NOVEL P2Y12 RECEPTOR ANTAGONISTS – PRASUGREL AND TICAGRELOR

SYSTEMATIC REVIEW, INDIRECT COMPARISON TO CLOPIDOGREL IN CARDIOVASCULAR DISEASE, DESIGN OF A RANDOMIZED CONTROLLED TRIAL

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Thesis submitted to the Faculty of Graduate and Postdoctoral Studies in
Partial fulfillment of the requirements for the MSc degree in Epidemiology

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ABSTRACT

Antiplatelet therapy with clopidogrel is widely used in patients with coronary artery disease, but the recent development of the new $P2Y_{12}$ receptor antagonists prasugrel and ticagrelor will increase treatment options. An overview of systematic reviews was performed to summarize available evidence on clopidogrel. Current data on prasugrel and ticagrelor were identified by a systematic review and used for an indirect treatment comparison (ITC) of the drugs against each other and versus placebo in the absence of head-to-head clinical trials. Adjusted indirect comparison according to Bucher, Bayesian methods for mixed treatment comparisons using Winbugs, and generalized linear mixed models using SAS were employed for ITC, yielding almost identical results: prasugrel was favored regarding stent thrombosis and ticagrelor regarding major bleeding. However, substantial differences in trial design were identified, demanding caution when interpreting these results. On the basis of the obtained results, a randomized controlled trial was designed within the gap of current evidence.

ACKNOWLEDGEMENTS

During the completion of this thesis and my Masters in Epidemiology I could rely on several people I really would like to thank for their support.

I want to thank Dr. George A. Wells for all his guidance from my first steps in the program to the completion of my thesis. Beyond his profound expertise and invaluable support I was most impressed about his commitment he showed during each of our meetings. Despite his demanding schedule he always focused his attention to my needs to complete this project.

I also want to thank Dr. Doug Coyle for his continuous advice and support. I really appreciate all the insight he gave me while working with me on my thesis, in class and on an economic evaluation. This was not just essential for the completion of this work but represents an invaluable benefit for my scientific training.

My stay in Ottawa would not have been possible without Dr. J. George Fodor, whose personality and attitude are a real inspiration for me. I feel very privileged that I had the opportunity to join and work with him and his team, and most of all enjoy his enlightening company.

During the last two years I was confirmed how much I could count on my family and friends in Austria. Their long distance encouragement helped me tremendously with all aspects of my life in Canada.

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ACS	Acute coronary syndrome
ARC	Academic research consortium
CABG	Coronary artery bypass graft
CAC	Clinical adjudication committee
CAD	Coronary artery disease
CMR	Cardiac magnetic resonance
CVD	Cardiovascular disease
CYP	Cytochrome P450
DAPT	Dual antiplatelet therapy
EDV	End-diastolic volume
EMA	European Medicine Agency
EF	Ejection fraction
ESV	End-systolic volume
FDA	Food and Drug Administration
ITC	Indirect treatment comparison
LV	Left ventricular
LD	Loading dose
NSTE-ACS	Non ST-segment elevation acute coronary syndrome
NSTEMI	Non ST-segment elevation myocardial infarction
MD	Maintenance dose
MI	Myocardial infarction
MTC	Mixed treatment comparison
PCI	Percutaneous coronary intervention
RCT	Randomized controlled trial
RCDB	Randomized, controlled, double-blind
SCAD	Stable coronary artery disease
STEMI	ST-segment elevation myocardial infarction
TIMI	Thrombolysis In Myocardial Infarction
UA	Unstable angina

1 INTRODUCTION

1.1 Rationale

Platelets play a central role in the pathogenesis of atherothrombosis, and antiplatelet therapy is considered a cornerstone for the prevention and treatment of cardiovascular disease (CVD), including coronary heart disease, stroke and peripheral vascular disease. The use of aspirin has long been seen as the standard of care in cardiovascular disease, and its antithrombotic action depends on the irreversible inhibition of the platelet cyclooxygenase activity, which prevents the formation and release of platelet agonist thromboxane A_2.[1] In patients with established vascular occlusive disease, i.e. in secondary cardiovascular prevention, long-term aspirin therapy is of substantial net benefit with a yearly 25% reduction of serious vascular events, such as non-fatal myocardial infarction, non-fatal stroke and vascular death.[2, 3] However, multiple pathways contribute to platelet activation and the high residual morbidity and mortality in aspirin treated patients has led to the development of newer antiplatelet agents.[4] Thienopyridines - inhibiting ADP induced platelet activation by blockade of the platelet $P2Y_{12}$ receptor - are widely used in combination with aspirin or as monotherapy for secondary CVD prevention. The first available thienopyridine was ticlopidine, which has been shown to be effective in treating patients with acute coronary syndromes (ACS), in particular those who received a coronary artery stent.[5-8] Subsequently, it was replaced by clopidogrel, that was found to be at least as efficacious as ticlopidine in preventing major adverse cardiac events, but with a better safety-tolerability profile, in particular a lower risk of neutropenia and thrombotic thrombocytopenic purpura.[9-11] Recent literature has emphasized several limitations of clopidogrel use, including potential drug-drug interactions, slow onset of action, irreversibility of platelet inhibition, and a wide variability of platelet response, including both increased and decreased responsiveness.[12, 13] A growing number of studies have linked poor antiplatelet response to clopidogrel with adverse clinical outcomes, particularly recurrent ischemic events and stent thrombosis.[14-17] Pharmacogenetic studies have further related genetic polymorphisms in the hepatic cytochrome P450 (CYP) 2C19 system to an alteration in the metabolite levels of clopidogrel.[18-22] There seems to be a gene-dose effect for certain variants (such as CYP2C19 *2 for ischemic and CYP2C19 *17 for bleeding events) with an increased risk for bleeding, myocardial infarction, stent thrombosis and death.[18-21]

These limitations fostered the development of novel drugs with a more consistent and predictable antiplatelet efficacy compared to clopidogrel. Several new agents have been or are currently tested in phase II and phase III trials, and the most promising results are available for prasugrel[23] and ticagrelor.[24] Prasugrel is a third-generation thienopyridine, which has to be converted to an active form before binding irreversibly to the $P2Y_{12}$ receptor and inhibiting platelet aggregation.[25] Recently, it received approval by Health Canada, the US Food and Drug Administration (FDA) and the European Medicine Agency (EMA) for use in patients with ACS undergoing percutaneous coronary intervention (PCI). Ticagrelor is a direct-acting and reversible inhibitor of the $P2Y_{12}$ receptor, that has a shorter half-life and requires twice-daily dosing.[26] Ticagrelor has been approved recently by health authorities in North America and Europe for the prevention of atherothrombotic events in patients with ACS including patients managed medically, and those who undergo revascularization.

No head-to-head comparison for these two drugs is currently available or under way. Thus, the rationale of this thesis was to summarize current data for these two drugs by performing a systematic review for each drug versus clopidogrel, and to combine these results by the means of an indirect comparison of ticagrelor versus prasugrel in patients with ACS. We further sought to evaluate the potential of translating the results of the indirect comparison to patients with stable coronary artery disease and to indirectly compare the efficacy of these novel drugs to placebo.

1.2 Thesis objectives

The objectives of this thesis can be summarized as follows:

a. To identify and assess previous systematic reviews of clopidogrel in comparison to placebo by using AMSTAR (A Measurement Tool to Assess Systematic Reviews) in order to summarize the available evidence on clopidogrel treatment.
b. To perform a systematic review of randomized clinical trials addressing the efficacy and safety of the novel ADP-receptor antagonists, prasugrel and ticagrelor in comparison to the current thienopyridine standard clopidogrel.
c. To perform an indirect comparison of these drugs in patients with CVD, in particular in patients with acute coronary syndromes and undergoing percutaneous coronary

interventions. The potential of translating these results to patients with stable CAD will be addressed.

d. To identify areas with a need for more research and to design a clinical trial addressing these issues in line with requirements for Canadian Institute of Health Research (CIHR) funding programs.

1.3 Chapter description

Chapter 2 provides a short overview on the epidemiology of cardiovascular disease but its main emphasis is the role of antiplatelet therapy for the treatment of CVD. Currently available as well as investigational therapeutic strategies to prevent platelet activation are reviewed, focusing on clopidogrel, prasugrel and ticagrelor.

Chapter 3 gives an overview of systematic reviews on clopidogrel therapy. The systematic search strategy and its results, as well as the quality assessment of the identified reviews are presented. As all studies with prasugrel and ticagrelor were performed on top of aspirin, I was particularly interested in systematic reviews comparing dual antiplatelet therapy consisting of clopidogrel and aspirin to monotherapy. Six reviews met this criterion, and in total six different randomized clinical trials (and their substudies) were used in these systematic reviews. Due to the limited number of relevant trials, the data were extracted directly from the trials instead of using the combined evidence of the reviews.

The methods and results of the systematic review of prasugrel and ticagrelor in comparison to clopidogrel are presented in chapter 4. Efficacy and safety outcomes, and the subgroups explored, are presented. As the results of the meta-analysis are mainly driven by two large randomized clinical trials (RCT), namely TRITON and PLATO, a narrative comparison of their design and results is added to the discussion section.

Chapter 5 introduces several methodological approaches to perform an indirect treatment comparison, which were subsequently applied for indirectly comparing ticagrelor to prasugrel and both drugs to placebo. While conducting this thesis, a large clinical trial addressing the

limitations of clopidogrel therapy by doubling its dose, was published.[27, 28] The results of this trial were included into the indirect comparison as it might present a valid therapeutic alternative. The chapter concludes with a discussion of the findings and the problems encountered.

Chapter 6 comprises the design of an RCT in this area addressing the potential benefit of ticagrelor for all-cause and CV mortality. The so-called adenosine hypothesis postulates that the mortality benefit of ticagrelor might be due to an increase of adenosine levels rather than its antiplatelet efficacy. Adenosine has been shown to be cardio-protective by various mechanisms, in particular during reperfusion through revascularization of thrombotic occluded arteries. Such a benefit might translate into improved ventricular function and remodeling. Thus, the proposed trial seeks to investigate a potential role of ticagrelor on parameters of ventricular function and remodeling in patients after acute myocardial infarction. Prasugrel is used as active comparator as its antiplatelet activity is comparable to ticagrelor.

Chapter 7 gives closing remarks for this thesis.

2 ANTIPLATELET THERAPY IN CARDIOVASCULAR DISEASE

2.1 Epidemiology of cardiovascular disease

Cardiovascular disease and its most common manifestation coronary heart disease still rank first among causes of death in middle-aged and older individuals in the majority of the developed countries, as well as many developing countries.[29] CVD causes substantial disability and is a main factor for the increasing costs of healthcare systems, especially in the presence of an ageing population.[30] Despite a decline in CVD death rates in North America and Europe over the past decades,[29, 31, 32] projections suggest that CVD will remain the leading cause of death and loss of quality-adjusted life years by 2020.[33] An estimated 1.29 million Canadians reported having heart disease in 2005, which represents increases of 19% for men and 2% for women, relative to 1994.[34] A key goal of primary and secondary CVD prevention is the reduction of modifiable risk factors, such as smoking, sedentariness, nutritional imbalance, blood pressure elevation, impaired glucose tolerance and diabetes, dyslipidemia, increased body weight and obesity. In addition, established pharmacological treatments comprise antiplatelet therapy, in particular aspirin, statins and antihypertensive drugs. In secondary CVD prevention, the benefits of antiplatelet therapy are well established and clearly exceed the risks, such as bleeding.[3] For primary prevention, however, the balance is less clear, and the reduction in CV events needs to be weighted against any increase in bleeding events.

2.2 Platelets and cardiovascular disease

Platelets play a crucial role in haemostasis and thrombosis by preserving vascular integrity and preventing haemorrhage after injury.[35] For interaction with their environment, platelets are equipped with numerous receptors on their surface, on which various activating and inhibiting substances can bind. As a physiological response to injury, platelets rapidly adhere to the subendothelial matrix after endothelial damage. Upon activation, platelets aggregate with each other, which generates a prothrombotic surface, where other blood elements bind leading to activation of the coagulation cascade and fibrin accumulation. Thereby, a plug is formed that seals the damaged surface. However, the same process happens when an atherosclerotic plaque

ruptures, potentially leading to occlusive thrombus formation. As a consequence of vascular occlusion, hypoxia and infarction of distal tissues can occur. Partial or complete occlusion of a coronary artery might significantly reduce blood flow to the myocardium, thereby initiating an acute coronary syndrome.[36] Thus, in the majority of cases platelet rich thrombi are the underlying substrate of the clinical presentation with acute coronary syndromes. The cardinal sign of ACS is chest pain (angina) due to decreased blood flow in the coronary arteries with insufficient oxygen supply. The type and severity of a particular ACS is dependent on the interplay of several factors, such as the extent of coronary occlusion, the presence or absence of myocardial necrosis, and degree of collateralization. This defines then the clinical symptoms of ACS, which can range from unstable angina (UA) and non-ST-segment elevation myocardial infarction (NSTEMI) to ST-segment elevation myocardial infarction (STEMI). The latter is commonly known as a heart attack, and it is estimated that about one third of patients with STEMI will die within the first day, very often before the patient reaches the hospital. Lately, UA and NSTEMI are often combined in the expression NSTE-ACS (non-ST-segment elevation – acute coronary syndrome). The differentiation between these manifestations is based on electrocardiographic criteria (i.e. the presence of ST-segment elevation in the ECG) and the extent of rising biomarkers, which are released into the blood stream after myocardial necrosis. Importantly, all forms of ACS share a similar underlying pathophysiology, primarily the rupture of an atherosclerotic plaque resulting in intracoronary thrombus formation with massive involvement of platelets.

Due to the central role of platelets in arterial thrombosis and progression of atherosclerotic disease, antiplatelet therapy has proved beneficial in the treatment of stable coronary artery disease but in particular of ACS. The management of ACS has been revolutionized over the past two decades, leading to considerable reductions of mortality and adverse outcomes. Major advances were made in the areas of interventional cardiology and pharmacotherapy. Thus, percutaneous coronary interventions (PCI) have become routine procedures to re-open stenotic coronary arteries in both acute and elective clinical situations, i.e. ACS and stable CAD. The initially high incidence of restenosis was diminished by implantation of coronary stents, with even more favorable results by the development of drug-eluting stents.

Acute stent thrombosis could be significantly reduced by antithrombotic and antiplatelet therapies. In order to better target the elevated platelet reactivity central to the thrombus that underlies ACS, adjunctive antiplatelet agents to aspirin have been developed, first of all clopidogrel.

However, platelets have a physiological haemostatic role, and the downside of preventing ischemia is an enhanced risk of bleeding. Recent data emphasizes that bleeding following treatment for ACS is not benign, but that it is related to increased mortality.[37, 38] In these studies, bleeding events were found to be a risk factor for adverse outcomes equivalent or even greater than peri-procedural myocardial infarction.

Main predictors of high bleeding risk are advanced age, female sex and renal failure. Notably, these factors are also characteristic for patients with increased ischemic event rates after ACS. Therefore, the net clinical benefit of antiplatelet therapy has to take into account both ischemic and bleeding events. Currently, several antiplatelet drugs are available, that target differential key pathways of platelet activation, and additional agents are under development. However, by targeting the various components of platelet activation in ACS, the risk of bleeding is increasing. The next sections give an overview of current and investigational antiplatelet therapies.

2.3 Aspirin

For over five decades, aspirin has been the foundation of antiplatelet therapy, and this is still valid today.[1] Aspirin acts by inhibiting cyclooxygenase-1 (COX-1) within platelets, rendering the catalytic site of COX-1 inaccessible to arachidonic acid, which inhibits the generation of prostaglandin H_2 and subsequently thromboxane A_2.[39] Thromboxane A is a potent platelet activator and inhibition of its release prevents platelet activation through its thromboxane A_2 receptor. Oral aspirin is rapidly absorbed and plasma levels peak 30-40min after intake.[40] The platelet inhibitory effect lasts for the lifespan of the platelet, because inactivation of COX-1 is irreversible. In secondary prevention, aspirin was shown to reduce vascular death by ~15% and non-fatal vascular events by ~30%.[2, 3] In the subgroup of patients with NSTE-ACS analyzed in the meta-analysis of the Antithrombotic Trialists Collaboration,[2] vascular events (MI, stroke, or vascular death) were reduced by 46% (13.3% vs. 8.0%) using doses ranging from 74 to 325mg daily. In STEMI, the Second International Study of Infarct Survival (ISIS-2) demonstrated that aspirin therapy started within 12 hours of MI, significantly reduced the risk of mortality by 23% compared with placebo after 35 days.[41] Recent data suggests that in ACS patients, there is no difference in efficacy or safety between high (300-325mg) and low dose (75-100mg) aspirin at 30 days after the event.[27, 28]

Despite the significant mortality benefit of aspirin in secondary prevention, adverse CV events are still common. Accordingly, the concept of dual antiplatelet therapy has emerged by simultaneously inhibiting an additional pathway of platelet activation. Mostly, ADP receptor blockers are used in combination with aspirin, in particular in high-risk patients with ACS and/or undergoing percutaneous coronary intervention.

2.4 $P2Y_{12}$ receptor antagonists

Adenosine diphosphate (ADP) is an important agonist of platelet activation and has two types of receptors on the platelet surface: $P2Y_1$ and $P2Y_{12}$.[42] ADP signaling through $P2Y_1$ induces reversible platelet aggregation, while $P2Y_{12}$ activation leads to the formation of stable platelet aggregates and triggers the release of various substances, which are stored within platelet granulas and further enhance platelet activation. The $P2Y_{12}$ receptor is the target of various antiplatelet drugs, so called $P2Y_{12}$ or ADP receptor antagonists. There are two principle types of drugs that inhibit this receptor: thienopyridines and reversibly binding inhibitors.

Thienopyridines are a class of prodrugs that comprise ticlopidine, clopidogrel and prasugrel. After absorption, the drugs have to be converted to active metabolites, which then irreversibly bind and permanently inactivate the $P2Y_{12}$ receptor. Platelet function is inhibited proportionally to the extent of receptor blockade by the active metabolites.[43] Similar to the irreversibly inhibitory effect of aspirin, recovery of ADP-induced platelet aggregation after thienopyridine intake requires the release of new platelets from the bone marrow into the circulation. Thus, complete recovery of platelet function takes about 7 to 10 days, depending on the rate of platelet turnover.

Recently, three *reversibly binding $P2Y_{12}$ inhibitors* have been developed and utilized in clinical trials, ticagrelor, cangrelor, and elinogrel. They belong to different classes but share some similarities in their properties: In contrast to thienopyridines, no metabolic activation is needed, but the three drugs bind directly and reversibly to the ADP receptor. Platelets are only inhibited as long as plasma levels of the drugs are sufficiently high. When plasma levels fall, their inhibitory effects wear off as the drugs dissociate from the receptor.

The following section gives a short overview of the clinical data for the aforementioned drugs and highlights drug-specific characteristics, which influence their efficacy and safety.

2.4.1 Ticlopidine

Ticlopidine is a first generation thienopyridine, which has to be taken twice daily. It became the first approved $P2Y_{12}$ receptor antagonist by regulatory agencies and gained FDA approval for clinical use in the early 1990s. The active metabolite is generated in several steps, which involve cytochrome P450-dependent pathways. Ticlopidine therapy has been evaluated as monotherapy in stroke, unstable angina, myocardial infarction and intermittent claudication.[44] Most importantly, dual antiplatelet therapy (DAPT) with ticlopidine and aspirin was found to be highly effective in the prevention of acute and subacute stent thrombosis after PCI.[6-8] Prior treatment regimens using various combinations including aspirin, dipyridamole, dextran, heparin and warfarin were less effective and/or were accompanied by high bleeding rates.[45, 46] The introduction of DAPT was a major progress for patients undergoing PCI but ticlopidine therapy was limited by common side effects, such as gastrointestinal problems as well as hematological problems.[9-11] For example, transient neutropenia is seen in approximately 2.3% of patients taking ticlopidine, and its severe and potentially life-threatening form happens in nearly 1%. This necessitates periodic measurements of the white blood cell count.[11] Further, thrombotic thrombocytopenic purpura occurs rarely with ticlopidine (~1 per 4 800 treated patients), but - unless recognized and treated promptly - may lead to death.

2.4.2 Clopidogrel

Clopidogrel, which has to be taken once daily, has largely replaced ticlopidine owing to its improved side effect profile.[11, 47] Importantly, the rate of neutropenia is low (~0.1%) and is comparable between patients treated with clopidogrel or with aspirin. The process of clopidogrel conversion to its active metabolite is mediated by the liver cytochrome P450 (CYP) enzymes system.[48] Rapid conversion of clopidogrel to an inactive metabolite by plasma esterases can reduce the drug's antiplatelet effects.

In patients with stable atherosclerotic disease, clopidogrel showed a similar or moderately higher

efficacy than aspirin in the CAPRIE trial (Clopidogrel versus Aspirin in Patients at Risk for Cardiovascular events).[9] There were fewer gastrointestinal side effects with clopidogrel than with aspirin. Based on this data, monotherapy with clopidogrel is now recommended for secondary prevention of CVD in patients with aspirin intolerance.

The clinical benefit of adding clopidogrel to aspirin therapy (i.e. dual antiplatelet therapy, DAPT) has been demonstrated by several, large, multicenter, randomized, controlled trials in patients with unstable CV disease or undergoing PCI: CURE (Clopidogrel in unstable angina to prevent Recurrent Events) established the superiority of DAPT in patients with NSTEMI;[49] PCI-CURE and CREDO (Clopidogrel for the Reduction of Events during Observation) established the superiority of DAPT in patients undergoing PCI.[50, 51] COMMIT (Clopidogrel and metoprolol in myocardial Infarction Trial) and CLARITY-TIMI 28 (Clopidogrel as Adjunctive Reperfusion Therapy–Thrombolysis In Myocardial Infarction 28) proved the superiority of DAPT in patients with STEMI.[52, 53] However, in patients with stable cardiovascular disease or asymptomatic patients with multiple CV risk factors, the CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance) trial found that the combination of clopidogrel plus aspirin was not significantly more effective than aspirin alone in reducing the rate of myocardial infarction, stroke or death from cardiovascular causes.[54] Furthermore, the risk of moderate to severe bleeding was increased over the 28 months trial period. Similarly, adding aspirin to clopidogrel compared to clopidogrel monotherapy in high-risk patients with recent ischaemic stroke or transient ischaemic attack did not improve clinical outcome but was associated with an increase of life-threatening or major bleeding in the MATCH (Management of atherothrombosis with clopidogrel in high-risk patients with recent transient ischaemic attack or ischaemic stroke) trial.[55]

Over the past years, several drawbacks of clopidogrel therapy have been identified. Monitoring clopidogrel by platelet function tests revealed high interpatient response variability with clopidogrel hyporesponsiveness in many patients.[56] Several mechanisms for this variability in drug response have been identified, such as clinical, genetic and cellular factors.[57, 58] Importantly, there is evidence that such a poor response of clopidogrel in *in vitro* tests is associated with major adverse clinical events.[59] Drugs interactions may alter the effectiveness of clopidogrel by competitively changing its metabolization through cytochrome P450 in the liver. As an example, platelet function studies have shown that proton pump inhibitors, in particular omeprazole, reduce the inhibitory effect of clopidogrel on platelet aggregation.[60-62] There has been much

debate over whether this translates into clinically adverse outcomes with increased risk of ischemic events. Some, but not all observational studies have shown such an effect.[61, 63, 64] The only randomized controlled trial comparing proton pump inhibitors versus placebo in patients on clopidogrel (COGENT, Clopidogrel and the Optimization of Gastrointestinal Events trial) did not report an increase in CV events but found a benefit in terms of reduced gastrointestinal bleeds.[65] However, the trial was underpowered and there is still some concern about an interaction.

Another hot topic with respect to clopidogrel non-responsiveness is the existence of genetic variants, which lead to impaired active metabolite generation.[20] The metabolization of clopidogrel is achieved with a number of different isoenzymes of the cytochrome P450 system, including CYP2C19, which is believed to play a dominant role in the process. Previous studies demonstrated that the common loss-of-function CYP2C19*2 variant is associated with a blunted response to clopidogrel. Diminished platelet inhibition as shown by in vitro tests was linked to a higher rate of major adverse CV events, in particular stent thrombosis.[20-22] About 25% of the white population carries one loss-of-function variant of this gene, and about 2% carry two such alleles. These percentages are slightly higher in individuals of African ancestry and substantially greater in individuals of Asian ancestry. On the other side, another variant, CYP2C19*17, represents an enhanced function gene and is associated with rapid metabolism of clopidogrel. The heightened antiplatelet activity in platelet function tests was related with an increased risk of bleeding.[18] For the loss of function polymorphism, a gene-dose effect was described: Patients who carry 1 loss of function gene do worse than those with none, and patients who carry 2 genes (i.e. who are homozygous) do even worse. However, the clinical impact of these gene variants seems to depend on the clinical characteristics of the study population. A recent post-hoc analysis could not find any effect of loss-of-function CYP2C19 alleles with regard to safety or efficacy of clopidogrel in patients with ACS or atrial fibrillation participating in the CURE and ACTIVE A trials, respectively.[66] In contrast, the gain-of-function CYP2C19 allele was associated with a greater benefit of clopidogrel in the CURE trial (ACS patients), but not the ACTIVE A trial (patients with atrial fibrillation). Regarding the lack of an impact in ACTIVE A, one might argue that clinical events in patients with atrial fibrillation are not predominately a result of platelet-mediated processes. Thus, dual antiplatelet therapy is much less beneficial compared to oral anticoagulation in this patient population, and therefore the loss of function polymorphism might play a minor role. Importantly, only a small number of patients underwent PCI in the CURE trial

compared to recent ACS studies (14.5% versus around 70%) and during this era, only bare metal stents were used. Both aspects might have influenced the negative findings regarding loss of function variants and outcome. Thus, the relative importance of platelet-rich thrombi for the course of a disease might have to be taken into account when the role of antiplatelet therapy and the potential impact of agents or situations, which limit its efficacy, are investigated. While the genetic testing becomes more widespread available, the controversy over its value and role is ongoing.[67]

Further, identifying the CYP2C19 gene status only explains about 10% of the variation in clopidogrel response when measured by platelet activation tests.[68] As mentioned before, various environmental and clinical factors can affect clopidogrel metabolism and platelet function. It is still unclear how results of this platelet function tests translate to clinical outcomes and if clopidogrel non-responders identified by platelet function tests should be treated differently. Notably, the recently presented GRAVITAS (Gauging Responsiveness with A VerifyNow Assay-impact on Thrombosis And Safety) trial, which was the first RCT addressing the potential of adapting clopidogrel maintenance dose based on the results of platelet function tests, failed to show a benefit of doubling the dose in clopidogrel non-responders.[69] Possible explanations include the surprisingly low event rate (which might imply that platelet-related thrombosis was not so relevant) and the only modest effect of doubling clopidogrel on platelet inhibition (suggesting that doubling was not enough, and more potent agents could have done better). Another highly anticipated trial, TRIGGER-PCI, aimed to compare clopidogrel and prasugrel based on platelet reactivity testing in stable coronary artery disease patients undergoing PCI, while patients with ACS were excluded. The trial was stopped early (mid March 2011) after inclusion of only one quarter of the study population because the observed event rate was extremely low (below the 2.3% event rate in GRAVITAS). The investigators were not just concerned that they could not reach statistical significance but addressed the issue that – if the risk is so low – there cannot be much gained with a new therapy (such as prasugrel).[70] In the light of these trials, there is only a weak basis for a therapeutic impact of platelet function testing today.

Another drawback of clopidogrel therapy is a delayed onset of action, which is particularly important in clopidogrel naïve patients with ACS. An increase of the loading dose of clopidogrel from 300mg to 600mg enhanced the mean inhibition of platelet aggregation significantly and more rapidly, while a 900mg loading dose added little further effect.[71] A high loading dose (>300

mg) proved significantly superior to a standard loading dose (300mg) in terms of reducing early cardiac death or non-fatal MI post PCI in a recent meta-analysis.[72] Importantly, patients at highest risk, defined by the presence of elevated cardiac biomarkers, benefited the most with the increased loading dose.

In conclusion, clopidogrel has been accepted as the cornerstone of antiplatelet therapy in ACS. However, several limitations have been described, and novel $P2Y_{12}$ receptor inhibitors were developed to overcome these shortcomings.

2.4.3 Prasugrel

Similarly to clopidogrel, prasugrel is a thienopyridine and irreversibly blocks the $P2Y_{12}$ receptor. As a major advantage compared to clopidogrel, only a single cytochrome P450 dependent step (predominantly CYP3A and CYP2B6) is needed for metabolization, leading to a more efficient activation process.[73] Plasma concentrations of the active metabolite peak at ~ 30minutes after intake, which is once daily. Next to this faster onset of action, prasugrel is currently believed to be less susceptible to genetic variations or drug-drug interactions as compared to clopidogrel.[74] None of the common variants in the CYP genes tested significantly reduced the active metabolite generation of prasugrel or influenced its antiplatelet effect.[75] In pharmacodynamic studies, prasugrel inhibits ADP-induced platelet aggregation more rapidly, more consistently and at higher levels compared to clopidogrel. This also translates to a smaller number of hyporesponders as identified in platelet function tests during prasugrel treatment.[73]

In the PRINCIPLE (Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation) -TIMI 44 trial, prasugrel was compared to high dose clopidogrel in a crossover study in patients with coronary artery disease undergoing planned PCI. Prasugrel 60-mg loading dose showed higher levels of platelet inhibition using platelet function tests than 600 mg clopidogrel, and 10 mg prasugrel showed greater levels of platelet inhibition than 150 mg clopidogrel daily.[76] If this intensified platelet inhibition *in vitro* also translates to improved clinical outcome was the focus of two trials, the smaller phase II JUMBO (Joint Utilization of Medications to Block Platelets Optimally)-TIMI 26 trial and the large phase III TRITON (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel)-TIMI 38 trial.[23, 77] In JUMBO, 904 subjects undergoing elective or urgent PCI were randomized to 1 of 3 prasugrel dosing strategies (LD/MD: 40/7.5mg, 60/10mg, 60/15mg) compared with

clopidogrel (300/75mg). Follow up was 30 days. Bleeding rates were overall low but numerically more patients had bleeding in the combined prasugrel group compared with clopidogrel (HR 1.42, 95% CI 0.4 to 5.08). The study was not powered for efficacy events and a non-significant difference was observed for major CV events in favor of prasugrel (HR 0.76, 95% CI 0.46 to 1.24). In TRITON, 13 608 subjects with moderate to high-risk ACS were randomized to receive either clopidogrel (LD/MD: 300/75mg) or prasugrel (60/10mg). Median treatment duration was 14.5 months. Only clopidogrel-naïve patients were eligible. Further, only patients with planned PCI after coronary anatomy had been defined by angiography or with acute STEMI planned for primary PCI could be randomized.[78] The primary composite outcome of CV death, MI, or stroke was reduced from 12.1% to 9.9% (HR 0.81, 95% CI 0.73 to 0.90; P<0.001) with prasugrel compared to clopidogrel. The primary end point was driven by a 24% reduction in MI, while rates of CV death and stroke were not different. Major bleeding not related to coronary artery bypass graft (CABG) surgery was increased from 1.8% to 2.4% (HR 1.32, 95% CI 1.03 to 1.68; P=0.03). Regarding the generalizability and thus clinical relevance of the TRITON trial, criticism was raised regarding the late administration of the study drug (when coronary angiogram was available) for the majority of patients with NSTE-ACS and secondary PCI for STEMI, which is not in line with Canadian practice. Further, the rather low loading dose of the comparator (clopidogrel 300mg) might not reflect current practice adequately. Although the Health Canada-approved loading dose of clopidogrel in ACS is 300 mg, most centres in Canada use a 600 mg loading dose for patients requiring primary PCI.[79]
A detailed discussion of the results of TRITON overall and in various subgroups is included in chapter 4.

2.4.4 Ticagrelor

Ticagrelor is the first of a new class of antiplatelet drugs, the cyclopentyl-triazolo-pyrimidines. It binds reversibly to the $P2Y_{12}$ receptor at a different site than ADP and is thought to act through an allosteric mechanism.[80, 81] Ticagrelor has a rapid onset of action with a peak inhibitory effect at approximately 2 hours after intake.[82] The levels of platelet inhibition during maintenance therapy are more consistent and greater compared with clopidogrel in patients with stable CAD and ACS.[82-84] When clopidogrel hyporesponders are treated with ticagrelor, the mean inhibition of platelet activation is increased up to 40%, suggesting that ticagrelor overcomes clopidogrel

resistance.[85] The drug has a plasma half-life of 8-12 hours, and twice daily dosing is necessary. Ticagrelor is only minimally excreted renally, and very low levels (<=0.05%) of the parent compound and metabolite are found in the urine.[86] Individuals with mild hepatic insufficiency had moderately increased ticagrelor levels but no subsequent effects on the pharmacodynamics of the drug were found.[87] After therapy cessation, the inhibitory effect of ticagrelor declines rapidly over 72 hours and near-normal platelet reactivity can be expected after approximately 5 days. Drug-drug interactions of clinical significance include the CYP3A inhibitors ketoconazole and diltiazem, both of which have been shown to significantly increase ticagrelor plasma concentrations. As the drug does not require hepatic conversions, its antiplatelet effects are not subject to interindividual genetic variations in P450 enzymes.[88] Regarding side effects apart from bleeding complications, the most common adverse event reported with ticagrelor is dyspnea, which appears to be transient and dose-related.[89] In addition, a greater incidence of mostly asymptomatic ventricular pauses in ticagrelor patients, and a mild increase in uric acid levels were reported. These side effects may be due to the inhibition of adenosine uptake into erythrocytes by ticagrelor. It is speculated that this off-target effect of ticagrelor might also contribute to its CV benefits: increased concentrations of adenosine have been shown to improve recovery of cardiac function after ischemia by reducing the zone of no-reflow and the size of the infarct.[90] Accordingly, this non platelet-mediated effect of ticagrelor leading to increased endogenous adenosine concentrations could improve myocardial flow and decrease the size of myocardial infarcts.

The clinical trial portfolio of ticagrelor comprises mainly 2 studies: DISPERSE-2 (Dose Confirmation Study Assessing Antiplatelet Effects of AZD6140 versus Clopidogrel in Non-ST-segment Elevation Myocardial Infarction-2) and PLATO (The Study of Platelet Inhibition and Patient Outcomes).[24, 91] In DISPERSE-2 990 patients with NSTE-ACS were randomized to one of the following 3 treatments: (1) ticagrelor 90 mg twice daily, (2) ticagrelor 180 mg twice daily, or (3) clopidogrel 300 mg loading dose followed by 75 mg once daily. Treatments were given for up to 3 months, and those randomized to ticagrelor treatment were also sub-randomized to receive or not receive a 270 mg loading dose of ticagrelor. The primary outcome, major and minor bleeding, did not differ significantly among treatment groups at 4 weeks (8.1% in the clopidogrel group versus 9.8% in the ticagrelor 90 mg group and 8.0% in the ticagrelor 180 mg group). After three months a significant increase was observed for minor bleeding with the higher ticagrelor dose, but no differences for total or major bleeding. Regarding efficacy end points,

there were numerically fewer myocardial infarctions over 12 weeks with ticagrelor treatment (5.6% with clopidogrel versus 3.8% with ticagrelor 90 mg bid and 2.5% with ticagrelor 180 mg bid).

In PLATO, 18 624 patients with ACS were randomized to either ticagrelor (180 mg loading dose followed by 90 mg twice daily) or clopidogrel (300–600 mg loading dose followed by 75 mg once daily). All patients received additional aspirin therapy. The primary efficacy end point (death from vascular causes, myocardial infarction, or stroke) occurred in 9.8% of patients receiving ticagrelor and 11.7% of patients taking clopidogrel (HR: 0.84, 95% CI 0.77 to 0.92; P<0.001). Notably, secondary analyses of the components of the primary end point showed that not just MI but also CV death was reduced significantly. The primary safety end point of any major bleeding event was similar between the ticagrelor (11.6%) and clopidogrel (11.2%) groups (P =0.43). Non CABG-related major bleeding according to the PLATO bleeding classification was higher in the ticagrelor treatment arm (4.5% versus 3.8%; P=0.03).
A detailed description of the study design and outcomes is given in chapter 4.

2.4.5 Further investigational $P2Y_{12}$ inhibitors

Two additional $P2Y_{12}$ inhibitors have been tested in clinical trials: cangrelor and elinogrel. *Cangrelor* is a reversible $P2Y_{12}$ inhibitor, which is only active when administered intravenously.[92] As an advantage high levels of platelet inhibition can be achieved within minutes. The drug has an ultra-short half-life and the effects wear off in 1-2min.[93] So far, cangrelor was tested in two large clinical trials, CHAMPION (Cangrelor versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition) –PCI and CHAMPION-PLATFORM.[94, 95] The studies compared a strategy using cangrelor followed by 600mg clopidogrel compared to clopidogrel administration alone in patients undergoing PCI, predominantly for ACS. The major difference between the two trials was the timing of the administration of the study drugs. In the CHAMPION PCI trial, both study drugs (cangrelor and clopidogrel) were started within 30 minutes before PCI. In the CHAMPION-PLATFORM trial, cangrelor was started at the beginning of PCI, whereas clopidogrel was not administered before the end of PCI. Despite the rapid onset of action, cangrelor did not have a significant effect on the incidence of the primary end point (death from any cause, myocardial infarction, or ischemia-

driven revascularization). In view of the negative findings, alternative applications of cangrelor are currently investigated: The BRIDGE study will investigate the application of cangrelor in patients, who are treated with thienopyridines but need to stop before CABG surgery. Continuous infusion of cangrelor or placebo will be administered until the day of surgery.

Elinogrel is another reversibly binding $P2Y_{12}$ inhibitor, and both intravenous and oral formulations are available.[96] Promising results for this novel compound were demonstrated in preclinical and early-phase clinical testing.[97] No large clinical trials are available with this compound yet, but a phase III clinical trial was recently announced (ECLIPSE, Elinogrel to Clarify the Optimal Inhibition of Platelets in Secondary Prevention). Interestingly, the trial will be performed in patients with stable CAD and not ACS.

2.5 Other currently approved antiplatelet strategies

ADP antagonists are a mainstay in antiplatelet therapy, but several other drugs have been approved for the treatment of cardiovascular disease in addition to aspirin. Table 1 gives an overview of these agents.

Table 1. FDA-approved antiplatelet agents[35]

Drug	Mechanism of action	Admini-stration	Frequency	Side effects	Limitations
Abciximab	Glycoprotein IIb/IIIa antagonist	Intravenous	Once	Bleeding Thrombocytopaenia	Requires iv administration
Eptifibatide	Glycoprotein IIb/IIIa antagonist	Intravenous	Once	Bleeding Thrombocytopaenia	Requires iv administration
Tirofiban	Glycoprotein IIb/IIIa antagonist	Intravenous	Once	Bleeding Thrombocytopaenia	Requires iv administration
Dipyridamole	Inhibition of cyclic nucleotide phosphodi-esterase and adenosine uptake	Oral	Two or three times daily	Headache Dizziness Hypotension Flushing GI-toxicity: Nausea Vomiting Diarrhoea Abdominal pain	Benefit mostly in combination with low dose aspirin

Cilostazol	Inhibition of cyclic nucleotide phospho-diesterase 3	Oral	Twice daily	Bleeding Headache Diarrhoea Palpitations Dizziness Rash Pancytopenia	Side effects lead to discontinuation in ~15% of patients

In addition, various antiplatelet drugs are currently under development, which are directed against other platelet surface targets, such as proteinase-activated receptor 1 (PAR1), platelet glycoprotein IV (GPIV), integrin α2β1, 5-hydroxytryptamine receptor 2A ($5HT_{2a}$), and prostaglandin E2 receptor EP3 subtype (EP_3).[35] The ultimate goal is to better separate reduced thrombotic events from increased bleeding events. The PAR1 antagonist vorapaxar, an inhibitor of thrombin-induced platelet activation, is the most advanced agent on the road towards clinical use with two ongoing phase III clinical trials (TRA-CER and TRA-2P-TIMI 50) in patients with ACS and stable CVD. In January 2011, changes to the study protocol were announced upon recommendation of the Data Safety Monitoring Board (DSMB). In the TRACER study, patients should discontinue the study drug and investigators were advised to begin to close out the study as a sufficient number of events were collected. In the TRA-2P trial, the study drug will be continued in patients with CV or peripheral arterial disease (approximately 75 percent of the patients enrolled in the study), but will be immediately discontinued in patients, who experienced a stroke prior to entry into the study or during the course of the study, as an increase in intracranial hemorrhage was observed. These announcements might be another indicator how difficult it has become for a new antiplatelet treatment regimen to further reduce ischemic events without increasing bleeding events.

3 OVERVIEW OF SYSTEMATIC REVIEWS ON CLOPIDOGREL

3.1 Objective

The overview of systematic reviews on clopidogrel was conducted to summarize existing evidence on the efficacy and safety of clopidogrel therapy in cardiovascular disease. The aim was to identify the relevant information in order to perform an indirect comparison of the new agents, prasgurel and ticagrelor, to placebo, which was directly compared only with clopidogrel. If feasible, the synthesized evidence of appropriate systematic reviews should be used in the indirect comparison. Alternatively, data from the individual trials included in the systematic reviews could be extracted and used directly.

3.2 Methods

3.2.1 Search strategy

The *population of interest* included adult participants with known cardiovascular, cerebrovascular or peripheral arterial disease. Patients with atrial fibrillation (valvular and non-valvular), congestive heart failure, pre-eclampsia, eclampsia or pulmonary hypertension were excluded.

Regarding the *interventions of interest* systematic reviews of 1) dual antiplatelet therapy with clopidogrel and aspirin in comparison to aspirin and placebo/control, 2) clopidogrel in comparison to aspirin as well as 3) clopidogrel in comparison to placebo/control were included. Preliminary search results showed a relevant proportion of systematic reviews that combined results from trials using ticlopidine or clopidogrel into one thienopyridine intervention arm. Thus, the search strategy was widened to comprise both clopidogrel and ticlopidine. Systematic reviews comparing ticlopidine and clopidogrel were included as well as reviews comparing various antiplatelet strategies when the comparisons of interest were addressed in subgroup analysis. Systematic reviews of single or aspirin-combined clopidogrel/ticlopidine therapy versus anticoagulant therapy or other antiplatelet therapy (e.g. cilostazol, dipyridamole) were excluded. Antiplatelet therapy evaluated as part of wider treatment strategies (e.g. optimal treatment strategies post MI) was not included.

Systematic reviews without realization of a meta-analysis (i.e. narrative reviews) were included and are reported as a subcategory.

For the search strategy no restrictions on *outcomes* were applied.

For the overview and data extraction, several outcomes of interest were included: Primary outcome comprised all-cause mortality. Secondary measures included death due to coronary, cerebrovascular or peripheral arterial disease (i.e. vascular or cardiovascular death), myocardial infarction, stroke, the composite of these three, and, if available, stent thrombosis.

Bleeding events were collected as safety outcome. However, bleeding can be categorized according to various criteria. If available, bleeding events defined by TIMI (Thrombolysis In Myocardial Infarction) criteria were extracted.

The medical subject headings and key words used for the systematic search of the electronic databases Embase and Medline through July 14th, 2010 are presented in Appendix 1. In addition, the Cochrane database was searched using the keywords clopidogrel, ticlopidine or thienopyridine in title, abstract and keywords. The references of retrieved studies were checked for additional reviews of potential interest. No language restrictions were enforced.

3.2.2 Quality Assessment

The methodological quality of the reviews was assessed using the AMSTAR measurement tool (A Measurement Tool to Assess Systematic Reviews).[98] The tool consists of 11 items and has good face and content validity. The time required to complete an assessment is about 10-15 minutes, which underlines the feasibility of the tool.

The following 11 questions are addressed:

1. Was an ‘a priori’ design provided?
2. Was there duplicate study selection and data extraction?
3. Was a comprehensive literature search performed?
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?
5. Was a list of studies (included and excluded) provided?

6. Were the characteristics of the included studies provided?

7. Was the scientific quality of the included studies assessed and documented?

8. Was the scientific quality of the included studies used appropriately in formulating conclusions?

9. Were the methods used to combine the findings of studies appropriate?

10. Was the likelihood of publication bias assessed?

11. Were potential conflicts of interest included?

For each question, which is answered with yes, one point is given. A systemativ review with 11 to 8 points is considered of excellent, 7 to 4 points of moderate and below 4 points of poor quality.

3.3 Results

3.3.1 Search Results

In total, 2906 references were retrieved by the aforementioned search strategies yielding 2648 references after duplicate removal. 2589 references were excluded based on title or abstract because of non-relevance to the research question. 59 full-text articles were retrieved and screened. One additional review was identified by review of reference lists yielding 60 articles for full-text screening.

23 articles were excluded due to the following reasons:

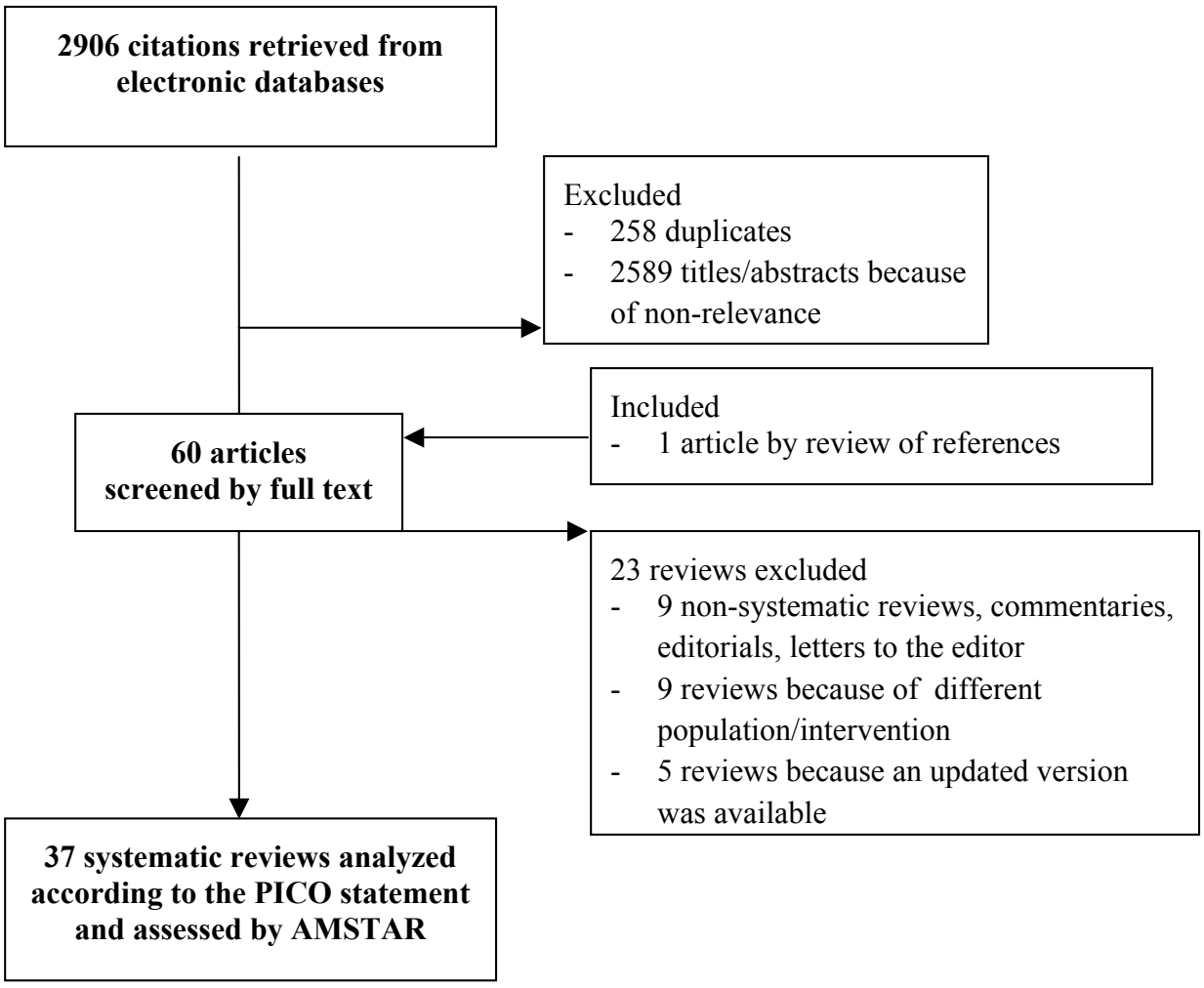
- 9 studies were excluded because they represented non-systematic narrative/clinical reviews, commentaries, editorials or letters to the editor.
- 9 studies were excluded because a different intervention or study population was addressed in the systematic review.
- 5 studies were excluded because an updated systematic review was available.

A list of the excluded reviews is shown in Appendix 2.

37 systematic reviews were analyzed according to the PICO statement and assessed by the AMSTAR tool.

A schematic of the reviewing process is shown given in Figure 1.

Figure 1. Flow diagram of systematic review inclusion



3.3.2 Results of the quality assessment

The majority of systematic reviews had an excellent (12) or moderate (13) quality rating, and 7 reviews had a poor rating. However, the reviews with a poor rating mostly focused on different aspects such as cost-effectiveness or the systematic review was only a minor aspect within a manuscript. For 5 reviews, the AMSTAR rating was not applicable because the reviews did not intend to perform a formal meta-analysis. In this case, several categories of the AMSTAR cannot be addressed. The most frequently missing category asked if a conflict of interest statement was reported for both the systematic review authors and the authors of the original studies included in the review. Only one systematic review reported this specifically.

Results of the AMSTAR rating are depicted in APPENDIX 3.

3.3.3 Results of the overview

According to the available information on the interventions and outcomes, the systematic reviews were categorized into subgroups:

a) Comparison of dual antiplatelet therapy with clopidogrel and aspirin versus monotherapy with aspirin or clopidogrel; 6 systematic reviews.[99-104]

b) Comparison of thienopyridine (clopidogrel, ticlopidine) monotherapy versus aspirin or control; 4 systematic reviews.[100, 105-107]

c) Comparison of ticlopidine versus clopidogrel; 4 systematic reviews.[11, 47, 108, 109]

d) Systematic reviews without performance of a meta-analyis; 6 systematic reviews.[110-115]

e) Systematic reviews addressing multiple interventions combining various antiplatelet treatment strategies with comparisons of interest (clopidogrel plus aspirin versus placebo plus aspirin) as subgroup analysis; 9 systematic reviews.[2, 45, 116-122]

f) Systematic review focusing on specific aspects of the intervention beyond the scope of the research question: e.g. effect of clopidogrel loading dose, pre-treatment, therapy duration and network analysis; 5 systematic reviews.[72, 123-126]

g) Systematic reviews focusing only on the safety outcome bleeding; 3 systematic reviews.[127-129]

Subgroup a) comprised the interventions of interest for the subsequent indirect treatment comparison and results are shown in detail including the AMSTAR rating in Table 2. The remaining reviews are listed in Appendix 4.

Table 2. Overview of most relevant systematic reviews: Comparison of DAPT with clopidogrel and aspirin versus monotherapy with aspirin or clopidogrel

Berg 2008 (search through: n/a); **Research question**: Cost-effectiveness of clopidogrel pre- and long-term treatment – based on MA of PCI-CURE, CREDO, PCI-CLARITY; **AMSTAR 2/poor**				
Population	**Intervention**	**Comparator**	**Outcome**	**Included RCT**
Study populations of PCI-CURE, CREDO, PCI-CLARITY	Aspirin plus Clopidogrel (pre-treatment, long-term)	Aspirin, Clopidogrel for 28 days post PCI	Combined endpoint MI and CV death; major bleedings;	PCI-CURE, CREDO, PCI-CLARITY, long-term: PCI-CURE, CREDO

Berger 2009 (search through May 2007); **Research question**: to compare the efficacy and safety of clopidogrel in women and men; **AMSTAR 9/excellent**				
Population	**Intervention**	**Comparator**	**Outcome**	**Included RCT**
Patients at high risk for CV events	Clopidogrel plus Aspirin, only RCT (open or blinded)	Placebo plus Aspirin	Composite MACE (CV mortality, nonfatal MI, stroke), MI , stroke, CV and all-cause mortality, major bleeding as defined in each study	CREDO CURE CLARITY COMMIT CHARISMA
Subgroup analysis– enrollment for ACS		Including CURE, CLARITY, COMMIT		
Subgroup analysis – established disease		All trial but excluding CV risk group from CHARISMA		

Bowry 2008 (search through Aug 2008); **Research question**: to determine the role of dual antiplatelet therapy for patients with vascular disease; **AMSTAR 7/moderate**

Population	Intervention	Comparator	Outcome	Included RCT
Patients with CV disease	Aspirin plus clopidogrel	Monotherapy with either aspirin or clopidogrel	Primary: MACE (composite of death, stroke, MI). Secondary: MI, all-cause mortality, and ischemic stroke. primary safety: major bleeding (decrease in hb of 5 g/dl or >2 units of blood)	CREDO CURE (substudy: PCI-CURE) CLARITY (substudy: PCI-CLARITY) COMMIT CHARISMA MATCH
Subgroup analysis– ACS		Including CURE, CLARITY, COMMIT		
Subgroup analysis – PCI		Including PCI-CURE, CREDO, PCI-CLARITY		
Subgroup analysis– other		Including MATCH, CHARISMA		
Subgroup analysis – short follow-up		Including COMMIT, CLARITY		
Subgroup analysis– long follow-up>30days		Including CURE, CREDO, MATCH, CHARISMA		

Helton 2007 (search through May 06); **Research question**: to determine the impact of clopidogrel plus aspirin on individual outcomes death, MI or stroke; **AMSTAR 8/excellent**

Population	Intervention	Comparator	Outcome	Included RCT
Patients with established CVD or multiple CVRF	Aspirin plus Clopidogrel	Aspirin and Placebo	**Individual** Outcomes: all-cause and CV mortality, MI, stroke or bleeding (major, fatal, hemorrhagic); composite (all-cause mortality, MI, stroke)	CURE CREDO CLARITY COMMIT CHARISMA

Main 2004 (search through April 03); **Research question**: to determine clinical effectiveness and the cost-effectiveness of clopidogrel in ACS; **AMSTAR 8/excellent**

Population	Intervention	Comparator	Outcome	Included RCT
Patients with UA or NSTEMI (studies excluded with only NSTEMI pts undergoing PCI)	Clopidogrel combined with standard therapy including Aspirin	Standard therapy including Aspirin	CV and all-cause mortality, MI, stroke, refractory ischemia, HF, revascularization, UA, other vascular events, major and minor bleeding, other adverse events	CURE

Squizzato 2007 (search through May 06); **Research question**: effects of adjunct clopidogrel to standard long-term ASA for preventing CV events in people at high risk of CVD and those with established CVD; **AMSTAR 10/excellent**

Population	Intervention	Comparator	Outcome	Included RCT
Patients with known CAD, ischemic CVD, PAD or at high risk of CVD; only RCT with FU>30d	Aspirin plus Clopidogrel	Aspirin and Placebo; Aspirin monotherapy	Primary: all CV events; Secondary: MI, UA, HF, ischemic stroke, Revascularization procedures, All-cause and CVD mortality, Major and minor bleeding	CHARISMA, CURE (CREDO excluded because of open label clopidogrel one month post PCI)

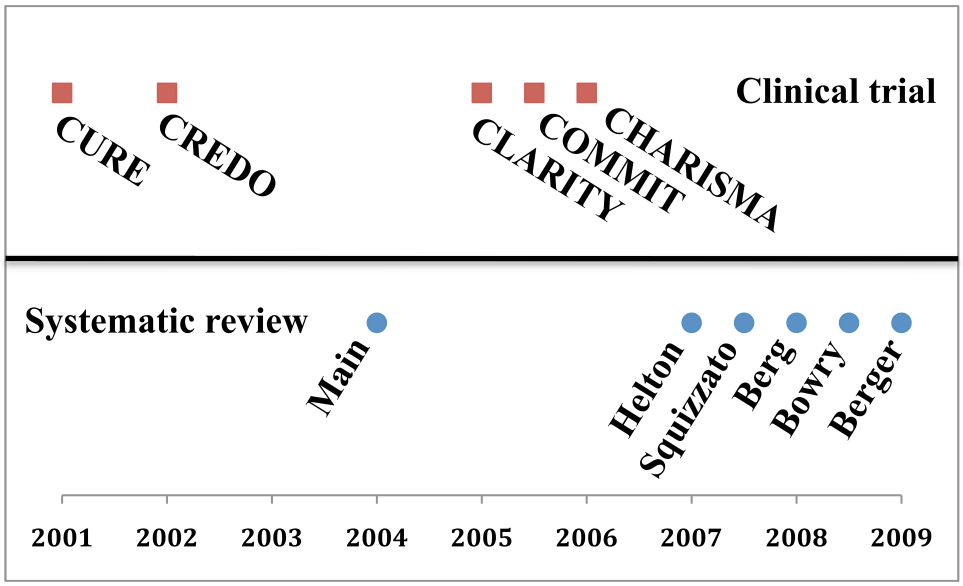
3.4 Summary

The overview of systematic reviews revealed that only a limited number of trials with the intervention of interest for the indirect treatment comparison are available. In total, six different studies were used in these systematic reviews. In addition, two sub-studies reported the results from patients undergoing PCI. One study (MATCH) compared DAPT with clopidogrel and aspirin to clopidogrel and placebo. However, for the indirect treatment comparison studies of clopidogrel versus placebo in addition to aspirin were of interest, and so this study was not eligible. As the number of available studies was small, the results from the trials were extracted directly instead of using the synthesized evidence of the systematic reviews. The data were then

entered into RevMan in order to generate estimates (odds ratios and 95% confidence intervals) for all outcomes and subgroups. These results are given in Appendix 5. These data were then used for the indirect treatment comparison, which is outlined in detail in chapter 5.

