COMPARATIVE EFFECTIVENESS AND SAFETY OF LIPID LOWERING AGENTS FOR THE TREATMENT OF DYSLIPIDEMIA IN HIV-POSITIVE INDIVIDUALS

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Submitted to the University of Ottawa
in partial fulfillment of the requirements
of the degree of Master of Science in Interdisciplinary Health Sciences

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ABSTRACT

As the HIV-positive population ages, managing non-AIDS-related comorbidities such as cardiovascular disease (CVD) complicates HIV care. Effectively treating risk factors for CVD will help reduce its burden in the HIV-infected population. However, the evidence base for the efficacy of statins as lipid-lowering therapies in HIV-infected patients has yet to be synthesized. Most trials do not compare statins directly to each other. In the absence of head-to-head evidence, the relative treatment effects of different statins can be indirectly obtained through a network meta-analysis (NMA). This NMA aims to evaluate the use of statins for treating dyslipidemia in HIV-infected individuals. Bayesian methods were used for obtaining treatment effect estimates and probabilistic rankings of treatments. Among lipid-lowering therapies, statins were most effective in treating dyslipidemia. All statins were found to offer the same treatment benefits. To our knowledge, this is the first NMA on this topic. It provides clinicians, health economists, and policy decision-makers with precise and reliable estimates for making definitive recommendations for the use of statins in dyslipidemic HIV-positive patients.

RÉSUMÉ

Le nombre de personnes vieillissant avec le VIH et développant des comorbidités, telles que les maladies cardiovasculaires, ne cesse d'augmenter. Il est impératif de pallier ces comorbidités car elles représentent un réel défi pour la provision des soins de santé. Traiter les facteurs de risque cardiovasculaires de façon efficace permettrait de réduire leur fardeau sur la qualité de vie des personnes vivant avec le VIH. Cependant, le peu d'évidence existant sur l'efficacité d'hypolipidémiants, telles que les statines, chez les personnes atteintes par le VIH n'a pas encore été synthétisé. De plus, les essais cliniques réalisés ne comparent que rarement l'usage de différentes statines directement. Adopter des méthodes de synthèse d'évidence, telle que la méta-analyse en réseau, permet de mobiliser toutes les connaissances acquises sur le sujet et de comparer l'efficacité des statines indirectement. Ainsi, l'objectif de cette thèse est d'évaluer l'efficacité et l'innocuité d'un traitement par statine pour la dyslipidémie chez les personnes vivant avec le VIH. Le classement et les effets relatifs des traitements furent estimés par l'intermédiaire de méthodes Bayésiennes. Parmi les différents types d'hypolipidémiants, les statines paressent être les plus efficaces. Toutes les statines offrent des bénéfices thérapeutiques similaires. Cette méta-analyse en réseau est la première en son genre. Les résultats obtenus informent aussi bien le milieu clinique que les politiques de santé, de façon fiable et précise, et permettront d'élaborer des recommandations sur les traitements par statine pour la dyslipidémie chez les personnes vivant avec le VIH.

ACKNOWLEDGEMENTS

I would first like to thank my supervisor, Professor Edward Mills, for without his vision, this thesis would not have been possible and I simply would not have had the same opportunities. His support and advice have inspired me and have helped me define my career path. For that, I am forever grateful.

I would also like to express my gratitude to my dear friend and classmate, Ghayath Janoudi, for his valuable contribution to this thesis as second reviewer. I feel very fortunate to have collaborated with him and look forward to working together again.

In addition, I am grateful to Professors Raywat Deonandan and Jeffrey Jutai for their support and kind words of encouragement in the last two years, as members of my thesis advisory committee.

Finally, I would like to thank my friends and family. If writing a thesis is a long and isolating journey, my journey would not have been the same without them standing by my side. The unconditional love and support of my parents and siblings, and the countless laughs and good times shared with my friends brighten every single one of my days. I cannot thank them enough for simply being present, and it warms my heart to know that I can always count on them. I am truly blessed to have such amazing human beings in my life.

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ABBREVIATIONS

AIDS: Acquired Immune Deficiency Syndrome
ALT: Alanine Aminotransferase
BMI: Body Mass Index
CDC: Centers for Disease Control and Prevention
CD4: Cluster of Differentiation 4
CI: Confidence Interval
CPK: Creatine Phosphokinase
CrI: Credible Interval
CVD: Cardiovascular Disease
DIC: Deviance Information Criterion
FDA: Food and Drug Administration
GI: Gastrointestinal
GRADE: Grading of Recommendations Assessment, Development and Evaluation
HDL-c: High Density Lipoprotein cholesterol
HIV: Human Immunodeficiency Virus
HMG-CoA: 3-hydroxy-3-methyl-glutaryl-CoA
IDSA/ACTG: Infectious Disease Society of America/AIDS Clinical Trials Group
LDL-c: Low Density Lipoprotein cholesterol
MCMC: Markov Chain Monte Carlo
MeSH: Medical Subject Headings
MI: Myocardial Infarction
NICE: National Institute for Health and Care Excellence
NMA: Network Meta-analysis
NNRTI: Non-Nucleoside Reverse Transcriptase Inhibitor
NRTI: Nucleot(s)ide Reverse Transcriptase Inhibitor
OR: Odds Ratio
PI: Protease Inhibitor
PICO: Population, Intervention, Comparators, Outcome
PLHA: People Living with HIV/AIDS
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO: International Prospective register of systematic reviews
RCT: Randomized Controlled Trial
RNA: Ribonucleic Acid
Sd: Standard deviation
TG: Triglycerides
Total-c: Total cholesterol
UNAIDS: Joint United Nations Programme on HIV/AIDS

PART I: INTRODUCTION

1. The HIV/AIDS paradigm shift: From death sentence to chronic condition

With the advent and expansion of combination antiretroviral therapy (ART) in 1996, the life expectancy of people living with HIV/AIDS (PLHA) has dramatically increased. With a timely diagnosis, access to health care, and adherence to ART, the estimated life expectancy of PLHA is almost identical to that of their uninfected counterparts.[1] Findings from a cohort study of 22,937 patients from the United States and Canada suggest that a 20-year-old HIV-infected individual on stable ART can expect to live into their early 70s.[2] A national observational cohort study of 4,612 patients in the Netherlands corroborates these findings and suggest that 25-year-old HIV-infected individuals who are asymptomatic at 24 weeks after starting ART had an estimated 52.7 life-years remaining, compared with 53.1 life-years for 25-year-old uninfected persons.[3] Moreover, the 2013 annual UNAIDS report claims that for the first time since the start of the HIV epidemic, 10% of the adult PLHA in low- and middle-income countries and 30% of the adult PLHA population in high-income countries are over 50 years of age.[4] Likewise, the CDC predicts that 50% of HIV-infected individuals living in the U.S. will be over 50 in 2015.[5] In a context of access to health care, successful virologic suppression, and adequate immune recovery, the paradigm of care for HIV-positive patients has shifted: HIV-infection is no longer considered a death sentence and is now instead perceived as a chronic, yet manageable, condition.

However, success in the management of HIV-infection has brought on a new set of challenges. As they grow older, PLHA are prone to the same age-associated comorbidities burdening the general population. HIV-infected persons are now

developing non-AIDS related comorbidities such as cardiovascular disease, non-AIDS-defining cancers, renal and hepatic diseases, osteoporosis, and neurological impairments.[6] This results in an important decline in their quality of life and it changes the relative proportion of AIDS-defining and non-AIDS- defining causes of death in PLHA. Non-AIDS-defining causes of death are now gradually becoming major causes of death in HIV-infected persons.[6-9] Furthermore, PLHA seem to develop age-associated comorbidities earlier than individuals in the general population, leading several experts to suggest that being HIV-infected may also translate into experiencing premature aging.[10] While the commonly observed phenomenon of early senescence in PLHA is linked to an exacerbated risk of developing age-associated non-AIDS conditions, it is mainly thought to be due to the interaction of factors such as chronic HIV-infection, poor lifestyle habits (such as smoking), long-term exposure to ART, and the process of aging itself.[11] As the proportion of older PLHA increases in all regions of the world, managing chronic comorbidities in HIV-infected individuals constitutes an important public health challenge.

The HIV Medicine Association of the Infectious Diseases Society of America recently updated their evidence-based guidelines for the management of PLHA.[12] They make several recommendations for managing HIV-infection as a chronic condition with multiple non-AIDS related comorbidities and for providing integrated primary care to HIV-positive patients. Recommendations are made using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines.[13] The authors specify both the level of strength for each

recommendation made and the type of quality of the evidence these recommendations are based on. Many are only moderately strong recommendations and are based on "moderate" or "low" quality evidence, particularly those regarding the management of comorbidities such as cardiovascular disease. These recommendations are, in fact, more often based on cohort studies than on randomized trials, and only a limited number is based on evidence synthesis studies such as systematic reviews or meta-analyses. As an increasing amount of high quality data is generated, synthesizing the available evidence is of importance for informing decision-makers and shaping continuing care treatment strategies in PLHA.

2. Cardiovascular disease in people living with HIV/AIDS

In the era of antiretroviral therapy, cardiovascular disease (CVD) has become a major cause of morbidity and mortality in PLHA.[14] HIV-infected individuals have about a two-fold increased risk for CVD than their uninfected counterparts.[15] While the details of the pathophysiology of cardiovascular diseases in HIV-infected patients have yet to be fully elucidated, it is thought that biologic and environmental factors may interact to increase the risk of developing CVD in this subset of the population.[16] Three main factors are frequently identified in the literature as being associated with an increased risk of CVD in PLHA: HIV infection itself, use of ART, and traditional comorbid risk factors for CVD (e.g. family status, smoking, lack of exercise, and obesity).

HIV as a risk factor: Several studies and reviews have identified HIV as an independent risk factor for CVD.[17,18] HIV infection has been associated with an increased risk of heart failure[19], stroke[20], and sudden cardiac death.[21] Even HIV-positive individuals on stable ART with suppressed viral loads are still at a higher risk of CVD compared with uninfected individuals.[18] This increased risk is thought to be due to the fact that HIV-positive individuals often have high viral loads prior to ART initiation, affecting organ damage, and that low levels of residual viral replication remain after they initiate treatment.[22] Moreover, evidence from cross-sectional studies associates HIV-infection with a higher risk of metabolic disorders such as diabetes mellitus, abnormal lipid profiles, and alterations of body fat distribution (lipodystrophy).[23,24] These disorders are well-established independent contributors to higher risk of CVD.[25] In addition, immune activation and inflammation persist in the majority of PLHA, even in those able to achieve viral suppression by adhering to ART.[26-28] A long-term consequence of chronic HIV replication is chronic inflammation of the vascular endothelium[22] One study's findings suggest that the vasculature of HIV-infected patients are the same as those of uninfected individuals 25 years older.[29] Long-term HIV-infection thus results in chronic inflammation of the vascular endothelium, leading to accelerated vascular aging and putting HIV-infected individuals at a higher risk of CVD than uninfected persons early-on in their lives. Therefore, regardless of whether or not patients are on stable ART, HIV-infection is considered to be an independent risk factor for CVD because not only does it increase the probability of having CVD events and

developing risk factors for CVD, it also contributes to the accelerated aging of the cardiovascular system in PLHA.

ART as a risk factor: Findings from the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study- an international prospective cohort study investigating the effects of ART on CVD in over 33,000 patients - suggest that ART also plays a role in excess risk of CVD in PLHA.[30-32] Friis-Moller et al. found a relative rate for myocardial infarction (MI) of 1.26 per year of ART exposure in PLHA, suggesting that the use of ART puts HIV-positive individuals at an increased risk of CVD.[31] There are different types and classes of ART- each being associated with different levels of toxicity. Numerous studies have found that protease inhibitors (PIs) are the most common type of ART associated with an increased risk of CVD.[31,33,34] For instance, Friis-moller et al. report that the rate of MI among patients who were not exposed to PIs was 1.53 per 1000 person-years compared with 6.01 per 1000 person-years for patients exposed to PIs for more than 6 years. Risks per additional year of exposure to PIs were lower after adjustment for Nucleot(s)ide Reverse Transcriptase Inhibitors (NRTI) exposure, diabetes mellitus, hypertension, and lipid levels.[31] This suggests that metabolic changes such as alterations in lipid profiles affect the risk for developing CVD in patients receiving PIs. On the other hand, data on the association between other types of ART and CVD are less conclusive. Data from the D:A:D study indicates that the use of neither non-nucleoside reverse transcriptase (NNRTIs) or NRTIs was significantly associated with an increased risk in MI.[31] However the duration of NNRTI and NRTI use was shorter than the duration of PI exposure. These findings should thus be interpreted with caution because the

length of time on ART is an important factor in determining its metabolic and physiological consequences, and it could play a confounding role in assessing the comparative impact of different types of ART on the risk for CVD. Nevertheless, the literature contains compelling evidence suggesting that exposure to ART constitutes an independent risk factor for CVD because it is associated with a higher risk for CVD event occurrence and an increased incidence of CVD risk factors, such as abnormal changes in lipid profiles.

Traditional comorbid risk factors: Numerous studies have revealed that smoking, alcohol consumption and/or cocaine use, hypertension, insulin resistance, and dyslipidemia, are more prevalent in PLHA than in the general population.[22,35,36] Moreover, older age is considered to be one of the strongest factors associated with a higher risk of CVD in PLHA. The risk of myocardial infarction increases by 6 to 9% for every year aged in PLHA.[37] This risk increased with longer ART exposure for up to 6 to 7 years of exposure.[37,38] Traditional CVD risk factors such as older age, smoking, substance abuse, hypertension, diabetes, and dyslipidemia, have all been associated with an excess risk of CVD in PLHA.

3. Dyslipidemia in people living with HIV/AIDS

Dyslipidemia, a disorder in which patients have abnormal blood lipid concentrations, is highly prevalent in PLHA.[39] HIV replication, chronic inflammation, and exposure to ART have all been identified as contributing factors to the development of dyslipidemia in the HIV-infected population.[22] ART is most often recognized as being the most important contributor to variations in lipid levels. PIs,

NRTIs, and NNRTIs have all been identified as playing a major role in changes in lipid metabolism, abnormalities in fat, insulin resistance, and dyslipidemia.[40] While different PIs have varying effects on lipid levels, individuals with long-term exposure to this specific class of ART often experience hypertriglyceridemia (triglyceride levels above 500mg/dL), low levels of high-density lipoprotein cholesterol (HDL-c) and high levels of low-density lipoprotein cholesterol (LDL-c).[22,40] On the other hand, NRTIs have been associated with changes in triglyceride (TG) levels, and NNRTIs have been associated with increases in total cholesterol (Total-c) levels, HDL-c, LDL-c, and TG.[22] Therefore, combined with the highly prevalent traditional risk factors for CVD, long-term HIV-infection and exposure to ART put HIV-infected persons at a higher risk of developing lipid abnormalities than their individuals in the general population.

4. Treatment of dyslipidemia in HIV-infected persons

In 2003, the Infectious Disease Society of America and the Adult AIDS Clinical Trials Group (IDSA/ACTG) published guidelines for the evaluation and management of dyslipidemia in PLHA.[41] It is important to note however that, since the publication of these guidelines, several new randomized clinical trials have been published on the efficacy and safety of lipid-lowering medications in HIV-infected individuals, and some therapies, such as rosuvastatin and pitavastatin, are now FDA-approved and commonly prescribed. The IDSA/ACTG recommend lifestyle changes, such as following a healthy diet and a regular exercise regimen, as the initial step in the management of dyslipidemia and CVD risk in PLHA. However, a recent meta-

analysis of dietary intervention studies conducted in HIV-positive patients found that such lifestyle changes did not significantly or importantly alter lipid levels and only had a small effect on triglyceride concentrations.[42] This suggests that lifestyle changes alone are not enough to change the course of dyslipidemia in the HIV-infected population. It also suggests that, in light of more recent data, the recommendations made for clinical practice in the IDSA/ACTG guidelines do not adequately represent the current level of knowledge on effective means for managing lipid abnormalities in PLHA.

When lipid-lowering therapies are needed, the IDSA/ACTG suggest prescribing HMG-CoA reductase inhibitors (statins), fibric acid derivatives (fibrates), and/or and niacin.[41] One of the main challenges in the management of dyslipidemia in PLHA is selecting the lipid-lowering medication that will effectively normalize lipid levels, all the while maintaining an acceptable safety profile given the potential drug-drug interactions with ART.

Statins: In the general population, statin therapy is widely used as first-line therapy for dyslipidemia (defined as total-c > 200 mg/dL, LDL-c > 130 mg/dL, HDL-c < 40, TG > 150mg/dL).[41] Their efficacy in normalizing lipid levels and reducing the risk of CVD in both primary and secondary prevention is well-established.[43,44] There are 7 different types of statins with different pharmacokinetic properties, drug interaction profiles, and risks of myotoxicity: simvastatin, lovastatin, atorvastatin, pravastatin, rosuvastatin, fluvastatin, and pitavastatin.[45] Cerivastatin, an 8th formulation that was marketed by Bayer, was voluntarily withdrawn from the market in 2001 due to concerns about rhabdomyolysis.[46]

While there is a plethora of evidence for the use of these various statins in the general population, the evidence base for the use of statins in HIV-positive individuals is much more limited. The IDSA/ACTG guidelines identify pravastatin, atorvastatin, and fluvastatin as being the most effective and least toxic statins for PLHA.[41] In addition, data from clinical trials published after 2003 suggests that the relatively new statins, rosuvastatin and pitavastatin, are also both well tolerated and effective in normalizing lipid profiles.[47-51]

However, it is important to note that the choice in type of statin prescribed to HIV-infected patients is further complicated by the fact that there are known drug-drug interactions between statins and ART. Some statins, such as lovastatin and simvastatin, are metabolized by the same cytochrome as PIs: cytochrome P450 isoenzyme CYP3a4.[52] The use of such statins in patients whose ART regimens include PIs could thus result in increased statin/ART toxicity due to interference with the metabolism of PIs and elevated plasma levels of statins or ART. Moreover, since several studies associate both lovastatin and simvastatin with a higher risk of liver and muscle toxicity when used with PIs and/or NNRTIs, the IDSA/ACTG guidelines state that these two statins are contraindicated in all HIV-infected patients, regardless of their type of ART regimens.[39,41,52] Since most HIV-positive patients have ART regimens involving PIs, the main statins prescribed to PLHA are the ones using metabolic pathways that are not dependent on CYP3a4. Pravastatin, rosuvastatin, atorvastatin, fluvastatin, and pitavastatin are considered to be the safest statins to prescribe to PLHA.[41,53,54]

Fibrates: Fibrates are recommended as the first-line therapy choice for hypertriglyceridemia (defined as TG>500mg/dL) in both the general population[55] and in PLHA because they are thought to specifically target triglycerides.[41] Since their metabolism is not dependent on CYP3a4, their drug-drug interactions with ART are less of a concern than with statins. Several different types of fibrates exist, although limited data are available on their comparative efficacy and on clinical outcomes of their use in PLHA. Findings from a recent review suggest that fenofibrate- the most commonly prescribed fibrate for HIV-positive patients with elevated TG levels[56]- is both effective and safe for the treatment of mixed dyslipidemia and hypertriglyceridemia in HIV-positive persons.[57] Findings from randomized trials evaluating the comparative efficacy and safety of fenofibrate and pravastatin found that combining pravastatin and fenofibrate is an effective and safe way to treat mixed dyslipidemia in PLHA.[58,59] However, other studies have associated the co-administration of fibrates and statins with a risk of hepatotoxicity.[54] The lack of evidence for the comparative effectiveness and safety of fibrates in PLHA has led physicians to prescribe fibrates only when triglyceride concentrations exceed 500 mg/dL, as per clinical indication.[41]

Ezetimibe: Before 2003, no data was yet available in the peer-reviewed literature on the efficacy of ezetimibe. For this reason, the IDSA/ACTG guidelines do not include recommendations about its use in PLHA. However, recent reviews explain that ezetimibe is a cholesterol absorption inhibitor and is sometimes prescribed in both the general population and PLHA to reduce hepatic cholesterol levels and increase the clearance of cholesterol from the blood.[39,53] In HIV-positive patients

with poor response to statins, it has been associated with a reduction of LDL-c levels.[60] Moreover, several studies suggest that it has a high tolerability profile in PLHA on ART because it does not interact with CYP3A4.[53,60,61]

Niacin: In the general population, niacin is given to target elevated TG levels and increase low HDL-c levels.[55] There is very little published evidence on the use of niacin in the HIV-infected population. Niacin has only been associated with effective management of dyslipidemia in PLHA in two studies[62,63] However both studies report mild elevations in fasting glucose, suggesting that niacin may induce insulin resistance. For this reason, niacin is not commonly prescribed for the management of dyslipidemia in PLHA, especially in patients who may already be insulin resistant.

5. Bridging the gap between research and practice

Treating dyslipidemia in the HIV-infected population has its own set of challenges, not encountered in the general population. For example, antiretroviral medications can both cause changes in lipid profiles and interact with lipid-lowering therapies. For this reason, certain statins are considered safe in the general population but are contraindicated in PLHA. Moreover, several high quality randomized trials have been conducted since the publication of the available, but outdated, IDSA/ACTG guidelines. Thus, there is an urgent need to synthesize the available evidence on the use of lipid lowering medications in PLHA. Doing so will not only serve to update the current guidelines but will also bridge the gap between research and practice.

PART II: METHODOLOGY

Chapter 1: Systematic Review

1. Rationale for the review

As the HIV-positive population ages, managing chronic non-AIDS related comorbidities such as CVD adds a layer of complexity to HIV care. Effectively treating risk factors for CVD will help reduce its burden on both the quality of life and mortality rates in PLHA on stable ART regimens. However, current guidelines for the management of dyslipidemia, a highly prevalent risk factor for CVD, in PLHA are outdated. Since the publication of these guidelines, several randomized trials have been conducted on the use of various lipid-lowering therapies in HIV-positive individuals.

While the evidence-base for this topic is increasing, it has yet to be synthesized or evaluated in the context of comparative effectiveness. To support clinical and policy decision-making, evidence from direct comparisons between competing treatments should ideally be used. Unfortunately, the efficacy of lipid-lowering therapies in treating dyslipidemic PLHA is mostly evaluated against standard care or placebo controlled trials. In the absence of head-to-head evidence, a network meta-analysis is a highly valuable tool to assess the comparative efficacy of competing interventions. Combining the evidence from different pairwise comparisons across a range of interventions allows us to make definitive recommendations based on all the available data from published clinical trials.

Using Bayesian methods is particularly useful to policy decision-makers because it allows for a flexible interpretation of the treatment effect estimates.

NB. The protocol for this review was registered with the PROSPERO Centre for Reviews and Dissemination and made publicly available in January 2014 (ID number: CRD42014007077). The PROSPERO protocol can be found in the **Appendix.**

2. Research questions

The *objective* of this study is to compare the relative efficacy and safety of different statins for the treatment of dyslipidemia in HIV-infected individuals.

The following *research questions* were formulated based on the PICO (**P**articipants, **I**nterventions, **C**omparisons, and **O**utcomes) model:

- How does the use of statins affect the average change in cholesterol across HIV-positive patients?
- Are certain statins more effective than others in lowering the cholesterol levels of HIV-positive patients?
- How safe is the use of statins in HIV-positive patients?

3. Eligibility criteria

Inclusion and exclusion criteria were pre-specified for each PICO component and can be found in **Table 1**. Only randomized clinical trials (RCTs) were included

because randomization is a way to prevent systematic differences in patient baseline characteristics from acting as confounding variables. Moreover, non-randomized studies may over or under estimate true treatment effects due to important baseline differences between groups.[64] For this reason, observational studies were excluded. Studies had to have a minimum of 6-week follow-up. Intention-to-treat analysis had to have been conducted or could at least be inferred from the data reported in each publication's methods section. Authors had to at least report that all study participants had been included in the analysis for the groups to which they were originally assigned. Duplicate publications of findings from the same trial were excluded.

The **participants** in each included study had to be HIV-infected individuals with lipid abnormalities, from any age and gender, and statin-naïve for the past 3 months. Studies conducted on dyslipidemic HIV-negative patients, dyslipidemic HIV-positive individuals on ART with two or more non-AIDS related comorbidities or with Hepatitis C co-infections, and individuals who had already been on any sort of lipid-lowering medication before the start of the trial were excluded.

Studies evaluating the use of any type of statin as **interventions** for dyslipidemia were included. Trials reporting on the efficacy of approved lipid-lowering therapies in HIV-positive individuals were excluded if they did not include a statin arm. RCTs of atorvastatin, fluvastatin, pitavastatin, pravastatin, or rosuvastatin were included. Trials reporting on the use of lovastatin or simvastatin were excluded as the latter therapies are widely contraindicated in HIV-positive patients.[39,45]

Studies investigating the use of other types of statins or other lipid-lowering therapies, and control (placebo or standard care/dietary change) as **comparators** were included. Single arm studies were excluded.

Trials reporting average change in total-c, LDL-c, HDL-c, and TG levels in their **outcomes** were included for evaluating intervention efficacy. Studies reporting on number of adverse events such as myalgia, myositis, rhabdomyolysis, creatine kinase elevations, liver function elevations, gastrointestinal disturbances, and severe unexpected adverse events were included to assess the comparative safety of the interventions of interest.

Table 1. Study selection criteria based on the PICO model

Population	**Included:** HIV-infected individuals with lipid abnormalities; From any age and gender; Statin-naïve for the past 3 months
	Excluded: HIV-negative patients; Dyslipidemic HIV-positive individuals on ART with two or more non-AIDS related comorbidities; Individuals who had already been on any sort of lipid-lowering medication before the start of the trial; Hepatitis C Virus co-infected patients
Interventions	**Included:** Any type of statin (HMG-CoA Reductase Inhibitors)
	Excluded: Evaluating other sorts of lipid-lowering therapies without statin arm
Comparators	**Included:** Placebo; Standard care/dietary change; Other lipid-lowering therapies; Statins compared amongst themselves
	Excluded: Single arm studies
Outcomes	*Primary:* Average change in total, LDL, and HDL cholesterol levels; Average change in triglyceride levels. *Secondary:* Myositis, myalgia/myositis/rhabdomyolysis, creatine phosphokinase elevations, liver function elevations, gastrointestinal disturbances, and severe unexpected adverse events
Study Design	**Included:** Randomized experimental studies; randomized controlled trials (RCTs); Studies with minimum 6-week follow-up; Intent-to-treat analysis done or could at least be inferred from data reported in methods
	Excluded: Observational studies, studies reporting results from less than 6-weeks follow-up; studies using the same data but published at different times and with minor changes

4. Search strategies

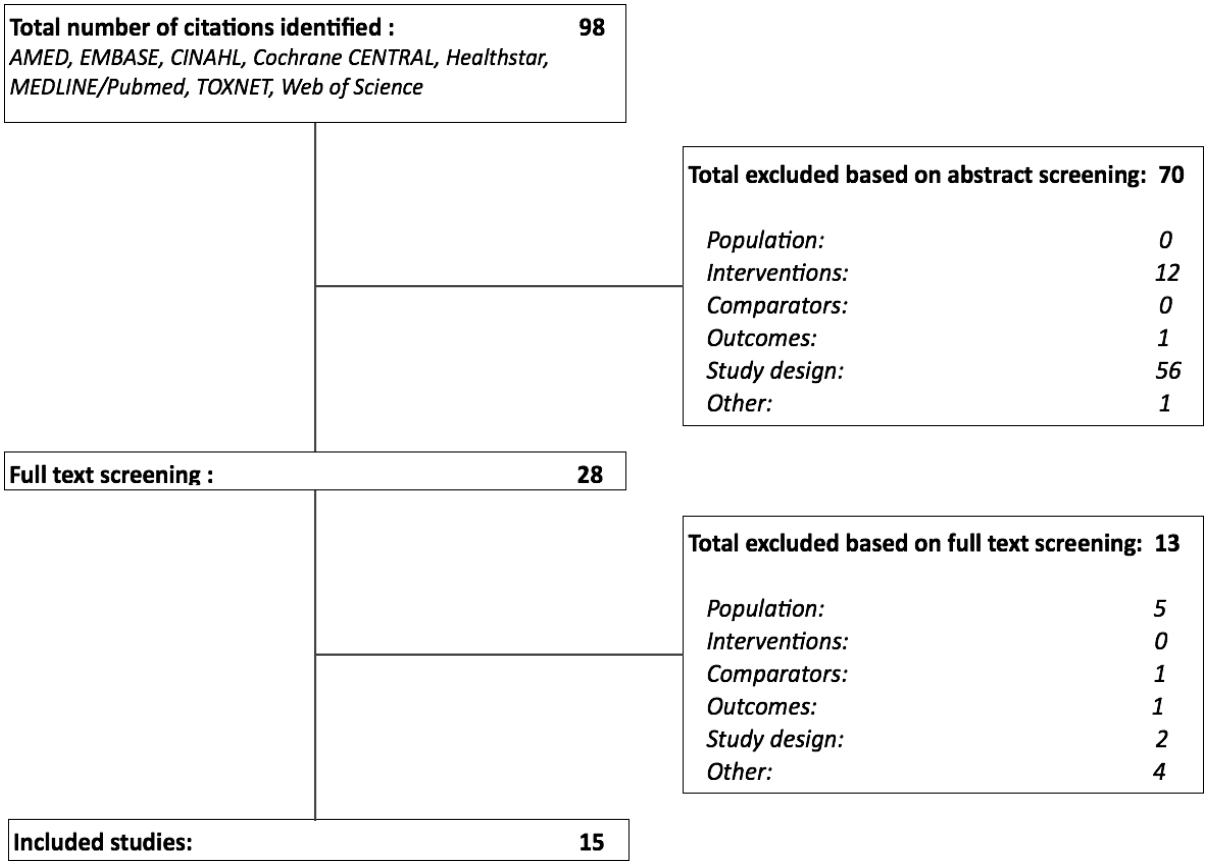
A medical librarian in the faculty of Health Sciences Library was consulted in order to double-check search strategies and retrieve all relevant studies. The following 8 databases were searched: AMED, EMBASE, CINAHL, Cochrane CENTRAL, Healthstar, MEDLINE/Pubmed, TOXNET, and Web of Science from inception to 05/01/2015. Conducting sensitive and broad search strategies in a wide variety of databases helps minimize selection bias.[65] Together, these databases are generally considered to be the most important sources for clinical trial references.[66] Searches were not limited by language, gender, or location of trial research center. Only published reports were considered; letters, posters, and abstracts were excluded. Within each PICO component of the research question, a wide variety of search terms were combined with the Boolean 'OR' operator. Both free-text and subject headings (i.e. Medical Subject Headings (MeSH) in MEDLINE/Pubmed) were used. PICO components were then combined with the Boolean 'AND' operator. Manual searches for eligible RCTs were also performed using reference lists from published review articles and all references were crosschecked. Searches included all results made from database conception to November 28, 2014. Searches were last updated in March 2015. Details of the strategies used to search each database can be found in the **Appendix**.

5. Study selection process

All search results were merged in the Endnote reference management software (*Version X7.1*). Two investigators (Laura Mesana and Ghayath Janoudi)

independently scanned all of the abstracts retrieved after running the database-specific search strategies. Any irrelevant abstracts were removed. After obtaining full text reports of RCTs evaluating the use of statins in the population of interest, both reviewers assessed in duplicate their eligibility for inclusion in the review, following the PICO model. Duplicate reports of the same study were identified based on author names, specific details about the interventions (i.e. dose and frequency), the number of participants per arm, baseline characteristics, and duration of follow-up. The reviewers met after each phase of the screening process to discuss the eligibility decisions. Any disagreement was resolved by consulting a neutral third party. Some of the primary authors of individual RCTs were contacted when information on trial and/or patient characteristics were missing for determining final eligibility. **Figure 1** is a flow chart depicting the study selection process.

Figure 1. Flow chart of the study selection process



6. Data collection process

The two independent reviewers collected data from the included RCTs using the same data extraction sheet. Details were gathered about trial characteristics, relevant patient characteristics, and treatment effects on the pre-determined outcomes of interest.

Trial characteristics included: treatment duration, follow-up time, sample size, details about intervention arms such as type of intervention, dosage, dosage frequency, route of administration, allocation concealment details, previous

exposure to ART, type of ART exposure, concomitant use of ART, type of ART regimen, and time on ART.

Patient characteristics included: Age, gender, ethnicity, body mass index (BMI), percent smokers, percent transmission groups, percent with known hypertension, baseline LDL-c, HDL-c, total-c, and TG levels, baseline glucose levels, baseline insulin concentration, and baseline HIV-related clinical parameters (CD4 cell count, plasma HIV-RNA levels, % of prior AIDS events)

Outcomes components evaluated both the efficacy and safety of the different interventions**.** All efficacy outcomes of interests were continuous. They consisted of average changes from baseline in total-c, LDL-c, HDL-c, and TG levels in each arm. All safety outcomes were dichotomous. They consisted of number of patients in each arm with adverse events. Adverse events of interest consisted of alanine aminotransferase elevations (to assess the effect of interventions on liver function), creatine phosphokinase elevations and the occurrence of myalgia, myositis, and rhabdomyolysis (to assess the effect of interventions on muscle damage), the occurrence of gastrointestinal disturbances (such as diarrhea, nausea, and dyspepsia), and the number of treatment discontinuations due to adverse events. When trials did not report results based on an intent-to-treat analysis, outcomes were extracted as all patients randomized.

7. Risk of bias assessment

Variation in the quality of the research methods used in each included trial can introduce bias into their findings and thus influence the outcomes of a

systematic review or meta-analysis.[67] For this reason, the methodological quality of each included RCT was assessed using the *Cochrane Collaboration's tool for assessing risk of bias*. Items such as sequence generation, allocation sequence concealment, blinding, incomplete outcome data, and selective outcome reporting were evaluated. Each criteria in the "risk of bias" table is assessed by answering a question, where answers 'Yes' indicate a low risk of bias, 'No' indicate a high risk of bias, and 'Unclear' indicate uncertainty over the potential risk for bias due to lack of information. Assessing the risk of bias in this fashion is of key importance because bias due to design flaws such as lack of allocation concealment may lead to biased treatment effects.[68]

The presence of selection bias was assessed by evaluating sequence generation and allocation concealment. That way, systematic differences between baseline characteristics of the groups were identified and compared. Performance bias was identified by collecting details on the blinding of participants, personnel, and outcome assessors. In doing so, differences between groups were identified. Attrition bias was assessed by evaluating incomplete outcome data and how the blinding of participants, personnel and outcome assessors was conducted. Evaluating how the blinding of participants was conducted also helped assess detection bias, or systematic differences between groups in how outcomes are determined. Finally, outcome reporting bias was evaluated by looking at selective outcome reporting. Detailed guidelines on how to use the *Cochrane Collaboration's tool for assessing risk of bias* can be found in the **Appendix.**

8. Reporting guidelines

This review follows the PRISMA statement for reporting systematic reviews and meta-analyses[69]. This 27-item checklist helps increase the clarity and transparency of our NMA's report. In doing so, it increases its value to clinicians, health economists, and policy-makers. The PRISMA checklist can be found in the **Appendix**.

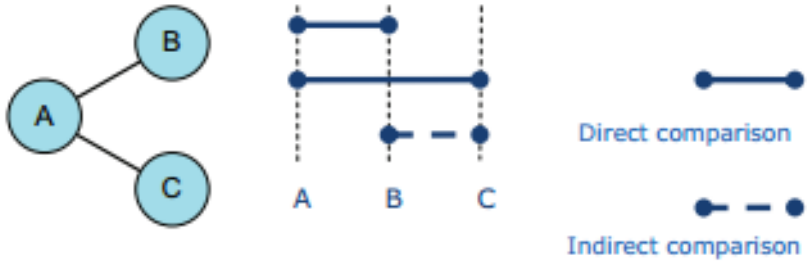
Chapter 2: Network Meta-Analysis

1. Introduction to network meta-analysis

Clinical trials often assess competing treatments for the same condition against placebo or a control such as the standard treatment of care. Trials making direct comparisons between competing interventions are rare, particularly when there are more than two active treatments available for treating a given condition. For example, five different statins are commonly prescribed to HIV-positive patients with dyslipidemia, yet very few RCTs directly compare these different statins to each other. Instead, most RCTs compare statins to a control arm (i.e. placebo or dietary changes) or to other types of lipid-lowering therapies (i.e. fibrates). Consequently, making definitive recommendations for the use of these medications can be a challenging task.

A network meta-analysis (NMA) synthesizes the evidence on comparative effects of more than two alternative interventions for the same condition.[70] This allows us to compare treatment effects of interventions that have never been directly evaluated against each other through the use of indirect treatment comparisons. In the absence of head-to-head evidence, indirect treatment comparisons can provide valuable information on the relative efficacy of competing treatments and can help clinicians and decision-makers select the most effective intervention.[71] For instance, an indirect estimate for the comparison of treatment A vs. B can be obtained by using the direct estimates from RCTs comparing treatments A vs. C and B vs. C (See **Figure 2**).[72]

Figure 2. Example of direct vs. indirect comparison comparisons



Note: This figure was taken from a report written by the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices.[72] Here, interventions B and C have never been directly compared to each other but they have been commonly compared to treatment A. We can thus make an indirect comparison of B vs. C, using the evidence from the direct comparisons of A vs. B and A vs. C.

A NMA thus expands the scope of conventional pair-wise meta-analysis by using direct evidence obtained within RCTs in conjunction with the indirect evidence gathered in comparisons of interventions across trials. Combining data from indirect and direct comparisons helps build a network of evidence where interventions that have not been compared directly are linked through common comparators, allowing us to make use of all available data from published RCTs. Therefore, NMAs do not only allow researchers to analyze studies with multiple intervention groups but they also help synthesize a greater share of the available evidence than traditional meta-analysis.

2. Network meta-analysis in a Bayesian framework

There are two main frameworks in which NMAs are conducted. The frequentist approach views probability as a limiting long run frequency and uncertainty is said to be due to chance.[73] The results of a frequentist analysis are presented as point

estimates of treatment effects along with their associated 95% confidence intervals (CIs) and a P values. Confidence intervals cannot be directly interpreted in terms of probabilities about treatment effects. They only mean that, under repeated sampling they would contain the true population parameter 95% of the time. P values measure whether results are statistically significant or not. They do not inform us on the probability that the hypothesis of whether one treatment is better than another is true or false. Instead, they provide information about the probabilities for error in the hypothesis test statistic. The usefulness of P values and 95% CIs is thus limited in contexts of decision-making under uncertainty. When comparing more than two treatments within the same network of interventions, P values are associated with each pairwise comparison in the network and do not provide information about the ranking of treatments. Such inferential outputs are not easy to interpret when the aim is to evaluate the relative efficacies of several different types of interventions and make statements about each treatment's ranking probabilities. The use of a frequentist framework is therefore not the most appropriate method for decision-making under uncertainty.

On the other hand, the Bayesian framework is grounded in Bayes theorem, a more philosophical approach to statistical inferences. Probability is seen as a personal degree of belief and applies to any event or statement about which we are uncertain.[73] Inferences about treatment effects can be made by combining the data collected from RCTs with prior information, in order to obtain posterior distribution of the variables of interest. These posterior probability distributions represent the likely values for the treatment effect of each intervention relative to another, and

are summarized as a treatment effect point estimates with their associated 95% credible intervals (CrIs). In contrast with the 95% CIs, the 95% CrIs can be interpreted as meaning that there is a 95% chance that the true effect size lies between the interval's boundaries. Bayesian methods thus allow us to make direct probability statements about treatment effects because the posterior distribution is in essence a probability distribution. Probabilities are, however, not without their own limitations as a comparator can be highly ranked as probabilistically the highest likelihood of treatment effect, but without achieving statistical significance, as the probability is based on the point estimate rather than CrI.

