders. *Journal of Headache and PainConference: 2nd European Headache and Migraine Trust International Congress - EHMTIC Nice France*Conference Start: 20101028 Conference End: 20101031Conference Publication: (varpagings)11 ()(pp S97), 2010Date of Public. 2010.

194. Tazaki Y, Sakai F, Tashiro K, Hirai S, Goto F, Maruyama S, et al. [Clinical Evaluation of SN-308 (Sumatriptan) Tablet on Migraine: Dose Finding Study by Double-Blind Cross-Over Method]. *Rinsho Iyaku (Journal of Clinical Therapeutics and Medicines)*. 1997;13(21):5567-94.
195. Tazaki Y, Sakai F, Tashiro K, Hirai S, Maruyama S, Goto F, et al. [Study on Clinical Usefulness of SN-308 (Sumatriptan) Subcutaneous Injection in Migraine: Dose Finding Study by Envelope Method]. *Rinsho Iyaku (Journal of Clinical Therapeutics and Medicines)*. 1993;9(5):1077-93.
196. Tepper SJ, Millson DS. Zolmitriptan (Zomig, 311C90) is efficacious in migraine on awakening. *Journal of the Neurological Sciences*. 1997;150 Suppl:S106.
197. Tfelt-Hansen P. The effectiveness of combined oral lysine acetylsalicylate and metoclopramide (Migpriv) in the treatment of migraine attacks. Comparison with placebo and oral sumatriptan. *Functional Neurology*. 2000;15 Suppl 3:196-201.
198. Tfelt-Hansen P, Goadsby PJ. Naratriptan is effective and well tolerated in the acute treatment of migraine [comment]. *Neurology*. 1999;52(6):1300-1.
199. Tfelt-Hansen P, Henry P, Mulder LJ, Scheldewaert RG, Schoenen J, Chazot G. [The combination of oral lysine-acetylsalicylate and metoclopramide compared with oral sumatriptan in the treatment of migraine attacks. A randomized, double-blind, placebo-controlled clinical trial]. *Ugeskrift for Laeger*. 1996;158(45):6435-9.
200. Tietjen GE, Athanas K, Utley C, Herial NA, Khuder SA. The combination of naratriptan and prochlorperazine in migraine treatment. *Headache*. 2005;45(6):751-3.
201. Utiger D, Eichenberger U, Bernasch D, Baumgartner RW, Bartsch P. Transient minor improvement of high altitude headache by sumatriptan. *High Alt Med Biol*. 2002;3(4):387-93.
202. Valade D, Seeburger JL, Cady RK, Winner P, MacGregor A, Ge Y, et al. Rizatriptan treatment of acute migraine in patients taking Topiramate for migraine prophylaxis. *Journal of Headache and PainConference: 2nd European Headache and Migraine Trust International Congress - EHMTIC Nice FranceConference Start: 20101028 Conference End: 20101031Conference Publication: (varpagings)11 ()(pp S97), 2010Date of Public. 2010*.
203. Visser WH, Ferrari MD, Bayliss EM, Ludlow S, Pilgrim AJ. Treatment of migraine attacks with subcutaneous sumatriptan: first placebo-controlled study. The Subcutaneous Sumatriptan International Study Group. *Cephalalgia*. 1992;12(5):308-13.
204. Visser WH, Jiang K. Effect of rizatriptan versus sumatriptan on migraine associated symptoms [abstract]. *Neurology*. 1998;50(4 Suppl 4):A375.
205. Visser WH, Klein KB, Cox RC, Jones D, Ferrari MD. 311C90, a new central and peripherally acting 5-HT_{1D} receptor agonist in the acute oral treatment of migraine: a double-blind, placebo-controlled, dose-range finding study. *Neurology*. 1996;46(2):522-6.
206. Wells NE, Steiner TJ. Effectiveness of eletriptan in reducing time loss caused by migraine attacks. *Pharmacoeconomics*. 2000;18(6):557-66.
207. Wendt J, Cady R, Singer R, Peters K, Webster C, Kori S, et al. A randomized, double-blind, placebo-controlled trial of the efficacy and tolerability of a 4-mg dose of subcutaneous sumatriptan for the treatment of acute migraine attacks in adults. *Clinical Therapeutics*. 2006;28(4):517-26.
208. Wilkinson M. L-ASA compared to sumatriptan and parenteral placebo in the acute treatment of migraine. *Cephalalgia*. 1999;19(6):542.
209. Winner P, Ricalde O, Le FB, Saper J, Margul B. A double-blind study of subcutaneous dihydroergotamine vs subcutaneous sumatriptan in the treatment of acute migraine. *Archives of Neurology*. 1996;53(2):180-4.
210. Zhao YB, Zhang GP, Chen QT, Han DL, Ma XP. [A clinical trial with sumatriptan in patients with acute migraine]. *The Chinese Journal of Clinical Pharmacology*. 1994;10(3):143-7.

Appendix 3: Assessment of inconsistency

Two analyses we conducted, one using the standard consistency model and the other using an inconsistency model. The residual deviance and DIC statistics of the consistency and inconsistency models were then compared. To help identify the loops in which inconsistency is present, the posterior mean deviance of the individual data points in the inconsistency model were plotted against their posterior mean deviance in the consistency model.

In general, the consistency model has a lower posterior mean of the residual deviance and DIC and hence is a better fit than the inconsistency model for all outcomes.

Table A3.1. Summary of the goodness of fit of the consistency and inconsistency models

Outcome	Measure	Consistency Model	Inconsistency Model
2 hour relief	Deviance	290.6 versus 271 datapoints	299.4 versus 271 datapoints
	DIC	1941.35	1959.83
2 hour freedom from pain	Deviance	237.6 versus 228 datapoints	253.6 versus 228 datapoints
	DIC	1553.57	1575.91
24 hour relief	Deviance	88.98 versus 93 datapoints	90.71 versus 93 datapoints
	DIC	654.33	661.357
24 hour freedom from pain	Deviance	117.4 versus 114 datapoints	120.6 versus 114 datapoints
	DIC	777.162	782.309
Rescue medication	Deviance	243 versus 232 datapoints	266.8 versus 232 datapoints
	DIC	1660.51	1672.07

For most outcomes, the posterior mean deviance contributions are very similar and close to 1, for both models and there is limited evidence of inconsistency. However, a few data points in the 2 hour relief analysis have higher values of the posterior mean deviance in the consistency model than the inconsistency model. These five points (circled below) in the lower right hand quadrant correspond to arms in the Sunrshine 2006 (SD Eletriptan Tablet, SD Rizatriptan ODT), Misra 2010 (NSAID), Goadsby 2000 (HD Eletriptan Tablet), and Wells 2001-2003 (SD Eletriptan Tablet) studies. Similarly, there were six points for rescue medication and the studies correspond to the MOSCC group 1991 (HD Sumatriptan and Ergots), Thompson 1992 (HD Sumatriptan and Aspirin+ with antiemetic), and Silberstein 2008 (Placebo and Ergots). (50, 67, 106, 152, 153)

Figure A3.1 2 hour headache relief - Plot of posterior mean deviance of the individual data points in the inconsistency model against their posterior mean deviance in the consistency model

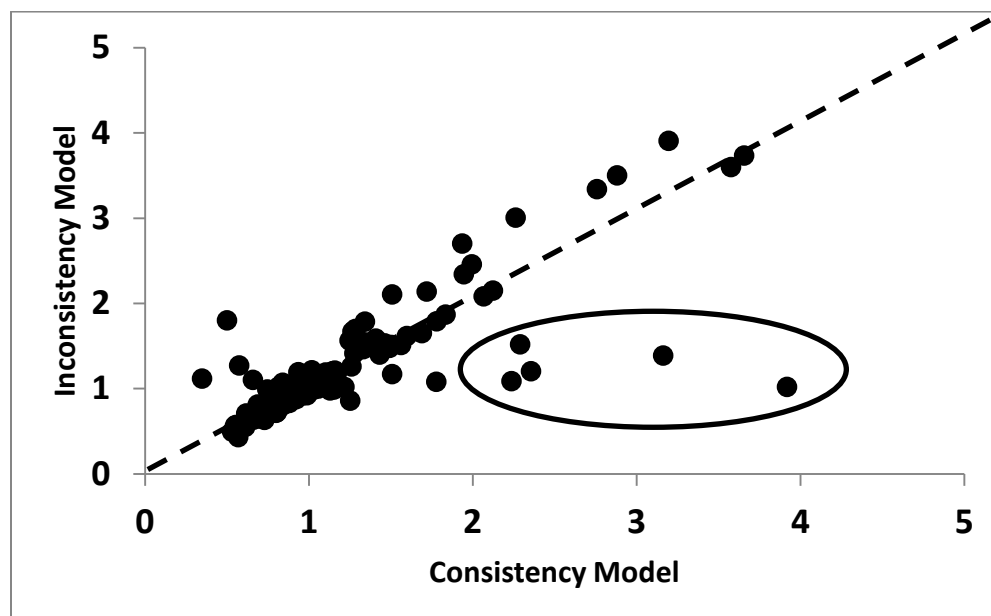


Figure A3.2. 2 hour freedom from pain - Plot of posterior mean deviance of the individual data points in the inconsistency model against their posterior mean deviance in the consistency model

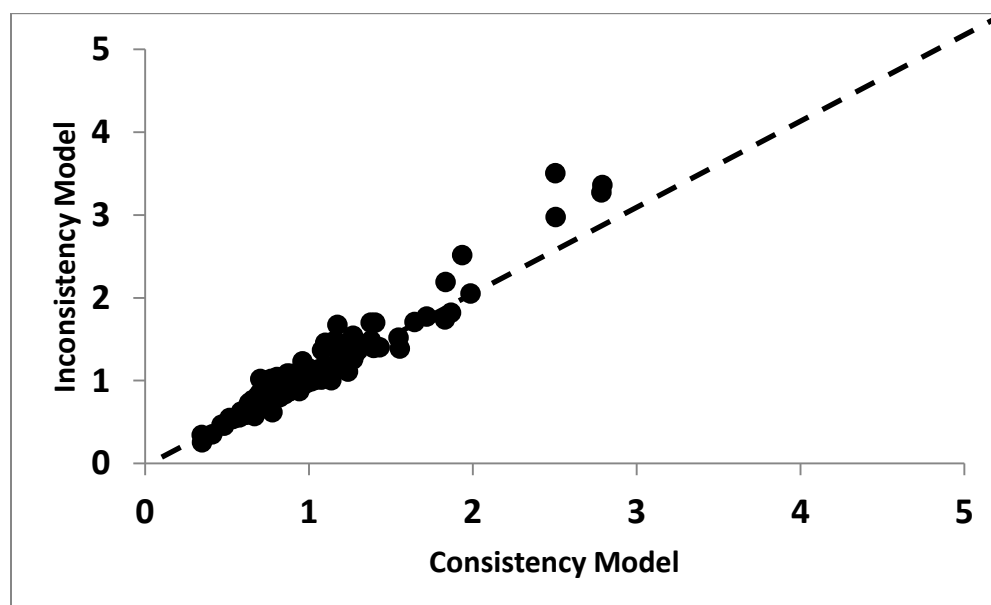


Figure A3.3. 24 hour sustained headache relief - Plot of posterior mean deviance of the individual data points in the inconsistency model against their posterior mean deviance in the consistency model

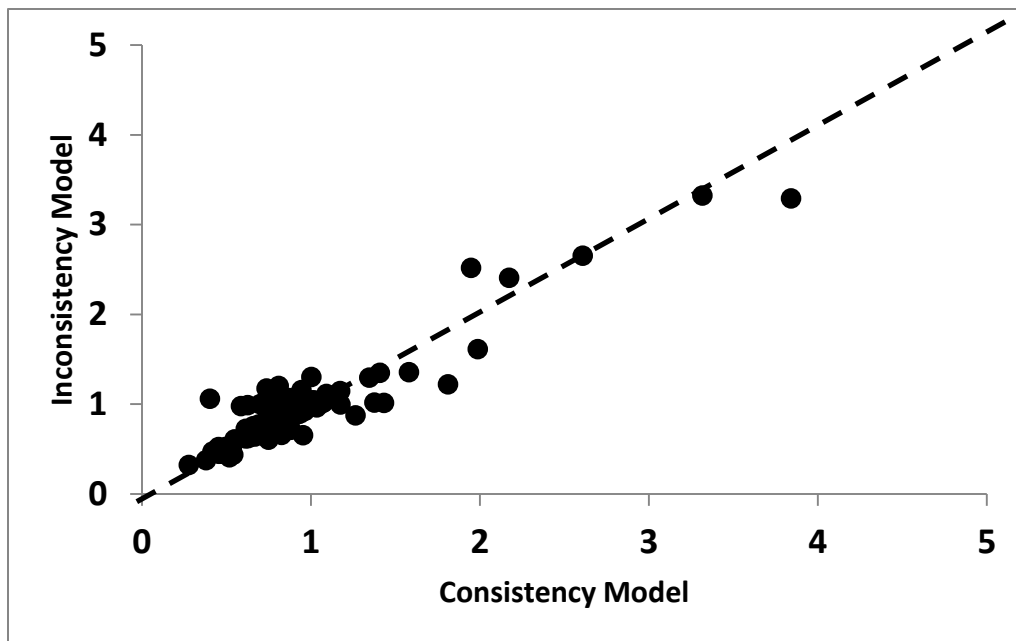


Figure A3.4. 24 hour sustained freedom from pain - Plot of posterior mean deviance of the individual data points in the inconsistency model against their posterior mean deviance in the consistency model

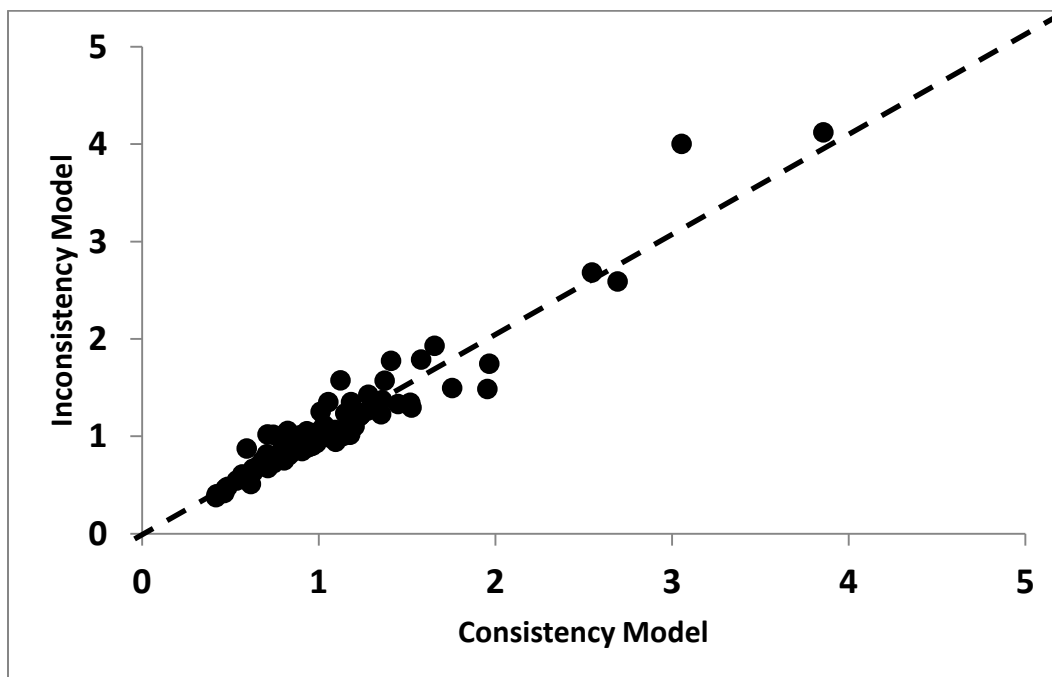
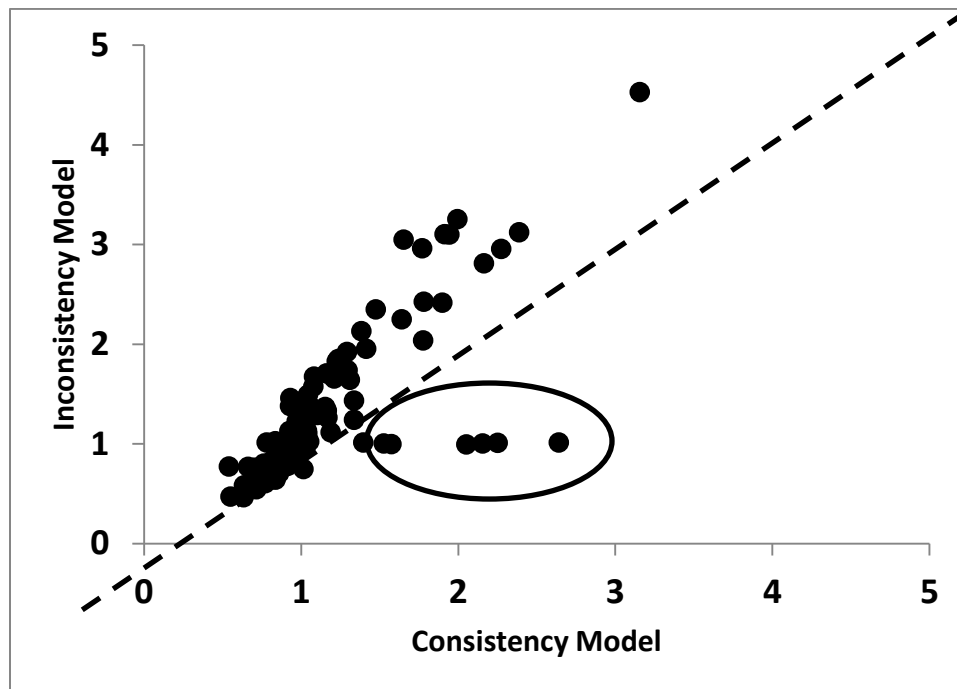


Figure A3.5. Use of rescue medication - Plot of posterior mean deviance of the individual data points in the inconsistency model against their posterior mean deviance in the consistency model



Appendix 4: Comparisons among standard dose triptans

Table A4a –Odds ratios for head-to-head comparisons of standard dose monotherapy triptan treatment - 2 hour headache relief

Placebo										
2.53 (2.01,3.21)	NSAID									
2.94 (1.22,7.18)	1.16 (0.47,2.93)	Acetamenophin								
2.35 (1.30,4.24)	0.93 (0.49,1.73)	0.8 (0.28,2.31)	Aspirin							
4.19 (3.51,5.00)	1.66 (1.24,2.20)	1.43 (0.58,3.49)	1.78 (0.97,3.30)	SD Eletriptan Tablet						
2.71 (2.37,3.11)	1.07 (0.85,1.35)	0.92 (0.37,2.24)	1.15 (0.64,2.08)	0.65 (0.53,0.80)	SD Suma-triptan Tablet					
3.66 (3.02,4.45)	1.45 (1.07,1.95)	1.25 (0.51,3.00)	1.56 (0.84,2.91)	0.87 (0.68,1.13)	1.35 (1.07,1.71)	SD Rizatriptan Tablet				
2.02 (1.52,2.69)	0.8 (0.55,1.15)	0.69 (0.27,1.73)	0.86 (0.45,1.66)	0.48 (0.34,0.67)	0.74 (0.54,1.02)	0.55 (0.39,0.78)	SD Frova-triptan Tablet			
2.56 (2.02,3.25)	1.01 (0.73,1.40)	0.87 (0.35,2.17)	1.09 (0.58,2.06)	0.61 (0.46,0.82)	0.95 (0.73,1.22)	0.7 (0.52,0.95)	1.27 (0.88,1.84)	SD Almo-triptan Tablet		
2.75 (2.29,3.32)	1.09 (0.82,1.45)	0.94 (0.38,2.29)	1.17 (0.63,2.17)	0.66 (0.52,0.84)	1.02 (0.82,1.25)	0.75 (0.58,0.97)	1.36 (0.97,1.92)	1.07 (0.81,1.42)	SD Zolmi-triptan Tablet	
2.2 (1.52,3.20)	0.87 (0.56,1.35)	0.75 (0.29,1.95)	0.94 (0.47,1.88)	0.53 (0.36,0.78)	0.81 (0.55,1.21)	0.6 (0.40,0.89)	1.09 (0.68,1.74)	0.86 (0.55,1.34)	0.8 (0.53,1.21)	SD Nara-triptan Tablet

Table A4b –Odds ratios for head-to-head comparisons of standard dose monotherapy triptan treatment - 2 freedom from pain

Placebo										
2.35 (1.79,3.11)	NSAID									
2.41 (0.85,6.57)	1.02 (0.35,2.93)	Acetaminophen								
2.66 (1.33,5.28)	1.13 (0.54,2.34)	1.11 (0.33,3.80)	Aspirin							
5.43 (4.31,6.89)	2.31 (1.63,3.30)	2.26 (0.81,6.54)	2.04 (0.99,4.22)	SD Eletriptan Tablet						
3.22 (2.73,3.82)	1.37 (1.05,1.80)	1.34 (0.49,3.84)	1.21 (0.61,2.42)	0.59 (0.45,0.78)	SD Suma- triptan Tablet					
4.86 (3.88,6.15)	2.07 (1.47,2.93)	2.02 (0.75,5.68)	1.83 (0.89,3.80)	0.89 (0.65,1.23)	1.51 (1.15,1.99)	SD Riza- triptan Tablet				
4.48 (2.83,7.28)	1.91 (1.11,3.32)	1.87 (0.62,5.78)	1.69 (0.74,3.90)	0.82 (0.49,1.41)	1.39 (0.85,2.32)	0.92 (0.55,1.57)	SD Frova- triptan Tablet			
2.73 (2.11,3.56)	1.17 (0.81,1.68)	1.14 (0.40,3.30)	1.03 (0.50,2.14)	0.5 (0.36,0.71)	0.85 (0.64,1.13)	0.56 (0.40,0.79)	0.61 (0.35,1.04)	SD Almo- triptan Tablet		
3.14 (2.47,4.00)	1.34 (0.94,1.91)	1.31 (0.47,3.77)	1.18 (0.58,2.45)	0.58 (0.42,0.79)	0.97 (0.74,1.28)	0.65 (0.47,0.88)	0.7 (0.41,1.18)	1.15 (0.83,1.58)	SD Zolmi- triptan Tablet	
1.79 (1.13,2.84)	0.76 (0.44,1.30)	0.74 (0.25,2.29)	0.67 (0.30,1.55)	0.33 (0.20,0.53)	0.55 (0.34,0.90)	0.37 (0.23,0.59)	0.4 (0.20,0.77)	0.65 (0.39,1.11)	0.57 (0.34,0.95)	SD Nara- triptan Tablet

Table A4c –Odds ratios for head-to-head comparisons of standard dose monotherapy triptan treatment - 24 hour headache relief

Placebo								
2.00 (1.63,2.47)	NSAID							
2.02 (0.92,4.46)	1.01 (0.44,2.30)	Acetaminophen						
4.37 (3.67,5.25)	2.19 (1.69,2.83)	2.17 (0.96,4.88)	SD Eletriptan Tablet					
2.41 (2.10,2.77)	1.21 (0.99,1.46)	1.19 (0.54,2.67)	0.55 (0.45,0.67)	SD Sumatriptan Tablet				
2.02 (1.49,2.74)	1.01 (0.70,1.45)	1 (0.46,2.20)	0.46 (0.32,0.66)	0.84 (0.60,1.17)	SD Rizatriptan Tablet			
2.71 (1.98,3.71)	1.35 (0.94,1.97)	1.34 (0.58,3.15)	0.62 (0.44,0.87)	1.12 (0.81,1.57)	1.34 (0.87,2.07)	SD Almotriptan Tablet		
2.94 (2.40,3.64)	1.47 (1.11,1.95)	1.46 (0.64,3.27)	0.67 (0.53,0.85)	1.22 (0.98,1.53)	1.46 (1.02,2.10)	1.09 (0.81,1.46)	SD Zolmitriptan Tablet	
3.06 (2.14,4.34)	1.53 (1.02,2.27)	1.52 (0.62,3.59)	0.7 (0.49,0.98)	1.27 (0.88,1.81)	1.52 (0.94,2.44)	1.13 (0.70,1.79)	1.04 (0.70,1.53)	SD Naratriptan Tablet

Table A4d –Odds ratios for head-to-head comparisons of standard dose monotherapy triptan treatment, Freedom from pain at 24 hours

Placebo								
1.85 (1.36,2.52)	NSAID							
1.58 (0.49,4.59)	0.86 (0.25,2.60)	Acetaminophen						
4.63 (3.50,6.10)	2.51 (1.67,3.73)	2.94 (0.97,9.84)	SD Eletriptan Tablet					
2.79 (2.31,3.38)	1.51 (1.12,2.05)	1.76 (0.60,5.77)	0.6 (0.44,0.82)	SD Sumatriptan Tablet				
2.97 (2.19,3.98)	1.61 (1.05,2.45)	1.88 (0.65,5.99)	0.64 (0.43,0.95)	0.83 (0.54,1.30)	SD Rizatriptan Tablet			
2.48 (1.77,3.49)	1.34 (0.86,2.12)	1.57 (0.51,5.32)	0.53 (0.36,0.82)	0.92 (0.63,1.35)	0.83 (0.54,1.30)	SD Almotriptan Tablet		
2.74 (2.04,3.66)	1.48 (0.98,2.22)	1.73 (0.57,5.77)	0.59 (0.42,0.84)	0.72 (0.40,1.28)	0.92 (0.63,1.35)	1.11 (0.76,1.58)	SD Zolmitriptan Tablet	
2.13 (1.28,3.50)	1.15 (0.63,2.06)	1.35 (0.41,4.77)	0.46 (0.27,0.76)	0.76 (0.44,1.28)	0.72 (0.40,1.28)	0.86 (0.47,1.55)	0.78 (0.44,1.36)	SD Naratriptan Tablet

Table A4e –Odds ratios for head-to-head comparisons of standard dose monotherapy triptan treatment, Use of Rescue medications

Placebo									
0.55 (0.42,0.71)	NSAID								
0.47 (0.24,0.94)	0.86 (0.41,1.79)	Aspirin							
0.25 (0.20,0.31)	0.46 (0.33,0.64)	0.53 (0.26,1.09)	SD Eletriptan Tablet						
0.48 (0.40,0.57)	0.87 (0.66,1.15)	1.02 (0.51,2.03)	1.91 (1.47,2.49)	SD Sumatriptan Tablet					
0.4 (0.32,0.50)	0.73 (0.53,1.03)	0.85 (0.41,1.76)	1.61 (1.19,2.17)	0.84 (0.64,1.11)	SD Rizatriptan Tablet				
0.42 (0.19,0.96)	0.77 (0.33,1.82)	0.89 (0.30,2.62)	1.68 (0.72,3.95)	0.88 (0.38,2.04)	1.05 (0.45,2.46)	SD Frovatriptan Tablet			
0.44 (0.33,0.59)	0.8 (0.55,1.19)	0.94 (0.45,1.97)	1.76 (1.24,2.50)	0.92 (0.67,1.27)	1.1 (0.76,1.58)	1.05 (0.44,2.48)	SD Almotriptan Tablet		
0.36 (0.28,0.48)	0.66 (0.46,0.97)	0.77 (0.37,1.61)	1.46 (1.05,2.01)	0.76 (0.56,1.04)	0.91 (0.65,1.27)	0.87 (0.36,2.04)	0.82 (0.58,1.18)	SD Zolmitriptan Tablet	
0.41 (0.28,0.60)	0.74 (0.47,1.18)	0.87 (0.39,1.90)	1.64 (1.08,2.46)	0.85 (0.57,1.29)	1.02 (0.67,1.54)	0.97 (0.39,2.39)	0.93 (0.58,1.48)	1.12 (0.71,1.77)	SD Naratriptan Tablet

Appendix 5: Adjustment for control group response rate

Table A5.1: Comparison of Unadjusted and Adjusted Analyses (OR, 95% CrI)

		Random-effect Model - unadjusted	Random-effect Model - Adjusted
1	Placebo	NA	NA
2	NSAID	2.56 (2.03,3.27)	2.63 (2.11,3.30)
3	Acetaminophen	2.92 (1.19,7.27)	4.01 (1.79,9.28)
4	Aspirin	2.36 (1.29,4.34)	2.54 (1.44,4.48)
5	SD Eletriptan Tablet	4.14 (3.45,4.97)	3.98 (3.37,4.70)
6	SD Sumatriptan Tablet	2.76 (2.41,3.16)	2.88 (2.54,3.26)
7	SD Rizatriptan Tablet	3.66 (3.40,4.80)	4.42 (3.67,5.34)
8	SD Frovatriptan Tablet	2.02 (1.51,2.71)	1.84 (1.42,2.39)
9	SD Almotriptan Tablet	2.58 (2.02,3.30)	2.83 (2.26,3.55)
10	SD Zolmitriptan Tablet	2.82 (2.35,3.40)	3.01 (2.54,3.59)
11	SD Naratriptan Tablet	2.07 (1.37,3.16)	2.18 (1.48,3.19)
12	SD BI 44370 TA Tablet	3.70 (1.76,7.81)	3.03 (1.53,6.04)
13	HD Sumatriptan Tablet	3.14 (2.72,3.62)	3.27 (2.87,3.72)
14	SD Rizatriptan ODT	6.23 (4.09,9.53)	5.82 (3.99,8.51)
15	SD Sumatriptan Nasal Spray	3.05 (2.1,4.43)	3.70 (2.66,5.13)
16	SD Sumatriptan Subcutaneous Injection	8.96 (6.06,13.34)	6.62 (4.84,9.17)
17	SD Sumatriptan patch	2.56 (1.59,4.11)	1.91 (1.24,2.93)
18	SD Zolmitriptan Nasal Spray	2.93 (1.71,4.98)	3.20 (1.92,5.34)
19	SD Zolmitriptan ODT	5.27 (2.76,10.18)	4.51 (2.53,8.05)
20	Ergots	1.68 (1.12,2.51)	1.64 (1.11,2.41)
21	Aspirin with antiemetic	2.88 (1.97,4.21)	2.98 (2.07,4.28)
22	Triptan with Acetaminophen	11.0 (3.93,35.37)	15.03 (5.84,44.41)
23	Triptan with NSAID	4.59 (3.39,6.20)	4.68 (3.51,6.27)

24	Acetaminophen, dichloralphenazone, and isometheptene	1.69 (0.65,4.40)	1.85 (0.71,4.72)
25	LD Eletriptan Tablet	2.89 (1.91,4.36)	2.90 (1.96,4.31)
26	LD Sumatriptan Tablet	2.20 (1.62,3.01)	2.40 (1.79,3.23)
27	LD Rizatriptan Tablet	2.88 (2.06,4.04)	3.30 (2.40,4.52)
28	LD Frovatriptan Tablet	1.03 (0.62,1.68)	0.91 (0.57,1.44)
29	LD Almotriptan Tablet	2.11 (1.39,3.18)	2.54 (1.74,3.74)
30	LD Zolmitriptan Tablet	2.19 (1.02,4.67)	2.32 (1.11,4.75)
31	LD BI 44370 TA Tablet	1.70 (0.77,3.70)	1.41 (0.67,2.88)
32	HD Eletriptan Tablet	5.38 (4.41,6.60)	5.18 (4.29,6.23)
33	HD Rizatriptan Tablet	4.92 (2.52,9.64)	4.78 (2.51,9.11)
34	HD Frovatriptan Tablet	1.85 (1.18,2.91)	1.64 (1.08,2.47)
35	HD Almotriptan Tablet	2.81 (1.86,4.26)	3.32 (2.25,4.93)
36	HD Zolmitriptan Tablet	2.90 (2.28,3.71)	2.92 (2.33,3.69)
37	HD BI 44370 TA Tablet	4.72 (2.29,9.90)	3.91 (2.00,7.70)
38	SD Tonaberstat	1.21 (0.65,2.27)	1.24 (0.67,2.23)
39	LD Tonaberstat	1.09 (0.58,2.05)	1.11 (0.61,2.02)
40	LD Rizatriptan ODT	3.39 (1.83,6.27)	3.42 (1.93,6.05)
41	LD Sumatriptan Nasal Spray	1.96 (1.31,2.92)	2.37 (1.65,3.39)
42	LD Sumatriptan Suppositories	6.65 (2.66,17.38)	6.17 (2.9,13.37)
43	LD Zolmitriptan Nasal Spray	2.58 (1.52,4.40)	2.83 (1.7,4.760)
44	HD Zolmitriptan Nasal Spray	4.53 (3.28,6.30)	4.92 (3.61,6.71)
45	HD Sumatriptan Subcutaneous Injection	6.45 (2.34,18.70)	5.63 (2.47,12.99)
	Resdeviance	290.6 versus 271 datapoints	283.1 versus 271 datapoints
	DIC	1941.35	1946
	Beta	NA	Beta= -0.58 (-0.41,-0.75)

Appendix 6: Number of Patients and Studies for each outcome

	2h Headache		2h Freedom		24h Sustained		24h sustained		Use of rescue medications	
	# RCTs	# Patients	# RCTs	# Patients	# RCTs	# Patients	# RCTs	# Patients	# RCTs	# Patients
Placebo	82	13602	78	13806	23	5741	39	8284	80	13377
TABLET SD										
Almotriptan	7	2120	8	2334	2	906	4	1019	7	1918
Eletriptan	13	3143	11	2935	6	1966	7	1418	13	3555
Frovatriptan	5	1840	5	1804	--	--	--	--	1	131
Naratriptan	3	512	3	512	2	363	2	327	4	704
Rizatriptan	11	2676	12	2390	5	606	6	1191	13	2926
Sumatriptan	23	5807	21	5150	11	3116	13	3442	17	4451
Zolmitriptan	10	3491	9	3069	5	1523	4	1794	8	2291
TABLET LD										
Almotriptan Tablet	2	527	1	360	1	360	--	--	--	--
Eletriptan Tablet	3	514	3	407	1	290	3	553	4	697
Frovatriptan Tablet	2	229	2	229	--	--	--	--	1	122
Naratriptan Tablet	--	--	--	--	--	--	--	--	1	117
Rizatriptan Tablet	3	752	2	294	--	--	--	--	3	503
Sumatriptan Tablet	4	850	1	150	1	336	--	--	1	336
Zolmitriptan Tablet	1	52	1	52	1	52	--	--	1	52
TABLET HD										
Almotriptan Tablet	2	352	2	352	--	--	--	--	2	352
Eletriptan Tablet	10	2042	7	1621	3	872	4	949	8	1759
Frovatriptan Tablet	2	338	2	338	--	--	--	--	1	126
Rizatriptan Tablet	1	82	1	82	--	--	--	--	--	--
Sumatriptan Tablet	23	5210	20	4165	7	2446	8	1824	22	4497
Zolmitriptan Tablet	6	2084	5	1747	3	770	2	927	3	614

ODT SD										
Rizatriptan	7	517	3	410	--	--	--	--	1	41
Zolmitriptan	--	--	1	231	1	231	--	--	--	--
Zumatriptan	1	231	--	--	--	--	--	--	--	--
ODT LD										
Rizatriptan	2	373	2	373	--	--	--	--	--	--
ODT HD										
Zolmitriptan	--	--	--	--	--	--	--	--	2	560
NASAL SPRAY SD										
Sumatriptan	4	738	1	29	--	--	--	--	--	--
Zolmitriptan	--	--	--	--	--	--	--	--	--	--
Zumatriptan	1	238	--	--	--	--	--	--	--	--
NASAL SPRAY LD										
Sumatriptan	3	511	--	--	--	--	--	--	--	--
Zolmitriptan	1	224	--	--	--	--	--	--	--	--
NASAL SPRAY HD										
Zolmitriptan	--	1635	2	1399	1	935	2	1399	2	1399
SUBCUTANEOUS INJECTION SD										
Sumatriptan	6	742	2	295	--	--	2	295	8	1114
Zolmitriptan	--	--	--	--	--	--	--	--	--	--
SUBCUTANEOUS INJECTION HD										
Sumatriptan	--	49	1	49	--	--	--	--	1	49
Zolmitriptan	--	--	--	--	--	--	--	--	1	76
PATCH SD										
Sumatriptan	2	468	2	468	--	--	--	--	1	137
SUPPOSITORIES LD										
Sumatriptan	1	66	1	66	--	--	--	--	--	--
NON TRIPTAN SINGLE THERAPIES										
NSAID										
Acetaminophen	1	45	1	45	1	45	1	45	--	--
Aspirin	1	146	1	147	--	--	--	--	1	146

Ergots	3	503	1	203	1	10	--	--	2	568
COMBINATION THERAPIES										
Aspirin with antiemetic	3	660	3	660	--	--	--	--	3	660
Triptan with acetaminophen	1	49	1	49	1	49	1	49	--	--
Triptan with NSAID	3	988	9	2777	3	988	9	2777	9	2597
OTHER THERAPIES										
SD BI 44370 TA Tablet	1	72	1	72	1	72	1	72	2	144
HD BI 44370 TA Tablet	1	79	1	79	1	79	1	79	2	155
LD BI 44370 TA Tablet	1	71	1	71	1	71	1	71	2	142
SD Tonaberstat	1	137	1	137	--	--	--	--	--	--
LD Tonaberstat	1	134	1	134	--	--	--	--	--	--
Acetaminophen, Dichloralphenazone, and Isometheptene	1	65	--	--	--	--	--	--	--	--

CHAPTER 5: NETWORK META-ANALYSIS OF RARE EVENTS: AN APPLICATION EXAMINING RISK OF SERIOUS INFECTION WITH BIOLOGICS

The risk of serious infection with biologics in treating patients with rheumatoid arthritis

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CHAPTER 5: NETWORK META-ANALYSIS OF RARE EVENTS: AN APPLICATION EXAMINING RISK OF SERIOUS INFECTION WITH BIOLOGICS

The risk of serious infection with biologics in treating patients with rheumatoid arthritis

SUMMARY:

In this chapter, we conduct a network meta-analysis of a rare event. We conduct a network meta-analysis comparing the risk of serious infection with biologics in treating patients with rheumatoid arthritis.

LINKS:

This article was published in Lancet following peer review and can also be viewed on the journal's website at: [http://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(14\)61704-9/abstract](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(14)61704-9/abstract)

The online appendices will be available here:

[http://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(14\)61704-9/supplemental](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(14)61704-9/supplemental)

A pdf is also presented in Appendix

CONTRIBUTION:

I was responsible for drafting the initial manuscript in collaboration with Dr. Jas Singh and Dr. George Wells as well as other supervisors and co-authors. I conducted all network meta-analyses, and generated all tables and figures related to findings from the network meta-analysis. Dr. Jas Singh and I also responded to feedback on the network meta-analysis that was provided during the peer review process with guidance from supervisors and other co-authors.

ABSTRACT

Background: Serious infections are a major concern for patients considering treatments for rheumatoid arthritis (RA). Evidence is inconsistent on whether biologics are associated with an increased risk of serious infection compared to traditional disease-modifying anti-rheumatic drugs (DMARDs).

Methods: A systematic literature search was undertaken using MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, and www.clinicaltrials.gov from inception through February 11, 2014. We conducted a network meta-analysis of published trials to assess the risk of serious infections of biologics in RA patients, compared to traditional DMARDs.

Findings: The systematic review identified 106 trials that included RA patients on biologic and reported on serious infections. Compared to traditional DMARDs, standard-dose biologic (odds ratio [OR], 1.31; 95% credible interval [CrI], 1.09 to 1.58), high-dose biologic (OR, 1.90; 95% CrI, 1.50 to 2.39) and combination biologic therapy (OR, 4.14; 95% CrI, 1.87 to 9.05) were associated with an increased risk of serious infections, while low-dose biologics (OR, 0.93; 95% CrI, 0.65 to 1.33) were not. The risk was lower in patients who are methotrexate naïve compared with traditional DMARD- or anti-TNF-biologic-experienced. The absolute increase in the number of serious infections per 1000 patients treated each year compared to traditional DMARDs ranged from 6 for standard-dose biologic to 55 for combination biologic therapy.

Interpretation: Standard-dose and, high-dose and combination biologics (with/without traditional DMARDs) are associated with an increase in serious infections compared to traditional DMARDs in RA, while low-dose biologics are not. Clinicians should discuss the balance between benefit and harm with the individual RA patient before initiating biologic therapy.

INTRODUCTION

Biologics are a breakthrough new class of disease-modifying treatment options for rheumatoid arthritis (RA), with large clinical and radiographic improvements.^{1 2} Nine biologics are now approved for RA by the U.S. Food and Drug Administration and European Medicines Agency. Biologics are used to treat moderate to severe RA in patients who have not responded adequately to traditional DMARDs such as methotrexate (MTX).^{3,4} Infections, and in particular serious infections, are one of the greatest worries for patients considering biologics.

There is debate over whether biologic therapies are associated with serious infectious in patients with RA, the magnitude of this risk, and whether the risk varies among subpopulations of patients within RA.⁵ The clinical perception leans towards a belief that serious infection is an issue but this is not backed-up by consistent research evidence. The confusion lies in the four published systematic reviews with meta-analyses⁶⁻⁹ on the risk of serious infection with biologics in patients with RA. The first meta-analysis⁹, that included only three of the currently used biologics in only 9 trials, found an association, but the next three meta-analyses in RA including more biologics and a far greater sample size⁶⁻⁸ failed to find any association of standard-dose biologics with an increased risk of serious infections.

Further, discordant results have also been reported for non-randomized studies assessing the risk of serious infection in RA,¹⁰⁻¹⁶ with some studies showing an association¹⁴⁻¹⁶ and others showing no association.¹⁰⁻¹³ Accordingly, there has been debate around the risk of serious infection with biologics in RA. Several-fold more trials are now available to perform a conclusive study to address this question. As well, all four meta-analyses in RA patients⁶⁻⁹ were limited in that they restricted the patient population (e.g., MTX-naïve patients),⁸ only considered a few biologics in their analyses,⁶⁻⁹ consisted primarily of studies which were more than a decade old,⁹ or failed to integrate findings across low, standard or high-dose biologics (i.e., conducted analyses separately).⁶⁻⁹ Availability of more robust evidence is critical for the development of RA treatment guidelines, which have been predominantly based on observational studies in the past.³

The objective of our study was to compare the risk of serious infections with biologics to non-biologic traditional DMARDs for the treatment of RA and subpopulations within RA using network meta-analysis (NMA) to synthesize data from randomized controlled trials (RCTs).

METHODS

A systematic review that included both a traditional meta-analysis and NMA was conducted to assess the risk of serious infection comparing biologics with each other, placebo or a control treatment (traditional DMARDs or their combinations) in RA. NMA considers direct and indirect evidence on the benefits and harms among multiple treatments simultaneously, whereas traditional meta-analysis only considers direct evidence between two treatment strategies.⁶ This systematic review, meta-analysis and NMA was performed according to the guidance specified in the Cochrane Handbook for Intervention Reviews,¹⁷ ISPOR NMA Guidance^{18,19} and the preferred reporting items for systematic reviews and meta-analyses

(PRISMA) statement.²⁰

We included RCTs in adults with RA treated with any of the nine biologics approved for the treatment of RA, alone or in combination as compared to each other, placebo or traditional DMARD (or DMARD combinations). Biologics included tumor necrosis factor blockers (etanercept, adalimumab, infliximab, golimumab, certolizumab pegol), interleukin (IL)-1 antagonist (anakinra), IL-6 antagonist (tocilizumab), anti-CD28 (abatacept), and anti-B cell (rituximab) biologic in any dose. The comparator was placebo, traditional DMARDs (including MTX, alone or in combination) or another biologic. We included tofacitinib doses as separate nodes in the network to improve precision of effect estimates for biologics (i.e. by borrowing strength from indirect evidence) and facilitate future updates of this review but do not report findings for tofacitinib at this time for many reasons (**Appendix 1**). Serious infection was the outcome of interest, defined as serious infection in each study (mostly included infections associated with death, hospitalization, or the use of intravenous antibiotics).

Search and Systematic Review Methods

A Cochrane librarian (TR) performed a literature search (**Appendix 2**) and retrieved published trials of biologics or tofacitinib based on the above criteria in: a] the Cochrane Central Register of Controlled Trials (CENTRAL, via the Cochrane Library), Medline (from 1946), and EMBASE databases (from 1947) up to February 11, 2014; b] data from the two previously published Cochrane systematic reviews of biologics^{21,22}; c] data from two reviews comparing traditional DMARD monotherapy with traditional DMARD combination therapies,^{23,24} and d] through a search of the www.clinicaltrials.gov website. The search protocols for both Cochrane reviews are accessible online.^{21,22} Search terms included

biologics, rheumatoid arthritis and their synonyms (Appendix 2). Studies were eligible for inclusion if they included any of the biologics and reported serious infections; no restrictions were applied by the length of follow-up. Two reviewers assessed titles and abstracts (SN, MT), full text articles (SN, TC) and extracted the data (SN, MT) independently; any disagreements were resolved by consensus and when needed, by a third reviewer (JS). Data on serious infections and the total number of patients in each treatment arm and key patient and study characteristics (**Appendix 3**) were extracted using a standardized data abstraction sheet. The risk of bias was assessed using the Cochrane Risk of Bias Tool.²⁵

Statistical Methods

The odds ratio (OR) of serious infection was the primary measure of treatment effect. Absolute risk differences per 1,000 patients treated were also calculated using the mean annualized baseline risk of serious infection in traditional DMARD arms of included studies greater than 6 months in duration. We conducted traditional meta-analyses, cumulative meta-analyses (meta-analyses over time), and Bayesian NMA. Traditional and cumulative meta-analyses (comparing standard-dose (approved) biologic versus traditional DMARD) were conducted using Comprehensive Meta-analysis (BioStat, Englewood, US). The Mantel Haenszel method using a fixed effects model and an adjusted continuity correction factor centered around 0.5 to handle zero cells.²⁶

Bayesian NMA were conducted using WinBUGS software (MRC Biostatistics Unit, Cambridge, UK).²⁷ A binomial likelihood model,²⁸ which allows for the use of multi-arm trials, was used for Bayesian NMA because many studies included multi-arms trials. Both fixed and random-effects NMA were conducted, although the random-effects model with an informative prior²⁹ on the between study variance was used for the primary analysis. Point

estimates and 95% credible intervals (CrI) for ORs were derived using Markov Chain Monte Carlo methods. We assessed model fit and inconsistency³⁰ using standard approaches (**See online appendix**).

For traditional and cumulative meta-analyses, we used the standard-doses of the biologics, provided in **Appendix 3**. For the NMA, we included all doses (low, standard, high) of biologics. Pre-specified study and patient characteristics were assessed to ensure similarity and to investigate the potential impact of heterogeneity on effect estimates (**See Appendix 3**. In particular, we stratified results by the following pre-defined populations: MTX-naïve, MTX-experienced, and anti-TNF-biologic-experienced. We also conducted numerous sensitivity analyses related to methods for handling zero events.²⁶

RESULTS

Study characteristics of included trials

We identified 106 randomized trials published between 1992 and 2014 involving 42,330 RA patients (**Figure 1, Appendix 4**). There were 24 (23%), 71 (67%), 11 (10%) studies conducted in patients who were MTX-naïve, traditional DMARD-experienced, and anti-TNF-biologic-experienced, respectively (**Table 1; Figure 2**). Study and patient characteristics, overall and for each of these three populations, are summarized in **Table 1**. Treatment duration ranged from 2-36 months, and the mean RA duration ranged from 0.1-13.5 years (**Table 1**). RCTs reported serious infection on an intention-to-treat (ITT; 70%) or modified ITT (30%) basis. Detailed characteristics of included studies are summarized in **Appendix 4** and the risk of bias assessment in **Appendix 5**.

Traditional Meta-Analysis – Standard-dose biologics

There were 59 trials comparing standard-dose biologic +/-traditional DMARD. Of the 59 trials, 53 (89%) reported at least one serious infection in the study. There were a total of 525 serious infections among the 59 trials, involving 68 comparisons of standard-dose biologic +/-traditional DMARD (342 events) with traditional DMARD monotherapy (183 events). A significant increase in serious infections with biologics was found (OR, 1.27; 95% CI, 1.05 to 1.52; p=0.012) (**Figure 3**). The risk of serious infections with biologics varied depending on previous treatment experience, being statistically significantly higher in MTX-experienced, but not statistically significant in patients who were MTX-naïve or anti-TNF-biologic-experienced (**Figure 3**).

Stratified analyses adjusting for differences in other patient and study-level characteristics were conducted and are presented in **Appendix 6**. A clinically important and statistically significantly higher risk of serious infections with biologic compared to traditional DMARDs was also seen in: duration of follow-up 6-12 months; biologic when used in combination with traditional DMARDs; established RA (2 to 10 years of disease duration); studies published between 2000 and 2004; studies with a low risk of bias; and when the comparator was traditional DMARD plus placebo (**Appendix 6**). The results did not vary substantively when different statistical models were used (**Appendix 7**). Detailed findings from the traditional meta-analysis are reported in **Appendix 5**.

Cumulative Meta-Analysis – Standard-dose biologics

Cumulative meta-analysis (**Figure 4**) showed that an increased risk of serious infection associated with using standard-dose biologic became evident in 2004, when 5,537 patients

had been randomized and 129 events had occurred (OR, 1.63; 95% CI, 1.08 to 2.45; $p=0.02$). Subsequent trials increased the number of patients to 22,608 and the number of events to 525 for this treatment comparison. This resulted in a reduction in the odds ratio with a narrowing of CI (OR, 1.27; 95% CI, 1.05 to 1.52; $p=0.012$), although the point estimate remained above 1 for years following 2004 and very similar from 2007 onwards.

Network meta-analysis

Standard-dose biologics +/- traditional DMARD (OR, 1.31; 95% CrI, 1.09 to 1.58) were associated with an increased risk of serious infection (**Figure 3, Appendix 8, 9 and 9a**). High-dose biologics +/- traditional DMARD (OR, 1.90; 95% CrI, 1.50 to 2.39) and combination biologic therapy (OR, 4.14; 95% CrI, 1.87 to 9.05) were associated with an increased risk of serious infection while low-dose biologics +/- traditional DMARD (OR, 0.93; 95% CrI, 0.65 to 1.33) were not. These findings aligned with traditional meta-analyses (**Appendix 10**).

There were differences observed among the *a priori defined* RA populations. In patients who are MTX-naïve, standard-dose biologics +/- traditional DMARD (OR, 1.08; 95% CrI, 0.75 to 1.53) and high-dose biologics +/- traditional DMARD (OR, 1.73; 95% CrI 0.89 to 3.52) were not associated with a statistically significant increase in risk of serious infection (**Figure 3**). In contrast, in MTX-experienced patients, standard-dose biologics +/- traditional DMARD (OR, 1.48; 95% CrI, 1.17 to 1.90) and high-dose biologics +/- traditional DMARD (OR, 2.07; 95% CrI, 1.57 to 2.74) were associated with an increased risk of serious infections. Information on combination biologic therapy was only available for MTX-experienced and anti-TNF-biologic-experienced patients and was associated with a significant increase in serious infections in both patient groups (**Figure 3**).

Absolute risk of serious infection

In patients using traditional DMARDs, the median absolute annual risk of a serious infection reported was approximately 2% or 20 per 1000 patients treated each year. The absolute increase in the number of serious infections compared to traditional DMARDs was: 6 per 1000 for standard-dose biologic therapy+/- traditional DMARD, 17 per 1000 for high-dose biologic therapy+/- traditional DMARD, and 55 per 1000 for combination biologic therapy.

DISCUSSION

There is uncertainty around the risk of serious infection of biologic therapies in RA and the magnitude of effect. Although the first meta-analysis showed an association, when more trials were completed, three subsequent meta-analyses found that standard-dose biologics were not associated with an increased risk of serious infection compared with traditional DMARDs. Now that there is evidence from 42,330 patients with RA from 106 RCTs, this increased sample size provides a more precise estimate of an increased risk of serious infection. To the best of our knowledge, this is the most comprehensive meta-analysis of RCTs on the risk of serious infections in RA, adhering to recommended PRISMA reporting standards.²⁰ Our analysis greatly exceeds the sample size in the largest meta-analysis of 18 RCTs conducted in RA to date (N=8,808)⁷ by >5 times and includes 88 more RCTs (**Appendix 11**). We included data from nine biologics; reported detailed stratified analyses; integrated findings for all doses of biologics; presented findings on both the relative and absolute scale, and tested the robustness of findings with sensitivity analyses (see appendices).

We found standard-dose, high-dose, and combination biologics (with/without DMARDs) are associated with more serious infections compared to traditional DMARDs. Our comprehensive study investigated biologic dose in RA in more detail than previous studies (**Appendix 11**). Bongartz et al.⁹ found that two of the three biologics studied (infliximab, adalimumab) were associated with significantly increased odds of serious infections (OR, 2.0; 95% CI, 1.3 to 3.1), compared to placebo in 9 trials up to 2005 including 5,005 patients. In contrast, several recent meta-analyses including more biologics and more RCTs reported different findings.⁶⁻⁸ Salliot et al.⁷ examined 12 RCTs up to 2007 (N=6,879) and reported that the risk of serious infections with rituximab and abatacept did not differ from placebo, but was significantly higher with high-doses of anakinra versus low-dose anakinra (OR, 9.63; 95% CI, 1.31 to 70.91) and versus placebo (OR, 3.40; 95% CI 1.11 to 10.46, respectively). Leombruno et al.⁶ analyzed 18 RCTs of three anti-TNF biologics up to 2007 (N=8,808) and found no significant increase in serious infections (OR, 1.21; 95% CI, 0.89 to 1.63), but found higher risk in patients receiving 2-3 times higher than recommended doses of anti-TNF biologic in unadjusted and pooled meta-analysis, but not in exposure-adjusted analyses. Thompson et al.⁸ included 6 RCTs of five anti-TNF biologics in early RA up to 2009 (N=3,419) and found no significant increase in odds of serious infections with biologics compared to MTX (OR, 1.28; 95% CI, 0.82 to 2.00).

Our findings focus solely on results reported in RCTs. These studies are often limited in that elderly and high-risk patients are often underrepresented, and that treatments are often compared with placebo as opposed to active treatments. Indeed, the RCTs included in our analysis were largely compared with placebo. Accordingly, our risk estimates mostly represent biologics + DMARD versus DMARD comparisons. However, “no treatment” may

not be considered a realistic comparator in clinical practice. As such, we conducted several analyses where we compared biologics with combination or triple DMARD therapy. For these analyses, the odds ratio was slightly higher (**Appendix 6, 9 and 10**) but more uncertain because this comparison was only based on data from 4 recent RCTs comparing biologics plus DMARD with combination or triple DMARD therapy. However, the majority of these trials for this comparison did indeed report a higher number of serious infections among the biologic group. Complementary evidence to meta-analyses of RCTs is provided by non-randomized studies. A recent review has summarized the range of effect estimates reported in non-randomized studies, where effect estimates for biologics versus DMARDs have ranged from 1.0 to 2.2.³¹ While there have been differences among non-randomized studies, these studies have reported that there is an association with infection that is higher early in the course of treatment, but that declines with time.^{31,32} However, the latter finding should be interpreted with caution – studies investigating the long-term use of DMARD treatment are limited to highly selected populations who are adherent and responding well to DMARDs.

These findings have practical implications. The benefits of biologic therapy for patients with RA are well known, and now these patients, at time of decision-making regarding treatment with biologics, can consider these benefits alongside the absolute risk increase of serious infections with biologic therapy (6 per 1000 for standard-dose biologic to 55 per 1000 for combination biologic therapy). Clinical guidelines should also reflect this finding that this risk differs by several patient characteristics, such as previous DMARD exposure, concurrent use of traditional DMARD or not, established vs. early RA, is important information that should also be discussed.

Our study findings must be interpreted considering the following limitations. Our analysis includes studies, which span a 15-year period. Patients enrolled in early studies may differ from those included in more recent studies. We conducted a sensitivity analysis investigating this issue. We found that the point estimate for the odds ratio remained above unity over the 15-year period (**Appendix 6**) but decreased from 1995-1999 (OR, 1.59; 95% CrI, 0.29 to 8.79) to 2010-2014 (OR, 1.11; 95% CrI, 0.76 to 1.62). It is unclear whether the decrease in relative effect is evidence that the risk of biologics causing serious infections is declining over time or attributable to changes in regions where recent trials were performed or duration of placebo application among included studies (i.e., increased use of rescue medications for placebo arm); slight change in the inclusion/exclusion criteria of included RCTs may have occurred over time including that greater proportion of RCTs in recent years excluded patients with positive TB tests. Future research is needed in this area.

There are a number of other limitations, which warrant consideration. We observed variability across studies in terms of duration of RA, duration of follow-up and other covariates (**Appendix 12**). Therefore, we report findings for a number of sub-groups of patients to allow comparisons across patient groups (**Figure 3; Appendices 6 and 8**). Second, meta-analyses and NMA of less frequent outcomes are more challenging due to the inherent difficulties in handling of zero cells. To manage this issue, we conducted a number of analyses using different statistical models and assumptions.²⁶ Results were consistent using alternative approaches (**Appendix 7**). Most studies presented the data using ITT or modified ITT, rather than as-treated analyses, which may underestimate the serious infection risk. In addition, withdrawals were labeled due to adverse events, but not serious infections and some patients may have discontinued biologic before these qualified for serious

infections. However the magnitude is likely small, given the low number of withdrawals and crossovers reported. Data on compliance with drugs was not reported in most RCTs; however, these expensive drugs are usually dispensed and adherence recorded as part of the RCT conduct. Finally, our analyses only incorporate published data. Future work should focus on integrating more unpublished data⁵ if it becomes available. The lack of detailed patient level data, particularly on steroid use, also limits interpretation of these analyses.

CONCLUSIONS

Standard-dose and high-dose biologics (with/without DMARDs) are associated with an increase in serious infections compared to traditional DMARDs in RA, while low-dose biologics are not. This new knowledge, when balanced against the demonstrated clinically important benefits of biologics, will help patients and their physicians make evidence-based decisions that align with their values, preferences and tolerance of risks of harm and benefits.

TABLES AND FIGURES

Table 1: Summary of patient and study characteristics among populations of patients with rheumatoid arthritis

	All Populations	Traditional DMARD naïve	Traditional DMARD experienced	TNF Experienced
Number of trials	106 (100%)	24 (22.6%)	71 (67%)	11 (10.4%)
No. of patients in trials	42,330 (100%)	8,375 (19.8%)	29,167 (68.9%)	4,788 (11.3%)
No. of patients with serious infection	965 (100%)	227 (23.5%)	646 (66.9%)	92 (9.5%)
Median year of Publication (range)	2008 (1992-2013)	2006 (1992-2013)	2008 (1994-2013)	2008 (2005-2013)
No. of treatment nodes	10	5	10	6
No. of 2-arm trials	63	19	38	6
No. of multi-arm trials	43	5	33	5
Mean follow-up duration, months (range)	9 (1,60)	13.1 (3,24)	8 (1,60)	6.3 (2,12)
Proportion of trials with duration ≥12 months	31.1%	70.8%	25.4%	18.2%
Mean RA duration, years (range)	6.9 (0.1,13.5)	0.7 (0.1,3.5)	8.5 (2.2,13.5)	10.8 (6.4,12.9)
Mean annualized baseline risk of serious infection in traditional DMARDs arms (range)*	2% (0%, 9.2%)	2% (0%, 9.2%)	2% (0%, 8%)	2.4% (0%, 4.5%)

DMARD= disease-modifying anti-rheumatic drugs; MTX=methotrexate; RCT=randomized controlled trial; TNF= Tumor necrosis factor

* Only included trials greater than 6 months in duration for calculation

Figure 1: PRISMA Diagram of selection of studies

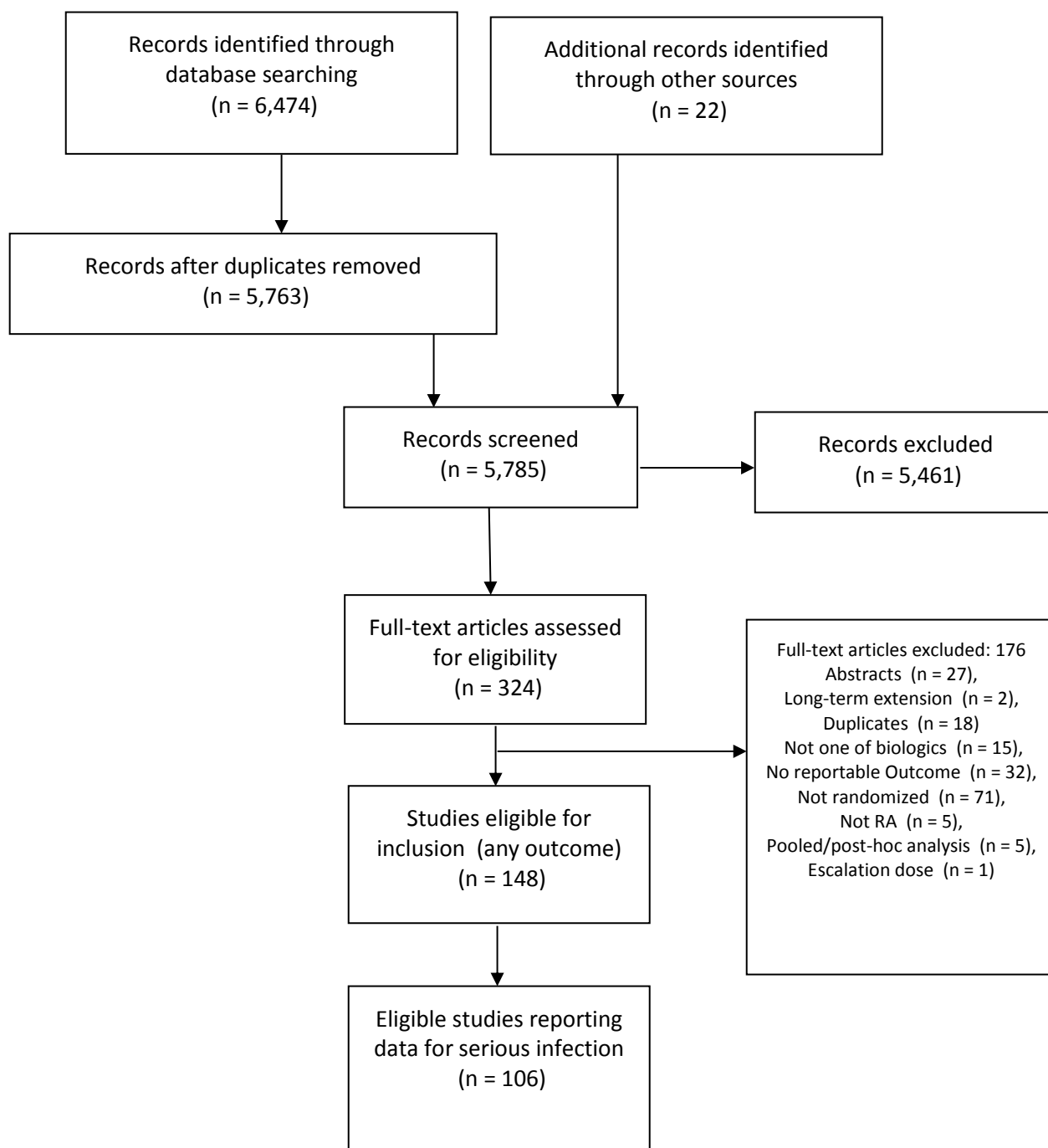
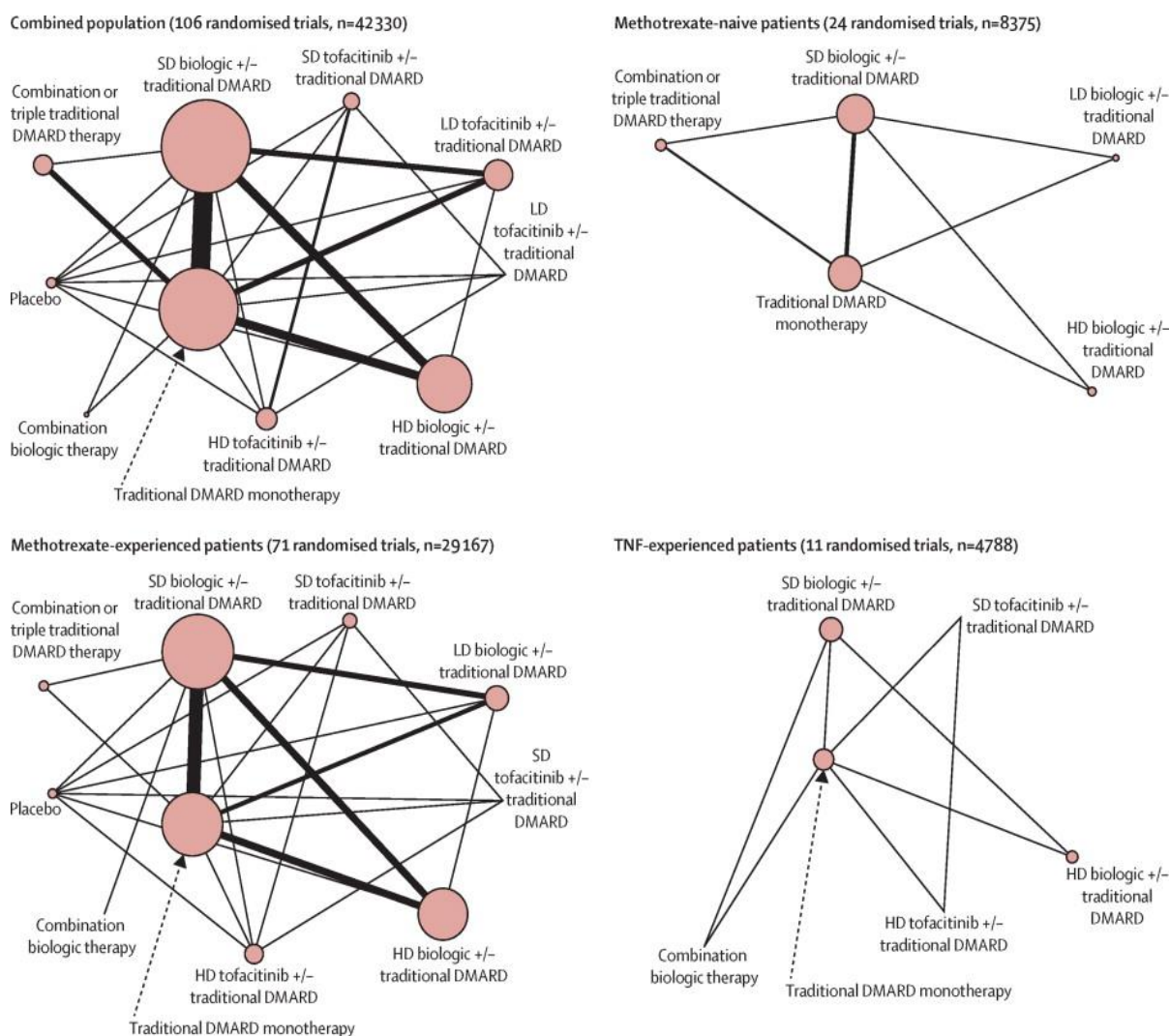
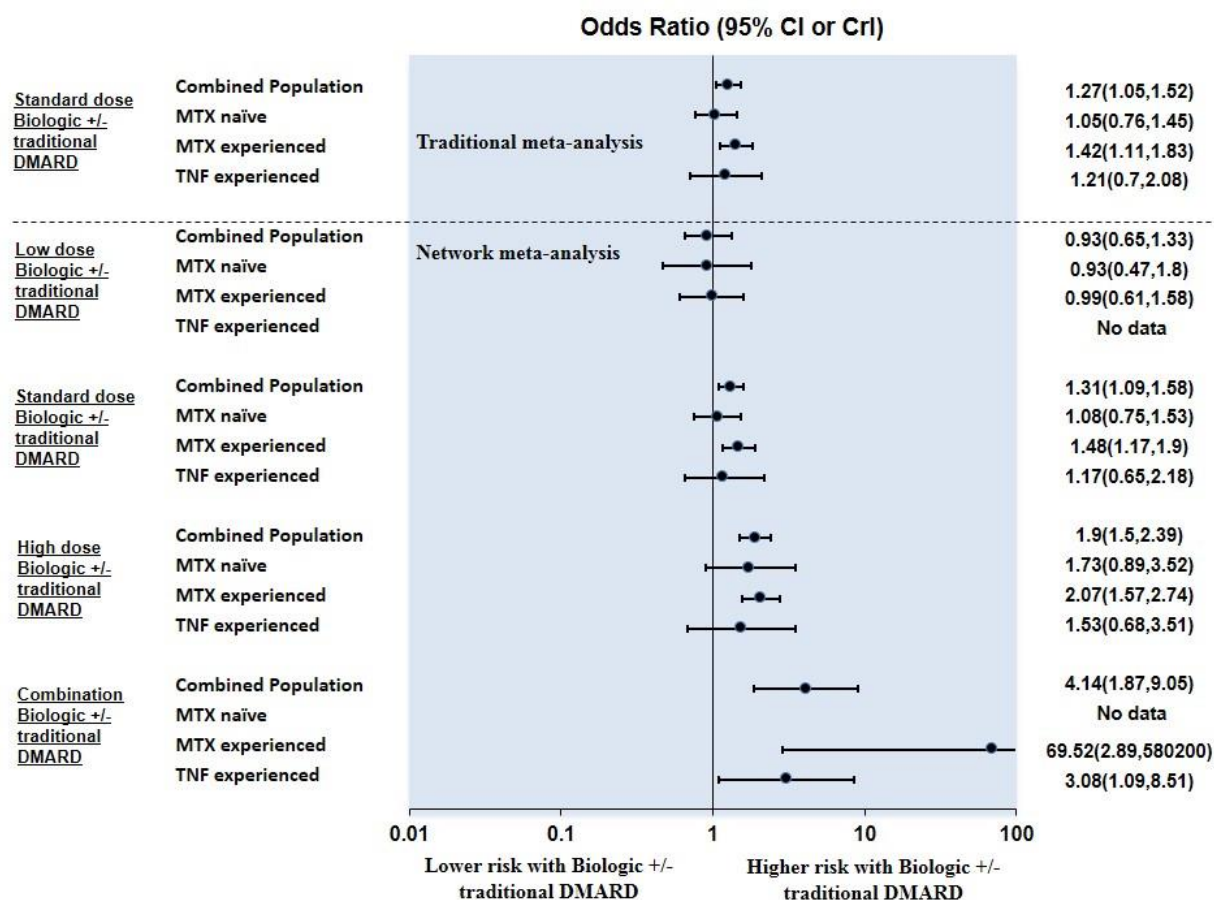


Figure 2: Evidence networks for serious infection among populations. The width of the lines is proportional to the number of randomized controlled trials comparing each pair of treatments, and the size of each treatment node is proportional to the number of randomized participants (sample size).



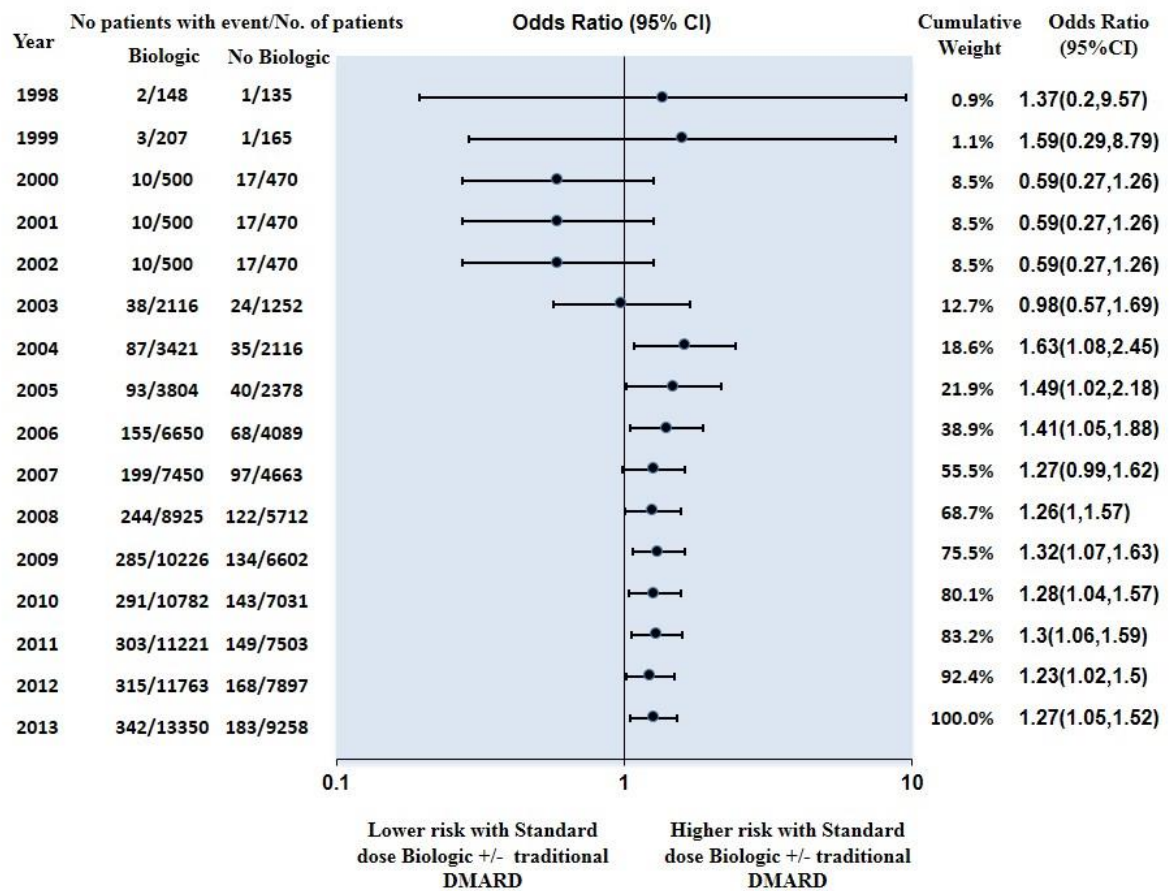
DMARD= disease-modifying anti-rheumatic drugs; MTX=methotrexate; RCT= randomized controlled trial

Figure 3: Summary of findings from traditional meta-analysis and network meta-analysis for serious infection among populations compared with traditional DMARD monotherapy.



CI= confidence interval; CrI= Credible interval; DMARD= disease-modifying anti-rheumatic drugs;
RCT= randomized controlled trial

Figure 4: Cumulative meta-analysis – Risk of serious infection among patients using standard dose biologics +/- traditional DMARD compared with traditional DMARD monotherapy



DMARDs= disease-modifying anti-rheumatic drugs; RCT= randomized controlled trial

REFERENCES

1. Scott DL, Wolfe F, Huizinga TW. Rheumatoid arthritis. *Lancet* 2010; **376**(9746): 1094-108.
2. Tugwell P, Singh JA, Wells GA. Biologicals for rheumatoid arthritis. *BMJ* 2011; **343**: d4027.
3. Singh JA, Furst DE, Bharat A, et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. *Arthritis Care Res (Hoboken)* 2012; **64**(5): 625-39.
4. Smolen JS, Landewe R, Breedveld FC, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Ann Rheum Dis* 2014; **73**(3): 492-509.
5. Ioannidis JP, Karassa FB, Druyts E, Thorlund K, Mills EJ. Biologic agents in rheumatology: unmet issues after 200 trials and \$200 billion sales. *Nature reviews Rheumatology* 2013; **9**(11): 665-73.
6. Leombruno JP, Einarson TR, Keystone EC. The safety of anti-tumour necrosis factor treatments in rheumatoid arthritis: meta and exposure-adjusted pooled analyses of serious adverse events. *Ann Rheum Dis* 2009; **68**(7): 1136-45.
7. Salliot C, Dougados M, Gossec L. Risk of serious infections during rituximab, abatacept and anakinra treatments for rheumatoid arthritis: meta-analyses of randomised placebo-controlled trials. *Ann Rheum Dis* 2009; **68**(1): 25-32.

8. Thompson AE, Rieder SW, Pope JE. Tumor necrosis factor therapy and the risk of serious infection and malignancy in patients with early rheumatoid arthritis: a meta-analysis of randomized controlled trials. *Arthritis Rheum* 2011; **63**(6): 1479-85.
9. Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. *JAMA : the journal of the American Medical Association* 2006; **295**(19): 2275-85.
10. Dixon WG, Symmons DP, Lunt M, Watson KD, Hyrich KL, Silman AJ. Serious infection following anti-tumor necrosis factor alpha therapy in patients with rheumatoid arthritis: lessons from interpreting data from observational studies. *Arthritis Rheum* 2007; **56**(9): 2896-904.
11. Schneeweiss S, Setoguchi S, Weinblatt ME, et al. Anti-tumor necrosis factor alpha therapy and the risk of serious bacterial infections in elderly patients with rheumatoid arthritis. *Arthritis Rheum* 2007; **56**(6): 1754-64.
12. Wolfe F, Caplan L, Michaud K. Treatment for rheumatoid arthritis and the risk of hospitalization for pneumonia: associations with prednisone, disease-modifying antirheumatic drugs, and anti-tumor necrosis factor therapy. *Arthritis Rheum* 2006; **54**(2): 628-34.
13. Grijalva CG, Chen L, Delzell E, et al. Initiation of tumor necrosis factor-alpha antagonists and the risk of hospitalization for infection in patients with autoimmune diseases. *JAMA : the journal of the American Medical Association* 2011; **306**(21): 2331-9.
14. Askling J, Forel CM, Brandt L, et al. Time-dependent increase in risk of hospitalisation with infection among Swedish RA patients treated with TNF antagonists. *Ann*

Rheum Dis 2007; **66**(10): 1339-44.

15. Strangfeld A, Eveslage M, Schneider M, et al. Treatment benefit or survival of the fittest: what drives the time-dependent decrease in serious infection rates under TNF inhibition and what does this imply for the individual patient? *Ann Rheum Dis* 2011; **70**(11): 1914-20.
16. Galloway JB, Hyrich KL, Mercer LK, et al. Anti-TNF therapy is associated with an increased risk of serious infections in patients with rheumatoid arthritis especially in the first 6 months of treatment: updated results from the British Society for Rheumatology Biologics Register with special emphasis on risks in the elderly. *Rheumatology (Oxford)* 2011; **50**(1): 124-31.
17. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. Available at <http://handbook.cochrane.org>: The Cochrane Collaboration; 2011.
18. Hoaglin DC, Hawkins N, Jansen JP, et al. Conducting indirect-treatment-comparison and network-meta-analysis studies: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 2. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research* 2011; **14**(4): 429-37.
19. Jansen JP, Fleurence R, Devine B, et al. Interpreting indirect treatment comparisons and network meta-analysis for health-care decision making: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 1. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research* 2011; **14**(4): 417-28.
20. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS medicine* 2009; **6**(7): e1000097.

21. Singh JA, Wells GA, Christensen R, et al. Adverse effects of biologics: a network meta-analysis and Cochrane overview. *Cochrane Database Syst Rev* 2011; (2): CD008794.
22. Singh JA, Christensen R, Wells GA, et al. Biologics for rheumatoid arthritis: an overview of Cochrane reviews. *Cochrane Database Syst Rev* 2009; (4): CD007848.
23. Gaujoux-Viala C, Nam J, Ramiro S, et al. Efficacy of conventional synthetic disease-modifying antirheumatic drugs, glucocorticoids and tofacitinib: a systematic literature review informing the 2013 update of the EULAR recommendations for management of rheumatoid arthritis. *Ann Rheum Dis* 2014.
24. Katchamart W, Trudeau J, Phumethum V, Bombardier C. Methotrexate monotherapy versus methotrexate combination therapy with non-biologic disease modifying anti-rheumatic drugs for rheumatoid arthritis. *Cochrane Database Syst Rev* 2010; (4): CD008495.
25. Higgins JP, Altman DG, Sterne JA. Chapter 8: Assessing risk of bias in included studies. *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from <http://www.cochrane-handbook.org>. In: Higgins JP, Green S, eds.; 2011.
26. Bradburn MJ, Deeks JJ, Berlin JA, Russell Localio A. Much ado about nothing: a comparison of the performance of meta-analytical methods with rare events. *Statistics in medicine* 2007; **26**(1): 53-77.
27. Spiegelhalter D, Thomas A, Best N. WinBUGS user manual. Version 1.4, January 2003. MRC Biostat. Unit 2.
<https://faculty.washington.edu/jmiyamot/p548/spiegelhalter%20winbugs%20user%20manual.pdf>. 2003.
28. Dias S, Sutton AJ, Ades AE, Welton NJ. Evidence synthesis for decision making 2: a

generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials. *Medical decision making : an international journal of the Society for Medical Decision Making* 2013; **33**(5): 607-17.

29. Turner RM, Davey J, Clarke MJ, Thompson SG, Higgins JP. Predicting the extent of heterogeneity in meta-analysis, using empirical data from the Cochrane Database of Systematic Reviews. *International journal of epidemiology* 2012; **41**(3): 818-27.

30. Dias S, Welton NJ, Sutton AJ, Caldwell DM, Lu G, Ades AE. Evidence synthesis for decision making 4: inconsistency in networks of evidence based on randomized controlled trials. *Medical decision making : an international journal of the Society for Medical Decision Making* 2013; **33**(5): 641-56.

31. Bernatsky S, Habel Y, Rahme E. Observational studies of infections in rheumatoid arthritis: a metaanalysis of tumor necrosis factor antagonists. *J Rheumatol* 2010; **37**(5): 928

32. Novosad SA, Winthrop KL. Beyond tumor necrosis factor inhibition: the expanding pipeline of biologic therapies for inflammatory diseases and their associated infectious sequelae. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2014; **58**(11): 1587-98.

APPENDICES

Appendix 1 (on line): Search Strategy

Database: Cochrane Library, Issue 2, 2014

Description:

ID	Search
#1	MeSH descriptor: [Antibodies, Monoclonal] explode all trees
#2	MeSH descriptor: [Monokines] explode all trees
#3	MeSH descriptor: [Receptors, Interleukin-1] explode all trees
#4	MeSH descriptor: [Receptors, Interleukin-6] explode all trees
#5	MeSH descriptor: [Immunoglobulin G] explode all trees
#6	MeSH descriptor: [Immunoconjugates] explode all trees
#7	MeSH descriptor: [Polyethylene Glycols] explode all trees
#8	MeSH descriptor: [Immunoglobulin Fab Fragments] explode all trees
#9	MeSH descriptor: [T-Lymphocytes] explode all trees
#10	adalimumab:ti,ab
#11	humira:ti,ab
#12	trudexa:ti,ab
#13	abatacept:ti,ab
#14	orencia:ti,ab
#15	anakinra:ti,ab
#16	kineret:ti,ab
#17	Certolizumab:ti,ab
#18	cimzia:ti,ab
#19	Etanercept:ti,ab
#20	enbrel:ti,ab
#21	Golimumab:ti,ab
#22	simponi:ti,ab
#23	rituximab:ti,ab
#24	rituxan:ti,ab
#25	mabthera:ti,ab
#26	Tocilizumab:ti,ab
#27	actemra:ti,ab
#28	RoActemra:ti,ab
#29	infliximab:ti,ab
#30	remicade:ti,ab
#31	(#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30)
#32	rheumatoid:ti,ab
#33	arthritis:ti,ab
#34	felty near/2 syndrome
#35	caplan near/2 syndrome
#36	rheumatoid nodule

- #37 sjogren* near/2 syndrome
- #38 still* next disease
- #39 arthritis near/2 rheumat*
- #40 MeSH descriptor: [Arthritis, Rheumatoid] explode all trees
- #41 (#32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40)
- #42 #31 and #41

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to 2014 February 11>
Search Strategy:

-
- 1 exp arthritis, rheumatoid/
 - 2 (arthritis adj2 rheumat\$).tw.
 - 3 (felty\$ adj2 syndrome).tw.
 - 4 (caplan\$ adj2 syndrome).tw.
 - 5 rheumatoid nodule.tw.
 - 6 (sjogren\$ adj2 syndrome).tw.
 - 7 still\$ disease.tw.
 - 8 or/1-7
 - 9 exp antibodies, monoclonal/
 - 10 exp monokines/ (117104)
 - 11 exp receptors, interleukin-1/
 - 12 exp receptors, interleukin-6/
 - 13 exp immunoglobulin g/
 - 14 exp immunoconjugates/
 - 15 exp polyethylene glycols
 - 16 exp immunoglobulin fab fragments/
 - 17 exp t-lymphocytes/
 - 18 Infliximab.tw.
 - 19 remicade.tw.
 - 20 adalimumab.tw.
 - 21 humira.tw.
 - 22 trudexa.tw.
 - 23 abatacept.tw.
 - 24 orenica.tw.
 - 25 anakinra.tw.
 - 26 kineret.tw.
 - 27 Certolizumab.tw.
 - 28 cimzia.tw.
 - 29 Etanercept.tw.
 - 30 enbrel.tw.
 - 31 Golimumab.tw.
 - 32 simponi.tw.
 - 33 rituximab.tw.
 - 34 rituxan.tw.
 - 35 mabthera.tw.
 - 36 Tocilizumab.tw.
 - 37 actemra.tw.
 - 38 RoActemra.tw.
 - 39 or/9-36
 - 40 randomized controlled trial.pt.

41 controlled clinical trial.pt.
 42 randomized.ab.
 43 placebo.ab.
 44 clinical trials as topic.sh.
 45 randomly.ab.
 46 trial.ti.
 47 or/40-46
 48 exp animals/ not humans.sh.
 49 47 not 48
 50 8 and 39 and 49
 51 limit 50 to ed=20080101-20130507
 52 limit 50 to yr="2008 -Current"
 53 18 or 19
 54 8 and 39 and 53
 55 limit 54 to ed=20060101-20130507
 56 limit 54 to yr="2006 -Current"
 57 51 or 52
 58 55 or 56
 59 57 or 58

Database: Embase Classic+Embase <1947 to 2014 February 11>
Search Strategy:

 1 exp arthritis, rheumatoid/
 2 (arthritis adj2 rheumat\$).tw.
 3 (felty\$ adj2 syndrome).tw.
 4 (caplan\$ adj2 syndrome).tw.
 5 rheumatoid nodule.tw.
 6 (sjogren\$ adj2 syndrome).tw.
 7 still\$ disease.tw.
 8 or/1-7
 9 exp monoclonal antibody/
 10 exp monokine/
 11 exp interleukin 1 receptor/
 12 exp interleukin 6 receptor/
 13 exp antibody conjugate/
 14 exp immunoglobulin G/
 15 exp macrogol derivative/
 16 exp "immunoglobulin F(ab) fragment"/
 17 exp T lymphocyte/
 18 infliximab.mp. or exp infliximab/
 19 remicade.mp.
 20 humira.mp. or exp adalimumab/
 21 trudexa.mp.
 22 abatacept.mp. or exp abatacept/
 23 orenia.mp.
 24 anakinra.mp. or recombinant interleukin 1 receptor blocking agent/
 25 kineret.mp.
 26 cimzia.mp. or exp certolizumab pegol/
 27 enbrel.mp. or exp etanercept/

28 simponi.mp. or exp golimumab/
 29 rituxan.mp. or exp rituximab/
 30 mabthera.mp.
 31 actemra.mp. or exp tocilizumab/
 32 RoActemra.mp.
 33 or/9-32
 34 8 and 33
 35 random:.tw.
 36 placebo:.mp.
 37 double-blind:.tw.
 38 or/35-37
 39 34 and 38

Tofacitinib search

Search Name: tofacitinib
Description:

ID	Search
#1	(tofacitinib or tasocitinib) in Trials
#2	(cp690550 or "cp-690550" or "cp 690550" or "cp-690,550" or "cp 690,550" or "cp-690 550" or "cp 690 550") in Trials
#3	(#1 or #2)
#4	(rheumat* near/5 arthrit*) in Trials
#5	MeSH descriptor: [Arthritis, Rheumatoid] explode all trees
#6	(stills or still's or felty* or sjogren* or sicca* or sjoegren* or vasculit* or arthrit* or caplan*) in Trials
#7	(#4 or #5 or #6)
#8	(#3 and #7)

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to 2014 February 11>

Search Strategy:

1	tofacitinib.mp.
2	tasocitinib.mp.
3	cp690550.mp.
4	"cp 690550".mp.
5	"cp 690 550".mp.
6	or/1-5
7	exp Arthritis, Rheumatoid/
8	(rheumatoid adj5 arthrit*).mp.
9	(stills or still's or felty* or sjogren* or sicca* or sjoegren* or vasculit* or arthrit* or caplan*).mp.
10	or/7-9
11	6 and 10

Database: Embase Classic+Embase <1947 to 2014 February 11>

Search Strategy:

-
- 1 tofacitinib.mp.
 - 2 tasocitinib.mp.
 - 3 Xeljanz.mp.
 - 4 cp690550.mp.
 - 5 "cp 690550".mp.
 - 6 "cp 690 550".mp.
 - 7 or/1-5
 - 8 exp Arthritis, Rheumatoid/
 - 9 (rheumatoid adj5 arthrit*).mp
 - 10 (stills or still's or felty* or sjogren* or sicca* or sjogren* or vasculit* or arthrit* or caplan*).mp.
 - 11 or/8-10
 - 12 7 and 11

Appendix 2 (on line): Sensitivity analysis removing tofacitinib treatment nodes from the analysis

Tofacitinib was not pooled with other biologics but treated as a separate treatment node within the analysis (**Figure 2**). We included tofacitinib in the primary analysis as a separate node to improve precision and because we wanted this review to be up-to-date and include all relevant treatment options for the management of rheumatoid arthritis. This is particularly important because we want this review to be dynamic and updated as new information evolves over time, including information on newer treatments such as tofacitinib. However, we opted to not include effect estimates on the risk of serious infection for tofacitinib in the main text at this time because 1) tofacitinib was not the focus of this review; 2) we do not report effect estimates for individual biologics, 3) conclusions regarding tofacitinib and the risk of serious infection may be premature because comparisons for tofacitinib may be underpowered at this time (similar to individual biologics), and 4) we observed some inconsistency for studies which included tofacitinib (**Appendix 10**).

We investigated the impact of including tofacitinib in the analysis as a separate node by running an analysis where we remove tofacitinib studies from the evidence network. Inclusion of tofacitinib in the evidence network had negligible impact on results (Table 1a) but allows us to easily update our analysis as new information become available. Results were nearly identical in analyses with and without tofacitinib, although inclusion of tofacitinib did result in a very small reduction in the between study standard deviation (0.1513 vs. 0.1524) and an increase in the number of studies (106 vs.98), patients (42,330 vs. 38,527), and patients who had a serious infection (965 vs. 934).

Appendix 2a – Comparison of effect estimates from Primary analysis and analysis removing tofacitinib from the evidence network

<u>Comparison</u>	<u>Primary Analysis</u>	<u>Sensitivity analysis removing tofacitinib</u>
Combination or triple traditional DMARD therapy vs Traditional DMARD monotherapy	0.84(0.48,1.48)	0.85(0.49,1.51)
SD Biologic +/- Traditional DMARD vs Traditional DMARD monotherapy	1.31(1.09,1.58)	1.31(1.10,1.59)
SD Tofacitinib +/- Traditional DMARD vs Traditional DMARD monotherapy	0.97(0.31,3.36)	NA
LD Biologic +/- Traditional DMARD vs Traditional DMARD monotherapy	0.93(0.65,1.33)	0.94(0.64,1.33)
LD Tofacitinib +/- Traditional DMARD vs Traditional DMARD monotherapy	2.32(0.6,10.74)	NA
HD Biologic +/- Traditional DMARD vs Traditional DMARD monotherapy	1.9(1.50,2.39)	1.89(1.50,2.38)
HD Tofacitinib +/- Traditional DMARD vs Traditional DMARD monotherapy	1.93(0.83,5.25)	NA
Combination Biologic vs Traditional DMARD monotherapy	4.14(1.87,9.05)	4.17(1.90,9.16)
Placebo vs SD Biologic +/- Traditional DMARD	0.57(0.19,1.28)	0.37(0.10,1.03)
Number of trials	106	98
No. of patients in trials	42,330	38,527
No. of patients with serious infection	965	934
Residual deviance	225.6 vs 265	207.3 vs 237
DIC	1040.87	953.69
Between study standard deviation	0.1513	0.1524

Appendix 3 (on line): Methods Supplement

Data Extraction – Patient and study characteristics

The following patient and study characteristics were extracted: Patient characteristics (age, RA duration); prior DMARD/biologic treatment (MTX naïve, MTX-experienced, non-MTX traditional DMARD experienced, or TNF-experienced); study characteristics (year and month of publication, length of follow-up, adaptive design); risk of bias in individual RCTs using the risk of bias tool as recommended by the Cochrane Collaboration (sequence generation, allocation concealment, blinding, incomplete outcome data, and selective outcome reporting), rating each item with (low, high or unclear bias) and each trial with an overall risk of bias in terms of low risk (low for all key domains), high risk (high for ≥ 1 key domains), and unclear risk (unclear for ≥ 1 key domains); intervention (type, dose and duration, concomitant MTX therapy and dose, monotherapy versus combination therapy; and comparator characteristics (placebo or active comparator with details on type, dose, concomitant methotrexate therapy, monotherapy versus combination therapy. The dose classification of each biologic is provided below. Doses above these doses were classified as high dose biologics and those below were classified as low dose biologics.

Appendix 3a. Dose classification of each biologic

Drug	Standard approved U.S. dose
Infliximab	3mg/kg intravenous every 8 weeks after initial dosing at 0, 2 and 6 weeks
Etanercept	25 mg subcutaneous twice weekly
Adalimumab	40 mg subcutaneous every 2 weeks
Golimumab	SQ: 50 mg subcutaneous every 4 weeks IV: 2 mg/kg given as an intravenous infusion at weeks 0 and 4, then every 8 weeks
Certolizumab	400 mg (given as two subcutaneous injections of 200 mg) initially and at Weeks 2 and 4, followed by 200 mg every other week. For maintenance dosing, 400 mg every 4 weeks can be considered.
Anakinra	100 mg subcutaneous every day
Abatacept	IV: (10 mg/kg every 4 weeks): every 4 weeks intravenously at 500 mg dose in patients <60 kg, 750 mg in patients 60-100 kg and 1000 mg in patients >100 kg, after the initial dosing regimen of baseline, 2 and 4-week infusions; SQ: After a single intravenous infusion as a loading dose (as per body weight categories above), 125 mg administered by a subcutaneous injection should be given within a day, followed by 125 mg subcutaneously once a week.
Tocilizumab	4 mg/kg intravenously every 4 weeks followed by an increase to 8 mg/kg based on clinical response
Rituximab	Two 1000 mg IV doses 2 weeks apart
Tofacitinib	5 mg bid PO

Assessment of model fit, convergence and inconsistency

Assessment of model fit was based on deviance information criterion (DIC) and comparison of residual deviance.¹ To ensure convergence was reached, trace plots and the Brooks-Gelman-Rubin statistic were assessed.¹ Three chains were fit in WinBUGS for each analysis, with at least 40,000 iterations, and a burn-in of at least 40,000 iterations.¹ To assess consistency (there is no conflict between direct and indirect evidence),² we compared deviance and DIC statistics in fitted consistency and inconsistency models.² We also plotted the posterior mean deviance of the individual data points in the inconsistency model against their posterior mean deviance in the consistency model to identify where inconsistency is present.

Assessment of Publication Bias

We assessed the publication bias for standard dose biologic versus non-biologic treatments by evaluating a funnel plot of the trial mean differences for asymmetry. The symmetry of such 'funnel plots' was assessed both visually, and formally with Egger's test.

Pre-specified sub-group and sensitivity analyses

We also pre-specified the following analyses: (1) MTX-naïve, MTX experienced (inadequate responders/failures) and TNF-experienced populations; (2) Anti-TNF biologics vs. other biologic; (3) individual biologics; (4) treatment duration with biologics: short (<6 months), intermediate duration (6 to 12 months) or long-duration (>1 year); (5) RA disease duration: categorized as early RA defined as duration of less than 2 years³ vs. established RA, duration 2 to 10 years vs. late RA defined as >10 years.⁴ Finally, we conducted detailed statistical analyses to ensure that findings were robust to type of analysis performed and assumptions around how to handle cells with zero events.

