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Antithrombotic Therapy in Patients Undergoing Coronary Artery Bypass Grafting: A Systematic Review and Network Meta-Analysis

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A thesis submitted in partial fulfillment of the requirements for the Master of Science degree in Epidemiology and Biostatistics

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Abstract

Comprehensive evidence on the comparative effects of various oral antithrombotic agents on the prevention of saphenous vein graft failure (SVGF) for patients undergoing coronary artery bypass is lacking. A systematic review and frequentist random-effects network meta-analysis of 18 RCTs (n=3,413 patients) comparing the effect of antithrombotic agents on SVGF and clinical outcomes was performed. Based on moderate quality evidence, among the six eligible interventions, dual-antiplatelet therapy with aspirin and clopidogrel was superior to aspirin monotherapy in reducing SVGF (OR: 0.63; 95% CI: 0.41-0.97). No statistical differences were found for major bleeding, mortality, and myocardial infarction between antithrombotic agents, owing to low number of events for most comparisons. Though significant heterogeneity or incoherence was not found, the quality of network evidence for these outcomes ranged from very low to moderate. Adequately-powered multi-arm RCTs are needed to ascertain the effects of antithrombotic therapies to help clinicians and patients achieve optimal treatment decisions.

Keywords

Coronary artery bypass, saphenous vein graft failure, antithrombotic therapy, network meta-analysis.

Co-Authorship Statement

Even though all chapters presented herein were written solely by Karla Solo, the author, the important contributions by the following individuals made the completion of this thesis possible. In addition to the author, Drs. Rodrigo Bagur (RB), Janet Martin (JM), and Ava John-Baptiste (AJB) were involved in the concept and design of the study. They also critically reviewed and provided feedback/suggestions on all chapters improving the overall quality of the thesis. Dr. Tawfiq Choudhury (TC) and Dr. AshlayAnne Huitema (AH), cardiology fellows at University Hospital, were the secondary reviewers who helped the author with study screening, risk of bias assessment, and data extraction. Lastly, the author performed the statistical analysis and assessed the quality of evidence.

Peer-review publications and presentations based on this thesis will be submitted incorporating feedback from the committee: Drs. Rodrigo Bagur, Janet Martin, and Ava John-Baptiste.

Dedication

This work is dedicated to God,
The cornerstone that directs my path (Psalm 119:105)

to my parents,
Your discipline contents me in any and every situation (Philippians 4:12)

to my siblings and niece,
The visible reminders to serve one another (1 Peter 4:10)

They have given me the love, faith, and support throughout my life.

Acknowledgments

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List of Abbreviations

ACC/AHA	American College of Cardiology/American Heart Association
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CCAB	On-pump Coronary Artery Bypass Graft
CI	Confidence Interval
CPB	Cardiopulmonary Bypass
CVA	Cerebrovascular Accident
CVD	Cardiovascular Disease
DOAC	Direct Oral Anticoagulant Agent
ESS	Effective Sample Size
GRADE	Grades of Recommendation, Assessment, Development, and Evaluation
ICC	Intracluster Correlation
IF	Inconsistency Factor
INR	International Normalized Ratio
IQR	Interquartile Range
ITT	Intention-to-Treat
LAD	Left Anterior Descending
LDL	Low Density Lipoprotein
LIMA	Left Internal Mammary Artery
LVEF	Left Ventricular Ejection Fraction
MACCE	Major Adverse Cardiac and Cerebrovascular Event
MI	Myocardial Infarction
NMA	Network Meta-Analysis
OIS	Optimal Information Size
OPCAB	Off-Pump Coronary Artery Bypass Graft
OR	Odds Ratio
PCI	Percutaneous Coronary Intervention
PICOS	Population, Intervention, Comparator, Outcome, and Study Design
PRISMA	Preferred Reporting Items for Systematic Review and Meta-Analysis
RBC	Red Blood Cells
RCT	Randomized Controlled Trial
RD	Risk Difference
RoB	Risk of Bias
RR	Risk Ratio
SE	Standard Error
SUCRA	Surface Under the Cumulative Ranking
SVG	Saphenous Vein Graft
SVGF	Saphenous Vein Graft Failure
TIA	Transient Ischemic Attack
TIMI	Thrombolysis in Myocardial Infarction
US	United States
Vit K A	Vitamin-K Antagonists

Preface

Among antithrombotic agents, aspirin monotherapy has been recommended as the mainstay of prevention of saphenous vein graft failure (SVGF) in patients undergoing coronary artery bypass graft (CABG) surgery, as supported in many clinical practice guidelines.¹⁻⁷ The scientific basis for this recommendation was evidence gathered from individual studies (randomized controlled trials (RCTs) and observational studies) and pairwise meta-analyses. However, there remain gaps in the evidence base for the guideline recommendation for prevention of SVGF after CABG. Although the conventional pairwise meta-analysis of well-designed RCTs (a quantitative method of synthesizing results from independent but similar RCTs to provide greater statistical power) is widely considered to be the highest level of evidence, this approach does not allow for a coherent assessment of more than two treatment strategies. This is problematic as clinicians and patients are challenged to choose from multiple antithrombotic drugs. Clinical-decision making is even more challenging because some of the medications have not been compared directly in RCTs. To date, no studies have been published that assess the comparative efficacy of all relevant antithrombotic agents on SVGF prevention among CABG patients in a unified analysis. Therefore, we designed a systematic review and network meta-analysis (NMA) in order to include all sources of evidence derived from RCTs comparing antithrombotic drugs in a single analysis to better inform clinical decision-making and guide further research in this area.

The following outline provides the overall framework for this thesis. The first chapter describes the clinical background regarding the current information related to CABG and oral antithrombotic agents as well as the rationale behind the present thesis work and discusses thesis objectives. Chapter 2 provides information on the methodological background to familiarize readers with the concepts and terminology of pairwise meta-analysis and NMA. Chapter 3 outlines the methods and statistical analyses used to answer our objectives. The results of the systematic review, quality assessment, and NMA are provided in Chapter 4. Finally, Chapter 5 discusses the interpretations of our findings, strengths and limitations, directions for future research, and overall conclusions.

Chapter 1

1 Literature Review

This chapter provides background clinical information relevant to the thesis. We provide a brief description of cardiovascular disease and the importance of coronary artery bypass surgery, including its inherent limitations as a treatment modality. We then summarize current knowledge about pharmacotherapies used to prevent saphenous vein graft failure, highlight notable gaps in the literature, and outline how the present study can expand the existing scientific knowledge.

1.1 Cardiovascular Disease Burden

Cardiovascular disease (CVD) is an umbrella term for all acute and chronic diseases that affect circulatory system in the heart, brain, and other parts of the body. CVD can be broadly divided into two types: atherosclerotic CVDs and other CVDs. Atherosclerosis is an inflammatory disease in which fatty material and cholesterol are accumulated in the walls of blood vessels. Atherosclerotic CVDs include coronary artery disease or CAD, which occurs when atherosclerotic plaque narrows the coronary arteries; cerebrovascular disease, which occurs when the plaque is in the blood vessels feeding the brain; and peripheral vascular disease, which occurs when the plaque reduces blood flow to the peripheral arteries. Other CVDs include congenital heart disease, rheumatic heart disease, deep vein thrombosis, and pulmonary embolism.

In 2015, CVD, the leading cause of global mortality, claimed the lives of more than 17 million (31%) individuals; of which, 80% of deaths occurred in developing countries.⁸ Although the mortality burden of CVD was mostly concentrated in developing countries, the overall burden remains high in developed countries including United States (US) and Canada. In US, nearly 37% of adults have a CVD and one of every three deaths occurs due to CVD,⁹ which is similar to the CVD-specific mortality rate in Canada.¹⁰ Despite

improved management and medical care, the number of deaths is expected to rise to more than 23.6 million by 2030 worldwide.¹¹

Not only does CVD take a toll on the health of individuals, it poses a substantial economic burden. It was estimated that the 2010 global total cost attributed to CVD was approximately US\$ 863 billion. The global economic burden of CVD will continue to increase owing to population aging and clustering of cardiovascular risk factors.^{12 13} Consequently, an increase in the global cost is expected with an annual total cost of US\$ 1,044 billion estimated by 2030 and a cumulative total cost of US\$ 20,032 billion between 2010 and 2030.¹⁴ In the US, the annual direct and indirect costs of CVD were estimated to be \$ 316 billion in 2012 and the annual total direct medical costs are projected to double by 2030.⁹ A similar trend is also forecasted to occur in developing countries such as China in which an increase from US\$ 721.58 million in 2012 to US\$ 1.71 billion in 2030 is expected.¹⁵ To address these global health challenges, there is a global initiative by World Health Organization to reduce premature deaths by 25% by 2025 via preventive measures, which may translate to a 34% reduction in premature deaths attributable to CVD, and ultimately, a decrease in overall global health and health care expenditures.^{16 17} The importance of reaching this goal highlights the need to improve medical prevention strategies, in addition to primary prevention strategies.

1.2 Coronary Artery Disease

Among atherosclerotic CVDs, CAD (also known as ischemic heart disease) is the most prevalent type of CVDs. CAD occurs when the coronary arteries, which supply blood to heart tissues, become narrowed and stiff due to the accumulation of atherosclerotic plaque. Left to its natural history of ischemic heart disease, these cholesterol-rich plaques can lead to myocardial infarction (MI), blockages of the artery that lead to the death of heart tissue, angina (chest pain), and ultimately death. Globally, CAD is the leading cause of CVD-specific mortality.¹¹ In the US, CAD accounts for 45% of all CVD deaths.⁹

Treatment strategies for CAD depend on various factors including anatomical factors (e.g., the severity of CAD), clinical factors (e.g., presence of comorbidities such as

diabetes), technical factors (e.g., whether revascularization is complete or incomplete), and patient-specific factors (e.g., patient values and preferences).¹⁸ As the first line therapy, medical management is used to control symptoms of disease in patients with stable CAD. Stable CAD is generally characterized by episodes of chest pain that are reversible but persist over time.¹⁹ The required pharmacological therapy, among others, includes antiplatelet therapy and statins, which should be given to all CAD patients. In patients with comorbidities such as chronic kidney disease, hypertension, diabetes, or impaired left ventricular ejection fraction (LVEF), an angiotensin-converting-enzyme inhibitor is also recommended to improve prognosis.²⁰ However, if symptoms persist despite medical therapy, coronary artery revascularization is required to treat the disease.^{18 21} Coronary artery revascularization can be achieved via percutaneous coronary intervention (PCI), or coronary artery bypass graft (CABG). PCI is a non-surgical procedure where a stent is placed in the narrowed vessel via a catheter, whereas CABG is open heart surgery that places bypass grafts by anastomosis (i.e., joining two blood vessels) to the heart around the diseased native arteries. Due to advanced technology in PCI and CABG, determining the optimal revascularization strategy is not always straightforward. In general, revascularization by PCI is recommended for the following types of patients: those with single-vessel CAD, multivessel CAD without proximal left anterior descending (LAD) involvement that is amenable to PCI and those deemed to have prohibitively high surgical risk.²¹ On the other hand, CABG is indicated for patients with lesions that are not amenable to PCI and who have coronary anatomies suitable for surgery. More specifically, suitable candidates for CABG are defined as patients with left main disease with >50% diameter stenosis, three-vessel disease with left ventricular dysfunction, or two-vessel disease with proximal LAD artery disease.^{21 22}

1.3 Coronary Artery Bypass Graft (CABG)

CABG was first introduced in the 1950s. Now, CABG is one of the most frequent surgical operations performed in the world. In the US in 2012, more than 200,000 patients underwent CABG with a rate of 64.6 per 100,000 population, which is similar to that of the same year in Canada (69 per 100,000).^{23 24}

CABG is used to restore blood flow to the heart with the goal of relieving angina symptoms and improving survival rates. Recent meta-analyses have observed that 84% of CABG patients remain angina-free within the first five postoperative years and that there is a 2.7% absolute risk reduction in mortality with CABG compared to PCI in patients with multivessel disease.^{25 26} The long-term success of CABG, however, depends on the patency of the grafts, of which there are two main types: arterial and venous conduits. The arterial grafts include (left or right) internal mammary artery, radial artery, and rarely gastro-epiploic artery. Among arterial grafts, left internal mammary artery (LIMA) to LAD coronary artery anastomosis has been recognized as a method of choice followed by right internal mammary artery and radial artery.^{4 21 27 28} Furthermore, compared to venous grafts, arterial grafts are the preferred conduit given their excellent long-term patency rates. However, total arterial revascularization is underused where <10% of CABG patients receive total arterial grafts.²⁹ In practice, arterial grafts are mostly used in combination with saphenous vein grafts (SVGs).