Prior information can reflect prior beliefs about potential values of the relative treatment effects.[74] Priors can be specified based on clinical judgment and contribute information to the analyses, or they can be "flat" and left unspecified.[74] Since there is no definitive evidence supporting treatment effects of statins in managing dyslipidemia in PLHA, non-informative prior information was used to minimize the impact of potentially subjective prior information on the estimates obtained. Choosing to use non-informative prior distributions of treatment effects forces posterior distributions to be almost entirely driven by the observed data.[75]

An important utility of adopting a Bayesian framework is that all evaluated interventions can be ranked using the posterior probability distribution.[76] A simulation-based method called Markov Chain Monte Carlo is used to calculate the rank for each treatment according its performance in each simulation. Competing treatments can thus be ranked according to their respective probabilities of being the best, second best, third best, etc. For instance, posterior distributions of pooled

treatment effects of statins on cholesterol levels can be interpreted as mean differences but can also be interpreted in terms of probabilities. More precisely, one can say that there is X% probability that statin A results in a greater reduction of LDL-c than statin B. Being able to calculate the probability that each intervention is the most effective in the network also provides knowledge users with a measure of decision uncertainty, making Bayesian NMAs a more practical tool for clinical decision-making than NMAs conducted under a frequentist framework. In sum, the use of Markov Chain Monte Carlo helps obtain more precise treatment effect estimates and increases the certainty in the analytical outputs.

In health technology assessment, multiple parties often interpret the same evidence in different ways.[74] Within a Bayesian framework, predictive statements can be explicitly derived from the probabilistic rankings inferred by the model, leaving little room for misinterpretation. The outputs of a Bayesian analysis are more straightforward to interpret than those of a frequentist NMA and are thus directly relevant to health policy because they provide clinicians, health-economists, and decision-makers with an intuitive platform for probabilistic decision-making in a context of uncertainty. For this reason, the outputs of a Bayesian NMA make it a suitable methodology and potentially powerful tool for decision theory and policy-making.

3. Feasibility assessments

An important and simple requirement for being able to conduct a NMA is to have a connected network. In other words, each intervention evaluated should be

connected to every other treatment in the network through a chain of pair-wise comparisons.[71] Several other factors are also important. For instance, similarity and consistency assumptions must hold true in order to ensure that data from different trials can be pooled and that indirect and direct evidence can be adequately combined. Moreover, heterogeneity should be explored in order to assess the degree of variation of true treatment effects between the included trials.

In this NMA, feasibility assessments were conducted for each outcome of interest. We first assessed whether the evidence from all included RCTs formed a connected network and calculated how many RCTs contributed to each outcome's evidence network. We then analyzed the distribution of each study and patient characteristics across trials. Finally, we proceeded to conduct analyses assessing inconsistency and heterogeneity in the network.

a. Similarity assumption

Before combining direct and indirect evidence in a NMA, the degree of similarity between all included RCTs should be assessed.[72] Since the advantages of randomization only hold true when comparing treatment effects within the same trial, comparisons of between-trial treatment effects have to be made with caution as there is a risk that trial and patients characteristics differ sufficiently that they can act as treatment effect modifiers. Identifying imbalances in the distribution of these characteristics across trials is of importance to avoid making biased indirect comparisons.

In this NMA, clinical similarity was assessed by collecting and reviewing data on patient characteristics, interventions, settings, treatment duration, and length of

follow-up. Trials were compared based on the following characteristics: type of intervention, dosage, dosage frequency, route of administration, allocation concealment details, concomitant use of ART, type of ART regimen, time on ART, age, gender, BMI, baseline LDL-c, HDL-c, total-c, and TG levels, and baseline HIV-related clinical parameters (CD4 cell count, plasma HIV-RNA levels, % of prior AIDS events). Methodological similarity was assessed through the quality assessment using the *Cochrane Collaboration's tool for assessing risk of bias* (See **Appendix**).

b. Consistency assumption

When combining direct and indirect evidence, an imbalance in patient and trial characteristics can result in the violation of the consistency assumption.[72] Inconsistencies can mainly be examined in closed loops of evidence, where each intervention in the loop has been compared directly with all the others.[70] Every comparison in a closed loop is comprised of both direct and indirect evidence. It is thus important to assess whether or not there are inconsistencies between indirect and direct treatment effect comparisons.

In this NMA, the consistency assumption was verified by plotting posterior mean deviance estimates for each treatment effect obtained with a consistency model against the posterior mean deviance estimates obtained with an inconsistency model. The consistency model is based on the assumption that treatment effects do not differ across trials and types of comparisons, while the inconsistency model is based on the assumption that treatment effects differ across trials and types of comparisons. This method allowed us to identify the loops in

which inconsistency was present. Given the small number of studies reporting on safety outcomes, inconsistency was only assessed for the efficacy outcomes.

c. Heterogeneity

Variation in trial and patient characteristics among studies included in the network may act as effect modifiers among studies comparing the same interventions, resulting in between-study heterogeneity.[77] Similarly to variations in similarities between trials and consistency assumption violations, heterogeneity can be a threat to the internal validity of NMAs, as it can act as a modifier of the relative treatment effects.

In this NMA, the between-trial treatment effect standard deviation (sd) was set as the heterogeneity parameter, τ, in the Bayesian model. The between-trial sd was chosen because it reflects the degree of variation of true treatment effects between studies. For larger τ values, potential sources of heterogeneity were investigated by observing differences in study level covariates. The National Institute for Clinical Evaluation (NICE) recommends conducting a meta-regression in order to explore sources of heterogeneity in NMAs.[78] However, it is recommended that at least 10 trials per adjustment variable are required in order to achieve stability in the meta-regression results.[79] Since there were not enough studies available per study-level covariates of interest to perform a statistically valid meta-regression analysis, sensitivity analyses were conducted instead. Sensitivity analyses aim to explore potential effect modifiers by removing trials that show peculiarities in study-level covariates from the analysis. Estimates of each intervention's treatment effect obtained from analyzing the totality of studies are

compared with estimates of treatment effects obtained from the analysis after potentially effect-modifying trials have been removed. Based on findings from the literature review, the following trial and patient characteristics were selected for sensitivity analyses: Treatment duration, time on ART, and baseline LDL-c levels.

4. Statistical analysis

a. Bayesian Markov Chain Monte Carlo

An advantage of using a Bayesian approach to conduct a NMA is that it allows for the use of a simulation-based methodology. The posterior probability distributions from which relative treatment effects and probability statements are inferred are obtained through a simulation-based approach known as the Markov Chain Monte Carlo (MCMC) model. More precisely, the rank attributed to every treatment in the network is calculated according to the performance of interventions in each simulation.[75] The use of MCMC for predicting treatment ranks is particularly useful when the number of treatments in the network is large and differences in comparative treatments effects are small.[75]

The MCMC process first starts by running a very large number of iterations for a sequence (chain) of initial values. After the first (burn-in) values have been excluded, a random sample of the posterior distribution is obtained for each parameter in the model. Consequently, we can infer a stable estimate of the posterior distribution for each variable of interest. The distribution of these variables informs us on the probability that they will take a specific value.[80]

In this NMA, the posterior distributions were obtained for each outcome of interest by running three chains consisting of widely different and randomly generated initial values. Each chain used 100, 000 iterations with a burn-in number of 50,000, a thin interval of 1, and updates of 100. The number of burn-in values was decided based on the Gelman-Rubin method for assessing chain convergence in MCMC models.[81] This approach consists of identifying how many burn-in values it takes for each chain to converge to the same distribution. Much like one-way analysis of variance, the aim of the Gelman-Rubin approach is to compare the variation within each chain to variation between the chains. Gelman-Rubin diagnostic plots are used to provide a more formal assessment of convergence.[80] Three lines appear on this plot: the blue line depicts the variation within the chains, the green line represents the variation between the chains, and the red line is the ratio of between to within chain variation. Convergence is said to have happened when the red line converges to one, and the blue and green line converge to the same value.[80]

b. Model specification

Just as in traditional meta-analyses, NMAs can be performed using fixed effects or random effects models. The main difference between these two fundamentally different approaches centers around the concept of heterogeneity (i.e. the variation in true relative treatment effects for each pairwise comparison, both within and between trials). The fixed effects model assumes that differences in true relative treatment effects are only caused by differences in treatments: there is no heterogeneity in relative treatment effects other than that caused by differences

in the types of interventions compared. On the other hand, the random effects model assumes that differences in study-level covariates can in fact cause heterogeneity: true relative treatment effects across studies are exchangeable and heterogeneity is constant between different comparisons.[76]

The choice of model type is based on assessments of model fit and the posterior mean residual deviance $\overline{D}$. In Bayesian analyses, deviance is a likelihood-based measure. The lower the residual deviance in the model, the better the fit.[82] When comparing models, the deviance information criterion (DIC) is computed. The DIC adds a penalty term, equal to the effective number of parameters in the model, to the residual deviance and provides us with a standardized measure of model fit. As such, complex models involving a large number of parameters are penalized, and we are able to assess which approach provides the best fit to the data. The model with the smallest DIC is said to provide the better fit because it would best predict a replicate dataset that has the same structure as the current one.[83] DIC differences of more than 5 to 7 points are considered to be significant enough to rule out the model with the highest DIC.[83] Most Bayesian modeling guides recommend the use of both the DIC and residual deviance parameter in order to compare the fit of fixed and random effect models.[80]

c. Outputs

The main outputs of Bayesian NMAs are posterior distributions of relative treatment effects for each outcome. Outcomes were assessed with the Lu-Ades method for combining direct and indirect evidence.[84] This method allows for the use

of all available comparisons between treatments while preserving the effects of within-trial randomization.

All results for efficacy outcomes are reported as posterior means with their corresponding 95% credibility intervals (CrIs). All results for safety outcomes are reported as odds ratios (ORs) with their corresponding 95% CrIs. [74] The relative treatment effects are displayed in forest plots for each outcome.

The probability for each intervention to rank best, second best, third best, and so on was assessed by using the results from pairwise meta-analyses of each treatment compared with control and counting the proportion of MCMC iterations in which each intervention had the highest treatment effect, second highest, etc… For efficacy outcomes, treatments providing patients with the largest reduction in total-c, LDL-c or triglyceride levels were interpreted as being the best. Treatments providing patients with the smallest reduction in HDL-c were considered to the best for that specific outcome. For safety outcomes, treatments associated with the smallest amounts of adverse events were interpreted as being the best. These rank probabilities are depicted in rankograms. Rankograms are a graphical display of each treatment's probability of occupying a particular rank in the network hierarchy, where the most effective treatment is ranked first.[70]

d. Software

All analyses were conducted in WinBUGS (*Version 1.4.3*) and R (*Version 3.1.2*). Model specification and MCMC simulation were conducted in WinBUGS and inconsistency in the network was assessed in R. The annotated WinBUGS code written to specify the model can be found in the **Appendix**. The WinBUGS code used

for this NMA is based on the National Institute for Health and Care Excellence (NICE) Decision Support Unit *Technical Support Documents for Evidence Synthesis*.[85,86] Forest plots and rankograms were developed in R. The R code used to obtain these figures is provided in the **Appendix.**

PART III: RESULTS

Chapter 1: Evidence Base

1. Study selection process

The literature search identified 98 citations, after removal of exact duplicates. Of these, 12 were excluded because they did not meet the 'interventions' PICO component inclusion criteria for this NMA, 1 was excluded because it did not meet the 'outcomes' component, 56 were excluded because they were not randomized trials, and 1 was excluded as 'other', because it had nothing to do with any of the PICO components. The abstract screening process thus yielded a total of 28 relevant abstract. The full-texts of these articles were retrieved and screened. Of these, 5 were excluded because they did not meet the 'population' PICO component inclusion criteria for this NMA, 1 was excluded because it did not meet the 'comparators' component, 1 was excluded because it did not meet the 'outcomes' component, 2 were excluded because they were not RCTs, and 4 were excluded as 'other', mainly because they were duplicate trials of already included RCTs from slightly different authors. A flow chart depicting the study selection process can be found in **Figure 1.** The list of excluded studies during the full-text review process can be found in **Table 2**. Any disagreement between reviewers was resolved by referring to a neutral third party.

Figure 1. Flow chart of the study selection process

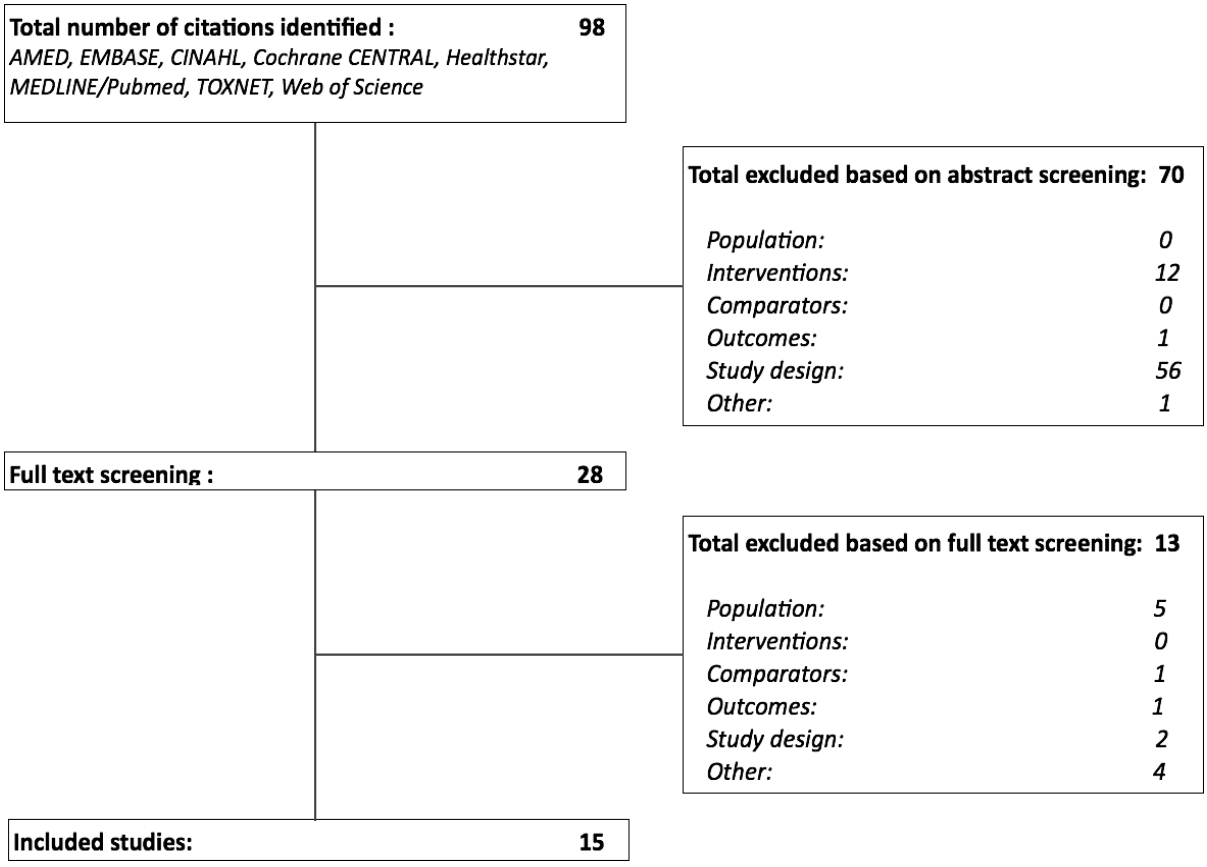


Table 2. List of excluded studies at full-text screening

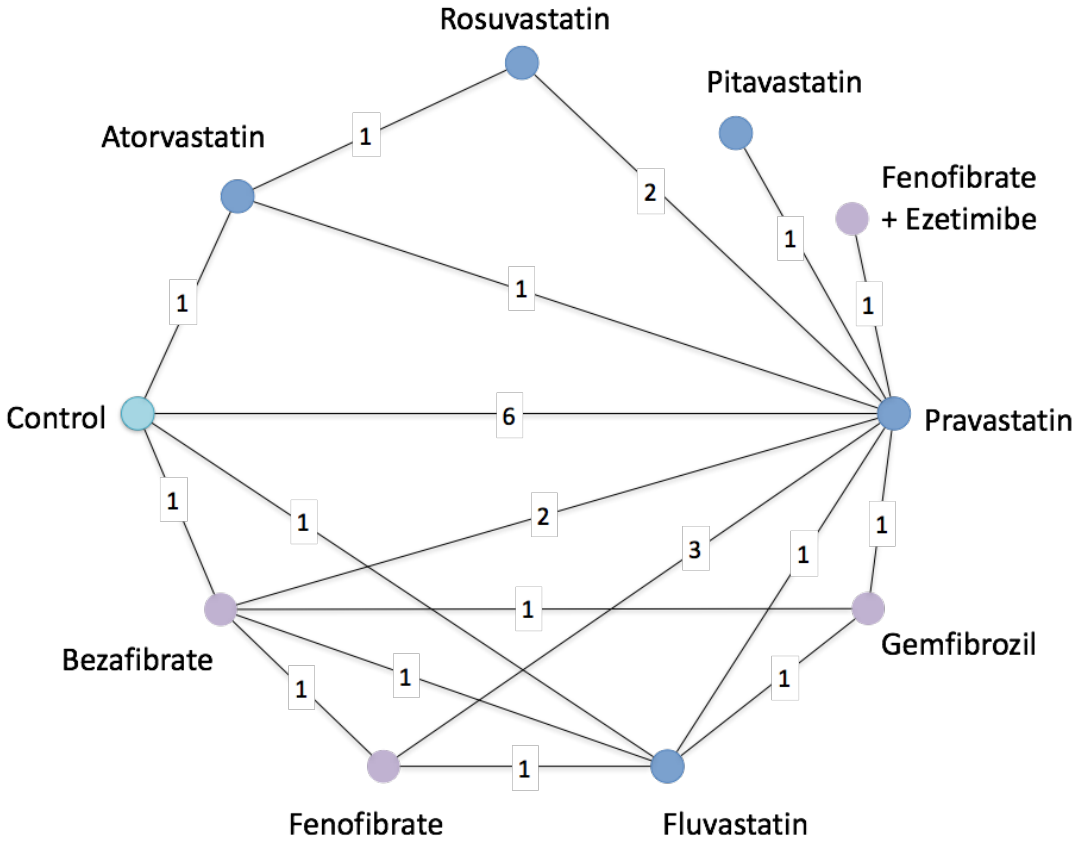
Author, year	Reason	Details
Aslangul et al, 2010[95]	Other	Duplicate of Bittar et al, 2012
Baker et al, 2012[96]	Population	Not hyperlipidemic at baseline (=LDL>160)
Calmy et al 2010[97]	Population	Not hyperlipidemic at baseline (=LDL>160)
Eckard et al, 2014[98]	Other	Not hyperlipidemic at baseline (=LDL>160)
Funderburg et al, 2014[99]	Population	Not hyperlipidemic at baseline (=LDL>160)
Ganesan et al, 2011[100]	Population	Not hyperlipidemic at baseline (=LDL>160)
Joshi et al, 2014[101]	Other	Duplicate of Sponseller et al, 2013
Montoya et al, 2012[102]	Population	Not hyperlipidemic at baseline (=LDL>160)
Munoz et al, 2013[103]	Study design	Not an RCT
Negredo et al, 2006[60]	Outcomes	Lack of outcomes of interest
Nicolini et al, 2014[104]	Other	Duplicate of Grandi et al, 2014
Samineni et al, 2012[105]	Comparators	No true control arm
Stein et al, 2004[106]	Study design	Not an RCT

2. Trial characteristics

Combined, the 15 eligible RCTs involved 1,258 patients. There were 2 eligible RCTs using atorvastatin,[48,87] 2 using bezafibrate,[47,49] 1 using fenofibrate in combination with ezitimibe,[88] 3 using fenofibrate alone,[47,58,59] 2 using fluvastatin,[47,89] 1 using gemfibrozil,[47] 1 using pitavastatin,[51] 13 using pravastatin,[47-51,58,59,88,90-94] and 2 using rosuvastatin.[48,50] Out of the 15 trials, there were 12 two-armed trials, 2 three-armed trials, and 1 five-armed trial. Control (placebo or standard care/dietary change) was compared to pravastatin in 7

eligible trials,[49,90-94] to bezafibrate in 1 trial,[49] to fluvastatin in 1 trial,[89] and to atorvastatin in 1 trial.[87] Pravastatin was compared to fenofibrate in 3 RCTs,[58,59,88] to rosuvastatin in 2 trials,[48,50] to bezafibrate in 2 trials,[47,49] to fluvastatin in 1 trial,[47] to gemfibrozil in 1 trial,[47] to atorvastatin in 1 trial,[48] to fenofibrate in combination with ezitimibe in 1 trial,[88] and to pitavastatin in 1 trial.[51] **Figure 3** depicts the overall network of available treatment comparisons for all outcomes combined.

Figure 3. Overall network of evidence diagram (15 trials)



Note: *Nodes* represent interventions. Different *colors* signify different types of lipid lowering therapies (blue: statins, purple: fibrates). *Lines* indicate direct comparisons made. *Numbers* indicate the number of trials that make a particular direct comparison.

The study characteristics (i.e. trial length, intervention arm details, number of patients, and allocation concealment details) of all 15 eligible RCTs can be found in **Table 3.** The mean duration of treatment across trials was 27.8 weeks (sd=19.3 weeks), and the mean duration of follow-up trial time was 31.3 weeks (sd=19.6 weeks). Six trials out of fifteen were double blinded (participants and key study personnel). All trials were done in health centers from developed countries. Eleven trials were conducted in Europe, three in North America, and one in Australia.

Table 3. Characteristics of the 15 included trials

Study	Interventions	Multicenter (Y/N)	Double blind (Y/N)	Treatment duration (days)	Follow-up duration (days)	Region
Aberg et al, 2005[58]	Pravastatin; Fenofibrate	N	N	84	336	USA
Bittar et al, 2012[50]	Pravastatin; Rosuvastatin	Y	Y	45	45	France
Bonnet et al, 2007[90]	Control; Pravastatin	N	Y	84	84	France
Calza et al, 2008[48]	Atorvastatin; Pravastatin; Rosuvastatin	N	N	365	365	Italy
Calza et al, 2005[49]	Bezafibrate; Control; Pravastatin	N	N	365	365	Italy
Calza et al, 2003[47]	Bezafibrate; Gemfibrozil; Fenofibrate; Fluvastatin; Pravastatin	N	N	365	365	Italy
Doser et al, 2002[89]	Control; Fluvastatin	N	Y	28	28	Switzerland
Fichtenbaum et al, 2010[59]	Fenofibrate; Pravastatin	Y	N	84	336	USA
Grandi et al, 2014[88]	Pravastatin; Ezetimibe + Fenofibrate	N	N	182	182	Italy
Hurlimann et al, 2006[91]	Control; Pravastatin	N	Y	56	56	Switzerland
Macallan et al, 2008[92]	Control; Pravastatin	N	N	336	336	UK

Study	Interventions	Multicenter (Y/N)	Double blind (Y/N)	Treatment duration (days)	Follow-up duration (days)	Region
Mallon et al, 2006[93]	Control; Pravastatin	N	Y	84	84	AUS
Masiá et al, 2009[87]	Control; Atorvastatin	N	N	168	168	UK
Moyle et al, 2001[94]	Control; Pravastatin	N	N	168	168	UK
Sponseller et al, 2013[51]	Pitavastatin; Pravastatin	Y	Y	84	365	USA

Note: Y = Yes, N = No. Control = placebo or standard care/dietary change

The specific study characteristics of all 15 eligible RCTs can be found in **Table 4**. Included trials were well matched with regards to similarity characteristics. Patients from all included studies were on ART prior to trial start and for the entire study duration. All studies' ART regimens contained protease inhibitors. The average time of ART exposure prior to trial start was 8.8 years. All trials involved patients that were on protease inhibitor-containing ART regimens.

Table 4. HIV/AIDS-specific trial characteristics of the 15 included trials

Study	Interventions	Previous exposure to ART (Y/N)	Concomitant use of ART (Y/N)	Type of ART regimen	Time on ART (years)
Aberg et al, 2005[58]	Pravastatin; Fenofibrate	Y	Y	PI	--
Bittar et al, 2012[50]	Pravastatin; Rosuvastatin	Y	Y	PI	9(5-13) [a]
Bonnet et al, 2007[90]	Control; Pravastatin	Y	Y	PI; NRTI	--
Calza et al, 2008[48]	Atorvastatin; Pravastatin; Rosuvastatin	Y	Y	PI; NRTI	5.2(2.2)[b]
Calza et al, 2005[49]	Bezafibrate; Control; Pravastatin	Y	Y	PI; NRTI	2.35[c]
Calza et al, 2003[47]	Bezafibrate; Gemfibrozil; Fenofibrate; Fluvastatin; Pravastatin	Y	Y	PI	28.1(9.5)[b]
Doser et al, 2002[89]	Control; Fluvastatin	Y	Y	PI	2.66(0.25)[d]
Fichtenbaum et al, 2010[59]	Fenofibrate; Pravastatin	Y	Y	PI; NRTI; NNRTI	--
Grandi et al, 2014[88]	Pravastatin; Ezetimibe + Fenofibrate	Y	Y	PI; NRTI	8(6.2)[b]
Hurlimann et al, 2006[91]	Control; Pravastatin	Y	Y	PI; NRTI; NNRTI	4.8(2.3-5.9)[a]
Macallan et al, 2008[92]	Control; Pravastatin	Y	Y	--	--
Mallon et al, 2006[93]	Control; Pravastatin	Y	Y	PI; NRTI; NNRTI	--

Study	Interventions	Previous exposure to ART (Y/N)	Concomitant use of ART (Y/N)	Type of ART regimen	Time on ART (years)
Masiá et al, 2009[87]	Control; Atorvastatin	Y	Y	PI; NNRTI	10(8-15)[a]
Moyle et al, 2001[94]	Control; Pravastatin	Y	Y	PI; NRTI	--
Sponseller et al, 2013[51]	Pitavastatin; Pravastatin	Y	Y	PI; NRTI; NNRTI	--

Note: Control: placebo or standard care/dietary change; PI: Protease Inhibitor; NRTI: Nucleoside Reverse Transcriptase Inhibitor; NNRTI: Non-Nucleoside Reverse Transcriptase Inhibitor. (a) Median(Inter Quartile Range), (b) Mean(Standard Deviation), (c) Mean, (d) Mean(Standard Error)

3. Patient characteristics

The baseline patient characteristics (i.e. age, gender, ethnicity, BMI, percent smokers, percent transmission groups, percent with known hypertension, baseline LDL-c, HDL-c, total-c, and TG levels, baseline glucose levels, baseline insulin concentration, and baseline HIV-related clinical parameters) of all 15 eligible RCTs can be found in **Tables 5, 6, and 7**. Only three trials prescribed different doses of pravastatin to patients (20mg instead of the more common 40mg dose).[47-49] The mean age of patients was 43.4 years (sd=4.5). The mean proportion of male patients across trials was 82.9 sd 13.1%. Baseline cholesterol and triglyceride levels confirmed that all patients from the included trials were dyslipidemic, and those lipid levels were similar across trials. Baseline CD4 cell counts ranged from trial averages of 290 to 598 cells/mL, indicating a reasonably good status of patients' immune systems in all included RCTs.

Table 5. General baseline patient characteristics of the 15 included trials

Study	Intervention	Treatment duration (days)	Treat-ment dose	Treatment frequency	Number of patients randomized	Estimate age (years)	Estimate BMI (kg/m^2)	% Male	% Female
Aberg et al, 2005[58]	Pravastatin	84	40 mg	Daily	87	35-44[a]	--	91.8	8.2
Aberg et al, 2005[58]	Fenofibrate	84	200 mg	Daily	88	35-44[a]	--	90.9	9.1
Bittar et al, 2012[50]	Pravastatin	45	40 mg	Daily	37	48(42-52)[b]	--	81.1	18.9
Bittar et al, 2012[50]	Rosuvastatin	45	10 mg	Daily	39	47(42-56)[b]	--	77.0	23.0
Bonnet et al, 2007[90]	Control	84	--	Daily	9	41(38-50)[b]	--	78.0	22.0
Bonnet et al, 2007[90]	Pravastatin	84	40 mg	Daily	12	42(39-47)[b]	--	92.0	8.0
Calza et al, 2008[48]	Atorvastatin	365	10 mg	Daily	32	38.1(11.2)[c]	--	56.3	43.8
Calza et al, 2008[48]	Pravastatin	365	20 mg	Daily	34	37.4(10.6)[c]	--	73.5	26.5
Calza et al, 2008[48]	Rosuvastatin	365	10 mg	Daily	28	36.3(9.5)[c]	--	60.0	40.0
Calza et al, 2005[49]	Bezafibrate	365	400 mg	Daily	31	37.9[d]	--	67.7	32.3
Calza et al, 2005[49]	Control	365	--	Daily	65	38.2[d]	--	57.1	42.9
Calza et al, 2005[49]	Pravastatin	365	20 mg	Daily	36	40.4[d]	--	58.3	41.7

Study	Intervention	Treatment duration (days)	Treat-ment dose	Treatment frequency	Number of patients randomized	Estimate age (years)	Estimate BMI (kg/m^2)	% Male	% Female
Calza et al, 2003[47]	Bezafibrate	365	400 mg	Daily	25	--	--	--	--
Calza et al, 2003[47]	Gemfibrozil	365	600 mg	Twice daily	22	--	--	--	--
Calza et al, 2003[47]	Fenofibrate	365	200 mg	Daily	22	--	--	--	--
Calza et al, 2003[47]	Fluvastatin	365	20 mg	Daily	18	--	--	--	--
Calza et al, 2003[47]	Pravastatin	365	20 mg	Daily	12	--	--	--	--
Doser et al, 2002[89]	Control	28	--	Daily	16	40.5(1.8)[e]	22.4(0.8)[e]	87.5	12.5
Doser et al, 2002[89]	Fluvastatin	28	40 mg	Daily	16	40.5(1.8)[e]	22.4(0.8)[e]	87.5	12.5
Fichtenbaum et al, 2010[59]	Fenofibrate	84	200 mg	Daily	37	46(28-62)[b]	25.4(22.2-27.1)[b]	100.0	0.0
Fichtenbaum et al, 2010[59]	Pravastatin	84	40 mg	Daily	37	42.5(31-57)[b]	26.4(24.0-30.9)[b]	91.9	8.1
Grandi et al, 2014[88]	Pravastatin	182	40 mg	Daily	20	45(9)[c]	25.4(3.1)[c]	85.0	15.0
Grandi et al, 2014[88]	Ezetimibe + Fenofibrate	182	200 mg	Daily	21	47(7)[c]	24.9(3.6)[c]	85.7	14.3
Hurlimann et al, 2006[91]	Control	56	--	Daily	29	43[f]	22.9(21.4-25.1)[b]	79.0	21.0

Study	Intervention	Treatment duration (days)	Treat-ment dose	Treatment frequency	Number of patients randomized	Estimate age (years)	Estimate BMI (kg/m^2)	% Male	% Female
Hurlimann et al, 2006[91]	Pravastatin	56	40 mg	Daily	29	43[f]	22.9(21.4-25.1)[b]	79.0	21.0
Macallan et al, 2008[92]	Control	336	--	Daily	26	43.3(7.8)[c]	22.8(2.66)[c]	--	--
Macallan et al, 2008[92]	Pravastatin	336	40 mg	Daily	11	43.3(7.8)[c]	22.8(2.66)[c]	--	--
Mallon et al, 2006[93]	Control	84	--	Daily	17	43(9)[b]	25(21.5-28.5)[b]	100.0	0.0
Mallon et al, 2006[93]	Pravastatin	84	40 mg	Daily	16	52(12)[b]	24(23-24)[b]	90.6	9.4
Masiá et al, 2009[87]	Control	168	--	Daily	36	47.8(44.2-56.99)[h]	24.3(22.3-25.9)[b]	88.9	11.1
Masiá et al, 2009[87]	Atorvastatin	168	10 mg	Daily	32	53.7(45.3-58.2)[h]	26.3(22.9-28.8)[b]	90.6	9.4
Moyle et al, 2001[94]	Control	168	--	Daily	12	--	23.6(21.9-25.3)[g]	100.0	0.0
Moyle et al, 2001[94]	Pravastatin	168	40 mg	Daily	14	--	23.1(21.7-24.4)[g]	100.0	0.0
Sponseller et al, 2013[51]	Pitavastatin	84	4 mg	Daily	121	50.1(7.5)[c]	27.2(4.5)[c]	84.1	15.9
Sponseller et al, 2013[51]	Pravastatin	84	40 mg	Daily	126	49.2(8.7)[c]	28.2(4.9)[c]	88.1	11.9

Note: Control: placebo or standard care/dietary change. (a) Median range, (b) Median(Inter Quartile Range), (c) Mean(Standard Deviation), (d) Mean, (e) Mean, (f) Median, (g) Mean(95% Confidence Interval), (h) Median(Range)

Table 6. Dyslipidemia-related baseline patient characteristics for the 15 included RCTs

Study	Intervention	Number of patients randomized	Total cholesterol concentration estimate	LDL Cholesterol concentration estimate	HDL Cholesterol concentration estimate	Triglyceride levels estimate
Aberg et al, 2005[58]	Pravastatin	87	261.5(183-639) mg/dL[a]	162(67-248) mg/dL[a]	34(21-52) mg/dL[a]	311.5(118-2516) mg/dL[a]
Aberg et al, 2005[58]	Fenofibrate	88	275.5(185-531) mg/dL[a]	149.5(58-291) mg/dL[a]	34(6-54) mg/dL[a]	336.5(118-2516) mg/dL[a]
Bittar et al, 2012[50]	Pravastatin	37	7.24(0.94) mmol/L[b]	4.94(0.9) mmol/L[b]	1.38(0.35) mmol/L[b]	2.57(1.7) mmol/L[b]
Bittar et al, 2012[50]	Rosuvastatin	39	7.31(1.22) mmol/L[b]	5.05(1.13) mmol/L[b]	1.38(0.38) mmol/L[b]	2.69(1.29) mmol/L[b]
Bonnet et al, 2007[90]	Control	9	6.4(6.1-7.7) mmol/L[d]	3.9(3.7-4.8) mmol/L[d]	1(0.8-1.1) mmol/L[d]	3.2(2.1-4.4) mmol/L[d]
Bonnet et al, 2007[90]	Pravastatin	12	6.1(5.8-6.3) mmol/L[d]	4.1(3.7-4.6) mmol/L[d]	0.9(0.8-1.1) mmol/L[d]	2(1.1-3.3) mmol/L[d]
Calza et al, 2008[48]	Atorvastatin	32	289(31) mg/dL[b]	180(28) mg/dL[b]	49(18) mg/dL[b]	269(77) mg/dL[b]
Calza et al, 2008[48]	Pravastatin	34	275(29) mg/dL[b]	173(17) mg/dL[b]	54(25) mg/dL[b]	179(89) mg/dL[b]
Calza et al, 2008[48]	Rosuvastatin	28	282(28) mg/dL[b]	177(21) mg/dL[b]	51(20) mg/dL[b]	274(74) mg/dL[b]
Calza et al, 2005[49]	Bezafibrate	31	264.2 mg/dL[e]	--	--	314.5 mg/dL[e]
Calza et al, 2005[49]	Control	65	215 mg/dL[e]	--	--	296.8 mg/dL[e]
Calza et al, 2005[49]	Pravastatin	36	257.5 mg/dL[e]	--	--	296.8 mg/dL[e]

Study	Intervention	Number of patients randomized	Total cholesterol concentration estimate	LDL Cholesterol concentration estimate	HDL Cholesterol concentration estimate	Triglyceride levels estimate
Calza et al, 2003[47]	Bezafibrate	25	244.2(86.2) mg/dL [b]	--	--	329.8(106.5) mg/dL[b]
Calza et al, 2003[47]	Gemfibrozil	22	244.2(86.2) mg/dL[b]	--	--	329.8(106.5) mg/dL[b]
Calza et al, 2003[47]	Fenofibrate	22	244.2(86.2) mg/dL[b]	--	--	329.8(106.5) mg/dL[b]
Calza et al, 2003[47]	Fluvastatin	18	244.2(86.2) mg/dL[b]	--	--	329.8(106.5) mg/dL[b]
Calza et al, 2003[47]	Pravastatin	12	244.2(86.2) mg/dL[b]	--	--	329.8(106.5) mg/dL[b]
Doser et al, 2002[89]	Control	16	7.5(0.4) mmol/L[c]	--	1.1(0.1) mmol/L[c]	6.3(2.2) mmol/L[c]
Doser et al, 2002[89]	Fluvastatin	16	8(0.5) mmol/L[c]	--	1.2(0.1) mmol/L[c]	4.5(0.9) mmol/L[c]
Fichtenbaum et al, 2010[59]	Fenofibrate	37	281(252-325) mg/dL[d]	148(132-176) mg/dL[d]	34(30-39) mg/dL[d]	375(262-457) mg/dL[d]
Fichtenbaum et al, 2010[59]	Pravastatin	37	260(249-289) mg/dL[d]	160(145-179) mg/dL[d]	35(32-41) mg/dL[d]	307(225-399) mg/dL[d]
Grandi et al, 2014[88]	Pravastatin	20	248(39) mg/dL[b]	149(32) mg/dL[b]	47(11) mg/dL[b]	263(96) mg/dL[b]
Grandi et al, 2014[88]	Ezetimibe + Fenofibrate	21	241(34) mg/dL[b]	149(33) mg/dL[b]	44(10) mg/dL[b]	265(118) mg/dL[b]
Hurlimann et al, 2006[91]	Control	29	6.4(6.0-7.4) mmol/L[d]	3.7(2.8-4.2) mmol/L[d]	1.2(1.1-1.6) mmol/L[d]	3(2.1-4.0) mmol/L[d]

Study	Intervention	Number of patients randomized	Total cholesterol concentration estimate	LDL Cholesterol concentration estimate	HDL Cholesterol concentration estimate	Triglyceride levels estimate
Hurlimann et al, 2006[91]	Pravastatin	29	6.4(6.0-7.4) mmol/L[d]	3.7(2.8-4.2) mmol/L[d]	1.2(1.1-1.6) mmol/L[d]	3(2.1-4.0) mmol/L[d]
Macallan et al, 2008[92]	Control	26	5.7(1.3) mmol/L[b]	3.44(1.01) mmol/L[b]	1.19(0.28) mmol/L[b]	2.19(1.37-3.58) mmol/L[b]
Macallan et al, 2008[92]	Pravastatin	11	5.7(1.3) mmol/L[b]	3.44(1.01) mmol/L[b]	1.19(0.28) mmol/L[b]	2.19(1.37-3.58) mmol/L[b]
Mallon et al, 2006[93]	Control	17	7.6(1.4) mmol/L[d]	--	1.1(0.4) mmol/L[d]	4.9(7.8) mmol/L[d]
Mallon et al, 2006[93]	Pravastatin	16	7.6(1.7) mmol/L[d]	--	1.1(0.4) mmol/L[d]	3.8(4.1) mmol/L[d]
Masiá et al, 2009[87]	Control	36	202(175.8-228.5) mg/dL[d]	131(108.8-145.3) mg/dL[d]	44(38.8-52.2) mg/dL[d]	142.5(90-177) mg/dL[d]
Masiá et al, 2009[87]	Atorvastatin	32	213.5(194.3-237.5) mg/dL[d]	141(115-160) mg/dL[d]	48.8(36.1-53.9) mg/dL[d]	158.5(99.5-227.8) mg/dL[d]
Moyle et al, 2001[94]	Control	12	7.4(6.8-7.9) mmol/L[f]	4.68(3.89-5.47) mmol/L[f]	0.87(0.72-1.02) mmol/L[f]	4.06(2.20-5.97) mmol/L[f]
Moyle et al, 2001[94]	Pravastatin	14	7.5(6.7-8.3) mmol/L[f]	4.65(4.1-5.2) mmol/L[f]	0.94(0.79-1.08) mmol/L[f]	3.96(2.84-6.52) mmol/L[f]
Sponseller et al, 2013[51]	Pitavastatin	121	284.4(32.4) mg/dL[b]	155.1(25.9) mg/dL[b]	49.6(15) mg/dL[b]	174.2(93.8) mg/dL[b]
Sponseller et al, 2013[51]	Pravastatin	126	238.1(31) mg/dL[b]	154.6(23.9) mg/dL[b]	49.1(11.8) mg/dL[b]	172.4(73.2) mg/dL[b]

Note: Control: placebo or standard care/dietary change. (a) Median(Min, Max), (b) Mean(Standard Deviation), (c) Mean(Standard Error), (d) Median(Inter Quartile Range), (e) Mean, (f) Mean(95% Confidence Interval)

Table 7. HIV/AIDS-related baseline patient characteristics for the 15 included RCTs

Study	Intervention	% Prior AIDS events	Estimate CD4 cell count	Estimate plasma HIV-RNA levels
Aberg et al, 2005[58]	Pravastatin	--	462(91-1843) cells/mL[a]	1.7 copies/mL[e]
Aberg et al, 2005[58]	Fenofibrate	--	416(23-1480) cells/mL[a]	1.7 copies/mL[e]
Bittar et al, 2012[50]	Pravastatin	27	448(315-548) cells/uL[a]	86% <400 copies/mL
Bittar et al, 2012[50]	Rosuvastatin	18	482(313-659) cells/uL[a]	90% <400 copies/mL
Bonnet et al, 2007[90]	Control	--	484(429-653) cells/mm^3[a]	1.7 copies/mL[e]
Bonnet et al, 2007[90]	Pravastatin	--	465(330-525) cells/mm^3[a]	1.7 copies/mL[e]
Calza et al, 2008[48]	Atorvastatin	6.2	381(189) cells/mm^3[b]	--
Calza et al, 2008[48]	Pravastatin	8.8	411(209) cells/mm^3[b]	--
Calza et al, 2008[48]	Rosuvastatin	10.7	352(172) cells/mm^3[b]	--
Calza et al, 2005[49]	Bezafibrate	--	528 cells/mm^3[b]	--
Calza et al, 2005[49]	Control	--	479 cells/mm^3[b]	--
Calza et al, 2005[49]	Pravastatin	--	535 cells/mm^3[b]	--
Calza et al, 2003[47]	Bezafibrate	--	311(89) cells/uL[b]	--
Calza et al, 2003[47]	Gemfibrozil	--	311(89) cells/uL[b]	--
Calza et al, 2003[47]	Fenofibrate	--	311(89) cells/uL[b]	--
Calza et al, 2003[47]	Fluvastatin	--	311(89) cells/uL[b]	--
Calza et al, 2003[47]	Pravastatin	--	311(89) cells/uL[b]	--
Doser et al, 2002[89]	Control	--	535(63) cells/mL[c]	4.03(3.84) copies/mL[c]
Doser et al, 2002[89]	Fluvastatin	--	535(63) cells/mL[c]	4.03(3.84) copies/mL[c]

Study	Intervention	% Prior AIDS events	Estimate CD4 cell count	Estimate plasma HIV-RNA levels
Fichtenbaum et al, 2010[59]	Fenofibrate	--	358(276-573) cells/mL [a]	78% <50 copies/mL
Fichtenbaum et al, 2010[59]	Pravastatin	--	462(312-690) cells/mL [a]	78% <50 copies/mL
Grandi et al, 2014[88]	Pravastatin	--	598(238) cells/mm^3 [b]	--
Grandi et al, 2014[88]	Ezetimibe + Fenofibrate	--	592(285) cells/mm^3 [b]	--
Hurlimann et al, 2006[91]	Control	34	484(328-633) cells/mL [a]	100% <50 copies/mL
Hurlimann et al, 2006[91]	Pravastatin	34	484(328-633) cells/mL [a]	100% <50 copies/mL
Macallan et al, 2008[92]	Control	--	421(313-615) cells/uL [a]	--
Macallan et al, 2008[92]	Pravastatin	--	421(313-615) cells/uL [a]	--
Mallon et al, 2006[93]	Control	47	442 cells/mL[e]	--
Mallon et al, 2006[93]	Pravastatin	25	502(171-833) cells/mL [a]	--
Masiá et al, 2009[87]	Control	58.3	440(300-737.5) cells/mm^3 [a]	0.5 copies/mL [e]
Masiá et al, 2009[87]	Atorvastatin	43.8	440(300-737.5) cells/mm^3 [a]	0.5 copies/mL [e]
Moyle et al, 2001[94]	Control	--	290(224-405) cells/uL[d]	--
Moyle et al, 2001[94]	Pravastatin	--	407(290-471) cells/uL [d]	--
Sponseller et al, 2013[51]	Pitavastatin	--	648.5(246.8) cells/mm^3 [b]	1.2(0.3) copies/mL [b]
Sponseller et al, 2013[51]	Pravastatin	--	563.7(211.3) cells/mm^3 [b]	1.1(0.2) copies/mL [b]

Note: Control: placebo or standard care/dietary change. (a) Median(Inter Quartile Range), (b) Mean(Standard Deviation), (c) Mean(Standard Error), (d) Mean(95% Confidence Interval), (e) Median

4. Risk of bias assessment

Results from the quality assessment of the 15 included RCTs can be found **in Table 8.** According to the *Cochrane Collaboration's tool for assessing risk of bias* criteria, all included trials are of similar quality. Several trials did not always report details for some components of the Cochrane tool, namely for allocation concealment and incomplete outcome details. Therefore, we were not able to make a definitive decision with regards to the extent of risk of bias for these sections of the Cochrane tool. However, all trials seem to bear a reasonably low risk of bias overall.