Handling Zero Cells

We also conducted numerous sensitivity analyses related to methods for handling zero cells.^{5, 6} We conducted numerous analyses to ensure robustness of results irrespective of how zeroes were handled (**Appendix 6**). We also did not exclude double/multiple zeroes cells to provide analytic consistency and because exclusion may cause an artificial small increase the effect size of serious infection.⁵ Finally, since treatment arms within some studies have differential sample size, we did not apply a constant 0.5 continuity correction which would have biased estimates but instead applied an adjusted continuity correction factor centered around 0.5 and accounting for differential sample sizes among the arms.⁶

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References

1. Spiegelhalter, D., Thomas, A. & Best, N. WinBUGS user manual. MRC Biostat. Unit 2, (2004).
2. Dias, S., Welton, N.J., Sutton, A.J., et al. NICE Technical Support Document 4: Inconsistency in Networks of Evidence Based on Randomised Controlled Trials. 1–39 (2011). at www.nicedsu.org.uk

3. Boers M. Rheumatoid arthritis. Treatment of early disease. *Rheumatic diseases clinics of North America* 2001;27:405-14.
4. Singh JA, Christensen R, Wells GA, et al. Biologics for rheumatoid arthritis: an overview of Cochrane reviews (Protocol). *Cochrane Database of Systematic Reviews* 2009.
5. Bradburn MJ, Deeks JJ, Berlin JA, Russell Localio A. Much ado about nothing: a comparison of the performance of meta-analytical methods with rare events. *Statistics in medicine* 2007; **26**(1): 53-77.
6. Friedrich JO, Adhikari NK, Beyene J. Inclusion of zero total event trials in meta-analyses maintains analytic consistency and incorporates all available data. *BMC medical research methodology* 2007; **7**: 5.

Appendix 4 (on line): Summary of Included Trials

Author and Year	N	Patient Population	Treatment 1	Treatment 2	Treatment 3	Treatment 4	Treatment 5	MTX	Duration of RA	Biologic-naïve	DMARD-naïve	Mono-Biologic	TIME of Outcome abstracted	Trial Duration
Abe 2006	147	MTX experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	HD Biologic +/- Traditional DMARD	NA	NA	7.5-30	7.9	yes	no	yes	3 months	3 months
Bathon (ERA) 2000	632	MTX naïve	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	LD Biologic +/- Traditional DMARD	NA	NA	7.5-30	1	no	no	yes	24 months	24 months
Bejarano 2008	148	MTX naïve	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	NA	NA	NA	7.5-30	0.7	yes	no	yes	13 months	13 months
Breedveld 2006	799	MTX naïve	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	NA	NA	NA	7.5-30	0.8	yes	no	yes	24 months	24 months
Bresnihan 1998	472	DMARD experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	LD Biologic +/- Traditional DMARD	HD Biologic +/- Traditional DMARD	NA	n/a	3.9	yes	no	yes	6 months	6 months
Burmester 2013	399	TNF experienced	Traditional DMARD monotherapy	SD Tofacitinib +/- Traditional DMARD	HD Tofacitinib +/- Traditional DMARD	NA	NA	7.5-30	12.3	no	no	yes	6 months	6 months
Chen 2009	47	DMARD experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	NA	NA	NA	7.5-30	6	no	no	yes	3 months	3 months
Choy 2012	247	MTX experienced	Traditional DMARD monotherapy	HD Biologic +/- Traditional DMARD	NA	NA	NA	7.5-30	9.7	no?	no	yes	6 months	6 months
Cohen 2004	501	MTX experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	NA	NA	NA	7.5-30	11.5	yes	no	yes	6 months	12 months
Cohen 2002	137	MTX experienced	Traditional DMARD monotherapy	LD Biologic +/- Traditional DMARD	NA	NA	NA	7.5-30	7.4	yes	no	yes	6 months	6 months

Author and Year	N	Patient Population	Treatment 1	Treatment 2	Treatment 3	Treatment 4	Treatment 5	MTX	Duration of RA	Biologic-naive	DMARD-naive	Mono-Biologic	TIME of Outcome abstracted	Trial Duration
Cohen 2006	520	TNF experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	NA	NA	NA	7.5-30	12.1	no	no	yes	6 months	24 months
Combe 2009	254	DMARD experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	NA	NA	NA	n/a	5.6	no	no	yes	24 months	24 months
Conaghan 2013	50	MTX experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	NA	NA	NA	7.5-30	2.2	0	0	yes	4 months	12 months
de Jong 2013	179	MTX naïve	Traditional DMARD monotherapy	Combination or triple traditional DMARD therapy	NA	NA	NA	7.5-30	0.4	no	no	yes	3 months	3 months
Detert 2013	172	MTX naïve	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	NA	NA	NA	7.5-30	0.14	yes	yes	yes	6 months	11 months
Dougados 1999	137	MTX naïve	Traditional DMARD monotherapy	MTX + non-MTX traditional DMARD	NA	NA	NA	7.5-30	0.2	no	no	yes	12 months	12 months
Durez 2007	29	MTX naïve	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	NA	NA	NA	7.5-30	0.4	no	no	yes	12 months	12 months
Edwards 2004	120	MTX experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	NA	NA	NA	7.5-31	10.4	yes	no	yes	6 months	12 months
Emery (RADIATE) 2008a	498	TNF experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	HD Biologic +/- Traditional DMARD	NA	NA	7.5-30	12.6	no	no	yes	4 months	6 months
Emery (COMET) 2008	542	MTX naïve	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	NA	NA	NA	7.5-30	0.7	yes	no	yes	12 months	24 months
Emery (DANCER) 2006	483	DMARD experienced	Traditional DMARD	SD Biologic +/- Traditional	LD Biologic +/- Traditional	NA	NA	7.5-30	10.8	no	no	yes	6 months	6 months

Author and Year	N	Patient Population	Treatment 1	Treatment 2	Treatment 3	Treatment 4	Treatment 5	MTX	Duration of RA	Biologic-naive	DMARD-naive	Mono-Biologic	TIME of Outcome abstracted	Trial Duration
			monotherapy	DMARD	DMARD									
Emery (GO-BEFORE) 2009	637	MTX naive	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	HD Biologic +/- Traditional DMARD	NA	NA	7.5-30	3.5	no	no	yes	6 months	12 months
EMERY (SERENE) 2010a	512	MTX experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	LD Biologic +/- Traditional DMARD	NA	NA	7.5-30	7.1	yes	no	yes	6 months	11 months
Fleischman 2003	1399	DMARD experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	NA	NA	NA	n/a	10.2	yes	no	yes	6 months	6 months
Fleischman_Marc h 2012	331	DMARD experienced	SD Tofacitinib +/- Traditional DMARD	LD Tofacitinib +/- Traditional DMARD	HD Tofacitinib +/- Traditional DMARD	Placebo	NA	7.5-30	8.1	no?	no	no	3 months	6 months
Fleischmann (FAST4WARD) 2009	220	DMARD experienced	SD Biologic +/- Traditional DMARD	Placebo	NA	NA	NA	n/a	8.7	no	no	yes	6 months	6 months
Fleischmann _ August 2012	610	DMARD experienced	SD Tofacitinib +/- Traditional DMARD	HD Tofacitinib +/- Traditional DMARD	Placebo	NA	NA	7.5-30	8.1	no?	no	yes	3 months	6 months
Furst 2003	636	DMARD experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	NA	NA	NA	n/a	9.3	yes	no	yes	6 months	6 months
Gabay (ADACTA) 2013	326	MTX experienced	Traditional DMARD monotherapy	HD Biologic +/- Traditional DMARD	NA	NA	NA	n/a	6.8	yes	no	yes	6 months	6 months
Genovese (TOWARD) 2008	1220	DMARD experienced	Traditional DMARD monotherapy	HD Biologic +/- Traditional DMARD	NA	NA	NA	7.5-30	9.8	yes	no	yes	6 months	6 months
Genovese 2004	241	MTX	Traditional DMARD	Combination	NA	NA	NA	7.5-30	9.9	no	no	no	6 months	6 months

Author and Year	N	Patient Population	Treatment 1	Treatment 2	Treatment 3	Treatment 4	Treatment 5	MTX	Duration of RA	Biologic-naive	DMARD-naive	Mono-Biologic	TIME of Outcome abstracted	Trial Duration
		experienced	monotherapy	Biologic										
Genovese 2005	391	TNF experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	NA	NA	NA	no	12.2	no	no	yes	6 months	6 months
Greenwald 2011*	54	TNF experienced	Traditional DMARD monotherapy	Combination Biologic	NA	NA	NA	7.5-30	10.4	no	no	no	6 months	6 months
Haagsma 1994	40	MTX experienced	Traditional DMARD monotherapy	Combination or triple traditionall DMARD therapy	NA	NA	NA	7.5-30	5	no	no	yes	5.5 months	5.5 months
Haagsma 1997	71	MTX naïve	Traditional DMARD monotherapy	Combination or triple traditionall DMARD therapy	NA	NA	NA	7.5-30	0.3	no	no	yes	12 months	12 months
Hanyu 1999	37	MTX experienced	Traditional DMARD monotherapy	Combination or triple traditionall DMARD therapy	NA	NA	NA	7.5-30	13.5	no	no	yes	60 months	60 months
Heijde (TEMPO Pt reported outcomes) 2007	682	DMARD experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	NA	NA	NA	7.5-30	6.4	yes	no	yes	36 months	36 months
Hetland 2006	160	MTX naïve	Traditional DMARD monotherapy	Combination or triple traditionall DMARD therapy	NA	NA	NA	7.5-30	0.3	no	no	yes	12 months	12 months
Ichikawa 2005	47	MTX naïve	Traditional DMARD monotherapy	Combination or triple traditionall DMARD therapy	NA	NA	NA	7.5-30	0.8	no	no	yes	22 months	22 months
Jones 2010	572	TNF experienced	Traditional DMARD	HD Biologic +/- Traditional	NA	NA	NA	7.5-30	6.4	yes	no	yes	6 months	6 months

Author and Year	N	Patient Population	Treatment 1	Treatment 2	Treatment 3	Treatment 4	Treatment 5	MTX	Duration of RA	Biologic-naive	DMARD-naive	Mono-Biologic	TIME of Outcome abstracted	Trial Duration
			monotherapy	DMARD										
Kaine 2011	120	MTX experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	NA	NA	NA	<=10	6.6	no	no	yes	4 months	9 months
Kavanaugh (OPTIMA) 2013	1032	MTX naïve	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	NA	NA	NA	7.5-30	0.3	yes	no	yes	6 months	6 months
Kay 2008	104	MTX experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	HD Biologic +/- Traditional DMARD	NA	NA	7.5-30	7.8	no	no	yes	4 months	11 months
Keystone (GO-FORWARD) 2010	444	MTX experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	HD Biologic +/- Traditional DMARD	NA	NA	7.5-31	5.9	no	no	yes	4 months	12 months
Keystone 2004	619	MTX experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	LD Biologic +/- Traditional DMARD	NA	NA	7.5-30	11	yes	no	yes	12 months	12 months
Keystone 2004	420	MTX experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	NA	NA	NA	7.5-30	8.9	no	no	yes	4 months	4 months
Keystone 2008	982	MTX experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	HD Biologic +/- Traditional DMARD	NA	NA	7.5-30	6.2	no	no	no	6 months	12 months
Kim 2007	128	DMARD experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	NA	NA	NA	7.5-30	6.8	yes	no	yes	6 months	6 months
Kim 2012	300	MTX experienced	Combination or triple traditional DMARD therapy	SD Biologic +/- Traditional DMARD	NA	NA	NA	7.5-30	6.7	yes	no	yes	4 months	4 months
Kremer 2002	263	MTX experienced	Traditional DMARD	Combination or triple traditional	NA	NA	NA	7.5-30	11.6	no	no	yes	5.5 months	5.5 months

Author and Year	N	Patient Population	Treatment 1	Treatment 2	Treatment 3	Treatment 4	Treatment 5	MTX	Duration of RA	Biologic-naive	DMARD-naive	Mono-Biologic	TIME of Outcome abstracted	Trial Duration
			monotherapy	DMARD therapy										
Kremer 2005	339	DMARD experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	LD Biologic +/- Traditional DMARD	NA	NA	7.5-30	9.7	no	no	yes	6 months	12 months
Kremer 2006	652	MTX experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	NA	NA	NA	7.5-30	8.7	no	no	yes	12 months	12 months
Kremer 2009	195	TNF experienced	Traditional DMARD monotherapy	SD Tofacitinib +/- Traditional DMARD	HD Tofacitinib +/- Traditional DMARD	NA	NA	n/a	8.7	no	no	yes	2 months	3 months
Kremer 2010	645	MTX experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	LD Biologic +/- Traditional DMARD	NA	NA	7.5-30	7.9	no	no	yes	4 months	11 months
Kremer 2010	1190	MTX experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	HD Biologic +/- Traditional DMARD	NA	NA	7.5-30	9.2	no	no	yes	12 months	24 months
Kremer 2012	442	MTX experienced	Traditional DMARD monotherapy	SD Tofacitinib +/- Traditional DMARD	LD Tofacitinib +/- Traditional DMARD	HD Tofacitinib +/- Traditional DMARD	NA	7.5-30	9.6	no	no	yes	3 months	6 months
Kremer 2013	795	DMARD Experienced	Traditional DMARD monotherapy	SD Tofacitinib +/- Traditional DMARD	HD Tofacitinib +/- Traditional DMARD	NA	NA	n/a	8.9	no	no	yes	3 months	12 months
Lan 2004	58	MTX experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	NA	NA	NA	7.5-30	8.5	no	no	yes	3 months	3 months
Lipsky 2000	261	MTX experienced	Traditional DMARD	SD Biologic +/- Traditional	HD Biologic +/- Traditional	NA	NA	7.5-30	10	yes	no	yes	12 months	12 months

Author and Year	N	Patient Population	Treatment 1	Treatment 2	Treatment 3	Treatment 4	Treatment 5	MTX	Duration of RA	Biologic-naive	DMARD-naive	Mono-Biologic	TIME of Outcome abstracted	Trial Duration
			monotherapy	DMARD	DMARD									
Maini (CHARISMA) 2006	359	MTX experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	LD Biologic +/- Traditional DMARD	HD Biologic +/- Traditional DMARD	NA	7.5-30	9.6	no	no	yes	5 months	5 months
Maini 1998	101	MTX experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	LD Biologic +/- Traditional DMARD	HD Biologic +/- Traditional DMARD	NA	7.5-30	10	yes	no	yes	6 months	6 months
Marchesoni 2003	58	MTX naïve	Traditional DMARD monotherapy	Combination or triple traditionall DMARD therapy	NA	NA	NA	7.5-30	0.9	no	no	yes	12 months	12 months
Miyasaka (CHANGE) 2008	352	DMARD experienced	SD Biologic +/- Traditional DMARD	LD Biologic +/- Traditional DMARD	HD Biologic +/- Traditional DMARD	Placebo	NA	n/a	9.9	yes	no	yes	6 months	6 months
Moreland (TEAR) 2012	500	MTX naïve	Traditional DMARD monotherapy	Combination or triple traditionall DMARD therapy	SD Biologic +/- Traditional DMARD	NA	NA	7.5-30	0.3	yes	yes	yes	6 months	6 months
Nishimoto (SAMURAI) 2007	306	DMARD experienced	Traditional DMARD monotherapy	HD Biologic +/- Traditional DMARD	NA	NA	NA	<=10	2.4	no	no	yes	12 months	12 months
Nishimoto (SATORI) 2009	127	MTX experienced	Traditional DMARD monotherapy	HD Biologic +/- Traditional DMARD	NA	NA	NA	<=10	8.6	yes	no	yes	6 months	6 months
O'Dell 1996	102	MTX experienced	Traditional DMARD monotherapy	Combination or triple traditionall DMARD therapy	NA	NA	NA	7.5-30	8.6	no	no	yes	24 months	24 months
O'Dell 2006	48	MTX naïve	Traditional DMARD monotherapy	Combination or triple traditionall DMARD	NA	NA	NA	7.5-30	0.4	no	no	yes	24 months	24 months

Author and Year	N	Patient Population	Treatment 1	Treatment 2	Treatment 3	Treatment 4	Treatment 5	MTX	Duration of RA	Biologic-naive	DMARD-naive	Mono-Biologic	TIME of Outcome abstracted	Trial Duration
therapy														
O'Dell 2013	441	MTX experienced	Combination or triple traditional DMARD therapy	SD Biologic +/- Traditional DMARD	NA	NA	NA	7.5-30	5.2	yes	no	yes	6 months	12 months
Ogrendik 2007	76	MTX experienced	Traditional DMARD monotherapy	Combination or triple traditional DMARD therapy	NA	NA	NA	7.5-30	12	no	no	yes	6 months	6 months
Pavelka 2009	141	MTX experienced	SD Biologic +/- Traditional DMARD	HD Biologic +/- Traditional DMARD	NA	NA	NA	n/a	13	no	no	yes	12 months	12 months
Quinn 2005	20	MTX naive	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	NA	NA	NA	7.5-30	0.5	yes	yes	yes	12 months	24 months
Rau 2004	54	MTX experienced	Traditional DMARD monotherapy	LD Biologic +/- Traditional DMARD	NA	NA	NA	7.5-30	11.1	no	no	yes	1 month	1 month
Rubbert-Roth 2010	378	MTX experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	LD Biologic +/- Traditional DMARD	NA	NA	7.5-30	8.8	yes	no	yes	11 months	11 months
Schiff 2008	431	MTX experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	NA	NA	NA	7.5-30	7	yes	no	yes	6 months	12 months
Smolen (GO-AFTER) 2009a	461	TNF experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	HD Biologic +/- Traditional DMARD	NA	NA	n/a	9.4	no	no	yes	6 months	6 months
Smolen (RAPID 2) 2008	619	MTX experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	HD Biologic +/- Traditional DMARD	NA	NA	7.5-30	6	no	no	yes	6 months	12 months

Author and Year	N	Patient Population	Treatment 1	Treatment 2	Treatment 3	Treatment 4	Treatment 5	MTX	Duration of RA	Biologic-naive	DMARD-naive	Mono-Biologic	TIME of Outcome abstracted	Trial Duration
Smolen 2008 (OPTION)	623	MTX experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	HD Biologic +/- Traditional DMARD	NA	NA	7.5-30	7.6	no	no	yes	4 months	8 months
Smolen 2013	604	MTX experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	LD Biologic +/- Traditional DMARD	NA	NA	7.5-30	6.9	yes	no	yes	22 months	22 months
St. Clair (ASPIRE) 2004	1040	MTX naïve	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	HD Biologic +/- Traditional DMARD	NA	NA	7.5-30	0.8	yes	no	yes	12 months	12 months
Taciolglu 2003	55	MTX naïve	Traditional DMARD monotherapy	Combination or triple traditional DMARD therapy	NA	NA	NA	7.5-30	0.6	no	no	yes	12 months	12 months
Tada (PRECEPT) 2012	70	DMARD experienced	SD Biologic +/- Traditional DMARD	LD Biologic +/- Traditional DMARD	NA	NA	NA	<=10	9	no	no	yes	12 months	12 monthss
Tak 2012	748	MTX naïve	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	LD Biologic +/- Traditional DMARD	NA	NA	7.5-30	0.9	yes	yes	yes	24 months	24 months
Takeuchi 2013	316	DMARD Experienced	SD Biologic +/- Traditional DMARD	HD Biologic +/- Traditional DMARD	Placebo	NA	NA	n/a	8.9	no?	no	yes	4 months	6 months
Takeuchi 2013b	548	DMARD Experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	HD Biologic +/- Traditional DMARD	NA	NA	<=10	3	yes?	no	yes	12 months	12 months
Takeuchi 2014	334	MTX naïve	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	NA	NA	NA	<=10	0.3	yes	yes	yes	6 months	6 months
Tanaka (GO-	269	MTX	Traditional DMARD	SD Biologic +/- Traditional	HD Biologic +/-	NA	NA	<=10	8.6	yes	no	yes	3 months	6 months

Author and Year	N	Patient Population	Treatment 1	Treatment 2	Treatment 3	Treatment 4	Treatment 5	MTX	Duration of RA	Biologic-naive	DMARD-naive	Mono-Biologic	TIME of Outcome abstracted	Trial Duration
FORTH) 2012		experienced	monotherapy	DMARD	Traditional DMARD									
Tanaka 2011	112	MTX experienced	Traditional DMARD monotherapy	SD Tofacitinib +/- Traditional DMARD	LD Tofacitinib +/- Traditional DMARD	HD Tofacitinib +/- Traditional DMARD	NA	<=10	7.6	no	no	yes	3 months	3 months
Tugwell 1995	148	MTX experienced	Traditional DMARD monotherapy	MTX + non-MTX traditional DMARD	NA	NA	NA	7.5-30	10.3	no	no	yes	6 months	6 months
van de Putte 2003	284	DMARD experienced	SD Biologic +/- Traditional DMARD	LD Biologic +/- Traditional DMARD	HD Biologic +/- Traditional DMARD	Placebo	NA	no	10	yes	no	yes	3 months	3 months
Van de Putte 2004	544	DMARD experienced	SD Biologic +/- Traditional DMARD	LD Biologic +/- Traditional DMARD	HD Biologic +/- Traditional DMARD	Placebo	NA	n/a	10.6	yes	no	yes	6 months	6 months
van der Heijde 2013	718	MTX experienced	Traditional DMARD monotherapy	SD Tofacitinib +/- Traditional DMARD	HD Tofacitinib +/- Traditional DMARD	NA	NA	7.5-30	9.1	no	no	yes	12 months	12 months
Vollenhoven (SWEFOT) 2012	258	MTX naive	Combination or riple traditional DMARD therapy	SD Biologic +/- Traditional DMARD	NA	NA	NA	7.5-30	0.5	no	yes	yes	24 months	24 months
Vollenhoven 2012a	717	MTX experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	HD Tofacitinib +/- Traditional DMARD	NA	NA	7.5-30	7.8	no	no	yes	3 months	12 months
Weinblatt (Go FURTHER)	592	MTX experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	NA	NA	NA	7.5-30	7	yes	no	yes	6 months	6 months

Author and Year	N	Patient Population	Treatment 1	Treatment 2	Treatment 3	Treatment 4	Treatment 5	MTX	Duration of RA	Biologic-naive	DMARD-naive	Mono-Biologic	TIME of Outcome abstracted	Trial Duration
Weinblatt 1999	89	MTX experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	NA	NA	NA	7.5-30	13	yes	no	yes	6 months	6 months
Weinblatt 2003	271	DMARD experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	LD Biologic +/- Traditional DMARD	HD Biologic +/- Traditional DMARD	NA	7.5-30	12.2	yes	no	yes	6 months	6 months
Weinblatt 2006	121	TNF experienced	SD Biologic +/- Traditional DMARD	Combination Biologic	NA	NA	NA	n/a	12.9	no	no	no	12 months	12 months
Weinblatt 2006	1377	TNF experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	Combination Biologic	NA	NA	7.5-30	11.3	no	no	yes	12 months	12 months
Weinblatt 2008	200	TNF experienced	SD Biologic +/- Traditional DMARD	HD Biologic +/- Traditional DMARD	NA	NA	NA	7.5-30	10	no	no	yes	3 months	3 months
Weinblatt 2012	1063	DMARD Experienced	Traditional DMARD monotherapy	HD Biologic +/- Traditional DMARD	NA	NA	NA	n/a	8.7	no?	no	yes	3 months	3 months
Weisman 2007	535	DMARD experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	NA	NA	NA	7.5-30	10.1	yes	no	yes	4 months	4 months
Westhovens (START) 2006	1084	MTX experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	HD Biologic +/- Traditional DMARD	NA	NA	7.5-30	7.5	yes	no	yes	5 months	24 months
Westhovens 2009a	509	MTX naïve	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	NA	NA	NA	7.5-30	0.5	no	no	yes	12 months	24 months
Williams 1992	220	MTX naïve	Traditional DMARD monotherapy	MTX + non-MTX traditional DMARD	NA	NA	NA	7.5-30	0.9	no	no	yes	6 months	6 months
Yazici 2012	619	DMARD	Traditional DMARD	HD Biologic +/- Traditional	NA	NA	NA	n/a	8.5	no	no	yes	4 months	6 months

Author and Year	N	Patient Population	Treatment 1	Treatment 2	Treatment 3	Treatment 4	Treatment 5	MTX	Duration of RA	Biologic- naive	DMARD- naive	Mono- Biologic	TIME of Outcome abstracted	Trial Duration
		experienced	monotherapy	DMARD										

Appendix 5 (on line): Risk of Bias assessment; + = low risk of bias; - = high risk of bias; ? = unclear risk of bias

	Random sequence generation	Allocation concealment	Blinding of assessor	Blinding of participants	Incomplete outcome data	Selective reporting	Major baseline imbalance	Funding source	Risk of Bias
Abe 2006	?	?	?	?	+	+	+	?	Unclear
Bathon 2000	?	-	-	-	-	?	+	+	High
Breedveld 2006	?	?	+	+	-	?	+	-	Low
Burmester 2013	+	+	?	?	-	?	+	-	Low
Chen 2009	?	?	?	?	-	?	+	?	Unclear
Combe 2009	?	?	?	?	-	+	-	-	Unclear
Durez 2007	?	?	+	?	+	+	+	?	Unclear
Emery 2006	?	?	?	?	-	-	+	-	Unclear
Emery 2008a	?	?	?	?	-	+	+	-	Unclear
Emery 2009	+	+	+	+	+	?	+	?	Low
Fleischmann 2009	+	?	+	?	-	+	+	-	Unclear
Gabay 2013	+	+	?	?	-	?	+	-	Low
Genovese 2008	?	?	+	?	-	?	+	-	Unclear
Greenwald 2011	?	?	?	?	-	?	+	-	Unclear
Jones 2010	?	?	?	?	-	?	+	-	Unclear
Kavanaugh 2013	+	+	?	?	-	?	+	-	Low
Kay 2008	?	?	+	+	-	?	+	-	Low
Keystone 2004a	?	?	+	+	-	?	+	-	Low

Keystone 2008	?	?	+	?	+	+	+	-	Unclear
Keystone 2009	+	+	+	+	-	+	+	-	Low
Kim 2012	?	?	-	-	-	?	+	-	High
Kremer 2005	+	+	?	?	-	+	+	-	Low
Kremer 2010	+	+	?	+	-	?	+	-	Low
Lan 2004	?	?	?	?	-	-	+	-	Unclear
Maini 1999	+	+	?	?	-	+	+	-	Low
Maini 2006	+	+	+	+	-	+	+	-	Low
Nishimoto 2007	+	+	-	-	-	?	+	-	High
Nishimoto 2009	?	?	?	?	-	?	+	-	Unclear
Pavelka 2009	?	?	?	?	-	?	+	+	Unclear
Putte 2003	?	?	?	?	-	?	+	-	Unclear
Rubbert-Roth 2010	+	+	?	?	-	?	+	-	Low
Smolen 2008	+	+	+	?	-	?	+	-	Low
Smolen 2009	?	?	-	-	?	+	+	-	High
Smolen 2009a	+	+	+	+	-	?	+	-	Low
Smolen 2013	+	+	-	-	-	?	+	-	High
St. Clair 2004	+	+	-	-	-	+	+	-	High
Tada 2012	+	+	-	-	?	?	+	-	High
Tak 2012	?	?	?	?	-	?	+	-	Unclear
Tanaka 2011	?	?	?	?	-	?	+	-	Unclear
Tanaka 2012	?	?	?	?	-	?	+	-	Unclear

Vollenhoven 2012	+	+	-	-	+	?	+	-	High
Vollenhoven 2012a	+	+	?	?	-	?	+	-	Low
Weinblatt 2008	?	?	?	?	-	?	+	-	Unclear
Weinblatt 2013	+	+	?	?	-	?	+	-	Low
Weisman 2007	?	?	?	?	-	?	+	-	Unclear
Westhovens 2006	+	?	+	+	-	+	+	-	Low
Westhovens 2009a	?	?	?	?	-	+	+	-	Unclear
Yazici 2012	?	?	?	?	-	?	+	-	Unclear
Dougados 1999	?	?	+	?	+	?	+	-	Unclear
Haagsma 1997	+	?	?	+	+	?	-	-	Unclear
Hetland 2006	+	+	+	+	+	?	-	-	Low
Ichikawa 2005	?	?	?	+	+	?	+	-	Unclear
Marchesoni 2003	+	?	?	-	+	?	+	+	High
O'Dell 2006	+	+	?	?	-	?	+	?	Low
Tacioglu 2003	?	-	?	-	-	?	+	?	High
Williams 1992	+	?	?	+	?	?	+	+	Unclear
Moreland 2012	+	+	+	+	+	?	-	-	Low
de Jong 2013	+	?	+	-	+	?	-	-	High
Keystone (GO-FORWARD) 2010	+	+	+	+	+	?	?	-	Low
Lipsky 2000	?	?	+	-	-	?	+	-	High
Emery (SERENE)	?	?	?	?	+	?	+	-	Unclear

2010a									
van der Heijde 2013	+	?	+	+	+	?	+	-	Low
Rau 2004	?	?	?	?	+	?	+	-	Unclear
Kremer 2012	?	?	?	+	+	?	+	-	Unclear
Kremer 2010	?	?	+	+	+	?	+	-	Low
O'Dell 2013	?	?	+	?	-	?	+	-	Unclear
Haagsma 1994	?	?	-	-	+	?	+	?	High
Kremer 2002	+	+	+	+	+	?	+	-	Low
Hanyu 1999	?	?	-	-	-	?	+	?	High
Ogrendik 2007	?	?	?	?	+	?	+	?	Unclear
Tugwell 1995	?	?	+	+	+	?	+	-	Low
O'Dell 1996	+	+	+	+	-	?	+	-	Low
Weinblatt (Aug.) 2006	+	+	+	+	-	?	+	-	Low
Cohen 2006	?	?	+	+	-	+	+	-	Low
Weinblatt (Sept.) 2006	?	?	?	?	?	?	-	-	Unclear
Kremer 2009	?	?	?	?	+	?	+	-	Unclear
Heijde (TEMPO) 2007	?	?	+	+	-	-	+	-	Low
Flesichmann (Aug.) 2012	+	+	?	?	?	?	-	-	Low
Bresnihan 1998	?	?	+	+	+	?	+	-	Low
Flesichmann	?	?	?	+	+	?	+	-	Unclear

(March) 2012									
Weinblatt 2012	+	?	?	?	+	?	+	-	Unclear
Choy 2012	+	?	+	+	-	?	+	-	Low
Kaine 2011	?	?	?	+	+	?	+	-	Unclear
Kremer 2013	?	?	?	?	+	?	-	-	Unclear
Takeuchi 2013	?	?	+	+	-	?	+	-	Low
Takeuchi 2013b	+	+	+	+	+	?	+	-	Low
Takeuchi 2014	?	?	+	+	+	?	+	-	Low
Conaghan 2013	+	+	+	+	+	?	+	-	Low
Detert 2013	?	?	+	+	+	?	+	-	Low
Bejarano 2008	+	+	+	+	+	?	+	-	Low
Quinn 2005	+	+	?	+	?	?	-	-	Low
Cohen 2004	?	?	+	?	+	?	+	-	Unclear
Edwards 2004	?	?	?	+	+	-	+	-	Unclear
Schiff 2008	?	?	+	+	+	?	+	-	Low
Emery 2008 (COMET)	+	+	+	+	-	?	+	-	Low
Kremer 2006	+	+	?	+	+	?	+	-	Low
Cohen 2002	?	?	+	?	?	?	+	-	Unclear
Genovese 2004	?	?	+	+	+	?	+	-	Low
Weinblatt 1999	?	?	+	?	+	?	+	-	Unclear
Genovese 2005	?	?	?	+	+	?	+	-	Unclear
Furst 2003	?	?	+	?	+	?	+	-	Unclear

Miyasaka 2008	?	?	?	?	+	+	?	-	Unclear
Van De Putte 2004	+	?	?	?	-	+	+	-	Unclear
Flesichmann 2003	?	?	+	+	+	+	+	-	Low
Kim 2007	?	?	?	?	-	-	+	-	Unclear
Weinblatt 2003	?	?	?	+	+	+	+	-	Unclear

+ = low risk of bias
 - = high risk of bias
 ? = unclear risk of bias

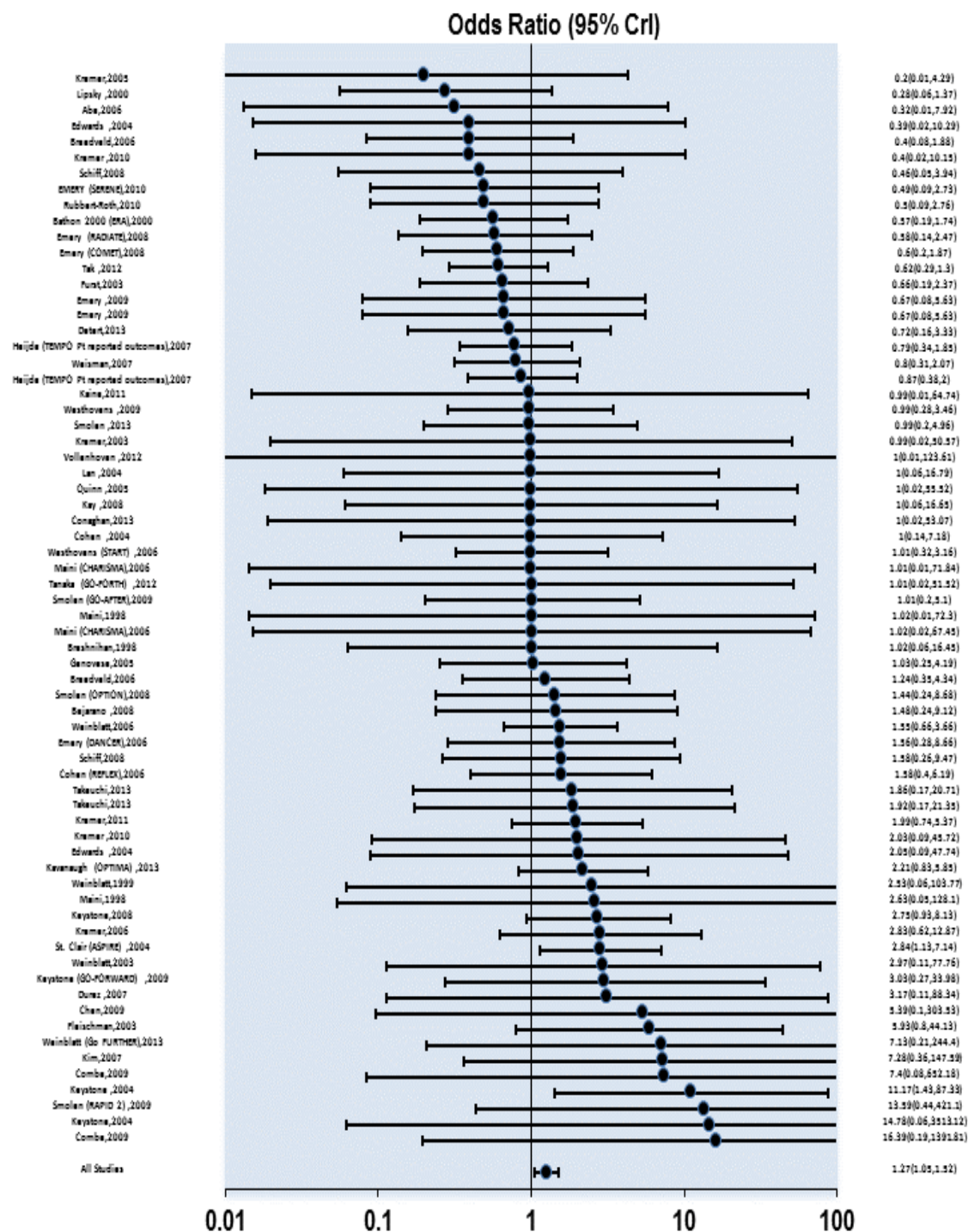
Appendix 6 (on line): Summary of findings from traditional meta-analyses on risk of serious infection for standard dose biologics (Odds ratios (95% CI)) in rheumatoid arthritis

	<u>All Populations</u>	<u>Traditional DMARD naïve</u>	<u>Traditional DMARD experienced</u>	<u>TNF Experienced</u>
<u>All standard dose biologics</u>	1.27(1.05,1.52)	1.05(0.76,1.45)	1.43(1.11,1.83)	1.21(0.71,2.08)
<u>Biologic +/- traditional DMARD</u>				
Abatacept	1.26(0.75,2.11)	0.99(0.28,3.46)	1.19(0.47,3.05)	1.41(0.67,2.90)
Adalimumab	1.86(1.15,3.01)	1.52(0.82,2.80)	2.55(1.16,5.66)	NA
Anakinra	2.71(0.86,8.57)	NA	2.71(0.86,8.57)	NA
Certolizumab	3.61(1.31,9.99)	NA	3.61(1.31,9.99)	NA
Etanercept	0.97(0.60,1.57)	0.60(0.2,1.80)	1.08(0.64,1.85)	NA
Golimumab	1.14(0.41,3.11)	0.67(0.08,5.63)	1.71(0.34,8.67)	1.01(0.2,5.10)
Infliximab	1.33(0.78,2.28)	2.71(1.11,6.62)	0.76(0.37,1.57)	NA
Rituximab	0.75(0.44,1.26)	0.62(0.29,1.30)	0.70(0.28,1.73)	1.58(0.40,6.19)
Tocilizumab	1.35(0.66,2.75)	NA	1.81(0.77,4.22)	0.58(0.14,2.47)
Tofacitinib*	1.40(0.46,4.33)	NA	1.94(0.53,7.09)	0.52(0.05,5.02)
<u>Anti-TNF vs non-TNF biologic</u>				
Anti-TNF biologic	1.34(1.06,1.69)	1.21(0.83,1.77)	1.44(1.07,1.94)	1.01(0.2,5.10)
Non-TNF biologic	1.15(0.85,1.56)	0.7(0.37,1.32)	1.40(0.89,2.18)	1.24(0.70,2.20)
<u>Duration of follow-up</u>				
Less than 6 months	1.07(0.66,1.73)	NA	1.16(0.69,1.94)	0.58(0.14,2.47)
6 to 12 months	1.59(1.15,2.19)	1.37(0.70,2.71)	1.77(1.18,2.67)	1.21(0.53,2.79)
Greater than or equal to 12 months	1.14(0.88,1.47)	0.97(0.67,1.40)	1.28(0.86,1.92)	1.55(0.66,3.66)
<u>Duration of Rheumatoid arthritis</u>				
Early RA - less than 2 years	1.07(0.77,1.48)	1.07(0.77,1.49)	1.00(0.06,16.79)	NA
Established RA - 2 to 10 years	1.35(1.02,1.77)	0.67(0.15,3.02)	1.39(1.05,1.85)	1.01(0.2,5.10)
Late RA - greater than 10 years	1.418(0.96,2.07)	NA	1.57(0.93,2.63)	1.24(0.70,2.20)
<u>Biologic Monotherapy</u>				
Biologic used in combination with Traditional DMARD	1.34(1.09,1.69)	1.17(0.82,1.67)	1.47(1.12,1.92)	1.21(0.71,2.083)
Biologic not used in combination with Traditional DMARD	0.89(0.54,1.48)	0.61(0.27,1.34)	1.18(0.60,2.34)	NA
<u>Traditional DMARD monotherapy vs. combination therapy</u>				
Traditional DMARD monotherapy	1.27(1.05,1.52)	1.05(0.76,1.45)	1.43 (1.11,1.84)	1.21(0.71,2.08)
Traditional DMARD combination or triple therapy*	1.85(0.85,4.10)	1.21(0.38,3.79)	2.68(0.88,8.23)	NA
<u>Year of study</u>				
1995-1999	1.59(0.29,8.79)	NA	1.59(0.29,8.79)	NA

2000-2004	1.63(1.07,2.48)	1.54(0.80,2.96)	1.69(0.98,2.93)	NA
2005-2009	1.22(0.95,1.56)	0.85(0.50,1.45)	1.39(1.002,1.93)	1.21(0.71,2.08)
2010-2014	1.11(0.76,1.62)	1.00(0.60,1.67)	1.25(0.71,2.20)	NA
<u>Risk of Bias</u>				
Studies with low risk of bias	1.31(1.02,1.69)	1.05(0.66,1.67)	1.43(1.01,2.03)	1.46(0.75,2.81)
Studies with high risk of bias	1.34(0.80,2.25)	1.54(0.80,2.96)	1.50(1.02,2.22)	NA
Studies with unclear risk of bias	1.18(0.87,1.61)	0.74(0.40,1.38)	1.05(0.45,2.48)	0.78(0.29,2.09)
<u>Use of corticosteroids</u>				
Remove RCTs, with greater than 5% difference in proportion of patients using corticosteroids between arms or do not report data	1.44(1.12,1.85)	1.20(0.82,1.77)	1.65(1.13,2.40)	1.56 (0.75,3.22)
Remove RCTs with greater than 10% difference in proportion of patients using corticosteroids between arms or do not report data	1.27(1.01,1.61)	1.20(0.82,1.77)	1.34(0.96,1.87)	1.24(0.70,2.20)

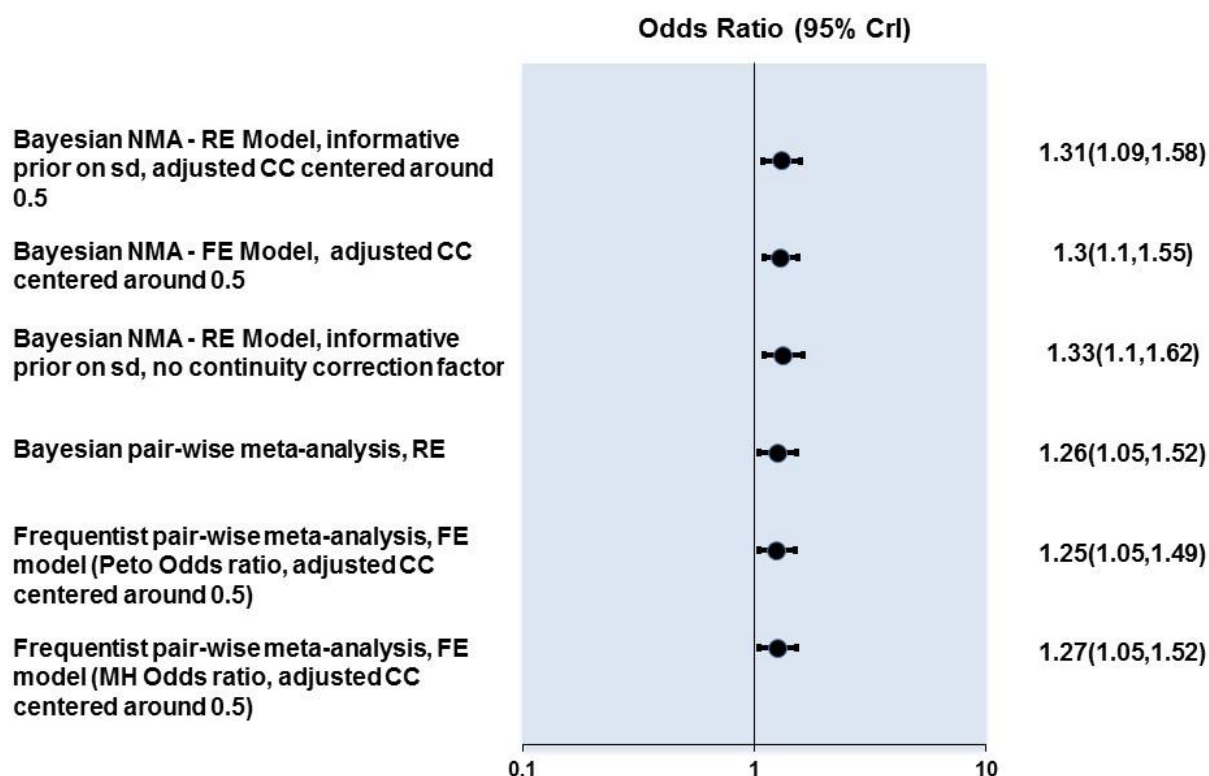
* Studies using Tofacitinib or Traditional DMARD combination or triple therapy are not included in other calculations because they are treated as separate nodes in evidence network
CI= confidence interval; DMARD= disease-modifying antirheumatic drugs; MTX=methotrexate; TNF= Tumor necrosis factors; NA=not available

Appendix 6a. Forest plot for traditional meta-analyses on risk of serious infection for standard dose biologics (Odds ratios (95% CI)) in rheumatoid arthritis



Appendix 7 (on line): Summary of sensitivity analyses for Bayesian network meta-analysis (95% Credible interval)

We did not exclude double/multiple zeroes cells from the Primary analysis to provide analytic consistency and because exclusion may cause an artificial small increase the effect size of serious infection.² Since treatment arms within some studies have differential sample size, we did not apply a constant 0.5 continuity correction, which would have biased estimates but instead applied an adjusted continuity correction factor centered around 0.5 and accounting for differential sample sizes among the arms.¹ Further, we conducted numerous analyses to ensure robustness of results irrespective of how zeroes were handled.¹ Results were similar using a variety of statistical methods:



CC= continuity correction; FE= fixed-effects; MH= Mantel–Haenszel; NMA= network meta-analysis; RE= random-effects; sd= standard deviation

Appendix 8 (on line): Comparison of fixed versus random-effects model of therapies compared to traditional DMARD therapy, using Bayesian network meta-analysis (95% Credible interval)

	Fixed-effects model	Random-Effects model
Combination or triple traditional DMARD therapy vs. Traditional DMARD monotherapy	0.85 (0.48,1.47)	0.84 (0.48,1.48)
SD Biologic +/- Traditional DMARD vs. Traditional DMARD monotherapy	1.3 (1.1,1.55)	1.31 (1.09,1.58)
LD Biologic +/- Traditional DMARD vs. Traditional DMARD monotherapy	0.94 (0.66,1.33)	0.93 (0.65,1.33)
HD Biologic +/- Traditional DMARD vs. Traditional DMARD monotherapy	1.88 (1.51,2.34)	1.9 (1.5,2.39)
Combination Biologic vs. Traditional DMARD monotherapy	4.05 (1.89,8.42)	4.14 (1.87,9.05)

DMARD= disease-modifying antirheumatic drugs; HD= high dose; LD= low dose; SD= standard dose; DIC, deviance information criterion

* Model includes double zero cells rather than excluding double zeroes, which may inflate serious infection risk estimates. However, inclusion of double zeroes also artificially improves the model fit statistics

Appendix 9 (on line): Summary of findings from Bayesian network meta-analyses (NMA) on the risk of serious infection (Odds ratios (95% CrI) for all doses of biologics in rheumatoid arthritis*

	All Populations (106 Studies; N=42,330)	MTX naïve (24 Studies; N=8,775)	MTX experienced (71 Studies; N=29,167)	TNF Experienced (11 Studies; N=4,788)
<u>Compared to traditional DMARD monotherapy</u>				
MTX + non-MTX traditional DMARD	0.84(0.48,1.48)	0.99(0.44,2.14)	0.73(0.3,1.69)	NA
SD Biologic +/- Traditional DMARD	1.31(1.09,1.58)	1.08(0.75,1.53)	1.48(1.17,1.9)	1.17(0.65,2.18)
LD Biologic +/- Traditional DMARD	0.93(0.65,1.33)	0.93(0.47,1.8)	0.99(0.61,1.58)	NA
HD Biologic +/- Traditional DMARD	1.9(1.5,2.39)	1.73(0.89,3.52)	2.07(1.57,2.74)	1.53(0.68,3.51)
Combination Biologic	4.14(1.87,9.05)	NA	69.52(2.89,580200)	3.08(1.09,8.51)
Placebo	0.57(0.19,1.28)	NA	0.64(0.23,1.47)	NA
<u>Compared to combination or triple traditional DMARD therapy</u>				
SD Biologic +/- Traditional DMARD	1.56(0.9,2.73)	1.08(0.5,2.54)	2.04(0.89,4.94)	NA
LD Biologic +/- Traditional DMARD	1.11(0.59,2.14)	0.94(0.34,2.62)	1.36(0.53,3.58)	NA
HD Biologic +/- Traditional DMARD	2.26(1.26,4.07)	1.73(0.66,5.09)	2.83(1.2,7.01)	NA
Combination Biologic	4.94(1.88,12.77)	NA	97.06(3.57,836800)	NA
Placebo	0.67(0.2,1.74)	NA	0.87(0.23,2.92)	NA
<u>Compared to SD Biologic +/- traditional DMARD</u>				
LD Biologic +/- Traditional DMARD	0.71(0.5,1.01)	0.86(0.43,1.66)	0.67(0.42,1.03)	NA
HD Biologic +/- Traditional DMARD	1.45(1.16,1.81)	1.59(0.84,3.2)	1.4(1.06,1.8)	1.31(0.57,3)
Combination Biologic	3.15(1.45,6.92)	NA	46.43(2,387900)	2.63(0.99,6.62)
Placebo	0.44(0.15,0.96)	NA	0.43(0.16,0.96)	NA
<u>Compared to LD Biologic +/- traditional DMARD</u>				
HD Biologic +/- Traditional DMARD	2.03(1.38,3.02)	1.86(0.76,4.81)	2.09(1.31,3.43)	NA
Combination Biologic	4.44(1.9,10.45)	NA	70.91(2.88,562000)	NA
Placebo	0.61(0.2,1.45)	NA	0.64(0.23,1.54)	NA
<u>Compared to HD Biologic +/- traditional DMARD</u>				
Combination Biologic	2.18(0.96,4.92)	NA	33.67(1.42,287000)	2(0.59,6.6)
Placebo	0.3(0.1,0.67)	NA	0.31(0.11,0.7)	NA
<u>Compared to Combination Biologic</u>				
Placebo	0.14(0.04,0.43)	NA	0.01(0,0.25)	NA

CrI= credible interval; DMARD= disease-modifying antirheumatic drugs; TNF= Tumor necrosis factors; NA=not available

* Tofacitinib was included in the network to enhance precision of biologic effect estimates. The effect estimates for tofacitinib are available in Appendix 10 although they should be interpreted with caution due to limited power and inconsistency between direct and indirect evidence (Appendix 9).

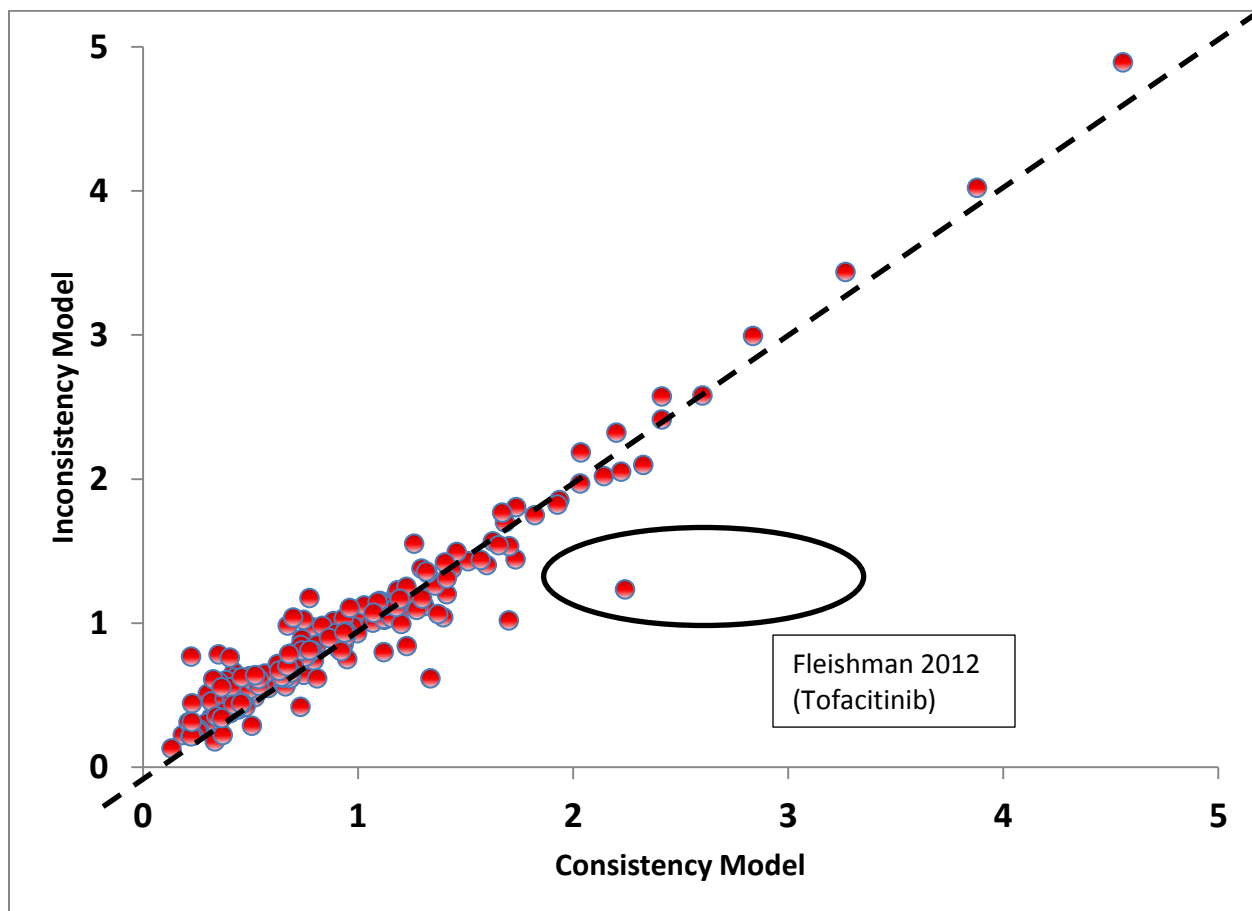
Appendix 9a. Summary of findings from Bayesian network meta-analyses on risk of serious infection (Odds ratios (95% CrI)) - All populations. Odds ratios for serious infections are calculated based on row-defining treatment versus column-defining treatment. To obtain ORs for comparisons in the opposite direction, reciprocals should be taken. Significant results are in bold.

Traditional DMARD monotherapy						
0.84 (0.48,1.48)	Combination or triple DMARD therapy					
1.31 (1.09,1.58)	1.56 (0.9,2.73)	SD Biologic +/- Traditional DMARD				
0.93 (0.65,1.33)	1.11 (0.59,2.14)	0.71 (0.5,1.01)	LD Biologic +/- Traditional DMARD			
1.9 (1.5,2.39)	2.26 (1.26,4.07)	1.45 (1.16,1.81)	2.03 (1.38,3.02)	HD Biologic +/- Traditional DMARD		
4.14 (1.87,9.05)	4.94 (1.88,12.77)	3.15 (1.45,6.92)	4.44 (1.9,10.45)	2.18 (0.96,4.92)	Combination Biologic	
0.57 (0.19,1.28)	0.67 (0.2,1.74)	0.44 (0.15,0.96)	0.61 (0.2,1.45)	0.3 (0.1,0.67)	0.14 (0.04,0.43)	Placebo

Appendix 10 (on line): Assessment of inconsistency

We plotted the posterior mean deviance of the individual data points in the inconsistency model against their posterior mean deviance in the consistency model to help identify loops where inconsistency is present. In our analysis, the posterior mean deviance contributions are very similar and close to 1, for both models. The consistency model has a lower posterior mean of the residual deviance (225.6 vs. 229.1 each versus 265) and DIC (1040.87 vs. 1048.45) and hence is a better fit. One point shows a lower value of the posterior mean deviance in the inconsistency model but these values are not too far from 1. This point is from the Fleishman 2012 study that compares different doses of tofacitinib with placebo.

Appendix 10a- Plot of posterior mean deviance of the individual data points in the inconsistency model against their posterior mean deviance in the consistency model



The effect estimates for Combination or triple traditional DMARD therapy vs Traditional DMARD monotherapy, SD Tofacitinib +/- Traditional DMARD vs Traditional DMARD monotherapy, HD Biologic +/- Traditional DMARD vs SD Biologic +/- Traditional DMARD, and Placebo vs SD Tofacitinib +/- Traditional DMARD are also on different sides of unity.

Appendix 10b - Comparison of effect estimates from consistency and inconsistency models where there were data available for comparison

<u>Comparison</u>	<u>Consistency Model</u>	<u>Inconsistency Model</u>
Combination or triple traditional DMARD therapy vs Traditional DMARD monotherapy	0.84(0.48,1.48)	1.07(0.53,2.13)
SD Biologic +/- Traditional DMARD vs Traditional DMARD monotherapy	1.31(1.09,1.58)	1.26(1.05,1.52)
SD Tofacitinib +/- Traditional DMARD vs Traditional DMARD monotherapy	0.97(0.31,3.36)	1.72(0.47,6.37)
LD Biologic +/- Traditional DMARD vs Traditional DMARD monotherapy	0.93(0.65,1.33)	0.87(0.59,1.29)
LD Tofacitinib +/- Traditional DMARD vs Traditional DMARD monotherapy	2.32(0.6,10.74)	3.06(0.5,17.08)
HD Biologic +/- Traditional DMARD vs Traditional DMARD monotherapy	1.9(1.5,2.39)	1.95(1.51,2.49)
HD Tofacitinib +/- Traditional DMARD vs Traditional DMARD monotherapy	1.93(0.83,5.25)	2.6(0.97,7.54)
Combination Biologic vs Traditional DMARD monotherapy	4.14(1.87,9.05)	3.06(1.02,7.81)
SD Biologic +/- Traditional DMARD vs Combination or triple traditional DMARD therapy	1.56(0.90,2.73)	2.98(1.04,9.14)
LD Biologic +/- Traditional DMARD vs SD Biologic +/- Traditional DMARD	0.71(0.50,1.01)	0.7(0.27,1.68)
HD Biologic +/- Traditional DMARD vs SD Biologic +/- Traditional DMARD	1.45(1.16,1.81)	1(0.54,1.82)
Combination Biologic vs SD Biologic +/- Traditional DMARD	3.15(1.45,6.92)	12.42(1.98,378.8)
Placebo vs SD Biologic +/- Traditional DMARD	0.44(0.15,0.96)	0.26(0.07,0.74)
LD Tofacitinib +/- Traditional DMARD vs SD Tofacitinib +/- Traditional DMARD	2.36(0.68,9.6)	6.58(0.49,150.81)
HD Tofacitinib +/- Traditional DMARD vs SD Tofacitinib +/- Traditional DMARD	2.00(0.90,4.72)	5.18(0.85,78.96)
Placebo vs SD Tofacitinib +/- Traditional DMARD	0.57(0.13,2.14)	3.18(0.24,57.92)

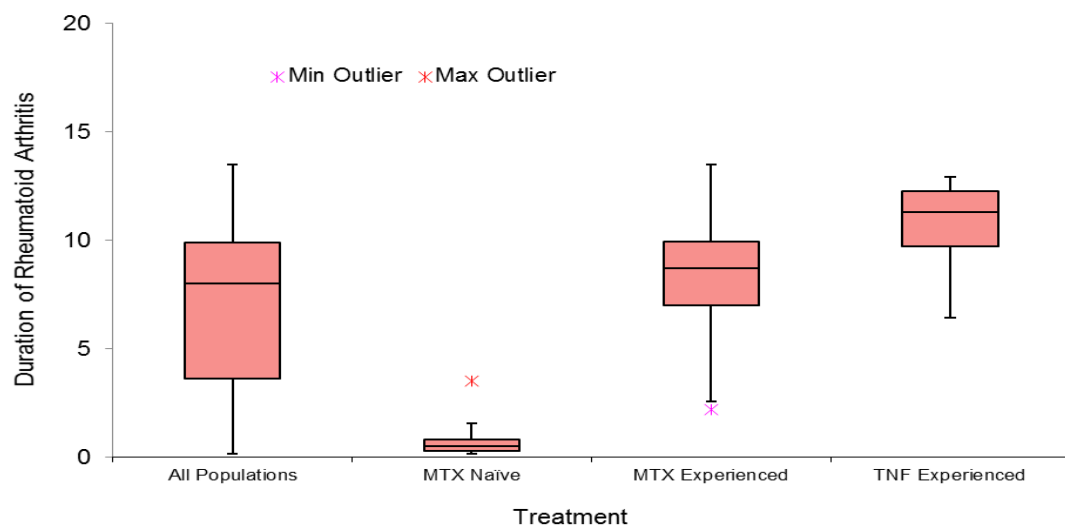
Appendix 11(on line): Summary of published meta-analyses assessing the risk of serious infection in patients with rheumatoid arthritis

Study	No. of RCTs	No. of patients	Biologics considered in Study	Search dates	Population Considered			Conclusion
					MTX naïve	MTX experienced	TNF experienced	
Bongartz 2006	9	5,005	Infliximab, adalimumab	Up to December 2005	Yes	Yes	No	Increased risk of serious infections in patients with rheumatoid arthritis treated with anti-TNF antibody therapy
Salliot et al 2009	12	6,879	rituximab, abatacept, anakinra	Up to October 2007	Yes	Yes	Yes	No increased risk of serious infections in patients with rheumatoid arthritis treated with biologics
Leombruno 2008	18	8,808	Infliximab, adalimumab, etanercept	Up to December 2007	Yes	Yes	Yes	No increased risk of serious infections in patients with rheumatoid arthritis treated with biologics
Thompson et al 2012	6	3,419	Infliximab, adalimumab, etanercept	Up to August 2009	Yes	No	No	No increased risk of serious infections in patients with rheumatoid arthritis treated with biologics

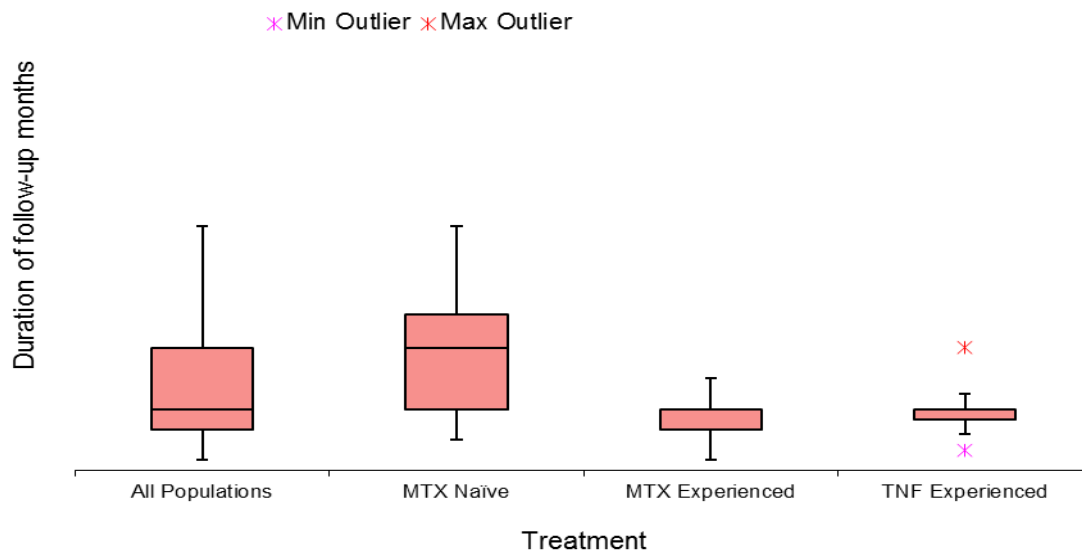
MTX=methotrexate; No= Number; RCT= randomized controlled trial; No= Number; TNF= tumor necrosis factor alpha

Appendix 12 (on line): Box-plots comparing characteristics of populations

Duration of rheumatoid arthritis



Duration of follow-up



CHAPTER 6A: NETWORK META-ANALYSIS OF BENEFITS AND HARMS: AN APPLICATION USING TREATMENT FOR ACUTE VENOUS THROMBOEMBOLISM

Clinical and Safety Outcomes of Treatment of Acute Venous Thromboembolism: A Systematic Review and Meta-Analysis

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CHAPTER 6A: NETWORK META-ANALYSIS OF BENEFITS AND HARMS: AN APPLICATION USING TREATMENT FOR ACUTE VENOUS THROMBOEMBOLISM

Clinical and Safety Outcomes of Treatment of Acute Venous Thromboembolism: A Systematic Review and Meta-Analysis

SUMMARY:

In this chapter, we conduct a network meta-analysis summarizing and comparing the clinical outcomes and safety outcomes of eight anticoagulation options (unfractionated heparin (UFH) and vitamin K antagonist (VKA), low-molecular-weight heparin (LMWH) and VKA, fondaparinux/VKA, LMWH/dabigatran, LMWH/edoxaban, rivaroxaban, apixaban and LMWH alone) for treatment of acute venous thromboembolism.

LINKS:

This article was published in JAMA following peer review and can also be viewed on the journal's website at: <http://jama.jamanetwork.com/article.aspx?articleid=1904827>

The online appendices will be available here:

<http://jama.jamanetwork.com/article.aspx?articleid=1904827>

A pdf of the published manuscript is presented in Appendix C.

CONTRIBUTION:

I was responsible for drafting the methods and results section of the manuscript with guidance from Dr. Lana Castellucci and Dr. Marc Carrier as well as other supervisors and co-authors. I conducted all network meta-analyses, and generated all tables and figures related to findings from the network meta-analysis. I was also responsible for developing appendices 2 and 4-9. Dr. Lana Castellucci and Dr. Marc Carrier and I also responded to feedback on the network meta-analysis that was provided during the peer review process with guidance from supervisors and other co-authors.

ABSTRACT

Importance: Many different anticoagulant strategies have been evaluated for the treatment of acute venous thromboembolism (VTE), yet little guidance exists regarding which drug is most effective and safe.

Objective: To summarize and compare the clinical outcomes and safety outcomes of eight anticoagulation options (unfractionated heparin (UFH) and vitamin K antagonist (VKA), low-molecular-weight heparin (LMWH) and VKA, fondaparinux/VKA, LMWH/dabigatran, LMWH/edoxaban, rivaroxaban, apixaban and LMWH alone) for treatment of acute VTE.

Data Sources: A systematic literature search was conducted using MEDLINE, EMBASE, and the EBM reviews from inception through February 28, 2014.

Study Selection: Eligible studies were randomized controlled trials reporting rates of recurrent VTE and major bleeding in patients with VTE. 1197 studies were identified and forty-five trials including 44,989 patients were included in the analyses.

Data extraction and Synthesis: Two reviewers independently extracted trial-level data including number of patients, duration of follow up, and outcomes. The data were pooled using network meta-analysis.

Main outcomes and Measures: The primary clinical and safety outcomes were recurrent VTE and major bleeding, respectively. Hazard ratios (95% credible interval (CrI)) were generated.

Results: Compared to LMWH/VKA, a treatment strategy using UFH/VKA was associated with an increased risk of recurrent VTE (HR: 1.4; 95% CrI: 1.2 to 1.8). The proportion of patients experiencing recurrent VTE during 3 months of treatment were 1.84%; 95% CrI: 1.33 to 2.51% for UFH/VKA and 1.3%; 95% CrI: 1.02 to 1.62% for LMWH/VKA. The risk of major bleeding was lower with rivaroxaban (HR: 0.6; 95% CrI: 0.4 to 0.9) and apixaban (HR: 0.3; 95% CrI: 0.2 to 0.6) compared to LMWH/VKA, with a lower proportion of patients experiencing a major bleeding event during 3 months of anticoagulation (0.49%; 95% CrI: 0.29 to 0.85%, and 0.28%; 95% CrI: 0.14 to 0.50%, and 0.89%; 95% CrI: 0.66 to 1.16%, respectively).

Conclusion and Relevance: Using meta-analytic pooling, there were no statistically significant differences for efficacy and safety among the treatment strategies when compared with LMWH/VKA. Findings suggest that UFH/VKA may be the least effective strategy and that rivaroxaban and apixaban may be associated with the lowest risk for bleeding. PROSPERO registry – (CRD42014008671)

INTRODUCTION

Venous thromboembolism (VTE), manifested as deep vein thrombosis (DVT) or pulmonary embolism (PE), is a common medical condition and is the third leading cause of cardiovascular mortality.¹⁻⁷ Untreated acute PE is associated with a mortality rate of up to 25%.⁸ Anticoagulant therapy is effective at treating VTE and preventing recurrent events and death associated with these recurrent VTE.⁹

The traditional immediate treatment of acute VTE involves the initial use of parenteral anticoagulants (unfractionated heparin (UFH), low-molecular-weight-heparin (LMWH) or fondaparinux) with transition to vitamin K antagonist (VKA), and the parenteral anticoagulant is continued for a minimum of 5 days and until the international normalized ratio (INR) is 2.0 or above for at least 24 hours.¹⁰ In patients with acute DVT or PE, LMWH or fondaparinux is recommended over UFH.¹⁰

The traditional approach to acute VTE may be cumbersome for patients given that the initial phase is administered parenterally and that the use of VKA requires frequent laboratory monitoring and food and drug restrictions due to interactions.¹¹ Direct oral anticoagulants (DOACs) including direct Xa inhibitors (rivaroxaban, apixaban and edoxaban) and a direct thrombin inhibitor (dabigatran) may offer an attractive alternative to the traditional acute treatment of VTE. Recent studies have evaluated the efficacy and safety of DOACs (with and without initial parenteral anticoagulant therapy) for the acute treatment of VTE.

Clinicians are left with many potential treatment options regarding management of acute VTE and little guidance exists as to which drug is most effective yet safe. While individual studies have shown promising results, several therapies have been assessed in only a single trial, and direct comparisons are rarely available. Therefore, we sought to summarize and

compare the clinical outcomes and safety of various management options (UFH/VKA, LMWH/VKA, fondaparinux/VKA, LMWH/dabigatran, LMWH/edoxaban, rivaroxaban, apixaban and LMWH alone) for the treatment of acute VTE using network meta-analysis.

PATIENTS / METHODS

Data Sources and Searches

A systematic search of the literature was conducted on MEDLINE (1946 to February 28, 2014), EMBASE (1947 to February 28, 2014) and the EBM reviews (Cochrane Database of Systematic Review (2005-January 2014); ACP Journal Club (1981 to February 2014); Database of Abstract of Reviews of Effects (1st Quarter 2014); Cochrane Central Register of Controlled Trials (January 2014); Cochrane Methodology Register (3rd Quarter 2012); Health Technology Assessment (1st Quarter 2014); NHS Economic Evaluation (1st Quarter 2014)) using an OVID interface. References of included studies and narrative reviews were reviewed for additional potential studies. The protocol and systematic search strategy of the review is documented online (PROSPERO registry - CRD42014008671). The systematic search strategy is documented in online Appendix 1. There were no restrictions on language.

Study Selection

Potentially relevant articles were reviewed in full length to ensure that they satisfied three criteria: 1) prospective enrollment of patients with objectively confirmed acute symptomatic VTE (lower extremity DVT and/or PE) and qualifying recurrent events were symptomatic and objectively confirmed; 2) Patients randomized to UFH/VKA, LMWH/VKA, fondaparinux/VKA, LMWH/dabigatran, LMWH/edoxaban, rivaroxaban, apixaban or LMWH alone; studies had to compare two different anticoagulation strategies; 3) one or

more of the primary or secondary outcomes were reported. Studies were excluded if: 1) Patients were randomized to placebo or observation; 2) Patients were randomized to idraparinux or ximelagatran; 3) Only patients with cancer-associated thrombosis were included; 4) Study design was Phase 1 or 2; and 5) Trials evaluated extended VTE treatment for secondary prevention.

Outcome Measures

The primary outcome measures were recurrent VTE and major bleeding episodes. Recurrent VTE was defined as a new non-compressible segment on compression leg vein ultrasound imaging, new intra-luminal filling defect on venography, newly abnormal impedance plethysmography test, new high probability ventilation/perfusion scan or a new pulmonary artery filling defect on computed tomography or pulmonary angiography. A major bleeding episode was defined as clinically overt bleeding and associated with at least 1 of the following: 1) A fall in hemoglobin levels of at least 2 g/dL; 2) Transfusion of ≥ 2 units of packed red blood cells; 3) Intracranial or retroperitoneal or involved a body cavity; or 4) Death; or as defined by the investigators of each individual study.¹²

Secondary outcome measures included fatal recurrent VTE and fatal bleeding episodes. Fatal recurrent VTE was diagnosed by autopsy, a high-probability ventilation/perfusion scan or new intra-luminal filling defect detected on computed tomography or venography prior to death, or a high clinical suspicion of fatal PE as defined by the investigators of each individual study. A fatal bleeding episode was defined as a major bleeding episode directly leading to death or a death that was reported as associated with bleeding.

Data Extraction and Quality Assessment

Two reviewers (LAC, MC) independently assessed eligibility of articles identified in the initial search strategy for inclusion in the review and discussed those deemed potentially eligible; independently extracted data (baseline characteristics, definition of outcomes, numbers of events) using a standardized data abstraction form; and assessed studies' methodological quality using the Risk of Bias Assessment Tool from the Cochrane Handbook for randomized trials.¹³ Corresponding authors of manuscripts were contacted if primary or secondary outcomes could not be extracted from the original manuscript.

Data Synthesis and Analysis

Outcomes were allocated according to the intention-to-treat principle. Bayesian network meta-analyses and direct frequentist pair-wise meta-analyses were conducted for all outcomes. Bayesian network meta-analyses were conducted using a Poisson likelihood model.¹⁴ The different treatment strategies were treated as separate nodes (UFH/VKA, LMWH/VKA, fondaparinux/VKA, LMWH/dabigatran, LMWH/edoxaban, rivaroxaban, apixaban or LMWH alone) (Figure 1). All networks were constructed using NodeXL.¹⁵

Hazard ratios (HR) and 95% credible intervals (CrI) were modeled using Markov Chain Monte Carlo methods. The proportion of patients expected to have an event during use of each treatment for a period of 3 and 6 months was calculated, assuming a rate of 5.3 per 100 patient-years (~2.6% over 6 months) and 3.6 events per 100 patient-years (~1.8% over 6 months) for recurrent VTE and major bleeding for LMWH/VKA, respectively.^{16;17} The probability that each drug was the most efficacious regimen was calculated by counting the proportion of iterations of the Markov chain in which each drug had the highest HR.¹⁴

Random-effects network meta-analyses with vague priors were conducted for the analyses.¹⁴ Fixed-effects models were also conducted, along with an analysis using a binomial likelihood model and random-effects model with informative priors.^{18;19} Assessment of model fit was based on comparison of residual deviance to number of unconstrained data points, assessment of the deviance information criterion, and between study standard deviation.^{14;20;21} To ensure convergence was reached, trace plots and the Brooks-Gelman-Rubin statistic were assessed.²² Analyses were performed using WinBUGS version 1.4.3 (MRC Biostatistics Unit, Cambridge, UK).

A priori sub-group analysis was conducted to adjust for index VTE (DVT or PE) and for differences in study duration. We assessed inconsistency by comparing the deviance and DIC statistics in fitted consistency and inconsistency models.²³ We also plotted the posterior mean deviance of the individual data points (each arm of the trial) in the inconsistency model against their posterior mean deviance in the consistency model.²³ Results from our network meta-analysis were also qualitatively compared with direct frequentist pair-wise estimates. Frequentist pair-wise meta-analyses were conducted using Comprehensive Meta-Analysis Version 2.2.064 (Biostat, New Jersey, United States).

RESULTS

A total of 1197 citations were identified by our literature search and 45 manuscripts (44, 989 patients) were included in the analyses (Figure 2 and online Appendix 1).^{17;24-67} Twenty-two clinical trials compared UFH/VKA (number of events/number of patients: 357/7133) to LMWH/VKA (533/20,246),²⁴⁻⁴⁵ 12 compared UFH/VKA (357/7133) to LMWH alone (81/1897),⁴⁶⁻⁵⁷ three compared LMWH/VKA (533/20,246) to LMWH alone (81/1897),⁵⁹⁻⁶¹

two compared fondaparinux/VKA (85/2201) to LMWH/VKA (533/20,246) or UFH/VKA (357/7133)^{58;62} and six compared LMWH/VKA (533/20,246) to one of the DOACs (dabigatran (2) (60/2553), apixaban (1) (59/2691), edoxaban (1) (66/4118) and rivaroxaban (2) (86/4150)).^{17;63-67} Two of the included studies compared UFH/VKA (357/7133), LMWH/VKA (533/20,246) and LMWH alone (81/1897).^{26;27} The baseline characteristics of the included studies are depicted in Table 1 and online Appendix 2. The sample size ranged from 60 to 8240 patients, with a median sample size of 298. The median follow-up period was 3 months (range 3 to 8.2 months). Eleven RCTs evaluated treatment of patients with any VTE (both DVT and PE),^{17;26;37;39;43-45;57;63-65} seven studies assessed patients with PE,^{33;38;41;52;53;58;67} and the remaining 27 studies evaluated treatment of patients with DVT.^{24;25;27-32;34-36;40;42;46-51;54-56;59-62;66} Quality assessment is reported in online Appendix 3.

All studies were included in the evaluation for recurrent VTE. Results of Bayesian network meta-analyses are presented in Table 2 and Figure 3. In comparison to LMWH/VKA, all treatment strategies showed a reduction in recurrent VTE events; UFH/VKA was the least effective regimen compared to LMWH/VKA and conferred an increase in recurrent VTE with HR 1.42 (95% CrI: 1.15 to 1.79). When UFH/VKA was used as the comparator, LMWH/VKA and LMWH alone were associated with a reduction in recurrent VTE event rates (Table 2). Stepwise comparison of all remaining treatment strategies did not reveal significant differences in rates of recurrent VTE (Table 2). LMWH/edoxaban and apixaban were associated with the greatest probability of being the best therapy among all treatment strategies evaluated, 33.1 % and 31.6 %, respectively (online Appendix 4).

The proportion of patients experiencing a recurrent VTE during 3 months of treatment was

higher for UFH/VKA compared to LMWH/VKA (1.84%; 95% CrI: 1.33 to 2.51% and 1.30%; 95% CrI: 1.02 to 1.62%, respectively) (online Appendix 5). In comparison to LMWH/VKA the number needed to treat to harm (NNTH) using UFH/VKA was 188 patients at three months (online Appendix 5).

Comparison of random-effects Bayesian network meta-analyses with direct frequentist meta-analysis pairwise comparisons were similar in magnitude and direction of effect estimates for recurrent VTE rates, with the exception of fondaparinux/VKA and LMWH alone. UFH/VKA was the least effective therapy compared to LMWH/VKA (online Appendix 6). Subgroup analyses were conducted to evaluate recurrent VTE event rates for patients presenting with index DVT and index PE (Table 2). Compared to LMWH/VKA, use of UFH/VKA in patients with index DVT was the least effective treatment strategy and was associated with an increased risk of recurrent VTE (HR: 1.74; 95% CrI: 1.27 to 2.44). All remaining treatment regimens were not different compared to LMWH/VKA in this population. Additional sensitivity analysis was performed for variation in study treatment duration (online Appendix 7). Effect estimates from the sensitivity analyses were similar to the primary analysis except for UFH/VKA, which had a slightly higher rate of recurrent VTE (HR: 1.88; 95% CrI: 1.13 to 3.38 compared to HR: 1.42; 95% CrI: 1.15 to 1.80 in the primary analysis).

The analysis of major bleeding events included 42 trials (44,434 patients) (Figure 1 and Appendix 2). Twenty-two clinical trials compared UFH/VKA (number of events/number of patients: 169/6975) to LMWH/VKA (361/20,124),²⁴⁻⁴⁵ 10 compared UFH/VKA (169/6975) to LMWH alone (28/1622),^{46;49-57} two compared LMWH/VKA (361/20,124) to LMWH

alone (28/1622),^{59;60} two compared fondaparinux/VKA (50/2201) to LMWH/VKA (361/20,124) or UFH/VKA (169/6975)^{58;62} and six compared LMWH/VKA (361/20,124) to one of the DOACs (dabigatran (2) (35/2553), apixaban (1) (15/2691), edoxaban (1) (56/4118) and rivaroxaban (2) (40/4150)).^{17;63-67} Two of the included studies compared UFH/VKA (169/6975), LMWH/VKA (361/20,124) and LMWH alone (28/1622).^{26;27} The results of network meta-analysis pairwise comparisons are available in Table 2. Compared to LMWH/VKA, rivaroxaban and apixaban demonstrated the lowest bleeding risk (HR: 0.55; 95% CrI: 0.35 to 0.89 and HR: 0.31; 95% CrI: 0.15 to 0.62, respectively). All other treatment regimens conferred similar risk of bleeding to LMWH/VKA. Additional pairwise comparisons revealed either rivaroxaban or apixaban, or both, were also the safest therapies compared to UFH/VKA (rivaroxaban: HR: 0.47; 95% CrI: 0.27 to 0.8 and apixaban; HR: 0.26; 95% CrI: 0.12 to 0.54); fondaparinux/VKA (apixaban: HR 0.3; 95% CrI: 0.12 to 0.68); LMWH/dabigatran (apixaban: HR: 0.42; 95% CrI: 0.17 to 0.99); and LMWH/edoxaban (apixaban: HR: 0.37; 95% CrI: 0.15 to 0.89).

The difference in proportion of patients experiencing a major bleeding event compared to LMWH/VKA was lower for both rivaroxaban and apixaban use for three months duration of treatment (0.89%; 95% CrI: 0.66 to 1.16%, 0.49%; 95% CrI: 0.29 to 0.85%, and 0.28%; 95% CrI: 0.14 to 0.50%, respectively) (online Appendix 5). Compared to LMWH/VKA use of rivaroxaban was associated with a number need to treat to benefit (NNTB) of 258 patients at three months. For apixaban the NNTB was 165 patients at three months (online Appendix 5). Apixaban was associated with the greatest probability of being the least harmful therapy (88.9%), among all treatment regimens assessed (online Appendix 4).

Network meta-analysis using both random-effects and a fixed-effects model were considered and yielded similar results, albeit with wider credible intervals in the random-effects model (online Appendix 8). Hazard ratios also align with odds ratios reported in the binomial likelihood model (online Appendix 11). The network meta-analysis for major bleeding yielded a reasonable fit to the data, while there were a few studies that did not fit particularly well for recurrent VTE (online Appendix 10). Exclusion of these studies did not alter our main findings, although it did improve model fit and reduce between study standard deviation (online Appendix 10). We found no evidence of inconsistency (online Appendix 9).

Fatal events were rare. Fatal recurrent VTE and fatal bleeding events were reported in 165 (0.37%) and 64 (0.14%) patients, respectively.

DISCUSSION

To our knowledge this network meta-analysis is the largest review, including nearly 45,000 patients, assessing the clinical outcomes and safety of different anticoagulation strategies for the treatment of acute VTE. We provide estimates on symptomatic recurrent VTE and major bleeding outcomes (both patient-important outcomes), which are clinically relevant and are what clinical practice guideline recommendations are based upon.⁶⁸ All the management options, with the exception of UFH/VKA, had similar clinical outcomes compared to a management strategy using LMWH/VKA. Treatment using UFH/VKA was associated with a higher risk of recurrent VTE during the follow-up period (HR: 1.42; 95% CrI: 1.15 to 1.79). Despite not being as effective as LMWH/VKA, there are clinical circumstances which necessitate the use of UFH including patients with severe renal insufficiency and those with

massive or submassive PE who are potential candidates for thrombolysis or thrombectomy.

Management strategies using rivaroxaban or apixaban, without preceding parenteral anticoagulation, appear to be associated with a reduction in the risk of major bleeding episodes compared to LMWH/VKA ((HR: 0.55; 95% CrI: 0.35 to 0.89) and (HR: 0.31; 95% CrI: 0.15 to 0.62), respectively). Apixaban was associated with a significant reduction in the risk of major bleeding episodes when compared to all the other different treatment options except rivaroxaban and LMWH alone. These risks for recurrent VTE and major bleeding events are key pieces of information to help clinicians assess the benefit/harm balance of the various treatment options and tailor their therapeutic approaches accordingly.

The decision to use LMWH/VKA as the comparator for the network meta-analysis was based on the current clinical practice guidelines recommending LMWH or fondaparinux over UFH for the initial treatment of acute DVT or PE.¹⁰ Our results are consistent with these recommendations. Both treatment strategies using LMWH/VKA and fondaparinux/VKA were associated with lower risk of recurrent VTE and major bleeding episodes (Table 2). The most recent version of the clinical practice guidelines was published before results of several clinical trials assessing the efficacy and safety of the DOACs for the treatment of acute VTE were available. Therefore, there is very little guidance for clinicians on the use of these new oral anticoagulants in this patient population. A number of DOACs are now approved therapies for the indication of acute DVT and PE (rivaroxaban and dabigatran in the US). Both dabigatran (150 mg PO BID) and edoxaban (60 mg PO daily) were assessed following an initial 5 days of LMWH whereas apixaban (10 mg PO BID for 7 days, then 5 mg PO

BID) and rivaroxaban (15 mg PO BID X 21 days, then 20 mg PO daily) were evaluated without the use of initial LMWH.^{17;63-67} Our network meta-analysis demonstrated that treatment options using DOACs have similar clinical outcomes as the more traditional strategies using LMWH/VKA. As previously mentioned, strategies using DOACs seem to be associated with a lower risk of major bleeding episodes which is most pronounced for rivaroxaban and apixaban. Apixaban was also associated with significantly less bleeding when compared to LMWH/dabigatran and LMWH/edoxaban (Table 2).

Our study included trials assessing patients with acute VTE only and those evaluating use of anticoagulation for secondary prevention of VTE were not included in this analysis. A prior systematic review and network meta-analysis on the use of long-term oral anticoagulation for the secondary prevention of VTE has already been published.⁶⁹ Our findings are consistent with the results of two recently published systematic reviews and meta-analyses on the treatment of acute VTE.^{70;71} Although comparisons on the different DOACs for the treatment of acute VTE have already been published, our review is more comprehensive as it is not limited to the inclusion of the studies assessing the DOACs and includes studies assessing UFH/VKA, LMWH/VKA and fondaparinux/VKA, thereby providing clinicians with an overall appraisal of all possible therapies. We also report the proportions of patients experiencing an event (and differences between treatments) after using each treatment for a period of 3 and 6 months for both outcomes in online Appendix 5.

It is important to note limitations of our study. First, the length of follow-up varied across studies. Trials assessing DOACs were longer in duration than those for UFH/VKA, fondaparinux/VKA or LMWH alone, resulting in potential variations in event rates in the

LMWH/VKA arms (online Appendix 7: eFigures 7a and 7b). We conducted a sensitivity analysis restricting studies to those that had a minimum of 6 months of treatment (14 studies including 30,027 patients) (online Appendix 7: eFigure 7c). Results of the sub-group analysis aligned with the primary analysis (online Appendix 7: eFigure 7c and eTable 7), suggesting minimal impact of treatment duration across studies. Second, the proportion of patients experiencing an outcome event during three and six months of anticoagulation (online Appendix 5) were generated assuming a rate of 5.3 per 100 patient-years (~2.6% over 6 months) and 3.6 events per 100 patient-years (~1.8% over 6 months) for recurrent VTE and major bleeding, respectively, in the LMWH/VKA arm.^{16;17} Although there was considerable variation in event rates in LMWH/VKA arms when all studies are considered, the outcome rates were similar when only studies at least 6 months in duration were considered. The use of another trial to derive baseline rates for LMWH/VKA is unlikely to substantially alter estimates on differences in proportion of patients experiencing an event at three and six months (online Appendix 7: eFigures 7a and 7c). Third, patients treated with LMWH alone are a heterogeneous group as LMWH dosing varied across studies. Fourth, patient-level longitudinal data are required to establish more robust conclusions in specific patient populations. Other risk factors including severity of the index event (e.g. segmental PE vs. massive PE), presence of risk factors for major bleeding (i.e. recent bleeding or surgery), or other on-going risk factors for VTE (e.g. cancer, body mass index, etc.) may influence the risk of recurrent VTE and bleeding events, as well as choice of treatment. Fifth, no trials have directly compared the different DOACs as all trials assessing the efficacy of DOACs were compared with LMWH/VKA. Future direct comparison trials, patient-level network meta-analyses, or high quality non-randomized studies are required to confirm our findings. Sixth, our analysis does not incorporate costs or preference for the different outcomes. Future

studies need to be conducted to determine the most cost-effective management option.

Seventh, the strength of evidence (bias and consistency assessments, etc.) for our analysis was not evaluated using the GRADE guidelines⁷². Finally, the data included in the network meta-analysis was extracted from randomized controlled trials and in the absence of phase 4 studies are not generalizable to all patients with acute VTE.

CONCLUSIONS

Using meta-analytic pooling, there were no statistically significant differences for efficacy and safety among the treatment strategies when compared with LMWH/VKA. Findings suggest that UFH/VKA may be the least effective strategy and that rivaroxaban and apixaban may be associated with the lowest risk for bleeding.