As shown in Figure 2, two studies were published in 2001 and 2002 and three studies in 2005 and 2006. The systematic reviews were published one to three years thereafter.

Figure 2. Time line of clinical trials and systematic reviews



4 METAANALYSIS OF TICAGRELOR AND PRASUGREL TRIALS

4.1 Introduction

Systematic reviews have become a hallmark of evidence-based medicine. Their main objective is to present an unbiased summary of all relevant studies of adequate quality in order to evaluate effectiveness of treatment strategies and answer relevant therapeutic questions.[130] If a quantitative, i.e. statistical, approach to synthesize evidence is included, this is termed meta-analysis. Several requirements have to be fulfilled for a precise, unbiased estimate of the effects of an intervention. Decisions taken during the execution of a systematic review should be reproducible for the reader.

The following systematic reviews for prasugrel and ticagrelor were conducted in line with the Cochrane Handbook for Systematic Reviews of Interventions.[131] Potential deviations are reported.

4.2 Methods

4.2.1 Study inclusion criteria

Studies were included if the **PICO** criteria as outlined below were met.

- Types of studies

Only randomized controlled trials published in peer-review journals were included.

- Types of participants

Studies that enrolled patients with known cardiovascular, cerebrovascular and/or disease peripheral arterial disease were included.

- Types of intervention and comparator

Studies randomizing patients to dual antiplatelet therapy (DAPT) with aspirin and clopidogrel versus aspirin and ticagrelor or aspirin and prasugrel are included in the systematic review. To date, no trials were performed using prasugrel or ticagrelor as monotherapy without adjunct

aspirin treatment. No time limit was applied for the duration of DAPT but subgroup analysis addressed duration of treatment and follow-up. For multi-dose trials, only the dosage, which is equivalent to the one for which approval was sought at regulatory boards in North America and Europe was included, i.e. prasugrel 10mg daily (60 mg loading dose) and ticagrelor 90mg bid (180mg loading dose). If none of these were used, the most similar dosage was chosen. Dosage of the comparator clopidogrel was not pre-specified as dosing according to current guidelines was expected (i.e.75 mg daily).

- Types of outcome measures

The primary clinical outcome for this review was all-cause mortality. However, a number of additional outcomes were addressed. Regarding efficacy outcomes, a composite endpoint of CV death, non-fatal myocardial infarction and stroke as well as the individual components were included. For cerebrovoascular events, ischemic or –if not reported - total stroke events were included. If appropriate, stent thrombosis (defined as definite or probable according to Academic Research Consortium criteria,[132] see Appendix 6A) was included.

Regarding safety outcomes, bleeding events were included comprising the categories major, minor and 'major or minor'. In addition, non CABG-related major bleeding was analyzed if reported separately. However, different criteria for major and minor bleeding are currently used in clinical trials. Bleeding according to TIMI (Thrombolysis In Myocardial Infarction) criteria was used if available.[133] Otherwise, bleeding results were extracted as described in the trials. Epistaxis was considered as minimal bleeding and thus not included. Bleeding classification according to TIMI criteria is shown in Appendix 6B.

4.2.2 Search methods

A computerized search strategy was created with the help of an information scientist in order to address efficacy and safety outcomes simultaneously. The following electronic databases were searched through August 25th 2010 using an OVID interface:

- CDSR (Cochrane Database of Systematic Reviews), The Cochrane library, 2010
- EMBASE, 1980 to 2010, week 33
- MEDLINE, 1950 to present AND in-process & other non-indexed citations

In addition, bibliographies of included articles, relevant systematic and non-systematic reviews were searched for possible references not otherwise found. Hand-searching of selected cardiovascular journals and conference proceedings was performed. Medline results were updated on a weekly basis until February 7th, 2011 and new studies included if appropriate.

No language or methodological limits were applied. The full search strategies in Embase and Medline are presented in Appendix 7. The following keywords were used to search CDSR: clopidogrel and prasugrel; clopidogrel and ticagrelor.

In addition, reviews for the advisory committee of the American Food and Drug Administration (FDA), Division of Cardiovascular and Renal Products, on prasugrel and ticagrelor were used as information source. The reviews can be found at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022307s000TOC.cfm for prasugrel and http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM220192.pdf for ticagrelor.

4.2.3 Methods of the systematic review

4.2.3.1 Selection of studies

Eligibility assessments of titles and abstracts were performed in an un-blinded standardized manner. Uncertainties were resolved by discussion and consensus with the supervisor. Any RCT of potential interest was obtained in full text format. The inclusion criteria were then applied and a final decision was made for inclusion. No attempt was undertaken to blind authors or centers of publication before performance of the study selection as there is only weak evidence that this would improve results but clearly complicates the review process.[131]

In the case of the inclusion of multiple published reports or outcomes from one study, the multiple publications were linked together and referred to by the included study. The primary study publication was used for data extraction. If necessary, data extraction was also performed for additional publications.

4.2.3.2 Data extraction and management

All information was extracted using a standardized data abstraction form created in excel, which was based on the Cochrane Consumers and Communication Review Groups's data extraction template.

Abstraction included 1) characteristics of trial participants including age, sex, stage and severity of disease (e.g. ACS, ST elevation myocardial infarction) and method of diagnosis (e.g. ECG chances, biomarkers as troponin T), key inclusion and exclusion criteria; 2) type of intervention including dose (in particular use of a loading dose), duration and co-medication; 3) results of efficacy and safety outcomes of the intervention.

All extracted data were checked for accuracy by two independent reviewers (E.F., A.H.).

4.2.3.3 Quality Assessment

For quality assessment two assessment tools were piloted: the checklist proposed by the Scottish Intercollegiate Guidelines network (SIGN50) [134] and the Cochrane Collaboration's tool for assessing risk of bias.[135]

The SIGN 50 assessment form comprises three sections: (i) assessing internal validity (10 questions), (ii) performing an overall assessment of the study by rating the methodological quality based on answers to questions from section 1 (4 questions), and (iii) extracting useful data from the studies in order to complete evidence tables facilitating cross-study comparisons (9 questions). Answers from the checklists are not weighted. The risk of bias is classified as either:

- Low. All or most of the criteria from the assessment of internal validity are satisfied. Study conclusions would not likely be altered if methods were changed.
- Moderate. Some of the criteria from the assessment of internal validity are satisfied. Study conclusions would not likely be altered if methods were changed.
- High. Few or none of the criteria from the assessment of internal validity are satisfied.

The SIGN50 tool overlapped substantially with the data extraction form and was more time consuming without any evidence of additional benefit compared to the Cochrane tool. The latter

was subsequently preferred. It is also implemented in RevMan 5.0, which was used for all analyses.

The Cochrane instrument is a two-part tool addressing six specific domains (namely sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and "other issues"). Each domain includes one or more specific entries in a ' Risk of bias' table, which was created in line with the Cochrane template in excel. The first part involves describing what was reported to have happened in the study. The second part involves assigning a judgment relating to the risk of bias for that entry by answering a pre-specified question about the adequacy of the study in relation to the entry. A judgment of 'YES' indicated low risk of bias, 'NO' indicates high risk of bias, and 'UNCLEAR' indicates unclear or unknown risk of bias. Figures can be generated in RevMan showing the results of this assessment.

As proposed in the Cochrane Handbook for Systematic reviews of Interventions, two entries were made for the domain 'Blinding' because assessments had to be made separately for blinding of the study drug and blinding of outcome assessments.

For a specific study, information for the description can be obtained from a single published report, but may also be obtained from a mixture of study reports, protocols, published comments on the study and contacts with investigators.[131] Within this review, we encountered an additional aspect as some information was solely available from the aforementioned reviews for the FDA advisory committees.

4.2.3.4 Assessment of heterogeneity

First, clinical heterogeneity was assessed through clinical judgment. The outcome data were combined by meta-analysis only when the population characteristics of the studies and interventions were sufficiently homogenous.

Second, statistical heterogeneity was assessed in two steps. Forest plots were visually inspected for the absence of overlap in the confidence intervals as this would suggest heterogeneity. A formal assessment was made using the I^2 test statistics, which quantifies the percentage of the variability that is due to heterogeneity rather than chance.[136, 137] As a rule of thumb, a value above 25% suggests *mild*, above 50% suggests *moderate* and above 75% *high* heterogeneity. In case of

relevant statistical heterogeneity (I^2 >50%), it should be explored using sensitivity analysis and influence analysis. The presence or absence of heterogeneity would also influence the subsequent method of analysis. If it could not be explained, results should be presented using both a random and fixed effects model. If no heterogeneity was present, a fixed-effects model would be employed. Thereby, the size of treatment effect is assumed to be the same (fixed) across all studies and the variation between the studies is due only to the play of chance. In RevMan, the random-effects meta-analysis by DerSimonian and Laird is implemented. The assumption is made that the studies included are estimating different treatment effects. The summary effect refers to the centre of the point estimate and the associated confidence intervals are wider than in fixed effect models if the I^2 statistic is greater than zero. If very large heterogeneity is encountered, it may even be inappropriate to calculate an overall effect measure.

4.2.3.5 Data synthesis

RevMan 5.0 software from the Cochrane Collaboration was used for all statistical analyses. All outcomes of interest were dichotomous and analyzed by a fixed-effects model using the Mantel Haenszel methods on the basis of the intention to treat principle. This method of analysis has better statistical properties when the event rates are low, as this is the case for several outcomes in this review, in particular for stroke, stent thrombosis and bleeding events. For each outcome the weighted Odds Ratio and corresponding 95% confidence interval were calculated for the overall treatment effect. If one treatment group has zero events, a 0.5 adjustment is automatically made to the numerator, while no adjustments are made to the cells for studies containing zero events in both the intervention and control group. Thus, these studies do not contribute to the overall treatment effect.

4.2.3.6 Assessment of publication bias

Reporting bias was assessed by constructing funnel plots for each outcome. In funnel plots, the vertical axis gives a measure of the precision of the estimate of the treatment effect. So the smaller the confidence interval, the more precise the study, and the further up the study will be placed. The horizontal axis measures the treatment effect on a log scale, so that the distance from

0.1 to 1 is the same as from 1 to 10. The point estimate from each study is then plotted, and a vertical line added, where the pooled estimate from the meta-analysis lies. Less precise studies (with fewer participants and events) would be expected to be more affected by the play of chance, and so more widely scattered about the pooled estimate. As studies get bigger with more events, they should be closer to the pooled estimate and this should produce a triangular shape, or inverted funnel. An asymmetric plot might be an indicator for publication bias.

4.2.3.7 Subgroup analysis

Subgroups of interest included trials with short and long-term follow-up as well as patients undergoing percutaneous coronary intervention, which indicates a procedure to re-open stenotic or coronary arteries. In most cases, stents are implanted to ensure long-term patency. Further, studies were classified according to clinical symptoms into trials including patients with acute coronary syndrome, stable coronary artery disease or both (i.e. mixed). In acute coronary syndrome, coronary blood flow is decreased due to thrombotic artery occlusion leading to insufficient oxygen supply and acute clinical symptoms (such as chest pain, dyspnea, tachycardia, hemodynamic shock). In patients with stable disease, atherosclerotic arteries provide sufficient oxygen supply at rest, but patients can become symptomatic during physical activity due to the higher oxygen demand.

4.2.3.8 Sensitivity analysis

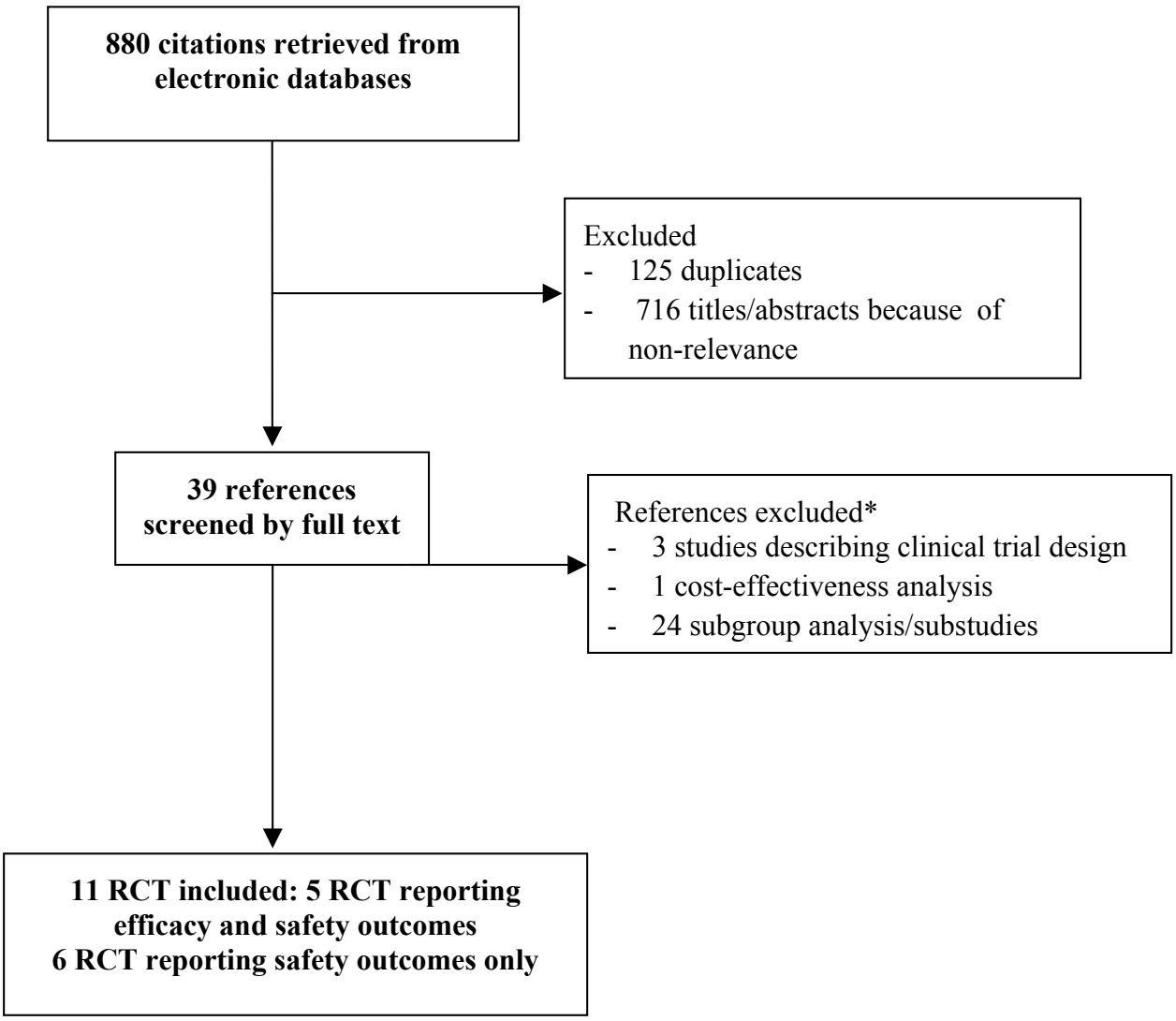
If relevant heterogeneity in trial design or clinical population was present, sensitivity analysis would be conducted.

4.3 Results

4.3.1 Results of the search

The systematic search strategy identified 755 study reports of potential interest for the review after de-duplication. 716 reports were excluded upon inspection of the title and/or abstract, thus 39 references were screened by full text. The review process is depicted in Figure 3.

Figure 3. Schematic of the RCT reviewing process



* A list of excluded studies is shown in Appendix 8. One additional included study was published later and identified by the weekly update of the Medline search (SWAP trial).[138] Searching of conference proceedings identified no additional trial but sub-reports of already published studies.

4.3.2 Included studies

From the 12 RCT included, 7 studies compared prasugrel versus clopidogrel comprising 15 110 patients.[23, 76, 77, 138-141] Notably, one large clinical trial, TRITON-Timi-38, contributed 13 608 patients.[23]

Five studies compared ticagrelor versus clopidogrel comprising 20 029 patients.[24, 82, 85, 91, 142] Again, one clinical trial, PLATO, contributed the majority of patients, namely 18 624.[24]

Both efficacy and safety outcomes were reported in three prasugrel trials and in two ticagrelor trials. The remaining seven trials reported only safety outcomes (bleeding) because their primary objectives were pharmaco-dynamic analyses. All studies were reported in English.

Main characteristics of the included studies are depicted in Appendix 9.

4.3.2.1 Characteristics of the patients

The majority of included patients suffered from unstable coronary artery disease, i.e. unstable angina, non-ST-elevation myocardial infarction as well as ST-elevation myocardial infarction as this was a prerequisite for the inclusion in the TRITON and PLATO study. Some smaller trials also included patients with stable coronary artery disease.

The percentage of patients undergoing stent implantation differed between the clinical trials with nearly all patients (99%) undergoing PCI in the two large prasugrel trials, TRITON and JUMBO.[23, 77] Apart from these two trials, individualized results for patients undergoing coronary stenting were only available for the PLATO trial. Patients with planned invasive strategy were identified at study entry and published as a sub-report in the PLATO-invasive analysis.[143]

4.3.2.2 Characteristics of the intervention/comparator

In all trials, patients received co-medication with another antiplatelet agent, aspirin, albeit the dosage was not consistent between and within the trials and ranged from low dose therapy (81mg daily) to high dose therapy (up to 325 mg daily).

The maintenance dose of the comparator clopidogrel was 75mg daily in all but two trials, which investigated prasugrel versus clopidogrel. In PRINCIPLE-Timi 44, double dose clopidogrel, i.e.

150mg daily, was used.[76] Another trial, which was only included in safety analysis as no efficacy results were reported, also used double dose clopidogrel.[140] However, relevant differences were found regarding the loading dose of clopidogrel ranging from 300mg to 900mg. Some trials in stable patients without planned coronary intervention did not use a loading dose.

Regarding the study drug, different dosages were used in early, dose-finding trials, while later studies used the established dosing: 60mg loading dose and 10mg maintenance dose daily of prasugrel, 180mg loading dose and 90mg maintenance dose twice daily of ticagrelor. As mentioned before, in studies with multiple dosages the closest to the established dosing was included for this analysis.

Another important aspect is timing and duration of the intervention. The optimal timing of loading dose (of both clopidogrel or novel ADP antagonists) in patients presenting with unstable disease scheduled to undergo coronary angiography is still under debate[108] and different strategies were used in the included clinical trials. Thus, the PLATO trial adopted a strategy of early loading before the coronary anatomy was known, while in the TRITON trial patients were randomized and treated with the study drug or the comparator only when the coronary angiogram was available and found to be suitable for interventional therapy. As mentioned before, interventional cardiologists in Canada and other countries often favor a 600mg loading dose that is given early before coronary angiography. Thus, the rather low loading dose of clopidogrel and its late administration limit the generalizability of the TRITON trial to clinical routine.

Duration of therapy and follow-up differed substantially between the included studies. Three studies had a cross-over design with a total study duration of 28 days and two of these studies reported safety outcomes only.[76, 85, 140] For this analysis, only results from the pre-cross over phase were used. Another 7 studies had rather short treatment durations between 14 days and 3 months.[77, 82, 91, 138, 139, 141, 142] The two large RCT had a median study duration of 14.5 months for the TRITON and 277 days for the PLATO trial, respectively.

4.3.2.3 Characteristics of the outcomes

In analogy to treatment duration, the follow-up periods differed largely between 14 days and 15 months. Importantly, only in two trials (TRITON and PLATO) the primary endpoint was a

composite of cardiovascular death, non-fatal myocardial infarction and stroke while in all other trials the primary endpoints were either safety results, i.e. bleeding events, or pharmaco-dynamic data of platelet function testing. As all crossover studies were pharmaco-dynamic studies looking at platelet reactivity measures, the study populations were small with low event rates. In these studies, only one myocardial infarction in the clopidogrel group[76] and one minor bleeding event in the prasugrel group[140] happened in the post-crossover period, which were not included for analysis. The `RESPOND´ study by Gurbel 2010 did not mention, in which period the bleeding events happened, but summarized the data together.[85]

Although the two most influential trials (TRITON and PLATO) both used an endpoint adjudication committee, relevant differences exist with respect to definition of outcomes. In particular, non-fatal myocardial infarction was classified in a differential manner. Differences between these trials are discussed in detail later. Sub-classification of total major bleeding events into CABG-related and non-procedure related was only available in the two large, phase III trials, TRITON and PLATO.

4.3.3 Quality assessment

Overall, a relatively low risk of bias was identified. All studies provided adequate sequence generation, addressed outcomes completely and were free of selective reporting bias. Allocation concealment and blinding of outcomes had a low risk of bias in about half of the studies with an unclear risk in the remaining studies. Regarding blinding of the study drug, only one small study did not blind the intervention.[139] The late loading of patients in the TRITON trial after the coronary anatomy was known was considered a potential source of other bias as this might have favored prasugrel due to its faster onset of action. Further, early trial suspension of the ACAPULCO study by Montalescot might have introduced bias.[140] The authors based this decision on the publication of the TRITON study. Thereby, subgroups of patients were identified, who are at increased risk of bleeding. As the study design of the ACAPULCO trial did not exclude these patients, the authors stopped the trial.

The results of the risk of bias assessment in RevMan are shown in Figure 4 and Figure 5.

Figure 4. Risk of bias graph: Authors' judgments about each risk of bias item presented as percentages across all included studies

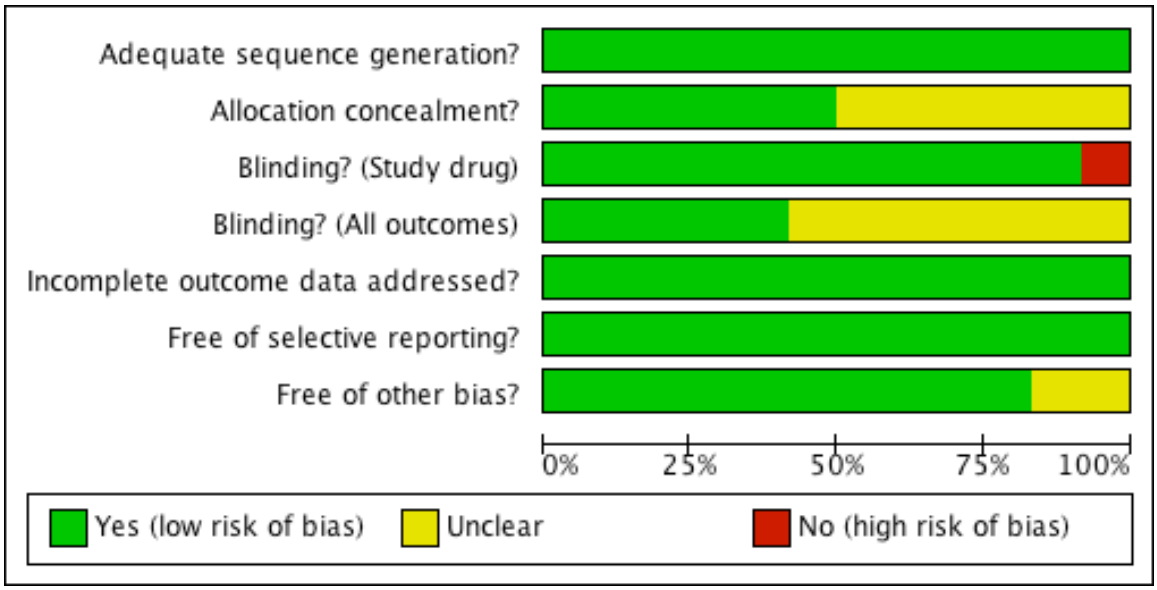
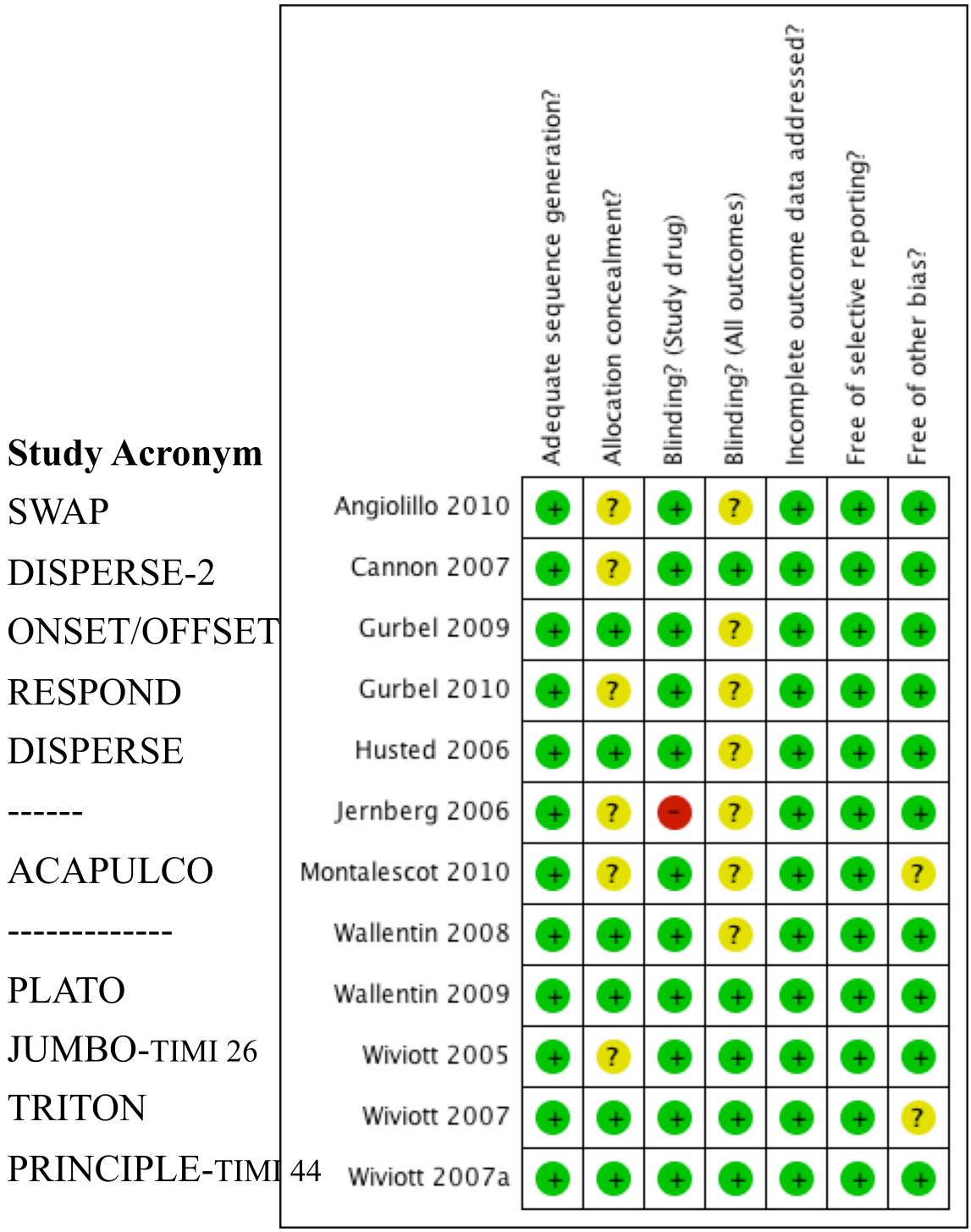


Figure 5. Risk of bias summary: Authors' judgments about each risk of bias item for each included study



4.3.4 Publication bias

The informative value of the funnel plots is limited due to the small number of included trials, in particular with respect to efficacy outcomes. No major concern of publication bias was raised by these plots. Representative funnel plots for both efficacy and safety outcomes are found in Appendix 10.

4.3.5 Main results of the meta-analysis

All results are shown as odds ratios and 95% confidence intervals using fixed effects models. Results from the comparison ticagrelor versus clopidogrel are presented first, followed by the comparison prasugrel versus clopidogrel. Forest plots show all included studies stratified by length of follow-up according to clinical presentation. By visual inspection of the forest plots no signal for relevant heterogeneity (i.e. absence of overlap of confidence intervals) was seen.

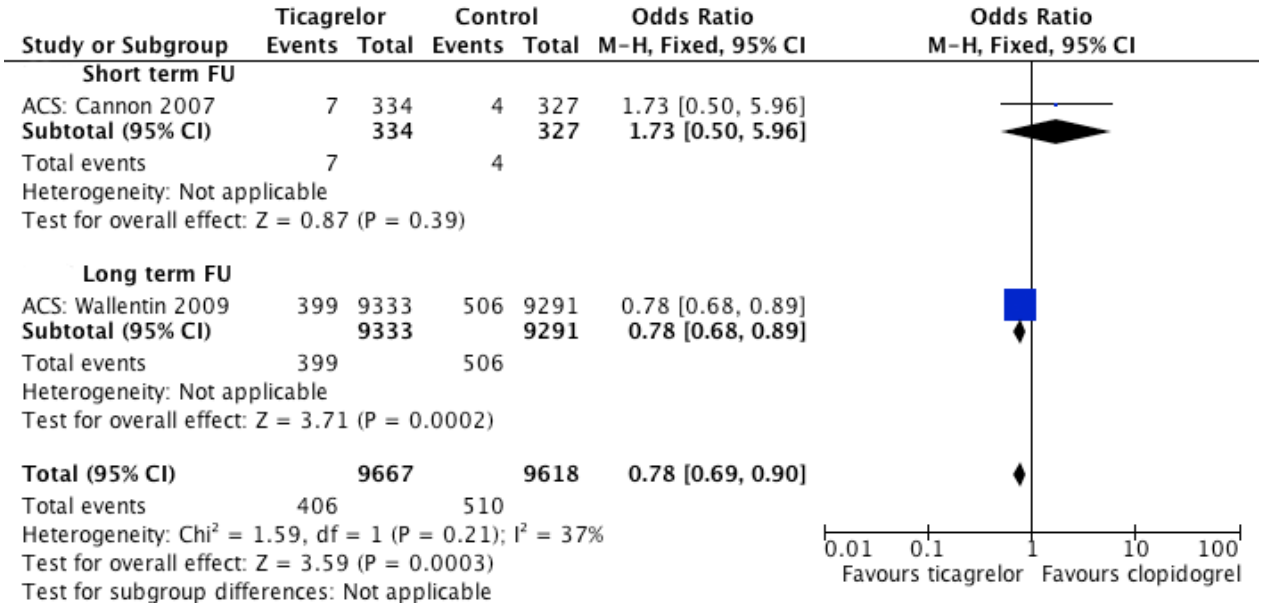
The relative weight of the two large clinical trials, TRITON and PLATO, was >92% in all analyses and even higher (>96%) for efficacy outcomes. Thus, when total event rates are reported, this mainly reflects the results from these two trials. Further, meta-analyses did not change any conclusion of these two trials and that was seen for both efficacy and safety outcomes.

4.3.5.1 All-cause mortality

A) Ticagrelor

Total mortality was 4.1% in the ticagrelor and 5.3% in the clopidogrel group. This relatively high mortality rate was also seen in the invasive subgroup (3.9% and 5%, respectively). Overall, ticagrelor treatment reduced all cause mortality significantly (OR 0.78, 95% CI 0.69-0.90). Heterogeneity was 37% by I^2 test statistics (mild). Results are shown in Figure 6a.

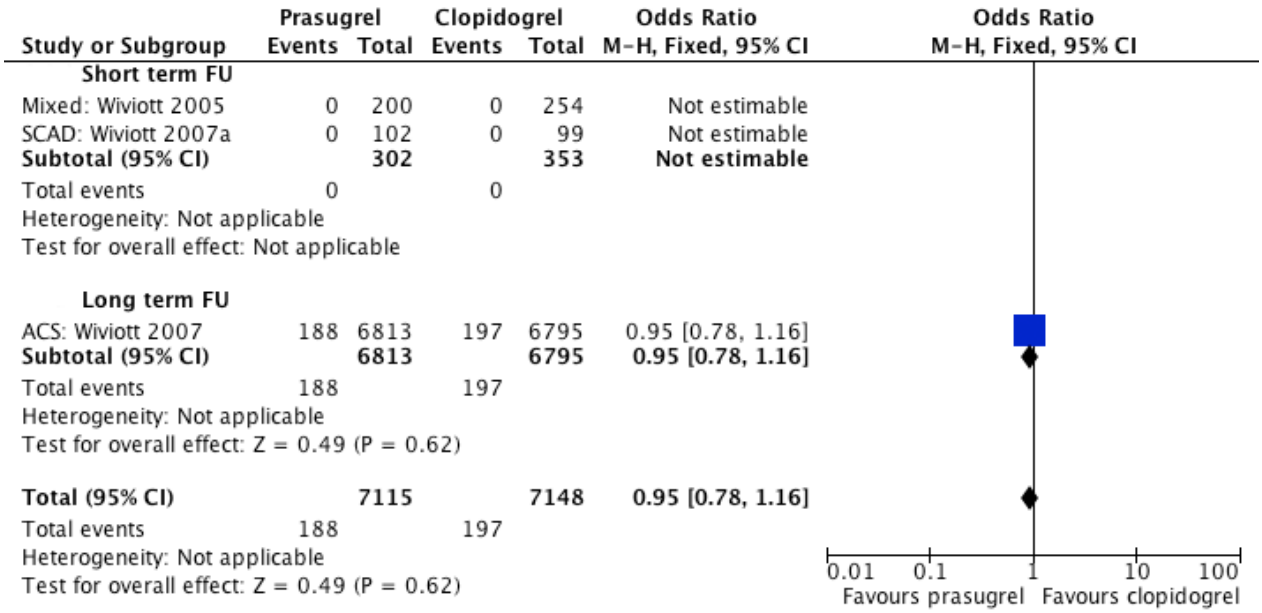
Figure 6a. Forest plot Ticagrelor versus Clopidogrel – all-cause mortality



B) Prasugrel

Total mortality was 2.5% in the prasugrel and 2.8% in the clopidogrel group. Overall, prasugrel treatment did not reduce all cause mortality significantly (OR 0.96, 95% CI 0.78-1.17). I^2 test statistics is not applicable as only one study reported events. Results are shown in Figure 6b.

Figure 6b. Forest plot Prasugrel versus Clopidogrel – all-cause mortality

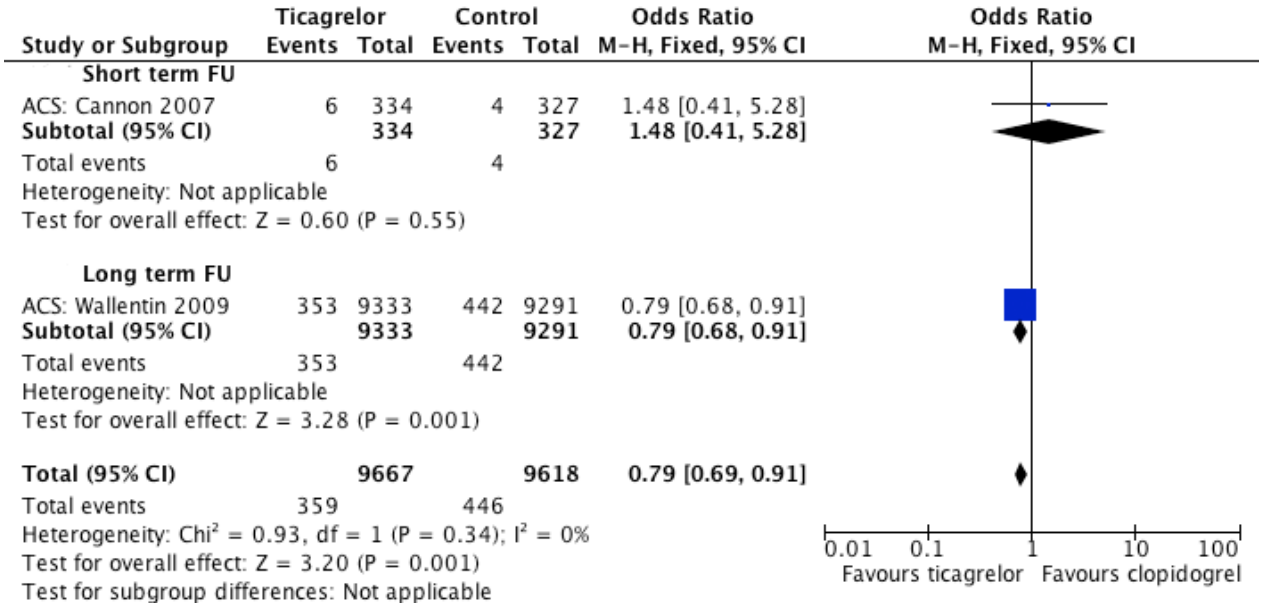


4.3.5.2 Cardiovascular mortality

A) Ticagrelor

CV mortality was 3.7% in the ticagrelor and 4.6% in the clopidogrel group. Overall, ticagrelor treatment reduced CV mortality significantly (OR 0.80, 95% CI 0.69-0.92). No statistical heterogeneity was observed by I^2 test statistics. Results are shown in Figure 7a.

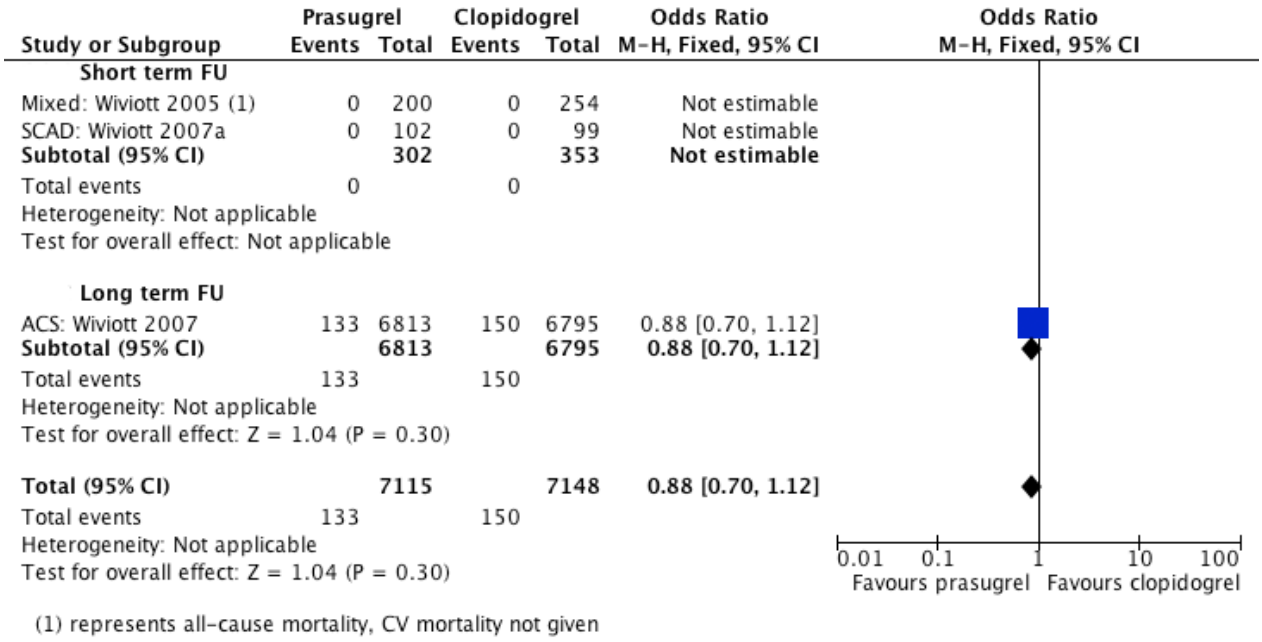
Figure 7a. Forest plot Ticagrelor versus Clopidogrel – CV mortality



B) Prasugrel

CV mortality was 1.9% in the prasugrel and 2.1% in the clopidogrel group. Similar to total mortality, CV mortality was not reduced significantly by prasugrel (OR 0.88, 95% CI 0.70-1.12). Deaths happened only in the TRITON study and thus no heterogeneity can be calculated. Results are shown in Figure 7b.

Figure 7b. Forest plot Prasugrel versus Clopidogrel – CV mortality



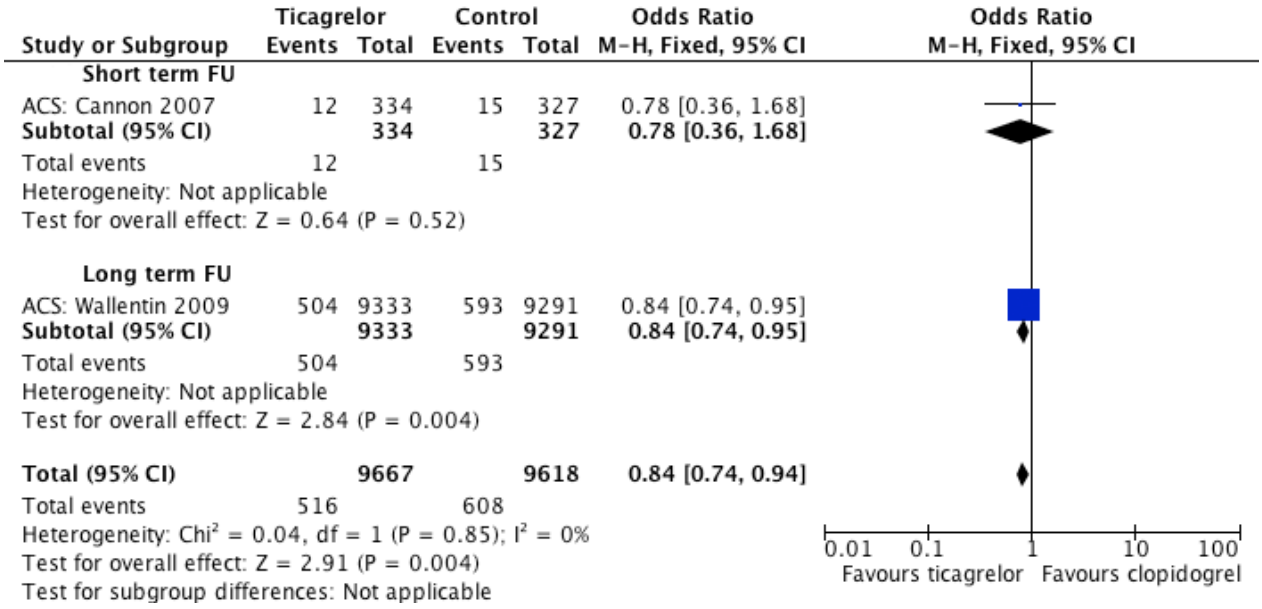
(1) represents all-cause mortality, CV mortality not given

4.3.5.3 Non-fatal myocardial infarction

A) Ticagrelor

Non-fatal myocardial infarction (excluding silent MI diagnosed by ECG only) occurred in 5.3% in the ticagrelor and in 6.3% in the clopidogrel group. Ticagrelor significantly reduced MI (OR 0.80, 95% CI 0.69-0.92). No statistical heterogeneity was observed by I^2 test statistics. Results are shown in Figure 8a.

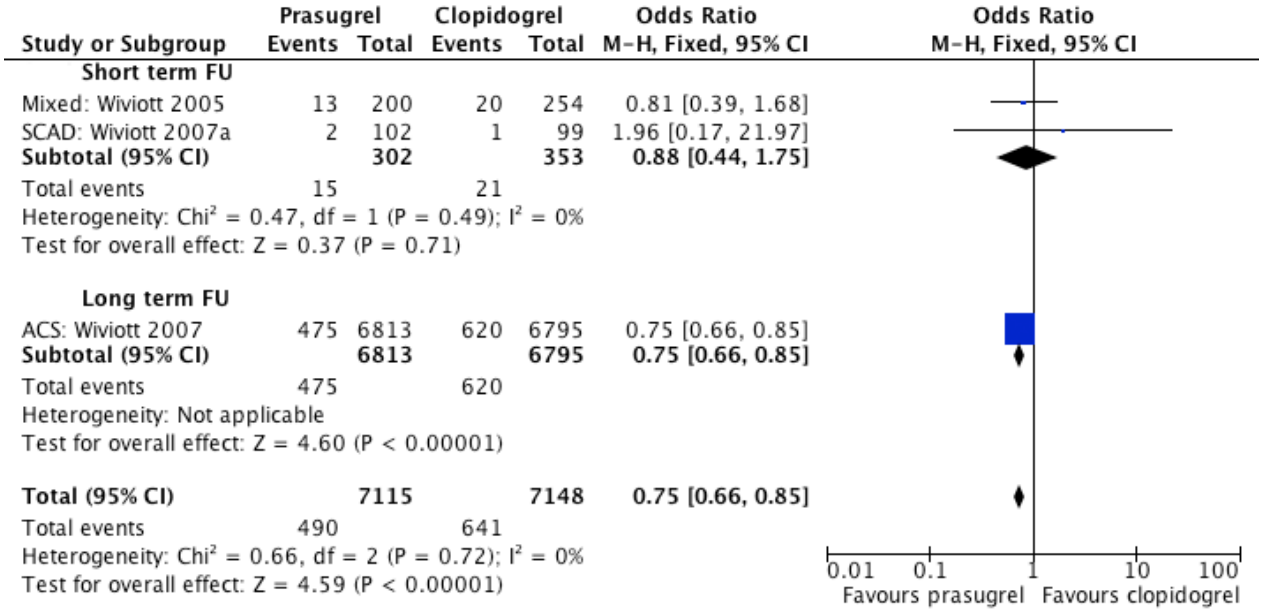
Figure 8a. Forest plot Ticagrelor versus Clopidogrel – Non-fatal MI



B) Prasugrel

Non-fatal MI occurred in 6.9% in the prasugrel group compared to 9.0% in the clopidogrel group. Prasugrel significantly reduced MI (OR 0.75, 95% CI 0.66-0.85). No statistical heterogeneity was observed by I^2 statistics. Results are shown in Figure 8b. Compared to other studies in the field, a rather high rate of non-fatal MI was reported, which is mostly due to the chosen classification scheme in the TRITON study. Thus, about two-third of the events comprised periprocedural MIs (related to PCI or CABG), which were often identified by biomarker rise rather than clinical symptoms.

Figure 8b. Forest plot Prasugrel versus Clopidogrel – Non-fatal MI

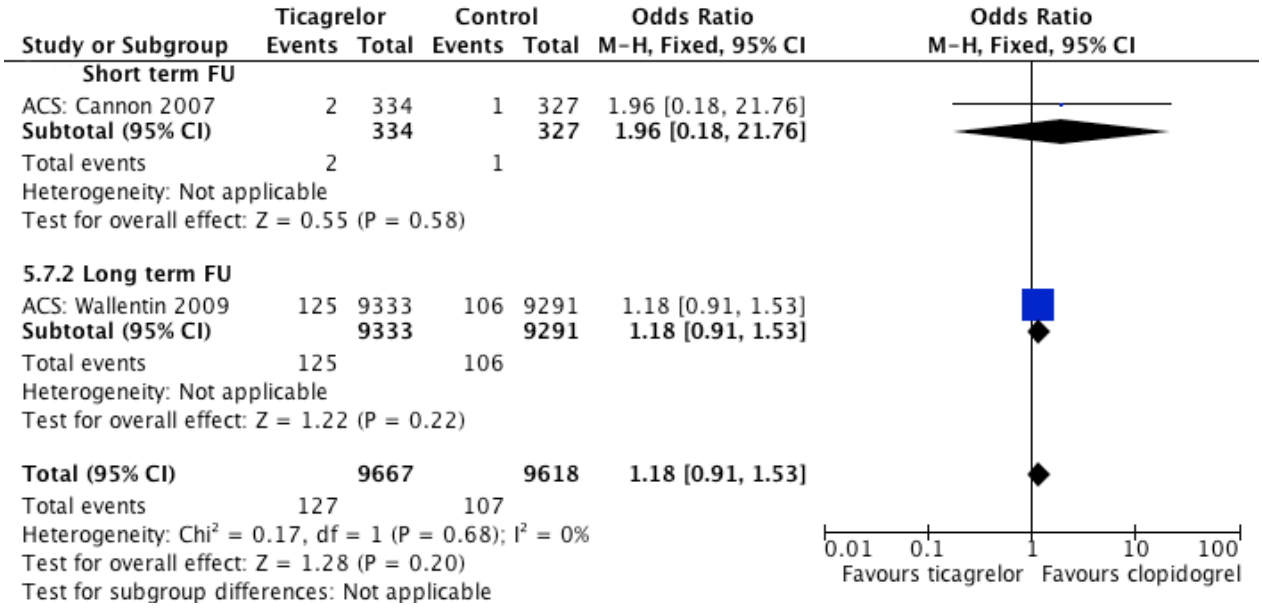


4.3.5.4 Stroke

A) Ticagrelor

Stroke occurred in 1.3% in the ticagrelor and in 1.1% in the clopidogrel group. Ticagrelor treatment did not change the risk of stroke significantly (OR 1.17, 95% CI 0.91-1.52). No statistical heterogeneity was observed by I^2 test statistics. Results are shown in Figure 9a.

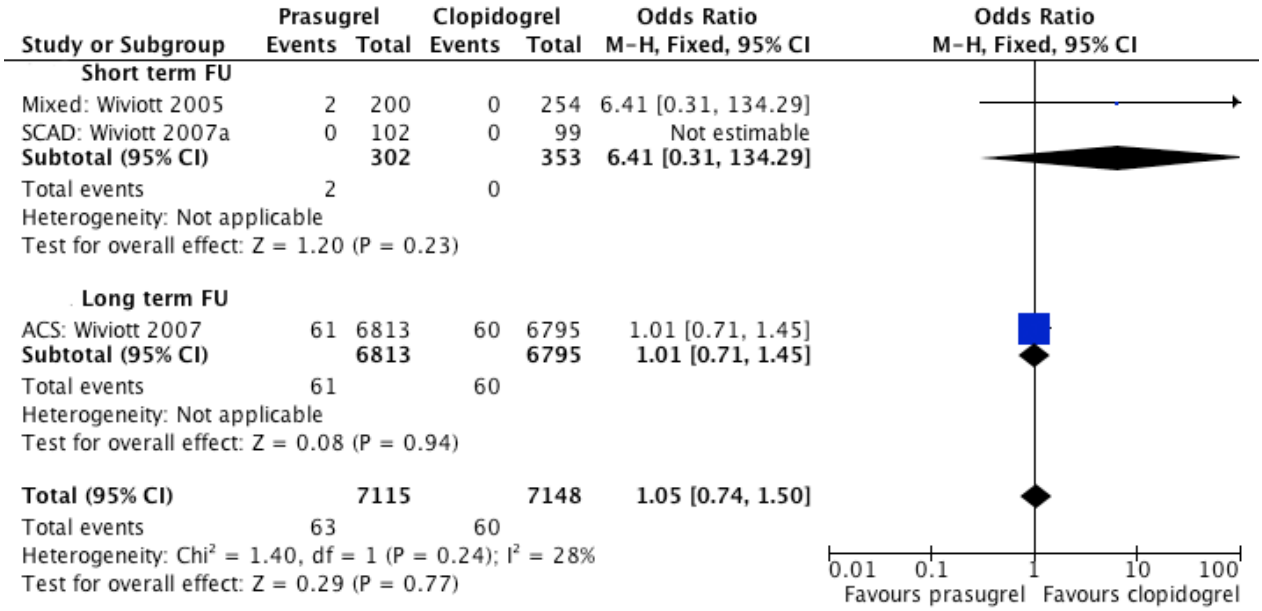
Figure 9a. Forest plot Ticagrelor versus Clopidogrel – Stroke



B) Prasugrel

Stroke occurred in 0.9% in the prasugrel and in 0.8% in the clopidogrel group. Prasugrel treatment did not change the risk of stroke significantly (OR 1.03, 95% CI 0.72-1.46). Statistical heterogeneity was 28% by I^2 test statistics (mild). Results are shown in Figure 9b.