Table 8. Risk of bias assessment summary table

Study	Sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective outcome reporting	Other Source of bias
Aberg et al, 2005[58]	UNCLEAR	UNCLEAR	NO (Open-label trial)	YES (Missing data have been imputed using appropriate methods)	UNCLEAR	YES (The study appears to be free of other sources of bias)
Bittar et al, 2012[50]	YES (computer random number generator)	UNCLEAR	NO (Open-label trial)	UNCLEAR	YES (The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way)	YES (The study appears to be free of other sources of bias)

Study	Sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective outcome reporting	Other Source of bias
Bonnet et al, 2007[90]	UNCLEAR	UNCLEAR	NO (Open-label trial)	UNCLEAR	YES (The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way)	YES (The study appears to be free of other sources of bias)
Calza et al, 2008[48]	YES (computer random number generator)	YES (Central allocation)	YES (double-blind trial)	UNCLEAR	UNCLEAR	UNCLEAR
Calza et al, 2005[49]	UNCLEAR	UNCLEAR	NO (Open-label trial)	UNCLEAR	UNCLEAR	YES (The study appears to be free of other sources of bias)

Study	Sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective outcome reporting	Other Source of bias
Calza et al, 2003[47]	YES (computer random number generator)	UNCLEAR	NO (Open-label trial)	YES (Missing outcomes not enough to have a clinically relevant impact on observed effect size)	UNCLEAR	YES (The study appears to be free of other sources of bias)
Doser et al, 2002[89]	YES (computer random number generator)	UNCLEAR	NO (Open-label trial)	UNCLEAR	UNCLEAR	YES (The study appears to be free of other sources of bias)
Fichtenbaum et al, 2010[59]	UNCLEAR	UNCLEAR	YES (double-blind trial)	UNCLEAR	UNCLEAR	UNCLEAR

Study	Sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective outcome reporting	Other Source of bias
Grandi et al, 2014[88]	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	YES (The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way)	YES (The study appears to be free of other sources of bias)
Hurlimann et al, 2006[91]	UNCLEAR	UNCLEAR	YES (double-blind trial)	UNCLEAR	UNCLEAR	UNCLEAR

Study	Sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective outcome reporting	Other Source of bias
Macallan et al, 2008[92]	YES - block randomization (sealed envelopes generated from an external source)	YES - block randomization (sealed envelopes from an external source)	NO (Open-label trial)	YES (Missing data have been imputed using appropriate methods)	YES (The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way)	YES (The study appears to be free of other sources of bias)
Mallon et al, 2006[93]	YES (computer random number generator)	UNCLEAR	YES (double-blind trial)	UNCLEAR	YES (The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way)	YES (The study appears to be free of other sources of bias)

Study	Sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective outcome reporting	Other Source of bias
Masiá et al, 2009[87]	YES (computer random number generator)	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	YES (The study appears to be free of other sources of bias)
Moyle et al, 2001[94]	YES (Random sealed enveloped)	YES (Sealed enveloped by a pharmasicit)	NO (Open-label trial)	UNCLEAR	UNCLEAR	YES (The study appears to be free of other sources of bias)
Sponseller et al, 2013[51]	UNCLEAR	UNCLEAR	YES (Double Blind (Subject, Investigator))	UNCLEAR	UNCLEAR	UNCLEAR

Note: 'YES': low risk of bias; 'NO': High risk of bias; 'UNCLEAR': uncertain risk of bias

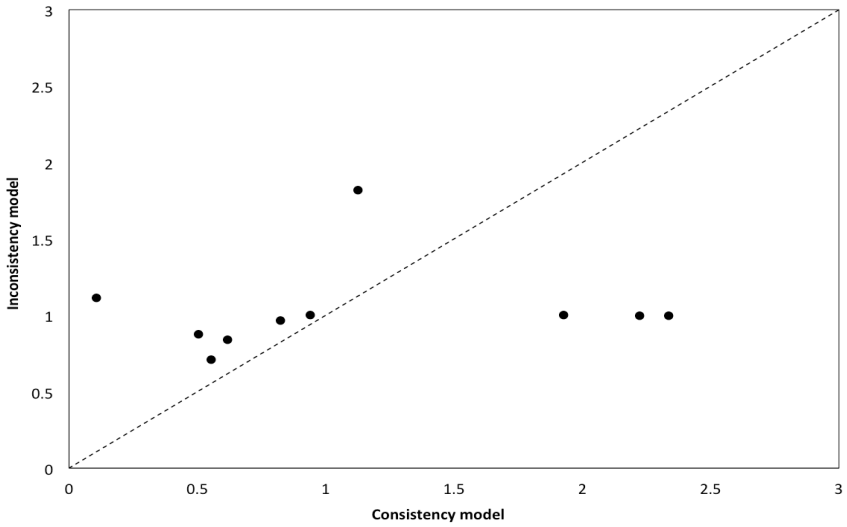
Chapter 2: Network Meta-Analysis

1. Feasibility assessment

a. Consistency

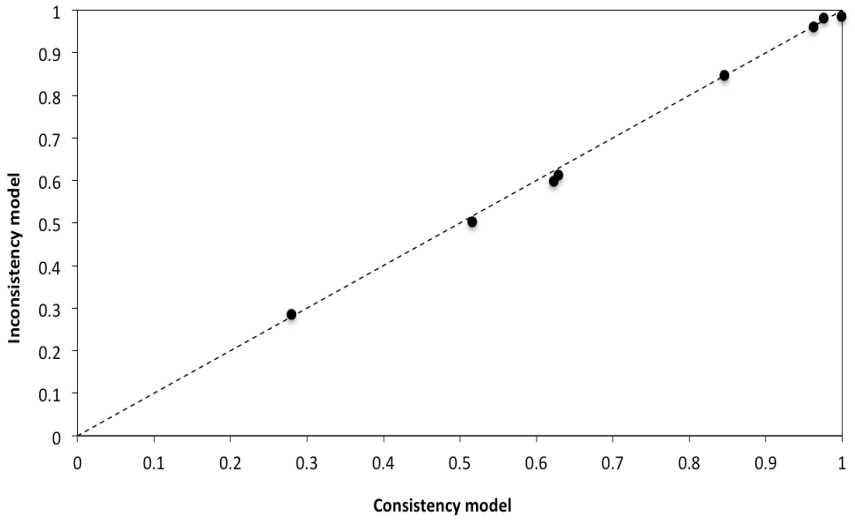
Results from the assessment of inconsistency between direct and indirect evidence are shown in **Figures 4 to 7**. The posterior mean deviance estimates obtained with the consistency model are compared to those obtained with the inconsistency model. Both sets of estimates are based on running 100,000 iterations on three chains after a burn-in period of 50,000 iterations. The inconsistency plot for the total cholesterol network shows that several comparisons had posterior mean deviances that were larger in the consistency model than in the inconsistency model. This suggests that the consistency model did not fit these data points well, and that there must be some inconsistency in the treatment comparisons associated with these data points. The loop identified as having the most inconsistency with regards to treatment effects on total cholesterol was the bezafibrate-control-pravastatin comparison loop. However, no inconsistency was present in the networks evaluating LDL, HDL, and triglycerides outcomes, as the posterior mean deviance estimates were similar for both models. Therefore, overall the inconsistency plots suggest that evidence for inconsistency is only present in some comparisons between treatments for the total cholesterol outcome.

Figure 4. Inconsistency plot- Total cholesterol



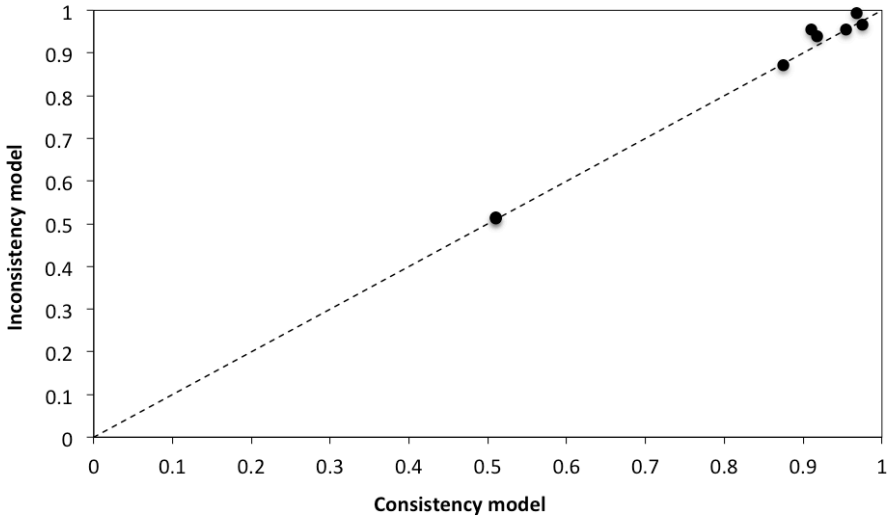
Note: Individual data points represent the posterior mean deviance contributions for the consistency (horizontal axis) and the inconsistency model (vertical axis). The data points are plotted along a line of equality. Inconsistency is detected in some comparisons as some points that do not align have larger deviances in the consistency model

Figure 5. Inconsistency plot- LDL cholesterol



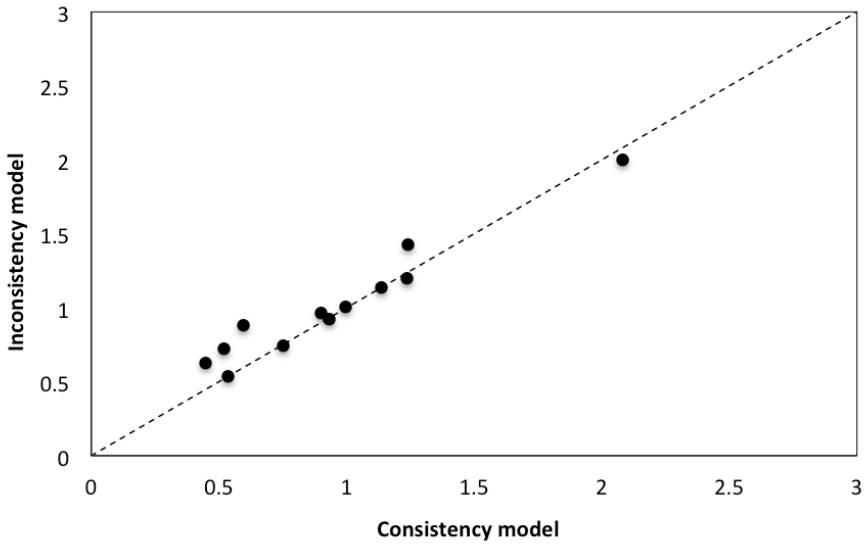
Note: Individual data points represent the posterior mean deviance contributions for the consistency (horizontal axis) and the inconsistency model (vertical axis). The data points are plotted along a line of equality. No inconsistency is detected as data points align.

Figure 6. Inconsistency plot- HDL cholesterol



Note: Individual data points represent the posterior mean deviance contributions for the consistency (horizontal axis) and the inconsistency model (vertical axis). The data points are plotted along a line of equality. No inconsistency is detected as data points align.

Figure 7. Inconsistency plot- Triglycerides



Note: Individual data points represent the posterior mean deviance contributions for the consistency (horizontal axis) and the inconsistency model (vertical axis). The data points are plotted along a line of equality. No inconsistency is detected as data points align.

b. Heterogeneity

The posterior mean of the heterogeneity parameter, τ, can be found in **Tables 9 to 17** for each outcome of interest. It represents the mean posterior distribution for the standard deviation of each true effect size and thus reflects how different the true treatment effects are between studies. Overall, heterogeneity was low to moderate. A larger τ was observed for efficacy outcomes than for safety outcomes, suggesting that more heterogeneity is present in the efficacy analyses than in the safety analyses. It is important to note that efficacy outcomes were evaluated using continuous outcomes while adverse events were typically dichotomous. Continuous values are prone to identify greater heterogeneity as they are more precise than dichotomous data. Heterogeneity was further explored through sensitivity analyses. Based on the results of this assessment, sensitivity analyses were only conducted for total-c and LDL-c outcomes. Their results are presented in **section 12** of this chapter.

Table 9. DIC summary statistics table for assessment of model fit- Total cholesterol

	Dbar	**pD**	**DIC**	**Tau**
Random Effects	270.625	23.326	293.95	2.419
Fixed Effects	270.587	23.071	293.658	--

Note*:* Dbar: Residual deviance (posterior mean); DIC: Deviance Information Criterion; Tau: Heterogeneity parameter (posterior mean)

Table 10. DIC summary statistics table for assessment of model fit- LDL cholesterol

	Dbar	pD	DIC	Tau
Random Effects	231.609	19.386	250.995	2.437
Fixed Effects	231.404	19.166	250.57	--

Note*:* Dbar: Residual deviance (posterior mean); DIC: Deviance Information Criterion; Tau: Heterogeneity parameter (posterior mean)

Table 11. DIC summary statistics table for assessment of model fit- HDL cholesterol

	Dbar	pD	DIC	Tau
Random Effects	131.415	21.279	152.694	1.883
Fixed Effects	132.646	19.866	152.512	--

Note*:* Dbar: Residual deviance (posterior mean); DIC: Deviance Information Criterion; Tau: Heterogeneity parameter (posterior mean)

Table 12. DIC summary statistics table for assessment of model fit- Triglycerides

	Dbar	pD	DIC	Tau
Random Effects	308.394	22.739	331.133	2.444
Fixed Effects	308.072	22.169	330.241	--

Note*:* Dbar: Residual deviance (posterior mean); DIC: Deviance Information Criterion; Tau: Heterogeneity parameter (posterior mean)

Table 13. DIC summary statistics table for assessment of model fit- ALT elevations

	Dbar	pD	DIC	Tau
Random Effects	56.726	10.766	67.493	0.9441
Fixed Effects	55.588	9.219	64.807	--

Note*:* Dbar: Residual deviance (posterior mean); DIC: Deviance Information Criterion; Tau: Heterogeneity parameter (posterior mean)

Table 14. DIC summary statistics table for assessment of model fit- CPK elevations

	Dbar	pD	DIC	Tau
Random Effects	49.063	10.474	59.538	0.9938
Fixed Effects	51.626	8.546	60.173	--

Note*:* Dbar: Residual deviance (posterior mean); DIC: Deviance Information Criterion; Tau: Heterogeneity parameter (posterior mean)

Table 15. DIC summary statistics table for assessment of model fit- GI disturbances

	Dbar	pD	DIC	Tau
Random Effects	29.894	5.804	35.699	1.005
Fixed Effects	29.405	5.11	34.515	--

Note*:* Dbar: Residual deviance (posterior mean); DIC: Deviance Information Criterion; Tau: Heterogeneity parameter (posterior mean)

Table 16. DIC summary statistics table for assessment of model fit- Myalgia, Myositis, Rhabdomyolysis

	Dbar	pD	DIC	Tau
Random Effects	69.634	13.26	82.894	0.8394
Fixed Effects	68.076	10.782	78.858	--

Note*:* Dbar: Residual deviance (posterior mean); DIC: Deviance Information Criterion; Tau: Heterogeneity parameter (posterior mean)

Table 17. DIC summary statistics table for assessment of model fit- Discontinuation due to adverse events

	Dbar	pD	DIC	Tau
Random Effects	106.38	19.807	126.187	0.6084
Fixed Effects	104.643	15.963	120.606	--

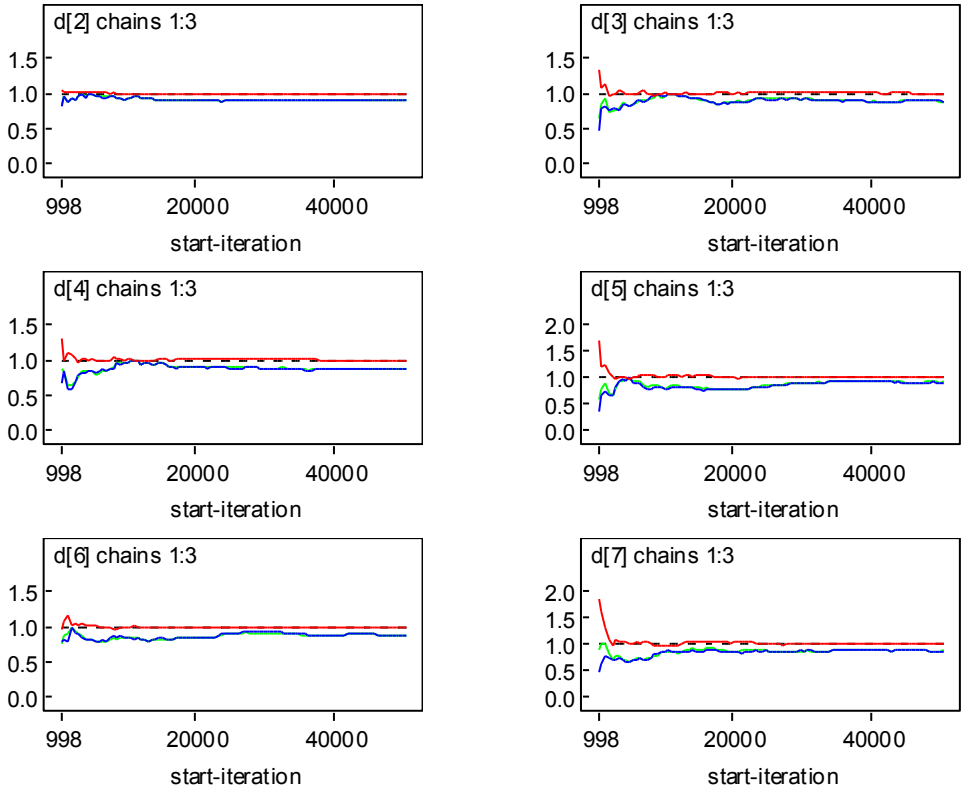
Note*:* Dbar: Residual deviance (posterior mean); DIC: Deviance Information Criterion; Tau: Heterogeneity parameter (posterior mean)

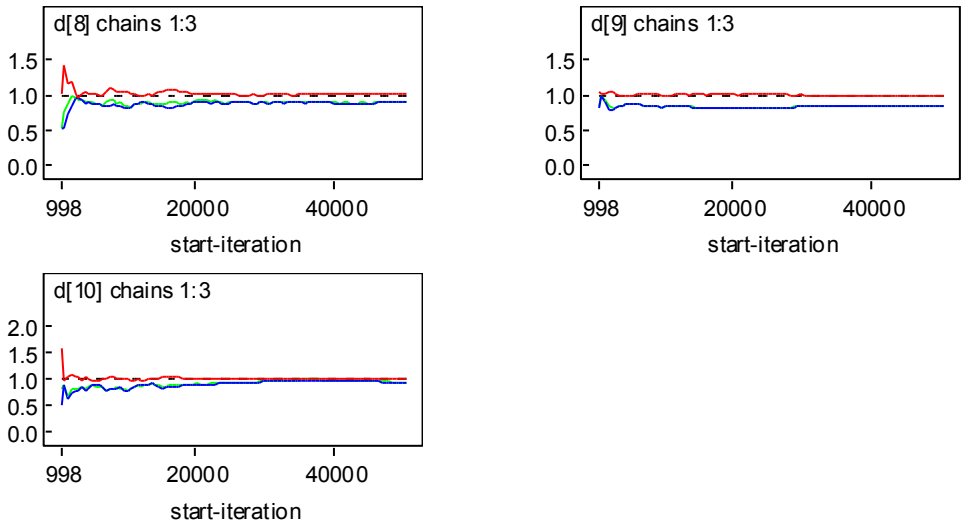
2. Model specification

a. Model convergence

The Gelman-Rubin plots confirmed that the chains converged before 20,000 iterations for each outcome of interest. Convergence for each treatment effect relative to control is depicted by the red line clearly converging to 1 in each plot displayed in **Figures 17 to 25**.

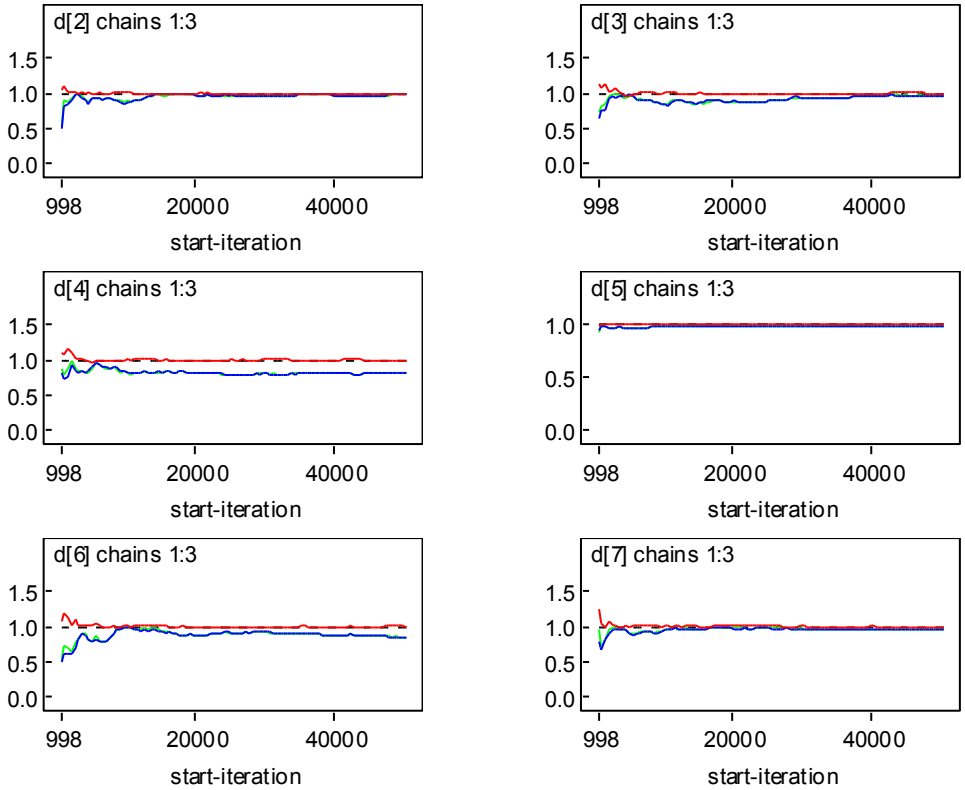
Figure 17. Gelman-Rubin plots for assessment of model convergence- Total cholesterol

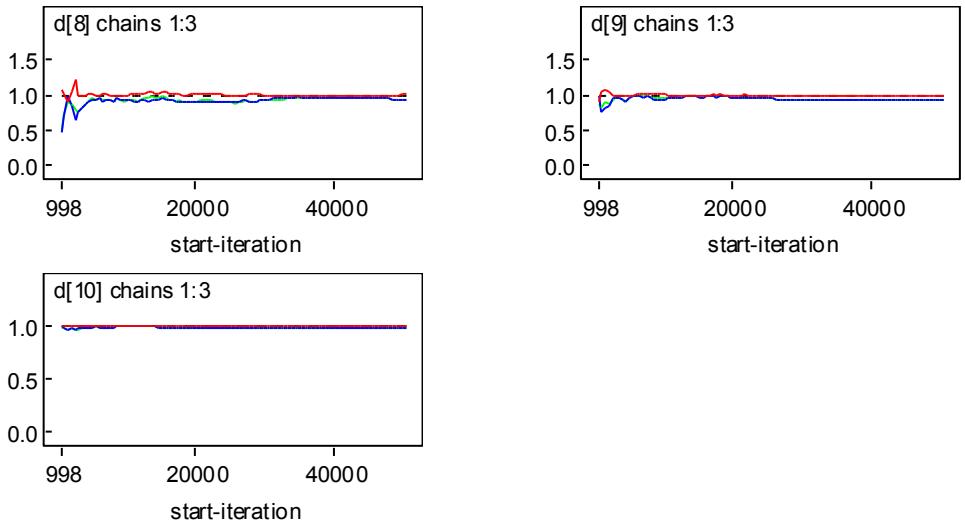




Note: *Blue line* = variation within the chains; *Green line* = variation between the chains; *Red line* = ratio of between to within chain variation. *Convergence* = Red line converges to one and Blue and Green line converge to the same value.

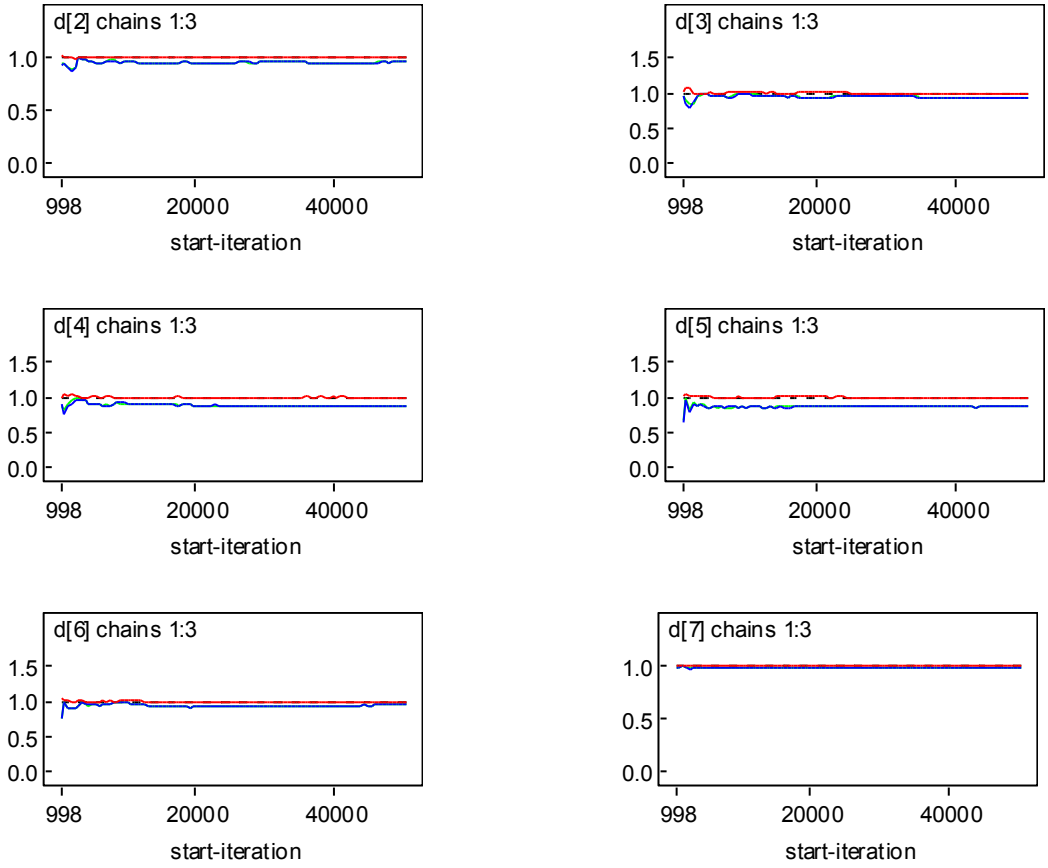
Figure 18. Gelman-Rubin plots for assessment of model convergence- LDL cholesterol

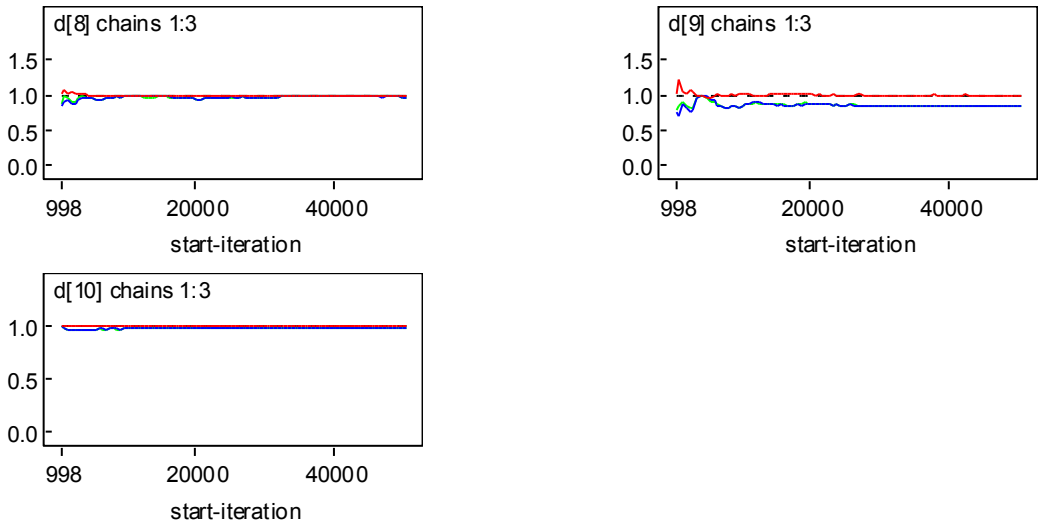




Note: *Blue line* = variation within the chains; *Green line* = variation between the chains; *Red line* = ratio of between to within chain variation. *Convergence* = Red line converges to one and Blue and Green line converge to the same value.

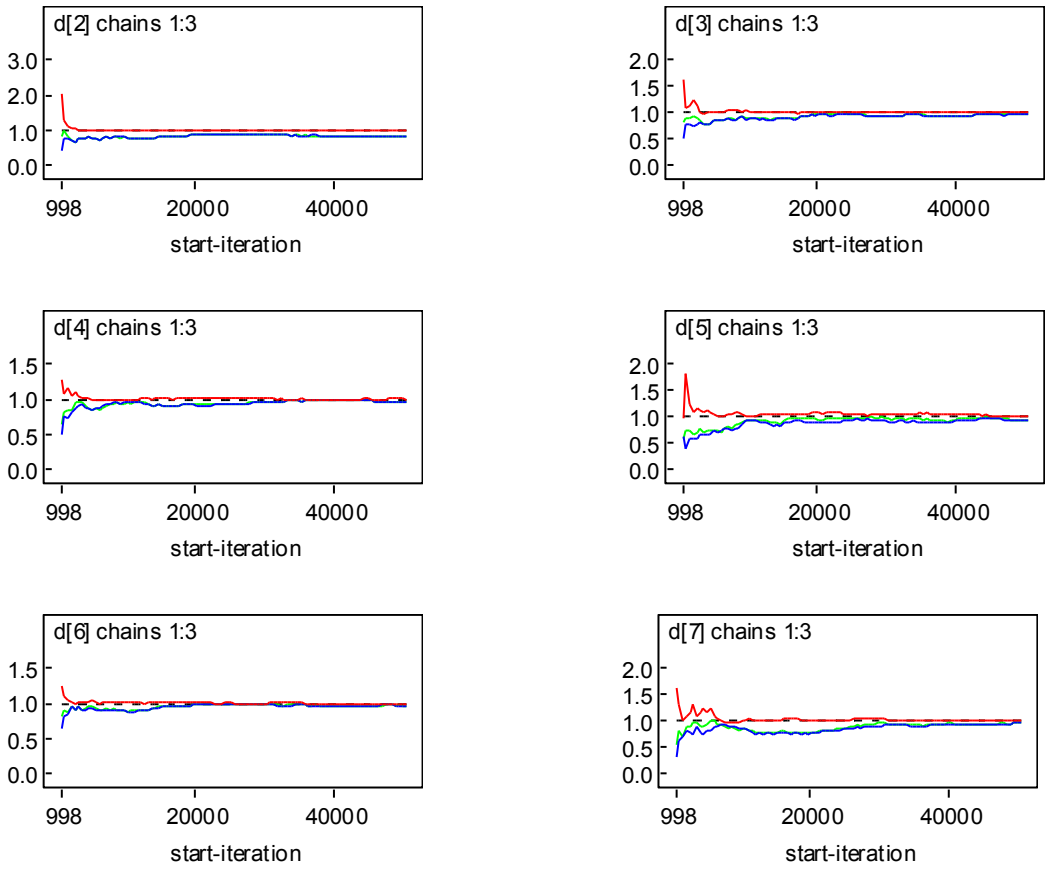
Figure 19. Gelman-Rubin plots for assessment of model convergence- HDL cholesterol

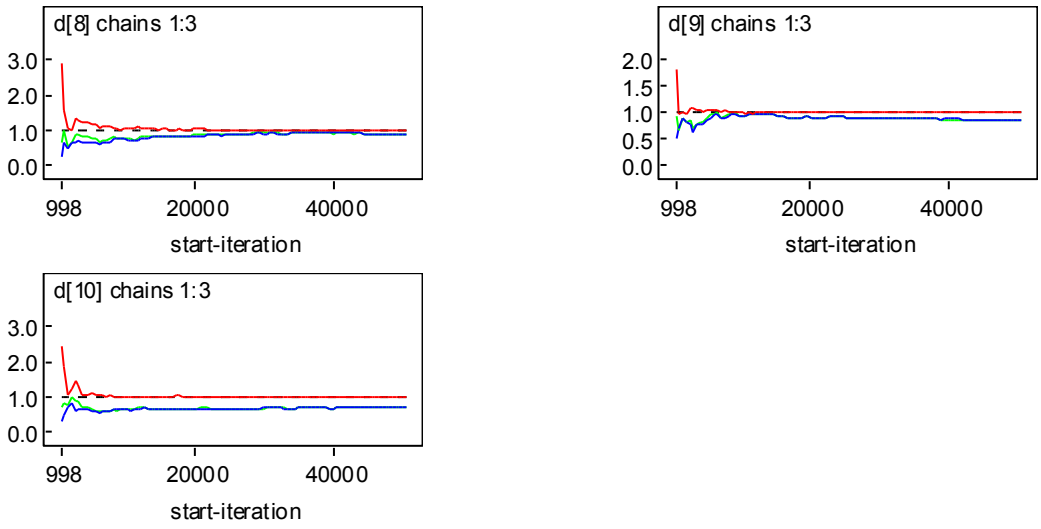




Note: *Blue line* = variation within the chains; *Green line* = variation between the chains; *Red line* = ratio of between to within chain variation. *Convergence* = Red line converges to one and Blue and Green line converge to the same value.