TABLES AND FIGURES

Table 1(a): Baseline Characteristics and Outcomes of RCTs of Treatment of Acute VTE (DVT and PE) Comparing UFH/VKA vs. LMWH/VKA

Patient Population	Study, Year (reference)	Treatment Regimen	Sample Size (n)	Duration of Drug Treatment (months)	Recurrent VTE events	Fatal Recurrent VTE events	Major Bleeding Events	Fatal Bleeding Events
<u>DVT</u>	Collaborative European Study, 1991	UFH/VKA	81	3	2	0	4	0
		LMWH/VKA	85		3	1	2	0
	Hull et al, 1992	UFH/VKA	219	3	15	3	11	0
		LMWH/VKA	213		6	0	6	0
	Lopaciuk et al, 1992	UFH/VKA	75	3	3	0	1	0
		LMWH/VKA	74		0	0	0	0
	Prandoni et al, 1992	UFH/VKA	85	6	12	3	6	1
		LMWH/VKA	85		6	3	2	0
	Simonneau et al, 1993	UFH/VKA	67	3	2	0	0	0
		LMWH/VKA	67		0	0	0	0
	Fiessinger et al, 1996	UFH/VKA	133	5.3 ^a	3	0	2	0
		LMWH/VKA	120		5	0	0	0
	Koopman et al, 1996	UFH/VKA	198	3	10	0	4	1
		LMWH/VKA	202		8	0	1	0
	Levine et al, 1996	UFH/VKA	253	3	17	2	3	0
		LMWH/VKA	247		13	0	5	2
	Kirchmaier et al. 1998	UFH/VKA	130	6	4	1	5	0
		LMWH/VKA ^b	128		0 ^b	0 ^b	10 ^b	1 ^b
		LMWH/VKA ^b	127		2 ^b	0 ^b	2 ^b	0 ^b
	Harenberg et al, 2000	UFH/VKA	273	6	17	3	13	2
		LMWH/VKA	265		6	0	7	0
	Breddin et al, 2001	UFH/VKA	375	3	24	3	2	0
		LMWH/VKA ^b	388		7 ^b	1 ^b	3 ^b	0 ^b
		LMWH/VKA ^b	374		13 ^b	3 ^b	2 ^b	0 ^b
	Kakkar et al, 2003	UFH/VKA	98	3	4	1	1	0
		LMWH/VKA	105		1	0	0	0

Patient Population	Study, Year (reference)	Treatment Regimen	Sample Size (n)	Duration of Drug Treatment (months)	Recurrent VTE events	Fatal Recurrent VTE events	Major Bleeding Events	Fatal Bleeding Events
		LMWH alone	94		3	0	1	0
	Riess et al, 2003	UFH/VKA	593	6	27	5	7	0
		LMWH/VKA	627		22	2	6	0

Patient Population	Study, Year (reference)	Treatment Regimen	Sample Size (n)	Duration of Drug Treatment (months)	Recurrent VTE events	Fatal Recurrent VTE events	Major Bleeding Events	Fatal Bleeding Events
<u>PE</u>	Meyer et al, 1995	UFH/VKA	31	3	1	0	0	0
		LMWH/VKA	29		0	0	0	0
	Simonneau et al, 1997	UFH/VKA	308	3	6	3	8	2
		LMWH/VKA	304		5	3	6	1
	Findik et al, 2002	UFH/VKA	30	3	3	0	0	0
		LMWH/VKA	29		1	0	0	0
<u>All VTE</u>	Columbus Investigators, 1997	UFH/VKA	511	3	25	3	12	2
		LMWH/VKA	510		27	3	16	0
	Hull et al, 2000	UFH/VKA	103	3	7	1	2	0
		LMWH/VKA	97		0	0	1	0
	Merli et al, 2001	UFH/VKA	290	3	12	2	6	2
		LMWH/VKA	298		13	1	5	5
		LMWH alone	312		9	2	4	0
	Prandoni et al, 2004	UFH/VKA	360	3	15	3	4	1
		LMWH/VKA	360		14	4	3	0
	Kearon et al, 2006	UFH/VKA	355	3	13	0	6	1
		LMWH/VKA	353		12	1	12	1
	Leizorovicz et al, 2011	UFH/VKA	270	3	3	1	10	0
		LMWH/VKA	269		7	1	12	2

a Median duration of treatment used

b Treatment arms used similar regimens and results are combined

DVT = Deep vein thrombosis; LMWH = Low molecular weight heparin; PE = Pulmonary embolism; RCTs = Randomized Controlled Trials; UFH = Unfractionated heparin; VKA = Vitamin K antagonist; VTE = Venous thromboembolism

Table 1(b): Baseline Characteristics and Outcomes of RCTs of Treatment of Acute VTE (DVT and PE) Comparing LMWH alone vs. UFH/VKA or LMWH/VKA

Patient Population	Study, Year (reference)	Treatment Regimen	Sample Size (n)	Duration of Drug Treatment (months)	Recurrent VTE events	Fatal Recurrent VTE events	Major Bleeding Events	Fatal Bleeding Events
<u>DVT</u>	Bratt et al, 1990	UFH/VKA	55	3	0	0	NR	NR
		LMWH alone	55		1	0	NR	NR
	Lindmarker et al, 1994	UFH/VKA	103	3	0	0	NR	NR
		LMWH alone	101		2	0	NR	NR
	Pini et al, 1994	UFH/VKA	94	3	4	0	3	0
		LMWH alone	93		6	0	3	0
	Das et al, 1996	LMWH/VKA	55	3	2	0	0	0
		LMWH alone	50		5	0	0	0
	Belcaro et al, 1999 ^a	UFH/VKA	97	3	6	0	0	0
		LMWH alone	98		6	0	0	0
	Gonzalez-Fajardo et al, 1999	UFH/VKA	80	3	19	0	2	0
		LMWH alone	85		8	1	1	0
	Lopaciuk et al, 1999	LMWH/VKA	95	3	7	1	1	0
		LMWH alone	98		2	0	1	0
	Veiga et al, 2000	UFH/VKA	50	3	1	0	2	1
		LMWH alone	50		2	0	0	0
	Ramacciotti et al, 2004	UFH/VKA	97	3	5	0	3	0
		LMWH alone	104		2	0	2	0
	Chong et al, 2005	UFH/VKA	148	6	14	0	3	0
		LMWH alone	150		4	0	0	0
	Daskalopoulos et al, 2005	UFH/VKA	52	6	4	1	4	1
		LMWH alone	50		2	0	2	1
	Romera et al, 2009	LMWH/VKA	122	6	7	0	NR	0
		LMWH alone	119		5	0	NR	0
<u>PE</u>	Beckman et al, 2003	UFH/VKA	20	3	0	0	2	0
		LMWH alone	40		3	1	1	0
	Perez de Llano et al, 2003	UFH/VKA	21	6	2	0	0	0
		LMWH alone	29		3	0	1	1
<u>All VTE</u>	Hull et al, 2007	UFH/VKA	368	3	21	2	17	0

	LMWH alone	369	18	1	12	0

a Third study arm excluded

DVT = Deep vein thrombosis; LMWH = Low molecular weight heparin; NR = not reported; PE = Pulmonary embolism; RCTs = Randomized Controlled Trials; UFH = Unfractionated heparin; VKA = Vitamin K antagonist; VTE = Venous thromboembolism

Table 1(c): Baseline Characteristics and Outcomes of RCTs of Treatment of Acute VTE (DVT and PE) Comparing Fondaparinux vs. UFH/VKA or LMWH/VKA

Patient Population	Study, Year (reference)	Treatment Regimen	Sample Size (n)	Duration of Drug Treatment (months)	Recurrent VTE events	Fatal Recurrent VTE events	Major Bleeding Events	Fatal Bleeding Events
<u>DVT</u>	Buller et al, 2004	LMWH/VKA	1107	3	45	5	26	0
		Fondaparinux/VKA	1098		43	5	28	5
<u>PE</u>	Buller et al, 2003	UFH/VKA	1110	3	56	15	26	1
		Fondaparinux/VKA	1103		42	16	22	1

DVT = Deep vein thrombosis; LMWH = Low molecular weight heparin; PE = Pulmonary embolism; RCTs = Randomized Controlled Trials; UFH = Unfractionated heparin; VKA = Vitamin K antagonist; VTE = Venous thromboembolism

Table 1(d): Baseline Characteristics and Outcomes of RCTs of Treatment of Acute VTE (DVT and PE) Comparing DOACs vs. LMWH/VKA

Patient Population	Study, Year (reference)	Treatment Regimen	Sample Size (n)	Duration of Drug Treatment (months) ^a	Recurrent VTE events	Fatal Recurrent VTE events	Major Bleeding Events	Fatal Bleeding Events
<u>DVT</u>	Bauersachs et al, 2010	LMWH/VKA	1718	6.2	51	6	20	5
		Rivaroxaban	1731	6.4	36	4	14	1
<u>PE</u>	Buller et al, 2012	LMWH/VKA	2413	7	44	6	52	3
		Rivaroxaban	2419	7.1	50	10	26	2
<u>All VTE</u>	Schulman et al, 2009	LMWH/VKA	1265	6	27	3	24	1
		LMWH/Dabigatran	1274		30	1	20	1
	Schulman et al, 2014	LMWH/VKA	1289	6	28	0	22	1
		LMWH/Dabigatran	1279		30	1	15	0
	Buller et al, 2013	LMWH/VKA	4122	8.2	80	NR	66	10
		LMWH/Edoxaban	4118		66	NR	56	2
	Agnelli et al, 2013	LMWH/VKA	2704	6	71	15	49	2
		Apixaban	2691		59	12	15	1

a DOAC trials used median treatment duration

DOAC = Direct Oral Anticoagulant; DVT = Deep vein thrombosis; LMWH = Low molecular weight heparin; NR = not reported; PE = Pulmonary embolism; RCTs = Randomized Controlled Trials; UFH = Unfractionated heparin; VKA = Vitamin K antagonist; VTE = Venous thromboembolism

Table 2: Hazard Ratios^a (95% Credible Interval) for Treatment Comparisons within the Network Meta-analysis for Recurrent VTE (index VTE, DVT or PE only) and Major Bleeding

<u>Treatment</u>	<u>Recurrent VTE by Index Event</u>			
	<u>Recurrent VTE</u>	<u>Index DVT</u>	<u>Index PE^b</u>	<u>Major Bleeding</u>
<u>Compared with UFH/VKA</u>				
Fondaparinux/VKA	0.71 (0.45,1.12)	0.55 (0.22,1.34)	0.76 (0.5,1.12)	0.9 (0.54,1.49)
LMWH/dabigatran	0.78 (0.45,1.31)	NA	NA	0.64 (0.35,1.14)
LMWH/edoxaban	0.58 (0.3,1.08)	0.55 (0.22,1.32)	0.36 (0.1,1.12)	0.71 (0.4,1.24)
Rivaroxaban	0.64 (0.38,1.03)	0.4 (0.16,0.97)	0.67 (0.2,1.98)	0.47 (0.27,0.8)
Apixaban	0.59 (0.31,1.09)	0.47 (0.19,1.17)	0.53 (0.15,1.7)	0.26 (0.12,0.54)
LMWH alone	0.7 (0.5,0.95)	0.61 (0.4,0.99)	2.19 (0.46,17.09)	0.6 (0.35,1.03)
<u>Compared with Fondaparinux/VKA</u>				
LMWH/dabigatran	1.1 (0.55,2.1)	NA	NA	0.7 (0.35,1.46)
LMWH/edoxaban	0.82 (0.38,1.7)	0.99 (0.3,3.22)	0.47 (0.12,1.57)	0.79 (0.39,1.61)
Rivaroxaban	0.89 (0.46,1.67)	0.72 (0.22,2.37)	0.89 (0.25,2.8)	0.52 (0.27,1.02)
Apixaban	0.83 (0.38,1.73)	0.86 (0.26,2.86)	0.7 (0.18,2.38)	0.3 (0.12,0.68)
LMWH alone	0.97 (0.57,1.71)	1.1 (0.44,3.07)	2.91 (0.59,23.24)	0.66 (0.34,1.44)
<u>Compared with LMWH/dabigatran</u>				
LMWH/edoxaban	0.75 (0.35,1.64)	NA	NA	1.13 (0.54,2.26)
Rivaroxaban	0.81 (0.41,1.61)	NA	NA	0.74 (0.38,1.45)
Apixaban	0.75 (0.35,1.65)	NA	NA	0.42 (0.17,0.99)
LMWH alone	0.9 (0.5,1.67)	NA	NA	0.93 (0.46,2.11)
<u>Compared with LMWH/edoxaban</u>				
Rivaroxaban	1.09 (0.52,2.27)	0.73 (0.22,2.39)	1.9 (0.94,3.98)	0.65 (0.33,1.33)
Apixaban	1.01 (0.43,2.35)	0.86 (0.27,2.86)	1.5 (0.65,3.48)	0.37 (0.15,0.89)
LMWH alone	1.19 (0.61,2.43)	1.11 (0.45,3.07)	6.35 (0.9,70.48)	0.84 (0.41,1.91)
<u>Compared with Rivaroxaban</u>				
Apixaban	0.93 (0.44,1.95)	1.18 (0.37,3.99)	0.79 (0.38,1.6)	0.56 (0.24,1.33)
LMWH alone	1.1 (0.63,2)	1.52 (0.6,4.29)	3.31 (0.5,35.17)	1.27 (0.64,2.82)

Compared with Apixaban

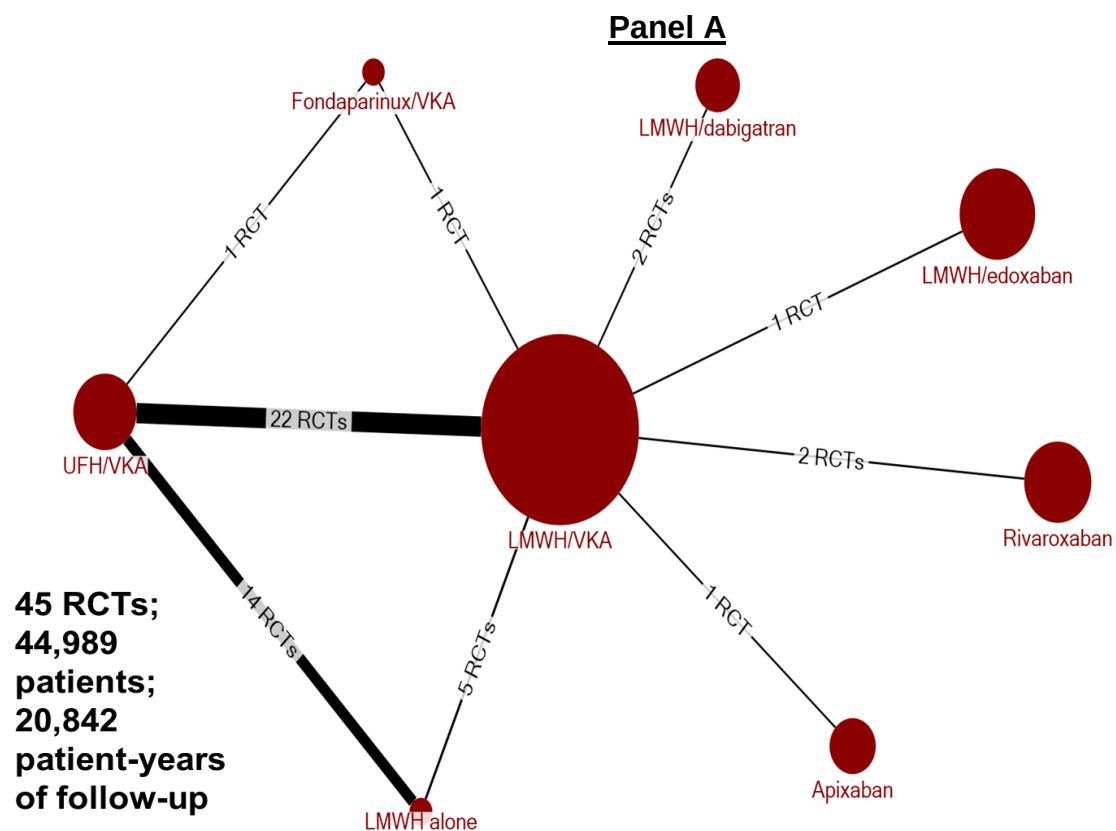
LMWH alone	1.18 (0.6,2.41)	1.28 (0.5,3.56)	4.24 (0.6,47.45)	2.31 (0.94,5.53)

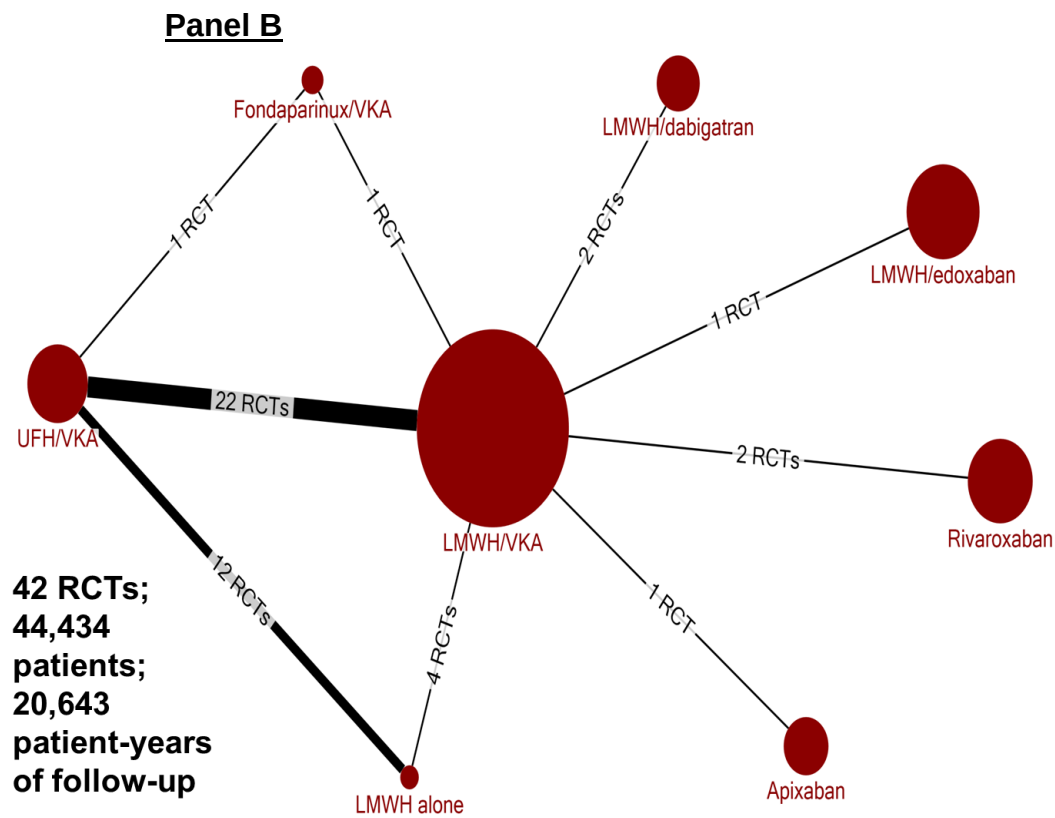
DVT = deep vein thrombosis; LMWH = low molecular weight heparin; NA = not assessable; PE = pulmonary embolism; UFH = unfractionated heparin; VKA = vitamin K antagonist; VTE = venous thromboembolism

aHazard ratios (HR) > 1 favours the treatment arm listed in the Treatment column; HR < 1 favours the comparison treatment.

bFixed-effects model was used because Index PE evidence network was comprised of connections consisting of either a few studies or single studies

Figure 1: (A) Evidence network for recurrent venous thromboembolism (VTE) and (B) Evidence network for major bleeding





The width of the lines for each connection in the evidence network are proportional to the number of RCTs comparing each pair of treatments, and the size of each treatment node is proportional to the patient-years of follow-up .

LMWH = low molecular weight heparin; RCT = randomized controlled trial; UFH= unfractionated heparin; VKA = vitamin K antagonist; VTE = venous thromboembolism

Figure 2: Flow Diagram

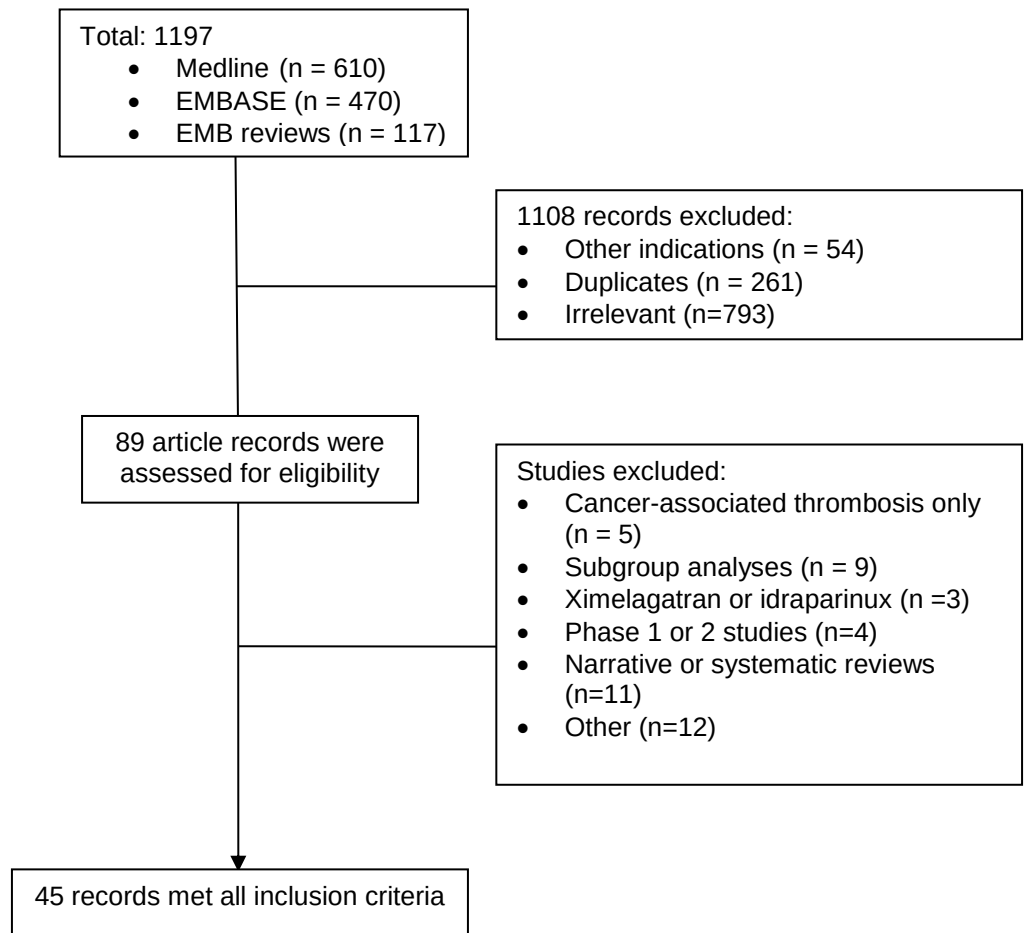
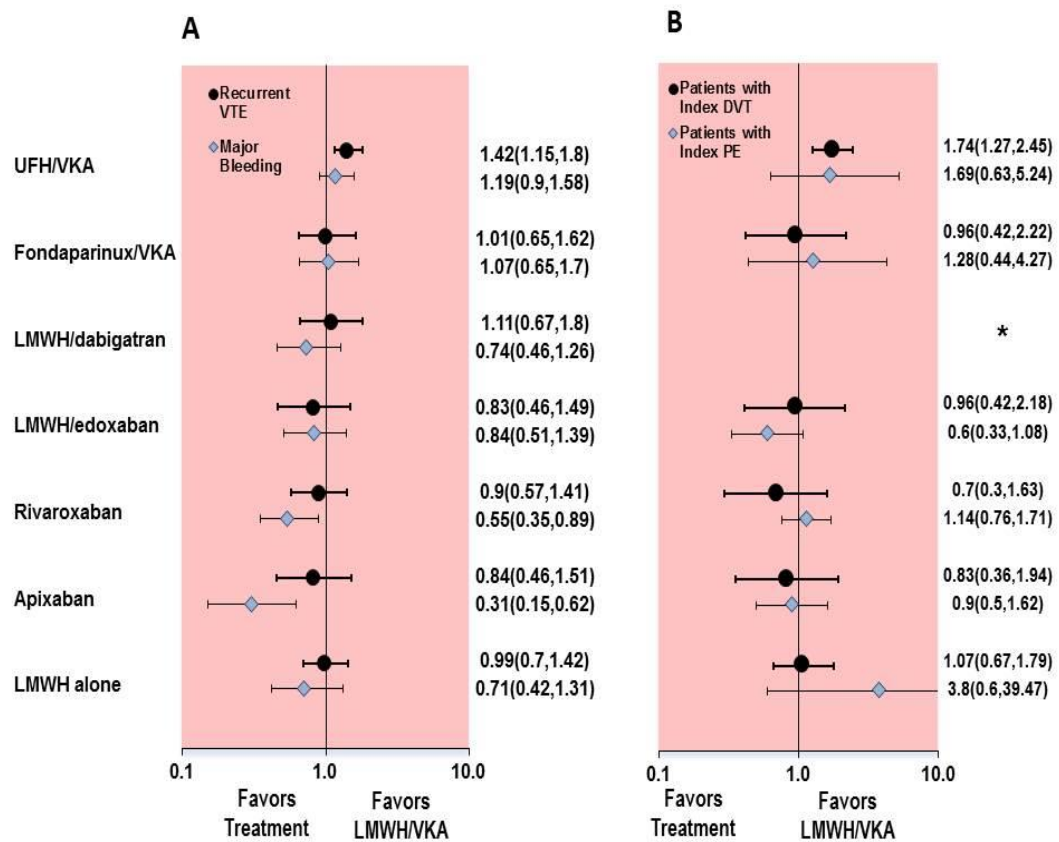


Figure 3: Network meta-analysis: Forest plot of hazard ratios (95% credible interval) relative to LMWH/VKA for (A) Recurrent VTE and major bleeding; and (B) Recurrent VTE by index event



* Data not stratified by Index DVT/PE

DVT = deep vein thrombosis; LMWH = low molecular weight heparin; PE = pulmonary embolism; UFH = unfractionated heparin; VKA = vitamin K antagonist; VTE = venous thromboembolism

REFERENCES

- (1) Cohen AT, Agnelli G, Anderson FA et al. Venous thromboembolism (VTE) in Europe. The number of VTE events and associated morbidity and mortality. *Thromb Haemost* 2007;98:756-764.
- (2) Ageno W, Prandoni P, Romualdi E et al. The metabolic syndrome and the risk of venous thrombosis: a case-control study. *J Thromb Haemost* 2006;4:1914-1918.
- (3) Heit JA. The epidemiology of venous thromboembolism in the community: implications for prevention and management. *J Thromb Thrombolysis* 2006;21:23-29.
- (4) White RH. The epidemiology of venous thromboembolism. *Circulation* 2003;107:I-4-I-8.
- (5) Prins MH, Marchiori A. Risk of recurrent venous thromboembolism--expanding the frontier. *Thromb Haemost* 2002;87(1):1-3.
- (6) Silverstein MD, Heit JA, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ, III. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. *Arch Intern Med* 1998;158:585-593.
- (7) Anderson FA, Jr., Wheeler HB, Goldberg RJ et al. A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism. The Worcester study. *Arch Intern Med* 1991;151:933-938.
- (8) Barritt DW, Jordan SC. Anticoagulant drugs in the treatment of pulmonary embolism. A controlled trial. *Lancet* 1960;1:1309-1312.
- (9) Carrier M, Le Gal G, Wells PS, Rodger MA. Systematic review: case-fatality rates of recurrent venous thromboembolism and major bleeding events among patients treated for venous thromboembolism. *Ann Intern Med* 2010;152(9):578-589.
- (10) Kearon C, Akl EA, Comerota AJ et al. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;141(2 Suppl):e419S-e494S.
- (11) Ansell JE, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G. Pharmacology and management of the vitamin K antagonists: ACCP Evidence-Based Clinical Practice Guidelines. *Chest* 2008;133:160S-198S.
- (12) Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost* 2005;3(4):692-694.
- (13) Higgins JPT. Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2. *Cochrane Database Syst Rev* [serial online] 2009.
- (14) Dias S, Welton NJ, Sutton AJ, Ades A. NICE DSU technical support document 2: A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials. 2011.
- (15) Hansen D, Shneiderman B, Smith MA. Analyzing Social Media Networks with NodeXL: Insights from a Connected World. Elsevier Inc., 2010.
- (16) Fleurence RL, Hollenbeak CS. Rates and probabilities in economic modelling: transformation, translation and appropriate application. *Pharmacoeconomics* 2007;25(1):3-6.
- (17) Agnelli G, Buller HR, Cohen A et al. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med* 2013;369(9):799-808.
- (18) Turner RM, Davey J, Clarke MJ, Thompson SG, Higgins JP. Predicting the extent of heterogeneity in meta-analysis, using empirical data from the Cochrane Database of Systematic Reviews. *Int J Epidemiol* 2012;41(3):818-827.
- (19) Thorlund K, Thabane L, Mills EJ. Modelling heterogeneity variances in multiple treatment

comparison meta-analysis--are informative priors the better solution? BMC Med Res Methodol 2013;13:2.

(20) Cipriani A, Furukawa TA, Salanti G et al. Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. Lancet 2009;373(9665):746-758.

(21) Spiegelhalter DJ, Best NG, Carlin BP, Van der Linde A. Bayesian measures of model complexity and fit. Journal of the Royal Statistical Society: Series B (Statistical Methodology) 2002;64:583-639.

(22) Spiegelhalter D, Thomas A, Best N. WinBUGS user manual. 2004. MRC Biostatistics Unit 2. Ref Type: Online Source

(23) Dias S, Welton NJ, Sutton AJ, Caldwell DM, Lu G, Ades AE. Evidence synthesis for decision making 4: inconsistency in networks of evidence based on randomized controlled trials. Med Decis Making 2013;33(5):641-656.

(24) Kirchmaier CM, Wolf H, Schäfer H, Ehlers B, Breddin HK. Efficacy of a low molecular weight heparin administered intravenously or subcutaneously in comparison with intravenous unfractionated heparin in the treatment of deep venous thrombosis. Int Angiol 1998;17(3):135-145.

(25) Breddin HK, Hach-Wunderle V, Nakov R, Kakkar VV. Effects of a low molecular weight heparin on thrombus regression and recurrent thromboembolism in patients with deep vein thrombosis. N Engl J Med 2001;344(9):626-631.

(26) Merli G, Spiro TE, Olsson CG et al. Subcutaneous enoxaparin once or twice daily compared with intravenous unfractionated heparin for treatment of venous thromboembolic disease. Ann Intern Med 2001;134(3):191-202.

(27) Kakkar VV, Gebaska M, Kadziola Z, Saba N, Carrasco P. Low-molecular-weight heparin in the acute and long-term treatment of deep vein thrombosis. Thromb Haemost 2003;89(4):674-680.

(28) Duroux P, Beclere A. A randomised trial of subcutaneous low molecular weight heparin (CY216) compared with intravenous unfractionated heparin in the treatment of deep vein thrombosis. A Collaborative European Multicentre Study. Thromb Haemost 1991;65(3):251-256.

(29) Hull RD, Raskob GE, Pineo GF et al. Subcutaneous low-molecular-weight Heparin compared with continuous intravenous Heparin in the treatment of proximal vein thrombosis. N Engl J Med 1992;326(15):975-982.

(30) Lopaciuk S, Meissner AJ, Filipecki S et al. Subcutaneous low molecular weight heparin versus subcutaneous unfractionated heparin in the treatment of deep vein thrombosis: a Polish multicenter trial. Thromb Haemost 1992;68(1):14-18.

(31) Prandoni P, Lensing AWA, Buller HR et al. Comparison of subcutaneous low-molecular-weight heparin with intravenous standard heparin in proximal deep-vein thrombosis. Lancet 1992;339(8791):441-445.

(32) Simonneau G, Charbonnier B, Decousus H et al. Subcutaneous low molecular weight Heparin compared with continuous intravenous unfractionated heparin in the treatment of proximal deep vein thrombosis. Arch Intern Med 1993;153:1541-1546.

(33) Meyer G, Brenot F, Pacouret G et al. Subcutaneous low-molecular-weight heparin fragmin versus intravenous unfractionated heparin in the treatment of acute non massive pulmonary embolism: an open randomized pilot study. Thromb Haemost 1995;74(6):1432-1435.

(34) Levine MN, Gent M, Hirsh J et al. A comparison of low molecular weight heparin administered primarily at home with unfractionated heparin administered in the hospital for proximal deep vein thrombosis. N Engl J Med 1996;334(11):677-681.

(35) Koopman MMW, Prandoni P, Piovella F et al. Treatment of venous thrombosis with intravenous unfractionated heparin administered in the hospital as compared with subcutaneous low molecular weight heparin administered at home. N Engl J Med 1996;334(11):682-687.

(36) Fiessinger JN, Lopez-Fernandez M, Gatterer E et al. Once-daily subcutaneous Dalteparin, a

low molecular weight heparin, for the initial treatment of acute deep vein thrombosis. *Thromb Haemost* 1996;76(2):195-199.

(37) Columbus Investigators, ten Cate JW. Low molecular weight heparin in the treatment of patients with venous thromboembolism. *N Engl J Med* 1997;337(10):657-662.

(38) Simonneau G, Sors H, Charbonnier B et al. A Comparison of low-molecular-weight heparin with unfractionated heparin for acute pulmonary embolism. *N Engl J Med* 1997;337(10):663-669.

(39) Hull RD, Raskob GE, Brant RF et al. Low-molecular-weight heparin vs heparin in the treatment of patients with pulmonary embolism. *Arch Intern Med* 2000;160(2):229-236.

(40) Harenberg J, Schmidt JA, Koppenhagen K, Tolle A, Huisman MV, Buller HR. Fixed-dose, body-weight-independent subcutaneous LMW Heparin versus adjusted dose unfractionated intravenous Heparin in the initial treatment of proximal venous thrombosis. *Thromb Haemost* 2000;83(5):652-656.

(41) Findik S, Erkan ML, Selcuk MB, Albayrak S, Atici AG, Doru F. Low-molecular-weight heparin versus unfractionated heparin in the treatment of patients with acute pulmonary thromboembolism. *Respiration* 2002;69(5):440-444.

(42) Riess H, Koppenhagen K, Tolle A et al. Fixed-dose, body weight-independent subcutaneous low molecular weight heparin certoparin compared with adjusted-dose intravenous unfractionated heparin in patients with proximal deep venous thrombosis. *Thromb Haemost* 2003;90(2):252-259.

(43) Prandoni P, Carnovali M, Marchiori A. Subcutaneous adjusted-dose unfractionated heparin vs fixed-dose low-molecular-weight heparin in the initial treatment of venous thromboembolism. *Arch Intern Med* 2004;164(10):1077-1083.

(44) Kearon C, Ginsberg JS, Julian JA et al. Comparison of fixed-dose weight-adjusted unfractionated heparin and low-molecular-weight heparin for acute treatment of venous thromboembolism. *JAMA* 2006;296:935-942.

(45) Leizorovicz A, Siguret V, Mottier D et al. Safety profile of tinzaparin versus subcutaneous unfractionated heparin in elderly patients with impaired renal function treated for acute deep vein thrombosis: the Innohep(R) in Renal Insufficiency Study (IRIS). *Thromb Res* 2011;128(1):27-34.

(46) Belcaro G, Barsotti A, Nicolaides AN et al. Comparison of low-molecular-weight Heparin, administered primarily at home, with unfractionated Heparin, administered in hospital, and subcutaneous Heparin, administered at home for deep-vein thrombosis. *Angiology* 1999;50(10):781-787.

(47) Bratt G, Aberg W, Johansson M, Tornebohm E, Granqvist S, Lockner D. Two daily subcutaneous injections of Fragmin as compared with intravenous standard heparin in the treatment of deep venous thrombosis (DVT). *Thromb Haemost* 1990;64(4):506-510.

(48) Lindmarker P, Holmstrom H, Granqvist S, Johnsson H, Lockner D. Comparison of once-daily subcutaneous Fragmin with continuous intravenous unfractionated Heparin in the treatment of deep vein thrombosis. *Thromb Haemost* 1994;72(2):186-190.

(49) Pini M, Aiello S, Manotti C et al. Low molecular weight heparin versus warfarin in the prevention of recurrences after deep vein thrombosis. *Thromb Haemost* 1994;72(2):191-197.

(50) Gonzalez-Fajardo JA, Arreba E, Castrodeza J et al. Venographic comparison of subcutaneous low-molecular weight heparin with oral anticoagulant therapy in the long-term treatment of deep venous thrombosis. *J Vasc Surg* 1999;30(2):283-292.

(51) Veiga F, Escriba A, Maluenda MP et al. Low molecular weight Heparin (Enoxaparin) versus oral anticoagulant therapy (Acenocoumarol) in the long-term treatment of deep venous thrombosis in the elderly: a randomized trial. *Thromb Haemost* 2000;84:559-564.

(52) Beckman JA, Dunn K, Sasahara AA, Goldhaber SZ. Enoxaparin monotherapy without oral anticoagulation to treat acute symptomatic pulmonary embolism. *Thromb Haemost* 2003;89(6):953-958.

- (53) Perez de Llano LA, Baloira VA, Veres RA, Veiga F, Golpe GR, Pajuelo FF. [Multicenter, prospective study comparing enoxaparin with unfractionated heparin in the treatment of submassive pulmonary thromboembolism]. *Arch Bronconeumol* 2003;39(8):341-345.
- (54) Ramacciotti E, Araujo GR, Lastoria S et al. An open-label, comparative study of the efficacy and safety of once-daily dose of enoxaparin versus unfractionated heparin in the treatment of proximal lower limb deep-vein thrombosis. *Thromb Res* 2004;114:149-153.
- (55) Chong BH, Brighton TA, Baker RI, Thurlow P, Lee CH. Once-daily enoxaparin in the outpatient setting versus unfractionated heparin in hospital for the treatment of symptomatic deep-vein thrombosis. *J Thromb Thrombolysis* 2005;19(3):173-181.
- (56) Daskalopoulos ME, Daskalopoulou SS, Tzortzis E et al. Long-term treatment of deep venous thrombosis with a low molecular weight heparin (tinzaparin): a prospective randomized trial. *Eur J Vasc Endovasc Surg* 2005;29(6):638-650.
- (57) Hull RD, Pineo GF, Brant RF et al. Self-managed long-term low-molecular-weight heparin therapy: the balance of benefits and harms. *Am J Med* 2007;120:72-82.
- (58) Buller HR, Davidson BL, Decousus H et al. Subcutaneous fondaparinux versus intravenous unfractionated heparin in the initial treatment of pulmonary embolism. *N Engl J Med* 2003;349:1695-1702.
- (59) Das SK, Cohen AT, Edmondson RA, Melissari E, Kakkar VV. Low-molecular-weight heparin versus warfarin for prevention of recurrent venous thromboembolism: a randomized trial. *World J Surg* 1996;20(5):521-526.
- (60) Lopaciuk S, Bielska-Falda H, Noszczyk W et al. Low molecular weight heparin versus acenocoumarol in the secondary prophylaxis of deep vein thrombosis. *Thromb Haemost* 1999;81(1):26-31.
- (61) Romera A, Cairols MA, Vila-Coll R et al. A randomised open-label trial comparing long-term sub-cutaneous low-molecular-weight heparin compared with oral-anticoagulant therapy in the treatment of deep venous thrombosis. *Eur J Vasc Endovasc Surg* 2009;37(3):349-356.
- (62) Buller HR, Davidson BL, Decousus H et al. Fondaparinux or Enoxaparin for the initial treatment of symptomatic deep venous thrombosis. A randomized trial. *Ann Intern Med* 2004;140:867-873.
- (63) Schulman S, Kearon C, Kakkar AK et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med* 2009;361(24):2342-2352.
- (64) Schulman S, Kakkar AK, Goldhaber SZ et al. Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. *Circulation* 2014;129(7):764-772.
- (65) Buller HR, Decousus H, Grosso MA et al. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *N Engl J Med* 2013;369(15):1406-1415.
- (66) Einstein Investigators, Bauersachs R, Berkowitz SD et al. Oral Rivaroxaban for Symptomatic Venous Thromboembolism. *N Engl J Med* 2010;363(26):2499-2510.
- (67) Buller HR, Prins MH, Lensin AW et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med* 2012;366(14):1287-1297.
- (68) Guyatt GH, Eikelboom JW, Gould MK et al. Approach to outcome measurement in the prevention of thrombosis in surgical and medical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;141(2 Suppl):e185S-e194S.
- (69) Castellucci LA, Cameron C, Le GG et al. Efficacy and safety outcomes of oral anticoagulants and antiplatelet drugs in the secondary prevention of venous thromboembolism: systematic review and network meta-analysis. *BMJ* 2013;347:f5133.
- (70) Fox BD, Kahn SR, Langleben D, Eisenberg MJ, Shimony A. Efficacy and safety of novel oral anticoagulants for treatment of acute venous thromboembolism: direct and adjusted indirect meta-

analysis of randomised controlled trials. *BMJ* 2012;345:e7498.

(71) van der Hulle T, Kooiman J, den Exter PL, Dekkers OM, Klok FA, Huisman MV. Effectiveness and safety of novel oral anticoagulants compared with vitamin K-antagonists in the treatment of acute symptomatic venous thromboembolism- a systematic review and meta-analysis. *J Thromb Haemost* 2013.

(72) Guyatt GH, Oxman AD, Vist G et al. GRADE guidelines: 4. Rating the quality of evidence--study limitations (risk of bias). *J Clin Epidemiol* 2011;64(4):407-415.

APPENDICES

Castellucci LA, Cameron C, LeGal G, et al. Clinical and safety outcomes associated with treatment of acute venous thromboembolism: a systematic review and meta-analysis. JAMA. doi:10.1001/jama.2014.10538

Appendix 1. Medline search strategy

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Appendix 11. Summary of network meta-analysis odds ratios (95%CrI) using a binomial likelihood model – random-effects model with informative priors.

Reference Section

This supplementary material has been provided by the authors to give readers additional information about their work.

Appendix 1. Medline search strategy

Example of MeSH and key word terms used for the systematic search strategy. The search strategy below was used to conduct the MEDLINE review*

exp Venous Thrombosis/
exp Venous Thromboembolism/
Deep vein thrombosis.mp.
Pulmonary embolism.mp. or exp Pulmonary Embolism/
exp Warfarin/
exp Acenocoumarol/
Direct thrombin inhibitor.mp.
dabigatran.mp.
rivaroxaban.mp.
apixaban.mp.
direct Xa inhibitor.mp.
Pradax\$.mp.
xarelto.mp.
eliquis.mp.
coumadin.mp.
exp Heparin, low molecular weight/
randomized controlled trial.pt.
controlled clinical trial.pt.
random allocation.sh.
double blind method.sh.
single-blind method.sh.
((singl\$ or doubl\$ or trebl\$ or tripl\$) adj (blind\$ or mask\$)).ti,ab.
random\$.ti,ab.

*Search completed on February 28th, 2014

Appendix 2. Summary of data on network geometry for each network

	<u>Recurrent VTE</u>	Major Bleeding
Total number of studies	45	42
Total number of studies with 2-arms	43	40
Total number of studies with multi-arms	2	2
Total number of patients	44989	44434
Total number of patient-years	20842	20643
Total number of patients who had an event	1327	754
Total number of treatments compared	8	8
Theoretical number of direct comparisons	28	28
Total number of comparisons with no direct comparisons	19/28(67.9%)	19/28(67.9%)
Total number of events/patients/patient-years for each treatment		
LMWH/VKA	533/20246/9821	361/20124/9760
UFH/VKA	357/7133/2134	169/6975/2095
Fondaparinux/VKA	85/2201/550	50/2201/550
LMWH/dabigatran	60/2553/1277	35/2553/1277
LMWH/edoxaban	66/4118/2814	56/4118/2814
Rivaroxaban	86/4150/2340	40/4150/2340
Apixaban	59/2691/1346	15/2691/1346
LMWH alone	81/1897/561	28/1622/463
Total number of studies for each comparison		
UFH/VKA vs LMWH/VKA	22 RCTs	22 RCTs
Fondaparinux/VKA vs LMWH/VKA	1 RCT	1 RCT
LMWH/dabigatran vs LMWH/VKA	2 RCTs	2 RCTs
LMWH/edoxaban vs LMWH/VKA	1 RCT	1 RCT
Rivaroxaban vs LMWH/VKA	2 RCTs	2 RCTs
Apixaban vs LMWH/VKA	1 RCT	1 RCT
LMWH alone vs LMWH/VKA	5 RCTs	4 RCTs
Fondaparinux/VKA vs UFH/VKA	1 RCT	1 RCT
LMWH/dabigatran vs UFH/VKA	0 RCTs	0 RCTs
LMWH/edoxaban vs UFH/VKA	0 RCTs	0 RCTs
Rivaroxaban vs UFH/VKA	0 RCTs	0 RCTs
Apixaban vs UFH/VKA	0 RCTs	0 RCTs
LMWH alone vs UFH/VKA	14 RCTs	12 RCTs

	<u>Recurrent VTE</u>	Major Bleeding
Total number of studies for each comparison		
LMWH/dabigatran vs Fondaparinux/VKA	0 RCTs	0 RCTs
LMWH/edoxaban vs Fondaparinux/VKA	0 RCTs	0 RCTs
Rivaroxaban vs Fondaparinux/VKA	0 RCTs	0 RCTs
Apixaban vs Fondaparinux/VKA	0 RCTs	0 RCTs
LMWH alone vs Fondaparinux/VKA	0 RCTs	0 RCTs
LMWH/edoxaban vs LMWH/dabigatran	0 RCTs	0 RCTs
Rivaroxaban vs LMWH/dabigatran	0 RCTs	0 RCTs
Apixaban vs LMWH/dabigatran	0 RCTs	0 RCTs
LMWH alone vs LMWH/dabigatran	0 RCTs	0 RCTs
Rivaroxaban vs LMWH/edoxaban	0 RCTs	0 RCTs
Apixaban vs LMWH/edoxaban	0 RCTs	0 RCTs
LMWH alone vs LMWH/edoxaban	0 RCTs	0 RCTs
Apixaban vs Rivaroxaban	0 RCTs	0 RCTs
LMWH alone vs Rivaroxaban	0 RCTs	0 RCTs
LMWH alone vs Apixaban	0 RCTs	0 RCTs

LMWH = low molecular weight heparin; RCT= randomized controlled trial; UFH = unfractionated heparin; VKA = vitamin K antagonist; VTE = venous thromboembolism.

Appendix 3. Study Quality

Study, Year (reference)	Adequate Sequence Generation	Allocation Concealment	Blinding	Incomplete Outcome Data Addressed	Free of Selective Outcome Reporting	Free of Other Bias
Collaborative European Study, 1991 ¹	Unclear	Unclear	No	Yes	Yes	Yes
Hull et al, 1992 ²	Yes	Yes	Yes	Yes	Yes	Yes
Lopaciuk et al, 1992 ³	Yes	Yes	No	Yes	Yes	Yes
Prandoni et al, 1992 ⁴	Yes	Unclear	No	Yes	Yes	Yes
Simonneau et al, 1993 ⁵	Yes	Yes	No	Unclear	Yes	Yes
Fiessinger et al, 1996 ⁶	Unclear	Unclear	No	Yes	Yes	Yes
Koopman et al, 1996 ⁷	Unclear	Yes	No	Unclear	Yes	Yes
Levine et al, 1996 ⁸	Yes	Yes	No	Yes	Yes	Yes
Kirchmaier et al, 1998 ⁹	Unclear	Yes	No	Yes	Yes	Yes
Harenberg et al, 2000 ¹⁰	Unclear	Unclear	No	Yes	Yes	Yes
Breddin et al, 2001 ¹¹	Unclear	Unclear	No	Yes	Yes	Yes
Kakkar et al, 2003 ¹²	Unclear	Yes	No	Yes	Yes	Yes
Riess et al, 2003 ¹³	Yes	Yes	No	Yes	Yes	Yes
Meyer et al, 1995 ¹⁴	Unclear	Unclear	No	Yes	Yes	Yes
Simonneau et al, 1997 ¹⁵	Yes	Yes	No	Unclear	Yes	Yes
Findik et al, 2002 ¹⁶	Unclear	Unclear	No	Yes	Yes	Yes
Columbus Investigators, 1997 ¹⁷	Yes	Yes	No	Yes	Yes	Yes
Hull et al, 2000 ¹⁸	Yes	Yes	Yes	Yes	Yes	Yes
Merli et al, 2001 ¹⁹	Yes	Yes	No	Yes	Yes	Yes
Prandoni et al, 2004 ²⁰	Yes	Yes	No	Yes	Yes	Yes
Kearon et al, 2006 ²¹	Yes	Yes	No	Yes	Yes	Yes
Leizorovicz et al, 2011 ²²	Yes	Yes	No	Yes	Yes	Yes
Bratt et al, 1990 ²³	Unclear	Unclear	No	Unclear	Unclear	Yes
Lindmarker et al, 1994 ²⁴	Unclear	Yes	No	Unclear	Yes	Yes
Pini et al, 1994 ²⁵	Yes	Yes	No	Yes	Yes	Yes
Das et al, 1996 ²⁶	Yes	Yes	No	Yes	Yes	Yes
Belcaro et al, 1999 ²⁷	Unclear	Unclear	No	No	Yes	Yes
Gonzalez-Fajardo et al, 1999 ²⁸	Yes	Unclear	No	Yes	Yes	Yes
Lopaciuk et al, 1999 ²⁹	Unclear	Yes	No	Yes	Yes	Yes
Veiga et al, 2000 ³⁰	Unclear	Yes	No	Yes	Yes	Yes
Ramacciotti et al, 2004 ³¹	Yes	No	No	Yes	Yes	Yes
Chong et al, 2005 ³²	Unclear	Unclear	No	Yes	Yes	Yes
Daskalopoulos et al, 2005 ³³	Yes	Yes	No	Yes	Yes	Yes
Romera et al, 2009 ³⁴	Yes	Yes	No	Yes	Yes	Yes
Beckman et al, 2003 ³⁵	Unclear	Unclear	No	Yes	Yes	Yes
Perez de Llano et al, 2003 ³⁶	Unclear	Unclear	No	Yes	Yes	Yes

Hull et al, 2007 ³⁷	Yes	Yes	No	Yes	Yes	Yes
Buller et al, 2004 ³⁸	Yes	Yes	Yes	Yes	Yes	Yes
Buller et al, 2003 ³⁹	Yes	Yes	No	Yes	Yes	Yes
Bauersachs et al, 2010 ⁴⁰	Yes	Yes	No	Yes	Yes	Yes
Buller et al, 2012 ⁴¹	Yes	Yes	No	Yes	Yes	Yes

Study, Year (reference)	Adequate Sequence Generation	Allocation Concealment	Blinding	Incomplete Outcome Data Addressed	Free of Selective Outcome Reporting	Free of Other Bias
Schulman et al, 2009 ⁴²	Yes	Yes	Yes	Yes	Yes	Yes
Schulman et al, 2014 ⁴³	Yes	Yes	Yes	Yes	Yes	Yes
Buller et al, 2013 ⁴⁴	Yes	Yes	Yes	Yes	Yes	Yes
Agnelli et al, 2013 ⁴⁵	Yes	Yes	Yes	Yes	Yes	Yes

Appendix 4. Probability best therapy

We assessed the probability that each treatment was the most efficacious for each outcome by calculating the hazard ratio for each drug compared with LMWH/VKA, and counting the proportion of iterations in which each drug had the most favorable hazard ratio compared with LMWH/VKA.

eTable 4a. Probability of best therapy (%)

Treatment	Recurrence of VTE	Major Bleeding
LMWH/VKA	0.3%	0.0%
UFH/VKA	0.0%	0.0%
Fondaparinux/VKA	6.6%	0.1%
LMWH/dabigatran	5.1%	1.0%
LMWH/edoxaban	33.1%	0.5%
Rivaroxaban	16.5%	7.4%
Apixaban	31.6%	88.9%
LMWH alone	6.7%	2.2%

LMWH = low molecular weight heparin; UFH = unfractionated heparin; VKA = vitamin K antagonist; VTE = venous thromboembolism.

A simple numerical summary of these probabilities – the surface under the cumulative ranking (SUCRA) was calculated. The SUCRA would be 100% when a treatment is certain to be the best and 0% when a treatment is certain to be the worst. SUCRA values enable the ranking of treatments overall for a particular outcome. For example, for recurrent VTE the SUCRA value for LMWH/edoxaban is 72.5%, which is better than other treatments. By contrast, UFH/VKA has a SUCRA of 5.1% for recurrent VTE meaning it is more certain to be worst for this outcome.

eTable 4b. Surface under the cumulative ranking values (%)

Treatment	Recurrence of VTE	Major Bleeding
LMWH/VKA	48.7%	27.8%
UFH/VKA	5.1%	9.5%
Fondaparinux/VKA	48.6%	23.2%
LMWH/dabigatran	37.0%	55.7%
LMWH/edoxaban	72.5%	45.9%
Rivaroxaban	64.5%	78.6%
Apixaban	71.2%	97.7%
LMWH alone	52.5%	61.7%

LMWH = low molecular weight heparin; UFH = unfractionated heparin; VKA = vitamin K antagonist; VTE = venous thromboembolism.

Appendix 5. Proportion of patients experiencing outcomes events

We report the proportion of patients expected to have a recurrent VTE or major bleeding event while using each treatment for a period of 3 and 6 months. These values were calculated, assuming a rate of 5.3 per 100 patient-years (~2.6% over 6 months) and 3.6 events per 100 patient-years (~1.8% over 6 months) for recurrent VTE and major bleeding, respectively, in the LMWH/VKA arm of the Amplify trial.^{45;46} The hazard ratios were then applied to this log-rate.⁴⁷ Using this value, we calculate the difference in the proportion of patients expected to have an event relative to LMWH/VKA and number needed to treat to benefit (or harm).

eTable 5a. Recurrent VTE

Treat ment	Proportion of patients expected to have recurrent VTE (95% CrI)	Difference in proportion of patients expected to have recurrent VTE relative to LMWH/VKA (95% CrI)*	NNTB(NNTH) relative to LMWH/VKA
At 3 months			

LMWH /VKA	1.3% (1.02%, 1.62%)	Reference	Reference
UFH/VKA	1.84% (1.33%, 2.51%)	0.53% (0.19%, 1.04%)	(188)
Fondaparinux	1.31% (0.79%, 2.18%)	0.01% (-0.47%, 0.79%)	(14071)
LMWH /dabigatran	1.44% (0.82%, 2.43%)	0.14% (-0.44%, 1.04%)	(733)
LMWH /edoxaban	1.07% (0.57%, 1.99%)	-0.22% (-0.73%, 0.63%)	447
Rivaroxaban	1.16% (0.7%, 1.91%)	-0.13% (-0.57%, 0.53%)	756
Apixaban	1.08% (0.62%, 1.87%)	-0.22% (-0.78%, 0.6%)	460
LMWH alone	1.28% (0.83%, 1.95%)	-0.02% (-0.41%, 0.54%)	5247
At 6 months			
LMWH /VKA	2.58% (2.03%, 3.22%)	Reference	Reference
UFH/VKA	3.64% (2.64%, 4.96%)	1.05% (0.37%, 2.05%)	(95)
Fondaparinux	2.59% (1.57%, 4.32%)	0.01% (-0.93%, 1.56%)	(7117)
LMWH /dabigatran	2.85% (1.62%, 4.8%)	0.27% (-0.87%, 2.03%)	(372)
LMWH /edoxaban	2.13% (1.14%, 3.95%)	-0.44% (-1.44%, 1.23%)	226
Rivaroxaban	2.31% (1.39%, 3.79%)	-0.26% (-1.14%, 1.03%)	383
Apixaban	2.15% (1.23%, 3.7%)	-0.43% (-1.54%, 1.19%)	233
LMWH alone	2.54% (1.66%, 3.86%)	-0.04% (-0.81%, 1.06%)	2658

CrI = credible interval; LMWH = low molecular weight heparin; NNTB = number need to treat to benefit; NNTH = number need to treat to harm; UFH = unfractionated heparin; VKA = vitamin K antagonist; VTE = venous thromboembolism
 *A minus sign (-) indicates that a lower proportion of patients is expected to have an event.

Bold type font indicates significant values.

eTable 5b. Major Bleeding

Treatment	Proportion of patients expected to have a major bleeding event (95% CrI)	Difference in proportion of patients expected to have a major bleeding event relative to LMWH/VKA (95% CrI)*	NNTB(NNTH) relative to LMWH/VKA
At 3 months			
LMWH/VKA	0.89% (0.66%, 1.16%)	Reference	Reference
UFH/VKA	1.05% (0.69%, 1.56%)	0.16% (-0.09%, 0.53%)	(609)

Fond a parinu	0.94% (0.54%, 1.64%)	0.06% (-0.32%, 0.64%)	(1779)
LMW H/dabi gatan	0.66% (0.37%, 1.2%)	-0.22% (-0.51%, 0.23%)	453
LMW H/edo xaban	0.75% (0.42%, 1.32%)	-0.14% (-0.45%, 0.35%)	732
Rivaro xaban	0.49% (0.29%, 0.85%)	-0.39% (-0.63%, -0.1%)	258
Apix a	0.28% (0.14%, 0.5%)	-0.6% (-0.92%, -0.28%)	165
LMW H alone	0.63% (0.34%, 1.16%)	-0.25% (-0.55%, 0.27%)	398
At 6 months			
LMW H/VK A	1.77% (1.32%, 2.31%)	Reference	Reference
UFH/V KA	2.09% (1.37%, 3.09%)	0.33% (-0.18%, 1.05%)	(307)
Fond a parinu	1.87% (1.07%, 3.26%)	0.11% (-0.63%, 1.27%)	(898)
LMW H/dabi gatan	1.32% (0.74%, 2.39%)	-0.44% (-1.02%, 0.45%)	228
LMW H/edo xaban	1.49% (0.84%, 2.63%)	-0.27% (-0.9%, 0.69%)	369
Rivaro xaban	0.98% (0.57%, 1.7%)	-0.77% (-1.26%, -0.2%)	130
Apix a	0.56% (0.29%, 0.99%)	-1.2% (-1.82%, -0.56%)	83
LMW H alone	1.26% (0.67%, 2.3%)	-0.5% (-1.1%, 0.52%)	200

CrI = credible interval; LMWH = low molecular weight heparin; NNTB = number need to treat to benefit; NNTH = number need to treat to harm; UFH = unfractionated heparin; VKA = vitamin K antagonist; VTE = venous thromboembolism

*A minus sign (-) indicates that a lower proportion of patients is expected to have an event.

Bold type font indicates significant values.

Appendix 6. Comparison of random-effects bayesian network meta-analysis with direct frequentist meta-analysis estimate for recurrent VTE

The effect estimates from the Bayesian network meta-analysis aligned closely with frequentist pair-wise meta-analyses. There was some heterogeneity within individual comparisons using direct frequentist meta-analysis, particularly for rivaroxaban ($I^2=61\%$). However, the heterogeneity can be explained by the use of different index events among included studies. There were two rivaroxaban studies and each used a different index event (index DVT and index PE^{40;41}). We stratified recurrent VTE analyses by index event in Figure 3 (main manuscript) to account for this heterogeneity.

Treatment	NMA, Recurrent VTE HR (95% CrI) vs LMWH/VKA	Direct estimates, Recurrent VTE Rate ratio (95% CI) vs LMWH/VKA
UFH/VKA	1.42 (1.15, 1.80)	1.40 (1.12, 1.77); I²=13%
Fondaparinux/VKA	1.01 (0.65, 1.62)	0.96 (0.63, 1.46); I ² =NA
LMWH/dabigatran	1.11 (0.67, 1.8)	1.09 (0.76, 1.57); I ² =0%
LMWH/edoxaban	0.83 (0.46, 1.49)	0.83 (0.60, 1.14); I ² =NA
Rivaroxaban	0.9 (0.57, 1.41)	0.90 (0.56, 1.44); I ² =61%
Apixaban	0.84 (0.46, 1.51)	0.84 (0.59, 1.18); I ² =NA
LMWH alone	0.99 (0.7, 1.42)	0.84 (0.41, 1.74); I ² =30%

CI = confidence interval; CrI = Credible Interval; HR = hazard ratio; LMWH = low molecular weight heparin; NA = not assessable; NMA = network meta-analysis; UFH = unfractionated heparin; VKA = vitamin K antagonist; VTE = venous thromboembolism

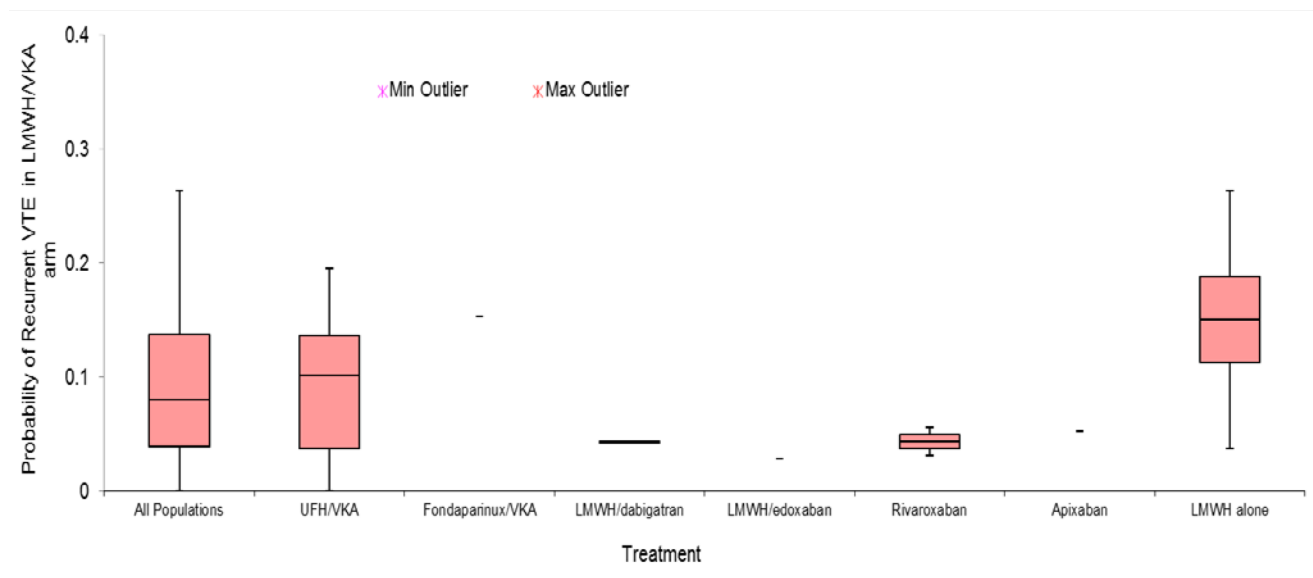
Bold type font indicates significant values.

Appendix 7. Sensitivity analysis for duration of study

We present box plots to illustrate the rationale for the sensitivity analyses undertaken to investigate the impact of study duration. The bottom and top of the box in each box plot are the first (Q1) and third (Q3) quartiles, and the band inside the box is the median value. The ends of the whisker are set at $1.5 \times \text{interquartile range (IQR)}$ above the third quartile (Q3) and $1.5 \times \text{IQR}$ below the first quartile (Q1), where $\text{IQR} = Q3 - Q1$. If the minimum or maximum values are outside this range, then they are shown as outliers. The small dashes indicate one point is available (Fondaparinux/VKA, LMWH/edoxaban, apixaban) while a long bar indicates two studies with very similar findings (LMWH/dabigatran) and the IQR is not visible unless you zoom in (narrow box plot).

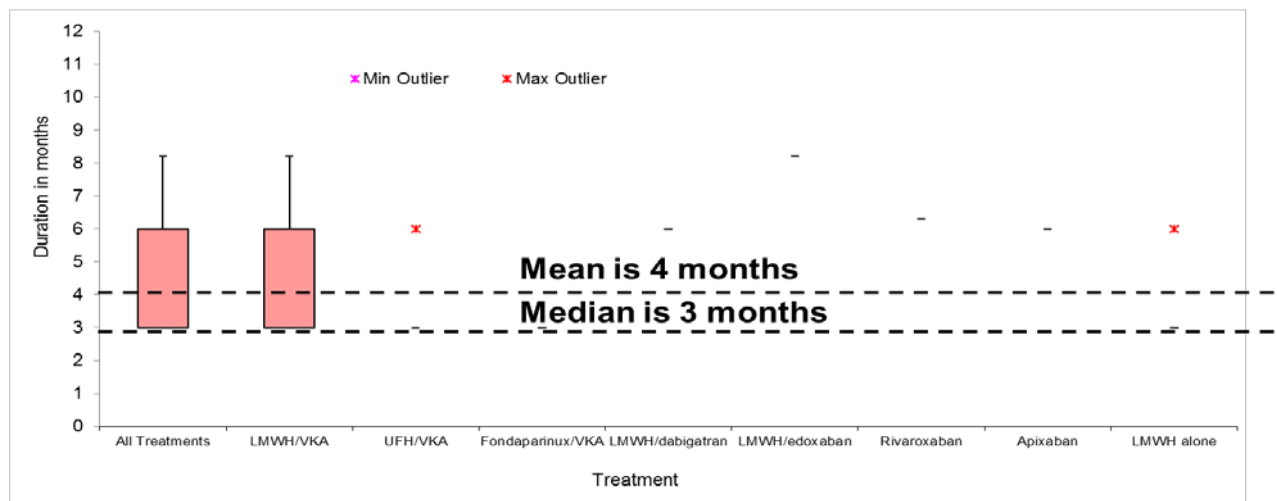
The probability of recurrent VTE is higher in the LMWH/VKA arm of patients using UFH/VKA, Fondaparinux/VKA, and LMWH alone. Probabilities are calculated using the formulas defined by Fluerence et al to convert between probabilities and rates over different time points.⁴⁶ This appears partly attributable to the variation in treatment duration, although it is also attributable to combining of index PE and index DVT outcomes in the box plot (which has been stratified in Table 2 and Figure 3 of the manuscript).

eFigure 7a. Box plot comparing treatments in terms of probability of recurrent VTE in LMWH/VKA arm



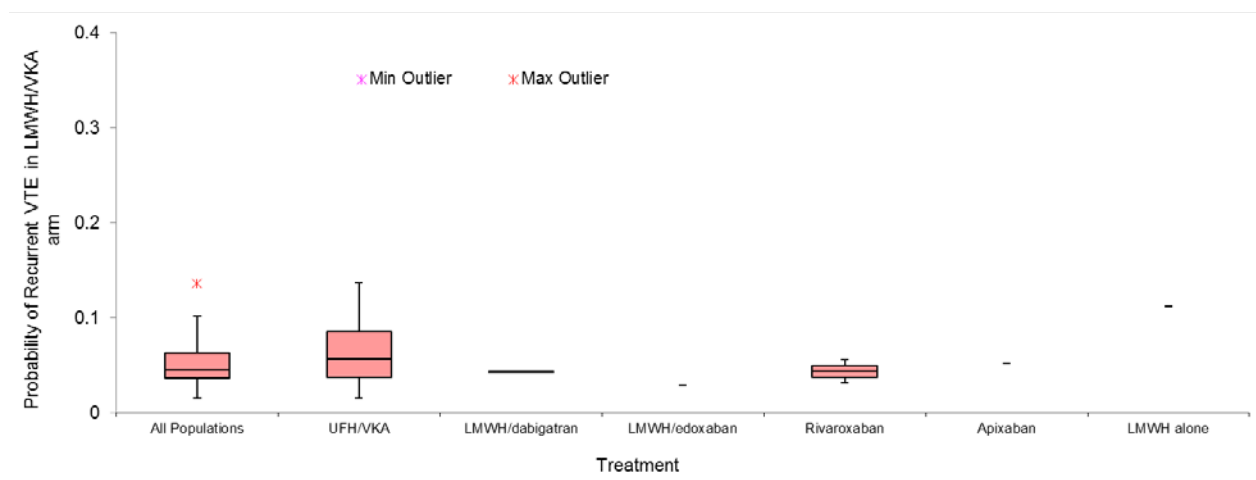
In general, the studies including direct oral anticoagulants were longer in duration than those for UFH/VKA, Fondaparinux/VKA, LMWH alone (eFigure 7b) resulting in potential variations in the probability of recurrent VTE in the LMWH/VKA arms.

eFigure 7b. Box plot comparing treatments in terms of study treatment duration



We ran the reference case analyses using a Poisson likelihood model. However, we also conducted a sub- group analysis which investigated whether duration of treatment may have impacted results. For this analysis, we restricted studies to those that were 6 months in treatment duration or longer. This resulted in a smaller network (14 studies with 17,053 patient-years of follow-up versus 45 studies with 20,842 patient- years of follow-up). Fondaparinux/VKA was also removed from the network given all studies involving this treatment were less than 6 months in duration. Restriction of the network to studies 6 months in treatment duration or longer resulted in more homogeneous estimates of the probability of recurrent VTE in the LMWH/VKA arm compared to the reference case network (eFigure 7c versus eFigure 7a).

eFigure 7c. Box plot comparing treatments in terms of probability of recurrent VTE in LMWH/VKA arm when restricted to trials with at least 6 months of treatment



The results for the sub-group analysis yielded similar results to the primary analysis, with the exception being that the UFH/VKA effect estimate is slightly higher in the sub-group analysis (1.88 vs 1.42) and LMWH alone is slightly lower (0.79 vs 0.99). These do not change statistical significance from the primary analysis. The relative ordering of the SUCRA values are also similar to the primary analysis. SUCRA values enable the ranking of treatments overall for a particular outcome. The SUCRA would be 100% when a treatment is certain to be the best and 0% when a treatment is certain to be the worst.

eTable 7. Comparison of results from primary analysis and sub-group analysis for study treatment duration

Treatment	Primary Analysis		Sub-group Analysis	
	Recurrent VTE HR (95% CrI) vs LMWH/VKA	SUCRA	Recurrent VTE HR (95% CrI) vs LMWH/VKA	SUCRA
LMWH/VKA	Reference	48.7%	Reference	45.7%
UFH/VKA	1.42 (1.15, 1.80)	5.1%	1.88 (1.13, 3.38)	3.2%
Fondaparinux/VKA	1.01 (0.65, 1.62)	48.6%	NA	NA
LMWH/dabigatran	1.11 (0.67, 1.8)	37.0%	1.09 (0.60, 2.0)	38.1%
LMWH/edoxaban	0.83 (0.46, 1.49)	72.5%	0.83 (0.38, 1.77)	67.3%
Rivaroxaban	0.9 (0.57, 1.41)	64.5%	0.9 (0.50, 1.57)	60.0%
Apixaban	0.84 (0.46, 1.51)	71.2%	0.83 (0.38, 1.81)	66.7%
LMWH alone	0.99 (0.7, 1.42)	52.5%	0.79 (0.34, 1.83)	69.0%

CrI = credible intervals; HR= hazard ratio; LMWH = low molecular weight heparin; NA = not available; SUCRA = Surface under the cumulative ranking curve; UFH = unfractionated heparin; VKA = vitamin K antagonist; VTE = venous thromboembolism

Bold type font indicates significant values.

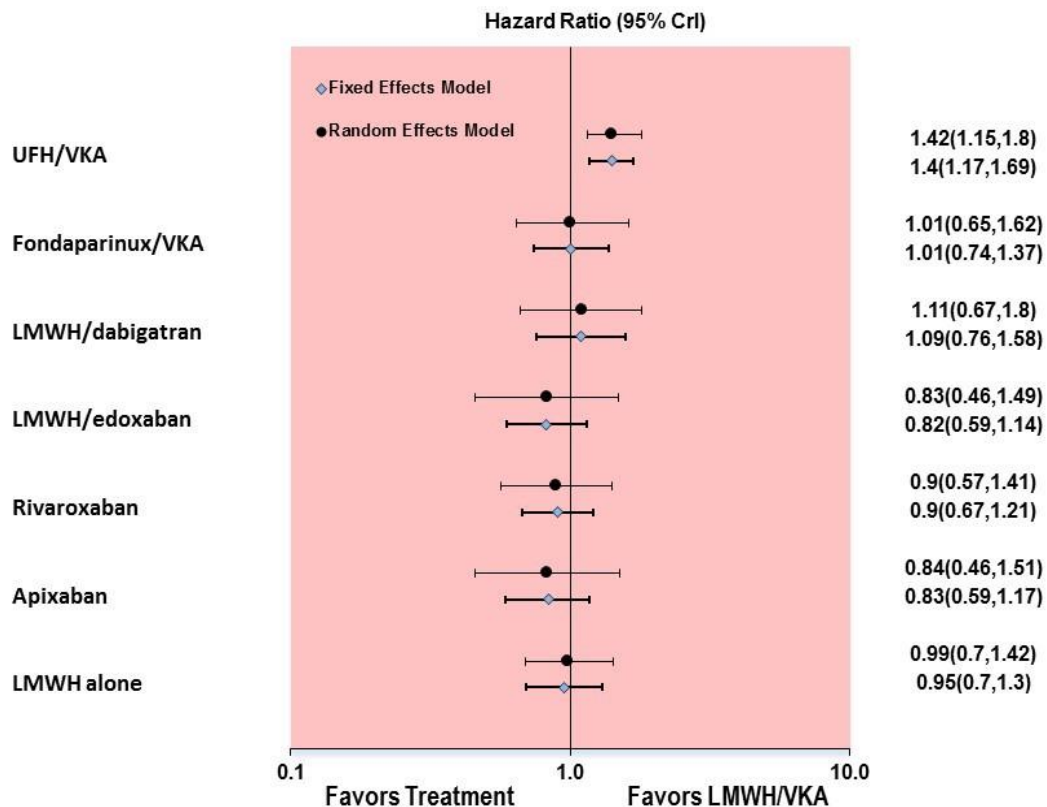
Appendix 8. Summary of analyses to support choice of model for network meta-analyses

We considered a random-effects model with a vague prior and a fixed-effects model for recurrent VTE. The random-effects model was chosen because it has a lower total residual deviance (107 vs 113.1 each vs. 92 data points) and DIC (504.1 vs 503.7) and hence is a better fit to the data, although they are very similar for both models. The between study standard deviation for the random-effects model is 0.202. The total

residual deviance for both random- and fixed-effects models was higher than the number of unconstrained data points (107 vs 113.1 each vs. 92 data points); however, this was largely driven by inclusion of 4 studies – Hull et al.¹⁸, Lopaciuk et al.³, Lindmarker et al.²⁴, and Leizorovicz et al.²² (See Appendix 10).

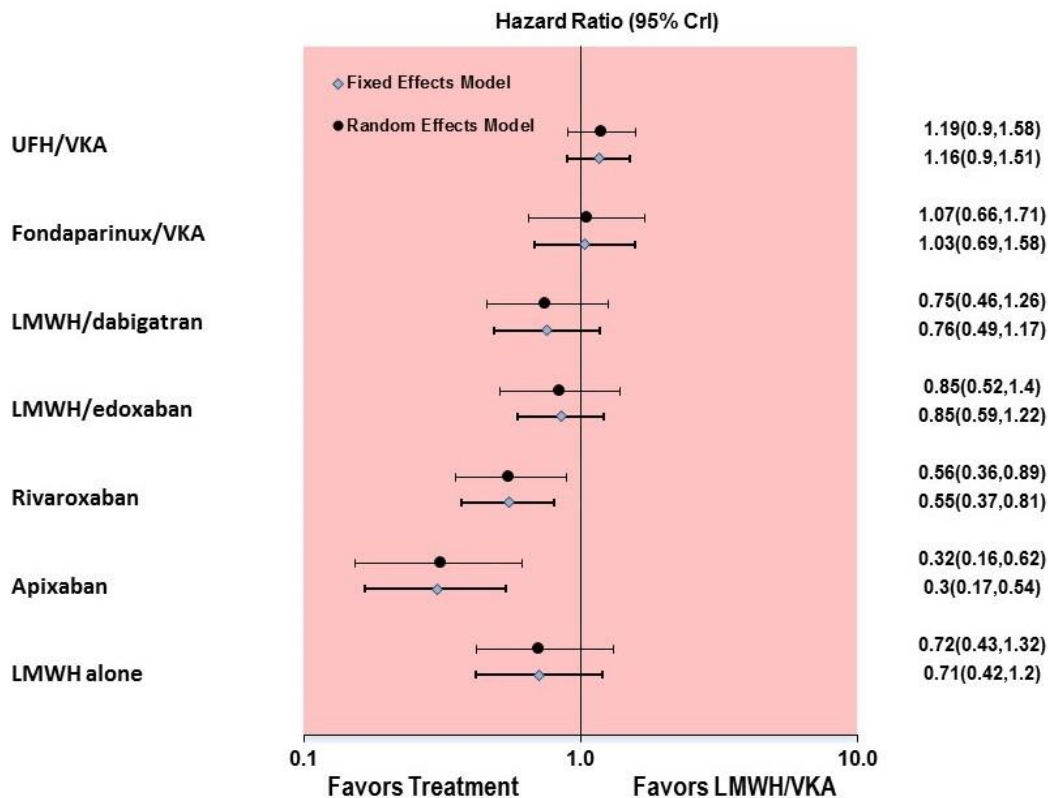
Removal of these 4 studies from the analyses improved fit but did not alter findings substantially (See Appendix 10).

eFigure 8a. Recurrent VTE. Comparison of fixed- and random-effects models for each treatment versus LMWH/VKA



We considered a random-effects model and a fixed-effects model for major bleeding. The random-effects model was chosen because it has a lower residual deviance (71.2 vs 71.4 each vs 86 data points) and similar DIC (370.3 vs 368.3), although they are very similar for both models. The between study standard deviation for the random-effects model for major bleeding was 0.139. The total residual deviance for both random- and fixed-effects models was higher than the number of unconstrained data points (71.2 vs 71.4 each vs 86 data points) indicating good model fit; however, the some of the fit is driven by inclusion of 5 studies with multiple zero event cells.

eFigure 8b. Major bleeding. Comparison of Fixed- and Random-Effects models for each treatment versus LMWH/VKA



The model fit statistics for the major bleeding analysis seemed to be better than the recurrent VTE analysis. The between study standard deviation was lower (0.139 vs 0.202) and the total residual deviance was closer to the number of unconstrained data points (even if we exclude the double/multiple zero cells).

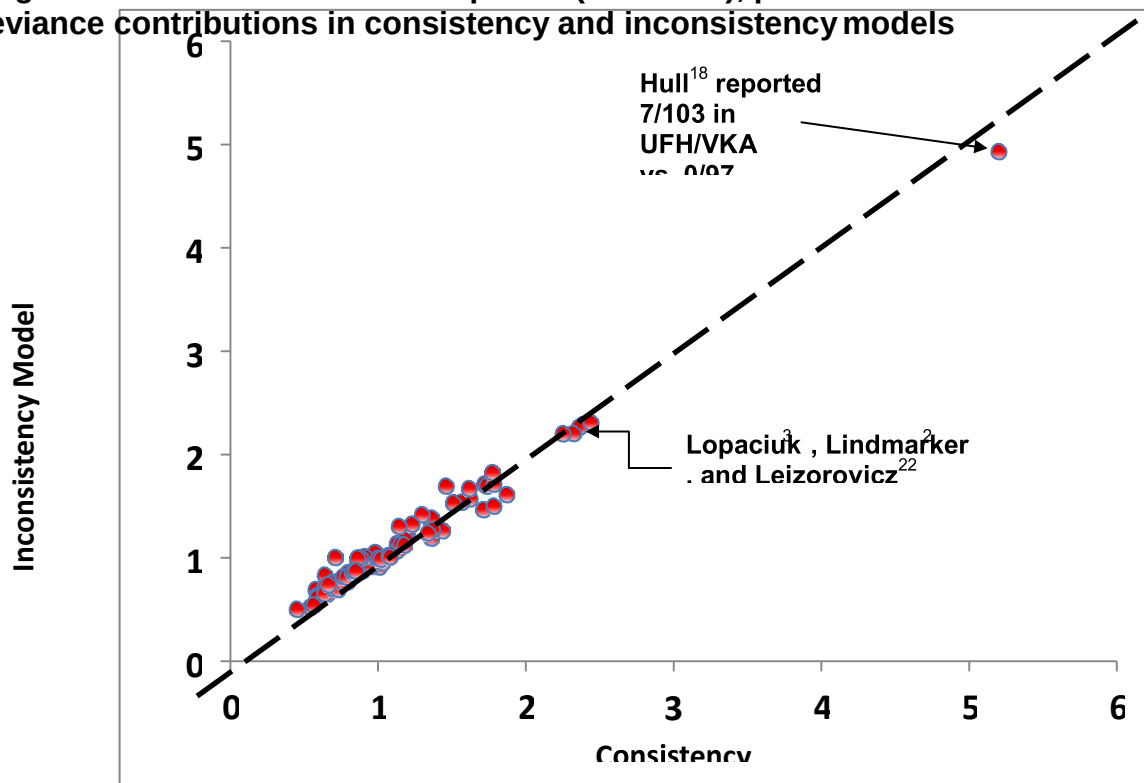
Accordingly, we conducted numerous sensitivity analyses related to recurrent VTE. In particular, we conducted an analysis where we stratify by index PE/DVT (Figure 3 and Table 2 of manuscript). We also conducted an analysis where we only considered studies 6 months or longer treatment duration (Appendix

7) and another analysis removing studies that did not fit the model well (Appendix 10). The results for the latter 2 analyses did not alter findings substantially, while there were some differences when results were stratified by index event.

Appendix 9. Assessment of inconsistency.

We plotted the posterior mean deviance of the individual data points (each arm) in the inconsistency model against their posterior mean deviance in the consistency model to help identify loops where inconsistency is present. In our analysis, the posterior mean deviance contributions are very similar and close to 1, for both models. The consistency model has a similar total residual deviance of the residual deviance (107 vs 106.3 each versus 92 data points) and DIC (504.1 vs 506.3). However, the between study standard deviation was lower for the consistency model (0.202 vs 0.250), and hence the consistency model appears to fit the data slightly better. The parameter estimates are also similar for both models and there is considerable overlap in the 95% credible intervals (see table below) suggesting no evidence of inconsistency in the network, although this should be interpreted with caution as there may not be sufficient power to detect inconsistency.

eFigure 9. Plot of individual data points (each arm), posterior mean deviance contributions in consistency and inconsistency models



LMWH = low molecular weight heparin; UFH = unfractionated heparin; VKA = vitamin K antagonist

eTable 9. Comparison of hazard ratios (95% CrI) from consistency and inconsistency models

Treatment Comparison	Consistency Model	Inconsistency Model
UFH/VKA vs LMWH/VKA	1.42 (1.15,1.80)	1.47 1.16,1.91)
Fondaparinux/VKA vs LMWH/VKA	1.01 (0.65,1.62)	0.96 (0.47,1.98)
LMWH/dabigatran vs LMWH/VKA	1.11 (0.67,1.8)	1.1 (0.63,1.9)
LMWH/edoxaban vs LMWH/VKA	0.83 (0.46,1.49)	0.82 (0.42,1.62)
Rivaroxaban vs LMWH/VKA	0.9 (0.57,1.41)	0.9 (0.54,1.49)
Apixaban vs LMWH/VKA	0.84 (0.46,1.51)	0.84 (0.42,1.65)
LMWH alone vs LMWH/VKA	0.99 (0.7,1.42)	0.86 (0.46,1.53)
Fondaparinux/VKA vs UFH/VKA	0.71 (0.45,1.12)	0.76 (0.37,1.52)
LMWH alone vs UFH/VKA	0.7 (0.5,0.95)	0.75 (0.49,1.15)
Residual deviance	107 vs 92	106.3 vs 92
DIC	504.1	506.3
Between-study standard deviation	0.202	0.250

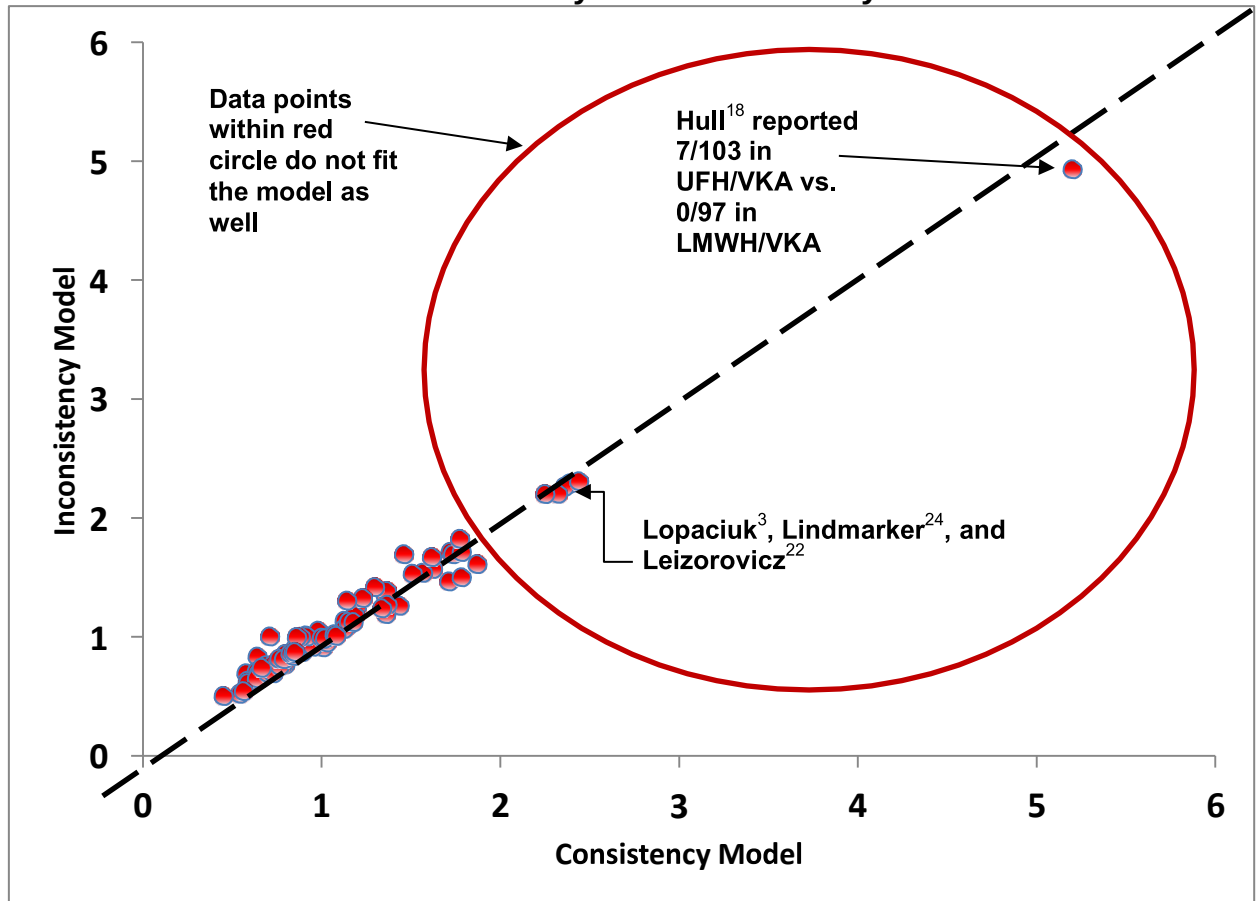
CrI = credible interval; LMWH = low molecular weight heparin; UFH = unfractionated heparin; VKA = vitamin K antagonist; VTE = venous thromboembolism

Bold type font indicates significant values.

Appendix 10. Exclusion of studies contributing to poor fit for recurrent VTE network meta-analysis

The total residual deviance for both random-effects models was higher than the number of unconstrained data points (107 vs 92 data points); however, this was largely driven by inclusion 4 studies – Hull et al.¹⁸, Lopaciuk et al.³, Lindmarker et al.²⁴, and Leizorovicz et al.²²

eFigure 10. Plot of individual data points (each arm), posterior mean deviance contributions in consistency and inconsistency models



Exclusion of these 4 studies improved model fit. The between study standard deviation decreased (15.00 vs. 20.02) and the total residual deviance is closer to the number of unconstrained data points (88.22 vs 84 vs 113.1 vs 92). However, the findings did not change substantially. Despite this improvement in model fit, these 4 studies remained in the primary analysis for analytic completeness and because it did not alter findings/conclusions.

eTable 10. Comparison of results for recurrent VTE from primary analysis and sub-group analysis based on study duration.

Treatment	Primary Analysis		Sensitivity analysis removing 4 studies with poor fit to the model	
	Recurrent VTE HR (95%)	SU CR A	Recurrent VTE HR (95% CrI) vs LMWH/VKA	SUCRA
LMWH/VKA	Referenc	48.7%	Reference	48.6%
UFH/VKA	1.42 (1.15,1.80)	5.1 %	1.43 (1.15,1.73)	4.2%
Fondaparinux/VKA	1.01 (0.65,1.62)	48.6%	1.04 (0.68,1.63)	44.6%
LMWH/dabigatran	1.11 (0.67,1.8)	37.0%	1.12 (0.69,1.72)	36.3%
LMWH/edoxaban	0.83 (0.46,1.49)	72.5%	0.81 (0.5,1.37)	75.7%
Rivaroxaban	0.9 (0.57,1.41)	64.5%	0.92 (0.61,1.33)	63.1%
Apixaban	0.84 (0.46,1.51)	71.2%	0.84 (0.5,1.4)	72.8%
LMWH alone	0.99 (0.7,1.42)	52.5%	0.96 (0.67,1.46)	54.9%
Total residual deviance versus number of unconstrained data points	113.1 vs 92		88.22 vs 84	
DIC	504.1		463.1	
Between study standard deviation	0.202		0.150	

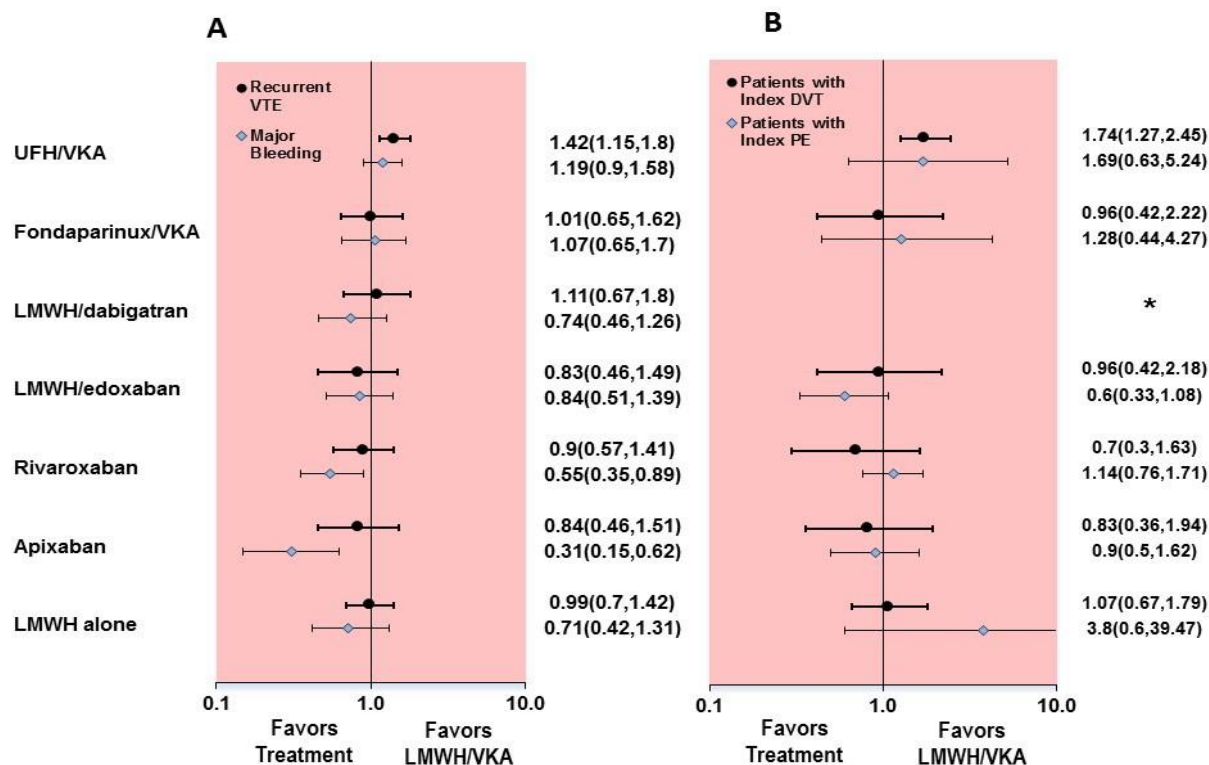
CrI = credible intervals; HR= hazard ratio; LMWH = low molecular weight heparin; SUCRA. Surface under the cumulative ranking curve; UFH = unfractionated heparin; VKA = vitamin K antagonist

Bold type font indicates significant values.

Appendix 11. Summary of network meta-analysis odds ratios using a binomial likelihood model – random-effects model with informative priors

We conducted an analysis using a binomial likelihood model which accounts for multi-arm trials. The primary analysis using this model was a random-effects model with informative priors.^{48;49} The findings for the odds ratios from the binomial likelihood model aligned closely with hazard ratios from the Poisson likelihood model used in the primary analysis.

eFigure 11. Summary of network meta-analysis odds ratios (95% CrI) using a binomial likelihood model (compared to LMWH/VKA)



* Data not stratified by Index DVT/PE

CrI = credible interval; DVT = deep vein thrombosis; LMWH = low molecular weight heparin; PE = pulmonary embolism; UFH = unfractionated heparin; VKA = vitamin K antagonist; VTE = venous thromboembolism

Reference

- (1) Duroux P, Beclere A. A randomised trial of subcutaneous low molecular weight heparin (CY216) compared with intravenous unfractionated heparin in the treatment of deep vein thrombosis. A Collaborative European Multicentre Study. *Thromb Haemost* 1991;65(3):251-256.
- (2) Hull RD, Raskob GE, Pineo GF et al. Subcutaneous low-molecular-weight Heparin compared with continuous intravenous Heparin in the treatment of proximal vein thrombosis. *N Engl J Med* 1992;326(15):975-982.
- (3) Lopaciuk S, Meissner AJ, Filipecki S et al. Subcutaneous low molecular weight heparin versus subcutaneous unfractionated heparin in the treatment of deep vein thrombosis: a Polish multicenter trial. *Thromb Haemost* 1992;68(1):14-18.
- (4) Prandoni P, Lensing AWA, Buller HR et al. Comparison of subcutaneous low-molecular-weight heparin with intravenous standard heparin in proximal deep-vein thrombosis. *Lancet* 1992;339(8791):441-445.
- (5) Simonneau G, Charbonnier B, Decousus H et al. Subcutaneous low molecular weight Heparin compared with continuous intravenous unfractionated heparin in the treatment of proximal deep vein thrombosis. *Arch Intern Med* 1993;153:1541-1546.
- (6) Fiessinger JN, Lopez-Fernandez M, Gatterer E et al. Once-daily subcutaneous Dalteparin, a low molecular weight heparin, for the initial treatment of acute deep vein thrombosis. *Thromb Haemost* 1996;76(2):195-199.
- (7) Koopman MMW, Prandoni P, Piovella F et al. Treatment of venous thrombosis with intravenous unfractionated heparin administered in the hospital as compared with subcutaneous low molecular weight heparin administered at home. *N Engl J Med* 1996;334(11):682-687.
- (8) Levine MN, Gent M, Hirsh J et al. A comparison of low molecular weight heparin administered primarily at home with unfractionated heparin administered in the hospital for proximal deep vein thrombosis. *N Engl J Med* 1996;334(11):677-681.
- (9) Kirchmaier CM, Wolf H, Schäfer H, Ehlers B, Breddin HK. Efficacy of a low molecular weight heparin administered intravenously or subcutaneously in comparison with intravenous unfractionated heparin in the treatment of deep venous thrombosis. *Int Angiol* 1998;17(3):135-145.
- (10) Harenberg J, Schmidt JA, Koppenhagen K, Tolle A, Huisman MV, Buller HR. Fixed-dose, body-weight-independent subcutaneous LMW Heparin versus adjusted dose unfractionated intravenous Heparin in the initial treatment of proximal venous thrombosis. *Thromb Haemost* 2000;83(5):652-656.
- (11) Breddin HK, Hach-Wunderle V, Nakov R, Kakkar VV. Effects of a low molecular weight heparin on thrombus regression and recurrent thromboembolism in patients with deep vein thrombosis. *N Engl J Med* 2001;344(9):626-631.
- (12) Kakkar VV, Gebaska M, Kadziola Z, Saba N, Carrasco P. Low-molecular-weight heparin in the acute and long-term treatment of deep vein thrombosis. *Thromb Haemost*

- 2003;89(4):674-680.
- (13) Riess H, Koppenhagen K, Tolle A et al. Fixed-dose, body weight-independent subcutaneous low molecular weight heparin certoparin compared with adjusted-dose intravenous unfractionated heparin in patients with proximal deep venous thrombosis. *Thromb Haemost* 2003;90(2):252-259.
 - (14) Meyer G, Brenot F, Pacouret G et al. Subcutaneous low-molecular-weight heparin fragmin versus intravenous unfractionated heparin in the treatment of acute non massive pulmonary embolism: an open randomized pilot study. *Thromb Haemost* 1995;74(6):1432-1435.
 - (15) Simonneau G, Sors H, Charbonnier B et al. A Comparison of low-molecular-weight heparin with unfractionated heparin for acute pulmonary embolism. *N Engl J Med* 1997;337(10):663-669.
 - (16) Findik S, Erkan ML, Selcuk MB, Albayrak S, Atici AG, Doru F. Low-molecular-weight heparin versus unfractionated heparin in the treatment of patients with acute pulmonary thromboembolism. *Respiration* 2002;69(5):440-444.
 - (17) Columbus Investigators, ten Cate JW. Low molecular weight heparin in the treatment of patients with venous thromboembolism. *N Engl J Med* 1997;337(10):657-662.
 - (18) Hull RD, Raskob GE, Brant RF et al. Low-molecular-weight heparin vs heparin in the treatment of patients with pulmonary embolism. *Arch Intern Med* 2000;160(2):229-236.
 - (19) Merli G, Spiro TE, Olsson CG et al. Subcutaneous enoxaparin once or twice daily compared with intravenous unfractionated heparin for treatment of venous thromboembolic disease. *Ann Intern Med* 2001;134(3):191-202.
 - (20) Prandoni P, Carnovali M, Marchiori A. Subcutaneous adjusted-dose unfractionated heparin vs fixed-dose low-molecular-weight heparin in the initial treatment of venous thromboembolism. *Arch Intern Med* 2004;164(10):1077-1083.
 - (21) Kearon C, Ginsberg JS, Julian JA et al. Comparison of fixed-dose weight-adjusted unfractionated heparin and low-molecular-weight heparin for acute treatment of venous thromboembolism. *JAMA* 2006;296:935-942.
 - (22) Leizorovicz A, Siguret V, Mottier D et al. Safety profile of tinzaparin versus subcutaneous unfractionated heparin in elderly patients with impaired renal function treated for acute deep vein thrombosis: the Innohep(R) in Renal Insufficiency Study (IRIS). *Thromb Res* 2011;128(1):27-34.
 - (23) Bratt G, Aberg W, Johansson M, Tornebohm E, Granqvist S, Lockner D. Two daily subcutaneous injections of Fragmin as compared with intravenous standard heparin in the treatment of deep venous thrombosis (DVT). *Thromb Haemost* 1990;64(4):506-510.
 - (24) Lindmarker P, Holmstrom H, Granqvist S, Johnsson H, Lockner D. Comparison of once-daily subcutaneous Fragmin with continuous intravenous unfractionated Heparin in the treatment of deep vein thrombosis. *Thromb Haemost* 1994;72(2):186-190.
 - (25) Pini M, Aiello S, Manotti C et al. Low molecular weight heparin versus warfarin in the prevention of recurrences after deep vein thrombosis. *Thromb Haemost* 1994;72(2):191-197.
 - (26) Das SK, Cohen AT, Edmondson RA, Melissari E, Kakkar VV. Low-molecular-weight heparin versus warfarin for prevention of recurrent venous thromboembolism: a randomized trial. *World J Surg* 1996;20(5):521-526.

- (27) Belcaro G, Barsotti A, Nicolaides AN et al. Comparison of low-molecular-weight Heparin, administered primarily at home, with unfractionated Heparin, administered in hospital, and subcutaneous Heparin, administered at home for deep-vein thrombosis. *Angiology* 1999;50(10):781-787.
- (28) Gonzalez-Fajardo JA, Arreba E, Castrodeza J et al. Venographic comparison of subcutaneous low-molecular weight heparin with oral anticoagulant therapy in the long-term treatment of deep venous thrombosis. *J Vasc Surg* 1999;30(2):283-292.
- (29) Lopaciuk S, Bielska-Falda H, Noszczyk W et al. Low molecular weight heparin versus acenocoumarol in the secondary prophylaxis of deep vein thrombosis. *Thromb Haemost* 1999;81(1):26-31.
- (30) Veiga F, Escriba A, Maluenda MP et al. Low molecular weight Heparin (Enoxaparin) versus oral anticoagulant therapy (Acenocoumarol) in the long-term treatment of deep venous thrombosis in the elderly: a randomized trial. *Thromb Haemost* 2000;84:559-564.
- (31) Ramacciotti E, Araujo GR, Lastoria S et al. An open-label, comparative study of the efficacy and safety of once-daily dose of enoxaparin versus unfractionated heparin in the treatment of proximal lower limb deep-vein thrombosis. *Thromb Res* 2004;114:149-153.
- (32) Chong BH, Brighton TA, Baker RI, Thurlow P, Lee CH. Once-daily enoxaparin in the outpatient setting versus unfractionated heparin in hospital for the treatment of symptomatic deep-vein thrombosis. *J Thromb Thrombolysis* 2005;19(3):173-181.
- (33) Daskalopoulos ME, Daskalopoulou SS, Tzortzis E et al. Long-term treatment of deep venous thrombosis with a low molecular weight heparin (tinzaparin): a prospective randomized trial. *Eur J Vasc Endovasc Surg* 2005;29(6):638-650.
- (34) Romera A, Cairols MA, Vila-Coll R et al. A randomised open-label trial comparing long-term sub-cutaneous low-molecular-weight heparin compared with oral-anticoagulant therapy in the treatment of deep venous thrombosis. *Eur J Vasc Endovasc Surg* 2009;37(3):349-356.
- (35) Beckman JA, Dunn K, Sasahara AA, Goldhaber SZ. Enoxaparin monotherapy without oral anticoagulation to treat acute symptomatic pulmonary embolism. *Thromb Haemost* 2003;89(6):953-958.
- (36) Perez de Llano LA, Balloira VA, Veres RA, Veiga F, Golpe GR, Pajuelo FF. [Multicenter, prospective study comparing enoxaparin with unfractionated heparin in the treatment of submassive pulmonary thromboembolism]. *Arch Bronconeumol* 2003;39(8):341-345.
- (37) Hull RD, Pineo GF, Brant RF et al. Self-managed long-term low-molecular-weight heparin therapy: the balance of benefits and harms. *Am J Med* 2007;120:72-82.
- (38) Buller HR, Davidson BL, Decousus H et al. Fondaparinux or Enoxaparin for the initial treatment of symptomatic deep venous thrombosis. A randomized trial. *Ann Intern Med* 2004;140:867-873.
- (39) Buller HR, Davidson BL, Decousus H et al. Subcutaneous fondaparinux versus intravenous unfractionated heparin in the initial treatment of pulmonary embolism. *N Engl J Med* 2003;349:1695-1702.
- (40) Einstein Investigators, Bauersachs R, Berkowitz SD et al. Oral Rivaroxaban for Symptomatic Venous Thromboembolism. *N Engl J Med* 2010;363(26):2499-2510.
- (41) Buller HR, Prins MH, Lensin AW et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med* 2012;366(14):1287-1297.

- (42) Schulman S, Kearon C, Kakkar AK et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med* 2009;361(24):2342-2352.
- (43) Schulman S, Kakkar AK, Goldhaber SZ et al. Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. *Circulation* 2014;129(7):764-772.
- (44) Buller HR, Decousus H, Grosso MA et al. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *N Engl J Med* 2013;369(15):1406-1415.
- (45) Agnelli G, Buller HR, Cohen A et al. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med* 2013;369(9):799-808.
- (46) Fleurence RL, Hollenbeak CS. Rates and probabilities in economic modelling: transformation, translation and appropriate application. *Pharmacoeconomics* 2007;25(1):3-6.
- (47) Dias S, Welton NJ, Sutton AJ, Ades A. NICE DSU technical support document 2: A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials. 2011.
- (48) Turner RM, Davey J, Clarke MJ, Thompson SG, Higgins JP. Predicting the extent of heterogeneity in meta-analysis, using empirical data from the Cochrane Database of Systematic Reviews. *Int J Epidemiol* 2012;41(3):818-827.
- (49) Thorlund K, Thabane L, Mills EJ. Modelling heterogeneity variances in multiple treatment comparison meta-analysis--are informative priors the better solution? *BMC Med Res Methodol* 2013;13:2.