Figure 9b. Forest plot Prasugrel versus Clopidogrel – Stroke

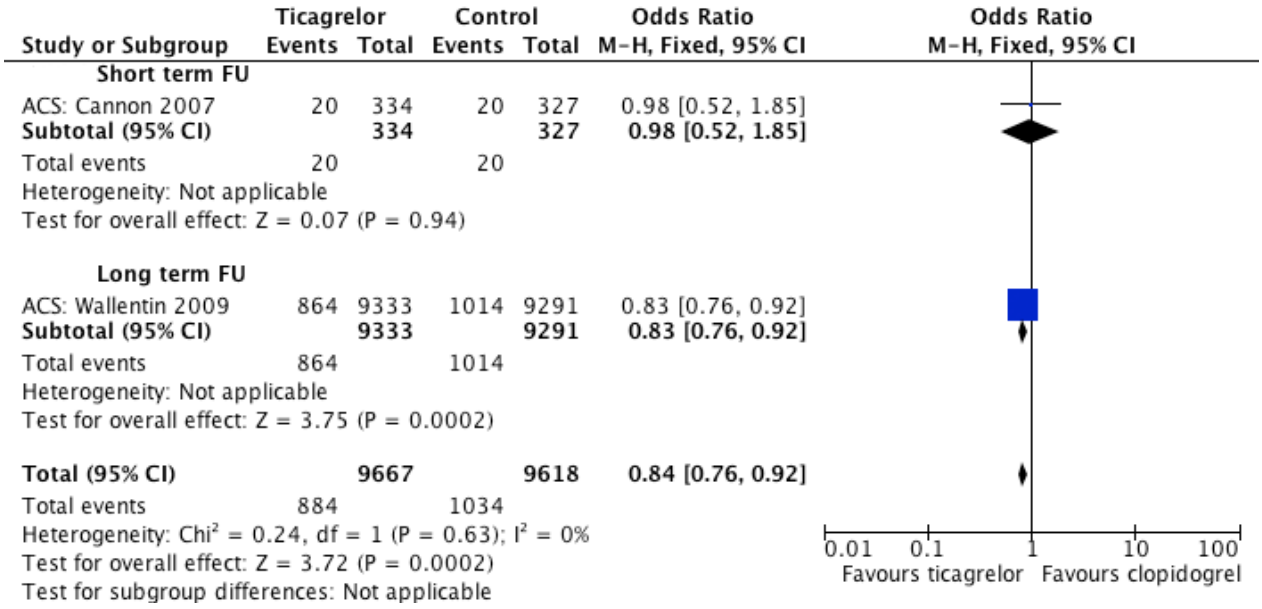


4.3.5.5 Composite endpoint of CV death, MI and stroke

A) Ticagrelor

The composite endpoint occurred in 9.1% in the ticagrelor and in 10.8% in the clopidogrel group and was significantly reduced by ticagrelor (OR 0.84, 95% CI 0.76-0.92). No statistical heterogeneity was observed by I^2 test statistics. Results are shown in Figure 10a.

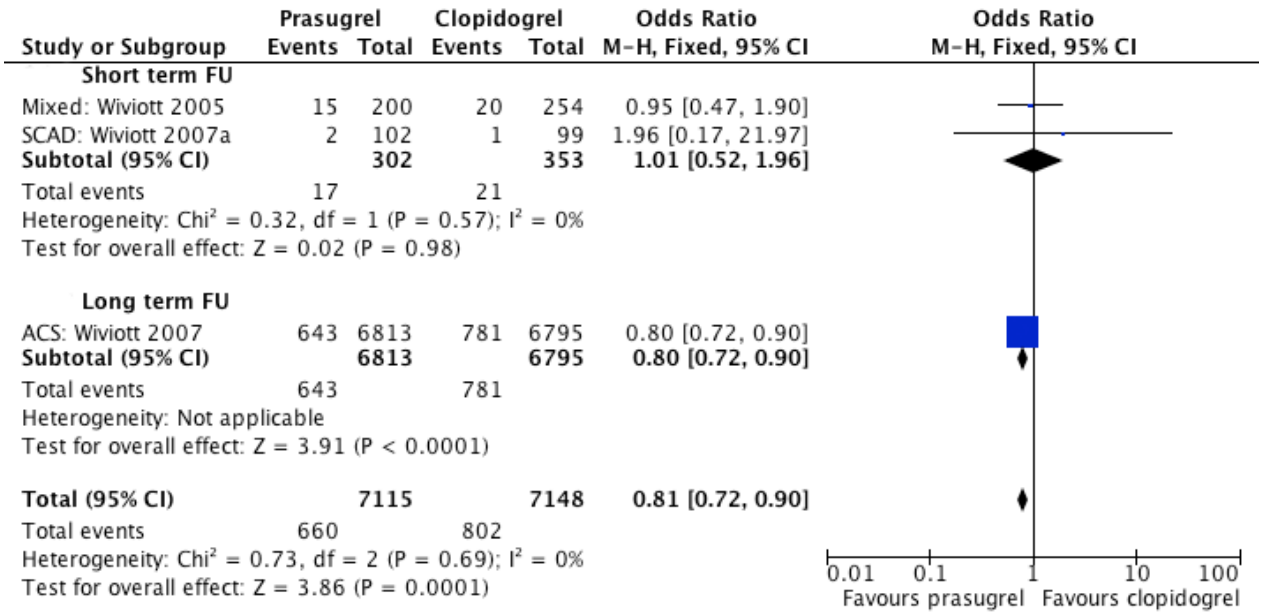
Figure 10a. Forest plot Ticagrelor versus Clopidogrel – Composite endpoint



B) Prasugrel

The composite endpoint occurred in 9.3% in the prasugrel and in 11.2% in the clopidogrel group and was significantly reduced by prasugrel (OR 0.81, 95% CI 0.72-0.90). No statistical heterogeneity was observed by I^2 test statistics. Results are shown in Figure 10b.

Figure 10b. Forest plot Prasugrel versus Clopidogrel – Composite endpoint

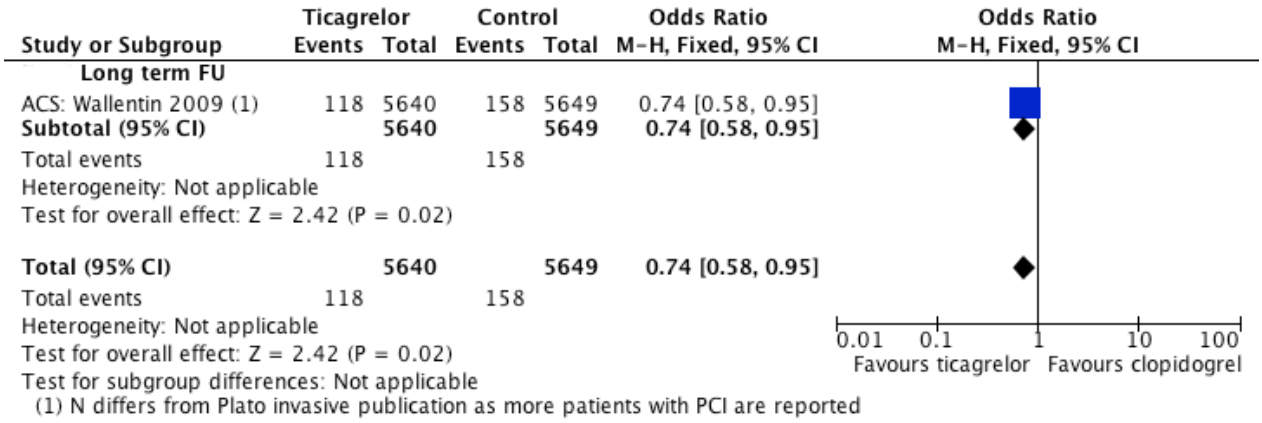


4.3.5.6 Definite or probable stent thrombosis

A) Ticagrelor

Stent thrombosis is only reported in patients undergoing stent implantation and consequently, the total number at risk differs from the previous outcomes. Only PLATO reported stent thrombosis, which was found in 2.1% in the ticagrelor and 2.8% in the clopidogrel group. Ticagrelor significantly reduced stent thrombosis (OR 0.74, 95% CI 0.58-0.95). No statistical heterogeneity can be calculated. Results are shown in Figure 11a.

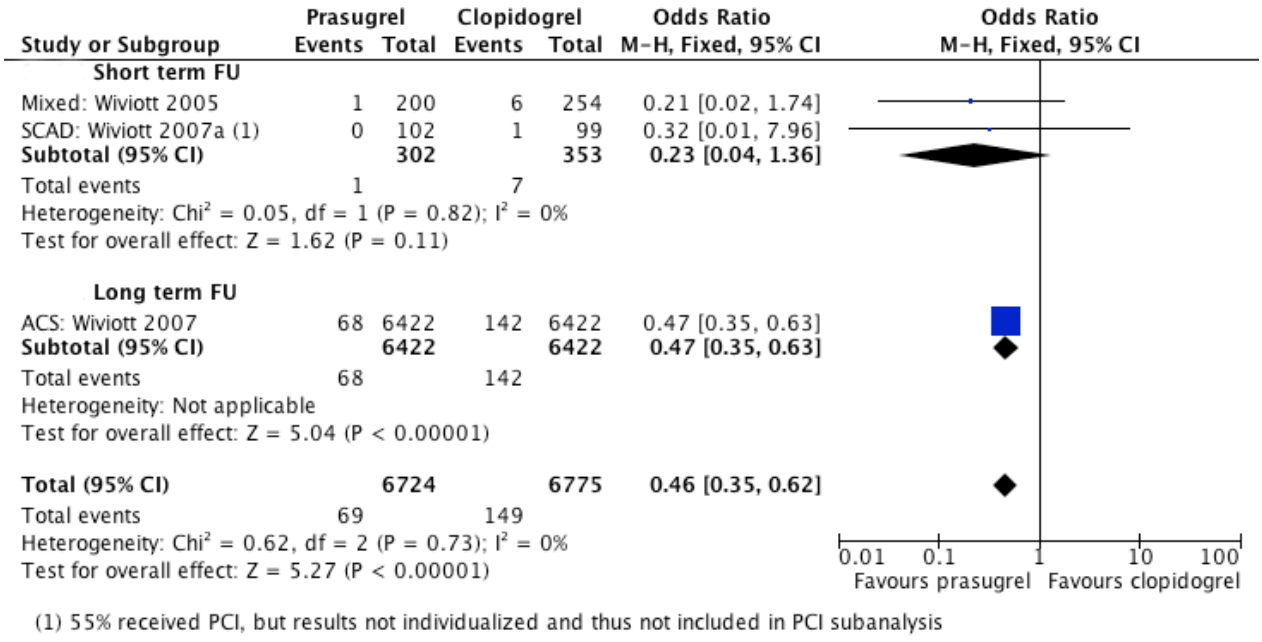
Figure 11a. Forest plot Ticagrelor versus Clopidogrel – Stent thrombosis



B) Prasugrel

The number of definite or probable stent thrombosis was available from the study Wiviott07a and the TRITON study. In the trial Wiviott 2005 (i.e. JUMBO Timi 25), clinical target vessel thrombosis was described instead of stent thrombosis. Overall, the rate of stent thrombosis was 1% with prasugrel and 2.2% clopidogrel. Thus, prasugrel significantly reduced the risk of stent thrombosis (OR 0.46, 95% CI 0.35 - 0.61). No statistical heterogeneity was observed. Results are shown in Figure 11b.

Figure 11b. Forest plot Prasugrel versus Clopidogrel – Stent thrombosis



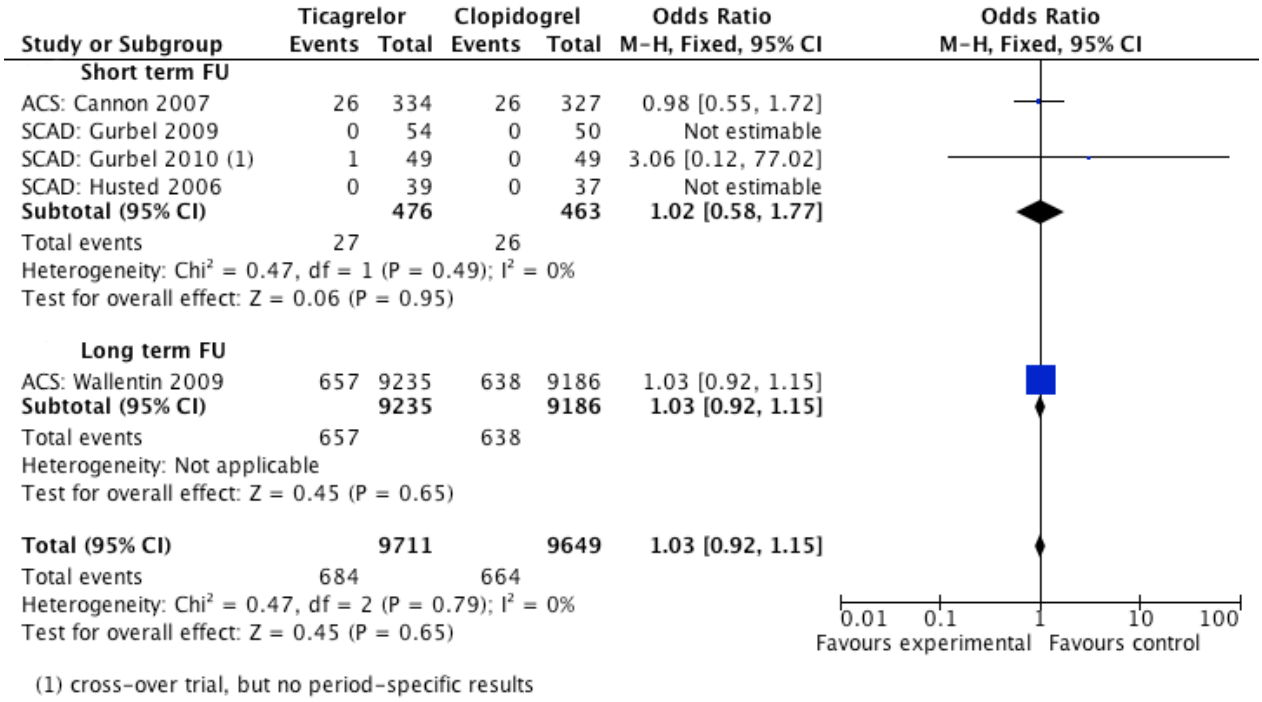
(1) 55% received PCI, but results not individualized and thus not included in PCI subanalysis

4.3.5.7 Total major bleeding

A) Ticagrelor

Total major bleeding rates were 7.0% with ticagrelor and 6.9% with clopidogrel treatment. No significant difference was observed for the risk of total major bleeding (OR 1.03, 95%CI 0.92, 1.15). No statistical heterogeneity was observed. Results are shown in Figure 12a.

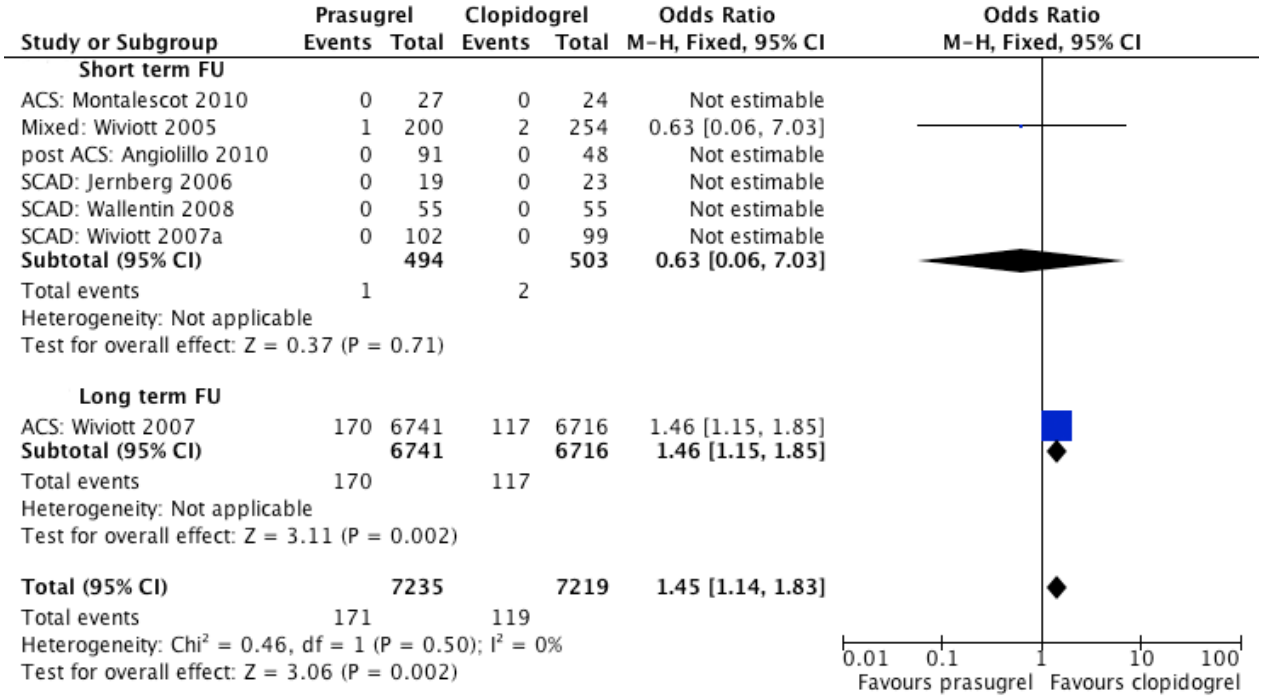
Figure 12a. Forest plot Ticagrelor versus Clopidogrel – major bleeding



B) Prasugrel

Total major bleeding rates were 2.4% with prasugrel and 1.7% with clopidogrel treatment. Significant higher major bleeding rates were observed with prasugrel treatment (OR 1.45, 95%CI 1.14, 1.83). No statistical heterogeneity was observed. Results are shown in Figure 12b.

Figure 12b. Forest plot Prasugrel versus Clopidogrel – major bleeding

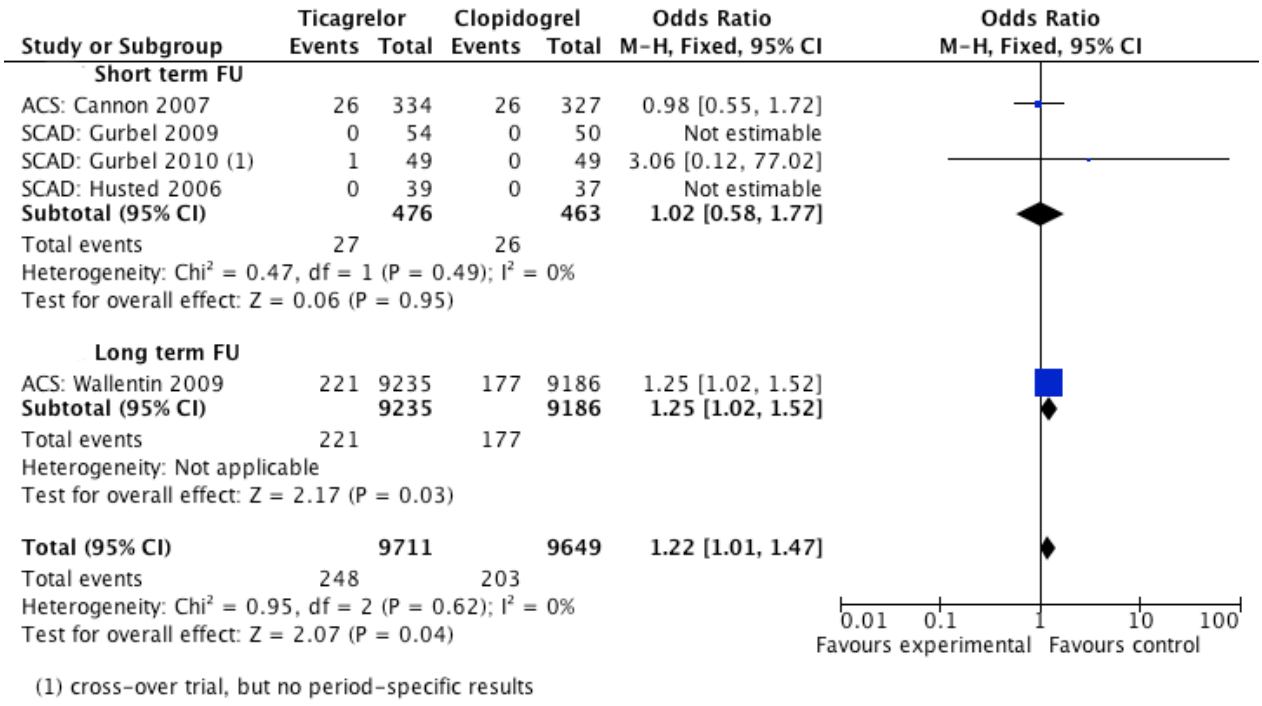


4.3.5.8 Non CABG-related major bleeding

A) Ticagrelor

Non CABG-related major bleeding rates were 2.6% with ticagrelor and 2.1% with clopidogrel treatment. Significant higher major bleeding rates not related to CABG were observed with ticagrelor treatment (OR 1.22, 95%CI 1.01, 1.47). No statistical heterogeneity was observed. Results are shown in Figure 13a.

Figure 13a. Forest plot Ticagrelor versus Clopidogrel – non CABG-related major bleeding

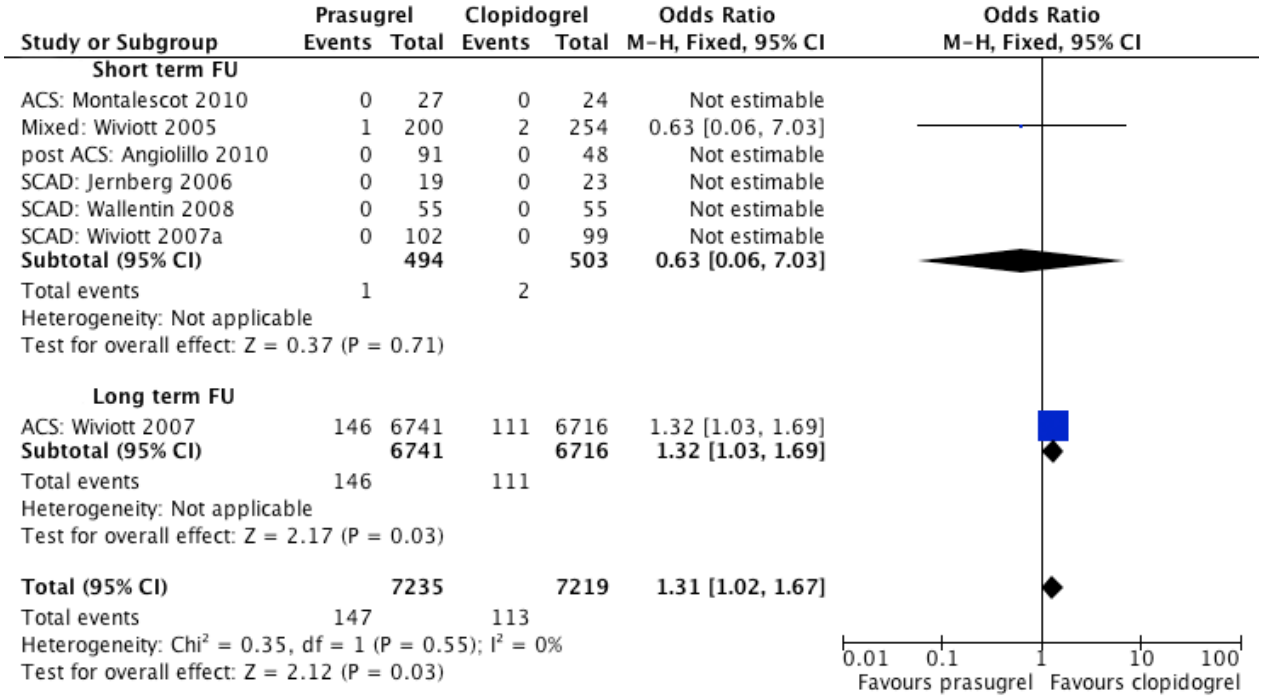


(1) cross-over trial, but no period-specific results

B) Prasugrel

Non CABG-related major bleeding rates were 2.0% with prasugrel and 1.6% with clopidogrel treatment. Significant higher major bleeding rates not related to CABG were observed with prasugrel treatment (OR 1.31, 95%CI 1.02, 1.67). No statistical heterogeneity was observed. Results are shown in Figure 13b.

Figure 13b. Forest plot Prasugrel versus Clopidogrel – non CABG-related major bleeding

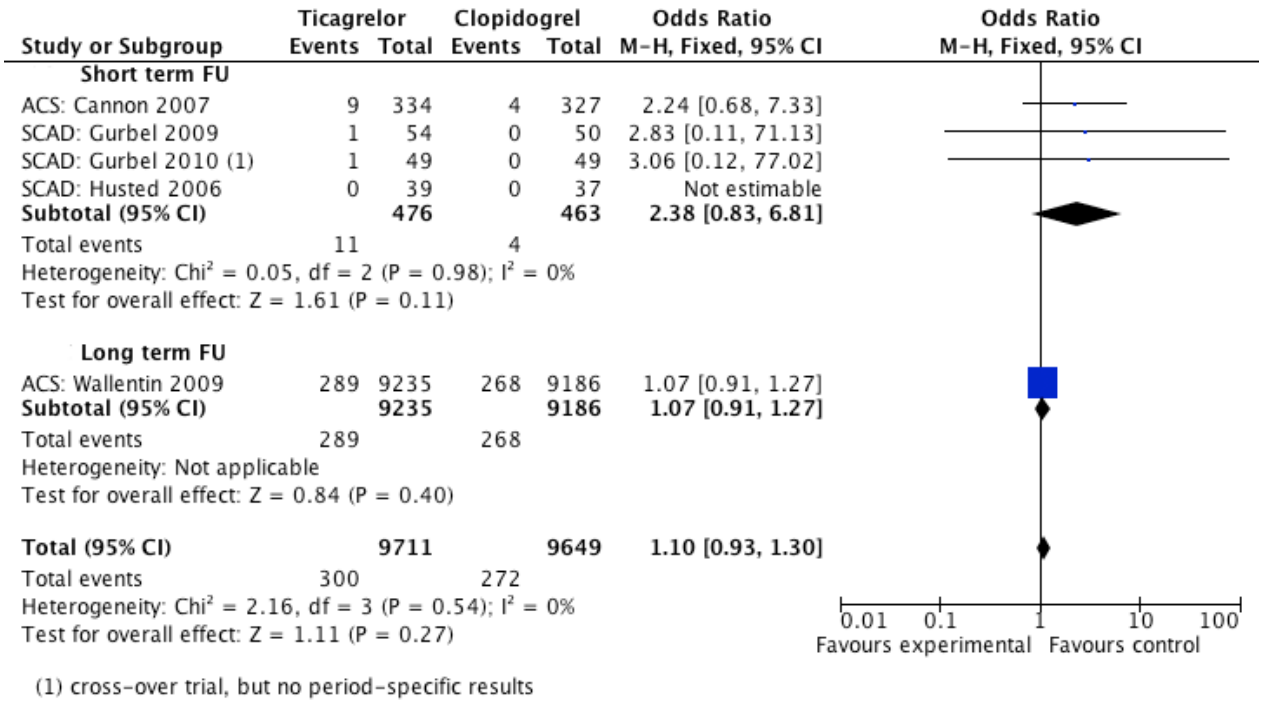


4.3.5.9 Minor bleeding

A) Ticagrelor

Minor bleeding rates were 3.1% with ticagrelor and 2.8% with clopidogrel treatment. Minor bleeding rates did not differ significantly between ticagrelor and clopidogrel treatment (OR 1.10, 95%CI 0.93, 1.30). No statistical heterogeneity was observed. Results are shown in Figure 14a.

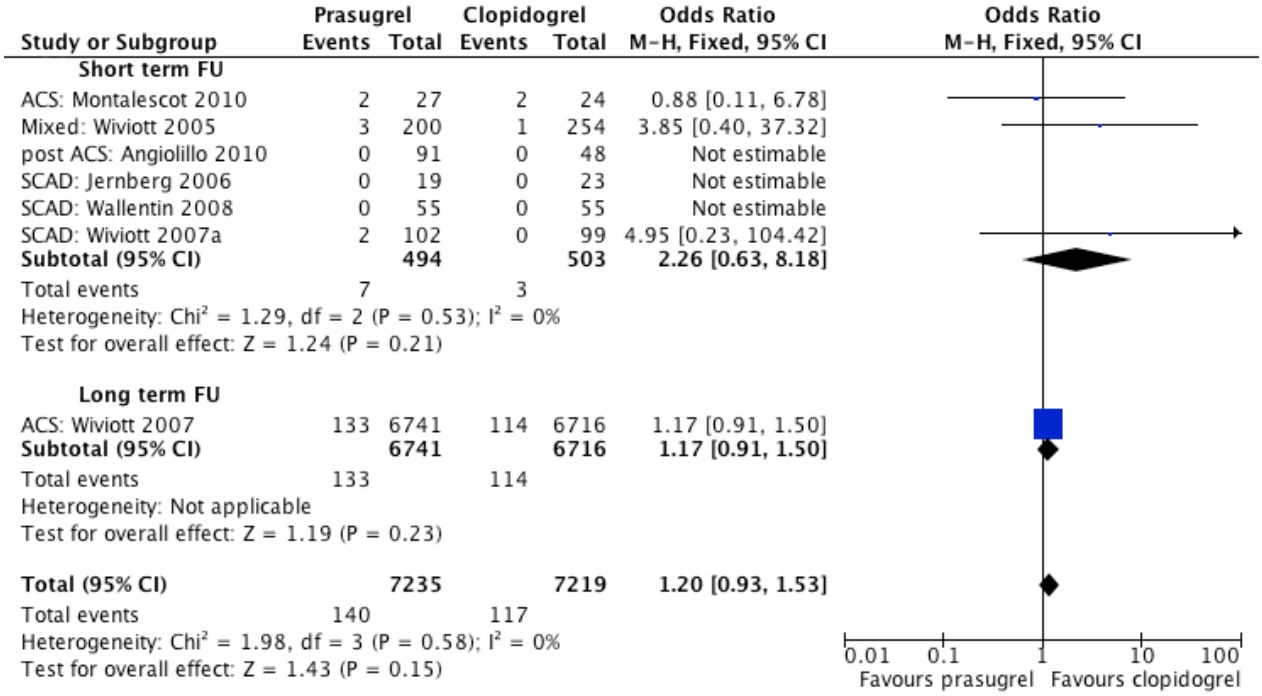
Figure 14a. Forest plot Ticagrelor versus Clopidogrel – minor bleeding



B) Prasugrel

Minor bleeding rates were 1.9% with prasugrel and 1.6% with clopidogrel treatment. Minor bleeding rates did not differ significantly between prasugrel and clopidogrel treatment (OR 1.20, 95%CI 0.93, 1.53). No statistical heterogeneity was observed. Results are shown in Figure 14b.

Figure 14b. Forest plot Prasugrel versus Clopidogrel – minor bleeding

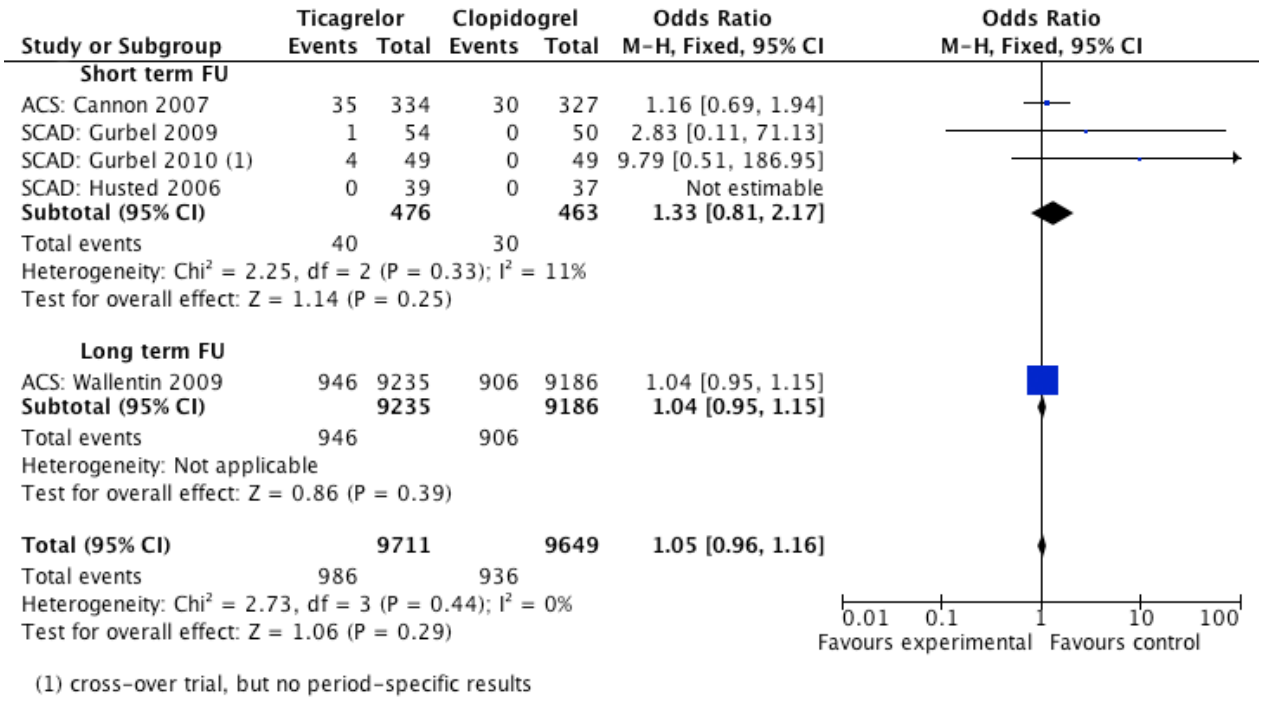


4.3.5.10 Major or minor bleeding

A) Ticagrelor

Combined major or minor bleeding rates were 10.2% with ticagrelor and 9.7% with clopidogrel treatment. Combined major or minor bleeding rates did not differ significantly between ticagrelor and clopidogrel treatment (OR 1.05, 95%CI 0.96, 1.16). No statistical heterogeneity was observed. Results are shown in Figure 15a.

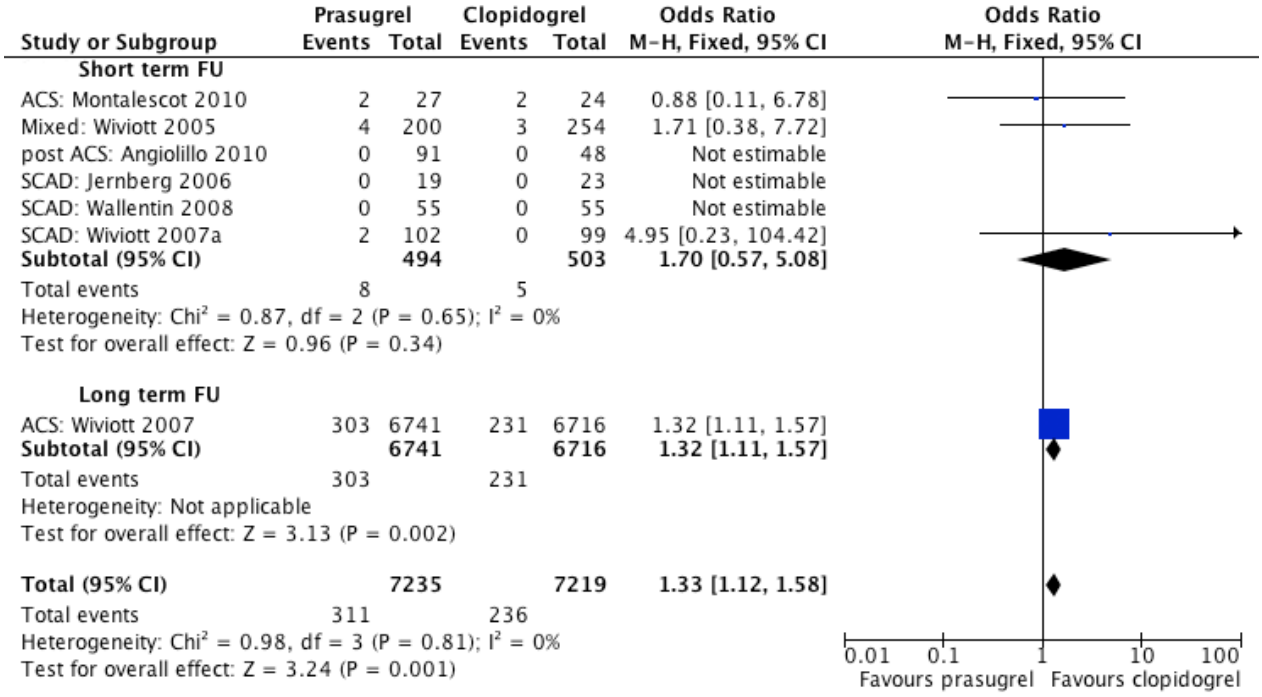
Figure 15a. Forest plot Ticagrelor versus Clopidogrel – major or minor bleeding



B) Prasugrel

Combined major or minor bleeding rates were 4.3% with prasugrel and 3.3% with clopidogrel treatment. Significantly higher combined major or minor bleeding rates were observed with prasugrel treatment (OR 1.33, 95%CI 1.12, 1.58). No statistical heterogeneity was observed. Results are shown in Figure 15b.

Figure 15b. Forest plot Prasugrel versus Clopidogrel – major or minor bleeding



4.3.6 PCI subgroup results

PCI subgroup results are shown in Table 3, corresponding forest plots are found in Appendix 11.

Table 3. Subgroup analysis comprising PCI trials

		OR (95%CI)	
TICAGRELOR	**Overall results**	**Long-term FU**	**Short-term FU**
All-cause mortality	0.80 (0.67, 0.94)	0.80 (0.67, 0.94)	no study available
CV mortality	0.81 (0.67, 0.97)	0.81 (0.67, 0.97)	no study available
Non-fatal MI	0.79 (0.68, 0.92)	0.79 (0.68, 0.92)	no study available
Stroke	1.08 (0.78, 1.50)	1.08 (0.78, 1.50)	no study available
Composite endpoint	0.83 (0.74, 0.93)	0.83 (0.74, 0.93)	no study available
Stent thrombosis	0.63 (0.49, 0.82)	0.63 (0.49, 0.82)	no study available
Total major bleeding	0.99 (0.87, 1.13)	0.99 (0.87, 1.13)	no study available
Non CABG-related major bleeding	1.22 (0.97, 1.55)	1.22 (0.97, 1.55)	no study available
Minor bleeding	0.99 (0.81, 1.19)	0.99 (0.81, 1.19)	no study available
Major or minor bleeding	0.98 (0.88, 1.10)	0.98 (0.88, 1.10)	no study available
		OR (95%CI)	
PRASUGREL	**Overall results**	**Long-term FU**	**Short-term FU**
All-cause mortality	0.95 (0.78, 1.16)	0.95 (0.78, 1.16)	not estimable
CV mortality	0.88 (0.70, 1.12)	0.88 (0.70, 1.12)	not estimable
Non-fatal MI	0.75 (0.66, 0.85)	0.75 (0.66, 0.85)	0.81 (0.39, 1.68)
Stroke	1.05 (0.74, 1.50)	1.01 (0.71, 1.45)	6.41 (0.31, 134.29)
Composite endpoint	0.81 (0.72, 0.90)	0.80 (0.72, 0.90)	0.95 (0.47, 1.90)
Stent thrombosis	0.46 (0.35, 0.62)	0.47 (0.35, 0.63)	0.21 (0.02, 1.74)
Total major bleeding	1.45 (1.14, 1.83)	1.46 (1.15, 1.85)	0.63 (0.06, 7.03)
Non CABG-related major bleeding	1.31 (1.02, 1.67)	1.32 (1.02, 1.69)	0.63 (0.06, 7.03)
Minor bleeding	1.19 (0.92, 1.52)	1.17 (0.91, 1.50)	3.85 (0.40, 37.32)
Major or minor bleeding	1.33 (1.11, 1.58)	1.32 (1.15, 1.57)	1.71 (0.38, 7.72)

4.3.7 ACS subgroup results

For efficacy outcomes, ACS subgroup results can be derived from the main results. For bleeding outcomes, ACS subgroup results are not readily available from the overall forest plots because more studies are available. All ACS subgroup results are shown in Table 4, corresponding forest plots for the bleeding outcomes are found in Appendix 12.

Table 4. Subgroup analysis comprising ACS trials

		OR (95%CI)	
TICAGRELOR	**Overall results**	**Long-term FU**	**Short-term FU**
All-cause mortality	0.78 (0.69, 0.90)	0.78 (0.68, 0.89)	1.73 (0.50, 5.96)
CV mortality	0.79 (0.69, 0.91)	0.79 (0.68, 0.91)	1.48 (0.41, 5.28)
Non-fatal MI	0.84 (0.74, 0.94)	0.84 (0.74, 0.95)	0.78 (0.36, 1.68)
Stroke	1.18 (0.91, 1.53)	1.18 (0.91, 1.53)	1.96 (0.18, 21.76)
Composite endpoint	0.84 (0.76, 0.92)	0.83 (0.76, 0.92)	0.98 (0.52, 1.85)
Stent thrombosis	0.74 (0.58, 0.95)	0.74 (0.58, 0.95)	no study available
Total major bleeding	1.02 (0.92, 1.14)	1.03 (0.92, 1.15)	0.98 (0.55, 1.72)
Non CABG-related major bleeding	1.21 (1.01, 1.47)	1.25 (1.02, 1.52)	0.98 (0.55, 1.72)
Minor bleeding	1.09 (0.92, 1.29)	1.07 (0.91, 1.27)	2.24 (0.68, 7.33
Major or minor bleeding	1.05 (0.95, 1.15)	1.04 (0.95, 1.15)	1.16 (0.69, 1.94)
		OR (95%CI)	
PRASUGREL	**Overall results**	**Long-term FU**	**Short-term FU**
All-cause mortality	0.95 (0.78, 1.16)	0.95 (0.78, 1.16)	no study available
CV mortality	0.88 (0.70, 1.12)	0.88 (0.70, 1.12)	no study available
Non-fatal MI	0.75 (0.66, 0.85)	0.75 (0.66, 0.85)	no study available
Stroke	1.01 (0.71, 1.45)	1.01 (0.71, 1.45)	no study available
Composite endpoint	0.80 (0.72, 0.90)	0.80 (0.72, 0.90)	no study available
Stent thrombosis	0.47 (0.35, 0.63)	0.47 (0.35, 0.63)	no study available
Total major bleeding	1.46 (1.15, 1.85)	1.46 (1.15, 1.85)	Not estimable
Non CABG-related major bleeding	1.32 (1.03, 1.69)	1.32 (1.03, 1.69)	Not estimable
Minor bleeding	1.16 (0.90, 1.49)	1.17 (0.91, 1.50)	0.88 (0.11, 6.78)
Major or minor bleeding	1.32 (1.11, 1.57)	1.32 (1.11, 1.57)	0.88 (0.11, 6.78)

4.4 Discussion

4.4.1 Comparison with other meta-analyses of new ADP antagonists

To synthesize the data on ticagrelor and prasugrel a meta-analysis of each drug was performed in comparison to the standard intervention clopidogrel. As mentioned before, the meta-analysis was mainly influenced by two large phase III clinical trials, PLATO and TRITON, which contributed over 90% of all patients, and results of this meta-analysis are in line with the trial results. In the literature, different approaches were employed for systematic reviews on new ADP-antagonists. In a recent meta-analysis, all new $P2Y_{12}$ inhibitors were compared together versus clopidogrel.[144] Thus, eight randomized controlled trials with prasugrel, ticagrelor, cangrelor and elinogrel were included. In this analysis, the new antiplatelet drugs reduced all-cause mortality after PCI compared with clopidogrel and were especially effective in patients undergoing PCI for ST-segment elevation MI. Although statistical heterogeneity was mostly low (except for MI and stent thrombosis in the PCI subgroup: 67% and 55%, respectively), the clinical trials differed largely in their design indicating clinical heterogeneity. Cangrelor is an intravenous drug and was administered only during PCI for up to 4 hours.[94, 95] Elinogrel is available as intravenous and oral compound but in this meta-analysis only one trial administering a single elinogrel bolus before PCI was included.[97] For ticagrelor and prasugrel, the PLATO and TRITON study and their substudies were included with treatment durations of one year and more. Thus, the clinical relevance of this meta-analysis seems questionable. Another recently published meta-analysis performed a comparison of the combined results of prasugrel and ticagrelor trials with clopidogrel in patients with acute coronary syndromes.[145] In a subsequent step, an indirect comparison between prasugrel and ticagrelor was performed.

The evidence regarding prasugrel and ticagrelor is mainly driven by the results of two large clinical trials, TRITON and PLATO. Both trials investigated the role of a new ADP antagonist in comparison to standard clopidogrel on top of aspirin in patients with ACS. Despite the similarity in the research question, the trials differ substantially in the way the scientific problem was addressed. Before performing an indirect comparison of these drugs, the following section summarizes differences in design and results of the TRITON and PLATO trial

4.4.2 Key aspects of TRITON and PLATO

4.4.2.1 Design

Rationale and design of TRITON and PLATO, both international, multi-center, randomized, double-blind, active-controlled trials, were published previously.[78, 146] Important differences exist in timing of randomization and study inclusion. In TRITON, clopidogrel-naïve patients with moderate to high-risk NSTE-ACS (i.e. TIMI risk score≥3) could only be randomized after diagnostic coronary angiography had confirmed anatomy suitable for PCI. In the STEMI subpopulation, which should comprise 20-30% of the total population and was therefore capped after inclusion of 3500 subjects, only patients within 12 hours of symptom onset, in whom primary PCI was planned, were allowed to be pretreated with the study drug before coronary angiography. Study medication should be administered at any time between randomization and 1 hour after the patient left the cardiac catheterization laboratory.
In PLATO, patients with either moderate to high risk NSTE-ACS within 24 hours of symptom onset or acute STEMI planned for primary PCI were eligible. Patients pre-treated with clopidogrel could be included and study medication should be administered as early as possible after the index event, i.e. before coronary angiography in most cases but in any case before PCI.

Timing of intervention might explain why prasugrel showed a more marked early benefit over clopidogrel compared with ticagrelor. The lack of early pretreatment with clopidogrel before PCI in the majority of patients and the relatively low loading dose of clopidogrel (300mg) could have supported the very early benefit of the study drug in TRITON, which was not seen in PLATO. The slower onset of action and less consistent effect of the 300mg loading dose clopidogrel (compared to 600mg)[147] might have contributed to the early reduction in mortality in the STEMI cohort treated with prasugrel and the pronounced difference in early outcomes in diabetic patients in TRITON as these two high-risk patient populations might benefit most from rapid, intensive antiplatelet therapy.[148, 149] On the other hand, more effective pre-treatment regimens of clopidogrel were used in the PLATO study, with 46% of patients receiving open-label clopidogrel before randomization and nearly 20% of patients receiving at least 600 mg total loading dose. Although some comments claim that clopidogrel loading could have been improved further, this has likely contributed to the smaller initial difference between ticagrelor

and clopidogrel. Specifically, Kaplan-Meier event curves did not begin to separate until after 30 days.

4.4.2.2 Overall results and pitfalls for approval

Table 5 gives a comparative overview of key results of the two trials.

Table 5. Key results of TRITON and PLATO

	TRITON			PLATO		
	P	**C**	**HR (95%CI)**	**T**	**C**	**HR (95%CI)**
1° endpoint*	9.9%	12.1%	0.81 (0.73,0.90)	9.8%	11.7%	0.84 (0.77, 0.92)
All-cause mortality	3.0%	3.2%	0.95 (0.78,1.16)	4.5%	5.9%	0.78 (0.69, 0.89)
CV death	2.1%	2.4%	0.89 (0.70,1.12)	4.0%	5.1%	0.79 (0.69, 0.91)
Non-fatal MI	7.3%	9.5%	0.76 (0.67,0.85)	5.8%	6.9%	0.84 (0.75, 0.95)
Stent thrombosis[#]	1.1%	2.4%	0.48 (0.36,0.64)	2.2%	2.9%	0.75 (0.59, 0.95)
TIMI major bleeding[+]	2.5%	1.7%	1.46 (1.15,1.85)	7.9%	7.7%	1.03 (0.93, 1.15)
Non CABG TIMI major bleeding	2.4%	1.8%	1.32 (1.03,1.68)	2.8%	2.2%	1.25 (1.03, 1.53)

P indicates prasugrel, C indicates clopidogrel, T indicates ticagrelor.

* Composite of CV death, MI, stroke. [#]Definite or probable stent thrombosis according to ARC criteria. [+]TRITON did not report KM estimates of total major bleeding. Results are percentages and odds ratio (95%CI).

In TRITON, the difference in the primary endpoint favoring prasugrel was driven by a reduction of non-fatal MI events, while mortality and stroke rates were similar. Initially, the applied classification scheme for MI in TRITON caused some debate. The inclusion of peri-procedural events identified merely by typical rise and fall of cardiac biomarkers (but without a pre-requisite of specific ECG changes or clinical symptoms) was questioned as 1) the rate of non-fatal MI was high compared to prior ACS trials, and 2) a substantial percentage of MI were identified by the clinical adjudication committee (CAC) through biomarker search but were not reported by local investigators.[150, 151] The study authors subsequently reported a detailed analysis of all types of MI according to a previously published universal definition.[152] Each MI was classified as spontaneous, secondary, or sudden cardiac death (types 1, 2, and 3) or procedure related (type 4 related with PCI and type 5 related with CABG), which predominantly comprise MIs identified by biomarkers. A consistent significant reduction of MI was described across the spectrum of MIs of varying type, size and timing.[153, 154] Thus, prasugrel significantly reduced the overall risk

of MI (7.4% versus 9.7%; HR 0.76, 95% CI 0.67 to 0.85). This benefit was present for procedure-related (types 4 or 5) MIs (4.9% versus 6.4%; HR 0.76, 95% CI 0.66 to 0.88) and nonprocedural (type 1, 2, or 3) MIs (2.8% versus 3.7%; HR 0.72, 95% CI 0.59 to 0.88). In a secondary analyses starting at 30 days, patients treated with prasugrel had a lower risk of any MI (2.9% versus 3.7%; P=0.014) until study end.

PLATO applied a more stringent MI classification excluding silent MI (ECG diagnosis only) in the pre-specified primary analysis. Overall, MI rates were lower than in TRITON but a significant reduction was also achieved by ticagrelor compared with clopidogrel.
However, the most striking aspect of PLATO was the significant reduction of CV and all-cause mortality leading to a 22% relative risk reduction for total mortality in the ticagrelor arm. Importantly, a hierarchical statistical test sequence was pre-specified in PLATO to address the issue of multiple testing. The secondary composite efficacy end points were tested in a specific order, until the first non-significant result was found. In PLATO, stroke rates did not differ significantly between the ticagrelor and clopidogrel group, which was tested before all-cause and CV mortality. Thus, the analyses of mortality rates have to bee seen as exploratory only but this is often not mentioned when the trial results are discussed.
Historically, only two large RCT of antiplatelet agents achieved a mortality reduction: In the COMMIT trial, clopidogrel saved more lives, when over 45 000 Chinese patients presenting with acute MI were randomized to treatment with clopidogrel or placebo on top of aspirin until hospital discharge or maximally up to 4 weeks (mean treatment duration 15 days).[52] Importantly, patients scheduled for primary PCI were excluded, which limits the trial's relevance for current clinical practice. Further, in ISIS-2, which was done in the 1980ies, aspirin exhibited an absolute mortality reduction in patients with MI when given for four weeks after the event.[41] Both trials showed early benefits of short-term treatment, while in PLATO the mortality reduction had a totally different pattern as it was accrued over time. The most important difference is that in both historic trials the comparator was placebo, while PLATO was superior to clopidogrel with respect to mortality. This remarkable mortality reduction was unexpected and is even more impressive when compared to the reduction in MI: in PLATO, the mortality reduction (difference of 107 deaths between the two treatment arms) exceeds the MI prevention benefit (difference of 89 events favoring ticagrelor). Several explanations were discussed why ticagrelor might reduce mortality, ascribing it to a play of chance (which seems unlikely as the benefit is so large) and to

off-target effects, e.g. by inhibiting the adenosine reuptake of red blood cells with improved microcirculatory flow.[155]

Others suggested that the avoidance of clinically significant bleeding might have allowed the life-saving effect of reducing MI and stent thrombosis to emerge. The occurrence of hemorrhage complications as a trade off of antiplatelet and antithrombotic therapy has been strongly linked to subsequent mortality before.[37, 156, 157] Therefore, the key difference between ticagrelor and clopdiogrel might be the reversible binding of ticagrelor. Even if patients on the two treatments would have a bleeding event that has a similar severity, the consequences and subsequent effects could be less severe with ticagrelor as the drug effect wears off faster and functional platelets become available. However, these assumptions are mere speculations.

Overall, ticagrelor did not increase major bleeding compared to clopidogrel. In PLATO, most major bleeding was CABG-related (~75%), and most CABG-related bleeding events were classified as major (~80%, using the PLATO classification). The reversible effects of ticagrelor might offer an advantage in patients proceeding to CABG surgery and investigators were advised to stop ticagrelor at least 24 hours and up to 72 hours before surgery to allow the level of platelet inhibition to decline substantially. Analyses of patients undergoing CABG in the PLATO trial showed that there was no excess of CABG-related bleeding with ticagrelor regardless of bleeding type (major/minor) or which classification was used.[158] Although non CABG-related major bleeding was significantly higher in the ticagrelor treatment arm, the high, but equal number of procedure related bleeds neutralized the effect of more spontaneous bleeding and led to a lack of significance between the treatment groups in the primary safety outcome of total major bleeding.

Both non CABG-related and CABG-related major bleeding was significantly increased with prasugrel compared to clopidogrel. The higher rates of CABG-related bleeding seen with prasugrel likely reflect the irreversible $P2Y_{12}$ receptor inhibition by prasugrel as well as the study design of TRITON, by which it was not intended that patients would proceed to CABG surgery. So, there could have been a relatively high number of urgent CABG procedures, which were done before the antiplatelet effects of the drug had sufficiently weared off. In TRITON only 0.35% of all patients underwent CABG during index hospitalization, while in PLATO 4.5% of all patients received CABG as index procedure.

An important difference between the bleeding results of TRITON and PLATO is that fatal bleeding was increased with prasugrel compared with clopidogrel (0.4% vs 0.1%; P=0.002), but

this was not the case for ticagrelor versus clopidogrel (0.3% vs 0.3%; P=0.66).