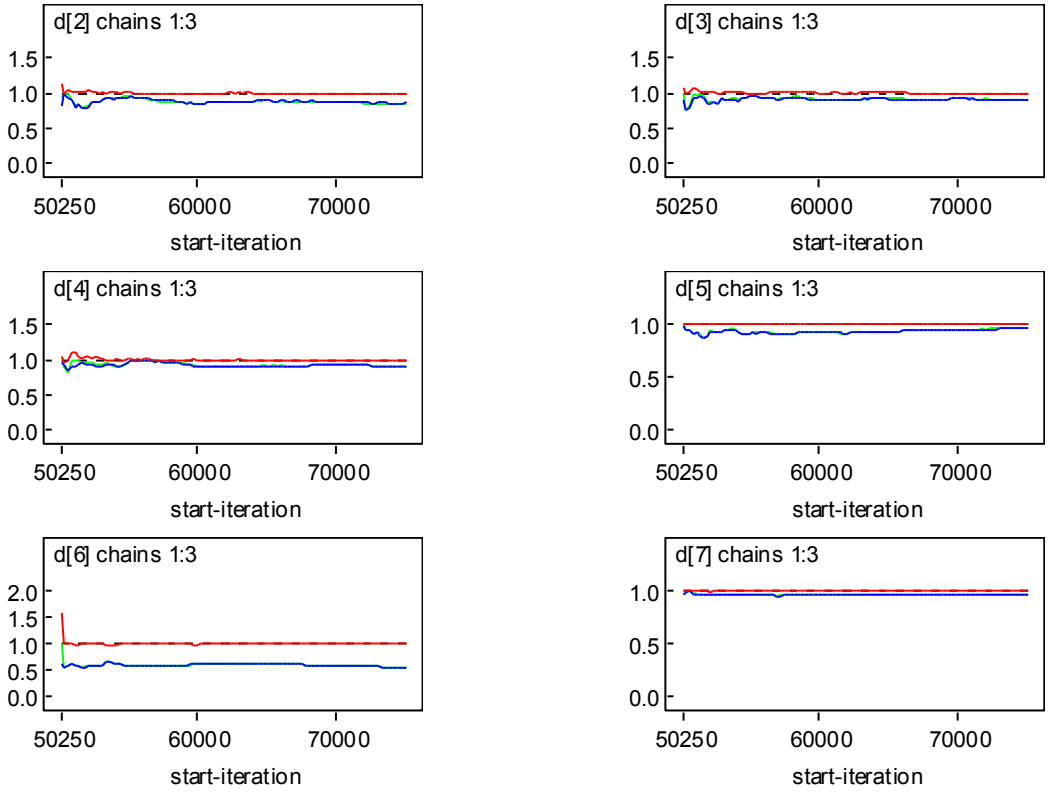
Figure 20. Gelman-Rubin plots for assessment of model convergence- Triglycerides

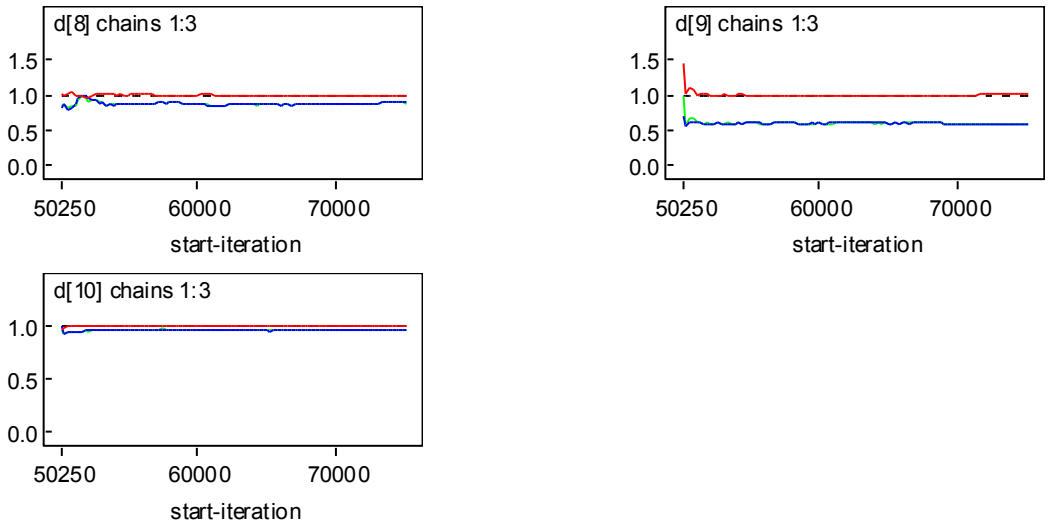




Note: *Blue line* = variation within the chains; *Green line* = variation between the chains; *Red line* = ratio of between to within chain variation. *Convergence* = Red line converges to one and Blue and Green line converge to the same value.

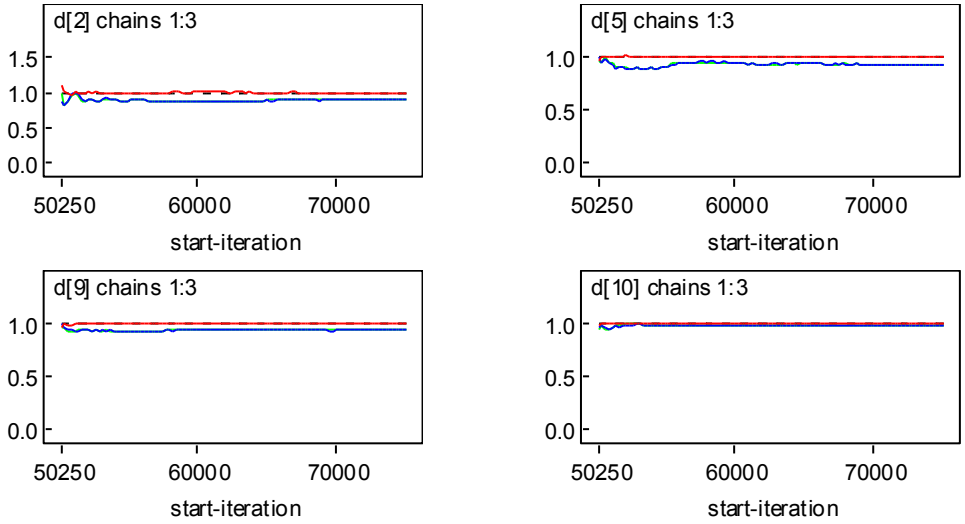
Figure 21. Gelman-Rubin plots for assessment of model convergence- Alanine aminotransferase





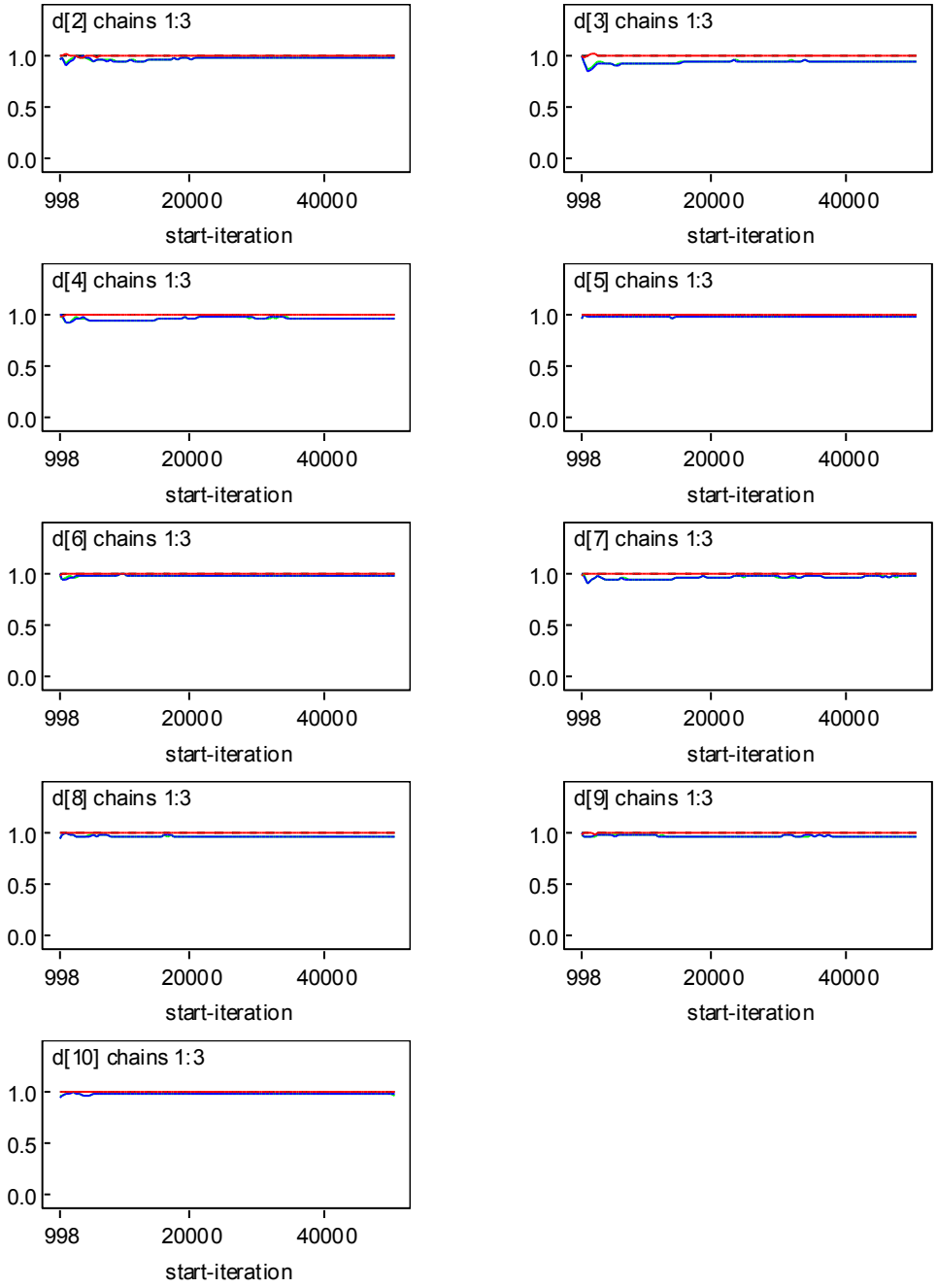
Note: *Blue line* = variation within the chains; *Green line* = variation between the chains; *Red line* = ratio of between to within chain variation. *Convergence* = Red line converges to one and Blue and Green line converge to the same value.

Figure 22. Gelman-Rubin plots for assessment of model convergence- Creatine phosphokinase



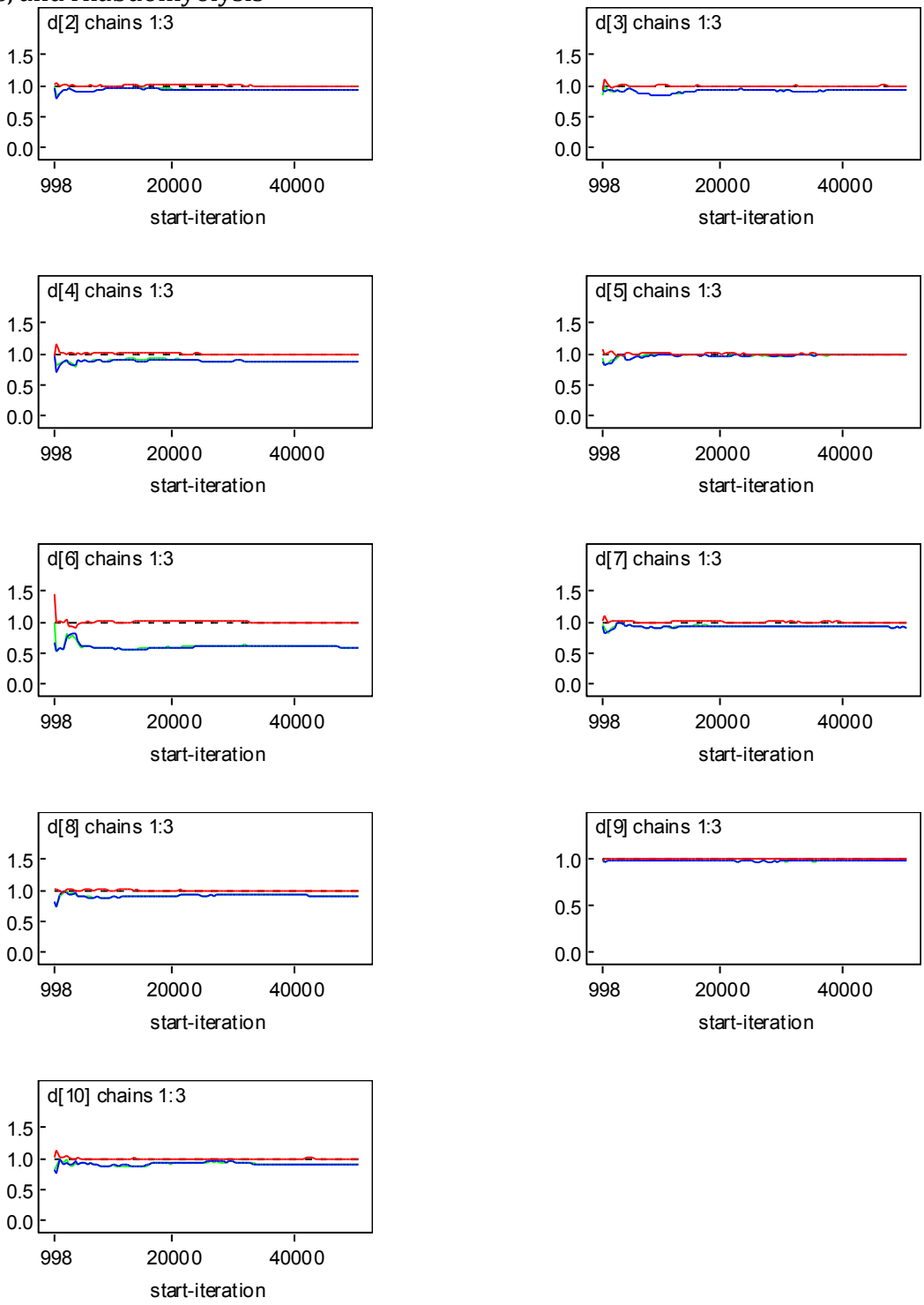
Note: *Blue line* = variation within the chains; *Green line* = variation between the chains; *Red line* = ratio of between to within chain variation. *Convergence* = Red line converges to one and Blue and Green line converge to the same value.

Figure 23. Gelman-Rubin plots for assessment of model convergence- Gastrointestinal disturbances



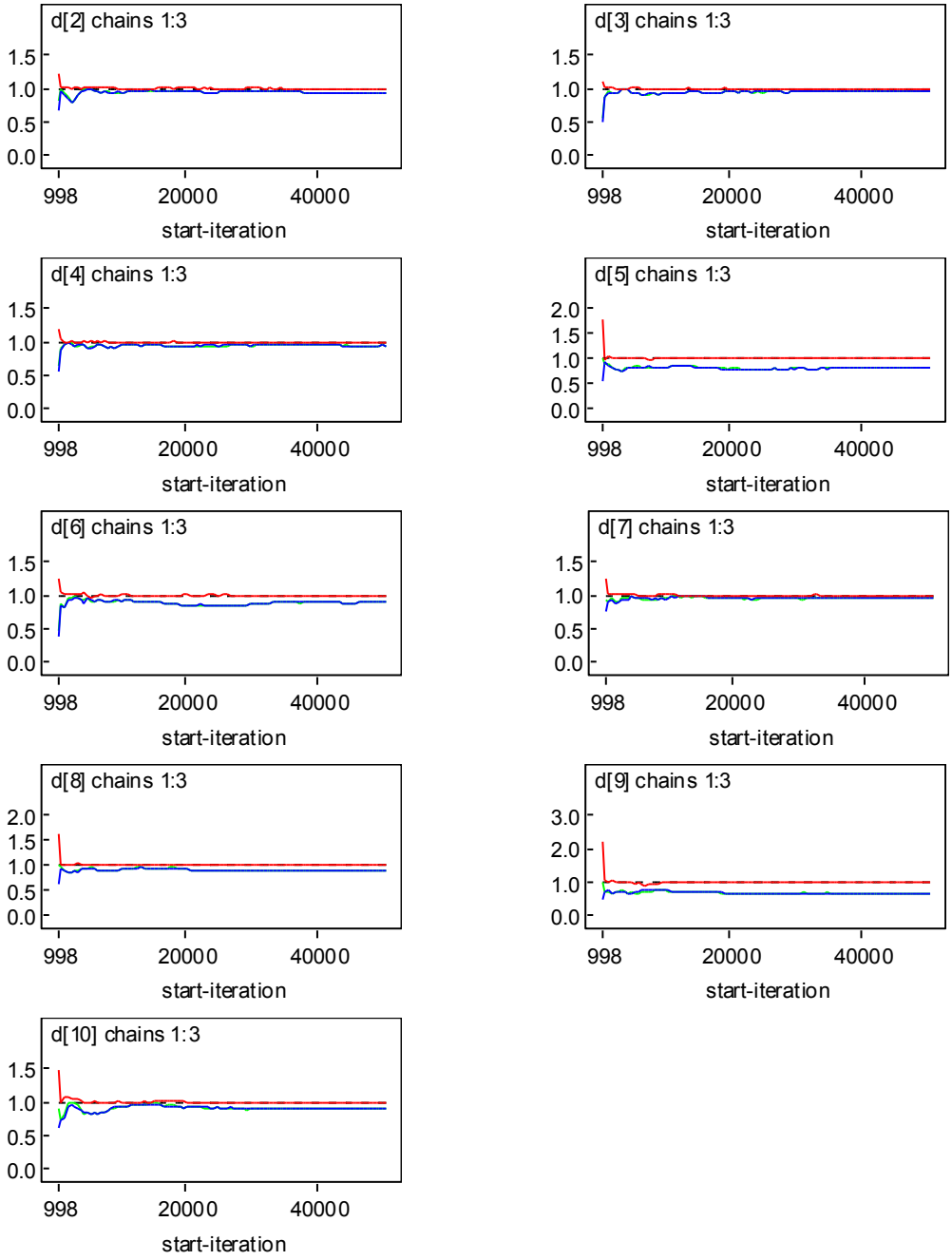
Note: *Blue line* = variation within the chains; *Green line* = variation between the chains; *Red line* = ratio of between to within chain variation. *Convergence* = Red line converges to one and Blue and Green line converge to the same value.

Figure 24. Gelman-Rubin plots for assessment of model convergence- Myalgia, myositis, and rhabdomyolysis



Note: *Blue line* = variation within the chains; *Green line* = variation between the chains; *Red line* = ratio of between to within chain variation. *Convergence* = Red line converges to one and Blue and Green line converge to the same value.

Figure 25. Gelman-Rubin plots for assessment of model convergence- Discontinuations due to adverse events



Note: *Blue line* = variation within the chains; *Green line* = variation between the chains; *Red line* = ratio of between to within chain variation. *Convergence* = Red line converges to one and Blue and Green line converge to the same value.

b. Model fit

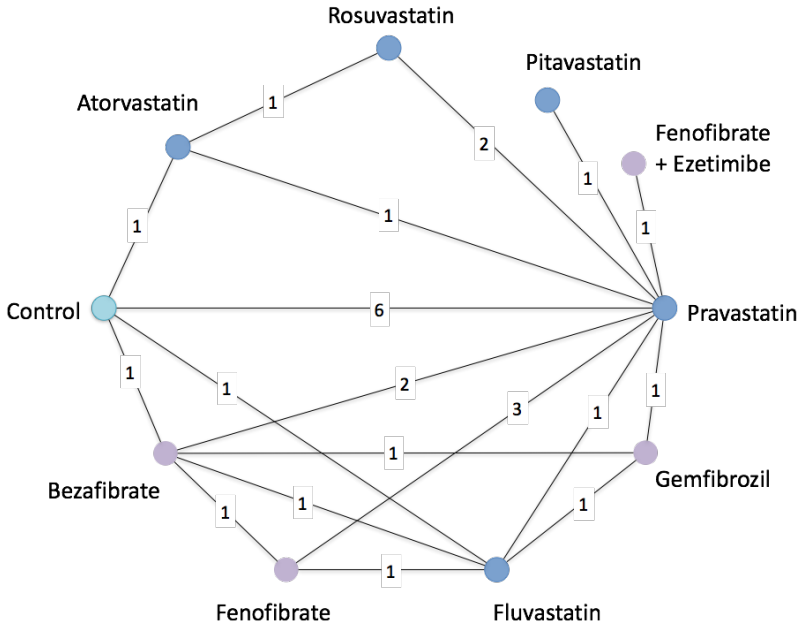
Tables 9 to 17 summarize the results obtained from the model fit assessment (See above in **section 1.b** of this chapter). DIC statistics for both the random and fixed effects models were compared. No considerable differences were seen between the use of random and fixed effects models. However, as NMAs combine both direct and indirect comparisons, we made the conservative assumption that there may be additional and unaccounted for heterogeneity in the network, and opted to only use treatment effect summaries obtained with a random effects method over those obtained with the fixed effect method.

3. Total cholesterol

a. Network of evidence

All 15 trials reported total cholesterol outcome data on a total of 1,218 patients. The network consisted of 5 different statins (Atorvastatin, fluvastatin, pitavastatin, pravastatin, and rosuvastatin), 3 different fibrates (Bezafibrate, fenofibrate, gemfibrozil), and of another lipid-lowering therapy, ezetimibe, given in combination with fenofibrate. All interventions were adequately connected in the network, allowing for indirect comparisons to be made and for each intervention to be compared to every other treatment in the network. Pravastatin appeared in 13 trials and was directly compared to every other intervention in the network, making it the most commonly compared treatment. **Figure 8** shows a geometrical representation of the network of evidence on the outcome for total cholesterol.

Figure 8. Diagram of the network of evidence on the outcome for total cholesterol (15 trials)



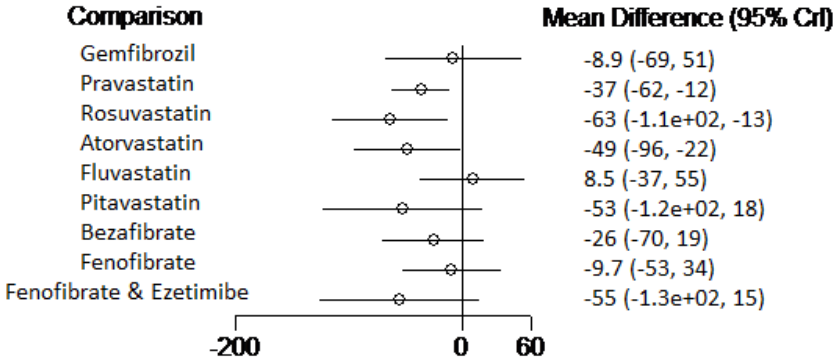
b. Summary statistics

Among different statins, rosuvastatin was found to be the most effective in reducing total cholesterol levels. Although only 2 trials constituted the direct evidence for its use, combining indirect and direct estimates showed that patients on rosuvastatin tend to have the largest average change in total cholesterol from baseline, compared to control (-63 mg/dL, CrI = -110, -13). Analyses revealed that fluvastatin increased total cholesterol levels from baseline by 8.5 mg/dL (CrI = -37, 55), indicating that this statin is the least efficacious in reducing total cholesterol levels.

Among all lipid-lowering interventions, rosuvastatin was still the most effective, and fluvastatin the least effective, in reducing total cholesterol levels from baseline. The combination of fenofibrate & ezetimibe was found to be the second most effective in reducing total cholesterol levels compared to control (Mean

difference = -55, CrI = -130, 15). However, not only is this finding non-significant, but the node corresponding to this intervention was one of the least well connected in the network as only 1 RCT of relatively small size (n=21 patients for the fenofibrate & ezetimibe arm) contributed to the pool of direct evidence for the efficacy of that treatment. Overall, fibrates showed smaller mean differences in total cholesterol levels from baseline than statins compared to control. **Figure 26** is a forest plot displaying the results of analyses for each treatment effect compared to control. **Table 18** provides more detailed summary statistics of these relative treatment effects.

Figure 26. Forest plot: Treatment effects on total cholesterol levels compared to control (15 trials)



Note: CrI = Credible interval. Mean difference values are given in mg/dL. A mean difference > 0 favours control (more reduction from baseline occurred with control than with the active treatment) vs. a mean difference < 0 favours the active treatment (more reduction from baseline with the active treatment).

Table 18. Estimated relative treatment effects and 95%CrI- Total cholesterol levels

	Mean Difference[a]	95% CrI
Vs. Control		
Pravastatin	-37	-62, -12
Rosuvastatin	-63	-110, -13
Atorvastatin	-49	-96, -22
Fluvastatin	8.5	-37, 55
Pitavastatin	-53	-120, 18
Bezafibrate	-26	-70, 19
Fenofibrate	-9.7	-53, 34
Fenofibrate + Ezetimibe	-55	-130, 15
Gemfibrozil	-8.9	-69, 51
Vs. Pravastatin		
Rosuvastatin	-26	-72, 20
Atorvastatin	-12	-59, 34
Fluvastatin	45	-0.30, 91
Pitavastatin	-16	-82, 50
Bezafibrate	11	-31, 54
Fenofibrate	27	-11, 65
Fenofibrate + Ezetimibe	-18	-84, 47
Gemfibrozil	28	-29, 85
Vs. Rosuvastatin		
Atorvastatin	14	-41, 69
Fluvastatin	72	7.9, 140
Pitavastatin	10	-70, 91
Bezafibrate	38	-24, 100
Fenofibrate	54	-5.4, 110
Fenofibrate + Ezetimibe	8.4	-72, 88
Gemfibrozil	54	-18, 130
Vs. Atorvastatin		
Fluvastatin	58	-5.1, 120
Pitavastatin	-3.8	-84, 77
Bezafibrate	23	-38, 85
Fenofibrate	39	-20, 99
Fenofibrate + Ezetimibe	-5.8	-86, 74
Gemfibrozil	40	-32, 110

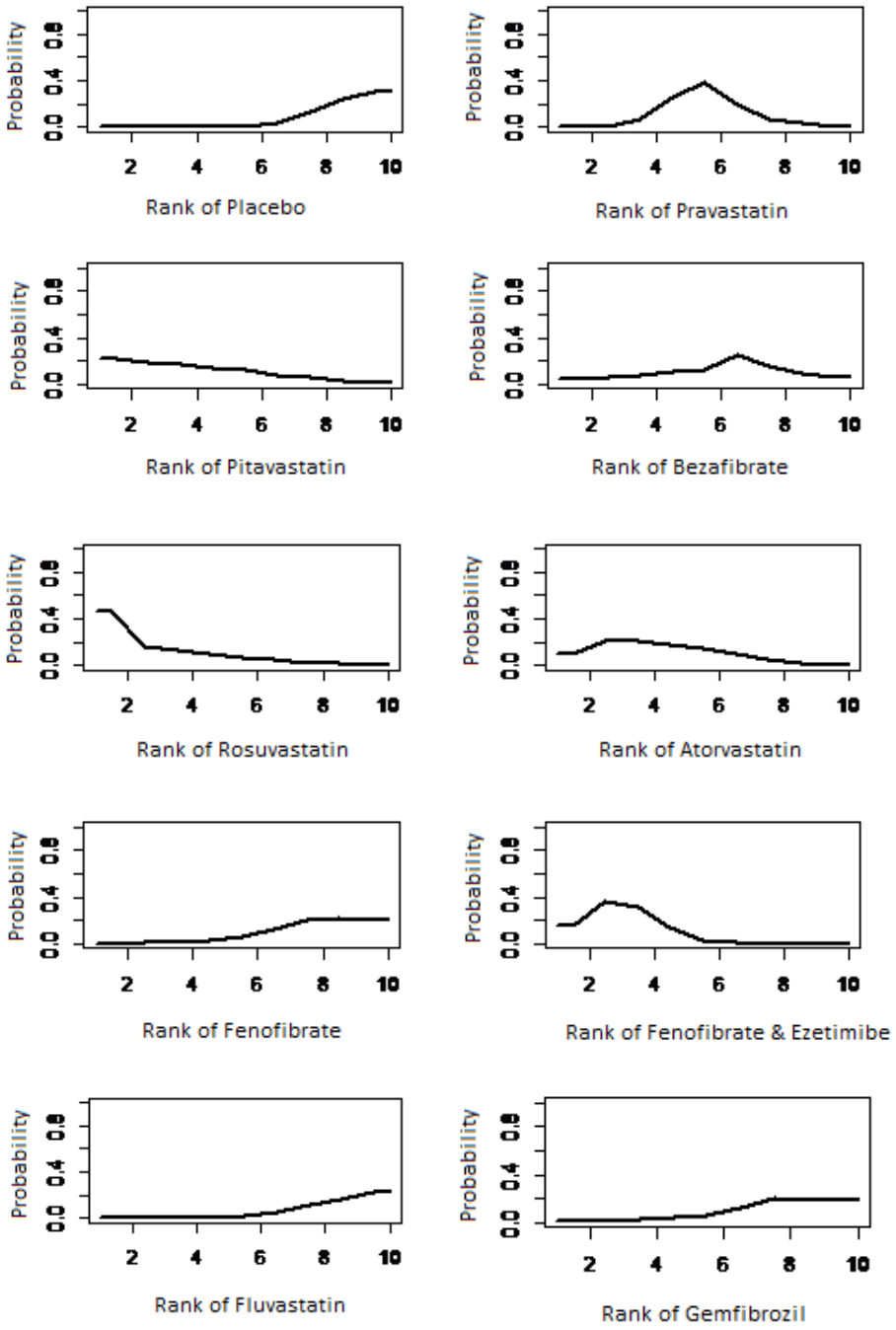
	Mean Difference[a]	95% CrI
Vs. Fluvastatin		
Pitavastatin	-61	-140, 19
Bezafibrate	-34	-88, 19
Fenofibrate	-18	-71, 34
Fenofibrate + Ezetimibe	-63	-140, 16
Gemfibrozil	-17	-80, 45
Vs. Pitavastatin		
Bezafibrate	27	-51, 110
Fenofibrate	43	-33, 120
Fenofibrate + Ezetimibe	-2.0	-95, 91
Gemfibrozil	44	-43, 130
Vs. Bezafibrate		
Fenofibrate	16	-34, 67
Fenofibrate + Ezetimibe	-29	-110, 49
Gemfibrozil	17	-44, 78
Vs. Fenofibrate		
Fenofibrate + Ezetimibe	-45	-120, 30
Gemfibrozil	0.77	-59, 61
Vs. Gemfibrozil		
Fenofibrate + Ezetimibe	-46	-130, 40

Note: Control: placebo or standard care/dietary change. (a) Mean difference < 0 shows an advantage of treatment over the reference. CrI = Credible Interval. Mean differences units = mg/dL

c. Rank probabilities

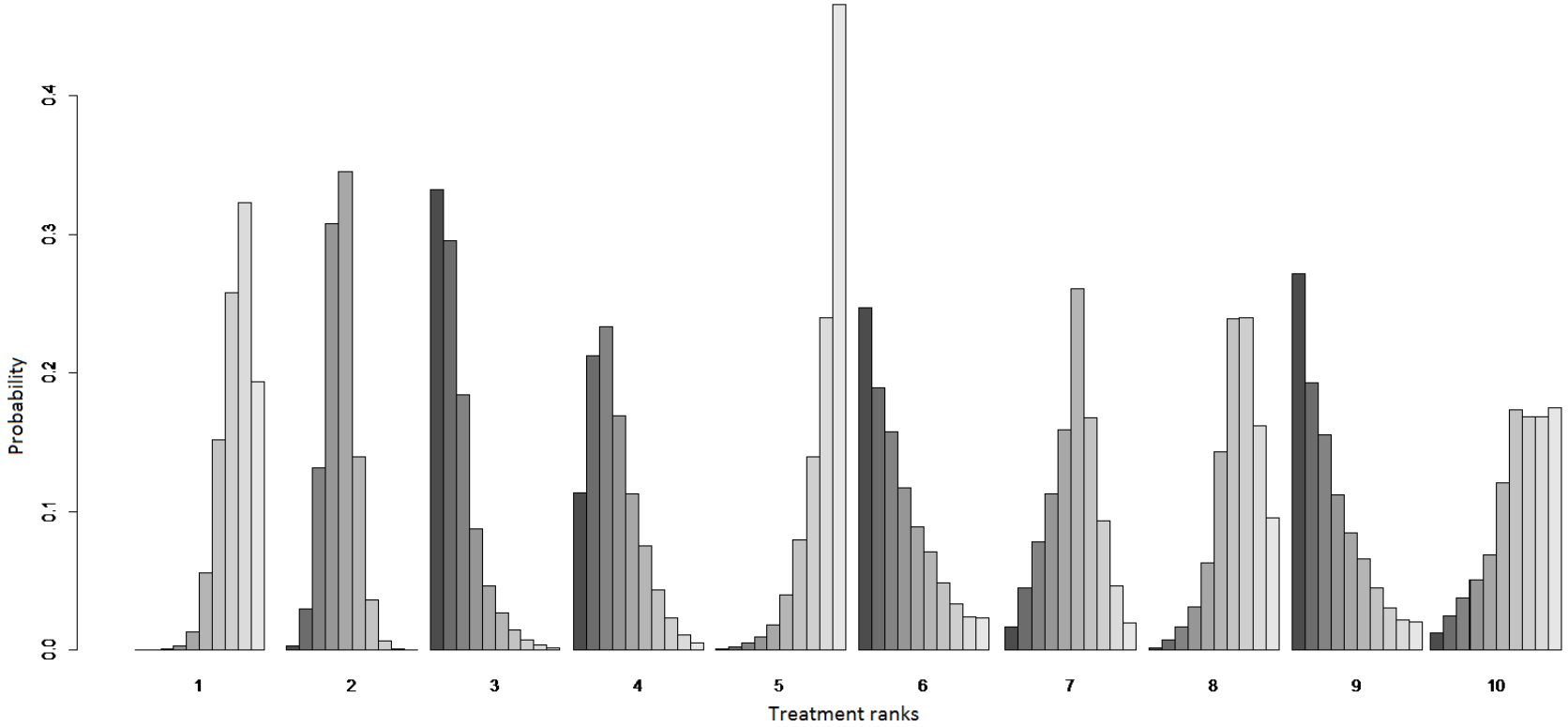
Among all lipid-interventions evaluated, rosuvastatin had the highest probability (33%) of ranking first. In other words, there is a 33% chance that rosuvastatin is the best treatment for reducing total cholesterol levels from baseline. Among statins, pitavastatin had the second highest probability of being the best treatment after rosuvastatin (25%). Among all lipid-lowering interventions, the treatment combination of fenofibrate and ezetimibe had the second highest probability of ranking first (27%). **Figures 35 and 44** are graphical representations of each treatment's probability of taking a specific rank in terms of efficacy at reducing total cholesterol levels.

Figure 35. Rankogram: Graphical representation of the hierarchy of treatments for total cholesterol (15 trials)



Note: Each graph represents each treatment's probability to take a specific rank. Rankings indicate probabilities of being the best treatment, the second best, the third best, and so forth. On the horizontal axis are the 10 possible ranks. On the vertical axis is the probability of a treatment to take a given rank.

Figure 44. Barplots for the ranking probabilities of competing treatments- Total cholesterol



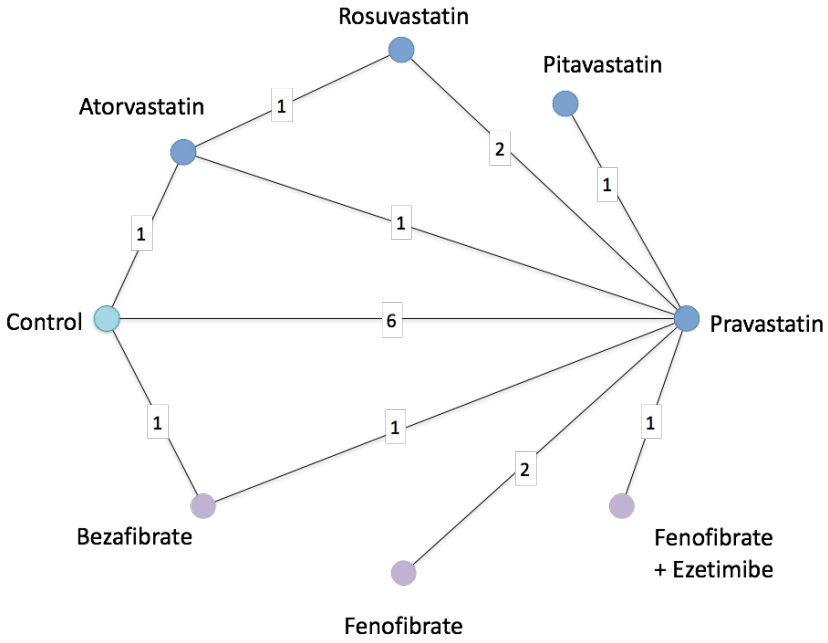
Note: This histogram shows the share of probabilities among competing treatment to rank at a specific place. Numbers correspond to different treatments (1: Control, 2: Pravastatin, 3: Rosuvastatin, 4: Atorvastatin, 5: Fluvastatin, 6: Pitavastatin, 7: Bezafibrate, 8: Fenofibrate, 9: Fenofibrate & Ezetimibe, 10: Gemfibrozil). The size of each bar corresponds to the probability of each treatment to be at a specific rank.

4. LDL cholesterol

a. Network of evidence

Out of the 15 included trials, 13 reported LDL cholesterol outcome data on a total of 1,080 patients. The network consisted of 5 different statins (Atorvastatin, fluvastatin, pitavastatin, pravastatin, and rosuvastatin), and 2 different fibrates (Bezafibrate, fenofibrate). All interventions were adequately connected in the network, allowing for indirect comparisons to be made and for each intervention to be compared to every other treatment in the network. Pravastatin appeared in 13 trials and was directly compared to every other intervention in the network, making it the most commonly compared treatment. **Figure 9** shows a geometrical representation of the network of evidence on the outcome for LDL cholesterol.

Figure 9. Diagram of the network of evidence on the outcome for LDL cholesterol (13 trials)

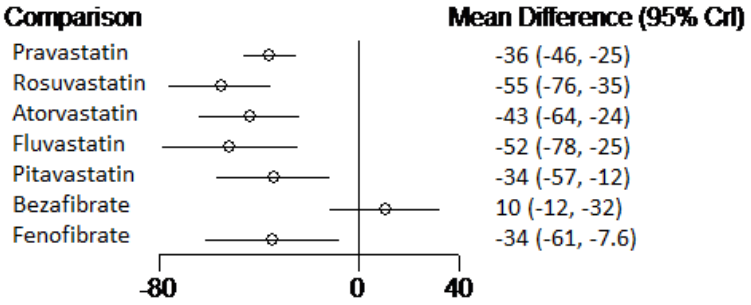


b. Summary statistics

Among different statins, rosuvastatin was found to be the most effective in reducing LDL cholesterol levels. Although, just as for the outcome for total cholesterol, only 2 trials constituted the direct evidence for its use, combining indirect and direct estimates showed that patients on rosuvastatin tend to have the largest average change in LDL cholesterol from baseline, compared to control (-55 mg/dL, CrI = -76, -35). In contrast with the findings for total cholesterol levels, fluvastatin showed the second highest reduction in LDL cholesterol levels from baseline, compared to control (mean difference = -52 mg/dL, CrI = -78, -25).

Among all lipid-lowering interventions, rosuvastatin was the most effective in reducing LDL cholesterol levels from baseline. Overall, fibrates showed the two smallest mean differences in LDL cholesterol levels from baseline compared to control. In fact, analyses show that bezafibrate increased LDL cholesterol levels from baseline by 10 mg/dL (CrI = -12, 32), indicating that it is the least efficacious lipid-lowering therapy in reducing LDL cholesterol levels. **Figure 27** is a forest plot displaying the results of analyses for each treatment effect compared to control. **Table 19** provides more detailed summary statistics of these relative treatment effects.

Figure 27. Forest plot: Treatment effects on LDL cholesterol levels compared to control (13 trials)



Note: CrI = Credible interval. Mean difference values are given in mg/dL. A mean difference > 0 favours control (more reduction from baseline occurred with control than with the active treatment) vs. a mean difference < 0 favours the active treatment (more reduction from baseline with the active treatment).