**CHAPTER 6B: BENEFIT-HARM ASSESSMENT USING DATA
DERIVED FROM NETWORK META-ANALYSIS: AN APPLICATION
USING TREATMENTS FOR ACUTE VENOUS
THROMBOEMBOLISM**

**Benefit-harm assessment using data derived from network meta-analysis: An
application using treatments for acute venous thromboembolism**

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CHAPTER 6B: BENEFIT-HARM ASSESSMENT USING DATA DERIVED FROM NETWORK META-ANALYSIS: AN APPLICATION USING TREATMENTS FOR ACUTE VENOUS THROMBOEMBOLISM

**Benefit-harm assessment using data derived from network meta-analysis: An
application using treatments for acute venous thromboembolism**

SUMMARY:

In this chapter, we conduct a benefit-harm assessment using data derived from network meta-analysis the clinical outcomes and safety outcomes of eight anticoagulation options in Chapter 6A for treatment of acute venous thromboembolism. In the previous Chapter, we presented findings for outcomes separately using standard tables and figures. In this Chapter we investigate alternative approaches for integrating findings between two outcomes.

LINKS:

This manuscript was not yet submitted for publication.

CONTRIBUTION:

I was responsible drafting the manuscript with guidance from supervisors. I conducted all analyses and generated all tables and figures related to findings from the network meta-analysis.

ABSTRACT

Objective: To present some simple graphical ways to illustrate benefits and harms of treatments derived from network meta-analysis, and provide an Excel-based tool so other can create similar graphical outputs.

Study Design and Setting: We reanalyzed a published network meta-analysis comparing various treatment of acute venous thromboembolism using Bayesian approaches, and explored new forms of graphical presentations of results for benefits and harms.

Results: We present the findings for benefits and harms derived from network meta-analysis using various approaches. Conventionally, research in this area has focused on presenting benefits and harms as relative effect measures or using probabilities and ranks. Findings have also traditionally not considered findings for benefits and harms together. We focus on methods for presenting findings on the absolute scale and integrating data related to a benefit and harm. We report findings using 7 approaches: scatterplot plots with error bars; confidence ellipses; bar charts with error bars, outcome acceptability curves, icon arrays, icon arrays depicting quality adjusted life days gained, and acceptability curves varying the decision makers' ratio for preference of outcomes.

Conclusions: We provide a multitude of ways to present findings on the benefits and harms of drugs derived from network meta-analysis on the absolute scale. We also provide a user friendly Excel-based tool to assist others in conducting benefit harms assessments using data derived from network meta-analyses.

INTRODUCTION

For many medical questions of interest, decision makers are interested in knowing which treatment has the best balance of benefit and harms among a multitude of treatments. Network meta-analysis offers and methodology for integrating all the data from multiple comparisons simultaneously thereby allowing one to compare the benefits and harms of multiple interventions. The use of this methodology has increased dramatically over the years.¹ However, the majority of papers²⁻⁵ published in this area has focused on presenting findings on the relative scale or have converted outputs to ranks or probability that a treatment is best. Further, outcomes on benefits and harms are considered independently of each other.

In this article, we aim to discuss alternative approaches for presenting benefits and harms findings derived from network meta-analysis to facilitate better interpretation. We first describe a case study we will be using to illustrate our approaches to conveying findings. In the Presenting the Evidence Section, we present various approaches that can be used to present benefits and harms derived from network meta-analysis on the absolute scale: scatterplot plots with error bars; confidence ellipses; bar charts with error bars, icon arrays, and icon arrays depicting quality adjusted life days gained. We advocate that the use of the absolute scale is advantageous for presenting findings related to benefits and harms simultaneously, as they are more conducive to healthcare decision making and take into account differences in the actual risk of an event unlike relative effects or other measures such as probability best, ranks and SUCRA.^{3,4} Finally, we discuss how future methods work should evolve to improve our ability to compare the benefits and harms of multiple

treatments derived from network meta-analysis.

CASE STUDY

In Figures 1 and 2, we present the evidence network and results for a network meta-analysis evaluating various treatments for the treatments of acute venous thromboembolism. The methods used to identify studies included in the network meta-analysis have been described previously.⁶ A total of 45 randomized studies comparing 8 different treatments (UFH/VKA, LMWH/VKA, fondaparinux/VKA, LMWH/dabigatran, LMWH/edoxaban, rivaroxaban, apixaban or LMWH alone) were included in the analysis of venous thromboembolism, encompassing a total of 44,989 participants and 20,842 years of follow-up. For major bleeding, a total of 42 randomized studies comparing 8 different treatments were included, encompassing a total of 44,434 participants and 20,643 years of follow-up. The authors conducted a Bayesian random effects network meta-analysis using a Poisson model to compare the overall risk of venous thromboembolism and major bleeding among the different treatments.

The findings in the *JAMA* paper were largely presented on the relative scale (**Figure 2**), although data on absolute risk of events was reported in the text.⁶

PRESENTING THE EVIDENCE IN ABSOLUTE TERMS

In Table 1 and 2, we report the proportion of patients expected to have a recurrent VTE or major bleeding event while using each treatment for a period of 3 and 6 months. These values were calculated assuming a rate of 5.3 per 100 patient-years (~2.6% over 6 months) and 3.6 events per 100 patient-years (~1.8% over 6 months) for recurrent VTE and major bleeding, respectively, in the LMWH/VKA arm of the Amplify trial.^{45;46} The hazard ratios

were then applied to this log-rate.⁴⁷ Using this value, we calculated the difference in the proportion of patients expected to have an event relative to LMWH/VKA and number needed to treat to benefit (or harm).

Scatterplot with error bars

In **Figure 3**, we plot the absolute risk difference for recurrent VTE and major bleeding, each relative to LMWH/VKA at 6 months for each treatment using a scatterplot. A scatterplot is a graph for analyzing data on two variables. One variable is plotted on the horizontal axis and the other is plotted on the vertical axis. In network meta-analysis, after relative effect estimates are converted to the absolute scale, one can plot the differences relative to a common comparator. We also represent the credible intervals for our estimates using error bars. Error bars are a graphical representation of the uncertainty of the effect estimates. From **Figure 3**, it can be seen for example that UFH/VKA is associated with an increase in both recurrent VTE and major bleeding compared with LMWH/VKA, and the absolute risk increase is approximately 1% and 0.5% for recurrent VTE and major bleeding respectively. It can also be seen that there is more uncertainty around the LMWH/edoxaban effect estimates compared with UFH/VKA (smaller error bars).

Confidence ellipses

In **Figure 4**, we present findings using confidence ellipses. A confidence ellipse is an alternative to presenting a scatterplot with error bars. Similar to the scatterplot with error bars, findings for two variables are presented where one variable is plotted on the horizontal axis and the other is plotted on the vertical axis. However, rather than provide mean (or median) effect estimates and credible intervals using error bars, confidence ellipses present an ellipse reflecting the 95% credible intervals for each of the outcomes. From **Figure 3**, one can easily see for example that UFH/VKA is associated with an increase in both recurrent

VTE and major bleeding compared with LMWH/VKA, and the absolute risk increase is approximately 1% and 0.5% for recurrent VTE and major bleeding respectively.

Bar chart with error bars

In Figure 5, we present absolute risks using a bar chart with error bars. A bar chart or bar graph is a rectangular graph with height proportional to the values they represent. The bars can be plotted vertically or horizontally. Within the bars, the user sometimes includes error bars to convey uncertainty around the mean estimate (height of the bar). From Figure 5, we can see clearly that UFH/VKA is associated with the highest risk of recurrent VTE and major bleeding, whereas LMWH/edoxaban is associated with the lowest risk of recurrent VTE and apixaban the lowest risk of major bleeding.

Icon arrays depicting absolute risk of an event

In Figure 6, we convey the absolute risk of recurrent VTE (red) and major bleed (green) at 6 months out of 100 patients for each of the treatments using a grid of icon arrays. Icon arrays are a risk communication graphic made up of a matrix of unique elements representing individual people within the at-risk population. They are used to communicate numbers of patients who had a particular event within an at-risk population. From the icon arrays, we are able to see that UFH/VKA is associated with a higher absolute risk of recurrence of VTE compared with other treatments. We also see that there are not major differences between other treatments in terms of absolute risk. 1 or 2 patients out of 100 will experience a recurrent VTE while 1 or 2 will experience a major bleeding depending on the treatment.

Icon arrays depicting quality adjusted life hours (or days) gained (or lost) for each treatment

In Figure 7, we convey hours of perfect health gained for each treatment using efficacy data derived from the network meta-analysis for recurrent and major bleed. We apply the QALYs derived from a recently published quality of life study in patients with acute venous thromboembolism.⁷ Each clock in the figure represents one hour of perfect health gained over a 12 month time horizon. From the figure, we are able to see that UFH/VKA is associated with a reduction of approximately 5 hours of perfect health whereas apixaban is associated with an increase of approximately 14 hours, each relative to LMWH/VKA. It is not surprising that the gains in quality of life are small given the small absolute risk differences depicted in Figures 6 and 6.

Acceptability curve showing the probability that each treatment is most effective

In Figure 8, we convey an acceptability curve showing the probability that each treatment is most effective, across a range of decision-makers' ratios for major bleed to VTE. In this figure, a value of 1 means major bleeding are valued equally by decision makers' in terms of severity whereas a value higher than 1 values major bleeding more than VTE and a value less than 1 values VTE more than major bleeding. From the figure, we are able to see that apixaban is associated with the highest probability of being most effective across a decision makers ratio for major bleed to VTE. It is not surprising that the probability that apixaban is most effective increases as decision makers value major bleeding a being more severe outcome than VTE.

DISCUSSION

We have illustrated an application of benefit-harms assessment using data derived from a network meta-analysis. We build off findings reported in a previously published network meta-analysis⁶ comparing treatments for acute treatment of venous thromboembolism. In accordance with best practices for benefit-harm assessment,^{8,9} we focused on presenting findings on the absolute scale.

We found the various figures presented in this paper helped convey the information to decision makers in a more user friendly manner. Indeed, CADTH used our scatterplot with errors bars methods for a recent therapeutic review.¹⁰ The accompanying Excel-based tool to will be useful to others if they are interested in generating similar figures for network meta-analysis. Where possible, we attempted to capture uncertainty around benefits and harms in our figures. Indeed, we included error bars on our scatterplots and box-plots. We illustrated findings using confidence ellipses which inherently capture uncertainty. Our icon arrays or quality adjusted life hours gained/lost figures do not report information around uncertainty, however, icon arrays are known to be useful for conveying risk information to patients and healthcare decision makers.¹¹ Similarly, converting findings to hours (or days) of perfect health gained is also useful for conveying information to decision makers.

Our paper expanded on previous papers which too outlined how to convey findings from a network meta-analysis. Previous papers,^{3,4} however, focused largely on reporting findings

using relative effect measures, or using probabilities or ranks. Indeed, Cipriani et al² reported findings on relative effects using league tables, and also reported a findings for benefits/harms using rankograms in a recently published paper in *Lancet* comparing new generation antidepressants. Several authors have also demonstrated how to convey information on probability of a certain rank using barplots;³ Chiamani et al⁴ also illustrated how to convey rankings in relation to SUCRA in a recent publication. While these previous approaches are intuitive to the reader, there are limitations with using such figures when conveying information in a benefit-harm framework, particularly when using probabilities or ranks. Relative effects do not capture information on differences in underlying risk, whereas probabilities and ranks may exaggerate small differences in relative effects. Further, the aforementioned approaches would not reflect if a benefit has a four-fold risk compared with the harm. Similarly, a treatment may receive a rank of 1 when in reality there are minimal differences between it and the treatment ranked #4 in absolute terms. By contrast, the approaches presented in this paper account for the aforementioned considerations.

There are several other limitations that warrant consideration. We only considered two outcomes, and these outcomes were analyzed separately versus simultaneously thereby not accounting for potential correlation between outcomes. Further research is needed which enables network meta-analysis to consider multiple outcomes simultaneously. Indeed, Ades et al¹² have conducted some research using competing risk models which could be particularly useful for integrating benefit-harm assessments of multiple outcomes. Van Valkenhoef et al⁵ has also conducted some research related to incorporating multiple benefits and harms.

Another limitation related to us having to assume a particular baseline rate and subsequently

apply relative effects to the assumed rate. For example, we assumed a rate of 5.3 per 100 patient-years (~2.6% over 6 months) and 3.6 events per 100 patient-years (~1.8% over 6 months) for recurrent VTE and major bleeding, respectively, in the LMWH/VKA arm of the Amplify trial. The hazard ratios were subsequently applied to this log-rate. We opted to use this approach because relative effects such as hazard ratios are more reliable outputs from a network meta-analysis from an analytic standpoint. Nonetheless, if the user selects and inappropriate rate, and will impact the absolute effect estimates. Particular care must be taken when selecting baseline event rates to ensure that are appropriate, and sensitivity analyses should be conducted around this parameter.

The majority of our figures do not account for the health related quality of life associated with each outcome. For example, if the harm is more burdensome to patients than the benefit, this is not reflective in most figures. To account for this potential issue, we included one figure which captures impact of each outcome on quality and quantity of life. The impact of each outcome on health related quality of life was derived from a recent publication by Hogg et al⁷ which estimated health related quality of life in patients with acute venous thromboembolism. For this figure, we depict the number of perfect days of health lost for each treatment. This approach of integrating health related quality of life will undoubtedly be useful for extensions of these approaches to multiple outcomes which are difficult to convey in 2-D.

CONCLUSIONS

We have demonstrated the application of benefit-harm assessment derived from a network meta-analysis using findings from a published network meta-analysis comparing treatments

for treatment of acute venous thromboembolism. We also developed a user friendly Excel-based tool to assist others in generating similar figures presented in this paper for conveying benefits and harms for two outcomes derived from a network meta-analysis. The application of benefit-harms assessment underpinned by a network meta-analysis will undoubtedly increase with increased use of progressive licensing agreements where regulators are required to monitor the balance of benefits and harms of multiple treatments over the life cycle of the various products. Hopefully, the figures provided here and the accompanying Excel-based tool will help facilitate benefit-harm assessments using data derived from network meta-analysis.

TABLES AND FIGURES

Table 1: Proportion of patients experiencing recurrent VTE

Treatment	Proportion of patients expected to have recurrent VTE (95% CrI)	Difference in proportion of patients expected to have recurrent VTE relative to LMWH/VKA (95% CrI)*	NNTB(NNTH) relative to LMWH/VKA
At 3 months			
LMWH/VKA	1.3% (1.02%, 1.62%)	Reference	Reference
UFH/VKA	1.84% (1.33%, 2.51%)	0.53% (0.19%, 1.04%)	(188)
Fondaparinux/VKA	1.31% (0.79%, 2.18%)	0.01% (-0.47%, 0.79%)	(14071)
LMWH/dabigatran	1.44% (0.82%, 2.43%)	0.14% (-0.44%, 1.04%)	(733)
LMWH/edoxaban	1.07% (0.57%, 1.99%)	-0.22% (-0.73%, 0.63%)	447
Rivaroxaban	1.16% (0.7%, 1.91%)	-0.13% (-0.57%, 0.53%)	756
Apixaban	1.08% (0.62%, 1.87%)	-0.22% (-0.78%, 0.6%)	460
LMWH alone	1.28% (0.83%, 1.95%)	-0.02% (-0.41%, 0.54%)	5247
At 6 months			
LMWH/VKA	2.58% (2.03%, 3.22%)	Reference	Reference
UFH/VKA	3.64% (2.64%, 4.96%)	1.05% (0.37%, 2.05%)	(95)
Fondaparinux/VKA	2.59% (1.57%, 4.32%)	0.01% (-0.93%, 1.56%)	(7117)
LMWH/dabigatran	2.85% (1.62%, 4.8%)	0.27% (-0.87%, 2.03%)	(372)
LMWH/edoxaban	2.13% (1.14%, 3.95%)	-0.44% (-1.44%, 1.23%)	226
Rivaroxaban	2.31% (1.39%, 3.79%)	-0.26% (-1.14%, 1.03%)	383
Apixaban	2.15% (1.23%, 3.7%)	-0.43% (-1.54%, 1.19%)	233
LMWH alone	2.54% (1.66%, 3.86%)	-0.04% (-0.81%, 1.06%)	2658

CrI= credible interval; LMWH = low molecular weight heparin; NNTB = number need to treat to benefit; NNTH = number need to treat to harm; UFH = unfractionated heparin; VKA = vitamin K antagonist; VTE = venous thromboembolism

*A minus sign (-) indicates that a lower proportion of patients is expected to have an event.

Bold type font indicates significant values.

Table 2: Proportion of patients experiencing major bleeding

Treatment	Proportion of patients expected to have a major bleeding event (95% CrI)	Difference in proportion of patients expected to have a major bleeding event relative to LMWH/VKA (95% CrI)*	NNTB(NNTH) relative to LMWH/VKA
At 3 months			
LMWH/VKA	0.89% (0.66%, 1.16%)	Reference	Reference
UFH/VKA	1.05% (0.69%, 1.56%)	0.16% (-0.09%, 0.53%)	(609)
Fondaparinux/VKA	0.94% (0.54%, 1.64%)	0.06% (-0.32%, 0.64%)	(1779)
LMWH/dabigatran	0.66% (0.37%, 1.2%)	-0.22% (-0.51%, 0.23%)	453
LMWH/edoxaban	0.75% (0.42%, 1.32%)	-0.14% (-0.45%, 0.35%)	732
Rivaroxaban	0.49% (0.29%, 0.85%)	-0.39% (-0.63%, -0.1%)	258
Apixaban	0.28% (0.14%, 0.5%)	-0.6% (-0.92%, -0.28%)	165
LMWH alone	0.63% (0.34%, 1.16%)	-0.25% (-0.55%, 0.27%)	398
At 6 months			
LMWH/VKA	1.77% (1.32%, 2.31%)	Reference	Reference
UFH/VKA	2.09% (1.37%, 3.09%)	0.33% (-0.18%, 1.05%)	(307)
Fondaparinux/VKA	1.87% (1.07%, 3.26%)	0.11% (-0.63%, 1.27%)	(898)
LMWH/dabigatran	1.32% (0.74%, 2.39%)	-0.44% (-1.02%, 0.45%)	228
LMWH/edoxaban	1.49% (0.84%, 2.63%)	-0.27% (-0.9%, 0.69%)	369
Rivaroxaban	0.98% (0.57%, 1.7%)	-0.77% (-1.26%, -0.2%)	130
Apixaban	0.56% (0.29%, 0.99%)	-1.2% (-1.82%, -0.56%)	83
LMWH alone	1.26% (0.67%, 2.3%)	-0.5% (-1.1%, 0.52%)	200

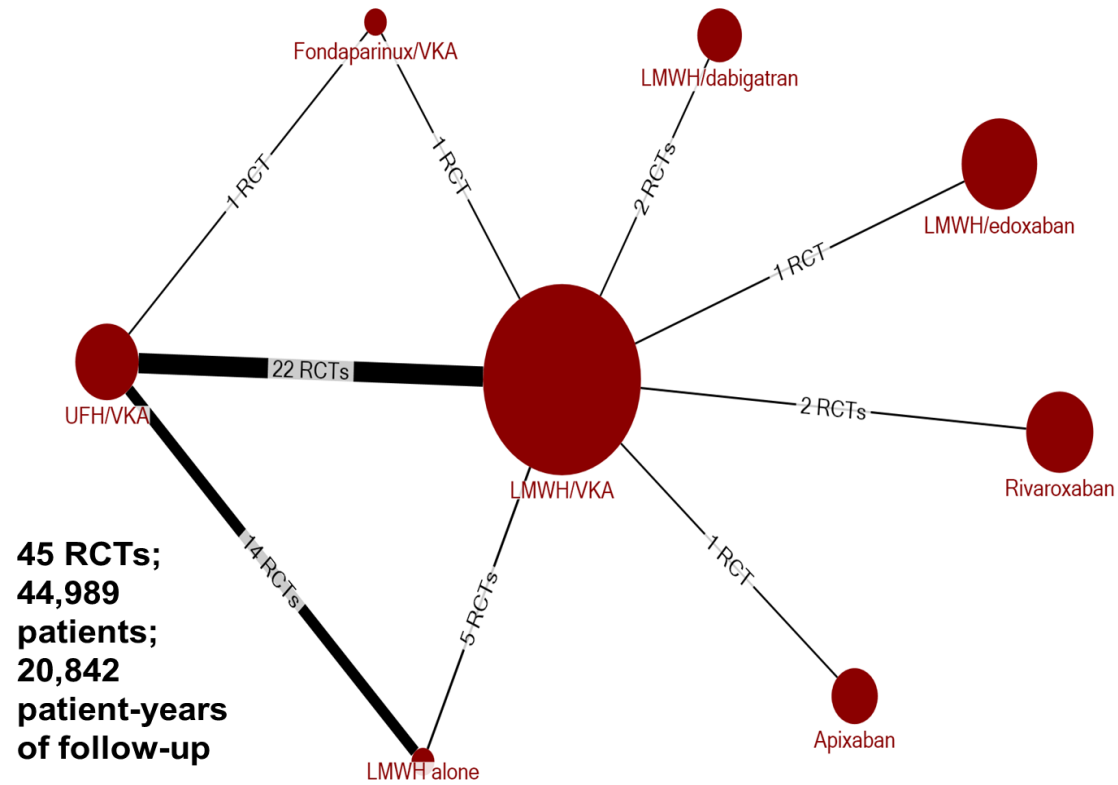
CrI = credible interval; LMWH = low molecular weight heparin; NNTB = number need to treat to benefit; NNTH = number need to treat to harm; UFH = unfractionated heparin; VKA = vitamin K antagonist; VTE = venous thromboembolism

*A minus sign (-) indicates that a lower proportion of patients is expected to have an event.

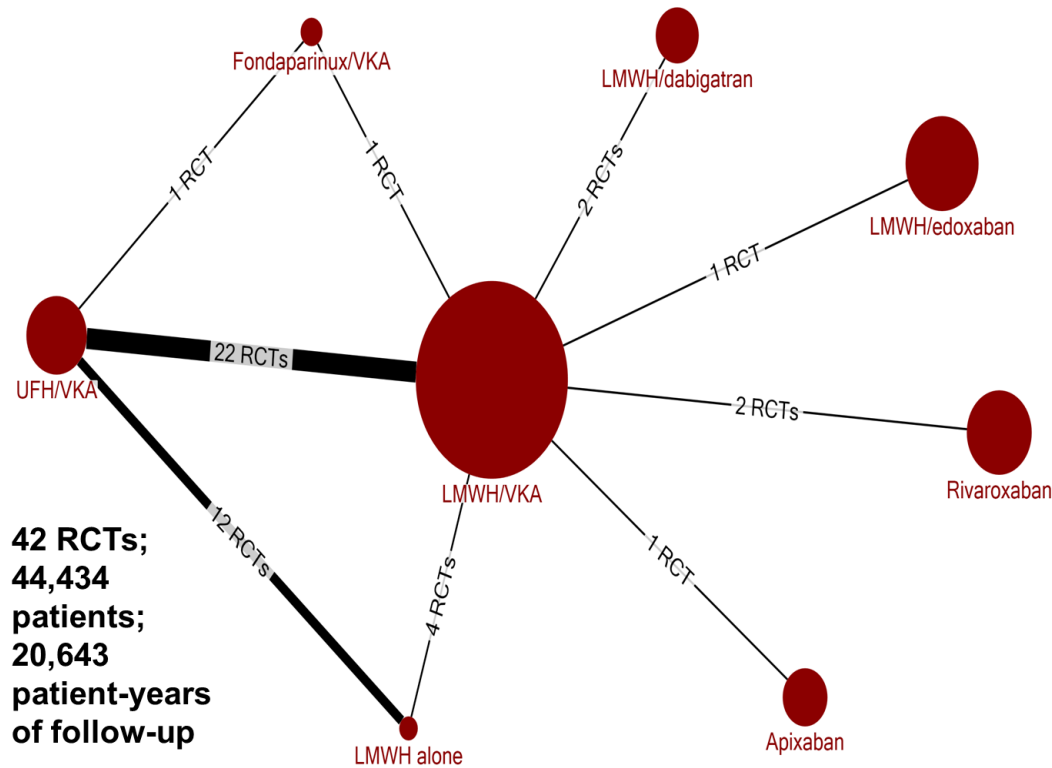
Bold type font indicates significant values.

Figure 1: (A) Evidence network for recurrent venous thromboembolism (VTE) and (B) Evidence network for major bleeding

Panel A



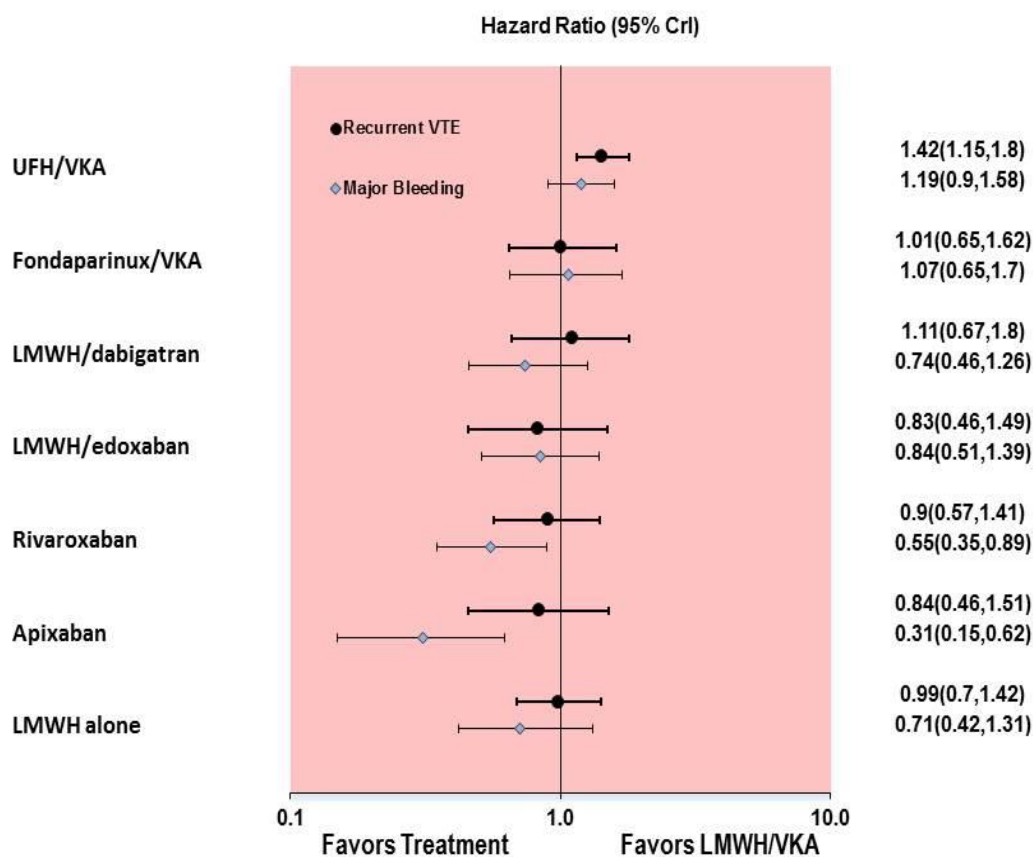
Panel B



The width of the lines for each connection in the evidence network are proportional to the number of RCTs comparing each pair of treatments, and the size of each treatment node is proportional to the patient-years of follow-up .

LMWH = low molecular weight heparin; RCT = randomized controlled trial; UFH= unfractionated heparin; VKA = vitamin K antagonist; VTE = venous thromboembolism

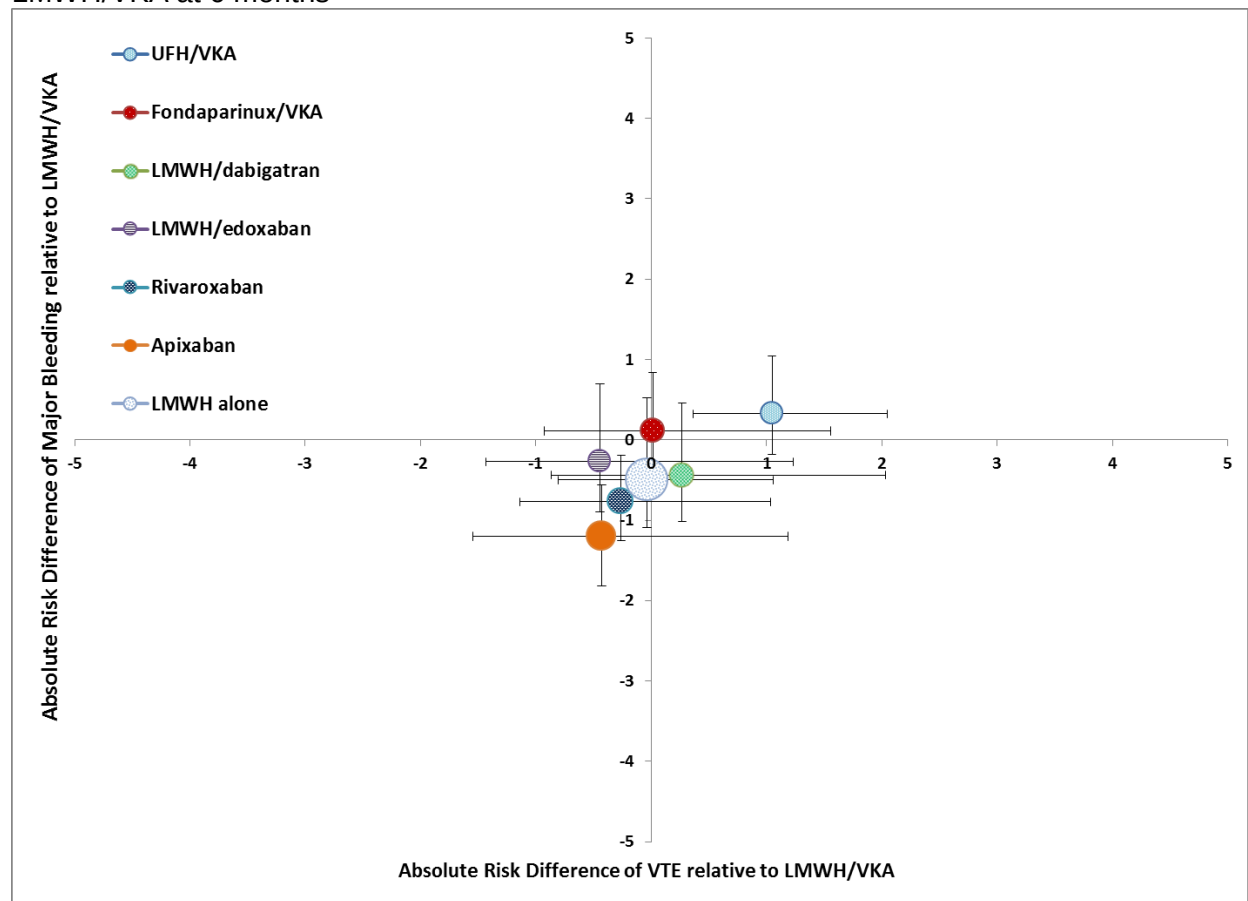
Figure 2: Network meta-analysis: Forest plot of hazard ratios (95% credible interval) relative to LMWH/VKA for Recurrent VTE and major bleeding; and Recurrent VTE by index event



* Data not stratified by Index DVT/PE

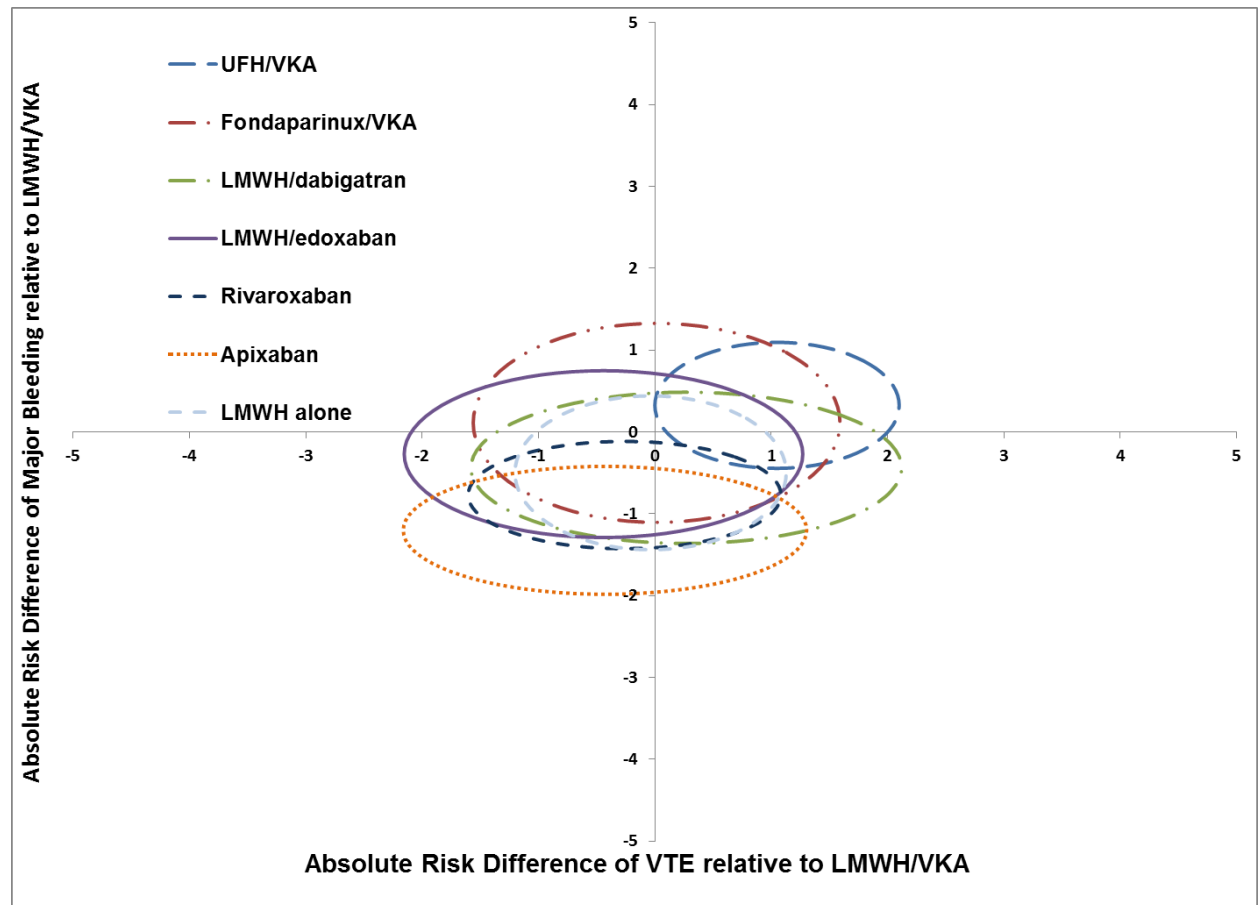
DVT = deep vein thrombosis; LMWH = low molecular weight heparin; PE = pulmonary embolism;
 UFH = unfractionated heparin; VKA = vitamin K antagonist; VTE = venous thromboembolism

Figure 3: Scatterplot with error bars for recurrent VTE and major bleeding, each relative to LMWH/VKA at 6 months



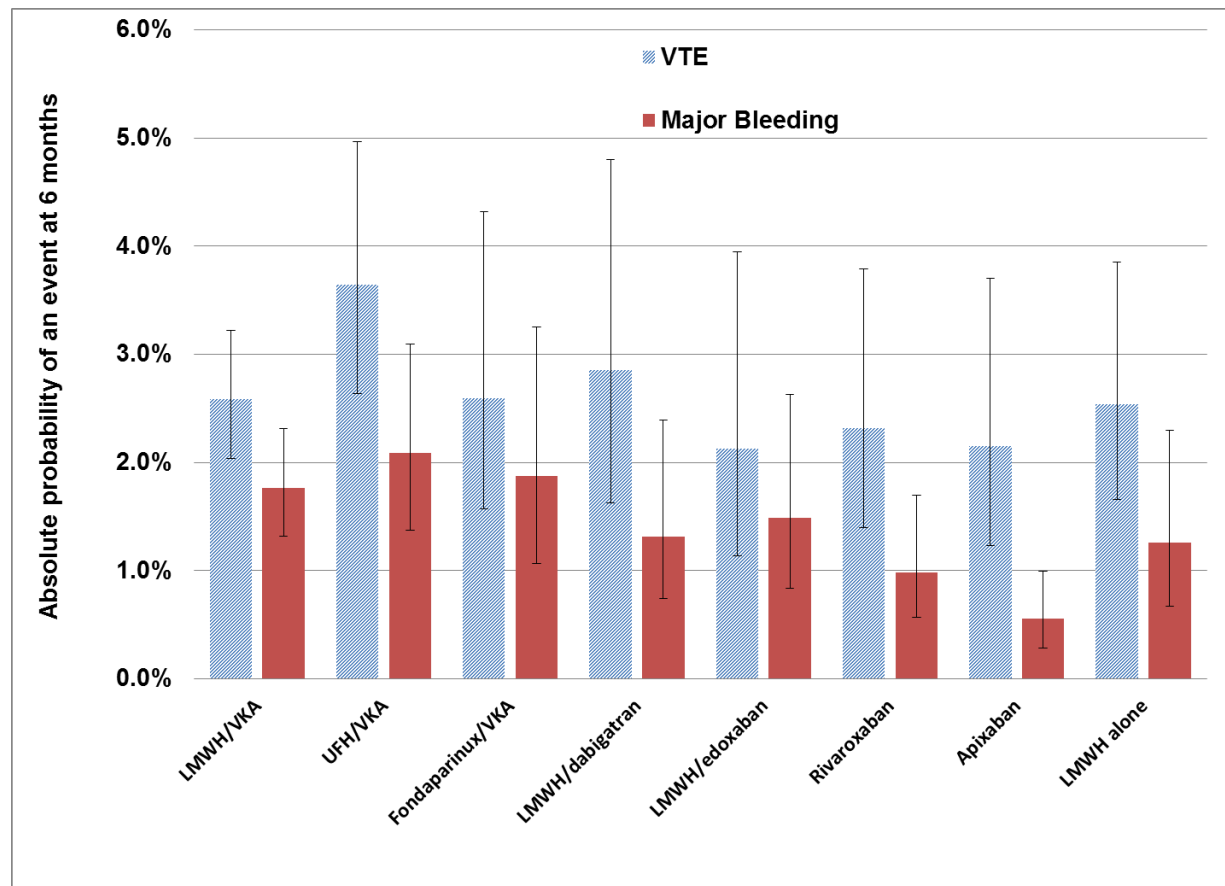
LMWH = low molecular weight heparin; UFH = unfractionated heparin; VKA = vitamin K antagonist; VTE = venous thromboembolism

Figure 4: Scatterplot with confidence ellipses for recurrent VTE and major bleeding, each relative to LMWH/VKA at 6 months



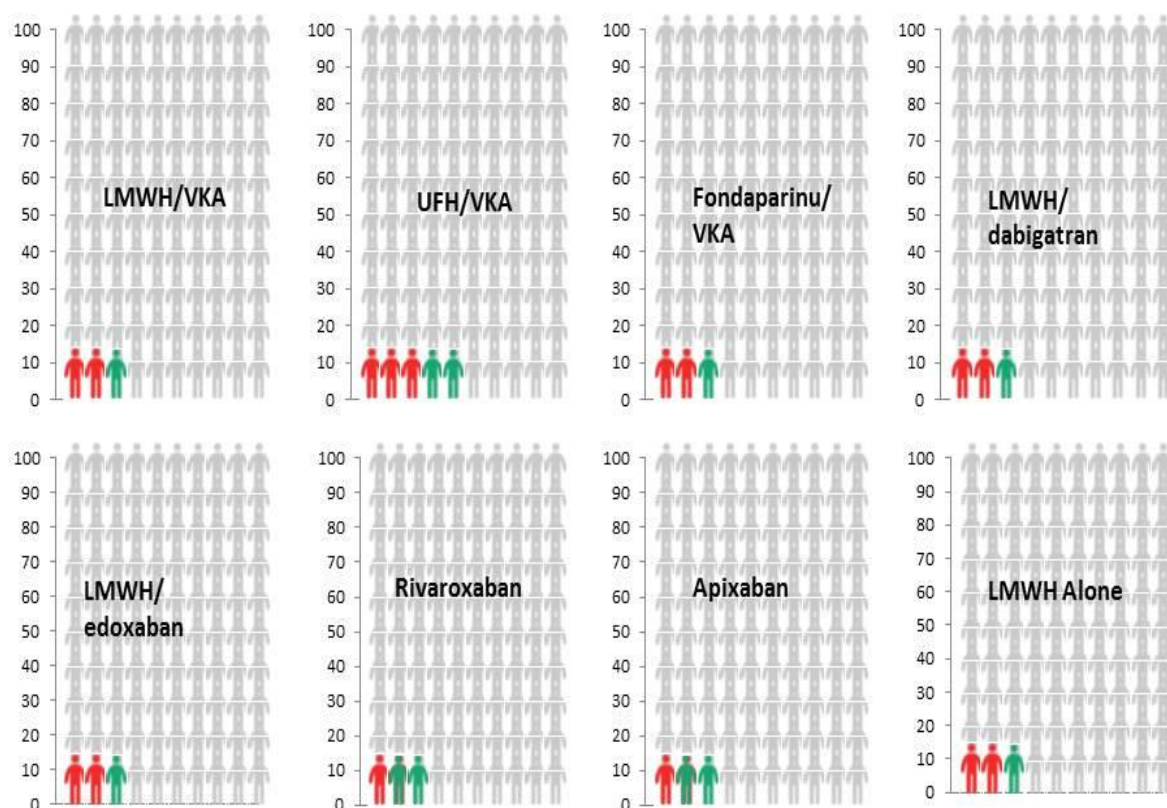
LMWH = low molecular weight heparin; UFH = unfractionated heparin; VKA = vitamin K antagonist; VTE = venous thromboembolism

Figure 5: Bar Chart with error bars for absolute probability of VTE and major bleeding at 6 months



LMWH = low molecular weight heparin; UFH = unfractionated heparin; VKA = vitamin K antagonist; VTE = venous thromboembolism

Figure 6: Icon Arrays with number of patients having a recurrent VTE (red) and major bleed (green) out of 100 patients at 6 months



LMWH = low molecular weight heparin; UFH = unfractionated heparin; VKA = vitamin K antagonist; VTE = venous thromboembolism

Figure 7: Icon Arrays with hours of perfect health gained or lost

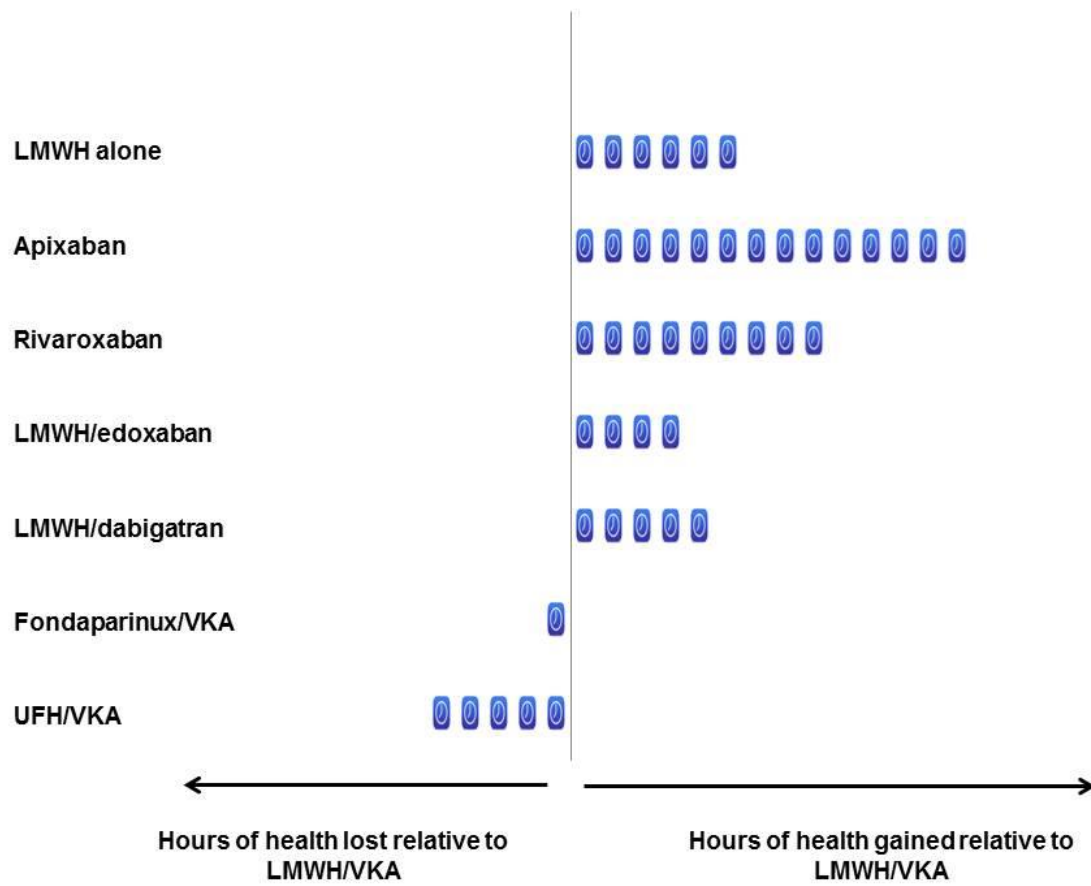
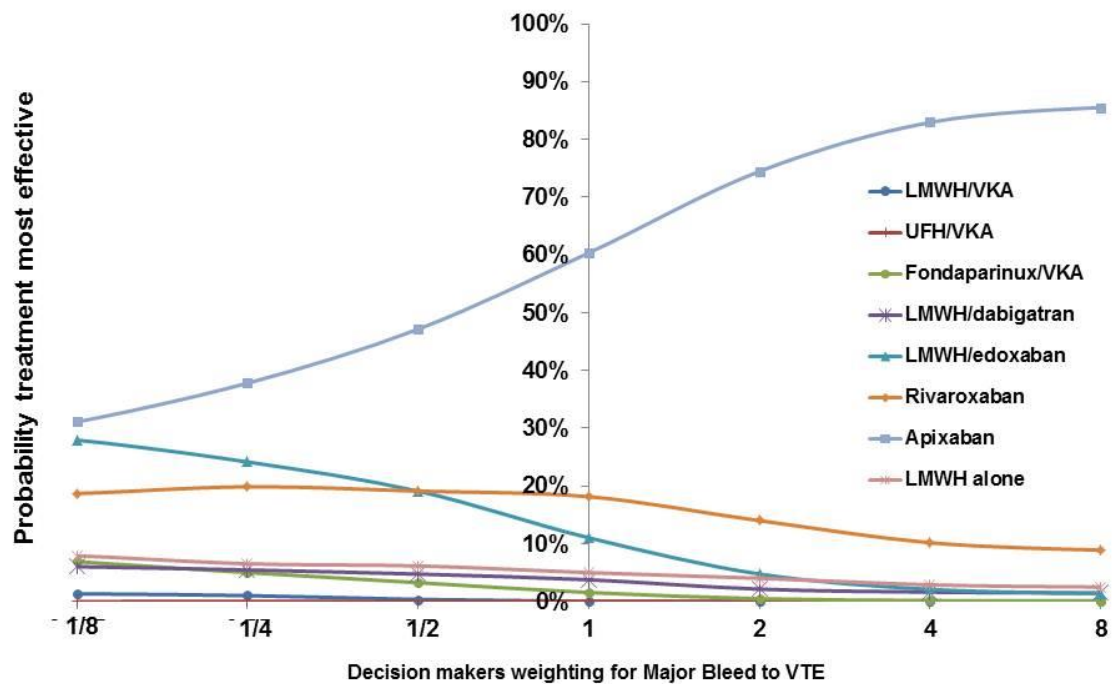


Figure 8: Acceptability curve showing the probability that each treatment is most effective, across a range of decision-makers' ratios for major bleed to VTE (i.e., value of 1 means major bleeding are valued equally in terms of severity whereas a value higher than 1 values major bleeding more than VTE and a value less than 1 values VTE more than major bleeding)



REFERENCES

1. Nikolakopoulou A, Chaimani A, Veroniki AA, Vasiliadis HS, Schmid CH, Salanti G. Characteristics of Networks of Interventions : A Description of a Database of 186 Published Networks. 2014;9(1):1-10. doi:10.1371/journal.pone.0086754.
2. Cipriani A, Furukawa T a, Salanti G, et al. Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. *Lancet*. 2009;373(9665):746-758. doi:10.1016/S0140-6736(09)60046-5.
3. Salanti G, Ades A, Ioannidis J. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *J Clin Epidemiol*. 2011;64(2):163-171. doi:10.1016/j.jclinepi.2010.03.016.
4. Chaimani A, Higgins JPT, Mavridis D, Spyridonos P, Salanti G. Graphical tools for network meta-analysis in STATA. *PLoS One*. 2013;8(10):e76654. doi:10.1371/journal.pone.0076654.
5. Van Valkenhoef G, Tervonen T, Zhao J, de Brock B, Hillege HL, Postmus D. Multicriteria benefit-risk assessment using network meta-analysis. *J Clin Epidemiol*. 2012;65(4):394-403. doi:10.1016/j.jclinepi.2011.09.005.
6. Castellucci L a., Cameron C, Le Gal G, et al. Clinical and Safety Outcomes Associated With Treatment of Acute Venous Thromboembolism. *JAMA*. 2014;312(11):1122. doi:10.1001/jama.2014.10538.
7. Hogg K, Kimpton M, Carrier M, Coyle D, Forgie M, Wells P. Estimating quality of life in acute venous thrombosis. *JAMA Intern Med*. 2013;173(12):1067-1072. doi:10.1001/jamainternmed.2013.563.
8. West SL, Squiers L, McCormack L, et al. *Quantitative Summary of the Benefits and Risks of Prescription Drugs : A Literature Review*.; 2011.
9. Garrison LP. Regulatory Benefit-Risk Assessment and Comparative Effectiveness Research. *Pharmacoeconomics*. 2010;28(10):855-865.
10. Wells G, Coyle D, Cameron C, Steiner S, Kelly S. *Safety, Effectiveness, and Costeffectiveness of New Oral Anticoagulants Compared with Warfarin in Preventing Stroke and Other Cardiovascular Events in Patients with Atrial Fibrillation*.; 2012.
11. Woloshin S, Schwartz L. Communicating Data About the Benefits and Harms of Treatment. *Ann Intern Med*. 2011;155(2):87-96.

12. Ades a E, Mavranouzouli I, Dias S, Welton NJ, Whittington C, Kendall T. Network meta-analysis with competing risk outcomes. *Value Health*. 2010;13(8):976-983. doi:10.1111/j.1524-4733.2010.00784.x.

CHAPTER 7A: NETWORK META-ANALYSIS INCORPORATING NON RANDOMIZED STUDIES: PITFALLS AND OPPORTUNITIES

Network meta-analysis incorporating non-randomized studies for assessing medical product safety: pitfalls and opportunities

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CHAPTER 7A: NETWORK META-ANALYSIS INCORPORATING NON RANDOMIZED STUDIES: PITFALLS AND OPPORTUNITIES

Network meta-analysis incorporating non-randomized studies for assessing medical product safety: pitfalls and opportunities

SUMMARY:

In this chapter, we present an overview of the pitfalls and opportunities for incorporating non-randomized studies for assessing medical product safety in network meta-analysis. The methods discussed in this section are subsequently applied in Chapter 7B. This Chapter was completed during the 3-month period where I was awarded the Michael Smith Foreign Study Supplement to time at the Harvard University Department of Population Medicine at Harvard Medical School and Harvard Pilgrim Health Care Institute.

LINKS:

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CONTRIBUTION:

I was responsible drafting the manuscript with guidance from Dr. Darren Toh and other supervisors. I generated all figures and tables related to pitfalls and opportunities for incorporating non-randomized studies for assessing medical product safety in network meta-analysis

INTRODUCTION

Many medical conditions exist for which there are multiple treatment options. However, evidence based on pair-wise meta-analysis only considers two treatments at a time. Accordingly, new meta-analytic methods have emerged to permit simultaneous comparison of multiple treatment options across studies that compare two or more treatments.^{5,6} These methods are most commonly referred to as *network meta-analysis*.^{5,6} For well-established methodological reasons, randomized controlled trials (RCTs) have been the study design most typically incorporated into network meta-analysis.⁷ However, there may be valid reasons to consider the inclusion of non-randomized studies, e.g., when studying unintended adverse safety events in the general population (See Box 1).¹⁻⁴

Network meta-analysis incorporating non-randomized studies has the potential to provide useful comparative safety evidence about multiple treatment options for medical conditions. It can maximize the utility of the information available for a particular condition. It could also utilize the data available in newly developed distributed health data networks, such as the Mini-Sentinel program in the United States.^{8,9} and Canadian Network for Observational Drug Effect Studies (CNODES)¹⁰ in Canada. These distributed health data networks have data on more than 150 million and 40 million individuals, respectively.^{9,10}

There have been few network meta-analyses incorporating non-randomized studies,¹¹⁻¹⁴ and these studies have derived data from the published literature. Some network meta-analyses including non-randomized studies have restricted their analysis to certain non-randomized study designs,¹¹ while others have included broad array of non-randomized

study designs^{12–14} and included unadjusted estimates.^{12,13}

In this paper, we describe network meta-analysis involving non-randomized studies; discuss some of its promises and challenges, offer insights on opportunities for improving the application of this methodology, and highlight the potential application of network meta-analysis in multi-center distributed health data networks.

WHAT IS NETWORK META-ANALYSIS?

A network meta-analysis (sometimes called *mixed or multiple treatments meta-analysis*) is a method for comparing more than two interventions, some of which may not have been compared directly head-to-head in the same RCT or observational study (Figure 1).^{5,6,15}

While a network meta-analysis respects randomization within individual studies, it is not randomized evidence – even if based entirely on RCTs – because the studies themselves were not randomized.^{5,6} The key assumption underlying any meta-analysis is *transitivity* of the studies.^{5,6,16} That is, all studies measure the same underlying relative treatment effects and any observed differences are due to chance. Stated another way, all treatments included in the network meta-analysis are ‘jointly randomizeable’.^{5,6,16} For example, in Figure 1, AC trials do not have B arms and AB trials do not have treatment C arms; however, the assumption underlying a network meta-analysis is that if an AB trial would have included a C arm, it would measure the same underlying relative effect for AC as the AC trials included in the network.^{5,6,16} To assess transitivity, one can collect information about the studies, and carefully consider whether they appear similar enough to be compared based on inspection of this information (Figure 1).^{5,6,16} Another way to assess transitivity is compare baseline event rates in the common treatment(s).^{5,6,16} In a standard pair-wise meta-analysis (i.e., within AB

or AC comparisons), effect modifiers may be different from one trial to the next (between-study heterogeneity).^{17,18} When the amount of between-study heterogeneity is large, it may be inappropriate to pool the effect estimates from these individual studies.^{17,18}

Lack of transitivity in network meta-analysis can produce disagreement between direct (solid lines in Panel A of Figure 1) and indirect evidence (dashed lines in Panel A of Figure 1) with respect to the estimates of the outcome – also known as inconsistency.^{18,19} There are various statistical methods to evaluate inconsistency when closed loops are available (i.e., both direct and indirect evidence are available to allow a comparison),¹⁹ although caution should be taken when interpreting the results of an assessment of consistency, as issues of heterogeneity and power may limit its applicability.

CONFOUNDING IN RANDOMIZED TRIALS AND NON-RANDOMIZED STUDIES

With a sufficiently large sample, well-designed RCTs are expected to achieve high internal validity by balancing all measured and unmeasured prognostic factors across intervention groups through random allocation (Figure 2 – Panel A).^{18,20} However, in non-randomized studies, allocation to treatment groups depends on other factors which may be unmeasured and which may result in systematically different patient characteristics between groups.^{20–22} Confounding occurs when treatment groups differ in their underlying risk for the outcome;^{18,20} unadjusted confounding in non-randomized studies thus produce biased effect estimates (Figure 2 – Panel A).²³

CONDUCT OF NETWORK META-ANALYSIS OF NON-RANDOMIZED STUDIES

Both Frequentist and Bayesian approaches have been used for conducting network meta-analyses,^{6,24,25} although the methods have been largely applied to RCTs.⁷ The two approaches have been shown to give similar results,²⁶ although the latter may be advantageous when combining results with randomized evidence or integrating findings with other types of evidence such as health economic evaluations.²⁷ The statistical implementation of a network meta-analysis incorporating non-randomized studies, irrespective of the method, must be handled with care. The validity of network meta-analysis is based on the underlying assumption that there is no imbalance in the distribution of effect modifiers across the different types of direct treatment comparisons.^{6,24,25} This can be a strong assumption for network meta-analyses including non-randomized studies.

An advantage of non-randomized studies is their inclusion of more representative patients who receive treatments in real-world settings. However, without stringent criteria for including studies, use of pair-wise non-randomized studies increases the potential to include patients who are not similar, which could bias effect estimates in a network meta-analysis (Figure 2 – Panel C). This is analogous to including separate trials with different inclusion/exclusion criteria in the network, but with additional risk of bias given these studies have may still also be limited by unmeasured confounding. Accordingly, evidence networks will be more robust, albeit not guaranteed, when comprised of treatments which are typically used for similar disease severity for the same indication, i.e., a network consisting

of a number of comparisons of different sulfonylureas for type 2 diabetes will more likely adhere to the transitivity assumption than a network which consists of a broad mix of comparators (e.g., metformin, sulfonylureas, insulin) used in a wide array of populations along the disease continuum. Similarly, if the network incorporates studies where the patient characteristics which do affect treatment choice (e.g. age) are similar, then they are more likely to adhere to the transitivity assumption.

The network meta-analytic methods chosen will depend on the study designs of non-randomized studies. Some non-randomized study designs and some may be better suited for network meta-analysis than others. Network meta-analyses should not include unadjusted effect estimates derived from non-randomized studies – these are prone to selection and performance bias. Network meta-analyses should only include non-randomized studies exploiting approaches to limit the extent of confounding. There are various approaches to limit the extent of confounding.²⁸ A popular approach to adjust for confounding in non-randomized studies is based on the use of propensity scores. A propensity score is the probability of receiving a particular treatment of interest based on measured baseline characteristics.^{20–22,28} It is particularly useful in studies of rare outcomes where adequate confounder adjustment may not be feasible using traditional covariate adjustment methods.^{20–22,28} Propensity score matching, a commonly used propensity score approach, allows one to design and analyze a non-randomized study so that it mimics some of the characteristics of a RCT. Matching on the propensity score is particularly attractive for network meta-analysis because it allows one to design and analyze a non-randomized study such that it mimics some of the characteristics of a RCT. For example, 1:1 matching allows

one to easily compare the patient characteristics of matched cohorts included in the analysis, analogous to RCTs (Figure 3).^{4,20–22,28} Nonetheless, similar to most methods that are used to deal with non-randomized data, all propensity score matching methods control only for measured confounders, but not for unmeasured confounders.^{20–22,28}

COMPARING AND COMBINING FINDINGS FROM NON-RANDOMIZED STUDIES WITH RCTS

Considering both non-randomized and randomized study designs together may provide investigators with a more comprehensive picture regarding the risk profiles of medical products.²⁹ Figure 4 presents two scenarios. In the first scenario, findings from non-randomized studies align with those reported in RCTs (Panel A). In the second scenario, the findings reported in non-randomized studies do not align with those reported in RCTs (Panel B). Investigators and decision makers are generally more likely to have confidence in estimates in the scenario where findings from both study designs are consistent compared with the scenario where there are discrepancies. However, the discrepancies may yield insight regarding residual confounding and effect modification that may not have been noticed had both study designs not been considered.

There are various approaches to combining randomized and non-randomized studies. Naive pooling, using either Frequentist or Bayesian network meta-analysis methods, is the simplest approach and does not differentiate between randomized and non-randomized studies.²⁹ Alternatively, non-randomized studies could be incorporated as prior information if a Bayesian approach is used. Another approach – a Bayesian hierarchical model – is the most

flexible,²⁹ and allows for bias adjustment while also accounting for heterogeneity between-trial designs.¹⁷ There has been limited research in this area, especially the latter two approaches. Furthermore, there is a lack of consensus on what degree of bias adjustment to apply. A recently published study assessing the safety of antifibrinolytics in cardiac surgery used naïve pooling of studies using propensity score methods.¹¹ In that study, the findings from the non-randomized studies largely aligned with those reported in the RCTs for most comparisons; however, inclusion of non-randomized studies led to more precise estimates for comparisons with limited RCT data.¹¹

FUTURE DIRECTIONS

Non randomized study methods have traditionally compared one treatment versus a single alternative.^{20–22,28} However, non-randomized methods are emerging which permit the comparison among multiple treatment options.^{30,31} The potential application of methods on multiple treatment options may be particularly beneficial when incorporating in network meta-analysis, given the requirement of the underlying “transitivity assumption” among multiple treatments. The consideration of multiple treatments simultaneously increases the likelihood that patients are more similar among compared with inclusion of multiple conventional two-way non-randomized comparisons, albeit at a potential cost of reduced precision.^{30,31}

Typically, non-randomized studies for meta-analyses are identified by conducting a systematic review of the literature. However, non-randomized studies identified using such an approach may differ with respect to study design, intricacies in methods used,

methodological quality, and so forth. For example, one study may have used high dimensional propensity score matching, whereas another used conventional covariate adjustment approaches but didn't include some relevant covariates. Over the past number of years, we have seen an increase in the development of distributed health data networks⁹ to assist in the conduct of non-randomized studies. In the United States, The Mini-Sentinel Distributed Database⁸ has been developed and consists of 18 Data Partners and for over 150 million individuals,³² while the Canadian Network for Observational Drug Effect Studies (CNODES)¹⁰ includes health and prescription records of over 40 million people from eight jurisdictions in Canada and abroad. These networks permit comparative safety and other evaluations across multiple databases without creation of a central data warehouse, avoiding numerous obstacles.⁸⁻¹⁰ The distributed approach lets data partners maintain control over their data, thereby minimizing concerns about patient privacy and data security.^{9,10,33} The studies performed in these networks often use common protocols, data models, or both, which improves the comparability of analysis performed at each site.⁸⁻¹⁰ Researchers involved in these networks may also be more adept at selecting the appropriate study design to control for confounders. As such, distributed health data networks offer a valuable data source for examining the comparative efficacy and safety of drugs. Given the large sample size and more homogeneous methods employed by these networks,^{9,10,33} it will be difficult to justify excluding such non-randomized information from systematic reviews and network meta-analyses when data is available. Network meta-analysis is well-suited for incorporating data from these distributed health data networks when there are multiple treatment options (versus two) under consideration.³⁴ Indeed, CNODES has used pair-wise meta-analysis to combine data within CNODES. Mini-Sentinel has also used pair-wise meta-

analysis to combine results across data partners.³⁵

Currently, data from the new distributed health data networks is only made available to those involved in the networks; future work is needed investigating the advantages and disadvantages of making aggregate safety data from these networks more assessable for analysis by using repositories such as ClinicalTrials.gov.

Future studies are needed which compare and contrast findings from the different approaches that combine randomized and non-randomized studies in network meta-analysis. The use of methods which combine randomized and non-randomized studies will undoubtedly increase with increasing number of available alternatives; improvement in data bases and methods, and the global movement towards progressive licensing³⁶ and product listing agreements³⁷ where information on a medical product is monitored throughout its lifecycle for regulatory and reimbursement purposes.

CONCLUSIONS

Non-randomized studies, either analyzed alone or in combination with RCTs, offer several advantages. Inclusion of non-randomized studies may improve precision, allow for a wider array of treatments to be considered (i.e., expands network), and provide real-world estimates. However, bias due to unmeasured confounding is a threat to validity. This potential bias could be propagated (or exaggerated) when incorporated into network meta-analysis. Network meta-analyses should only include non-randomized studies exploiting approaches to limit the extent of confounding. Certain approaches to limit the extent of

confounding (e.g., propensity score matching) may more closely mimic the characteristics of randomized studies and allow one to more easily examine whether patients included in the network meta-analysis are similar among comparisons. Analysts conducting networks meta-analyses involving non-randomized studies must ensure that comparisons are indeed similar enough in terms of patient characteristics to be pooled. Findings from evidence networks considering a mix of treatments and populations along the disease continuum should be interpreted with caution. Methods are evolving which permit investigators to combine or compare findings with randomized studies versus looking at these study designs in isolation of one another. The use of these methods will undoubtedly increase in the future in light of the increasing need to consider multiple treatments simultaneously; improved methodologies; increased development of distributed health data networks; and increased use of progressive licensing and product listing agreements requiring collection of data over the life cycle of a drug.

BOXES, TABLES, AND FIGURES

SUMMARY POINTS

- Network meta-analysis is increasingly used to allow comparison of multiple treatment alternatives simultaneously, some of which may not have been compared directly in primary research studies.
- The majority of network meta-analyses published to date have incorporated data from randomized controlled trials only; however, in many instances, inclusion of non-randomized studies may be desirable.
- Network meta-analyses should not include unadjusted effect estimates derived from non-randomized studies – these are prone to selection and performance bias. Network meta-analyses should only include non-randomized studies which use approaches to limit the extent of confounding.
- Some approaches to limit the extent of confounding may be better suited for network meta-analysis than others. For example, studies employing propensity score matching to balance the distribution of risk factors across groups may be more attractive than studies employing multivariable analysis, because they mimic some of the characteristics of randomized controlled trials. Further, they allow comparison of the patient characteristics of matched cohorts.
- Network meta-analyses including a broad mix of treatments and populations along the disease continuum should be interpreted with caution, especially those incorporating non-randomized studies. Although this may improve patient representativeness, it may make it difficult to yield reliable estimates of treatment effects due to residual confounding or effect modification. However, the application of network meta-analysis may yield insight regarding these issues.
- Network meta-analysis has the potential to be used in distributed health data networks such as Mini-Sentinel in the United States and the Canadian Network for Observational Drug Effect Studies in Canada.
- Multiple approaches to combining non-randomized and randomized data are feasible, and in many instances it may be worthwhile to combine and/or compare findings from both types of data sources versus consideration of each data source in isolation.

Box 1**Advantages of network meta-analysis incorporating non-randomized studies for assessing medical product safety**

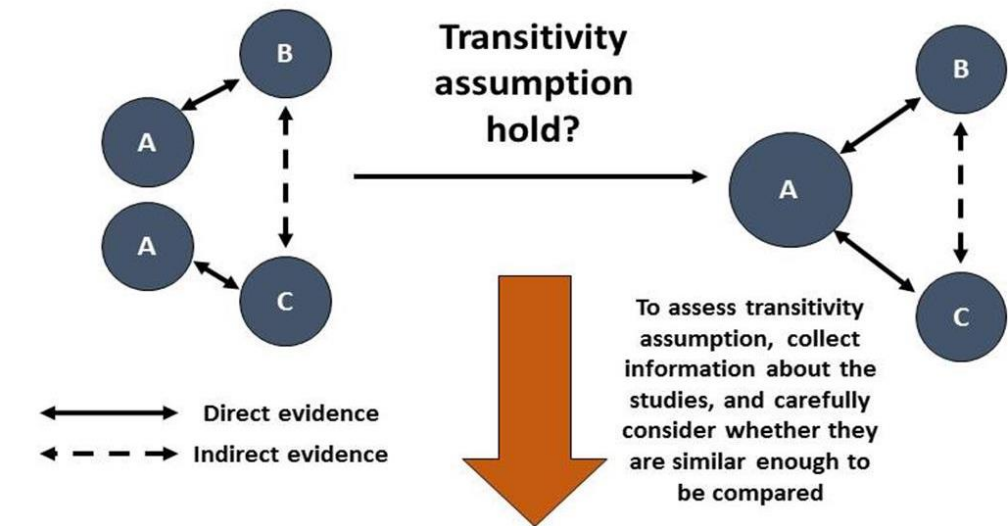
- Non-randomized studies can complement randomized controlled trials or address some of their limitations, such as short follow-up time, small sample size, highly selected population, high cost, and ethnical restrictions.
- Network meta-analysis of non-randomized studies can consider multiple treatments simultaneously, including active treatments that may not have been studied in randomized controlled trials.

Disadvantages of network meta-analysis incorporating non-randomized studies for assessing medical product safety

- Non randomized studies do not control for unmeasured confounders. If there are issues with unmeasured confounding in underlying studies, these will be propagated (and potentially exaggerated) when integrated into a network meta-analysis.
- Greater risk of violating the transitivity assumption of network meta-analysis, especially if broad populations are considered
- The application of network meta-analysis in non-randomized studies is more complex and less understood than traditional approaches for stakeholders.

Figure 1: Network meta-analysis and assessment of the transitivity assumption*

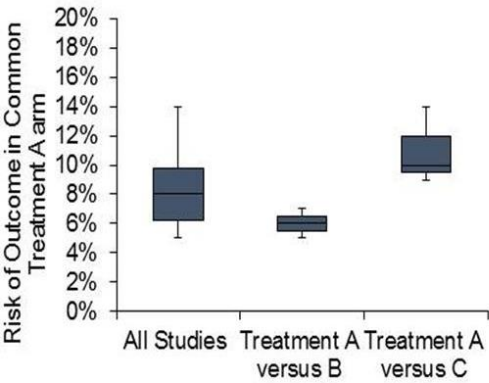
A: Network meta-analysis and assessment of transitivity assumption



B: Summary of patient and study characteristics

	All studies	Drug A versus B	...	Drug A versus C
Age	68 (2)	62 (2)		72 (3)
Duration of diabetes	15 years (2 years)	10 years (2 years)		20 years (2 years)
.....				
Concomitant medication	15%	10%		20%

C: Box Plot on risk of outcome in common arm



* We have compared patient and study characteristics at the comparison level although they can also be conducted at the treatment level (e.g., A, B, and C)

Figure 2: Potential bias resulting in network meta-analyses incorporating non-randomized studies

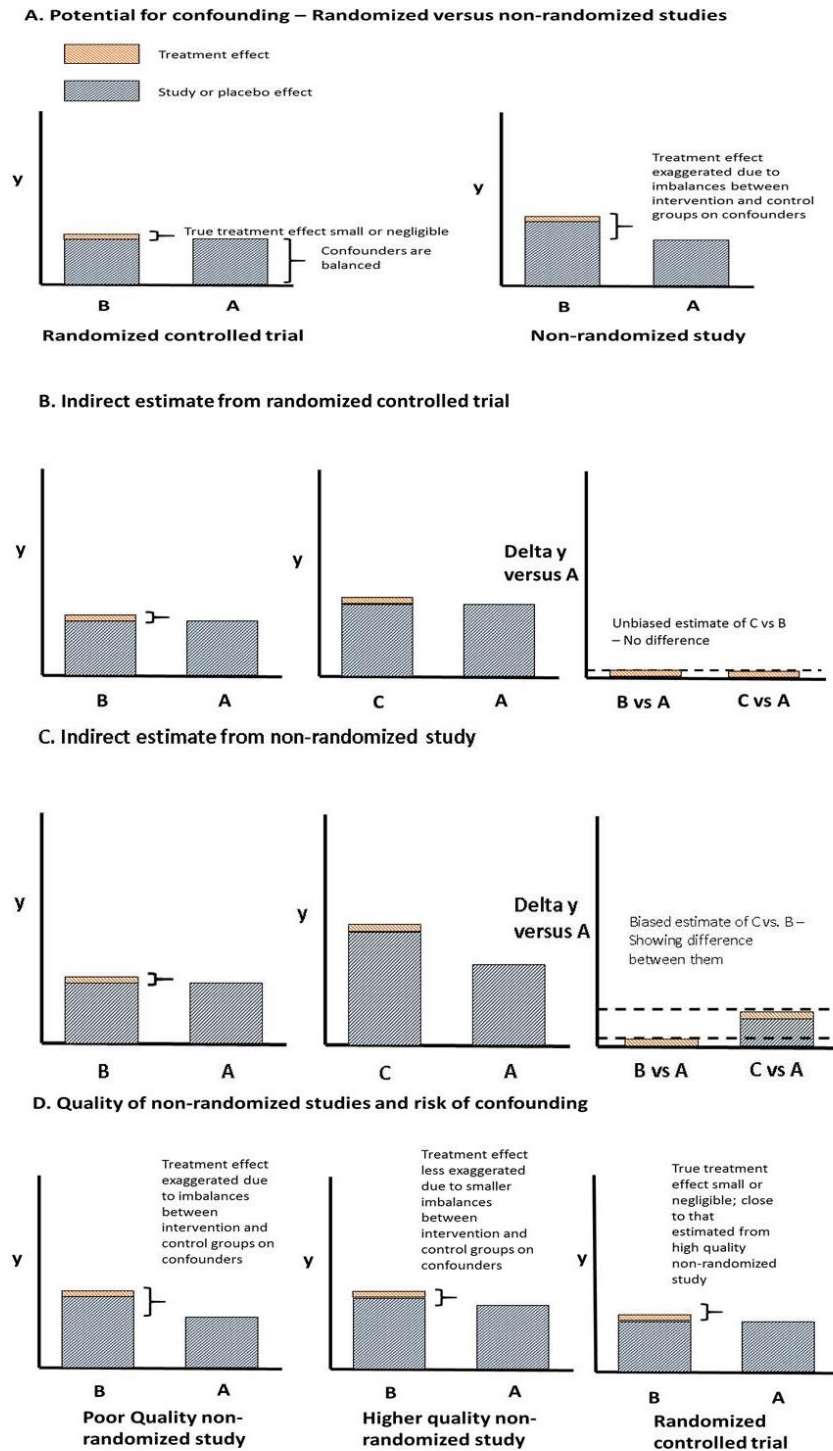


Figure 3: Illustration of hypothetical propensity score distributions between two treatment groups and of a commonly used approach, propensity score-matching (adapted from Schneeweiss et al.¹⁻⁴) A model predicting the probability of treatment A given patients' baseline characteristics (propensity scores) developed and the propensity score is estimated for each patient. The propensity score distributions can be separately plotted for both treatment groups. The propensity score distribution for those treated with Drug A is plotted as a solid line while those for Drug B are shown using a dashed line. The top image shows the propensity score distributions before matching while the bottom image shows the distribution of the propensity score after matching.

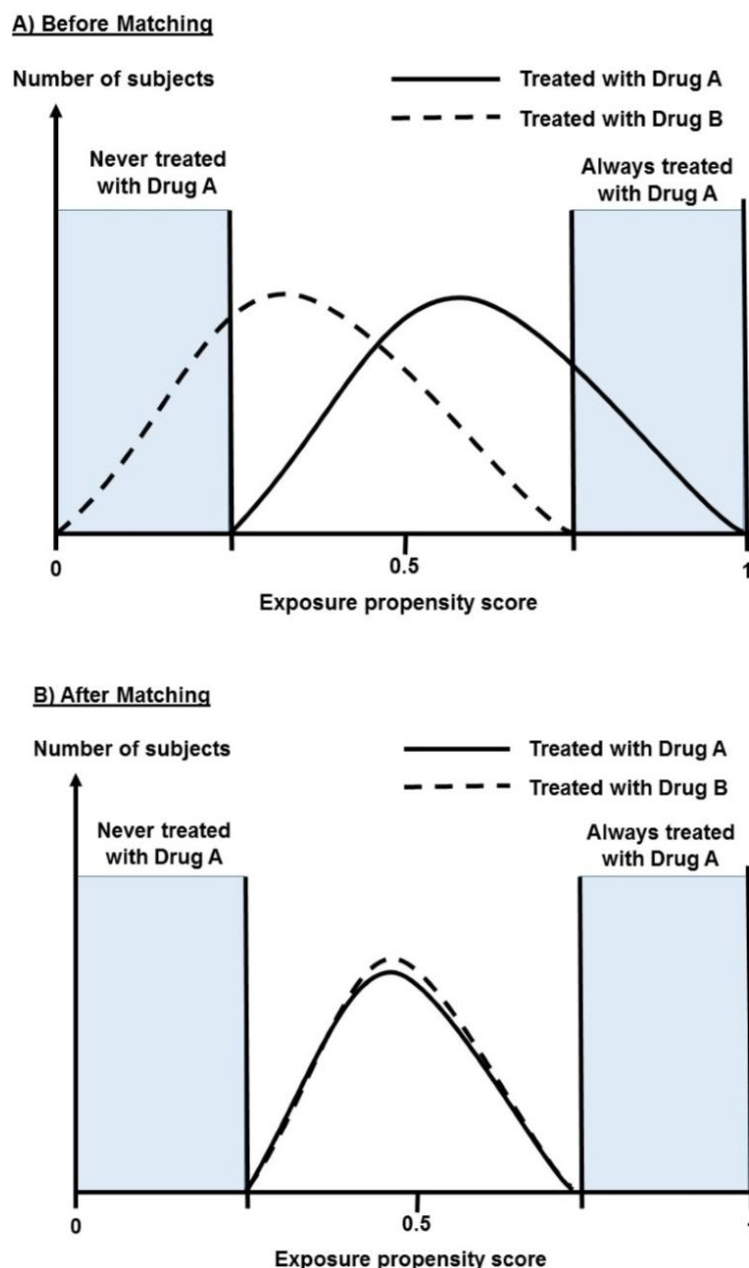
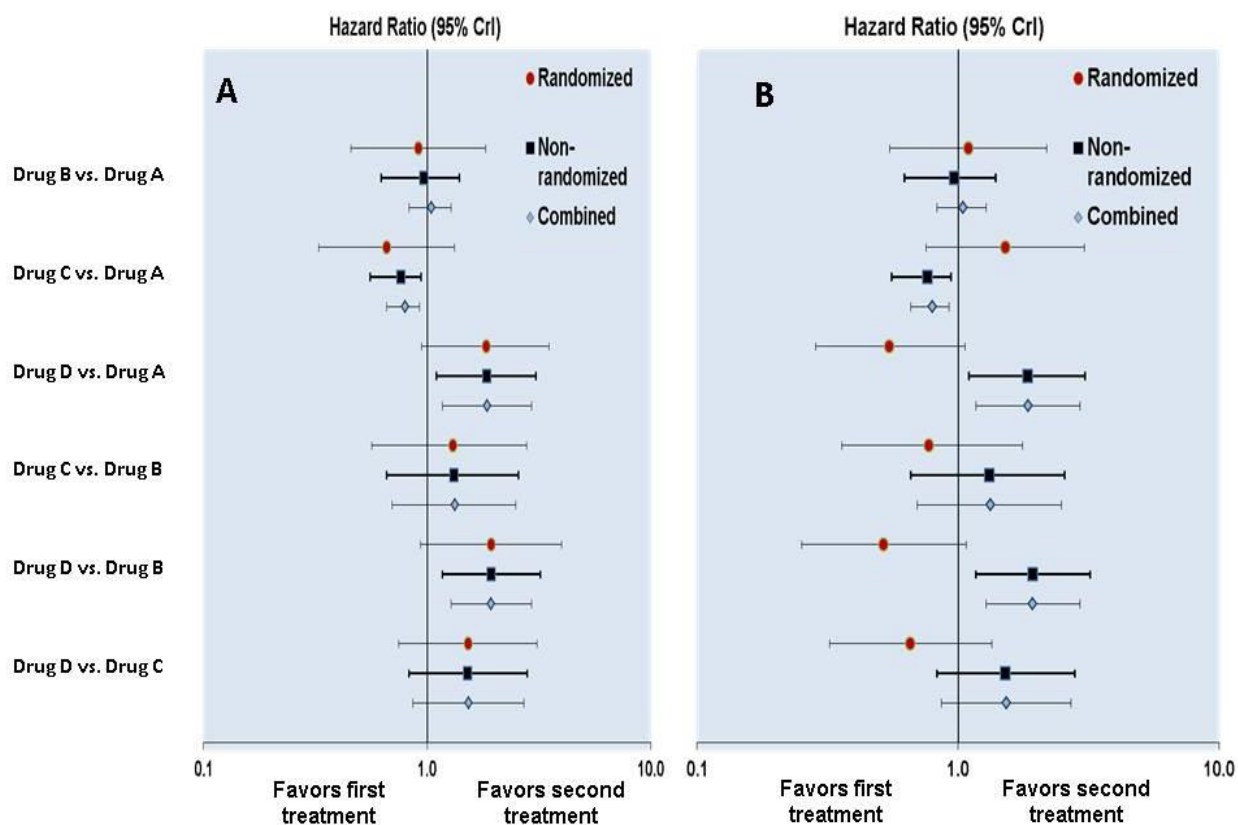


Figure 4: Combining and comparing findings from network meta-analyses using non-randomized studies, randomized studies, or both. We assume for this example a network which consists of 4 treatments, namely A, B, C, and D. Panel A illustrates a scenario in which findings from non-randomized studies and randomized studies align with each other; Panel B illustrates a scenario in which they do not align.



REFERENCES

1. Gibbons, R. D. *et al.* Post-approval drug safety surveillance. *Annu. Rev. Public Health* **31**, 419–37 (2010).
2. Singh, S. & Loke, Y. K. Drug safety assessment in clinical trials: methodological challenges and opportunities. *Trials* **13**, 138 (2012).
3. Vandenbroucke, J. & Psaty, B. Benefits and risks of drug treatments: how to combine the best evidence on benefits with the best data about adverse effects. *Jama* **300**, 2417–2419 (2008).
4. Schneeweiss, S. A basic study design for expedited safety signal evaluation based on electronic healthcare data. *Pharmacoepidemiol. Drug Saf.* 858–868 (2010). doi:10.1002/pds
5. Caldwell, D. M., Ades, a E. & Higgins, J. P. T. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. *BMJ* **331**, 897–900 (2005).
6. Dias, S., Sutton, A. J., Ades, a E. & Welton, N. J. Evidence synthesis for decision making 2: a generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials. *Med. Decis. Making* **33**, 607–17 (2013).
7. Nikolakopoulou, A. *et al.* Characteristics of Networks of Interventions : A Description of a Database of 186 Published Networks. **9**, 1–10 (2014).
8. Behrman, R. E. *et al.* Developing the Sentinel System--a national resource for evidence development. *N. Engl. J. Med.* **364**, 498–9 (2011).
9. Brown, J., Holmes, J., Shah, K. & Hall, K. Distributed health data networks: a practical and preferred approach to multi-institutional evaluations of comparative effectiveness, safety, and quality of care. *Med. Care* **48**, 45–51 (2010).
10. Suissa, S. *et al.* CNODES : the Canadian Network for Observational Drug Effect Studies. *Open Med.* **6**, 134–140 (2012).
11. Hutton, B. *et al.* Risks of harms using antifibrinolytics in cardiac surgery: systematic review and network meta-analysis of randomised and observational studies. *BMJ* **345**, e5798–e5798 (2012).
12. Vlaar, P. J. *et al.* Culprit vessel only versus multivessel and staged percutaneous coronary intervention for multivessel disease in patients presenting with ST-segment elevation myocardial infarction: a pairwise and network meta-analysis. *J. Am. Coll. Cardiol.* **58**, 692–703 (2011).

13. Stegeman, B. H. *et al.* Different combined oral contraceptives and the risk of venous thrombosis: systematic review and network meta-analysis. *BMJ* **347**, f5298 (2013).
14. Robertson, C. *et al.* Relative effectiveness of robot-assisted and standard laparoscopic prostatectomy as alternatives to open radical prostatectomy for treatment of localised prostate cancer: a systematic review and mixed treatment comparison meta-analysis. *BJU Int.* **112**, 798–812 (2013).
15. Ioannidis, J. P. a. Integration of evidence from multiple meta-analyses: a primer on umbrella reviews, treatment networks and multiple treatments meta-analyses. *CMAJ* **181**, 488–93 (2009).
16. Van Valkenhoef, G., Tervonen, T., Zwinkels, T., de Brock, B. & Hillege, H. ADDIS: A decision support system for evidence-based medicine. *Decis. Support Syst.* **55**, 459–475 (2013).
17. Dias, S., Sutton, A. J., Welton, N. J. & Ades, a E. Evidence synthesis for decision making 3: heterogeneity--subgroups, meta-regression, bias, and bias-adjustment. *Med. Decis. Making* **33**, 618–40 (2013).
18. Jansen, J. P. & Naci, H. Is network meta-analysis as valid as standard pairwise meta-analysis? It all depends on the distribution of effect modifiers. *BMC Med.* **11**, 159 (2013).
19. Dias, S. *et al.* Evidence synthesis for decision making 4: inconsistency in networks of evidence based on randomized controlled trials. *Med. Decis. Making* **33**, 641–56 (2013).
20. Freemantle, N., Marston, L. & Walters, K. Making inferences on treatment effects from real world data: propensity scores, confounding by indication, and other perils for the unwary in observational research. *BMJ* **6409**, 1–5 (2013).
21. Rosenbaum, P. & Rubin, D. The central role of the propensity score in observational studies for causal effects. *Biometrika* 41–55 (1983).
22. Austin, P. C. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. *Multivariate Behav. Res.* **46**, 399–424 (2011).
23. Deeks, J. J. *et al.* Evaluating non-randomised intervention studies. *Health Technol. Assess.* **7**, iii–x, 1–173 (2003).
24. Higgins, J. P. T. *et al.* Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. *Res. Synth. Methods* **3**, 98–110 (2012).

25. White, I. R., Barrett, J. K., Jackson, D. & Higgins, J. P. T. Consistency and inconsistency in network meta-analysis: model estimation using multivariate meta-regression. *Res. Synth. Methods* **3**, 111–125 (2012).
26. Chaimani, A., Higgins, J. P. T., Mavridis, D., Spyridonos, P. & Salanti, G. Graphical tools for network meta-analysis in STATA. *PLoS One* **8**, e76654 (2013).
27. Cooper, N. J., Sutton, A. J., Abrams, K. R., Turner, D. & Wailoo, A. Comprehensive decision analytical modelling in economic evaluation: a Bayesian approach. *Health Econ.* **13**, 203–26 (2004).
28. Biondi-Zoccai, G. *et al.* Are propensity scores really superior to standard multivariable analysis? *Contemp. Clin. Trials* **32**, 731–40 (2011).
29. Schmitz, S., Adams, R. & Walsh, C. Incorporating data from various trial designs into a mixed treatment comparison model. *Stat. Med.* (2013). doi:10.1002/sim.5764
30. Rassen, J. A. *et al.* One-to-many propensity score matching in cohort studies. *Pharmacoepidemiol. Drug Saf.* **21 Suppl 2**, 69–80 (2012).
31. Rassen, J. A. *et al.* Matching by propensity score in cohort studies with three treatment groups. *Epidemiology* **24**, 401–9 (2013).
32. Mini-Sentinel Data Core. *Mini-Sentinel Distributed Database Summary Report - Year 4*. 4 (2014). at <http://www.mini-sentinel.org/data_activities/distributed_db_and_data/details.aspx?ID=162>
33. Toh, S., Gagne, J. & Rassen, J. Confounding adjustment in comparative effectiveness research conducted within distributed research networks. *Med. Care* **51**, 4–10 (2013).
34. Fireman, B., Toh, S. & Butler, M. A protocol for active surveillance of acute myocardial infarction in association with the use of a new antidiabetic pharmaceutical agent. ... *Drug Saf.* **21**, 282–290 (2012).
35. Toh, S., Reichman, M. E., Houstoun, M. & Southworth, M. R. Comparative Risk for Angioedema Associated With the Use of Drugs That Target the Renin-Angiotensin-Aldosterone System. **172**, 1582–1589 (2014).
36. Eichler, H.-G. *et al.* Adaptive licensing: taking the next step in the evolution of drug approval. *Clin. Pharmacol. Ther.* **91**, 426–37 (2012).
37. Morgan, S. & Thomson, P. Inter-jurisdictional cooperation on pharmaceutical product listing agreements: views from Canadian provinces. *BMC Heal. Serv.* ... **13**, 34 (2013).

CHAPTER 7B: NETWORK META-ANALYSIS INCORPORATING NON RANDOMIZED STUDIES: AN APPLICATION USING ACUTE MYOCARDIAL INFARCTION IN ASSOCIATION WITH USE OF ANTI-DIABETIC AGENTS

**Network meta-analysis using observational data from distributed health data
networks: An application using acute myocardial infarction in association with use of
anti-diabetic agents**

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CHAPTER 7B: NETWORK META-ANALYSIS INCORPORATING NON RANDOMIZED STUDIES: AN APPLICATION USING ACUTE MYOCARDIAL INFACRTION IN ASSOCIATION WITH USE OF ANTI-DIABETIC AGENTS

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SUMMARY:

In this chapter, we present network meta-analysis incorporating non-randomized studies. We compare the risk of acute myocardial infarction in association with use of anti-diabetic agents using data from the Mini-Sentinel Distributed Health Data Database. The methods discussed in this section are based on Chapter 7A. This Chapter was completed during the 3-month period where I was awarded the Michael Smith Foreign Study Supplement to time at the Harvard University Department of Population Medicine at Harvard Medical School and Harvard Pilgrim Health Care Institute.

LINKS:

This manuscript was not submitted for publication.

CONTRIBUTION:

I was responsible drafting the manuscript with guidance from Dr. Darren Toh and other supervisors. I conducted all analyses and generated all figures and tables related to incorporating non-randomized studies for assessing medical product safety in network meta-analysis using this case study.

ABSTRACT

Estimates of comparative benefits and harms between multiple treatments are crucial for decision making in health care. Network meta-analysis provides a powerful methodology to obtain such estimates. In recent years, we have seen an increase in the use of this methodology for combining data from randomized controlled trials; however, limited research has been conducted around using this method for combining data from the real-world. In this paper, we investigate the strengths and limitations of applying this methodology using observational data derived from the Mini-Sentinel distributed health data network – the largest of its kind in the world. The use of observational data from distributed health data networks may be more desirable than including observational studies identified in a systematic review given these networks have large patient populations; use common data models or protocols; and typically use more rigorous methodologies to control for confounding. However, the use of data from distributed health data networks still pose challenges. Data derived from these networks do not control for unknown confounders which may introduce or exaggerate bias when incorporated into network meta-analysis. There is also potential for double counting events within data partners in the distributed health data network when multiple pair-wise PSM and DRS analyses are conducted. The strengths and limitations of this methodology are illustrated using an application in type 2 diabetes, where we conduct network meta-analyses of real-world data on acute myocardial infarction using two approaches: propensity score matching and disease risk score stratification into a network meta-analysis. We also compare and combine data derived from distributed the distributed health data network with randomized controlled trials.

INTRODUCTION

A network meta-analysis (sometimes called *mixed or multiple treatments meta-analysis*) is a statistical approach aimed at combining data on multiple interventions simultaneously.¹⁻³ By comparison, traditional meta-analysis only considers two interventions at a time.¹⁻³ By combining data on multiple interventions of interest, network meta-analyses can provide a more comprehensive picture on the body of evidence on a particular topic. Most network meta-analyses only consider randomized controlled trials for strong methodological reasons – randomization is the only means of controlling for unknown differences between comparison groups, as well as those that are known and measured.

However, there may be instances where consideration of observational studies in network meta-analysis is desirable, particularly for less common events.⁴⁻⁷ Randomized controlled trials are often too short in duration, or do not contain large enough sample sizes to identify less common events.⁴⁻⁷ They may also contain patients who are not representative of the general population.⁴⁻⁷ In these cases, it is possible to include information from observational studies, although inclusion of such data in network meta-analyses must be handled with care to minimize the risk of bias.

Typically, observational studies for meta-analyses are identified by conducting a systematic review of the literature. However, observational studies identified using such an approach may differ with respect to study design, intricacies in methods used, methodological quality, etc. For example, one study may have used high dimensional propensity score matching,

whereas another used conventional covariate adjustment approaches but didn't include some relevant covariates. Inclusion of heterogeneous or low quality data into meta-analyses, and in particular network meta-analysis, may introduce bias.

Over the past number of years, we have seen an increase in the development of distributed health data networks⁸ to assist in the conduct of observational studies. In the United States, The Mini-Sentinel Distributed Database (MSDD)⁹ has been developed and consists of 18 Data Partners and for over 150 million individuals,¹⁰ while the Canadian Network for Observational Drug Effect Studies (CNODES)¹¹ – includes health and prescription records of over 40 million people from eight jurisdictions in Canada and abroad. In each of these distributed health data networks, data from multiple databases are integrated but not combined into a centralized data repository. The use of a distributed health data network versus a centralized data repository allows data holders to retain physical control over use of their data, overcoming many obstacles related to confidentiality, regulation, and proprietary interests.^{8,9,11}

The use of observational studies derived distributed health data networks in network meta-analysis offer other advantages over traditional approaches of pooling all observational studies identified in a systematic review. The researchers involved in these networks may be more adept at selecting the appropriate study design to control to control for confounders. The effect estimates derived from distributed health data networks may also be more homogenous than those derived from the published literature given data partners within these networks often use common data models^{8,9} or protocols¹¹ to conduct analyses. Despite these

potential strengths, it is important to note that while using data derived from these methods may help minimize bias (compared to including all published observational studies irrespective of methods/design), it does not obviate bias – these studies still do not control for unknown confounders.

In this paper, we provide a general framework for analyzing observational data derived from distributed health data networks using network meta-analyses using an illustrative example in type 2 diabetes. To accomplish this, we analyze data on the risk of myocardial infarction in type 2 among oral anti-diabetes drug using real world data from the MSDD in the United States. We also compare and combine findings from Mini-Sentinel distributed health data network with those reported in RCTs, and then discuss the strengths and limitations of the methods employed, and opportunities for enhancing the application of methods.

THE CASE STUDY

Saxagliptin is an oral dipeptidyl peptidase-4 (DPP-4) inhibitor used in the treatment of type 2 diabetes mellitus. It was approved in July 2009 by the FDA as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus, and can be used as either monotherapy or combination therapy.¹² In 2010, the FDA selected saxagliptin to be the first product tested using active surveillance in the newly developed MSDD. A protocol¹² was developed which outlined the methods for the active surveillance of acute myocardial infarction in users of saxagliptin compared to users of comparator agents, using data from MSDD. In short, the active surveillance of saxagliptin used a “new user” parallel cohort design, where new users of saxagliptin after August 1, 2009 were identified, and followed up

over time to examine the risk of AMI, and the incidence of AMI was compared with new users of comparator drugs.¹² The comparators considered were: sitagliptin, long-acting insulin, pioglitazone, and second-generation sulfonylureas as a class (glimepiride, glipizide, and glyburide).¹² The analysis considered a number of approaches to adjust for confounders including matching 1:1 by an exposure propensity score (PS) and stratification by a disease risk score (DRS). The covariates for inclusion in each PS and DRS analyses were identified *a priori*. Due to the limited time that saxagliptin was on the market in the US at the time of the analysis (2009 and onwards), an addendum to the protocol was made to also include an active surveillance of sitagliptin from 2006 onwards alongside the active surveillance of saxagliptin. Sitagliptin is also an oral DPP-4 inhibitor but it was approved in October 2006, and as a result had more time to accumulate data on risk of myocardial infarction. The methods employed in the sitagliptin active surveillance using MSDD were very similar to those outlined in the original protocol for saxagliptin active surveillance.¹²

METHODS

Data sources

Observational studies. We identified observational data for the analysis using data from Mini-Sentinel distributed database (MSDD) – a pilot project sponsored by the U.S. Food and Drug Administration (FDA) – for monitoring the safety of FDA-regulated medical products.^{8–10} The MSDD consists of 18 Data Partners and data for over 150 million individuals in the United States.^{8–10} Seventy percent of the data within the MSDD include both medical and drug coverage.¹⁰ The MSDD include data on patients enrolled in or profit and non-for-profit health plans between January 2000 through June 2014: Aetna, HealthCore, the HMO Research Network (6 sites), Humana, Kaiser Permanente (6 sites),

Lovelace Clinic Foundation, OptumInsight, and Vanderbilt.¹⁰ Data from the HMO Research Network and Kaiser Permanente are each pooled thereby resulting in data for 7 data partners for purposes of this analysis.¹⁰

Randomized controlled trials. We identified randomized controlled trials using two recently published meta-analyses^{13,14} investigating the cardiovascular safety of sulfonylureas and dipeptidyl peptidase-4 inhibitors. We also searched ClinicalTrials.gov to identify studies reporting data beyond the search dates of these meta-analyses. The inclusion criteria for randomized studies were: 1) patients with type 2 diabetes who have been treated for at least 52 weeks, 2) compared two of the following: saxagliptin, sitagliptin, pioglitazone, and second-generation sulfonylureas (glimepiride, glipizide, and glyburide); and 3) report data for acute myocardial infarction. Studies comparing any of these treatments with either placebo or insulin were excluded.

Data synthesis

We conducted both traditional meta-analyses and Bayesian network meta-analyses.

Traditional meta-analyses were conducted using Comprehensive meta-analysis version 2.2.064 (BioStat, Englewood, US) and Bayesian meta-analyses using WinBUGS software version 1.4.3 (MRC Biostatistics Unit, Cambridge, UK).