The explanation of beneficial effects of ticagrelor in the PLATO trial became even more complicated during the review of the drug for approval by the FDA. A statistically insignificant trend towards worse outcome with ticagrelor versus clopidogrel was found among the North American patients in the study, who made up 1800 of the total 18 000 patients (1° endpoint; US: HR=1.27, 95% CI 0.92-1.75; Canada: HR=1.17, 95% CI 0.59-2.31). The sponsor's explanation focused on a possible interaction between ticagrelor and high dose aspirin, which is used more frequently in North America compared to the rest of the world.[159] However, the biological plausibility of this interaction is limited and others assume that aspirin dosing does not explain the disparate outcome results but rather suggest a spurious finding. Finally, CADTH and the FDA approved the drug in in the first half of 2011 with a recommendation for the use of low-dose aspirin. Before approval criticism about the trial conduct emerged. Differences in primary site monitoring by the study sponsor in most countries versus a third-party contract research organization in the USA were speculated to be an alternative explanation for the diverging outcomes.[160] Further, the high all-cause and CV mortality rate (see table 5) in PLATO has started another debate. Serebruany considered the observed rates `excessive´ when compared to other trials in the area,[161] and highlighted that all-cause mortality rates in the US (where no ticagrelor benefit was observed) are much lower (3.84% in the ticagrelor arm). In a reply, the argument was brought forward, that a higher portion of patients with STEMI (40%) facing higher early mortality was enrolled in PLATO.[162] However, this cannot easily explain the high rates as also among STEMI patients the rates were much higher when compared to TRITON (CV mortality rates in STEMI patients: PLATO ~ 5%; TRITION ~ 1.9%). In the light of this intense discussion, affirmation of the beneficial effects seems crucial. However, the recently started, second large clinical trial with ticagrelor, PEGASUS-TIMI 54, in patients with a history of MI 12-36 months in the past won't be finished before February 2014.

The authors of the TRITON trial, which was performed by the TIMI study group of Harvard Medical School, recently published a manuscript underlining the consistency of the treatment effects throughout the world.[163] Despite differences in patient demographics, procedural techniques and adjunctive medications, prasugrel treatment was associated with a similar reduction in ischemic events and increased bleeding in all participating countries. However, the

FDA approval of prasugrel was hampered by the observation that there was a numeric excess of cancer-related deaths in the prasugrel group.[164] As the trial was too short that the tumors might be `new´, the concern is about tumor stimulation rather than carcinogenicity. After assessment of the temporal sequence between adverse events including bleeding, anemia and iron deficiency and tumor cases by the FDA review, the sponsor's view that the observed difference between the prasugrel and clopidogrel groups was due to ascertainment bias (i.e. increased bleeding associated with prasugrel leading to early tumor detection) was excluded. To clarify this issue, the company is now collecting baseline cancer history and cancer adverse event data from the ongoing trial TRILOGY-ACS, where 10 300 subjects with medically managed acute coronary syndrome are randomized to prasugrel or clopidogrel. Prasugrel seems to exert most of its benefit early (within the first month) but significantly increases bleeding continuously with time. In addition, the potential for tumor promotion remains a serious question for long-term use. In the light of these aspects, several comments suggested a short-term treatment with prasugrel and subsequent switch to clopidogrel when the risk of ischemic events has declined. However, this concept has never been tested and is not recommended by guidelines.

4.4.2.3 Special subpopulations

Compared to TRITON, where 99% of all participants underwent PCI, PLATO comprised a more diverse ACS population due to its study design including invasively (72%) and medically (28%) managed patients. Hazard ratios were generally similar for all types of index ACS (e.g. STEMI versus NSTE-ACS) except no benefit was observed in the small subgroups of patients with unstable angina (17%), which has to be interpreted cautiously as a post-hoc subgroup analysis.[86, 159] Secondary subgroup publications reported a benefit consistent with those in the overall results in patients with a planned invasive strategy,[143] with STEMI undergoing primary PCI,[165] with diabetes[166] or renal dysfunction.[86] In patients undergoing CABG, a reduced CV and all-cause mortality was found among patients on ticagrelor, which was directionally consistent but substantially greater (more than 2-fold) compared with the parent study.[158] Again, no prima facie explanation is available for this observation, in particular as bleeding and transfusions of blood products were similar between the study groups. Interestingly, the timing of surgery influenced the results. In the PLATO study, the study drug was discontinued up to 7 days before CABG. For

patients in whom study drug was discontinued >4 days before CABG, mortality was not different between the two groups. Both drugs can be expected to have some biological activity within the first days after discontinuation, and the antiplatelet effect of ticagrelor at three days after drug cessation is considered to be comparable to clopidogrel at 5 days after cessation. The striking mortality difference within the first four days favoring ticagrelor, might point to a beneficial effect of ticagrelor, a harmful effect of clopidogrel, or some combination of the two.[167] In an editorial comment, another hypothesis was posed: in the case of bleeding, young platelets with increased reactivity are released, which may contribute to a greater risk of thrombotic complications. As ticagrelor binds reversibly, re-distribution of the drug could attenuate the reactivity of these platelets and thereby reduce adverse thrombotic events and subsequent CV mortality.[167]

Several subgroup analyses in TRITON focused on patients, who were at increased risk of ischemic events because of co-morbidities (diabetes) or medical interventions (STEMI). Parallel to the overall cohort, the primary endpoint was significantly reduced in STEMI patients, but in contrast to the whole study population there was no increased bleeding in STEMI patients treated with prasugrel compared with those randomized to clopidogrel.[148] The benefit was most pronounced in the first 30 days, and was maintained until study end. All-cause and CV mortality rates, however, were similar between the two treatments at 15 months, despite statistically significant early benefits at 30 days. Interestingly, a post hoc analysis revealed that ischemic event rates at 15 months were significantly lower with prasugrel only in STEMI patients with an anterior MI, which might be the highest risk patients. Inherent to the trial design, several limitations have to be addressed. As mentioned before, prasugrel was compared with a 300mg loading dose of clopidogrel rather than the more potent 600mg dose, which is considered current standard of care for primary PCI. STEMI patients enrolled in the study between 12 hours and 14 days after symptom onset, which were designated to secondary PCI, likely did not receive the full benefit of clopidogrel because of inadequate preloading as coronary anatomy had to be known before patients could be randomized. Overall, 72% of STEMI patients received the study drug during PCI, whereas just 27% were preloaded within 24 hours prior to the procedure.
In patients with diabetes, prasugrel reduced the primary endpoint significantly by 30% without increasing the risk of bleeding suggesting greater clinical benefit.[149]

Three subgroups were identified from the overall trial, in whom prasugrel should be avoided. Outcomes were worse in the prasugrel group for patients with a history of stroke or transient ischemic attack, mainly due to higher rates of intracranial hemorrhage, while patients older than 75 years or weighing less than 60 kg appeared to have no benefit.

In conclusion, TRITON and PLATO addressed a similar research question and the scenario seems suitable for an indirect comparison, which will be performed in the subsequent section. However, substantial differences in trial design have to be kept in mind for the interpretation of the results of this indirect comparison.

5 INDIRECT TREATMENT COMPARISON

5.1 Introduction

Indirect treatment comparisons aim to provide information in areas, where available trials have not directly compared the specific treatments or interventions of interest. As an example, a class of various drugs has been studied in placebo-controlled RCTs, but there are no trials (or only a limited number) in which the drugs have been directly compared with each other.[168, 169] However, one has to keep in mind that such indirect comparisons are subject to greater bias (especially selection bias) than head-to-head randomized comparisons, as the benefit of randomization does not hold across trials.

Key aim of the analysis was to provide an indirect comparison for ticagrelor versus prasugrel. Further, both drugs were directly compared to clopidogrel, but no direct comparisons with placebo are available so far, which was also performed.

5.2 Methods

5.2.1 Selection of studies

Studies with ticagrelor or prasugrel as intervention were identified as outlined in chapter 4 by a systematic search. In order to perform an indirect comparison of the new ADP antagonist to placebo, trials testing clopidogrel versus placebo had to be identified. Existing evidence regarding clopidogrel in comparison to placebo was summarized by an overview of systematic reviews as outlined in chapter 3.

Indirect comparisons aim to compare multiple interventions simultaneously and thus it is important that all relevant interventions for the research question are included. Due to increasing data on clopidogrel hyporesponsiveness, an increase of clopidogrel dose was suggested by several authors. While conducting this thesis, the first large randomized clinical trial using a high dose clopidogrel strategy compared to standard clopidogrel was published.[27] As this regimen might be a valid alternative to new ADP antagonists the trial was included in the indirect treatment comparison although the intervention was rather short (1 week) and total follow-up was 30 days.

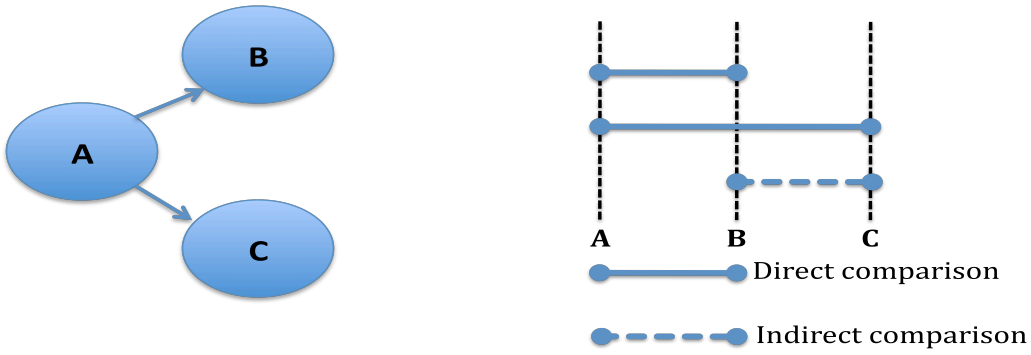
In addition, the PRINCIPLE-Timi-44 trial also used double dose clopidogrel as comparator to prasugrel and was consequently included as high dose clopidogrel trial in this analysis.
Only trials, which reported both efficacy and safety outcomes were used for indirect comparisons.

To limit clinical heterogeneity two relevant subgroups were specified: 1) patients with acute coronary syndrome and 2) patients undergoing percutaneous coronary intervention. Analyses were performed for all trials and long-term trials only (i.e. at least 6 months minimum treatment duration).

5.2.2 Adjusted indirect comparisons using the Bucher approach

The adjusted indirect comparison (AIC), first reported by Bucher et al in 1997,[170] aims to construct an indirect comparison of two competing interventions B and C adjusted according to the results of their direct comparison with a common control A (see Figure 16). Thus, the indirect comparison between B and C is anchored on A and the advantage of randomized controlled trials can be at least partly preserved in the indirect comparison. An important assumption of AIC is similarity, meaning that covariates, which could be effect modifier of the relative treatment effect of the intervention, have to be similar across the trials.

Figure 16. Indirect treatment comparison



The direct effect estimate can be taken from a single RCT or through separate meta-analysis of the trials of each intervention.

Using OR the equation would look as follows:

$\ln OR_{BC} = \ln OR_{AC} - \ln OR_{AB}$

$\text{Variance}(\ln OR_{BC}) = \text{Variance}(\ln OR_{AC}) + \text{Variance}(\ln OR_{AB})$

This method may also be used for other measures, such as relative risk, risk difference and mean difference. In this thesis, the Bucher approach was used to perform an indirect comparison between prasugrel and ticagrelor based on clopidogrel. In a second step, prasugrel as well as ticagrelor were compared to placebo, based again on clopidogrel.

5.2.3 Network analysis

As a step forward, network analysis makes it possible to interpret the available randomized evidence from networks of trials, going beyond simple pairwise comparisons. In network analysis, all available evidence can be taken into account from both direct and indirect comparisons, multiple treatments can be compared simultaneously and it does not depend on the chosen comparator treatment.

Frequentist and Bayesian approaches have been developed for implementation of network analysis and both methods were used within this thesis.

5.2.3.1 Mixed treatment comparison

Mixed treatment comparison (MTC) models were conducted using Bayesian methods, as introduced by Lu and Ades.[171] Sampling was performed by Monte Carlo chain simulation, as implemented in the software package WinBUGS version 1.4.3. WinBUGS is the Windows version of BUGS (Bayesian inference Using Gibbs Sampling). The computer software was originally developed by a statistical research project at the MRC biostatistical unit in Cambridge, UK. It can be downloaded free of charge from www.mrc-bsu.cam.ac.uk/bugs/welcome.shtml.

The codes to perform the MTC methods including an explanatory introduction are found on the website https://www.bris.ac.uk/cobm/research/mpes/mtc.html, where four codes can be downloaded for 1) fixed effect models, 2) simple random effect models for 2-arm trials (where no

correlations induced by multi-arm trials has to be considered), 3) random effects models for 3-arm trials, and 4) random effects models for multi-arm trials.

In this thesis, fixed effects models were used assuming that there is a single true value underlying all studies. The fixed effects model aims to estimate this common-truth effect and the uncertainty around it. For each comparison non-informative, vague priors were used. The study data were then combined with the priors to derive posterior distributions for all unknown model parameters, which are reported as odds ratios with 95% credible intervals – the Bayesian equivalent of a classical confidence interval.

Implementation of the final code, details on necessary modifications, convergence assessment and problems encountered with random effect models are shown in Appendix 13.

5.2.3.2 Network analysis using SAS

Network analysis was performed using PROC GLIMMIX provided in SAS version 9.2, which performs estimation and statistical inference for generalized linear mixed models. A generalized linear mixed model is a statistical model that extends the class of generalized linear models (GLM) by incorporating normally distributed random effects.

In general, a GLM can be defined in terms of several model components:
• a linear predictor ŋ that is a linear combination of regression coefficients: $\eta_i = x'_i\beta$
• a link function $g(\cdot)$ that relates the mean of the data to the linear predictor, $g(E[Y_i]) = \eta_i$
• a response distribution for Y_i from the exponential family of distributions

The exponential family of distributions is very broad and contains many important distributions. For example, the binary, binomial, Poisson, negative binomial, normal, beta, gamma, and inverse Gaussian distribution are members of this family.

For our analysis, a binomial model was separately fit for each outcome to estimate odds ratios and confidence intervals. The model included a fixed treatment effect as well as a random study effect.
Implementation and modifications of the final code are shown in Appendix 14.

5.3 Results

5.3.1 Included studies

In total, 11 studies (and their substudies) were included. From the 5 trials comparing clopidogrel to placebo,[49, 51-54] three trials were performed in ACS patients (one long-term), [49, 52, 53] and three studies were available for the PCI subgroup (two long-term).[50, 51, 172] One high-dose clopidogrel versus standard-dose clopidogrel trial in patients with ACS was included (short-term),[27] and a subgroup analysis also reported results in patients undergoing PCI.[28] Key characteristics of clopidogrel trials are shown in Appendix 15.

Two ticagrelor trials in patients with ACS were included (one long-term trial also reporting PCI sub-analysis).[24, 91] Two trials compared prasugrel to clopidogrel including one long-term ACS-PCI trial.[23, 77] One short-term trial compared high dose clopidogrel to prasugrel.[76]
Key trial characteristics are shown in Appendix 9.

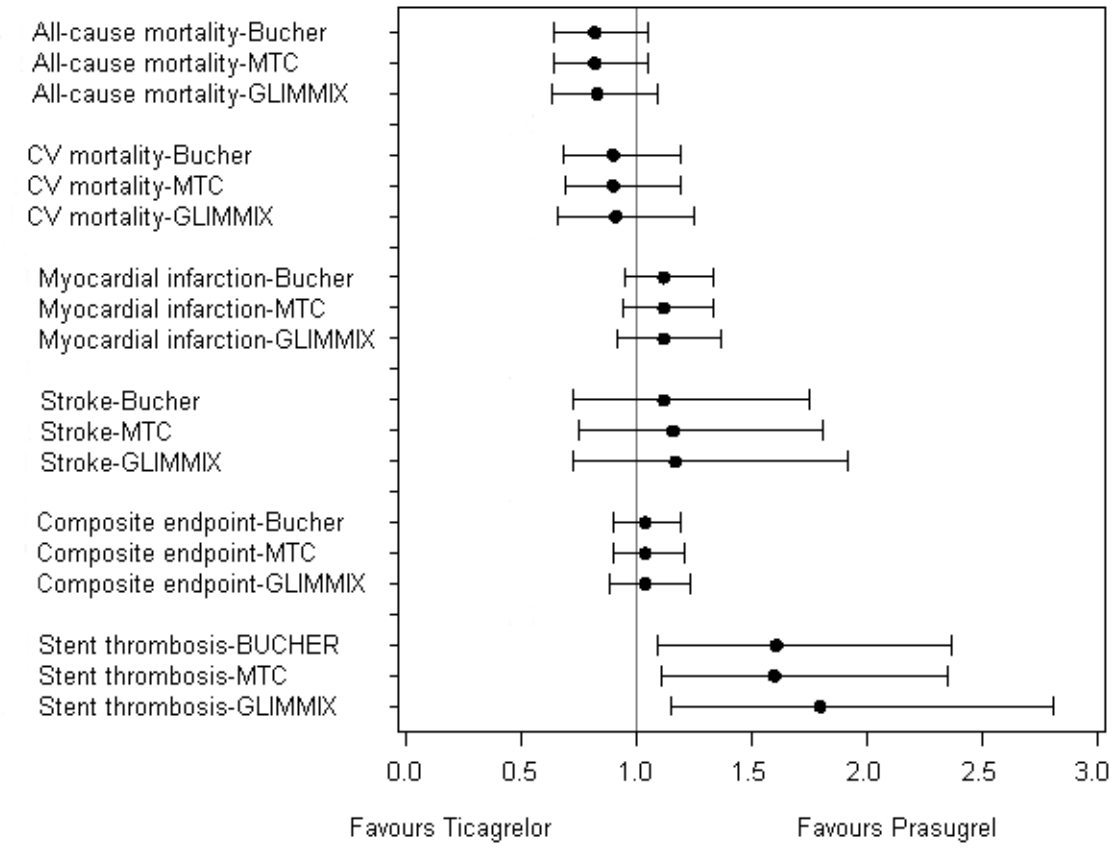
5.3.2 Indirect treatment comparison results

The following section gives key examples of the obtained results. First, the results of indirectly comparing ticagrelor with prasugrel are given for the ACS subgroup in Table 17 (efficacy outcomes) and Table 18 (bleeding outcomes), as this is one of the clinically most important subgroups and a major focus of this thesis. In this analysis, results from all three statistical approaches are presented.

Second, two outcomes are presented in detail showing results from all subgroups for all possible direct and indirect comparisons using MTC (Figures 19-26). The residual results comparing all ADP antagonists versus placebo are presented in Appendix 16.

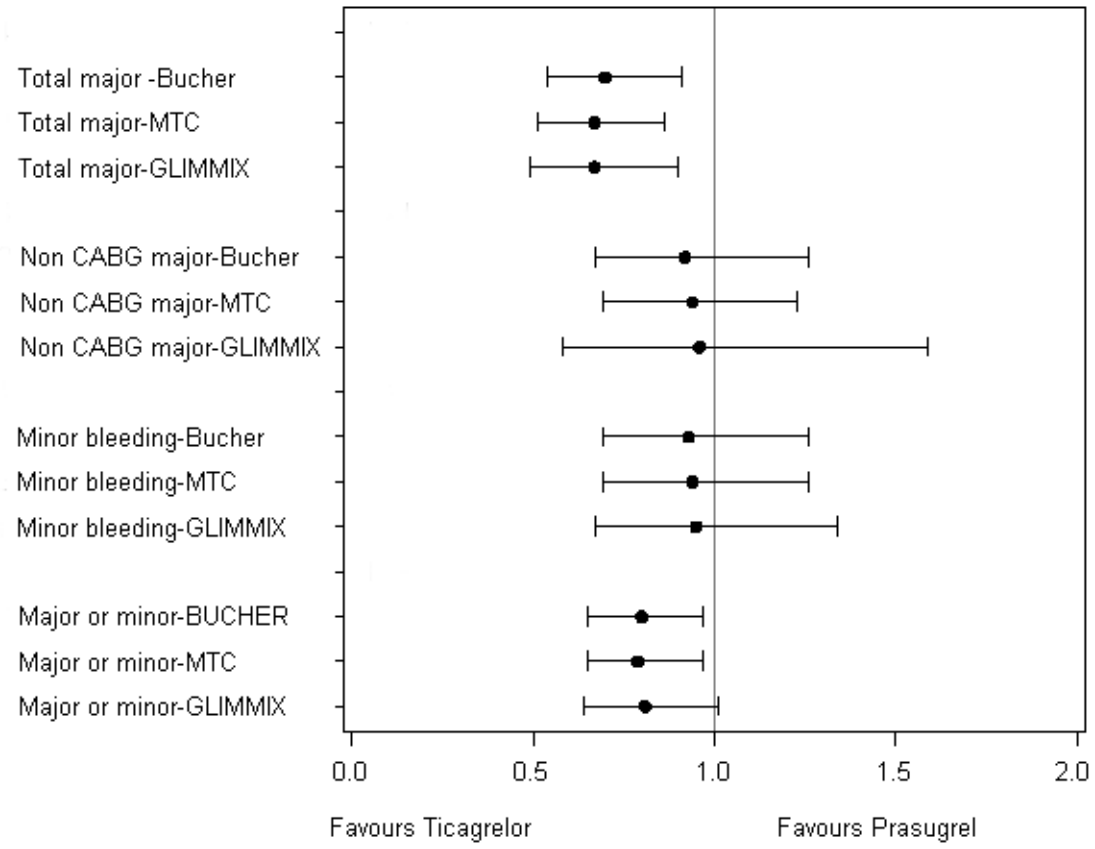
5.3.2.1 Ticagrelor versus prasugrel in ACS

Figure 17. ITC efficacy results (Ticagrelor versus Prasugrel)



Importantly, in this analysis results from ACS trials were taken into account. Using PCI trials only, the increased risk of stent thrombosis for ticagrelor vanished. When results from PLATO-invasive (instead of PLATO overall) were applied, a non-significant difference was seen for the comparison ticagrelor versus prasugrel with respect to stent thrombosis: OR 1.37, 95% CI 0.92 to 2.04 (Bucher approach).

Figure 18. ITC safety results (Ticagrelor versus Prasugrel)



A *sensitivity analysis* studied the impact of excluding clopidogrel versus placebo trials and high dose versus clopidogrel trials from the MTC and GLIMMIX models on the comparison ticagrelor versus prasugrel. Exclusion of these trials should not influence the ITC results, as these trials do not contribute any information on the comparison of interest. The corresponding table of results is shown in Appendix 16B. No relevant differences between these two approaches were seen for the fixed effects MTC model. This is in clear contrast to results from the random effects MTC model, where major differences were found with a smaller number of trials (results shown in Appendix 13). For GLIMMIX, the point estimates of the odds ratios were nearly identical but the CI tended to be larger when only three trials were included instead of seven. For two outcomes

(stent thrombosis and non CABG-related major bleeding), only two trials were available, which was associated with pronounced larger CI.

5.3.2.2 Examples of MTC analyses

The following figures 19-26 show MTC results for all subgroups for one efficacy (composite endpoint) and one safety (total major bleeding) outcome.

Figure Legend: All available trials for each comparison are given, and long-term trials are capitalized. Results from MTC models are given in Italics with grey background (OR, 95% credible interval). In addition, results from meta-analyses are shown for direct comparisons (OR, 95% confidence interval).

Figure 19. MTC composite endpoint – all trials

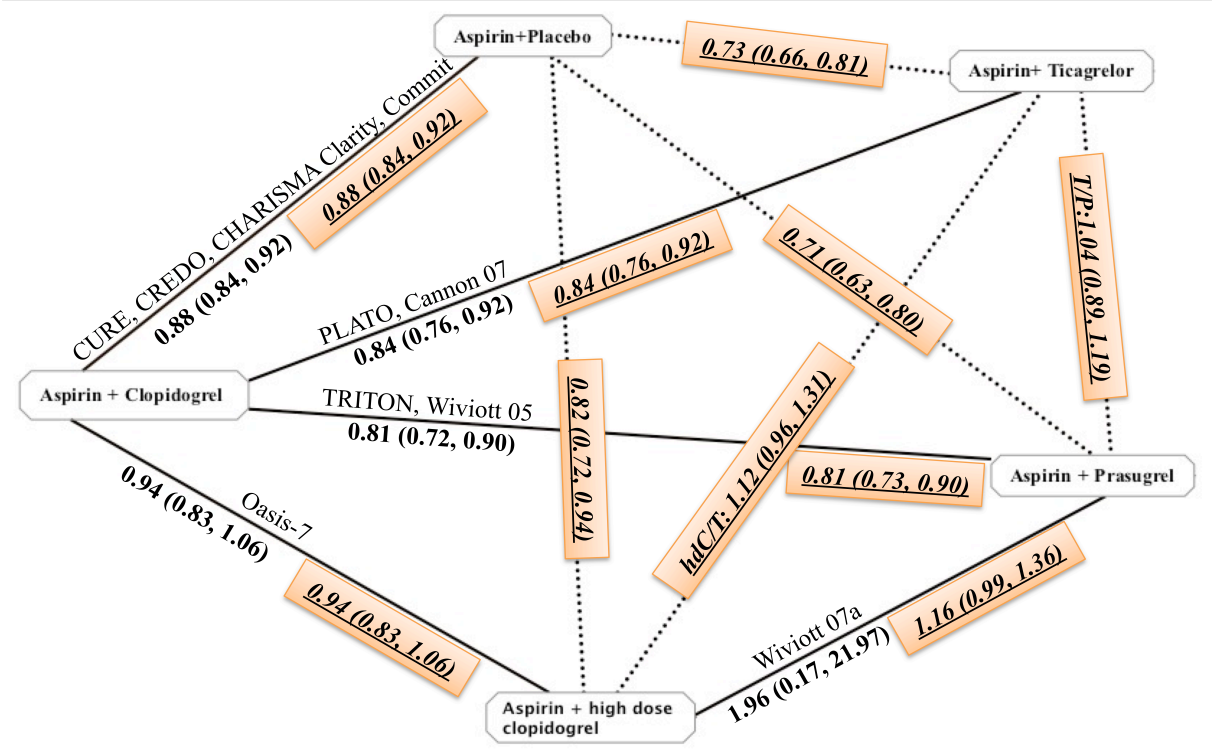


Figure 20. MTC composite endpoint – all ACS trials

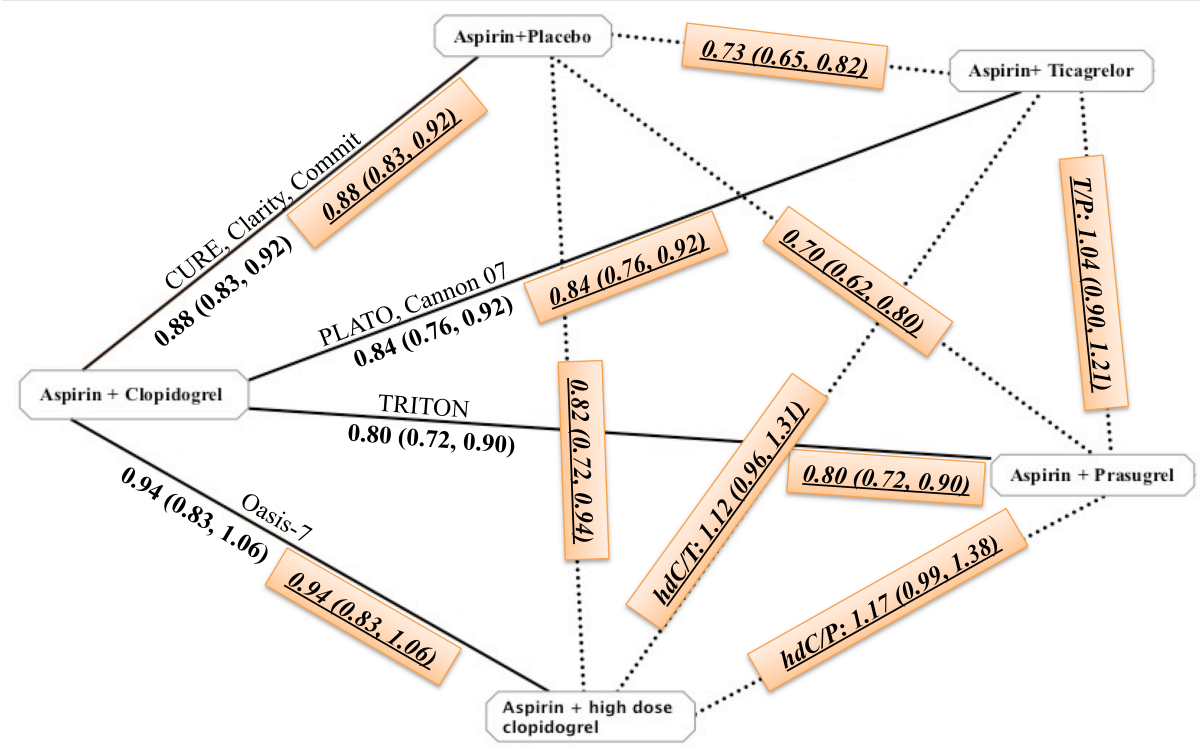


Figure 21. MTC composite endpoint – long-term ACS trials

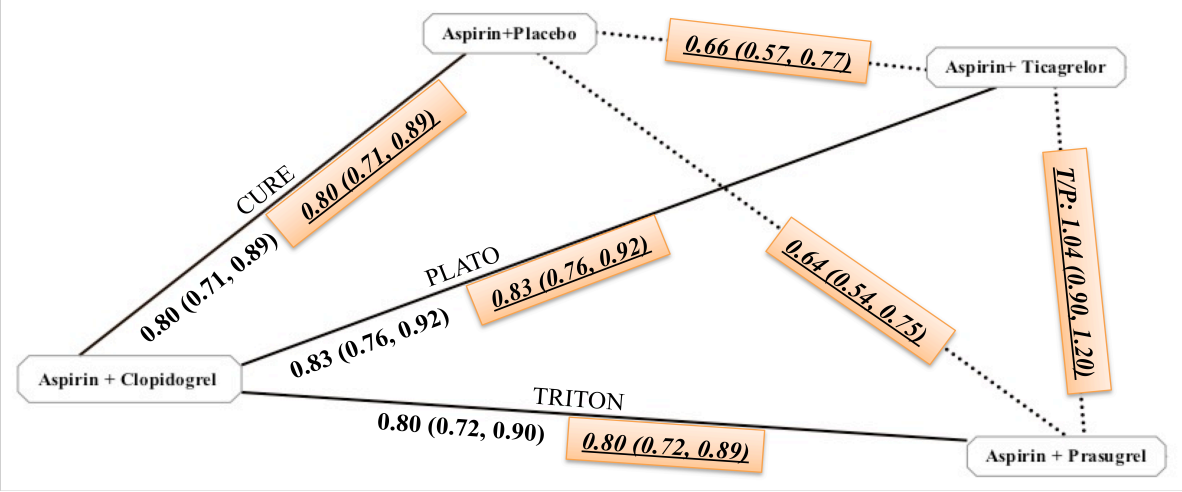


Figure 22. MTC composite endpoint – all PCI trials

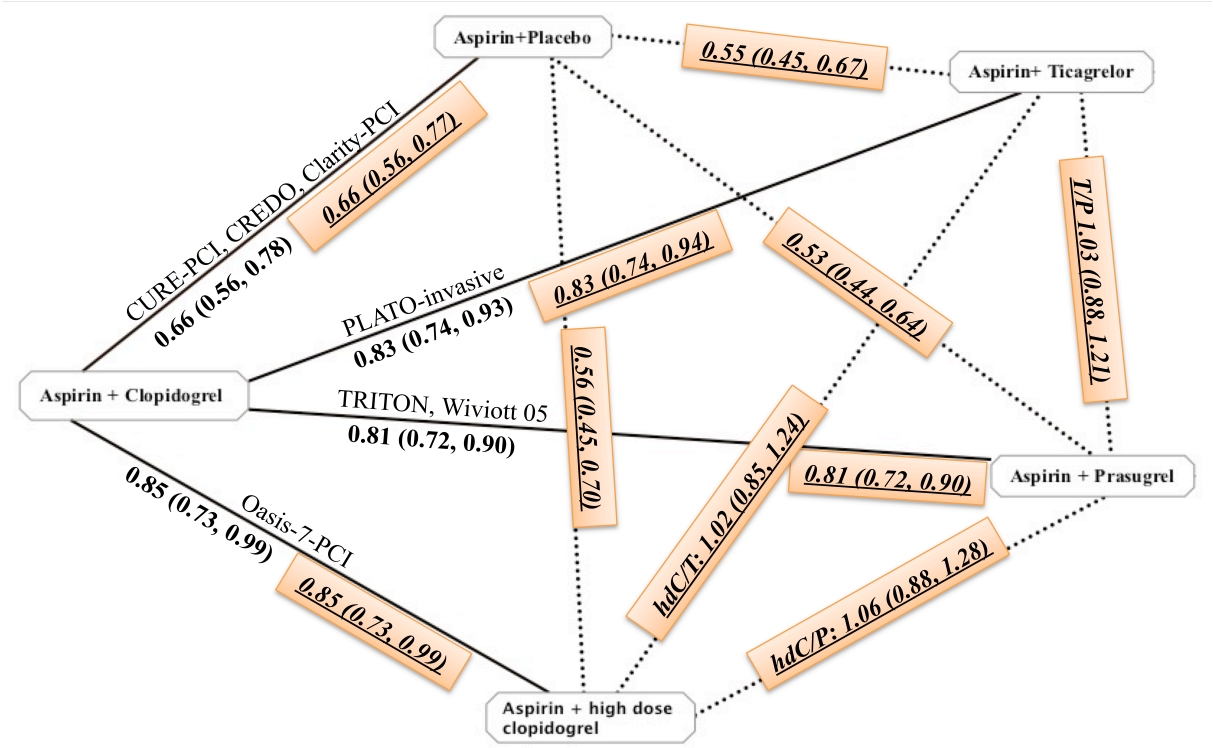
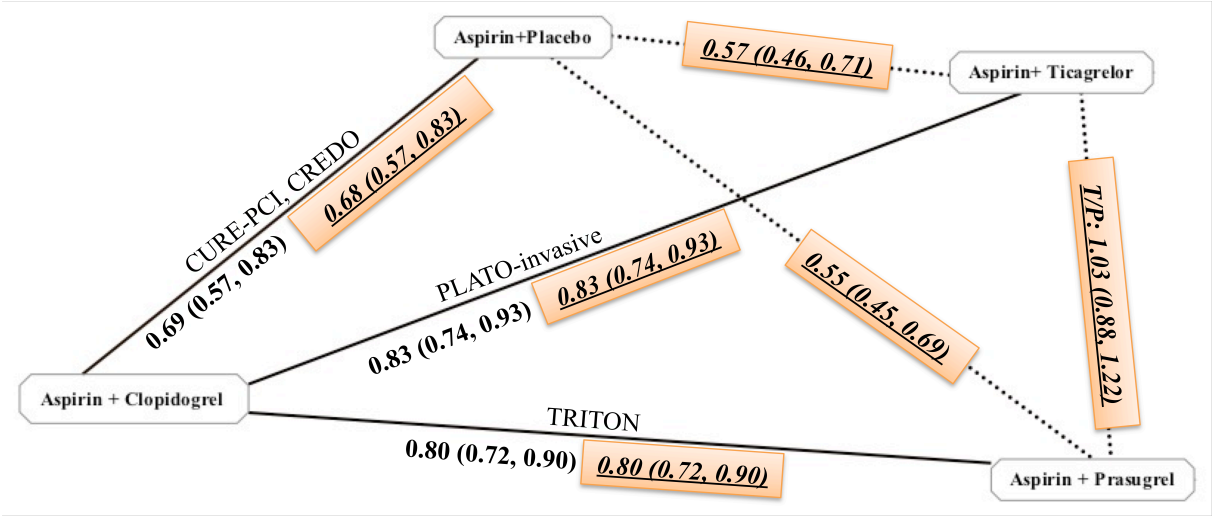


Figure 23. MTC composite endpoint – long-term PCI trials



As an exploratory analysis, the impact of including a small trial directly comparing ticagrelor and prasugrel in the ACS subpopulation was studied. In each arm 200 individuals experiencing 20 events were assumed. However, results did not change (Ticagrelor versus Prasugrel: OR1.04; 95% CI 0.91, 1.20).

The following figures show total major bleeding events for all subgroups.

Figure 24. MTC total major bleeding – all trials

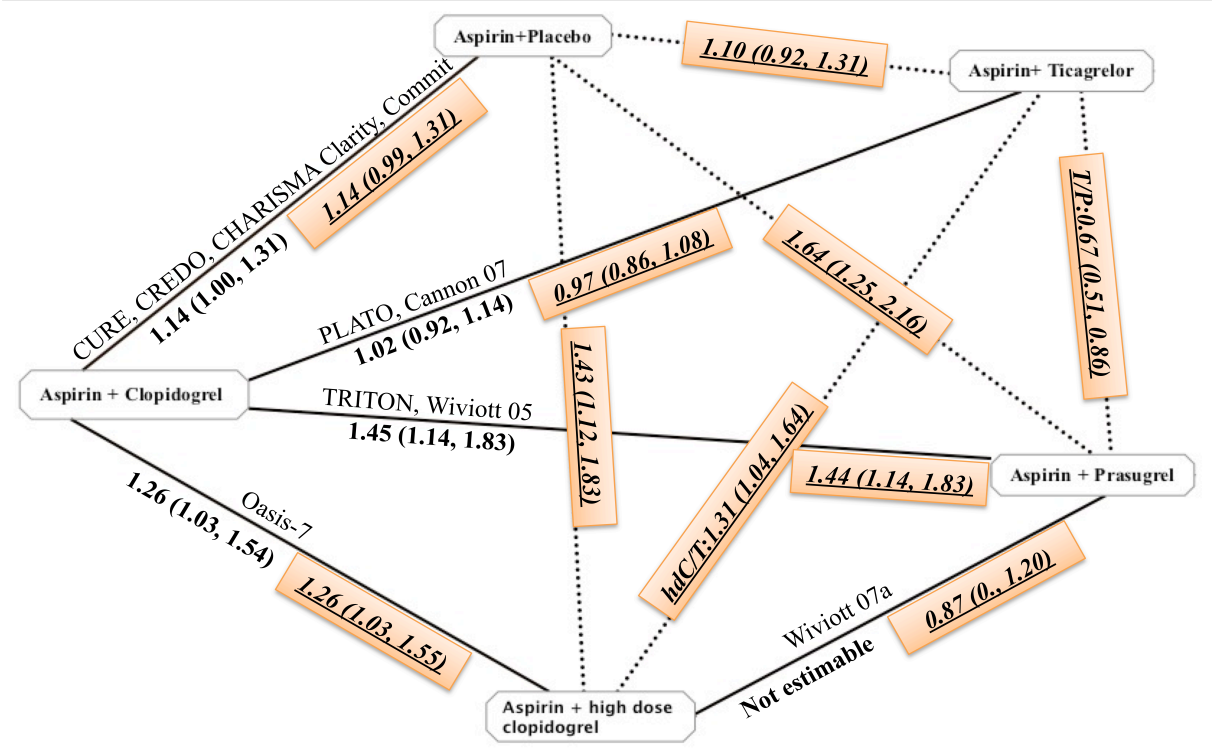


Figure 25. MTC total major bleeding – all ACS trials

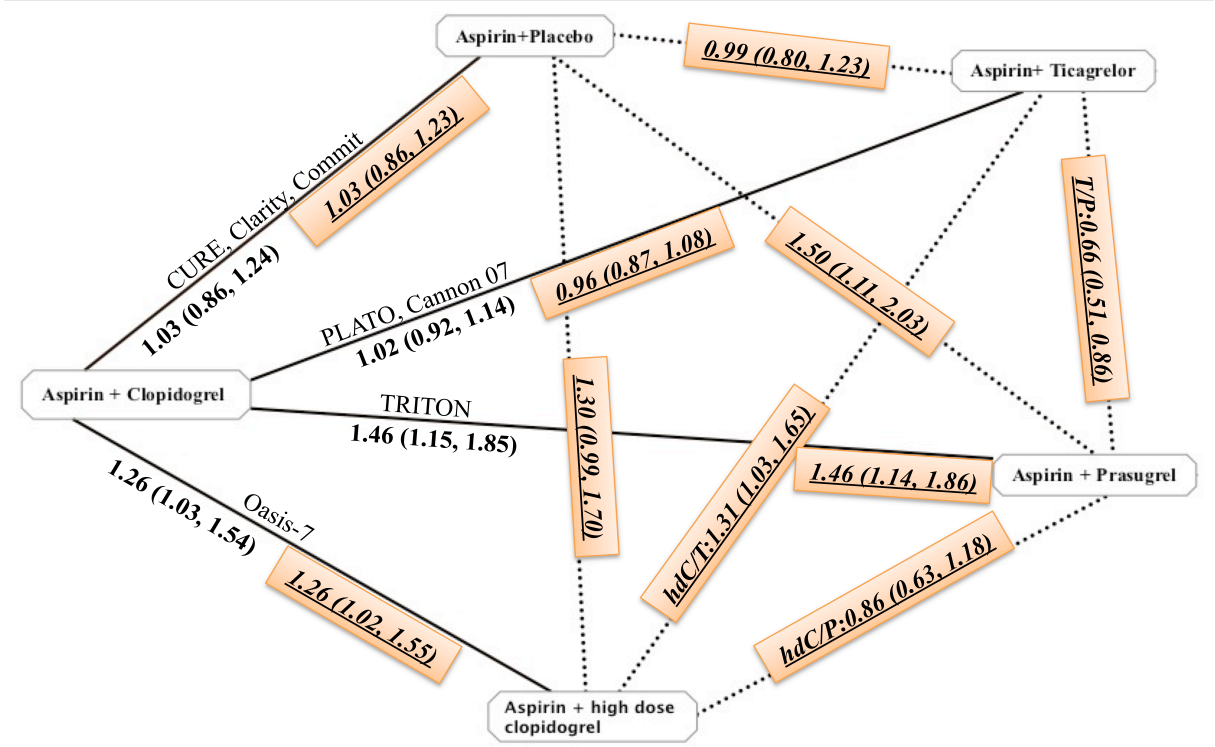


Figure 26. MTC total major bleeding – long-term ACS trials

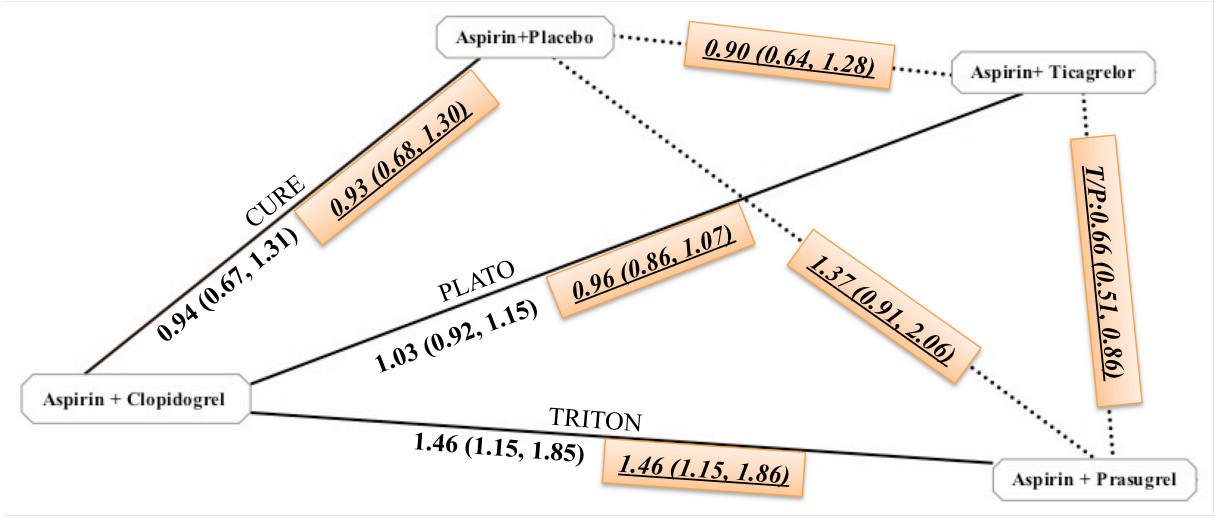


Figure 27. MTC total major bleeding – all PCI trials

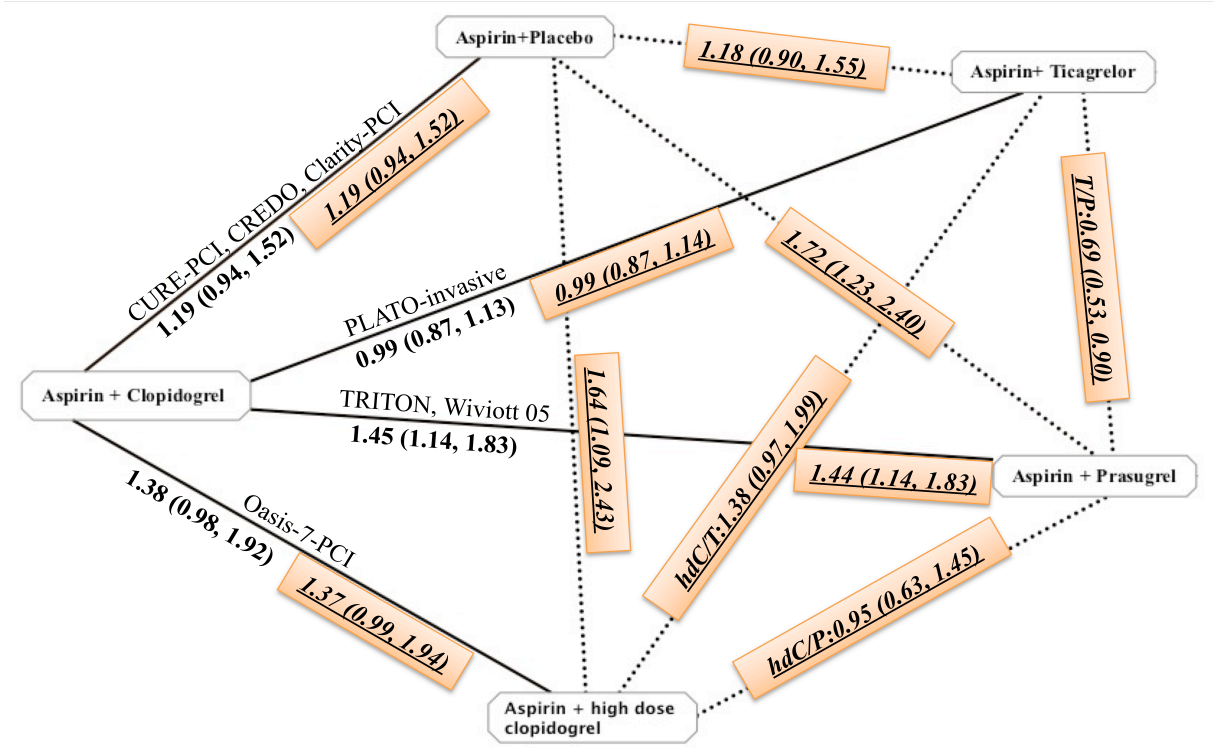
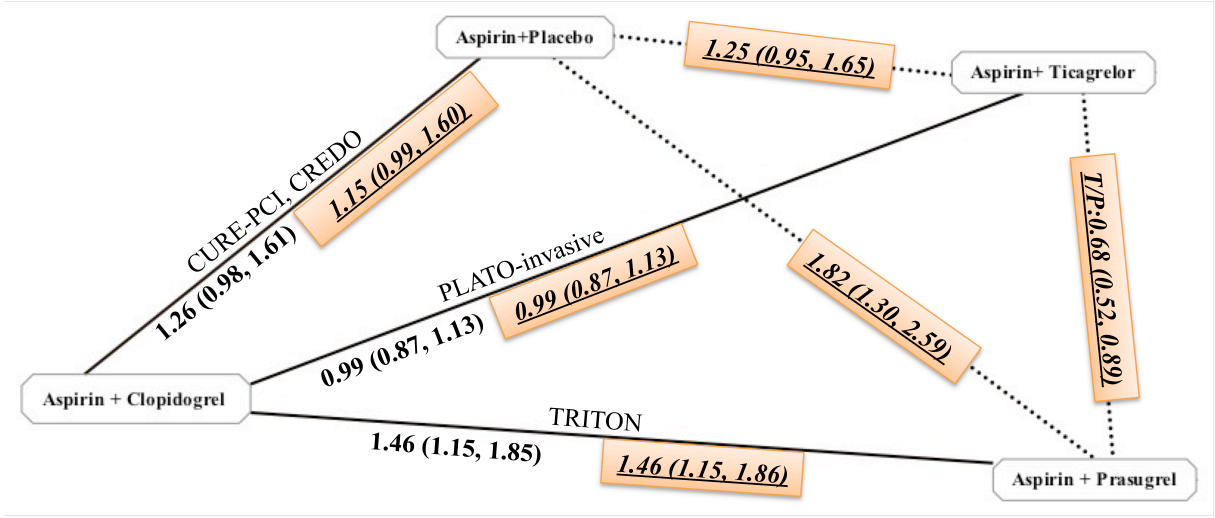


Figure 28. MTC total major bleeding – long-term PCI trials



As an exploratory analysis the impact of including a small trial directly comparing ticagrelor and prasugrel in the ACS subpopulation was studied. In each arm 200 individuals experiencing 10 major bleeding events were assumed. However, results did not change relevantly (Ticagrelor versus Prasugrel: OR 0.68; 95% CI 0.53, 0.88).

When direct comparisons were available, indirect estimates from modeling corresponded very well to direct estimates from meta-analyses.

5.4 Discussion

5.4.1 Considerations about indirect treatment comparisons

In the era of evidence-based decision making, several approaches and concepts have been developed to optimally synthesize data and present available information. When looking at the hierarchy of research designs, results of randomized controlled trials are considered as the highest level of evidence.[173] Meta-analysis are used for secondary evaluation of RCT by combining data from many studies in order to guide medical practice and health policy.[174] As a step forward ITC offers an attractive approach for areas, where no direct comparisons are available. Since its use is growing in popularity, various problems have been identified and it might not be always obvious, where biases or errors might arise from.[175, 176] The following section attempts to address several of these issues, as they might be relevant for this thesis.

Before performing an ITC using the Bucher approach, the available evidence is summarized using conventional meta-analysis and the homogeneity assumption should be fulfilled. The results from standard meta-analyses did not suggest relevant statistical heterogeneity in chapter 4. Related to this assessment, a *similarity assumption* should be appraised for ITC. Using the data of this thesis as an example, the relative efficacy of e.g. prasugrel would be assumed to be the same in all trials included in the indirect comparison. Such a generalizability of a relative treatment effect requires clinical and methodological trial similarity. It is important to evaluate if moderators of treatment effects differ between the trials and if the methods how the RCT were conducted are comparable. Efficacy of treatments may depend on patient characteristics, interventions, settings, length of follow-up, and outcomes measured. In this example, prasugrel was nearly exclusively tested in patients undergoing PCI. However, the drug might work

differently in a medically managed population than in a PCI population. To emphasize trial similarity, several subgroup analyses were performed in this thesis. As an alternative differences (co-variates) could be adjusted for by meta-regression, which also has been implemented for MTC in Winbugs.[177, 178] A recent survey of published systematic reviews with an indirect approach underlined that trial similarity was often addressed by a narrative comparison of trial characteristics (as it was included at the end of chapter 4), but this is prone to subjectiveness.[175]

In network analyses with closed loops, it is possible to examine *consistency (coherence)* between direct and indirect effect estimates.[171, 179] Inconsistency is present when these estimates reach different conclusions, which has been related to various potential reasons.[176] In the presented ITC of this thesis, there was only one small trial comparing high-dose clopidogrel to prasugrel, which closed a loop. Apart from this trial, the shape of the network was a star design. As it is shown in figure 19, the point estimates from direct and indirect evidence for the aforementioned comparison high-dose clopidogrel versus prausgrel differed substantially, but the direct estimate had very wide confidence intervals. The relevance of the head-to-head comparison is limited by the fact that the trial comprised only 201 patients, and thus no conclusions can be drawn regarding (in)consistency. In all other analyses of the star shaped network, the remaining direct and indirect estimates were very similar but due to the lack of closed loops, this does not allow us to make any inferences about consistency either.

The shape of the network also hampers an assessment of *diversity* and *co-occurrence*.[180] Diversity depends on the variety of treatments and the dispersion of evidence. Although the available treatments are evenly represented in the network (not considering the small, aforementioned prasugrel versus high-dose clopidogrel trial), there is only a small number of them and thus low diversity. Co-occurrence indicates if specific pairwise comparisons are preferred or avoided but this cannot be applied to a star-shaped network at all.

In this thesis, three different methodological approaches were used to derive indirect estimates, which gave mostly similar results. This observation has been addressed systematically before.[181] When applied to comparisons of interest with low complexity, such as the star-shaped network, adjusted indirect comparison according to Bucher yielded relative estimates equal to the mixed treatment comparison using Winbugs.

In general, the precision of indirect estimates from ITC is lower than that of direct estimates that would have been obtained through head-to-head trials.[168] It has been suggested that to achieve the same level of precision one might need four times as many trials for an indirect than for a direct estimate. Therefore, several assumptions have to be fulfilled, such as 1) all within study variances are equal within and across pair-wise comparisons of treatment, 2) between-study variances are equal across pair-wise comparisons of treatments and 3) each pair-wise comparison of treatments includes an equal number of studies.
In a recent simulation study, it has been emphasized that ITC (using the Bucher approach) suffers from low power.[182] The authors demonstrated that power is particularly limited when only a small number of trials (n=1 or n=5) are included in any treatment arm, which is the case in this thesis. Although they did not address the effect of trial sample size, which is high in our example, this also underlines, how difficult it is to achieve valid results. Further, Wells and co-workers showed that the degree of bias and precision of indirect point estimation is also influenced by the likelihood of the events of interest.[169] Lower event rates (below 0.1 to 0.2) are at higher risk of bias, and this also has to be kept in mind for the presented results, especially for rare outcomes such as stroke, stent thrombosis and non CABG-related bleeding.

Due to the paucity of available trials and comparisons with an absence of closed loops and the observed questionable trial similarity no attempt was made to formally translate the results into stable coronary artery disease as it was planned in the original thesis proposal. Instead, it was preferred to present overall results including all trials in patients with stable and unstable CAD and to show results in subpopulations such as patients undergoing PCI and patients with ACS.

5.4.2 Considerations about a potential clinical impact of the findings

For clinicians, a key question in the interpretation of synthesized evidence would be `Can the evidence be translated to individual patient level?´. In general, due to the aforementioned limitations results from ITC have to be interpreted cautiously.