Table 19. Estimated relative treatment effects and 95%CrI- LDL cholesterol levels

	Mean Difference[a]	95% CrI
Vs. Control		
Pravastatin	-36	-46, -25
Rosuvastatin	-55	-76, -35
Atorvastatin	-43	-64, -24
Fluvastatin	-52	-78, -25
Pitavastatin	-34	-57, -12
Bezafibrate	10	-12, 32
Fenofibrate	-34	-61, -7.6
Vs. Pravastatin		
Rosuvastatin	36	25, 46
Atorvastatin	-19	-38, -1.7
Fluvastatin	-16	-40, 9.1
Pitavastatin	1.7	-21, 24
Bezafibrate	46	-27, 65
Fenofibrate	1.3	-23, 26
Vs. Rosuvastatin		
Atorvastatin	11	-10, 33
Fluvastatin	3.2	-27, 35
Pitavastatin	21	-7.7, 50
Bezafibrate	65	39, 92
Fenofibrate	20	-9.6, 52

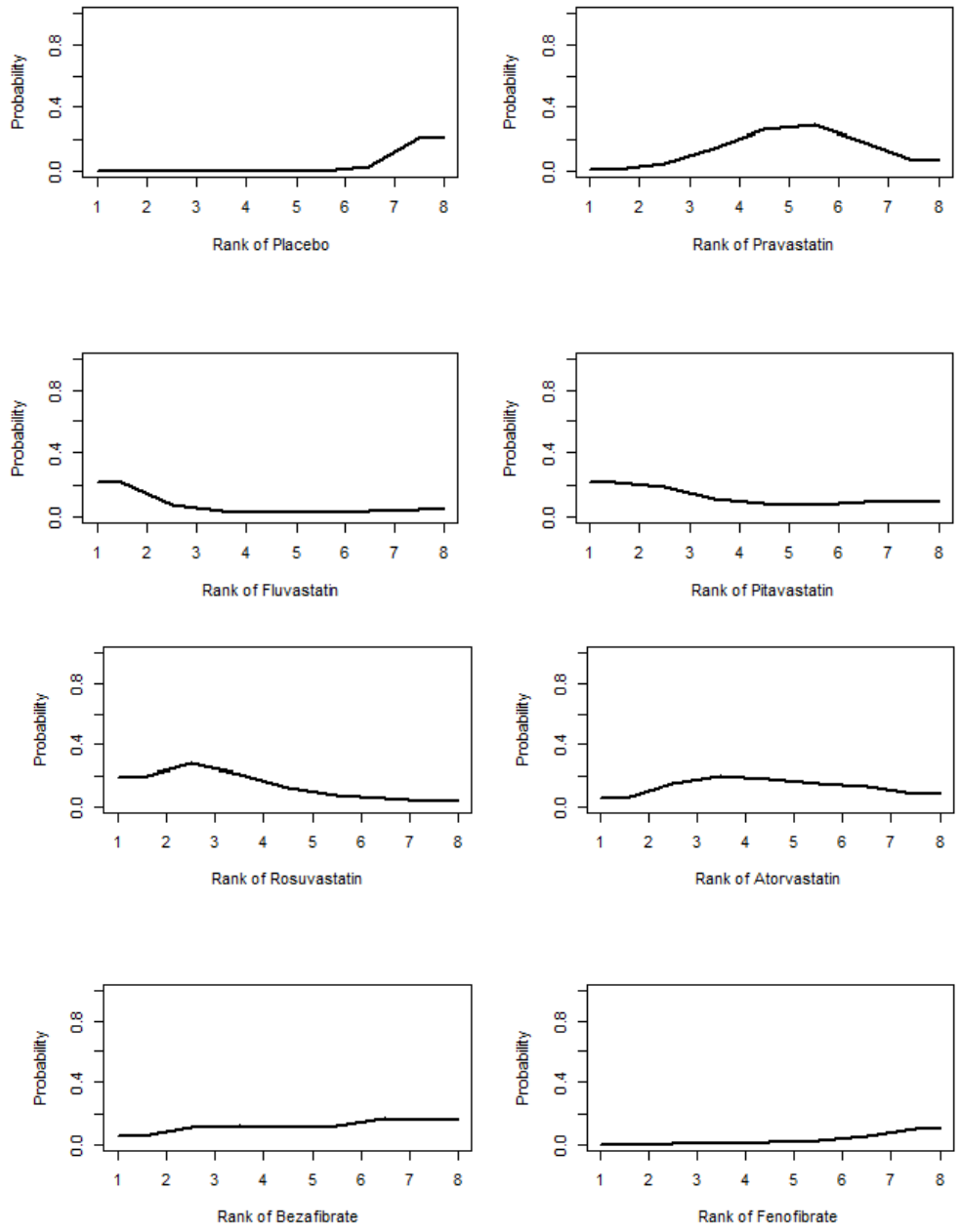
Vs. Atorvastatin		
Fluvastatin	-8.2	-39, 24
Pitavastatin	9.3	-19, 39
Bezafibrate	54	27, 81
Fenofibrate	8.9	-22, 41
Vs. Fluvastatin		
Pitavastatin	9.3	-19, 39
Bezafibrate	54	27, 81
Fenofibrate	8.9	-22, 41
Vs. Pitavastatin		
Bezafibrate	44	15, 74
Fenofibrate	-0.38	-34, 34
Vs. Bezafibrate		
Fenofibrate	-45	-76, -13

Note: Control: placebo or standard care/dietary change. (a) Mean difference < 0 shows an advantage of treatment over the reference. CrI = Credible Interval. Mean differences units = mg/dL

c. Rank probabilities

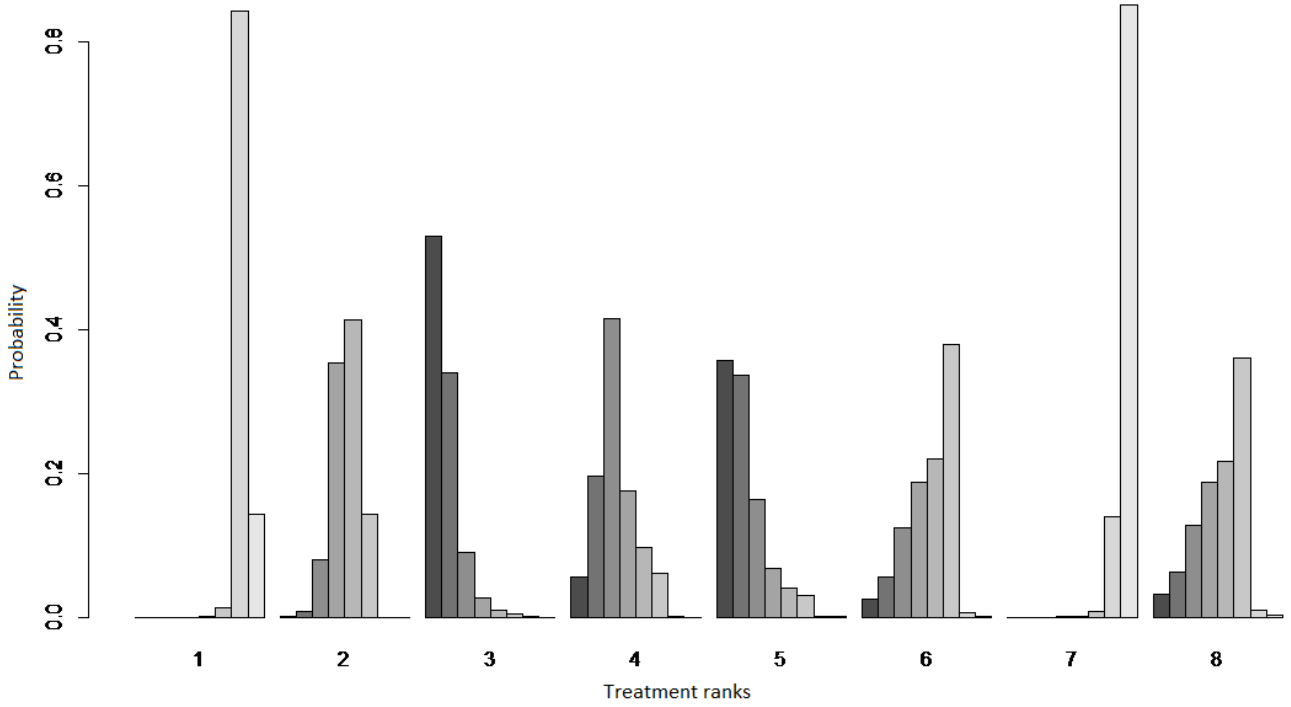
Among all lipid-interventions evaluated, rosuvastatin had the highest probability (53%) of ranking first. These findings mirror those obtained for total cholesterol levels. Among statins, fluvastatin had the second highest probability of being the best treatment after rosuvastatin (36%). Atorvastatin had the highest probability of ranking third in the hierarchy of interventions (42%). Pravastatin had the highest probability ranking 5th, thus of being the least effective statin (21.97%). Among all lipid-lowering interventions, fibrates had the highest probability of occupying the two lowest ranks in the network's treatment hierarchy. Bezafibrate had the highest probability of ranking last (85%). Fenofibrate had the highest probability of ranking second last (36%). **Figures 36 and 45** are graphical representations of each treatment's probability of taking a specific rank in terms of efficacy at reducing LDL cholesterol levels.

Figure 36. Rankogram: Graphical representation of the hierarchy of treatments for LDL cholesterol (13 trials)



Note: Each graph represents each treatment's probability to take a specific rank. Rankings indicate probabilities of being the best treatment, the second best, the third best, and so forth. On the horizontal axis are the 8 possible ranks. On the vertical axis is the probability of a treatment to take a given rank.

Figure 45. Barplots for the ranking probabilities of competing treatments- LDL cholesterol



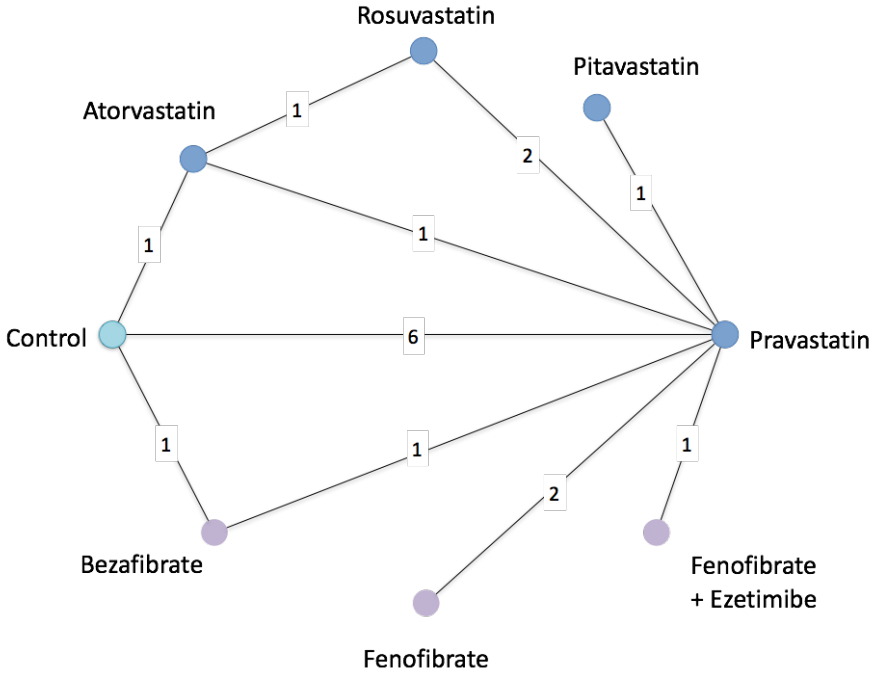
Note: This histogram shows the share of probabilities among competing treatment to rank at a specific place. Numbers correspond to different treatments (1: Control, 2: Pravastatin, 3: Rosuvastatin, 4: Atorvastatin, 5: Fluvastatin, 6: Pitavastatin, 7: Bezafibrate, 8: Fenofibrate). The size of each bar corresponds to the probability of each treatment to be at a specific rank.

5. HDL cholesterol

a. Network of evidence

Out of the 15 included trials, 13 reported HDL cholesterol outcome data on a total of 1,080 patients. The network consisted of 5 different statins (Atorvastatin, fluvastatin, pitavastatin, pravastatin, and rosuvastatin), and 2 different fibrates (Bezafibrate, fenofibrate). All interventions were adequately connected in the network, allowing for indirect comparisons to be made and for each intervention to be compared to every other treatment in the network. Pravastatin appeared in 13 trials and was directly compared to every other intervention in the network, making it the most commonly compared treatment. **Figure 10** shows a geometrical representation of the network of evidence on the outcome for HDL cholesterol.

Figure 10. Diagram of the network of evidence on the outcome for HDL cholesterol (13 trials)



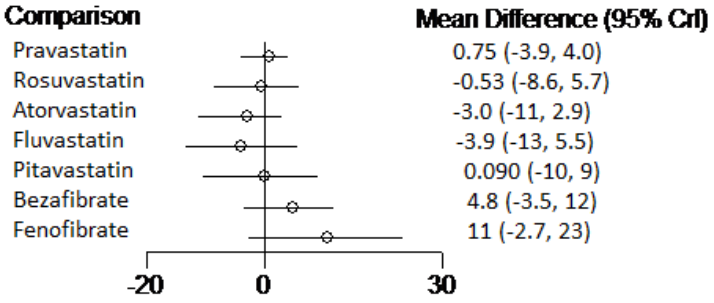
b. Summary statistics

The summary statistics for HDL cholesterol levels should be interpreted with caution. Dyslipidemia is mainly defined by having elevated total and LDL cholesterol levels and abnormally low HDL cholesterol levels.[55] Therefore, in contrast with total and LDL cholesterol levels, interventions providing the greatest reduction in HDL-c concentrations are not considered to be the most efficacious in treating abnormal HDL cholesterol levels. On the contrary, treatments that increase HDL-c levels are considered to be the best options for patients with low baseline HDL-c levels.[55]

Among different statins, pravastatin and pitavastatin were found to be the most effective in treating abnormal HDL cholesterol levels. These two statins were the only ones that did not decrease HDL cholesterol levels from baseline, compared to control (Pravastatin: mean difference = 0.75 mg/dL, CrI = -3.9, 4; Pitavastatin: mean difference = 0.090 mg/dL, CrI = -10, 9). All other statins showed small reductions in HDL cholesterol levels from baseline.

Among all lipid-lowering interventions, fibrates were found to be more effective than statins in increasing HDL cholesterol levels. Fenofibrate increased HDL-c levels from baseline by 11 mg/dL (CrI = -2.7, 23), indicating that it is the most efficacious in increasing HDL cholesterol levels. **Figure 28** is a forest plot displaying the results of analyses for each treatment effect compared to control. **Table 20** provides more detailed summary statistics of these relative treatment effects.

Figure 28. Forest plot: Treatment effects on HDL cholesterol levels compared to control (13 trials)



Note: CrI = Credible interval. Mean difference values are given in mg/dL. A mean difference > 0 favours the active treatment (increase in HDL levels from baseline occurred with the active treatment) vs. a mean difference < 0 favours control (more reduction in HDL levels from baseline with the active treatment).

Table 20. Estimated relative treatment effects and 95%CrI- HDL cholesterol levels

	Mean Difference[a]	95% CrI
Vs. Control		
Pravastatin	0.75	-3.9, 4.0
Rosuvastatin	-0.53	-8.6, 5.7
Atorvastatin	-3.0	-11, 2.9
Fluvastatin	-3.9	-13, 5.5
Pitavastatin	0.090	-10, 9
Bezafibrate	4.8	-3.5, 12
Fenofibrate	11	-2.7, 23
Vs. Pravastatin		
Rosuvastatin	-1.3	-7.7, 4.7
Atorvastatin	-3.7	-11, 2.4
Fluvastatin	-4.6	-14, 6.1
Pitavastatin	-0.71	-9.5, 8.1
Bezafibrate	4.0	-2.4, 10
Fenofibrate	10	-2.3, 22
Vs. Rosuvastatin		
Atorvastatin	-2.4	-10, 4.7
Fluvastatin	-3.3	-14, 9.3
Pitavastatin	0.57	-10, 12
Bezafibrate	5.3	-3.5, 14
Fenofibrate	11	-2.3, 25

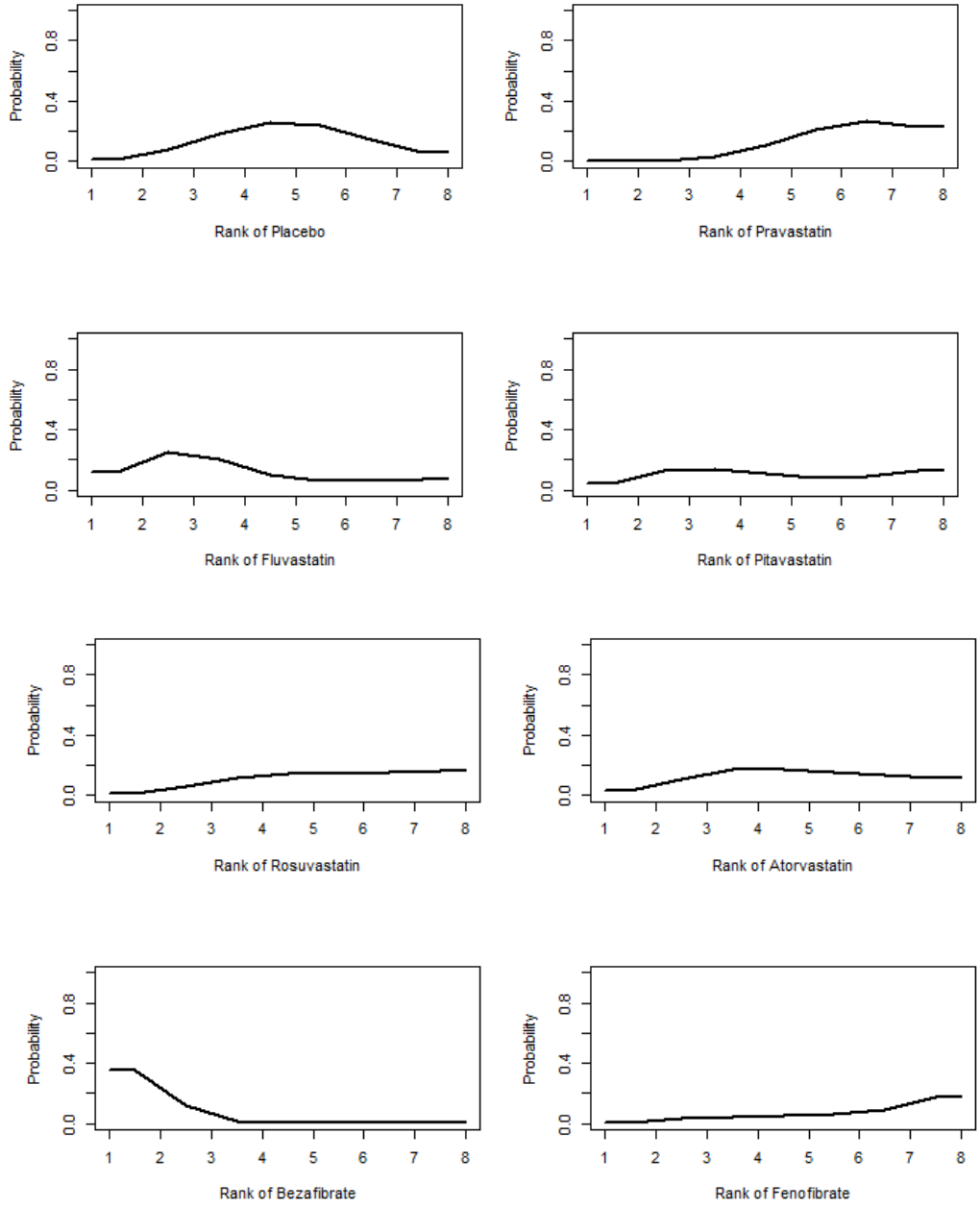
Vs. Atorvastatin		
Fluvastatin	-0.84	-11, 12
Pitavastatin	3	-7.5, 15
Bezafibrate	7.7	-1.0, 17
Fenofibrate	14	0.14, 28
Vs. Fluvastatin		
Pitavastatin	3.9	-10, 17
Bezafibrate	8.6	-4.1, 20
Fenofibrate	15	-1.9, 30
Vs. Pitavastatin		
Bezafibrate	4.7	-6.2, 16
Fenofibrate	11	-4.3, 26
Vs. Bezafibrate		
Fenofibrate	6	-7.9, 20

Note: Control: placebo or standard care/dietary change. (a) Mean difference < 0 shows an advantage of treatment over the reference. CrI = Credible Interval. Mean differences units = mg/dL

c. Rank probabilities

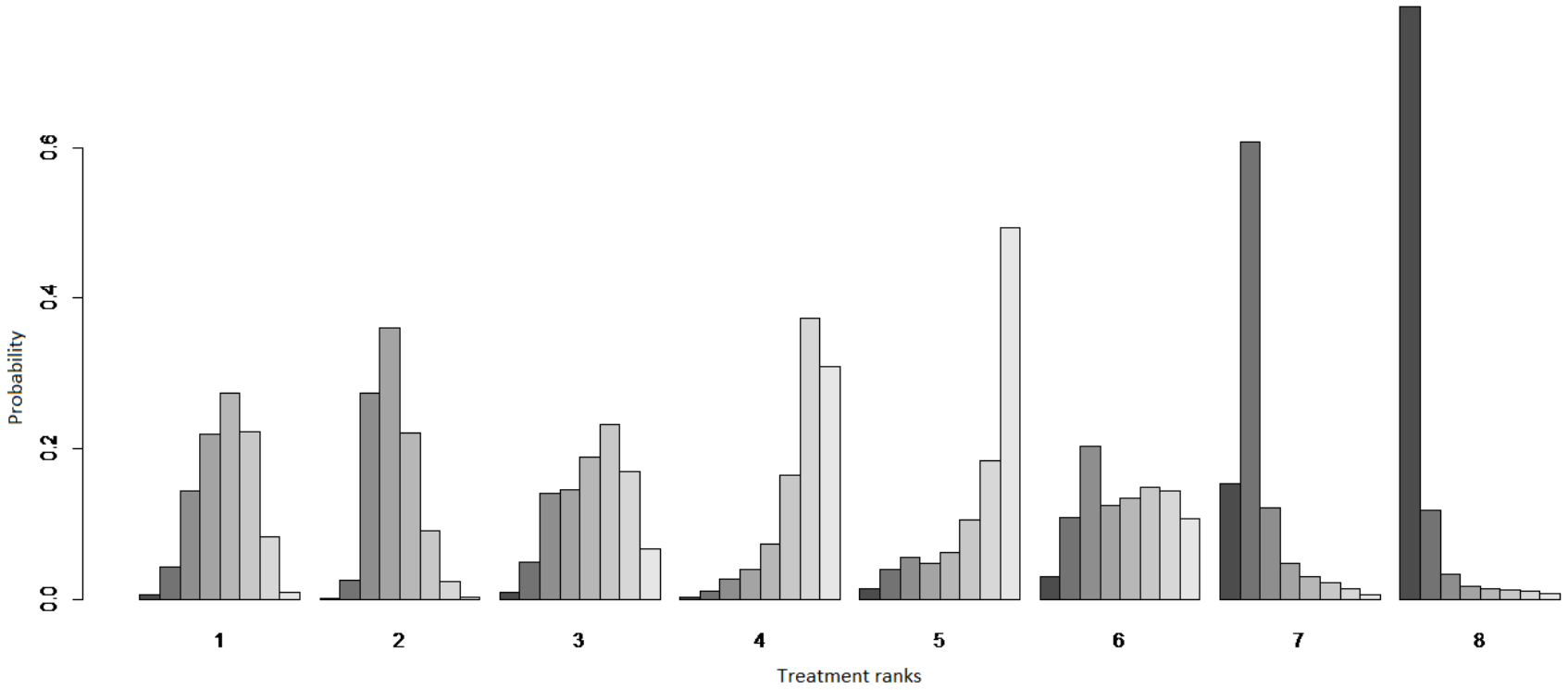
Among all lipid-interventions evaluated, fenofibrate had the highest probability (44%) of ranking first. **Figures 37 and 46** are graphical representations of each treatment's probability of taking a specific rank in terms of efficacy at increasing HDL cholesterol levels.

Figure 37. Rankogram: Graphical representation of the hierarchy of treatments for HDL cholesterol (13 trials)



Note: Each graph represents each treatment's probability to take a specific rank. Rankings indicate probabilities of being the best treatment, the second best, the third best, and so forth. On the horizontal axis are the 8 possible ranks. On the vertical axis is the probability of a treatment to take a given rank.

Figure 46. Barplots for the ranking probabilities of competing treatments- HDL cholesterol



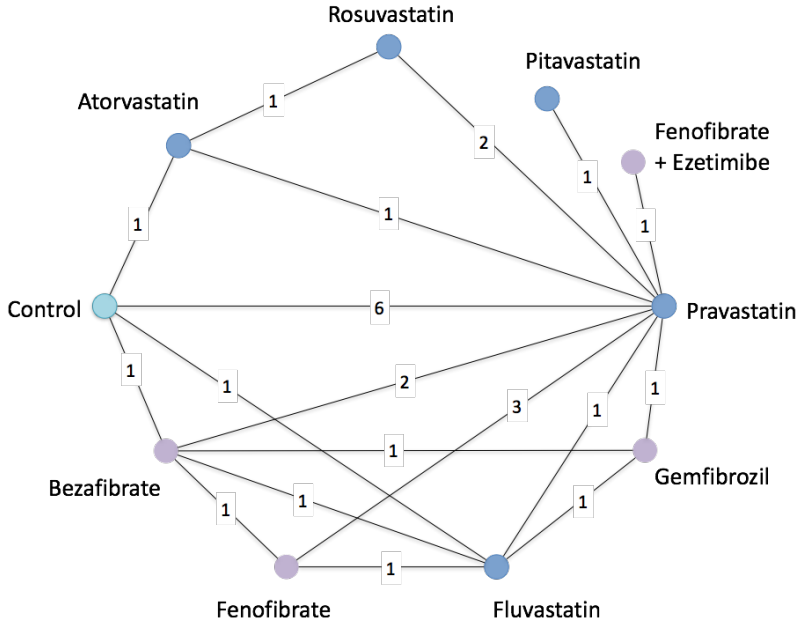
Note: This histogram shows the share of probabilities among competing treatment to rank at a specific place. Numbers correspond to different treatments (1: Control, 2: Pravastatin, 3: Rosuvastatin, 4: Atorvastatin, 5: Fluvastatin, 6: Pitavastatin, 7: Bezafibrate, 8: Fenofibrate). The size of each bar corresponds to the probability of each treatment to be at a specific rank.

6. Triglycerides

a. Network of evidence

All 15 trials reported triglyceride levels outcome data on a total of 1,218 patients. The network consisted of 5 different statins (Atorvastatin, fluvastatin, pitavastatin, pravastatin, and rosuvastatin), 3 different fibrates (Bezafibrate, fenofibrate, gemfibrozil), and of another lipid-lowering therapy, Ezetimibe, given in combination with Fenofibrate. All interventions were adequately connected in the network, allowing for indirect comparisons to be made and for each intervention to be compared to every other treatment in the network. Pravastatin appeared in 13 trials and was directly compared to every other intervention in the network, making it the most commonly compared treatment. **Figure 11** shows a geometrical representation of the network of evidence on the outcome for triglycerides.

Figure 11. Diagram of the network of evidence on the outcome for triglycerides (15 trials)

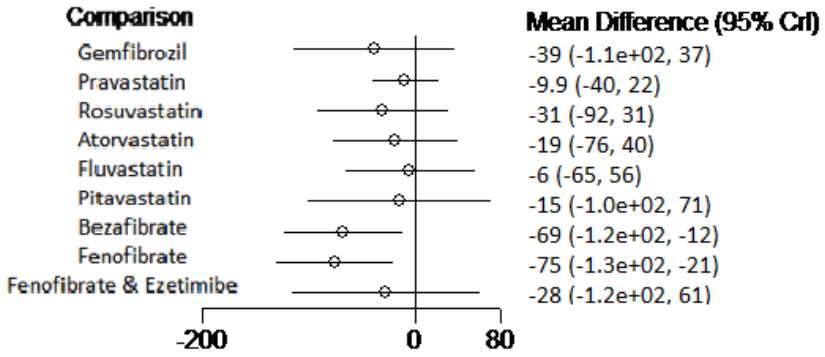


b. Summary statistics

Among different statins, rosuvastatin was found to be the most effective in reducing triglyceride levels. Although only 2 trials constituted the direct evidence for its use, combining indirect and direct estimates showed that patients on rosuvastatin tend to have the largest average change in triglyceride levels from baseline, compared to control (-31 mg/dL, CrI = -92, 31). Fluvastatin was found to be the least efficacious statin in reducing triglyceride levels from baseline (Mean difference = -6 mg/dL, CrI = -65, 56). These findings mirror those obtained for total cholesterol levels.

Among all lipid-lowering interventions, fibrates were found to be more effective than statins in reducing triglyceride levels. Fenofibrate showed the greatest reduction in triglyceride levels from baseline, compared to control (-75 mg/dL, CrI = -130, -21), and bezafibrate showed the second greatest reduction (-69 mg/dL, CrI = -120, -12). **Figure 29** is a forest plot displaying the results of analyses for each treatment effect compared to control. **Table 21** provides more detailed summary statistics of these relative treatment effects.

Figure 29. Forest plot: Treatment effects on triglyceride levels compared to control (15 trials)



Note: CrI = Credible interval. Mean difference values are given in mg/dL. A mean difference > 0 favours control (more reduction from baseline occurred with control than with the active treatment) vs. a mean difference < 0 favours the active treatment (more reduction from baseline with the active treatment).

Table 21. Estimated relative treatment effects and 95%CrI- Triglyceride levels

	Mean Difference[a]	95% CrI
Vs. Control		
Pravastatin	-9.9	-40, 22
Rosuvastatin	-31	-92, 31
Atorvastatin	-19	-76, 40
Fluvastatin	-6	-65, 56
Pitavastatin	-15	-100, 71
Bezafibrate	-69	-120, -12
Fenofibrate	-75	-130, -21
Fenofibrate + Ezetimibe	-28	-120, 61
Gemfibrozil	-39	-110, 37
Vs. Pravastatin		
Rosuvastatin	-21	-77, 35
Atorvastatin	-8.9	-66, 48
Fluvastatin	3.8	-54, 65
Pitavastatin	-5.2	-86, 75
Bezafibrate	-59	-110, -5.5
Fenofibrate	-65	-110, -19
Fenofibrate + Ezetimibe	-18	-100, 64
Gemfibrozil	-29	-100, 43

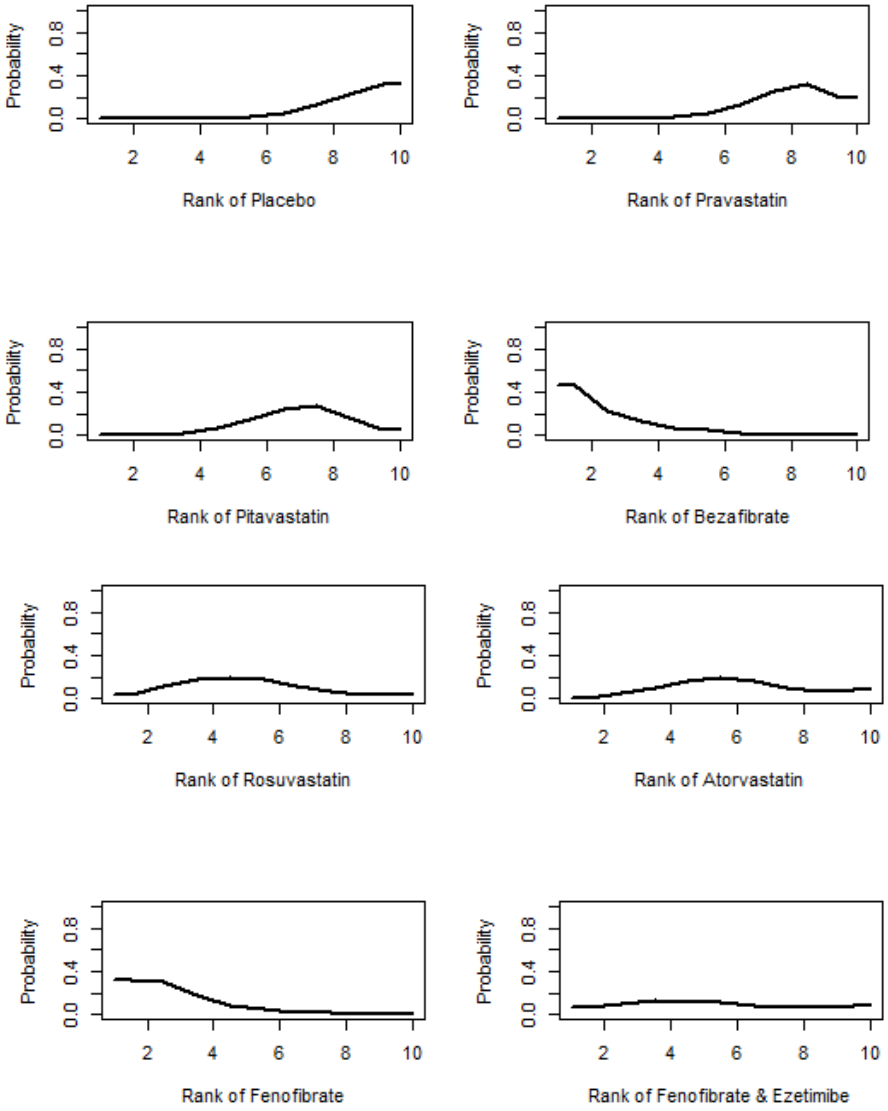
Vs. Rosuvastatin		
Atorvastatin	12	-55, 80
Fluvastatin	25	-55, 110
Pitavastatin	16	-82, 110
Bezafibrate	-38	-110, 39
Fenofibrate	-44	-120, 28
Fenofibrate + Ezetimibe	3	-97, 100
Gemfibrozil	-8.3	-98, 82
Vs. Atorvastatin		
Fluvastatin	13	-66, 94
Pitavastatin	3.8	-95, 100
Bezafibrate	-50	-130, 26
Fenofibrate	-56	-130, 16
Fenofibrate + Ezetimibe	-9.2	-110, 91
Gemfibrozil	-20	-110, 70
Vs. Fluvastatin		
Pitavastatin	-9.1	-110, 90
Bezafibrate	-62	-130, 4.6
Fenofibrate	-69	-140, -4.4
Fenofibrate + Ezetimibe	-22	-120, 79
Gemfibrozil	-33	-110, 44
Vs. Pitavastatin		
Bezafibrate	-53	-150, 44
Fenofibrate	-60	-150, 33
Fenofibrate + Ezetimibe	-13	-130, 100
Gemfibrozil	-24	-130, 84
Vs. Bezafibrate		
Fenofibrate	-6.5	-71, 55
Fenofibrate + Ezetimibe	40	-57, 140
Gemfibrozil	29	-47, 110
Vs. Fenofibrate		
Fenofibrate + Ezetimibe	47	-47, 140
Gemfibrozil	36	-38, 110
Vs. Gemfibrozil		
Fenofibrate + Ezetimibe	11	-98, 120

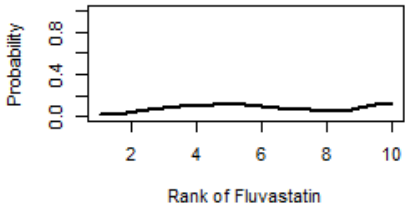
Note: Control: placebo or standard care/dietary change. (a) Mean difference < 0 shows an advantage of treatment over the reference. CrI = Credible Interval. Mean differences units = mg/dL

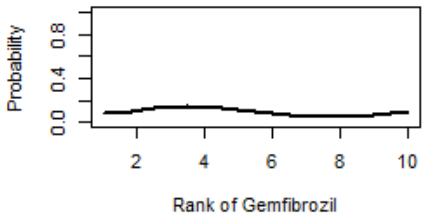
c. Rank probabilities

Among all lipid-interventions evaluated, fibrates had the highest probability of taking the highest ranks in the network's hierarchy of intervention. **Figures 38 and 47** are graphical representations of each treatment's probability of taking a specific rank in terms of efficacy at reducing triglyceride levels.

Figure 38. Rankogram: Graphical representation of the hierarchy of treatments for triglycerides (15 trials)

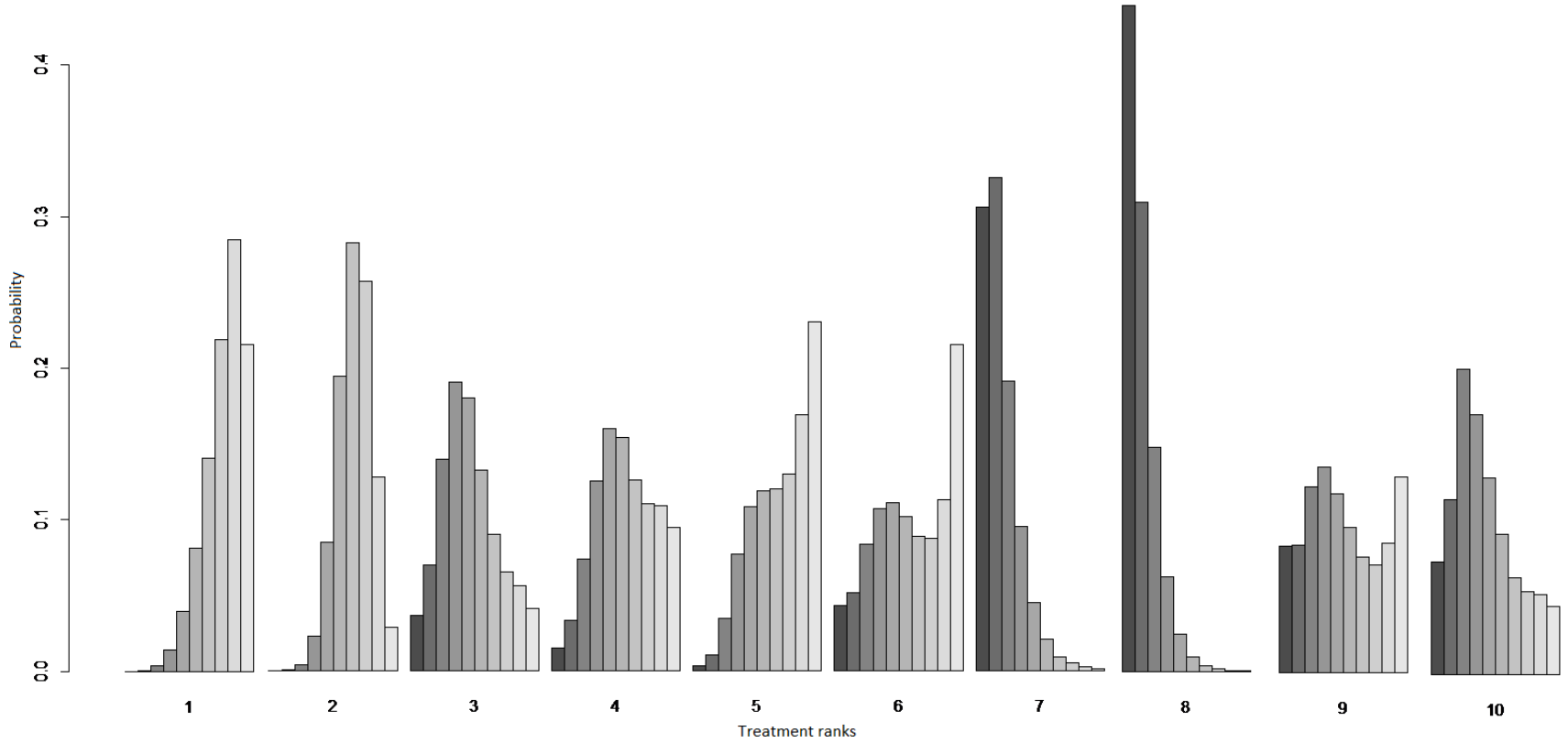






Note: Each graph represents each treatment's probability to take a specific rank. Rankings indicate probabilities of being the best treatment, the second best, the third best, and so forth. On the horizontal axis are the 10 possible ranks. On the vertical axis is the probability of a treatment to take a given rank.