We conducted traditional frequentist meta-analysis, where the log hazard ratios (relative risks for RCTs) and standard errors for each data partner or RCT were pooled. We conducted three analyses where we: 1) pooled observational data from each data partner using 1:1 propensity score matching; 2) pooled observational data from each data partner using disease risk stratification; 3) pooled data from randomized controlled trials. Both fixed and random-

effects models were used. We assessed the appropriateness of pooling data across data partners and RCTs by assessing heterogeneity. We used the I^2 test for heterogeneity for traditional meta-analysis.

We used a Bayesian approach for network meta-analyses, where point estimates and 95% credible intervals for hazard ratios (HR) were derived using Markov Chain Monte Carlo (MCMC) methods. Vague priors, such as $N(0, 100^2)$, were assigned for basic parameters throughout.² We assessed the appropriateness of pooling data across data partners and/or RCTs by assessing heterogeneity, including assessment of deviance information criterion (DIC), between study standard deviation, and comparison of residual deviance to number of unconstrained data points.^{2,15,16} To ensure convergence was reached, trace plots and the Brooks-Gelman-Rubin statistic were assessed. Three chains were fit in WinBUGS for each analysis, with at least 20,000 iterations, and a burn-in of at least 20,000 iterations. We formally assessed inconsistency, by comparing the deviance, between study variance, and DIC statistics in fitted consistency and inconsistency models.¹⁶ We also plotted the posterior mean deviance of the individual data points in the inconsistency model against their posterior mean deviance in the consistency model to identify any loops in where inconsistency is present.¹⁶

In the main analyses, we did not pool effect estimates using different study designs, i.e., observational data from MSDD were not pooled with randomized controlled trials. However, we compared findings between study designs and ran additional analyses where we pooled data from different study designs using naïve pooling.¹⁷ We also investigated the impact of conducting additional analyses to see how results varied by: 1) cardiovascular disease (CVD) versus non-CVD; 2) per protocol versus ITT; 3) AMIs known to be principal diagnosis

versus of myocardial infarction versus including AMIs where the principal diagnosis is unknown; and 4) excluding patients where AMIs may have been counted in multiple comparisons. Data partner specific estimates were not available for these analyses, but pooled analyses across all sites indicate that the conduct of such analyses is unlikely to impact findings (**Appendix 1**).

RESULTS

Overall, 1,980 and 4,890 AMIs which occurred among one of the 4 oral antidiabetes drugs examined using for propensity-score matching and disease risk score stratification respectively (Figure 1). The majority of the AMI events for each analysis were derived from comparisons versus sitagliptin, and these patients also had longer patient-years of follow-up (Figure 1). For PSM analyses, there were a few data partners which did not have sufficient data for comparisons, particularly those for saxagliptin (Figure 1). However, all data partners had sufficient data in analysis using disease risk score stratification (**Appendix 2**).

Within the traditional meta-analysis, no treatments were associated with differences in risk of acute myocardial infarction compared with saxagliptin (**Figure 2**). Compared with sitagliptin, sulfonylureas were associated with a statistically significant risk of acute myocardial infarction (HR 1.44, 95% CI; 1.16—1.79). We noted a moderate amount of heterogeneity for the sulfonylureas versus sitagliptin comparisons ($I^2=35$), although 6 of 7 data partners reported values above unity (**Figure 3**).

Within the network meta-analysis, sulfonylureas were associated with an increased risk of

acute myocardial infarction compared with sitagliptin (HR 1.4, 95% CrI; 1.12—1.7) when using propensity score matching (PSM), and sitagliptin (HR 1.34, 95% CrI; 1.13—1.54) and saxagliptin (HR 1.24, 95% CI; 1.03—1.45) when using disease risk score stratification. Sulfonylureas were also associated with an increased risk of myocardial infarction compared with pioglitazone, using either PSM (HR 1.51, 95% CrI 1.12—1.98) or DRS (HR 1.42, 95% CrI 0.114—1.72), although these comparisons were not formally considered directly in the saxagliptin or sitagliptin active surveillance (**Figure 1**).

The risk of myocardial infarction for sulfonylureas versus sitagliptin/saxagliptin ranged from 0.89 to 9.06 (**Figure 6**), with pooled estimates not reported a difference (RR 1.25, 95% CI 0.49—3.17). The risk of myocardial infarction for sulfonylureas versus other dipeptidyl peptidase-4 inhibitors ranged from 1.99 to 3.04, while pooling all dipeptidyl peptidase-4 inhibitors was not associated with a difference (RR 1.59, 95% CI 0.82—3.09). Analyses pooling observational data from MSDD with randomized controlled trials were similar to those reported using MSDD alone, irrespective of the methods used (**Figure 6**).

DISCUSSION

We have provided a general framework for conducting network meta-analyses using observational data derived from distributed health data networks such as MSDD in the United States and CNODES in Canada. We illustrate the application using a case study¹² comparing the risk of acute myocardial infarction in association with use of anti-diabetic agents using data from Mini-Sentinel, and also discuss some of the advantages, opportunities and challenges with applying these methods. To the best of our knowledge, this is the first

application of network meta-analysis using data derived from distributed health data networks.

For sound methodological reasons, the majority of network meta-analyses conducted to date only consider randomized controlled trials – RCTs control for both known and unknown confounders a key element to adhere to the exchangeability assumption underpinning a network meta-analysis.^{1,18} However, in some instances it may be desirable to consider observational data despite the known methodological limitations. We felt consideration of observational data was appropriate in our case study given the limited information that was provided on risk of AMI among anti-diabetes drugs in RCTs. Indeed, we only identified 18 RCTs with greater than 52 weeks of follow-up comparing either saxagliptin or sitagliptin with each other, pioglitazone, or sulfonylureas among these studies only 56 AMIs were observed. By contrast, we had 1,980 and 4,890 AMIs in PSM and DRS analyses respectively in the MSDD.

We focused solely on data derived from the MSDD. Studies conducted within distributed health data networks such as MSDD often use common methods and/or study design. This particularly true within MSDD where data partners use a standardized data structure and standardized analyses are run identically at each Data Partner site.^{8,9} By contrast, CNODES uses a common protocol approach to enhance similarity of analyses among data partners.¹¹ As a result, studies undertaken within distributed health data networks may result in more homogeneous effect estimates than traditional approaches where a systematic review is undertaken to identify observational studies and these are summarized and/or pooled. Indeed,

we observed fairly homogenous effect estimates for comparisons across sites, especially for analyses using DRS stratification where more AMIs are considered. By contrast, had a systematic review been undertaken, there may have been considerably more heterogeneity, given identified studies (if available) would likely differ with respect to study design, intricacies in methods used, methodological quality, etc. Indeed, in one of the few published network meta-analysis which included observational studies¹⁹ using a broad array of methods and designs found large variation in effect estimates.

In traditional meta-analysis, only two treatments are considered at a time.¹ This approach is not optimal for decision making where multiple treatments are often of interest, which was the case for our illustrative example. In our example,¹² the Food and Drug Administration (FDA) was interested in how saxagliptin compared with multiple treatments. Further complicating matters, a parallel active surveillance of sitagliptin was conducted alongside the saxagliptin active surveillance, increasing the number of pair-wise comparisons that needed to be considered. The use of network meta-analysis allowed us to integrate data from the multiple saxagliptin and sitagliptin comparisons into a unified analysis, and present findings in a more cohesive manner which may be more suitable for decision making. It also allowed us to obtain estimates for analyses that were not provided in the AMI active surveillance project, i.e., sulfonylureas versus pioglitazone, and could be used to validate findings.

Studies often consider observational data and randomized controlled trial data in isolation from one another. However, methods are emerging¹⁷ which permit the combination of findings from different study designs. Indeed, we compared the risk of myocardial infarction

within our framework using some of these methods.¹⁷ By not restricting our analysis to one study design, we were able to get a more holistic view of the body of evidence on this topic. It was reassuring that findings for the sulfonylurea versus dipeptidyl peptidase-4 inhibitor comparisons were trending in the same direction in randomized controlled trials.

Rather than focusing solely on the analyses which combine study designs, we opted to present both study-level RCT results alongside each other. This was partly because the number of AMI's in the Mini-Sentinel distributed health data network far outnumbered those reported in RCTs (even when only considering PSM analyses), thereby contributing an overwhelming majority of weight in effect estimates which pooled both RCTs and observational studies. However, we also opted for this approach because we felt it was more conducive to decision-making – decision makers are able to get a better sense of how results compare between study designs irrespective of whether they are pooled or not. Pooling different study designs may mask differences observed by study design.

Nonetheless, it should be noted that the network meta-analysis based on randomized controlled trials is limited. We identified few studies with follow-up of at least 52 weeks in duration, and these studies often had small sample sizes and/or few AMIs. Although the findings for SUs versus sitagliptin and SU versus pioglitazone were similar in magnitude to those reported in the network meta-analysis of data from Mini-Sentinel distributed data network, they were not statistically significant. Given the small number of events observed, the results are sensitive to inclusion of additional RCTs. For example, if one large RCT were published and did not identify an increased risk of myocardial infarction for sulfonylureas, it

could dramatically alter findings in the RCT network. Until more information become available, definitive conclusions cannot be drawn from the RCT network.

Placebo-controlled comparisons, or data for comparisons with insulin were not considered in this analysis. Patients using placebo or insulin may be systematically different than those using oral anti-diabetes drugs, potentially violating the exchangeability assumption underpinning each network meta-analysis. The use of more stringent inclusion/exclusion criteria is paramount when conducting network meta-analyses of observational studies given these studies do not account for unmeasured confounders.

We considered a broad type 2 diabetes population and did not stratify by line of diabetes therapy, e.g., inadequately controlled on metformin; inadequately controlled on two or more oral diabetes drugs, inadequately controlled on insulin, etc. This decision was a consequence of the available observational data, although we recognize there may be differences among subpopulations of patients with type 2 diabetes in terms of susceptibility for myocardial infarction, which may be masked by pooling. Indeed, other network meta-analyses in diabetes^{20,21} have stratified populations by line of diabetes therapy to avoid this issue. Future research is needed investigating the shortcomings of using broad patient populations within networks for safety assessments in general, and for this specific case study before definitive conclusions can be drawn.

Our analysis is also limited in that comparisons within each data partner conducted analyses comparing two treatments at a time. While patient groups within a two treatment comparison

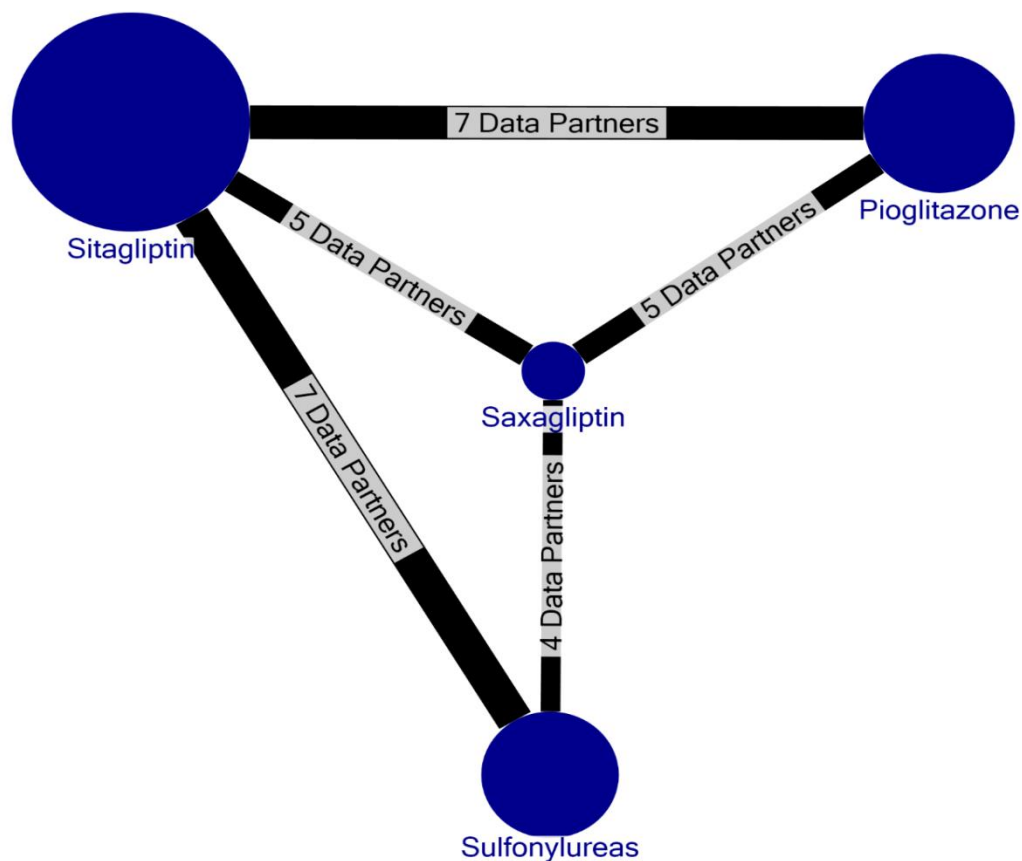
may be balanced with respect to known covariates when using either PSM or DRS methods, there is still a possibility of differences between comparisons. The risk of differences between comparisons is particularly pronounced when comparing treatments which are used along different times of the disease continuum, such as comparing insulin with orals in the case of diabetes, although there still may be differences among the oral anti-diabetes treatments. Further, to maximize available data, AMI's were double or triple counted (**Figure 5**). For example, a patient using sitagliptin who had an MI in the sitagliptin versus SU comparison may also count as a patient who had an MI in a sitagliptin versus pioglitazone comparison (**Figure 5**). In the future, if one of the main objectives of an analysis is to compare how the risk of a harm (or benefit) for a particular treatment compares with multiple treatment options in the real-world, then studies could consider matching on multiple treatments simultaneously²² from the outset within each data partner. This will not only resolve the double counting issue, but also ensure that patient populations for treatments are more similar in terms of known confounders, and more closely adhere to the exchangeability assumption, albeit at a potential cost of reduced precision.^{22,23}.

In summary, network meta-analysis can be used to integrate observational data from distributed health data networks when comparisons among multiple treatments are needed. However, before conducting such analyses, it is imperative that researchers understand the methodological limitations and ensure that treatments and/or populations included in evidence networks are similar enough to be compared. The use of observational data from distributed health data networks may be more desirable than including observational studies identified in a systematic review. However, use of data from distributed health data networks

still pose challenges. Data derived from these networks do not control for unknown confounders, and there is potential for double counting events within data partners in the distributed health data network when multiple pair-wise PSM and DRS analyses are conducted. Despite these limitations, network meta-analysis provides a more holistic view of the evidence, especially when findings from observational data are compared and combined with randomized controlled trials. We illustrated the strengths, limitations, and opportunities for improving this methodology using real-world safety issue based on data derived from the Mini-Sentinel distributed database – the world’s largest distributed health data network.

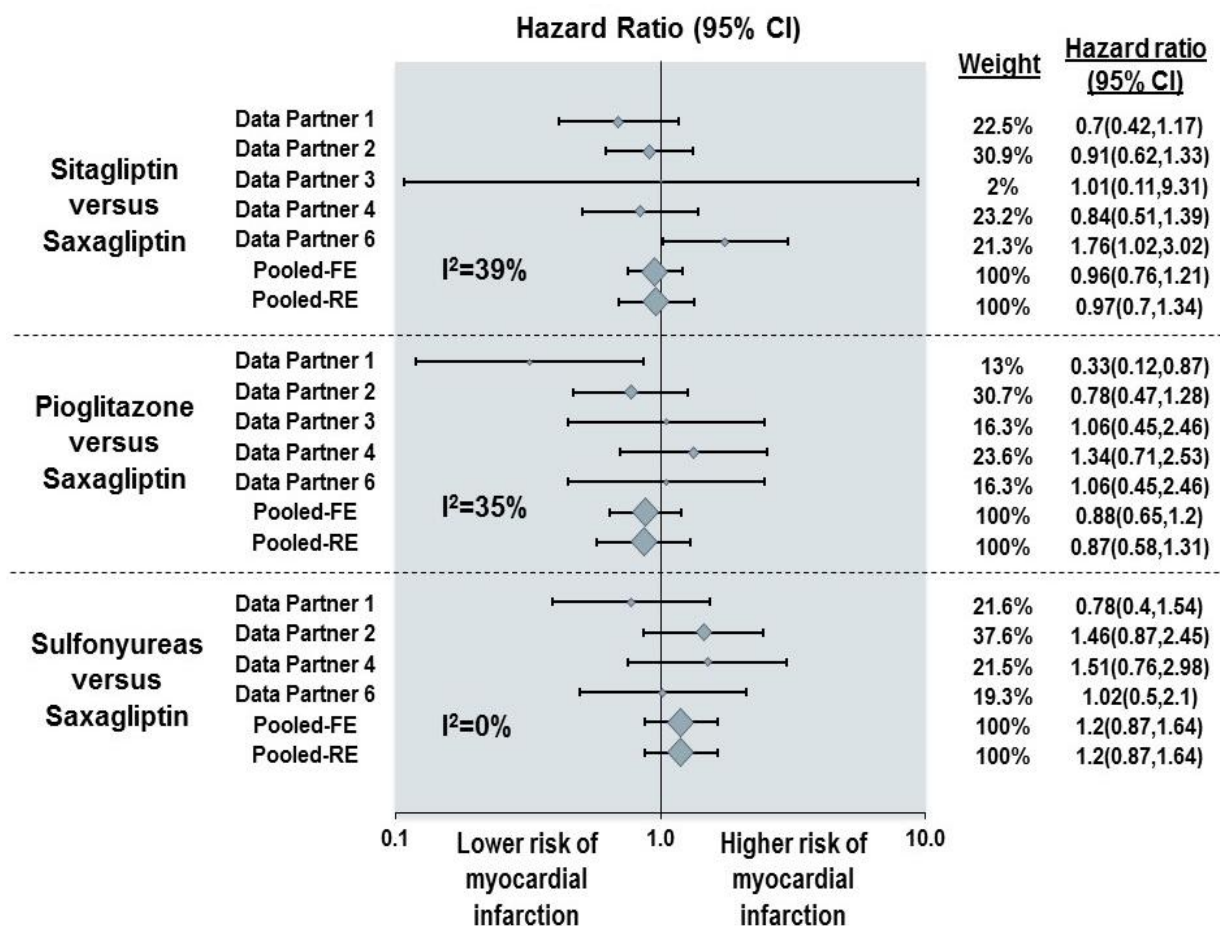
TABLES AND FIGURES

Figure 1: Evidence network* for acute myocardial infarction – Propensity-score matching analysis using per protocol analyses which censor follow-up after run out of study drug



* Size of node reflect of patient-years of follow-up and width of connections reflective of number of data partners

Figure 2: Forest plot of traditional frequentist meta-analyses for comparisons versus saxagliptin– Propensity-score matching analysis using per protocol analyses which censor follow-up after run out of study drug and AMI is principal diagnosis



* For simplicity, we have shown comparisons at the treatment level although they can also be conducted at the comparison level (B vs A)

Figure 3: Forest plot of traditional frequentist meta-analyses for comparisons versus sitagliptin– Propensity-score matching analysis using per protocol analyses which censor follow-up after run out of study drug and AMI is principal diagnosis

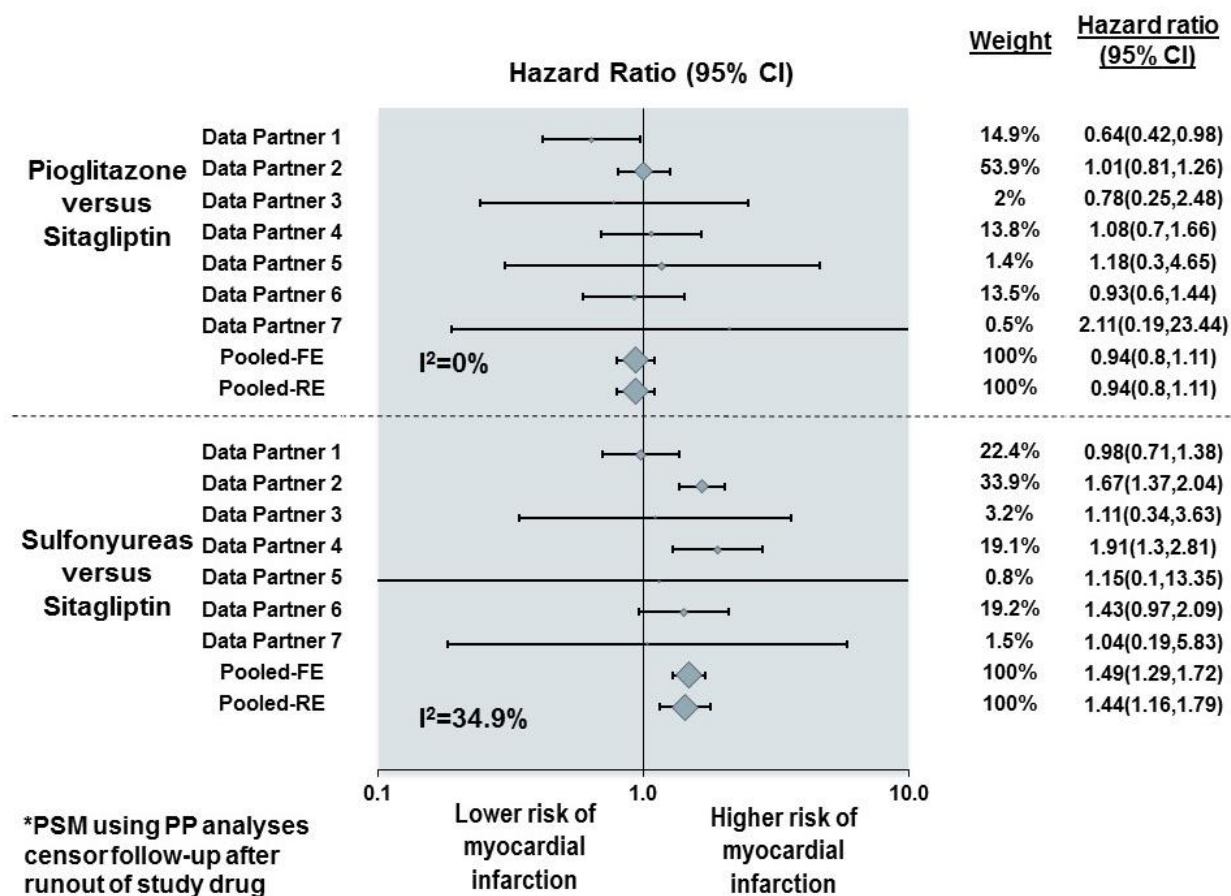


Figure 4: Bayesian network meta-analysis using propensity-score matching (PSM) and disease risk score stratification (DRS) – AMI is principal diagnosis and per protocol analyses which censor follow-up after run out of study drug

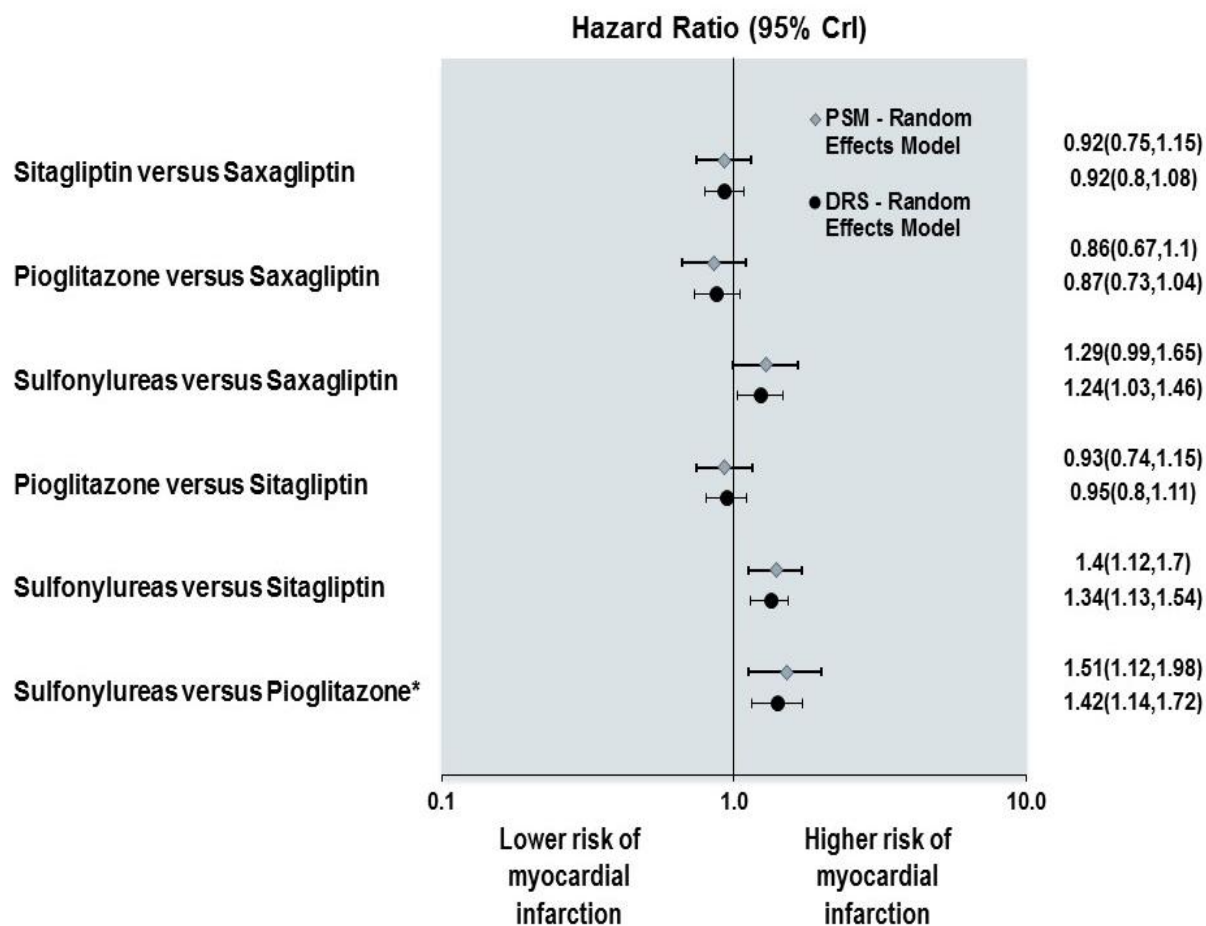


Figure 5: Methodological challenges with the data available from Mini-Sentinel AMI assessment

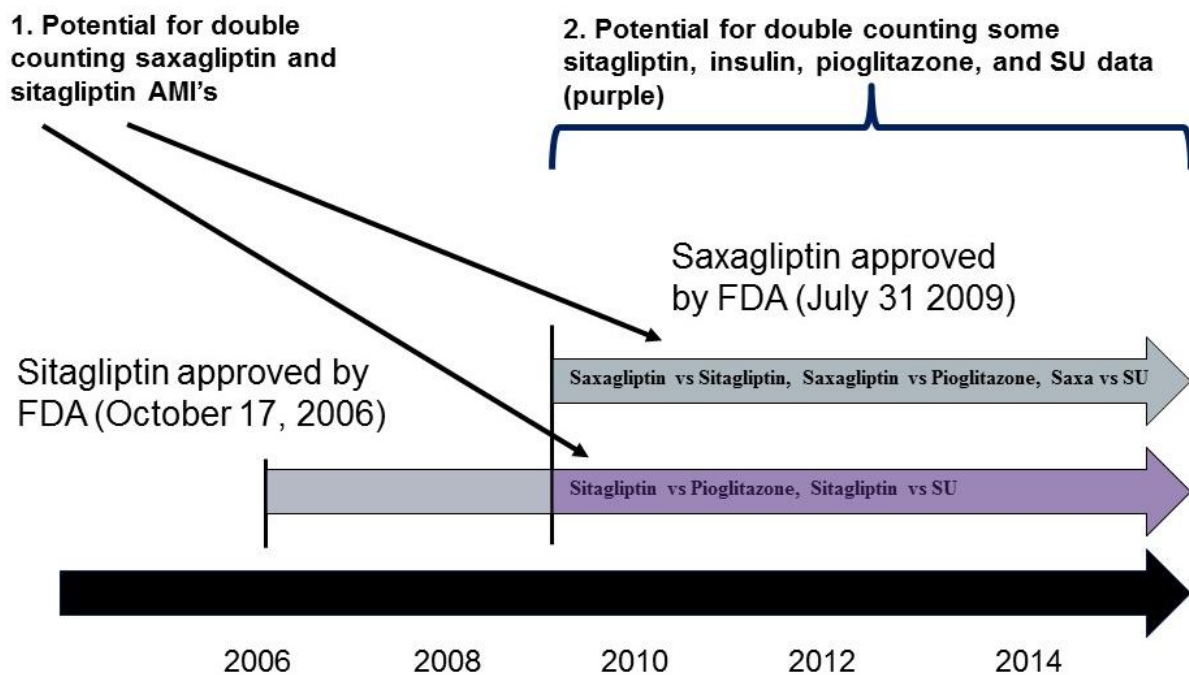
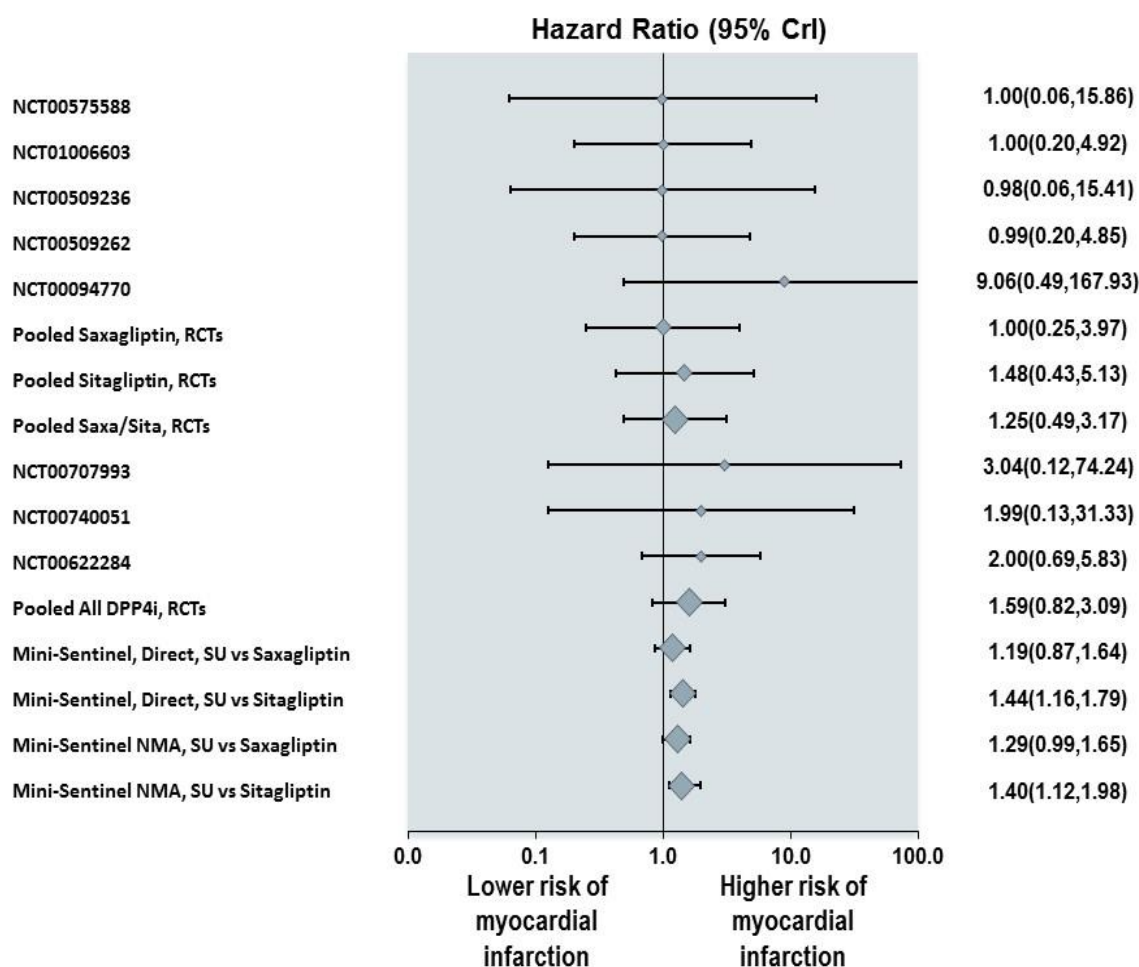


Figure 6: Comparison of data for sulfonylurea versus dipeptidyl peptidase-4 inhibitor comparisons derived using real-world data from distributed health data networks with data from randomized controlled trials.



DPP4-I = dipeptidyl peptidase 4 inhibitor; NCT= ClinicalTrials.gov ID; RCT= randomized controlled trial; SU- sulphonylurea

REFERENCES

1. Caldwell, D. M., Ades, a E. & Higgins, J. P. T. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. *BMJ* **331**, 897–900 (2005).
2. Dias, S., Sutton, A. J., Ades, a E. & Welton, N. J. Evidence synthesis for decision making 2: a generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials. *Med. Decis. Making* **33**, 607–17 (2013).
3. Ioannidis, J. P. a. Integration of evidence from multiple meta-analyses: a primer on umbrella reviews, treatment networks and multiple treatments meta-analyses. *CMAJ* **181**, 488–93 (2009).
4. Gibbons, R. D. *et al.* Post-approval drug safety surveillance. *Annu. Rev. Public Health* **31**, 419–37 (2010).
5. Singh, S. & Loke, Y. K. Drug safety assessment in clinical trials: methodological challenges and opportunities. *Trials* **13**, 138 (2012).
6. Vandenbroucke, J. & Psaty, B. Benefits and risks of drug treatments: how to combine the best evidence on benefits with the best data about adverse effects. *Jama* **300**, 2417–2419 (2008).
7. Schneeweiss, S. A basic study design for expedited safety signal evaluation based on electronic healthcare data. *Pharmacoepidemiol. Drug Saf.* 858–868 (2010). doi:10.1002/pds
8. Brown, J., Holmes, J., Shah, K. & Hall, K. Distributed health data networks: a practical and preferred approach to multi-institutional evaluations of comparative effectiveness, safety, and quality of care. *Med. Care* **48**, 45–51 (2010).
9. Behrman, R. E. *et al.* Developing the Sentinel System--a national resource for evidence development. *N. Engl. J. Med.* **364**, 498–9 (2011).
10. Mini-Sentinel Data Core. *Mini-Sentinel Distributed Database Summary Report - Year 4*. 4 (2014). at <http://www.mini-sentinel.org/data_activities/distributed_db_and_data/details.aspx?ID=162>
11. Suissa, S. *et al.* CNODES : the Canadian Network for Observational Drug Effect Studies. *Open Med.* **6**, 134–140 (2012).
12. Fireman, B., Toh, S. & Butler, M. A protocol for active surveillance of acute myocardial infarction in association with the use of a new antidiabetic pharmaceutical agent. ... *Drug Saf.* **21**, 282–290 (2012).

13. Monami, M., Ahrén, B., Dicembrini, I. & Mannucci, E. Dipeptidyl peptidase-4 inhibitors and cardiovascular risk: a meta-analysis of randomized clinical trials. *Diabetes. Obes. Metab.* **15**, 112–20 (2013).
14. Monami, M., Genovese, S. & Mannucci, E. Cardiovascular safety of sulfonylureas: a meta-analysis of randomized clinical trials. *Diabetes. Obes. Metab.* **15**, 938–53 (2013).
15. Dias, S., Sutton, A. J., Welton, N. J. & Ades, a E. Evidence synthesis for decision making 3: heterogeneity--subgroups, meta-regression, bias, and bias-adjustment. *Med. Decis. Making* **33**, 618–40 (2013).
16. Dias, S. *et al.* Evidence synthesis for decision making 4: inconsistency in networks of evidence based on randomized controlled trials. *Med. Decis. Making* **33**, 641–56 (2013).
17. Schmitz, S., Adams, R. & Walsh, C. Incorporating data from various trial designs into a mixed treatment comparison model. *Stat. Med.* (2013). doi:10.1002/sim.5764
18. Jansen, J. P. & Naci, H. Is network meta-analysis as valid as standard pairwise meta-analysis? It all depends on the distribution of effect modifiers. *BMC Med.* **11**, 159 (2013).
19. Vlaar, P. J. *et al.* Culprit vessel only versus multivessel and staged percutaneous coronary intervention for multivessel disease in patients presenting with ST-segment elevation myocardial infarction: a pairwise and network meta-analysis. *J. Am. Coll. Cardiol.* **58**, 692–703 (2011).
20. McIntosh, B. *et al.* Choice of therapy in patients with type 2 diabetes inadequately controlled with metformin and a sulphonylurea: a systematic review and mixed-treatment comparison meta-analysis. *Open Med.* **6**, e62–74 (2012).
21. McIntosh, B. *et al.* Second-line therapy in patients with type 2 diabetes inadequately controlled with metformin monotherapy: a systematic review and mixed-treatment comparison meta-analysis. *Open Med.* **5**, e35–48 (2011).
22. Rassen, J. A. *et al.* Matching by propensity score in cohort studies with three treatment groups. *Epidemiology* **24**, 401–9 (2013).
23. Rassen, J. A. *et al.* One-to-many propensity score matching in cohort studies. *Pharmacoepidemiol. Drug Saf.* **21 Suppl 2**, 69–80 (2012).

CHAPTER 8: MICROSOFT EXCEL-BASED TOOL FOR CONDUCTING NETWORK META-ANALYSIS

A Microsoft-Excel- based tool for running and critically appraising network meta-analyses – an overview and application of NetMetaXL

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CHAPTER 8: MICROSOFT EXCEL-BASED TOOL FOR CONDUCTING NETWORK META-ANALYSIS

A Microsoft-Excel- based tool for running and critically appraising network meta-analyses – an overview and application of NetMetaXL

SUMMARY:

In this chapter, we present an Excel-based Tool for running and critically appraising network meta-analyses. The application of NetMetaXL is demonstrated using data from a network meta-analysis published previously which compares combined resynchronization and implantable defibrillator therapy in left ventricular dysfunction.

LINKS:

This article was published in *Systematic Reviews* following peer review and can also be viewed on the journal's website at:

<http://www.systematicreviewsjournal.com/content/pdf/2046-4053-3-110.pdf>

A pdf of the final publication is presented in Appendix C

CONTRIBUTION:

I was responsible for writing the manuscript, with guidance from supervisors and other co-authors. I provided and validated the WinBUGS code underpinning the tool and Dr. Stephen Brown coded the tool in Visual Basic. I conducted all network meta-analyses, and generated all tables and figures related to findings from NetMetaXL in this manuscript. I also responded to all feedback on NetMetaXL that was provided during the peer review process with guidance from supervisors and other co-authors.

ABSTRACT

Background

The use of network meta-analysis has increased dramatically in recent years. WinBUGS, a freely available Bayesian software package, has been the most widely used software package to conduct network meta-analyses. However, the learning curve for WinBUGS can be daunting, especially for new users. Furthermore, critical appraisal of network meta-analyses conducted in WinBUGS can be challenging given its limited data manipulation capabilities and the fact that generation of graphical output from network meta-analyses often relies on different software packages than the analyses themselves.

Methods

We developed a freely available Microsoft-Excel-based tool called NetMetaXL, programmed in Visual Basic for Applications, which provides an interface for conducting a Bayesian network meta-analysis using WinBUGS from within Microsoft Excel. This tool allows the user to easily prepare and enter data, set model assumptions, and run the network meta-analysis, with results being automatically displayed in an Excel spreadsheet. It also contains macros that use NetMetaXL's interface to generate evidence network diagrams, forest plots, league tables of pairwise comparisons, probability plots (rankograms), and inconsistency plots within Microsoft Excel. All figures generated are publication quality, thereby increasing the efficiency of knowledge transfer and manuscript preparation.

Results

We demonstrate the application of NetMetaXL using data from a network meta-analysis published previously which compares combined resynchronization and implantable defibrillator therapy in left ventricular dysfunction. We replicate results from the previous publication while demonstrating result summaries generated by the software.

Conclusions

Use of the freely available NetMetaXL successfully demonstrated its ability to make running network meta-analyses more accessible to novice WinBUGS users by allowing analyses to be conducted entirely within Microsoft Excel. NetMetaXL also allows for more efficient and transparent critical appraisal of network meta-analyses, enhanced standardization of reporting, and integration with health economic evaluations which are frequently Excel-based.

BACKGROUND

Meta-analysis is a statistical method commonly used to combine summary estimates of treatment effects from a collection of studies to establish the benefits and harms of competing interventions. An important limitation of standard meta-analysis (i.e., pairwise meta-analysis) is that it compares only two treatments at a time [1]. However, many medical conditions exist for which there are a multitude of possible treatment alternatives. Accordingly, new meta-analytic methods have emerged which permit simultaneous comparison of multiple treatments. This new method is referred to as *network meta-analysis* (NMA) (other terms such as *mixed-treatment comparison meta-analysis* and *multiple treatments meta-analysis* have also been used) [1,2]. Not surprisingly, the increasing need to compare multiple treatments for medical conditions has been mirrored by the dramatic rise in the use of network meta-analysis in recent years [3,4].

Both Frequentist and Bayesian approaches for conducting network meta-analysis are feasible [1,5-7]. Among them, the latter has been the more commonly used framework, likely because the methods have evolved more quickly, because Bayesian methods provide greater flexibility to use more complex models and different outcome types, and because Bayesian methods are easily integrated into health economic evaluations. WinBUGS is a freely available software package available for Bayesian data analysis and has been the most widely used package to conduct network meta-analyses to date [3]. However, the learning curve for using WinBUGS to conduct network meta-analyses successfully can be daunting for new users, given the challenges of understanding WinBUGS code. WinBUGS also has limited data manipulation, data annotation, and graphical illustration capabilities. Given these challenges, the preparation of tables and figures to present insightful summaries of

findings from network meta-analyses often requires use of an additional software package [7], thereby adding time and an additional layer of complexity to complete reports. As a result, current approaches do not allow analysts to simply update and reanalyze models quickly and efficiently. Further, the variability in software used and the lack of standardization has led to inconsistency in the reporting of analyses to health technology assessment (HTA) organizations and journals, thereby complicating the review process. Given these challenges, more user-friendly software is needed to facilitate the ability to perform, consistently report, and critically appraise network meta-analyses for a broader group of researchers. More integrated and user-friendly software will dramatically improve the transparency and reproducibility of findings from network meta-analyses.

The objectives of this paper are to use an illustrative example to demonstrate how our Microsoft-Excel-based Network Meta-analysis Tool (NetMetaXL) can be used to simplify running and reporting network meta-analyses and to highlight how NetMetaXL can be used to facilitate consistent reporting and more efficient and transparent critical appraisal of network meta-analyses submitted to HTA organizations such as the Canadian Agency for Drugs and Technologies in Health (CADTH) and the National Institute for Health and Care Excellence (NICE), as well as to journals which publish network meta-analyses.

METHODS

The Illustrative example

Table 1 presents the illustrative dataset derived from a network meta-analysis evaluating combined resynchronization and implantable defibrillator therapy in left ventricular dysfunction [8]. The methods used to identify studies included in the network meta-analysis and to collect trial-level data have been described previously [8]. A total of 12 randomized

studies comparing 5 different treatments (medical resynchronization, cardiac resynchronization, implantable defibrillator, combined resynchronization and defibrillator, and amiodarone) were included in the review, encompassing a total of 1,616 deaths in 8,307 participants. The authors conducted a Bayesian random effects network meta-analysis to compare the overall risk of mortality among the different treatments.

Application of NetMetaXL using an illustrative example

This tool was designed to allow users to run network meta-analyses, as well as to appraise Bayesian network meta-analyses using WinBUGS via a more user-friendly Microsoft Excel interface. The current versions of NetMetaXL only allow the user to apply Bayesian network meta-analysis for binomial data and logistic regression models. This section describes how users can use this tool in the context of the illustrative example above. It is critical that users of NetMetaXL receive training on network meta-analysis. Users should be educated on key concepts related to network meta-analysis and how to interpret findings for decision-making purposes. Users are also encouraged to consult with a statistician when using this tool.

Step 1: Software installation

The application of NetMetaXL requires installation of Microsoft Excel 2007 or higher, as well as installation of the WinBUGS 1.4.3 package. NetMetaXL will work using Windows XP, Windows 7, or Windows 8. Before opening NetMetaXL, the user will install the WinBUGS 1.4.3 package and download and install the patch for WinBUGS 1.4.3 and the key for unrestricted use as described on the WinBUGS website. Detailed instructions on installing WinBUGS are available on the WinBUGS website. After the user has installed WinBUGS, the user can download the latest version of the NetMetaXL package from www.NetMetaXL.com. Any user can download the tool and administrator access is required.

This Excel-based tool is also part of the CADTH online repository of Microsoft-based tools for enhancing the application of HTAs: www.cadth.ca/en/resources/hta-excel-tools. NetMetaXL is programmed in Visual Basic for Applications within Excel and links to WinBUGS using Visual Basic. After NetMetaXL and WinBUGS have been downloaded and installed, the user will open NetMetaXL and go to the WinBUGS Setting tab visible in the menu bar at the top of the screen. Within this tab, under Program Settings, the user will indicate where the WinBUGS executable file that was downloaded is located on their computer's hard drive. For example, the user can click the file folder icon next to the WinBUGS Directory (cell D41) and then browse to specify the location of the WinBUGS Directory (e.g., C:\Program Files\WinBUGS14\).

Step 2: Setup of specifications for analysis

After NetMetaXL has been installed and is linked to WinBUGS, the user is ready to begin conducting or appraising network meta-analyses. The user should then open the file and save it using a study-specific name. Within NetMetaXL, the user will see a WinBUGS menu bar in the top right of Microsoft Excel. WinBUGS is a software for conducting Bayesian analysis using Markov chain Monte Carlo simulation [9]. A Bayesian analysis using WinBUGS requires two main ingredients: prior distributions for the unknown parameters and a likelihood function derived from a model that specifies the relation between the unknown parameters and the observed data [10,11]. A prior distribution of a parameter represents the uncertainty about the parameter before the current data are examined [10,12-16]. The prior chosen may be informative or ‘vague.’ The latter is thought to ‘let the data drive the analysis,’ but the use of a ‘vague’ prior should not be used unthinkingly especially when data is sparse because a vague prior may actually influence the analysis [10,12-16]. Multiplying

the prior and the likelihood function together leads to the posterior distribution of the parameter. The posterior distribution is used to carry out all inferences [10,12-16].

To run the Bayesian analysis using WinBUGS, a series of procedures are required, all of which are automated within NetMetaXL. In particular, the user must check that the model is properly specified, load the data, and select the number of chains (or samples) to specify the initial values for certain parameter estimates; set up monitors to store the sampled parameter values; run the simulation; check convergence for the parameter estimates; and then obtain a summary of the posterior distribution of the selected parameter estimates.

The user will also see a number of worksheets, each devoted to different aspects of preparing the data for Bayesian analysis and generating graphical summaries of the results after the analysis has been run. The majority of settings for the setup of specifications for analysis are located within the WinBUGS Settings worksheet. Within this worksheet, the user specifies analysis characteristics such as WinBUGS Settings (e.g., number of burn-in iterations for assessing convergence of parameter estimates); statistical settings such as which model parameters to capture (e.g., odds ratio, treatment rankings), whether the outcome being considered is 'bad' (e.g., dead at the end of the study) or 'good' (e.g., alive at the end of the study) from the patient's perspective, informative prior settings (NetMetaXL applies vague priors for log odds ratios but allows the user to use informative priors for between-study heterogeneity variances derived from based on a publication by Turner et al. [14] which is potentially useful when data is sparse), and initial values for parameter estimates (NetMetaXL selects these randomly from a uniform distribution within the ranges chosen for

log odds ratios and log odds) which should be checked in WinBUGS data sheet; and Program Settings (e.g., location to save files).

Step 3: Data input

After the user specifies the WinBUGS and statistical settings on the WinBUGS Settings worksheet, the dataset for analysis in NetMetaXL can next be entered. To input the data, the user selects the Data Input tab. A screenshot displaying the dataset is presented in Table 1. An additional file showing the screenshot with the dataset in NetMetaXL is also provided [see Additional file 1]. To begin inserting the data, the user must specify the name of each treatment under consideration in row 5; the tool has currently been designed to handle up to 15 interventions of interest and up to 50 studies. The choice of treatment 1, also known as the reference treatment, is an important consideration. Ideally, the user will select the treatment with the most studies as the reference treatment. After the user specifies the treatment names, the user inserts the number of observed events and total sample size for the intervention groups in each study beginning in row 7. In accordance with the most commonly used Bayesian implementation of network meta-analysis, users are able to input more than two treatment groups for a given study and the software will account for correlation between trial arms. As the user inputs the data for all studies and treatments, cells C2–C5 will update automatically to reflect properties of the evidence base under study in terms of the total number of included studies and patients in the treatment network. In the case of our illustrative example, once data input is complete, cells C2–C5 will indicate that the evidence base consists of 12 studies and 5 treatments and will also indicate that 8 of the included studies include medical therapy as one of their treatment arms (our chosen control treatment,

labeled as treatment 1 in our network). After the data is inserted, the user is ready to begin running network meta-analyses using NetMetaXL.

Step 4: Preparing the data for WinBUGS

There is a 'Convert Data' button within the menu bar. When the user selects this button, there will be a prompt asking: 'Correct for zero values?'. If the user selects, 'Yes,' NetMetaXL will adjust all zero cells using an adjusted continuity correction factor accounting for potential differences in sample size and centered around 0.5 [17]. If the user selects 'No,' zero cells will be included in the analysis and no adjustment is applied. An advantage of the Bayesian approach is that special precautions do not usually need to be taken in the case of the occasional trial with a zero cell count [18]. NetMetaXL allows users to run the analysis with zeroes when there are occasional zero cells and attempt to resolve the issue by adjusting otherwise, although in some cases the results will remain unstable even after adjusting [18]. The zero cell correction within NetMetaXL keeps all studies for analytic consistency (i.e., does not delete studies entered by the user) even those with multiple zero cells although these do not contribute to the relative effect estimation and can cause computational problems when networks are sparse. Because studies with zero cells remain, model fit statistics for these analyses should be interpreted with caution given they make certain model fit statistics artificially look better. The users of this tool should always consult with a statistician, but especially when dealing with zero cells. After the user selects either of these choices, NetMetaXL will convert the data provided into the appropriate format for analysis within WinBUGS. WinBUGS requires the data to be in a specific format and for the user to specify the initial values. The data after the conversion is reported within the

WinBUGS data tab. NetMetaXL will also perform this step automatically when pushing the ‘Run WinBUGS’ button.

RESULTS

There are key outputs to consider when interpreting a network meta-analysis. Notably, the user should carefully review the geometry of the evidence network, which provides information related to the number of studies performed comparing the different treatments, the numbers of patients who have been studied for each treatment, and so forth. After ensuring convergence has been reached and there is no relevant inconsistency in the evidence, one can use the output from the consistency model to draw conclusions about the relative effects of treatments [19]. This information is often displayed in tabular or graphical format such as a forest plot or league table. Alternatively, information of relative effects is sometimes converted to a probability a treatment is best, second best, and so on, or the ranking of each treatment. More recently, these two measures have been combined into a single measure called the surface under the cumulative ranking curve (SUCRA) [19], which is expressed as a percentage—the SUCRA would be 100% when a treatment is certain to be the best and 0% when a treatment is certain to be the worst. The outputs for these elements in NetMetaXL are described in steps 5–9 below.

Step 5: Visualizing the treatment network

After the user selects the WinBUGS tab from the menu bar in NetMetaXL, the user can generate a treatment network diagram by selecting the Generate Diagram button. After the user clicks this button, an evidence network will be generated (see Figure 1). As has become common practice in reports of network meta-analyses [7], the width of each edge in the evidence network is proportional to the number of randomized controlled trials comparing

each pair of treatments, and the size of each treatment node is proportional to the number of randomized participants (sample size). A tabular description of the evidence network is also provided within the Data Summary worksheet. The user has the capability to indicate the treatment names to be used on the network diagram in cells C25–C29. For example, instead of labeling the nodes simply as A–E as in Additional file 1 2, the user can input the treatment names for each node (or preferred abbreviations which are a preferable option when dealing with longer treatment names). After the labels are changed in cells C25–C29, the user can push the Generate Diagram button again from the WinBUGS tab in the toolbar, and the names in cells C25–C29 will appear within the network diagram. The nodes can also be moved, if desired, and the connections can automatically be redrawn by clicking the ReDraw Connections button. The user can copy the evidence network by holding control and selecting the nodes and connections and subsequently pasting the evidence network into other programs such as PowerPoint.

Step 6: Running network meta-analyses using NetMetaXL

To run network meta-analyses within NetMetaXL, the user selects the Run WinBUGS button within the menu bar. After selecting the Run WinBUGS button, NetMetaXL will open WinBUGS to run the network meta-analyses and will then close WinBUGS after transferring back to NetMetaXL the results for all the prespecified parameters of interest specified in the WinBUGS Settings tab during the setup of the analysis in WinBUGS Settings tab. These analysis functions and others are provided within the WinBUGS tab within the menu bar in the upper right of NetMetaXL. NetMetaXL generates commonly used graphical summaries of results including forest plots, league tables, and probability bar plots (or rankograms); a separate worksheet is devoted to each type of graphical output. To begin the analyses, the

user clicks the Run WinBUGS button from the WinBUGS tab in the menu bar of NetMetaXL once data have been appropriately formatted as outlined in step 3. After the user clicks this button, a dialog box will open where the user will select the different network meta-analyses to be conducted (Figure 2). For example, the user can run analyses using a fixed effects model, a random effects model using vague priors as outlined in NICE Evidence Synthesis Series [18], and/or a random effects model using informative variance priors [14]. For the random effects model using vague priors, we assume use the following prior: $sd \sim \text{dunif}(0,2)$. For the random effects model using informative variance priors, the user indicates the type of outcome under consideration as well as the type of treatment (e.g., placebo, active pharmacological treatment). NetMetaXL uses these selections and bases the informative variance priors on evidence on the extent of heterogeneity observed in previous meta-analyses, as described in Turner et al. [14] For all analyses, we assume vague priors on baselines [$\text{dnorm}(0,10000)$] and basic parameters [$\text{dnorm}(0,10000)$]. After the user selects the analyses to be conducted using the check boxes within the dialog box, the user then selects Run WinBUGS from within the dialog box; this will launch WinBUGS and will automatically run analyses and import results based on the various models selected back into NetMetaXL in fixed effects (FE) Results or random effects (RE) Results worksheets. The WinBUGS results are also saved as an *.odc file in the directory specified in the Program Settings (WinBUGS Setting tab). The WinBUGS code used for generating all the network meta-analyses is based on the NICE Decision Support Unit Series [5,18]. The WinBUGS model codes are stored within NetMetaXL on the worksheets titled FE model, RE Model, RE Inconsistency Model, and FE Inconsistency Model. The user also has the option to open

WinBUGS directly and examine the underlying WinBUGS code if need be using the Open WinBUGS button in the toolbar.

NetMetaXL captures all the WinBUGS output [see Additional file 2] and stores them in FE Results or RE Results worksheets. NetMetaXL will capture output results from WinBUGS for any parameters selected in the WinBUGS Settings tab (e.g., odds ratios). The user should refer to FE and RE model tabs to see the statistics behind the parameter calculations.

Step 7: Checking convergence in NetMetaXL

We fit three chains for the Markov chain Monte Carlo (MCMC) Bayesian network meta-analysis. The use of multiple chains is a useful way to check MCMC convergence. The user selects the initial values for each of these chains randomly from a uniform distribution. The user can select the bounds for the uniform distribution in the WinBUGS Settings worksheet. The user is encouraged to review the following paper [20] for additional detail on selecting initial values. Convergence is assessed in NetMetaXL using the Brooks-Gelman-Rubin method and by checking whether the Monte Carlo error is less than 5% of the sd of the effect estimates and between-study variance. These diagnostics are provided when the user runs the analysis. NetMetaXL will check whether the Monte Carlo error is less than 5% of the sd of the effect estimates and between-study variance and gives the user the option to view the Brooks-Gelman-Rubin plots from the WinBUGS output. The Brooks-Gelman-Rubin method compares within-chain and between-chain variances to calculate the potential scale reduction factor [21]. A potential scale reduction factor is presented in red in the figure, and a value close to one indicates when approximate convergence has been reached.

Step 8: Generating a graphical summary of findings from network meta-analysis

NetMetaXL captures all the WinBUGS output and then uses VBA macros to construct different graphical representations common to reports of network meta-analyses [19]. NetMetaXL is capable of generating forest plots and league tables to summarize all pairwise comparisons between the competing treatments, as well as probability bar plots (or rankograms). A forest plot generated by NetMetaXL for our illustrative example is presented in Figure 3. On the forest plot worksheet, the user can select the analyses they would like reported in the forest plot. For example, the user can present findings for only one model (e.g., fixed effects model) or can also choose to report findings using both the fixed and random effects models. The user can also select the spacing, marker size, and plot size in cells D7–D9 to maximize the quality of the figure. The forest plots then illustrate the median effect estimate for each pairwise comparison within the network meta-analysis for each model fit, along with corresponding 95% credible intervals.

In addition to generating forest plots, the user can also generate league tables within NetMetaXL to summarize all possible pairwise comparisons between the interventions. The summary league table for our illustrative example is shown in Figure 4. The league table arranges the presentation of summary estimates by ranking the treatments in order of most pronounced impact on the outcome under consideration, based on SUCRA [19]. SUCRA, the surface under the cumulative ranking [19], is a simple numerical summary of the probabilities. It is 100% when a treatment is certain to be the best and 0% when a treatment is certain to be the worst. SUCRA values enable the ranking of treatments overall for a particular outcome. For example, in our illustrative example, combined resynchronization and defibrillation is listed in the top left of the diagonal of the league table because it was

associated with the most favorable SUCRA for mortality reduction, while medical therapy is listed in the bottom right of the diagonal of the league table because it was associated with the least favorable results. For interpretation purposes, the results are read from top to bottom and left to right. For example, using the random effects model with vague priors (as was used in Lam and Owen [8]), combined resynchronization and defibrillation compared with cardiac synchronization is associated with an odds ratio of 0.84 (0.57–1.22), suggesting it is trending towards being better than cardiac synchronization in terms of mortality, whereas cardiac resynchronization versus medical therapy is associated with an odds ratio of 0.66 (0.50–0.89).

Probability bars (or rankograms) [19] are also generated and reported within NetMetaXL, which report the probability that each treatment is ranked first, second, and so on for a particular outcome. These rankograms are depicted as stacked vertical bar charts within NetMetaXL for all treatments. The user can also output line graphs for all treatments or generate bar charts or line graphs for individual treatments.

Step 9: Assessment of inconsistency

Assessment of inconsistency is crucial in the conduct of any network meta-analysis. Inconsistency can be thought of as a conflict between ‘direct’ and ‘indirect’ evidence [5]. Similar to heterogeneity, inconsistency is caused by imbalances in effect modifiers from study to study, specifically by an imbalance in the distribution of effect modifiers in the direct and indirect evidence [5]. NetMetaXL allows users to assess inconsistency by comparing the deviance residuals and DIC statistics in fitted consistency and inconsistency models [5]. These are reported in a table in the Inconsistency results worksheet. We refer the readers to the NICE Technical Support Documents (TSD) series for the methods employed

[5]. NetMetaXL also plots the posterior mean deviance of the individual data points in the inconsistency model against their posterior mean deviance in the consistency model to identify any loops in the treatment network where inconsistency is present (Figure 5) [5]. NetMetaXL also allows the user to select the points on the inconsistency plot and see which study and treatment is represented by that point. For example, by double-clicking on the point in Figure 5 within NetMetaXL, we see that this point is from the cardiac resynchronization arm of the COMPANION study. This feature will be particularly useful for network meta-analyses where there are a number of points in the bottom right of the inconsistency plot, indicating potential inconsistency [5].

DISCUSSION

Summary of main findings

We have shown how use of NetMetaXL can enhance the ability of users to run WinBUGS-based network meta-analyses entirely within Microsoft Excel. We have replicated findings from a network meta-analysis [8] published in the BMJ on combined resynchronization and implantable defibrillator therapy in left ventricular dysfunction using NetMetaXL. The approach and steps used in this illustrative example can be applied to running other network meta-analyses of dichotomous outcomes entirely through the Microsoft-Excel-based NetMetaXL tool, without requiring the user to directly use the WinBUGS software. In the future, we plan on developing similar tools for other outcome measures.

There are several software packages available to run network meta-analyses. The majority of network meta-analyses conducted to date have used WinBUGS [3], although new routines have been developed which allow network meta-analyses to be conducted with STATA [6,7,22], R [23], and SAS [24]. These approaches to conducting network meta-analyses share

a similar feature—they require programming knowledge of the software package being used. This is not a problem for statisticians who use these packages regularly or reviewers who are well versed in network meta-analyses and these software. However, this is a challenge for non-statisticians or reviewers who are not familiar with the packages but would like to run or critically appraise a network meta-analysis. Some of these packages (e.g., WinBUGS) have poor data manipulation functionality, data annotation, and graphical illustration capabilities, thereby requiring results to be transferred between multiple software packages, adding an additional layer of complexity.

This has led to the development of more user-friendly and integrated packages such as the Aggregate Data Drug Information System (ADDIS) [25]. Similar to our NetMetaXL tool, ADDIS [25] also provides users with a more user-friendly software package to run network meta-analyses without directly using WinBUGS (or JAGS or OpenBUGS) code. However, the current version of ADDIS (ADDIS 1) uses a stand-alone software package. Using Microsoft Excel offers some advantages over a stand-alone package like ADDIS such as the following: 1) it allows users to use a software that they are familiar with, 2) there is more potential for others to develop add-ons to the Excel-based tool (versus stand-alone package) given the wide user base, and 3) it allows the data and results to be more easily integrated with decision analytic models and health economic evaluations which are frequently Excel-based compared to stand-alone packages. Indeed, this was noted in a recent publication [26] where they developed an Excel-based tool to perform HTAs entirely within Microsoft Excel. This Excel-based tool developed by Bujkiewicz et al. [26] called the transparent interactive decision interrogator (TIDI) also integrated with WinBUGS but used R, another software with a steep learning curve for non-statisticians. Although the example in TIDI was not

specific to network meta-analysis, TIDI [26] could also be used for conducting and critically appraising network meta-analyses as well. Despite the advantages of using Excel, there are also disadvantages. Excel is a free-form tool and accordingly there are opportunities for both user and programmer error. Users should double- and triple-check data inserted into NetMetaXL. To reduce the risk of programmer error, we used standard WinBUGS code provided in the NICE TSD series and had an independent statistician review the WinBUGS coding.

Application of NetMetaXL

Network meta-analysis is increasingly being used to provide estimates of effect for treatments that may not have been compared directly in clinical trials. NetMetaXL represents a step forward in improving the ability of novice users to run network meta-analyses. We have illustrated this application for running network meta-analyses in NetMetaXL using the combined resynchronization and implantable defibrillator therapy illustrative example. Another useful application of NetMetaXL would be related to critical appraisal of network meta-analyses by HTA organizations such as CADTH or NICE, or network meta-analyses submitted to journals. Inclusion of a NetMetaXL file, along with a technical report or publication, would undoubtedly facilitate more efficient and transparent critical appraisal of network meta-analyses. In addition, it would provide some standardization to the format of the analysis and graphical reporting.

HTA organizations and major medical journals should encourage authors to submit the data for their systematic reviews and network meta-analyses using NetMetaXL or a similar software package. Currently, the data used in HTAs or published network meta-analyses is often not adequately reported, presented in a wide range of styles, or often embedded in

images such as forest plots, making it challenging to extract data quickly, replicate findings, and critically appraise the study. The use of data repositories such as the Systematic Review Data Repository [27] and the Dryad Digital Repository has improved accessibility of data. However, these repositories only require that the data and code are uploaded to the repository and are often made available for use in less user-friendly packages such as R, STATA, or SAS. These repositories do not require that data are formally integrated with the analysis. Accordingly, critical appraisal of network meta-analyses, especially for non-statisticians, is still a challenge even when data is submitted to these repositories because users are still often left without the tools to quickly validate the analyses. By contrast, NetMetaXL will allow users to quickly validate the submitted analysis and test robustness of results to excluding certain studies, use of informative/non-informative priors, and choice of fixed/random effects models.

Some organizations in the healthcare sector have recognized the limitation of not providing the unified data and model on which an analysis is based. Indeed, HTA organizations often require manufacturers of drugs and devices to provide a user-friendly health economic model, in specified software, in addition to a technical report to facilitate critical appraisal of their product; however, this is not the standard for network meta-analyses submitted to HTA organizations. These health economic models are often Microsoft Excel based and give reviewers much more information than is provided in a 100-page technical report, let alone a 2,700–4,000-word publication. Given that type of easy access to and control of the original authors' data, model, and analysis, reviewers at HTA organizations are able to run additional analyses to test model uncertainty and alternative assumptions. The impact that these Microsoft-Excel-based models have had on critical appraisal of manufacturers' health

economic models is evident by examining the public summary documents from HTA organizations such as CADTH and NICE. It is not uncommon for recommendations from HTA bodies to report that reanalyses conducted by their staff found the cost-effectiveness estimates were less favorable than those submitted by the manufacturer. The same impact could potentially be seen if this increased level of transparency was applied to network meta-analyses.

Limitations of NetMetaXL

There are a number of limitations with NetMetaXL to note. Currently, this version of NetMetaXL only allows users to consider a maximum of 15 treatment options and 50 studies. This will prevent its application to more complex networks with multiple dosing strategies, complex interventions, or well-established disease areas where there are more than 15 treatment options. The current version of NetMetaXL is also only applicable for dichotomous outcomes. However, we will develop similar tools for other outcome types (e.g., continuous), will continue to update and refine the Microsoft-Excel-based tool, and will make new versions freely available online, including additional capabilities to adjust for heterogeneity including meta-regression analysis and inclusion of more sophisticated methods for assessing inconsistency. All versions of NetMetaXL will be housed on www.NetMetaXL.com. This tool is the first in a series of Excel-based tools being developed with support from CADTH. These Excel-based tools are being developed to enhance the application of HTAs in Canada and abroad. There will also be a link to NetMetaXL on the PRISMA website to enhance uptake and improve transparency of network meta-analyses in published medical journals.

With availability of user-friendly software such as NetMetaXL, concerns arise about network meta-analysis being undertaken and implemented inappropriately by novice users. It is critical that users of NetMetaXL receive training on network meta-analysis. Users should be educated on key concepts related to network meta-analysis such as heterogeneity and inconsistency and how to interpret findings for decision-making purposes. Users are also encouraged to consult with a statistician when using this tool.

Another disadvantage of NetMetaXL is that Microsoft Excel keeps the data locally (unless integrated with the cloud-based Microsoft 360 or other cloud systems) and does not foster sharing of information/data. This may be advantageous to drug or device manufacturers when submitting confidential data and network meta-analyses to HTA organizations such as CADTH and NICE. However, such an environment is not good for the society as a whole. Rather than keeping data in silos, there is a need to foster a research environment where data are shared and can be dynamically updated by multiple collaborators to improve research productivity. The earlier-mentioned ADDIS software [25] is in the process of launching a web-based platform (ADDIS 2) where researchers can collaborate to perform systematic reviews, data extraction, evidence synthesis, and decision analysis. Undoubtedly, such an integrated system should improve the efficiency, transparency, and critical appraisal of systematic reviews and network meta-analyses dramatically by making data more accessible to researchers and collaboration more seamless. As a result, we are strong ambassadors of the research that ADDIS [25] is striving towards. However, until use of such a system becomes widespread and readily available, NetMetaXL will serve as a step in the right direction towards making the conduct of network meta-analyses more accessible to non-statisticians and facilitating more efficient and transparent critical appraisal of network meta-

analyses, standardization in reporting, and more seamless integration with health economic evaluation.

CONCLUSIONS

We have demonstrated the application of a freely available Microsoft-Excel-based tool—NetMetaXL—using an example of a published network meta-analysis. NetMetaXL can make running and reporting network meta-analyses more accessible to novice users, as all aspects of data entry, analysis, and reporting are conducted entirely within Excel and require no specialized programming knowledge. The application of this Microsoft-Excel-based tool could also facilitate more efficient and transparent critical appraisal of network meta-analyses submitted to HTA organizations such as CADTH or NICE, or journals which publish network meta-analyses. The use of this tool may also help standardize reporting and enhance integration with health economic evaluations.

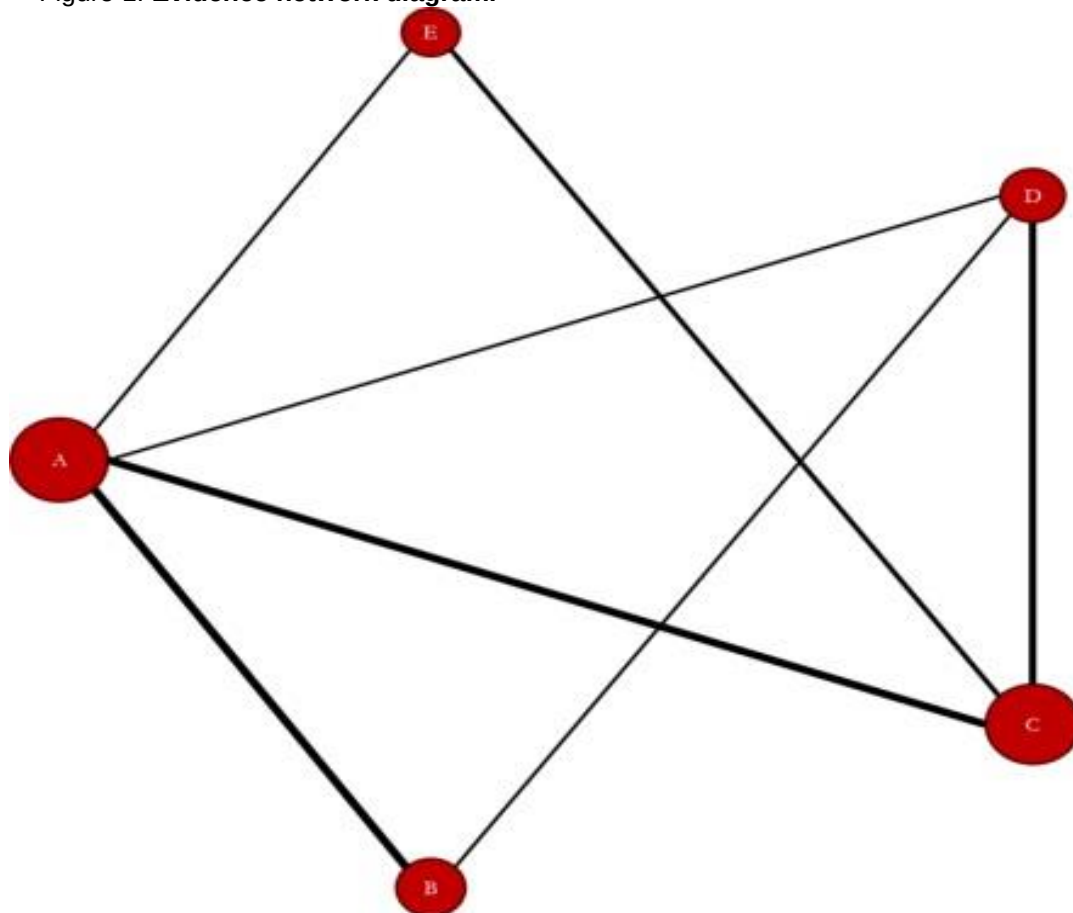
TABLES AND FIGURES

Table 1 Dataset used for illustrative example

Study number	Study name	Medical		Cardiac resynchronization		Implantable defibrillator		Combined resynchronization and defibrillator		Amiodarone	
		Number of events	Number of patients	Number of events	Number of patients	Number of events	Number of patients	Number of events	Number of patients	Number of events	Number of patients
1	CARE_HF-ext	154	404	101	409						
2	COMPANION	77	308	131	617			105	595		
3	MIRACLE	16	225	12	228						
4	MUSTIC-SR	0	29	1	29						
5	SCD-HeFT	244	847			182	829			240	845
6	MADIT-II	97	490			105	742				
7	DEFINITE	40	229			28	229				
8	CAT	17	54			13	50				
9	MIRACLE-ICD-I					5	182	4	187		
10	MIRACLE-ICD-II					2	101	2	85		
11	CONTAK-CD					16	245	11	245		
12	AMIOVIRT					6	51			7	52

The data is derived from Lam and Owen [8].

Figure 1. **Evidence network diagram.**



A medical therapy, B cardiac resynchronization, C implantable defibrillator, D combined resynchronization and defibrillator, E amiodarone.

Figure 2 Analysis dialog box from NetMetaXL

Select Analyses to Run

☐ Fixed Effects

☐ Random Effects (Vague Prior)

☐ Random Effects (Informative Prior)

Intervention Type: Pharmacological vs Control/Placebo
Pharmacological vs Pharmacological
Non-Pharmacological (Any)

Outcome Type: All Cause Mortality
Semi-Objective
Subjective

☐ Inconsistency Fixed Effects

☐ Inconsistency Random Effects

Random Effects: Vague
Informative

Run WinBUGS

Figure 3 Forest plot from NetMetaXL

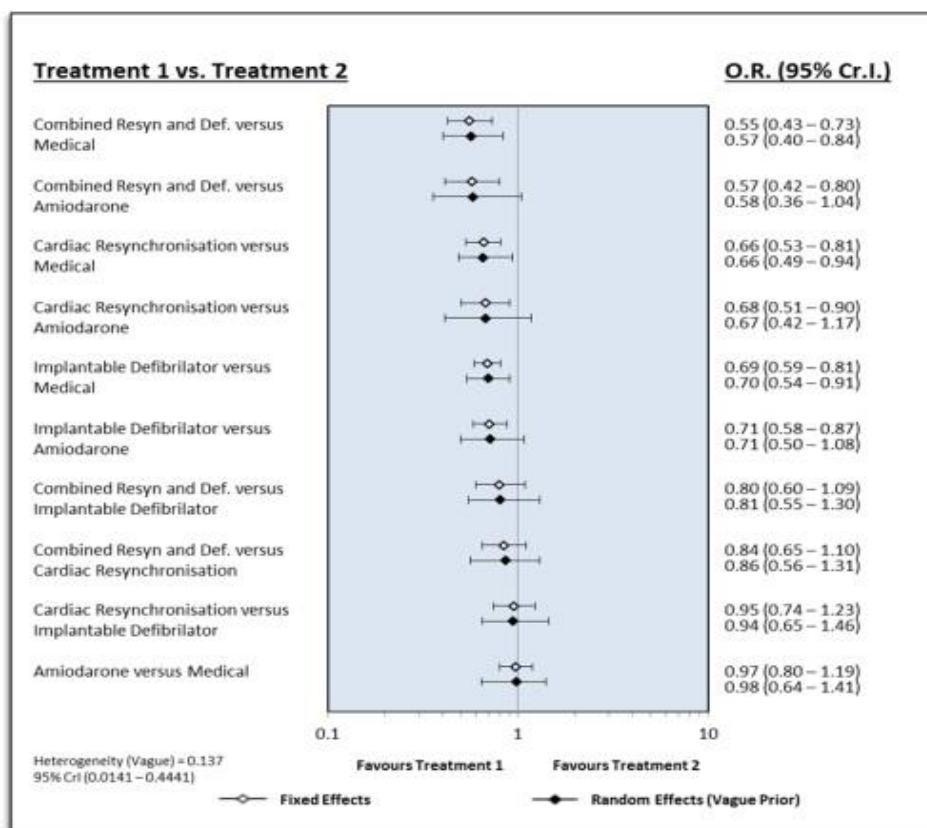
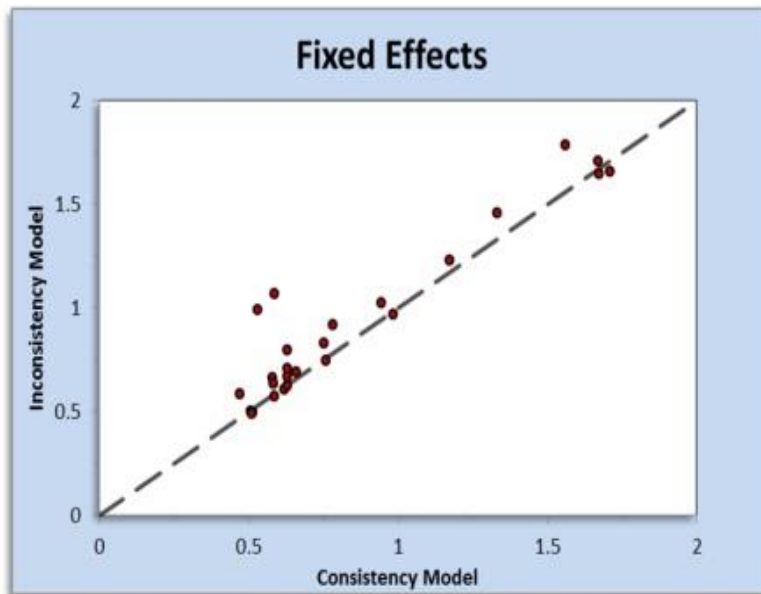


Figure 4 League table from NetMetaXL

Combined Resyn and Def.				
0.84 (0.65 – 1.10)	Cardiac Resynchronization			
0.80 (0.60 – 1.09)	0.95 (0.74 – 1.23)	Implantable Defibrillator		
0.57 (0.42 – 0.80)	0.68 (0.51 – 0.90)	0.71 (0.58 – 0.87)	Amiodarone	
0.55 (0.43 – 0.73)	0.66 (0.53 – 0.81)	0.69 (0.59 – 0.81)	0.97 (0.80 – 1.19)	Medical

Figure 5 Inconsistency plot from NetMetaXL



REFERENCES

1. Caldwell DM, Ades AE, Higgins PT: **Simultaneous comparison of multiple treatments: combining direct and indirect evidence.** *BMJ* 2005, **331**:897–900.
2. Jansen JP, Crawford B, Bergman G, Stam W: **Bayesian meta-analysis of multiple treatment comparisons: an introduction to mixed treatment comparisons.** *Value Health* 2008, **11**:956–964.
3. Nikolakopoulou A, Chaimani A, Veroniki AA, Vasiliadis HS, Schmid CH, Salanti G: **Characteristics of networks of interventions: a description of a database of 186 published.** *Networks* 2014, **9**:1–10.
4. Lee AW: **Review of mixed treatment comparisons in published systematic reviews shows marked increase since 2009.** *J Clin Epidemiol* 2014, **67**:138–143.
5. Dias S, Welton NJ, Sutton AJ, Caldwell DM, Lu G, Ades AE: **Evidence synthesis for decision making 4: inconsistency in networks of evidence based on randomized controlled trials.** *Med Decis Making* 2013, **33**:641–656.
6. Higgins JPT, Jackson D, Barrett JK, Lu G, Ades AE, White IR: **Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies.** *Res Synth Meth* 2012, **3**:98–110.
7. Chaimani A, Higgins JPT, Mavridis D, Spyridonos P, Salanti G: **Graphical tools for network meta-analysis in STATA.** *PLoS One* 2013, **8**:e76654.
8. Lam SKH, Owen A: **Combined resynchronisation and implantable defibrillator therapy in left ventricular dysfunction: Bayesian network meta-analysis of randomised controlled trials.** *BMJ* 2007, **335**:925.
9. Spiegelhalter D, Thomas A, Best N: **WinBUGS user manual.** *MRC Biostat Unit* 2004, **2**. January.
10. Spiegelhalter DJ, Abrams KR, Myles JP: *Bayesian Approaches to Clinical Trials and Health-Care Evaluation.* 1st edition: Wiley; 2004:408.
11. Sutton AJ, Abrams KR: **Bayesian methods in meta-analysis and evidence synthesis.** *Stat Methods Med Res* 2001, **10**:277–303.
12. Lambert P, Sutton A: **How vague is vague? A simulation study of the impact of the use of vague prior distributions in MCMC using WinBUGS.** *Stat ...* 2005, **24**:2401–2428.
13. Gelman A: **Prior distributions for variance parameters in hierarchical models.** In. 2006:515–533.

14. Turner RM, Davey J, Clarke MJ, Thompson SG, Higgins JP: **Predicting the extent of heterogeneity in meta-analysis, using empirical data from the Cochrane Database of Systematic Reviews.** *Int J Epidemiol* 2012, **41**:818–827.
15. Thorlund K, Thabane L, Mills EJ: **Modelling heterogeneity variances in multiple treatment comparison meta-analysis—are informative priors the better solution?** *BMC Med Res Methodol* 2013, **13**:1.
16. Dias S, Welton NJ, Sutton AJ, Ades A: *NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials.* 2011:1–96.
17. Sweeting MJ, Sutton AJ, Lambert PC: **What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data.** *Stat Med* 2004, **23**:1351–1375.
18. Dias S, Sutton AJ, Ades AE, Welton NJ: **Evidence synthesis for decision making 2: a generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials.** *Med Decis Making* 2013, **33**:607–617.
19. Salanti G, Ades A, Ioannidis J: **Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial.** *J Clin Epidemiol* 2011, **64**:163–171.
20. Van Valkenhoef G, Lu G, de Brock B, Hillege H, Ades AE, Welton NJ: **Automating network meta-analysis.** *Res Synth Meth* 2012, **3**:285–299.
21. Brooks S, Gelman A: **General methods for monitoring convergence of iterative simulations.** *J Comput Graph Stat* 1998, **7**:434–455.
22. White IR, Barrett JK, Jackson D, Higgins JPT: **Consistency and inconsistency in network meta-analysis: model estimation using multivariate meta-regression.** *Res Synth Meth* 2012, **3**:111–125.
23. Rücker G: **Network meta-analysis, electrical networks and graph theory.** *Res Synth Meth* 2012, **3**:312–324.
24. Jones B, Roger J, Lane PW, Lawton A, Fletcher C, Cappelleri JC, Tate H, Moneuse P: **Statistical approaches for conducting network meta-analysis in drug development.** *Pharm Stat* 2011, **10**:523–531.
25. Van Valkenhoef G, Tervonen T, Zwinkels T, de Brock B, Hillege H: **ADDIS: A decision support system for evidence-based medicine.** *Decis Support Syst* 2013, **55**:459–475.
26. Bujkiewicz S, Jones HE, Lai MCW, Cooper NJ, Hawkins N, Squires H, Abrams KR, Spiegelhalter DJ, Sutton AJ: **Development of a transparent interactive decision**

interrogator to facilitate the decision-making process in health care. *Value Health* 2011, **14**:768–776.

27. Ip S, Hadar N, Keefe S, Parkin C, Iovin R, Balk EM, Lau J: **A Web-based archive of systematic review data.** *Syst Rev* 2012, **1**:15.

CHAPTER 9: DISCUSSION AND CONCLUSION

Network meta-analysis is increasingly used to support regulatory and reimbursement decisions, both in Canada and in other countries around the world. In this thesis, I have conducted applied research to address real world problems for decision makers, and simultaneously explored several key methodological issues related to conducting network meta-analysis. As noted earlier, many research questions in my thesis were undertaken to directly support decision making within provincial and national organizations such as CADTH,³³ the Ontario Drug Policy Research Network,⁵⁷ and the Food and Drug Administration. However, we also addressed several methodological aspects throughout my thesis while addressing these real world problems.

Summary of Main Clinical Findings

As noted above, several Chapters were used to support decision making, notably Chapters 2, 4, 5, 6A, and 7. For these Chapters, we conducted a network meta-analysis related to a particular decision problem. In Chapter 2, the comparative efficacy and safety of antithrombotic treatments for non-valvular atrial fibrillation and among sub-populations was examined. We found that new oral anticoagulants were associated with modest reductions in the absolute risk of stroke and major bleeding compared with standard adjusted dose VKA. In Chapter 4, we conducted a network meta-analysis comparing triptans for acute treatment of migraine. We found that triptans are effective for migraine relief. In particular, standard dose triptans are associated with better outcomes than ergots, and most triptans are associated with equal or better outcomes compared with NSAIDs, ASA, and acetaminophen. We also found that use of triptans in combination with ASA or acetaminophen, or using alternative modes of administration such as injectables, may be

associated with slightly better outcomes than standard dose triptan tablets. In Chapter 5, we conducted a network meta-analysis of a rare event – risk of serious infection with biologics in treating patients with rheumatoid arthritis. Multiple evidence structures were considered initially. However, given the limited data available on individual treatments, a class level network was applied. This is the largest network meta-analysis investigating risk of serious infection among biologics in rheumatoid arthritis using rigorous network meta-analysis methods. We found that standard-dose and, high-dose and combination biologics (with/without traditional DMARDs) are associated with an increase in serious infections compared to traditional DMARDs in RA, while low-dose biologics are not.

In Chapter 6, we conducted a network meta-analysis summarizing and comparing the clinical outcomes and safety outcomes of eight anticoagulation options for treatment of acute venous thromboembolism. There were no statistically significant differences for efficacy and safety among the treatment strategies when compared with LMWH/VKA. Findings suggest that UFH/VKA may be the least effective strategy and that rivaroxaban and apixaban may be associated with the lowest risk for bleeding. Finally, in Chapter 7B, a network meta-analysis incorporating non-randomized studies was conducted exploring the risk of acute myocardial infarction in association with use of anti-diabetic agents using data from the Mini-Sentinel Distributed Health Data Database (MSDD). We found that sulfonylureas were associated with an increased risk of acute myocardial infarction compared with sitagliptin, saxagliptin and pioglitazone.

By focusing on timely and relevant clinical issues, we were able to generate impactful

research. Indeed, Chapter 2 of my thesis formed the basis of a CADTH Therapeutic Review which supported two recommendations (Apixaban and Rivaroxaban) by the Common Drug Review; Chapter 5 supported a listing recommendation by the Ontario Drug Policy Research Network; and Chapter 7 will be used to support a regulatory review of the safety of saxagliptin currently being undertaken by the Food and Drug Administration. Although other Chapters have not directly support decision making, it is likely they will be subsequently used to support policy or proactive decisions or advance methods, particularly Chapters 4 and 6 which were published in top tier general medical journals such as *JAMA* and *Lancet*. Indeed, some of these Chapters have already been downloaded or cited a number of times. A summary of uptake of Chapters in this thesis are provided in Table 2.

Summary of Main Methodological Findings

As noted previously, my thesis was able to simultaneously explore approaches to address several key methodological issues in network meta-analysis, in addition to supporting healthcare decision making. In Chapter 2, we focused on incorporating findings from FDA Public Summary Documents. Indeed, the analysis was not restricted traditional systematic review methods which largely consider published randomized controlled trials but also included FDA Public Summary Documents. In doing so, information not available in published papers was obtained. Indeed, sub-group data for rivaroxaban on the intention-to-treat population was now available. This allowed us to use standard methods across comparisons in our network meta-analysis. Future network meta-analyses may consider using FDA Public Summary documents to obtain additional information if they run into similar issues where published studies report alternate methods, but more detailed information is available in FDA Public Summary Documents.

In Chapter 3, a rapid network meta-analysis using only data reported in ClinicalTrials.gov was reported. The opportunities and pitfalls of using rapid network meta-analysis of using ClinicalTrials.gov was investigated by replicating Chapter 2 of my thesis but only using data from ClinicalTrials.gov. Considerable time was saved by not conducting a primary systematic review of primary studies. It took approximately a week to identify studies and extract data from ClinicalTrials.gov compared to a several months for conducting a systematic review of primary studies. However, data from older studies was not captured which were conducted before the ClinicalTrials.gov database was introduced in 2008. Future studies are needed investigating situations where application of ClinicalTrials.gov versus a systematic review of primary studies is most appropriate. The use of ClinicalTrials.gov may be particularly advantageous when timelines are really tight and when all treatments included in the evidence network were introduced within the past few years (i.e., post 2008).

In Chapter 4, a network meta-analysis of a complex network was conducted – triptans for acute treatment of migraine. Presenting information from networks where there are a large number of treatments is challenging, which was the case for the triptans network. Indeed, for the 2 hour relief analysis, there were 45 different treatments considered, which would require a league table which could report data on 990 comparisons. Presenting such a massive amount of data is challenging within a publication or large technical report. To support decision making, data is summarized using an approach not commonly employed for network meta-analysis. Rather than presenting relative effect measures for each pair-

wise comparison, the percentage of patients who achieved relief within 2 hours for the key treatments is presented. This allowed us to minimize the amount of comparative data but at the same time gave us space to report data for multiple outcomes in one table. Further, it allowed the discussion to focus on absolute effects which is often better suited for decision making.

In Chapter 5, a network meta-analysis of a rare outcome was conducted investigating the risk of serious infection among people treated with biologics. For this analysis, a network which included multiple doses of biologics and combination therapies was constructed, as well as the new oral biologic tofacitinib. Some of the connections in the network were comprised of few events due to the rarity of the outcome. Several analyses were conducted to account for zero cells in the network, although these analyses did not have a substantial impact on our findings. Future research in the area of zero events in nodes is needed, especially for networks which examine treatments at the drug level versus class-level where there is likely to be a larger number of connections with zero events. For our analysis, we merged biologics into one node, which avoided some of the potential issues with zero or few events among individual treatments.

In Chapter 6, a network meta-analysis comparing the benefits and harms of treatments for acute venous thromboembolism was conducted, as well as a subsequent benefit-harm assessment. Findings from the initial network meta-analysis were published in *JAMA*. In the *JAMA* paper, findings using standard approaches in network meta-analysis were reported – tables, forest plots, evidence networks, etc. VTE and major bleeding outcomes were

reported separately and not integrated in a formal way. In Part B of Chapter 6, various benefit-harm assessment methodologies were investigated to integrate VTE and major bleeding findings derived from the network meta-analysis. We integrated the findings using icon arrays, as scatterplots. These approaches allow the reader to view findings from both benefits and harms simultaneously. We only considered one benefit and harm for our analysis – future studies are needed investigating how to convey information succinctly for multiple benefits and harms.

In Chapter 7, findings from a network meta-analysis including non-randomized studies was reported. Before implementing the analysis, a methods paper was submitted to *BMJ Open* describing the challenges and pitfalls of conducting such an analysis, with a particular emphasis on using data from distributed health data networks. A network meta-analysis investigating the risk of acute myocardial infarction for saxagliptin was subsequently conducted which compared with use of anti-diabetic agents. For this analysis, data from the Mini-Sentinel distributed health data network was used which includes data from 18 data partners in the United States and over 150 million people.⁵⁸ To the best of our knowledge, this is the first network meta-analysis focusing solely on using data from newly formed distributed health data networks. The use of observational data from distributed health data networks may be more desirable than including observational studies identified in a systematic review given these networks have large patient populations; use common data models or protocols; and typically use more rigorous methodologies to control for confounding. Nonetheless, they are not without their own unique challenges, notably they do not account for unknown confounders, potential for double counting events within data

partners, and use of pair-wise comparisons. The use of data from distributed health data networks will undoubtedly increase and future research is needed in this area.

Tools to support future network meta-analyses

In addition to the core chapters of my thesis which apply network meta-analysis to support either a regulatory or reimbursement decision, I developed an Excel-based tool to help novice users conduct and critically appraise network meta-analyses more easily. This tool was developed in collaboration with a programmer/consultant who attended one of our network meta-analysis short courses. I subsequently drafted a paper describing how to use this tool, which was published in *Systematic Reviews* in late September 2014.⁵⁹ The tool is available for download on the CADTH website: <http://www.cadth.ca/en/resources/hta-excel-tools> . It has been downloaded over 600 times since September and the article has been assessed almost 5,000 times. The tool is a first in a series of Microsoft-Excel based tools that CADTH will be developing in 2014/15 to support health technology assessments. Each tool will consist of an Excel-based tool, a user guide and/or publication, and YouTube video to enhance use.

Advantages and disadvantages of addressing real world decision making while simultaneously addressing a methodological issue

As described throughout this thesis, the information used in this thesis was used to support healthcare decision making. In light of limited research dollars, it is important to balance methodological research and applied research which can be used to support decision making. Rather than dedicating each chapter to addressing one methodological issue in significant detail, several applied research problems were addressed while addressing an

interesting methodological issue at the same time. Many theses focus on addressing one or the other. In doing so, PhD students may become well versed in a particular methodological area but not develop a broad skill set that can be applied beyond academia. By contrast, in addition to gaining experience addressing problems for healthcare decision makers, the structure of my thesis enabled me to become well versed in a variety of clinical areas ranging from atrial fibrillation to migraines, and also develop applied methods expertise that can be broadly applied within organizations in Canada such as government, health technology assessment bodies, academia, consultancies, or the pharmaceutical industry.

For this thesis, I collaborated with a large number of groups in Ottawa and beyond. I interacted and fostered relationships with world class researchers beyond my PhD program. By collaborating with individuals and groups who have already conducted a systematic review and extracted relevant data, I was able to save valuable time and resources and focus on the conducting network meta-analysis as opposed to data extraction. Indeed, two chapters of my thesis were published in *JAMA* and *Lancet*. Had I opted to conduct my own primary systematic review, data extraction and network meta-analysis as part of my PhD program, it seems unlikely that the chapters would have been published in top tier journals given others would have likely published their findings first. Indeed, papers on the same topics have been published since our paper was published.⁶⁰ The same applies for the paper related to the network meta-analysis Excel-based tool. By collaborating with the programmer/consultant, I was able to focus on ensuring the network meta-analysis code underpinning the tool was appropriate and drafting the paper, as opposed to learning Visual Basic. This allowed the paper to get published quickly and

into the hands of users. Indeed, the paper has been downloaded almost 5000 times since September 2014 and given the ‘*Highly Assessed*’ designation.

Despite these advantages, a main disadvantage of this approach was that we were not able to address many methodological issues in sufficient detail in my PhD. Time that could have been dedicated to address a methodological issue in detail was devoted to supporting decision making in real time. Similarly, the discussion of methodological aspects was limited by the space requirements in clinical journals that were often targeted.

Nonetheless, we attempted to include this methodological information within the supplemental appendices of these Chapters and allude to the main issues in the discussion of each chapter. Future research and publications dedicated to these methodological issues are needed, particularly for the methodological aspects identified within the clinical chapters in this thesis.

Conclusion

In summary, my thesis investigated key methodological research related to network meta-analysis whilst simultaneously provided pragmatic research to support regulatory and reimbursement decision making. By interacting closely with decision makers, I was able to deliver timely and impactful research to support healthcare decision making. It is my hope that this thesis and the approaches used within it will be disseminated to enhance research capacity in conducting network meta-analysis in Canada and abroad.