In the presented indirect comparison of ticagrelor and prasugrel, no significant differences were seen for most outcomes. Prasugrel seemed to be associated with a lower risk of stent thrombosis compared to ticagrelor in the total ACS population. When the analysis was restricted to the PCI

sub-group this observation was no longer statistically significant. At first view, this result is puzzling as one might assume that in the PLATO trial the ACS population undergoing PCI is the same as the planned invasively managed sub-population but the difference arises from the word *planned* and is inherent to the study design of PLATO. As mentioned before, the investigators had to specify at randomization if they intended to perform PCI in a particular patient and these patients were included in the pre-specified analysis of the planned invasively managed subgroup. In this analysis comprising 9 877 patients with *planned* stent implantation, ticagrelor was minimally more effective with respect to stent thrombosis than in the study population receiving *planned or unplanned* stents, which comprised 11 289 patients. However, prasugrel was no longer significantly superior to ticagrelor in the ITC for stent thrombosis.

Next to the importance of dual antiplatelet therapy, several predictors of stent thrombosis have been identified including undersizing of coronary stents, intermediate (50 to <70% stenosis) coronary artery disease proximal or distal to the culprit lesion, reduced flow after stenting (TIMI flow grade <3), dissection, bifurcational lesions, reduced left ventricular ejection fraction (<30%) and presence of malignancies.[183] The design of PLATO and TRITON varied substantially in the way the study population was selected. In particular, in TRITON patients were randomized after the coronary angiogram was available, which might introduce selection bias. Several of the predictors of stent thrombosis (e.g. diffuseness of the disease with proximal or distal stenosis, bifurcational lesions, the risk of dissection) are related to coronary anatomy and one cannot exclude that investigators are reluctant to include higher risk interventions into a trial. In the light of these considerations and the borderline superiority of prasugrel for stent thrombosis, one has to be cautious to favor one drug over the other.

Similarly, safety results from the ITC suggested a smaller risk of total major bleeding with ticagrelor compared to prasugrel but this was mainly due to the equal bleeding rates for patients undergoing CABG with ticagrelor compared to clopidogrel in PLATO as has been discussed in chapter 4. Comparing non CABG-related major bleeding rates, no difference was seen between prasugrel and ticagrelor.

In addition, we indirectly compared high dose clopidogrel, prasugrel and ticagrelor with placebo. These results might be helpful to ponder the benefits and risks of DAPT in specific patient populations. Ticagrelor was the only drug that significantly reduced all-cause and CV mortality, which is in line with the results of head-to-head comparisons against clopidogrel. All compounds

significantly reduced the composite endpoint (of vascular death, MI, stroke) as well as myocardial infarction with more pronounced effects in the PCI subgroup, while no effect was found for rates of stroke. Thus, the lack of efficacy against stroke was not just seen in comparison to the active comparator clopidogrel but also against placebo. Notably, clopidogrel treatment was associated with a reduced stroke risk compared with placebo in a meta-analysis (results are given in Appendix 5). For stent thrombosis, only prasugrel achieved a significant reduction compared to placebo. All compounds were related to a significant increase in the risk of bleeding, except total major bleeding associated with ticagrelor. Non CABG-related major bleeding was increased by 90% up to 270% dependent on the compound and subgroup, which underlines that DAPT is associated with significant risks for the patient and should be only given when clearly indicated.

6 DESIGN OF A RANDOMIZED CONTROLLED TRIAL

6.1 The Need for a Trial

6.1.1 What is the problem to be addressed?

Platelets play a pivotal role in arterial thrombotic events including myocardial infarction and coronary stent thrombosis. The options of effective antiplatelet therapy are increasing, and novel ADP antagonists such as prasugrel, ticagrelor, cangrelor, and elinogrel show excellent platelet inhibition in pharmocodynamic studies using in vitro platelet function tests.[35] However, the results of clinical phase II and III studies differ to some extent and only one drug so far, ticagrelor, demonstrated a significant reduction in all-cause and CV mortality in the PLATO trial.[24] This benefit has caused many speculations about its origin, as a mortality reduction is not commonly observed in trials of antiplatelet therapy.[184] In the past, only two antiplatelet trials (ISIS-2, COMMIT) succeeded to significantly reduce mortality, both showing an early benefit against placebo.[41, 52] In contrast, the mortality benefit of ticagrelor in the PLATO trial emerged late, grew over time between three and nine months and was achieved against the active comparator clopidogrel, another potent platelet inhibitor.[24] This unique pattern suggests beneficial effects beyond pure inhibition of platelet activation. Potential explanations comprise a better safety profile of ticagrelor with respect to bleeding events due to its reversibility of action or off-target effects related to the inhibition of adenosine uptake by erythrocytes.[185] Despite numerous subsequent analyses of the PLATO results, there are no definite data available delineating the specific mechanisms by which ticagrelor reduces mortality more than can be explained by reduction of thrombotic events through platelet inhibition. Critical reviews challenge the trial results by questioning their validity and considering the mortality benefit paradoxical and unnatural.[160, 161] To clarify this issue is of high scientific interest.

Cardioprotective effects of adenosine and its role for ventricular remodeling after acute MI

It has been hypothesized that the striking mortality benefit in the PLATO trial is related to an increased availability of adenosine promoted by ticagrelor treatment.[186]

Adenosine is an endogenous nucleoside found in large quantities in myocardial and endothelial cells exhibiting its effects through binding to four G-protein coupled receptors, A1, A2A, A2B, and A3.[155, 187] Intra-vascular adenosine has an extremely short half-life (1-2 sec in humans) due to rapid uptake by endothelial cells and erythrocytes. Since the 1980s adenosine is commonly used as an antiarrhythmic drug for the treatment of patients with supraventricular tachycardias.[188] Beyond that, a variety of additional potential therapeutic applications have been proposed related to its anti-inflammatory, anti-fibrotic and cardioprotective effects.[189] Elevated adenosine levels were found in response to metabolic stress and cell damage, suggesting a role in tissue protection and healing.

A cardioprotective role of adenosine was in particular postulated in myocardial infarction when ischemic myocardium undergoes reperfusion.[155] Over the past decades, it has been demonstrated that early reperfusion is the best treatment of acute MI by re-opening the occluded coronary artery through PCI or thrombolysis. However, reperfusion per se also exerts negative effects, as it is associated with embolization of atherothrombotic material into the microcirculation, vasoconstriction, platelet and neutrophil activation, stimulation of proinflammatory mediators and myocardial oedema.[190] This so called ischemia-reperfusion injury is associated with coronary microvascular dysfunction and cardiomyocyte necrosis leading to larger infarct size and increased mortality.[191] Thus, reduction of this reperfusion injury is of high clinical interest, as it would lead to myocardial salvage, which should translate into improved ventricular size and function. The characteristic changes of ventricular volume, wall thickness and shape after acute MI are also termed ventricular remodeling. All these parameters have been closely linked to prognosis,[192-194] and can be accurately quantified by imaging techniques.[195]

Due to its multifaceted cardioprotective properties, a therapeutic potential has been repeatedly attributed to adenosine as adjunctive therapy in acute MI in order to reduce reperfusion injury.[155, 190]

6.1.2 What is the principal research question to be addressed?

The proposed trial aims to study if ticagrelor treatment leads to improved ventricular size and function after myocardial infarction, thereby supporting the hypothesis that ticagrelor has adenosine-related cardioprotective effects independent of its antiplatelet efficacy. As active

comparator prasugrel will be used, which is another potent platelet inhibitor without postulated effects on adenosine levels.

Study hypothesis

Ticagrelor has beneficial effects on left ventricular remodeling six months after myocardial infarction when compared to prasugrel.

6.1.3 Why is a trial needed now? Evidence from the literature - professional and consumer consensus and pilot studies should be cited if available.

Animal studies and clinical trials utilizing adenosine in acute myocardial infarction

In animal models of acute myocardial ischemia, adenosine was found to be cardioprotective when administered in the peri-reperfusion period (i.e. during re-opening of an occluded coronary artery). In these dog and rabbit models of acute myocardial infarction, adenosine administration reduced infarct size, which was associated with improved regional ventricular function in the ischemic zone.[196-198]

In humans, small trials reported a reduced infarct size after intravenous or intracoronary adenosine application during reperfusion through fibrinolysis or PCI in patients with acute MI.[199-201] Post hoc analysis further suggested improved clinical outcome in high-risk patients with anterior MI.[202] The largest study so far, AMISTAD II, a double-blind, placebo-controlled randomized trial included 2118 patients with anterior STEMI undergoing thrombolysis or primary angioplasty within 6 hours of symptom onset.[203] Patients received either a 3h-infusion of adenosine (at two different dosages 50 or 70 µg/kg/min) or placebo. No difference was seen for the primary endpoint of death, new onset of congestive heart failure (CHF) developing after 24 hours, or re-hospitalization for CHF. However, post-hoc analyses suggested a marked reduction of infarct size in the high-dose group and an improved clinical outcome in patients treated early (within 3.17h of symptom onset).[204]

These potential effects of adenosine on infarct size were also addressed in a recent randomized controlled trial including 112 patients with STEMI undergoing PCI, who were randomized to high-dose intracoronary administration of adenosine (4mg) distal to the occlusion site immediately before initial balloon inflation or placebo.[205] After 4 months, infarct size as assessed

with cardiac magnetic resonance imaging was similar in both groups suggesting no effect of single adenosine administration prior to acute coronary revascularization.

Acadesine is an adenosine-regulating agent that increases adenosine concentrations in ischemic tissues. A recent study hypothesized that administration of acadesine in patients undergoing coronary bypass surgery could have beneficial effects in those patients suffering from post-reperfusion MI after CABG by increasing interstitial adenosine concentrations in ischemic tissue.[206] In total, 2698 patients undergoing CABG were randomized to receive intraoperative administration (intravenously and in the cardioplegia solution) of acadesine or placebo. In those patients with perioperative MI (n=100, 3.7%), acadesine administration was associated with a reduced 30-day and 2-year mortality. To confirm this finding, a randomized clinical trial aiming to include 7500 patients undergoing CABG was launched in April 2009 (clinicaltrials.gov: NCT 00872001). However, the trial was stopped early in the third quarter of 2010 upon recommendation of the independent Data Safety Monitoring Board because a pre-specified interim analysis suggested futility and a low probability of the trial meeting its primary efficacy endpoint.

Potential adenosine-related benefits of ticagrelor

In the light of the aforementioned studies, a clear confirmation of the benefits of adenosine as a cardioprotective agent following reperfusion of ischemic myocardium is missing as several studies failed to show such a benefit. However, in these studies only a single short-term administration of adenosine was used, while ticagrelor is taken and would exhibit a potential adenosine benefit over a much longer time course.

Regarding its mechanism of action, ticagrelor was shown to inhibit adenosine uptake of washed human erythrocytes in a dose-dependent manner, similar to that provided by dipyridamole, but 10 times less potent.[185, 207] Further, ticagrelor augmented adenosine-mediated coronary arterial blood flow in a dog model of occlusion and hyperemia.[207]

Interestingly, there was no evidence in a recent systematic review that dipyridamole, which also has adenosine related effects, reduces the risk of vascular death in patients who present with arterial vascular disease (including those with acute MI), but it only reduced the risk of further vascular events in patients with cerebral ischaemia.[208] No signal for a mortality benefit was also

found in the recently published PROFESS trial, where over 20 000 patients after ischemic stroke were randomized to aspirin plus extended release dipyridamole versus clopidogrel for a mean treatment duration of 2.5 years.[209]

However, it has been postulated that the benefit of adenosine is related to improved coronary microcirculatory flow after thrombotic occlusion and reperfusion in patients with ACS, which then might translate into beneficial effects on ventricular remodeling. In contrast to the PLATO trial, the studies of dipyridamole did not focus on this specific setting. In PLATO, ventricular remodeling as a marker of improved microcirculatory flow was not determined. The large ongoing trial with ticagrelor, PEGASUS-TIMI-54 (Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin; clinicaltrial.gov: NCT01225562), will not address this question either as patients with stable CAD, who had a heart attack within 1 to 3 years ago, will be included.

Therefore, a trial is needed to clarify if ticagrelor improves ventricular remodeling, which then would support the adenosine hypothesis for the observed striking mortality benefit in PLATO.

6.1.4 Give references to any relevant systematic review and discuss the need for your trial in the light of the(se) review(s). If you believe that no relevant previous trials have been done, give details of your search strategy for existing trials.

No prior study or systematic review of ticagrelor specifically focused on potential adenosine mediated effects on ventricular remodeling in humans. A systematic review of the efficacy of ticagrelor as an antiplatelet agent in cardiovascular disease was performed prior to the design of the proposed RCT. No study was identified by the systematic search that examined the effect of ticagrelor treatment on ventricular remodeling after acute myocardial infarction.

6.1.5 How will the results of this trial be used? E.g. Inform decision-making /improve understanding.

The results will help to improve our understanding of the unexpected, long-term mortality benefit of ticagrelor compared to clopidogrel in patients after acute coronary syndromes as observed in the PLATO trial. Interestingly, no prior studies with short-term adenosine administration have definitely proven that adenosine improves outcome in CVD and long-term applications have not

been investigated yet. Nevertheless, adenosine has been repeatedly brought forward as a mediator of the long-term mortality benefits of ticagrelor compared to clopidogrel. Increased understanding in this specific field might also help developing drugs for a sustained mortality benefit independent from platelet inhibition.

6.2 The Proposed Trial

6.2.1 What is the proposed trial design? E.g. Open-label, double or single blinded, etc.

The study is designed as a double-blind, two-arm, randomized active-controlled trial.

6.2.2 What are the planned trial interventions? Both experimental and control.

Patients will be randomly assigned to oral maintenance treatment with ticagrelor 90mg twice daily or prasugrel 10mg once daily in a 1:1 ratio. Randomization and initiation of treatment should be performed as early as possible but not >12 hours after onset of ischemic chest pain. Patients randomized to ticagrelor will receive a loading dose of 180mg of ticagrelor study medication (2 active plus 4 placebo tablets), patients randomized to prasugrel a loading dose of 60mg prasugrel study medication (6 active tablets). Patients taking clopidogrel maintenance therapy can be included without protocol modifications but clopidogrel has to be stopped immediately.

Concomitant medication

For patients not previously on aspirin, a loading dose of 325mg is preferred (160-500mg allowed). Patients already taking aspirin can be re-loaded. After stent placement, long-term aspirin therapy should consist of aspirin 75-100mg daily. Higher aspirin doses are not allowed due to the potential interaction of high dose aspirin and ticagrelor.

All other decisions regarding concomitant medications are left to the treating physician. Patients may receive unfractionated heparin, low-molecular-weight heparin, any approved direct thrombin inhibitor, and/or glycoprotein IIb/IIIa receptor antagonists. Patients, who require oral anticoagulation, must not be included.

6.2.3 What are the proposed practical arrangements for allocating participants to trial groups? E.g., randomization method. If stratification or minimization is to be used, give reasons and factors to be included.

Randomization numbers will be generated using a validated IVR (interactive voice response) system that automates the random assignment of patient numbers to randomization numbers in an unbiased fashion to conceal randomization codes from patients and investigator staff. The randomization schedule will be blocked by site. No further stratification is planned.

6.2.4 What are the proposed methods for protecting against other sources of bias? E.g. Blinding or masking.

The identity of the treatments is concealed by the use of study drugs that are identical in packaging, labeling, schedule of administration, and appearance.

Patients, investigator staff, persons performing the assessments, and data analysts will remain blinded to the identity of the treatment from the time of randomization until database lock.

Randomization data will be kept strictly confidential until the time of unblinding, and is not accessible by anyone else involved in the study with the exception of authorized persons.

6.2.5 What are the planned inclusion/exclusion criteria?

The study population will comprise patients with acute anterior ST segment elevation myocardial infarction, who are enrolled within 12 hours of onset of symptoms and scheduled to undergo primary PCI.

Diagnostic criteria for STEMI comprise a history of new chest discomfort or ischemic symptoms of greater than 20minutes duration at rest and electrocardiographic evidence of anterior STEMI. Electrocardiographic requirements are new persistent ST-segment elevation at the J-point of ≥0.2 mV in precordial ECG leads in men, or ≥0.15 mV in precordial ECG leads V2-V3 and/or ≥ 0.10 mV in other precordial leads in women; or (presumed) new left bundle branch block.[152]

Patients scheduled for primary PCI are not likely to undergo CABG and were also randomized in TRITON before coronary angiogram was available.[23] Thus, the potential risk of CABG-related bleeding associated with prasugrel will be small. The restriction to anterior MI aims to enroll a more homogenous study population. In general, patients with anterior MI have a worse prognosis, and the area at risk and final infarct size are significantly larger in anterior than non-anterior MI.[210] Thus, the anticipated mean benefit from an improved therapy in anterior infarction is greater, easier to detect and has potentially more clinical significance. Noteworthy, a significant interaction for anterior versus non-anterior MI was found in the STEMI subgroup of the TRITON trial, where the clinical benefit of prasugrel was restricted to patients with anterior MI.[148] Detailed exclusion criteria are found in table 6.

Table 6. Exclusion criteria for the proposed RCT

	Cardiovascular exclusion criteria
1	STEMI without planned primary PCI
2	Cardiogenic shock at the time of randomization
3	Refractory ventricular arrhythmias
	Bleeding risk and study drug related exclusion criteria
4	Planned surgery
5	Age >75 years
6	History of ischemic or hemorrhagic stroke
7	Body weight <60kg
8	Active internal bleeding or history of bleeding diathesis
9	Clinical findings, in the judgment of the investigator, associated with an increased risk of bleeding
10	Intracranial neoplasm, arteriovenous malformation, or aneurysm
11	International normalized ratio known to be greater than 1.5 at the time of screening
12	Platelet count of less than 100000/mm^3 at the time of screening
13	Anemia (hemoglobin <10 g/dL) at the time of screening
14	Oral anticoagulation or other antiplatelet therapy that cannot be safely discontinued for the duration of the study
15	Concomitant oral or IV therapy with strong CYP3A inhibitor (ketaconazole, itraconazole, voricaonazole, telithromycin, clarithromycin, nefazodone, ritonavir, saquinavir, nelfinavir, indinavir, atazanavir, grapefruit juice >1 L/d), CYP3A substrates with narrow therapeutic indices (cyclosporine, quinidine) or strong CYP3A inducers (rifampin/rifampicin, phenytoin, carbamazepine)
16	Increased risk of bradycardiac events
17	Dialysis required
	General exclusion criteria
18	Legal age <18 years or incompetent to provide written informed consent
19	Women who are known to be pregnant, have given birth within the past 90 d, or are breast-feeding
20	Treatment within the last 30 d with an investigational drug or are presently enrolled in

	another drug or device study
21	Previously completed or withdrawn from this study or any other study investigating prasugrel or ticagrelor
22	Concomitant medical illness that in the opinion of the investigator is associated with reduced survival over the expected treatment period
23	Known severe hepatic dysfunction
24	Any condition associated with poor treatment compliance, including alcoholism, mental illness, or drug dependence
25	Intolerance of or allergy to aspirin, ticagrelor, or prasugrel
26	Inability to fulfill protocol requirements and/or follow-up procedures
27	Involvement in the planning or conduct of the study

6.2.6 What is the proposed duration of treatment period?

Duration of treatment with the study drug is planned for 12 months for each patient. After the study period, choice of antiplatelet therapy is at the discretion of the treating physician.

6.2.7 What is the proposed frequency and duration of follow-up?

Baseline assessment will be performed as soon as possible after PCI. Follow-up visits are scheduled at day 2-3 and after 1, 3, 6 and 12 months.

6.2.8 What are the proposed primary and secondary outcome measures?

In patients after MI successfully treated with PCI, LV dilation at 6 months but not the observed specific pattern over time (early, late, progressive remodeling) was associated with poor long-term prognosis.[211] Thus, assessment of the pattern of LV dilation might be less important for risk stratification in individual patients than measurement of LV volumes at baseline and after 6 months.[195]

Therefore, primary outcome measure of the trial will be change in left ventricular end-systolic volume (LVESV) measured by three dimensional (3D) echocardiography from baseline to 6 months. Different patterns of change in LVESV between the study groups will be assessed in a secondary analysis. Follow-up measurements 12 months after the index event will provide information if a potential benefit at 6 months can be sustained.

Other secondary study end points include other echocardiographic assessments of cardiac size and function (left ventricular end-diastolic volume (LVEDV), left ventricular ejection fraction (LVEF)). As a substudy in centers equipped with cardiac magnetic resonance imaging (C-MRI), patients without contraindications will also undergo C-MRI at selected time points (day 2-3 and 6 months), which is considered the reference standard for ventricular volume assessment and can also provide information on microvascular obstruction.[212-214]

As an increase of left ventricular ESV indicates adverse remodeling and is a powerful predictor of death, it can be used as surrogate marker for clinical outcome after MI.[194] Similarly, end diastolic volume and left ventricular ejection fraction are each prognostic for subsequent mortality risk.[192-194]

Further secondary outcomes of interest comprise clinically important safety and efficacy parameters.
For safety, all bleeding events (major, minor, minimal according to TIMI classification) will be collected.
Major cardiovascular events will be recorded: CV and all-cause mortality, MI, stroke and a composite of these as well as stent thrombosis (according to ARC criteria).

6.2.9 How will the outcome measures be measured at follow-up?

The development of 3D echocardiography has resulted in improved image quality with better accuracy and reproducibility in LV volume and function quantification than 2D echocardiography.[215, 216] With respect to assessment of LVEF, the accuracy and reproducibility of 3D echocardiography is comparable to C-MRI, the current reference method for measurement of LVEF. For this study, 3D echocardiography is advantageous over cardiac magnetic resonance imaging because it is more widely available, portable, can be performed rapidly and also in individuals with implanted ferromagnetic objects. In addition, when compared to C-MRI an excellent agreement, small mean differences and low test-retest variability have been described.[217, 218] As recommended for volume measurements, contrast-enhanced 3D echocardiography will be performed as non-contrast 3D images may underestimate volumes.[219]

C-MRI is considered the reference standard for non-invasive assessment of functional and volumetric parameters with a high spatial and temporal resolution.[212-214] Beyond geometric measurements, contrast (i.e. gadolinium) enhanced C-MRI has the ability to show microvascular obstruction and thereby to predict the patient risk of adverse remodeling after MI.[220, 221]
Thus, additional performance of C-MRI is planned as a substudy in certain centers to capture microvascular obstruction early after MI (day 2-3) and to validate 3D echocardiographic for determination of the primary outcome after 6months.
A Core Laboratory will be established for assessment of results from imaging studies.

6.2.10 What is the proposed sample size? Include both control and treatment groups, a brief description of the power calculations detailing the outcome measures on which these have been based, and give event rates, means and medians, etc., as appropriate. What is the justification for the size of difference that the trial is powered to detect? Does the sample size calculation take into account the anticipated rates of non-compliance and loss to follow-up given below.

Consideration about the minimally clinically important effect size

In a recent meta-analysis, short-term trial-level therapeutic effects of a drug or device on LV remodeling (measured by left ventricular ESV, EDV, EF) were associated with longer-term trial-level effect on mortality.[222] This meta-analysis focused on studies in patients with reduced ejection fraction and used two methodological approaches to elaborate on the relation between size of change in ESV and effect on mortality. First, placebo corrected change in ESV from each individual remodeling trial was plotted against the mortality OR in each trial. A significant correlation between effect sizes in the mortality trials and the effect sizes on ESV in the remodeling studies was reported. A decrease of 10 ml in the mean ESV change corresponded to a relative OR of 0.96 for mortality (95% CI: 0.93 to 0.99). Further, in logistic regression analyses, an even more pronounced association between the mean change in ESV due to therapy and effects on mortality was described, based on a per 10-ml decrease in the mean change in ESV (OR: 0.56, 95% CI: 0.53 to 0.60).

Several drugs, that have been shown to improve prognosis after MI, also have been shown to reduce left ventricular remodeling. Studies in this area can be used to derive an estimate of effect size.

An echocardiographic substudy of the CAPRICORN trial, reported the effects of the betablocker carvedilol on left ventricular remodeling after MI.[223] Over 90% of patients received ACE inhibitors, and about 40% underwent revascularization by PCI or thrombolysis. At six months, the intervention group had a significant reduction of LVESV by 9.2 ml (95% CI: -17.1 to -1.3ml) compared to placebo.

A recent study investigated the effect of eplerenone on LV remodeling after MI on top of recommended secondary preventive therapy and included a large proportion of patients undergoing revascularization through PCI (78%).[224] After adjustment for covariates, a reduction of LVESV by 6.1ml/m^2 body surface area (standard deviation 2.7ml/m^2) was achieved. As the latter estimate is given per m^2 body surface area (BSA), this corresponds to a 10.7ml reduction assuming an average body surface area of 1.75 m^2 (men 1.9m^2, women 1.6m^2). In this trial, the authors assumed a treatment difference of 10ml in LVESV as clinically important for their sample size estimation.

The sample size calculation of the recently published ASPIRE (Effect of the direct renin inhibitor aliskiren on left ventricular remodelling following myocardial infarction with systolic dysfunction) trial was based on a 3.1 ml difference in change in LVESV (measured by echocardiography).[225]

Sample size calculation

In the light of the aforementioned literature, a 5ml difference in change in LVESV is chosen as effect size for sample size calculation. It is essential to avoid results of borderline statistical significance as this might lead to a continuation of the discussion if ticagrelor exerts an effect on ventricular remodeling supporting the adenosine hypothesis. Therefore, an effect size is chosen, which is at the lower boundary what might be considered clinically important.

Based on prior studies,[223, 225, 226] the standard deviation of LVESV is assumed to 30ml.

Thus, a sample size of approximately 282 patients per group is estimated to provide ≥80% power at the 0.05 level of statistical significance to detect a change of 5ml between the groups after 6

months using a 30ml standard deviation for LVESV. Assuming a 15% drop-out rate, the study aims to recruit 664 patients.

The following formula was applied for sample size calculation:

$n= 2x [(Z^{0.975}+Z^{0.8})/ES]^2$, where ES (estimated size effect) = (|mu1-mu2|/standard deviation).

6.2.11 Are there likely to be any problems with compliance? On what evidence are the compliance figures based?

In patients after STEMI, compliance can be expected to be good. Patients will benefit from close monitoring after the event and the opportunity to address their concerns regarding their illness with a specialist.

In the STEMI sub-study of PLATO premature study drug discontinuation was reported in about 19%, which was lower than in the total PLATO population (23%).[165] Non-compliance was reported in 0.5% of the study population. Adverse events (5.5%) and unwillingness (8.3%) were described more often as reason for drug discontinuation.

As the time to the primary end point is shorter in the proposed study than the median PLATO STEMI follow-up time (280 days), a 15% drop out rate was considered for sample size calculation, which also takes into account the expected one-year mortality rate of 3-4%.

6.2.12 What is the likely rate of loss to follow-up? On what evidence is the loss to follow-up rate based?

Loss to follow-up can be considered to be low based on results from previous trials in patients with STEMI. In TRITON and PLATO, loss to follow-up was ≤0.1%.

6.2.13 Give details of the planned analyses.

Descriptive statistics will be performed for continuous and categorical variables to summarize results before statistical analyses.

Data will be analyzed on an intention-to-treat basis using linear mixed-effects regression models, implemented in SAS version 9.2 (PROC MIXED), which allows to account for correlation among the repeated measures of LVESV over time. If baseline variables would differ between the groups, adjustment for covariates can be performed. Significant interaction between main effects will be explored. A p-value<0.05 will be considered statistically significant and all tests will be 2-tailed.
In addition, a per-protocol analysis will be performed. Bleeding events will be analyzed in an as-treated study population.

6.2.14 Are there any planned subgroup analyses?

No subgroup analyses are planned.

6.2.15 What is the proposed frequency of analyses? (Including any interim analyses.)

No interim analysis is planned. Analyses will be performed after the trial is finished and follow-up completed.

6.2.16 Will the trial address any economic issues? (This is not a requirement. However, please justify the inclusion/exclusion of any health economic studies and give details of any study proposed.)

The trial focuses on mechanistic effects of ticagrelor rather than hard clinical outcomes. Thus, no economic analysis is planned. However, results from the trial can be incorporated into a network meta-analysis of ticagrelor, prasugrel and clopidogrel, which has already been performed. Results from the network analysis can be used as basis for the clinical assumptions of a subsequent economic evaluation.

7 CLOSING REMARKS

Clopidogrel has been the second top selling drug (based on its costs) in the world over the last few years, and despite being on the market since 1997 sales were still growing by over 20% ten years later.[227] Throughout the last decade, extensive research has been carried out to evaluate the role of clopidogrel in the prevention and treatment of cardiovascular disease. Several drawbacks of clopidogrel therapy have been described such as a delayed onset of action and large inter-individual variability in platelet response, although the clinical impact of these observations is less clear. Clopidogrel's limitations and the high economic impact of antiplatelet therapy have stimulated an intensive search for alternative antiplatelet agents. Over the last years, various new compounds were tested in clinical trials, but so far only two agents are on their way into clinical routine. As of May 2011, prasugrel has been approved by Canadian, American and European health authorities, while ticagrelor is only approved in Europe.

Key goal of this thesis was an indirect comparison of these two compounds. Despite the availability of results from large clinical trials with ten thousands of participants, the data seem not sufficient to draw valid conclusions from such a comparison. Further, many issues regarding these trials have been raised after their publication, which cannot be incorporated either.
In a comment in the New England Journal of Medicine, Dr. Ellis Unger, one of the FDA's major reviewers for the approval of prasugrel, wrote: "Ultimately, deciding which drug is preferable will be a matter of individual clinical judgment. The FDA made sure that prasugrel's label clearly articulates the balance between efficacy and risk—a balance that physicians will need to assess carefully when choosing treatment for individual patients."[228] This statement emphasizes the need for `personalized medicine´, where treatment should be tailored to the individual characteristics of each patient. Genetics and other personalized approaches have been postulated to represent the future of cardiovascular healthcare but according to a recent US survey, less than 7% of patients seen by practicing cardiologists are currently treated with such an approach.[229]
The availability of three agents for antagonizing platelet ADP receptors may make it possible to individualize antiplatelet therapy, but this requires profound knowledge of the characteristics of each drug and the corresponding trials. Drug labeling might not be sufficient to address all aspects, which should be taken into account, and past experience showed that it could rather cause confusion than support clinicians. The latest FDA clopidogrel label, announced in March 2010, outlined the availability of genetic tests to identify poor responders of clopidogrel and

advised clinicians to consider other antiplatelet medications or alternative dosing strategies for clopidogrel non-responders. However, evidence was and is sparse for the use of different treatment strategies in response to genetic testing. Twelve weeks after the release of the label, a committee of the US cardiac associations (ACC/AHA) released several recommendations in a 20-page document. These recommendations included statements that, doctors should adhere to the existing guidelines for antiplatelet therapy and that, while the evidence is thin, some patients at moderate or high risk for poor outcomes, such as those undergoing elective high-risk PCI procedures, might be candidates for genetic or platelet-function testing.[230, 231]
Lately, recommendations of the FDA Cardiovascular and Renal Drugs Advisory Committee during the review process of ticagrelor proposed that the lack of benefit with ticagrelor in the United States should be included in product labeling.[159] Given that the drug will be finally approved and this label included, it seems challenging to incorporate country-specific aspects of evidence when managing and informing patients in daily clinical routine.

Thus, one of the key messages that can be drawn from this thesis is how challenging it can be to compare individual trials even within one well-defined area of medicine. As more drugs are on the horizon the situation will become if anything more complicated.

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APPENDIX 1 SEARCH STRATEGY FOR OVERVIEW OF SYSTEMATIC REVIEWS

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1950 to Present>

Search Strategy:

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1 ("review" or "review academic" or "review tutorial").pt. (1539440)

2 (medline or medlars or embase or pubmed).tw,sh. (45712)

3 (scisearch or psychinfo or psycinfo).tw,sh. (4103)

4 (psychlit or psyclit).tw,sh. (823)

5 cinahl.tw,sh. (4746)

6 ((hand adj2 search$) or (manual$ adj2 search$)).tw,sh. (4570)

7 (electronic database$ or bibliographic database$ or computeri?ed database$ or online database$).tw,sh. (7477)

8 (pooling or pooled or mantel haenszel).tw,sh. (35997)

9 (retraction of publication or retracted publication).pt. (3069)

10 (peto or dersimonian or der simonian or fixed effect).tw,sh. (1870)

11 or/2-10 (88755)

12 1 and 11 (36785)

13 meta-analysis.pt. (25367)

14 meta-analysis.sh. (25367)

15 (meta-analys$ or meta analys$ or metaanalys$).tw,sh. (45700)

16 (systematic$ adj5 review$).tw,sh. (27717)

17 (systematic$ adj5 overview$).tw,sh. (563)

18 (quantitativ$ adj5 review$).tw,sh. (2988)

19 (quantitativ$ adj5 overview$).tw,sh. (132)

20 (quantitativ$ adj5 synthesis$).tw,sh. (1011)

21 (methodologic$ adj5 review$).tw,sh. (2314)

22 (methodologic$ adj5 overview$).tw,sh. (154)

23 (integrative research review$ or research integration).tw. (69)

24 or/13-23 (69537)

25 12 or 24 (90429)
26 Platelet Aggregation Inhibitors/ (20411)
27 (clopidogrel or plavix or iscover).mp. (5232)
28 ticlopidine/ (4949)
29 thienopyridine*.mp. (695)
30 27 or 28 or 29 (6830)
31 26 or 30 (22704)
32 exp Cardiovascular Diseases/ (1579036)
33 31 and 32 (13550)
34 25 and 33 (587)
35 limit 33 to systematic reviews (824)
36 34 or 35 (1061)
****

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1950 to Present>

Search Strategy:

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1 (clopidogrel or plavix or iscover or platelet aggregat* or antiplatelet* or anti-platelet* or platelet inhibit* or antithrombocyt* or anti-thrombocyt*).ti. (12755)
2 limit 1 to in process (204)
****

Database: EMBASE <1980 to 2010 Week 27>

Search Strategy:

---

1 exp review/ (1049029)
2 (medline or medlars or embase or pubmed).ti,ab,sh. (42229)
3 (scisearch or psychlit or psyclit).ti,ab,sh. (1054)
4 (psycinfo or psychinfo).ti,ab,sh. (2712)

5 cinahl.ti,ab,sh. (3232)

6 ((hand adj2 search$) or (manual$ adj search$)).tw. (3176)

7 ((electronic adj database$) or (bibliographic adj database$)).tw. (3912)

8 ((pooled adj analys$) or pooling).tw. (6568)

9 (peto or dersimonian or (fixed adj effect) or mantel haenszel).tw. (2779)

10 RETRACTED ARTICLE/ (3431)

11 or/2-10 (56880)

12 1 and 11 (27110)

13 exp meta analysis/ (38901)

14 meta?analys$.tw,sh. (39572)

15 (systematic$ adj5 review$).tw,sh. (35941)

16 (systematic$ adj5 overview$).tw,sh. (498)

17 (quantitativ$ adj5 review$).tw,sh. (11201)

18 (quantitativ$ adj5 overview$).tw,sh. (122)

19 (methodologic$ adj5 review$).tw,sh. (1847)

20 (methodologic$ adj5 overview$).tw,sh. (138)

21 ((integrative adj5 research adj5 review$) or (research adj5 integration)).tw. (674)

22 (quantitativ$ adj5 synthesi$).tw,sh. (1905)

23 or/13-22 (77878)

24 12 or 23 (93619)

25 antithrombocytic agent/ (17089)

26 (clopidogrel or plavix or iscover).mp. (18470)

27 ticlopidine/ (9520)

28 clopidogrel/ (18301)

29 thienopyridine*.mp. (1223)

30 thienopyridine derivative/ (645)

31 or/26-30 (23997)

32 25 or 31 (35389)

33 exp Cardiovascular Diseases/ (1478198)

34 32 and 33 (29723)

35 24 and 34 (1641)

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APPENDIX 2 LIST OF EXCLUDED SYSTEMATIC REVIEWS
(after full text retrieval)

Study ID/First Author	Year	Reason for exclusion
No author (J Fam Practice)	2005	Practice Recommendation referring to systematic review by Tran et al
Altmann	1994	Comparison of antiplatelet versus control, no clopdiogrel/ticlopidine subgroup analysis
Baumgartner	2008	Editorial
Belvis	2008	Narrative review
Collins	2004	Comparison of antithrombotic versus control, no clopdiogrel/ticlopidine subgroup analysis
Cowley	2009	Narrative review
Dorffler-Melly	2003	Updated version available
Dorffler-Melly	2005	No comparison of interest (no thienopyridine subgroup analysis)
Engelter	2003	Comparison multiple antiplatelets versus control
Engelter	2004	No comparison of interest, short version of Engelter 2003
Felmeden	2005	Different study population (hypertensives)
Gubitz	2000	Updated version available
Hankey	2000	Updated version available
Hankey	2000	Updated version available
Lip	2004	Different study population (hypertensives)
Majid	2001	Narrative review
Misson	1998	Narrative review of CAPRIE
Mood	2008	Narrative review
Reaume	2008	Narrative review
Robinson	2000	SR re glycoprotein antagonists (cost-effectiveness analysis)
Sandercock	2003	Updated version available
Sze	1998	No studies with thienopyridines included
Wong	2006	Narrative review

APPENDIX 3 RESULTS OF AMSTAR RATING

AMSTAR Items

1. Was an ‘‘a priori’’ design provided?
2. Was there duplicate study selection and data extraction?
3. Was a comprehensive literature search performed?
4. Was the status of publication (i.e., grey literature) used as an inclusion criterion?
5. Was a list of studies (included and excluded) provided?
6. Were the characteristics of the included studies provided?
7. Was the scientific quality of the included studies assessed and documented?
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?
9. Were the methods used to combine the findings of studies appropriate?
10. Was the likelihood of publication bias assessed?
11. Were potential conflicts of interest included?

Author	Year	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Score SUM	Quality rating
ATC*	2002	yes	no	yes	yes	yes	yes	yes	yes	yes	no	no	8	excellent
Basili	2010	no	no	yes	yes	yes	yes	yes	yes	yes	no	no	7	moderate
Berg	2008	no	no	no	no	no	yes	no	no	yes	no	no	2	poor
Berger	2009	yes	no	yes	yes	yes	yes	yes	yes	yes	yes	no	9	excellent
Bhatt	2002	no	no	no	yes	no	yes	no	no	yes	no	no	3	poor
Biondi-Zocai	2007	no	yes	no	yes	no	yes	yes	yes	yes	yes	no	7	moderate
Biondi-Zocai	2004	no	yes	yes	yes	no	yes	yes	yes	yes	yes	no	8	excellent

* ATC indicates Antihrombotic trialists collaboration

Author	Year	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Score SUM	Quality rating
Bowry	2008	no	yes	yes	yes	no	yes	yes	yes	yes	no	no	7	moderate
Brown	2008	no	yes	yes	yes	yes	yes	yes	yes	yes	yes	no	9	excellent
Casella	2003	no	yes	no	yes	yes	yes	no	no	yes	no	no	5	moderate
Eshaghian	2007	AMSTAR not applicable												
Girolami	1999	no	yes	no	yes	no	yes	yes	yes	yes	yes	no	7	moderate
Girolami	2000	no	yes	no	no	no	yes	yes	yes	yes	no	no	5	moderate
Hackam	2007	AMSTAR not applicable												
Helton	2007	no	yes	yes	yes	no	yes	yes	yes	yes	yes	no	8	excellent
Jones	2004	yes	no	yes	yes	yes	yes	yes	yes	yes	yes	yes	10	excellent
Lotrionte	2007	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	no	10	excellent
Main	2004	yes	no	yes	no	yes	yes	yes	yes	yes	yes	no	8	excellent
McQuaid	2006	no	yes	yes	yes	no	yes	yes	yes	yes	no	no	7	moderate
Mehta	2000	no	no	no	no	no	yes	no	no	yes	no	no	2	poor
Motovska	2008	AMSTAR not applicable												
Patel	2009	no	yes	yes	yes	no	yes	yes	yes	yes	no	no	7	moderate
Purkayastha	2006	no	yes	yes	no	no	no	no	no	yes	no	no	3	poor
Robless	2001	no	yes	yes	no	no	yes	yes	yes	yes	no	no	6	moderate
Rogowski	2009	yes	yes	yes	yes	no	yes	yes	yes	yes	no	no	8	excellent

Author	Year	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Score SUM	Quality rating
Sabatine	2008	yes	yes	no	no	no	yes	no	yes	yes	no	no	5	moderate
Sandercock	2008	no	yes	yes	yes	yes	yes	yes	yes	yes	yes	no	9	excellent
Schleinitz	2004	no	no	yes	yes	no	yes	no	yes	yes	yes	no	6	moderate
Serebruany	2008	no	yes	yes	no	yes	yes	no	no	yes	no	no	5	moderate
Serebruany	2004	no	yes	yes	no	no	yes	no	no	no	no	no	3	poor
Squizzato	2007	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	no	10	excellent
Sudlow	2009	yes	yes	yes	yes	yes	yes	yes	yes	yes	no	no	9	excellent
Thijs	2008	no	no	yes	no	no	yes	no	no	yes	no	no	3	poor
Tran	2004	AMSTAR not applicable												
Usman	2009	no	no	no	no	no	yes	no	no	yes	no	no	2	poor
Vlaar	2008	no	yes	yes	yes	no	yes	no	yes	yes	no	no	6	moderate
Zusman	1999	AMSTAR not applicable												

APPENDIX 4 SYSTEMATIC REVIEWS WITH INTERVENTIONS OF SECONDARY INTEREST

b) Comparison of thienopyridine (clopidogrel, ticlopidine) monotherapy versus aspirin or control

Sudlow 2009 (search through July 08); **Research question**: to determine effectiveness and safety of thienopyridine derivatives versus aspirin for preventing stroke and other serious vascular events in high vascular risk patients; **AMSTAR 9/excellent**

Population	Intervention	Comparator	Outcome	Included RCT
Patients at high risk of occlusive arterial disease due to previous clinical manifestations of atherosclerotic arterial disease of the cerebral, coronary or peripheral circulations	Thienopyridines; RCT with follow-up of at least 1 month	Aspirin	Primary: Composite of stroke, MI, or vascular death; Secondary: individual outcomes as stroke (ischemic, hem.), MI, all-cause/vascular death; safety incl. intra- and extracranial - /GI-haemorrhage, neutropenia, thrombocytopenia	Ticlopidine trials: Japanese-B, Schoop 1983, TASS,Sadowski 1995, AAASPS, De Lucia 2000, Li 2000, Zhu 2001, STAMI Clopidogrel trial: CAPRIE

Mehta 2000 (search through: n/a); **Research question**: to determine effects of thienopyridines in patients with vascular disease, part of CURE study protocol; **AMSTAR 2/poor**

Population	Intervention	Comparator	Outcome	Included RCT
Patients with cardio-, cerebrovascular or peripheral arterial disease	1) Thienopyridines 2) Thienopyridine plus aspirin	1) Placebo/ Control or Aspirin 2) Aspirin alone or Aspirin plus OAK	Primary outcome: Vascular death, MI or stroke	1) **vs control**: CATS, Balsano 90, STIMS; **vs ASA**: TASS, CAPRIE 2) **vs ASA**: ISAR, STARS, MATTIS, FANTASTIC; **vs ASA+OAK**: STARS, HALL

Jones 2004 (search through April 2003); **Research question**: to determine the clinical effectiveness and cost-effectiveness of clopidogrel and dipyridamole in secondary prevention of vascular occlusive events; **AMSTAR 10/excellent**

Population	Intervention	Comparator	Outcome	Included RCT
Patients with established PAD, or history of MI, ischemic stroke or TIA (NSTEMI excluded)	1) Clopidogrel; 2) Dipyridamole, alone or combined with Aspirin; subgroups: stroke, MI, PAD	Aspirin	Composite of MI, ischemic stroke, vascular death and individual outcomes as used in CAPRIE trial	Ad 1) CAPRIE Ad 2) ESPS-2

Purkayastha 2006 (search through 2004; scientific letter); **Research question**: to determine the effect of clopidogrel on outcome post CABG; **AMSTAR 3/poor**

Population	Intervention	Comparator	Outcome	Included RCT
Patients undergoing CABG	Clopidogrel while CABG	Clopidogrel stopped ≥7days before CABG, i.e. versus control	Intra-op blood loss, transfusion/ventilation requirements, adverse events, length of hospital stay, mortality, and re-exploration rates	11 comparative studies, no list/references of included studies available

c) Comparison of ticlopidine versus clopidogrel

Bhatt 2002 (search through Dec 00); **Research question**: to determine whether clopidogrel is at least as efficacious as ticlopidine; **AMSTAR 3/poor**

Population	Intervention	Comparator	Outcome	Included RCT
Patients receiving coronary stents	Clopidogrel plus Aspirin	Ticlopidine plus Aspirin	Primary: MACE 30-days (death, MI, TVR, subacute stent thrombosis), Secondary: all-cause mortality	**RCT**: CLASSICS, TOPPS, Müller00; **Single-centre registries**: CCF, Lenox Hill, Mayo, N. Memorial, S. Illinois, Wash. Hosp., Wessex

Biondi-Zocai 2004 (search through Oct 03); **Research question**: to compare clopidogrel versus ticlopidine, additional analysis re loading dose; **AMSTAR 8/excellent**

Population	Intervention	Comparator	Outcome	Included RCT
Patients undergoing PCI; only RCTs included	Clopidogrel plus Aspirin	Ticlopidine plus Aspirin	Primary: all-cause mortality; Secondary: death and MI; bleeding, hematological adverse events	Atmaca03, Piamsoomboon01, CLASSICS 00, Mueller 03, Taniuchi01

Biondi-Zocai 2007 (search through March 06); **Research question**: to compare clopidogrel versus ticlopidine, focusing on clopidogrel front-loading; **AMSTAR 7/moderate**

Population	Intervention	Comparator	Outcome	Included RCT
Patients undergoing PCI; only RCTs included	Clopidogrel plus Aspirin; a priori stratification for loading dose	Ticlopidine plus Aspirin	Primary: Composite of death, non-fatal MI; Secondary: death, MI, TVR, neutro-, thrombopenia	Atmaca, CLASSICS, Juergens, Mueller, Parodi, Piamsomboon, Taniuchi

Casella 2003 (search through Dec 01); **Research question**: to compare clopidogrel versus ticlopidine on top of aspirin; **AMSTAR 5/moderate**

Population	Intervention	Comparator	Outcome	Included RCT
Patients undergoing PCI	Clopidogrel plus Aspirin;	Ticlopidine plus Aspirin	Primary: Composite of death and non-fatal MI; major adverse side effects	Moussa 99, Mishkel 99, Berger 99, Bertrand 00, Mueller 00, Calver 00, L'Allier 00, Taniuchi 01, Dangas01,Wang99

d) Systematic reviews without performance of a meta-analyis

Esaghian 2007 (search through Nov 06); **Research question**: to review the evidence regarding clopidogrel from clinical trials; **AMSTAR not applicable**

Population	Intervention	Comparator	Outcome	Included RCT
Patients with atherothrombotic cardiovascular disease	1) Clopidogrel, monotherapy 2) clopidogrel combined with aspirin	Placebo and/or aspirin	CV death, MI, stroke	1) CAPRIE 2) CURE CREDO CLARITY COMMIT CHARISMA

Hackam 2007 (search through Jan 07); **Research question**: to review the optimal antithrombotic prophylaxis for patients with PAD; **AMSTAR not applicable**

Population	Intervention	Comparator	Outcome	Included RCT
Patients with peripheral arterial disease	Aspirin, thienopyridine, picotamine, oral anticoagulation	Placebo or active treatment	Review of available RCT (with PAD subgroup), systematic reviews and consensus guidelines	Re thienopyridine: CAPRIE, CHARISMA, CREDO, EMATAP, STIMS

Motovska 2008 (search through July 08); **Research question**: to review the evidence from clinical trials and registries concerning the benefits and risks of clopidogrel in relation to dose and timing of treatment and its use in particular patient populations (stratified by risk factors for MACE); **AMSTAR not applicable**

Population	Intervention	Comparator	Outcome	Included RCT
Patients with CAD, categorized into 1.) STEMI 2.) NSTEMI 3.) elective PCI	RCT and registries: Different doses and times of clopidogrel administration a) pretreatment 300mg b) pretreatment 600mg c) pretreatment 600mg d) prasugrel (2 RCT: Triton, ongoing Principle-TIMI-44)	RCT and registries: Clopidogrel a) post PCI 300mg b) pretreatment 300mg c) post PCI 300 mg d) clopidogrel (Triton trial: 300mg pre-treatment)	Outcome data on mortality, reinfarction, stroke, or their combination (MACE); Bleeding risk	RCTs: **1.) STEMI:** a) CLARITY b) ongoing OASIS 7 c) ongoing CIPAMI **2.) NSTEMI:** a) PCI-CURE b) Cuisset 2006, OASIS-7 c) n/a **3.) elective PCI:** a) CREDO b) ARMYDA-2 c) PRAGUE-8, ARMYDA-5

Patel 2009 (search through May 08); **Research question**: to review whether clopidogrel use after CABG is based on good trial data; no MA due to study heterogeneity **AMSTAR 7/moderate**

Population	Intervention	Comparator	Outcome	Included RCT
Pts after on- or off-pump bypass **But**: due to low quality off-pump studies not included	on-pump: a) Clopidogrel plus aspirin, b) Clopidogrel mono	a) Aspirin plus placebo, b) aspirin or ticlopidine	Primary end point of the individual studies (death, stroke, MI); major bleeding	a) CURE CHARISMA CREDO b) CAPRIE, Lim 2004, David 1999

Tran 2004 (search through Aug 04); **Research question**: to review the current state of evidence regarding oral antiplatelet treatment; **AMSTAR not applicable**

Population	Intervention	Comparator	Outcome	Included RCT
Pts. with cerebrovascular, coronary artery and peripheral arterial disease	aspirin ticlopidine clopidogrel dipyridamole	Mainly vs control; In part vs each other	vascular events (modified results of Anitplatelet Trialist meta-analysis)	Subcategories: Stroke (21studies) CAD (46 studies) PAD (42 studies)

Zusman 1999 (search through: not available); **Research question**: Antiplatelet Therapy to prevent vascular events: Literature Review and Evidence-Based Guidelines; **AMSTAR not applicable**

Population	Intervention	Comparator	Outcome	Included RCT
Pts with atherosclerotic vascular disease at risk of ischemic events	Antiplatelet therapy (aspirin, ticlopidine, clopidogrel, dipyridamole)	Mainly vs control; Individual results from selected studies	MI, stroke, vascular death (modified results of Anitplatelet Trialist meta-analysis)	Pts with Prior or acute MI: 20 studies; prior stroke: 18 studies; other high risk: 104 studies

e) Systematic reviews address various antiplatelet treatment strategies with comparisons of interest in subgroup analysis

APTC 2002 (search through Sept 97); **Research question**: to review the effects of antiplatelet therapy among patients at high risk of occlusive vascular events; **AMSTAR 8/excellent**

Population	Intervention	Comparator	Outcome	Included RCT
Patients with acute or previous vascular disease or some other predisposing condition	Antiplatelet regimen	Control or other antiplatelet regimen	Primary: serious vascular event (non-fatal MI, stroke (hem or not), death from vascular or unknown cause), major extracranial bleeding	197 studies versus control, 90 studies versus another antiplatelet regimen

Basili 2010 (search through: not available); **Research question**: to review if antiplatelet treatment reduced CV events in PAD and to analyze if specific antiplatelet treatment had a different impact on clinical outcome; **AMSTAR 7/moderate**

Population	Intervention	Comparator	Outcome	Included RCT
Pts with claudication and/or ABI ≤0.99	Antiplatelets including thienopyridines, aspirin or picotamide	Control or other antiplatelet	Primary - CV event defined as non-fatal MI, stroke, CV death	26 trials from ATC - MA plus CLIPS POPADAD CHARISMA

Brown 2008 (search through Jan 08); **Research question**: to review if antiplatelet treatment in patients with symptomatic PAD undergoing infrainguinal bypass surgery improves graft patency, limb salvage and survival; **AMSTAR 9/excellent**

Population	Intervention	Comparator	Outcome	Included RCT
Patients undergoing femoro popliteal or femoro distal bypass grafting for the treatment of IC and critical limb ischaemia	(1) Aspirin (ASA) or ASA and dipyridamol (DIP) (2) ASA or ASA and DIP (3) ASA (4) ASA (5) ASA and DIP (6) Ticlopidine (7) ASA 8) ASA	(1) vs nothing or placebo (2) vs pentoxifylline (3) vs indobufen (4) vs vitamin K antagonists (5) vs low molecular weight heparin (6) vs placebo (7) vs prostaglandin E1 8) vs naftidrofuryl	Primary: graft patency rate; Secondary: secondray graft patency after secondary intervention, lower limb flow, limb salvage rate, CV events, death, QoL	(1) Clyne87; Donaldson 85; Goldman 84; Green 82; Kohler 84; McCollum 91 (2) Lucas 84; Raithel 87 (3) D' Addato92 (4) BOA 00; Schneider 79 (5) Edmondson 94 (6) Becquemin97 (7) Gruss 91 (8) Noppeney 88

Girolami 2000 (search through 1997); **Research question**: to evaluate the efficacy of conservative adjuvant therapy after revascularisation procedures; **AMSTAR 5/moderate**

Population	Intervention	Comparator	Outcome	Included RCT
Patients with peripheral arterial disease	**Antiplatelet drugs**: aspirin and dipyridamole, ticlopidine, suloctidil, picotamide, indobufen, cilostazol, **Anticoagulant drugs:** low molecular weight heparins, sulodexide, vitamin K inhibitors, defibrotide **Subgroup analysis:** ticlopidine versus control	Control or other antiplatelet regimen	Vessel patency, amputation, vascular events, mortality	32 studies, Subgroup: ticlopidine versus control: Arcan 1988, Fagher 1994

Girolami 1999 (search through June 98); **Research question**: to evaluate the effectiveness of antithrombotic drugs in pts with intermittent claudication; **AMSTAR 7/moderate**

Population	Intervention	Comparator	Outcome	Included RCT
Patients with claudication Fontaine stage II	Active drugs: aspirin, dipyridamol, ticlopidine, LMWH, cilostazol, triflusal, suloctidil, picotamide, indobufen, sulodexide	Placebo/control, or other active drug	Walking distance, ABI, calf blood flow, n of lower limb arterial occlusions, n of peripheral revascularization procedures , amputations, cerebro- or cardiovascular events, death	54 studies (44 active drug versus placebo/ control), Clopidogrel versus aspirin: CAPRIE

McQuaid 2006 (search through Dec 04); **Research question**: to review the relative and absolute risk of clinically relevant **adverse events** with the antiplatelet agents, aspirin and clopidogrel; **AMSTAR 7/moderate**