Figure 47. Barplots for the ranking probabilities of competing treatments- Triglycerides



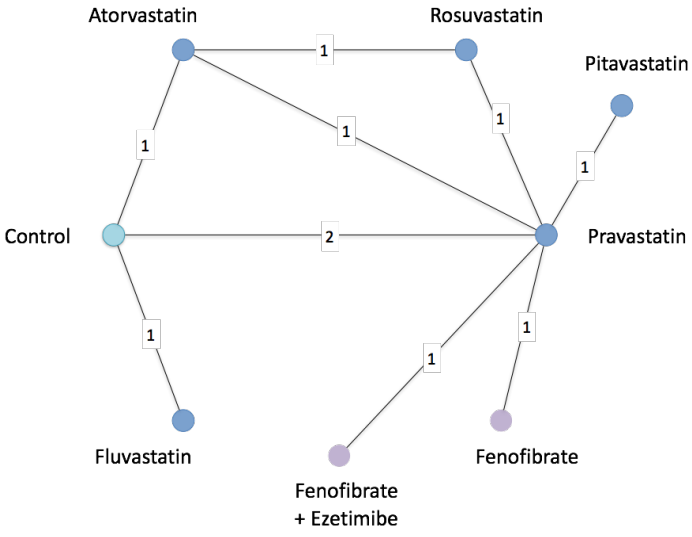
Note: This histogram shows the share of probabilities among competing treatment to rank at a specific place. Numbers correspond to different treatments (1: Control, 2: Pravastatin, 3: Rosuvastatin, 4: Atorvastatin, 5: Fluvastatin, 6: Pitavastatin, 7: Bezafibrate, 8: Fenofibrate, 9: Fenofibrate & Ezetimibe, 10: Gemfibrozil). The size of each bar corresponds to the probability of each treatment to be at a specific rank.

7. Alanine aminotransferase (ALT) elevations

a. Network of evidence

Eight trials out of fifteen reported data on ALT level elevations. The 8 trials included a total of 344 patients, of whom 8 had ALT elevations. The network consisted of 5 different statins (Atorvastatin, fluvastatin, pitavastatin, pravastatin, and rosuvastatin), 1 fibrate (Fenofibrate), and of another lipid-lowering therapy, Ezetimibe, given in combination with Fenofibrate. All interventions were adequately connected in the network, allowing for indirect comparisons to be made and for each intervention to be compared to every other treatment in the network. Pravastatin appeared in 6 trials and was compared to all other interventions in the network but one, making it the most commonly compared treatment. **Figure 12** shows a geometrical representation of the network of evidence on the outcome for ALT.

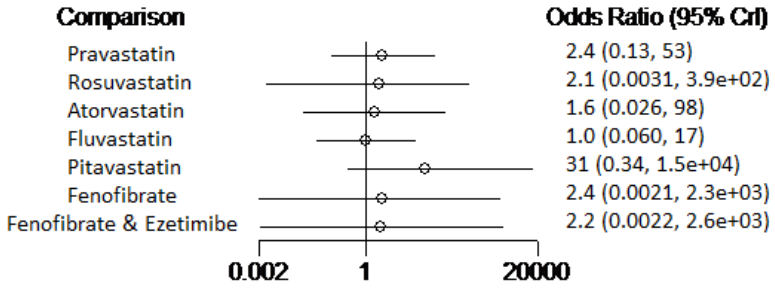
Figure 12. Diagram of the network of evidence for the alanine aminotransferase outcome (8 trials)



b. Summary statistics

No major differences from control were found among the lipid-lowering interventions evaluated with respect to elevation of ALT levels. Only pitavastatin was associated with higher odds of being associated with elevated ALT levels. However, there were too few numbers of adverse events reported to increase the certainty in the relative treatment effect estimates obtained- as indicated by the wide credible intervals associated with the odds ratios for each comparison. **Figure 30** is a forest plot displaying the results of analyses for each treatment effect compared to control. **Table 22** provides the odds ratios and their associated credible intervals for all relative treatment effect estimates obtained.

Figure 30. Forest plot: Treatment effects on freedom from elevations in ALT levels compared to control (8 trials)



Note: CrI = Credible interval. An Odds Ratio > 1 favours control (fewer adverse events occurred with control than with the active treatment) vs. an Odds Ratio < 1 favours the active treatment (fewer adverse events occurred with the active treatment).

Table 22. Estimates of ORs and 95%CrI from network meta-analysis of alanine aminotransferase endpoint

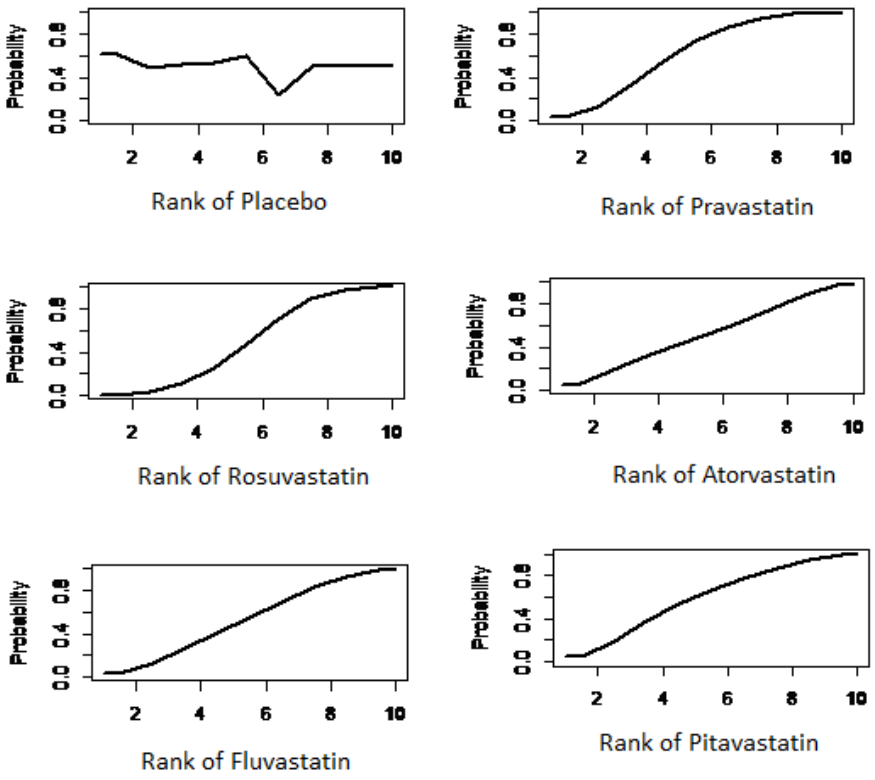
Control	0.42 (0.019, 7.5)	0.46 (0.0019, 350)	0.63 (0.0076, 40)	0.99 (0.059, 17)	0.031 (0.00055, 2.9)	0.44 (0.00051, 440)	0.42 (0.00034, 480)
2.4 (0.13, 53)	**Pravastatin**	1.2 (0.0086, 550)	1.5 (0.022, 110)	2.4 (0.044, 160)	0.084 (0.00026, 2.1)	1.1 (0.0022, 660)	1.0 (0.0018, 720)
2.1 (0.0031, 3900)	0.89 (0.0018, 100)	**Rosuvastatin**	1.3 (0.0022, 300)	2.1 (0.0018, 1000)	0.059 (0.00017, 27)	0.92 (0.00016, 3200)	0.85 (0.00019, 3000)
1.6 (0.026, 98)	0.66 (0.010, 36)	0.80 (0.0036, 410)	**Atorvastatin**	1.6 (0.011, 280)	0.048 (0.00051, 11)	0.73 (0.00044, 1700)	0.69 (0.00038, 1300)
1.0 (0.060, 17)	0.41 (0.0065, 23)	0.47 (0.00095, 580)	0.63 (0.0036, 91)	**Fluvastatin**	0.030 (0.00033, 6.4)	0.46 (0.00030, 830)	0.42 (0.00023, 810)
31 (0.34, 15000)	11 (0.46, 2900)	19 (0.037, 64000)	21 (0.091, 20000)	34 (0.16, 31000)	**Pitavastatin**	16 (0.012, 67000)	15 (0.011, 72000)
2.4 (0.0021, 2300)	0.97 (0.0015, 510)	1.2 (0.00039, 6200)	1.4 (0.00060, 2300)	2.2 (0.0012, 3400)	0.062 (0.00015, 83)	**Fenofibrate**	0.91 (0.00014, 6000)
2.2 (0.0022, 2600)	0.92 (0.0016, 580)	1.2 (0.00032, 6200)	1.5 (0.00078, 2600)	2.4 (0.0012, 4400)	0.068 (0.00014, 87)	1.1 (0.00017, 6900)	**Fenofibrate & Ezetimibe**

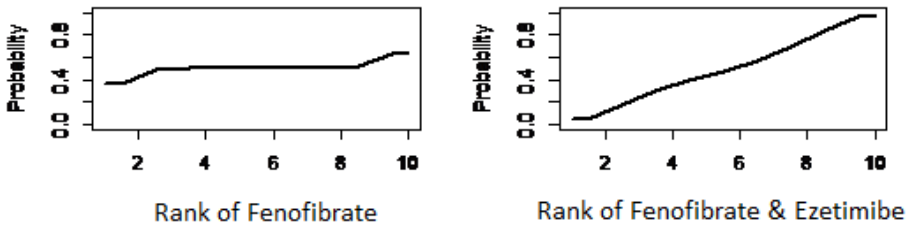
Note: Control = placebo or standard care/dietary change. OR = Odds Ratio. CrI = Credible Interval

c. Rank probabilities

Among all lipid-lowering interventions assessed, most had high probabilities of offering similarly low odds of elevations in ALT levels compared to control or placebo. Only pitavastatin had the highest probability of ranking last or being associated with the highest odds for ALT elevations (51%). **Figures 39 and 48** are graphical representations of each treatment's probability of taking a specific rank in terms of freedom from elevations in ALT levels.

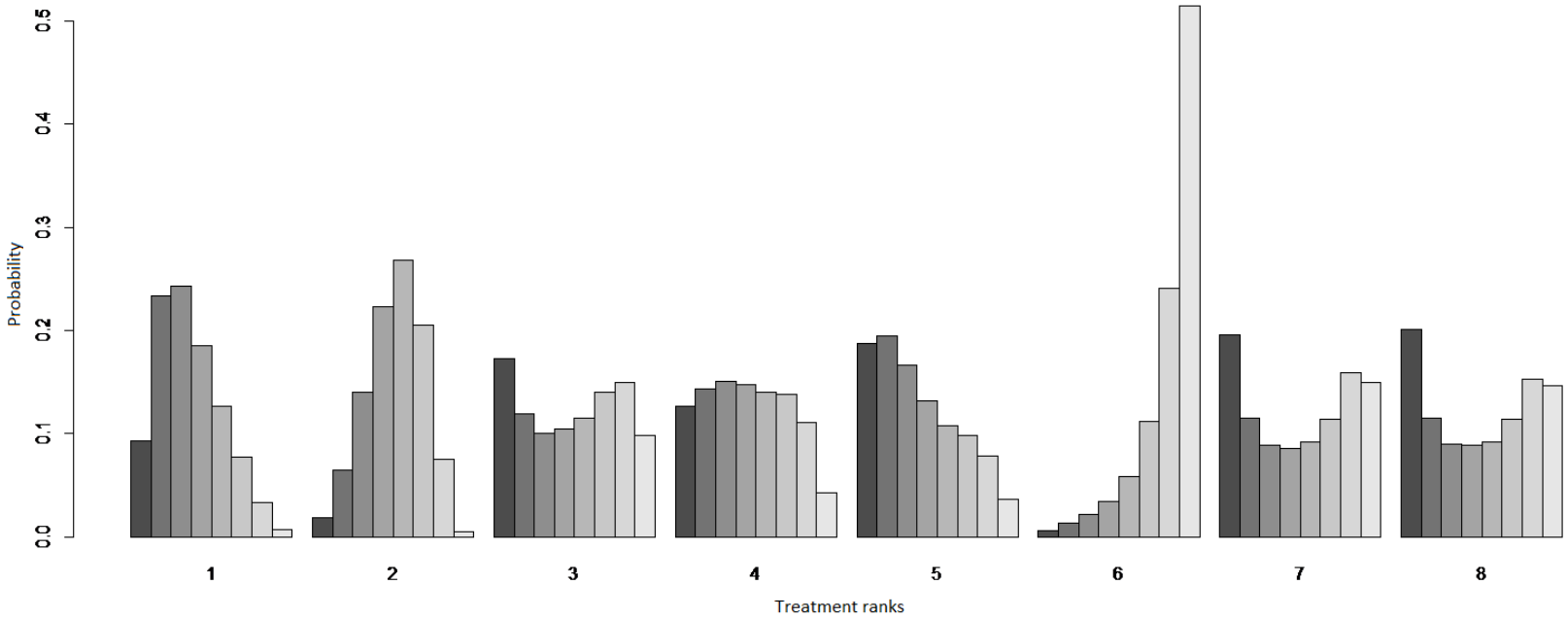
Figure 39. Rankogram: Graphical representation of the hierarchy of treatments for alanine aminotransferase (8 trials)





Note: Each graph represents each treatment's probability to take a specific rank. Rankings indicate probabilities of being the best treatment, the second best, the third best, and so forth. On the horizontal axis are the 10 possible ranks. On the vertical axis is the probability of a treatment to take a given rank.

Figure 48. Barplots for the ranking probabilities of competing treatments- Alanine aminotransferase



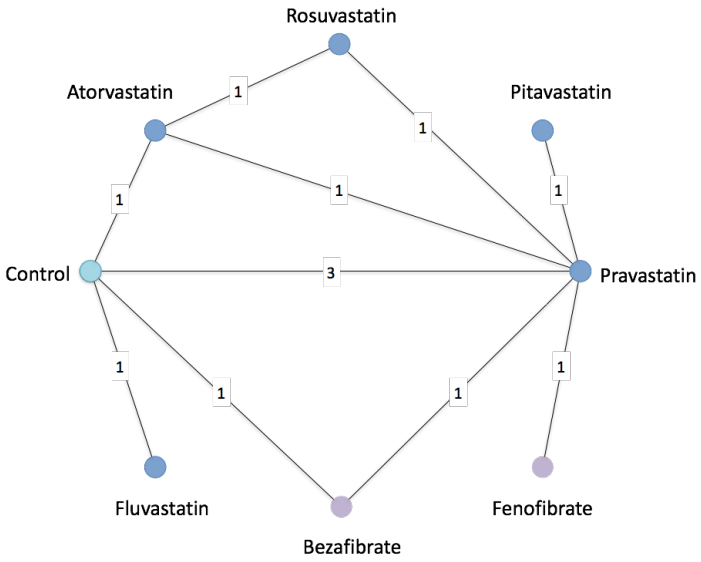
Note: This histogram shows the share of probabilities among competing treatment to rank at a specific place. Numbers correspond to different treatments (1: Control, 2: Pravastatin, 3: Rosuvastatin, 4: Atorvastatin, 5: Fluvastatin, 6: Pitavastatin, 7: Fenofibrate, 8: Fenofibrate + Ezetimibe). The size of each bar corresponds to the probability of each treatment to be at a specific rank.

8. Creatine phosphokinase (CPK) elevations

a. Network of evidence

Eight trials out of fifteen reported data on CPK level elevations. The 8 trials included a total of 692 patients, of whom 9 had CPK elevations. The network consisted of 5 different statins (Atorvastatin, fluvastatin, pitavastatin, pravastatin, and rosuvastatin), and 2 fibrates (Bezafibrate and fenofibrate). All interventions were adequately connected in the network, allowing for indirect comparisons to be made and for each intervention to be compared to every other treatment in the network. Pravastatin appeared in 6 trials and was compared to all other interventions in the network but one, making it the most commonly compared treatment. **Figure 13** shows a geometrical representation of the network of evidence on the outcome for CPK.

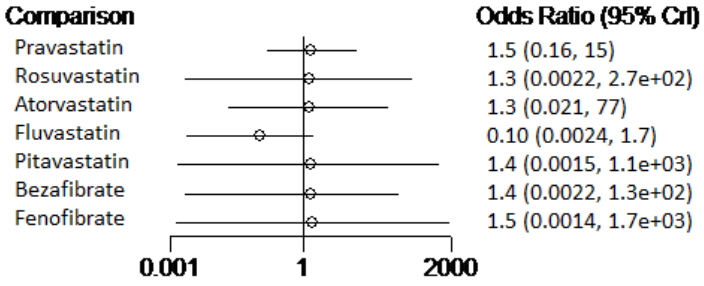
Figure 13. Diagram of the network of evidence for the creatine phosphokinase outcome (8 trials)



b. Summary statistics

No major differences from control were found among the lipid-lowering interventions evaluated with respect to elevation of CPK levels. Only fluvastatin was associated with higher odds of preventing increased levels of CPK upon use of lipid-lowering therapy (OR = 0.10, CrI = 0.0024, 1.7), but this was non-significant. There were too few numbers of adverse events reported to increase the certainty in the relative treatment effect estimates obtained- as indicated by the wide credible intervals associated with the odds ratios for most of the treatment comparisons made. **Figure 31** is a forest plot displaying the results of analyses for each treatment effect compared to control. **Table 23** provides the odds ratios and their associated credible intervals for all relative treatment effect estimates obtained.

Figure 31. Forest plot: Treatment effects on freedom from elevations in CPK levels compared to control (8 trials)



Note: CrI = Credible interval. An Odds Ratio > 1 favours control (fewer adverse events occurred with control than with the active treatment) vs. an Odds Ratio < 1 favours the active treatment (fewer adverse events occurred with the active treatment).

Table 23. Estimates of ORs and 95%CrI from network meta-analysis of creatine phosphokinase endpoint

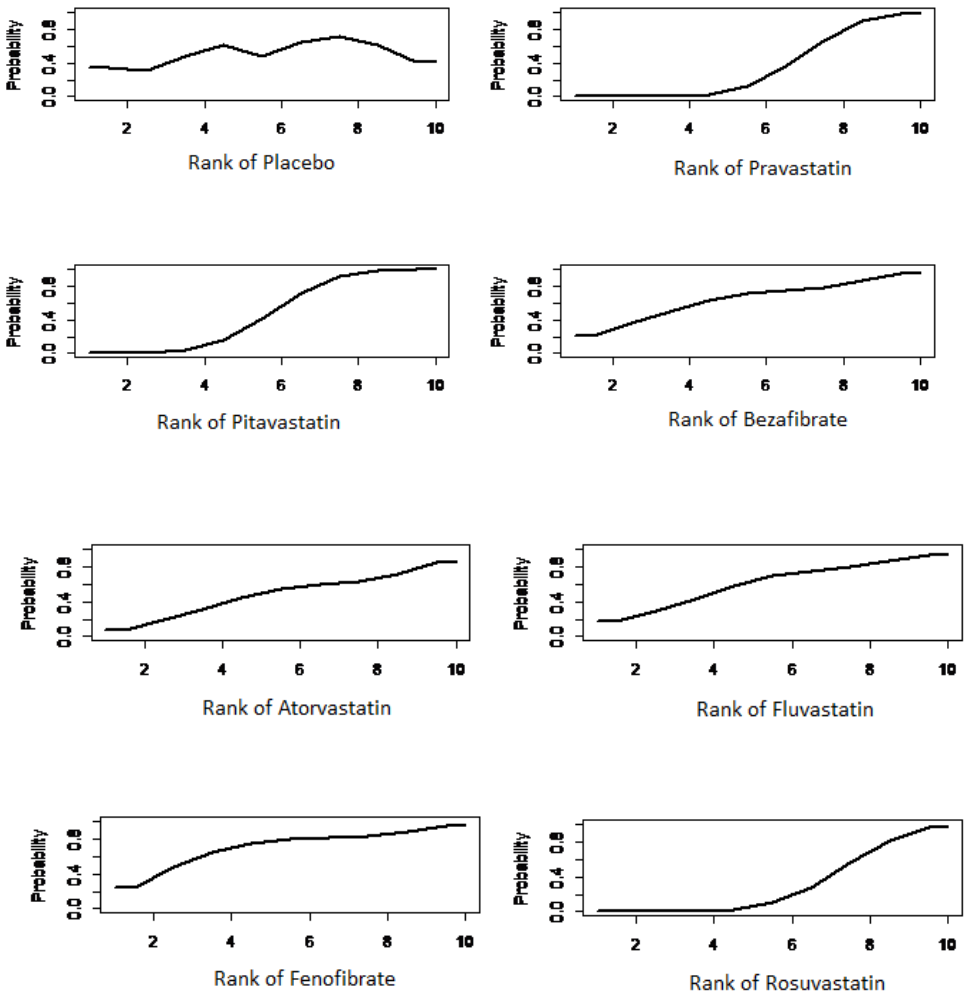
Control	0.70 (0.068, 6.5)	0.77 (0.0041, 470)	0.81(0.015, 49)	9.7 (0.59, 460)	0.68 (0.00076, 70)	0.71 (0.0078, 350)	0.69 (0.00074, 650)
1.4 (0.16, 15)	**Pravastatin**	1.1 (0.0073, 620)	1.2 (0.023, 73)	15 (0.41, 1200)	1.0 (0.0015, 710)	1.0 (0.011, 560)	1.0 (0.0015, 660)
1.3 (0.0021, 240)	0.88 (0.0016, 140)	**Rosuvastatin**	1.1 (0.0016, 220)	13 (0.012, 8900)	0.87 (0.00011, 3300)	0.97 (0.00046, 2400)	0.85 (0.00011, 3100)
1.2 (0.020, 65)	0.85 (0.014, 44)	0.94, (0.0046, 630)	**Atorvastatin**	13 (0.084, 2700)	0.85 (0.00043, 1700)	0.94 (0.0025, 1200)	0.86 (0.00040, 1600)
0.10 (0.0022, 1.7)	0.068 (0.0082, 2.5)	0.074 (0.00011, 86)	0.078 (0.00037, 12)	**Fluvastatin**	0.063 (0.00031, 110)	0.071 (0.00021, 60)	0.064 (0.00032, 110)
0.5 (0.0014, 1300)	0.98 (0.0014, 650)	1.1 (0.00030, 9200)	0.2 (0.00060, 2300)	16 (0.0090, 32000)	**Pitavastatin**	1.1 (0.00040, 7600)	0.99 (0.00012, 8700)
1.4 (0.0029, 130)	0.96 (0.0018, 89)	1.0 (0.00042, 220)	1.1 (0.00086, 400)	14 (0.017, 4800)	0.89 (0.00013, 2500)	**Bezafibrate**	0.90 (0.00013, 2500)
1.4 (0.0015, 1300)	0.98 (0.0015, 660)	1.2 (0.00033, 8700)	1.2 (0.00061, 2500)	16 (0.0091, 31000)	1.0 (0.00011, 8300)	1.1 (0.00040, 7500)	**Fenofibrate**

Note: Control = placebo or standard care/dietary change. OR = Odds Ratio. CrI = Credible Interval

c. Rank probabilities

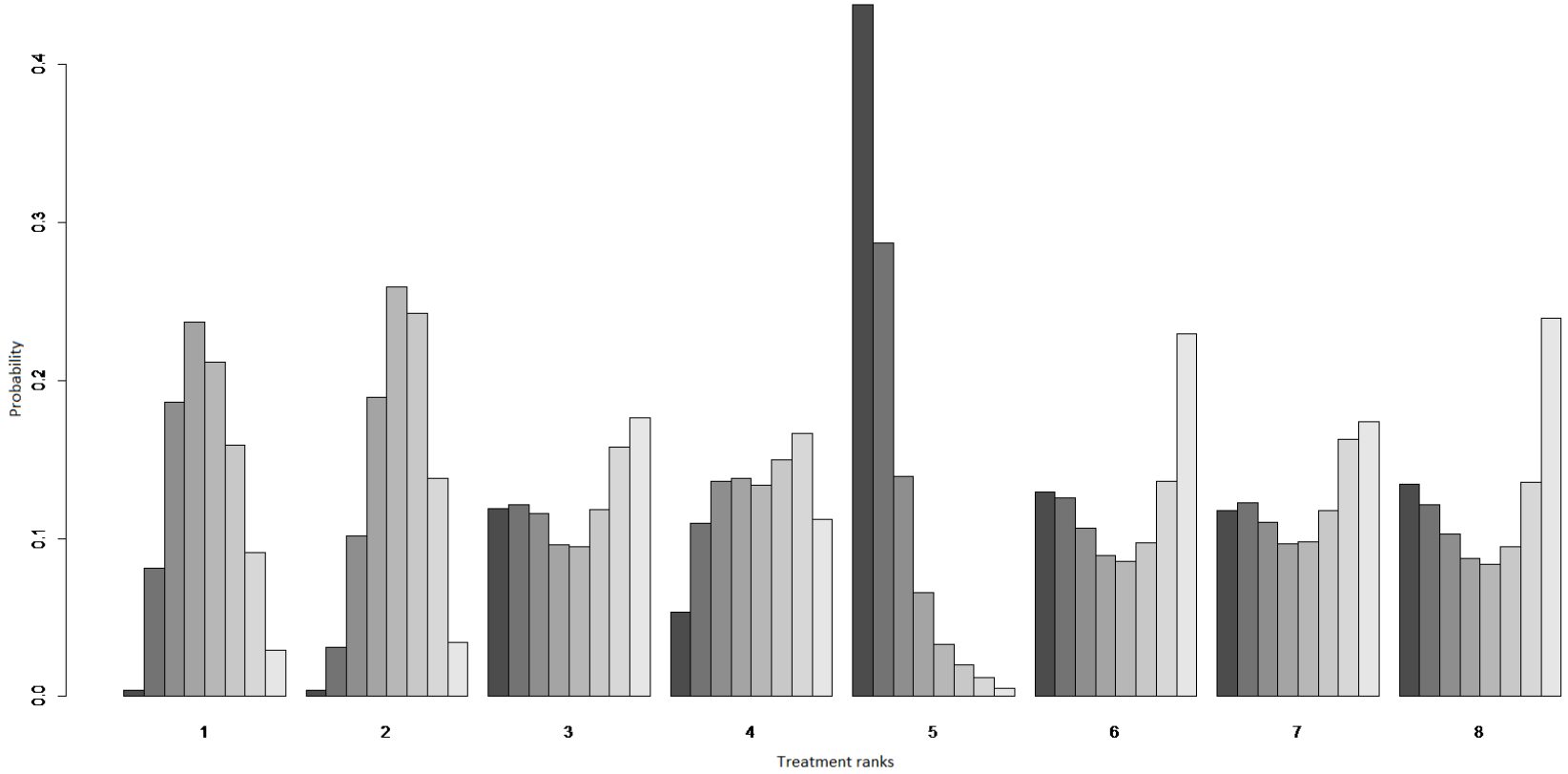
Among all lipid-lowering interventions assessed, most had high probabilities of offering similarly low odds of elevations in CPK levels compared to control or placebo. Only fluvastatin had the highest probability of ranking first or being associated with the lowest odds for CPK elevations (44%). **Figures 40 and 49** are graphical representations of each treatment's probability of taking a specific rank in terms of in terms of freedom from elevations in CPK levels.

Figure 40. Rankogram: Graphical representation of the hierarchy of treatments for creatine phosphokinase (8 trials)



Note: Each graph represents each treatment's probability to take a specific rank. Rankings indicate probabilities of being the best treatment, the second best, the third best, and so forth. On the horizontal axis are the 10 possible ranks. On the vertical axis is the probability of a treatment to take a given rank.

Figure 49. Barplots for the ranking probabilities of competing treatments- Creatine phosphokinase



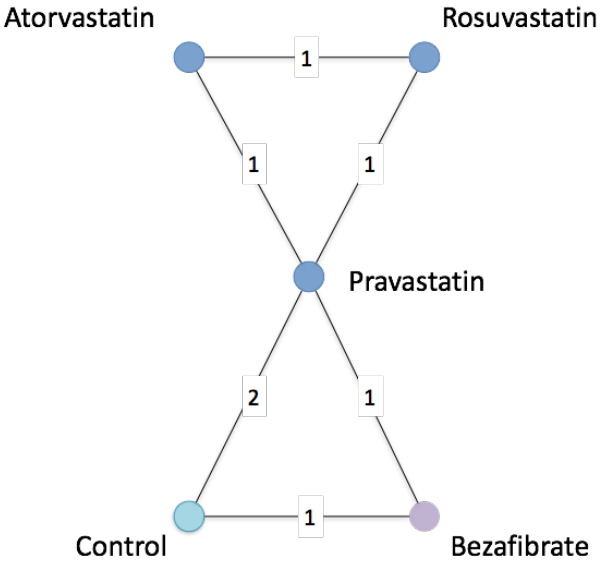
Note: This histogram shows the share of probabilities among competing treatment to rank at a specific place. Numbers correspond to different treatments (1: Control, 2: Pravastatin, 3: Rosuvastatin, 4: Atorvastatin, 5: Fluvastatin, 6: Pitavastatin, 7: Bezafibrate, 8: Fenofibrate). The size of each bar corresponds to the probability of each treatment to be at a specific rank.

9. Gastrointestinal disturbances

a. Network of evidence

Three trials out of fifteen reported data on gastrointestinal (GI) adverse events. The 3 trials included a total of 261 patients, of whom 29 had GI disturbances. The network consisted of 3 statins (Atorvastatin, pravastatin, and rosuvastatin) and 1 fibrate (Bezafibrate). All interventions were adequately connected in the network, allowing for indirect comparisons to be made and for each intervention to be compared to every other treatment in the network. **Figure 14** shows a geometrical representation of the network of evidence on the outcome for GI disturbances.

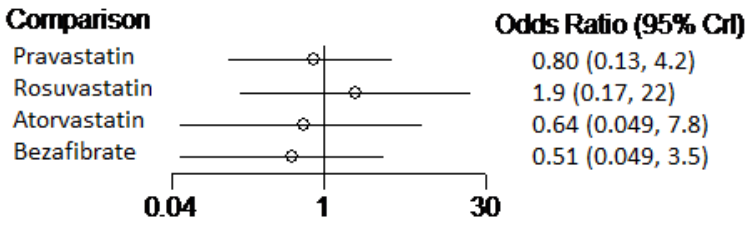
Figure 14. Diagram of the network of evidence for the gastrointestinal disturbances outcome (3 trials)



b. Summary statistics

Rosuvastatin had the highest odds of being associated with more GI adverse events (OR = 1.9, CrI = 0.17, 22), but this was not statistically significant. Among all lipid-lowering interventions assessed, bezafibrate had the lowest odds of being associated with GI adverse events (OR = 0.51, CrI = 0.049, 3.5). Among statins, atorvastatin had the lowest odds of being associated with GI disturbances (OR = 0.64, CrI = 0.049, 7.8). **Figure 32** is a forest plot displaying the results of analyses for each treatment effect compared to control. **Table 24** provides the odds ratios and their associated credible intervals for all relative treatment effect estimates obtained.

Figure 32. Forest plot: Treatment effects on freedom from gastrointestinal disturbances compared to control (3 trials)



Note: CrI = Credible interval. An Odds Ratio > 1 favours control (fewer adverse events occurred with control than with the active treatment) vs. an Odds Ratio < 1 favours the active treatment (fewer adverse events occurred with the active treatment).

Table 24. Estimates of ORs and 95%CrI from network meta-analysis of gastrointestinal disturbances endpoint

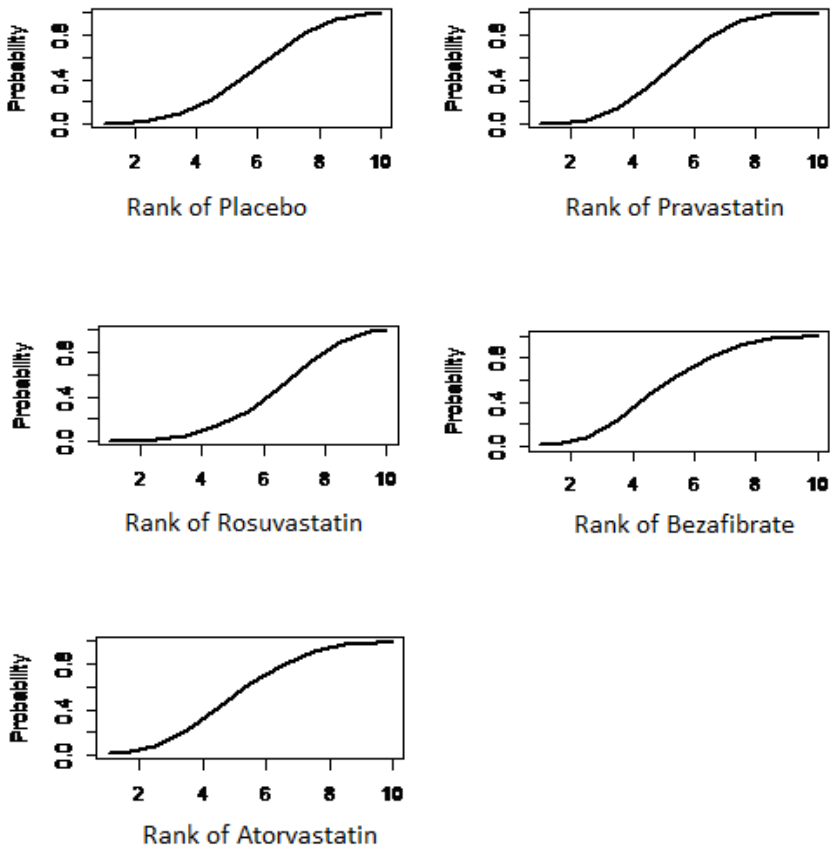
Control	1.2 (0.24, 7.6)	0.52 (0.046, 6.1)	1.6 (0.13, 20)	1.9 (0.28, 20)
0.80 (0.13, 4.2)	**Pravastatin**	0.42 (0.072, 2.3)	1.2 (0.19, 8.1)	1.5 (0.18, 18)
1.9 (0.16, 22)	2.4 (0.44, 14)	**Rosuvastatin**	3.0 (0.52, 18)	3.8 (0.24, 72)
0.64 (0.049, 7.7)	0.81 (0.12, 5.1)	0.34 (0.054, 1.9)	**Atorvastatin**	1.3 (0.073, 26)
0.52 (0.051, 3.5)	0.65 (0.056, 5.6)	0.26 (0.014, 4.1)	0.79 (0.039, 14)	**Bezafibrate**

Note: Control = placebo or standard care/dietary change. OR = Odds Ratio. CrI = Credible Interval

c. Rank probabilities

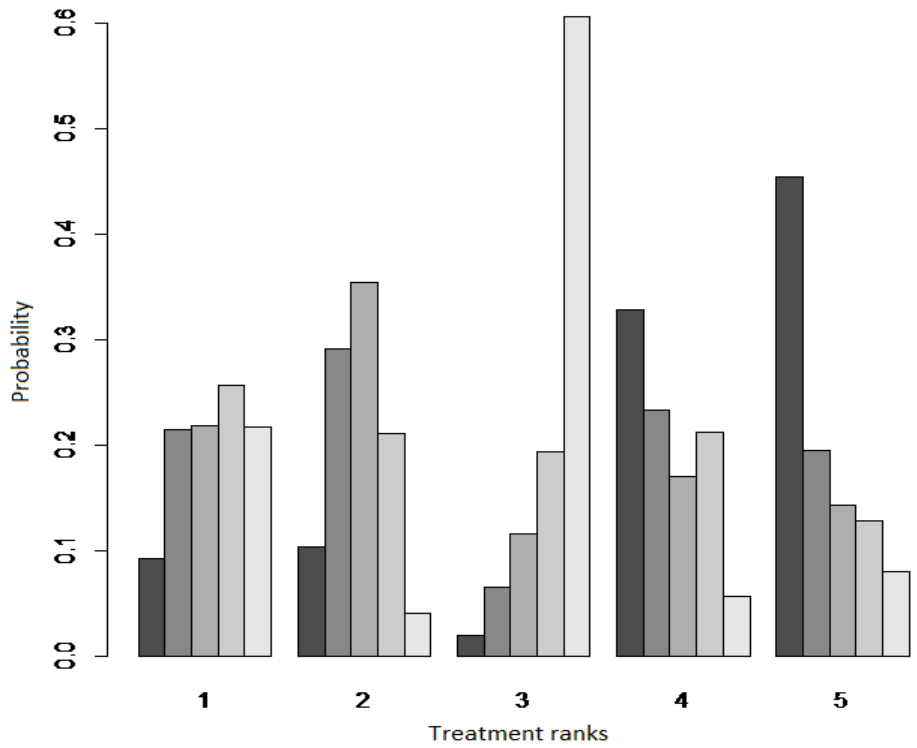
Figures 41 and 50 are graphical representations of each treatment's probability of taking a specific rank in terms of freedom from GI disturbances.

Figure 41. Rankogram: Graphical representation of the hierarchy of treatments for gastrointestinal disturbances (3 trials)



Note: Each graph represents each treatment's probability to take a specific rank. Rankings indicate probabilities of being the best treatment, the second best, the third best, and so forth. On the horizontal axis are the 10 possible ranks. On the vertical axis is the probability of a treatment to take a given rank.

Figure 50. Barplots for the ranking probabilities of competing treatments- Gastrointestinal disturbances



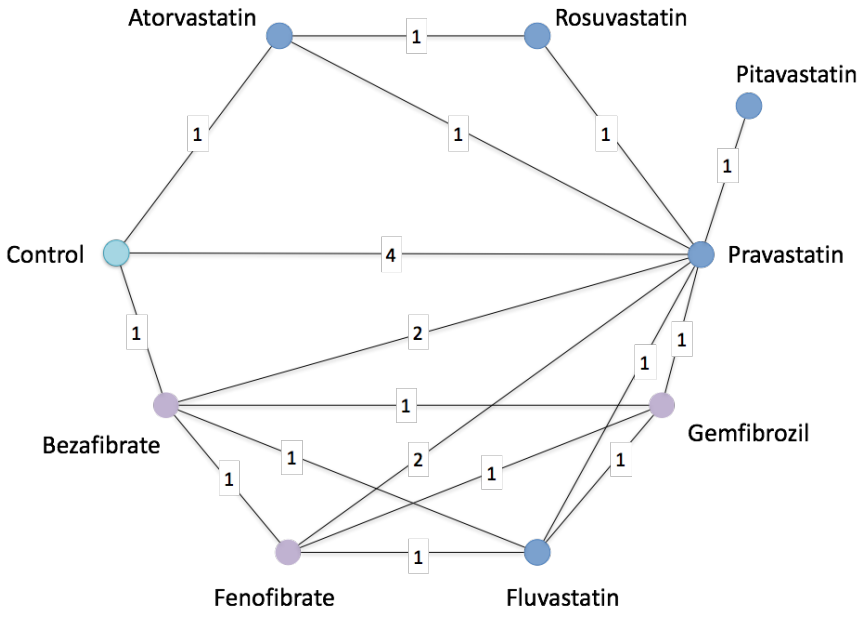
Note: This histogram shows the share of probabilities among competing treatment to rank at a specific place. Numbers correspond to different treatments (1: Control, 2: Pravastatin, 3: Rosuvastatin, 4: Atorvastatin, 5: Bezafibrate1: Control, 2: Pravastatin, 3: Rosuvastatin, 4: Atorvastatin, 5: Bezafibrate). The size of each bar corresponds to the probability of each treatment to be at a specific rank.

10. Myalgia, myositis, or rhabdomyolysis

a. Network of evidence

Nine trials out of fifteen reported data on myalgia, myositis, and rhabdomyolysis adverse events. The 9 trials included a total of 882 patients, of whom 9 had adverse events. The network consisted of 5 different statins (Atorvastatin, fluvastatin, pitavastatin, pravastatin, and rosuvastatin) and 3 fibrates (Bezafibrate, fenofibrate, gemfibrozil). All interventions were adequately connected in the network, allowing for indirect comparisons to be made and for each intervention to be compared to every other treatment in the network. **Figure 15** shows a geometrical representation of the network of evidence on the outcome for myalgia, myositis, or rhabdomyolysis.