1.3.1 Importance of assessing saphenous vein graft failure

SVGs remain the most commonly used grafts during CABG because of the benefits afforded by the sufficient length to accommodate many anastomoses and ease of harvest. Unfortunately, the concern regarding thrombus formation and progression of atherosclerosis is predominantly related to SVGs. Compared to arterial grafts, SVGs are more vulnerable to thrombotic/atherosclerotic occlusion due to their wall structure, biochemical composition, and responses to high pressure in an arterial environment.³⁰ Up to 25% of SVGs occlude at one year, 15% to 35% at five years, and 29% to 68% at ≥ 10 years, while most (up to 95%) of LIMA grafts remain patent even after 10 years post-CABG.²¹

Though consistent evidence is limited, some argue that the occurrence of adverse cardiovascular events post CABG may be explained by the presence of SVG failure (SVGF, defined as occlusion that blocks blood supply to the heart through the SVG). The mechanism of SVGF starts with the formation of thrombus that involves the localization of platelet adhesion and the activation of coagulation cascade system on the vein luminal

surface.³¹⁻³⁶ This formation is the major pathological process of SVGF within the first month of CABG. Between one to 12 postoperative months, intimal hyperplasia is the main reason for SVGF, which occurs when smooth muscle cells migrating from the media to the intima of veins continue to proliferate and undergo apoptosis.³⁴⁻³⁶ Beyond 12 months, atherosclerosis takes over the process of SVGF. Compared to that in native diseased arteries, atherosclerosis in SVGs is more likely to rupture and dislodge which may result in life-threatening blockages of blood vessels potentially leading to MI, angina, or even death.³⁴ A subgroup analysis of patients who returned for catheterization within one- and three- postoperative years showed that SVGF was associated with early and late angina.³⁷ In addition, another subgroup study of a clinical trial showed that patients with SVGF were more likely to experience MI or death than those without SVGF.³⁸ It is important to note that these studies are subject to bias because of a high rate of loss to follow-up and a failure to adjust for confounders. After controlling for potential confounders, the differences in death or MI rates between those who had SVGF and those who did not were no longer apparent at four to five years after CABG.³⁹ Moreover, although an observational analysis by Halabi *et al*⁴⁰ showed that early SVGF (one to 18 months) was associated with an increased 10-year risk of major cardiovascular events, this occurrence was mainly driven by repeat revascularization, “a faulty endpoint for clinical trials” that is associated with referral bias as the procedure is more likely to be performed in symptomatic patients.^{41 42} This significant difference can be expected because of the high incidence of repeat revascularization relative to MI or death post CABG providing greater statistical power to detect differences. Using separate multivariable analyses, Lopes *et al*³⁹ showed a significant association between repeat revascularization and SVGF but not with other patient-relevant outcomes (i.e., MI or death) at four years after CABG. Whether there is a causal relationship between SVGF and clinical outcomes and whether repeat revascularization should be part of the composite clinical outcomes, they remain unclear.⁴³ Nonetheless, SVGF is still considered an important indicator to guide the decision-making process regarding the management of subsequent treatments. If graft failure is detected, it is recommended to perform repeat revascularization (PCI or rarely re-do CABG) to treat restenosis.²¹ However, repeat revascularization is not without hazards. It is known that PCI places

CABG patients at risk of MI, mortality, and additional repeat revascularizations, and that re-do CABG is associated with a higher mortality rate compared to initial CABG.²¹ It is therefore of clinical interest to prevent graft failure, especially SVGF given its frequent occurrence, to avoid unnecessary invasive procedures and their inherent complications.

Importantly, emerging evidence suggests that SVG patency rates can potentially be improved by pharmacological therapy. Since platelets and coagulation factors contribute to the pathophysiology of SVG disease, antiplatelet therapy and anticoagulant therapy should, in theory, prevent SVGF as these agents inhibit clotting factors of platelet and coagulation.³¹⁻³⁶

1.3.2 Determinants of saphenous vein graft failure

There are several factors that can affect the development of SVGF either at the patient-level or graft-level. The well-known patient-level risk factors include traditional cardiovascular risk factors such as diabetes, hypertension, dyslipidemia, and smoking.⁴⁴⁴⁵ ⁴⁶ ⁴⁷ Although females tend to have poorer clinical outcomes following CABG, it is unclear whether sex is predictive of SVGF.⁴⁸

In addition to patient-level factors, native vessel diameter and surgical technique are the graft-related features that predict SVG patency. It was shown that there was a 90% patency rate for SVGs that were grafted to vessels >2.0 mm in diameter versus 52% for vessels ≤2.0 mm.⁴⁹ In terms of surgical factors, the ‘no-touch’ technique of harvesting SVGs, whereby the vein is harvested along with its surrounding tissue to avoid creating spasm, is found to be linked to a reduction of SVGF.⁵⁰ Another graft-level predictor of graft failure is blood flow competition between the native coronary artery and the graft, a phenomenon that occurs when a bypass graft competes with a native vessel to supply blood to a distal heart vessel. A high competitive flow, especially through a native coronary artery with stenosis <70%, accelerates the process of atherosclerosis in the grafts.⁵¹⁻⁵³ However, this occurrence happens predominantly in arterial grafts, and the association between competitive flow and SVGF remains uncertain.⁵⁴

Other factors that may be associated with the patency of SVGs include use of cardiopulmonary bypass (CPB), time to surgery (urgent or elective), antifibrinolytic use, and antithrombotic therapy use. A meta-analysis of 12 randomized controlled trials (RCTs) showed a statistically significant 41% increase in risk of occlusion of SVGs in those who underwent CABG without CPB (known as off-pump CABG or OPCAB) than those with CPB (known as on-pump CABG or CCAB).⁵⁵ Moreover, though there is little evidence to show an association between SVGF and time to surgery, it has been suggested that compared with elective surgery, patients undergoing urgent surgery were likely to receive fewer internal mammary artery grafts and more SVGs.^{56 57} Moreover, the relationship between antifibrinolytic therapy and SVGF remains unclear due to conflicting results. A RCT showed that aprotinin increased 10-day occlusion of SVGs,⁵⁸ whereas the use of tranexamic acid did not significantly increase the short-term rate of SVGF.⁵⁹ Lastly, the use of pharmacotherapy including lipid-lowering drugs and antithrombotic agents was associated with improved SVG patency.^{34 36 60}

1.3.3 Prophylactic pharmacotherapy options for saphenous vein graft failure

It has been established that antithrombotic therapy and lipid-lowering drugs are the medical therapies used to inhibit the process of SVG disease.^{34 36}

1.3.3.1 Lipid-lowering agents

The main goal of lipid-lowering drugs is to reduce blood low-density lipoprotein (LDL) cholesterol, a fat-like substance in vein graft atherosclerosis that influences the process of SVG disease.⁴⁵ Lipid-lowering agents include statins and fibrates. Of these, statins are the most commonly prescribed drugs.

Epidemiological studies have shown that statins slow the development of SVG disease. In a RCT of 1,351 patients who had prior (1 to 11 years) CABG, the aggressive lovastatin (40 to 80 mg/day) therapy was shown to reduce the incidence of SVGF and progression of SVG atherosclerosis at four years post randomization compared to the moderate lovastatin (2.5 to 5 mg/day) therapy.⁶¹ Moreover, a recent multivariable analysis of a

RCT showed that among 113 CABG patients who were on statins, those who achieved LDL levels <100 mg/dL had a lower occurrence of SVGF than those who did not.⁶² Currently, preoperative statins are recommended for patients undergoing CABG and should be restarted early after surgery.^{3 4 6}

1.3.3.2 Antithrombotic therapy

The main goal of antithrombotic agents is to prevent the formation of thrombus, which consists of fibrin and platelets, and the progression of thrombosis. Oral antithrombotic therapy is identified in two main categories: oral antiplatelet therapy (aspirin, indobufen, dipyridamole, ticlopidine, clopidogrel, ticagrelor, and prasugrel) and oral anticoagulation therapy (warfarin, acenocoumarol, phenprocoumon, dabigatran, rivaroxaban, and apixaban). In terms of adverse effects, all of these agents put patients at varying risk of bleeding. Though they share the same main goal and common side effect, they have different mechanisms of action. Antiplatelet agents prevent the activation of platelets, reducing the aggregation of platelets on the injured vascular wall by inhibiting receptors on platelets. By contrast, anticoagulation therapy prevents clots by interrupting the coagulation cascade.³⁴

Antiplatelet therapy. Aspirin prevents platelet adhesion to the vein wall by decreasing the production of thromboxane A₂, a hormone released by activated platelets that stimulates other platelets and augments platelet aggregation, with the goal of improving graft patency and clinical outcomes. Compared to placebo, aspirin administered early after CABG for one year was shown to improve 60-day and one-year SVG patency.^{63 64} In terms of clinical outcomes, a recent meta-analysis of RCTs showed that the beneficial effect of preoperative aspirin was also apparent in the reduction of cardiovascular events in CABG patients.⁶⁵ Given its favourable effects, it is not surprising to have multiple guidelines recommending the use of pre- and post-operative aspirin for the prevention of SVG occlusion and the secondary cardiovascular prevention.¹⁻⁷

Clopidogrel, ticlopidine, prasugrel, and ticagrelor selectively inhibit adenosine diphosphate receptors, causing platelet dysfunction. Clopidogrel, ticagrelor, and prasugrel are more potent than aspirin. The combination of these antiplatelet agents with aspirin has

been studied in many clinical settings with the expectation of synergistic antithrombotic effects, especially in patients with aspirin resistance i.e., patients who do not completely respond to aspirin and continue to suffer from the clinical manifestations of thrombosis.⁶⁶ For non-responders, the use of a second antiplatelet agent may therefore be justified to maximize SVG patency as patients who had occluded vein grafts are more likely to be non-responders than those who did not.⁶⁷ However, one side effect of antiplatelet therapy is increased bleeding risk. Using dual or poly antiplatelet agents may potentially improve effectiveness but at the expense of a much higher risk of bleeding.

Dipyridamole and indobufen are antiplatelet drugs that inhibit the activity of platelet cyclooxygenase and cyclic guanosine monophosphate phosphodiesterase type V enzyme, respectively.^{5 68} Unlike other antiplatelet agents mentioned previously, these drugs are often not used in current practice, especially for SVGF prevention, because of their side-effects and the fact that they have been preferred over more effective and safer agents such as aspirin.

Anticoagulation therapy. Warfarin, acenocoumarol, and phenprocoumon are vitamin-K antagonists, which inhibit blood clot formation by reducing the vitamin-K dependent coagulation factors.⁶⁹ Unlike other antithrombotic agents, vitamin-K antagonists need frequent laboratory monitoring to minimize bleeding complications associated with the drugs. To address this problem, direct oral anticoagulant agents (DOACs) including apixaban, rivaroxaban, and dabigatran have been developed.

1.4 Gaps in the Current Literature and Rationale of the Thesis

Clinical practice guidelines play a role in providing current summaries of best available evidence to health policy-makers, clinicians, researchers, patients, and other healthcare providers with the goal of improving patient outcomes and promoting appropriate use of optimal therapy.^{1-7 70} In many guidelines,^{1-7 70} the strength of recommendations and the level of evidence are presented to assist healthcare providers in making informed clinical decisions. The strength of recommendations of a specific therapy is graded based on the

size of treatment effect ranging from Class I to Class III, where Class I indicates that the therapy should be administered, Class II denotes that additional studies are helpful to strengthen the recommendation, and Class III suggests that the therapy is harmful or has no benefit. The level of evidence, on the other hand, is weighted according to the quality of evidence (risk of bias and precision of treatment effect) ranging from Level A to Level C, where Level A indicates that data were obtained from high quality of evidence (meta-analysis or multiple RCTs), Level B means that data were sourced from lower quality of evidence (a single RCT or observational studies with conflicting results), and Level C suggests that data were from poor quality of evidence (case studies or expert opinions).

Today, there are many clinical guidelines that have been developed focusing on the prevention of SVGF after CABG. The majority of existing guidelines have strongly and consistently emphasized the importance of aspirin (alone) administration before and early after CABG in improving graft patency (Class of recommendation: I).¹⁻⁷ However, the scientific basis for this recommendation primarily relies on the available direct evidence of varying quality. The majority of earlier guidelines, including American College of Cardiology/American Heart Association (ACC/AHA)¹⁻³ and American College of Chest Physicians⁵ guidelines, developed recommendations for SVGF prevention based on multiple observational studies and underpowered RCTs. In recent guidelines by AHA (2015),⁶ recommendations were based on higher quality evidence (Level of Evidence: I). In these guidelines, the writing group appraised and used multiple RCTs and a meta-analysis of RCTs published by Fremes *et al.*⁷¹ to evaluate the benefit of various oral antithrombotic agents in SVGF prevention. However, this meta-analysis included an intervention (i.e., dipyridamole) that is not being widely used today and rarely for the prevention of SVGF. This is potentially problematic as the conclusions made based on studies with irrelevant comparators may not be applicable in the current practice, where aspirin monotherapy is the standard prophylactic treatment. Moreover, since the publication of this meta-analysis, important evidence from RCTs with newer agents has emerged, enriching the totality of evidence to better inform decision-making. Therefore, revising guidelines with inclusion of more updated information and more relevant interventions is crucial.

In 2016, ACC/AHA developed and published more recent guidelines for SVGF prevention.⁷⁰ Unlike many other existing guidelines that highly recommended the use of aspirin monotherapy, these guidelines proposed a different recommendation. The 2016 guidelines suggested that the addition of clopidogrel to aspirin (known as dual-antiplatelet therapy with aspirin and clopidogrel) may be reasonable for SVGF prevention. However, this recommendation requires additional studies to strengthen the recommendation (Class of recommendation: IIb) and is based on lower quality of evidence (Level of evidence: Level B – Non-Randomized). Using this recommendation poses several challenges: 1) the recommendation based on lower quality of evidence may not be very helpful in guiding clinical decision making, especially when the intervention involves risks to the patients. 2) Although the 2016 ACC/AHA guidelines considered prophylactic treatments that are used in current practice, these guidelines primarily focused on two treatments, aspirin monotherapy and dual-antiplatelet therapy with aspirin and clopidogrel and failed to place recommendations for other relevant alternatives to prevent SVGF. The focus on two clinical therapies may lead to uninformed clinical decisions regarding the optimal prophylactic treatment for CABG patients. 3) In addition to the narrow focus in the practice guidelines on aspirin monotherapy and dual-antiplatelet therapy with aspirin and clopidogrel, in the absence of an appropriate statistical analysis, objective assessments of optimal therapy are not possible.

Clinicians and patients are constantly challenged to make an optimal choice from among the multiple antithrombotic regimens proposed for potential prevention of SVGF. Despite the importance of providing optimal prophylactic treatments to CABG patients, most available antithrombotic agents have not been compared directly in randomized trials, and furthermore no studies have been published that assess the comparative effects of all oral antithrombotic agents in the prevention of SVGF after CABG. There are a number of ways to assess the efficacy of multiple antithrombotic agents, including designing a multi-arm head-to-head RCT, performing a series of pairwise meta-analyses, and conducting a network meta-analysis (NMA, also known as multiple treatment comparison). However, well-designed RCTs comparing all relevant interventions have not yet been performed, and conducting such RCTs can be challenging due to the high cost and time required for studies of adequate power to detect differences between active

comparators. Furthermore, several other pairwise meta-analyses comparing a subset of relevant antithrombotic therapies have been recently published.^{72 73} Although a pairwise meta-analysis of well-designed RCTs is widely considered to be the highest level of evidence, this approach does not allow for a coherent assessment of more than two antithrombotic therapies nor allow for comparison of therapies that have not been directly compared in RCTs. Naively comparing across treatments with a series of pairwise meta-analyses is also not recommended because of a failure to appropriately handle the study effect (i.e. the effect of patient/study characteristics that equally contribute to the intervention and comparator). Only the treatment effect (and not the study effect) of each RCT should be compared to obtain an unbiased estimate from an indirect comparison.⁷⁴ Among the aforementioned options, NMA of RCTs may represent a better option to determine the efficacy of all relevant antithrombotic agents as it can compare multiple treatments simultaneously even when the treatments have not yet been compared directly, while preserving the within-study randomization. Hence, in the present study, we used a NMA approach, to conduct multiple treatment comparisons.