Population	Intervention	Comparator	Outcome	Included RCT
Adults assigned to antiplatelet therapy (primary or secondary prevention in pts with CAD, hypertension, Afib, valvular heart disease, post CABG/ PCI, CVD, PAD, or TVT prophylaxis)	Antiplatelet therapy with low dose aspirin or clopidogrel	Placebo, low-dose aspirin (compared with clopidogrel), clopidogrel (compared with aspirin), or combined aspirin and clopidogrel	Bleeding, non-CV deaths, discontinuations due to adverse events, or symptoms other than bleeding or CV events	22 RCT

Robless 2001 (search through Jan 99); **Research question**: to evaluate the effects of antiplatelets in reducing vascular mortality rates and CV events (MI, stroke); **AMSTAR 6/moderate**

Population	Intervention	Comparator	Outcome	Included RCT
Pts with PAD and patients undergoing vascular intervention (PTA, surgery)	At least 4 weeks of aspirin, dipyridamol, indobufen,sulfinpyrazone, picotamide, suloctidil, ticlopidine or clopidogrel	Control or aspirin	Non-fatal MI, non-fatal stroke, vascular/unexplained death, hemorrhagic side effects	Clopidogrel versus aspirin: CAPRIE Ticlopidine versus aspirin/placebo: 15 trials

Sandercock 2008 (search through June 07); **Research question**: to review the efficacy and safety of antiplatelet therapy in acute ischaemic stroke; **AMSTAR 9/excellent**

Population	Intervention	Comparator	Outcome	Included RCT
Patients within 2 weeks of onsest of presumed ischaemic stroke	Single antiplatelet agent or a combination of antiplatelet agents (Aspirin, thienopyridines, dipyridamole, TX-A2/fibrinogen/ IIb/IIIa antagonists	Control or Placebo	Primary: dead or dependent on help from other people for their daily life activities of daily living 1mo after stroke; Secondary: death, VTE, recurrent stroke, intra-, extra-cranial haemorrhage, complete recovery	Abciximab 2000, AbESTT 2005, AbESTT-II/C 2008, CAST 1997, Ciufetti 1990, IST 1997, MAST-I 1995, Pince 1981, Rödén-Jullig 2003, Turpie 1983, Utsumi 1988,

Schleinitz 2004 (search through May 03); **Research question**: to compare ≥2 oral anti-thrombotic strategies in patients undergoing coronary stenting to determine which treatment optimally prevents adverse cardiac events in the 30 days following stent insertion; **AMSTAR 6/moderate**

Population	Intervention	Comparator	Outcome	Included RCT
Pts. undergoing coronary stent placement	Ticlopidine plus aspirin	1) aspirin 2) aspirin+coumadin 3)aspirin+clopidogrel 4) aspirin+cilostazol	30-day outcome of MACE, including MI, TVR, CV death or angiographically visualized stent thrombosis	1) Hall, STARS 3) TOPPS Piamsonboon CLASSICS Muller

f) Systematic review focusing on specific aspects of the intervention beyond the scope of the research question: effect of clopidogrel loading dose, pre-treatment, therapy duration and previous network analysis

Lotrionte 2007 (search through Dec 06); **Research question**: to review the optimal clopidogrel loading dose during PCI; **AMSTAR 10/excellent**				
Population	**Intervention**	**Comparator**	**Outcome**	**Included RCT**
Pts. with CAD scheduled for catherization and/or PCI	High clopidogrel loading >300mg	Standard clopidogrel loading 300 mg	Primary: 1-mo cardiac death or non-fatal MI; Second.: cardiac death, nonfatal MI, urgent TVR, stent thrombosis within 1mo; bleeding	ALBION 2006, Angiolillo 2004, ARMYDA-2 2005, CLEARPLATELETS 2005, Cuisset 2006, Gurbel 2005, ISAR-CHOICE 2005, Muller 2001, Seyfarth 2002, Wolfram 2006

Rogowski 2009 (search through Feb 07); **Research question**: to review the effect of different treatment durations of clopidogrel in patients with non-ST-segment elevation acute coronary syndromes: a systematic review and value of information analysis; focus **1)** on optimal duration and **2)** effects of withdrawal ; **AMSTAR 8/excellent**				
Population	**Intervention**	**Comparator**	**Outcome**	**Included RCT**
Patients with **1)** NSTE-ACS, namely UA or NSTEMI; **Broadened**: STEMI, PCI, stroke, PAD **2)** NSTE-ACS, STEMI, PCI, stroke, PAD	**1)** clopidogrel plus aspirin **2)** any thienopyridine (ticlopidine, clopidogrel, prasugrel) with or without aspirin	**1)** Placebo with aspirin or aspirin alone **2)** Control treatment	**1)** Primary: non-fatal MI, IHD w/o MI, death, bleeding; Secondary: refractory and severe ischaemia, HF, UA, revasc., other vascular or adverse events **2)** Changes in platelet biomarker, occurrence of adverse events	CURE Vavuranikis 06

Sabatine 2008 (search through Aug 07); **Research question**: to review whether clopidogrel pretreatment is beneficial stratified by the use of IIb/IIIa antagonists; **AMSTAR 5/moderate**

Population	Intervention	Comparator	Outcome	Included RCT
Pts undergoing percutaneous coronary interventions	Pretreatment with 300mg clopidogrel loading dose; Use of IIb/IIIa antagonists was at discretion of treating physician	Placebo pretreatment - 300mg clopidogrel loading dose at time of PCI;	Primary: composite CV death, MI, or stroke after PCI; safety: rate of TIMI major or minor bleeding	PCI-CURE CREDO PCI-CLARITY

Thijs 2008 (search through March 03); **Research question**: to use network meta-analysis to compare commonly used antiplatelet regimens in the prevention of serious vascular events after transient ischaemic attack (TIA) or stroke; **AMSTAR 3/poor**

Population	Intervention	Comparator	Outcome	Included RCT
Patients at secondary prevention after TIA/stroke	Aspirin+dipyridamole; Thienopyridine+aspirin; Thienopyridine; Aspirin; short term studies <3 mo excluded	Placebo; one antiplatelet strategy versus another	Non-fatal stroke, non-fatal MI, vascular death	Thieno vs Aspirin: AAASPS, Caprie stroke, TASS, Li 00; Thieno vs Ctrl: CATS, Russel 85; Thieno +Aspirin vs Thieno: MATCH, TOPALS; Thieno+Aspirin vs ASA: CHARISMA

Vlaar 2008 (search through: not available); **Research question**: to compare the incidence of initial coronary artery patency and short-term outcome of pts with clopidogrel pretreatment versus pts who did not receive clopidogrel before initial coronary angiography; **AMSTAR 6/moderate**

Population	Intervention	Comparator	Outcome	Included RCT
Unselected patients with STEMI undergoing primary PCI; RCTs only	Pretreatment with clopidogrel	Clopidogrel not received before initial coronary angiography	Primary: initial coronary artery patency before primary PCI; Secondary: short-term mortality, death, reinfarction, in-hospital major bleeding	26 studies with 38 treatment groups

g) Systematic reviews focusing only on the safety outcome bleeding

Serebruany 2008 (search through 2006); **Research question**: to quantitate the risks of bleeding with single versus combination antiplatelet therapy; **AMSTAR 5/moderate**

Population	**Intervention**	**Comparator**	**Outcome**	**Included RCT**
Patients participating in appropriate RCTs; FU at least 1month	Dual antiplatelet therapy incl. iv/oral IIb/IIIa blockers (8/2 trials); thienopyridines (6 trials); dipyridamole (2 trials) on top of aspirin	Single antiplatelet therapy with aspirin; or clopidogrel (MATCH trial)	Bleeding: major (16 trials) minor (9 trials) fatal (6 trials) intracranial (8 trials)	18 RCT

Serebruany 2004 (search through 2002); **Research question**: to evaluate the risk of hemorrhage in the major classes of antiplatelet agents; **AMSTAR 3/poor**

Population	**Intervention**	**Comparator**	**Outcome**	**Included RCT**
Patients participating in appropriate RCTs; FU at least 1month	Aspirin < 100 mg, Aspirin>/= 100 mg, dipyridamole, ADP-receptor blockers, i.v./oral GP IIb/IIIa inhibitors		Weighted average bleeding rate (total, major, minor, stroke, GI)	18 RCT

Usmann 2009 (search through: not available); **Research question**: to evaluate antithrombotic agents for secondary stroke prevention, focusing on bleeding risk; **AMSTAR 2/poor**

Population	**Intervention**	**Comparator**	**Outcome**	**Included RCT**
Patients taking anithrombotic agents for secondary stroke– prevention after non cardio-embolic strokes; FU at least 1 year; only RCTs	Aspirin, clopidogrel, aspirin plus dipyridamole, OAK, aspirin plus clopidogrel	Control or aspirin alone or clopidogrel alone	Annualized rates of total and major (necessitating hospital admission) bleeding events per 100 PY	13 trials

APPENDIX 5 RESULTS FROM CLOPIDOGREL VERSUS PLACEBO STUDIES

CLOPIDOGREL VERSUS PLACEBO	
	ALL TRIALS OR (95%CI)
All-cause mortality	0.94 (0.89, 0.99)
CV mortality	0.94 (0.89, 1.00)
Non-fatal MI	0.82 (0.76, 0.89)
Stroke	0.82 (0.72, 0.93)
Composite endpoint	0.88 (0.84, 0.92)
Stent thrombosis*	0.92 (0.51, 1.67)
Total major bleeding	1.14 (1.00, 1.31)
Non CABG-related major bleeding	1.58 (1.25, 2.00)
Minor bleeding	1.35 (1.24, 1.46)
Major or minor bleeding	1.29 (1.21, 1.39)

CLOPIDOGREL VERSUS PLACEBO, OR (95%CI)		
	ACS TRIALS	**Long-term ACS TRIALS**
All-cause mortality	0.93 (0.88, 0.99)	0.92 (0.80, 1.07)
CV mortality	0.93 (0.89, 0.99)	0.92 (0.79, 1.08)
Non-fatal MI	0.81 (0.74, 0.88)	0.77 (0.66, 0.89)
Stroke	0.84 (0.72, 0.97)	0.87 (0.64, 1.18)
Composite endpoint	0.88 (0.83, 0.92)	0.80 (0.71, 0.89)
Total major bleeding	1.03 (0.86, 1.24)	0.94 (0.67, 1.31)
Non CABG-related major bleeding	1.52 (1.18, 1.97)	1.52 (1.18, 1.97)
Minor bleeding	1.34 (1.22, 1.46)	2.18 (1.79, 2.65)
Major or minor bleeding	1.28 (1.18, 1.38)	1.79 (1.51, 2.11)

CLOPIDOGREL VERSUS PLACEBO, OR (95%CI)		
	PCI TRIALS	**Long-term PCI TRIALS**
All-cause mortality	0.80 (0.58, 1.12)	0.92 (0.63, 1.36)
CV mortality	0.80 (0.58, 1.12)	0.92 (0.63, 1.36)
Non-fatal MI	0.70 (0.58, 0.83)	0.72 (0.58, 0.88)
Stroke	0.54 (0.27, 1.07)	0.76 (0.32, 1.80)
Composite endpoint	0.66 (0.56, 0.78)	0.69 (0.57, 0.83)
Stent thrombosis*	0.92 (0.51, 1.67)	0.92 (0.51, 1.67)
Total major bleeding	1.19 (0.94, 1.52)	1.26 (0.98, 1.61)
Non CABG-related major bleeding*	1.92 (1.04, 3.54)	1.92 (1.04, 3.54)
Minor bleeding	1.26 (0.97, 1.64)	1.22 (0.92, 1.60)
Major or minor bleeding	1.24 (1.03, 1.49)	1.25 (1.04, 1.52)

*Only reported in the CREDO trial.

APPENDIX 6

A ARC (ACADEMIC RESEARCH CONSORTIUM) CRITERIA FOR STENT THROMBOSIS

Definite, **Probable, and Possible Stent Thrombosis**

Definite stent thrombosis is considered to have occurred by either angiographic or pathological confirmation:

- The presence of a thrombus that originates in the stent or in the segment 5 mm proximal or distal to the stent and presence of at least 1 of the following criteria within a 48-hour time window:
  - Acute onset of ischemic symptoms at rest
  - New ischemic ECG changes that suggest acute ischemia
  - Typical rise and fall in cardiac biomarkers (refer to definition of spontaneous MI)
  - Nonocclusive thrombus: Intracoronary thrombus is defined as a (spheric, ovoid, or irregular) noncalcified filling defect or lucency surrounded by contrast material (on 3 sides or within a coronary stenosis) seen in multiple projections, or persistence of contrast material within the lumen, or a visible embolization of intraluminal material downstream.
  - Occlusive thrombus: TIMI 0 or TIMI 1 intrastent or proximal to a stent up to the most adjacent proximal side branch or main branch (if originates from the side branch).
- Evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy.

Probable stent thrombosis - Clinical definition of probable stent thrombosis is considered to have occurred after intracoronary stenting in the following cases:

- Any unexplained death within the first 30 days
- Irrespective of the time after the index procedure, any MI that is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause

Possible stent thrombosis - Clinical definition of possible stent thrombosis is considered to have occurred with any unexplained death from 30 days after intracoronary stenting until end of trial follow-up.

The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is not considered a confirmed stent thrombosis (silent occlusion).

B TIMI (THROMBOLYSIS IN MYOCARDIAL INFARCTION) BLEEDING CRITERIA

TIMI-defined Major Intracranial, or clinically significant overt signs of hemorrhage associated with a drop in hemoglobin of > 5 g/dL (or, when hemoglobin is not available, an absolute drop in hematocrit of > 15%)
TIMI-Life threatening A subset of TIMI-Major that meets any of the following: is fatal; leads to hypotension requiring treatment with intravenous inotropic agents; requires surgical intervention for ongoing bleeding; necessitates the transfusion of 4 or more units of blood (whole blood or packed red blood cells) over a 48-hour period; is a symptomatic ICH
TIMI-defined Minor Any clinically overt sign of hemorrhage (including imaging) that is associated with a fall in hemoglobin of 3 to <=5 g/dL (or, when hemoglobin is not available, a fall in haematocrit of 9 to<=15%) NOTE: TRITON used 3 to <5 g/dL
TIMI-defined Minimal Any clinically overt sign of hemorrhage (including imaging) that is associated with a fall in hemoglobin <3 g/dL (or, when hemoglobin is not available, a fall in hematocrit of <9%)

APPENDIX 7 SEARCH STRATEGY FOR PRASUGREL AND TICAGRELOR RCT

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1950 to Present>

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1 (clopidogrel or plavix or iscover).mp. (5337)
2 ticlopidine/ (5022)
3 thienopyridine*.mp. (713)
4 Platelet Aggregation Inhibitors/ (20580)
5 1 or 2 or 3 or 4 (22914)
6 prasugrel.mp. (343)
7 CS-747.mp. (24)
8 LY640315.mp. (11)
9 6 or 7 or 8 (346)
10 ticagrelor.mp. (81)
11 azd6140.mp. (55)
12 10 or 11 (121)
13 exp cardiovascular disease/ (1586018)
14 5 and (9 or 12) (366)
15 13 and 14 (230)
16 (prasugrel or ticagrelor).ti,ab. (337)
17 (CS-747 or LY640315 or azd6140).ti,ab. (79)
18 16 or 17 (361)
19 limit 18 to in process (35)
20 randomized controlled trial.pt. (297107)
21 controlled clinical trial.pt. (82205)
22 randomized.ab. (211555)
23 placebo.ab. (124428)
24 clinical trials as topic.sh. (150234)
25 randomly.ab. (156298)
26 trial.ti. (91006)
27 20 or 21 or 22 or 23 or 24 or 25 or 26 (706875)
28 15 and 27 (114)
29 19 or 28 (149)

Database: EMBASE <1980 to 2010 Week 33>

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1 antithrombocytic agent/ (21612)
2 (clopidogrel or plavix or iscover).mp. (20411)
3 ticlopidine/ (10594)
4 clopidogrel/ (19994)
5 thienopyridine*.mp. (1408)
6 thienopyridine derivative/ (721)
7 or/1-6 (41323)
8 prasugrel.mp. (1019)
9 CS-747.mp. (110)
10 LY640315.mp. (14)
11 8 or 9 or 10 (1023)
12 ticagrelor.mp. (389)
13 azd6140.mp. (75)
14 12 or 13 (417)
15 7 and (11 or 14) (1076)
16 exp cardiovascular disease/ (2179822)
17 15 and 16 (966)
18 randomized controlled trial.sh. (267389)
19 randomization.sh. (51238)
20 double blind procedure.sh. (95216)
21 single blind procedure.sh. (12658)
22 exp clinical trials/ (815508)
23 (clin$ adj25 trial$).ti,ab. (218707)
24 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab. (124473)
25 placebo.sh. (163503)
26 placebo$.ti,ab. (146039)
27 random$.ti,ab. (581520)
28 methodology.sh. (1167349)
29 comparative study.sh. (594747)
30 exp evaluation studies/ (157101)
31 follow up.sh. (469147)
32 prospective study.sh. (151887)
33 (control$ or prospectiv$ or volunteer$).ti,ab. (2556498)
34 or/18-33 (5127850)
35 17 and 34 (731)

APPENDIX 8 LIST OF EXCLUDED RCT

Study ID/First Author	Year	Reason for exclusion
Antmann	2008	Subgroup analysis of Triton trial in patients undergoing PCI re early and late benefits
Bonaca	2007	Sub-analysis of the JUMBO-TIMI 26 trial re biomarkers
Braun	2008	Sub-analysis of Wallentin et al Eur Heart J 2008 re platelet function
Chin	2010	Rationale and design of TRILOGY-ACS trial
Ernest	2008	Sub-analysis of Jernberg et al Eur Heart J 2006 re pharmacokinetics of prasugrel
Jakubowski	2010	No relevant outcome reported, integrated database results from 8 clinical trials
Mahoney	2010	Cost-effectiveness analysis of Triton
Michelson	2009	Substudy of Triton re platelet activation markers
Montalescot	2009	Subgroup analysis of Triton trial in patients undergoing PCI for STEMI
Morrow	2009	Subgroup analysis of Triton trial; analysis of spontaneous and procedural MI
Murphy	2008	Subgroup analysis of Triton trial; analysis of recurrents CV events
O'Donoghue	2009	Subgroup analysis of Triton trial; analysis of IIb/IIIa glycoprotein co-administration
O'Donoghue	2009	Analysis of PPI co-administration using two RCT
Pride	2009	Subgroup analysis of Triton trial re patients undergoing PCI w/o stent implantation
Serebruany	2006	Subgroup analysis of JUMBO trial re patients undergoing PCI w/o stent implantation
Varenhorst	2009	Sub-analysis of Wallentin et al Eur Heart J 2008 re role of genetic variations
Varenhorst	2009	Sub-analysis of Wallentin et al Eur Heart J 2008 re platelet function
Wiviott	2008	Subgroup analysis of Triton trial; analysis of patients with diabetes mellitus
Wiviott	2008	Subanalysis of Triton trial; reduction of ischemic events/stent thrombosis
Wiviott	2006	Rational and design of Triton
Wrishko-19	2009	Substudy of Triton trial; pharmacokinetic analysis
Cannon	2010	Subgroup analysis of Plato trial; analysis of patients with planned invasive strategy
Husted	2009	Subgroup analysis of Disperse-2 trial; bleeding events in patients undergoing CABG
Husted	2010	Subanalysis of the DISPERSE-2 trial re inflammatory biomarker
James	2009	Rational and design of Plato
Storey	2010	Subanalysis of the ONSET/OFFSET trial re dyspnea/pulmonary function
Storey	2007	Subanalysis of the DISPERSE-2 trial re platelet function
Storey	2009	Subanalysis of the DISPERSE and DISPERSE-2 trials re the role of genetic variations

APPENDIX 9 CHARACTERISTICS OF PRASUGREL AND TICAGRELOR STUDIES

Table A. Characteristics of included studies comparing ticagrelor with clopidogrel

Author Year ACRONYM	Number in treatment T control C group	Study design	Follow-up, maximum (mean or median)	Population: STEMI (%) NSTE-ACS (%) (comprising STEMI+UA) SCAD (%)	Characteristics: - Age (median/mean) - Female (%) - Dyslipidemia (%) - Hypertension (%) - Diabetes - Smoking (%)	%PCI:	Ticagrelor T (mg) Clopidogrel C (mg)	Aspirin dose (mg)	Included endpoints 1) Efficacy 2) Bleeding
Wallentin **2009** **PLATO**	T 9333 C 9291	Phase III, RCDB	12 months (277 days)	38% STEMI 59% NSTE-ACS 3% other or missing diagnosis	- 62 - 28 - 47 - 65 - 25 - 36	64%	T 180 LD/ 90 MD bid C 300-600 LD / 75 MD	75-100 recommended, 325 allowed	1) total & CV mortality, MI, stroke, stent thrombosis composite, 2) total major, non-CABG major, minor, major or minor
Substudy: **Cannon** **2009** **PLATO-invasive**	T 6732 C 6676	Phase III, RCDB	12 months (278 days)	49% STEMI 51% NSTE-ACS	- 61 - 25 - nr - nr - 23 - nr	77%	T 180 LD/ 90 MD bid C 300-600 LD / 75 MD	75-100 recommended, 325 allowed	1) total & CV mortality, MI, stroke, stent thrombosis composite, 2) total major, non-CABG major, minor, major or minor
Cannon **2007** **DISPERSE-2**	T 663 C 327	Phase II, RCDB, multi-dose	12 weeks (56 days)	100% NSTE-ACS	- 63 - 34 - nr - nr - 24 - nr	42%	T 270 LD or placebo, 90 or 180 bid MD C 300-600 LD/ 75 MD	75-100 mg daily	1) total & CV mortality, MI, stroke, composite, 2) total major, minor, major or minor
Husted **2006** **DISPERSE**	T 163 C 37	RCDB, multi-dose, pharmaco-kinetic study	28 days	100% SCAD	- 63 - 27 - nr - 51 - 17 - 34	0%	T 50,100 or 200 bid or 400 MD C 75 MD	75-100 mg daily	1) NO 2) major, minor, major or minor

Table A continued

Author Year ACRONYM	Number in treatment T control C group	Study design	Follow-up, maximum (mean or median)	Population: STEMI (%) NSTE-ACS (%) (comprising STEMI+UA) SCAD (%)	Characteristics: - Age (median/mean) - Female (%) - Dyslipidemia (%) - Hypertension (%) - Diabetes - Smoking (%)	%PCI:	Ticagrelor T (mg) Clopidogrel C (mg)	Aspirin dose (mg)	Included endpoints 1) Efficacy 2) Bleeding
Gurbel **2009** **ONSET/OFF SET**	T 54 C 50	RCDB, pharmaco-kinetic study	6 weeks	100% SCAD	- 64 - 24 - 96 - 75 - 22 - nr	0%	T 180 LD, 90 MD bid C 600 LD/75 MD	75-100 mg daily	1) NO 2) major, minor, major or minor
Gurbel **2010** **RESPOND**	T 49 C 49	RCDB, pharmaco-kinetic, cross-over study	29 days	100% SCAD	- 65 - 22 - 94 - 81 - 26 - nr	0%	T 180 LD, 90 MD bid C 600 LD/75 MD	75-100 mg daily	1) NO 2) major, minor, major or minor

Table B Characteristics of included studies comparing prasugrel with clopidogrel

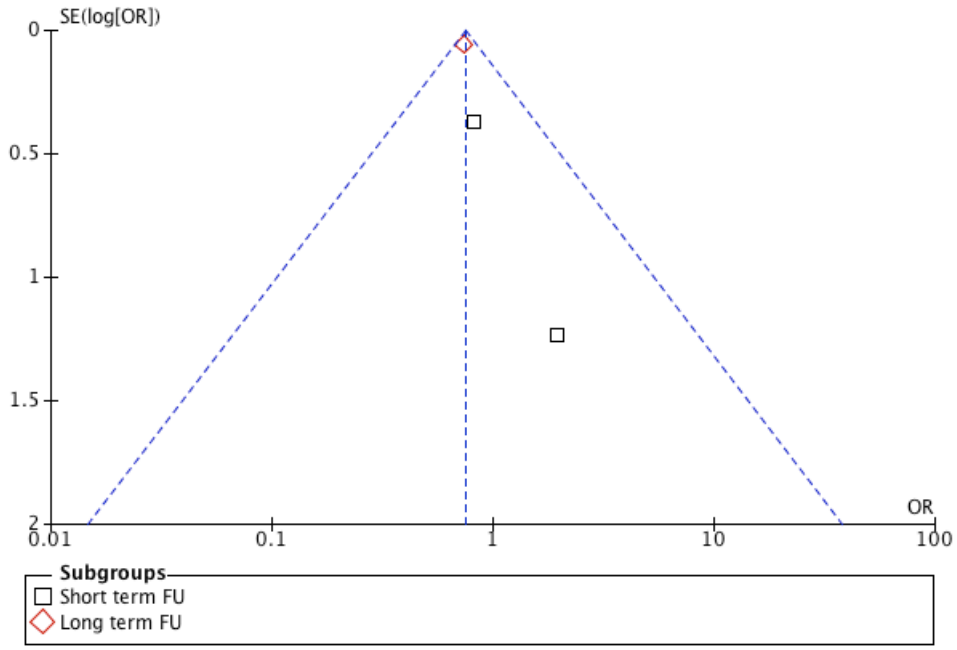
Author Year ACRONYM	Number in treatment P control C group	Study design	Follow-up, maximum (mean or median)	Population: STEMI (%) NSTE-ACS (%) (comprising STEMI+UA) SCAD (%)	Characteristics: - Age (median/mean) - Female (%) - Dyslipidemia (%) - Hypertension (%) - Diabetes - Smoking (%)	%PCI:	Prasugrel P (mg) Clopidogrel C (mg)	Aspirin dose (mg)	Included endpoints 1) Efficacy 2) Bleeding
Wiviott **2007** **TRITON-TIMI 38**	P 6813 C 6795	Phase III, RCDB	15 months (14.5 months)	26% STEMI 74% NSTE-ACS	- 61 - 26 - 56 - 64 - 23 - 38	99%	P 60 LD/ 10 MD C 300 LD/75 MD	75-162 mg daily recommended	1) total & CV mortality, MI, stroke, stent thrombosis composite, 2) total major, non-CABG major, minor, major or minor
Wiviott **2005** **JUMBO-TIMI 26**	P 650 C 254	Phase II, multi-dose, RCDB	30 days	40% NSTE-ACS 60% SCAD	- 59 - 23 - nr - nr - 26 - 27	99%	P LD/MD: 60/15, 60/10, 40/7.5 C 300 LD/75 MD	325 mg daily	1) total & CV mortality, MI, stroke, target vessel, revasc. composite, 2) major, minor, major or minor
Wiviott **2007** **PRINCIPLE TIMI 44**	P 102 C 99	Phase II, cross-over, RCDB, pharmaco-kinetic	28 days, cross-over at day 15	100% SCAD	- 64 - 25 - 88 - 82 - 30 - 17	55%	P 60 LD/ 10 MD C 600 LD/75 MD	325 mg daily	1) total & CV mortality, MI, stroke, stent thrombosis, composite, 2) major, minor, major or minor
Jernberg **2006**	P 78 C 23	Phase II, partially blinded, pharmaco-kinetic	28 days	100% SCAD	- 64 - 21 - 48 - 69 - 10 - 17	0%	P LD/MD: 60/15, 60/10, 40/7.5, 40/5 C 300 LD/75 MD	325 mg daily	1) NO 2) major, minor, major or minor

Table B continued

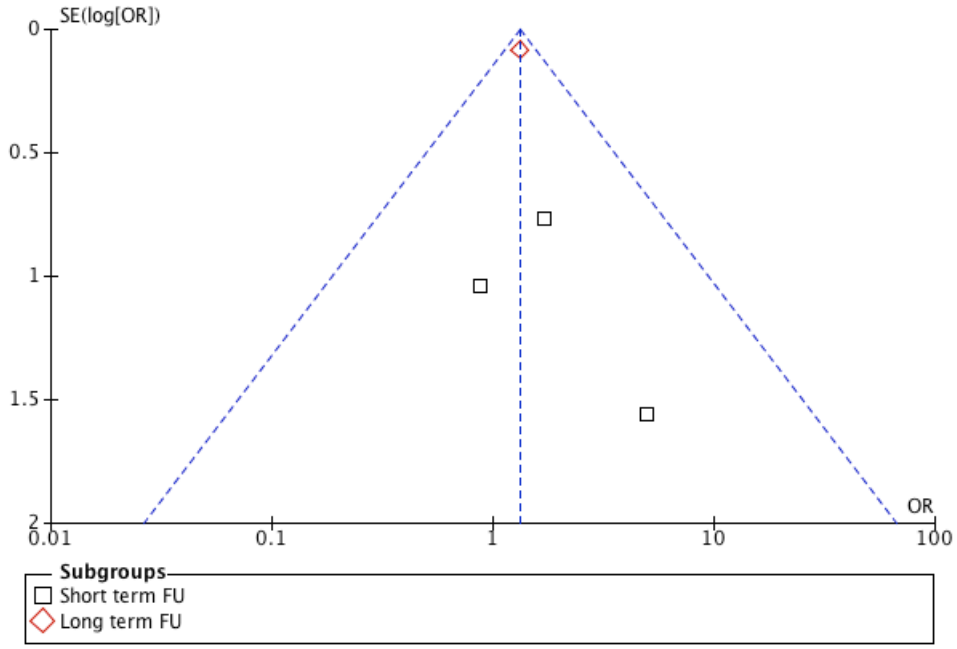
Author Year ACRONYM	Number in treatment P control C group	Study design	Follow-up, maximum (mean or median)	Population: STEMI (%) NSTE-ACS (%) (comprising STEMI+UA) SCAD (%)	Characteristics: - Age (median/mean) - Female (%) - Dyslipidemia (%) - Hypertension (%) - Diabetes - Smoking (%)	% PCI	Prasugrel P (mg) Clopidogrel C (mg)	Aspirin dose (mg)	Included endpoints 1) Efficacy 2) Bleeding
Wallentin **2008**	P 55 C 55	Phase II, RCDB, pharmaco-kinetic	28 days	100% SCAD	- 63 - 8 - 90 - 65 - 18 - nr	0%	P 60 LD/ 10 MD C 600 LD / 75 MD	325 mg daily	1) NO 2) major, minor, major or minor
Montalescot **2010** **ACAPULCO**	P 27 C 24	RCDB, cross-over, pharmaco-kinetic study	28 days, cross-over at day 15	100% NSTE-ACS	- 61 - 16 - 16 - 66 - 20 - 30	66%	900 LD clopidogrel in all patients; P 10 MD C 150 MD	100 mg daily	1) NO 2) major, minor, major or minor
Angiolillo **2010** **SWAP**	P 91 C 48	Phase II, RCDB, pharmaco-kinetic study	14 days	100% SCAD >14 d post NSTE-ACS/STEMI	- 57 - 31 - 81 - 81 - 28 - 29	0%	P 60 LD or placebo, 10 MD C placebo LD / 75 MD	81-325 mg daily	1) NO 2) major, minor, major or minor

APPENDIX 10 REPRESENTATIVE FUNNEL PLOTS

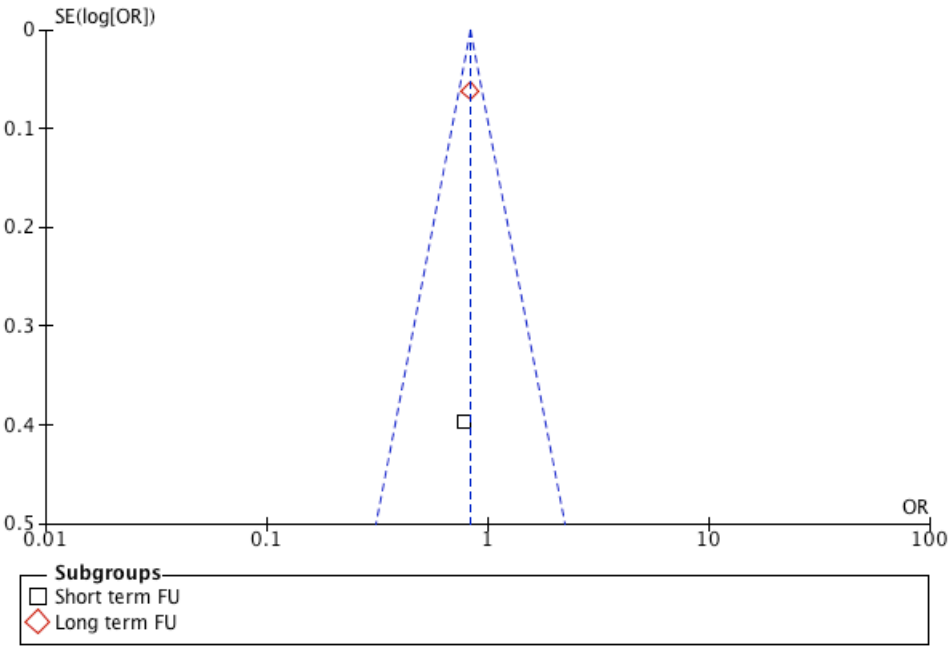
Outcome: non fatal myocardial infarction for all prasugrel trials



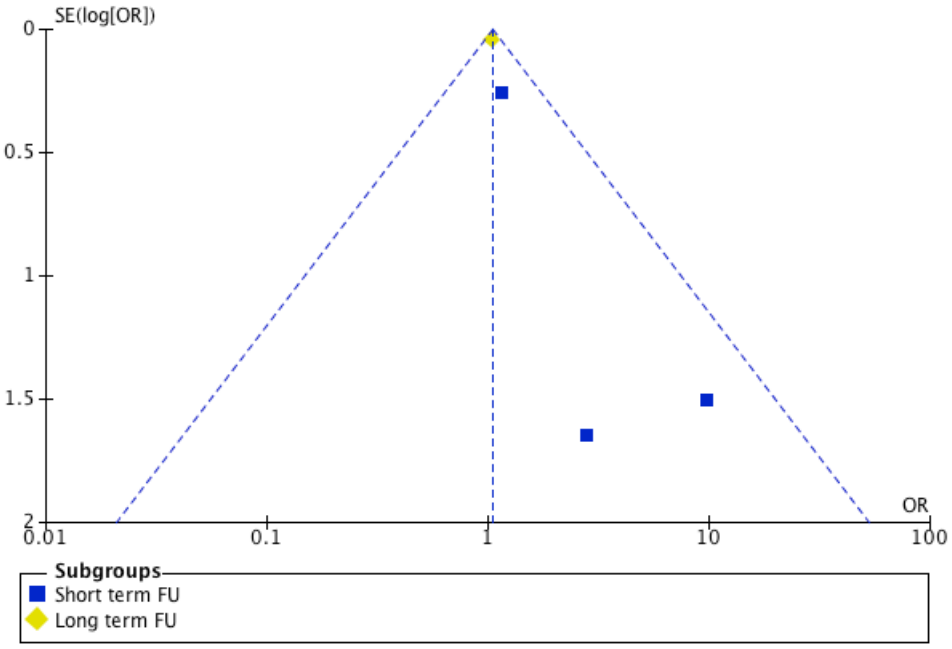
Outcome: Major or minor bleeding for all prasugrel trials



Outcome: non fatal myocardial infarction for all ticagrelor trials



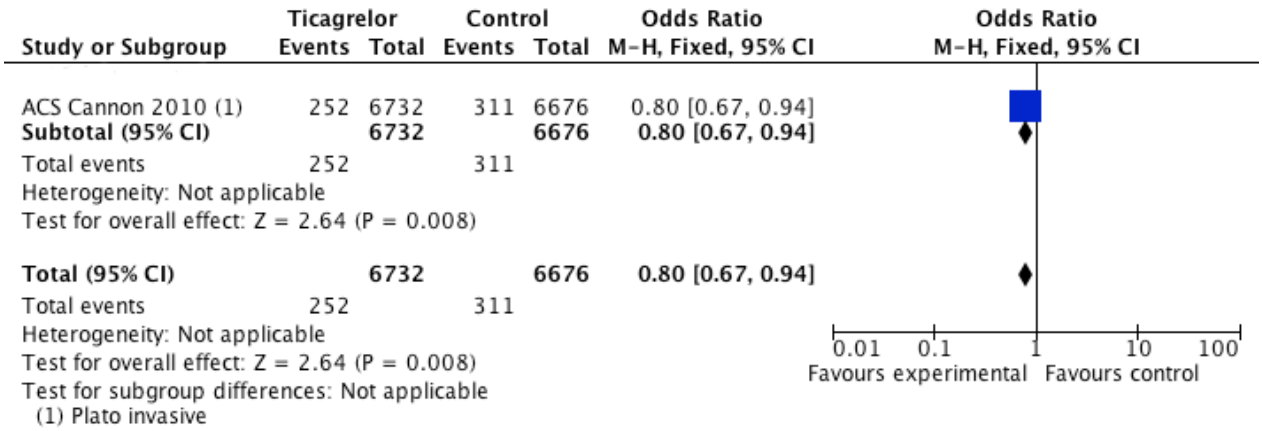
Outcome: Major or minor bleeding for all ticagrelor trials



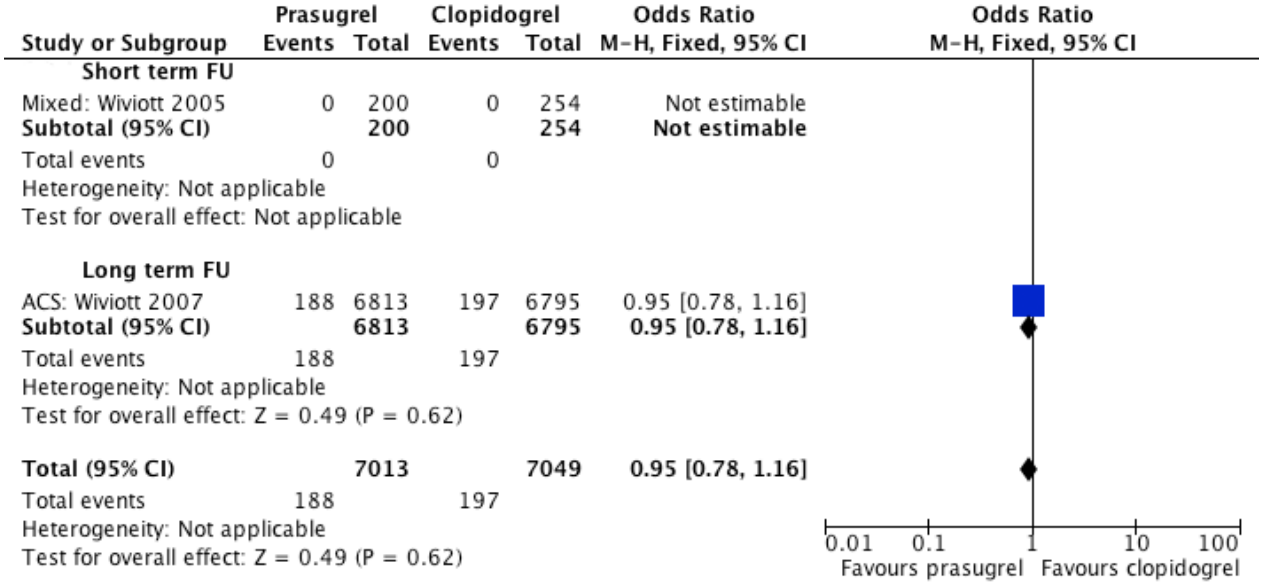
APPENDIX 11 FOREST PLOTS FOR PCI SUBGROUP (ALL OUTCOMES)