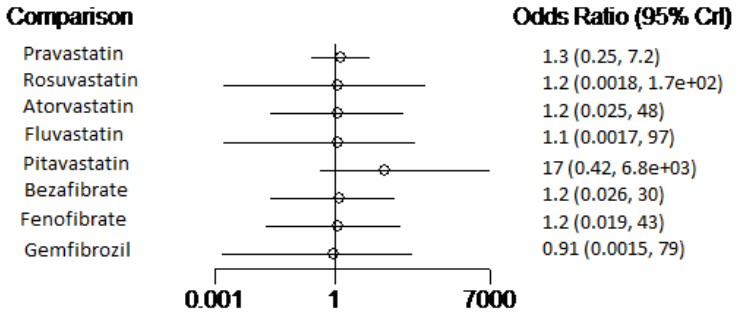
Figure 15. Diagram of the network of evidence for the myalgia, myositis, or rhabdomyolysis outcome (9 trials)



b. Summary statistics

No major differences from control were found among the lipid-lowering interventions evaluated with respect to these adverse events. **Figure 33** is a forest plot displaying the results of analyses for each treatment effect compared to control. **Table 25** provides the odds ratios and their associated credible intervals for all relative treatment effect estimates obtained.

Figure 33. Forest plot: Treatment effects on freedom from myalgia, myositis, or rhabdomyolysis compared to control (9 trials)



Note: CrI = Credible interval. An Odds Ratio > 1 favours control (fewer adverse events occurred with control than with the active treatment) vs. an Odds Ratio < 1 favours the active treatment (fewer adverse events occurred with the active treatment).

Table 25. Estimates of ORs and 95%CrI from network meta-analysis of myalgia, myositis, and rhabdomyolysis endpoints

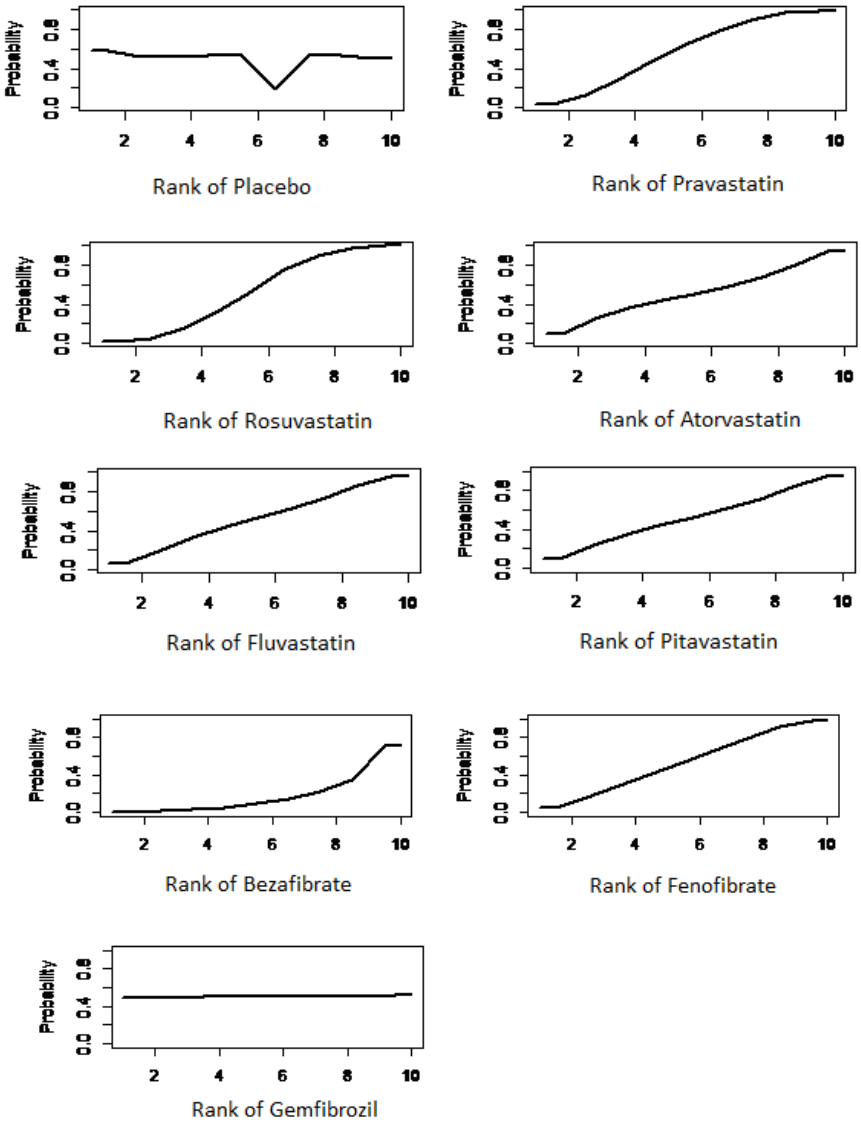
Control	0.76 (0.14, 4.0)	0.84 (0.0058, 570)	0.86 (0.021, 40)	0.90 (0.010, 570)	0.059 (0.00015, 2.4)	0.83 (0.033, 39)	0.86 (0.023, 52)	1.1 (0.013, 650)
1.3 (0.25, 7.2)	**Pravastatin**	1.1 (0.0088, 640)	1.1 (0.029, 53)	1.2 (0.017, 630)	0.082 (0.00023, 2)	1.1 (0.054, 42)	1.1 (0.042, 51)	1.4 (0.021, 750)
1.2 (0.0018, 170)	0.92 (0.0016, 110)	**Rosuvastatin**	1.0 (0.0018, 150)	1.1 (0.00063, 2300)	0.057 (0.00017, 26)	1.0 (0.00092, 410)	1.0 (0.00084, 460)	1.4 (0.00069, 2900)
1.2 (0.025, 48)	0.90 (0.019, 35)	1.0 (0.0066, 560)	**Atorvastatin**	1.1 (0.0038, 1200)	0.065 (0.00083, 9.6)	1.0 (0.0074, 150)	1.1 (0.0068, 170)	1.4 (0.0046, 1600)
1.1 (0.0017, 97)	0.86 (0.0016, 60)	0.88 (0.00043, 1600)	0.88 (0.00081, 260)	**Fluvastatin**	0.053 (0.00016, 16)	0.96 (0.0014, 110)	0.96 (0.0015, 130)	1.2 (0.0017, 890)
17 (0.42, 6800)	12 (0.51, 4300)	17 (0.039, 60000)	15 (0.10, 12000)	19 (0.064, 61000)	**Pitavastatin**	16 (0.16, 12000)	16 (0.13, 13000)	23 (0.082, 83000)
1.2 (0.026, 30)	0.92 (0.024, 19)	0.98 (0.0024, 4100)	0.99 (0.0065, 130)	1.0 (0.0092, 720)	0.063 (0.00084, 6.2)	**Bezafibrate**	1.0 (0.014, 65)	1.3 (0.011, 630)
1.2 (0.019, 43)	0.88 (0.019, 24)	1.0 (0.0022, 1200)	0.94 (0.0059, 150)	1.0 (0.0077, 690)	0.063 (0.00078, 7.5)	0.97 (0.015, 74)	**Fenofibrate**	1.2 (0.0098, 730)
0.91 (0.0015, 79)	0.71 (0.0013, 48)	0.74 (0.00035, 1400)	0.73 (0.00063, 220)	0.84 (0.0011, 600)	0.044 (0.00012, 12)	0.78 (0.0016, 88)	0.80 (0.0014, 100)	**Gemfibrozil**

Note: Control = placebo or standard care/dietary change. OR = Odds Ratio. CrI = Credible Interval

c. Rank probabilities

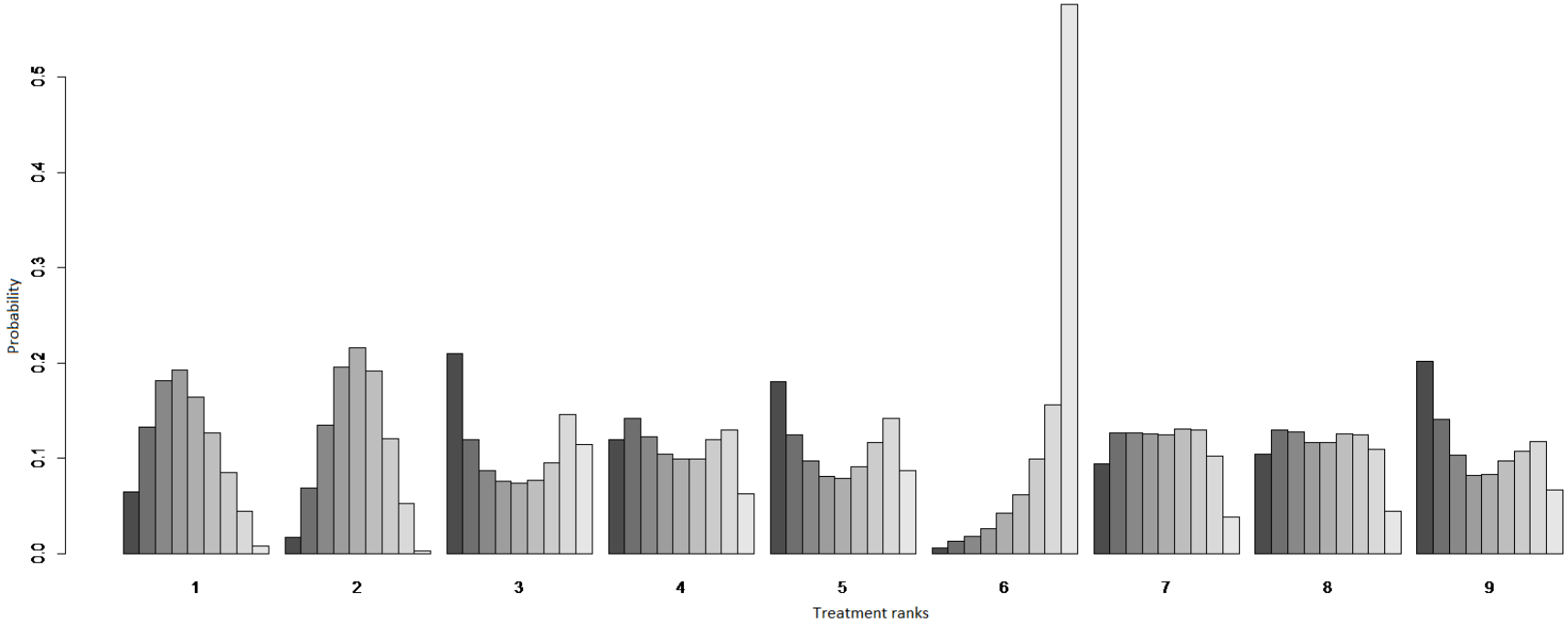
Figures 42 and 51 are graphical representations of each treatment's probability of taking a specific rank in terms of freedom from myalgia, myositis, and rhabdomyolysis.

Figure 42. Rankogram: Graphical representation of the hierarchy of treatments for myalgia, myositis, or rhabdomyolysis (9 trials)



Note: Each graph represents each treatment's probability to take a specific rank. Rankings indicate probabilities of being the best treatment, the second best, the third best, and so forth. On the horizontal axis are the 10 possible ranks. On the vertical axis is the probability of a treatment to take a given rank.

Figure 51. Barplots for the ranking probabilities of competing treatments- Myalgia, myositis, or rhabdomyolysis



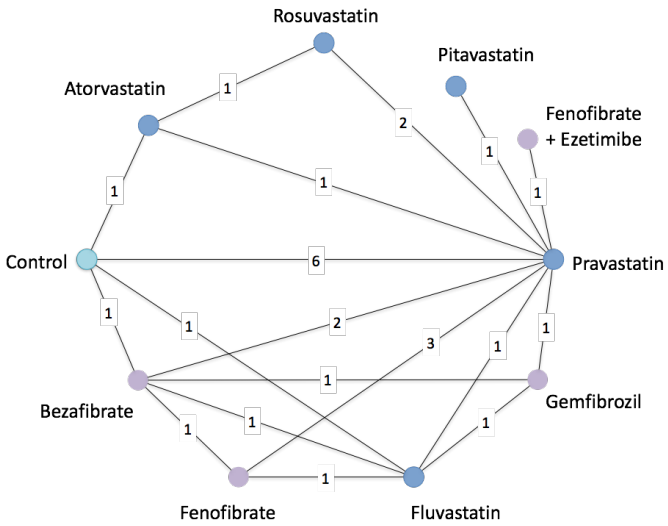
Note: This histogram shows the share of probabilities among competing treatment to rank at a specific place. Numbers correspond to different treatments (1: Control, 2: Pravastatin, 3: Rosuvastatin, 4: Atorvastatin, 5: Fluvastatin, 6: Pitavastatin, 7: Bezafibrate, 8: Fenofibrate, 9: Fenofibrate & Ezetimibe). The size of each bar corresponds to the probability of each treatment to be at a specific rank.

11. Treatment discontinuation due to adverse events

a. Network of evidence

All trials reported data on discontinuations of treatment due to adverse events. Out of the total 1,218 patients, 8 discontinued treatment due to adverse events. The network consisted of 5 different statins (Atorvastatin, fluvastatin, pitavastatin, pravastatin, and rosuvastatin), 3 fibrates (Fenofibrate, bezafibrate, and gemfibrozil), and of another lipid-lowering therapy, Ezetimibe, given in combination with Fenofibrate. All interventions were adequately connected in the network, allowing for indirect comparisons to be made and for each intervention to be compared to every other treatment in the network. Pravastatin appeared in 6 trials and was compared to all other interventions in the network, making it the most commonly compared treatment. **Figure 16** depicts a geometrical representation of the network of evidence on the outcome for discontinuation due to adverse events.

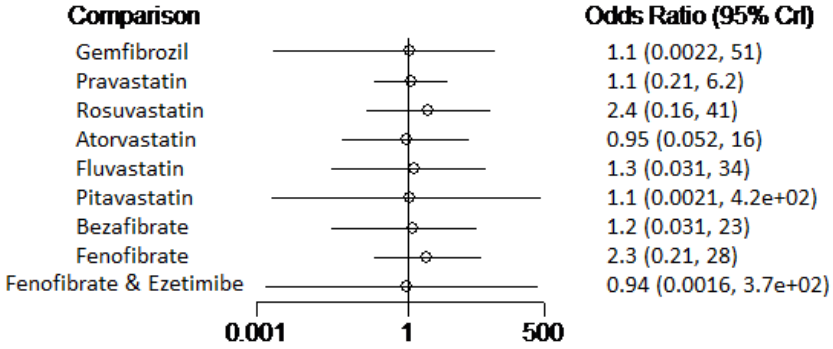
Figure 16. Diagram of the network of evidence for discontinuations due to adverse events (15 trials)



b. Summary statistics

No major differences from control were found among the lipid-lowering interventions evaluated with respect to discontinuations due to adverse events. **Figure 34** is a forest plot displaying the results of analyses for each treatment effect compared to control. **Table 26** provides the odds ratios and their associated credible intervals for all relative treatment effect estimates obtained.

Figure 34. Forest plot: Discontinuations of allocated treatments due to adverse events compared to control (15 trials)



Note: CrI = Credible interval. An Odds Ratio > 1 favours control (fewer adverse events occurred with control than with the active treatment) vs. an Odds Ratio < 1 favours the active treatment (fewer adverse events occurred with the active treatment).

Table 26. Estimates of ORs and 95%CrI from network meta-analysis of treatment discontinuation due to adverse events

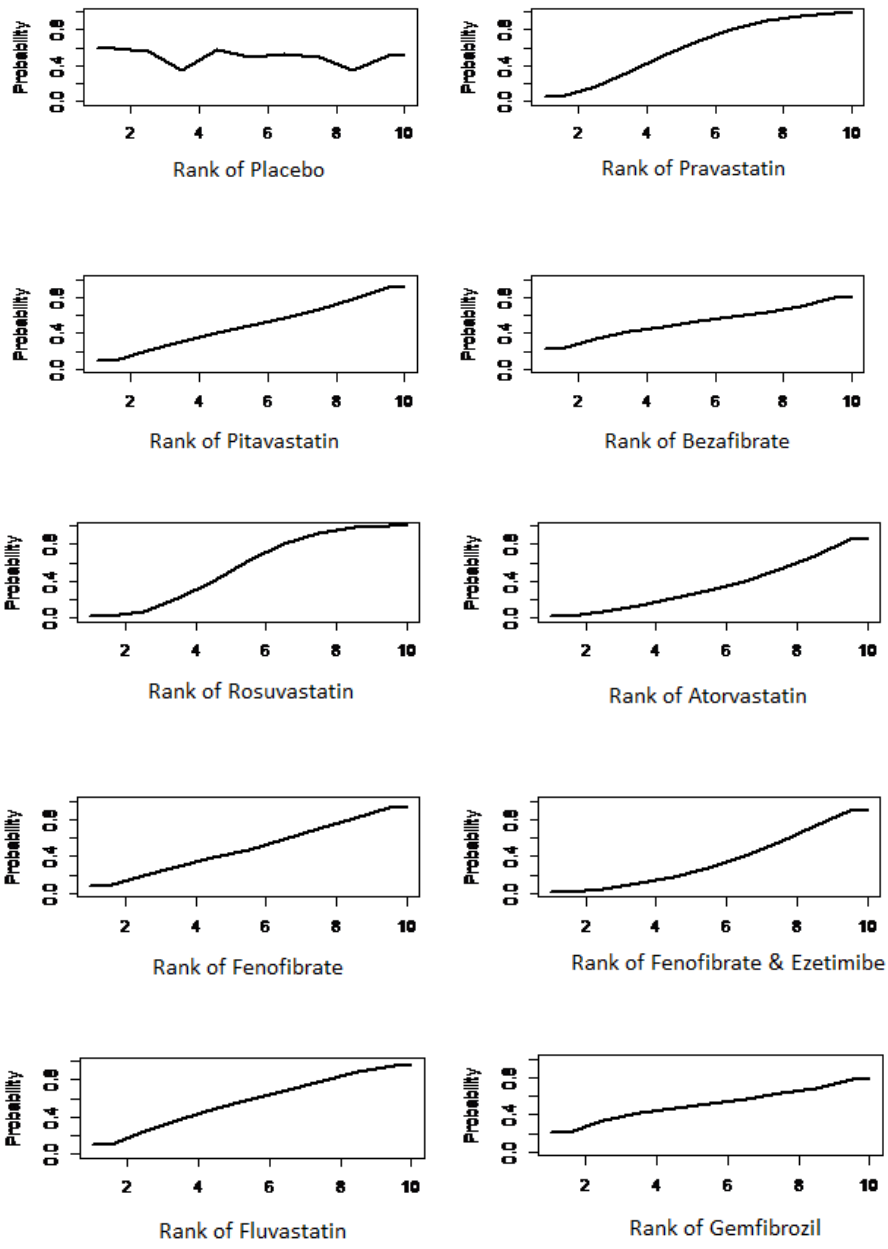
Control	0.91 (0.17, 5)	0.44 (0.026, 7.0)	1.1 (0.063, 22)	0.76 (0.034, 32)	0.99 (0.0029, 500)	0.77 (0.043, 30)	1.1 (0.0028, 550)	0.45 (0.040, 5.0)	0.90 (0.018, 350)
1.1 (0.20, 5.8)	**Pravastatin**	0.49 (0.040, 4.9)	1.2 (0.091, 20)	0.82 (0.037, 38)	1.1 (0.0038, 430)	0.87 (0.054, 26)	1.2 (0.0041, 490)	0.51 (0.069, 3)	0.96 (0.023, 360)
2.3 (0.14, 38)	2.0 (0.21, 25)	**Rosuvastatin**	2.5 (0.19, 48)	1.7 (0.033, 160)	2.2 (0.0063, 1400)	1.9 (0.048, 110)	2.4 (0.0053, 1700)	1.0 (0.052, 21)	2.1 (0.024, 100)
0.91 (0.046, 16)	0.83 (0.051, 11)	0.41 (0.021, 5.3)	**Atorvastatin**	0.70 (0.012, 61)	0.91 (0.0016, 600)	0.72 (0.016, 51)	0.94 (0.0018, 630)	0.41 (0.015, 9.4)	0.84 (0.081, 500)
1.3 (0.031, 29)	1.2 (0.027, 27)	0.58 (0.0064, 30)	1.4 (0.016, 83)	**Fluvastatin**	1.2 (0.0018, 100)	1.1 (0.016, 63)	1.3 (0.0015, 120)	0.60 (0.011, 16)	1.2 (0.011, 510)
1.0 (0.0020, 350)	0.93 (0.0023, 260)	0.44 (0.00069, 160)	1.1 (0.0017, 610)	0.83 (0.00098, 570)	**Pitavastatin**	0.84 (0.0013, 560)	1.0 (0.00038, 3700)	0.46 (0.00084, 150)	1.0 (0.00091, 2700)
1.3 (0.033, 23)	1.2 (0.038, 19)	0.53 (0.0089, 21)	1.4 (0.020, 64)	0.94 (0.016, 63)	1.2 (0.0018, 790)	**Bezafibrate**	1.2 (0.0019, 880)	0.55 (0.015, 12)	1.1 (0.014, 370)
2.2 (0.20, 25)	2.0 (0.33, 14)	0.97 (0.048, 19)	2.4 (0.11, 69)	1.7 (0.063, 93)	2.2 (0.0065, 1200)	1.8 (0.086, 68)	**Fenofibrate & Ezetimibe**	0.42 (0.00081, 180)	2 (0.046, 720)
0.95 (0.0018, 350)	0.87 (0.0021, 250)	0.41 (0.00060, 190)	1.1 (0.0016, 570)	0.74 (0.0087, 690)	0.98 (0.00027, 2600)	0.80 (0.0011, 540)	2.4 (0.0055, 1200)	**Fenofibrate**	0.97 (0.00081, 2900)
1.1 (0.0029, 56)	1.0 (0.0028, 44)	0.49 (0.00097, 42)	1.2 (0.0020, 120)	0.84 (0.0020, 87)	0.99 (0.00037, 110)	0.88 (0.0027, 74)	1.0 (0.00035, 1200)	0.51 (0.0014, 22)	**Gemfibrozil**

Note: Control = placebo or standard care/dietary change. OR = Odds Ratio. CrI = Credible Interval

c. Rank probabilities

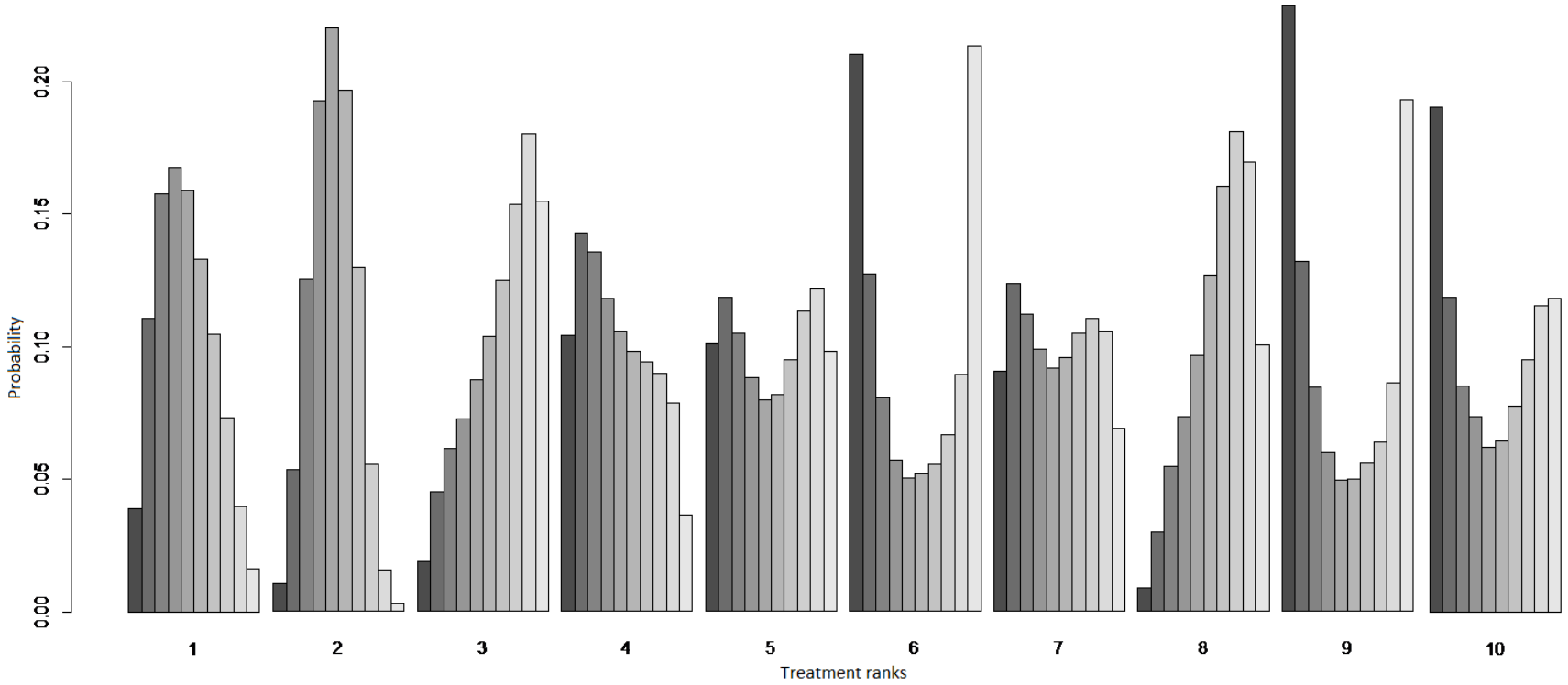
Figures 43 and 52 are graphical representations of each treatment's probability of taking a specific rank in terms of freedom from discontinuations due to adverse events.

Figure 43. Rankogram: Graphical representation of the hierarchy of treatments for treatment discontinuations due to adverse events (15 trials)



Note: Each graph represents each treatment's probability to take a specific rank. Rankings indicate probabilities of being the best treatment, the second best, the third best, and so forth. On the horizontal axis are the 10 possible ranks. On the vertical axis is the probability of a treatment to take a given rank.

Figure 52. Barplots for the ranking probabilities of competing treatments - Discontinued treatment due to adverse events



Note: This histogram shows the share of probabilities among competing treatment to rank at a specific place. Numbers correspond to different treatments (1: Control, 2: Pravastatin, 3: Rosuvastatin, 4: Atorvastatin, 5: Fluvastatin, 6: Pitavastatin, 7: Bezafibrate, 8: Fenofibrate, 9: Fenofibrate & Ezetimibe, 10: Gemfibrozil). The size of each bar corresponds to the probability of each treatment to be at a specific rank.

12. Sensitivity analyses

a. Treatment duration

Trials that evaluated the use of lipid-lowering interventions for over 6 months were removed from analyses in order to examine the potential effect-modification of treatment duration. This resulted in 5 trials[47-49,88,92] being removed from the total cholesterol analyses and 4 trials[48,49,88,92] being removed from the LDL cholesterol analyses. Consequently, fenofibrate, fenofibrate & ezetimibe and gemfibrozil were no longer part of the total cholesterol network of evidence. Similarly, bezafibrate, fenofibrate, fenofibrate & ezetimibe and gemfibrozil were no longer part of the LDL cholesterol network of evidence. The effect-modification of treatment duration on these treatments' relative efficacies was therefore not assessed.

The results of this sensitivity analysis were highly similar to those of the analysis using all available data. For total cholesterol, rosuvastatin was found to be the most effective in reducing total cholesterol levels compared to control (mean difference = -65 mg/dL, CrI = -130, 3.1). Analyses revealed that fluvastatin increased total cholesterol levels from baseline by 66 mg/dL (CrI = 4.8, 130), indicating that, regardless of how long it is taken for, this statin is the least efficacious in reducing total cholesterol levels. For LDL cholesterol, rosuvastatin was also found to be the most effective in reducing total cholesterol levels compared to control (mean difference = -59 mg/dL, CrI = -110, -5.6). In contrast with the findings for total cholesterol levels- and just as in the analysis using all of the available data- fluvastatin showed the second highest reduction in LDL cholesterol

levels from baseline, compared to control (mean difference = -51 mg/dL, CrI = -100, 1.8). Thus, treatment duration does not seem to modify the relative treatment effects obtained in the analysis of total and LDL cholesterol levels. **Table 27** provides more detailed summary statistics of these relative treatment effects.

Table 27. Estimated relative treatment effects and 95%CrI- Sensitivity analysis for treatment duration

	Total Cholesterol		LDL Cholesterol	
	Mean Difference[a]	**95% CrI**	**Mean Difference[a]**	**95% CrI**
Vs. Control				
Pravastatin	-35	-65, -5.2	-35	-59, -11
Rosuvastatin	-65	-130, 3.1	-59	-110, -5.6
Atorvastatin	-51	-110, 8.1	-46	-97, 5.0
Fluvastatin	66	4.8, 130	-51	-100, 1.8
Pitavastatin	-51	-120, 15	11	-31, 52
Bezafibrate	-10	-63, 43	--	--
Vs. Pravastatin				
Rosuvastatin	-29	-90, 31	-24	-72, 24
Atorvastatin	-16	-82, 50	-11	-67, 45
Fluvastatin	100	33, 170	-16	-62, 31
Pitavastatin	-16	-75, 44	46	12, 79
Bezafibrate	25	-19, 69	--	--
Vs. Rosuvastatin				
Atorvastatin	14	-77, 100	13	-61, 87
Fluvastatin	130	39, 220	8.6	-58, 76
Pitavastatin	13	-71, 98	70	11, 130
Bezafibrate	54	-21, 130	--	--
Vs. Atorvastatin				
Fluvastatin	120	32, 200	-4.8	-77, 68
Pitavastatin	-0.030	-88, 90	57	-9, 120
Bezafibrate	41	-38, 120	--	--
Vs. Fluvastatin				
Pitavastatin	-120	-210, -26	62	3.6, 120
Bezafibrate	-76	-160, 5.4	--	--
Vs. Pitavastatin				
Bezafibrate	-41	-110, 33	--	--

Note: Control: placebo or standard care/dietary change. (a) Mean difference < 0 shows an advantage of treatment over the reference. CrI = Credible Interval

b. Time on ART

Trials with patients who had been on stable ART regimen for over 10 years were removed from analyses in order to examine the potential effect-modification of time on ART. This resulted in 2 trials[47,87] being removed from the total cholesterol analyses and 1 trial[87] being removed from the LDL cholesterol analyses. Consequently, gemfibrozil was no longer part of the network of evidence, and the effect-modification of time on ART on its relative efficacy was not assessed.

The results of this sensitivity analysis were similar to those of the analysis using all available data. For total cholesterol, rosuvastatin was found to be the most effective in reducing total cholesterol levels compared to control (mean difference = -70 mg/dL, CrI = -120, -25). Analyses revealed that fluvastatin increased total cholesterol levels from baseline by 66 mg/dL (CrI = 9.3, 120), indicating that, regardless of how long patients had been taking ART, this statin is the least efficacious in reducing total cholesterol levels. For LDL cholesterol, rosuvastatin was also found to be the most effective in reducing total cholesterol levels compared to control (mean difference = -54 mg/dL, CrI = -79, -31). In contrast with the findings for total cholesterol levels- and just as in the analysis using all of the available data- fluvastatin showed the second highest reduction in LDL cholesterol levels from baseline, compared to control (mean difference = -51 mg/dL, CrI = -82, -20). Thus, time on ART does not seem to modify the relative treatment effects obtained in the analysis of total and LDL cholesterol levels. **Table 28** provides more detailed summary statistics of these relative treatment effects.

Table 28. Estimated relative treatment effects and 95%CrI- Sensitivity analysis for time on ART

	Total Cholesterol		LDL Cholesterol	
	Mean Difference[a]	**95% CrI**	**Mean Difference[a]**	**95% CrI**
Vs. Control				
Pravastatin	-44	-67, -22	-36	-48, -23
Rosuvastatin	-70	-120, -25	-54	-79, -31
Atorvastatin	-54	-110, 1.3	-42	-72, -14
Fluvastatin	66	9.3, 120	-51	-82, -20
Pitavastatin	-60	-120, -1.6	-34	-60, -8.6
Bezafibrate	-45	-93, 5.3	10	-14, 35
Fenofibrate	-19	-66, 28	-34	-65, -3.5
Fenofibrate & Ezetimibe	-62	-120, -3.7	--	--
Vs. Pravastatin				
Rosuvastatin	-26	-65, 13	-19	-40, 1.3
Atorvastatin	-10	-61, 40	-6.9	-34, 19
Fluvastatin	110	49, 170	-16	-44, 12
Pitavastatin	-16	-70, 38	1.4	-25, 27
Bezafibrate	-0.67	-50, 50	46	24, 67
Fenofibrate	25	-16, 66	1.3	-27, 29
Fenofibrate & Ezetimibe	-18	-72, 36		
Vs. Rosuvastatin				
Atorvastatin	15	-36, 67	12	-14, 39
Fluvastatin	140	64, 210	3.1	-31, 39
Pitavastatin	9.8	-57, 77	20	-12, 54
Bezafibrate	25	-37, 89	65	35, 95
Fenofibrate	51	-5.8, 110	20	-14, 55
Fenofibrate & Ezetimibe	7.8	-59, 75	--	--
Vs. Atorvastatin				
Fluvastatin	120	41, 200	-8.8	-47, 30
Pitavastatin	-5.6	-80, 69	8.4	-28, 46
Bezafibrate	9.7	-60, 82	53	19, 87
Fenofibrate	35	-30, 100	8.2	30, 47
Fenofibrate & Ezetimibe	-7.6	-82, 67	--	--

	Total Cholesterol		LDL Cholesterol	
	Mean Difference[a]	**95% CrI**	**Mean Difference[a]**	**95% CrI**
Vs. Fluvastatin				
Pitavastatin	-130	-210, -45	17	-21, 55
Bezafibrate	-110	-180, -35	62	26, 97
Fenofibrate	-85	-160, -12	17	-23, 57
Fenofibrate & Ezetimibe	-130	-210, -47	--	--
Vs. Pitavastatin				
Bezafibrate	15	-57, 89	45	11, 78
Fenofibrate	41	-27, 110	-0.17	-38, 38
Fenofibrate & Ezetimibe	-1.9	-79, 74	--	--
Vs. Bezafibrate				
Fenofibrate	26	-40, 89	-45	-80, -9.5
Fenofibrate & Ezetimibe	-17	-91, 55	--	--
Vs. Fenofibrate				
Fenofibrate & Ezetimibe	-43	-110, 25	--	--

Note: Control: placebo or standard care/dietary change. (a) Mean difference < 0 shows an advantage of treatment over the reference. CrI = Credible Interval

c. Baseline severity of dyslipidemia

Trials with patients who had baseline LDL cholesterol levels over 170 mg/dL were removed from analyses in order to examine the potential effect-modification of baseline severity of dyslipidemia. This resulted in 1 trial[48] being removed from all analyses. Consequently, fenofibrate & ezetimibe and gemfibrozil were no longer part of the network of evidence, and the effect-modification of baseline severity of dyslipidemia on their relative efficacies was not assessed.

The results of this sensitivity analysis were highly similar to those of the analysis using all available data. For total cholesterol, rosuvastatin was found to be the most effective in reducing total cholesterol levels compared to control (mean difference = -66 mg/dL, CrI = -150, 17). Analyses revealed that fluvastatin increased total cholesterol levels from baseline by 8.9 mg/dL (CrI = -44, 62), indicating that, regardless of how severe baseline dyslipidemia is, this statin is the least efficacious in reducing total cholesterol levels. For LDL cholesterol, rosuvastatin was also found to be the most effective in reducing total cholesterol levels compared to control (mean difference = -55 mg/dL, CrI = -80, -31). In contrast with the findings for total cholesterol levels- and just as in the analysis using all of the available data- fluvastatin showed the second highest reduction in LDL cholesterol levels from baseline, compared to control (mean difference = -52 mg/dL, CrI = -85, -19). Thus, baseline severity of dyslipidemia does not seem to modify the relative treatment effects obtained in the analysis of total and LDL cholesterol levels. **Table 29** provides more detailed summary statistics of these relative treatment effects.

Table 29. Estimated relative treatment effects and 95%CrI- Sensitivity analysis for baseline severity of dyslipidemia

	Total Cholesterol		LDL Cholesterol	
	Mean Difference	**95% CrI**	**Mean Difference**	**95% CrI**
Vs. Control				
Gemfibrozil	-8.6	-78, 60	--	--
Pravastatin	-37	-66, -6.7	-36	-50, -22
Rosuvastatin	-66	-150, 17	-55	-80, -31
Atorvastatin	-51	-130, 25	-44	-68, -21
Fluvastatin	8.9	-44, 62	-52	-85, -19
Pitavastatin	-53	-130, 29	-34	-61, -7.3
Bezafibrate	-26	-77, 26	9.9	-16, 36
Fenofibrate	-9.4	-60, 41	-35	-67, -2.2
Fenofibrate & Ezetimibe	-55	-140, 27	--	--
Vs. Pravastatin				
Gemfibrozil	28	-38, 93	--	--
Rosuvastatin	-29	-110, 48	-19	-41, 1.5
Atorvastatin	-15	-96, 67	-7.8	-31, 14
Fluvastatin	45	-7.5, 99	-16	-46, 14
Pitavastatin	-16	-92, 60	1.7	-26, 29
Bezafibrate	11	-38, 60	46	23, 68
Fenofibrate	27	-16, 70	1.3	-28, 31
Fenofibrate & Ezetimibe	-18	-94, 58	--	--
Vs. Rosuvastatin				
Gemfibrozil	57	-44, 160	--	--
Atorvastatin	15	-97, 130	11	-14, 37
Fluvastatin	75	-18, 170	3.4	-33, 40
Pitavastatin	13	-95, 120	21	-13, 55
Bezafibrate	40	-51, 130	65	35, 96
Fenofibrate	56	-32, 150	20	-16, 57
Fenofibrate & Ezetimibe	11	-97, 120	--	--

	Total Cholesterol		LDL Cholesterol	
	Mean Difference	**95% CrI**	**Mean Difference**	**95% CrI**
Vs. Atorvastatin				
Gemfibrozil	43	-61, 150	--	--
Fluvastatin	60	-33, 150	-8	-45, 30
Pitavastatin	-1.4	-110, 110	9.5	-25, 44
Bezafibrate	25	-66, 120	54	22, 86
Fenofibrate	42	-50, 130	9.1	-27, 47
Fenofibrate & Ezetimibe	-3.4	-120, 110	--	--
Vs. Fluvastatin				
Gemfibrozil	-18	-89, 54	--	--
Pitavastatin	-62	-150, 31	18	-23, 58
Bezafibrate	-34	-96, 27	62	24, 99
Fenofibrate	-18	-79, 42	17	-25, 59
Fenofibrate & Ezetimibe	-63	-160, 29	--	--
Vs. Pitavastatin				
Gemfibrozil	44	-57, 140	--	--
Bezafibrate	27	-63, 120	-44	8.9, 79
Fenofibrate	43	-44, 130	-0.49	-40, 40
Fenofibrate & Ezetimibe	-2	-110,110	--	--
Vs. Bezafibrate				
Gemfibrozil	17	-53, 87	--	--
Fenofibrate	16	-42, 74	-45	-81, -7.5
Fenofibrate & Ezetimibe	-29	-120, 61	--	--
Vs. Fenofibrate				
Gemfibrozil	0.83	-68, 70	--	--
Fenofibrate & Ezetimibe	-45	-130, 42	--	--
Vs. Gemfibrozil				
Fenofibrate & Ezetimibe	-46	-150, 54	--	--

Note: Control: placebo or standard care/dietary change. (a) Mean difference < 0 shows an advantage of treatment over the reference. CrI = Credible Interval

PART IV: CLOSING REMARKS

1. Discussion

This is the first NMA comparing lipid-lowering therapies for the treatment of dyslipidemia in HIV-positive individuals. It allows for more precise treatment comparisons and helps make inferences about relative treatment effects for comparisons that had never been previously made. Including all of the available evidence from the RCTs found in the literature allowed for more informed estimates. Using network meta-analysis methods[84] to combine both direct and indirect evidence yielded more informed estimates of the relative effects of statins that had never been compared head-to-head in existing RCTs, while maintaining the benefits of randomization. Moreover, the use of Bayesian methods provided us with a better understanding of how different lipid-lowering therapies rank in terms of efficacy and safety when compared against each other and not solely to a control. Such probability-based methods provide clinicians, health economists, and policy-makers with an intuitive platform for decision-making under uncertainty.