1.5 Thesis Objectives

This thesis addresses two main research objectives:

Objective 1 – Systematic Review

To systematically review the literature to identify RCTs that assessed the efficacy of various antithrombotic therapies for the prevention of SVGF in patients undergoing CABG.

Objective 2 –Meta-analysis

- a) To conduct a pairwise meta-analysis of relevant RCTs to provide a summary of direct estimates of the effects of antithrombotic agents (alone or in-combination with other antithrombotic agents) versus placebo/control or other antithrombotic agents on graft patency and clinical outcomes of interest in patients undergoing CABG.
- b) To perform a NMA of relevant RCTs to evaluate the comparative efficacy of antithrombotic agents (alone or in-combination with other antithrombotic agents)

versus placebo/control or other antithrombotic agents in the prevention of SVGF among patients undergoing CABG.

- c) To perform a NMA of relevant RCTs to evaluate the effect of antithrombotic agents (alone or in-combination with other antithrombotic agents) versus placebo/control or other antithrombotic agents on clinical outcomes in patients undergoing CABG.
- d) To generate a treatment ranking for each outcome of interest.
- e) To assess the quality of direct and network evidence provided by included RCTs.

Chapter 2

2 Literature Review for Methodological Background

This chapter provides a brief background on quantitative and qualitative methodology used in this thesis. Specifically, we introduce the concepts with a detailed review of the underlying assumptions of pairwise meta-analysis and NMA and explain the importance of the Grading of Recommendation, Assessment, Development, and Evaluation approach in assessing the quality of randomized evidence for outcomes reported in evidence synthesis.

2.1 Pairwise Meta-Analysis

2.1.1 Introduction

According to the Cochrane Collaboration,⁷⁵ a systematic review is defined as “a review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research, and to collect and analyze data from the studies that are included in the review.” In a review, studies that address a similar research question can be pooled together to provide a meaningful summary. When sufficient data are available, the findings of included studies can also be quantitatively synthesized through meta-analysis to obtain a more precise single summary estimate.⁷⁶

There are a number of summary estimates that can be used to present the study findings. The selection depends on the available data and the type of outcome of interest. When means and standard deviations are available from the original studies, the standardized or unstandardized mean difference or response rate are the common effect sizes. For binary outcomes where the number of events and non-events in two study arms are reported, the risk ratio (RR), odds ratio (OR), and risk difference (RD) are the preferred effect sizes.

For studies that report a correlation between two continuous variables, a correlation coefficient can be calculated and used as a summary estimate.⁷⁶

2.1.2 Heterogeneity

On average, randomization balances the distributions of any prognostic factors across study groups in a RCT. In the absence of systematic errors, the difference in event rates (or any outcome measures) between the groups is the effect of the treatment on the outcome of interest relative to a comparator (known as the treatment effect). Despite the benefit of randomization, treatment effect may vary between groups of participants in a RCT. This is expected as some people with certain characteristics that are effect modifiers (i.e., characteristics that modify the treatment effects) may respond to treatments differently. The true variation in treatment effects within a RCT is called within-study heterogeneity.⁷⁷ For instance, a RCT of statins may include a mixture of participants with and without prior exposure to aspirin.

In a meta-analysis comparing two interventions, the distribution of study and patient characteristics may not be balanced across RCTs because randomization does not occur at study level (i.e., participants are not randomized to different studies). As a result, a between-study variation in these characteristics is expected. If these characteristics are effect modifiers, then this variation is called between-study heterogeneity. For example, if some of the trials comparing treatment A with C, are not comparable in terms of distribution of effect modifiers (e.g., severity of disease, selection of patients, or regimens) and, hence, their observed effect sizes are not similar, then between-study heterogeneity is present. In a pairwise meta-analysis of individual patient-level data, there are two sources of heterogeneity: within-study heterogeneity and between-study heterogeneity. Without individual patient-level data, we can only assess between-study heterogeneity in an aggregate pairwise meta-analysis.⁷⁷ In a meta-analysis, between-study heterogeneity may arise from three sources: clinical, methodological, and statistical.

Clinical heterogeneity: Clinical heterogeneity is assumed to occur when studies included in the review are not sufficiently similar in clinical characteristics, such as baseline patient characteristics, intervention characteristics, and outcome measurements.

Methodological heterogeneity. Methodological heterogeneity occurs when the included studies are not comparable in terms of risk of bias and study design (e.g., clustered RCTs versus non-clustered RCTs. Compared with non-clustered RCTs, clustered RCTs produce less precise estimates).

Combining studies that are clinically and methodologically diverse may increase the generalizability of findings; however, the combination can have a negative impact on internal validity. The more diverse a targeted population, the greater the chance of heterogeneity.⁷⁵ Furthermore, evaluating similarity among studies is based on qualitative assessment of study and patient characteristics, which can be subjective. The involvement of clinical experts and methodologists is therefore strongly recommended in the process of making decisions about combining studies in order to produce a meaningful and valid summary of estimates.⁷⁸

Statistical heterogeneity: statistical heterogeneity refers to variability in treatment effect size estimates across studies, including magnitude and/or direction of effect that is beyond the expected play of chance. The source of this heterogeneity may arise from the combined impact of clinical and methodological heterogeneity, biases, or random chance.⁷⁵

Statistical heterogeneity can be detected using statistical tests such as Cochran Q-statistic,⁷⁹ Generalized Q-statistic, and Cochran Q-statistic adjusted for small-study effects.⁸⁰ Of these, the Cochran Q-statistic is the most commonly used test and it performs well in controlling the type I error rate (false positive rate).⁸¹ The extent of statistical heterogeneity can then be quantified using statistical measures such as H^2 index,⁸² I^2 statistics,⁸³ D^2 index,⁸⁴ and G^2 index.⁸⁰ Among these measures, I^2 statistic is the most common.⁸⁵ The I^2 statistic describes the percentage of variation in study estimates amongst studies that is attributable to heterogeneity and beyond what chance alone could explain.⁸⁶ An I^2 of 75% indicates that 75% of the observed variance comes from true differences across individual studies, and thus there is substantial heterogeneity. When between-study heterogeneity is detected, it is important to explore

its potential sources by performing subsequent analyses such as meta-regression, subgroup analyses, and/or sensitivity analyses.

Subgroup analysis: The variation in effect sizes across different subgroups (studies of similar characteristics) can be explored using subgroup analysis. For example, a meta-analysis comparing dual-antiplatelet therapy with aspirin and clopidogrel versus aspirin monotherapy included a mixture of RCTs with low and high aspirin doses (with no variation in doses within RCTs). Subgroup analysis by dose may be performed to explore the impact of dose on the treatment effect. These subgroups may be patient-level variables if individual-patient level data are available or study-level variables if only aggregate patient data are available. It is important to note that the subgroup effects are often misleading and should be considered hypothesis-generating rather than conclusive.⁸⁷

Meta-regression: If the source of heterogeneity is a categorical or continuous variable, then meta-regression can be used instead of subgroup analysis. Meta-regression is used to explore the relationship between study-level variables and treatment effects. Some examples of study-level variables used in meta-regression include treatment doses and year of publication. There are several limitations inherent in subgroup analysis and meta-regression.

First, when we perform subgroup analysis or meta-regression, randomization is broken in cases where the original trial did not stratify randomization based on the subgroup variable of interest. These analyses therefore are observational by nature and suffer the limitations of any observational studies such as confounding. Second, the statistical power by which to detect a difference among subgroups (in subgroup analysis) or to detect a significant association between covariates and effect size (in meta-regression) is usually low.⁷⁶ Third, if study-level covariates vary between patients within a study, then the analyses are subject to ecological bias such that an association may exist at the study level, but may not be true at the patient-level.⁸⁸ Lastly, in practice, these analyses are often performed multiple times with a number of covariates or subgroups. Though there is no consensus on how to handle the issue of multiple testing in meta-analysis,

investigators should be mindful of its consequence, in particular as it relates to the inflation of risk of type I errors (>5%).⁷⁶

Sensitivity analysis: If subgroup analysis and meta-regression cannot be performed, sensitivity analysis is particularly useful to explore the potential heterogeneity. For example, sensitivity analyses can be done by excluding studies that had very different baseline risks from most included studies.

2.1.3 Statistical models

The choices of statistical models in a meta-analysis are fixed-effects and random-effects models.

2.1.3.1 Fixed-effects pairwise meta-analysis

In the fixed-effects, all included studies are assumed to share a common effect size and any variation in observed effects is a result of sampling error.⁸⁹ In other words, a fixed effects meta-analysis is based on the assumption that there is no between-study heterogeneity. The observed effects Y_i from individual studies included in a meta-analysis are sampled from a distribution with one true effect size, μ and variance σ^2 . The observed effect Y_i is:

$$Y_i = \mu + \varepsilon_i$$

where ε_i is the within-study error of the i^{th} study and assumed to be normally distributed, $\varepsilon_i \sim N(0, v_i)$. v_i denotes the within-study variance of the i^{th} study.

2.1.3.2 Random-effects pairwise meta-analysis

It may not be realistic to assume that the effect sizes are identical across studies.⁸² In fact, it is reasonable to expect slight variation between studies that we characterize as between-study heterogeneity. The studies are required to be similar to ensure internal validity but not identical. A random-effects model assumes that there is a common normal distribution of true effect estimates.⁸⁹ In other words, the true treatment effects

may vary from study to study. In this model, we need to consider two levels of sampling. First, the true effect size θ_i in the i^{th} study is distributed about μ , the mean of all true effects, with a variance τ^2 . The difference between θ_i and μ refers to between-study error (s_i). Second, the observed effect Y_i in the i^{th} study is distributed about θ_i , the true effect size in the i^{th} study, with a variance σ^2 . The difference between Y_i and θ_i refers to variability due to sampling error, within-study error (ε_i). The summary estimate represents the population mean of all true effects. In a random-effects model, the observed effect Y_i of the i^{th} study is:

$$Y_i = \mu + s_i + \varepsilon_i$$

where $s_i \sim N(0, \tau^2)$ and $\varepsilon_i \sim N(0, v_i)$. v_i denotes the within-study variance for the i^{th} study and τ^2 denotes between-study variance. In a fixed-effects model, $s_i = 0$.

2.2 Network meta-analysis

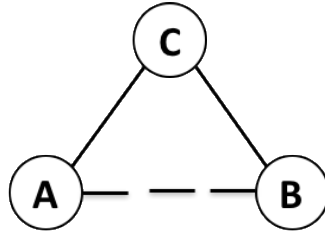
2.2.1 Introduction

A pairwise meta-analysis is useful when the pooled information is derived from studies comparing two interventions. However, clinicians and patients are often challenged to choose from multiple treatment options. Clinical decision-making becomes even more challenging when head-to-head comparisons are not available for some of the alternatives. NMA, also known as mixed treatment comparison (MTC), is a promising method that overcomes these issues. NMA synthesizes evidence from direct comparisons (between two treatments, A and B, without the need of a common comparator) and indirect comparisons (between two treatments, A and B, via a common comparator, C) and simultaneously combines both sources of evidence via mixed comparisons to obtain treatment effect estimates for all relative pairwise comparisons for a particular outcome of interest, even when the treatments have never been compared head-to-head.⁹⁰

The effect of treatment A relative to treatment B can be obtained directly through a head-to-head comparison. When direct evidence does not exist, indirect evidence can be estimated by deriving direct comparisons between treatment A versus C and treatment B

versus C, where C is a common comparator.⁹¹ The simplest way to obtain indirect estimates in a closed loop within the network is to use Butcher's method, the adjusted indirect comparison.⁹¹

Figure 1. Direct and indirect comparisons.



Each node represents a treatment, solid lines represent pairwise direct comparisons, and a dash line represents an indirect comparison.

In Figure 1, we can calculate the probability of an event if patients receive treatment A versus treatment B using Butcher's method. The indirect treatment effect of A versus B can be estimated by (computations are carried out on a log scale using the odds, $Odds = \frac{p}{1-p}$, as a function of probability, p)

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

The variance:

$$Var(\log OR_{AB}) = Var(\log OR_{AC}) + Var(\log OR_{BC})$$

The 95% CI for the indirect estimate can be calculated

$$95\% CI (\log OR_{AB}) = \log OR_{AB} \pm 1.96\sqrt{Var(\log OR_{AB})}$$

For the purpose of this example, odds ratio is used, however, the method can be extended to other outcomes. Butcher's method is limited as it is used to estimate an indirect effect.

NMA is an extension of Butcher's method and can produce direct and indirect estimates, and combine (mix) them to gain precision.

In terms of statistical models, the same considerations for pairwise meta-analyses are applied when choosing between a fixed-effect and a random-effects model in the NMA. If investigators believe that the included studies are reflective of a single population and expected to have an identical treatment effect and the generalizability of the findings are not of interest, then the fixed-effect model may be used.⁹² Fixed-effect models are more likely to be considered appropriate in cases where studies are conducted by the same investigators under the same protocol or if studies are very similar in all important factors clinically, methodologically, and statistically. However, this rarely happens in real practice as it is reasonable to expect some degree of variation between studies. As a result, the random-effects model is more commonly used as it incorporates known and unknown heterogeneity.⁹²

Synthesizing the totality of evidence in a NMA improves the statistical power by which to detect effects and therefore increases the precision in the network estimates.⁹⁰ This statistical method can also produce a ranking for all treatment options, which may assist policy makers or clinicians with decision-making.⁹³ NMA is especially valuable when study data are pooled from RCTs as randomization (balance in prognostic factors and other important characteristics between treatment groups) within a RCT is maintained.⁹⁴

However, NMA is not without drawbacks. Even though within-study randomization is preserved in direct comparisons of RCTs, interventions were not randomized across studies in NMA.⁹⁴ As a result, indirect comparisons are observational by nature and may bear some of the limitations of observational studies, such as bias due to confounding^{77 90} and selection bias.⁹⁵ Confounding bias arises when the imbalance in the effect modifiers between direct comparisons confound treatment effects. Additionally, selection bias occurs when researchers selectively choose treatment comparators based on the expectation of magnitude and direction of treatment effects, which can be minimized by including all relevant comparators or random selection. To ensure unbiased indirect

estimates, there are two main assumptions that need special care: homogeneity and transitivity, with its statistical extension, known as coherence.