Table 2 – Impact of Chapter from Thesis

Chapter	Impact
<u>Chapter 2: Network meta-analysis involving sub-group data</u> Cameron C, Coyle D, Richter T, Kelly S, Gauthier K, Steiner S, Carrier M, Coyle K, Bai A, Moulton K, Clifford T, Wells GA (2014). Systematic Review and Network Meta-analysis comparing Antithrombotic Agents for the Prevention of Stroke and Major Bleeding in Patients with Atrial Fibrillation. <i>BMJ Open</i>.	- supported CDR recommendations for apixaban and rivaroxaban - Supported Therapeutic Review Recommendations by CADTH - Among the most highly downloaded articles in BMJ Open - ranks in the 92nd percentile of all articles in terms of quality and quantity of online attention received
<u>Chapter 3: Rapid network meta-analysis using ClinicalTrials.gov</u> Cameron C, Coyle D, Wells GA, Clifford T (2014). Rapid network meta-analysis using ClinicalTrials.gov: An application comparing Antithrombotic Agents for the Prevention of Stroke and Major Bleeding in Patients with Atrial Fibrillation. (To be submitted in 2015)	- Presented preliminary methods/results at CADTH 2014 Symposium - Submitted to <i>Systematic Reviews</i> in 2015
<u>Chapter 4: Network meta-analysis involving complex networks</u> Cameron C, Kelly S, Hsieh SC, Murphy M, Chen L, Kotb A, Peterson J, Coyle D, Skidmore B, Gomes T, Clifford T, George Wells GA (2015). Triptans in the acute treatment of migraine: A systematic review and network meta-analysis (Submitted to <i>Headache</i>)	- Published in <i>Headache</i> in July 2015 - Supported Ontario Drug Policy Network Triptans recommendation
<u>Chapter 5: Network meta-analysis when events are rare</u> Singh JA,*Chris Cameron C,* Noorbaloochi S, Cullis T, Tucker M, Christensen R, Tanjong Ghogomu E, Coyle D, Clifford T, Tugwell P, Wells GA (2014). The risk of serious infection with biologics in treating patients with rheumatoid. (Accepted in <i>Lancet</i>)	- Published in <i>Lancet</i> - will support CADTH recommendations in 2015 – will inform CIHR DSEN grant to update work on biologics for rheumatoid arthritis
<u>Chapter 6: Network meta-analysis including benefits and harms</u> Part A: Castellucci L*, Cameron C*, Le Gal G, Rodger M, Coyle D, Wells P, Clifford T, Gandara E, Wells G, Carrier M (2014). Clinical and Safety Outcomes of Treatment of Acute Venous Thromboembolism: A Systematic Review and Meta-Analysis. <i>JAMA</i>. 312 (11): 122-1135 *Co-first authors Part B: Cameron C, Clifford T, Wells GA, Coyle D (2014). Benefit-harm assessment of treatments for Acute Venous Thromboembolism. (To be submitted in 2015)	- will support CADTH recommendations in 2015 – will form the basis of a CIHR DSEN grant to update work on new oral anticoagulants for prevention of venous thromboembolism - Paper in Part A rank in the 99th percentile of all articles in terms of quality and quantity of online attention received - Among the most highly downloaded articles in <i>JAMA</i> during the time they were published - Part B to be submitted in 2015
<u>Chapter 7: Network meta-analysis incorporating non-randomized studies</u> Part A: Cameron C, Fireman B, Clifford T, Coyle D, Hutton B,	- Part A paper submitted to <i>Systematic Reviews</i> in June 2015 - Presented findings to Food and Drug Administration in August and

Chapter	Impact
Wells GA, Dormuth C, Platt R, Toh S (2015). Network meta-analysis incorporating non-randomized studies for assessing medical product safety: pitfalls and opportunities. (Submitted to <i>BMJ Open</i> in March 2015) Part B: Cameron C, Fireman B, Clifford T, Coyle D, Wells GA, Toh S (2015). Network meta-analysis using observational data from distributed health data networks: An application using acute myocardial infarction in association with use of anti-diabetic agents (To be submitted in 2015 – under embargo by FDA)	October 2014 - Will support FDA Mini-Sentinel review safety review investigating risk of myocardial infarction in Saxagliptin - Part B will be submitted to Journal of Clinical Epidemiology in 2015
<u>Supplementary paper – Excel-based Network meta-analysis Tool</u> S Brown*, B Hutton, T Clifford, D Coyle, D Grima, G Wells, C Cameron* (2014). A Microsoft-Excel-based tool for running and critically appraising network meta-analyses-an overview and application of NetMetaXL. <i>Systematic Reviews</i>. 3 (110) *Co-first authors	- Tool downloaded over 1000 times and article assessed almost 7000 times since September 2014 - rank in the 93rd percentile of all articles in terms of quality and quantity of online attention received - Among the most highly downloaded articles in Systematic Reviews since published – designated as a highly assessed article

BIBLIOGRAPHY (for CHAPTER 1 and CHAPTER 9)

1. Sutton a J, Abrams KR. Bayesian methods in meta-analysis and evidence synthesis. *Stat Methods Med Res.* 2001;10(4):277-303.
<http://www.ncbi.nlm.nih.gov/pubmed/11491414>.
2. Ried K. Interpreting and understanding meta-analysis graphs. *Aust Fam Physician.* 2006;35(8):635-638.
3. Alves C, Batel-marques F, Macedo AF. Data sources on drug safety evaluation : a review of recent published meta-analyses. *Pharmacoepidemiol Drug Saf.* 2012;21(October 2011):21-33.
4. Gibbons RD, Amatya AK, Brown CH, et al. Post-approval drug safety surveillance. *Annu Rev Public Health.* 2010;31:419-437.
doi:10.1146/annurev.publhealth.012809.103649.
5. Singh S, Loke YK. Drug safety assessment in clinical trials: methodological challenges and opportunities. *Trials.* 2012;13(1):138. doi:10.1186/1745-6215-13-138.
6. Caldwell DM, Ades a E, Higgins JPT. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. *BMJ.* 2005;331(7521):897-900.
doi:10.1136/bmj.331.7521.897.
7. Wells GA, Sultan SA, Chen L, Khan M CD. *Indirect Evidence: Indirect Treatment Comparisons in Meta-Analysis.*; 2009.
<http://scholar.google.com/scholar?hl=en&btnG=Search&q=intitle:Indirect+Evidence:+Indirect+Treatment+Comparisons+in+Meta-Analysis#7>. Accessed October 1, 2011.
8. Jansen JP, Crawford B, Bergman G, Stam W. Bayesian meta-analysis of multiple treatment comparisons: an introduction to mixed treatment comparisons. *Value Health.* 2008;11(5):956-964. doi:10.1111/j.1524-4733.2008.00347.x.
9. Drug Safety and Effectiveness Network (DSEN). <http://www.cihr-irsc.gc.ca/e/40269.html>.
10. Trelle S, Reichenbach S, Wandel S, et al. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. *BMJ.* 2011;342(jan11 1):c7086-c7086.
doi:10.1136/bmj.c7086.
11. Kearney PM, Baigent C, Godwin J, Halls H, Emberson JR, Patrono C. Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. *BMJ.* 2006;332(7553):1302-1308. doi:10.1136/bmj.332.7553.1302.

12. White WB, West CR, Borer JS, et al. Risk of cardiovascular events in patients receiving celecoxib: a meta-analysis of randomized clinical trials. *Am J Cardiol.* 2007;99(1):91-98. doi:10.1016/j.amjcard.2006.07.069.
13. Dias S, Welton NJ, Sutton AJ, Ades A. *NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials.*; 2011. www.nicesdu.org.uk. Accessed October 1, 2011.
14. Spiegelhalter D, Thomas A, Best N. WinBUGS user manual. *MRC Biostat Unit.* 2004;2(January). <http://voteview.org/manual14.pdf>. Accessed October 1, 2011.
15. Briggs A, Claxton K, Sculpher M. *Decision Modelling for Health Economic Evaluation.* Oxford University Press, USA; 2006.
16. Briggs a, Sculpher M. An introduction to Markov modelling for economic evaluation. *Pharmacoeconomics.* 1998;13(4):397-409. <http://www.ncbi.nlm.nih.gov/pubmed/10178664>.
17. Friedrich JO, Adhikari NKJ, Beyene J. Inclusion of zero total event trials in meta-analyses maintains analytic consistency and incorporates all available data. *BMC Med Res Methodol.* 2007;7:5. doi:10.1186/1471-2288-7-5.
18. Bradburn MJ, Deeks JJ, Berlin J a, Russell Localio a. Much ado about nothing: a comparison of the performance of meta-analytical methods with rare events. *Stat Med.* 2007;26(1):53-77. doi:10.1002/sim.2528.
19. Salanti G, Ades A, Ioannidis J. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *J Clin Epidemiol.* 2011;64(2):163-171. doi:10.1016/j.jclinepi.2010.03.016.
20. Salanti, Georgia, Kavvoura, F, Ioannidis J. Exploring the geometry of treatment networks. *Ann Intern Med.* 2008;148:544-553.
21. Dias S, Sutton AJ, Welton NJ, Ades A. *NICE Technical Support Document 3: Heterogeneity: Subgroups, Meta-Regression, Bias and Bias-Adjustment.*; 2011. www.nicesdu.org.uk.
22. Dias S, Welton NJ, Caldwell DM, Ades a E. Checking consistency in mixed treatment comparison meta-analysis. *Stat Med.* 2010;29(7-8):932-944. doi:10.1002/sim.3767.
23. Dias, S., Welton, N.J., Sutton, A.J., Caldwell, D.M., Guobing, L. & Ades AE. *NICE Technical Support Document 4: Inconsistency in Networks of Evidence Based on Randomised Controlled Trials.*; 2011. www.nicesdu.org.uk. Accessed October 1, 2011.

24. Jansen JP. Network meta-analysis of individual and aggregate level data. *Res Synth Methods*. 2012;3(2):177-190. doi:10.1002/jrsm.1048.
25. Ades a E, Claxton K, Sculpher M. Evidence synthesis, parameter correlation and probabilistic sensitivity analysis. *Health Econ*. 2006;15(4):373-381. doi:10.1002/hec.1068.
26. Ades a E. A chain of evidence with mixed comparisons: models for multi-parameter synthesis and consistency of evidence. *Stat Med*. 2003;22(19):2995-3016. doi:10.1002/sim.1566.
27. Ades a E, Welton NJ, Caldwell D, Price M, Goubar A, Lu G. Multiparameter evidence synthesis in epidemiology and medical decision-making. *J Health Serv Res Policy*. 2008;13 Suppl 3(October):12-22. doi:10.1258/jhsrp.2008.008020.
28. Bujkiewicz S, Jones HE, Lai MCW, et al. Development of a transparent interactive decision interrogator to facilitate the decision-making process in health care. *Value Health*. 2011;14(5):768-776. doi:10.1016/j.jval.2010.12.002.
29. Cooper NJ, Sutton AJ, Abrams KR, Turner D, Wailoo A. Comprehensive decision analytical modelling in economic evaluation: a Bayesian approach. *Health Econ*. 2004;13(3):203-226. doi:10.1002/hec.804.
30. Claxton K, Neumann PJ, Araki SS, Weinstein MC. Bayesian Value-of-Information Analysis : in Two-Sector BAYESIAN VALUE-OF-INFORMATION ANALYSIS : AN APPLICATION TO A POLICY MODEL OF ALZHEIMER ' S DISEASE. 2000.
31. Ioannidis JP a. Integration of evidence from multiple meta-analyses: a primer on umbrella reviews, treatment networks and multiple treatments meta-analyses. *CMAJ*. 2009;181(8):488-493. doi:10.1503/cmaj.081086.
32. Cnt T. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. *Lancet*. 2013;6736(13):1-11. doi:10.1016/S0140-6736(13)60900-9.
33. *Antithrombotic Agents for the Prevention of Stroke and Systemic Embolism in Patients with Atrial Fibrillation.*; 2013.
http://www.cadth.ca/media/pdf/TR0003_AntithromboticAgents-AF_ScienceReport-e.pdf.
34. McDonagh MS, Peterson K, Balshem H, Helfand M. US Food and Drug Administration documents can provide unpublished evidence relevant to systematic reviews. *J Clin Epidemiol*. 2013. doi:10.1016/j.jclinepi.2013.05.006.

35. Glasziou PP, Shepperd S, Brassey J. Can we rely on the best trial? A comparison of individual trials and systematic reviews. *BMC Med Res Methodol.* 2010;10:23. doi:10.1186/1471-2288-10-23.
36. Allen I OI. Creative nonfiction. *JAMA.* 1999;282(7):634-635. <http://dx.doi.org/10-1001/pubs.JAMA-ISSN-0098-7484-282-7-jbk0818>.
37. Singh J, Wells G. Adverse effects of biologics: a network meta-analysis and Cochrane overview. *Cochrane Database Syst Rev.* 2012;3:1-82. <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008794.pub2/full>. Accessed February 8, 2013.
38. Singh S, Loke YK, Spangler JG, Furberg CD. Risk of serious adverse cardiovascular events associated with varenicline: a systematic review and meta-analysis. *Can Med Assoc J.* 2011;183(12):1359-1366. doi:10.1503/cmaj.110218.
39. Van Valkenhoef G, Tervonen T, Zhao J, de Brock B, Hillege HL, Postmus D. Multicriteria benefit-risk assessment using network meta-analysis. *J Clin Epidemiol.* 2012;65(4):394-403. doi:10.1016/j.jclinepi.2011.09.005.
40. Guo JJ, Pandey S, Doyle J, Bian B, Lis Y, Raisch DW. A review of quantitative risk-benefit methodologies for assessing drug safety and efficacy-report of the ISPOR risk-benefit management working group. *Value Health.* 2010;13(5):657-666. doi:10.1111/j.1524-4733.2010.00725.x.
41. West SL, Squiers L, McCormack L, et al. *Quantitative Summary of the Benefits and Risks of Prescription Drugs : A Literature Review.*; 2011. <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/RiskCommunicationAdvisoryCommittee/UCM275355.pdf>.
42. McGettigan P, Henry D. Cardiovascular risk with non-steroidal anti-inflammatory drugs: systematic review of population-based controlled observational studies. *PLoS Med.* 2011;8(9):e1001098. doi:10.1371/journal.pmed.1001098.
43. Eichler H-G, Oye K, Baird LG, et al. Adaptive licensing: taking the next step in the evolution of drug approval. *Clin Pharmacol Ther.* 2012;91(3):426-437. doi:10.1038/clpt.2011.345.
44. Hutton B, Joseph L, Fergusson D, Mazer CD, Shapiro S, Tinmouth A. Risks of harms using antifibrinolytics in cardiac surgery: systematic review and network meta-analysis of randomised and observational studies. *BMJ.* 2012;345(sep11 2):e5798-e5798. doi:10.1136/bmj.e5798.
45. Schmitz S, Adams R, Walsh C. Incorporating data from various trial designs into a mixed treatment comparison model. *Stat Med.* 2013;(January). doi:10.1002/sim.5764.

46. Rassen JA, Shelat AA, Franklin JM, Glynn RJ, Solomon DH, Schneeweiss S. Matching by propensity score in cohort studies with three treatment groups. *Epidemiology*. 2013;24(3):401-409. doi:10.1097/EDE.0b013e318289dedf.
47. Coyle D, Buxton M, O'Brien B. Stratified cost- • effectiveness analysis: a framework for establishing efficient limited use criteria. *Health Econ*. 2003;427(August 2002):421-427. doi:10.1002/hec.788.
48. McIntosh B, Cameron C, Singh SR, et al. Second-line therapy in patients with type 2 diabetes inadequately controlled with metformin monotherapy: a systematic review and mixed-treatment comparison meta-analysis. *Open Med*. 2011;5(1):e35-e48. <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3205809&tool=pmcentrez&rendertype=abstract>.
49. Citrome L. A systematic review of meta-analyses of the efficacy of oral atypical antipsychotics for the treatment of adult patients with schizophrenia. *Expert Opin Pharmacother*. 2012;13(11):1545-1573. doi:10.1517/14656566.2011.626769.
50. Siontis KC, Hernandez-boussard T. Overlapping meta-analyses on the same topic : survey of published studies. 2013;4501(July):1-11. doi:10.1136/bmj.f4501.
51. Boyd C, Singh S, Varadhan R, et al. *Methods Research Report Methods for Benefit and Harm Assessment in Systematic Reviews*. Rockville, MD; 2012. www.ncbi.nlm.nih.gov/books/NBK115750/.
52. *Health Product Vigilance Framework*. Health Canada; 2012. http://www.hc-sc.gc.ca/dhp-mps/pubs/medeff/_fs-if/2012-hpvf-cvps/index-eng.php.
53. Garrison LP. Regulatory Benefit-Risk Assessment and Comparative Effectiveness Research. *Pharmacoeconomics*. 2010;28(10):855-865.
54. Garrison LP, Towse A, Bresnahan BW. Assessing a structured, quantitative health outcomes approach to drug risk-benefit analysis. *Health Aff (Millwood)*. 2007;26(3):684-695. doi:10.1377/hlthaff.26.3.684.
55. Lynd LD, Marra CA, Najafzadeh M, Sadatsafavi M. A quantitative evaluation of the regulatory assessment of the benefits and risks of rofecoxib relative to naproxen : an application of the incremental net-benefit framework y. *Pharmacoepidemiol Drug Saf*. 2010;(July):1172-1180.
56. Van Valkenhoef G, Tervonen T, Zwinkels T, de Brock B, Hillege H. ADDIS: A decision support system for evidence-based medicine. *Decis Support Syst*. 2013;55(2):459-475. doi:10.1016/j.dss.2012.10.005.

57. Wells G, Kelly S, Cameron C, Chen L. Triptans in the acute treatment of migraine. 2014;1-29. <http://www.odprn.ca/wp-content/uploads/2014/02/Triptan-SR-censored-feb-4-2014-final.pdf>. Accessed July 11, 2014.
58. Mini-Sentinel Data Core. *Mini-Sentinel Distributed Database Summary Report - Year 4.*; 2014. http://www.mini-sentinel.org/data_activities/distributed_db_and_data/details.aspx?ID=162.
59. Brown S, Hutton B, Clifford T, et al. A Microsoft-Excel-based tool for running and critically appraising network meta-analyses--an overview and application of NetMetaXL. *Syst Rev.* 2014;3(1):110. doi:10.1186/2046-4053-3-110.
60. Kakkos SK, Kirkilesis GI, Tsolakis I a. Efficacy and Safety of the New Oral Anticoagulants Dabigatran, Rivaroxaban, Apixaban, and Edoxaban in the Treatment and Secondary Prevention of Venous Thromboembolism: A Systematic Review and Meta-analysis of Phase III Trials. *Eur J Vasc Endovasc Surg.* 2014;48(5):565-575. doi:10.1016/j.ejvs.2014.05.001.

APPENDICES

APPENDIX A

Number of patient-years and myocardial infarction by randomised intervention (obtained from Trelle et al)¹⁰

Trial	Intervention	Patient years	Myocardial infarction†
ADAPT	Placebo	1982	13
ADAPT	Naproxen	1332	13
ADAPT	Celecoxib	1346	8
Aisen 2003	Placebo	115	1
Aisen 2003	Naproxen	124	0
Aisen 2003	Rofecoxib	126	3
Geusens 2004	Placebo	111	0
Geusens 2004	Naproxen	118	0
Geusens 2004	Lumiracoxib	234	2
APC	Placebo	1558	3
APC	Celecoxib	3124	18
IQ5-97-02-001	Placebo	120	0
IQ5-97-02-001	Celecoxib	285	2
PreSAP	Placebo	1570	4
PreSAP	Celecoxib	2331	9
Lehmann 2005	Placebo	98	1
Lehmann 2005	Celecoxib	99	0
Lehmann 2005	Lumiracoxib	200	0
APPROVe	Placebo	5711	18
APPROVe	Rofecoxib	5658	34
Reines 2004	Placebo	293	4
Reines 2004	Rofecoxib	273	2
Thal 2005	Placebo	1820	13
Thal 2005	Rofecoxib	1599	22
VICTOR	Placebo	986	1
VICTOR	Rofecoxib	928	6
ViP	Placebo	1102	5
ViP	Rofecoxib	1099	6
A3191152	Naproxen	130	0
A3191152	Celecoxib	131	0
SUCCESS-1 (USA/Canada)	Naproxen	165	1
SUCCESS-1 (USA/Canada)	Celecoxib	353	4

Trial	Intervention	Patient years	Myocardial infarction†
ADVANTAGE	Naproxen	526	1
ADVANTAGE	Rofecoxib	528	5
VIGOR	Naproxen	2008	4
VIGOR	Rofecoxib	2007	20
TARGET (0117)	Naproxen	4156	7
TARGET (0117)	Lumiracoxib	4197	15
CLASS (N49-98-02-035)	Ibuprofen	1123	9
CLASS (N49-98-02-035)	Celecoxib	1184	9
TARGET (2332)	Ibuprofen	3709	5
TARGET (2332)	Lumiracoxib	3795	5
CAESAR	Diclofenac	432	5
CAESAR	Celecoxib	415	4
CLASS (N49-98-02-102)	Diclofenac	1081	5
CLASS (N49-98-02-102)	Celecoxib	1136	10
Emery 1999	Diclofenac	125	0
Emery 1999	Celecoxib	133	1
SUCCESS-1 (World)	Diclofenac	745	0
SUCCESS-1 (World)	Celecoxib	1472	6
EDGE	Diclofenac	2607	11
EDGE	Etoricoxib	2789	19
EDGE II	Diclofenac	3251	25

APTC=Antiplatelet Trialists' Collaboration

†Includes fatal and non-fatal events.

APPENDIX B

Characteristics of Included Studies (obtained from Trelle et al)¹⁰

Study	Interventions	Population	No of patients*	Follow-up (weeks)	Low dose aspirin allowed	Concealed allocation†	Blinding‡	Events adjudicated§	Intention to treat¶	Source per Trelle et al ¹⁰
ADAPT	Placebo v naproxen (440 mg/d) v celecoxib (400 mg/d)	At risk for Alzheimer disease	2528	198	Yes	Yes	Yes	Yes	Yes	Journal article, trial website
Aisen 2003	Placebo v naproxen (440 mg/d) v rofecoxib (25 mg/d)	Alzheimer disease	351	60	Yes	Yes	Yes	No	Yes	Journal article, personal communication
Geusens 2004	Placebo v naproxen (1000 mg/d) v lumiracoxib (200, 400 mg/d)	Rheumatoid arthritis	1124	26	Yes	Yes	Yes	No	Yes	Journal article, personal communication
APC	Placebo v celecoxib (400,800 mg/d)	Adenomatous polyps (colon)	2035	160	Yes	Yes	Yes	Yes	Yes	Journal article, study register
IQ5-97-02-001	Placebo v celecoxib (400 mg/d)	At risk for Alzheimer disease	425	52	Yes	Yes	Yes	No	No	FDA reports, study register, personal communication
PreSAP	Placebo v celecoxib (400 mg/d)	Adenomatous polyps (colon)	1561	159	Yes	Yes	Yes	Yes	Yes	Journal article, personal communication
Lehmann 2005	Placebo v celecoxib (200 mg/d) v lumiracoxib (100 mg/d)	Osteoarthritis	1684	13	Yes	Yes	Yes	Yes	Yes	Journal article, personal communication
APPROVe	Placebo v rofecoxib (25 mg/d)	Adenomatous polyps (colon)	2586	229	Yes	Unclear	Yes	Yes	Yes	Journal article
Reines 2004	Placebo v rofecoxib (25 mg/d)	Alzheimer disease	692	65	Unclear	Yes	Yes	Yes	Yes	FDA reports
Thal 2005	Placebo v rofecoxib (25 mg/d)	At risk for Alzheimer	1457	210	Yes	Yes	Yes	Yes	Yes	Journal article

disease										
VICTOR	Placebo v rofecoxib (25 mg/d)	Adjuvant (colon cancer)	2327	235	Yes	Yes	Yes	Yes	No	FDA reports, journal article, study register, trial website
ViP	Placebo v rofecoxib (25 mg/d)	At risk for prostate cancer	4741	75	Yes	Yes	Yes	Yes	Yes	Study register
A3191152	Naproxen (1000 mg/d) v celecoxib (200 mg/d)	Osteoarthritis	589	26	Yes	Yes	Yes	No	No	Study register
SUCCESS-1 (USA/Canada)	Naproxen (1000 mg/d) v celecoxib (200, 400 mg/d)	Osteoarthritis	2736	12	Yes	Yes	Yes	No	No	Journal article, study register, personal communication
ADVANTAGE	Naproxen (1000 mg/d) v rofecoxib (25 mg/d)	Osteoarthritis	5557	14	Yes	Unclear	Yes	Yes	No	FDA reports, journal article
VIGOR	Naproxen (1000 mg/d) v rofecoxib (50 mg/d)	Rheumatoid arthritis	8076	54	No	Yes	Yes	Yes	Yes	FDA reports, journal article
TARGET (0117)	Naproxen (1000 mg/d) v lumiracoxib (400 mg/d)	Osteoarthritis	9511	56	Yes	Yes	Yes	Yes	No	FDA reports, journal article, personal communication
CLASS (N49-98-02-035)	Ibuprofen (2400 mg/d) v celecoxib (800 mg/d)	Osteoarthritis and rheumatoid arthritis	3975	65	Yes	Yes	Yes	No	No	FDA reports, personal communication
TARGET (2332)	Ibuprofen (2400 mg/d) v lumiracoxib (400 mg/d)	Osteoarthritis	8814	56	Yes	Yes	Yes	Yes	No	FDA reports, journal article, personal communication
CAESAR	Diclofenac (100 mg/d) v celecoxib (200 mg/d)	Osteoarthritis	916	52	Yes	Yes	Yes	No	No	FDA reports, study register, conference abstract, personal communication
CLASS (N49-98-02-102)	Diclofenac (150 mg/d) v celecoxib (800 mg/d)	Osteoarthritis and rheumatoid arthritis	3993	52	Yes	Yes	Yes	No	No	FDA reports, personal communication

Emery 1999	Diclofenac (150 mg/d) v celecoxib (400 mg/d)	Rheumatoid arthritis	655	24	No	Yes	Yes	No	No	Journal article, personal communication
SUCCESS-1 (World)	Diclofenac (100 mg/d) v celecoxib (200, 400 mg/d)	Osteoarthritis	10458	12	Yes	Yes	Yes	No	No	Journal article, study register, personal communication
EDGE	Diclofenac (150 mg/d) v etoricoxib (90 mg/d)	Osteoarthritis	7111	73	Yes	Yes	Yes	Yes	No	FDA reports, journal article
EDGE II	Diclofenac (150 mg/d) v etoricoxib (90 mg/d)	Rheumatoid arthritis	4086	150	Yes	Yes	Yes	Yes	No	Journal article
MEDAL	Diclofenac (150 mg/d) v etoricoxib (60, 90 mg/d)	Osteoarthritis and rheumatoid arthritis	23498	176	Yes	Yes	Yes	Yes	No	Journal article
Cannon 2000	Diclofenac (150 mg/d) v rofecoxib (12.5, 25 mg/d)	Osteoarthritis	784	52	No	Yes	Yes	No	No	FDA reports, journal article
Saag 2000	Diclofenac (150 mg/d) v rofecoxib (12.5, 25 mg/d)	Osteoarthritis	693	54	No	Yes	Yes	No	No	FDA reports, journal article
Fleischmann 2003**	Celecoxib (200 mg/d) v lumiracoxib (200, 400 mg/d)	Osteoarthritis	1376	13	Yes	Yes	Yes	No	No	Journal article, personal communication
Tannenbaum 2004**	Celecoxib (200 mg/d) v lumiracoxib (200, 400 mg/d)	Osteoarthritis	1459	13	Yes	Yes	Yes	No	Yes	Journal article, personal communication

FDA=US Food and Drug Administration.

*Number of randomized patients of included trial arms.

†Yes if investigators responsible for patient selection were unable to suspect before allocation which treatment was next in line (central randomisation, sequentially numbered, sealed, opaque assignment envelopes, coded drug packs).

‡Yes if drugs looked similar (for example, matching placebo) or double dummy was used.

§Relates to myocardial infarctions only. See web extra appendix 2 for more detailed description of external adjudication of events in individual trials.

¶Yes if all randomised patients were included in analysis.

**Placebo arm excluded (<100 patient years of follow-up).

APPENDIX C

PUBLISHED MANUSCRIPTS

BMJ Open Systematic review and network meta-analysis comparing antithrombotic agents for the prevention of stroke and major bleeding in patients with atrial fibrillation

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ABSTRACT

Objective: To examine the comparative efficacy and safety of antithrombotic treatments (apixaban, dabigatran, edoxaban, rivaroxaban and vitamin K antagonists (VKA) at a standard adjusted dose (target international normalised ratio 2.0–3.0), acetylsalicylic acid (ASA), ASA and clopidogrel) for non-valvular atrial fibrillation and among subpopulations.

Design: Systematic review and network meta-analysis.

Data sources: A systematic literature search strategy was designed and carried out using MEDLINE, EMBASE, the Cochrane Register of Controlled Trials and the grey literature including the websites of regulatory agencies and health technology assessment organisations for trials published in English from 1988 to January 2014.

Eligibility criteria for selecting studies:

Randomised controlled trials were selected for inclusion if they were published in English, included at least one antithrombotic treatment and involved patients with non-valvular atrial fibrillation eligible to receive anticoagulant therapy.

Results: For stroke or systemic embolism, dabigatran 150 mg and apixaban twice daily were associated with reductions relative to standard adjusted dose VKA, whereas low-dose ASA and the combination of clopidogrel plus low-dose ASA were associated with increases. Absolute risk reductions ranged from 6 fewer events per 1000 patients treated for dabigatran 150 mg twice daily to 15 more events for clopidogrel plus ASA. For major bleeding, edoxaban 30 mg daily, apixaban, edoxaban 60 mg daily and dabigatran 110 mg twice daily were associated with reductions compared to standard adjusted dose VKA. Absolute risk reductions with these agents ranged from 18 fewer per 1000 patients treated each year for edoxaban 30 mg daily to 24 more for medium dose ASA.

Conclusions: Compared with standard adjusted dose VKA, new oral anticoagulants were associated with modest reductions in the absolute risk of stroke and

Strengths and limitations of this study

- This network meta-analysis includes data on edoxaban from the recently published ENGAGE AF-TIMI 48 trial.
- The studies pooled in this meta-analysis include antiplatelet agents in addition to newer oral anticoagulants and standard adjusted dose vitamin K antagonists.
- We present findings on the relative and absolute scale, and graphically illustrate absolute risks using icon arrays.
- We report detailed a priori subgroup analyses for stroke or systemic embolism and major bleeding using data derived from FDA Public Summary Documents.
- Comparisons between antithrombotic treatments were largely comprised of single, albeit large, studies.
- There is notable heterogeneity and the small number of studies limits the analyses that can be conducted to account for heterogeneity in the absence of patient-level data.
- Icon arrays only consider the primary efficacy and safety endpoints of underlying studies and do not account for the different clinical consequences associated with each of the outcomes.

major bleeding. People on antiplatelet drugs experienced more strokes compared with anticoagulant drugs without any reduction in bleeding risk. To fully elucidate the comparative benefits and harms of antithrombotic agents across the various subpopulations, rigorously conducted comparative studies or network meta-regression analyses of patient-level data are required.

Systematic review registration number: PROSPERO registry—CRD42012002721.

INTRODUCTION

Atrial fibrillation (AF) is a common cardiac arrhythmia associated with increased morbidity and mortality.^{1 2} Patients with AF sustain an increased risk of arterial thromboembolism and stroke, which are associated with high recurrence and substantial debilitating impact. Therefore, antithrombotic strategies using anticoagulant drugs and antiplatelet agents are recommended for patients with AF presenting with risk factors for stroke. Antithrombotic therapy is also associated with a risk of bleeding; therefore, the beneficial effects on stroke prevention should always be compared against a patient's risk of major bleeding.^{1 2}

Existing guidelines recommend anticoagulant therapy for patients at intermediate or high risk of stroke.^{1 2} Although standard adjusted dose vitamin K antagonist (VKA) (eg, warfarin) has been the cornerstone treatment for reducing the risk of stroke or systemic embolism (SE) in this population, it is associated with several drawbacks² which have prompted the development of newer oral anticoagulants such as direct thrombin (dabigatran) and Xa (eg, apixaban, edoxaban, rivaroxaban) inhibitors.^{1 2} While some of these newer treatment options have been demonstrated to be efficacious in preventing stroke or SE compared to standard adjusted dose VKA, the relative efficacy and risk of bleeding of newer oral anticoagulants, both among themselves and in comparison to antiplatelet agents, is not clear, especially in certain subpopulations of patients, for example, CHADS₂ score <2 or ≥2; time in therapeutic range (TTR) <66% or ≥66%; Age <75 or ≥75 years. Therefore, the objective of this paper was to compare antithrombotic agents for the prevention of stroke and major bleeding in patients with non-valvular AF and among subpopulations.

METHODS

The published literature was identified by searching MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, BIOSIS Previews, PubMed and the Cochrane Central Register of Controlled Trials were searched through the Ovid interface to identify English-language clinical articles published from 1988 to 23 January 2014. Regular alerts were also established. Websites of regulatory agencies, Canadian and major international health technology assessment agencies, clinical practice guidelines as well as The Cochrane Library (2012, Issue 6) and University of York Centre for Reviews and Dissemination databases were searched. Complete details of the electronic search strategy, including any limits used, are reported in online supplementary appendix 1. The protocol was published online and was registered in the PROSPERO International Prospective Register of Systematic Reviews (PROSPERO registry—CRD42012002721).

The population of interest was individuals with non-valvular AF requiring anticoagulation (including all risk

levels and regardless of any comorbidities). The following treatments were included in the review: apixaban, dabigatran, edoxaban, rivaroxaban, standard adjusted dose VKA, acetylsalicylic acid (ASA), ASA and clopidogrel. Numerous outcomes were considered and results are reported elsewhere³; however, the focus of this publication is the outcomes of all-cause stroke or SE and major bleeding as defined by the International Society on Thrombosis and Haemostasis (ISTH) definition,⁴ which were the primary efficacy and safety outcomes used in the newer oral anticoagulant studies.

Active and placebo-controlled randomised controlled trials (RCTs) were selected for inclusion if they were published in English, included at least one antithrombotic treatment under review (using pre-specified doses), reported data for stroke/SE or major bleeding, and involved patients with non-valvular AF eligible to receive anticoagulant therapy, regardless of the level of stroke risk. Trials that included patients with contraindication to anticoagulant treatment were excluded. VKA trials were included if the dose was adjusted to a target international normalised ratio (INR) 2.0–3.0. Any dose of ASA was considered for inclusion, but ASA dose was stratified in the analysis as low (≤100 mg daily), medium (>100 mg to ≤300 mg daily) or high (>300 mg daily). We only included new oral anticoagulants which had at least one large phase III study. Three reviewers independently extracted the data on baseline characteristics, intervention(s) evaluated, including dose, duration and relevant co-medication, and results for each included article, using a standardised template. All extracted data were checked for accuracy by three independent reviewers. Any disagreements in the assessment of these data were resolved through discussion until consensus was reached. Quality assessment of RCTs was also performed independently by two reviewers using a standardised table based on major items from the SIGN 50 instrument for internal validity.⁵ The trial selection process is presented in a flow chart based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)⁶ statement (see online supplementary appendix 2).

Bayesian network meta-analyses were conducted using WinBUGS software (MRC Biostatistics Unit, Cambridge, UK). A binomial likelihood model⁷ which accounts for use of multi-arm trials was used for analyses, given outcomes were dichotomous and included multi-arm trials. Trials with zero cells in both arms or nodes, where there were no events, were excluded from the evidence networks because they do not contribute information or allow interpretable information.⁷ Both fixed and random-effects network meta-analyses were conducted, although the fixed-effects model was chosen for the reference case analysis, as the evidence network was largely comprised of single study connections. We modelled point estimates and 95% credible intervals for OR using Markov Chain Monte Carlo methods. The absolute risk difference per 1000 patients treated each year for each

outcome was also calculated, based on the standard adjusted dose VKA arm of the Randomised Evaluation of Long-Term Anti-coagulation Therapy (RE-LY) trial.⁸ The RE-LY trial⁸ was selected because it contained data for both CHADS₂ <2 and CHADS₂ ≥2 and had detailed data available from the Food and Drug Administration (FDA) Public Summary Report.⁹ We also assessed the probability that each treatment was the most efficacious regimen, the second best, the third best and so on.¹⁰ Vague or flat priors, such as N(0, 100²), were assigned for basic parameters throughout, although informative priors were considered.¹¹ Assessment of model fit was based on the deviance information criterion (DIC) and comparison of residual deviance to number of unconstrained data points.^{7 12} To ensure that convergence was reached, trace plots and the Brooks-Gelman-Rubin statistic were assessed.¹³ Three chains were fitted in WinBUGS for each analysis, with at least 40 000 iterations, and a burn-in of at least 40 000 iterations. We also qualitatively compared the results from our network meta-analysis with direct pairwise estimates. Frequentist pairwise meta-analyses were conducted using R (R Language and Environment for Statistical Computing, Vienna, Austria) and package meta.¹⁴

A key assumption behind network meta-analysis is that the analysed network is consistent, that is, there is no conflict between direct and indirect evidence.¹⁵ To assess inconsistency, we compared deviance and DIC statistics in fitted consistency and inconsistency models.¹⁵ We also plotted the posterior mean deviance of the individual data points in the inconsistency model against their posterior mean deviance in the consistency model to identify any loops where inconsistency was present (see online supplementary appendix 11).¹⁵ Additionally, the results from our network meta-analysis were qualitatively compared with direct frequentist pairwise estimates.

Network meta-analysis also requires that studies are sufficiently similar in order to pool their results.¹⁶ Available study and patient characteristics were assessed to ensure similarity and to investigate the potential impact of heterogeneity on effect estimates. Clinical and methodological heterogeneity was identified in a number of areas. The issues identified were similar to those reported in previous systematic reviews of anti-coagulant drugs (eg, differences in TTR, CHADS₂ score).¹⁷ Heterogeneity was assessed by conducting network meta-analysis with the following pre-specified subgroup data reported in the individual RCTs: TTR <66% or ≥66%; CHADS₂ score <2 or ≥2; Age <75 or ≥75 years.¹⁷ The data to conduct these subgroup analyses were derived from FDA Public Summary Documents when not available in the publications.^{9 18 19} Secondary evidence networks were constructed for each of the subgroup analyses. The WinBUGS code⁷ and data needed to replicate all analyses are available online.

RESULTS

Study characteristics of included studies

The systematic review included 16 individual RCTs (reported in 32 publications and FDA reports); all evaluated the efficacy and safety of antithrombotic agents: apixaban (5 mg twice daily), dabigatran (150 or 110 mg twice daily), edoxaban (30 or 60 mg daily), rivaroxaban (20 mg daily), standard adjusted dose VKA, ASA (low dose (<100 mg daily), medium dose (100–300 mg daily)), or low-dose ASA plus clopidogrel (75 mg daily) in patients with non-valvular AF. None of the included studies directly compared one new oral anticoagulant drug with another (see online supplementary appendix 4). Of the 82 396 randomised patients included in the primary analysis, five large multicentre trials account for 78 296 patients (96%): ENGAGE AF-TIMI 48 (n=21 105),²⁰ ARISTOTLE (n=18 201),²¹ RE-LY (n=18 113),⁸ ROCKET-AF (n=14 264)²² and ACTIVE-W (n=6706).²³ Most trials included stroke and SE as a primary efficacy outcome, while bleeding events were a frequent safety outcome. Follow-up ranged from 12 weeks to 3.5 years. All trials published results between 1989 and 2013. The mean CHADS₂ score was reported in eight trials, encompassing the vast majority of patients included in the systematic review. Reported CHADS₂ scores were consistent with a high-risk population (CHADS₂ ≥2), with patients from ROCKET-AF²² showing the highest risk for stroke (mean CHADS₂=3.5).

Mean age across the included trials ranged from 62 to 83 years (see online supplementary appendix 3). All trials included patients of both gender and had a higher proportion of male participants in most studies. However, the proportions of patients with a prior stroke or TIA varied substantially across the included trials, ranging from 3% in JAST to 55% in ROCKET-AF.²² The same observation can be made regarding the proportions of patients with other concomitant conditions, that is, congestive heart failure, hypertension, diabetes, myocardial infarction and prior VKA experience. TTR was reported in all but one trial that included a standard adjusted dose VKA treatment arm. Patient baseline characteristics are summarised in online supplementary appendix 3.

The studies were critically appraised individually and the details are reported elsewhere.³ Overall, there was substantial variation in study quality. However, large multicentre trials comparing newer anticoagulants with standard adjusted dose VKA, such as ENGAGE AF-TIMI 48 (n=21 105), ARISTOTLE (n=18 201), RE-LY (n=18 113) and ROCKET-AF (n=14 264), which account for the vast majority of patients included in the systematic review, appear to be methodologically rigorous.

Stroke or SE

The evidence network (figure 1) for the primary analysis was comprised of 12 RCTs representing eight treatments in addition to placebo/observation (N=82 396). Four RCTs

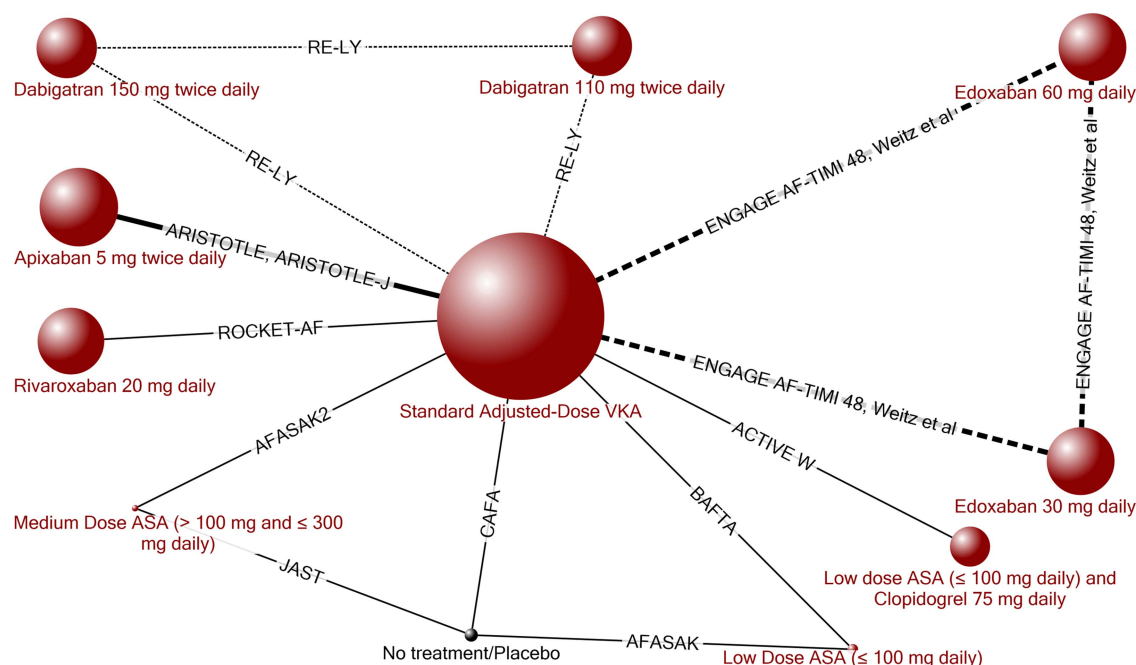


Figure 1 Evidence network for all-cause stroke or systemic embolism. (Four RCTs, PETRO,²⁴ WASPO²⁵ Chung *et al*²⁶ and Yamashita *et al*,²⁷ were not included in the analysis because they did not report data for this outcome or had zeros in both arms.) The width of the lines is proportional to the number of randomised controlled trials comparing each pair of treatments, and the size of each treatment node is proportional to the number of randomised participants (sample size). A dotted line indicates a three-arm randomised controlled trial and a black node indicates a node included in the analysis but not reported in the main text. ASA, acetylsalicylic acid; RCT, randomised controlled trial; VKA, vitamin K antagonist.

(Chung *et al*,²⁶ PETRO,²⁴ WASPO²⁵ and Yamashita *et al*²⁷) were not included in the analysis because they did not report data for this outcome or had zeros in both arms.

Dabigatran (150 mg twice daily) and apixaban were associated with reductions in stroke or SE relative to standard adjusted dose VKA (figure 2). The use of these two agents led to absolute risk reductions ranging from 4 to 6 fewer events per 1000 patients treated each year. In contrast, low-dose ASA and the combination of clopidogrel plus low-dose ASA appeared to have a higher risk of stroke or SE than standard adjusted dose VKA, leading to an increase in the number of stroke or SE ranging from 14 to 15 more events per 1000 patients treated each year (figure 4 and see online supplementary appendix 6). No differences were detected between standard adjusted dose VKA and each of the following interventions: dabigatran (110 mg twice daily), edoxaban (30 mg or 60 mg daily), rivaroxaban and medium-dose ASA (figure 3).

The estimates of effect derived from the direct pairwise comparisons aligned well with those obtained from the network meta-analysis in direction and magnitude (see online supplementary appendix 6). Furthermore, the posterior mean residual deviance (29.41) is close to the number of unconstrained data points (27), which is an indication of reasonable model fit. A number of subgroup analyses and alternative modelling strategies were conducted on the primary analysis, including adjusting for CHADS₂, TTR and age (table 1). We also conducted a sensitivity analysis where we included the AVERROES²⁸

and ACTIVE A²⁹ trials (see online supplementary appendix 12). These studies were excluded from the main analysis because we required patients to be eligible for anticoagulant therapy, including treatment with a VKA. The results differed slightly from the reference case (see online supplementary appendix 12). The primary analysis was conducted using a fixed-effects model because the network was comprised of single study connections; these results were also compared against those obtained using a random-effects model with informative and vague priors on the SD and found to be similar in magnitude, although wider credible intervals were observed (see online supplementary appendix 9).

Major bleeding

The evidence network for the primary analysis for major bleeding was comprised of 15 RCTs representing eight treatments in addition to placebo/observation (N=83 015). The evidence network for major bleeding is similar to the evidence network for stroke or SE (figure 1) but includes one extra RCT (WASPO²⁵) comparing medium-dose ASA with standard adjusted dose VKA, and two extra RCTs (Chung *et al*,²⁶ and Yamashita *et al*²⁷) comparing edoxaban with standard adjusted dose VKA (see online supplementary appendix 5).

Edoxaban 30 mg daily, apixaban, edoxaban 60 mg daily and dabigatran 110 mg twice daily were associated with reductions in the risk of major bleeding compared with standard adjusted dose VKA (figure 2). No differences for major bleeding were detected between

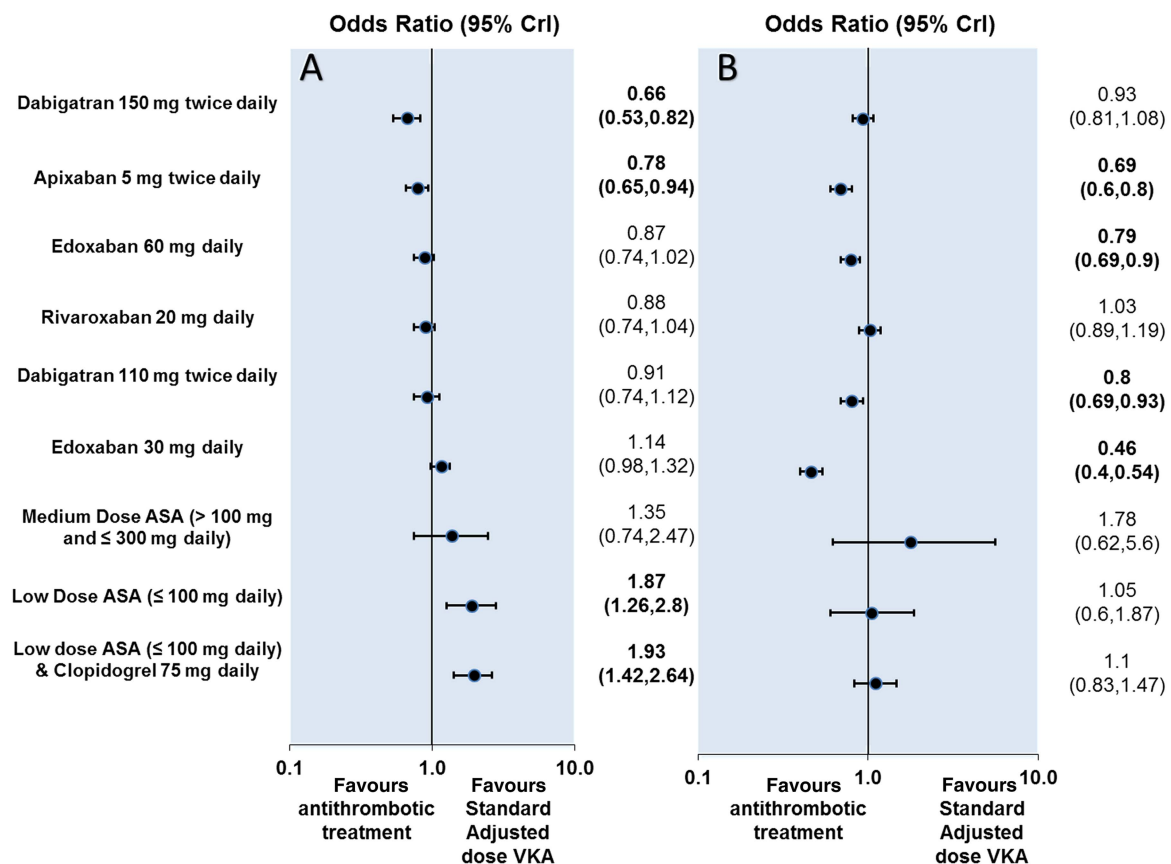


Figure 2 OR for all-cause stroke or systemic embolism (A) and major bleeding (B) in Bayesian network meta-analysis versus standard adjusted dose VKA. CrI, credible interval; VKA, vitamin K antagonist.

standard adjusted dose VKA and each of the remaining interventions: dabigatran 150 mg twice daily, rivaroxaban, clopidogrel plus low-dose ASA and all ASA dosages (figure 2). The absolute risk difference of major bleeding relative to standard adjusted dose VKA ranged from 18 fewer to 24 more events per 1000 patients treated per year (figure 4 and see online supplementary appendix 7). A summary of the results for the Bayesian and direct pairwise meta-analyses is shown in online supplementary appendix 7, and Bayesian network meta-analysis results are represented graphically in figure 2. Complete results from the Bayesian network meta-analysis for all possible comparisons are presented in figure 3.

The estimates of effect derived from the direct pairwise comparisons aligned well with those obtained from the network meta-analysis in direction and magnitude (see online supplementary appendix 7). Furthermore, the posterior mean residual deviance (38.0) is close to the number of unconstrained data points (35), which is an indication of reasonable model fit. A number of subgroup analyses and alternative modelling strategies were conducted on the primary analysis (table 1). We also conducted a sensitivity analysis where we included the AVERROES²⁸ and ACTIVE A²⁹ trial (see online supplementary appendix 12), as well as analyses using a random-effects model with vague and informative priors (see online supplementary appendix 9).

Benefit-harm assessment—stroke or SE versus major bleeding

Figure 3 summarises the results for all pairwise comparisons derived from the Bayesian fixed-effects network meta-analysis (see online supplementary appendix 9). Results relative to standard adjusted dose VKA have been discussed above. For pairwise comparisons among newer oral anticoagulants for stroke or SE, dabigatran 150 mg twice daily was associated with fewer events versus dabigatran 110 mg twice daily, edoxaban 30 mg daily, edoxaban 60 mg daily and rivaroxaban. Apixaban and rivaroxaban were also associated with fewer events compared to edoxaban 30 mg daily. There were no differences among low-dose ASA, medium-dose ASA, and clopidogrel plus low-dose ASA. However, low-dose ASA and the combination of clopidogrel plus low-dose ASA were associated with increases in stroke or SE compared to all newer oral anticoagulants. For major bleeding, apixaban and dabigatran 110 mg twice daily were associated with fewer events versus dabigatran 150 mg twice daily and rivaroxaban. Edoxaban 30 mg daily was associated with fewer events than other new oral anticoagulants, while edoxaban 60 mg daily was associated with fewer events compared with rivaroxaban and clopidogrel plus low-dose ASA. The risk of major bleeding for apixaban was lower compared to clopidogrel plus low-dose ASA. There were no differences associated with the ASA

Standard Adjusted-Dose VKA	0.93 (0.81,1.08)	0.69 (0.6,0.8)	0.79 (0.69,0.9)	1.03 (0.89,1.19)	0.8 (0.69,0.93)	0.46 (0.4,0.54)	1.78 (0.62,5.6)	1.05 (0.6,1.87)	1.1 (0.83,1.47)
0.66 (0.53,0.82)	Dabigatran 150 mg twice daily	0.74 (0.6,0.91)	0.84 (0.69,1.03)	1.1 (0.9,1.35)	0.86 (0.74,1.003)	0.5 (0.4,0.61)	1.91 (0.66,6.08)	1.13 (0.63,2.04)	1.18 (0.85,1.63)
0.78 (0.65,0.94)	1.19 (0.89,1.58)	Apixaban 5 mg twice daily	1.14 (0.93,1.38)	1.49 (1.21,1.82)	1.16 (0.94,1.43)	0.67 (0.54,0.83)	2.57 (0.89,8.18)	1.52 (0.85,2.75)	1.59 (1.16,2.2)
0.87 (0.74,1.02)	1.31 (1.002,1.73)	1.11 (0.87,1.41)	Edoxaban 60 mg daily	1.31 (1.08,1.59)	1.02 (0.83,1.25)	0.59 (0.5,0.69)	2.27 (0.78,7.17)	1.34 (0.75,2.41)	1.4 (1.02,1.92)
0.88 (0.74,1.04)	1.33 (1.01,1.76)	1.12 (0.87,1.43)	1.01 (0.8,1.28)	Rivaroxaban 20 mg daily	0.78 (0.63,0.96)	0.45 (0.37,0.56)	1.74 (0.6,5.48)	1.02 (0.57,1.85)	1.07 (0.78,1.48)
0.91 (0.74,1.12)	1.38 (1.11,1.74)	1.17 (0.88,1.53)	1.05 (0.81,1.37)	1.04 (0.8,1.36)	Dabigatran 110 mg twice daily	0.58 (0.47,0.72)	2.22 (0.77,7.03)	1.31 (0.73,2.37)	1.37 (0.99,1.9)
1.14 (0.98,1.32)	1.73 (1.32,2.26)	1.45 (1.15,1.84)	1.31 (1.13,1.54)	1.3 (1.04,1.63)	1.25 (0.97,1.61)	Edoxaban 30 mg daily	3.85 (1.32,12.18)	2.27 (1.26,4.1)	2.38 (1.72,3.3)
1.35 (0.74,2.47)	2.04 (1.08,3.9)	1.72 (0.92,3.24)	1.56 (0.84,2.91)	1.54 (0.83,2.88)	1.48 (0.79,2.8)	1.18 (0.64,2.21)	Medium Dose ASA (> 100 mg and ≤ 300 mg daily)	0.59 (0.17,1.94)	0.62 (0.19,1.84)
1.87 (1.26,2.8)	2.84 (1.81,4.5)	2.39 (1.55,3.72)	2.16 (1.42,3.34)	2.14 (1.4,3.31)	2.05 (1.32,3.23)	1.64 (1.08,2.53)	1.39 (0.74,2.61)	Low Dose ASA (≤ 100 mg daily)	1.05 (0.55,1.97)
1.93 (1.42,2.64)	2.93 (2.01,4.3)	2.46 (1.73,3.54)	2.23 (1.58,3.17)	2.2 (1.55,3.14)	2.11 (1.46,3.07)	1.69 (1.21,2.4)	1.43 (0.73,2.81)	1.03 (0.62,1.7)	Low dose ASA (≤ 100 mg daily) & Clopidogrel 75 mg daily

Figure 3 OR from network meta-analyses for stroke or systemic embolism and major bleeding for all pairwise comparisons. (Results between individual treatments, especially newer oral anticoagulants, should be interpreted with caution, given the limitations associated with using a fixed-effects model. See online supplementary appendix 9 for additional details.) ORs for recurrence of stroke or systemic embolism are below the diagonal (row-defining treatment vs column-defining treatment) and those for major bleeding are above the diagonal and in blue (column-defining treatment vs row-defining treatment). To obtain ORs for comparisons in the opposite direction, reciprocals should be taken (eg, the OR for standard dose warfarin compared with apixaban 5 mg twice daily for stroke or systemic embolism is $1/0.78=1.28$). Significant results are in bold. VKA, vitamin K antagonist.

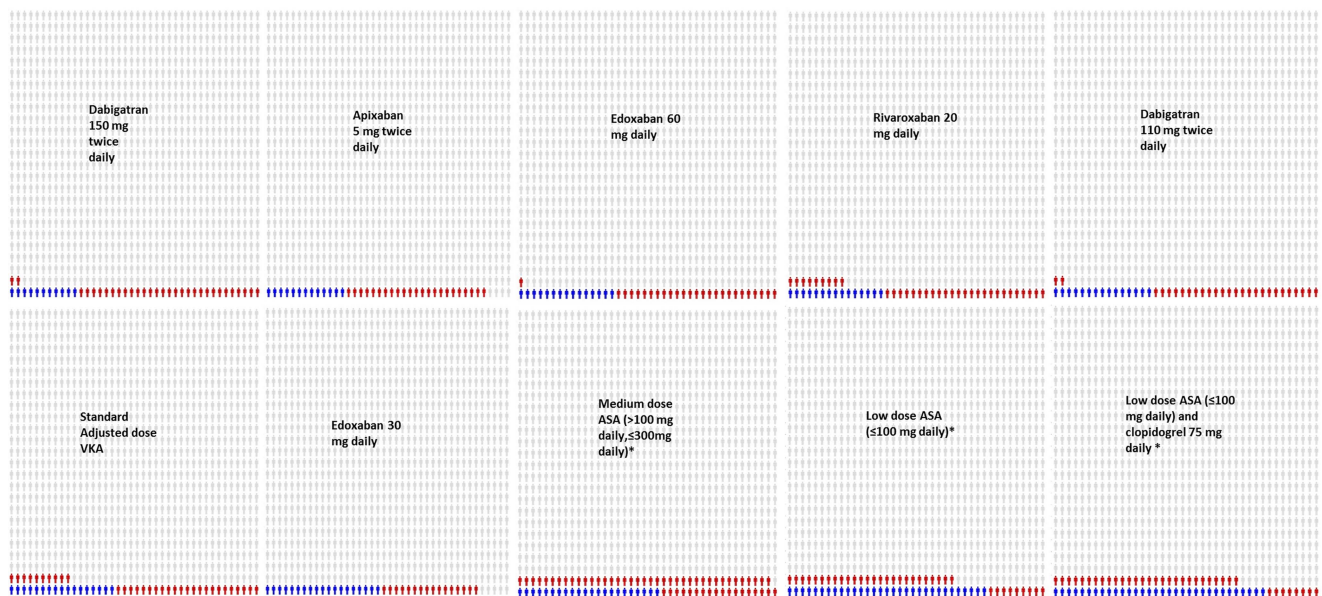


Figure 4 Icon array illustrating the absolute risks of Stroke or systemic embolism (blue) and major bleeding episodes (red) per 1000 patients treated. (Figures do not reflect uncertainty around effect estimates and there is more uncertainty (ie, wider credible intervals) for low-dose ASA, medium-dose ASA and clopidogrel plus low dose ASA (see online supplementary appendix 8). Underlying studies may also double count haemorrhage stroke.)

Table 1 Subgroup and sensitivity analyses for stroke or systemic embolism and major bleeding relative to standard adjusted dose VKA, OR±95% credible intervals versus standard adjusted dose VKA

	Reference case—fixed effect NMA	Subgroup analysis by CHADS ₂ score		Subgroup analysis by age		Subgroup analysis by TTR	
Treatment		CHADS ₂ <2	CHADS ₂ ≥2	Age <75 years	Age ≥75 years	TTR <66%	TTR ≥66%
Stroke or systemic embolism							
Dabigatran 150 mg twice daily	0.66 (0.53, 0.82)	0.61 (0.37, 0.999)	0.66 (0.52, 0.85)	0.63 (0.46, 0.87)	0.66 (0.48, 0.90)	0.54 (0.39, 0.73)	0.81 (0.58, 1.11)
Apixaban 5 mg twice daily	0.78 (0.65, 0.94)	0.86 (0.57, 1.28)	0.78 (0.63, 0.95)	0.85 (0.67, 1.07)	0.71 (0.53, 0.95)	0.79 (0.62, 1.003)	0.79 (0.60, 1.05)
Edoxaban 60 mg daily	0.87 (0.74, 1.02)	NA	0.87 (0.74, 1.01)	0.91 (0.73, 1.14)	0.83 (0.66, 1.04)	0.83 (0.65, 1.07) *	0.91 (0.73, 1.13)
Rivaroxaban 20 mg daily	0.88 (0.74, 1.04)	NA	0.88 (0.74, 1.04)	0.95 (0.75, 1.2)	0.80 (0.63, 1.03)	0.81 (0.65, 1.01)	0.72 (0.47, 1.10)
Dabigatran 110 mg twice daily	0.91 (0.74, 1.12)	1.00 (0.64, 1.55)	0.89 (0.71, 1.12)	0.93 (0.7, 1.24)	0.88 (0.66, 1.19)	0.91 (0.69, 1.19)	0.90 (0.66, 1.24)
Edoxaban 30 mg daily	1.14 (0.98, 1.32)	NA	1.14 (0.98, 1.32)	1.16 (0.94, 1.44)	1.13 (0.91, 1.40)	1.01 (0.80, 1.28)*	1.24 (1.01, 1.24)
Medium-dose ASA (>100 mg and ≤300 mg daily)	1.35 (0.74, 2.47)	1.97 (0.63, 6.73)†	NA	NA	NA	NA	NA
Low-dose ASA (≤100 mg daily)	1.87 (1.26, 2.8)	2.20 (1.18, 4.25)	2.10 (0.91, 5.15) ‡	NA	2.04 (1.33, 3.20)	NA	NA
Clopidogrel 75 mg daily and Low-dose aspirin (≤100 mg daily)	1.93 (1.42, 2.64)	3.16 (1.39, 8.22)	1.15 (0.84, 1.57)	NA	NA	1.52 (0.96, 2.45)	2.40 (1.59, 3.71)
Major bleeding							
Edoxaban 30 mg daily	0.46 (0.4, 0.54)	NA	0.46 (0.4, 0.54)	0.50 (0.41, 0.61)§	0.51 (0.41–0.62)§	0.45 (0.35, 0.58)*§	0.51 (0.43, 0.61)
Apixaban 5 mg twice daily	0.69 (0.6, 0.80)	0.59 (0.44, 0.78)	0.73 (0.62, 0.87)	0.73 (0.6, 0.89)	0.65 (0.52, 0.80)	0.57 (0.45, 0.71)	0.81 (0.67, 0.98)
Edoxaban 60 mg daily	0.79 (0.69, 0.9)	NA	0.79 (0.69, 0.90)	0.74 (0.62–0.90)§	0.82 (0.68–0.98)§	0.69 (0.55, 0.87) ast;§	0.83 (0.70, 0.97)
Dabigatran 110 mg twice daily	0.80 (0.69, 0.93)	0.65 (0.47, 0.89)	0.86 (0.73, 1.02)	0.62 (0.49, 0.77)	1.02 (0.84, 1.25)	0.74 (0.61, 0.91)	0.86 (0.69, 1.06)
Dabigatran 150 mg twice daily	0.93 (0.81, 1.08)	0.77 (0.57, 1.04)	1.01 (0.86, 1.19)	0.70 (0.56, 0.86)	1.19 (0.98, 1.45)	0.76 (0.62, 0.94)	1.15 (0.94, 1.40)
Rivaroxaban 20 mg daily	1.03 (0.89, 1.19)	NA	1.03 (0.89, 1.19)	0.93 (0.76, 1.13)	1.15 (0.93, 1.41)	0.92 (0.77, 1.10)	1.30 (1.01, 1.69)
Low-dose ASA (≤100 mg daily)	1.05 (0.6, 1.87)	0.83 (0.42, 1.64)	1.60 (0.55, 5.02) ‡	NA	1.01 (0.57, 1.78)	NA	NA
Clopidogrel 75 mg daily and low-dose aspirin (≤100 mg daily)	1.10 (0.83, 1.47)	1.51 (0.89, 2.61)	0.97 (0.69, 1.36)¶	NA	NA	0.66 (0.42, 1.02)	1.66 (1.12, 2.47)
Medium-dose ASA (>100 mg and <300 mg daily)	1.79 (0.63, 5.67)	1.48 (0.11, 19.07)†	NA	NA	NA	NA	NA

Significant results are in bold.

*Data provided from ENGAGE AF-TIMI 48²⁰ use TTR >60%.†Results may be slightly biased against medium-dose ASA. Based on study level results from CAFA and JAST studies. Although these studies consisted primarily of low-risk populations, some patients may have CHADS₂ scores greater than 2.‡Results may be slightly biased against LDASA. Derived from the BAFTA study where CHADS₂ subgroup data were stratified by CHADS₂ 1–2 (vs 0–1) and CHADS₂ 3–6 (vs 2–6).

§Based on overall time period where overall time period was defined as first dose to the last dose plus 3 days.

¶Estimated from the subgroup study by Healey *et al* (2008).^{29a}

ASA, acetylsalicylic acid; NA, not available; NMA, network meta-analysis; TTR, time in therapeutic range; VKA, vitamin K antagonist.

treatments, both for comparisons among themselves and compared to the anticoagulant treatments.

Figure 4 plots the absolute risk for stroke or SE and major bleeding per 1000 treated for the 10 treatments analysed. Data in figure 4 were obtained from the results presented in online supplementary appendix 6 and 7. Examination of the data in figure 4 suggests that the balance of benefits and harms of the new oral anticoagulants for stroke or SE and major bleeding is positive compared to standard adjusted dose VKA (decrease in stroke or SE and/or major bleeding) and largely similar among one another. Comparison of all anticoagulant treatment (including standard adjusted dose VKA) to ASA or ASA in combination with clopidogrel indicates that whereas the new oral anticoagulants decrease the risk of stroke or SE and major bleeding, ASA has a less favourable balance of benefits and harms, that is, fails to minimise the risk of stroke or SE and/or major bleeding.

DISCUSSION

We identified 16 RCTs comparing antithrombotic agents for the prevention of all cause stroke or SE and major bleeding in patients with AF. To the best of our knowledge, this is the most up-to-date systematic review and network meta-analysis^{30–34} to synthesise the available benefits and harms on newer oral anticoagulants, standard adjusted dose VKA and antiplatelet agents for the prevention of stroke and major bleeding in patients with non-valvular AF (see online supplementary appendix 13). Harenberg *et al*³⁰ recently summarised the published indirect comparisons and network meta-analyses evaluating newer oral anticoagulants for AF and an earlier unpublished version of our analysis¹⁷ was considered to be among the most comprehensive analyses at that time.³⁰ This network meta-analysis expands on that unpublished report.¹⁷ Overall, our findings align with those reported in previously published network meta-analyses^{30–31–33}; however, unlike previous analyses,³⁰ we include recently published edoxaban data,²⁰ and also include antiplatelet agents. We also present detailed evidence networks³⁵ to illustrate the body of evidence for each outcome; report analysis using multiple statistical models (see online supplementary appendix 9); report detailed a priori subgroup analyses for each outcome using data derived from FDA Public Summary Documents^{9–18}; present findings on the relative and absolute scale,^{36–37} and graphically illustrate results using icon arrays. Our network meta-analysis was registered in PROSPERO, and also adheres to PRISMA reporting standards (see online supplementary appendix 10). It also differs from a recently published traditional meta-analysis by Ruff *et al*,³² given that we report the comparison of newer oral anticoagulants versus each other and also include comparisons with antiplatelet agents.

For stroke or SE, dabigatran 150 mg and apixaban twice daily were associated with reductions in stroke or SE relative to standard adjusted dose VKA. In contrast,

low-dose ASA and the combination of clopidogrel plus low-dose ASA that appeared were associated with increases in stroke or SE relative to standard adjusted dose VKA. No differences were detected between standard adjusted dose VKA and each of the following interventions: dabigatran 110 mg twice daily, edoxaban 30 and 60 mg daily, rivaroxaban, medium-dose ASA and no treatment/placebo. The absolute risk reduction of stroke or SE relative to standard adjusted dose VKA ranged from 6 fewer to 15 more events per 1000 patients treated per year, with dabigatran 150 mg twice daily yielding the largest absolute risk reduction and clopidogrel plus low-dose ASA the largest absolute risk increase.

For major bleeding, edoxaban 30 mg daily, apixaban, edoxaban 60 mg daily and dabigatran 110 mg twice daily were associated with a decreased risk of major bleeding relative to standard adjusted dose VKA. No differences for major bleeding were detected between standard adjusted dose VKA and each of the remaining interventions: dabigatran 150 mg twice daily, rivaroxaban, clopidogrel plus low-dose ASA and all ASA dosages. The absolute risk difference of major bleeding relative to standard adjusted dose VKA ranged from 18 fewer to 24 more events per 1000 patients treated, with edoxaban 30 mg daily yielding the largest absolute risk reduction and medium-dose ASA the largest absolute risk increase. Results of network meta-analyses reflect the relative efficacy and safety profile of antiplatelet and anticoagulant drugs as documented by large clinical trials. Thus, international guidelines^{1–2} for prevention of stroke in patients with AF also recommended oral anticoagulation over antiplatelet therapy as the latter had only modest protective effects. With respect to the new oral anticoagulants, none of the guidelines has given a recommendation to prefer one of the new oral anticoagulants over another.^{1–2}

Network meta-analysis involves pooling of trials. We observed variability across studies included in the evidence network in terms of CHADS₂, age and TTR (see online supplementary appendices 3 and 4). For example, patients using rivaroxaban had a higher risk of stroke because ROCKET-AF²² included patients with CHADS₂ ≥ 2 . As such, we conducted subgroup analysis to adjust for differences in patient and study-level characteristics. We derived data for subgroup analyses from FDA Public Summary documents,^{9–18–19} which enhanced our ability to account for variability across studies (eg, use intention to treat population for rivaroxaban versus per-protocol as-treated population reported in publication²²). Results from these subgroup analyses differed slightly from those reported in the primary analysis, indicating that there may be differences in the benefits and harms across subgroups. This becomes more apparent when subgroup analyses are reported on the absolute scale.³ It is unclear whether the absolute risk reductions associated with these differences translate into clinically meaningful benefits in practice, especially in subpopulations of patients with a lower baseline risk

of stroke or SE. To fully elucidate the comparative benefits and harms of antithrombotic agents across the various subpopulations, rigorously conducted comparative studies^{38 39} or network meta-regression analyses of patient-level data⁴⁰ are required.

There are several limitations with the analysis we employed. First, there is notable heterogeneity in patients and study characteristics (see online supplementary appendices 3 and 4). However, the small number of studies limits the analyses that can be conducted to account for heterogeneity in the absence of patient-level data. Second, there is insufficient subgroup data available for other outcomes reported in the RCTs included. As a consequence, detailed analysis was limited to two outcomes—stroke and SE and major bleeding. Third, we reported the results from the fixed-effects model in the main text. We felt that this was appropriate as the nodes in evidence networks are connected largely by single studies. Effect estimates derived from the fixed-effects model aligned more closely with the direct estimates. Reporting results from the fixed-effects model in the main text most likely biases results in favour of the new oral anticoagulants, as treatments that achieved statistically significant results in the primary RCTs retained statistically significant findings when using the fixed-effects model, but not always when using the random-effects model due to the prior¹¹ on the between-study variance. Nevertheless, the results from the random-effects model have also been reported in online supplementary appendix 9, along with a detailed discussion around the limitations in using the fixed-effects model. Fourth, the absolute risk reduction for the network meta-analysis was calculated using the event rate in the standard adjusted dose VKA arm of the RE-LY study. The RE-LY trial was selected because it contained data for both CHADS₂ <2 and CHADS₂ ≥2 and had detailed data made publicly available following an FDA review of dabigatran. Use of a different study (eg, ARISTOTLE) for baseline event rate data is unlikely to change the results substantially, given that the event rates in standard adjusted dose VKA arms were similar across studies. Fifth, we present findings using graphics that have been largely applied in the network meta-analysis literature,⁴¹ such as a table with OR for all pairwise comparisons. This method of presenting findings on the relative scale is problematic when you are conducting assessments to compare the balance of benefits and harms, which need to be standardised. As such, we also provided results in absolute terms. We report our findings using icon arrays, although it should be noted that these results do not account for the utility values based on patient preferences for each of the outcomes;^{42 43} nor do they reflect uncertainty, although we report absolute reductions on the risk benefit plane reflecting uncertainty in online supplementary appendix 8. There are other methods available that can incorporate patient preferences for outcomes.^{42 43} Further, estimates of benefits and harms with several of the

therapies (eg, rivaroxaban) come from one trial, and thus such data are not particularly robust. Further research is needed that compares the balance of benefits and harms using other research methodologies, incorporating other relevant outcomes, patient preferences for each of the outcomes^{42 43} and additional studies when they become available. Finally, haemorrhagic stroke is also considered a major bleed in underlying studies. Accordingly, we may have double counted haemorrhage stroke in this analysis. Unfortunately, we are not able to account for this issue in all included studies. Nonetheless, it is important to note this limitation and highlight that this potentially biases results in favour of newer oral anticoagulants, given that these agents were associated with reductions in these events.

CONCLUSIONS

Compared with standard adjusted dose VKA, dabigatran 150 mg and apixaban twice daily were associated with reductions in the incidence of stroke or SE in patients with AF, whereas low-dose ASA and the combination of clopidogrel plus low-dose ASA increased the risk relative to standard adjusted dose VKA at preventing stroke or SE. Edoxaban 30 mg daily, apixaban, edoxaban 60 mg daily and dabigatran 110 mg twice daily were associated with reduced risk in major bleeding compared with standard adjusted dose VKA. Although the results of the current review revealed that there were differences in stroke or SE and major bleeding among antithrombotic agents in the management of patients with AF in relative terms, it is unclear whether the absolute risk reductions associated with these differences translate into clinically meaningful benefits in practice, especially in subpopulations of patients with a lower baseline risk of stroke or SE. Rigorously conducted comparative studies or network meta-regression analyses of patient-level data are required to fully elucidate the comparative benefits and harms of antithrombotic agents across the various subpopulations.

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Contributors CC conceived the study design, performed the data extraction and analysis, and drafted the manuscript. DC and GW conceived the study design, helped with the data analysis and reviewed the manuscript for important intellectual content. TR conceived the study design, performed the systematic review and data extraction, and reviewed the manuscript for important intellectual content. SK, SS, KG, AB, KM and KC performed the

systematic review and data extraction, and reviewed the manuscript for important intellectual content. TC, MC and KC conceived the study and reviewed the manuscript for important intellectual content. All authors have read and approved the final version of the manuscript.

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Competing interests None.

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REFERENCES

- Kirchhof P, Curtis AB, Skanes AC, *et al*. Atrial fibrillation guidelines across the Atlantic: a comparison of the current recommendations of the European Society of Cardiology/European Heart Rhythm Association/European Association of Cardiothoracic Surgeons, the American College of Cardiology Fou. *Eur Heart J* 2013;34:1471–4.
- Skanes AC, Healey JS, Cairns JA, *et al*. Focused 2012 update of the Canadian Cardiovascular Society atrial fibrillation guidelines: recommendations for stroke prevention and rate/rhythm control. *Can J Cardiol* 2012;28:125–36.
- Antithrombotic agents for the prevention of stroke and systemic embolism in patients with atrial fibrillation. 2013. http://www.cadth.ca/media/pdf/TR0003_AntithromboticAgents-AF_ScienceReport-e.pdf
- Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost* 2005;3:692–4.
- NHS Quality Improvement Scotland (NHS QIS). *SIGN 50. A guideline developer's handbook*. 2008. <http://www.sign.ac.uk/pdf/sign50.pdf>
- Moher D, Liberati A, Tetzlaff J, *et al*. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6:e1000097.
- Dias S, Sutton AJ, Ades A, *et al*. Evidence synthesis for decision making 2: a generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials. *Med Decis Making* 2013;33:607–17.
- Connolly S, Ezekowitz M. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;361:1139–51.
- Ingelheim B. Advisory committee briefing document: dabigatran etexilate [Internet]. 2010:1–168. <http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/cardiovas>
- Cipriani A, Furukawa TA, Salanti G, *et al*. Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. *Lancet* 2009;373:746–58.
- Turner RM, Davey J, Clarke MJ, *et al*. Predicting the extent of heterogeneity in meta-analysis, using empirical data from the Cochrane Database of Systematic Reviews. *Int J Epidemiol* 2012;41:818–27.
- Spiegelhalter DJ, Best NG, Carlin BP, *et al*. Bayesian measures of model complexity and fit. *J R Stat Soc Ser B (Statistical Methodol)* 2002;64:583–639.
- Spiegelhalter D, Thomas A, Best N. *WinBUGS user manual*. MRC Biostat Unit, 2004:2.
- meta: Meta-Analysis with R. <http://cran.r-project.org/web/packages/meta/index.html>
- Dias S, Welton NJ, Sutton AJ, *et al*. Evidence synthesis for decision making 4: inconsistency in networks of evidence based on randomized controlled trials. *Med Decis Making* 2013;33:641–56.
- Salanti G, Marinho V, Higgins JP. A case study of multiple-treatments meta-analysis demonstrates that covariates should be considered. *J Clin Epidemiol* 2009;62:857–64.
- Wells G, Coyle D, Cameron C, *et al*. Safety, effectiveness, and cost effectiveness of new oral anticoagulants compared with warfarin in preventing stroke and other cardiovascular events in patients with atrial fibrillation. 2012. http://www.cadth.ca/media/pdf/NOAC_Therapeutic_Review_final_report.pdf
- Johnson & Johnson Pharmaceutical Research & Development. Rivaroxaban for the prevention of stroke and non-central nervous system (CNS) systemic embolism in patients with atrial fibrillation. 2011;7939:222.
- McDonagh MS, Peterson K, Balshem H, *et al*. US Food and Drug Administration documents can provide unpublished evidence relevant to systematic reviews. *J Clin Epidemiol* 2013;66:1071–81.
- Giugliano RP, Ruff CT, Braunwald E, *et al*. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013;369:2093–104.
- Granger C, Alexander J. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;981–92.
- Patel M, Mahaffey K, Garg J. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011:883–91.
- Connolly S, Pogue J, Hart R, *et al*. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial Fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. *Lancet* 2006;367:1903–12.
- Ezekowitz MD, Reilly PA, Nehmiz G, *et al*. Dabigatran with or without concomitant aspirin compared with warfarin alone in patients with nonvalvular atrial fibrillation (PETRO Study). *Am J Cardiol* 2007;100:1419–26.
- Rash A, Downes T, Portner R, *et al*. A randomised controlled trial of warfarin versus aspirin for stroke prevention in octogenarians with atrial fibrillation (WASPO). *Age Ageing* 2007;36:151–6.
- Chung N, Jeon HK, Lien LM, *et al*. Safety of edoxaban, an oral factor Xa inhibitor, in Asian patients with non-valvular atrial fibrillation. *Thromb Haemost* 2011;105:535–44.
- Yamashita T, Koretsune Y, Yasaka M, *et al*. Randomized, multicenter, warfarin-controlled phase II study of edoxaban in Japanese patients with non-valvular atrial fibrillation. *Circ J* 2012;76:1840–7.
- Connolly S, Eikelboom J. Apixaban in patients with atrial fibrillation. *N Engl J Med* 2011;364:806–17.
- Connolly SJ, Pogue J, Hart RG, *et al*. Effect of clopidogrel added to aspirin in patients with atrial fibrillation. *N Engl J Med* 2009;360:2066–78.
- Healey JS, Hart RG, Pogue J, *et al*. Risks and benefits of oral anticoagulation compared with clopidogrel plus aspirin in patients with atrial fibrillation according to stroke risk: the atrial fibrillation clopidogrel trial with irbesartan for prevention of vascular events (ACTIVE-W). *Stroke* 2008;39:1482–6.
- Harenberg J, Weiss C. Clinical trials with new oral anticoagulants. Additive value of indirect comparisons also named network meta-analyses. *Hamostaseologie* 2013;33:62–70.
- Dogliotti A, Paolasso E, Giugliano RP. Current and new oral antithrombotics in non-valvular atrial fibrillation: a network meta-analysis of 79 808 patients. *Heart* 2014;100:396–405.
- Ruff CT, Giugliano RP, Braunwald E, *et al*. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet* 2013;6736:1–8.
- Assiri A, Al-Majzoub O, Kanaan AO, *et al*. Mixed treatment comparison meta-analysis of aspirin, warfarin, and new anticoagulants for stroke prevention in patients with nonvalvular atrial fibrillation. *Clin Ther* 2013;35:967–84.e2.
- Slot K, Berge E. Factor Xa inhibitors versus vitamin K antagonists for preventing cerebral or systemic embolism in patients with atrial fibrillation. *Stroke* 2013. <http://stroke.ahajournals.org/content/44/12/e165.short>
- Salanti G, Kavvoura FK, Ioannidis JP, *et al*. Exploring the geometry of treatment networks. *Ann Intern Med* 2008;148:544–53.
- Barratt A, Wyer PC, Hatala R, *et al*. Tips for learners of evidence-based medicine: 1. Relative risk reduction, absolute risk reduction and number needed to treat. *Can Med Assoc J* 2004;171:353–8.
- Schechtman E. Odds ratio, relative risk, absolute risk reduction, and the number needed to treat—which of these should we use? *Value Health* 2002;5:431–6.



38. Berger ML, Mamdani M, Atkins D, *et al.* Good research practices for comparative effectiveness research: defining, reporting and interpreting nonrandomized studies of treatment effects using secondary data sources: the ISPOR Good Research Practices for Retrospective Database Analysis Task Force. *Value Health* 2009;12:1044–52.
39. Berger ML, Dreyer N, Anderson F, *et al.* Prospective observational studies to assess comparative effectiveness: the ISPOR good research practices task force report. *Value Health* 2012;15:217–30.
40. Jansen JP. Network meta-analysis of individual and aggregate level data. *Res Synth Methods* 2012;3:177–90.
41. Salanti G, Ades A, Ioannidis J. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *J Clin Epidemiol* 2011;64:163–71.
42. Guo JJ, Pandey S, Doyle J, *et al.* A review of quantitative risk-benefit methodologies for assessing drug safety and efficacy-report of the ISPOR risk-benefit management working group. *Value Health* 2010;13:657–66.
43. Boyd C, Singh S, Varadhan R, *et al.* *Methods research report methods for benefit and harm assessment in systematic reviews*. 2012:52. <http://www.ncbi.nlm.nih.gov/books/NBK115750/>

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Systematic review and network meta-analysis comparing antithrombotic agents for the prevention of stroke and major bleeding in patients with atrial fibrillation

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Research Submission

Triptans in the Acute Treatment of Migraine: A Systematic Review and Network Meta-Analysis

Chris Cameron, *MSc; Shannon Kelly, *BSc; Shu-Ching Hsieh, PhD; Meghan Murphy, MSc; Li Chen, MSc; Ahmed Kotb, MSc; Joan Peterson, BA; Doug Coyle, PhD; Becky Skidmore, MLS; Tara Gomes, MHSc; Tammy Clifford, PhD; George Wells, PhD

Background.—Although triptans are widely used in the acute management of migraine, there is uncertainty around the comparative efficacy of triptans among each other and vs non-triptan migraine treatments. We conducted systematic reviews and network meta-analyses to compare the relative efficacy of triptans (alone or in combination with other drugs) for acute treatment of migraines compared with other triptan agents, non-steroidal anti-inflammatory drugs (NSAIDs), acetylsalicylic acid (ASA), acetaminophen, ergots, opioids, or anti-emetics.

Methods.—The Cochrane Library, MEDLINE, and EMBASE were searched for randomized controlled trials that compared triptans (alone or in combination with other drugs) with placebo-controlled or active migraine treatments. Study selection, data extraction, and quality assessment were completed independently by multiple reviewers. Outcome data were combined and analyzed using a Bayesian network meta-analysis. For each outcome, odds ratios, relative risks, and absolute probability of response were calculated.

Results.—A total of 133 randomized controlled trials met the inclusion criteria. Standard dose triptans relieved headaches within 2 hours in 42 to 76% of patients, and 2-hour sustained freedom from pain was achieved for 18 to 50% of patients. Standard dose triptans provided sustained headache relief at 24 hours in 29 to 50% of patients, and sustained freedom from pain in 18 to 33% of patients. Use of rescue medications ranged from 20 to 34%. For 2-hour headache relief, standard dose triptan achieved better outcomes (42 to 76% response) than ergots (38%); equal or better outcomes than NSAIDs, ASA, and acetaminophen (46 to 52%); and equal or slightly worse outcomes than combination therapy (62 to 80%). Among individual triptans, sumatriptan subcutaneous injection, rizatriptan ODT, zolmitriptan ODT, and eletriptan tablets were associated with the most favorable outcomes.

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Ethical Approval: Not required.

Conflicts of Interest: None.

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Interpretation/Conclusions.—Triptans are effective for migraine relief. Standard dose triptans are associated with better outcomes than ergots, and most triptans are associated with equal or better outcomes compared with NSAIDs, ASA, and acetaminophen. Use of triptans in combination with ASA or acetaminophen, or using alternative modes of administration such as injectables, may be associated with slightly better outcomes than standard dose triptan tablets.

Key words: triptan, efficacy, benefit, migraine, systematic review, network meta-analysis

(*Headache* 2015;55:221-235)

Migraine is a common and potentially disabling neurological condition characterized by recurrent moderate to severe pain generally occurring on one side of the head. Globally, it is estimated that over 10 to 15 percent of people suffer from migraines.¹ The condition causes short- and long-term disability, reduces quality of life, and often impacts work productivity, social relationships, and family life.²⁻⁴

The acute management of migraines includes the use of non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, ergots, opioids, and triptans. For many patients with moderate to severe migraine, triptans are considered the first-line therapy. There are now seven triptans (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan) available in Canada. The relative efficacy of each triptan among each other is uncertain since the majority of triptan studies have been placebo controlled. Further, while other reviews³⁻¹⁰ have attempted to examine the relative efficacy of triptans among each other and vs non-triptan migraine treatments, these studies have not considered multiple routes of administration (tablets, oral disintegrating tablets, injection, nasal spray, rectal suppositories), combination triptan therapy, or dose.

Therefore, as part of a larger initiative by the Ontario Drug Policy Research Network to evaluate triptans for the acute treatment of migraine in adults and provide recommendations for funding changes of these drugs in Ontario (<http://odprn.ca/drug-class-review/completed-reviews/triptans/>), we conducted a systematic review and network meta-analysis to address the following research question: What is the evidence for the efficacy, effectiveness, and safety of triptans (alone or in combination with other drugs) for acute treatment of migraines compared with: other triptan agents, NSAIDs, acetylsalicylic

acid (ASA), acetaminophen, ergots, opioids, or anti-emetics?

METHODS

Data Sources and Searches.—Published randomized controlled trials (RCTs) were identified using electronic search strategies developed and tested by an experienced medical information specialist in consultation with the review team. Using the OVID platform, we searched Ovid MEDLINE®, Ovid MEDLINE® In-Process & Other Non-Indexed Citations, and Embase Classic + Embase to identify English-language RCTs published from inception to October 6, 2013. Using the Cochrane Library on Wiley, the Cochrane Database of Systematic Reviews and CENTRAL were also searched. Strategies utilized a combination of controlled vocabulary (eg, migraine disorders, tryptamines) and keywords (eg, triptans, rizatriptan, sumatriptan). Vocabulary and syntax were adjusted across databases. Additional references were also sought through hand searching the bibliographies of relevant articles. Gray literature was searched using Google Scholar and the clinical trial sites listed in CADTH's Grey Matters (<http://cadth.ca/resources/grey-matters>). Complete details of the electronic search strategy, including any limits used, are reported in Appendix S1.

Study Selection.—The protocol was peer reviewed and published online prior to the start of the review. Studies were eligible for inclusion in the systematic review if they satisfied the population, intervention, comparator, and outcome (PICO) statement, including the study designs of interest outlined in our protocol.

The population of interest were adults 18 years and older with migraine specified by the International Headache Society (IHS 1988; IHS 2004, IHS ICDH-2).

Studies which included patients with cluster, tension or other headaches, chronic or recurrent migraines who are not experiencing an acute episode were not included. Active and placebo-controlled RCTs were selected for inclusion if they were published in English and included at least one triptan under review. The following triptans were included in the review: almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan. Triptans were allowed to be used alone or in combination with other drugs. All routes of administration (tablets, oral disintegrating tablets, injection, nasal spray, and rectal suppositories) and all doses (any frequency or strength) were included. Doses are classified according to Table 1. Allowable comparator groups include: placebo; other triptans used either alone or in combination with other acute migraine therapies; or other acute pharmacologic migraine treatment options (eg, NSAIDs, ASA, acetaminophen, ergots, opioids, antiemetics). Numerous outcomes were considered and results are reported elsewhere: <http://odprn.ca/drug-class-review/completed-reviews/triptans/>; however, the focus of this publication are: headache relief at 2 hours; freedom from pain at 2 hours; sustained headache response at 24 hours; sustained freedom from pain at 24 hours; and use of rescue medication. In general, headache relief was defined as a reduction in headache intensity from moderate or severe to mild or none at 2 or 24 hours, whereas freedom from pain was defined as the percentage of patients pain-free at 2 and 24 hours.

Screening, Data Extraction, and Quality Assessment.

—In the first phase of screening, the titles and abstracts of all identified citations were screened by two independent reviewers (MM, JP). In the second phase of screening, full manuscripts were retrieved and screened by two independent reviewers on the basis of our predefined patient population, intervention, comparison, outcomes, and study design of interest. We only included RCTs/crossovers that reported data for the first attack. Disagreements were resolved through discussion or through adjudication by a third reviewer (SK). For each included study, one of four reviewers independently (MM, JP, SCH, AK) extracted the data on characteristics of trial participants, study characteristics, and details on each study arm/pharmacological intervention, including but not limited to: dose, frequency, route of administration, co-medication/prophylaxis, and results of the clinical safety and efficacy outcomes for the overall study population and the *a priori* subgroups identified. All extracted data were checked for accuracy by another reviewer. Any disagreements in the assessment of these data were resolved through discussion until consensus was reached.

Quality assessment of RCTs was performed independently by four reviewers (MM, JP, SCH, AK) using a standardized table based on major items from the Cochrane Risk of Bias Tool.¹¹ The trial selection process is presented in a flowchart based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)^{12,13} statement (Fig. 1).

Table 1.—Dose Categorization for a Migraine Attack (and Number of RCTs/Number of Patients for 2-Hour Relief)†

	Low dose (Half)	Standard dose (Common)	High dose (Double)
Eletriptan	20 mg (3 RCTs/514 patients)	40 mg (13 RCTs/3143 patients)	80 mg (10 RCTs/2042 patients)
Sumatriptan	25 mg (4 RCTs/850 patients)	50 mg (23 RCTs/5870 patients)	100 mg (23 RCTs/5210 patients)
Rizatriptan	5 mg (3 RCTs/752 patients)	10 mg (11 RCTs/2676 patients)	20 mg (1 RCT/82 patients)
Frovatriptan	—	2.5 mg (5 RCTs/1840 patients)	5 mg (2 RCTs/338 patients)
Almotriptan	6.25 mg (2 RCTs/527 patients)	12.5 mg (7 RCTs/2120 patients)	25 mg (2 RCTs/352 patients)
Zolmitriptan	1.25 mg (1 RCT/52 patients)	2.5 mg (10 RCTs/3491 patients)	5 mg (6 RCTs/2084 patients)
Naratriptan	—	2.5 mg (3 RCTs/512 patients)	5 mg (No data)

†Numbers for other outcomes are reported in Appendix S6.

— = no low dose available/relevant for this medication.

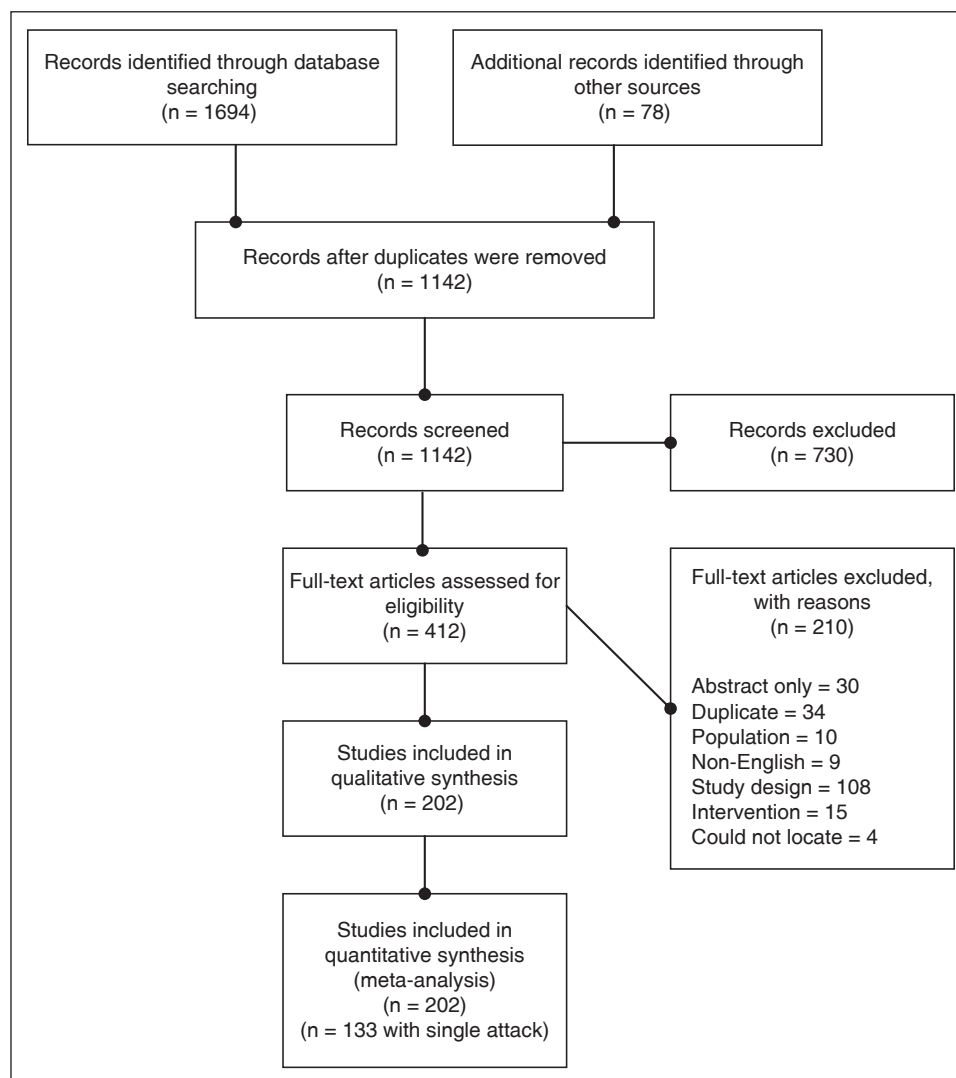


Fig 1.—PRISMA diagram.

Data Synthesis and Analysis.—We performed a Bayesian network meta-analysis. A Bayesian network meta-analysis requires two main elements: a likelihood function derived from a model that specifies the relation between the unknown parameters and the observed data, and prior distributions for the unknown parameters.¹⁴ A prior distribution of a parameter represents the uncertainty of parameter before the data are examined.^{14,15} The prior chosen may be informative or “vague” where the latter is thought to let the data drive the analysis. Multiplying the prior and the likelihood function leads to the posterior distribution of the parameter, which is used

to carry out all inferences in a Bayesian analysis.^{14,15} Methods for Bayesian network meta-analyses allow analysis of both placebo and active comparison studies simultaneously.¹⁴ Both direct and indirect pieces of evidence are combined. The results from indirect evidence combined with the direct evidence may strengthen the assessment between treatments evaluated using Bayesian network meta-analysis. Bayesian network meta-analyses were conducted using WinBUGS software version 1.4.3 (MRC Biostatistics Unit, Cambridge, UK). A binomial likelihood model which accounts for the use of multi-arm trials was used for the analyses given the datasets provided

were dichotomous outcomes and included multi-arm trials.¹⁴ Bayesian network meta-analyses were conducted for the following outcomes: headache relief within 2 hours; freedom from pain at 2 hours; sustained headache response at 24 hours; sustained freedom from pain at 24 hours; and use of rescue medication. Placebo was chosen as the reference group or index node in the model. Both random-effects network meta-analyses using informative priors and fixed-effects analyses were conducted;^{14,15} assessment of model fit and choice of model was based on assessment of the deviance information criterion (DIC) between study standard deviation and comparison of residual deviance to number of unconstrained data points.^{16,17}

Point estimates and 95% credible intervals for odds ratios (OR) were derived using Markov Chain Monte Carlo methods for all nodes in analysis. Risk ratios and absolute risk for an outcome of interest were estimated based on the ORs and the mean proportion of patients who experience the outcome in the placebo arms among included studies. Vague priors, such as $N(0, 100^2)$, were assigned for basic parameters throughout¹⁷ and informative priors for the variance parameter based on evidence on the extent of heterogeneity observed in previous meta-analyses, as described in Turner et al.¹⁵ To ensure convergence was reached, trace plots and the Brooks–Gelman–Rubin statistic were assessed.^{15,18} Three chains were fit in WinBUGS for each analysis, with at least 20,000 iterations, and a burn-in of at least 20,000 iterations.^{18,19}

We also qualitatively compared the results from our network meta-analysis with direct pairwise estimates. We formally assessed inconsistency by comparing the deviance between study variance and DIC statistics in fitted consistency and inconsistency models.²⁰ We also plotted the posterior mean deviance of the individual data points in the inconsistency model against their posterior mean deviance in the consistency model to identify any loops where inconsistency is present.²⁰ We also conducted a sensitivity analysis adjusting for control group response rate to address heterogeneity among included studies and generated a box plot to illustrate differences among included studies.

RESULTS

Search Results.—The initial literature search returned 1694 database abstracts and 78 gray literature documents (Fig. 1). After duplicates were removed, 1142 remained to be assessed for inclusion and 730 were excluded. Of the 412 full-text articles reviewed, 202 full-text publications were included after applying the PICO criteria. Of these, 69 were excluded from analysis as they did not present single migraine attack data. A total of 133 publications reported single migraine attack data in 133 unique RCTs. A complete list of included and excluded studies is available in Appendix S2.