1. All-cause mortality

A) Ticagrelor

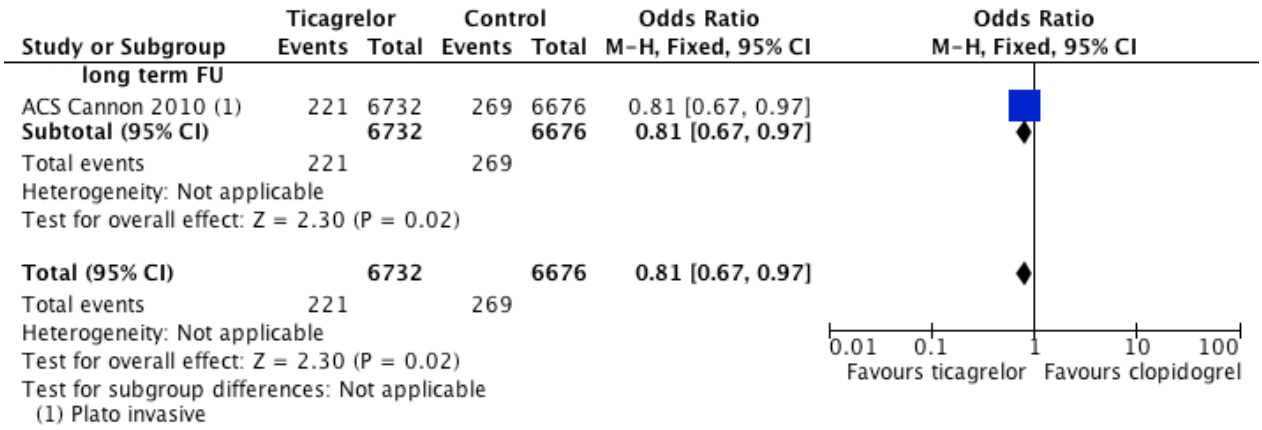


B) Prasugrel

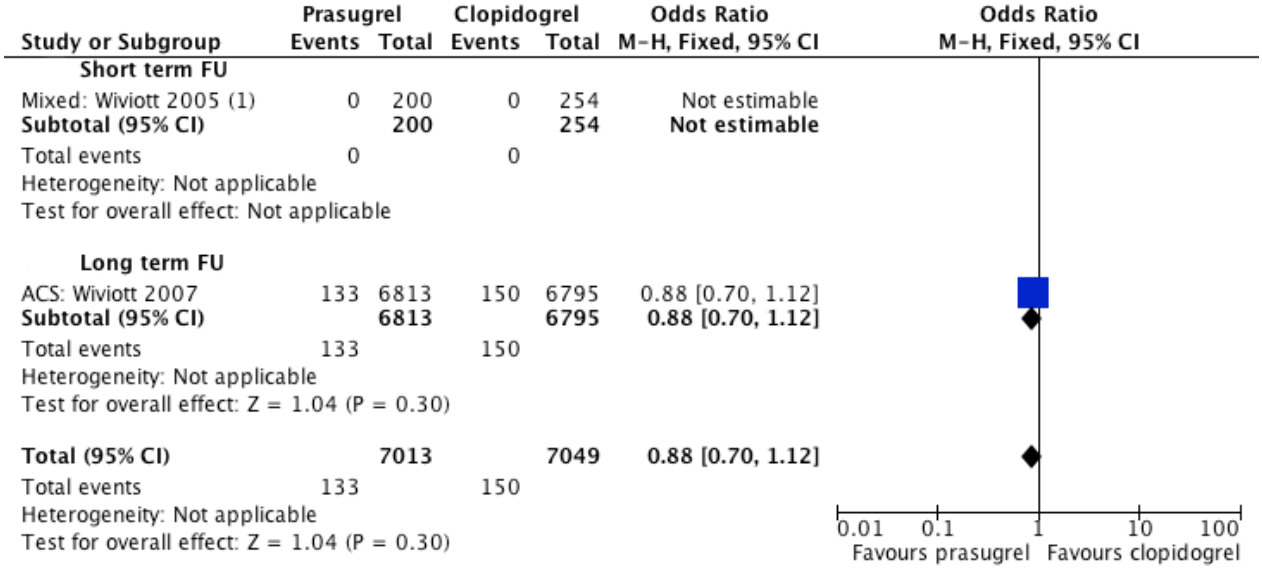


2. CV mortality

A) Ticagrelor

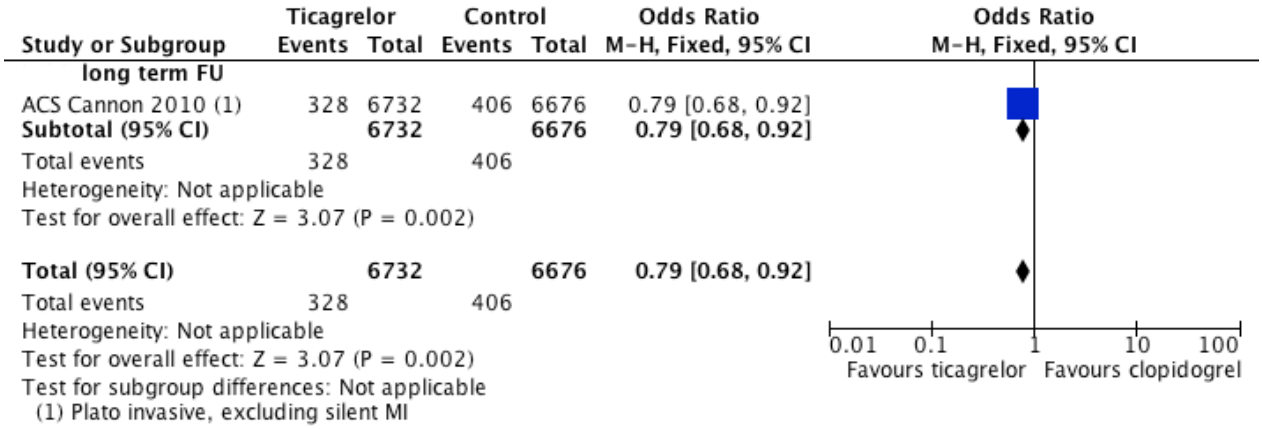


B) Prasugrel

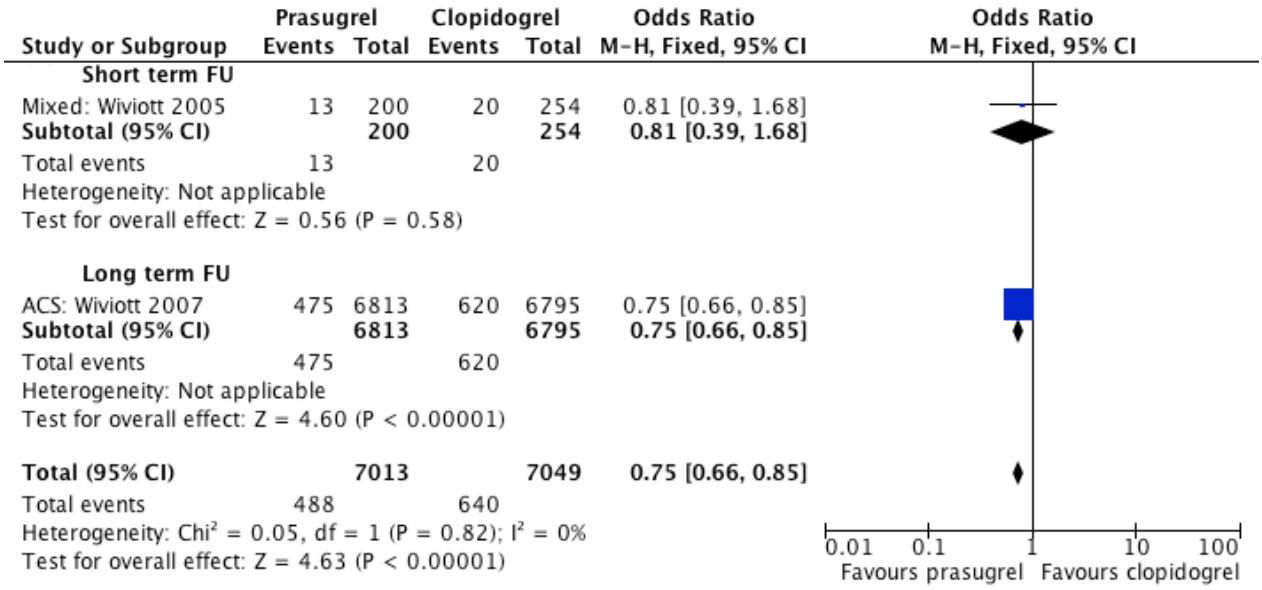


3. Non-fatal myocardial infarction

A) Ticagrelor

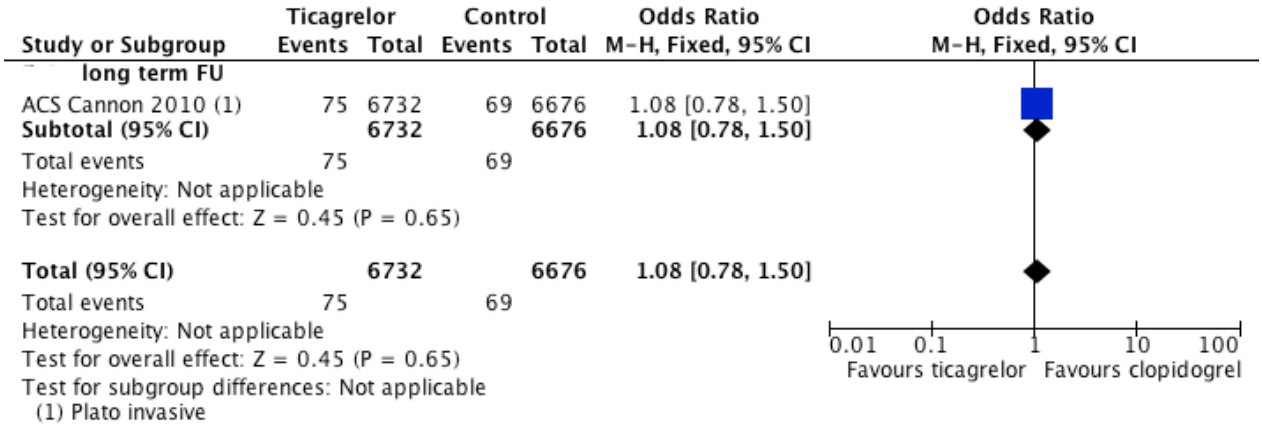


B) Prasugrel

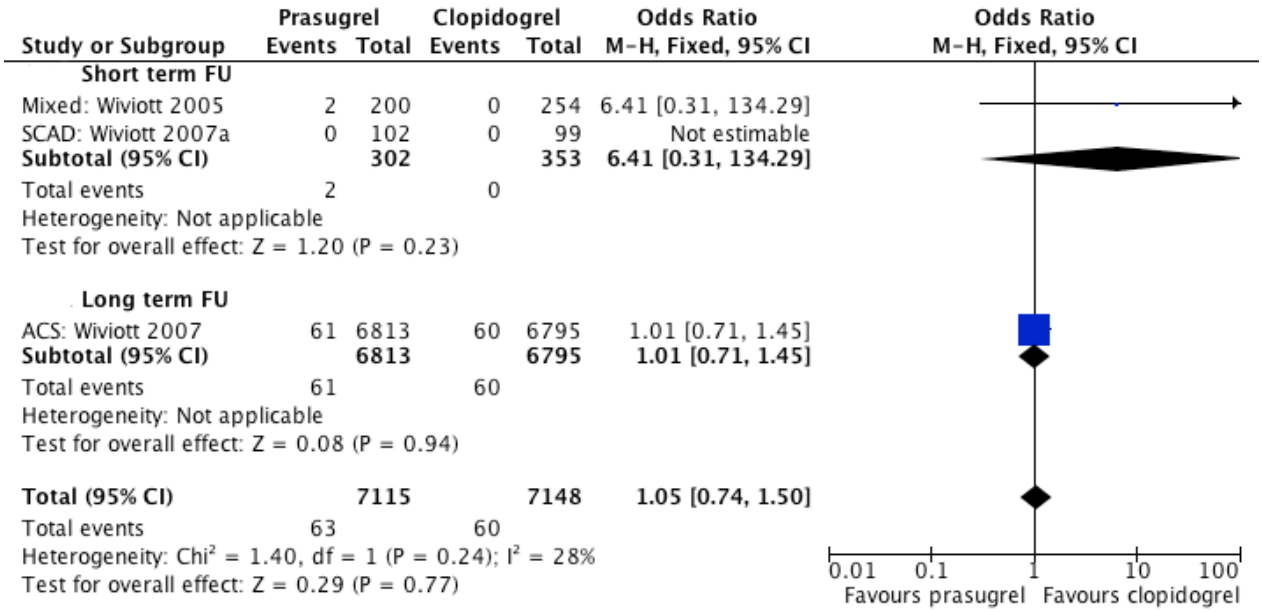


4. Stroke

A) Ticagrelor

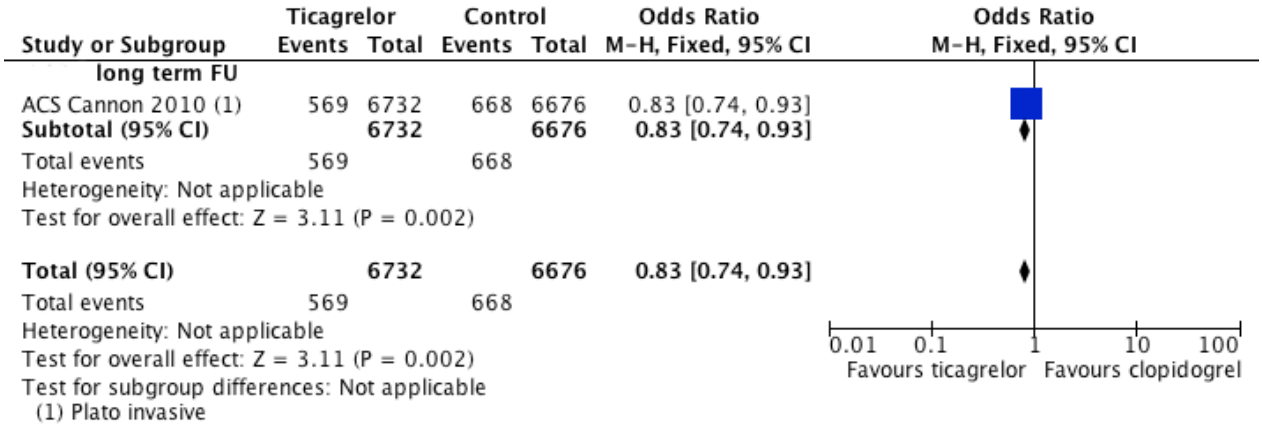


B) Prasugrel

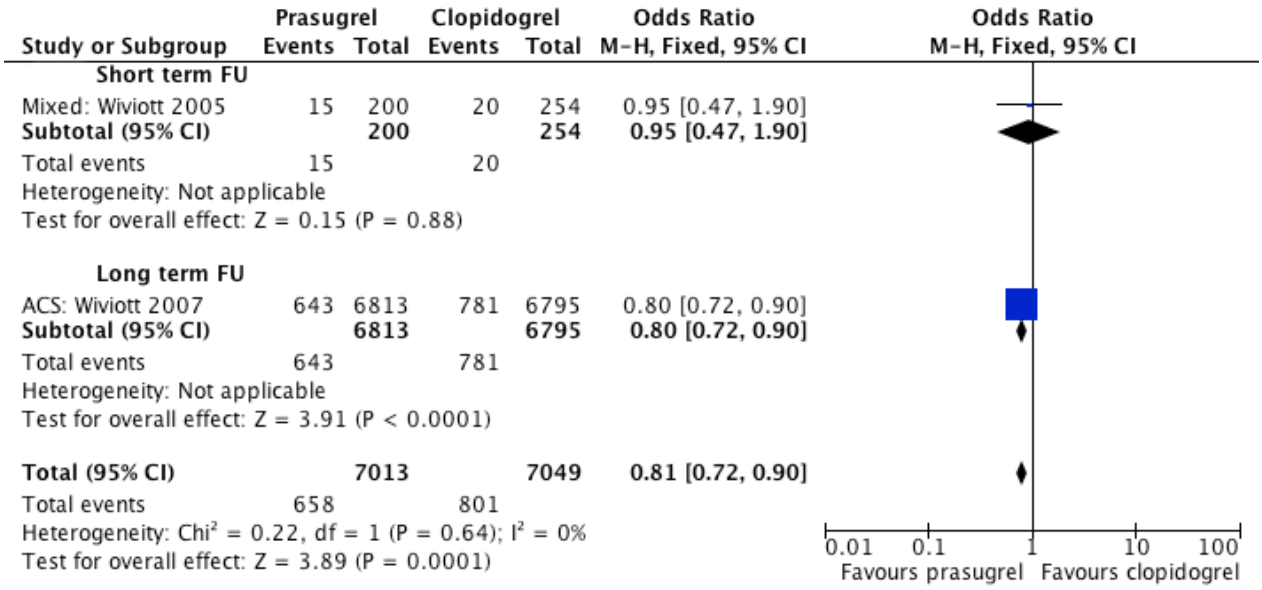


5. Composite of CV death, MI, stroke

A) Ticagrelor

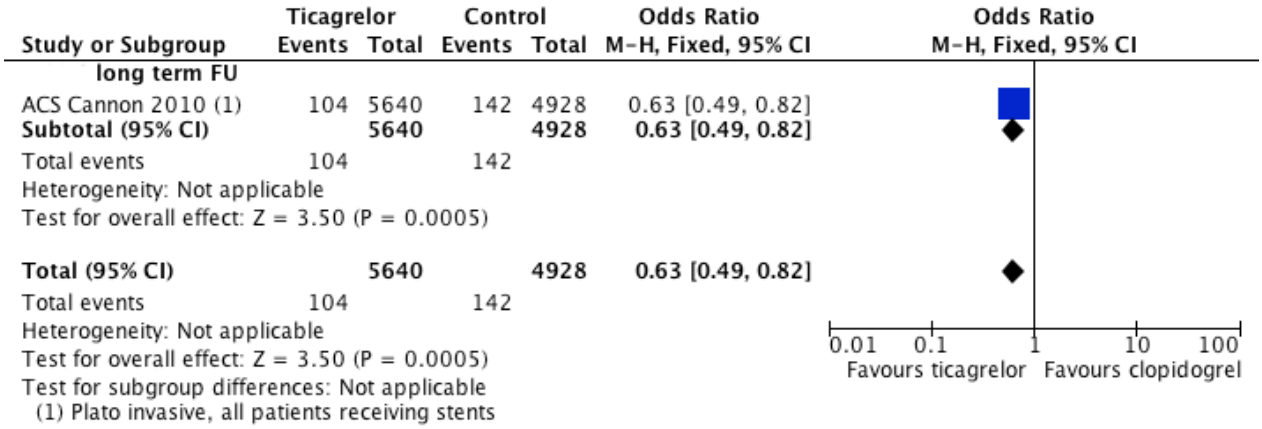


B) Prasugrel

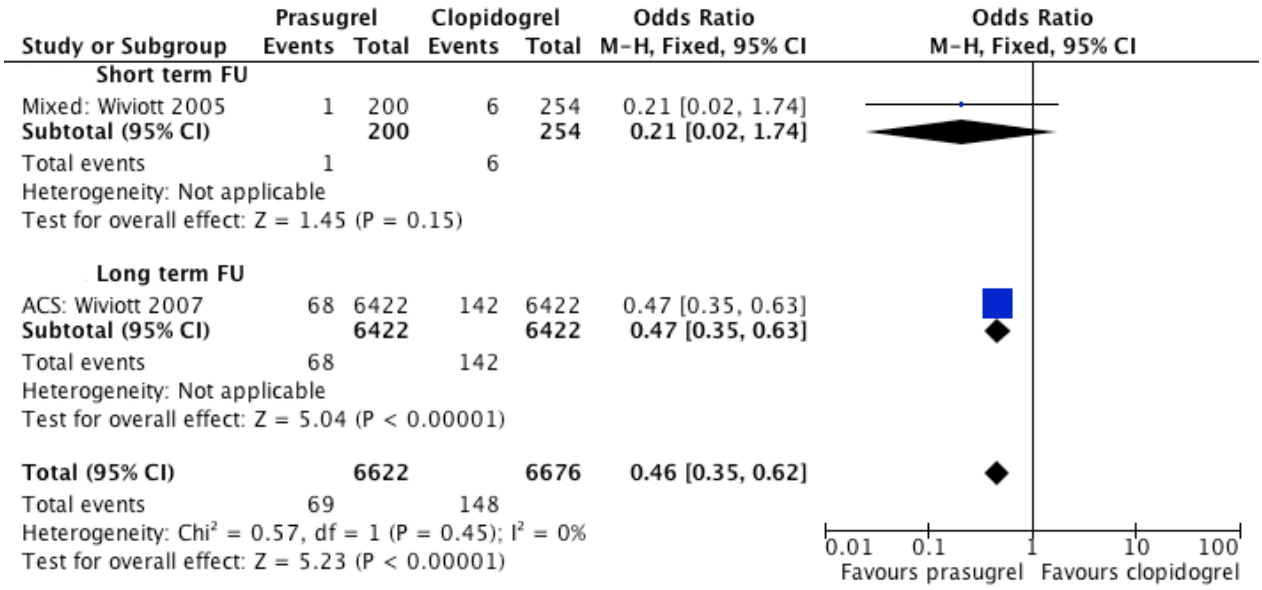


6. Stent thrombosis

A) Ticagrelor

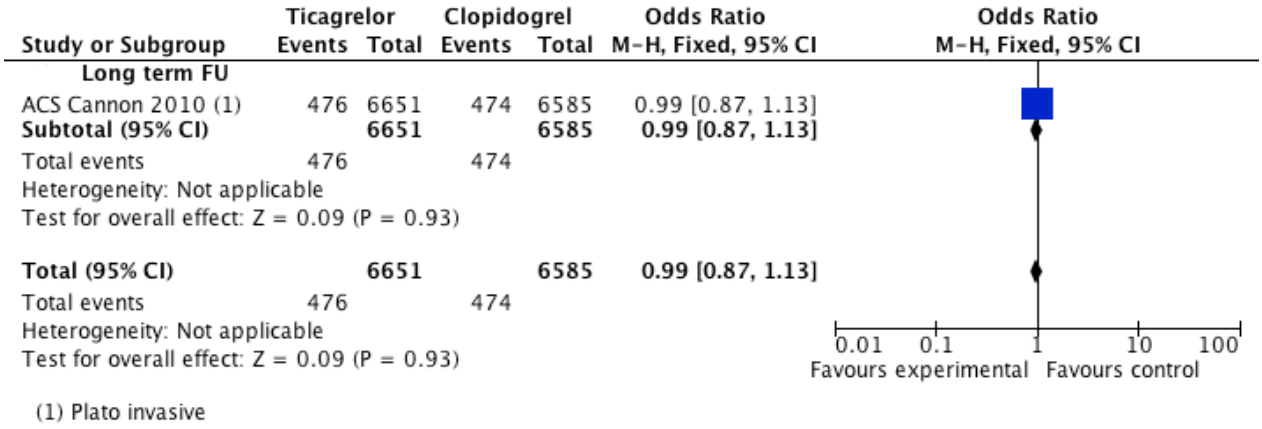


B) Prasugrel



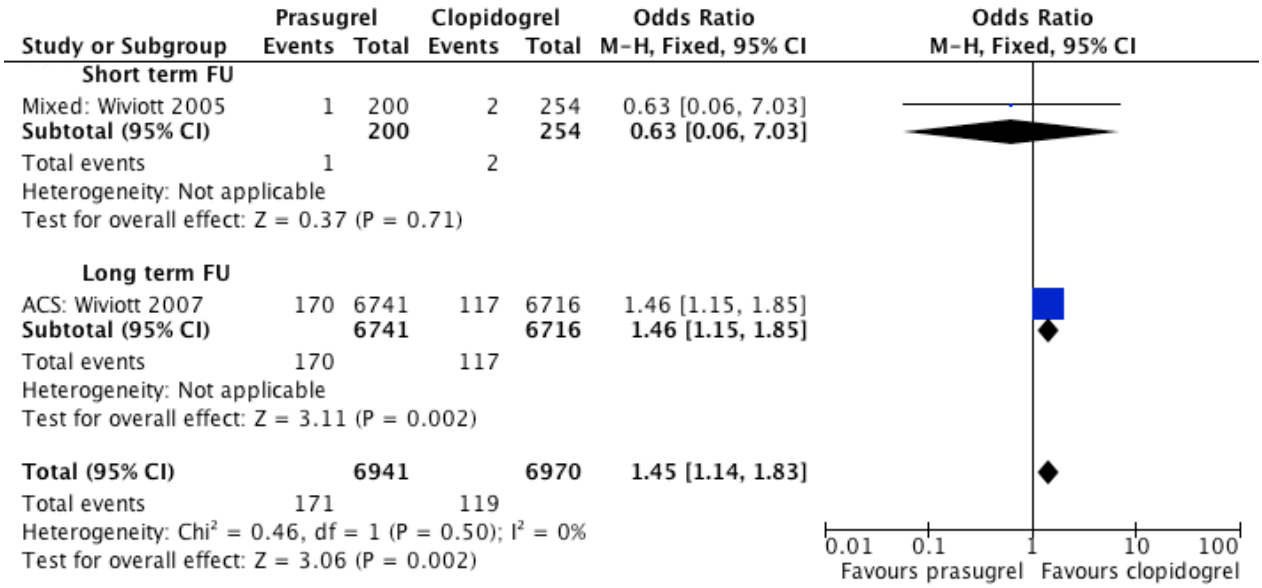
7. Total major bleeding

A) Ticagrelor



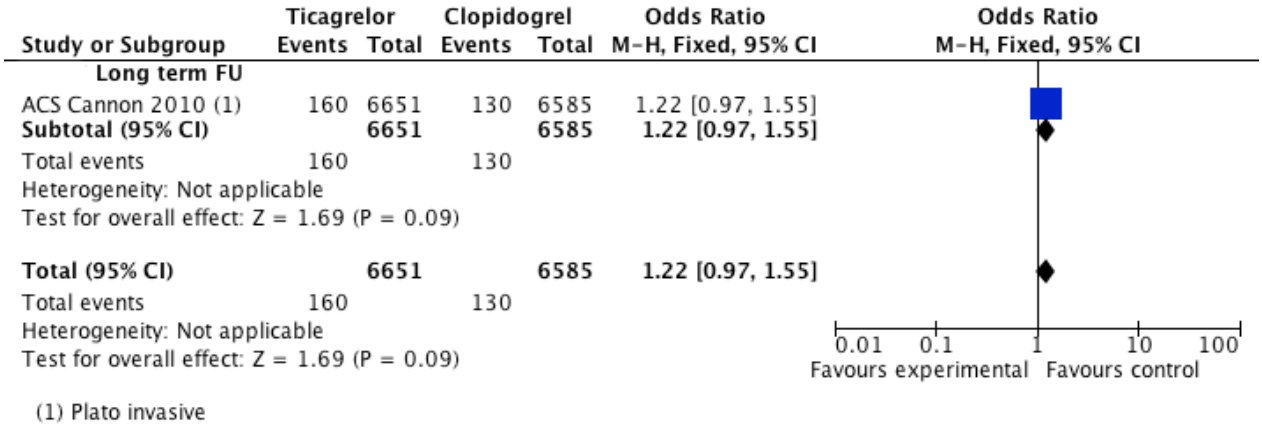
(1) Plato invasive

B) Prasugrel



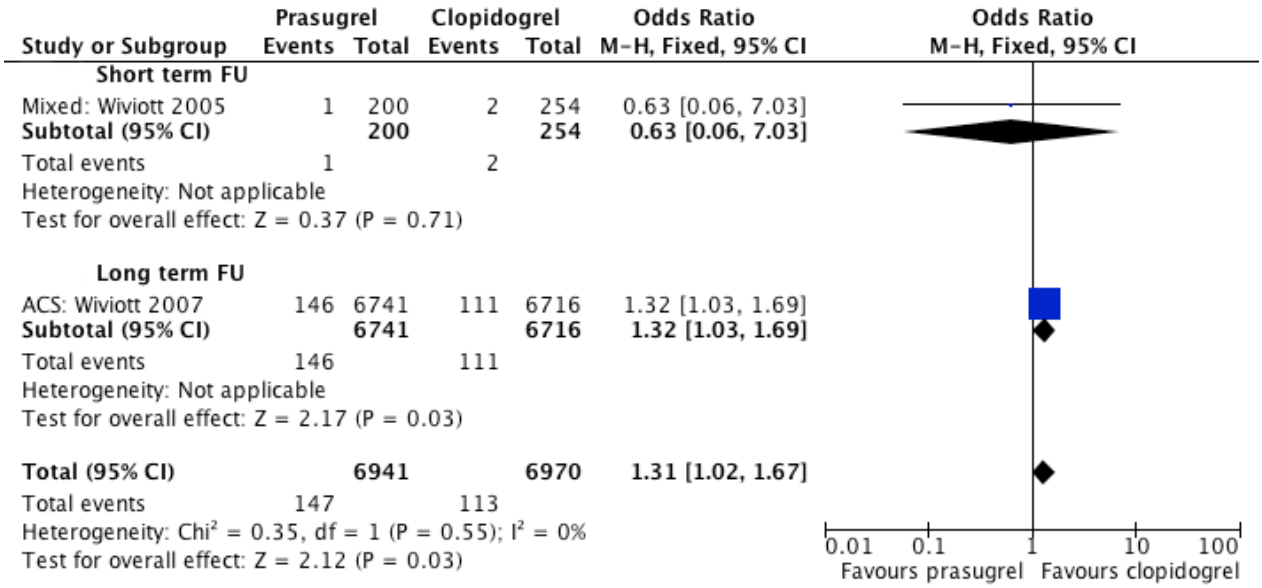
8. Non CABG-related major bleeding

A) Ticagrelor



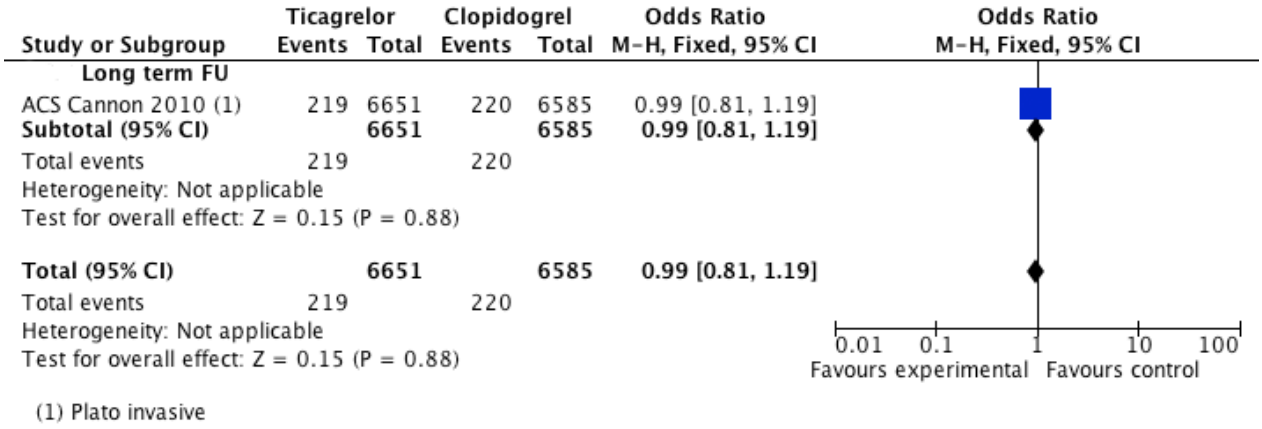
(1) Plato invasive

B) Prasugrel



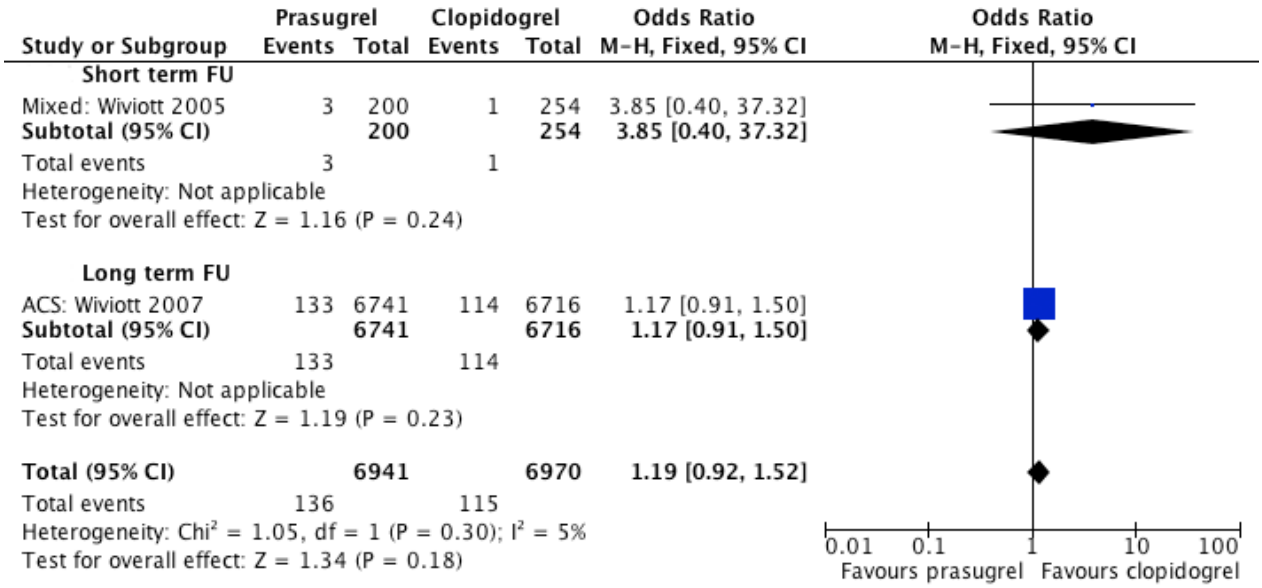
9. Minor bleeding

A) Ticagrelor



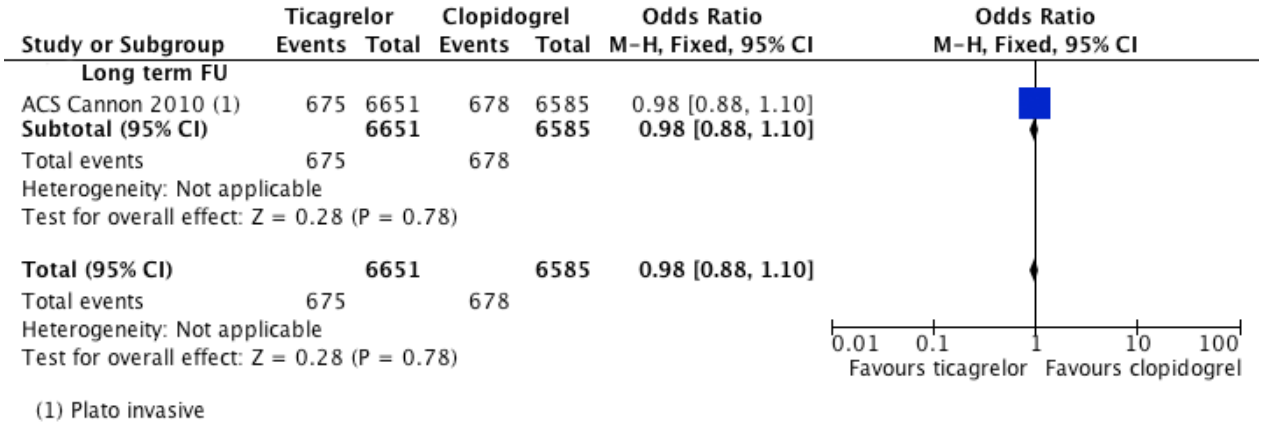
(1) Plato invasive

B) Prasugrel



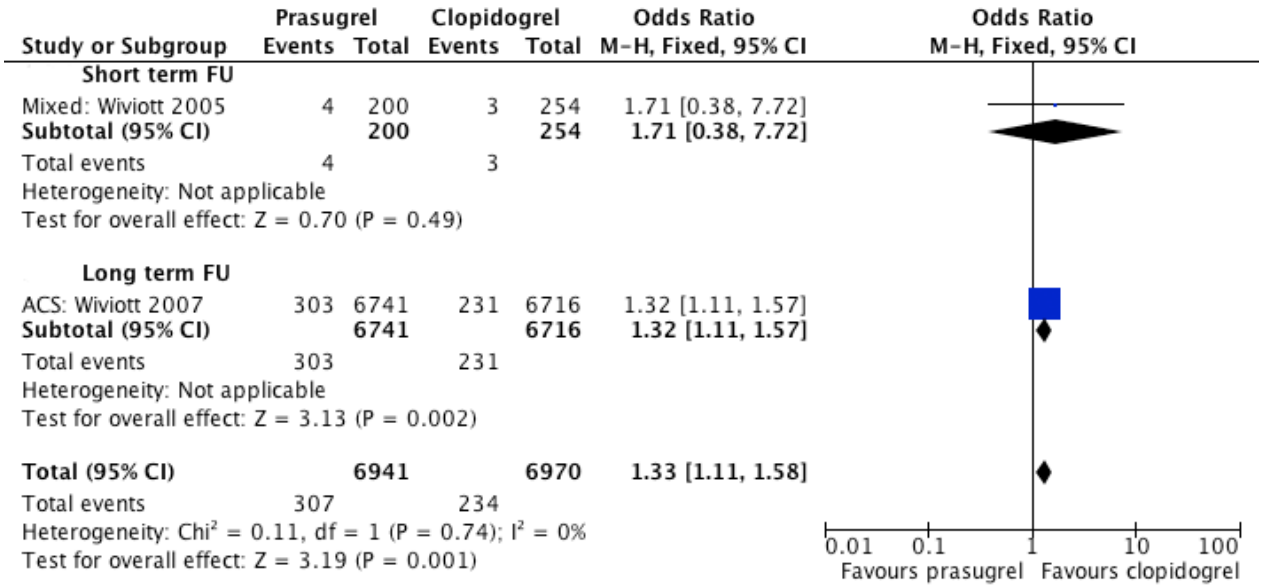
10. Major or minor bleeding

A) Ticagrelor



(1) Plato invasive

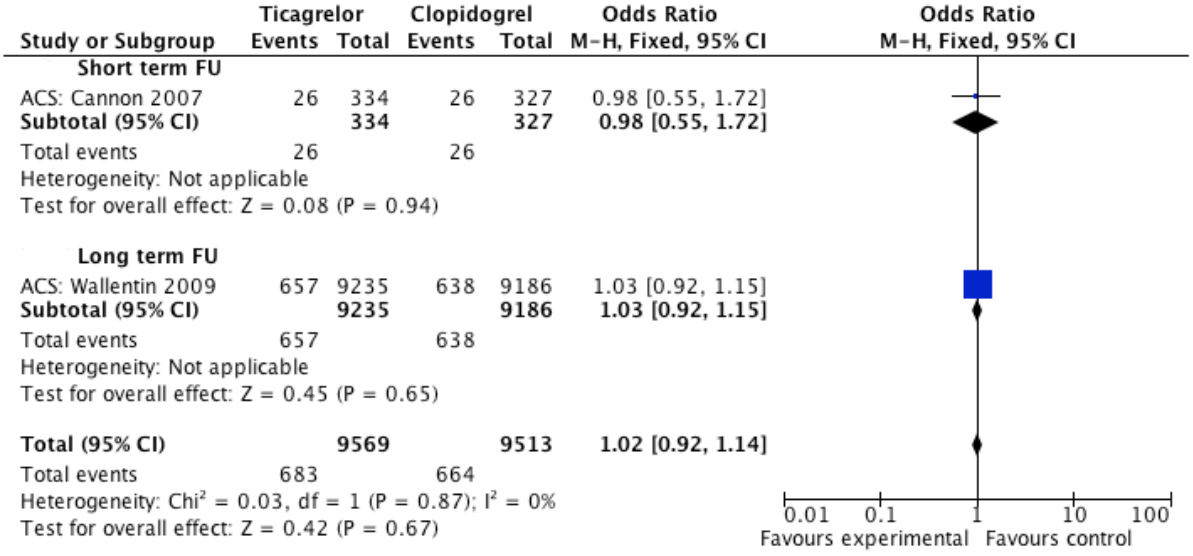
B) Prasugrel



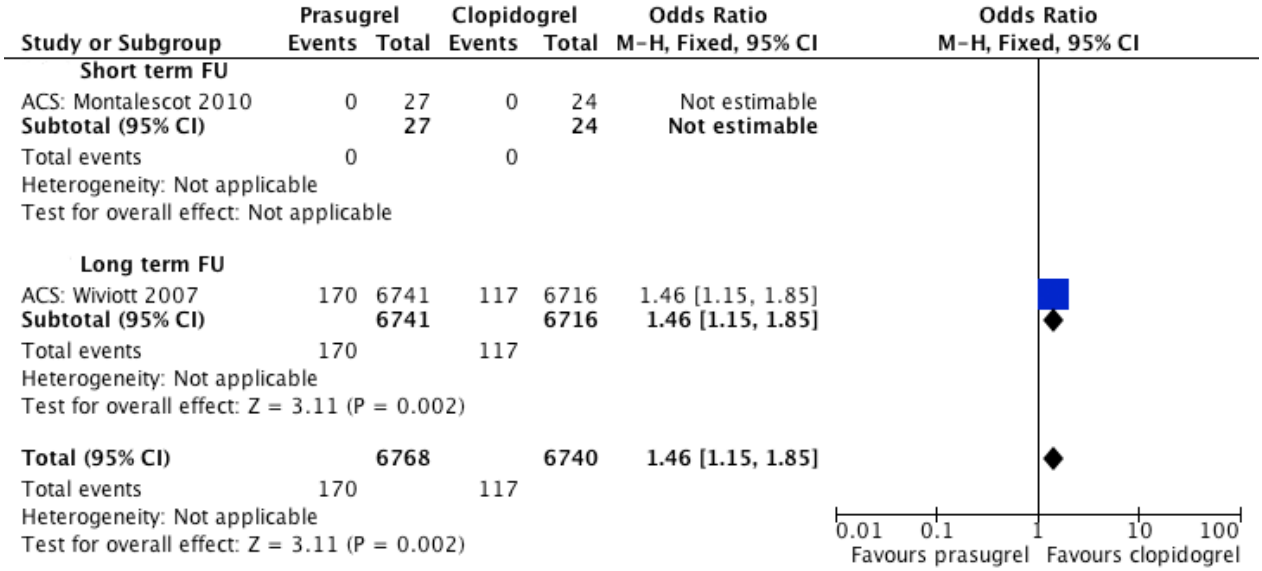
APPENDIX 12 FOREST PLOTS FOR ACS SUBGROUP (BLEEDING OUTCOMES)

1. Total major bleeding

A) Ticagrelor

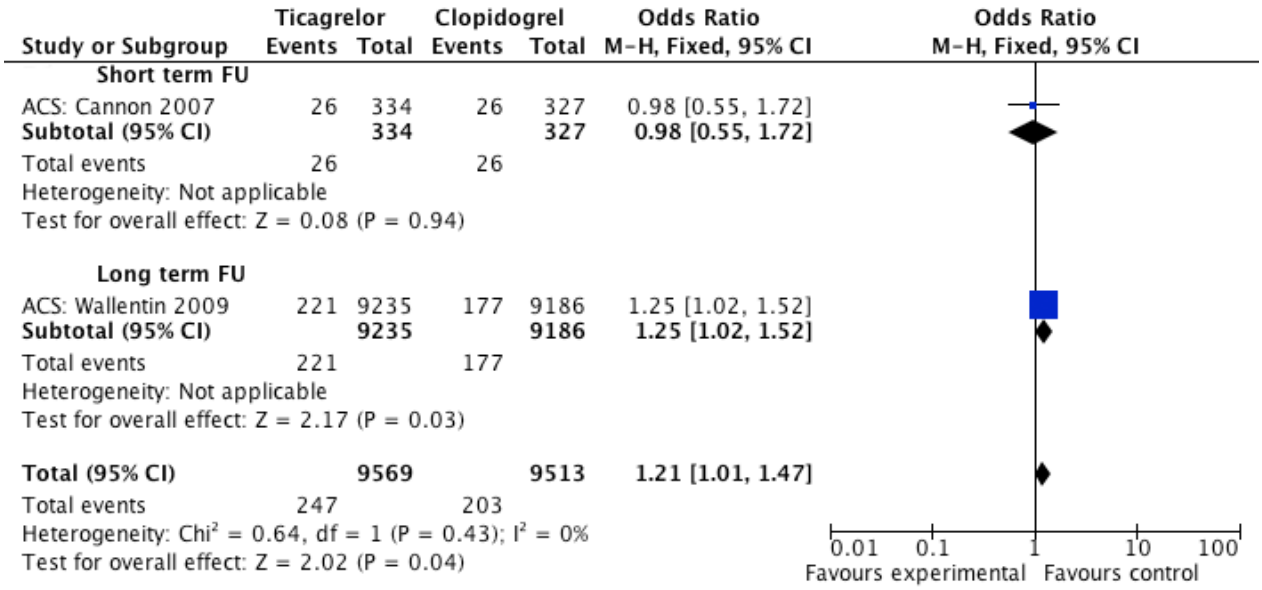


B) Prasugrel

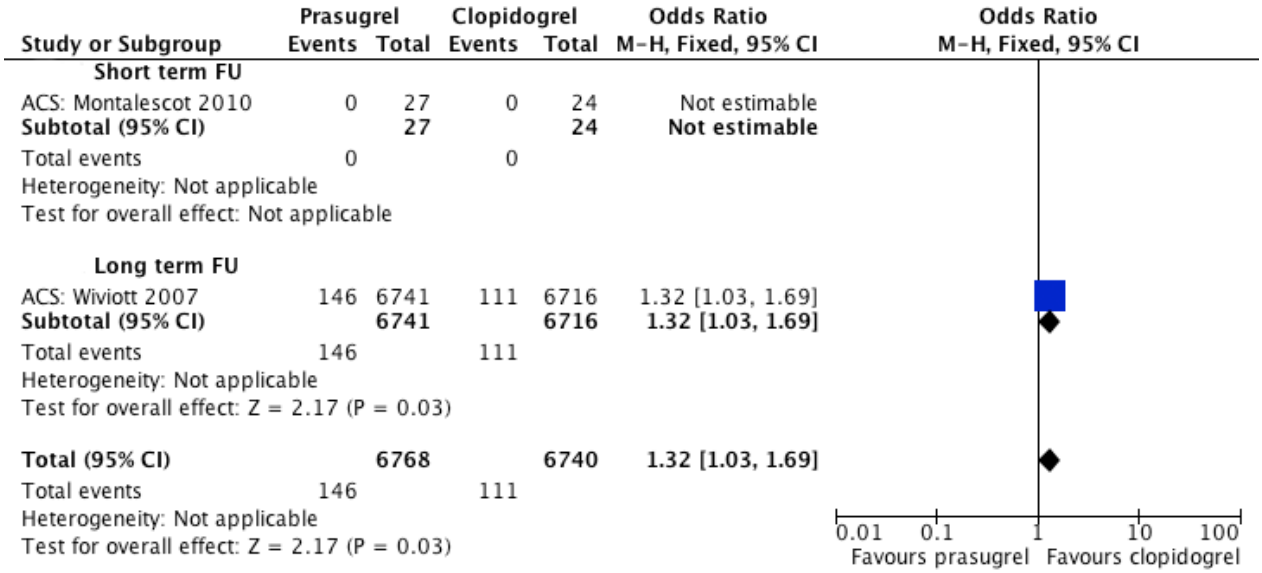


2. Non CABG-related major bleeding

A) Ticagrelor

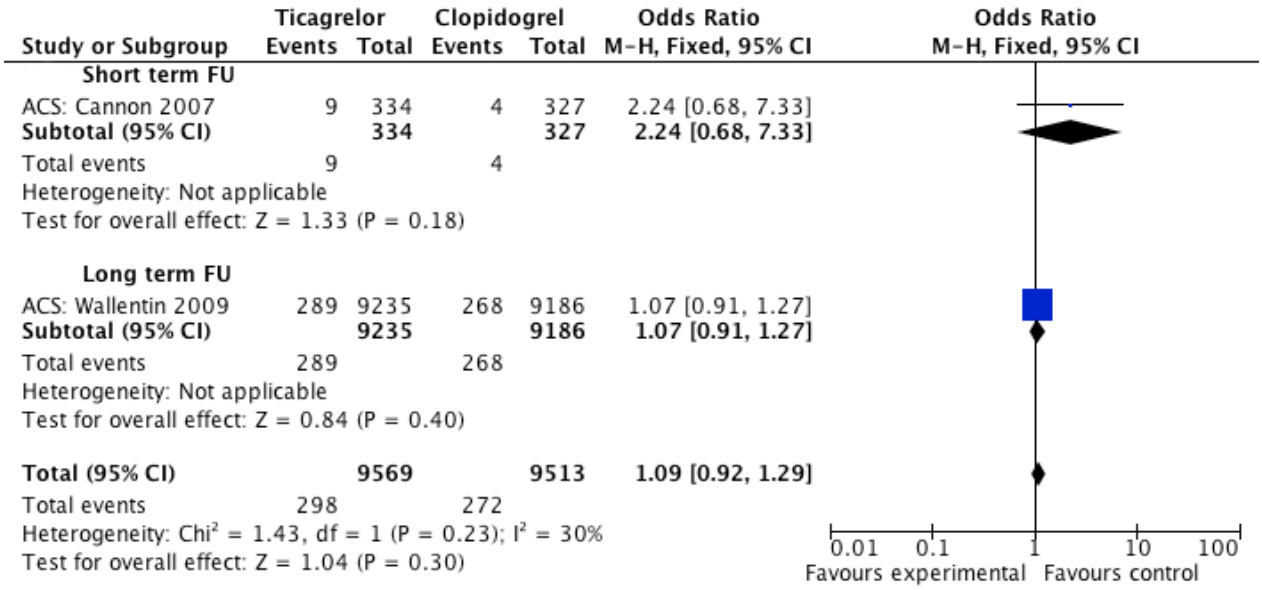


B) Prasugrel

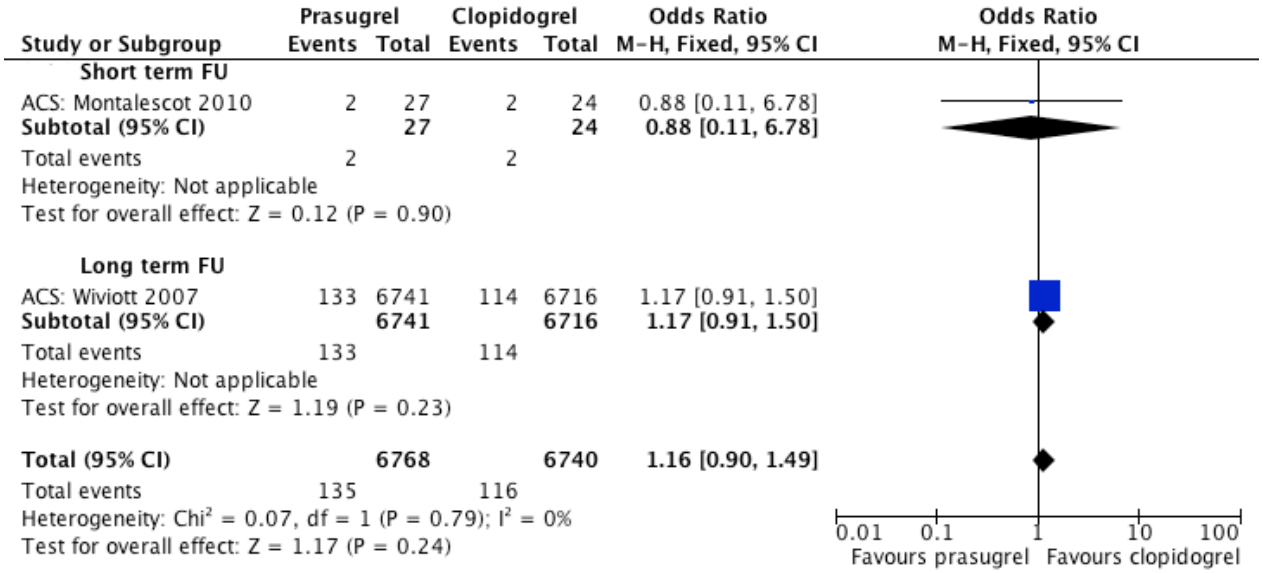


3. Minor bleeding

A) Ticagrelor

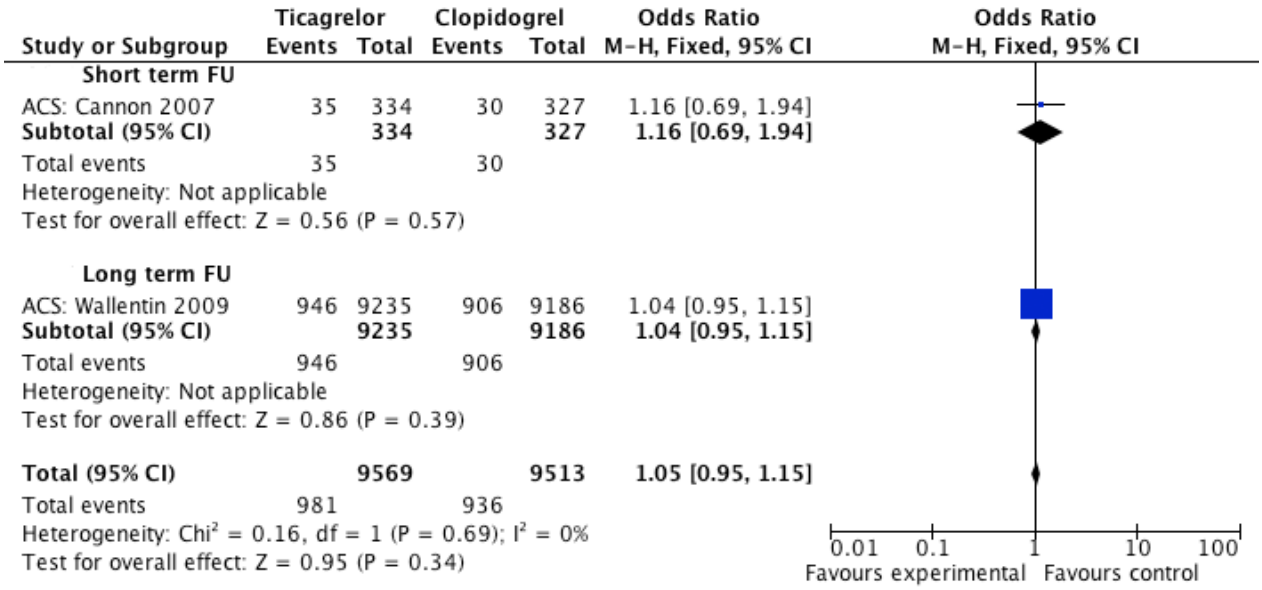


B) Prasugrel

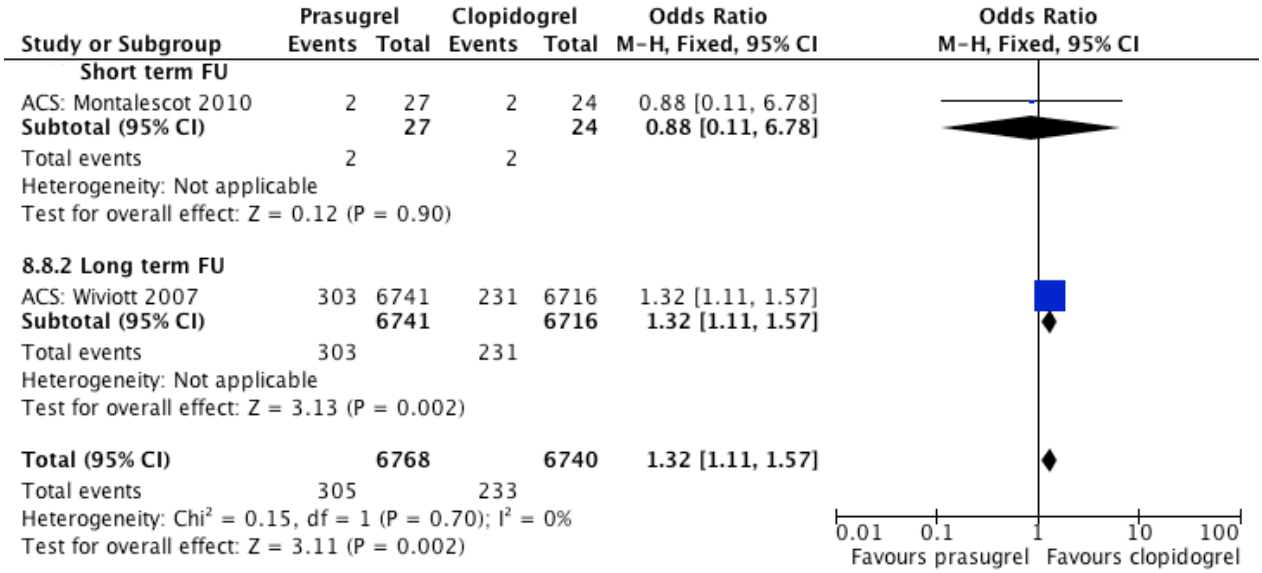


4. Major or minor bleeding

A) Ticagrelor



B) Prasugrel



APPENDIX 13 MTC MODELS IN WINBUGS

Section A: MTC Code implementation

WinBUGS (**B**ayesian inference **U**sing **G**ibbs **S**ampling) is a Windows computer software for the Bayesian analysis of statistical models using Markov Chain Monte Carlo (MCMC) methods. Bayesian inference can be used to fit complex models that include both direct and indirect comparisons. The WinBUGS code (i.e. model) used in this thesis was downloaded from https://www.bris.ac.uk/cobm/research/mpes/mtc.html.

When running a code in WinBUGS several steps have to be executed.
Data entry hast to be performed in a specific way and has two parts. First you tell WinBUGS, how many observations you have by entering the following constants within a bracket after "LIST": N= Number of arms, NS = Number of Studies, NT = Number of Treatments.
The data part comes next. The top line gives the variable names followed by brackets. Each line below the top line is considered as a data line by WinBUGS. "END" is put at the end and indicates the end of data entry to the program. At least one blank line has to be included after that, before other information can follow.

The treatments A, B, C,…become treatments number 1,2,3, … etc in the WinBUGS code. Placebo treatment is used as treatment A and coded with 1. The trials are then set out systematically, and this order is maintained in the WinBUGS data listing:
(a) first, all the trials including treatment A are listed,
(b) for this you should start with the AB trials, then the AC, AD, etc,
(c) next all trials including B but not A are listed,
(d) then those including C, but not A or B, etc … are listed.

The following example shows the data entry for the outcome 'all-cause mortality' for 11 trials and 5 treatments (placebo, clopidogrel, prasugrel, ticagrelor, high dose clopidogrel):
s[] indicates the study, t[] the treatment, r[] the numerator, n[] the denominator, b[] the comparator treatment (baseline) for that trial, $b[i] \leq t[i]$

LIST(N=22, NS=11, NT=5)

s[]	t[]	r[]	n[]	b[]
1	1	390	6303	1
1	2	359	6259	1
2	1	1845	22891	1
2	2	1726	22961	1
3	1	38	1739	1
3	2	45	1752	1
4	1	24	1063	1
4	2	18	1053	1
5	1	374	7801	1
5	2	371	7802	1
6	2	197	6795	1
6	3	188	6813	1
7	2	0	254	1
7	3	0	200	1
8	2	506	9291	1
8	4	399	9333	1
9	2	4	327	1
9	4	7	334	1
10	2	300	12566	1
10	5	287	12520	1
11	3	0	102	1
11	5	0	99	1

END

For running the code the specification tool has to be opened via ‘Model’ from the menu bar. The cursor is then placed within the model, and the model can be checked (using the *check model* button). WinBUGS will write a note ‘the model is syntactically correct’ and you can proceed loading the data. First, the word LIST has to be highlighted and the *load data* button pressed. Then, the first variable (i.e. s as shown above) has to be highlighted and the *load data* button pressed again. The *compile* button prepares the data structures for the sampling procedure. The *gen inits* button generates initial values for the model. The *load inits* button allows you to load pre-specified values for the chains specified in the box next to it. It is possible to run several chains at once and they can be started from various initial values.

In the update tool, which also can be opened via ‘Model’ from the menu bar, you can specify the number of MCMC updates to be carried out, thinning and over-relaxation (further explanations are given below). By pressing the update button the model would be started but first you have to tell WinBUGS, which variables of interest (i.e. results) should be stored. Therefore, the sample monitor tool can be opened via ‘Inference’ from the menu bar. In the field ‘node’ you can type the variables of interest, e.g. OR (for odds ratio), and then press the *set* button to save it. In this sample monitor, you can specify the beginning (*beg*) and end (*end*) of a subset of the stored sample for analysis. After the sampling further buttons become active: *trace* allows you to plot

the variable value against iteration number, *history* plots out the total trace for a variable, *density* plots a smoothed kernel density, *stats* produces a summary statistics (including the mean, sd, MC error, 2.5%, median, 97.5%) for the pre-defined variables of interest, *auto cor* plots the autocorrelation of the each variable, *quantiles* plots out the running mean with running 95% confidence interval against iteration number, *bgr diag* calculates Gelman-Rubin convergence statistics. Most of these results are used for convergence assessment as outlined below.
A variety of additional functions are available and a detailed description can be found in the WinBUGS manual, which can be downloaded via this weblink: http://www.mrc-bsu.cam.ac.uk/bugs/winbugs/manual14.pdf

As mentioned in the main section of the thesis a fixed effects model was implemented for all analyses. The following code was used:

Fixed effects model

```
model{
for(i in 1:N)  {   logit(p[i])<-mu[s[i]]+ d[t[i]] - d[b[i]]        #  model
                   r[i]~dbin(p[i],n[i])  }                         #  binomial likelihood
for(j in 1:NS)  {   mu[j]~dnorm(0,.0001)}                          # vague priors for trial baselines
d[1]<-0
for (k in 2:NT) {d[k] ~ dnorm(0,.0001) }                           # vague priors for basic parameters
mA ~ dnorm(0,1)                                                    # absolute log odds(success) on Treatment A
for (k in 1:NT) { rk[k]<- NT+1 - rank(T[],k)                       # Ranking and prob{treatment k is best}
best[k]<-equals(rk[k],1)}
for (c in 1:(NT-1))                                                # pairwise ORs
        {  for (k in (c+1):NT)
             {  lor[c,k] <- d[k] - d[c]
               log(or[c,k]) <- lor[c,k]  }}}
```

A detailed description and explanation for all available models (i.e. fixed effects models, simple random effects models, random effects models up to 3-arm trials, and multi-arm random effects models) by Ades AE et al. can be found using the following weblink:
www.bris.ac.uk/cobm/docs/intro%20to%20mtc.doc

After running this model, several posterior distributions for various variables of interest can be retrieved (when they have been set up in the sample monitoring tool): *d* gives the mean treatment effect (i.e. d_{AB} = mean treatment effect log odds ratio A versus B), *T* indicates the absolute efficacy T[k] of each treatment k, *p* gives the probability of response in the respective treatment

arms, *best* tells you the probability that each treatment is the best (CAVE: when you are interested in fatalities, this gives you the probability that the treatment is the worst), *lor* and *or* generate all possible log odds ratios and odds ratios.
Throughout this thesis, odds ratios and 95% credible intervals are reported.

In this thesis, a modification of the model had to be performed because the original model failed to run. The vague priors for trial baselines (mu[j]~dnorm(0,.0001)) had to be changed. Thus, the precision was increased (i.e. .01) and a weakly informative version of the prior created.
For each run, a burn-in period of 3,000 iterations and a further 7,000 iterations for estimation with a thinning factor of 80 were performed. This can be achieved by setting appropriate values in the sample monitor tool (*beg* and *end* fields). The burn-in is intended to allow the chain to stabilize and so remove the effects of the initial values. In the fixed effects models, convergence was reached soon, which is reflected in the Brooks Gelman plot below. Thinning means that every kth sampled iterate is kept (specified in the update tool).

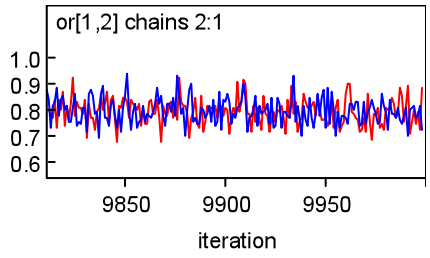
Convergence assessment

Convergence is reached, when inferences do not depend on the initial starting values of the chains but the Gibbs Sampler eventually reaches a stationary distribution. Convergence was assessed by several approaches: For history plots, two chains were simulated starting from different initial values of select unknown parameters. Then the histories of the chains were visualized against the iteration number; overlapping histories, that appear to mix with each other, were considered an indication for convergence. Further, Brooks-Gelman-Rubin plots were generated to control convergence. Therefore, multiple chains (at least 3) from dispersed initial values were run. The Gelman-Rubin convergence statistic R compares the ratio of the pooled chain variance to the within variance. These are two ways to estimate the posterior variance. Once convergence is reached, R=1. Gelman-Rubin statistic is shown in grey, which should converge to 1. In dark grey, the average width of the 80% intervals within each individual chain and the width of the 80% interval of the pooled runs (in light grey). The dark and light grey lines should stabilize to some number (not necessarily 1).
After each run, traceplots were examined for trends and Kernel density plots of the posteriors were checked. Kernel-density plots should be bell-shaped and not lumpy.

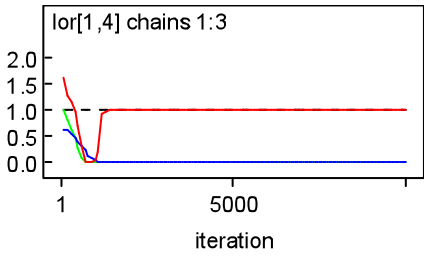
A large autocorrelation is indicated by a slow-mixing chain, which is stuck in one region of the posterior distribution. If large autocorrelation is detected, additional samples can be generated and thinned more.

Figure: Representative plots of convergence assessment

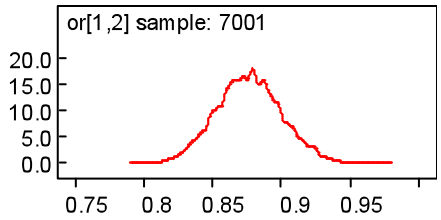
A) History plot



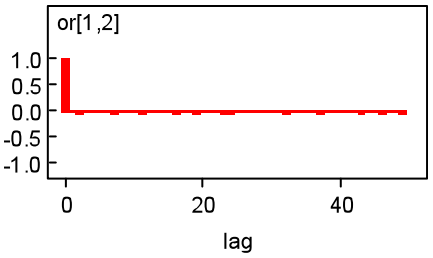
B) Brooks Gelman Rubin plot



C) Kernel density plot



D) Autocorrelation



The accuracy of the posterior estimates was also checked by inspection of the Monte Carlo error for each parameter of interest. The MC error is part of the statistical output (i.e. node statistics), which can be retrieved by pressing the *stats* button in the sample monitor tool after sampling. The MC error estimates to what extent simulation error contributes to the uncertainty in the estimation of the mean. The MC error should be less than about 5% of the sample standard deviation, which is also part of the statistical output.

No modifications were made to the seed, which specifies the random seed number used to initialize the random number generation procedure.

Random effects models

In addition, simple random effects models were run, for which the between-study variance parameter τ has to be estimated. In comparison to fixed effects models, the point estimates of the odds ratios were broadly similar but the credible intervals were extremely large and varied greatly. This has been described before (Lambert PC et al. *Stat Med.* 2005; 24(15):2401), and is frequently observed when only a small number of trials are available. Thus, the prior distributions, which are intended to be vague, may exert an unintentionally large degree of influence on any inferences. A smaller or a different choice of the prior distribution (instead of uniform) on the between study variance parameter τ may lead to marked variations of the results. Example of results, where various, less vague priors for the random effects standard deviations (sd~unif (0,2)) were used, are found in below in section C.

However, additional factors for the width of the credible intervals in random effects models were identified: next to the available evidence for each comparison (i.e. the number of studies comparing specific interventions, such as ticagrelor with clopidogrel), the total number of trials, which were included into the model, were also influential. When clopidogrel versus placebo trials were also included, the credible intervals were smaller for all comparisons, although the available evidence for ticagrelor versus clopidogrel was not increased. These models were prone to large autocorrelation, which was not observed with the smaller number of trials. Thinning (and in some cases over-relaxing) was crucial. An example for the influence of the number of included trials on the credible interval is given below in section B. Notably, for fixed effects models, the results for individual comparisons were not affected by the overall number of trials included into the model (see Appendix 16B, sensitivity analysis).

Due to these limitations and the fact that meta-analysis did not suggest relevant statistical heterogeneity only results from fixed effects models are reported within this thesis.