2.2.2 Assumptions

2.2.2.1 Homogeneity

Recall, within-study heterogeneity is observed within a study whereas between-study heterogeneity occurs when there is substantial variation in effect modifiers across studies of the same treatment contrast (defined as a comparison between two treatment agents). Since a NMA can analyze multiple treatment comparisons, there is an additional source of variation in treatment effects to be considered in a NMA, which is between-comparison heterogeneity. Between-comparison heterogeneity arises when the distribution of the effect modifier is imbalanced across treatment comparisons. A consequence of this imbalance is a biased indirect estimate.⁷⁷

2.2.2.2 Transitivity

Even if studies of the same treatment comparison are comparable (or homogeneous), the imbalance distribution of study characteristics that modify treatment effects across treatment comparisons will lead to biased indirect estimates.⁷⁷ For example, if sex is an effect modifier and more females were included in comparisons involving newer treatments than those in older treatments, then the indirect treatment effect is biased by sex. This is known as a violation of the transitivity assumption. There are five possible ways to interpret the transitivity assumption, also known as similarity or exchangeability.⁹⁴ First, treatment C is not systematically different between A-C and B-C studies in terms of effect modifiers. Second, arms in each study are missing at random and the choice of interventions is not associated with the treatment effects. Third, distribution of effect modifiers is balanced across treatment comparisons within the network irrespective of the degree of between-study heterogeneity. Fourth, subjects are eligible to take any of the competing treatments, and could, in principle, be randomized to any of them. Fifth, the effects of treatment A and C estimated directly and indirectly

come from the same distribution. In other words, any (known and unknown) differences between relative effects of A-C and B-C are attributable to heterogeneity.

The transitivity assumption cannot be evaluated using statistical tests.⁹⁴ Therefore, it is important to qualitatively identify potential violations of the transitivity assumption to aid in interpreting NMA results by considering the five expressions. However, in the presence of a closed loop (a path that begins and ends at the same treatment (node)), coherence, a synonym for transitivity, can be statistically tested. Transitivity requires a conceptual evaluation, whereas coherence is a statistical manifestation of transitivity across a closed loop.⁹⁶

2.2.2.3 Coherence

When both direct and indirect estimates are available, the combination of sources of evidence produces a more precise estimate, known as a mixed estimate. The mixed estimate becomes reliable when there is statistical agreement between direct and indirect evidence. When there is a conflict between the two sources of evidence in a closed loop, the use of mixed evidence may not be reliable; the disagreement suggests a violation of the coherence assumption.

Incoherence can be globally investigated (in the entire network) and locally (in a specific closed loop of evidence). Methods for assessing statistical local incoherence include:

- Loop-specific approach: This method estimates incoherence by generating an inconsistency factor (IF, the difference in absolute terms between indirect and direct estimates for a specific treatment contrast in a closed loop, which is expressed in the logarithmic scale) and its corresponding 95% confidence interval (CI).⁹⁷
- Composite test for incoherence: Unlike the loop-specific approach, this approach incorporates information from all direct comparisons that contribute to a specific indirect comparison. In other words, the estimated indirect summary effect is obtained from two or more different closed loops, and not from one specific loop.⁹⁸
- Node-splitting approach: This approach assesses incoherence by comparing direct evidence to indirect evidence via removal of a single direct pairwise comparison from the network.⁹⁹ Once the direct comparison is removed, the network is re-calculated to

obtain an indirect effect. The direct effect estimated before the removal is then compared with the indirect effect estimated after the removal using a Z-test.

The following are available methods for assessing incoherence globally:

- Lu and Ades Model: This approach is an extension of the loop-specific approach, where all IFs in the entire network are considered simultaneously. The null hypothesis that all IFs are zero is evaluated using the χ^2 test to identify the presence of global incoherence.⁹⁷
- Design-by-Treatment interaction model: The summary estimate of A versus C from two-arm studies of A versus C (AC design) may differ from the estimate obtained from three-arm studies of A versus B versus C (ABC design).¹⁰⁰ It is therefore important to consider the study design as another potential source of incoherence. Unlike the Lu and Ades model, the design-by-treatment interaction method can assess incoherence globally in the presence of multi-arm studies.¹⁰⁰
- Q-statistic in NMA: Krahn *et al* provided an equation to calculate the weighted distance between the network summary estimates and the direct summary estimates for a particular comparison.¹⁰¹ The weighted distance refers to the Q-statistic for incoherence. Hence, to statistically test incoherence, the null hypothesis that coherence is present is evaluated using the χ^2 test.

The fulfillment of transitivity and coherence assumptions results in reliable indirect evidence.¹⁰² However, the coherence assumption should be interpreted with caution. The number of studies contributing to a direct estimation is often small, yielding an underpowered statistical test. Therefore, the absence of statistically significant incoherence does not necessarily equal coherence. The likelihood of detecting incoherence is even lower in the presence of heterogeneity because of the wider 95% CI of an indirect estimate that overlaps with that of direct estimates, or vice versa.^{94 103}

2.2.3 Statistical framework

Frequentist and Bayesian approaches can be used to fit data to a model in order to make inference about the true value of a parameter of interest. The frequentist inference is a statistical inference that evaluates parameters based on a sampling distribution, where the

parameter of the population is assumed to be an unknown fixed constant. Consequently, probability statements cannot be made because the parameter is not a random, but fixed, quantity. To calculate probabilities, a random sample of observations is drawn from a sampling distribution of all possible random samples. These probabilities therefore are conditional on these random samples (and not actual data). Based on this sampling distribution, frequentist statistics performs inference on the parameter.¹⁰⁴

There are several different inference types about the parameter that frequentist approaches consider including hypothesis testing and interval estimation. Hypothesis testing is focused on what data from an analysis can explain by testing the null hypothesis that there is no difference between groups, $H_0: \pi = \pi_0$, against the alternative hypothesis that there is a significant difference, $H_a: \pi \neq \pi_0$, at a level of significance, α . The observed effect is tested under null hypothesis. The key question is, how likely is the observed effect, if the null hypothesis is true. If we fail to reject the null hypothesis, we would not accept the alternative hypothesis nor conclude that the null hypothesis is true. We can say that there is insufficient evidence of difference or the observed effect can be explained by chance alone. If we reject the null hypothesis, we would accept the alternative hypothesis that there is a significant difference.¹⁰⁴ Thus, analysis of study data is conditional on the null hypothesis being true. Direct probability statements about the true value of a parameter are not possible within the hypothesis testing framework of frequentist statistics. Another inference type is known as interval estimation. The 95% CI indicates that 95% of intervals calculated from repeated samples will be expected to include the true population effect and 5% of intervals will not. Analysis of study data using interval estimation is also conditional on the null hypothesis being true. The 95% CI does not provide a range of values for the true parameter, although it is often mistakenly interpreted this way. The only correct way of interpreting the 95% CI is to indicate that 95% of intervals so constructed will contain the true parameter value, conditional on the null hypothesis being true.

This contrasts with Bayesian statistics where parameters are assumed to be random. Since the parameters are random, probability statements can be made. In the Bayesian framework, the inference about parameters are updated with prior knowledge (known as

prior). To calculate probabilities, we form a posterior distribution by combining the prior information with the evidence from the actual data (formally, posterior \propto prior \times likelihood). In the Bayesian interpretation of the inference, the 95% credible intervals are estimated which indicates that there is a 95% probability that the true population effect lies within the interval.¹⁰⁴

In the context of a NMA, both approaches can be used. The Bayesian approach permits treatment rankings, i.e., the probability that a particular intervention for a particular health condition is best, second best, and so on. In addition, Bayesian posterior distributions can serve as inputs into probabilistic cost-effectiveness analyses.⁹³ However, the Bayesian approach requires appropriate prior distributions for model parameters and careful considerations to make selections. Even though it is recommended to use the non-informative priors to minimize the subjective selection of priors, sensitivity analyses with different priors are helpful to assess whether the results are stable and robust. With the exception of the most simple Bayesian analysis, complex computing algorithms are required to define the posterior distribution through sampling. The most commonly employed algorithm is Markov Chain Monte Carlo simulation. In Bayesian statistics, we need to ensure convergence of the Markov Chain Monte-Carlo algorithm to the posterior distribution; otherwise, the parameter estimations are not reliable. Similar to Bayesian, recently developed approaches within frequentist statistics allow for treatment ranking.¹⁰⁵ However, unlike Bayesian approaches, the frequentist approach does not rely on the use of prior information. The selection of priors can be based on subjective judgment, and it is likely that different priors produce different results.¹⁰⁶ For example, the between-study variance can be varied markedly across different prior distributions when the number of studies in a meta-analysis is small.¹⁰⁷ Since the frequentist approach does not consider any priors, this method provides more objective results relative to the Bayesian method.¹⁰⁴

2.3 Grading of Recommendation, Assessment, Development, and Evaluation (GRADE)

2.3.1 Introduction

Quality of evidence is highly variable as it depends on how well studies are conducted and whether appropriate designs/analyses are used. Inadequate research methods can produce biased study findings. Pairwise meta-analysis and NMA are quantitative approaches that do not evaluate the quality of evidence. The estimates derived from these approaches will reflect any biases inherent in the included studies or even increase the risk of bias if the study selection process is not systematic. Therefore, it is crucial to appraise the quality of each study included in a (pairwise or network) meta-analysis, in order to better understand the strength of the resulting evidence. The Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) working group has developed a widely used tool to rate the quality of evidence, known as the GRADE approach.^{108 109}

2.3.2 GRADE's approach to rating quality of evidence

The GRADE approach is a systematic method used in health care to guide in the process of making recommendations reflective of the certainty (confidence) in evidence. There are five concepts that need to be considered in GRADE when assessing the quality of evidence.¹¹⁰

Risk of bias: This concept focuses on the limitations of individual studies for a specific outcome that may threaten internal validity. There are many tools that have been developed to assess risk of bias including Cochrane Collaboration risk of bias (RoB) tool, Jadad scale, Delphi List, Newcastle-Ottawa Scale, Downs and Black, just to mention a few.¹¹¹ Of these, the Cochrane RoB tool is a commonly used tool to assess risk of bias of RCTs.¹¹² This tool assesses six different bias domains:

- Selection bias, which produces incomparable groups and imbalanced sample sizes leading to overrepresentation of groups of patients with certain characteristics. This bias domain is split into two groups:
 - Selection bias due to inappropriate random sequence generation, where the process of allocating interventions to participants is not random (e.g., quasi-random allocation based on patient identification).
 - Selection bias due to failure to conceal random allocation, where the investigators randomizing the participants are aware of the study intervention to which the next participant will be allocated (e.g., non-sequentially numbered, non-opaque, or non-sealed envelopes; or an open random allocation schedule).
- Performance bias, which results in behavior change or co-interventions, which occur differentially between treatment groups due to failure to blind participants and personnel.
- Detection bias, which overestimates or underestimates the treatment effect due to failure to blind outcome assessors.
- Attrition bias, which results in differential missing outcome data, i.e., the proportions of missing participants and reasons for missing data are not similar across treatment groups. This type of bias occurs when there is a high rate of loss to follow-up or a failure to follow the intention-to-treat (ITT) analysis with substantial departure from allocation. It is important to note that although the goal of ITT analysis is to preserve balance in the distribution of prognosis between study groups, it does not necessarily minimize bias introduced by large amounts of missing data.
- Reporting bias, which results in overestimation or underestimation of meta-analytic summary effects due to selective outcome reporting (e.g., reporting only statistically significant results)
- Other sources of bias that are beyond the specific domains mentioned above such as fraud, termination of study that is related to outcome data, and considerable changes in the protocol.

Once the risk of bias within a study is evaluated, the quality of evidence can be rated down or up for risk of bias treating all studies as a body of evidence. If most studies are at low risk of bias, then the evidence is of high quality. If studies at moderate risk of bias are a primary source of evidence, then the quality is rated down by one level. If most studies are at high risk of bias, then the evidence is rated down by two levels.¹¹²

Inconsistency: This concept focuses on variation (heterogeneity) in treatment effects across studies. If large statistical heterogeneity is detected, then, it is suggested to down-rate the quality of evidence for inconsistency.¹¹³

Indirectness: This concept focuses on differences in population, interventions, and outcomes between the included studies and those of interest. In other words, do patients or treatments or outcomes of interest differ from those in the included studies?¹¹⁴ In the context of NMA, the concept of indirectness has been expanded to include the risk of bias from indirect comparisons by assessing the coherence between indirect and direct estimates.¹¹⁵

Imprecision: This concept focuses on 95% CIs around the treatment effect.¹¹⁶ If the 95% CIs are wide and cross the clinical decision threshold (or line of no effect), the quality of evidence is down-rated for imprecision. If the 95% CI does not cross the threshold but both number of events and sample size are small or the optimal information size (OIS) is not met, then the quality of evidence is rated down.¹¹⁷

Publication bias: This concept focuses on studies that are not published, especially those that were deliberately not reported due to non-significant results.¹¹⁸ Egger's test and funnel plot are examples of methods that examine the precision and distribution of published effect sizes to explore the potential publication bias.⁷⁵

Based on these five concepts, the quality of evidence is rated separately for direct evidence, indirect evidence, and network evidence for each treatment comparison for a particular outcome of interest. As a first step, direct evidence is rated. Using GRADE the quality of direct evidence is rated as high, moderate, low, and very low. High quality evidence suggests that the degree of our confidence in effect estimates being close to the

truth is high, whereas very low-quality evidence indicates very little confidence in the summary estimates being close to the truth. The initial quality of randomized evidence starts as high-quality evidence and each concept is then considered to help in rating down or rating up the quality. The quality is rated down by one or two points for each concept depending on how serious the problem is. The quality can be rated up if the effect size is large or dose-response relationship is present.¹¹⁹ A second step involves rating the quality of indirect evidence. The quality of the indirect estimate is rated according to the ratings of the two direct comparisons contributing to that specific indirect estimate, where the rating of the comparison that contributes the most will be chosen, and based on the presence of intransitivity. Lastly, if both direct and indirect estimates are present, the quality of the network estimate is rated based on the rating of the source of evidence with the higher quality. Otherwise, it is rated based on the available source of evidence (i.e., direct or indirect estimates only).¹¹⁵

Chapter 3

3 Methods

This chapter includes a description of the methods undertaken to conduct the present thesis work. We describe the study selection process, including the eligibility criteria, information sources, and search strategy; the data extraction and analysis; and the assessment of study quality. The protocol of the present study was registered (PROSPERO no.: CRD42017065678) and has been submitted for publication,¹²⁰ and any post-hoc differences between protocol and NMA are highlighted in this chapter. This study is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension for NMA guidelines.¹²¹

3.1 Search Strategy

A pre-specified comprehensive and systematic literature search strategy was created before the start of the study in collaboration with an experienced medical librarian to identify relevant studies related to our research question. Five electronic databases (MEDLINE, EMBASE, CINAHL, Cochrane Library, and Web of Science) were searched for studies published as a journal article from inception until November 13, 2016, with no restriction by language or publication date placed on any searches. For each database, we structured a search strategy into relevant search concepts according to population, intervention/comparator, outcome, and study design (PICOS) using the following key terms: “coronary artery bypass”, “antithrombotic”, “graft occlusion or graft failure or repeat revascularization or percutaneous coronary intervention”, and “randomized controlled trial”. A complete detail of the search strategy can be found in eTables 1 to 5. Weekly auto-alerts for electronic databases during the course of this study were also set up to receive notifications for newly relevant published reports. To ensure all relevant studies were identified, we performed a grey literature search of trial registries (ClinicalTrials.gov, International Clinical Trials Registry Platform,

AstraZeneca, Bayer, and Bristol-Myers Squibb), USA Food and Drug Administration, electronic theses online service, and Gray Matters (eTable 6). We also manually screened reference lists of eligible studies and previous systematic reviews and pairwise meta-analyses to identify any additional relevant studies.