Characteristics of Included Studies.—A detailed list of included studies, patients and study characteristics is provided in the technical report. All included studies were published between 1991 and 2012. Most were large, multicenter studies conducted in a variety of countries worldwide, and often across many different countries. The number of randomized patients was often bigger than the number of participants included in the effect estimates for outcomes in each trial, due to the fact that most trials reported modified intention to treat outcome populations, ie, based on recruited patients who subsequently experienced a migraine event. The trials all recruited migraine sufferers who met the International Classification of Headache Disorders (ICHD) for migraine headaches,^{21–24} or used inclusion criteria with sufficient comparability to the ICHD criteria. All studies generally included patients affected with migraine with or without aura, and a small number also included some patients with menstrual migraine.^{25–27} Four RCTs reported solely on menstrual migraine in female participants.^{28–31} All participants self-administered their study medications. Trial participants were generally between the ages of 18 and 65, with an average age of approximately 40. Very few trials included participants older than 65, and trials of children and adolescents were excluded by the PICO statement. Trial participants were predominantly female. In 133 studies reporting first attack data, the mean percent of females included was over 80%. Patients included in studies were both treatment naïve and experienced. In general, a high proportion of studies included participants with at least one

previous treatment failure with a triptan. The risk of bias assessment for each study is available upon request.

Headache Relief at 2 Hours.—The evidence network for headache relief at 2 hours included 96 studies and a total of 56,180 participants (Table 2). Overall, 45 different treatments were considered, providing for 287 comparisons. There is some evidence of inconsistency in the network (Appendix S3). Standard dose (SD) triptans relieved headaches within 2 hours in 42 to 76% of patients, compared with 27% for placebo. Sumatriptan subcutaneous injection (76%), rizatriptan ODT (69%), zolmitriptan ODT (66%) had the largest effect on 2-hour headache relief among monotherapies, whereas ergots (38%), frovatriptan (42%), naratriptan (46%), and ASA (46%) were associated with less favorable outcomes. SD triptans yielded equal or slightly worse outcomes than triptan combination therapies (62% to 80%). Detailed results are reported in Table 3 including credible intervals around point estimates.

Freedom From Pain at 2 Hours.—The evidence network for freedom from pain at 2 hours included 88 studies and a total of 50,929 participants. Overall, 41 different treatments were considered, involving 236 comparisons. There was no evidence of inconsistency in the network (Appendix S3). With SD triptans, only 18 to 50% of patients had freedom from pain within 2 hours, compared with 11% for placebo. Rizatriptan ODT (50%), eletriptan tablet (39%), rizatriptan tablet (37%), sumatriptan subcutaneous injection (37%), and zolmitriptan ODT (37%) had

the largest effect on 2-hour freedom from pain among monotherapies, whereas ergots (16%), naratriptan (18%), NSAIDs (22%), and acetaminophen (22%) were associated with less favorable outcomes. SD triptans yielded equal or slightly worse outcomes than triptan combination therapies (37% to 51%). Detailed results are reported in Table 3 including credible intervals around point estimates.

Sustained Headache Relief at 24 Hours.—The evidence network for headache relief at 24 hours included 29 studies and a total of 22,963 participants. Overall, 24 different treatments were compared, involving 102 comparisons. There was no evidence of inconsistency in the network (Appendix S3). SD triptans provided sustained headache relief at 24 hours ranging from 29% to 50%, compared with 17% for placebo. Zolmitriptan ODT (50%) and eletriptan tablet (47%) had the largest effect on 24 hour headache relief among monotherapies, whereas ergots (8%), acetaminophen (29%), ASA (29%), and rizatriptan (29%) were associated with less favorable outcomes. SD triptans yielded equal or slightly worse outcomes than triptan combination therapies (46% to 50%). Detailed results are reported in Table 3 including credible intervals around point estimates.

Sustained Freedom From Pain at 24 Hours.—The evidence network for freedom from pain at 24 hours included 42 studies and a total of 27,755 participants. Overall, 20 different treatments were considered, involving 115 comparisons. There was no evidence of inconsistency in the network (Appendix S3). Eighteen to 33% of patients on SD triptans had sustained

Table 2.—Summary of Patient and Study Characteristics for Each Evidence Network:† Headache Relief at 2 Hours, Freedom From Pain at 2 Hours, Sustained Headache Relief at 24 Hours, Sustained Freedom From Pain at 24 Hours, and Use of Rescue Medications

	2-hour headache relief	2-hour freedom from pain	24-hour sustained headache relief	24-hour sustained freedom from pain	Use of rescue medications
Number of studies	96	88	29	42	88
Number of treatment nodes	45	41	24	20	34
Number of participants	56,180	50,929	22,963	27,775	48,363
Number of comparisons	287	236	102	115	222
Number of 2-arm trials	46	47	13	23	50
Number of multi-arm trials	50	41	16	19	38

†Evidence networks consisted of a large number of nodes, which makes it difficult to illustrate graphically.

Table 3.—Percent of Patients (and 95% Credible Interval) Achieving: Headache Relief at 2 Hours, Freedom From Pain at 2 Hours, Sustained Headache Relief at 24 Hours, Sustained Freedom From Pain at 24 Hours, and Use of Rescue Medications†,‡

	2-hour headache relief		2-hour freedom from pain		24-hour sustained headache relief		24-hour sustained freedom from pain		Use of rescue medications	
	% (95%CrI)	OR (95%CrI)	% (95%CrI)	OR (95%CrI)	% (95%CrI)	OR (95%CrI)	% (95%CrI)	OR (95%CrI)	% (95%CrI)	OR (95%CrI)
Placebo	26.70% (25.7%,27.7%)	NA	10.60% (10.0%,11.3%)	NA	17.00% (15.9%,18.2)	NA	9.60% (8.9%,10.3%)	NA	51.60% (50.4%,52.%)	—
TABLET SD										
Almotriptan	48.30% (42.4%,54.2%)	2.56 (2.0,3.3)	24.50% (20.1%,29.6%)	2.73 (2.1,3.6)	35.70% (29.2%,43.0)	2.71 (2.0,3.7)	20.80% (15.9%,26.8%)	2.48 (1.8,3.5)	32.00% (26.1%,38.5%)	0.44 (0.3,0.6)
Eletriptan	60.40% (56.1%,64.6%)	4.19 (3.5,5.0)	39.20% (34.1%,44.7%)	5.43 (4.3,6.9)	47.30% (43.4%,51.3%)	4.37 (3.7,5.3)	32.90% (27.5%,38.7%)	4.63 (3.5,6.1)	21.10% (17.9%,24.7%)	0.25 (0.2,0.3)
Frovatriptan	42.40% (35.6%,49.5%)	2.02 (1.5,2.7)	34.70% (25.4%,45.9%)	4.48 (2.8,7.3)	—	—	—	—	31.00% (16.5%,50.6%)	0.42 (0.2,1.0)
Naratriptan	44.50% (35.6%,53.8%)	2.2 (1.5,3.2)	17.50% (11.8%,25.0%)	1.79 (1.1,2.8)	38.60% (30.7%,46.8%)	3.06 (2.1,4.3)	18.40% (12.0%,26.8%)	2.13 (1.3,3.5)	30.30% (23.0%,38.8%)	0.41 (0.3,0.6)
Rizatriptan	57.10% (52.4%,61.9%)	3.66 (3.0,4.5)	36.60% (31.7%,42.0%)	4.86 (3.9,6.2)	29.30% (23.7%,35.5%)	2.02 (1.5,2.7)	23.90% (19.0%,29.5%)	2.97 (2.2,4.0)	30.00% (25.6%,34.8%)	0.4 (0.3,0.5)
Sumatriptan	49.70% (46.3%,53.1%)	2.71 (2.4,3.1)	27.70% (24.6%,31.0%)	3.22 (2.7,3.8)	33.10% (30.3%,36.0%)	2.41 (2.1,2.8)	22.80% (2.0%,26.0%)	2.79 (2.3,3.4)	33.80% (30.0%,37.8%)	0.48 (0.4,0.6)
Zolmitriptan	50.00% (45.5%,54.7%)	2.75 (2.3,3.3)	27.10% (22.7%,32.0%)	3.14 (2.5,4.0)	37.60% (33.4%,42.2%)	2.94 (2.4,3.6)	22.50% (18.0%,27.6%)	2.74 (2.0,3.7)	28.00% (22.8%,33.7%)	0.36 (0.3,0.5)
TABLET LD										
Almotriptan tablet	43.30% (33.9%,53.3%)	2.1 (1.4,3.1)	18.50% (11.1%,29.4%)	1.92 (1.0,3.5)	31.70% (24.0%,40.4%)	2.26 (1.5,3.3)	—	—	—	—
Eletriptan tablet	52.50% (44.3%,60.5%)	3.03 (2.2,4.2)	28.50% (20.8%,37.6%)	3.35 (2.2,5.1)	37.70% (29.8%,46.5%)	2.95 (2.1,4.3)	24.60% (18.3%,32.1%)	3.07 (2.1,4.5)	24.50% (18.7%,31.6%)	0.3 (0.2,0.4)
Frovatriptan tablet	27.30% (18.7%,38.0%)	1.03 (0.6,1.7)	12.60% (5.6%,24.4%)	1.21 (0.5,2.8)	—	—	—	—	36.70% (20.4%,56.7%)	0.54 (0.2,1.2)
Naratriptan tablet	—	—	—	—	—	—	—	—	35.30% (20.7%,53.4%)	0.51 (0.2,1.1)
Rizatriptan tablet	51.20% (43.1%,59.2%)	2.88 (2.1,4.0)	27.50% (18.8%,38.2%)	3.19 (2.0,5.2)	—	—	—	—	34.30% (24.3%,45.8%)	0.49 (0.3,0.8)
Sumatriptan tablet	44.20% (37.1%,51.7%)	2.17 (1.6,2.9)	24.90% (14.9%,38.0%)	2.79 (1.5,5.2)	29.80% (23.2%,37.1%)	2.07 (1.5,2.9)	—	—	46.40% (31.5%,62.0%)	0.81 (0.4,1.5)
Zolmitriptan tablet	44.00% (27.1%,62.2%)	2.16 (1.0,4.5)	21.00% (8.5%,41.7%)	2.24 (0.8,6.1)	29.50% (17.1%,45.6%)	2.04 (1.0,4.1)	—	—	33.10% (13.2%,58.8%)	0.46 (0.1,1.4)
TABLET HD										
Almotriptan tablet	50.60% (40.4%,60.8%)	2.81 (1.9,4.3)	32.40% (23.1%,43.2%)	4.04 (2.5,6.4)	—	—	—	—	28.00% (19.3%,38.6%)	0.36 (0.2,0.6)
Eletriptan tablet	66.20% (61.6%,70.6%)	5.38 (4.4,6.6)	48.00% (41.5%,54.7%)	7.78 (5.9,10.3)	50.50% (45.4%,55.9%)	4.98 (4.0,6.3)	38.90% (32.0%,46.2%)	6 (4.4,8.3)	18.10% (14.5%,22.3%)	0.21 (0.2,0.3)

Table 3.—Continued

	2-hour headache relief		2-hour freedom from pain		24-hour sustained headache relief		24-hour sustained freedom from pain		Use of rescue medications	
	% (95%CrI)	OR (95%CrI)	% (95%CrI)	OR (95%CrI)	% (95%CrI)	OR (95%CrI)	% (95%CrI)	OR (95%CrI)	% (95%CrI)	OR (95%CrI)
Frovatriptan tablet	40.30% (30.1%,51.5%)	1.85 (1.2,2.9)	35.20% (22.5%,50.7%)	4.58 (2.4,8.8)	—	—	—	—	32.30% (17.3%,51.8%)	0.45 (0.2,1.0)
Rizatriptan tablet	64.20% (47.9%,77.8%)	4.92 (2.5,9.6)	50.10% (32.3%,67.9%)	8.44 (4.0,17.9)	—	—	—	—	—	—
Sumatriptan tablet	53.40% (49.8%,56.9%)	3.14 (2.7,3.6)	32.10% (28.6%,35.8%)	3.99 (3.4,4.8)	36.00% (32.7%,39.4%)	2.75 (2.3,3.2)	27.90% (23.8%,32.4%)	3.65 (2.9,4.6)	27.40% (24.2%,30.8%)	0.35 (0.3,0.4)
Zolmitriptan tablet	51.40% (45.4%,57.5%)	2.9 (2.3,3.7)	31.00% (24.8%,38.3%)	3.79 (2.8,5.3)	38.30% (32.7%,44.3%)	3.02 (2.4,3.9)	23.90% (17.8%,31.8%)	2.97 (2.0,4.5)	33.40% (23.9%,44.6%)	0.47 (0.3,0.8)
ODT SD										
Rizatriptan	69.00% (59.6%,77.0%)	6.1 (4.1,9.2)	50.20% (34.5%,66.7%)	8.49 (4.4,17.0)	—	—	—	—	19.90% (6.2%,46.0%)	0.23 (0.1,0.8)
Zolmitriptan	65.80% (50.6%,78.3%)	5.28 (2.8,9.9)	36.60% (20.6%,56.8%)	4.87 (2.2,11.1)	—	—	—	—	—	—
ODT LD										
Rizatriptan	57.40% (44.6%,69.3%)	3.7 (2.2,6.2)	37.80% (23.2%,55.5%)	5.11 (2.6,10.6)	—	—	—	—	—	—
ODT HD										
Zolmitriptan	—	—	—	—	50.00% (38.0%,62.6%)	4.88 (3.0,8.2)	—	—	24.40% (16.0%,35.1%)	0.3 (0.2,0.5)
NASAL SPRAY SD										
Sumatriptan	52.60% (43.6%,61.5%)	3.04 (2.1,4.4)	21.20% (6.4%,53.4%)	2.26 (0.6,9.8)	—	—	—	—	—	—
Zolmitriptan	51.30% (38.8%,63.9%)	2.89 (1.7,4.9)	—	—	—	—	—	—	—	—
NASAL SPRAY LD										
Sumatriptan	41.80% (32.6%,51.5%)	1.97 (1.3,2.9)	—	—	—	—	—	—	—	—
Zolmitriptan	48.20% (35.6%,61.0%)	2.55 (1.5,4.3)	—	—	—	—	—	—	—	—
NASAL SPRAY HD										
Zolmitriptan	62.30% (54.4%,69.7%)	4.53 (3.3,6.3)	33.80% (24.5%,44.7%)	4.3 (2.7,6.8)	41.40% (34.6%,48.5%)	3.44 (2.6,4.6)	27.30% (20.5%,35.5%)	3.54 (2.5,5.2)	22.00% (14.9%,31.4%)	0.27 (0.2,0.4)
SUBCUTANEOUS INJECTION SD										
Sumatriptan	75.70% (67.6%,82.5%)	8.54 (5.7,12.9)	36.60% (25.1%,50.0%)	4.87 (2.8,8.5)	—	—	23.50% (15.8%,33.6%)	2.9 (1.8,4.8)	23.40% (17.7%,30.1%)	40.29 (0.2,0.4)
Zolmitriptan	—	—	—	—	—	—	—	—	35.00% (9.1%,74.1%)	0.51 (0.1,2.7)

SUBCUTANEOUS INJECTION HD									
Sumatriptan	70.10% (46.0%,87.2%)	6.45 (2.3,18.7)	29.10% (11.9%,57.0%)	3.46 (1.1,11.3)	-	-	-	25.50% (10.1%,50.2%)	0.32 (0.1,1.0)
PATCH SD									
Sumatriptan	48.30% (37.0%,60.0%)	2.56 (1.6,4.1)	20.60% (12.9%,31.4%)	2.19 (1.2,3.9)	-	-	-	26.20% (12.9%,45.6%)	0.33 (0.1,0.8)
SUPPOSITORIES LD									
Sumatriptan	70.80% (49.4%,86.1%)	6.64 (2.7,17.0)	44.70% (22.4%,71.1%)	6.8 (2.4,20.8)	-	-	-	-	-
NON TRIPTAN SINGLE THERAPIES									
NSAID	48.00%	2.53	21.80%	2.35	29.10%	2	16.40%	36.90%	0.55
Acetaminophen	(42.3%,53.9%)	(2.0,3.2)	(17.6%,26.8%)	(1.8,3.1)	(25.1%,33.5%)	(1.6,2.5)	(12.6%,20.9%)	(31.0%,43.1%)	(0.4,0.7)
	51.70%	2.94	22.20%	2.41	29.30%	2.02	14.30%	-	-
Aspirin	(30.8%,72.3%)	(1.2,7.2)	(9.2%,43.7%)	(0.9,6.6)	(16.0%,47.5%)	(0.9,4.5)	(5.0%,32.5%)	-	-
	46.10%	2.35	24%	2.66	-	-	-	33.40%	0.47
Ergots	(32.1%,60.7%)	(1.3,4.2)	(13.7%,38.4%)	(1.3,5.3)	-	-	-	(20.2%,50.1%)	(0.2,0.9)
	38.40%	1.71	15.50%	1.55	7.90%	0.42	-	24.00%	0.3
	(29.5%,47.9%)	(1.2,2.5)	(8.2%,27.1%)	(0.8,3.2)	(1.5%,28.2%)	(0.1,1.9)	-	(15.8%,34.9%)	(0.2,0.5)
COMBINATION THERAPIES									
Aspirin with anti-emetic	50.90% (41.9%,60.0%)	2.85 (2.0,4.1)	19.30% (13.0%,27.5%)	2.01 (1.3,3.2)	-	-	-	31.70% (23.0%,41.9%)	0.44 (0.3,0.7)
Triptan with acetaminophen	79.90% (59.6%,92.7%)	10.9 (4.1,35.0)	50.50% (29.4%,72.3%)	8.61 (3.5,22.1)	50.30%	4.93 (2.3,11.0)	29.30% (14.1%,50.8%)	-	-
Triptan with NSAID	62.30% (53.3%,68.9%)	4.53 (3.4,6.1)	36.80% (31.7%,42.1%)	4.91 (3.9,6.2)	46.20%	4.2 (3.4,5.2)	32.50% (28.3%,37.0%)	22.30% (18.5%,26.7%)	0.27 (0.2,0.3)
OTHER THERAPIES									
SD BI 44370 TA tablet	57.50% (39.3%,73.7%)	3.71 (1.8,7.7)	25.30% (12.0%,45.2%)	2.86 (1.2,7.0)	47.20%	4.36 (2.2,8.3)	28.90% (14.4%,49.0%)	26.70% (17.0%,39.3%)	0.34 (0.2,0.6)
HD BI 44370 TA tablet	63.40% (45.8%,78.2%)	4.76 (2.3,9.8)	32.40% (17.1%,52.8%)	4.04 (1.7,9.5)	54.30%	5.8 (3.0,11.2)	30.30% (15.5%,50.6%)	20.90% (12.9%,32.0%)	0.25 (0.1,0.4)
LD BI 44370 TA tablet	38.20% (22.1%,57.1%)	1.7 (0.8,3.7)	9.20% (2.8%,23.4%)	0.85 (0.2,2.6)	20.30%	1.24 (0.5,2.7)	7.00% (1.4%,20.1%)	48.60% (34.8%,62.8%)	0.89 (0.5,1.6)
SD Tonaberstat	30.20% (18.9%,44.6%)	1.19 (0.6,2.2)	5.90% (2.0%,14.4%)	0.53 (0.2,1.4)	-	-	-	-	-
LD Tonaberstat	28.00% (17.9%,42.2%)	1.07 (0.6,2.0)	7.00% (2.6%,16.3%)	0.64 (0.2,1.7)	-	-	-	-	-
Acetaminophen, dichloralphenazone, and isometheptene	37.70% (19.1%,60.9%)	1.66 (0.7,4.3)	-	-	-	-	-	-	-

NA = not applicable; ODT = oral disintegrating tablet; SD = standard dose.

†Percent of patients with the outcome are based on the odds ratios from the network meta-analysis and mean proportion of patients who experience the outcome in the placebo group.

‡Evidence networks include all treatments in this table although results did not change substantially when low dose or experimental agents were excluded.

- = no low dose available/relevant for this medication.

freedom from pain at 24 hours, compared with 10% for placebo. Eletriptan tablet (33%) and rizatriptan tablet (24%) had the largest effect on 24-hour freedom from pain among monotherapies, whereas acetaminophen (14%), ASA (16%), and naratriptan (18%) were associated with less favorable outcomes. SD triptans yielded equal or slightly worse outcomes than triptan combination therapies (29% to 33%). Detailed results are reported in Table 3 including credible intervals around point estimates.

Use of Rescue Medications.—The evidence network for the use of rescue medication included 88 studies and a total of 48,363 participants. Overall, 34 different treatments were considered, providing for 222 comparisons. There was evidence of inconsistency in the network (Appendix S3). With SD triptans, the percent of patients using rescue medications ranged from 20 to 34%, compared with 52% for placebo. The NNT in order for one patient to avoid use of rescue medication ranged from 4 to 6 patients. Eletriptan tablet (21%) and zolmitriptan tablet (24%) required the use of the least amount of rescue medications among monotherapies, whereas NSAIDs (37%), sumatriptan tablet (34%), and ASA (33%) used the most. SD triptans yielded equal or slightly worse outcomes than triptan combination therapies (22%). Detailed results are reported in Table 3 including credible intervals around point estimates.

Comparisons Among the SD Triptans.—Figure 2 provides comparisons among the SD triptan tablets. The gray circle indicates that the triptan identified in the “row” is associated with better outcomes than the “column” triptan; the black circle indicates that the “row” triptan is associated with worse outcome than the “column” triptan; the blank circle indicates that there is no difference between the “row” and “column” triptan; and a missing circle indicates that the outcome was not available for analysis. In general, there were more favorable results observed for eletriptan and rizatriptan (as indicated by the gray circles in the lower portion of the diagonal in Fig. 2). Results were less favorable for naratriptan and frovatriptan. Use of rescue medications was not significantly different between the triptans except for sumatriptan having a significantly favorable result compared with zolmitriptan. Detailed results are reported in Appendix S4.

Sensitivity Analyses.—Figure 3 presents a box plot illustrating control group response rates among treatments included in the network. From Figure 3, it can be seen that some treatments have lower or higher control group response rates than other treatments. We also report findings from a meta-regression analysis adjusting for these differences in control group response rate. Overall, findings for most treatments remained unchanged although those with lower

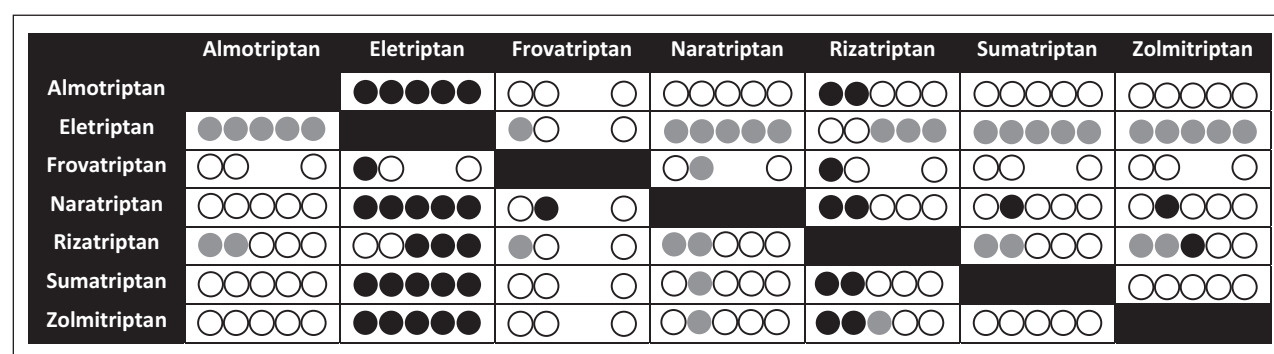


Fig 2.—Comparison among the standard dose triptan tablets on the 5 efficacy outcomes: headache relief at 2 hours, freedom from pain at 2 hours, sustained headache relief at 24 hours, sustained freedom from pain at 24 hours, and use of rescue medications.*
 *The 5 contiguous circles correspond, respectively, to the 5 efficacy outcomes: headache relief at 2 hours, freedom from pain at 2 hours, sustained headache relief at 24 hours, sustained freedom from pain at 24 hours, and use of rescue medications. The gray circle indicates that the “row” triptan is associated with better outcomes compared with “column” triptan; the black circle indicates that the “row” triptan is worse than the “column” triptan; the blank circle indicates that there is no difference between the “row” and “column” triptan; and a missing circle indicates that the outcome was not available for analysis.

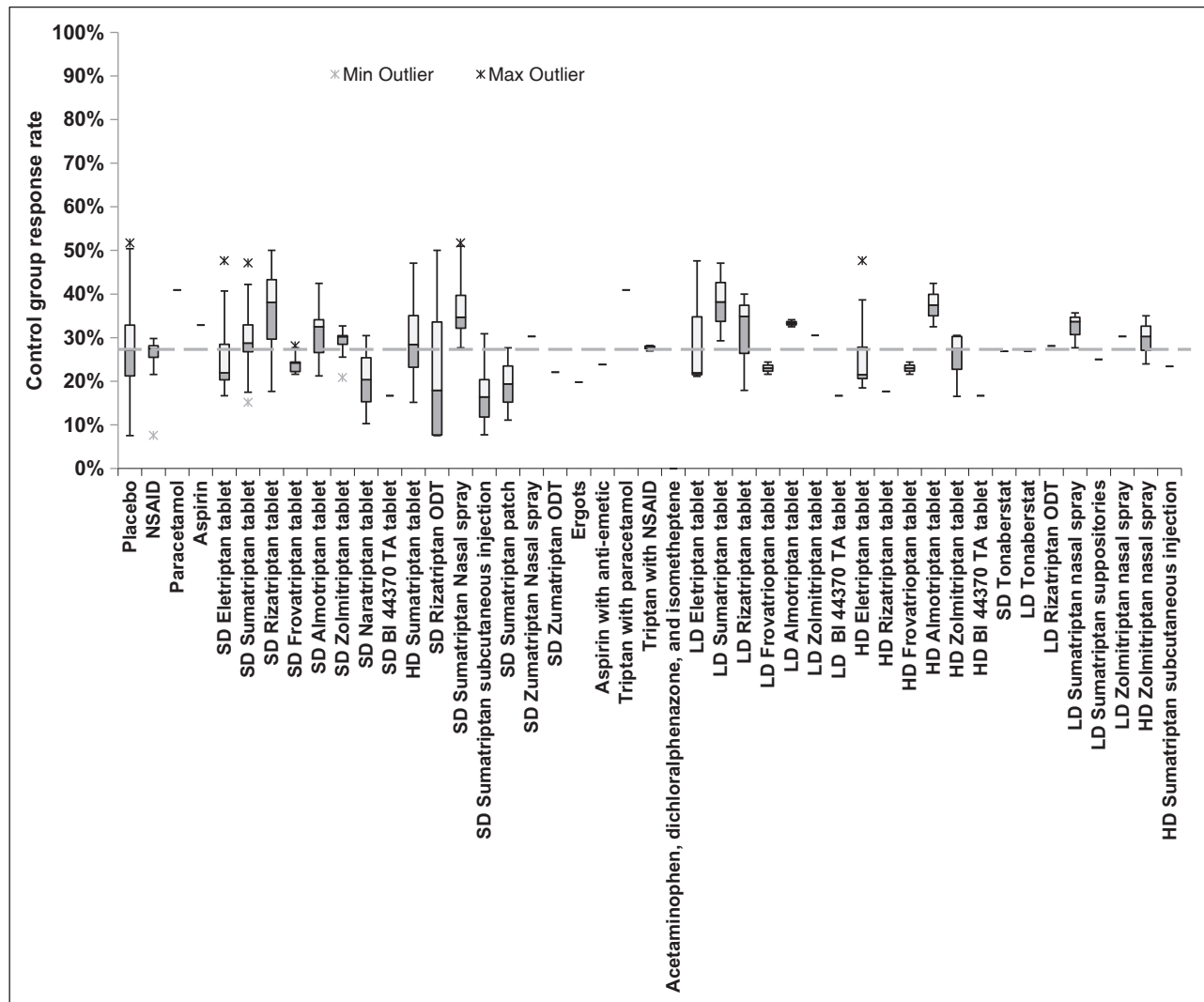


Fig 3.—Comparison of control group response rate among studies for 2-hour response.

control group response rates (eg, SD eletriptan tablet) became slightly less favorable, albeit still more favorable than SD triptan tablets (Appendix S5).

DISCUSSION

We found that SD triptans relieved headaches within 2 hours in 43 to 76% of patients. Freedom from pain within 2 hours was less common, with about 18 to 50% of patients experiencing freedom from pain within 2 hours. SD triptans provided sustained headache relief at 24 hours in 29 to 50% of patients, and sustained freedom from pain at 24 hours in 18 to 33% of patients. Use of rescue medications among patients using SD triptans ranged from 20 to 34%. Our find-

ings align with those reported in other systematic reviews,³⁻¹⁰ although the majority of other reviews only report estimates of relative effect for SD triptans.

SD triptans were associated with more favorable results than ergots for 2- and 24-hour outcomes, and equal or more favorable results than NSAIDs, ASA, and acetaminophen for 2-hour outcomes. These findings align with recommendations from the Canadian Headache Society Guidelines³ where they gave a strong recommendation for triptans, NSAIDs, ASA, and acetaminophen but did not recommend ergots for routine use in the acute management of migraine. Similarly, the National Institute for Health and Care

Excellence (NICE) in the UK does not recommend ergots for the acute treatment of migraine, but recommends oral triptans, NSAIDs, ASA, and acetaminophen for the acute treatment of migraine in patients who prefer monotherapy.³²

We found that combination therapies such as triptan and ASA or triptan plus acetaminophen, and certain modes of administration such as rizatriptan ODT and sumatriptan subcutaneous injection, were associated with slightly more favorable 2-hour results compared with SD triptans. However, there is potential that these findings may be due to systematic differences in the patient population and/or study design; that is, studies assessing efficacy of combination therapies or certain modes of administration may have been more extensively studied in a patient population that is systematically different, ie, more severe and/or treatment experienced. We attempted to adjust for this possible issue by conducting a meta-regression analysis adjusting for placebo response rate, a proxy that is often helpful in identifying patient populations or study designs that are systematically different (Fig. 3). We found that findings for combination therapies such as triptan and ASA or triptan plus acetaminophen remained stable after adjustment, whereas those using other modes of administration became slightly less favorable, albeit still more favorable than SD triptan tablets. Recent NICE guidance recommends combination therapy with an oral triptan and ASA or oral triptan plus acetaminophen, and findings from both our primary analysis and sensitivity analysis seem to support NICE recommendations.⁴

Among individual triptans, our analysis suggests that the majority of triptans, except frovatriptan and naratriptan, deliver similar pain relief in the acute management of migraines. However, our findings also suggest that eletriptan and rizatriptan may provide better pain relief than some of the other triptans. This latter finding should be interpreted in light of a number of caveats. First, findings for eletriptan became slightly less favorable after we adjusted for control groups response rate, albeit still more favorable than other triptans. Second, both eletriptan and rizatriptan are only available in tablet forms, whereas other triptans such as sumatriptan are available in

multiple formulations – which can be advantageous for patients given mixing of triptans is ill advised. Finally, we do not consider costs or cost-effectiveness in this paper. Other triptans such as sumatriptan are available as less expensive generics, whereas eletriptan is not yet available as a generic. Our companion pharmacoeconomic report has shown that use of less costly generic triptans could significantly reduce total expenditure on triptans.³² However, providing more open access to triptans will lead to a significant increase in their use with a high budget impact. NICE in the UK recommends to start with the triptan with the lowest acquisition cost initially, and if this is consistently ineffective, try one or more expensive alternative triptans.⁴ Consumer Reports recommends a similar approach, recommending sumatriptan initially because it is available as an inexpensive generic and offers the widest choice for mode of delivery.^{2,33}

Studies were not sufficiently powered or of adequate duration to measure differences in long-term complications or adverse events. Future research is needed in assessing the long-term use of triptans in the acute management of recurrent migraines.

As with all analyses, there are several limitations that warrant consideration. First, graphical aids in the form of network diagrams and forest plots are typically provided for network meta-analyses. However, our analysis consisted of upwards of 45-treatment nodes when the network was stratified by dose, mode of administration, and combination therapies. The inclusion of evidence structures with a large number of nodes (>20) makes presentation of network diagrams unwieldy. Similarly, presentation of forest plots or tables with all comparisons becomes challenging given the number of treatments and potential comparisons. As such, we provide tables which concisely report the main findings from them in tabular form compared with placebo (Table 3). We also report absolute probability of each comparison.

CONCLUSIONS

Triptans were found to be efficacious for the treatment of acute migraine. Forty-three to 76% of

patients experience pain relief at 2 hours when using SD triptan tablets. Most triptans were associated with equal or more favorable results than NSAIDs, ASA, acetaminophen, and more favorable results than ergots. Use of triptans in combination with aspirin or acetaminophen, or using different modes of administration such as injection, was associated with slightly better results than SD triptan tablets.

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(b) Acquisition of Data

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REFERENCES

- World Health Organization Factsheet No. 277: Headache Disorders (Available at: <http://www.who.int/mediacentre/factsheets/fs277/en/>). October 2012 (Accessed July 17, 2014).
- Using the Triptans to Treat: Migraine Headaches. Comparing Effectiveness, Safety, and Price: Consumer Reports Best Buy Drugs. March 2013.
- Worthington I, Pringsheim T, Gawel MJ, et al. Canadian Headache Society Guideline: Acute drug therapy for migraine headache. *Can J Neurol Sci.* 2013;40(5 Suppl. 3):S1-S80.
- NICE. Headaches: Diagnosis and Management of Headaches in Young People and Adults (Clinical guideline 150: Methods, Evidence and Recommendations): National Institute for Health and Clinical Excellence 2012. September 2012.
- Sumamo Schellenberg E, Dryden DM, Pasichnyk D, et al. Acute Migraine Treatment in Emergency Settings [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2012 Nov. (Comparative Effectiveness Reviews, No. 84.) Available at: <http://www.ncbi.nlm.nih.gov/books/NBK115368/>
- Asseburg C, Peura P, Oksanen T, Turunen J, Purmonen T, Martikainen J. Cost-effectiveness of oral triptans for acute migraine: Mixed treatment comparison. *Int J Technol Assess Health Care.* 2012;28:382-389.
- Ferrari MD, Loder E, McCarroll KA, Lines CR. Meta-analysis of rizatriptan efficacy in randomized controlled clinical trials. *Cephalalgia.* 2001;21:129-136.
- Ferrari MD, Roon KI, Lipton RB, Goadsby PJ. Oral triptans (serotonin 5-HT(1B/1D) agonists) in acute migraine treatment: A meta-analysis of 53 trials. *Lancet.* 2001;358:1668-1675.
- Johnston MM, Rapoport AM. Triptans for the management of migraine. *Drugs.* 2010;70:1505-1518.
- Thorlund K, Mills EJ, Wu P, et al. Comparative efficacy of triptans for the abortive treatment of migraine: A multiple treatment comparison meta-analysis. *Cephalalgia.* 2013;34:258-267.
- Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ.* 2011;343:d5928.
- Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration. *J Clin Epidemiol.* 2009;62:e1-e34.
- Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *J Clin Epidemiol.* 2009;62:1006-1012.

14. Dias S, Sutton AJ, Ades AE, Welton NJ. Evidence synthesis for decision making 2: A generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials. *Med Decis Making*. 2013;33:607-617.
15. Turner RM, Davey J, Clarke MJ, Thompson SG, Higgins JP. Predicting the extent of heterogeneity in meta-analysis, using empirical data from the Cochrane Database of Systematic Reviews. *Int J Epidemiol*. 2012;41:818-827.
16. Cooper NJ, Sutton AJ, Morris D, Ades AE, Welton NJ. Addressing between-study heterogeneity and inconsistency in mixed treatment comparisons: Application to stroke prevention treatments in individuals with non-rheumatic atrial fibrillation. *Stat Med*. 2009;28:1861-1881.
17. Dias S, Sutton A, Welton N, et al. NICE DSU Technical Support Document 2: Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials. May 2011 [cited 2012 June 13]; Available at: <http://www.nicedsu.org.uk/TSD6%20Software.final.08.05.12.pdf>.
18. Lunn DJ, Thomas A, Best N, Spiegelhalter D. WinBUGS – a Bayesian modelling framework: Concepts, structure, and extensibility. *Statistics and Computing* 2000;10:325-337.
19. Ades AE, Welton NJ, Caldwell D, Price M, Goubar A, Lu G. Multiparameter evidence synthesis in epidemiology and medical decision-making. *J Health Serv Res Policy*. 2008;13(Suppl. 3):12-22.
20. Dias S, Welton NJ, Sutton AJ, Caldwell DM, Lu G, Ades AE. Evidence synthesis for decision making 4: Inconsistency in networks of evidence based on randomized controlled trials. *Med Decis Making*. 2013;33:641-656.
21. Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders, 3rd edition (beta version). *Cephalalgia*. 2013;33:629-808.
22. Headache Classification Committee of the International Headache Society. Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. *Cephalalgia*. 1988;8(Suppl. 7):1-96.
23. Olesen J. The International Classification of Headache Disorders. *Headache*. 2008;48:691-693.
24. Olesen J, Steiner TJ. The International Classification of Headache Disorders, 2nd edn (ICDH-II). *J Neurol Neurosurg Psychiatry*. 2004;75:808-811.
25. Goadsby PJ, Massiou H, Pascual J, et al. Almotriptan and zolmitriptan in the acute treatment of migraine. *Acta Neurol Scand*. 2007;115:34-40.
26. Gruffydd-Jones K, Kies B, Middleton A, Mulder LJ, Rosjo O, Millson DS. Zolmitriptan versus sumatriptan for the acute oral treatment of migraine: A randomized, double-blind, international study. *Eur J Neurol*. 2001;8:237-245.
27. Sandrini G, Cerbo R, Del BE, et al. Efficacy of dosing and re-dosing of two oral fixed combinations of indomethacin, prochlorperazine and caffeine compared with oral sumatriptan in the acute treatment of multiple migraine attacks: A double-blind, double-dummy, randomised, parallel group, multicentre study. *Int J Clin Pract*. 2007;61:1256-1269.
28. Landy S, Savani N, Shackelford S, Loftus J, Jones M. Efficacy and tolerability of sumatriptan tablets administered during the mild-pain phase of menstrually associated migraine. *Int J Clin Pract*. 2004;58:913-919.
29. Mannix LK, Loder E, Nett R, et al. Rizatriptan for the acute treatment of ICHD-II proposed menstrual migraine: Two prospective, randomized, placebo-controlled, double-blind studies. *Cephalalgia*. 2007;27:414-421.
30. Mannix LK, Martin VT, Cady RK, et al. Combination treatment for menstrual migraine and dysmenorrhea using sumatriptan-naproxen: Two randomized controlled trials. *Obstet Gynecol*. 2009;114:106-113.
31. Nett R, Landy S, Shackelford S, Richardson MS, Ames M, Lener M. Pain-free efficacy after treatment with sumatriptan in the mild pain phase of menstrually associated migraine. *Obstet Gynecol*. 2003;102:835-842.
32. Coyle D, Lee K, Sabarre K. Triptans for Migraine Therapy: A Pharmacoeconomic Analysis. 2014. [Internet] Ontario Drug Policy Research Network. Available at: <http://odprn.ca/wp-content/uploads/2014/08/Triptan-PharmacoEcon-Report-CENSORED-for-review.pdf>
33. National Institute for Health and Clinical Excellence. Diagnosis and management of headaches in young people and adults. Clinical Guideline 150. September 2012. [Internet]. National Clinical Guideline Centre at The Royal College of Physicians, London. Available at: <http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0078140/pdf/TOC.pdf>

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Appendix S1.—Search strategy.

Appendix S2.—Included studies.

Appendix S3.—Assessment of inconsistency.

Appendix S4.—Comparisons among standard dose triptans.

Appendix S5.—Adjustment for control group response rate.

Appendix S6.—Number of patients and studies for each outcome.

Risk of serious infection in biological treatment of patients with rheumatoid arthritis: a systematic review and meta-analysis



Jasvinder A Singh*, Chris Cameron*, Shahrzad Noorbaloochi, Tyler Cullis, Matthew Tucker, Robin Christensen, Elizabeth Tanjong Ghogomu, Doug Coyle, Tammy Clifford, Peter Tugwell, George A Wells

Summary

Background Serious infections are a major concern for patients considering treatments for rheumatoid arthritis. Evidence is inconsistent as to whether biological drugs are associated with an increased risk of serious infection compared with traditional disease-modifying antirheumatic drugs (DMARDs). We did a systematic review and meta-analysis of serious infections in patients treated with biological drugs compared with those treated with traditional DMARDs.

Methods We did a systematic literature search with Medline, Embase, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov from their inception to Feb 11, 2014. Search terms included “biologics”, “rheumatoid arthritis” and their synonyms. Trials were eligible for inclusion if they included any of the approved biological drugs and reported serious infections. We assessed the risk of bias with the Cochrane Risk of Bias Tool. We did a Bayesian network meta-analysis of published trials using a binomial likelihood model to assess the risk of serious infections in patients with rheumatoid arthritis who were treated with biological drugs, compared with those treated with traditional DMARDs. The odds ratio (OR) of serious infection was the primary measure of treatment effect and calculated 95% credible intervals using Markov Chain Monte Carlo methods.

Findings The systematic review identified 106 trials that reported serious infections and included patients with rheumatoid arthritis who received biological drugs. Compared with traditional DMARDs, standard-dose biological drugs (OR 1.31, 95% credible interval [CrI] 1.09–1.58) and high-dose biological drugs (1.90, 1.50–2.39) were associated with an increased risk of serious infections, although low-dose biological drugs (0.93, 0.65–1.33) were not. The risk was lower in patients who were methotrexate naive compared with traditional DMARD-experienced or anti-tumour necrosis factor biological drug-experienced patients. The absolute increase in the number of serious infections per 1000 patients treated each year ranged from six for standard-dose biological drugs to 55 for combination biological therapy, compared with traditional DMARDs.

Interpretation Standard-dose and high-dose biological drugs (with or without traditional DMARDs) are associated with an increase in serious infections in rheumatoid arthritis compared with traditional DMARDs, although low-dose biological drugs are not. Clinicians should discuss the balance between benefit and harm with the individual patient before starting biological treatment for rheumatoid arthritis.

Funding Rheumatology Division at the University of Alabama at Birmingham.

Introduction

Biological drugs are a new class of disease-modifying treatment options for rheumatoid arthritis that have been reported to show large clinical and radiographic improvements compared with traditional drugs.^{1,2} Nine biological drugs are now approved by the US Food and Drug Administration and European Medicines Agency for treatment of rheumatoid arthritis. Biological drugs are used to treat moderate-to-severe rheumatoid arthritis in patients who have not responded adequately to traditional disease-modifying antirheumatic drugs (DMARDs), such as methotrexate.^{3,4} Infections, especially serious infections, are one of the greatest concerns for patients considering treatment with biological drugs.

Debate continues on whether biological therapies are associated with serious infections in patients with rheumatoid arthritis, the magnitude of this risk, and

whether the risk varies between subpopulations of patients with rheumatoid arthritis.⁵ In our experience, the clinical perception tends towards a belief that serious infection is an issue, but this notion is not backed up by consistent research evidence. The confusion originates from the four published systematic reviews with meta-analyses^{6–9} of the risk of serious infection in patients receiving biological drugs for rheumatoid arthritis. The first meta-analysis,⁹ which included three of the approved biological drugs in nine trials, reported an association. However, the next three meta-analyses,^{6–8} which included more biological drugs and far greater sample sizes, did not identify any association between standard-dose biological drugs and increased risk of serious infections. Furthermore, discordant results have also been reported for non-randomised studies that assessed the risk of serious infection in rheumatoid arthritis,^{10–16} with some

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studies^{14–16} detecting an association and others^{10–13} detecting no association. Accordingly, the risk of serious infection in biological treatment of patients with rheumatoid arthritis has been debated. Unlike previous analyses, many more trials are now available for a conclusive study to address this question. Additionally, all four meta-analyses^{6–9} in patients with rheumatoid arthritis^{6–9} had major limitations; they restricted the population of patients (eg, only methotrexate-naïve patients),⁸ only included a few biological drugs in their analyses,^{6–9} consisted mainly of studies that were more than a decade old,⁹ or did not integrate findings across low-dose, standard-dose, or high-dose biological drugs (ie, did analyses separately). Availability of more robust evidence is crucial for the development of guidelines for rheumatoid arthritis treatment, which have previously been based mainly on observational studies.³

We aimed to compare the risk of serious infections in rheumatoid arthritis between biological treatment and non-biological traditional treatment with DMARDs, and use network meta-analysis to compare subpopulations within rheumatoid arthritis, to synthesise data from randomised trials.

Methods

Search strategy and selection criteria

We did a systematic review that included both a traditional meta-analysis and network meta-analysis to assess the risk of serious infection in rheumatoid arthritis, comparing biological drugs with each other, placebo, or a control

treatment (traditional DMARDs or their combinations). Network meta-analysis includes direct and indirect evidence of benefits and harm among multiple treatments simultaneously, whereas traditional meta-analysis only considers direct evidence between two treatment strategies.⁶ We did this systematic review, meta-analysis, and network meta-analysis in accordance with the guidance specified in the Cochrane Handbook for Intervention Reviews,¹⁷ ISPOR network meta-analysis guidance,^{18,19} and the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement.²⁰

A Cochrane librarian (Tamara Rader) did a literature search (appendix pp 3–7) and retrieved published trials of biological drugs or tofacitinib based on the defined criteria. Data were retrieved from the following sources: the Cochrane Central Register of Controlled Trials (CENTRAL, via the Cochrane Library), Medline (from 1946), and Embase databases (from 1947) to Feb 11, 2014; the two previously published Cochrane systematic reviews of biological drugs;^{21,22} two reviews comparing traditional DMARD monotherapy with traditional DMARD combination therapies;^{23,24} and a search of ClinicalTrials.gov. The search protocols for both Cochrane reviews are accessible online.^{21,22} Search terms included “biologics”, “rheumatoid arthritis” and their synonyms (appendix pp 1–5). Studies were eligible for inclusion if they included any of the nine approved biological drugs and reported serious infections; no restrictions were applied by the length of follow-up.

Study selection and data extraction

We included randomised trials of rheumatoid arthritis in adults who were treated with any of the nine biological drugs approved for the treatment of rheumatoid arthritis, alone or in combination, if biological drugs were compared with each other, placebo, or traditional DMARDs (or DMARD combinations). Biological drugs included tumour necrosis factor (TNF) blockers (etanercept, adalimumab, infliximab, golimumab, certolizumab pegol), interleukin 1 antagonist (anakinra), interleukin 6 antagonist (tocilizumab), anti-CD28 (abatacept), and anti-B cell (rituximab) biological drugs in any dose. The comparators were placebo, traditional DMARDs (including methotrexate, alone or in combination), or another biological drug. We included tofacitinib doses as separate nodes in the network to improve precision of effect estimates for biological drugs (ie, by borrowing strength from indirect evidence) and help with future updates of this review, but we do not report findings for tofacitinib at this time (appendix p 6).

Independently, two reviewers assessed titles and abstracts (SN, MT) and full text articles (SN, TC), and extracted the data (SN, MT)—any disagreements were resolved by consensus and, when needed, a third reviewer (JAS). We extracted the data for serious infections, the total number of patients in each treatment group, and key characteristics of the patients and studies

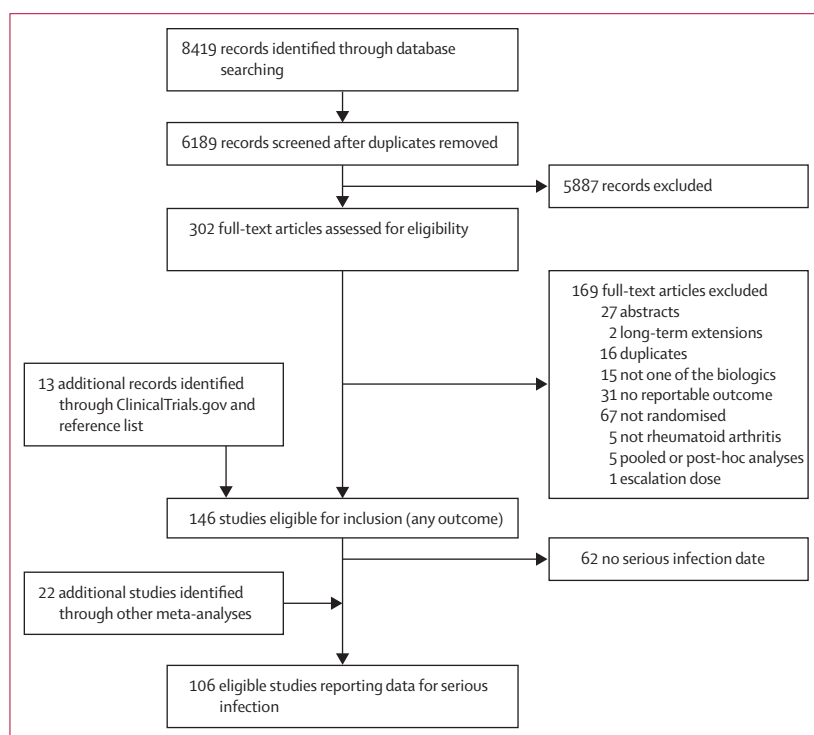


Figure 1: Study selection

(appendix pp 7–9) using a standardised data abstraction sheet. We assessed the risk of bias using the Cochrane Risk of Bias Tool.²⁵

Outcome

Serious infection was the outcome of interest, as defined in each study. Definitions mostly included infections associated with death, admission to hospital, or use of intravenous antibiotics.

Statistical analysis

The odds ratio (OR) of serious infection was the primary measure of treatment effect. We also calculated absolute risk differences per 1000 patients per year treated using the mean annualised baseline risk of serious infection in traditional DMARD groups of included studies more than 6 months in duration. We did traditional meta-analyses, cumulative meta-analyses (meta-analyses over time), and Bayesian network meta-analysis. We did traditional and cumulative meta-analyses (comparing standard-dose [approved] biological drug vs traditional DMARD) with Comprehensive Meta-Analysis (version 2.2.064). We used the Mantel-Haenszel method with a fixed effects model and an adjusted continuity correction factor centred around 0.5 to handle zero cells.²⁶

We used WinBUGS software (version 1.4.3) to do the Bayesian network meta-analysis.²⁷ We used a binomial likelihood model,²⁸ which allows for the use of multi-arm trials, for Bayesian network meta-analysis because many studies included multi-arms trials. We did both fixed-effects and random-effects network meta-analysis, although we used the random-effects model with an informative prior²⁹ for the between-study variance of the primary analysis. We derived point estimates and 95% credible intervals (CrI) for ORs using Markov Chain Monte Carlo methods. We assessed model fit and inconsistency³⁰ with standard approaches (appendix pp 8–10).

For traditional and cumulative meta-analyses, we used the standard-doses of the biological drugs (appendix pp 7–9). We included all doses of biological drugs (low, standard, and high) for the network meta-analysis. We assessed prespecified characteristics of studies and patients to ensure similarity and investigate the potential effect of heterogeneity on effect estimates (appendix pp 8–10). We stratified results by the following pre-defined populations: methotrexate-naive, methotrexate-experienced, and anti-TNF biological drug-experienced patients. We also did several sensitivity analyses related to methods for handling zero events.²⁶

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. JS, CC, and GAW had full access to all the data in the study and JS had final responsibility for the decision to submit for publication.

Results

We identified 106 randomised trials published between 1992 and Feb 11, 2014, which included 42 330 patients with rheumatoid arthritis (figure 1; appendix pp 10–21). We separated these studies into those that included methotrexate-naive, traditional DMARD-experienced, and anti-TNF biological drug-experienced patients (table; figure 2). Treatment duration ranged from 2 to 36 months, and the mean rheumatoid arthritis duration ranged from 0.1 to 13.5 years (table). Randomised trials reported serious infection on an intention-to-treat (70%) or modified intention-to-treat (30%) basis. The appendix shows the detailed characteristics of included studies (pp 10–21) and the risk of bias assessment (pp 22–27).

In the traditional meta-analysis, 59 trials assessed standard-dose biological drugs with or without traditional DMARD. Of these 59 trials, 53 (90%) reported at least

	All populations	Traditional DMARD-naive patients	Traditional DMARD-experienced patients	TNF-experienced patients
Number of trials	106 (100%)	24 (23%)	71 (67%)	11 (10%)
Number of patients in trials	42 330 (100%)	8375 (20%)	29 167 (69%)	4788 (11%)
Number of patients with serious infection	965 (100%)	227 (24%)	646 (67%)	92 (10%)
Median year of publication	2008 (1992–2013)	2006 (1992–2013)	2008 (1994–2013)	2008 (2005–2013)
Number of treatment nodes	10	5	10	6
Number of two-arm trials	63 (100%)	19 (30%)	38 (60%)	6 (10%)
Number of multi-arm trials	43 (100%)	5 (12%)	33 (77%)	5 (12%)
Mean follow-up duration (months)	9.0 (8.0, 1–60)	13.1 (6.9, 3–24)	8.0 (8.5, 1–60)	6.3 (3.2, 2–12)
Number of trials with duration ≥12 months	33 (31%)	17 (71%)	18 (25%)	2 (18%)
Mean rheumatoid arthritis duration (years)	6.9 (4.0, 0.1–13.5)	0.7 (0.7, 0.1–3.5)	8.5 (2.3, 2.2–13.5)	10.8 (2.0, 6.4–12.9)
Mean annualised baseline risk of serious infection in traditional DMARDs arms*	2% (2, 0–9%)	2% (2, 0–9%)	2% (2, 0–8%)	2% (2, 0–5%)

Data are n (%), year (range), mean (SD, range), or % (range). TNF=tumour necrosis factor. *Only included trials more than 6 months in duration for calculation. DMARD=disease-modifying antirheumatic drugs.

Table: Characteristics of patients and studies

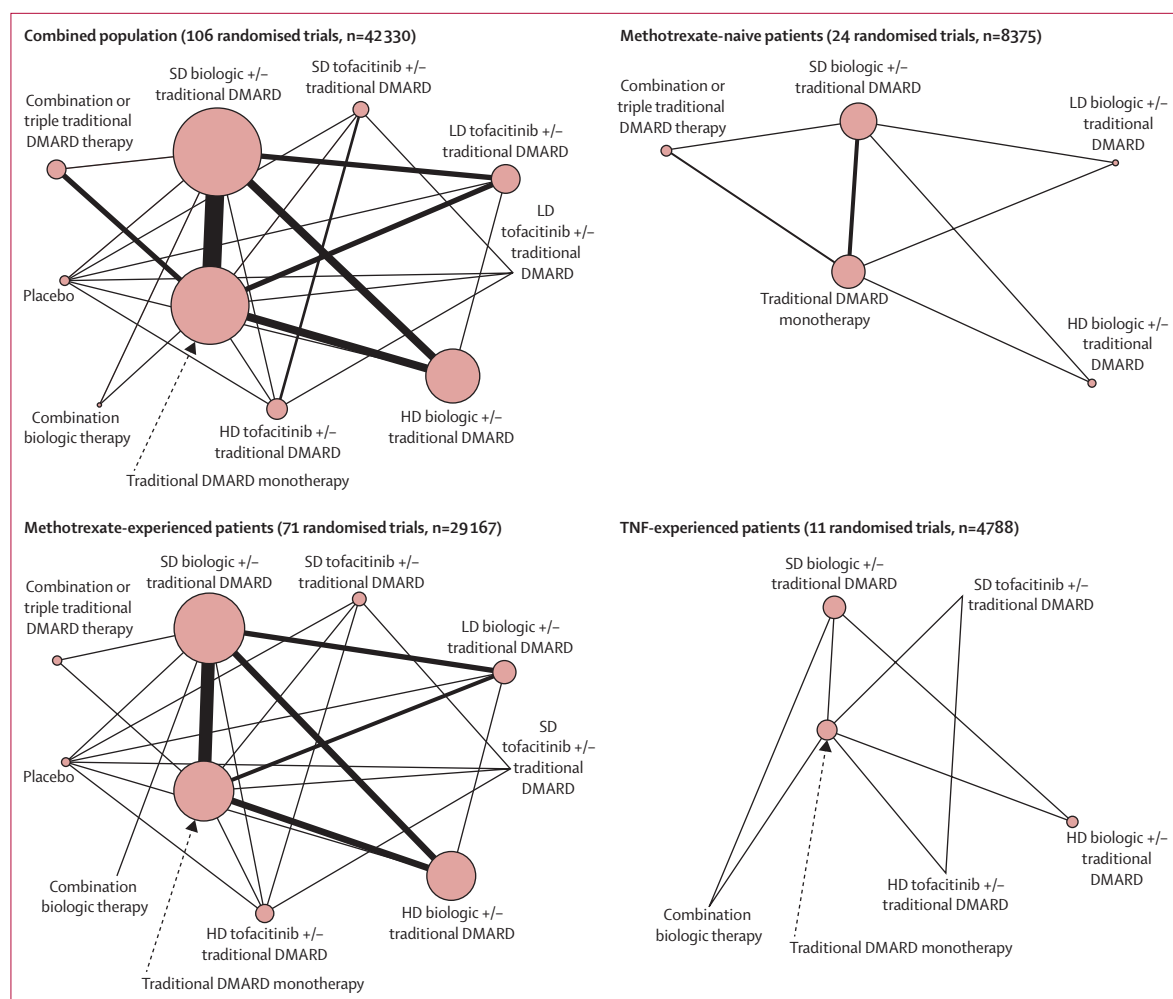


Figure 2: Evidence networks for serious infection in populations

The width of the lines is proportional to the number of randomised trials being compared in each pair of treatments. The size of each treatment node is proportional to the number of participants (sample size). Doses are defined in the appendix. DMARD=disease-modifying antirheumatic drugs. SD=standard dose. HD=high dose. LD=low dose.

one serious infection in the study. In total, 525 serious infections were reported in the 59 trials, including 68 comparisons between standard-dose biological drugs with or without traditional DMARD (342 events) and traditional DMARD monotherapy (183 events). We identified a significant increase in serious infections in patients receiving biological drugs (OR 1.27, 95% CI 1.05–1.52, $p=0.012$; figure 3). The risk of serious infections in patients treated with biological drugs varied depending on previous treatment experience; risk was significantly increased in methotrexate-experienced patients, but did not significantly differ in patients who were methotrexate-naïve or anti-TNF-biological drug-experienced (figure 3).

We did stratified analyses adjusting for differences in other patient-level and study-level characteristics and these are shown in appendix (pp 28–30). We detected clinically important and statistically significantly

increased risk of serious infections in patients treated with biological drugs compared with those treated with traditional DMARDs in several cases: when duration of follow-up was 6–12 months; when biological drugs were used in combination with traditional DMARDs; when patients had established rheumatoid arthritis (2–10 years disease duration); when studies were published between 2000 and 2004; when studies had a low risk of bias; and when the comparator was traditional DMARD plus placebo (appendix pp 28–30). The results did not vary substantially when different statistical models were used (appendix p 31). Detailed findings from the traditional meta-analysis are reported in the appendix (pp 28–30).

In the cumulative meta-analysis, our findings (figure 4) showed that use of standard-dose biological drugs was associated with a significantly increased risk of serious infection, which became evident in 2004, when

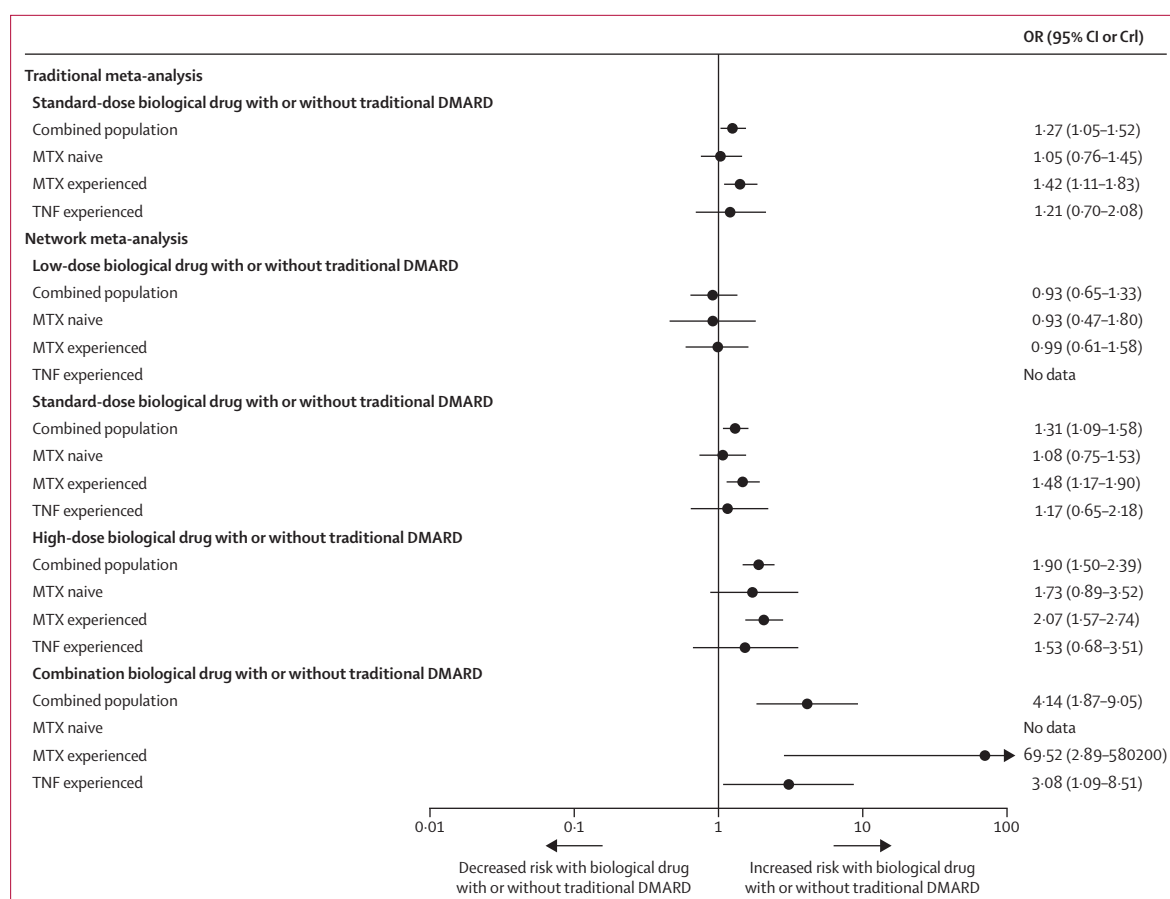


Figure 3: Traditional meta-analysis and network meta-analysis

Risk of serious infection among specified populations of patients compared with patients receiving traditional DMARD monotherapy. Data for the traditional meta-analysis are OR (95% CI) and data for the network meta-analysis are OR (95% CrI). OR=odds ratio. CrI=credible interval. DMARD=disease-modifying antirheumatic drugs.

5537 patients had been randomised and 122 events had occurred ($p=0.02$ at 2004). Subsequent trials increased the number of patients to 22608, and the number of events increased to 525 for this treatment comparison. This increase resulted in a reduction in the OR, with a narrowing of CI ($p=0.012$ at 2013), although the point estimate remained more than one for the years after 2004, and very similar from 2007 onwards.

In our network meta-analysis, standard-dose biological drugs with or without traditional DMARD were associated with an increased risk of serious infection (figure 3; appendix p 32–34). High-dose biological drugs with or without traditional DMARD and combination biological therapy were also associated with increased risk of serious infection, although low-dose biological drugs with or without traditional DMARD were not. These findings supported those of traditional meta-analyses (appendix pp 35–36).

We saw differences among the a-priori-defined populations with rheumatoid arthritis. In patients who were methotrexate-naïve, standard-dose biological drugs with or without traditional DMARD and high-dose

biological drugs with or without traditional DMARD were not associated with a significant increase in risk of serious infection (figure 3). By contrast, in methotrexate-experienced patients, standard-dose biological drugs with or without traditional DMARD and high-dose biological drugs with or without traditional DMARD were associated with an increased risk of serious infections. Information on combination biological therapy was only available for methotrexate-experienced and anti-TNF biological drug-experienced patients and showed a significant increase in serious infections in both groups of patients (figure 3), with wider confidence intervals.

In patients receiving traditional DMARDs, the median absolute reported annual risk of a serious infection was roughly 2%, or 20 per 1000 patients treated per year. The absolute increase in the number of serious infections compared with traditional DMARDs was six per 1000 patients per year for standard-dose biological therapy with or without traditional DMARD, 17 per 1000 patients per year for high-dose biological therapy with or without traditional DMARD, and 55 per 1000 patients per year for combination biological treatment.

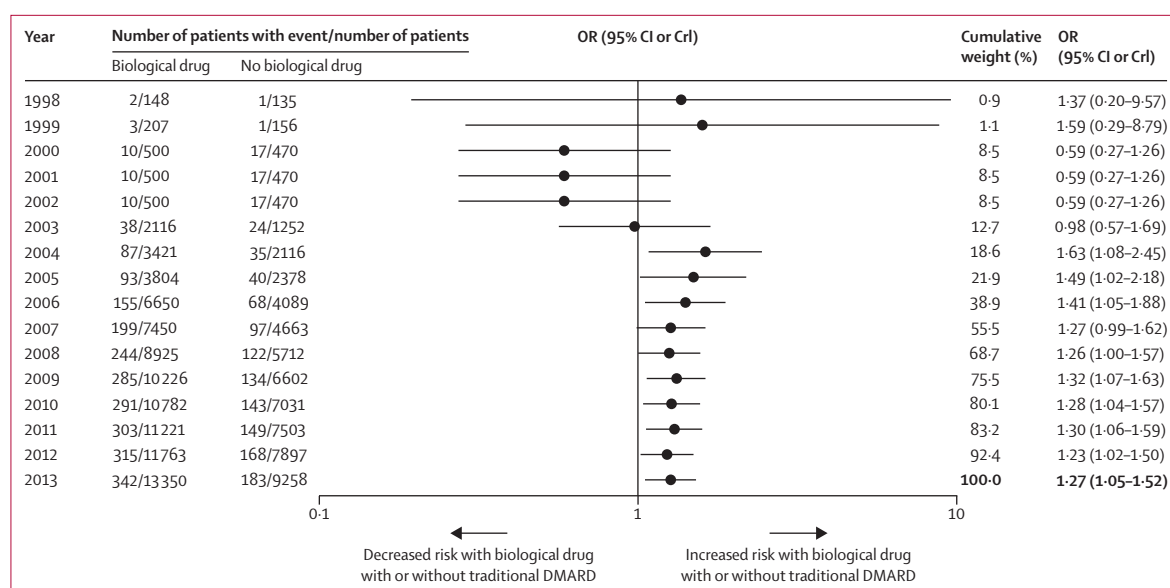


Figure 4: Cumulative meta-analysis

Risk of serious infection among specified populations of patients compared with patients receiving traditional DMARD monotherapy. OR=odds ratio. DMARDs=disease-modifying antirheumatic drugs.

Discussion

The risk of serious infection for patients receiving biological treatment for rheumatoid arthritis and the magnitude of this effect are uncertain. Although the first meta-analysis of the association between biological drugs and serious infections detected an association, three subsequent meta-analyses reported that standard-dose biological drugs were not associated with an increased risk of serious infection compared with traditional DMARDs. Evidence can now be drawn from data for 42 330 patients with rheumatoid arthritis from 106 randomised trials, and this increased sample size can provide a more precise estimate of the risk of serious infection. To the best of our knowledge, this study is the most comprehensive meta-analysis of randomised trials of the risk of serious infections in rheumatoid arthritis that adheres to the recommended PRISMA reporting standards.²⁰ Our analysis exceeds the sample size of the largest previous meta-analysis of risk of infection with biological treatment of rheumatoid arthritis (18 randomised trials and 8808 patients)⁷ more than five times, and includes 88 more randomised trials (appendix p 37). We included data from nine biological drugs, reported detailed stratified analyses, integrated findings for all doses of biological drugs, presented findings on both the relative and absolute scale, and tested the robustness of findings with sensitivity analyses (appendix).

We detected that standard-dose, high-dose, and combination biological drugs (with or without DMARDs) are associated with more serious infections than traditional DMARDs in patients with rheumatoid arthritis. Our comprehensive study investigated biological drug dose in rheumatoid arthritis in more detail than did previous studies (appendix p 37). Bongartz and colleagues⁹ reported

that two of the three biological drugs they studied (infliximab and adalimumab) were associated with significantly increased risk of serious infections (OR 2.0, 95% CI 1.3–3.1) compared with placebo in nine trials up to 2005, which included 5005 patients. By contrast, several later meta-analyses, which included more biological drugs and more randomised trials, reported different findings.^{6–8} Salliot and colleagues⁷ examined 12 randomised trials up to 2007 (6879 patients) and reported that the risk of serious infections with rituximab and abatacept did not differ from placebo, but was significantly increased with high doses of anakinra versus low-dose anakinra (9.63, 1.31–70.91) and versus placebo (3.40, 1.11–10.46). Leombruno and colleagues⁶ analysed 18 randomised trials of three anti-TNF biological drugs up to 2007 (8808 patients) and detected no significant increase in serious infections (1.21, 0.89–1.63). They did identify an increased risk in patients receiving two-to-three times the recommended doses of anti-TNF biological drugs in unadjusted and pooled meta-analysis, but not in exposure-adjusted analyses. Thompson and colleagues⁸ included six randomised trials of five anti-TNF biological drugs in early rheumatoid arthritis up to 2009 (3419 patients) and reported no significant increase in risk of serious infections with biological drugs compared with methotrexate (1.28, 0.82–2.00).

Our findings focus solely on results reported in randomised trials. These studies are often limited by underrepresentation of elderly and high-risk patients and the frequent comparison of treatments with placebo instead of active treatments. Indeed, most of the randomised trials included in our analysis compared the intervention in question with placebo. Accordingly, our risk estimates mainly represent comparisons of biological

drugs combined with DMARD versus DMARD. However, a no-treatment comparator might not be realistic in clinical practice. To compensate, we did several analyses in which we compared biological drugs with combination or triple DMARD therapy. For these analyses, the ORs were slightly higher (appendix pp 29–31, 33–36) but more uncertain because this comparison was only based on data from four randomised trials that compared biological drugs plus DMARD with combination or triple DMARD therapy. However, most trials for this comparison did report a higher number of serious infections in the biological drug group than in comparison groups. Non-randomised studies provide complementary evidence to meta-analyses of randomised trials. A 2010 review³¹ summarised the range of effect estimates reported in non-randomised studies, in which effect estimates for biological drugs versus DMARDs ranged from 1.0 to 2.2. While non-randomised studies differ, these studies have reported an association with infection that is strong early in the course of treatment, but decreases with time.^{31,32} However, the latter finding should be interpreted with caution—studies investigating the long-term use of DMARD treatment are limited to highly selected populations who are adherent to treatment and responding well to DMARDs.

These findings have practical implications. The benefits of biological therapy for patients with rheumatoid arthritis are well known,^{1,2} and now these patients can think about these benefits alongside the absolute risk increase of serious infections (six per 1000 per year for standard-dose biological drugs and 17 per 1000 per year for high-dose biological therapy) at the time when decisions about treatment with biological drugs are made. Clinical guidelines should also incorporate the fact that this risk varies with several characteristics of patients, such as previous DMARD exposure, concurrent use of traditional DMARD or not, and established versus early rheumatoid arthritis.

Our study findings must be interpreted considering several limitations. First, our analysis includes studies that span a 15 year period. Patients enrolled in early studies might have differed from those included in more recent studies. We did a sensitivity analysis to investigate this issue and noted that the point estimate for the OR remained greater than one during the 15 year period (appendix pp 29–31), but decreased from 1995–1999 (OR 1.59, 95% CrI 0.29–8.79) to 2010–2014 (1.11, 0.76–1.62). Whether the decrease in relative effect is evidence that the risk of biological drugs causing serious infections is decreasing over time, or attributable to changes in regions where recent trials were done or to duration of placebo among included studies (ie, increased use of rescue medications for placebo group) is unclear; slight changes in the inclusion and exclusion criteria of the randomised trials we included might have occurred over time, such as the fact that an increased proportion of randomised trials have excluded patients with positive tuberculosis tests in recent years. Future research is needed to study this effect.

Several other limitations need to be addressed. We detected variability between studies in terms of duration of rheumatoid arthritis, duration of follow-up, and other covariates (appendix p 38). Therefore, we reported findings for subgroups of patients to allow comparisons between groups of patients (figure 3; appendix pp 28–29, 32). Second, meta-analyses and network meta-analysis of infrequent outcomes are challenging because of the inherent difficulties in the handling of zero cells. To manage this issue, we did several analyses that used different statistical models and assumptions.²⁶ Results were consistent when we used alternative approaches (appendix p 31–32). Most studies presented the data by use of intention to treat or modified intention to treat, rather than as-treated analyses, which might underestimate the serious infection risk. Additionally, withdrawals were labelled if caused by adverse events, but not serious infections, and some patients might have discontinued biological drugs before these adverse events qualified as serious infections. However, we think the magnitude is probably small, in view of the low number of withdrawals and crossovers reported. Data for compliance with drugs were not reported in most randomised trials; however, these expensive drugs are usually dispensed and adherence recorded as part of the randomised trial conduct. Finally, our analyses only incorporate published data. Future work should focus on integration of more unpublished data⁵ if it becomes available. The scarcity of detailed patient-level data, especially on steroid use, also limits interpretation of these analyses.

Standard-dose and high-dose biological drugs (with or without DMARDs) are associated with an increase in serious infections compared with traditional DMARDs in rheumatoid arthritis, although low-dose biological drugs are not. This new knowledge, when balanced against the clinically important benefits of biological drugs, will help patients and their physicians to make evidence-based decisions that align with their values, preferences, and tolerance of risks of harm and benefits.

Contributors

JAS conceived the study design, did some of the data extraction, and drafted the report. CC conceived the study design, did some of the data extraction, did all of the analyses, and drafted the report. GAW conceived the study design and made major revisions to the report. PT and RC helped with the data analysis and reviewed the report for important intellectual content. SN, MT, and ETG did the systematic review and data extraction, and reviewed the report for important intellectual content. TC and DC conceived the study and reviewed the report for important intellectual content. All authors have read and approved the final version of the report.

Declaration of interests

JAS has received research grants from Takeda and Savient, and consultant fees from Savient, Takeda, Regeneron, and Allergan. JAS is a member of the executive of OMERACT, an organisation that develops outcome measures in rheumatology and receives arms-length funding from 36 companies; a member of the American College of Rheumatology's Guidelines Subcommittee of the Quality of Care Committee; and a member of the Veterans Affairs Rheumatology Field Advisory Committee. CC is a recipient of a Vanier Canada Graduate Scholarship from the Canadian Institutes of Health Research and has received funding from Canadian Network and Centre for Trials Internationally and is a trainee on

the CIHR Drug Safety and Effectiveness Network team grant. PT has received grants or honoraria from Bristol Myers, Chiltern International, and UCB. GAW has received a research grant and consultant fee from Bristol-Myers Squibb; consultant fees from Abbott, Amgen, and UCB; and done data safety monitoring for Novartis. RC has received consulting fees, honoraria, research or institutional support, educational grants, equipment, services or expenses from the following companies: Abbott, Astellas Pharma, Axellus, Bristol-Myers Squibb, Cambridge Nutritional Foods, Centocor, DSM Nutritional Products, HypoSafe, MSD, MundiPharma, NorPharma, Pharmavie, Pfizer, Roche, Sanofi-Aventis, and Scandinavian Clinical Nutrition. All other authors declare no competing interests.

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References

- 1 Scott DL, Wolfe F, Huizinga TW. Rheumatoid arthritis. *Lancet* 2010; **376**: 1094–108.
- 2 Tugwell P, Singh JA, Wells GA. Biologicals for rheumatoid arthritis. *BMJ* 2011; **343**: d4027.
- 3 Singh JA, Furst DE, Bharat A, et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. *Arthritis Care Res (Hoboken)* 2012; **64**: 625–39.
- 4 Smolen JS, Landewe R, Breedveld FC, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Ann Rheum Dis* 2014; **73**: 492–509.
- 5 Ioannidis JP, Karassa FB, Druyts E, Thorlund K, Mills EJ. Biologic agents in rheumatology: unmet issues after 200 trials and \$200 billion sales. *Nat Rev Rheumatol* 2013; **9**: 665–73.
- 6 Leombruno JP, Einarson TR, Keystone EC. The safety of anti-tumor necrosis factor treatments in rheumatoid arthritis: meta and exposure-adjusted pooled analyses of serious adverse events. *Ann Rheum Dis* 2009; **68**: 1136–45.
- 7 Salliot C, Dougados M, Gossec L. Risk of serious infections during rituximab, abatacept and anakinra treatments for rheumatoid arthritis: meta-analyses of randomised placebo-controlled trials. *Ann Rheum Dis* 2009; **68**: 25–32.
- 8 Thompson AE, Rieder SW, Pope JE. Tumor necrosis factor therapy and the risk of serious infection and malignancy in patients with early rheumatoid arthritis: a meta-analysis of randomized controlled trials. *Arthritis Rheum* 2011; **63**: 1479–85.
- 9 Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. *JAMA* 2006; **295**: 2275–85.
- 10 Dixon WG, Symmons DP, Lunt M, Watson KD, Hyrich KL, Silman AJ. Serious infection following anti-tumor necrosis factor alpha therapy in patients with rheumatoid arthritis: lessons from interpreting data from observational studies. *Arthritis Rheum* 2007; **56**: 2896–904.
- 11 Schneeweiss S, Setoguchi S, Weinblatt ME, et al. Anti-tumor necrosis factor alpha therapy and the risk of serious bacterial infections in elderly patients with rheumatoid arthritis. *Arthritis Rheum* 2007; **56**: 1754–64.
- 12 Wolfe F, Caplan L, Michaud K. Treatment for rheumatoid arthritis and the risk of hospitalization for pneumonia: associations with prednisone, disease-modifying antirheumatic drugs, and anti-tumor necrosis factor therapy. *Arthritis Rheum* 2006; **54**: 628–34.
- 13 Grijalva CG, Chen L, Delzell E, et al. Initiation of tumor necrosis factor-alpha antagonists and the risk of hospitalization for infection in patients with autoimmune diseases. *JAMA* 2011; **306**: 2331–39.
- 14 Askling J, Forred CM, Brandt L, et al. Time-dependent increase in risk of hospitalisation with infection among Swedish RA patients treated with TNF antagonists. *Ann Rheum Dis* 2007; **66**: 1339–44.
- 15 Strangfeld A, Eveslage M, Schneider M, et al. Treatment benefit or survival of the fittest: what drives the time-dependent decrease in serious infection rates under TNF inhibition and what does this imply for the individual patient? *Ann Rheum Dis* 2011; **70**: 1914–20.
- 16 Galloway JB, Hyrich KL, Mercer LK, et al. Anti-TNF therapy is associated with an increased risk of serious infections in patients with rheumatoid arthritis especially in the first 6 months of treatment: updated results from the British Society for Rheumatology Biologics Register with special emphasis on risks in the elderly. *Rheumatology (Oxford)* 2011; **50**: 124–31.
- 17 Higgins JPT, Green S, eds. *Cochrane handbook for systematic reviews of interventions* version 5.1.0 [updated March 2011]. London: The Cochrane Collaboration, 2011.
- 18 Hoaglin DC, Hawkins N, Jansen JP, et al. Conducting indirect-treatment-comparison and network-meta-analysis studies: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 2. *Value Health* 2011; **14**: 429–37.
- 19 Jansen JP, Fleurence R, Devine B, et al. Interpreting indirect treatment comparisons and network meta-analysis for health-care decision making: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 1. *Value Health* 2011; **14**: 417–28.
- 20 Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009; **6**: e1000097.
- 21 Singh JA, Wells GA, Christensen R, et al. Adverse effects of biologics: a network meta-analysis and Cochrane overview. *Cochrane Database Syst Rev* 2011; **2**: CD008794.
- 22 Singh JA, Christensen R, Wells GA, et al. Biologicals for rheumatoid arthritis: an overview of Cochrane reviews. *Cochrane Database Syst Rev* 2009; **4**: CD007848.
- 23 Gaujoux-Viala C, Nam J, Ramiro S, et al. Efficacy of conventional synthetic disease-modifying antirheumatic drugs, glucocorticoids and tofacitinib: a systematic literature review informing the 2013 update of the EULAR recommendations for management of rheumatoid arthritis. *Ann Rheum Dis* 2014; **73**: 510–15.
- 24 Katchamart W, Trudeau J, Phumethum V, Bombardier C. Methotrexate monotherapy versus methotrexate combination therapy with non-biologic disease modifying anti-rheumatic drugs for rheumatoid arthritis. *Cochrane Database Syst Rev* 2010; **4**: CD008495.
- 25 Higgins JP, Altman DG, Sterne JA. Chapter 8: Assessing risk of bias in included studies. In: Higgins JP, Green S, eds. *Cochrane handbook for systematic reviews of interventions* version 5.1.0 (updated March 2011). London: The Cochrane Collaboration, 2011.
- 26 Bradburn MJ, Deeks JJ, Berlin JA, Localio AR. Much ado about nothing: a comparison of the performance of meta-analytical methods with rare events. *Stat Med* 2007; **26**: 53–77.
- 27 Spiegelhalter D, Thomas A, Best N. WinBUGS user manual. Version 1.4, January 2003. Cambridge: Medical Research Council, 2003.
- 28 Dias S, Sutton AJ, Ades AE, Welton NJ. Evidence synthesis for decision making 2: a generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials. *Med Decis Making* 2013; **33**: 607–17.
- 29 Turner RM, Davey J, Clarke MJ, Thompson SG, Higgins JP. Predicting the extent of heterogeneity in meta-analysis, using empirical data from the Cochrane Database of Systematic Reviews. *Int J Epidemiol* 2012; **41**: 818–27.
- 30 Dias S, Welton NJ, Sutton AJ, Caldwell DM, Lu G, Ades AE. Evidence synthesis for decision making 4: inconsistency in networks of evidence based on randomized controlled trials. *Med Decis Making* 2013; **33**: 641–56.
- 31 Bernatsky S, Habel Y, Rahme E. Observational studies of infections in rheumatoid arthritis: a metaanalysis of tumor necrosis factor antagonists. *J Rheumatol* 2010; **37**: 928–31.
- 32 Novosad SA, Winthrop KL. Beyond tumor necrosis factor inhibition: the expanding pipeline of biologic therapies for inflammatory diseases and their associated infectious sequelae. *Clin Infect Dis* 2014; **58**: 1587–98.

Original Investigation

Clinical and Safety Outcomes Associated With Treatment of Acute Venous Thromboembolism

A Systematic Review and Meta-analysis

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IMPORTANCE Many anticoagulant strategies are available for the treatment of acute venous thromboembolism, yet little guidance exists regarding which drug is most effective and safe.

OBJECTIVE To summarize and compare the efficacy and safety outcomes associated with 8 anticoagulation options (unfractionated heparin [UFH], low-molecular-weight heparin [LMWH], or fondaparinux in combination with vitamin K antagonists); LMWH with dabigatran or edoxaban; rivaroxaban; apixaban; and LMWH alone) for treatment of venous thromboembolism.

DATA SOURCES A systematic literature search was conducted using MEDLINE, EMBASE, and the evidence-based medicine reviews from inception through February 28, 2014.

STUDY SELECTION Eligible studies were randomized trials reporting rates of recurrent venous thromboembolism and major bleeding in patients with acute venous thromboembolism. Of the 1197 studies identified, 45 trials including 44 989 patients were included in the analyses.

DATA EXTRACTION AND SYNTHESIS Two reviewers independently extracted trial-level data including number of patients, duration of follow-up, and outcomes. The data were pooled using network meta-analysis.

MAIN OUTCOMES AND MEASURES The primary clinical and safety outcomes were recurrent venous thromboembolism and major bleeding, respectively.

RESULTS Compared with the LMWH-vitamin K antagonist combination, a treatment strategy using the UFH-vitamin K antagonist combination was associated with an increased risk of recurrent venous thromboembolism (hazard ratio [HR], 1.42; 95% credible interval [CrI], 1.15-1.79). The proportion of patients experiencing recurrent venous thromboembolism during 3 months of treatment were 1.84% (95% CrI, 1.33%-2.51%) for the UFH-vitamin K antagonist combination and 1.30% (95% CrI, 1.02%-1.62%) for the LMWH-vitamin K antagonist combination. Rivaroxaban (HR, 0.55; 95% CrI, 0.35-0.89) and apixaban (HR, 0.31; 95% CrI, 0.15-0.62) were associated with a lower risk of bleeding than was the LMWH-vitamin K antagonist combination, with a lower proportion of patients experiencing a major bleeding event during 3 months of anticoagulation: 0.49% (95% CrI, 0.29%-0.85%) for rivaroxaban, 0.28% (95% CrI, 0.14%-0.50%) for apixaban, and 0.89% (95% CrI, 0.66%-1.16%) for the LMWH-vitamin K antagonist combination.

CONCLUSIONS AND RELEVANCE Using meta-analytic pooling, there were no statistically significant differences for efficacy and safety associated with most treatment strategies used to treat acute venous thromboembolism compared with the LMWH-vitamin K antagonist combination. However, findings suggest that the UFH-vitamin K antagonist combination is associated with the least effective strategy and that rivaroxaban and apixaban may be associated with the lowest risk for bleeding.

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 Author Audio Interview at jama.com

 Supplemental content at jama.com

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Venous thromboembolism, manifested as deep vein thrombosis or pulmonary embolism, is a common medical condition and is the third leading cause of cardiovascular mortality.¹⁻⁷ Untreated acute pulmonary embolism is associated with a mortality rate of up to 25%.⁸ Anticoagulant therapy is effective at treating acute venous thromboembolism and preventing recurrent events and death associated with recurrent venous thromboembolism.⁹

The traditional immediate treatment of acute venous thromboembolism involves the initial use of parenteral anticoagulants (unfractionated heparin [UFH], low-molecular-weight-heparin [LMWH], or fondaparinux) with transition to the vitamin K antagonist. Parenteral anticoagulant is continued for a minimum of 5 days and until the international normalized ratio is 2.0 or higher for at least 24 hours.¹⁰ In patients with acute deep vein thrombosis or pulmonary embolism, LMWH or fondaparinux is recommended over UFH.¹⁰

The traditional approach to acute venous thromboembolism may be cumbersome for patients given that the initial phase is administered parenterally and that the use of vitamin K antagonist requires frequent laboratory monitoring and food and drug restrictions due to adverse interactions.¹¹ Direct oral anticoagulants including direct Xa inhibitors (rivaroxaban, apixaban, and edoxaban) and a direct thrombin inhibitor (dabigatran) may offer an attractive alternative to the traditional treatment of acute venous thromboembolism. Recent studies have evaluated the efficacy and safety of direct oral anticoagulants (with and without initial parenteral anticoagulant therapy) for the treatment of acute venous thromboembolism.

Clinicians have many potential treatment options regarding management of acute venous thromboembolism and little guidance exists about which drug is most effective yet safe. Although individual studies have shown promising results, several therapies have been assessed in only a single trial, and direct comparisons are rarely available. Therefore, we sought to summarize and compare the clinical outcomes and safety associated with various management options (UFH-vitamin K antagonist, LMWH-vitamin K antagonist, fondaparinux-vitamin K antagonist, LMWH-dabigatran, and LMWH-edoxaban combinations; rivaroxaban; apixaban; and LMWH alone) for treating acute venous thromboembolism using network meta-analysis.

Methods

Data Sources and Searches

A systematic search of the literature was conducted on MEDLINE (1946 to February 28, 2014) and EMBASE (1947 to February 28, 2014) and, using the OVID interface, to search for evidence-based medicine reviews: Cochrane Database of Systematic Review (2005-January 2014); ACP Journal Club (1981-

February 2014); Database of Abstract of Reviews of Effects (first quarter, 2014); Cochrane Central Register of Controlled Trials (January 2014); Cochrane Methodology Register (third quarter, 2012); Health Technology Assessment (first quarter, 2014); and the National Health Service (NHS) Economic Evaluation (first quarter, 2014). References of included studies and narrative reviews were considered for additional potential studies. The protocol and systematic search strategy of the review is documented online (PROSPERO registry-CRD42014008671). The systematic search strategy is documented in eAppendix 1 in the Supplement. There were no language restrictions.

Study Selection

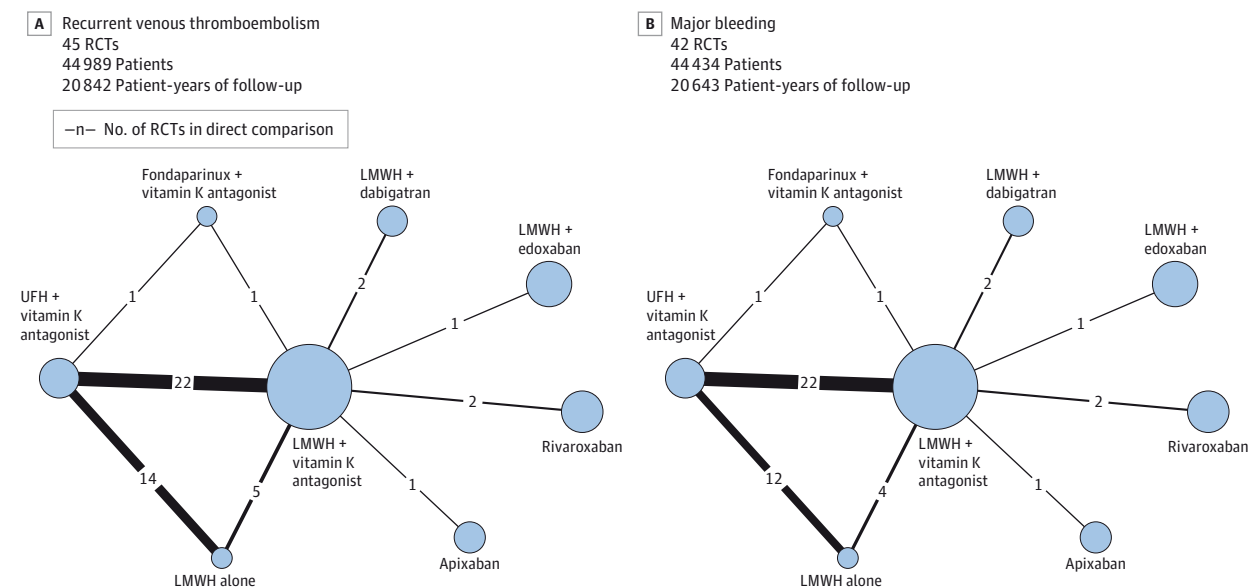
Potentially relevant articles were reviewed in full to ensure that they satisfied 3 criteria: (1) the study prospectively enrolled patients who had objectively confirmed symptomatic acute venous thromboembolism (lower extremity deep vein thrombosis, pulmonary embolism, or both) and who had qualifying recurrent venous thromboembolism events that were symptomatic and objectively confirmed; (2) patients were randomized to receive the UFH-vitamin K antagonist, LMWH-vitamin K antagonist, fondaparinux-vitamin K antagonist, LMWH-dabigatran, and LMWH-edoxaban combinations; rivaroxaban; apixaban; or LMWH alone and the study compared 2 different anticoagulation strategies; and (3) 1 or more of the primary or secondary outcomes were reported. Studies were excluded if (1) patients were randomized to placebo or observation; (2) patients were randomized to idraparinux or ximelagatran; (3) only patients with cancer-associated thrombosis were included; (4) study design was phase 1 or 2; and (5) trials evaluated extended venous thromboembolism treatment for secondary prevention.

Outcome Measures

The primary outcome measures were recurrent venous thromboembolism and major bleeding episodes. Recurrent venous thromboembolism was defined as a new noncompressible segment found on compression leg vein ultrasound imaging, new intraluminal filling defect on venography, newly abnormal impedance plethysmography test, new high-probability ventilation-perfusion scan, or new pulmonary artery filling defect on computed tomography or pulmonary angiography. A major bleeding episode was defined as clinically overt bleeding and associated with at least 1 of the following: (1) a decrease in hemoglobin levels of at least 2 g/dL; (2) transfusion of 2 or more units of packed red blood cells; (3) bleeding was intracranial or retroperitoneal or involved a body cavity; (4) death; or (5) a major bleeding episode as defined by the investigators of each individual study.¹²

Secondary outcomes included fatal recurrent venous thromboembolism and fatal bleeding episodes. Fatal recurrent venous thromboembolism was diagnosed by autopsy, a high-probability ventilation-perfusion scan or new intraluminal filling defect detected on computed tomography or venography prior to death, or a high clinical suspicion of fatal pulmonary embolism as defined by the investigators of each individual study. A fatal bleeding episode was defined as a ma-

Figure 1. Evidence Network for Recurrent Venous Thromboembolism and Major Bleeding



patient-years of follow-up. LMWH indicates low-molecular-weight heparin; RCT, randomized clinical trial; UFH, unfractionated heparin.

patient-years of follow-up. LMWH indicates low-molecular-weight heparin; RCT, randomized clinical trial; UFH, unfractionated heparin.

for bleeding episode directly leading to death or a death that was reported as associated with bleeding.

Data Extraction and Quality Assessment

Two reviewers (L.A.C., M.C.) independently assessed eligibility of articles identified in the initial search strategy for inclusion in the review and discussed those deemed potentially eligible; independently extracted data (baseline characteristics, definition of outcomes, numbers of events) using a standardized data abstraction form; and assessed studies' methodological quality using the Risk of Bias Assessment Tool from the Cochrane Handbook for randomized trials.¹³ Corresponding authors of manuscripts were contacted if primary or secondary outcomes could not be extracted from the original article.

Data Synthesis and Analysis

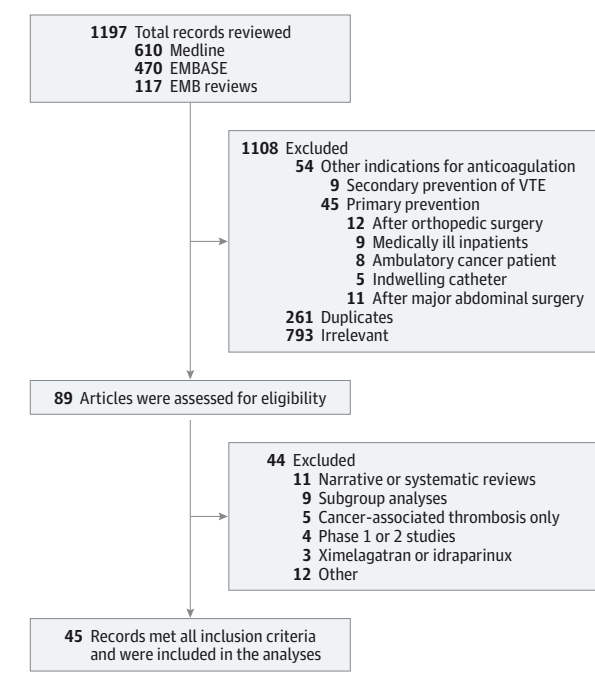
Outcomes were allocated according to the intention-to-treat principle. Bayesian network meta-analyses and direct frequentist pairwise meta-analyses were conducted for all outcomes. Bayesian network meta-analyses were conducted using a Poisson likelihood model.¹⁴ The different treatment strategies were treated as separate nodes (UFH-vitamin K antagonist, LMWH-vitamin K antagonist, fondaparinux-vitamin K antagonist, LMWH-dabigatran, or LMWH-edoxaban combinations; rivaroxaban; apixaban; or LMWH alone; **Figure 1**). All networks were constructed using NodeXL.¹⁵

Hazard ratios (HRs) and 95% credible intervals (CrIs) were modeled using Markov Chain Monte Carlo methods. The proportion of patients expected to have an event during use of each treatment (over 3 and 6 months) was calculated assuming a rate of 5.3 per 100 patient-years ($\approx 2.6\%$ over 6

months) and 3.6 per 100 patient-years ($\approx 1.8\%$ over 6 months) for recurrent venous thromboembolism and major bleeding respectively, for patients receiving the LMWH-vitamin K antagonist combination.^{16,17} The probability that each drug was associated with being the most efficacious treatment was calculated by counting the proportion of iterations of the Markov chain in which each drug had the highest HR.¹⁴ Random-effects network meta-analyses with vague priors were conducted for the analyses.¹⁴ Fixed-effects models were also conducted, along with an analysis using a binomial likelihood model and random-effects model with informative priors.^{18,19} Assessment of model fit was based on comparison of residual deviance to the number of unconstrained data points, assessment of the deviance information criterion, and between-study standard deviation.^{14,20,21} To ensure convergence was reached, trace plots and the Brooks-Gelman-Rubin statistic were assessed.²² Analyses were performed using WinBUGS version 1.4.3 (MRC Biostatistics Unit).