A recurring theme among critiques of the Bayesian approach is that the prior distribution influences the results obtained.[72] It is argued that grounding analyses on prior assumptions about the data can introduce potential subjectivity to the conclusions derived from a Bayesian interpretation of NMA results. Our choice to use non-informative priors for every parameter in the model helped avoid this potential limitation. By assuming that any treatment effect value was equally likely, the treatment effect estimates obtained from our parameters' posterior distributions were entirely driven by the data. In doing so, we were able to

objectively rank and make direct probability statements about the comparative treatment effects.

Moreover, although rank probability statements are a great advantage of using Bayesian methods, their use in networks consisting of small studies, has been debated.[107] Most of the trials included in this NMA can be classified as small studies. In networks comprised of small studies, solely looking at the probability for a treatment of being the best can result in false statements regarding the relative ranks of treatment within the network hierarchy of intervention**.** For instance, rank probabilities can be over or underestimated. A simulation study was conducted to assess the bias in identifying the best treatments within a Bayesian NMA framework.[107] The simulations showed that increasing the sample size of individual studies did not help to adjust the over or underestimation of treatment rank probabilities. Thus, we do not expect the relatively small size of our included trials to have biased our probability statements.

Despite our thorough search strategies and rigorous study selection methods, it is possible that some publication bias contributes to our analysis. Such bias is unavoidable in any literature-based analysis, as the limitations of an NMA are intricately tied to those of the published evidence base. For instance, there was some asymmetry in the evidence network. It seems that certain interventions are disproportionately evaluated (i.e. pravastatin), suggesting a potentially biased research agenda. Given this NMA's finding that pravastatin tends to rank among the least efficacious statins, reasons behind the network's asymmetry should be further investigated. Moreover, outcomes in some of the included trials were poorly

reported. For example, not all trials reported on adverse events and while two RCTs reported on changes in total cholesterol and triglyceride levels from baseline they did not report on changes in LDL and HDL cholesterol levels. This also suggests that publication bias in the evidence base may have contributed to bias in our analyses.

Furthermore, the validity of a NMA depends on the extent to which the findings of the included RCTs can be pooled together.[72] Assessing differences in patient and trial characteristics revealed that the trials were sufficiently similar to be combined in a network meta-analysis. However, although between-study heterogeneity ranged from low to moderate, it is possible that unexplained or unaccounted for heterogeneity may have affected the treatment effect estimates obtained. This is due to the fact that all literature-based evidence syntheses are comprised of studies that are different both clinically and methodologically. Significant differences between studies can thus bias the results of NMAs. However, the findings presented in this NMA were obtained through the use of a random-effects model. In other words, they are based on the assumption that each study has its own true treatment effect, due to differences in trial characteristics and in the distribution of patient-related effect modifiers.[108] Our analyses therefore did attempt to take potential unexplained heterogeneity into account through the use of a random-effects model.

Nevertheless, we conducted sensitivity analyses in order to explore potential sources of heterogeneity. Key outlier studies were excluded from the analyses. The width of the credible intervals did not significantly change around the relative efficacy estimates obtained, compared to those obtained using all of the available

data. This suggests that the potential effect-modifiers evaluated did not change the certainty around our estimates. There are perhaps other factors that could contribute to the heterogeneity found. The literature review suggests that the use of ART containing PIs could be an effect-modifier as well. However, all studies reported that their participants were on PI-containing ART regimens, precluding a sensitivity analysis exploring the potential effect-modification of the type of ART given to patients on the relative efficacy of statins. Similarly the effect of different medication dosage on relative treatment effects could not be assessed because doses did not differ across studies.

Due to the lack of trials providing head to head evidence on the use of statins, our estimates tend to disproportionately rely on indirect evidence. Indirect evidence contains lower precision than evidence obtained with a direct comparison. This explains why our credible intervals were often large. This limitation is important to take into consideration as it highlights the need for more trials evaluating lipid-lowering therapies among themselves instead of against control or standard treatment.

Moreover, the power of a NMA depends on both trial sample size and the number of trials available for each comparison.[108] Out of the 15 trials included in this NMA, few studies reported on safety outcomes. Of those that did, most were small and did not have any adverse events to report. The wide credible intervals reported represent a lack of precision in the estimates obtained and translate into uncertainty around our conclusions. Therefore, with regards to the safety of statins, the power of this NMA was lowered by the lack of evidence available in the

literature. This not only stresses the need for more research on the safety of lipid-lowering therapies, but also to better report on safety outcomes.

Finally, the external validity of this NMA is limited by the external validity of the included RCTs. For instance, since all trials were conducted in developed countries, and all patients were on stable antiretroviral therapy, the findings of this NMA are only applicable to developed countries and to patients who are on stable ART. Health care decision-makers will thus need to assess whether the results of this NMA can be generalized to their population of interest.

2. Recommendations

This NMA provides clinicians and policy-makers with strong evidence that statins are the most effective class of lipid-lowering therapies given for the treatment of dyslipidemia in HIV-positive patients on stable ART. The recommendations from this thesis can be summarized as follows:

- *Among all lipid-lowering therapies*, while fibrates are the most effective treatments for lowering triglyceride levels, overall, **rosuvastatin** is the most effective therapy for treating dyslipidemia in PLHA.
- *Among statins*, **all statins appear to offer treatment benefits.**
- Overall, all statins seem to offer similar odds of adverse events to control or placebo. However, more RCTs reporting on the safety of lipid-lowering therapies and better reporting measures for safety outcomes are needed.

- Future studies will also have to investigate the cost-effectiveness of statins, as the identification of the best statin should not be based solely on efficacy outcomes. Combined with this NMA, such studies will be of key importance to policy makers in order to update clinical guidelines.

APPENDIX

A. Ovid search strategy for MEDLINE/Pubmed, EMBASE, and AMED databases [Last conducted on 05/01/15]

Search	**Query**
1	HIV/
2	HIV Infections/
3	HIV-positive.mp
4	seropositive.mp
5	HIV-infected.mp
6	2 or 3 or 4 or 5
7	Dyslipidemias/
8	Hyperlipidemias
9	Dyslipidemic.mp
10	lipodystrophy.mp
11	lipoatrophy.mp
12	lipid abnormal$.mp
13	7 or 8 or 9 or 10 or 11 or 12
14	6 and 13 2745
15	Hydroxymethylglutaryl-CoA Reductase Inhibitors/
16	statin.mp
17	15 or 16
18	Cholesterol/
19	Lipids.mp
20	18 or 19
21	14 and 17 and 20

B. Ovid search strategy for Cochrane CENTRAL, HEALTHSTAR and AMED databases [Last conducted on 05/01/15]

Search	**Query**
1	HIV-infected.mp
2	Dyslipidemia.mp
3	HIV Infections
4	1 or 3
5	Hyperlipidemias
6	2 or 5
7	4 and 6
8	Hydroxymethylglutaryl-CoA Reducase Inhibitors/
9	statin.mp
10	8 or 9
11	Lipids/
12	Cholesterol
13	11 or 12
14	7 and 10 and 13

C. EBSCO search strategy for CINHAL and Web of Science databases [Last conducted on 05/01/15]

Search	**Query**
1	TX statin
2	TX HIV-positive
3	TX HIV-infected
4	TX dyslipidemia
5	TX hyperlipidemia
6	S4 OR S5
7	S2 OR S3
8	S1 AND S6 AND S7

D. Search strategy for Web of Science Thomson Reuters database [Last conducted on 05/01/15]

Search	**Query**
1	TX statin
2	TX HIV-positive
3	TX HIV-infected
4	TX dyslipidemia
5	TX hyperlipidemia
6	S4 OR S5
7	S2 OR S3
8	S1 AND S6 AND S7

E. Published PROSPERO protocol

UNIVERSITY of York
Centre for Reviews and Dissemination

NHS
National Institute for
Health Research

PROSPERO International prospective register of systematic reviews

Efficacy of statins in HIV-infected individuals with lipid abnormalities: a systematic review and network meta-analysis

Laura Mesana, Edward Mills

Citation
Laura Mesana, Edward Mills. Efficacy of statins in HIV-infected individuals with lipid abnormalities: a systematic review and network meta-analysis. PROSPERO 2014:CRD42014007077 Available from http://www.crd.york.ac.uk/PROSPERO_REBRANDING/display_record.asp?ID=CRD42014007077

Review question(s)
What is the effect of statins on average change in lipid levels across the antiretroviral-receiving HIV/AIDS population suffering from lipid abnormalities?

Which statins are most effective?

Searches
Medline (PubMed), EMBASE, Science Citation Index, Cochrane (CENTRAL), CINAHL, TRIP, Conference Papers Index, CDSR, DARE.

Types of study to be included
-Included: Randomized experimental studies, Randomized Controlled Trials (RCTs), Studies with minimum 6-weeks follow-up, Intent-to-treat analysis done or can at least be inferred from data reported in methods.

-Excluded: Observational studies, Studies reported results from less than 6-weeks follow-up, Studies using same data but published at different instances with minor changes.

Condition or domain being studied
Patients with HIV/AIDS on antiretroviral therapy have been found to suffer from lipid abnormalities, including elevated levels of total and LDL-cholesterol as well as triglyceride levels. Abnormal lipid levels are associated with increased risk for developing cardiovascular diseases. The latter are top causes of mortality among the general population.

Participants/ population
-Included: HIV/AIDS individuals on Antiretroviral Therapy (ART) with lipid abnormalities, Individuals from any age and gender

-Excluded: Individuals with lipid abnormalities but who are not infected with HIV/AIDS, HIV/AIDS individuals without lipid abnormalities, HIV/AIDS individuals who are on ART and have lipid abnormalities, but who also have at least two other non-AIDS related comorbidities, Individuals who had already been taking any sort of lipid-lowering medication before start of trial.

Intervention(s), exposure(s)
-Included: All types of statins.

-Excluded: Other sorts lipid-lowering therapies.

Comparator(s)/ control
-Included: Placebo, Other lipid-lowering therapies, Statins compared between themselves.

-Excluded: Non-controlled studies.

Context

HIV/AIDS patients on ART have been reported by numerous observational studies to show elevated lipid levels, a major risk factor for cardiovascular diseases. There is a lot of high-quality evidence for the use of statins as first-line therapy for lowering cholesterol levels in the general population. Such evidence is lacking in the HIV/AIDS population.

Outcome(s)

Primary outcomes

Average change in total, LDL, and HDL cholesterol levels.

Average change in triglyceride levels.

Not applicable.

Secondary outcomes

None.

Not applicable.

Data extraction, (selection and coding)

Two independent researchers will select studies for the review and extract data. A neutral third party will resolve discrepancies between the two reviewers' findings. Data relating to primary outcomes will be extracted from individual studies.

Risk of bias (quality) assessment

Risk of bias:

Having two independent reviewers finding RCTs and a neutral third party mediating discrepancies reduces selection bias, Including studies with both positive and negative studies prevents publication bias, Intent-to-treat analysis prevents attrition bias

Quality of individual studies:

Evaluate directness of individual studies: Research questions of individual studies should be similar to this review's research questions, Indirect information will be used very cautiously.

Random assignment to treatment arms is essential: Ensures treatment groups are comparable

Baseline characteristics should be available in publication: Randomization should lead to similar baseline characteristics among treatment arms

Concealment of allocation: RCTs with blinded participants will be considered as being a better quality of evidence, but non-blinding studies will be included in meta-analysis

Statistical significance of individual studies' findings should be reported: P-values, confidence intervals, etc.

Intent-to-treat analysis: All study participants should be analyzed in their original treatment group, Studies should report the number of participants who did not comply or adhere to treatment, dropped out, etc. Reason for such deviations should also be reported by the individual studies.

Strategy for data synthesis

Quantitative synthesis will be done by doing a meta-analysis of findings pooled from individual studies.

Random-Effects Model and Indirect Comparisons (Bayesian Network meta-analysis or adjusted indirect comparisons).

In order to compare which statin is most effective/compare statins' efficacies among themselves.

Done by pooling findings from reporting individual statin effect vs. placebo/other comparator and/or control.

Accounts for both within-study and between-study variance having occurred by chance.

Assumes heterogeneity in findings from different individual studies.

Analysis of subgroups or subsets
None planned.

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Details of any existing review of the same topic by the same authors
None.

Anticipated or actual start date
07 January 2014

Anticipated completion date
31 July 2014

Funding sources/sponsors
Edward Mills

Conflicts of interest
None known

Language
English

Country
Canada

Subject index terms status
Subject indexing assigned by CRD

Subject index terms
Antiretroviral Therapy, Highly Active; HIV Infections; HIV Protease Inhibitors; Humans; Hyperlipidemias; Hypolipidemic Agents; Lipid Metabolism

Stage of review
Ongoing

Date of registration in PROSPERO

08 January 2014

Date of publication of this revision
08 January 2014

Stage of review at time of this submission	Started	Completed
Preliminary searches	No	No
Piloting of the study selection process	No	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

F. The Cochrane Collaboration's tool for assessing risk of bias

The Cochrane Collaboration's tool for assessing risk of bias

Domain	Description	Review authors' judgement
Sequence generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.	Was the allocation sequence adequately generated?
Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.	Was allocation adequately concealed?
Blinding of participants, personnel and outcome assessors *Assessments should be made for each main outcome (or class of outcomes)*	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Was knowledge of the allocated intervention adequately prevented during the study?
Incomplete outcome data *Assessments should be made for each main outcome (or class of outcomes)*	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.	Were incomplete outcome data adequately addressed?
Selective outcome reporting	State how the possibility of selective outcome reporting was examined by the review authors, and what was found.	Are reports of the study free of suggestion of selective outcome reporting?
Other sources of bias	State any important concerns about bias not addressed in the other domains in the tool. If particular questions/entries were pre-specified in the review's protocol, responses should be provided for each question/entry.	Was the study apparently free of other problems that could put it at a high risk of bias?

Possible approach for *summary assessments* outcome (across domains) within and across studies

Risk of bias	Interpretation	Within a study	Across studies
Low risk of bias	Plausible bias unlikely to seriously alter the results.	Low risk of bias for all key domains.	Most information is from studies at low risk of bias.
Unclear risk of bias	Plausible bias that raises some doubt about the results	Unclear risk of bias for one or more key domains.	Most information is from studies at low or unclear risk of bias.
High risk of bias	Plausible bias that seriously weakens confidence in the results.	High risk of bias for one or more key domains.	The proportion of information from studies at high risk of bias is sufficient to affect the interpretation of the results.

Criteria for judging risk of bias in the 'Risk of bias' assessment tool

SEQUENCE GENERATION **Was the allocation sequence adequately generated? [Short form: *Adequate sequence generation*?]**	
Criteria for a judgement of 'YES' (i.e. low risk of bias).	The investigators describe a random component in the sequence generation process such as: ▪ Referring to a random number table; Using a computer random number generator; Coin tossing; Shuffling cards or envelopes; Throwing dice; Drawing of lots; Minimization*. *Minimization may be implemented without a random element, and this is considered to be equivalent to being random.
Criteria for the judgement of 'NO' (i.e. high risk of bias).	The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, for example: ▪ Sequence generated by odd or even date of birth; ▪ Sequence generated by some rule based on date (or day) of admission; ▪ Sequence generated by some rule based on hospital or clinic record number. Other non-random approaches happen much less frequently than the systematic approaches mentioned above and tend to be obvious. They usually involve judgement or some method of non-random categorization of participants, for example: ▪ Allocation by judgement of the clinician; ▪ Allocation by preference of the participant; ▪ Allocation based on the results of a laboratory test or a series of tests; ▪ Allocation by availability of the intervention.
Criteria for the judgement of 'UNCLEAR' (uncertain risk of bias).	Insufficient information about the sequence generation process to permit judgement of 'Yes' or 'No'.
ALLOCATION CONCEALMENT **Was allocation adequately concealed? [Short form: *Allocation concealment*?]**	
Criteria for a judgement of 'YES' (i.e. low risk of bias).	Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: ▪ Central allocation (including telephone, web-based, and pharmacy-controlled, randomization); ▪ Sequentially numbered drug containers of identical appearance; ▪ Sequentially numbered, opaque, sealed envelopes.
Criteria for the judgement of 'NO' (i.e. high risk of bias).	Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on: ▪ Using an open random allocation schedule (e.g. a list of random numbers); ▪ Assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); ▪ Alternation or rotation; ▪ Date of birth; ▪ Case record number; ▪ Any other explicitly unconcealed procedure.

Criteria for the judgement of 'UNCLEAR' (uncertain risk of bias).	Insufficient information to permit judgement of 'Yes' or 'No'. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement – for example if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed.
BLINDING OF PARTICIPANTS, PERSONNEL AND OUTCOME ASSESSORS **Was knowledge of the allocated interventions adequately prevented during the study? [Short form: *Blinding*?]**	
Criteria for a judgement of 'YES' (i.e. low risk of bias).	Any one of the following: ▪ No blinding, but the review authors judge that the outcome and the outcome measurement are not likely to be influenced by lack of blinding; ▪ Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken; ▪ Either participants or some key study personnel were not blinded, but outcome assessment was blinded and the non-blinding of others unlikely to introduce bias.
Criteria for the judgement of 'NO' (i.e. high risk of bias).	Any one of the following: ▪ No blinding or incomplete blinding, and the outcome or outcome measurement is likely to be influenced by lack of blinding; ▪ Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken; ▪ Either participants or some key study personnel were not blinded, and the non-blinding of others likely to introduce bias.
Criteria for the judgement of 'UNCLEAR' (uncertain risk of bias).	Any one of the following: ▪ Insufficient information to permit judgement of 'Yes' or 'No'; ▪ The study did not address this outcome.
INCOMPLETE OUTCOME DATA **Were incomplete outcome data adequately addressed? [Short form: *Incomplete outcome data addressed*?]**	
Criteria for a judgement of 'YES' (i.e. low risk of bias).	Any one of the following: ▪ No missing outcome data; ▪ Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); ▪ Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; ▪ For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; ▪ For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; ▪ Missing data have been imputed using appropriate methods.
Criteria for the judgement of 'NO' (i.e. high risk of bias).	Any one of the following: ▪ Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; ▪ For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; ▪ For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; ▪ 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomization; ▪ Potentially inappropriate application of simple imputation.

Criteria for the judgement of 'UNCLEAR' (uncertain risk of bias).	Any one of the following: ▪ Insufficient reporting of attrition/exclusions to permit judgement of 'Yes' or 'No' (e.g. number randomized not stated, no reasons for missing data provided); ▪ The study did not address this outcome.
SELECTIVE OUTCOME REPORTING **Are reports of the study free of suggestion of selective outcome reporting? [Short form: *Free of selective reporting*?]**	
Criteria for a judgement of 'YES' (i.e. low risk of bias).	Any of the following: ▪ The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; ▪ The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
Criteria for the judgement of 'NO' (i.e. high risk of bias).	Any one of the following: ▪ Not all of the study's pre-specified primary outcomes have been reported; ▪ One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; ▪ One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); ▪ One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; ▪ The study report fails to include results for a key outcome that would be expected to have been reported for such a study.
Criteria for the judgement of 'UNCLEAR' (uncertain risk of bias).	Insufficient information to permit judgement of 'Yes' or 'No'. It is likely that the majority of studies will fall into this category.
OTHER POTENTIAL THREATS TO VALIDITY **Was the study apparently free of other problems that could put it at a risk of bias? [Short form: *Free of other bias*?]**	
Criteria for a judgement of 'YES' (i.e. low risk of bias).	The study appears to be free of other sources of bias.
Criteria for the judgement of 'NO' (i.e. high risk of bias).	There is at least one important risk of bias. For example, the study: ▪ Had a potential source of bias related to the specific study design used; or ▪ Stopped early due to some data-dependent process (including a formal-stopping rule); or ▪ Had extreme baseline imbalance; or ▪ Has been claimed to have been fraudulent; or ▪ Had some other problem.
Criteria for the judgement of 'UNCLEAR' (uncertain risk of bias).	There may be a risk of bias, but there is either: ▪ Insufficient information to assess whether an important risk of bias exists; or ▪ Insufficient rationale or evidence that an identified problem will introduce bias.

G. Preferred reported items for systematic reviews and meta-analyses: The PRISMA statement checklist

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

H. Random effects model code for efficacy outcomes *(WinBUGS)*

```
# Normal likelihood, identity link
# Random effects model for multi-arm trials

model{                                  # *** PROGRAM STARTS
for(i in 1:ns){                         #   LOOP THROUGH STUDIES
w[i,1] <- 0                             # adjustment for multi-arm trials is zero for control arm
delta[i,1] <- 0                          # treatment effect is zero for control arm
    mu[i] ~ dnorm(0,.0001)                    # vague priors for all trial baselines
    for (k in 1:na[i]) {                       #  LOOP THROUGH ARMS
    var[i,k] <- pow(se[i,k],2)                  # calculate variances
    prec[i,k] <- 1/var[i,k]                        # set precisions
    y[i,k] ~ dnorm(theta[i,k],prec[i,k])         # normal likelihood
   theta[i,k] <- mu[i] + delta[i,k]              # model for linear predictor
#Deviance contribution
          dev[i,k] <- (y[i,k]-theta[i,k])*(y[i,k]-theta[i,k])*prec[i,k]
          }
#  summed residual deviance contribution for this trial
          resdev[i] <- sum(dev[i,1:na[i]])
for (k in 2:na[i]) {                                 # LOOP THROUGH ARMS
                    # trial-specific LOR distributions
delta[i,k] ~ dnorm(md[i,k],taud[i,k]) # mean of LOR distributions, with multi-arm trial
correction
      md[i,k] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k]       # precision of LOR distributions (with multi-
arm trial correction)
          taud[i,k] <- tau *2*(k-1)/k          # adjustment, multi-arm RCTs
          w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])    # cumulative adjustment for multi-arm
trials
          sw[i,k] <- sum(w[i,1:k-1])/(k-1)
          }
  }
    totresdev <- sum(resdev[])                #Total Residual Deviance
   d[1]<-0                                   # treatment effect is zero for control arm
# vague priors for treatment effects
   for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }
   sd ~ dunif(0,5)                           # vague prior for between-trial SD
   tau <- pow(sd,-2)                            # between-trial precision = (1/between-trial
variance)
# Provide estimates of treatment effects T[k] on the natural scale
# Given a Mean Effect, meanA, for 'standard' treatment A,
# with precision (1/variance) precA
       A ~ dnorm(meanA,precA)
         for (k in 1:nt) { T[k] <- A + d[k]  }
}                                       # *** PROGRAM ENDS
```

I. Fixed effects model code for efficacy outcomes *(WinBUGS)*

```
# Normal likelihood, identity link
# Fixed effects model
model{                                          # *** PROGRAM STARTS
for(i in 1:ns){                                 #   LOOP THROUGH STUDIES
   mu[i] ~ dnorm(0,.0001)                       # vague priors for all trial baselines
   for (k in 1:na[i]) {                         #  LOOP THROUGH ARMS
      var[i,k] <- pow(se[i,k],2)                # calculate variances
      prec[i,k] <- 1/var[i,k]                   # set precisions
      y[i,k] ~ dnorm(theta[i,k],prec[i,k])              # normal likelihood
# model for linear predictor
      theta[i,k] <- mu[i] + d[t[i,k]] - d[t[i,1]]
#Deviance contribution
      dev[i,k] <- (y[i,k]-theta[i,k])*(y[i,k]-theta[i,k])*prec[i,k]
    }
#  summed residual deviance contribution for this trial
   resdev[i] <- sum(dev[i,1:na[i]])
 }
totresdev <- sum(resdev[])                              #Total Residual Deviance
d[1]<-0                                         # treatment effect is zero for control arm
# vague priors for treatment effects
for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }
# Provide estimates of treatment effects T[k] on the natural scale
# Given a Mean Effect, meanA, for 'standard' treatment A,
# with precision (1/variance) precA
A ~ dnorm(meanA,precA)
for (k in 1:nt) { T[k] <- A + d[k]  }
}                                               # *** PROGRAM ENDS
```

J. Random effects model code for safety outcomes *(WinBUGS)*

```
# Binomial likelihood, logit link
# Random effects model for multi-arm trials

model{                                  # *** PROGRAM STARTS
for(i in 1:ns){                                 # LOOP THROUGH STUDIES
  w[i,1] <- 0                           # adjustment for multi-arm trials is zero for control
arm
  delta[i,1] <- 0                       # treatment effect is zero for control arm
  mu[i] ~ dnorm(0,1)                    # vague priors for all trial baselines
  for (k in 1:na[i]) {                  # LOOP THROUGH ARMS
    r[i,k] ~ dbin(p[i,k],n[i,k])        # binomial likelihood
    logit(p[i,k]) <- mu[i] + delta[i,k] # model for linear predictor
    rhat[i,k] <- p[i,k] * n[i,k]        # expected value of the numerators
#Deviance contribution
    dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
      +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))       }
#  summed residual deviance contribution for this trial
  resdev[i] <- sum(dev[i,1:na[i]])
  for (k in 2:na[i]) {                          # LOOP THROUGH ARMS
# trial-specific LOR distributions
    delta[i,k] ~ dnorm(md[i,k],taud[i,k])
# mean of LOR distributions (with multi-arm trial correction)
    md[i,k] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k]
# precision of LOR distributions (with multi-arm trial correction)
    taud[i,k] <- tau *2*(k-1)/k
# adjustment for multi-arm RCTs
    w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
    sw[i,k] <- sum(w[i,1:k-1])/(k-1)
   }
 }
totresdev <- sum(resdev[])                      # Total Residual Deviance
d[1]<-0                                 # treatment effect is zero for reference treatment
# vague priors for treatment effects
for (k in 2:nt){  d[k] ~ dnorm(0,1) }
sd ~ dunif(0,5)                         # vague prior for between-trial SD
tau <- pow(sd,-2)                       # between-trial precision = (1/between-trial
variance)
# Provide estimates of treatment effects T[k] on the natural (probability) scale
# Given a Mean Effect, meanA, for 'standard' treatment A,
# with precision (1/variance) precA
A ~ dnorm(meanA,precA)
for (k in 1:nt) { logit(T[k]) <- A + d[k]  }
# on alternative scales: Numbers Needed to Treat, Risk Difference, Relative Risks
# pairwise ORs and LORs for all possible pair-wise comparisons, if nt>2
for (c in 1:(nt-1)) {
```

```
for (k in (c+1):nt) {
or[c,k] <- exp(d[k] - d[c])
lor[c,k] <- (d[k]-d[c])
}
}
# ranking on relative scale
for (k in 1:nt) {
rk[k] <- nt+1-rank(d[],k) # assumes events are ?good?
# rk[k] <- rank(d[],k) # assumes events are ?bad?
best[k] <- equals(rk[k],1) #calculate probability that treat k is best
}
}                          # *** PROGRAM ENDS
```

K. Fixed effects model code for safety outcomes *(WinBUGS)*

```
# Binomial likelihood, logit link
# Fixed effects model

model{                                          # *** PROGRAM STARTS
for(i in 1:ns){                                 # LOOP THROUGH STUDIES
   mu[i] ~ dnorm(0,1)                           # vague priors for all trial baselines
   for (k in 1:na[i])  {                                # LOOP THROUGH ARMS
      r[i,k] ~ dbin(p[i,k],n[i,k])                    # binomial likelihood
# model for linear predictor
      logit(p[i,k]) <- mu[i] + d[t[i,k]] - d[t[i,1]]
# expected value of the numerators
      rhat[i,k] <- p[i,k] * n[i,k]
#Deviance contribution
      dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
          +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
    }
# summed residual deviance contribution for this trial
   resdev[i] <- sum(dev[i,1:na[i]])
   }
totresdev <- sum(resdev[])                      # Total Residual Deviance
d[1]<-0                                         # treatment effect is zero for reference treatment
# vague priors for treatment effects
for (k in 2:nt){  d[k] ~ dnorm(0,1) }
# Provide estimates of treatment effects T[k] on the natural (probability) scale
# Given a Mean Effect, meanA, for 'standard' treatment A,
# with precision (1/variance) precA
A ~ dnorm(meanA,precA)
for (k in 1:nt) { logit(T[k]) <- A + d[k]  }
     }                                          # *** PROGRAM ENDS
```

L. Random effects code for efficacy outcomes *(R)*

```
setwd("C:/R files/")
install.packages("R2WinBUGS")
library(R2WinBUGS)
install.packages("gemtc")
library(gemtc)

mydata = read.table('#Name of text file containing  outcome data#')
mydata
names(mydata) <- c("study", "treatment", "mean","std.dev", "sampleSize")
treatments <- read.table(textConnection('
id  description
1   "Placebo/Control"
2   "Pravastatin"
3   "Rosuvastatin"
4   "Atorvastatin"
5   "Fluvastatin"
6   "Pitavastatin"
7   "Bezafibrate"
8   "Fenofibrate"
9   "Fenofibrate & Ezetimibe"
10   "Gemfibrozil"'), header=TRUE)
alltreatments <- sort(unique(data[,"treatment"]))
for(t in 1:length(alltreatments)){
data[data[,"treatment"]==alltreatments[t],"treatment"] <- t
}
data <- data[order(as.numeric(data[,"study"]),as.numeric(data[,"treatment"])),]
treatments <- data.frame(id=as.character(1:length(alltreatments)),
description=alltreatments,stringsAsFactors=F)
gemtc_network_numbers <- mtc.network(data,treatments=treatments)
network <- mtc.network(data, description="TotalC Efficacy", treatments=treatments)
plot(network)
summary(network)
model.re <- mtc.model(network, type = "consistency", n.chain = 3,
        likelihood = "normal", link = "identity", linearModel = "random")
plot(model.re)
summary(model.re)
mtcresults.re <- mtc.run(model.re, n.adapt = 50000, n.iter=100000, thin=1,
sampler="R2WinBUGS")
summary(mtcresults.re)
plot(mtcresults.re)
forest(mtcresults.re)
summary(relative.effect(mtcresults.re,"1"))
forest(relative.effect(mtcresults.re,"1"))
summary(relative.effect(mtcresults.re,"2"))
forest(relative.effect(mtcresults.re,"2"))
summary(relative.effect(mtcresults.re,"3"))
rank.probability(mtcresults.re,preferredDirection=-1)
plot(rank.probability(mtcresults.re,preferredDirection=-1),beside=T)
```

```
"sucraplot.fun" = function(effectiveness, plotmfrow = c(3, 3))
{
	# effectiveness: the effectiveness matrix as DATABASE, each column is a treatment
	# plotmfrow is a vector of length two which defines the panels in the plot
	#Creates cumulative ranking curves extrapolated at the middle of each bar

	names <- names(effectiveness)
	nr.of.treat <- dim(effectiveness)[2]
	cumeffectiveness <- apply(effectiveness, 2, cumsum)
	par(mfrow = plotmfrow)
	for(i in 1:nr.of.treat) {
		plot(1:nr.of.treat, type = "none", ylim = c(0, 1), xlab =
			paste("Rank of", as.character(names[i])), ylab =
			"Cumulative Probability")
		#lines(stepfun(1:nr.of.treat, cumeffectiveness[, i]), lty = 2, col = 2, lwd = 2)
		lines(lwd = 2, c(1, c(1:c(nr.of.treat - 1)) + 0.5, nr.of.treat
			), cumeffectiveness[c(1, 1:c(nr.of.treat - 1), c(
			nr.of.treat - 1)), i])
	}

	for(i in 1:nr.of.treat) {
		plot(1:nr.of.treat, type = "none", ylim = c(0, 1), xlab =
			paste("Rank of", as.character(names[i])), ylab =
			"Probability")
		#lines(stepfun(1:nr.of.treat, cumeffectiveness[, i]), lty = 2, col = 2, lwd = 2)
		lines(lwd = 2, c(1, c(1:c(nr.of.treat - 1)) + 0.5, nr.of.treat
			), effectiveness[c(1, 1:c(nr.of.treat - 1), c(
			nr.of.treat - 1)), i])
	}
}
SUCRAdata = read.table('#insert text file name#')
SUCRAdata
eff<-SUCRAdata[1:100,2]
effectiveness=as.data.frame(matrix(eff, nrow=10,ncol=10,byrow=F))
names(effectiveness)=c("Placebo","Pravastatin","Rosuvastatin","Atorvastatin","Fluvastatin"
,"Pitavastatin","Bezafibrate","Fenofibrate","Fenofibrate & Ezetimibe", "Gemfibrozil")
sucraplot.fun(effectiveness, plotmfrow = c(5, 5))
```

M. Random effects code for safety outcomes (*R*)

```
setwd("C:/R files/")
install.packages("R2WinBUGS")
library(R2WinBUGS)
install.packages("gemtc")
library(gemtc)

mydata = read.table('#Name of text file containing  outcome data#')
mydata
names(mydata) <- c("study", "treatment", "responders", "sampleSize")
treatments <- read.table(textConnection('
id  description
1   "Placebo/Control"
2   "Pravastatin"
3   "Rosuvastatin"
4   "Atorvastatin"
5   "Fluvastatin"
6   "Pitavastatin"
7   "Bezafibrate"
8   "Fenofibrate"
9   "Fenofibrate & Ezetimibe"
10   "Gemfibrozil"'), header=TRUE)
alltreatments <- sort(unique(mydata[,"treatment"]))
for(t in 1:length(alltreatments)){
mydata[mydata[,"treatment"]==alltreatments[t],"treatment"] <- t
}
mydata <-
mydata[order(as.numeric(mydata[,"study"]),as.numeric(mydata[,"treatment"])),]
treatments <- data.frame(id=as.character(1:length(alltreatments)),
description=alltreatments,stringsAsFactors=F)
gemtc_network_numbers <- mtc.network(mydata,treatments=treatments)
network <- mtc.network(mydata, description="ALT Safety", treatments=treatments)
plot(network)
summary(network)
model.re <- mtc.model(network, type = "consistency", n.chain = 3,
        likelihood = "binom", link = "logit", linearModel = "random")
plot(model.re)
summary(model.re)
mtcresults.re <- mtc.run(model.re, n.adapt = 50000, n.iter=100000, thin=1,
sampler="R2WinBUGS")
summary(mtcresults.re)
plot(mtcresults.re)
forest(mtcresults.re)
ORandCIs <-
round(exp(summary(relative.effect(mtcresults.re,"1"))$summaries$quantiles[1:5,c("50%",
"2.5%", "97.5%")]), 2)
paste(ORandCIs[, 1], "(", ORandCIs[, 2], ", ", ORandCIs[, 3], ")", sep="")
```

```
ORandCIs <-
round(exp(summary(relative.effect(mtcresults.re,"1"))$summaries$quantiles[1:5,c("50%",
"2.5%", "97.5%")]), 2)
paste(ORandCIs[, 1], "(", ORandCIs[, 2], ", ", ORandCIs[, 3], ")", sep="")
ORandCIs <-
round(exp(summary(relative.effect(mtcresults.re,"2"))$summaries$quantiles[1:5,c("50%",
"2.5%", "97.5%")]), 2)
paste(ORandCIs[, 1], "(", ORandCIs[, 2], ", ", ORandCIs[, 3], ")", sep="")
summary(relative.effect(mtcresults.re,"1"))
forest(relative.effect(mtcresults.re,"1"))
summary(relative.effect(mtcresults.re,"2"))
forest(relative.effect(mtcresults.re,"2"))
summary(relative.effect(mtcresults.re,"3"))
rank.probability(mtcresults.re,preferredDirection=-1)
plot(rank.probability(mtcresults.re,preferredDirection=-1),beside=T)
"sucraplot.fun" = function(effectiveness, plotmfrow = c(3, 3))
{
        # effectiveness: the effectiveness matrix as DATABASE, each column is a treatment
        # plotmfrow is a vector of length two which defines the panels in the plot
        #Creates cumulative ranking curves extrapolated at the middle of each bar

        names <- names(effectiveness)
        nr.of.treat <- dim(effectiveness)[2]
        cumeffectiveness <- apply(effectiveness, 2, cumsum)
        par(mfrow = plotmfrow)
        for(i in 1:nr.of.treat) {
                plot(1:nr.of.treat, type = "none", ylim = c(0, 1), xlab =
                        paste("Rank of", as.character(names[i])), ylab =
                        "Cumulative Probability")
                #lines(stepfun(1:nr.of.treat, cumeffectiveness[, i]), lty = 2, col = 2, lwd = 2)
                lines(lwd = 2, c(1, c(1:c(nr.of.treat - 1)) + 0.5, nr.of.treat
                        ), cumeffectiveness[c(1, 1:c(nr.of.treat - 1), c(
                        nr.of.treat - 1)), i])
        }

        for(i in 1:nr.of.treat) {
                plot(1:nr.of.treat, type = "none", ylim = c(0, 1), xlab =
                        paste("Rank of", as.character(names[i])), ylab =
                        "Probability")
                #lines(stepfun(1:nr.of.treat, cumeffectiveness[, i]), lty = 2, col = 2, lwd = 2)
                lines(lwd = 2, c(1, c(1:c(nr.of.treat - 1)) + 0.5, nr.of.treat
                        ), effectiveness[c(1, 1:c(nr.of.treat - 1), c(
                        nr.of.treat - 1)), i])
        }
}
SUCRAdata = read.table('#Insert text file name#')
SUCRAdata
safe<-SUCRAdata[1:110,2]
Safety=as.data.frame(matrix(safe, nrow=10,ncol=10,byrow=F))
```

```
names(Safety)=c("Placebo","Pravastatin","Rosuvastatin","Atorvastatin","Fluvastatin","Pitav
astatin","Bezafibrate","Fenofibrate","Fenofibrate & Ezetimibe", "Gemfibrozil")
sucraplot.fun(Safety, plotmfrow = c(5, 5))
```

N. Inconsistency model code (*WinBUGS*)

```
# Normal likelihood, identity link, inconsistency model
# Random effects model

model{                                          # *** PROGRAM STARTS
for(i in 1:ns){                                  # LOOP THROUGH STUDIES
   delta[i,1]<-0                                 # treatment effect is zero in control arm
   mu[i] ~ dnorm(0,.0001)                        # vague priors for trial baselines
   for (k in 1:na[i]) {                          #  LOOP THROUGH ARMS
      var[i,k] <- pow(se[i,k],2)                 # calculate variances
      prec[i,k] <- 1/var[i,k]                    # set precisions
                              y[i,k] ~ dnorm(theta[i,k],prec[i,k]) # normal likelihood
      theta[i,k] <- mu[i] + delta[i,k]                          # model for linear predictor
#Deviance contribution
       dev[i,k] <- (y[i,k]-theta[i,k])*(y[i,k]-theta[i,k])*prec[i,k]
    }
# summed residual deviance contribution for this trial
  resdev[i] <- sum(dev[i,1:na[i]])
  for (k in 2:na[i]) {                           # LOOP THROUGH ARMS
# trial-specific LOR distributions
      delta[i,k] ~ dnorm(d[t[i,1],t[i,k]] ,tau)
    }
 }

totresdev <- sum(resdev[])                       # Total Residual Deviance
for (c in 1:(nt-1)) {                            # priors for all mean treatment effects
   for (k in (c+1):nt)  { d[c,k] ~ dnorm(0,.0001) }
 }
sd ~ dunif(0,5)                          # vague prior for between-trial SD
tau <- pow(sd,-2)                        # between-trial precision = (1/between-trial variance)

}                                                # *** PROGRAM ENDS
```

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