3.2 Eligibility Criteria

The study eligibility criteria were designed a priori in consultation with a team of clinical and statistical experts (RB and JM) to assure the most pertinent studies for the NMA and were specified in terms of PICOS. Eligible studies were selected based on the following criteria:

Patient Population: We included adult patients (aged 18 years or older) undergoing CABG surgery with at least one SVG who were eligible to receive any of the oral antithrombotic agents that are used in current practice for SVGF prevention (listed below), regardless of comorbidity, clinical setting (elective or urgent surgery), previous antithrombotic exposure, whether perioperative heparin or antifibrinolytic was administered, and whether CPB was used.

Interventions: The antithrombotic treatments included in this study are listed as follows: aspirin monotherapy, clopidogrel monotherapy, dual-antiplatelet therapy with aspirin and clopidogrel, dual-antiplatelet therapy with aspirin and ticagrelor, and vitamin-K antagonists (warfarin, acenocoumarol, or phenprocoumon). The decision about grouping warfarin, acenocoumarol, and phenprocoumon together was made in consultation with a clinical expert (RB) because these agents are members of the same drug class with similar mechanisms of action. Participants must have received at least one of these agents as a study medication within seven days pre- and/or post-CABG, regardless of drug regimen, timing of drug initiation (before or after CABG), and duration of treatment. A seven-day period was chosen arbitrarily but taking into consideration the lifetime of platelet cells (eight to nine days).¹²² Other antithrombotic agents were considered in the protocol, but not included in our NMA because of a lack of data (e.g., prasugrel and

DOACs) or because they are rarely used in current practice for the prevention of SVGF (e.g., dipyridamole and ticlopidine).

Comparator: The comparator could be placebo/inactive control or a different oral antithrombotic agent, regardless of drug regimen, duration of treatment, and timing of drug initiation. Placebo/control was defined as per study author definition. The comparator however could not be the same antithrombotic agent at a different dose as comparing the effects of drug dosages is beyond the scope of this study. Similar to the intervention group, participants must have received at least one of the products as a study medication within seven days before and/or after CABG.

Outcomes: Eligible studies must have reported the incidence of SVG occlusion (defined below) in intervention and comparator groups, as SVGF was the primary outcome of this NMA. There were no restraints on the units of analysis, methods or time of imaging assessment, and definitions of outcome. The lack of a universal definition for SVGF leads to a variety of definitions being reported in the literature, which results in inconsistencies in the reporting of events across studies and increased heterogeneity.⁴³ If several definitions were presented in the same study, to reduce heterogeneity in the analysis, we extracted SVGF data according to our preferred definition. Our preferred definition of SVGF was total occlusion in one or more SVGs detected angiographically and expressed on a per-patient basis.

If a study did not provide data using our preferred definition, we originally planned to use a predefined hierarchy, based on unit of patency analysis, percentage of stenosis in the graft lumen, and need for repeat revascularization to treat restenosis. However, due to the inadequate description of outcome measures in most included studies, we selected outcome data in the following order of preference: a) patients with at least one occluded SVG; b) repeat revascularization (repeat CABG or SVG-related PCI); and c) number of occluded SVG. The new definition of occlusion was no longer based on degree of stenosis, but rather on study author definition. We excluded studies with an unclear definition of repeat revascularization as it would be difficult to judge, without adequate descriptions, whether the procedure was performed to treat restenosis or different lesions.

Our pre-specified secondary outcomes included all-cause mortality, cerebrovascular accidents (CVA: stroke or transient ischemic attack [TIA]), MI (fatal or non-fatal), major adverse cardiac and cerebrovascular event (MACCE), major bleeding, minor bleeding, intracranial bleeding, heart failure, red blood cells (RBCs) transfusion, and admission to hospital due to cardiovascular cause. These outcomes were chosen based on their clinical importance. In our protocol, we planned to use Thrombolysis in Myocardial Infarction (TIMI) criteria for major bleeding. However, there were several studies that were published before the existence of TIMI criteria in the research. For fair comparisons, we decided to use the study author's definition. As per protocol, the remaining outcomes were defined by the study authors. Studies were included based on the availability of SVGF data and not on our secondary outcomes.

Study design: We included all parallel-group RCTs comparing one of the aforementioned oral antithrombotic agents as the intervention with a different antithrombotic agent or placebo/control as the comparator. RCTs with multiple eligible comparators (i.e. multi-arm studies) were included. Non-English language studies, observational comparative studies, non-comparative studies, editorials, secondary studies, subgroup analyses of eligible RCTs, and RCTs without extractable outcome data were excluded from the analysis. If duplicates were identified, we did not include them in this study because analyzing the same information more than once in meta-analysis may lead to overestimation of treatment effect.¹²³ In this case, studies with the most complete reports were selected. There were no constraints on sample size or publication date.

3.3 Screening

Once the literature search was performed, all citations were imported into Covidence Systematic Review Software (<https://www.covidence.org/>) for screening. A three-level screening procedure was used to ensure the most inclusive studies for the review. In level one screening, two reviewers (KS and AH, a cardiology fellow) independently screened titles and abstracts based on the pre-specified study eligibility criteria. The purpose of this step was to include as many studies as possible that were potentially relevant to our NMA. Prior to the screening of all titles and abstracts, screening was piloted to ensure

consistency between reviewers in using the screening criteria. Duplicates and irrelevant abstracts were excluded, but relevant abstracts published in non-English languages were kept at this stage. Any discrepancies were resolved by discussion with an experienced cardiologist (RB). In level two screening, the same reviewers independently screened the same set of full texts of reports included in level one. In this stage, non-English citations were excluded if the full-texts were not available in English. Again, a third reviewer (RB) was consulted to resolve any disagreements. The first two levels of screening were done independently and in duplicate to minimize the risk of measurement errors. Lastly, after completing the first two levels of screening, one reviewer (KS) checked reference lists of eligible studies and relevant reviews to find eligible studies that were not identified from the electronic searches, and a third reviewer (RB) was asked to confirm the study's eligibility. Reasons for exclusion were recorded.

3.4 Data Extraction for Descriptive Statistics

After the screening, we extracted information from the eligible studies. Data were extracted using a comprehensive data extraction form, which was pilot-tested on ten randomly-selected eligible studies by one reviewer (TC, an interventional cardiology fellow) and refined by another reviewer (KS) accordingly. One reviewer (KS) then extracted data from all included studies using the final version of the data extraction form and secondary reviewers (AH and TC) checked the extracted data for accuracy and completeness. Any disagreements were resolved by consulting a third reviewer (RB). The following information was collected for descriptive purposes:

Study characteristics: Inclusion and exclusion criteria, number of randomized patients per study arm, accrual period of the study, study setting (e.g., single or multicenter), clinical setting, CABG type (on- or off- pump), heparin or antifibrinolytic use during CABG, antithrombotic status prior to CABG, country of conduct, Cochrane risk of bias, and length of follow-up.

Patient characteristics: Mean age, mean number of bypass grafts per patient, mean of LVEF, proportion of male patients, and proportion of patients with diabetes mellitus,

hypertension, prior MI, prior CVA, or dyslipidemia. Data on chronic kidney disease, and heart failure at baseline were collected as per protocol, however these were not reported in this NMA due to limited or no data.

Intervention characteristics: Type, dose, and frequency of antithrombotic agents, definition of placebo/control, duration of treatment, and timing for the start of treatment.

Outcomes: Clinical event rates (number of patients with MACCE, major bleeding, CVA, MI, minor bleeding, intracranial bleeding, repeat revascularization, heart failure, or re-exploration for bleeding; number of patients that were hospitalized due to cardiovascular cause, number of deaths) per study arm; number of patients with at least one occluded SVG per study arm; number of occluded SVGs, number of total SVGs, and average number of SVGs analyzed per patient per study arm; rates of loss to follow-up (with reasons), time and method of outcome assessment, study author definitions of outcomes, and number of patients analyzed per study arm.

Publication details: Year of publication and first author.

Included studies had to have at least two eligible study arms. If studies had two or more eligible intervention arms of the same product but at different doses, we included the study arm that had the most complete follow-up data. If a study presented results from more than one time point separately in multiple publications, we kept all publications and treated them as a single study.

It is important to obtain data on these baseline characteristics as it allows us to visually assess the distributions of clinical characteristics of patients and methodological characteristics of studies both across included studies and across treatment comparisons, to understand the baseline risk profile of patients in each study, to appreciate changes (if any) in clinical practice over time, and to identify potential sources of heterogeneity.

3.5 Data Extraction for Meta-Analysis and Network Meta-Analysis

There are two different types of input data for meta-analysis and NMA: arm-level data (the observed outcomes are reported for each study arm) and contrast-level data (the relative effect measures are reported in a study). We extracted arm-level data from all included studies due to the availability of arm-specific data. As a base case, we included outcome data with the longest follow-up for studies that reported results at more than one time point as per Cochrane guidelines.⁷⁵

Our outcomes of interest were all binary. If enough studies (i.e., at least two studies per outcome) with direct comparisons were available, we performed pairwise meta-analysis and at least 10 studies per outcome for NMA. Outcomes included for pairwise meta-analysis were SVGF; number of deaths; number of patients with MI (fatal or non-fatal), CVA (any stroke or TIA), re-exploration for bleeding, major bleeding, MACCE and minor bleeding. Outcomes included for NMA were SVGF, major bleeding, all-cause mortality, and MI. We attempted to collect data on heart failure, admission to hospital due to cardiovascular cause, and need for RBC transfusions, but did not include them in the meta-analysis due to limited data.

It is important to obtain information about potential effect modifiers as it allows us to make comparisons between treatment contrasts and to evaluate whether the included studies were sufficiently similar. A similar distribution of these variables between studies suggests that homogeneity is likely to be present, and a similar prevalence of effect modifiers between treatment comparisons suggests that the transitivity assumption is less likely to be violated and that NMA is possible (details in Chapter 2.2.2). We therefore pre-specified several potential effect modifiers in our protocol as sources of heterogeneity and incoherence. Potential effect modifiers included antifibrinolytic use during surgery, timing for the start of treatment, CABG type, and clinical setting. These variables were chosen based on clinical expectations that they may influence SVG patency (see Chapter 1.3.2). Other potential effect-modifiers were SVG flow, diameter of diseased artery,

comorbidities, and sex. However, they were not included in our list as individual patient-level data is required.

3.6 Risk of Bias Within Individual Studies

To assess the methodological quality of eligible studies, one reviewer (KS) performed a risk of bias assessment which was double checked by secondary reviewers (TC and AH).⁷⁵ There are several quality assessment tools available for randomized studies.^{110 124-128} In this NMA, we evaluated the risk of bias of each included study using the Cochrane Collaboration RoB tool,¹¹⁰ which is the standard approach for quality assessment of randomized trials.¹²⁹ Unlike other existing tools, the Cochrane Collaboration RoB tool does not use checklists nor a numerical quality assessment scale based on the rationale that numeric scores are not sufficiently discriminatory to identify studies with high risk of bias beyond qualitative assessment alone.¹³⁰ Instead, this standard tool uses the domain-based rating system, which incorporates six bias domains (see Chapter 2.3.2). For each domain, we assessed the risk of bias related to trial results (i.e., internal validity) on an outcome level and whether potential sources of bias were addressed in the included studies.¹¹⁰ The judgement about risk of bias was made based on theoretical and empirical considerations as well as the unique circumstances of each study. The answer to each domain was assigned a score of “high risk”, “low risk”, or “unclear risk”, and as per Cochrane guidelines,⁷⁵ to ensure transparency in how assessments were made each domain was accompanied by a concise description on the basis of judgements and quotes supporting them.

No modifications to the Cochrane Collaboration RoB tool were made. Despite the difficulty of blinding vitamin-K antagonists, the risks of performance bias and detection bias were fairly assessed in all included studies regardless of the interventions. We assessed incomplete outcome data separately for primary and secondary outcomes because a higher rate of loss to follow-up for assessment of SVG patency was expected during the study.

3.7 Selection of Data for Analysis

3.7.1 Choice of interventions

Each intervention included in this NMA forms a node in the network. We clustered different regimens (dose and frequency) of an antithrombotic agent in the same node as comparing intervention regimens is beyond the scope of this NMA. We assumed that there would be no systematic differences in intervention effects (beyond sampling error) between regimens. We also kept aspirin monotherapy as a single node, regardless of whether aspirin was started before or after CABG, since aspirin has been strongly recommended to be administered preoperatively and restarted within six hours after surgery,⁶ and regardless of whether aspirin was interrupted or continuously taken before CABG (7 to 10 days), since an unpublished meta-analysis failed to show a significant difference between the two groups.¹³¹

3.7.2 Choice of time points

As stated before, if studies were followed by another publication in the same population, data from studies with the longest duration of follow-up were included as a base case.