A priori subgroup analysis was conducted to adjust for index acute venous thromboembolism (deep vein thrombosis or pulmonary embolism) and for differences in study duration. We assessed inconsistency by comparing the deviance and deviance information criterion statistics in fitted consistency and inconsistency models.²³ We also plotted the posterior mean deviance of the individual data points (each group of the trial) in the inconsistency model against their posterior mean deviance in the consistency model.²³ Results from our network meta-analysis were also qualitatively compared with direct frequentist pairwise estimates. Frequentist pairwise meta-analyses were conducted using Comprehensive Meta-Analysis Version 2.2.064 (Biostat).

Figure 2. Flow Diagram of Study Selection



Results

Of the 1197 citations identified, 45 articles (44 989 patients) were included in the analyses (Figure 2 and eAppendix 1 in the Supplement).^{17,24-67} Twenty-two clinical trials compared the UFH-vitamin K antagonist combination (357 events, 7133 patients) with the LMWH-vitamin K antagonist combination (533 events, 20 246 patients),²⁴⁻⁴⁵ 12 compared the UFH-vitamin K antagonist combination (357 events, 7133 patients) with LMWH alone (81 events, 1897 patients),⁴⁶⁻⁵⁷ 3 compared the LMWH-vitamin K antagonist combination (533 events, 20 246 patients) with LMWH alone (81 events, 1897 patients),⁵⁹⁻⁶¹ 2 compared the fondaparinux-vitamin K antagonist combination (85 events, 2201 patients) with the LMWH-vitamin K antagonist combination (533 events, 20 246 patients) or with the UFH-vitamin K antagonist (357 events, 7133 patients),^{58,62} and 6 compared the LMWH-vitamin K antagonist combination (533 events, 20 246 patients) with 1 of the direct oral anticoagulants: 2 dabigatran (60 events, 2553 patients), 1 apixaban (59 events, 2691 patients), 1 edoxaban (66 events, 4118 patients), and 2 rivaroxaban (86 events, 4150 patients).^{17,63-67} Two of the included studies compared 3 anticoagulation regimens: the UFH-vitamin K antagonist combination (357 events, 7133 patients), the LMWH-vitamin K antagonist combination (533 events, 20 246 patients), and LMWH alone (81 events, 1897 patients).^{26,27} The baseline characteristics of the included studies are shown in Table 1, Table 2, Table 3, and Table 4 and eAppendix 2 in the Supplement. The sample size ranged from 60 to 8240 patients, with a median sample size of 298. The median follow-up period was 3 months

(range, 3-8.2 months). Eleven randomized clinical trials (RCTs) evaluated treatment of patients with any acute venous thromboembolism (both deep vein thrombosis and pulmonary embolism),* 7 studies assessed patients with pulmonary embolism,^{33,38,41,52,53,58,67} and the remaining 27 studies evaluated treatment of patients with deep vein thrombosis.† Quality assessment is reported in eAppendix 3 in the Supplement.

All studies were included in the evaluation for recurrent venous thromboembolism. Results of Bayesian network meta-analyses are presented in Table 5 and Figure 3. In comparison with the LMWH-vitamin K antagonist combination, all treatment strategies except the UFH-vitamin K antagonist combination were associated with a lower rate of recurrent venous thromboembolism events. Compared with the LMWH-vitamin K antagonist combination, the UFH-vitamin K antagonist combination was associated with an increased rate of recurrent venous thromboembolism with an HR of 1.42 (95% CrI, 1.15-1.79). When the UFH-vitamin K antagonist combination was used as the comparator, the LMWH-vitamin K antagonist combination and LMWH alone were associated with a reduction in recurrent venous thromboembolism event rates (Table 5). Stepwise comparison of all remaining treatment strategies did not reveal significant differences in rates of recurrent venous thromboembolism (Table 5). The LMWH-edoxaban combination and apixaban were associated with the greatest probability of being the best therapy among all treatment strategies evaluated, 33.1% and 31.6 %, respectively. (For details, see eAppendix 4 in the Supplement.)

The UFH-vitamin K antagonist combination was associated with a higher percentage of patients experiencing recurrent venous thromboembolism during 3 months of treatment (1.84%; 95% CrI, 1.33%-2.51%) than patients taking the LMWH-vitamin K antagonist combination (1.30%; 95% CrI, 1.02%-1.62%; eAppendix 5 in the Supplement). Compared with the LMWH-vitamin K antagonist combination, the number needed to treat to harm using the UFH-vitamin K antagonist combination was 188 patients at 3 months (eAppendix 5 in the Supplement).

Comparison of random-effects Bayesian network meta-analyses with direct frequentist meta-analysis pairwise comparisons were similar in magnitude and direction of effect estimates for recurrent venous thromboembolism rates, with the exception of the fondaparinux-vitamin K antagonist combination and LMWH alone. The UFH-vitamin K antagonist combination was associated with lower efficacy than was the LMWH-vitamin K antagonist combination (eAppendix 6 in the Supplement). Subgroup analyses were conducted to evaluate recurrent venous thromboembolism event rates for patients presenting with index deep vein thrombosis and index pulmonary embolism (Table 5). Compared with the LMWH-vitamin K antagonist combination, use of the UFH-vitamin K antagonist combination in patients with index deep vein thrombosis was associated with the lowest efficacy and was associated

*References 17, 26, 37, 39, 43-45, 57, 63-65

†References 24, 25, 27-32, 34-36, 40, 42, 46-51, 54-56, 59-62, 66

Table 1. Baseline Characteristics of Randomized Clinical Trials of Treatment of Acute Venous Thromboembolism Comparing Unfractionated Heparin-Vitamin K Antagonist Combination With Low-Molecular-Weight Heparin-Vitamin K Antagonist Combination

Source	Sample Size	Duration of Drug Treatment, mo	Recurrent Venous Thromboembolism Events	Fatal Recurrent Venous Thromboembolism Events	Major Bleeding Events	Fatal Bleeding Events
Deep Vein Thrombosis						
Collaborative European Study, ²⁸ 1991						
UFH-VKA	81	3	2	0	4	0
LMWH-VKA	85		3	1	2	0
Hull et al, ²⁹ 1992						
UFH-VKA	219	3	15	3	11	0
LMWH-VKA	213		6	0	6	0
Lopaciuk et al, ³⁰ 1992						
UFH-VKA	75	3	3	0	1	0
LMWH-VKA	74		0	0	0	0
Prandoni et al, ³¹ 1992						
UFH-VKA	85	6	12	3	6	1
LMWH-VKA	85		6	3	2	0
Simonneau et al, ³² 1993						
UFH-VKA	67	3	2	0	0	0
LMWH-VKA	67		0	0	0	0
Fiessinger et al, ³⁶ 1996						
UFH-VKA	133	5.3 ^a	3	0	2	0
LMWH-VKA	120		5	0	0	0
Koopman et al, ³⁵ 1996						
UFH-VKA	198	3	10	0	4	1
LMWH-VKA	202		8	0	1	0
Levine et al, ³⁴ 1996						
UFH-VKA	253	3	17	2	3	0
LMWH-VKA	247		13	0	5	2
Kirchmaier et al, ²⁴ 1998						
UFH-VKA	130	6	4	1	5	0
LMWH-VKA ^b	128		0 ^b	0 ^b	10 ^b	1 ^b
LMWH-VKA ^b	127		2 ^b	0 ^b	2 ^b	0 ^b
Harenberg et al, ⁴⁰ 2000						
UFH-VKA	273	6	17	3	13	2
LMWH-VKA	265		6	0	7	0
Breddin et al, ²⁵ 2001						
UFH-VKA	375	3	24	3	2	0
LMWH-VKA ^b	388		7 ^b	1 ^b	3 ^b	0 ^b
LMWH-VKA ^b	374		13 ^b	3 ^b	2 ^b	0 ^b
Kakkar et al, ²⁷ 2003						
UFH-VKA	98	3	4	1	1	0
LMWH-VKA	105		1	0	0	0
LMWH alone	94		3	0	1	0
Riess et al, ⁴² 2003						
UFH-VKA	593	6	27	5	7	0
LMWH-VKA	627		22	2	6	0

(continued)

Table 1. Baseline Characteristics of Randomized Clinical Trials of Treatment of Acute Venous Thromboembolism Comparing Unfractionated Heparin–Vitamin K Antagonist Combination With Low-Molecular-Weight Heparin–Vitamin K Antagonist Combination (continued)

Source	Sample Size	Duration of Drug Treatment, mo	Recurrent Venous Thromboembolism Events	Fatal Recurrent Venous Thromboembolism Events	Major Bleeding Events	Fatal Bleeding Events
Pulmonary Embolism						
Meyer et al, ³³ 1995						
UFH-VKA	31	3	1	0	0	0
LMWH-VKA	29		0	0	0	0
Simonneau et al, ³⁸ 1997						
UFH-VKA	308	3	6	3	8	2
LMWH-VKA	304		5	3	6	1
Findik et al, ⁴¹ 2002						
UFH-VKA	30	3	3	0	0	0
LMWH-VKA	29		1	0	0	0
All Venous Thromboembolism						
Columbus Investigators, ³⁷ 1997						
UFH-VKA	511	3	25	3	12	2
LMWH-VKA	510		27	3	16	0
Hull et al, ³⁹ 2000						
UFH-VKA	103	3	7	1	2	0
LMWH-VKA	97		0	0	1	0
Merli et al, ²⁶ 2001						
UFH-VKA	290	3	12	2	6	2
LMWH-VKA	298		13	1	5	5
LMWH alone	312		9	2	4	0
Prandoni et al, ⁴³ 2004						
UFH-VKA	360	3	15	3	4	1
LMWH-VKA	360		14	4	3	0
Kearon et al, ⁴⁴ 2006						
UFH-VKA	355	3	13	0	6	1
LMWH-VKA	353		12	1	12	1
Leizorovicz et al, ⁴⁵ 2011						
UFH-VKA	270	3	3	1	10	0
LMWH-VKA	269		7	1	12	2

Abbreviations: LMWH, low-molecular-weight heparin; UFH, unfractionated heparin; VKA, vitamin K antagonist.

^a Median duration of treatment used.

^b Treatment groups used similar regimens and results are combined.

with an increased risk of recurrent venous thromboembolism (HR, 1.74; 95% CrI, 1.27-2.44). All remaining treatment regimens were not associated with differences in outcomes from the LMWH-vitamin K antagonist combination in this population. An additional sensitivity analysis was performed for variation in study treatment duration (eAppendix 7 in the Supplement). Estimates from the sensitivity analyses were similar to the primary analysis except for the UFH-vitamin K antagonist combination, which was associated with a higher rate of recurrent venous thromboembolism (HR, 1.88; 95% CrI, 1.13-3.38) than in the primary analysis (HR, 1.42; 95% CrI, 1.15-1.80).

The analysis of major bleeding events included 42 trials that involved 44 434 patients (Figure 1 and eAppendix 2 in the Supplement). Twenty-two clinical trials compared the UFH-vitamin K antagonist combination (169 events, 6975 patients) with the LMWH-vitamin K antagonist combination

(361 events, 20 124 patients),²⁴⁻⁴⁵ 10 compared the UFH-vitamin K antagonist combination (169 events, 6975 patients) with LMWH alone (28 events, 1622 patients),^{46,49-57} 2 compared the LMWH-vitamin K antagonist combination (361 events, 20 124 patients) with LMWH alone (28 events, 1622 patients),^{59,60} 2 compared the fondaparinux-vitamin K antagonist combination (50 events, 2201 patients) with the LMWH-vitamin K antagonist combination (361 events, 20 124 patients) or with the UFH-vitamin K antagonist combination (169 events, 6975 patients),^{58,62} and 6 compared the LMWH-vitamin K antagonist combination (361 events, 20 124 patients) with 1 of the direct oral anticoagulants: 2 dabigatran (35 events, 2553 patients), 1 apixaban (15 events, 2691 patients), 1 edoxaban (56 events, 4118 patients), and 2 rivaroxaban (40 events, 4150 patients).^{17,63-67} Two of the included studies compared the UFH-vitamin K antagonist combination (169 events, 6975 patients) with the LMWH-vitamin K

Table 2. Baseline Characteristics of Randomized Clinical Trials of Treatment of Acute Venous Thromboembolism Comparing Low-Molecular-Weight Heparin Alone vs Unfractionated Heparin-Vitamin K Antagonist or Low-Molecular-Weight Heparin-Vitamin K Antagonist Combinations

Source	Sample Size	Duration of Drug Treatment, mo	Recurrent Venous Thromboembolism Events	Fatal Recurrent Venous Thromboembolism Events	Major Bleeding Events	Fatal Bleeding Events
Deep Vein Thrombosis						
Bratt et al, ⁴⁷ 1990						
UFH-VKA	55	3	0	0	NR	NR
LMWH alone	55		1	0	NR	NR
Lindmarker et al, ⁴⁸ 1994						
UFH-VKA	103	3	0	0	NR	NR
LMWH alone	101		2	0	NR	NR
Pini et al, ⁴⁹ 1994						
UFH-VKA	94	3	4	0	3	0
LMWH alone	93		6	0	3	0
Das et al, ⁵⁹ 1996						
LMWH-VKA	55	3	2	0	0	0
LMWH alone	50		5	0	0	0
Belcaro et al, ⁴⁶ 1999 ^a						
UFH-VKA	97	3	6	0	0	0
LMWH alone	98		6	0	0	0
Gonzalez-Fajardo et al, ⁵⁰ 1999						
UFH-VKA	80	3	19	0	2	0
LMWH alone	85		8	1	1	0
Lopaciuk et al, ⁶⁰ 1999						
LMWH-VKA	95	3	7	1	1	0
LMWH alone	98		2	0	1	0
Veiga et al, ⁵¹ 2000						
UFH-VKA	50	3	1	0	2	1
LMWH alone	50		2	0	0	0
Ramacciotti et al, ⁵⁴ 2004						
UFH-VKA	97	3	5	0	3	0
LMWH alone	104		2	0	2	0
Chong et al, ⁵⁵ 2005						
UFH-VKA	148	6	14	0	3	0
LMWH alone	150		4	0	0	0
Daskalopoulos et al, ⁵⁶ 2005						
UFH-VKA	52	6	4	1	4	1
LMWH alone	50		2	0	2	1
Romera et al, ⁶¹ 2009						
LMWH-VKA	122	6	7	0	NR	0
LMWH alone	119		5	0	NR	0
Pulmonary Embolism						
Beckman et al, ⁵² 2003						
UFH-VKA	20	3	0	0	2	0
LMWH alone	40		3	1	1	0
Pérez de Llano et al, ⁵³ 2003						
UFH-VKA	21	6	2	0	0	0
LMWH alone	29		3	0	1	1
All Venous Thrombosis						
Hull et al ⁵⁷ , 2007						
UFH-VKA	368	3	21	2	17	0
LMWH alone	369		18	1	12	0

Abbreviations: LMWH, low-molecular-weight heparin; NR, not reported; UFH, unfractionated heparin; VKA, vitamin K antagonist.

^a Third study group excluded.

Table 3. Baseline Characteristics of Randomized Clinical Trials of Treatment of Acute Venous Thromboembolism Comparing Fondaparinux-Vitamin K Antagonist Combination vs Unfractionated Heparin-Vitamin K Antagonist or Low-Molecular-Weight Heparin-Vitamin K Antagonist Combinations

Source	Sample Size, No.	Duration of Drug Treatment, mo	Recurrent Venous Thromboembolism Events	Fatal Recurrent Venous Thromboembolism Events	Major Bleeding Events	Fatal Bleeding Events
Deep Vein Thrombosis						
Buller et al, ⁶² 2004						
LMWH-VKA	1107	3	45	5	26	0
Fondaparinux-VKA	1098		43	5	28	5
Pulmonary Embolism						
Buller et al, ⁵⁸ 2003						
UFH-VKA	1110	3	56	15	26	1
Fondaparinux-VKA	1103		42	16	22	1

Abbreviations: LMWH, low-molecular-weight heparin; UFH, unfractionated heparin; VKA, vitamin K antagonist.

Table 4. Baseline Characteristics of Randomized Clinical Trials of Treatment of Acute Venous Thromboembolism Comparing Direct Oral Anticoagulants vs Low-Molecular-Weight Heparin-Vitamin K Antagonist Combination

Source	Sample Size, No.	Duration of Drug Treatment, mo ^a	Recurrent Venous Thromboembolism Events	Fatal Recurrent Venous Thromboembolism Events	Major Bleeding Events	Fatal Bleeding Events
Deep vein Thrombosis						
Bauersachs et al, ⁶⁶ 2010						
LMWH-VKA	1718	6.2	51	6	20	5
Rivaroxaban	1731	6.4	36	4	14	1
Pulmonary Embolism						
Buller et al, ⁶⁷ 2012						
LMWH-VKA	2413	7	44	6	52	3
Rivaroxaban	2419	7.1	50	10	26	2
All Venous Thromboembolism						
Schulman et al, ⁶³ 2009						
LMWH-VKA	1265	6	27	3	24	1
LMWH-dabigatran	1274		30	1	20	1
Schulman et al, ⁶⁴ 2014						
LMWH-VKA	1289	6	28	0	22	1
LMWH-dabigatran	1279		30	1	15	0
Buller et al, ⁶⁵ 2013						
LMWH-VKA	4122	8.2	80	NR	66	10
LMWH-edoxaban	4118		66	NR	56	2
Agnelli et al, ¹⁷ 2013						
LMWH-VKA	2704	6	71	15	49	2
Apixaban	2691		59	12	15	1

Abbreviations: LMWH, low-molecular-weight heparin; NR, not reported; UFH, unfractionated heparin; VKA, vitamin K antagonist.

^a Direct oral anticoagulant trials used median treatment duration.

antagonist combination (361 events, 20 124 patients) and with LMWH alone (28 events, 1622 patients).^{26,27} The results of network meta-analysis pairwise comparisons are available in Table 5. Compared with the LMWH-vitamin K antagonist combination, rivaroxaban (HR, 0.55; 95% CrI, 0.35-0.89) and apixaban (HR, 0.31; 95% CrI, 0.15-0.62) were associated with the lowest bleeding risk. All other treatment regimens were associated with bleeding risks that did not differ from the LMWH-vitamin K antagonist combination. Additional pair-

wise comparisons showed that rivaroxaban, apixaban, or both were associated with the lowest bleeding rates compared with the UFH-vitamin K antagonist combination (HR, 0.47; 95% CrI, 0.27-0.80 for rivaroxaban and HR, 0.26; 95% CrI, 0.12-0.54 for apixaban); the fondaparinux-vitamin K antagonist combination (HR, 0.30; 95% CrI, 0.12-0.68 for apixaban); the LMWH-dabigatran combination (HR, 0.42; 95% CrI, 0.17-0.99 for apixaban); and the LMWH-edoxaban combination (HR, 0.37; 95% CrI, 0.15-0.89) for apixaban.

Table 5. Treatment Comparisons Within the Network Meta-analysis for Recurrent Venous Thromboembolism and Major Bleeding

Hazard Ratios (95% Credible Interval) ^a				
Treatment	Recurrent Venous Thromboembolism	Recurrent Venous Thromboembolism by Index Event ^b		Major Bleeding
		Deep Vein Thrombosis	Pulmonary Embolism	
Compared With Unfractionated Heparin-Vitamin K Antagonist Combination				
Fondaparinux-VKA	0.71 (0.45-1.12)	0.55 (0.22-1.34)	0.76 (0.50-1.12)	0.90 (0.54-1.49)
LMWH-dabigatran	0.78 (0.45-1.31)	NA	NA	0.64 (0.35-1.14)
LMWH-edoxaban	0.58 (0.30-1.08)	0.55 (0.22-1.32)	0.36 (0.10-1.12)	0.71 (0.40-1.24)
Rivaroxaban	0.64 (0.38-1.03)	0.40 (0.16-0.97)	0.67 (0.20-1.98)	0.47 (0.27-0.80)
Apixaban	0.59 (0.31-1.09)	0.47 (0.19-1.17)	0.53 (0.15-1.7)	0.26 (0.12-0.54)
LMWH alone	0.70 (0.50-0.95)	0.61 (0.40-0.99)	2.19 (0.46-17.09)	0.60 (0.35-1.03)
Compared With Fondaparinux-VKA Combination				
LMWH-dabigatran	1.10 (0.55-2.10)	NA	NA	0.70 (0.35-1.46)
LMWH-edoxaban	0.82 (0.38-1.70)	0.99 (0.30-3.22)	0.47 (0.12-1.57)	0.79 (0.39-1.61)
Rivaroxaban	0.89 (0.46-1.67)	0.72 (0.22-2.37)	0.89 (0.25-2.80)	0.52 (0.27-1.02)
Apixaban	0.83 (0.38-1.73)	0.86 (0.26-2.86)	0.70 (0.18-2.38)	0.30 (0.12-0.68)
LMWH alone	0.97 (0.57-1.71)	1.10 (0.44-3.07)	2.91 (0.59-23.24)	0.66 (0.34-1.44)
Compared With LMWH-Dabigatran				
LMWH-edoxaban	0.75 (0.35-1.64)	NA	NA	1.13 (0.54-2.26)
Rivaroxaban	0.81 (0.41-1.61)	NA	NA	0.74 (0.38-1.45)
Apixaban	0.75 (0.35-1.65)	NA	NA	0.42 (0.17-0.99)
LMWH alone	0.90 (0.50-1.67)	NA	NA	0.93 (0.46-2.11)
Compared With LMWH-Edoxaban				
Rivaroxaban	1.09 (0.52-2.27)	0.73 (0.22-2.39)	1.90 (0.94-3.98)	0.65 (0.33-1.33)
Apixaban	1.01 (0.43-2.35)	0.86 (0.27-2.86)	1.50 (0.65-3.48)	0.37 (0.15-0.89)
LMWH alone	1.19 (0.61-2.43)	1.11 (0.45-3.07)	6.35 (0.90-70.48)	0.84 (0.41-1.91)
Compared With Rivaroxaban				
Apixaban	0.93 (0.44-1.95)	1.18 (0.37-3.99)	0.79 (0.38-1.60)	0.56 (0.24-1.33)
LMWH alone	1.10 (0.63-20)	1.52 (0.60-4.29)	3.31 (0.50-35.17)	1.27 (0.64-2.82)
Compared With Apixaban				
LMWH alone	1.18 (0.60-2.41)	1.28 (0.50-3.56)	4.24 (0.60-47.45)	2.31 (0.94-5.53)

Abbreviations: LMWH, low-molecular-weight heparin; NA, not assessed; UFH, unfractionated heparin; VKA, vitamin K antagonist.

^a Hazard ratios greater than 1 favors the treatment group listed in the Treatment column; hazard ratios less than 1 favors the comparison treatment.

^b A fixed-effects model was used because the index pulmonary embolism evidence network comprised connections consisting of either a few studies or single studies.

For 3 months' duration of therapy, rivaroxaban (HR, 0.49%; 95% CrI, 0.29%-0.85%) and apixaban (HR, 0.28%; 95% CrI, 0.14%-0.50%) were associated with a lower proportion of patients experiencing a major bleeding event than patients receiving the LMWH-vitamin K antagonist combination (0.89%; 95% CrI, 0.66%-1.16%; eAppendix 5 in the Supplement). Compared with LMWH-vitamin K antagonist combination, rivaroxaban was associated with the number needed to treat to benefit of 258 patients at 3 months. Apixaban was associated with the number needed to treat to benefit of 165 patients at 3 months (eAppendix 5 in the Supplement). Apixaban was associated with the greatest probability of being the least harmful therapy (88.9%) among all treatment regimens assessed (eAppendix 4 in the Supplement).

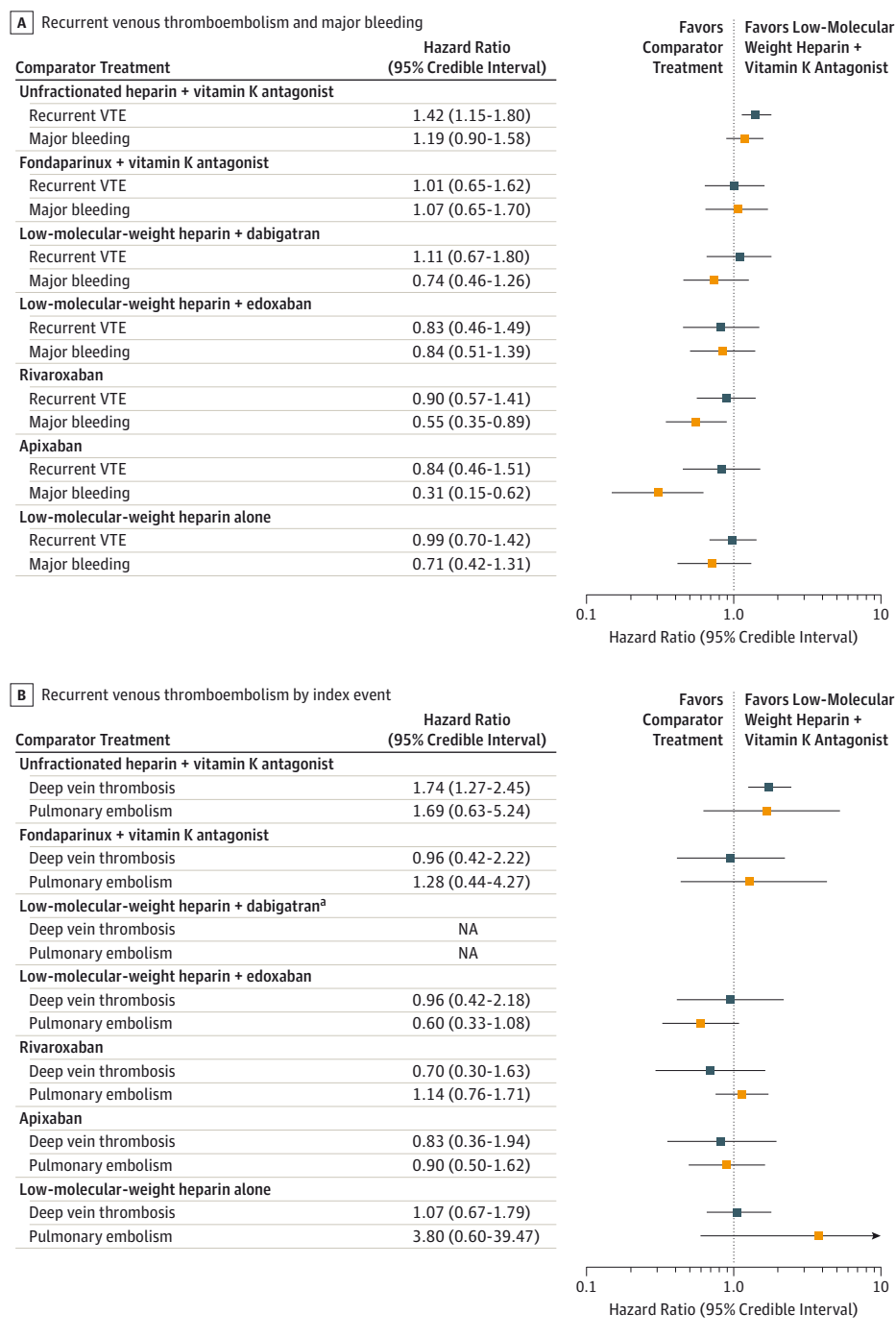
Network meta-analysis using both random-effects and a fixed-effects model were performed and yielded similar results, albeit with wider CrIs in the random-effects model (eAppendix 8 in the Supplement). Hazard ratios also align with

odds ratios reported in the binomial likelihood model (eAppendix 11 in the Supplement). The network meta-analysis for major bleeding yielded a reasonable fit to the data, even though there were a few studies that did not fit particularly well for recurrent venous thromboembolism (eAppendix 10 in the Supplement). Exclusion of these studies did not alter our main findings, although it did improve model fit and reduce between-study standard deviation (eAppendix 10 in the Supplement). We found no evidence of inconsistency (eAppendix 9 in the Supplement).

Fatal events were rare. One hundred sixty-five patients (0.37%) experienced fatal recurrent venous thromboembolism and 64 (0.14%), fatal bleeding events.

Discussion

To our knowledge, this network meta-analysis is the largest review, including nearly 45 000 patients, assessing the clini-

Figure 3. Network Meta-analysis Comparing Low-Molecular-Weight Heparin-Vitamin K Antagonist Combination for Recurrent Venous Thromboembolism and Major Bleeding

cal outcomes and safety associated with different anticoagulation strategies for the treatment of acute venous thromboembolism. We provide estimates on symptomatic recurrent venous thromboembolism and major bleeding outcomes (both patient-important outcomes), which are clinically relevant and are what clinical practice guideline recommendations are based on.⁶⁸ All management options, with the exception of the UFH-vitamin K antagonist combi-

nation, were associated with similar clinical outcomes compared with a management strategy using the LMWH-vitamin K antagonist combination. Treatment using the UFH-vitamin K antagonist combination was associated with a higher risk of recurrent venous thromboembolism during the follow-up period. Despite this, there are clinical circumstances that necessitate the use of UFH including for patients with severe renal insufficiency and those with mas-

sive or submassive pulmonary embolism who are potential candidates for thrombolysis or thrombectomy.

Management strategies using rivaroxaban or apixaban, without preceding parenteral anticoagulation, appear to be associated with a reduction in the risk of major bleeding episodes compared with the LMWH-vitamin K antagonist combination. Apixaban was associated with a significant reduction in the risk of major bleeding episodes compared with all the other treatment options except rivaroxaban and LMWH alone. These risks for recurrent venous thromboembolism and major bleeding events are important to help clinicians assess the benefit-harm balance of the various treatment options and tailor their therapeutic approaches accordingly.

The decision to use the LMWH-vitamin K antagonist combination as the comparator for the network meta-analysis was based on the current clinical practice guidelines recommending LMWH or fondaparinux over UFH for the initial treatment of acute deep vein thrombosis or pulmonary embolism.¹⁰ Our results are consistent with these recommendations. Both treatment strategies using the LMWH- and fondaparinux-vitamin K antagonist combinations were associated with lower risk of recurrent venous thromboembolism and major bleeding episodes (Table 5). The most recent version of the clinical practice guidelines assessing the efficacy and safety of the direct oral anticoagulants for the treatment of acute venous thromboembolism were available. Therefore, there is very little guidance for clinicians on the use of these new oral anticoagulants for this patient population. A number of direct oral anticoagulants are now approved therapies for the indication of acute deep vein thrombosis and pulmonary embolism (rivaroxaban, dabigatran, and apixaban in the United States). Both dabigatran (150 mg taken orally twice a day) and edoxaban (60 mg taken orally once a day) were assessed following an initial 5 days of LMWH, whereas apixaban (10 mg taken orally twice a day for 7 days, then 5 mg taken orally twice a day) and rivaroxaban (15 mg taken orally twice a day for 21 days, then 20 mg taken orally daily) were evaluated without the use of initial LMWH.^{17,63-67} Our network meta-analysis demonstrated that treatment options using direct oral anticoagulants are associated with similar clinical outcomes as the more traditional strategies using the LMWH-vitamin K antagonist combination. As previously mentioned, strategies using direct oral anticoagulants seem to be associated with a lower risk of major bleeding episodes, which is most pronounced for rivaroxaban and apixaban. Apixaban was also associated with significantly less bleeding when compared with the LMWH-dabigatran and LMWH-edoxaban combinations (Table 5).

Our study included trials assessing patients with acute venous thromboembolism only and those evaluating use of anticoagulation for secondary prevention of venous thromboembolism were not included in this analysis. A prior systematic review and network meta-analysis on the use of long-term oral anticoagulation for the secondary prevention of venous thromboembolism has been published.⁶⁹ Our

findings are consistent with the results of 2 recently published systematic reviews and meta-analyses on the treatment of acute venous thromboembolism.^{70,71} Compared with these prior reports, our review is more comprehensive because it is not limited to the inclusion of the studies assessing the direct oral anticoagulants and because included studies assessed the UFH-vitamin K antagonist, LMWH-vitamin K antagonist, and fondaparinux-vitamin K antagonist combinations, thereby providing clinicians with an overall appraisal of all possible therapies. We also report the proportions of patients experiencing an event (and differences between treatments) after using each treatment for a period of 3 and 6 months for both outcomes in eAppendix 5 in the Supplement.

It is important to note the limitations of our study. First, the length of follow-up varied across studies. Trials assessing direct oral anticoagulants were longer in duration than those assessing the UFH-vitamin K antagonist and fondaparinux-vitamin K antagonist combinations or LMWH alone, resulting in potential variations in event rates in the LMWH-vitamin K antagonist combination groups (eAppendix 7, eFigures 7A and 7B in the Supplement). We conducted a sensitivity analysis restricting studies to those that had a minimum of 6 months of treatment (14 studies including 30 027 patients) (eAppendix 7: eFigure 7C in the Supplement). Results of the subgroup analysis aligned with the primary analysis (eAppendix 7: eFigure 7C and eTable 7 in the Supplement), suggesting minimal effect of treatment duration across studies. Second, the proportion of patients experiencing an outcome event while taking anticoagulants for 3 and 6 months (eAppendix 5 in the Supplement) were generated assuming a rate of 5.3 per 100 patient-years ($\approx 2.6\%$ over 6 months) for recurrent venous thromboembolism and 3.6 events per 100 patient-years ($\approx 1.8\%$ over 6 months) for major bleeding in the LMWH-vitamin K antagonist combination group.^{16,17} Although there was considerable variation in event rates in the LMWH-vitamin K antagonist combination groups when all studies are considered, the outcome rates were similar when only studies at least 6 months in duration were considered. The use of another trial to derive baseline rates for the LMWH-vitamin K antagonist combination is unlikely to substantially alter estimates on differences in the proportion of patients experiencing an event at 3 and 6 months (eAppendix 7: eFigures 7A and 7C in the Supplement). Third, patients treated with LMWH alone are a heterogeneous group as LMWH dosing varied across studies. Fourth, patient-level longitudinal data are required to establish more robust conclusions in specific patient populations. Other risk factors including severity of the index event (eg, segmental pulmonary embolism vs massive pulmonary embolism), presence of risk factors for major bleeding (eg, recent bleeding or surgery), or other ongoing risk factors for acute venous thromboembolism (eg, cancer, body mass index, etc.) may influence the risk of recurrent venous thromboembolism and bleeding events, as well as choice of treatment. Fifth, no trials have directly compared the different direct oral anticoagulants, for all trials assessing the efficacy of direct oral anticoagulants were compared

with the LMWH-vitamin K antagonist combination. Future direct comparison trials, patient-level network meta-analyses, or high-quality nonrandomized studies are required to confirm our findings. Sixth, our analysis does not incorporate costs or preference for the different outcomes. Future studies need to be conducted to determine the most cost-effective management option. Seventh, the data included in the network meta-analysis was extracted from randomized trials and results are not generalizable to all patients with acute venous thromboembolism. Eighth, our search ended in March 2014.

Conclusions

Using meta-analytic pooling, there were no statistically significant differences in clinical and safety outcomes associated with most treatment strategies when compared with the LMWH-vitamin K antagonist combination. However, findings suggest that the UFH-vitamin K antagonist combination is associated with the least effective strategy and that rivaroxaban and apixaban may be associated with the lowest risk of bleeding.

ARTICLE INFORMATION

Author Contributions: Dr Carrier had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs Castellucci and Cameron contributed equally to this article.

Study concept and design: Castellucci, Cameron, Coyle, Carrier.

Acquisition, analysis, or interpretation of data: Castellucci, Cameron, Le Gal, Rodger, P.S. Wells, Clifford, Gandara, G. Wells, Carrier.

Drafting of the manuscript: Castellucci, Cameron, Rodger, Gandara, Carrier.

Critical revision of the manuscript for important intellectual content: All Authors.

Statistical analysis: Cameron, Coyle, Gandara, G. Wells, Carrier.

Administrative, technical, or material support: Clifford, Carrier.

Study supervision: Le Gal, Coyle, Clifford, G. Wells, Carrier.

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REFERENCES

- Cohen AT, Agnelli G, Anderson FA, et al; VTE Impact Assessment Group in Europe (VITAE). Venous thromboembolism (VTE) in Europe: the number of VTE events and associated morbidity and mortality. *Thromb Haemost*. 2007;98(4):756-764.
- Agno W, Prandoni P, Romualdi E, et al. The metabolic syndrome and the risk of venous thrombosis: a case-control study. *J Thromb Haemost*. 2006;4(9):1914-1918.
- Heit JA. The epidemiology of venous thromboembolism in the community: implications for prevention and management. *J Thromb Thrombolysis*. 2006;21(1):23-29.
- White RH. The epidemiology of venous thromboembolism. *Circulation*. 2003;107(23)(suppl 1):I4-I8.
- Prins MH, Marchiori A. Risk of recurrent venous thromboembolism—expanding the frontier. *Thromb Haemost*. 2002;87(1):1-3.
- Silverstein MD, Heit JA, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ III. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. *Arch Intern Med*. 1998;158(6):585-593.
- Anderson FA Jr, Wheeler HB, Goldberg RJ, et al. A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism: the Worcester DVT Study. *Arch Intern Med*. 1991;151(5):933-938.
- Barritt DW, Jordan SC. Anticoagulant drugs in the treatment of pulmonary embolism: a controlled trial. *Lancet*. 1960;1(7138):1309-1312.
- Carrier M, Le Gal G, Wells PS, Rodger MA. Systematic review: case-fatality rates of recurrent venous thromboembolism and major bleeding events among patients treated for venous thromboembolism. *Ann Intern Med*. 2010;152(9):578-589.
- Kearon C, Akl EA, Comerota AJ, et al; American College of Chest Physicians. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2)(suppl):e419S-e494S.
- Ansell JE, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest*. 2008;133(6)(suppl):160S-198S.
- Schulman S, Kearon C; Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antithrombotic medicinal products in non-surgical patients. *J Thromb Haemost*. 2005;3(4):692-694.
- Higgins JPT, Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2. Cochrane Database Syst Rev. 2009. <http://handbook.cochrane.org>. Accessed March 31, 2014.
- Dias S, Welton NJ, Sutton AJ, Ades A. NICE DSU technical support document 2: a generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials; 2011. <https://www.cc-arcc.ca/common/pages/UserFile.aspx?fileid=282149>. Accessed March 31, 2014.
- Hansen D, Shneiderman B, Smith MA. *Analyzing Social Media Networks with NodeXL: Insights from a Connected World*. Burlington, MA: Elsevier Inc; 2010.
- Fleurence RL, Hollenbeck CS. Rates and probabilities in economic modelling: transformation, translation and appropriate application. *Pharmacoeconomics*. 2007;25(1):3-6.
- Agnelli G, Buller HR, Cohen A, et al; AMPLIFY Investigators. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med*. 2013;369(9):799-808.
- Turner RM, Davey J, Clarke MJ, Thompson SG, Higgins JP. Predicting the extent of heterogeneity in meta-analysis, using empirical data from the Cochrane Database of Systematic Reviews. *Int J Epidemiol*. 2012;41(3):818-827.
- Thorlund K, Thabane L, Mills EJ. Modelling heterogeneity variances in multiple treatment comparison meta-analysis—are informative priors the better solution? *BMC Med Res Methodol*. 2013;13:2.
- Cipriani A, Furukawa TA, Salanti G, et al. Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. *Lancet*. 2009;373(9665):746-758.
- Spiegelhalter DJ, Best NG, Carlin BP, Van der Linde A. Bayesian measures of model complexity and fit. *J R Stat Soc Series B Stat Methodol*. 2002;64:583-639.
- Lunn DJ, Thomas A, Best N, Spiegelhalter D. WinBUGS—a Bayesian modelling framework:

concepts, structure, and extensibility. *Stat Comput*. 2000;10:325-337.

23. Dias S, Welton NJ, Sutton AJ, Caldwell DM, Lu G, Ades AE. Evidence synthesis for decision making 4: inconsistency in networks of evidence based on randomized controlled trials. *Med Decis Making*. 2013;33(5):641-656.
24. Kirchmaier CM, Wolf H, Schäfer H, Ehlers B, Breddin HK; Certoparin-Study Group. Efficacy of a low molecular weight heparin administered intravenously or subcutaneously in comparison with intravenous unfractionated heparin in the treatment of deep venous thrombosis. *Int Angiol*. 1998;17(3):135-145.
25. Breddin HK, Hach-Wunderle V, Nakov R, Kakkar VV; CORTES Investigators. Clivarin: Assessment of Regression of Thrombosis, Efficacy, and Safety. Effects of a low-molecular-weight heparin on thrombus regression and recurrent thromboembolism in patients with deep-vein thrombosis. *N Engl J Med*. 2001;344(9):626-631.
26. Merli G, Spiro TE, Olsson CG, et al; Enoxaparin Clinical Trial Group. Subcutaneous enoxaparin once or twice daily compared with intravenous unfractionated heparin for treatment of venous thromboembolic disease. *Ann Intern Med*. 2001;134(3):191-202.
27. Kakkar VV, Gebbska M, Kadziola Z, Saba N, Carrasco P; Bemiparin Investigators. Low-molecular-weight heparin in the acute and long-term treatment of deep vein thrombosis. *Thromb Haemost*. 2003;89(4):674-680.
28. Duroux P, Beclere A. A randomised trial of subcutaneous low molecular weight heparin (CY 216) compared with intravenous unfractionated heparin in the treatment of deep vein thrombosis. A collaborative European multicentre study. *Thromb Haemost*. 1991;65(3):251-256.
29. Hull RD, Raskob GE, Pineo GF, et al. Subcutaneous low-molecular-weight heparin compared with continuous intravenous heparin in the treatment of proximal-vein thrombosis. *N Engl J Med*. 1992;326(15):975-982.
30. Lopaciuk S, Meissner AJ, Filipiecki S, et al. Subcutaneous low molecular weight heparin versus subcutaneous unfractionated heparin in the treatment of deep vein thrombosis: a Polish multicenter trial. *Thromb Haemost*. 1992;68(1):14-18.
31. Prandoni P, Lensing AWA, Büller HR, et al. Comparison of subcutaneous low-molecular-weight heparin with intravenous standard heparin in proximal deep-vein thrombosis. *Lancet*. 1992;339(8791):441-445.
32. Simonneau G, Charbonnier B, Decousus H, et al. Subcutaneous low-molecular-weight heparin compared with continuous intravenous unfractionated heparin in the treatment of proximal deep vein thrombosis. *Arch Intern Med*. 1993;153(13):1541-1546.
33. Meyer G, Brenot F, Pacouret G, et al. Subcutaneous low-molecular-weight heparin fragmin versus intravenous unfractionated heparin in the treatment of acute non massive pulmonary embolism: an open randomized pilot study. *Thromb Haemost*. 1995;74(6):1432-1435.
34. Levine M, Gent M, Hirsh J, et al. A comparison of low-molecular-weight heparin administered primarily at home with unfractionated heparin administered in the hospital for proximal deep-vein thrombosis. *N Engl J Med*. 1996;334(11):677-681.
35. Koopman MMW, Prandoni P, Piovella F, et al; The Tasman Study Group. Treatment of venous thrombosis with intravenous unfractionated heparin administered in the hospital as compared with subcutaneous low-molecular-weight heparin administered at home. *N Engl J Med*. 1996;334(11):682-687.
36. Fiessinger JN, Lopez-Fernandez M, Gatterer E, et al. Once-daily subcutaneous dalteparin, a low molecular weight heparin, for the initial treatment of acute deep vein thrombosis. *Thromb Haemost*. 1996;76(2):195-199.
37. The Columbus Investigators. Low-molecular-weight heparin in the treatment of patients with venous thromboembolism. *N Engl J Med*. 1997;337(10):657-662.
38. Simonneau G, Sors H, Charbonnier B, et al; The THESEE Study Group. Tinzaparine ou Heparine Standard: Evaluations dans l'Embolie Pulmonaire. A comparison of low-molecular-weight heparin with unfractionated heparin for acute pulmonary embolism. *N Engl J Med*. 1997;337(10):663-669.
39. Hull RD, Raskob GE, Brant RF, et al; American-Canadian Thrombosis Study Group. Low-molecular-weight heparin vs heparin in the treatment of patients with pulmonary embolism. *Arch Intern Med*. 2000;160(2):229-236.
40. Harenberg J, Schmidt JA, Koppenhagen K, Tolle A, Huisman MV, Büller HR; EASTERN Investigators. Fixed-dose, body weight-independent subcutaneous LMW heparin versus adjusted dose unfractionated intravenous heparin in the initial treatment of proximal venous thrombosis. *Thromb Haemost*. 2000;83(5):652-656.
41. Findik S, Erkan ML, Selçuk MB, Albayrak S, Atici AG, Doru F. Low-molecular-weight heparin versus unfractionated heparin in the treatment of patients with acute pulmonary thromboembolism. *Respiration*. 2002;69(5):440-444.
42. Riess H, Koppenhagen K, Tolle A, et al; TH-4 Study Group. Fixed-dose, body weight-independent subcutaneous low molecular weight heparin Certoparin compared with adjusted-dose intravenous unfractionated heparin in patients with proximal deep venous thrombosis. *Thromb Haemost*. 2003;90(2):252-259.
43. Prandoni P, Carnovali M, Marchiori A; Galilei Investigators. Subcutaneous adjusted-dose unfractionated heparin vs fixed-dose low-molecular-weight heparin in the initial treatment of venous thromboembolism. *Arch Intern Med*. 2004;164(10):1077-1083.
44. Kearon C, Ginsberg JS, Julian JA, et al; Fixed-Dose Heparin (FIDO) Investigators. Comparison of fixed-dose weight-adjusted unfractionated heparin and low-molecular-weight heparin for acute treatment of venous thromboembolism. *JAMA*. 2006;296(8):935-942.
45. Leizorovicz A, Siguret V, Mottier D, et al; Innohep in Renal Insufficiency Study Steering Committee. Safety profile of tinzaparin versus subcutaneous unfractionated heparin in elderly patients with impaired renal function treated for acute deep vein thrombosis: the Innohep in Renal Insufficiency Study (IRIS). *Thromb Res*. 2011;128(1):27-34.
46. Belcaro G, Nicolaides AN, Cesarone MR, et al. Comparison of low-molecular-weight heparin, administered primarily at home, with unfractionated heparin, administered in hospital, and subcutaneous heparin, administered at home for deep-vein thrombosis. *Angiology*. 1999;50(10):781-787.
47. Bratt G, Aberg W, Johansson M, Törnebohm E, Granqvist S, Lockner D. Two daily subcutaneous injections of fragmin as compared with intravenous standard heparin in the treatment of deep venous thrombosis (DVT). *Thromb Haemost*. 1990;64(4):506-510.
48. Lindmarker P, Holmström M, Granqvist S, Johnsson H, Lockner D. Comparison of once-daily subcutaneous Fragmin with continuous intravenous unfractionated heparin in the treatment of deep vein thrombosis. *Thromb Haemost*. 1994;72(2):186-190.
49. Pini M, Aiello S, Manotti C, et al. Low molecular weight heparin versus warfarin in the prevention of recurrences after deep vein thrombosis. *Thromb Haemost*. 1994;72(2):191-197.
50. Gonzalez-Fajardo JA, Arreba E, Castrodeza J, et al. Venographic comparison of subcutaneous low-molecular weight heparin with oral anticoagulant therapy in the long-term treatment of deep venous thrombosis. *J Vasc Surg*. 1999;30(2):283-292.
51. Veiga F, Escribá A, Maluenda MP, et al. Low molecular weight heparin (enoxaparin) versus oral anticoagulant therapy (acenocoumarol) in the long-term treatment of deep venous thrombosis in the elderly: a randomized trial. *Thromb Haemost*. 2000;84(4):559-564.
52. Beckman JA, Dunn K, Sasahara AA, Goldhaber SZ. Enoxaparin monotherapy without oral anticoagulation to treat acute symptomatic pulmonary embolism. *Thromb Haemost*. 2003;89(6):953-958.
53. Pérez de Llano LA, Balloira Villar A, Veres Racamonde A, Veiga F, Golpe Gómez R, Pajuelo Fernández F. Multicenter, prospective study comparing enoxaparin with unfractionated heparin in the treatment of submassive pulmonary thromboembolism [in Spanish]. *Arch Bronconeumol*. 2003;39(8):341-345.
54. Ramacciotti E, Araújo GR, Lastoria S, et al; CLETRAT Investigators. An open-label, comparative study of the efficacy and safety of once-daily dose of enoxaparin versus unfractionated heparin in the treatment of proximal lower limb deep-vein thrombosis. *Thromb Res*. 2004;114(3):149-153.
55. Chong BH, Brighton TA, Baker RI, Thurlow P, Lee CH; ASTH DVT Study Group. Once-daily enoxaparin in the outpatient setting versus unfractionated heparin in hospital for the treatment of symptomatic deep-vein thrombosis. *J Thromb Thrombolysis*. 2005;19(3):173-181.
56. Daskalopoulos ME, Daskalopoulou SS, Tzortzis E, et al. Long-term treatment of deep venous thrombosis with a low molecular weight heparin (tinzaparin): a prospective randomized trial. *Eur J Vasc Endovasc Surg*. 2005;29(6):638-650.
57. Hull RD, Pineo GF, Brant RF, et al; LITE Trial Investigators. Self-managed long-term low-molecular-weight heparin therapy: the balance of benefits and harms. *Am J Med*. 2007;120(1):72-82.

58. Büller HR, Davidson BL, Decousus H, et al; Matisse Investigators. Subcutaneous fondaparinux versus intravenous unfractionated heparin in the initial treatment of pulmonary embolism. *N Engl J Med*. 2003;349(18):1695-1702.
59. Das SK, Cohen AT, Edmondson RA, Melissari E, Kakkar VV. Low-molecular-weight heparin versus warfarin for prevention of recurrent venous thromboembolism: a randomized trial. *World J Surg*. 1996;20(5):521-526, discussion 526-527.
60. Lopaciuk S, Bielska-Falda H, Noszczyk W, et al. Low molecular weight heparin versus acenocoumarol in the secondary prophylaxis of deep vein thrombosis. *Thromb Haemost*. 1999;81(1):26-31.
61. Romera A, Cairols MA, Vila-Coll R, et al. A randomised open-label trial comparing long-term sub-cutaneous low-molecular-weight heparin compared with oral-anticoagulant therapy in the treatment of deep venous thrombosis. *Eur J Vasc Endovasc Surg*. 2009;37(3):349-356.
62. Büller HR, Davidson BL, Decousus H, et al; Matisse Investigators. Fondaparinux or enoxaparin for the initial treatment of symptomatic deep venous thrombosis: a randomized trial. *Ann Intern Med*. 2004;140(11):867-873.
63. Schulman S, Kearon C, Kakkar AK, et al; RE-COVER Study Group. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med*. 2009;361(24):2342-2352.
64. Schulman S, Kakkar AK, Goldhaber SZ, et al; RE-COVER II Trial Investigators. Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. *Circulation*. 2014;129(7):764-772.
65. Büller HR, Decousus H, Grosso MA, et al; Hokusai-VTE Investigators. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *N Engl J Med*. 2013;369(15):1406-1415.
66. Bauersachs R, Berkowitz SD, Brenner B, et al; EINSTEIN Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med*. 2010;363(26):2499-2510.
67. Büller HR, Prins MH, Lensin AW, et al; EINSTEIN-PE Investigators. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med*. 2012;366(14):1287-1297.
68. Guyatt GH, Eikelboom JW, Gould MK, et al; American College of Chest Physicians. Approach to outcome measurement in the prevention of thrombosis in surgical and medical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2)(suppl):e185S-e194S.
69. Castellucci LA, Cameron C, Le Gal G, et al. Efficacy and safety outcomes of oral anticoagulants and antiplatelet drugs in the secondary prevention of venous thromboembolism: systematic review and network meta-analysis. *BMJ*. 2013;347:f5133.
70. Fox BD, Kahn SR, Langleben D, Eisenberg MJ, Shimony A. Efficacy and safety of novel oral anticoagulants for treatment of acute venous thromboembolism: direct and adjusted indirect meta-analysis of randomised controlled trials. *BMJ*. 2012;345:e7498.
71. van der Hulle T, Kooiman J, den Exter PL, Dekkers OM, Klok FA, Huisman MV. Effectiveness and safety of novel oral anticoagulants compared with vitamin K antagonists in the treatment of acute symptomatic venous thromboembolism: a systematic review and meta-analysis. *J Thromb Haemost*. 2014;12(3):320-328.

METHODOLOGY

Open Access

A Microsoft-Excel-based tool for running and critically appraising network meta-analyses—an overview and application of NetMetaXL

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Abstract

Background: The use of network meta-analysis has increased dramatically in recent years. WinBUGS, a freely available Bayesian software package, has been the most widely used software package to conduct network meta-analyses. However, the learning curve for WinBUGS can be daunting, especially for new users. Furthermore, critical appraisal of network meta-analyses conducted in WinBUGS can be challenging given its limited data manipulation capabilities and the fact that generation of graphical output from network meta-analyses often relies on different software packages than the analyses themselves.

Methods: We developed a freely available Microsoft-Excel-based tool called NetMetaXL, programmed in Visual Basic for Applications, which provides an interface for conducting a Bayesian network meta-analysis using WinBUGS from within Microsoft Excel. This tool allows the user to easily prepare and enter data, set model assumptions, and run the network meta-analysis, with results being automatically displayed in an Excel spreadsheet. It also contains macros that use NetMetaXL's interface to generate evidence network diagrams, forest plots, league tables of pairwise comparisons, probability plots (rankograms), and inconsistency plots within Microsoft Excel. All figures generated are publication quality, thereby increasing the efficiency of knowledge transfer and manuscript preparation.

Results: We demonstrate the application of NetMetaXL using data from a network meta-analysis published previously which compares combined resynchronization and implantable defibrillator therapy in left ventricular dysfunction. We replicate results from the previous publication while demonstrating result summaries generated by the software.

Conclusions: Use of the freely available NetMetaXL successfully demonstrated its ability to make running network meta-analyses more accessible to novice WinBUGS users by allowing analyses to be conducted entirely within Microsoft Excel. NetMetaXL also allows for more efficient and transparent critical appraisal of network meta-analyses, enhanced standardization of reporting, and integration with health economic evaluations which are frequently Excel-based.

Keywords: Network meta-analysis, Software, Microsoft Excel, WinBUGS, Systematic review, Health technology assessment

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Background

Meta-analysis is a statistical method commonly used to combine summary estimates of treatment effects from a collection of studies to establish the benefits and harms of competing interventions. An important limitation of standard meta-analysis (i.e., pairwise meta-analysis) is that it compares only two treatments at a time [1]. However, many medical conditions exist for which there are a multitude of possible treatment alternatives. Accordingly, new meta-analytic methods have emerged which permit simultaneous comparison of multiple treatments. This new method is referred to as *network meta-analysis* (NMA) (other terms such as *mixed-treatment comparison meta-analysis* and *multiple treatments meta-analysis* have also been used) [1,2]. Not surprisingly, the increasing need to compare multiple treatments for medical conditions has been mirrored by the dramatic rise in the use of network meta-analysis in recent years [3,4].

Both Frequentist and Bayesian approaches for conducting network meta-analysis are feasible [1,5-7]. Among them, the latter has been the more commonly used framework, likely because the methods have evolved more quickly, because Bayesian methods provide greater flexibility to use more complex models and different outcome types, and because Bayesian methods are easily integrated into health economic evaluations. WinBUGS is a freely available software package available for Bayesian data analysis and has been the most widely used package to conduct network meta-analyses to date [3]. However, the learning curve for using WinBUGS to conduct network meta-analyses successfully can be daunting for new users, given the challenges of understanding WinBUGS code. WinBUGS also has limited data manipulation, data annotation, and graphical illustration capabilities. Given these challenges, the preparation of tables and figures to present insightful summaries of findings from network meta-analyses often requires use of an additional software package [7], thereby adding time and an additional layer of complexity to complete reports. As a result, current approaches do not allow analysts to simply update and reanalyze models quickly and efficiently. Further, the variability in software used and the lack of standardization has led to inconsistency in the reporting of analyses to health technology assessment (HTA) organizations and journals, thereby complicating the review process. Given these challenges, more user-friendly software is needed to facilitate the ability to perform, consistently report, and critically appraise network meta-analyses for a broader group of researchers. More integrated and user-friendly software will dramatically improve the transparency and reproducibility of findings from network meta-analyses.

The objectives of this paper are to use an illustrative example to demonstrate how our Microsoft-Excel-based Network Meta-analysis Tool (NetMetaXL) can be used to

simplify running and reporting network meta-analyses and to highlight how NetMetaXL can be used to facilitate consistent reporting and more efficient and transparent critical appraisal of network meta-analyses submitted to HTA organizations such as the Canadian Agency for Drugs and Technologies in Health (CADTH) and the National Institute for Health and Care Excellence (NICE), as well as to journals which publish network meta-analyses.

Methods

The illustrative example

Table 1 presents the illustrative dataset derived from a network meta-analysis evaluating combined resynchronization and implantable defibrillator therapy in left ventricular dysfunction [8]. The methods used to identify studies included in the network meta-analysis and to collect trial-level data have been described previously [8]. A total of 12 randomized studies comparing 5 different treatments (medical resynchronization, cardiac resynchronization, implantable defibrillator, combined resynchronization and defibrillator, and amiodarone) were included in the review, encompassing a total of 1,616 deaths in 8,307 participants. The authors conducted a Bayesian random effects network meta-analysis to compare the overall risk of mortality among the different treatments.

Application of NetMetaXL using an illustrative example

This tool was designed to allow users to run network meta-analyses, as well as to appraise Bayesian network meta-analyses using WinBUGS via a more user-friendly Microsoft Excel interface. The current versions of NetMetaXL only allow the user to apply Bayesian network meta-analysis for binomial data and logistic regression models. This section describes how users can use this tool in the context of the illustrative example above. It is critical that users of NetMetaXL receive training on network meta-analysis. Users should be educated on key concepts related to network meta-analysis and how to interpret findings for decision-making purposes. Users are also encouraged to consult with a statistician when using this tool.

Step 1: Software installation

The application of NetMetaXL requires installation of Microsoft Excel 2007 or higher, as well as installation of the WinBUGS 1.4.3 package. NetMetaXL will work using Windows XP, Windows 7, or Windows 8. Before opening NetMetaXL, the user will install the WinBUGS 1.4.3 package and download and install the patch for WinBUGS 1.4.3 and the key for unrestricted use as described on the WinBUGS website. Detailed instructions on installing WinBUGS are available on the WinBUGS website. After the user has installed WinBUGS, the user can download the latest version of the NetMetaXL package from www.

Table 1 Dataset used for illustrative example

Study number	Study name	Medical		Cardiac resynchronization		Implantable defibrillator		Combined resynchronization and defibrillator		Amiodarone	
		Number of events	Number of patients	Number of events	Number of patients	Number of events	Number of patients	Number of events	Number of patients	Number of events	Number of patients
1	CARE_HF-ext	154	404	101	409						
2	COMPANION	77	308	131	617			105	595		
3	MIRACLE	16	225	12	228						
4	MUSTIC-SR	0	29	1	29						
5	SCD-HeFT	244	847			182	829			240	845
6	MADIT-II	97	490			105	742				
7	DEFINITE	40	229			28	229				
8	CAT	17	54			13	50				
9	MICRACLE-ICD-I					5	182	4	187		
10	MICRACLE-ICD-II					2	101	2	85		
11	CONTAk-CD					16	245	11	245		
12	AMIOVIRT					6	51			7	52

The data is derived from Lam and Owen [8].

NetMetaXL.com. Any user can download the tool and administrator access is required. This Excel-based tool is also part of the CADTH online repository of Microsoft-based tools for enhancing the application of HTAs: www.cadth.ca/en/resources/hta-excel-tools. NetMetaXL is programmed in Visual Basic for Applications within Excel and links to WinBUGS using Visual Basic. After NetMetaXL and WinBUGS have been downloaded and installed, the user will open NetMetaXL and go to the WinBUGS Setting tab visible in the menu bar at the top of the screen. Within this tab, under Program Settings, the user will indicate where the WinBUGS executable file that was downloaded is located on their computer's hard drive. For example, the user can click the file folder icon next to the WinBUGS Directory (cell D41) and then browse to specify the location of the WinBUGS Directory (e.g., C:\Program Files\WinBUGS14\).

Step 2: Setup of specifications for analysis

After NetMetaXL has been installed and is linked to WinBUGS, the user is ready to begin conducting or appraising network meta-analyses. The user should then open the file and save it using a study-specific name. Within NetMetaXL, the user will see a WinBUGS menu bar in the top right of Microsoft Excel. WinBUGS is a software for conducting Bayesian analysis using Markov chain Monte Carlo simulation [9]. A Bayesian analysis using WinBUGS requires two main ingredients: prior distributions for the unknown parameters and a likelihood function derived from a model that specifies the relation between the unknown parameters and the observed data

[10,11]. A prior distribution of a parameter represents the uncertainty about the parameter before the current data are examined [10,12-16]. The prior chosen may be informative or 'vague.' The latter is thought to 'let the data drive the analysis,' but the use of a vague prior should not be used unthinkingly especially when data is sparse because a vague prior may actually influence the analysis [10,12-16]. Multiplying the prior and the likelihood function together leads to the posterior distribution of the parameter. The posterior distribution is used to carry out all inferences [10,12-16].

To run the Bayesian analysis using WinBUGS, a series of procedures are required, all of which are automated within NetMetaXL. In particular, the user must check that the model is properly specified, load the data, and select the number of chains (or samples) to specify the initial values for certain parameter estimates; set up monitors to store the sampled parameter values; run the simulation; check convergence for the parameter estimates; and then obtain a summary of the posterior distribution of the selected parameter estimates.

The user will also see a number of worksheets, each devoted to different aspects of preparing the data for Bayesian analysis and generating graphical summaries of the results after the analysis has been run. The majority of settings for the setup of specifications for analysis are located within the WinBUGS Settings worksheet. Within this worksheet, the user specifies analysis characteristics such as WinBUGS Settings (e.g., number of burn-in iterations for assessing convergence of parameter estimates); statistical settings such as which model parameters to capture (e.g., odds ratio, treatment rankings), whether the outcome being considered

is 'bad' (e.g., dead at the end of the study) or 'good' (e.g., alive at the end of the study) from the patient's perspective, informative prior settings (NetMetaXL applies vague priors for log odds ratios but allows the user to use informative priors for between-study heterogeneity variances derived from based on a publication by Turner et al. [14] which is potentially useful when data is sparse), and initial values for parameter estimates (NetMetaXL selects these randomly from a uniform distribution within the ranges chosen for log odds ratios and log odds) which should be checked in WinBUGS data sheet; and Program Settings (e.g., location to save files).

Step 3: Data input

After the user specifies the WinBUGS and statistical settings on the WinBUGS Settings worksheet, the dataset for analysis in NetMetaXL can next be entered. To input the data, the user selects the Data Input tab. A screenshot displaying the dataset is presented in Table 1. An additional file showing the screenshot with the dataset in NetMetaXL is also provided [see Additional file 1]. To begin inserting the data, the user must specify the name of each treatment under consideration in row 5; the tool has currently been designed to handle up to 15 interventions of interest and up to 50 studies. The choice of treatment 1, also known as the reference treatment, is an important consideration. Ideally, the user will select the treatment with the most studies as the reference treatment. After the user specifies the treatment names, the user inserts the number of observed events and total sample size for the intervention groups in each study beginning in row 7. In accordance with the most commonly used Bayesian implementation of network meta-analysis, users are able to input more than two treatment groups for a given study and the software will account for correlation between trial arms. As the user inputs the data for all studies and treatments, cells C2–C5 will update automatically to reflect properties of the evidence base under study in terms of the total number of included studies and patients in the treatment network. In the case of our illustrative example, once data input is complete, cells C2–C5 will indicate that the evidence base consists of 12 studies and 5 treatments and will also indicate that 8 of the included studies include medical therapy as one of their treatment arms (our chosen control treatment, labeled as treatment 1 in our network). After the data is inserted, the user is ready to begin running network meta-analyses using NetMetaXL.

Step 4: Preparing the data for WinBUGS

There is a 'Convert Data' button within the menu bar. When the user selects this button, there will be a prompt asking: 'Correct for zero values?'. If the user selects, 'Yes', NetMetaXL will adjust all zero cells using an adjusted

continuity correction factor accounting for potential differences in sample size and centered around 0.5 [16]. If the user selects 'No', zero cells will be included in the analysis and no adjustment is applied. An advantage of the Bayesian approach is that special precautions do not usually need to be taken in the case of the occasional trial with a zero cell count [17]. NetMetaXL allows users the run the analysis with zeroes when there are occasional zero cells and attempt to resolve the issue by adjusting otherwise, although in some cases the results will remain unstable even after adjusting [17]. The zero cell correction within NetMetaXL keeps all studies for analytic consistency (i.e., does not delete studies entered by the user) even those with multiple zero cells although these do not contribute to the relative effect estimation and can cause computational problems when networks are sparse. Because studies with zero cells remain, model fit statistics for these analyses should be interpreted with caution given they make certain model fit statistics artificially look better. The users of this tool should always consult with a statistician, but especially when dealing with zero cells. After the user selects either of these choices, NetMetaXL will convert the data provided into the appropriate format for analysis within WinBUGS. WinBUGS requires the data to be in a specific format and for the user to specify the initial values. The data after the conversion is reported within the WinBUGS data tab. NetMetaXL will also perform this step automatically when pushing the 'Run WinBUGS' button.

Results

There are key outputs to consider when interpreting a network meta-analysis. Notably, the user should carefully review the geometry of the evidence network, which provides information related to the number of studies performed comparing the different treatments, the numbers of patients who have been studied for each treatment, and so forth. After ensuring convergence has been reached and there is no relevant inconsistency in the evidence, one can use the output from the consistency model to draw conclusions about the relative effects of treatments [18]. This information is often displayed in tabular or graphical format such as a forest plot or league table. Alternatively, information of relative effects is sometimes converted to a probability a treatment is best, second best, and so on, or the ranking of each treatment. More recently, these two measures have been combined into a single measure called the surface under the cumulative ranking curve (SUCRA) [18], which is expressed as a percentage—the SUCRA would be 100% when a treatment is certain to be the best and 0% when a treatment is certain to be the worst. The outputs for these elements in NetMetaXL are described in steps 5–9 below.

Step 5: Visualizing the treatment network

After the user selects the WinBUGS tab from the menu bar in NetMetaXL, the user can generate a treatment network diagram by selecting the Generate Diagram button. After the user clicks this button, an evidence network will be generated (see Figure 1). As has become common practice in reports of network meta-analyses [7], the width of each edge in the evidence network is proportional to the number of randomized controlled trials comparing each pair of treatments, and the size of each treatment node is proportional to the number of randomized participants (sample size). A tabular description of the evidence network is also provided within the Data Summary worksheet. The user has the capability to indicate the treatment names to be used on the network diagram in cells C25–C29. For example, instead of labeling the nodes simply as A–E as in Additional files 1 and 2, the user can input the treatment names for each node (or preferred abbreviations which are a preferable option when dealing with longer treatment names). After the labels are changed in cells C25–C29, the user can push the Generate Diagram button again from the WinBUGS tab in the toolbar, and the names in cells C25–C29 will appear within the network diagram. The nodes can also be moved, if desired, and the connections can automatically be redrawn by clicking the ReDraw Connections button. The user can copy the evidence network by

holding control and selecting the nodes and connections and subsequently pasting the evidence network into other programs such as PowerPoint.

Step 6: Running network meta-analyses using NetMetaXL

To run network meta-analyses within NetMetaXL, the user selects the Run WinBUGS button within the menu bar. After selecting the Run WinBUGS button, NetMetaXL will open WinBUGS to run the network meta-analyses and will then close WinBUGS after transferring back to NetMetaXL the results for all the prespecified parameters of interest specified in the WinBUGS Settings tab during the setup of the analysis in WinBUGS Settings tab. These analysis functions and others are provided within the WinBUGS tab within the menu bar in the upper right of NetMetaXL. NetMetaXL generates commonly used graphical summaries of results including forest plots, league tables, and probability bar plots (or rankograms); a separate worksheet is devoted to each type of graphical output. To begin the analyses, the user clicks the Run WinBUGS button from the WinBUGS tab in the menu bar of NetMetaXL once data have been appropriately formatted as outlined in step 3. After the user clicks this button, a dialog box will open where the user will select the different network meta-analyses to be conducted (Figure 2). For example, the user can run analyses using a fixed effects model, a random effects model using vague priors as outlined in

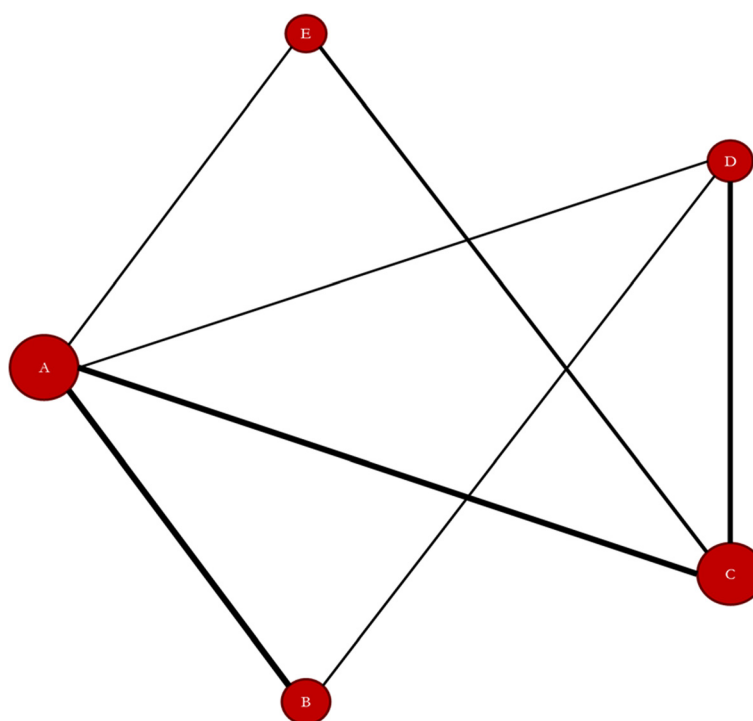


Figure 1 Evidence network diagram. A medical therapy, B cardiac resynchronization, C implantable defibrillator, D combined resynchronization and defibrillator, E amiodarone.

NICE Evidence Synthesis Series [17], and/or a random effects model using informative variance priors [14]. For the random effects model using vague priors, we assume use the following prior: $sd \sim \text{dunif}(0,2)$. For the random effects model using informative variance priors, the user indicates the type of outcome under consideration as well as the type of treatment (e.g., placebo, active pharmacological treatment). NetMetaXL uses these selections and bases the informative variance priors on evidence on the extent of heterogeneity observed in previous meta-analyses, as described in Turner et al. [14]. For all analyses, we assume vague priors on baselines [$\text{dnorm}(0,10000)$] and basic parameters [$\text{dnorm}(0,10000)$]. After the user selects the analyses to be conducted using the check boxes within the dialog box, the user then selects Run WinBUGS from within the dialog box; this will launch WinBUGS and will automatically run analyses and import results based on the various models selected back into NetMetaXL in fixed effects (FE) Results or random effects (RE) Results worksheets. The WinBUGS results are also saved as an *.odc file in the directory specified in the Program Settings (WinBUGS Setting tab). The WinBUGS code used for generating all the network meta-analyses is based on the NICE Decision Support Unit Series [5,17]. The WinBUGS model codes are stored within NetMetaXL on the worksheets titled FE model, RE Model, RE Inconsistency Model, and FE Inconsistency Model. The user also has the option to open WinBUGS directly and examine the underlying WinBUGS code if need be using the Open WinBUGS button in the toolbar.

NetMetaXL captures all the WinBUGS output [see Additional file 2] and stores them in FE Results or RE

Results worksheets. NetMetaXL will capture output results from WinBUGS for any parameters selected in the WinBUGS Settings tab (e.g., odds ratios). The user should refer to FE and RE model tabs to see the statistics behind the parameter calculations.

Step 7: Checking convergence in NetMetaXL

We fit three chains for the Markov chain Monte Carlo (MCMC) Bayesian network meta-analysis. The use of multiple chains is a useful way to check MCMC convergence. The user selects the initial values for each of these chains randomly from a uniform distribution. The user can select the bounds for the uniform distribution in the WinBUGS Settings worksheet. The user is encouraged to review the following paper [19] for additional detail on selecting initial values. Convergence is assessed in NetMetaXL using the Brooks-Gelman-Rubin method and by checking whether the Monte Carlo error is less than 5% of the sd of the effect estimates and between-study variance. These diagnostics are provided when the user runs the analysis. NetMetaXL will check whether the Monte Carlo error is less than 5% of the sd of the effect estimates and between-study variance and gives the user the option to view the Brooks-Gelman-Rubin plots from the WinBUGS output. The Brooks-Gelman-Rubin method compares within-chain and between-chain variances to calculate the potential scale reduction factor [20]. A potential scale reduction factor is presented in red in the figure, and a value close to one indicates when approximate convergence has been reached.

Step 8: Generating a graphical summary of findings from network meta-analysis

NetMetaXL captures all the WinBUGS output and then uses VBA macros to construct different graphical representations common to reports of network meta-analyses [18]. NetMetaXL is capable of generating forest plots and league tables to summarize all pairwise comparisons between the competing treatments, as well as probability bar plots (or rankograms). A forest plot generated by NetMetaXL for our illustrative example is presented in Figure 3. On the forest plot worksheet, the user can select the analyses they would like reported in the forest plot. For example, the user can present findings for only one model (e.g., fixed effects model) or can also choose to report findings using both the fixed and random effects models. The user can also select the spacing, marker size, and plot size in cells D7–D9 to maximize the quality of the figure. The forest plots then illustrate the median effect estimate for each pairwise comparison within the network meta-analysis for each model fit, along with corresponding 95% credible intervals.

In addition to generating forest plots, the user can also generate league tables within NetMetaXL to summarize all

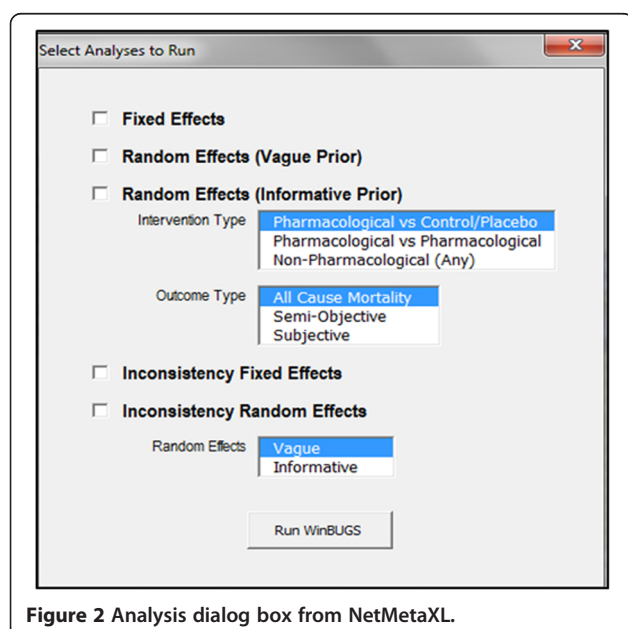


Figure 2 Analysis dialog box from NetMetaXL.

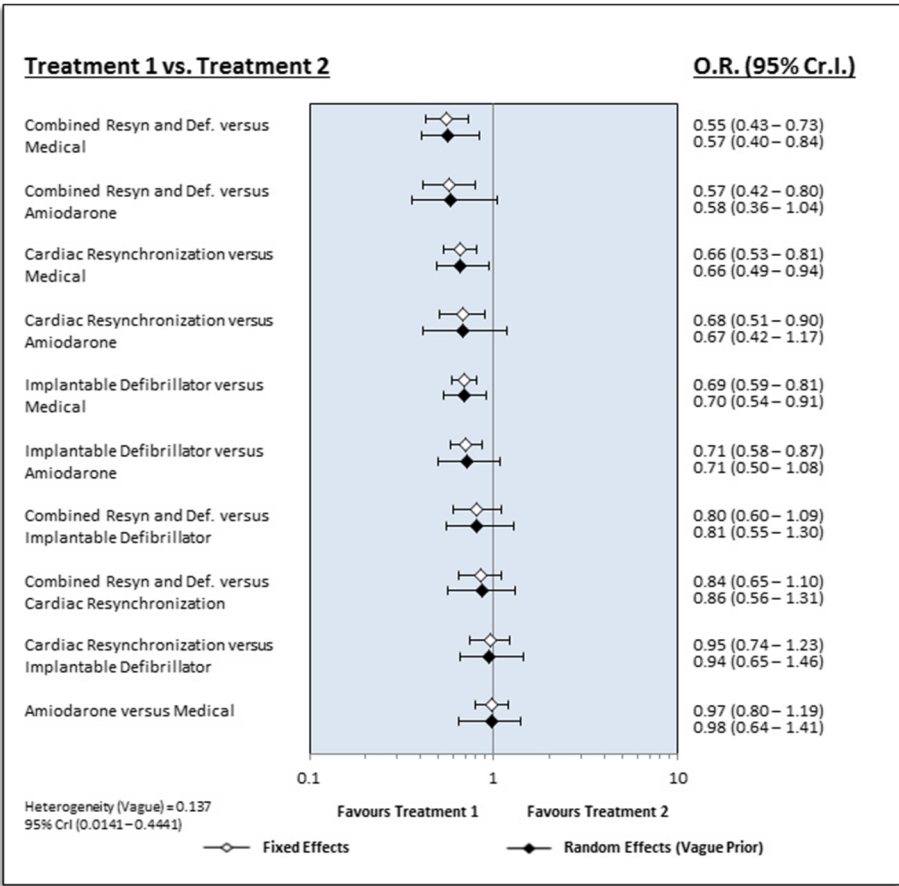


Figure 3 Forest plot from NetMetaXL.

possible pairwise comparisons between the interventions. The summary league table for our illustrative example is shown in Figure 4. The league table arranges the presentation of summary estimates by ranking the treatments in order of most pronounced impact on the outcome under consideration, based on SUCRA [18]. SUCRA, the surface under the cumulative ranking [18], is a simple numerical summary of the probabilities. It is 100% when a treatment

is certain to be the best and 0% when a treatment is certain to be the worst. SUCRA values enable the ranking of treatments overall for a particular outcome. For example, in our illustrative example, combined resynchronization and defibrillation is listed in the top left of the diagonal of the league table because it was associated with the most favorable SUCRA for mortality reduction, while medical therapy is listed in the bottom right of the

Combined Resyn and Def.				
0.84 (0.65 – 1.10)	Cardiac Resynchronization			
0.80 (0.60 – 1.09)	0.95 (0.74 – 1.23)	Implantable Defibrillator		
0.57 (0.42 – 0.80)	0.68 (0.51 – 0.90)	0.71 (0.58 – 0.87)	Amiodarone	
0.55 (0.43 – 0.73)	0.66 (0.53 – 0.81)	0.69 (0.59 – 0.81)	0.97 (0.80 – 1.19)	Medical

Figure 4 League table from NetMetaXL.

diagonal of the league table because it was associated with the least favorable results. For interpretation purposes, the results are read from top to bottom and left to right. For example, using the random effects model with vague priors (as was used in Lam and Owen [8]), combined resynchronization and defibrillation compared with cardiac synchronization is associated with an odds ratio of 0.84 (0.57–1.22), suggesting it is trending towards being better than cardiac synchronization in terms of mortality, whereas cardiac resynchronization versus medical therapy is associated with an odds ratio of 0.66 (0.50–0.89).

Probability bars (or rankograms) [18] are also generated and reported within NetMetaXL, which report the probability that each treatment is ranked first, second, and so on for a particular outcome. These rankograms are depicted as stacked vertical bar charts within NetMetaXL for all treatments. The user can also output line graphs for all treatments or generate bar charts or line graphs for individual treatments.

Step 9: Assessment of inconsistency

Assessment of inconsistency is crucial in the conduct of any network meta-analysis. Inconsistency can be thought of as a conflict between ‘direct’ and ‘indirect’ evidence [5]. Similar to heterogeneity, inconsistency is caused by imbalances in effect modifiers from study to study, specifically by an imbalance in the distribution of effect modifiers in the direct and indirect evidence [5]. NetMetaXL allows users to assess inconsistency by comparing the deviance residuals and DIC statistics in fitted consistency and inconsistency models [5]. These are reported in a table in the Inconsistency results worksheet. We refer the readers to the NICE Technical Support Documents (TSD) series for the methods employed [5]. NetMetaXL also plots the posterior mean deviance of the individual data points in the inconsistency model against their posterior mean deviance in the consistency model to identify any loops in the treatment network where inconsistency is present (Figure 5) [5]. NetMetaXL also allows the user to select the points on the inconsistency plot and see which study and treatment is represented by that point. For example, by double-clicking on the point in Figure 5 within NetMetaXL, we see that this point is from the cardiac resynchronization arm of the COMPANION study. This feature will be particularly useful for network meta-analyses where there are a number of points in the bottom right of the inconsistency plot, indicating potential inconsistency [5].

Discussion

Summary of main findings

We have shown how use of NetMetaXL can enhance the ability of users to run WinBUGS-based network meta-analyses entirely within Microsoft Excel. We have replicated

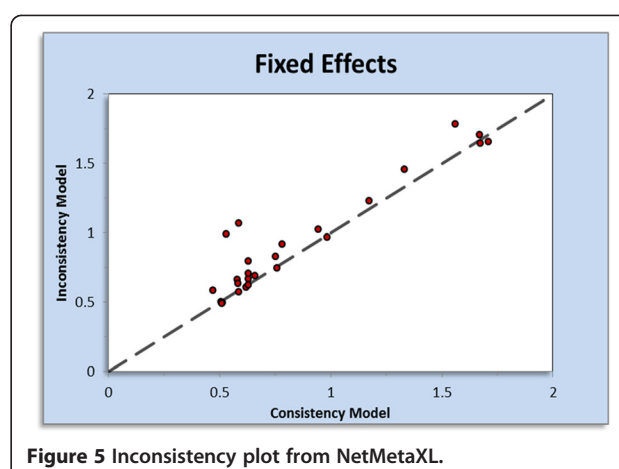


Figure 5 Inconsistency plot from NetMetaXL.

findings from a network meta-analysis [8] published in the BMJ on combined resynchronization and implantable defibrillator therapy in left ventricular dysfunction using NetMetaXL. The approach and steps used in this illustrative example can be applied to running other network meta-analyses of dichotomous outcomes entirely through the Microsoft-Excel-based NetMetaXL tool, without requiring the user to directly use the WinBUGS software. In the future, we plan on developing similar tools for other outcome measures.

There are several software packages available to run network meta-analyses. The majority of network meta-analyses conducted to date have used WinBUGS [3], although new routines have been developed which allow network meta-analyses to be conducted with STATA [6,7,21], R [22], and SAS [23]. These approaches to conducting network meta-analyses share a similar feature—they require programming knowledge of the software package being used. This is not a problem for statisticians who use these packages regularly or reviewers who are well versed in network meta-analyses and these software. However, this is a challenge for non-statisticians or reviewers who are not familiar with the packages but would like to run or critically appraise a network meta-analysis. Some of these packages (e.g., WinBUGS) have poor data manipulation functionality, data annotation, and graphical illustration capabilities, thereby requiring results to be transferred between multiple software packages, adding an additional layer of complexity.

This has led to the development of more user-friendly and integrated packages such as the Aggregate Data Drug Information System (ADDIS) [24]. Similar to our NetMetaXL tool, ADDIS [24] also provides users with a more user-friendly software package to run network meta-analyses without directly using WinBUGS (or JAGS or OpenBUGS) code. However, the current version of ADDIS (ADDIS 1) uses a stand-alone software package. Using Microsoft Excel offers some advantages over a stand-alone package like ADDIS such as the following: 1) it allows users

to use a software that they are familiar with, 2) there is more potential for others to develop add-ons to the Excel-based tool (versus stand-alone package) given the wide user base, and 3) it allows the data and results to be more easily integrated with decision analytic models and health economic evaluations which are frequently Excel-based compared to stand-alone packages. Indeed, this was noted in a recent publication [25] where they developed an Excel-based tool to perform HTAs entirely within Microsoft Excel. This Excel-based tool developed by Bujkiewicz et al. [25] called the transparent interactive decision interrogator (TIDI) also integrated with WinBUGS but used R, another software with a steep learning curve for non-statisticians. Although the example in TIDI was not specific to network meta-analysis, TIDI [25] could also be used for conducting and critically appraising network meta-analyses as well. Despite the advantages of using Excel, there are also disadvantages. Excel is a free-form tool and accordingly there are opportunities for both user and programmer error. Users should double- and triple-check data inserted into NetMetaXL. To reduce the risk of programmer error, we used standard WinBUGS code provided in the NICE TSD series and had an independent statistician review the WinBUGS coding.

Application of NetMetaXL

Network meta-analysis is increasingly being used to provide estimates of effect for treatments that may not have been compared directly in clinical trials. NetMetaXL represents a step forward in improving the ability of novice users to run network meta-analyses. We have illustrated this application for running network meta-analyses in NetMetaXL using the combined resynchronization and implantable defibrillator therapy illustrative example. Another useful application of NetMetaXL would be related to critical appraisal of network meta-analyses by HTA organizations such as CADTH or NICE, or network meta-analyses submitted to journals. Inclusion of a NetMetaXL file, along with a technical report or publication, would undoubtedly facilitate more efficient and transparent critical appraisal of network meta-analyses. In addition, it would provide some standardization to the format of the analysis and graphical reporting.

HTA organizations and major medical journals should encourage authors to submit the data for their systematic reviews and network meta-analyses using NetMetaXL or a similar software package. Currently, the data used in HTAs or published network meta-analyses is often not adequately reported, presented in a wide range of styles, or often embedded in images such as forest plots, making it challenging to extract data quickly, replicate findings, and critically appraise the study. The use of data repositories such as the Systematic Review Data Repository [26] and the Dryad Digital

Repository has improved accessibility of data. However, these repositories only require that the data and code are uploaded to the repository and are often made available for use in less user-friendly packages such as R, STATA, or SAS. These repositories do not require that data are formally integrated with the analysis. Accordingly, critical appraisal of network meta-analyses, especially for non-statisticians, is still a challenge even when data is submitted to these repositories because users are still often left without the tools to quickly validate the analyses. By contrast, NetMetaXL will allow users to quickly validate the submitted analysis and test robustness of results to excluding certain studies, use of informative/non-informative priors, and choice of fixed/random effects models.

Some organizations in the healthcare sector have recognized the limitation of not providing the unified data and model on which an analysis is based. Indeed, HTA organizations often require manufacturers of drugs and devices to provide a user-friendly health economic model, in specified software, in addition to a technical report to facilitate critical appraisal of their product; however, this is not the standard for network meta-analyses submitted to HTA organizations. These health economic models are often Microsoft Excel based and give reviewers much more information than is provided in a 100-page technical report, let alone a 2,700–4,000-word publication. Given that type of easy access to and control of the original authors' data, model, and analysis, reviewers at HTA organizations are able to run additional analyses to test model uncertainty and alternative assumptions. The impact that these Microsoft-Excel-based models have had on critical appraisal of manufacturers' health economic models is evident by examining the public summary documents from HTA organizations such as CADTH and NICE. It is not uncommon for recommendations from HTA bodies to report that reanalyses conducted by their staff found the cost-effectiveness estimates were less favorable than those submitted by the manufacturer. The same impact could potentially be seen if this increased level of transparency was applied to network meta-analyses.

Limitations of NetMetaXL

There are a number of limitations with NetMetaXL to note. Currently, this version of NetMetaXL only allows users to consider a maximum of 15 treatment options and 50 studies. This will prevent its application to more complex networks with multiple dosing strategies, complex interventions, or well-established disease areas where there are more than 15 treatment options. The current version of NetMetaXL is also only applicable for dichotomous outcomes. However, we will develop similar tools for other outcome types (e.g., continuous), will

continue to update and refine the Microsoft-Excel-based tool, and will make new versions freely available online, including additional capabilities to adjust for heterogeneity including meta-regression analysis and inclusion of more sophisticated methods for assessing inconsistency. All versions of NetMetaXL will be housed on www.NetMetaXL.com. This tool is the first in a series of Excel-based tools being developed with support from CADTH. These Excel-based tools are being developed to enhance the application of HTAs in Canada and abroad. There will also be a link to NetMetaXL on the PRISMA website to enhance uptake and improve transparency of network meta-analyses in published medical journals.

With availability of user-friendly software such as NetMetaXL, concerns arise about network meta-analysis being undertaken and implemented inappropriately by novice users. It is critical that users of NetMetaXL receive training on network meta-analysis. Users should be educated on key concepts related to network meta-analysis such as heterogeneity and inconsistency and how to interpret findings for decision-making purposes. Users are also encouraged to consult with a statistician when using this tool.

Another disadvantage of NetMetaXL is that Microsoft Excel keeps the data locally (unless integrated with the cloud-based Microsoft 365 or other cloud systems) and does not foster sharing of information/data. This may be advantageous to drug or device manufacturers when submitting confidential data and network meta-analyses to HTA organizations such as CADTH and NICE. However, such an environment is not good for the society as a whole. Rather than keeping data in silos, there is a need to foster a research environment where data are shared and can be dynamically updated by multiple collaborators to improve research productivity. The earlier-mentioned ADDIS software [24] is in the process of launching a web-based platform (ADDIS 2) where researchers can collaborate to perform systematic reviews, data extraction, evidence synthesis, and decision analysis. Undoubtedly, such an integrated system should improve the efficiency, transparency, and critical appraisal of systematic reviews and network meta-analyses dramatically by making data more accessible to researchers and collaboration more seamless. As a result, we are strong ambassadors of the research that ADDIS [24] is striving towards. However, until use of such a system becomes widespread and readily available, NetMetaXL will serve as a step in the right direction towards making the conduct of network meta-analyses more accessible to non-statisticians and facilitating more efficient and transparent critical appraisal of network meta-analyses, standardization in reporting, and more seamless integration with health economic evaluation.

Conclusions

We have demonstrated the application of a freely available Microsoft-Excel-based tool—NetMetaXL—using an example of a published network meta-analysis. NetMetaXL can make running and reporting network meta-analyses more accessible to novice users, as all aspects of data entry, analysis, and reporting are conducted entirely within Excel and require no specialized programming knowledge. The application of this Microsoft-Excel-based tool could also facilitate more efficient and transparent critical appraisal of network meta-analyses submitted to HTA organizations such as CADTH or NICE, or journals which publish network meta-analyses. The use of this tool may also help standardize reporting and enhance integration with health economic evaluations.

Additional files

Additional file 1: Screenshots of NetMetaXL. Multiple screenshots for selected steps within NetMetaXL: data input, generating network diagram, using dialogue box, generating forest plots, generating league tables, and generating inconsistency plots.

Additional file 2: Output from WinBUGS. Presentation of traditional output from WinBUGS for illustrative example—network meta-analysis evaluating combined resynchronization and implantable defibrillator therapy in left ventricular dysfunction [8].

Competing interests

DG is a partner at Cornerstone Research Group and SB is an employee of Cornerstone Research Group. BH has provided advice to Amgen Canada regarding methodological issues related to network meta-analysis. The authors declare that they have no competing interests.

Authors' contributions

CC drafted the manuscript, incorporated comments/feedback received on the manuscript, conceived the study design, validated the statistical/epidemiological analysis, provided the appropriate WinBUGS code to SB, assisted with developing the software package, and submitted the manuscript for publication. SB conceived the study design, wrote all the visual basic codes for running the network meta-analysis, developed the software package, incorporated comments/feedback related to the software, and reviewed the manuscript for important intellectual content. BH piloted NetMetaXL and provided feedback to CC and SB to incorporate into the tool. BH, DC, TC, DG, and GW conceived the study design and reviewed the manuscript for important intellectual content. All authors have read and approved the final version of the manuscript. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Authors' information

CC and SB are co-first authors. CC drafted the manuscript, validated the statistical/epidemiological analysis, provided the appropriate WinBUGS code to SB, and coordinated the development of the website to download NetMetaXL and track use of the tool; SB wrote all the visual basic codes for running the network meta-analysis, developed NetMetaXL, and reviewed the manuscript for important intellectual content.

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References

- Caldwell DM, Ades AE, Higgins PT: Simultaneous comparison of multiple treatments: combining direct and indirect evidence. *BMJ* 2005, **331**:897–900.
- Jansen JP, Crawford B, Bergman G, Stam W: Bayesian meta-analysis of multiple treatment comparisons: an introduction to mixed treatment comparisons. *Value Health* 2008, **11**:956–964.
- Nikolakopoulou A, Chaimani A, Veroniki AA, Vasiliadis HS, Schmid CH, Salanti G: Characteristics of networks of interventions: a description of a database of 186 published. *Networks* 2014, **9**:1–10.
- Lee AW: Review of mixed treatment comparisons in published systematic reviews shows marked increase since 2009. *J Clin Epidemiol* 2014, **67**:138–143.
- Dias S, Welton NJ, Sutton AJ, Caldwell DM, Lu G, Ades AE: Evidence synthesis for decision making 4: inconsistency in networks of evidence based on randomized controlled trials. *Med Decis Making* 2013, **33**:641–656.
- Higgins JPT, Jackson D, Barrett JK, Lu G, Ades AE, White IR: Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. *Res Synth Meth* 2012, **3**:98–110.
- Chaimani A, Higgins JPT, Mavridis D, Spyridonos P, Salanti G: Graphical tools for network meta-analysis in STATA. *PLoS One* 2013, **8**:e76654.
- Lam SKH, Owen A: Combined resynchronisation and implantable defibrillator therapy in left ventricular dysfunction: Bayesian network meta-analysis of randomised controlled trials. *BMJ* 2007, **335**:925.
- Lunn DJ, Thomas A, Best N, Spiegelhalter D: WinBUGS—a Bayesian modelling framework: concepts, structure, and extensibility. *Stat Comput* 2000, **10**:325–337.
- Spiegelhalter DJ, Abrams KR, Myles JP: *Bayesian Approaches to Clinical Trials and Health-Care Evaluation*. 1st edition. Chichester, West Sussex, PO19 8SQ, England: John Wiley & Sons Ltd; 2004:408.
- Sutton AJ, Abrams KR: Bayesian methods in meta-analysis and evidence synthesis. *Stat Methods Med Res* 2001, **10**:277–303.
- Lambert P, Sutton A: How vague is vague? A simulation study of the impact of the use of vague prior distributions in MCMC using WinBUGS. *Stat Med* 2005, **24**:2401–2428.
- Gelman A: Prior distributions for variance parameters in hierarchical models. In 2006:515–533.
- Turner RM, Davey J, Clarke MJ, Thompson SG, Higgins JP: Predicting the extent of heterogeneity in meta-analysis, using empirical data from the

- Cochrane Database of Systematic Reviews. *Int J Epidemiol* 2012, **41**:818–827.
- Thorlund K, Thabane L, Mills EJ: Modelling heterogeneity variances in multiple treatment comparison meta-analysis—are informative priors the better solution? *BMC Med Res Methodol* 2013, **13**:1.
- Sweeting MJ, Sutton AJ, Lambert PC: What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. *Stat Med* 2004, **23**:1351–1375.
- Dias S, Sutton AJ, Ades AE, Welton NJ: Evidence synthesis for decision making 2: a generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials. *Med Decis Making* 2013, **33**:607–617.
- Salanti G, Ades A, Ioannidis J: Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *J Clin Epidemiol* 2011, **64**:163–171.
- Van Valkenhoef G, Lu G, de Brock B, Hillege H, Ades AE, Welton NJ: Automating network meta-analysis. *Res Synth Meth* 2012, **3**:285–299.
- Brooks S, Gelman A: General methods for monitoring convergence of iterative simulations. *J Comput Graph Stat* 1998, **7**:434–455.
- White IR, Barrett JK, Jackson D, Higgins JPT: Consistency and inconsistency in network meta-analysis: model estimation using multivariate meta-regression. *Res Synth Meth* 2012, **3**:111–125.
- Rücker G: Network meta-analysis, electrical networks and graph theory. *Res Synth Meth* 2012, **3**:312–324.
- Jones B, Roger J, Lane PW, Lawton A, Fletcher C, Cappelleri JC, Tate H, Moneuse P: Statistical approaches for conducting network meta-analysis in drug development. *Pharm Stat* 2011, **10**:523–531.
- Van Valkenhoef G, Tervonen T, Zwinkels T, de Brock B, Hillege H: ADDIS: A decision support system for evidence-based medicine. *Decis Support Syst* 2013, **55**:459–475.
- Bujkiewicz S, Jones HE, Lai MCW, Cooper NJ, Hawkins N, Squires H, Abrams KR, Spiegelhalter DJ, Sutton AJ: Development of a transparent interactive decision interrogator to facilitate the decision-making process in health care. *Value Health* 2011, **14**:768–776.
- Ip S, Hadar N, Keefe S, Parkin C, Iovin R, Balk EM, Lau J: A Web-based archive of systematic review data. *Syst Rev* 2012, **1**:15.

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