Section B: Role of the number of included studies on the width of the credible intervals

All examples are shown for outcome `composite endpoint´ in the ACS subpopulation

Only three, large trials are included: One prasugrel (P, coded with 2) versus clopidogrel (C, coded with 1), one ticagrelor (T, coded with 3) versus clopidogrel, one high dose clopidogrel (Hd C, coded with 4) versus clopidogrel trial

Data input:

```
list(N=6, NS=3, NT=4)
s[]  t[]  r[]    n[]   b[]
1       1       781    6795   1
1       2       643    6813   1
2       1       1014   9291   1
2       3       864    9333   1
3       1       557    12566  1
3       4       522    12520  1
END
```

Results:

OR, 95% Credible Interval	
P vs C	0.80 (0.07, 9.72)
T vs C	0.83 (0.07, 10.14)
Hd C vs C	0.93 (0.07, 11.7)
P vs T	1.04 (0.03, 33.83)
P vs Hd C	1.17 (0.03, 41.4)
T vs Hd C	1.13 (0.03, 41.6)

Four trials are included: 3 trials as shown above plus one small ticagrelor versus clopidogrel trial (Cannon07)

Data input:

```
list(N=8, NS=4, NT=4)
s[]  t[]  r[]    n[]   b[]
1       1       781            6795   1
1       2       643            6813   1
2       1       1014           9291   1
2       3       864            9333   1
3       1       20             327    1
3       3       20             334    1
4       1       557            12566  1
4       4       522            12520  1
```

Results:

OR, 95% Credible Interval	
P vs C	0.80 (0.11, 5.63)
T vs C	0.86 (0.23, 3.51)
Hd C vs C	0.94 (0.14, 6.17)
P vs T	1.07 (0.11, 11.85)
P vs Hd C	1.17 (0.08, 18.59)
T vs Hd C	1.10 (0.11, 10.18)

All ACS trials included, i.e. 4 trials as shown above plus 3 clopidogrel versus placebo trials (Note coding changes, placebo=1, clopidogrel=2, prasugrel=3, ticagrelor=4, hd clopidogrel=5)

Data input:

```
list(N=14, NS=7, NT=5)
s[]  t[]  r[]    n[]    b[]
1       1       719    6303   1
1       2       582    6259   1
2       1       2310   22891  1
2       2       2121   22961  1
3       1       190    1739   1
3       2       159    1752   1
4       2       781    6795   1
4       3       643    6813   1
5       2       1014   9291   1
5       4       864    9333   1
6       2       20     327    1
6       4       20     334    1
7       2       557    12566  1
7       5       522    12520  1
END
```

Results:

OR, 95% Credible Interval	
P vs C	0.80 (0.43, 1.64)
T vs C	0.85 (0.51, 1.44)
Hd C vs C	0.94 (0.44, 1.74)
P vs T	1.06 (0.47, 2.40)
P vs Hd C	1.16 (0.40, 2.88)
T vs Hd C	1.10 (0.43, 2.43)
C vs Placebo	0.85 (0.61, 1.10)
P vs Placebo	0.69 (0.33, 1.38)
T vs Placebo	0.72 (0.39, 1.27)
Hd C vs Placebo	0.80 (0.33, 1.54)

Section C: Influence of various priors for SD, when the number of included studies is small

Using the data as shown in the first example of section B, various vague priors were used for the standard deviation of the random effects.

Random effects model default: sd~dunif(0,2)

node	mean	sd	MC error	2.5%	median	97.5%	start	sample
or[1,2]	1.94	10.88	0.1725	0.06765	0.7967	10.45	1000	4001
or[1,3]	1.86	5.545	0.08625	0.07348	0.8339	10.46	1000	4001
or[1,4]	2.049	5.698	0.09306	0.07575	0.938	10.91	1000	4001
or[2,3]	5.995	46.84	0.7135	0.03161	1.041	31.7	1000	4001
or[2,4]	6.579	47.05	0.7373	0.03606	1.156	36.01	1000	4001
or[3,4]	6.579	49.45	0.7234	0.03103	1.129	38.76	1000	4001

sd~dnorm(0,2)

node	mean	sd	MC error	2.5%	median	97.5%	start	sample
or[1,2]	1.178	9.441	0.1503	0.1699	0.7937	3.447	1000	4001
or[1,3]	1.088	1.748	0.02657	0.1894	0.8287	3.669	1000	4001
or[1,4]	1.319	4.926	0.08055	0.2114	0.9422	4.016	1000	4001
or[2,3]	2.155	12.02	0.1903	0.1216	1.038	8.998	1000	4001
or[2,4]	2.503	22.77	0.3503	0.1571	1.171	8.971	1000	4001
or[3,4]	2.545	19.74	0.3228	0.1423	1.129	9.326	1000	4001

sd~dunif(0,1.5)

node	mean	sd	MC error	2.5%	median	97.5%	start	sample
or[1,2]	1.276	2.336	0.03609	0.1325	0.8087	5.517	1000	4001
or[1,3]	1.238	1.792	0.03102	0.1245	0.8343	5.111	1000	4001
or[1,4]	1.446	2.209	0.02892	0.1424	0.9366	6.151	1000	4001
or[2,3]	2.447	8.428	0.1488	0.06287	1.037	13.31	1000	4001
or[2,4]	2.976	15.43	0.2338	0.0789	1.165	16.3	1000	4001
or[3,4]	2.652	8.806	0.1364	0.08527	1.142	15.55	1000	4001

sd~dunif(0,1)

node	mean	sd	MC error	2.5%	median	97.5%	start	sample
or[1,2]	0.9752	0.748	0.0139	0.2297	0.808	2.934	1000	4001
or[1,3]	0.9986	0.7736	0.01185	0.2462	0.8377	2.917	1000	4001
or[1,4]	1.133	1.026	0.01544	0.2669	0.9407	3.453	1000	4001
or[2,3]	1.54	2.393	0.03472	0.1699	1.034	6.386	1000	4001
or[2,4]	1.715	2.761	0.04086	0.1909	1.163	6.607	1000	4001
or[3,4]	1.647	2.373	0.03628	0.1995	1.125	6.727	1000	4001

sd~dunif(0,0.5)

node	mean	sd	MC error	2.5%	median	97.5%	start	sample
or[1,2]	0.8442	0.2784	0.004042	0.4297	0.8051	1.543	1000	4001
or[1,3]	0.8735	0.2784	0.004269	0.4439	0.8329	1.571	1000	4001
or[1,4]	0.9802	0.3006	0.00448	0.5034	0.9402	1.734	1000	4001
or[2,3]	1.13	0.5305	0.007329	0.4246	1.04	2.473	1000	4001
or[2,4]	1.267	0.5705	0.00773	0.4623	1.173	2.79	1000	4001
or[3,4]	1.225	0.5673	0.008998	0.4568	1.124	2.745	1000	4001

sd~dunif(0,0.1)

node	mean	sd	MC error	2.5%	median	97.5%	start	sample
or[1,2]	0.806	0.06587	0.001306	0.6786	0.8027	0.948	11000	3999
or[1,3]	0.8337	0.06276	9.857E-4	0.717	0.832	0.9655	11000	3999
or[1,4]	0.9424	0.08027	0.001778	0.7897	0.9387	1.116	11000	3999
or[2,3]	1.041	0.116	0.001902	0.8245	1.037	1.289	11000	3999
or[2,4]	1.177	0.1376	0.002857	0.9245	1.169	1.473	11000	3999
or[3,4]	1.137	0.1312	0.002629	0.9005	1.129	1.432	11000	3999

sd~dunif(0,0.075)

node	mean	sd	MC error	2.5%	median	97.5%	start	sample
or[1,2]	0.8033	0.05724	9.416E-4	0.6956	0.8006	0.9166	1000	4001
or[1,3]	0.8342	0.05475	9.503E-4	0.73	0.8328	0.9469	1000	4001
or[1,4]	0.9397	0.07153	0.001304	0.8042	0.9378	1.085	1000	4001
or[2,3]	1.044	0.1013	0.001681	0.8567	1.038	1.256	1000	4001
or[2,4]	1.176	0.1236	0.002201	0.9459	1.169	1.436	1000	4001
or[3,4]	1.131	0.115	0.001891	0.9214	1.124	1.368	1000	4001

sd~dunif(0,0.05)

node	mean	sd	MC error	2.5%	median	97.5%	start	sample
or[1,2]	0.8039	0.05142	0.001073	0.7069	0.804	0.9076	1000	4001
or[1,3]	0.8324	0.04746	9.21E-4	0.7422	0.8311	0.9286	1000	4001
or[1,4]	0.9393	0.06533	0.00159	0.8183	0.9382	1.074	1000	4001
or[2,3]	1.04	0.08958	0.002072	0.8728	1.036	1.223	1000	4001
or[2,4]	1.173	0.1102	0.002485	0.9663	1.171	1.4	1000	4001
or[3,4]	1.132	0.1016	0.002452	0.939	1.126	1.341	1000	4001

sd~dunif(0,0.025)

node	mean	sd	MC error	2.5%	median	97.5%	start	sample
or[1,2]	0.8014	0.04787	0.001543	0.713	0.8004	0.8983	1000	4001
or[1,3]	0.8326	0.04232	0.001233	0.754	0.8309	0.9185	1000	4001
or[1,4]	0.9387	0.05942	0.001858	0.827	0.9368	1.058	1000	4001
or[2,3]	1.043	0.08158	0.00235	0.8947	1.041	1.206	1000	4001
or[2,4]	1.176	0.1024	0.003351	0.9882	1.172	1.391	1000	4001
or[3,4]	1.13	0.09272	0.002866	0.9582	1.126	1.318	1000	4001

sd~dunif(0,0.01)

node	mean	sd	MC error	2.5%	median	97.5%	start	sample
or[1,2]	0.8032	0.04353	0.003008	0.7243	0.8002	0.8936	1000	4001
or[1,3]	0.8347	0.04205	0.002551	0.755	0.835	0.9187	1000	4001
or[1,4]	0.9418	0.05937	0.004162	0.828	0.94	1.06	1000	4001
or[2,3]	1.042	0.07595	0.005055	0.8941	1.041	1.202	1000	4001
or[2,4]	1.176	0.09562	0.006351	0.9998	1.176	1.37	1000	4001
or[3,4]	1.131	0.09032	0.005923	0.9655	1.127	1.317	1000	4001

sd~dunif(0,0.005)

update error after several iterations

node	mean	sd	MC error	2.5%	median	97.5%	start	sample
or[1,2]	0.735	0.1308	0.02867	0.3108	0.7726	0.8445	1000	435
or[1,3]	0.803	0.0557	0.01166	0.6269	0.8187	0.8646	1000	435
or[1,4]	0.9094	0.03571	0.006349	0.8405	0.9088	0.987	1000	435
or[2,3]	1.138	0.2712	0.05795	0.9603	1.055	2.017	1000	435
or[2,4]	1.315	0.4704	0.09839	1.045	1.188	2.808	1000	435
or[3,4]	1.138	0.09269	0.01807	1.019	1.125	1.395	1000	435

sd~dunif(0,0.001)

update error after several iterations

node	mean	sd	MC error	2.5%	median	97.5%	start	sample	
or[1,2]	3.052E-24	1.0E-10	3.849E-12	2.44E-24	3.085E-24	3.377E-24	1000	675	
or[1,3]	7.345E-31	1.0E-10	3.849E-12	5.476E-31	7.528E-31	8.223E-31	1000	675	
or[1,4]	1.134E+8	8.179E+6	1.599E+6	1.026E+8	1.118E+8	1.352E+8	1000	675	
or[2,3]	2.402E-7	6.454E-9	1.254E-9	2.214E-7	2.428E-7	2.448E-7	1000	675	
or[2,4]	3.761E+31	6.137E+30	1.198E+30	3.039E+31	3.625E+31	5.519E+31	1000	675	
or[3,4]	1.573E+38	3.098E+37	6.05E+36	1.248E+38	1.486E+38	2.462E+38	1000	675	

APPENDIX 14 NETWORK ANALYSIS WITH PROC GLIMMIX

Section A: PROC GLIMMIX

PROC GLIMMIX is a procedure in SAS for fitting **G**eneralized **L**inear **M**ixed **M**odels, where the data can have any distribution from the exponential family. Examples comprise the normal, beta and gamma distributions as continuous members and the binary, binomial and Poisson distributions as discrete members

Throughout this thesis the following model was used for all reported results:

```
1    PROC GLIMMIX data=antiplatelet;
2    CLASS Study Drug;
3    MODEL eDPT/nDPT = Drug / SOLUTION ODDSRATIO NOINT DDFM=SATTERTH;
4    RANDOM Study;
5    LSMEANS Drug / ILINK PDIFF CL;
6    RUN;
```

In line 1, the PROC GLIMMIX statement invokes the procedure. The *data=* option refers to the SAS-dataset (i.e. antiplatelet).
In line 2, the CLASS statement instructs the procedure to treat the variables *Study* and *Drug* as classification variables. It has to appear before the MODEL statement.
In line 3, the MODEL statement names the dependent variable (*eDPT/nDPT*) and the fixed effects (*Drug*). The events/trials syntax was used to specify the dependent variable. This syntax is specific to models for binomial data and so the GLIMMIX procedure automatically defaults to the binomial distribution. This distribution's default link is the logit link. The statement option for model building NOINT excludes the fixed-effects intercept from the model. SOLUTION and ODDSRATIO are model statement options for the statistical output. SOLUTION displays fixed-effects parameter estimates. ODDSRATIO displays odds ratios and confidence limits. DDFM= is a statement option for statistical computations and specifies the method for computing denominators degrees of freedom. In this case, the DDFM=SATTERTH option performs a general Satterthwaite approximation for the denominator degrees of freedom in the model.
In line 4, the RANDOM statement identifies the random effects, which was the variable *Study*. In general, multiple RANDOM statements would be possible.

In line 5, the LSMEANS statement computes least squares (LS) means of fixed effects (*Drug*). ILINK and CL are statement options of the statistical output. ILINK computes and displays estimates and standard errors of LS means on the inverse linked scale. CL constructs confidence limits for means and mean differences. PDIFF requests differences of LS means.
In line 6, the RUN statement tells SAS to process the preceding program statements.

Initially, a code was implemented including random effects for study and study*treatment. Using this code several problems were encountered. In some situations, GLIMMIX would give very large confidence intervals, while the point estimate often (but not always) would correspond to the results derived from the BUCHER or MTC approach. One example is shown in section B, Table 1 below. Here, the outcome all-cause mortality was examined, and in particular the results for all PCI trials did not fit. Interestingly, this did not depend on the number of trials as a good result was achieved for all ACS trials. In both analyses, 7 trials were included. Upon personal communication (K. Thorlund), the effect of data doubling was examined, which helped to stabilize the results but would generate too small a confidence interval, which might lead to overestimation of effects (see also Table 1, section B).

In a next step, reasons leading to the instability of the model were tried to identify. When very large confidence intervals were present, this was paralleled by a small number of the model's degrees of freedom. Removing or substituting zero event trials did not improve the results. Increasing the size of small trials (or excluding them) did not solve the problem either. Thus, the reason was not an imbalance of the study sizes. Adapting event rates between the trials in order to minimize differences did not change the results.

However, when individual trials were excluded stepwise, one trial could be identified to be problematic. When the trial Clarity-PCI was excluded, results improved substantially (shown below in section C). In total, three trials analyzing clopidogrel versus placebo were included in this analysis. While the number of events in CREDO and Cure-PCI were similar for the intervention and comparator group, in Clarity-PCI 24 events were found in the placebo and only 13 events in the clopidogrel group. When this "imbalance" was reduced by increasing the number of events in the clopidogrel arm, the results improved when 15 events (instead of 13) were included. The corresponding ORs are shown in section C.

When only a small number of trials are available, the model seems to be sensitive to heterogeneity of the results. This was also seen for other outcomes (not shown).

However, this problem could be avoided by changing the method to compute the denominator degrees of freedom for the test of fixed effects resulting from the MODEL and LSMEANS statements. Initially, the DDFM=SATTERTHWAITE option was used, which performs a general Satterthwaite approximation for the denominator degrees of freedom in a generalized linear mixed model. The small sample properties of this approximation have not been extensively investigated and results of the model improved by using DDFM=NONE. This specifies that no denominator degrees of freedom will be applied. PROC GLIMMIX then essentially assumes that infinite degrees of freedom are available in the calculation of p-values. An example is given in section C.

An alternative way to improve the odds ratios, was the exclusion of the second random effect factor "study*drug" from the model. It has been identified that the model cannot sustain the inclusion of the study*drug random effect, where the number of observations is lower than the number of model parameters to be estimated. This model achieved consistently results, which were in line with MTC and the Bucher approach. All analyses were finally performed with this model.

Section B: Effect of data multiplication in PROC GLIMMIX: Indirect comparison of antiplatelet drugs versus placebo using the outcome all-cause mortality as example

			Data Multiplication					
	Single	DF	**Double**	DF	**Triple**	DF	**Quadruple**	DF
All Trials (n=11)								
Clopidogrel vs Placebo	0.94 (0.88, 0.995)	17	0.94 (0.90, 0.98)	39	0.94 (0.91, 0.97)	61	0.94 (0.91, 0.96)	83
Prasugrel vs Placebo	0.88 (0.70, 1.10)	17	0.88 (0.75, 1.02)	39	0.88 (0.77, 0.99)	61	0.88 (0.79, 0.97)	83
Ticagrelor vs Placebo	0.73 (0.63, 0.86)	17	0.73 (0.66, 0.82)	39	0.73 (0.67, 0.80)	61	0.73 (0.68, 0.79)	83
Hd clop. vs Placebo	0.89 (0.74, 1.08)	17	0.89 (0.79, 1.01)	39	0.89 (0.81, 0.99)	61	0.89 (0.82, 0.98)	83
ACS trials (n=7)								
Clopidogrel vs Placebo	0.93 (0.87, 0.998)	9	0.93 (0.89, 0.97)	23	0.93 (0.90, 0.96)	37	0.93 (0.90, 0.96)	51
Prasugrel vs Placebo	0.88 (0.69, 1.12)	9	0.88 (0.75, 1.03)	23	0.88 (0.78, 0.997)	37	0.88 (0.79, 0.98)	51
Ticagrelor vs Placebo	0.73 (0.61, 0.86)	9	0.73 (0.65, 0.81)	23	0.73 (0.67, 0.79)	37	0.73 (0.68, 0.78)	51
Hd clop. vs Placebo	0.89 (0.73, 1.09)	9	0.89 (0.78, 1.01)	23	0.89 (0.80, 0.98)	37	0.89 (0.81, 0.97)	51
Long term ACS n=3)								
Clopidogrel vs Placebo	0.86 (0.27, 2.76)	2	0.92 (0.81, 1.04)	8	0.92 (0.85, 1.01)	14	0.92 (0.85, 0.99)	20
Prasugrel vs Placebo	0.73 (0.14, 3.68)	2	0.86 (0.70, 1.05)	8	0.85 (0.73, 0.998)	14	0.85 (0.75, 0.97)	20
Ticagrelor vs Placebo	0.71 (0.14, 3.48)	2	0.71 (0.60, 0.84)	8	0.71 (0.63, 0.81)	14	0.71 (0.64, 0.79)	20
PCI trials (n=7)								
Clopidogrel vs Placebo	0.80 (0.40, 1.58)	1	0.81 (0.63, 1.03)	23	0.81 (0.67, 0.99)	37	0.81 (0.69, 0.96)	51
Prasugrel vs Placebo	0.74 (0.03, 18.60)	1	0.76 (0.57, 1.02)	23	0.76 (0.61, 0.96)	37	0.76 (0.63, 0.93)	51
Ticagrelor vs Placebo	0.65 (0.03, 15.52)	1	0.65 (0.52, 0.81)	23	0.65 (0.52, 0.81)	37	0.65 (0.54, 0.79)	51
Hd clop. vs Placebo	0.75 (0.03, 19.85)	1	0.76 (0.49, 0.86)	23	0.76 (0.61, 0.96)	37	0.76 (0.63, 0.93)	51
Long term PCI (n=4)								
Clopidogrel vs Placebo	0.99 (0.59, 1.67)	4	1.01 (0.75, 1.34)	12	1.01 (0.81, 1.26)	20	1.01 (0.84, 1.22)	28
Prasugrel vs Placebo	0.94 (0.52, 1.70)	4	0.96 (0.69, 1.32)	12	0.96 (0.74, 1.24)	20	0.96 (0.78, 1.19)	28
Ticagrelor vs Placebo	0.80 (0.45, 1.42)	4	0.81 (0.59, 1.11)	12	0.82 (0.64, 1.04)	20	0.82 (0.66, 1.01)	28

Section C: Sensitivity analysis to improve results for outcome all-cause mortality, PCI trials

- **GLIMMIX Results as shown above (ddfm=satterth)**

Odds Ratio Estimates

DRUG	_DRUG	Estimate	DF	95% Confidence Limits	
clo	xplacebo	0.799	2.433	0.404	1.579
hd_clo	xplacebo	0.754	1	0.029	19.847
prasu	xplacebo	0.743	1	0.030	18.602
tica	xplacebo	0.654	1	0.028	15.520

- **GLIMMIX Results after exclusion of Clarity-PCI trial (ddfm=satterth)**

DRUG	_DRUG	Estimate	DF	95% Confidence Limits	
clo	xplacebo	0.921	7	0.580	1.463
hd_clo	xplacebo	0.868	7	0.512	1.473
prasu	xplacebo	0.870	7	0.516	1.466
tica	xplacebo	0.737	7	0.444	1.221

- **GLIMMIX Results with Clarity-PCI trial but increase of event rate in clopidogrel arm (ddfm=satterth)**

Original data			**events**	**total n**
Clarity-PCI	6	clo	**13**	933
Clarity-PCI	6	plac	24	930

DRUG	_DRUG	Estimate	DF	95% Confidence Limits	
clo	xplacebo	0.799	2.433	0.404	1.579
hd_clo	xplacebo	0.754	1	0.029	19.847
prasu	xplacebo	0.743	1	0.030	18.602
tica	xplacebo	0.654	1	0.028	15.520

14 events in clopidogrel arm

DRUG	_DRUG	Estimate	DF	95% Confidence Limits	
clo	xplacebo	0.817	2.416	0.434	1.540
hd_clo	xplacebo	0.770	1	0.049	12.184
prasu	xplacebo	0.768	1	0.051	11.641
tica	xplacebo	0.659	1	0.047	9.195

15 events in clopidogrel arm - IMPROVEMENT

DRUG	_DRUG	Estimate	DF	95% Confidence Limits	
clo	xplacebo	0.832	9	0.571	1.213
hd_clo	xplacebo	0.784	9	0.501	1.228
prasu	xplacebo	0.785	9	0.505	1.220
tica	xplacebo	0.667	9	0.436	1.019

16 events in clopidogrel arm

DRUG	_DRUG	Estimate	DF	95% Confidence Limits	
clo	xplacebo	0.844	9	0.580	1.229
hd_clo	xplacebo	0.795	9	0.508	1.244
prasu	xplacebo	0.796	9	0.513	1.236
tica	xplacebo	0.677	9	0.443	1.033

- **GLIMMIX Results with Clarity-PCI trial and change of DDFM (ddfm=NONE)**

Odds Ratio Estimates

DRUG	_DRUG	Estimate	DF	95% Confidence Limits	
Clo	Xplacebo	0.799	Infty	0.554	1.153
Hd_clo	Xplacebo	0.754	Infty	0.455	1.248
Prasu	Xplacebo	0.743	Infty	0.452	1.222
Tica	Xplacebo	0.654	Infty	0.401	1.065

APPENDIX 15 CHARACTERISTICS OF CLOPIDOGREL STUDIES

Table A. Characteristics of included studies comparing clopidogrel with placebo

Author Year ACRONYM	Number in treatment C Placebo P group	Study design	Follow-up, maximum (mean or median)	Population: STEMI (%) NSTE-ACS (%) (comprising STEMI+UA) SCAD (%)	Characteristics: - Age (median/mean) - Female (%) - Dyslipidemia (%) - Hypertension (%) - Diabetes - Smoking (%)	%PCI:	Clopidogrel C (mg) Placebo Comments	Aspirin dose (mg)	Included endpoints 1) Efficacy 2) Bleeding
Yusuf **2001** **CURE**	C 6259 P 6303	RCDB	12 months (9 months)	100% NSTE-ACS	- 64 - 38 - nr - 58 - 22 - 61	22%	C 300 LD / 75 MD Placebo	75-325 recommended	1) total & CV mortality, MI, stroke, composite, 2) total major, non-CABG major, minor, major or minor
Substudy **Mehta** **2001** **CURE-PCI**	C 1313 P 1345	RCDB	12 months (8 months)	100% NSTE-ACS	- 61 - 39 - nr - nr - 19 - 30	100%	C 300 LD / 75 MD Placebo Open label C for 4 weeks post PCI	75-325 recommended	1) CV mortality, MI, stroke, composite, 2) total major, minor, major or minor
Steinhubl **2002** **CREDO**	C 1053 P 1063	RCDB	12 months	14% recent MI 53% UA 33% SCAD	- 62 - 29 - 75 - 69 - 26 - 31	86%	C 300 LD / 75 MD Placebo Open label C for 4 weeks post PCI	81-325 recommended	1) total mortality, MI, stroke, target vessel revasc., composite, 2) total major, non-CABG major, minor, major or minor
Sabatine **2005** **CLARITY**	C 1752 P 1739	RCDB	30 days	100% STEMI after fibrinolysis	- 57 - 20 - 33 - 43 - 16 - 50	53%	C 300 LD / 75 MD up to 8 days or discharge Placebo	75-162 recommended	1) Total & CV mortality, MI, stroke, composite, 2) total major, minor, major or minor

Table A continued

Author Year ACRONYM	Number in treatment C Placebo P group	Study design	Follow-up, maximum (mean or median)	Population: STEMI (%) NSTE-ACS (%) (comprising STEMI+UA) SCAD (%)	Characteristics: - Age (median/mean) - Female (%) - Dyslipidemia (%) - Hypertension (%) - Diabetes - Smoking (%)	%PCI:	Clopidogrel C (mg) Placebo Comments	Aspirin dose (mg)	Included endpoints 1) Efficacy 2) Bleeding
Substudy **Sabatine** **2005** **PCI-CLARITY**	C 933 P 930	RCDB	30 days	100% STEMI after fibrinolysis	- 57 - 18 - 41 - 42 - 15 - 51	100%	C 300 LD / 75 MD up to 8 days or discharge Placebo Open label C post PCI	75-162 recommended	1) Total & CV mortality, MI, stroke, composite, 2) total major, minor, major or minor
Chen **2005** **COMMIT**	C 22961 P 22891	RCDB	28 days or discharge	100% STEMI	- 61 - 28 - nr - 43 - nr - nr	0%	C 300 LD / 75 MD Placebo	162	1) Total & CV mortality, MI, stroke, composite, 2) total major, minor, major or minor
Bhatt **2006** **CHARISMA**	C 7802 P 7801	RCDB	- (28 months)	78% documented vascular disease 21% multiple CV risk factors 1% neither	- 64 - 30 - 74 - 74 - 42 - 69	0%	C 75 MD Placebo	75-162 recommended	1) Total & CV mortality, MI, stroke, composite, 2) total major, minor, major or minor

Table B. Characteristics of included studies comparing high dose clopidogrel with standard dose clopidogrel

Author Year ACRONYM	Number in high dose clopidogrel hd C Control C group	Study design	Follow-up, maximum (mean or median)	Population: STEMI (%) NSTE-ACS (%) (comprising STEMI+UA) SCAD (%)	Characteristics: - Age (median/mean) - Female (%) - Dyslipidemia (%) - Hypertension (%) - Diabetes - Smoking (%)	%PCI:	Prasugrel P (mg) Clopidogrel C (mg)	Aspirin dose (mg)	Included endpoints 1) Efficacy 2) Bleeding
Mehta **2010** **OASIS-7**	hd C 12520 C 12566	RCDB	30 days	29% STEMI 71% NSTE-ACS	- 61 - 27 - 41 - 60 - 23 - 33	69%	hd C 600 LD/ 150 MD for 7d C 300 LD/75 MD	Randomization: 75-100 or 300-325 daily	1) total & CV mortality, MI, stroke, stent thrombosis composite, 2) total major, non-CABG major, minor, major or minor
Substudy: **Mehta** **2010** **OASIS-7-PCI**	hd C 8560 C 8703	RCDB	30 days	37% STEMI 63% NSTE-ACS	- 61 - 25 - 40 - 59 - 22 - 37	100%	hd C 600 LD/ 150 MD for 7d C 300 LD/75 MD	Randomization: 75-100 or 300-325 daily	1) total & CV mortality, MI, stroke, stent thrombosis composite, 2) total major, non-CABG major, minor, major or minor

APPENDIX 16 ITC RESULTS OVERVIEW

A) INDIRECT COMPARISON ADP - ANTAGONISTS VERSUS PLACEBO using different approaches

INDIRECT COMPARISON ADP - ANTAGONISTS VERSUS PLACEBO			
1. All cause mortality [1] OR (95% CI)	MTC	GLIMMIX	BUCHER
All trials			
Clopidogrel	0.94 (0.89, 0.99)	0.94 (0.88, 0.995)	
Prasugrel	0.89 (0.72, 1.10)	0.88 (0.70, 1.10)	0.89 (0.72, 1.09)
Ticagrelor	0.73 (0.63, 0.85)	0.73 (0.63, 0.86)	0.73 (0.63, 0.85)
High dose clopidogrel	0.90 (0.75, 1.07)	0.89 (0.74, 1.08)	0.90 (0.76, 1.07)
ACS trials			
Clopidogrel	0.93 (0.87, 0.99)	0.93 (0.87, 0.998)	
Prasugrel	0.89 (0.72, 1.09)	0.88 (0.69, 1.12)	0.89 (0.72, 1.09)
Ticagrelor	0.73 (0.63, 0.85)	0.73 (0.61, 0.86)	0.73 (0.62, 0.85)
High dose clopidogrel	0.89 (0.75, 1.07)	0.89 (0.73, 1.09)	0.90 (0.75, 1.07)
ACS trials with long term follow-up			
Clopidogrel	0.92 (0.80, 1.07)	0.92 (0.66, 1.27)	
Prasugrel	0.88 (0.68, 1.13)	0.86 (0.50, 1.48)	0.88 (0.68, 1.13)
Ticagrelor	0.72 (0.58, 0.87)	0.71 (0.46, 1.11)	0.72 (0.59, 0.88)
PCI trials			
Clopidogrel	0.80 (0.57, 1.11)	0.81 (0.55, 1.18)	
Prasugrel	0.76 (0.51, 1.12)	0.76 (0.49, 1.19)	0.77 (0.52, 1.14)
Ticagrelor	0.64 (0.44, 0.92)	0.65 (0.42, 0.99)	0.65 (0.44, 0.94)
High dose clopidogrel	0.75 (0.50, 1.11)	0.76 (0.49, 1.20)	0.76 (0.51, 1.11)
PCI trials with long term follow-up			
Clopidogrel	0.92 (0.62, 1.35)	0.99 (0.59, 1.67)	
Prasugrel	0.87 (0.56, 1.36)	0.94 (0.52, 1.70)	0.88 (0.57, 1.36)
Ticagrelor	0.73 (0.47, 1.11)	0.80 (0.45, 1.42)	0.74 (0.49, 1.13)

[1] CLARITY reported all cause mortality at a median of 3.5 days from the time of randomization. For CLARITY-PCI, only CV death at 30 days of follow-up was reported and included in this analysis. CURE-PCI reported only CV mortality, which was used instead of all-cause mortality for this analysis.

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2. CV mortality[1] OR (95% CI)	MTC	GLIMMIX	BUCHER
All trials			
Clopidogrel	0.93 (0.87, 0.99)	0.94 (0.88, 1.00)	
Prasugrel	0.82 (0.64, 1.05)	0.81 (0.62, 1.05)	0.83 (0.65, 1.07)
Ticagrelor	0.74 (0.63, 0.86)	0.75 (0.63, 0.88)	0.75 (0.64, 0.87)
High dose clopidogrel	0.88 (0.74, 1.05)	0.89 (0.73, 1.08)	0.90 (0.74, 1.08)
ACS trials			
Clopidogrel	0.93 (0.87, 0.99)	0.93 (0.86, 0.999)	
Prasugrel	0.82 (0.64, 1.04)	0.81 (0.61, 1.07)	0.82 (0.64, 1.06)
Ticagrelor	0.74 (0.63, 0.87)	0.74 (0.62, 0.88)	0.74 (0.63, 0.86)
High dose clopidogrel	0.89 (0.74, 1.07)	0.88 (0.71, 1.08)	0.89 (0.74, 1.07)
ACS trials with long term follow-up			
Clopidogrel	0.92 (0.79, 1.08)	0.92 (0.65, 1.30)	
Prasugrel	0.82 (0.61, 1.08)	0.80 (0.43, 1.48)	0.81 (0.61, 1.09)
Ticagrelor	0.73 (0.59, 0.90)	0.73 (0.46, 1.16)	0.73 (0.59, 0.91)
PCI trials			
Clopidogrel	0.80 (0.57, 1.11)	0.81 (0.55, 1.17)	
Prasugrel	0.70 (0.47, 1.05)	0.70 (0.44, 1.11)	0.71 (0.47, 1.08)
Ticagrelor	0.64 (0.44, 0.94)	0.66 (0.43, 1.01)	0.65 (0.45, 0.96)
High dose clopidogrel	0.76 (0.52, 1.15)	0.77 (0.49, 1.22)	0.77 (0.52, 1.16)
PCI trials with long term follow-up			
Clopidogrel	0.92 (0.63, 1.37)	0.98 (0.58, 1.65)	
Prasugrel	0.81 (0.51, 1.27)	0.86 (0.47, 1.57)	0.81 (0.52, 1.29)
Ticagrelor	0.74 (0.49, 1.15)	0.80 (0.45, 1.43)	0.73 (0.48, 1.10)

[1]The CREDO trial reported only all-cause mortality, which was used instead of CV mortality for this analysis. CLARITY reported CV mortality 30 days of follow-up (while all-cause mortality was reported at a median of 3.5 days).

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3. Myocardial infarction OR (95% CI)	MTC	GLIMMIX	BUCHER
All trials			
Clopidogrel	0.82 (0.76, 0.89)	0.82 (0.75, 0.90)	
Prasugrel	0.61 (0.53, 0.72)	0.62 (0.53, 0.73)	0.61 (0.53, 0.71)
Ticagrelor	0.69 (0.59, 0.80)	0.69 (0.59, 0.81)	0.69 (0.60, 0.79)
High dose clopidogrel	0.70 (0.58, 0.85)	0.69 (0.56, 0.85)	0.70 (0.58, 0.85)
ACS trials			
Clopidogrel	0.81 (0.74, 0.88)	0.81 (0.73, 0.90)	
Prasugrel	0.60 (0.52, 0.70)	0.61 (0.51, 0.73)	0.60 (0.52, 0.71)
Ticagrelor	0.68 (0.58, 0.78)	0.67 (0.56, 0.81)	0.68 (0.59, 0.78)
High dose clopidogrel	0.69 (0.57, 0.84)	0.68 (0.57, 0.81)	0.69 (0.57, 0.84)
ACS trials with long term follow-up			
Clopidogrel	0.77 (0.66, 0.89)	0.77 (0.56, 1.07)	
Prasugrel	0.57 (0.47, 0.69)	0.58 (0.38, 0.89)	0.58 (0.47, 0.70)
Ticagrelor	0.64 (0.53, 0.78)	0.65 (0.43, 0.99)	0.65 (0.53, 0.78)
PCI trials			
Clopidogrel	0.70 (0.58, 0.83)	0.69 (0.57, 0.85)	
Prasugrel	0.52 (0.42, 0.64)	0.52 (0.41, 0.67)	0.52 (0.42, 0.64)
Ticagrelor	0.55 (0.44, 0.70)	0.55 (0.42, 0.71)	0.55 (0.44, 0.69)
High dose clopidogrel	0.54 (0.41, 070)	0.52 (0.38, 0.71)	0.53 (0.41, 070)
PCI trials with long term follow-up			
Clopidogrel	0.72 (0.58, 0.88)	0.72 (0.55, 0.95)	
Prasugrel	0.53 (0.42, 0.67)	0.54 (0.39, 0.75)	0.54 (0.42, 0.68)
Ticagrelor	0.57 (0.44, 0.73)	0.56 (0.40, 0.79)	0.56 (0.44, 0.73)

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4. Stroke OR (95% CI)	MTC	GLIMMIX	BUCHER
All trials			
Clopidogrel	0.82 (0.72, 0.93)	0.81 (0.71, 0.92)	
Prasugrel	0.86 (0.58, 1.25)	0.81 (0.55, 1.19)	0.86 (0.59, 1.26)
Ticagrelor	0.97 (0.73, 1.30)	0.95 (0.70, 1.28)	0.97 (0.73, 1.29)
High dose clopidogrel	0.81 (0.56, 1.16)	0.74 (0.51, 1.09)	0.81 (0.56, 1.17)
ACS trials			
Clopidogrel	0.84 (0.72, 0.98)	0.82 (0.69, 0.98)	
Prasugrel	0.85 (0.57, 1.24)	0.83 (0.54, 1.28)	0.85 (0.57, 1.24)
Ticagrelor	0.99 (0.73, 1.34)	0.97 (0.70, 1.36)	0.99 (0.73, 1.34)
High dose clopidogrel	0.83 (0.57, 1.20)	0.75 (0.50, 1.14)	0.83 (0.57, 1.22)
ACS trials with long term follow-up			
Clopidogrel	0.86 (0.63, 1.17)	0.81 (0.44, 1.05)	
Prasugrel	0.87 (0.54, 1.41)	0.73 (0.31, 1.75)	0.88 (0.54, 1.42)
Ticagrelor	1.01 (0.67, 1.52)	0.99 (0.46, 2.11)	1.03 (0.68, 1.54)
PCI trials[1]			
Clopidogrel	0.52 (0.25, 1.03)	0.56 (0.28, 1.11)	
Prasugrel	0.55 (0.25, 1.17)	0.60 (0.27, 1.31)	0.57 (0.26, 1.22)
Ticagrelor	0.56 (0.26, 1.20)	0.63 (0.29, 1.37)	0.58 (0.28, 1.24)
High dose clopidogrel	0.44 (0.19, 1.02)	0.43 (0.18, 1.02)	0.46 (0.20, 1.06)
PCI trials with long term follow-up[1,2]			
Clopidogrel	0.74 (0.30, 1.70)	0.84 (0.02, 39.31)	
Prasugrel	0.75 (0.28, 1.87)	0.79 (0.01, 44.72)	0.77 (0.30, 1.97)
Ticagrelor	0.80 (0.31, 2.00)	0.99 (0.02, 52.44)	0.82 (0.33, 2.08)

[1] PCI CURE did not report strokes and is not included in this analysis.

[2] Three trials in this analysis, but the PROC GLIMMIX model has only 1 DF and gives large CI.

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5. Composite endpoint[1] OR (95% CI)	MTC	GLIMMIX	BUCHER
All trials			
Clopidogrel	0.88 (0.83, 0.92)	0.88 (0.83, 0.92)	
Prasugrel	0.71 (0.63, 0.80)	0.71 (0.62, 0.80)	0.71 (0.63, 0.80)
Ticagrelor	0.73 (0.66, 0.81)	0.74 (0.66, 0.82)	0.74 (0.67, 0.81)
High dose clopidogrel	0.82 (0.72, 0.94)	0.81 (0.70, 0.93)	0.82 (0.73, 0.94)
ACS trials			
Clopidogrel	0.88 (0.83, 0.92)	0.88 (0.82, 0.93)	
Prasugrel	0.70 (0.62, 0.80)	0.71 (0.61, 0.81)	0.70 (0.62, 0.80)
Ticagrelor	0.73 (0.65, 0.82)	0.73 (0.65, 0.83)	0.74 (0.66, 0.82)
High dose clopidogrel	0.82 (0.72, 0.94)	0.81 (0.70, 0.95)	0.82 (0.72, 0.94)
ACS trials with long term follow-up			
Clopidogrel	0.80 (0.71, 0.89)	0.81 (0.63, 1.04)	
Prasugrel	0.64 (0.54, 0.75)	0.66 (0.47, 0.92)	0.63 (0.54, 0.75)
Ticagrelor	0.66 (0.57, 0.77)	0.68 (0.49, 0.93)	0.66 (0.57, 0.77)
PCI trials			
Clopidogrel	0.66 (0.56, 0.77)	0.66 (0.55, 0.80)	
Prasugrel	0.53 (0.44, 0.64)	0.54 (0.43, 0.67)	0.54 (0.44, 0.65)
Ticagrelor	0.55 (0.45, 0.67)	0.55 (0.44, 0.69)	0.55 (0.45, 0.67)
High dose clopidogrel	0.56 (0.45, 0.70)	0.55 (0.43, 0.71)	0.56 (0.45, 0.70)
PCI trials with long term follow-up			
Clopidogrel	0.69 (0.57, 0.84)	0.73 (0.57, 0.93)	
Prasugrel	0.55 (0.45, 0.69)	0.59 (0.44, 0.79)	0.55 (0.44, 0.69)
Ticagrelor	0.57 (0.46, 0.71)	0.61 (0.45, 0.81)	0.57 (0.46, 0.71)

[1]Composite of CV mortality, non-fatal MI and non-fatal stroke; the CREDO trial reported all-cause mortality.

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6. Stent thrombosis[1] OR (95% CI)	MTC	GLIMMIX	BUCHER
PCI trials			
Clopidogrel	0.90 (0.49, 1.66)	1.07 (0.58, 1.96)	
Prasugrel	0.42 (0.21, 0.81)	0.48 (0.24, 0.96)	0.42 (0.22, 0.82)
Ticagrelor	0.65 (0.34, 1.28)	0.84 (0.43, 1.64)	0.58 (0.30, 1.11)
High dose clopidogrel	0.62 (0.33, 1.20)	0.73 (0.38, 1.40)	0.63 (0.34, 1.20)
PCI trials with long term follow-up			
Clopidogrel	0.91 (0.50, 1.64)	1.05 (0.35, 3.14)	
Prasugrel	0.43 (0.22, 0.82)	0.49 (0.14, 1.67)	0.43 (0.22, 0.84)
Ticagrelor	0.67 (0.34, 1.25)	0.79 (0.24, 2.62)	0.58 (0.30, 1.11)

[1]Definite or probable stent thrombosis. The JUMBO trial reported clinical target vessel thrombosis. CREDO reported urgent target vessel revascularization. PCI-CURE and PCI-CLARITY did not report stent thrombosis and are not included in this analysis. Thus, 5 trials are included with 3 long term trials.

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7. Total major bleeding[1] OR (95% CI)	MTC	GLIMMIX	BUCHER
All trials			
Clopidogrel	1.14 (0.99, 1.30)	1.14 (0.99, 1.32)	
Prasugrel	1.64 (1.25, 2.16)	1.63 (1.22, 2.18)	1.65 (1.26, 2.17)
Ticagrelor	1.10 (0.92, 1.31)	1.11 (0.92, 1.33)	1.16 (0.98, 1.37)
High dose clopidogrel	1.43 (1.12, 1.83)	1.43 (1.10, 1.86)	1.43 (1.13, 1.82)
ACS trials			
Clopidogrel	1.03 (0.86, 1.23)	1.04 (0.84, 1.28)	
Prasugrel	1.50 (1.11, 2.03)	1.51 (1.07, 2.14)	1.51 (1.11, 2.04)
Ticagrelor	0.99 (0.80, 1.23)	1.01 (0.79, 1.29)	1.05 (0.85, 1.31)
High dose clopidogrel	1.30 (0.99, 1.70)	1.31 (0.95, 1.79)	1.30 (0.99, 1.71)
ACS trials with long term follow-up			
Clopidogrel	0.93 (0.68, 1.30)	0.95 (0.46, 1.96)	
Prasugrel	1.37 (0.91, 2.06)	1.38 (0.57, 3.37)	1.36 (0.91, 2.05)
Ticagrelor	0.90 (0.64, 1.28)	0.92 (0.43, 1.97)	0.96 (0.68, 1.36)
PCI trials			
Clopidogrel	1.19 (0.94, 1.51)	1.19 (0.90, 1.56)	
Prasugrel	1.72 (1.23, 2.40)	1.70 (1.16, 2.51)	1.73(1.24, 2.40)
Ticagrelor	1.18 (0.90, 1.55)	1.18 (0.86, 1.62)	1.18 (0.90, 1.54)
High dose clopidogrel	1.64 (1.09, 2.43)	1.61 (1.00, 2.58)	1.64 (1.10, 2.46)
PCI trials with long term follow-up			
Clopidogrel	1.25 (0.99, 1.61)	1.25 (0.88, 1.77)	
Prasugrel	1.82 (1.30, 2.59)	1.79 (1.11, 2.90)	1.83 (1.30, 2.56)
Ticagrelor	1.25 (0.95, 1.65)	1.24 (0.84, 1.84)	1.24 (0.94, 1.63)

[1]Major bleeding was defined according to TIMI criteria, which was available for TRITON, PLATO, OASIS-7, CURE, and CLARITY (and their invasive substudies). CREDO used slightly modifies TIMI criteria. Severe bleeding according to the GUSTO (**G**lobal **U**tilization of **S**treptokinase and **T**issue Plasminogen Activator for **O**ccluded Arteries) definition was described in CHARISMA and used in this analysis. The other studies used study specific criteria for major bleeding.

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8. Non CABG major bleeding OR (95% CI)	MTC	GLIMMIX	BUCHER
All trials			
Clopidogrel	1.57 (1.25, 2.01)	1.53 (1.13, 2.08)	
Prasugrel	2.01 (1.48, 2.93)	2.00 (1.29, 3.11)	2.10 (1.49, 2.95)
Ticagrelor	1.96 (1.44, 2.70)	1.92 (1.28, 2.86)	1.98 (1.46, 2.70)
High dose clopidogrel	2.14 (1.54, 2.97)	2.02 (1.33, 3.05)	2.16 (1.56, 2.98)
ACS trials			
Clopidogrel	1.52 (1.18, 1.97)	1.49 (0.99, 2.25)	
Prasugrel	2.00 (1.40, 2.86)	1.96 (1.11, 3.46)	2.00 (1.40, 2.85)
Ticagrelor	1.89 (1.37, 2.65)	1.87 (1.11, 3.46)	1.89 (1.38, 2.61)
High dose clopidogrel	2.07 (1.47, 2.92)	1.97 (1.15, 3.37)	2.06 (1.48, 2.88)
ACS trials with long term follow-up			
Clopidogrel	1.52 (1.18, 1.97)	1.46 (0.85, 2.54)	
Prasugrel	2.00 (1.41, 2.87)	1.85 (0.88, 3.86)	2.00 (1.40, 2.85)
Ticagrelor	1.90 (1.37, 2.63)	1.82 (0.92, 3.60)	1.89 (1.38, 2.61)
PCI trials			
Clopidogrel	1.90 (1.04, 3.64)	1.81 (0.67, 4.87)	
Prasugrel	2.50 (1.31, 4.97)	2.38 (0.82, 6.93)	2.54 (1.31, 4.92)
Ticagrelor	2.32 (1.22, 4.61)	2.23 (0.77, 6.41)	2.35 (1.21, 4.53)
High dose clopidogrel	2.65 (1.39, 5.37)	2.46 (0.84, 7.22)	2.73 (1.40, 5.32)
PCI trials with long term follow-up			
Clopidogrel	1.91 (1.05, 3.52)	1.65 (0.46, 5.96)	
Prasugrel	2.50 (1.31, 4.88)	2.10 (0.53, 8.26)	2.54 (1.31, 4.92)
Ticagrelor	2.35 (1.22, 4.54)	2.01 (0.51, 7.84)	2.35 (1.21, 4.53)

[1]Non CABG related major bleeding was separately reported in TRITON, PLATO, OASIS-7, CREDO and CURE (and their invasive substudies except CURE PCI, which did not report this outcome).

Non CABG related major bleeding according to TIMI criteria was available for TRITON and PLATO. CREDO used slightly modified TIMI criteria. OASIS-7 and CURE used study specific criteria for major bleeding.

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9. Total minor bleeding[1] OR (95% CI)	MTC	GLIMMIX	BUCHER
All trials			
Clopidogrel	1.35 (1.24, 1.46)	1.34 (1.23, 1.47)	
Prasugrel	1.62 (1.25, 2.11)	1.56 (1.18, 2.06)	1.59 (1.22, 2.09)
Ticagrelor	1.47 (1.23, 1.77)	1.47 (1.20, 1.79)	1.47 (1.22, 1.78)
High dose clopidogrel	1.59 (1.38, 1.84)	1.59 (1.36, 1.85)	1.61 (1.39, 1.86)
ACS trials			
Clopidogrel	1.34 (1.22, 1.46)	1.34 (1.21, 1.48)	
Prasugrel	1.56 (1.19, 2.04)	1.53 (1.13, 2.07)	1.56 (1.20, 2.03)
Ticagrelor	1.46 (1.21, 1.77)	1.46 (1.17, 1.81)	1.45 (1.20, 1.76)
High dose clopidogrel	1.59 (1.37, 1.84)	1.59 (1.34, 1.89)	1.59 (1.38, 1.83)
ACS trials with long term follow-up			
Clopidogrel	2.18 (1.80, 2.67)	2.17 (1.41, 3.33)	
Prasugrel	2.53 (1.86, 3.51)	2.49 (1.24, 4.99)	2.54 (1.85, 3.49)
Ticagrelor	2.34 (1.82, 3.04)	2.33 (1.32, 4.10)	2.33 (1.79, 3.02)
PCI trials			
Clopidogrel	1.23 (0.97, 1.63)	1.25 (0.92, 1.69)	
Prasugrel	1.49 (1.04, 2.16)	1.45 (0.96, 2.20)	1.51 (1.05, 2.16)
Ticagrelor	1.24 (0.88, 1.71)	1.23 (0.85, 1.79)	1.25 (0.91, 1.73)
High dose clopidogrel	1.52 (1.13, 2.05)	1.52 (1.08, 2.14)	1.53 (1.13, 2.07)
PCI trials with long term follow-up			
Clopidogrel	1.21 (0.92, 1.61)	1.19 (0.80, 1.76)	
Prasugrel	1.41 (0.96, 2.07)	1.35 (0.80, 2.29)	1.43 (0.98, 2.07)
Ticagrelor	1.20 (0.85, 1.69)	1.17 (0.73, 1.88)	1.21 (0.87, 1.68)

[1] Minor bleeding defined according to TIMI criteria was available for TRITON, PLATO, and CLARITY (and their invasive substudies). CREDO used slightly modified TIMI criteria. Moderate bleeding according to the GUSTO (**G**lobal **U**tilization of **S**treptokinase and **T**issue Plasminogen Activator for **O**ccluded Arteries) definition was described in CHARISMA and used in this analysis. The other studies used study specific criteria for minor bleeding.

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10. Major or minor bleeding[1] OR (95% CI)	MTC	GLIMMIX	BUCHER
All trials			
Clopidogrel	1.29 (1.21, 1.39)	1.29 (1.20, 1.40)	
Prasugrel	1.73 (1.43, 2.08)	1.70 (1.39, 2.07)	1.73 (1.44, 2.07)
Ticagrelor	1.35 (1.20, 1.52)	1.36 (1.20, 1.54)	1.36 (1.21, 1.53)
High dose clopidogrel	1.56 (1.38, 1.77)	1.56 (1.36, 1.78)	1.57 (1.38, 1.78)
ACS trials			
Clopidogrel	1.28 (1.18,1.38)	1.28 (1.17, 1.40)	
Prasugrel	1.69 (1.39, 2.05)	1.67 (1.34, 2.09)	1.69 (1.39, 2.05)
Ticagrelor	1.34 (1.18, 1.51)	1.35 (1.17, 1.56)	1.35 (1.19, 1.53)
High dose clopidogrel	1.55 (1.36, 1.76)	1.55 (1.33, 1.80)	1.55 (1.36, 1.77)
ACS trials with long term follow-up			
Clopidogrel	1.79 (1.51, 2.12)	1.79 (1.24, 2.58)	
Prasugrel	2.37 (1.85, 3.01)	2.34 (1.38, 3.96)	2.36 (1.50, 3.70)
Ticagrelor	1.86 (1.53, 2.26)	1.87 (1.22, 2.85)	1.86 (1.21, 2.85)
PCI trials			
Clopidogrel	1.24 (1.03, 1.48)	1.23 (0.999, 1.52)	
Prasugrel	1.64 (1.27, 2.11)	1.62 (1.21, 2.17)	1.64 (1.28, 2.11)
Ticagrelor	1.22 (0.98, 1.51)	1.22 (0.95, 1.56)	1.21 (0.98, 1.50)
High dose clopidogrel	1.54 (1.22, 1.92)	1.53 (1.18, 1.98)	1.53 (1.23, 1.91)
PCI trials with long term follow-up			
Clopidogrel	1.25 (1.04, 1.51)	1.25 (0.95, 1.63)	
Prasugrel	1.66 (1.28, 2.13)	1.63 (1.13, 2.35)	1.65 (1.28, 2.12)
Ticagrelor	1.23 (0.995, 1.53)	1.23 (0.89, 1.68)	1.23 (0.99, 1.52)

[1]Major or minor bleeding defined according to TIMI criteria was available for TRITON, PLATO, and CLARITY (and their invasive substudies). CREDO used slightly modified TIMI criteria. Severe and moderate bleeding according to the GUSTO (**G**lobal **U**tilization of **S**treptokinase and **T**issue Plasminogen Activator for **O**ccluded Arteries) definition was described in CHARISMA and used in this analysis. The other studies used study specific

B) Sensitivity analysis: Excluding clopidogrel vs placebo and high dose clopidogrel trials vs clopidogrel trials for MTC and GLIMMIX (i.e. only ticagrelor and prasugrel trial included). Results for trials in patients with acute coronary syndrome

INDIRECT COMPARISON TICAGRELOR VERSUS PRASUGREL in ACS				
Outcome OR (95% CI)	MTC* including	GLIMMIX* including	MTC# excluding	GLIMMIX# excluding
All cause mortality	0.82 (0.64, 1.05)	0.83 (0.63, 1.09)	0.82 (0.65, 1.05)	0.83 (0.56, 1.22)
CV mortality	0.90 (0.69, 1.19)	0.91 (0.66, 1.25)	0.90 (0.68, 1.19)	0.91 (0.58, 1.41)
MI	1.12 (0.94, 1.33)	1.12 (0.92,1.37)	1.12 (0.94, 1.34)	1.11 (0.84, 1.47)
Stroke	1.16 (0.75, 1.81)	1.17 (0.72, 1.92)	1.17 (0.76, 1.80)	1.19 (0.61, 2.34)
Composite endpoint	1.04 (0.90, 1.21)	1.04 (0.88,1.23)	1.04 (0.91, 1.21)	1.04 (0.82, 1.31)
Stent thrombosis	1.60 (1.11, 2.35)	1.80 (1.15, 2.81)	1.61 (1.10, 2.33)	1.66 (0.16, 17.28)
Total major bleeding	0.67 (0.51, 0.86)	0.67 (0.49, 0.90)	0.66 (0.51, 0.86)	0.67 (0.44, 1.02)
Non CABG related major bleeding	0.94 (0.69, 1.32)	0.96 (0.58, 1.59)	0.95 (0.69, 1.31)	1.04 (0.20, 5.57)
Minor bleeding	0.94 (0.69, 1.26)	0.95 (0.67, 1.34)	0.94 (0.69, 1.27)	0.97 (0.60, 1.56)
Major or minor bleeding	0.79 (0.65, 0.97)	0.81 (0.64, 1.01)	0.79 (0.65, 0.97)	0.80 (0.58, 1.10)

*clopidogrel vs placebo and high dose clopidogrel trials vs clopidogrel included; 7 trials

clopidogrel vs placebo and high dose clopidogrel trials vs clopidogrel excluded; 3 trials