3.7.3 Choice of units of analysis

For the primary outcome, the choices for the units of analysis were the patient and the SVG/distal anastomosis. It is unclear whether the investigators in the included studies chose the unit of analysis based on clinical considerations or statistical efficiency. The patient approach may be more clinically relevant, as the interventions are naturally applied to the patient, and not the individual graft. Although patients generally received multiple grafts, studies that reported results expressed on a per patient basis typically presented SVG occlusion data as a proportion of patients with at least one occluded SVG. This outcome may have been chosen by investigators to avoid the issue of dependency between SVGs within a patient. In other words, this outcome may have been selected to satisfy the assumption of statistical independence, though at the expense of lower statistical power (inflated type II error).¹³²

On the other hand, the per graft approach may have been preferred as it does not compromise power.¹³² SVG occlusion data reported as per graft however present a particular statistical challenge because grafts in the same patient tend to respond similarly with respect to failure compared to grafts between different people, possibly because they are under the same circulatory system.^{132 133} Clustering effects must be therefore considered in the analysis, as otherwise the assumption of statistical independence is violated and it may result in over precision (i.e., underestimated standard errors, narrower CIs, and inflated type I error) because the same patient is potentially counted more than once (across multiple grafts). There are several statistical approaches used to handle clustering effects in the context of a meta-analysis, such as the ratio-estimator approach or the adjusted Mantel-Haenszel test.¹³⁴ To use one of these approaches, information such as the variance of the ratio estimate, intra-cluster correlation (ICC, the proportion of total variation in the outcome being measured at the patient level), and number of SVGs per patient are required. Due to limited individual patient-level data, we were unable to compute variance of the ratio estimate or ICC. However, we could calculate the effective sample size (ESS, defined as sample size after accounting for clustering effects) for each arm in studies that provided number of SVGs per patient. We considered it appropriate to use the ESS in the analysis rather than the original number of vein grafts provided by the included studies, as it accounts for the lack of independence. The ESS was estimated based on the design effect.¹³⁵ The design effect was a correction factor that included ICC and average number of SVGs per patient. The ICC was obtained from a published study.¹³³ Using Generalized Estimating Equation with an exchangeable correlation structure (i.e. the outcomes of the same patient are assumed equally correlated), the author estimated an ICC of 0.177 indicating a moderate degree of dependency. Then, the design effect was also applied to the number of events to obtain the number of occluded SVGs with clustering. As a result, the total number of SVGs and the number of occluded SVGs were reduced after correlation between SVGs was considered. We planned to use the originally reported outcome data if studies did not provide enough information. However, all studies provided sufficient data.

Unfortunately, not all included studies reported SVGF rates on a per-patient basis. There were studies that reported results both on a per-patient basis and a per-graft basis, but a

few reported results only from a per-graft analysis. To address the issue of partial reporting, the unit of analysis of this NMA depended on the consistency of effect estimates between the per-patient (patient with at least one occluded SVGs) and per-graft (with clustering) meta-analyses across treatment comparisons.

After conducting a separate meta-analysis for each unit of analysis, we found that the results between per patient and per graft were consistent (i.e., similar direction and large overlaps in the 95% CIs of effect sizes) in most comparisons. We therefore considered it appropriate to combine data from the two units of analysis: the patient and the SVG, for the NMA, assuming that there are no systematic differences between the units of analysis. In other words, we combined studies that reported the per-patient data with those that only reported the per-graft data and made an inference at the patient level (our base case). Inference at the patient level is highly preferable as treatments will be given on an individual basis. Unfortunately, we could not compare the consistency of results between the two levels using NMA as some studies did not provide sufficient data, which made it impossible to qualitatively compare results between NMAs with missing nodes. The credibility of this data-driven approach at the NMA level is unclear and therefore, the findings of the NMA should be interpreted with caution.

3.8 Statistical Analysis

Descriptive statistics were presented as percentages for categorical variables, and mean \pm standard deviation (SD) or median (range or interquartile range, [IQR]) for continuous variables. We performed pairwise meta-analysis using Review Manager version 5.3 (Nordic Cochrane Center, The Cochrane Collaboration) and NMA using the *network* command, a user-written command (Stata version 13.1).¹³⁶ ITT was followed whenever possible. A two-tailed p-value of less than 0.05 was considered statistically significant.

3.8.1 Direct treatment comparisons

Pairwise meta-analyses were conducted to produce direct estimates needed to supplement the NMA results and to evaluate a potential violation against the coherence assumption of the network. The random-effects model with an inverse-variance method was chosen

over the fixed-effect model because we anticipated true variation in effects across studies.¹³⁷ The included studies were clinically and methodologically similar, but not identical because they were conducted in different settings with different intervention regimens and patient characteristics. In addition, fixed-effect models are not recommended for common outcomes such as SVGF due to risk of over-precision.⁷⁸

Empirical studies have shown that, for binary outcomes, results using relative measures (e.g., OR and RR) are more consistent (i.e., less heterogeneous) than absolute measures (e.g., RD) due to their insensitivity to baseline risk.^{138 139} We therefore chose relative measures over absolute measures to ensure more consistent effect sizes across studies regardless of baseline risk, although absolute measures are better at communicating a clinical impact of the intervention. Compared to RRs, ORs are more commonly used in a NMA and preferable because of their mathematical properties (i.e., symmetric properties), which overcome inferential fallacies.^{140 141} An example of this fallacy is that a drug was suggested to both improve SVG patency and increase SVG occlusion. Given these considerations, the causal relationship between interventions and outcomes was estimated using OR and its corresponding 95% CI. For ease of comparison between direct and network estimates, ORs were also selected as the appropriate effect measure for the pairwise meta-analysis.

The extent of clinical and methodological heterogeneity was evaluated through visual examination of important differences in patient/study characteristics (e.g., CABG type, clinical setting) and risk of bias between studies. In addition, we assessed the extent of statistical heterogeneity in the meta-analysis using the I^2 index. An I^2 of either 25%, 50%, and 75% indicates low, moderate, and high heterogeneity, respectively.⁸⁶

Whether studies with zero events in both arms should be excluded or not remains unclear.¹⁴²⁻¹⁴⁴ For transparency, we included studies with zero events in both study arms for all endpoints in the meta-analyses.¹⁴⁴ A correction factor of 0.5 was applied when a study contained a zero event in one of the study arms, which is a widely acceptable approach to account for zero events.¹⁴⁴ In each direct comparison, publication bias was assessed if sufficient (i.e., ≥ 10 studies per comparison) data were available.¹⁴⁵

3.8.2 Indirect and mixed treatment comparisons

NMA allowed us to compare multiple treatments within a single analytic framework by combining the direct and indirect evidence. However, before concluding that NMA was feasible, we assessed the two important assumptions: transitivity and homogeneity.

First, we evaluated the transitivity assumption by considering the first four of its equivalent expressions (Chapter 2.2.2.2 Transitivity).⁷⁴ After checking the assumption of transitivity and determining that transitivity was reasonable (see details in Chapter 4.6), we performed NMA. In terms of statistical framework, there is no consensus on whether a frequentist or Bayesian framework should be used for NMA. Despite the conceptual benefits of Bayesian approaches (see details in Chapter 2.2.3), because they require specification of priors, and because the study results may vary based on the chosen prior, we opted to use the frequentist approach to NMA in this research work. We also used the random-effects approach for the NMA to account for heterogeneity. To illustrate information on the data structure, we produced a network plot for outcomes with sufficient data (≥ 10 studies) including SVGF, mortality, and MI. In addition to these outcomes, major bleeding was also included in the NMA, though with < 10 studies, because of its clinical relevance. We also produced the contribution matrix to summarize the contribution (in %) of each direct estimate to the network estimates.¹³⁶

Though there is no formal way to statistically test the transitivity assumption, we assessed the statistical manifestation of this assumption, known as coherence.⁹⁴ The indirect comparison is valid when there is an agreement in treatment effects between direct and indirect estimates. For the comparative analysis to be possible, both direct and indirect estimates must be available together in a closed loop. We assessed the coherence assumption in two ways (globally and locally). The design-by-treatment interaction model was used to explore for evidence of incoherence in the entire network.¹⁰⁰ This approach was chosen over the other methods (e.g., Lu and Ades model) because the presence of multi-arm studies would not influence the results.¹⁴⁶ P-value < 0.1 was considered to be statistically significant global incoherence. We also assessed the presence of local incoherence. The loop-specific approach was used to explore evidence

of local incoherence within a closed loop in a network, assuming a common loop-specific heterogeneity variance.¹⁴⁷ This approach was chosen over the composite test because the composite test considers multiple closed loops whereas our networks had only a single closed loop. Moreover, though our chosen approach and the node-splitting method share similar strengths (e.g., generally unbiased) and limitations (e.g., low power and unable to account for correlation induced by multi-arm trials), the loop-specific approach is more straightforward and requires less computations.¹⁴⁸ The IF and its corresponding 95% CI were estimated and reported. If the 95% CI excludes zero, local incoherence is detected statistically.¹⁴⁷

In addition to transitivity, we also assessed homogeneity. To evaluate the clinical and methodological heterogeneity, we visually compared the distribution of clinical characteristics and risk of bias across included studies. In terms of statistical heterogeneity, we obtained heterogeneity variance (τ^2) by squaring the standard deviation of treatment effects estimated from the NMA model. We assumed a common heterogeneity variance (τ^2) across all comparisons, as all treatments of interest are similar in a sense that they principally act to inhibit clotting factors.^{149 150} The magnitude of the estimated τ^2 was then compared with the empirical distribution of between-study heterogeneity variances to investigate the extent of heterogeneity.¹⁵¹ An estimated τ^2 of either <50%, 50% to 75%, and >75% quantile of the empirical distribution was considered low, moderate, and high heterogeneity, respectively.¹⁴⁹

Of note, when a treatment comparison is part of a closed loop, the network estimate is the weighted average of the two sources of evidence: direct and indirect evidence. When a treatment comparison provides either only direct evidence or only indirect evidence, the network estimate reflects only one of them.

3.8.2.1 Treatment ranking

We used the surface under the cumulative ranking (SUCRA) with 10,000 samples drawn from the distribution of summary treatment effects to calculate the mean rank for each intervention.¹³⁶ We ranked the interventions for each of the four outcomes. A larger SUCRA value indicates a more effective treatment.

3.8.2.2 Small-study effects

For outcomes that had sufficient data (≥ 10 placebo-controlled studies), a comparison adjusted funnel plot was created to explore the potential small-study effects in the network by comparing all active treatments against placebo/control.¹³⁶

3.9 GRADE

As per protocol, we assessed the quality of evidence using the GRADE approach (see details in Chapter 2.3.2). In this NMA, the OIS for SVGF ranged between 434 and 905 patients (in one arm), based on the following assumptions: alpha of 0.05, beta of 0.20, 10 to 20% of patients with SVGF, and medically worthwhile treatment effect of 5 to 15%. For MI, the OIS was about 2,073 patients per arm (incidence of 6.6%¹⁵² and a 2% absolute reduction with the therapy). For mortality, the OIS was about 18,330 patients per arm (rate of 0.5 to 14%¹⁵² and a 1% absolute reduction).

3.10 Missing Outcome Data

We tried to gather missing information by contacting the study authors. However, of 16 authors whom were contacted for further information, four responded but no one provided data needed for the NMA. Obtaining missing outcome data from secondary sources was also attempted.

In addition, we also used a statistical approach to handle missing data. Using empirical data, Spinelis *et al*¹⁵³ evaluated several different imputation assumptions: missing at random model, all missing failures model, all missing successes model, best-case model, worst-case model, common informative missing OR, treatment-specific informative missing OR (either on average missing at random, more missing failures, more missing successes, more failures in placebo, or more success in placebo). Compared with the other assumptions, the worst- and best- case models were found to increase heterogeneity markedly and were considered extreme assumptions. Moreover, this study found that the ‘all missing failure’ model was robust to small changes in the uncertainty and the

SUCRA values. Given this consideration, we handled missing outcome data using the ‘all missing failure’ model, which assumes that all missing patients have a negative event.

3.11 Sensitivity Analysis for SVGF

We did not perform our preplanned sensitivity analyses because the analyses would result in removal of nodes from the network altering the geometry of the network. Previous studies found that changing the network pattern may substantially change the effect sizes and/or treatment rankings and increase the likelihood of incoherence.¹⁵⁴⁻¹⁵⁶ Therefore, comparing results between primary analyses and sensitivity analyses with different network geometries may not be meaningful.

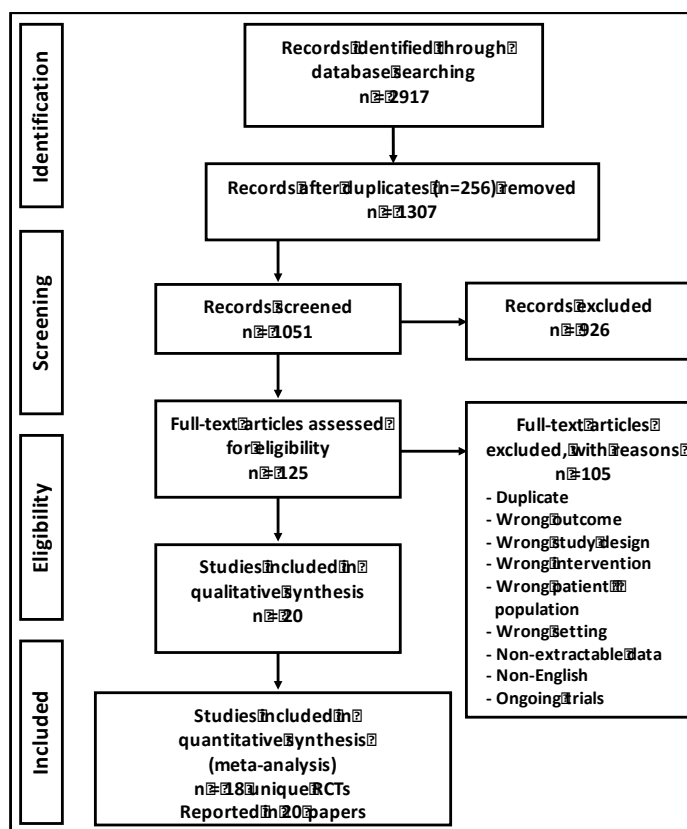
A series of post hoc sensitivity analyses was undertaken instead. First, we performed a sensitivity analysis including only per-graft data to determine the impact of unit of analysis on study findings. Another sensitivity analysis focused on duration of follow-up. The primary analyses for SVGF endpoint included studies with the longest follow-up data; however, this approach may lead to increased heterogeneity because the included studies had different lengths of follow-up. To explore the potential effect of duration of follow-up on treatment effects, a *post hoc* sensitivity analysis was performed by including only angiographic data that were collected closer to one year post CABG. In addition, we performed another *post hoc* sensitivity analysis excluding studies of OPCAB (only) surgery, a type of surgery that is less commonly used (~17%),¹⁵⁷ to explore the impact of outlier on study findings.

Chapter 4

4 Results

4.1 Literature Search

Figure 2 shows the study selection process. We identified a total of 2,917 titles and abstracts through the literature search. Of these, 125 articles were potentially eligible for inclusion and considered for full article review. One hundred and five articles were then excluded if they were duplicates or non-English, reported the wrong outcome (i.e., did not assess SVG patency), wrong interventions (e.g., combine aspirin with dipyridamole or ticlopidine), wrong patient population (e.g., randomization did not occur in proximity [seven days] to CABG), or wrong study design (e.g., subgroup analysis of RCTs), or if they were ongoing trials. Twenty articles describing 18 unique studies were deemed eligible and included. Of these, two articles were longer term follow-up of the original studies.^{64 158} The longest available follow-up for each of the 18 studies was used as our base case. The list of studies deemed to be excluded and the reasons for exclusion can be found in Supplementary Appendix eTable 7.

Figure 2. Study selection process

Flow diagram based on PRISMA

4.2 Study and Patient Characteristics

A total of 18 parallel-group RCTs^{64 158-174} with 3,413 patients (range: 20 to 635 patients per trial) and six eligible treatment arms met the inclusion criteria for our NMA. All included studies were published between 1979 and 2017, of which, 50%^{161 162 165 167 169-172 174} were single-center trials. Nine (50%) studies^{64 159-165 167} were placebo-controlled trials and 10 (56%)^{158 160 166 168-174} were head-to-head trials. Of 18 studies, one (6%)¹⁶⁰ was multi-arm with three eligible arms. Most trials (56%) performed CABG surgery in an elective setting, and five (28%) trials^{159 160 169 173 174} combined elective and urgent cases. Nine (50%) studies^{159 161-166 171 174} included patients who underwent CABG with CPB and two (11%)^{168 172} without CPB, whereas three (17%) studies^{158 169 170 174} included a mixture of patients with CPB and without CPB. Most studies were short-term studies, with a

longest time of angiographic follow-up ranging from eight days to eight years (\leq three-month follow-up from four studies,^{164 168 170 171} four- to 12-month follow-up from nine studies,^{159 161-163 167 169 172-174} and >12 -month-follow-up from five studies^{64 158 160 165 166}). In studies reporting duration of treatment (n=17 trials),^{64 158-168 170-174} the included patients received study medications as a single-dose 12 hours before CABG¹⁶⁴ or a regular-dose for one to 12 months. All studies reported SVGF on a per-graft basis as an outcome measure, but only 12 studies^{64 159-167 171 175} reported the outcome on a per-patient basis and 13 studies^{158-161 163-166 170-174} reported at least one of major clinical endpoints (major bleeding, mortality, CVA and/or MI). Detailed information for trial characteristics is summarized in Table 1 and eTable 8.

In studies that reported baseline characteristics, the mean age ranged from 44 to 83 years and 2,655 (89%) patients were male. A total of 528 (21%) patients underwent CABG without CPB and 2,596 (95%) were elective patients. There were 409 (18%) patients with diabetes, 824 (48%) with dyslipidemia, 1,445 (55%) with prior MI, 109 (14%) with prior PCI, 16 (3.7%) with prior CVA, and 1,361 (47%) with hypertension. Across studies, mean of SVGs per patient and percentage of male participants were comparable. The proportions of patients with at least one concomitant condition were also reasonably similar across studies. Overall, the included trials were deemed sufficiently similar in terms of observed demographic and clinical characteristics.

Five active interventions included in this NMA were aspirin monotherapy, clopidogrel monotherapy, vitamin-K antagonists, dual-antiplatelet therapy with aspirin and clopidogrel, and dual-antiplatelet therapy with aspirin and ticagrelor. These agents were compared either with inactive control/placebo or each other. Across treatment comparisons, the percentage of males was similar. The distribution of other baseline characteristics was generally balanced across comparisons, except for CABG type and timing for the start of treatment. CCAB patients were more prevalent in comparisons that included earlier studies (before 2000). In general, the timing for the start of treatment varied across treatment comparisons ranging from seven preoperative days to four postoperative days. Detailed information for patient characteristics is summarized in Table 2 and eTable 9.

Table 1. Summary of characteristics of trials included in pairwise meta-analysis and NMA (n=18 RCTs)

RCT Characteristics	No. of RCTs (%)
Year of publication	
1979 – 1989	6 (33)
1990 – 2000	4 (22)
2001 – 2011	4 (22)
2012 - 2017	4 (22)
Study type	
Single center	9 (50)
Multicenter	6 (33)
Not reported	3 (17)
Surgical setting	
Elective	10 (56)
Urgent	0 (0)
Both	5 (28)
Not reported	3 (17)
CABG type	
CCAB	9 (50)
OPCAB	2 (11)
Both	3 (17)
Not reported	4 (22)
Outcomes assessed*	
Vein graft failure (Per patient)	12 (67)
Vein graft failure (Per graft)	18 (100)
Major bleeding	8 (44)
Mortality	11 (61)
Myocardial infarction	10 (56)
CVA	7 (39)
Longest time of patency assessment	
≤3 months	4 (22)
>3 to 12 months	9 (50)
>12 months (up to 8 years)	5 (28)
Control interventions*	
Placebo/control	9 (50)
Aspirin (usual care)	9 (50)
Length of treatment	
<3 months	2 (11)
3 to 12 months	15 (83)
>12 months	0 (0)
Not reported	1 (5.6)

*RCTs can report more than one outcome or comparator.

4.3 Risk of Bias

Overall, the study-specific risk of bias ranged from low to high (eFigure 1 and eFigure 2). Most studies were judged to have a low risk of bias for random sequence generation (61%), blinding of patients (56%), blinding of outcome assessor (78%), selective reporting (78%), and other bias (94%). In terms of allocation concealment, 78% of studies did not report details.

Of five (28%) studies^{159-161 166 170} that reported failure to blind, three^{159 160 166} explained that the need for International Normalized Ratio (INR) monitoring of vitamin-K antagonists therapy prevented them from blinding patients and personnel. Eleven (61%) studies^{64 158-164 166 167 171} were at high risk of bias related to incomplete patency data owing to the high proportion of loss to follow up (16% to 49%) and/or uneven proportions and/or reasons for loss to follow up between arms. Unlike the primary outcome, all studies contributing to the secondary outcomes were judged to have a low risk of bias for incomplete outcome data. A greater risk of bias for the primary outcome is not surprising, as not all patients could return for angiographic assessment for various reasons including refusal or development of contraindications for angiography during follow-up (e.g., renal failure). In terms of selective reporting, three studies^{162 168 169} were at unclear risk of bias as they did not report data on at least one of our secondary clinical outcomes, and one study¹⁶⁷ was at high risk of bias because it did not report any clinical outcome data. In addition, only one trial¹⁶² had a high risk of bias due to other bias owing to the imbalance in a few clinical characteristics between study groups despite randomization.

Through visual inspection, the comparison-adjusted funnel plot appears symmetric suggesting that there was no evidence for small-study effects for placebo-controlled trials assessing SVGF (eFigure 4).

Table 2. Summary of baseline characteristics of patients undergoing CABG across treatment comparisons (n=18 RCTs)

Characteristics	No. of RCTs with data	Aspirin vs Control n=8 RCTs	Vit K A vs Control n=2 RCTs	Vit K A vs Aspirin n=2 RCTs	ASA/Clo vs Aspirin n=6 RCTs	ASA/Clo vs Clopidogrel n=1 RCT	ASA/Tic vs Aspirin n=1 RCT
Age (mean±SD)	14	58±7.72	53±8	58±8	61±8.16	62±9.94	62±8.67
Male	15	1212/1278 (95)	129/148 (87)	632/722 (88)	599/736 (81)	163/197 (83)	61/70 (87)
DM	12	45/560 (8)	18/111 (16)	74/722 (10)	168/756 (22)	108/197 (55)	21/70 (30)
HTN	14	528/1218 (43)	20/111 (18)	250/722 (35)	417/756 (55)	125/197 (64)	54/70 (77)
Dyslipidemia	8	27/116 (23)	NR	271/616 (44)	426/736 (58)	41/197 (21)	59/70 (84)
Prior MI	12	703/1076 (65)	74/111 (67)	401/722 (56)	253/623 (41)	105/197 (53)	12/70 (17)
Prior PCI	4	NR	NR	NR	77/524 (15)	24/197 (12)	8/70 (11)
Prior CVA	3	NR	NR	NR	16/436 (3.7)	NR	NR
CCAB	14	862/862 (100)	37/37 (100)	616/616 (100)	321/776 (41)	124/197 (63)	NR
Antifibrinolytic use	2	NR	NR	NR	399/399 (100)	NR	NR
Elective surgery	15	932/1006 (93)	73/145 (50)	695/755 (92)	776/776 (100)	186/197 (94)	47/70 (67)
Time of drug	18	7 preop to 5	3 to 4 postop	12 preop hours	Immediately	1 day	58 to 59

initiation (range)	postop days	days	to 4 postop days	postop to 48 hours	postop hours
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Values presented as n/N (%) unless stated otherwise. All information was obtained from first publications. ASA/Clo: Dual-antiplatelet therapy with aspirin and clopidogrel. ASA/Tic: Dual-antiplatelet therapy with aspirin and ticagrelor. NR: Not reported. Preop: preoperative. Postop: postoperative. Vit K A: Vitamin-K antagonists.

4.4 Direct Estimates

4.4.1 Primary outcome

A pairwise meta-analysis of eight RCTs (n= 1,182 patients) showed that dual-antiplatelet therapy with aspirin and clopidogrel significantly reduced SVGF compared to aspirin monotherapy (OR: 0.60; 95% CI: 0.42-0.88). In a separate meta-analysis of six RCTs (n= 1,085 patients), aspirin monotherapy significantly decreased the odds of SVGF by 38% (OR: 0.62; 95% CI: 0.43-0.90) relative to placebo/control. Furthermore, there was no evidence of significant differences among other treatment comparisons. The direct estimates were consistent in magnitude and direction between base case analyses and per-graft analyses for all comparisons (eTable 10).

4.4.2 Secondary outcomes

In a pairwise meta-analysis of four RCTs, of 506 patients assigned to aspirin monotherapy group, 34 (6.72%) patients underwent re-exploration for bleeding, and of 485 patients assigned to placebo/control group, 9 (1.86%) patients had the event (OR: 3.59; 95% CI: 1.67-7.73; eTable 10). No significant differences between interventions in major bleeding, mortality, MI, CVA, repeat revascularization, minor bleeding, and MACCE were found (eTable 10).

4.5 Network Estimates, Treatment Ranking, and Contribution of Direct Evidence

4.5.1 Primary outcome

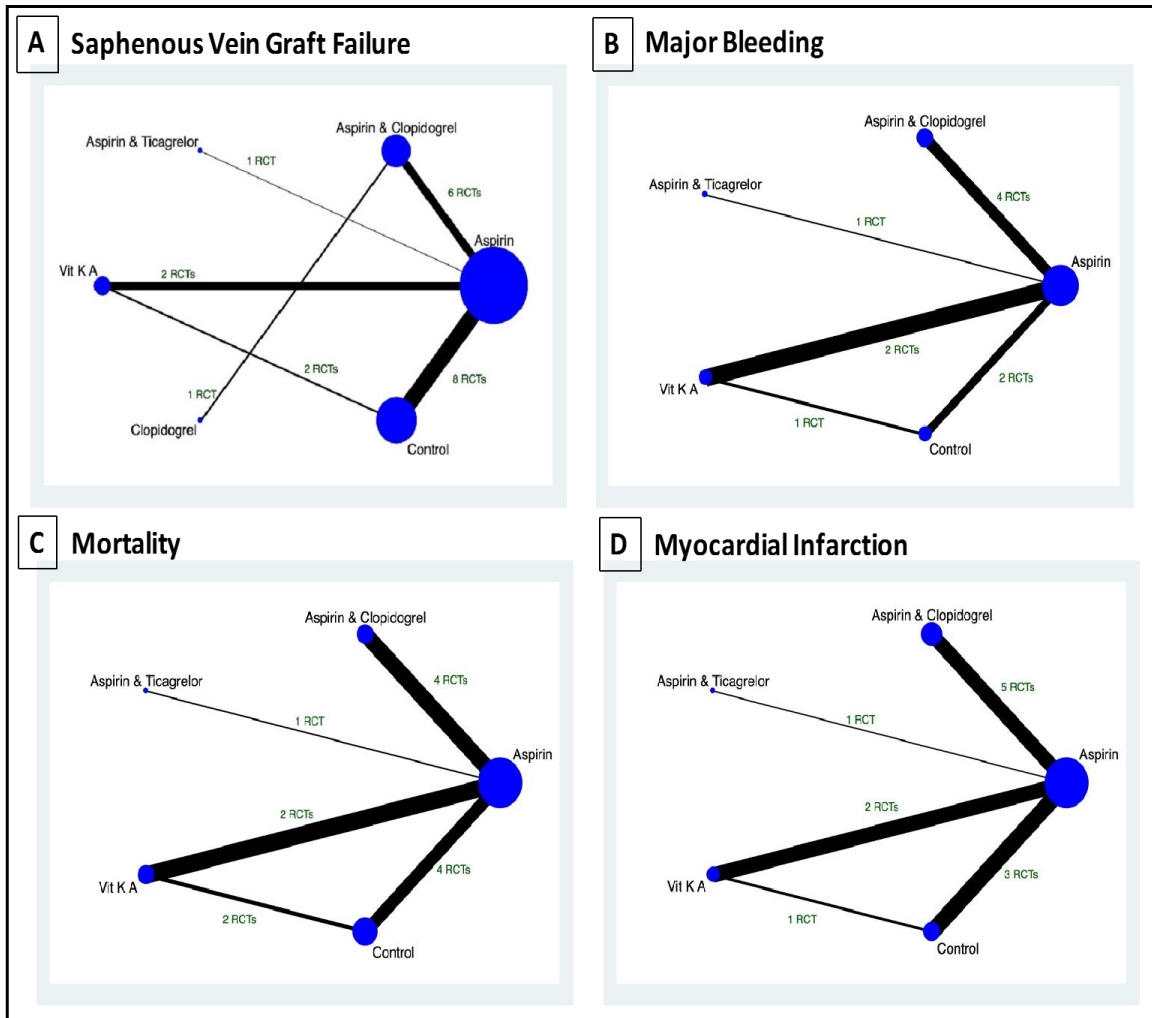
Figure 3 shows the network of evidence for SVGF. Eighteen studies^{64 158-174} with six treatment arms including 15 unique treatment comparisons were included in a NMA for SVGF. Of the 15 comparisons, four were statistically significant with three treatments were found to be more effective than placebo/control and one treatment was superior to aspirin monotherapy. More specifically, when compared with placebo/control, dual-antiplatelet therapy with aspirin and clopidogrel (OR: 0.40; 95% CI: 0.24-0.69), dual-

antiplatelet therapy with aspirin and ticagrelor (OR: 0.25; 95% CI: 0.07-0.94), and aspirin alone (OR: 0.64; 95% CI: 0.47-0.88) significantly reduced the odds of SVGF. In addition, dual-antiplatelet therapy with aspirin and clopidogrel had a statistically significant benefit in preventing SVGF relative to aspirin alone (OR: 0.63; 95% CI: 0.41-0.97). The network estimates were consistent in magnitude and direction between base case analyses and per-graft analyses for all comparisons, except for the network estimate of vitamin-K antagonists versus placebo/control (eTable 11). The difference is likely owing to a greater statistical power with the per-graft data (i.e., larger number of occluded SVGs and larger sample size in the two direct comparisons contributing to the network estimate) than with the base-case data. The direct and network estimates for all treatment comparisons can be found in Figure 4.

eTable 12 presents the SUCRA value for all interventions. According to the SUCRA, dual-antiplatelet therapy with aspirin and ticagrelor was ranked the best in preventing SVGF with a SUCRA of 89, followed by dual-antiplatelet therapy with aspirin and clopidogrel (SUCRA=80), vitamin-K antagonists (SUCRA=46), aspirin monotherapy (SUCRA=44), clopidogrel monotherapy (SUCRA=33), and placebo/control (SUCRA=8.4). The numerical values of SUCRA between the base-case analysis and the per-graft analysis were similar (eTable 12).

Lastly, the direct comparison of aspirin monotherapy and dual-antiplatelet therapy with aspirin and clopidogrel had the largest contribution to the network analyses (27.7%). Detailed information for contributions of direct evidence in the entire network can be found in eTable 13.

Figure 3. Network of RCTs comparing the effect of antithrombotic agents on saphenous vein graft failure (A), major bleeding (B), mortality (C), and myocardial infarction (D)



The size of the nodes (circles) and edges (lines) are proportional to the number of studies evaluating a particular treatment and the number of patients who contribute to the direct comparison, respectively.

Figure 4. Summary of direct and network estimates for SVGF

Control	0.77 (0.21-2.86)	0.64 (0.47-0.88)	0.63 (0.37-1.06)	0.25 (0.07-0.94)	0.40 (0.24-0.69)
--	Clopidogrel	0.83 (0.23-2.96)	0.81 (0.21-3.15)	0.32 (0.05-1.98)	0.52 (0.16-1.73)
0.62 (0.43-0.90)	--	Aspirin	0.98 (0.61-1.57)	0.39 (0.11-1.42)	0.63 (0.41-0.97)
0.68 (0.30-1.51)	--	0.94 (0.66-1.35)	Vit K A	0.40 (0.10-1.57)	0.64 (0.34-1.22)
--	--	0.39 (0.12-1.32)	--	Aspirin & Ticagrelor	1.62 (0.41-6.31)
--	0.52 (0.17-1.60)	0.60 (0.42-0.88)	--	--	Aspirin & Clopidogrel

Top diagonal (network estimates): column- versus row-defining treatment
Bottom (direct estimates): row- versus column-defining treatment

Estimates are presented as OR and its corresponding 95% CI. The bolded estimates are statistically significant.

4.5.2 Secondary outcomes

Figure 1 shows the network of treatment comparisons for secondary outcomes. Each outcome involves five arms with an identical set of interventions. Unlike the primary outcome, clopidogrel monotherapy was not part of the network for the secondary outcomes as the only study¹⁶⁹ evaluating clopidogrel monotherapy did not report data on any of our secondary outcomes.

In the NMA, there were eight studies^{158 160 165 166 171-174} including 1,690 patients for major bleeding, eleven studies^{158-161 163 165 166 170-173} including 2,396 patients for mortality, and ten studies^{158 160 164-166 170-174} including 2,644 patients for MI. For each of these secondary outcomes, there were 10 unique treatment comparisons in a network with no evidence of any statistically significant differences among these comparisons (eFigure 3 and eTable 11).

According to the SUCRA, placebo/control was the best strategy in reducing major bleeding with a SUCRA value of 83, followed by dual-antiplatelet with aspirin and

clopidogrel (SUCRA=60), aspirin monotherapy (SUCRA=47), dual-antiplatelet with aspirin and ticagrelor (SUCRA=46), and vitamin-K antagonists (SUCRA=14). In addition, dual-antiplatelet therapy with aspirin and clopidogrel (SUCRA=71) was most effective in preventing MI, but dual-antiplatelet therapy with aspirin and ticagrelor (SUCRA=66) was best for improving survival (eTable 12).

Lastly, the direct comparison of vitamin-K antagonists and aspirin monotherapy had the largest contribution to the network analysis for major bleeding and MI (34% and 37%, respectively, eTable 13). Dual-antiplatelet therapy with aspirin and clopidogrel versus aspirin monotherapy was the comparison with the most contribution to the entire network for mortality (24%).

4.6 Assessment of Transitivity, Homogeneity, and Coherence

We assessed the transitivity assumption using its own four expressions:

1. First, we suspected that not all treatments were sufficiently similar across trials. While trials investigating the effect of dual-antiplatelet therapy with aspirin and clopidogrel used similar regimens, higher aspirin doses were given to patients who participated in earlier studies. Also, for control arms, two trials^{159 161} provided no study medications to patients, while the remaining studies administered matching placebo. Therefore, the control arms in the vitamin-K antagonists studies may not be similar to control arms in earlier studies or in the aspirin monotherapy studies.
2. Second, we felt it is appropriate to conclude that the choice of comparator may not be influenced by the authors' expectations in the magnitude and/or direction of treatment effects. In early days, placebo was used as a comparator; but after the benefit of aspirin was established in published trials, most trials compared the intervention of interest with aspirin monotherapy. Hence, it may be justifiable to assume that the missing arms were missing at random.
3. Third, we visually inspected the network plot and qualitatively examined the comparability of the distribution of potential effect modifiers, which were pre-

specified, across treatment contrasts. We assumed that the effect modifiers were not systematically different between treatment comparisons (Table 2). Although the proportion of CCAB and the timing for the start of treatment varied across comparisons, we felt these differences may not have enough strength to substantially influence treatment effects. Due to limited data on antifibrinolytic use, it was not possible to compare the distribution of this variable across comparisons in this network.

4. Fourth, we felt it was appropriate to assume that the type of participants included in these studies could conceivably have been eligible to be randomized to any of the included interventions. Patients with a history of bleeding were excluded in all studies, thus, equipoise between participating in a vitamin-K antagonist trial and participating in a non-vitamin-K antagonist trial would equally apply, despite the known bleeding risk of vitamin-K antagonists.

In summary, though we could not definitively rule out the possibility of intransitivity, we judged that the assumption of transitivity sufficiently holds based on the current evidence since there was no good evidence to the contrary.

In terms of the homogeneity assumption, we identified low to moderate heterogeneity (I^2 of <75%) for all outcomes based on pairwise meta-analyses. In the network, the between-trial variance (τ^2) was 0.047, 5.38×10^{-22} , 1.93×10^{-17} , and 1.08×10^{-14} for SVGF, major bleeding, mortality, and MI, respectively (see eTable 11). The estimated τ^2 for SVGF was lower than the 50% quantile of heterogeneity estimates (up to 1.10) obtained from an empirical meta-analysis for a subjective outcome.¹⁴⁹ Similarly, the heterogeneity variance for all-cause mortality was lower than the corresponding 50% quantile of the empirical τ^2 (up to 0.007). Lastly, the heterogeneity variance for semi-objective outcomes (i.e., major bleeding and MI) was also lower than the 50% quantile of the empirical distribution (up to 0.016). Overall, we identified low heterogeneity in our networks, which suggests that heterogeneity is probably less likely to threaten internal validity.

With regards to the coherence assumption, there was a lack of evidence of local incoherence for all outcomes: SVGF (IF: 0.25 (95% CI: 0.00-1.42)), major bleeding (IF:

0.30 (95% CI: 0.00-1.12)), mortality (IF: 0.85 (95% CI: 0.00-5.22)), and MI (IF: 3.33 (95% CI: 0.00-7.06); see eTable 14). In addition, the design-by-treatment interaction model found no evidence of incoherence in the entire network for SVGF (P= 0.834), major bleeding (P= 0.632), mortality (P=0.476), and MI (P=0.191; see eTable 15).

4.7 Quality of Evidence

For the primary outcome, no serious risk of bias and no inconsistency was detected for all direct comparisons, except for those involving vitamin-K antagonists, in which blinding was a challenge. All direct comparisons were at risk of indirectness due to: 1) the use of aspirin at doses higher than the currently recommended (75 to 100 mg/day)²¹; 2) the use of a surrogate outcome (SVGF), which has not yet been validated for its relationship to the outcomes that matter, including acute MI and death; and 3) the short duration of treatment (e.g., one month) and follow-up (e.g., eight days) for SVGF, which are not very applicable to the real-world situation, where long term treatment and data are of interest. In addition, the evidence was rated down for imprecision because of the wide 95% CIs with small number of events and sample size for most direct comparisons. The overall quality of the direct evidence therefore ranged from very low to moderate, in which the comparisons of aspirin monotherapy versus placebo/control and dual-antiplatelet therapy with aspirin and clopidogrel versus aspirin monotherapy were of moderate quality. In terms of network evidence, the overall quality of evidence was very low, ranging from very low to moderate, primarily due to the wide 95% CIs of network estimates and the probable intransitivity. In the network, we found eight comparisons (53% of all comparisons) of very low quality, three (20%) of low quality, four (27%) of moderate quality. Notably, the network evidence for most comparisons of active drugs versus placebo/control was moderate quality because the magnitude of significant effect sizes reached <0.5 , and the only head-to-head comparison with moderate quality was dual-antiplatelet therapy with aspirin and clopidogrel versus aspirin monotherapy.

For secondary outcomes, there was no serious risk of bias and inconsistency for most direct comparisons, except for those studies using vitamin-K antagonists. Comparisons of any drugs versus aspirin monotherapy were at risk of indirectness as aspirin was

administered at higher doses than those that are currently used. For all direct comparisons, evidence was rated down for imprecision because the 95% CIs crossed the clinical decision threshold. The overall quality of direct evidence was therefore low, ranging from very low to moderate, in which the comparison of dual-antiplatelet therapy with aspirin and ticagrelor versus aspirin monotherapy was rated at moderate quality. In terms of network evidence, the overall quality was very low, ranging from very low to moderate, primarily due to the wide 95% CIs of network estimates and the possibility of intransitivity. In each of the networks, we found six comparisons (60% of all comparisons) of very low quality, three (30%) of low quality, one (10%) of moderate quality. Although the evidence for dual-antiplatelet therapy with aspirin and ticagrelor versus aspirin monotherapy was moderate quality, it is important to note that there was only one study available for this comparison. Detailed information regarding quality of direct and network evidence can be found in eTable 16 and eTable 17, respectively.

4.8 Post-hoc Sensitivity Analyses

To explore the potential impact of missing outcome data in the analyses, we conducted a sensitivity analysis for SVGF. eTable 18 and eTable 19 present the results of sensitivity analyses accounting for loss to follow-up. The results obtained from our primary analysis were similar to those from the ‘all missing failure’ models with respect to the effect estimates and the treatment rankings.

There were two studies with multiple follow-up data.^{158 160} When we included SVGF data that were collected closer to 1-year of CABG (a shorter follow-up i.e. up to two years) from these studies, the conclusions did not change substantially in terms of effect sizes, treatment rankings, and coherence (eTable 20).

Lastly, we performed another sensitivity analysis excluding studies^{168 172} that included only patients undergoing CABG without CPB (OPCAB) and found that the results were consistent with those obtained from the primary analyses (eTable 20), except for the comparison of dual-antiplatelet therapy with aspirin and clopidogrel versus aspirin monotherapy, which did not reach statistical significance. This may be owing to the

smaller sample size (i.e., lower statistical power) because of study removal or could be related to clinical differences in likelihood of SVGF in the context of OPCAB relative to CABG with CPB.

Chapter 5

5 Discussion

The aims of this chapter are to summarize the study findings, to compare them to the existing literature, and to discuss the limitations and the conclusions of the current NMA, including its implications for clinical practice and research.

5.1 Summary of Study Findings

A NMA was conducted to synthesize results from RCTs that assessed efficacy of different antithrombotic therapies in the prevention of SVGF to provide evidence-based guidance for optimal prophylactic management. In this NMA of 18 unique RCTs (n= 3,413 patients), we included six interventions for patients undergoing CABG and found that, based on moderate-quality evidence, patients receiving dual-antiplatelet therapy with aspirin and clopidogrel, a second-best treatment, had significantly lower odds of developing SVGF compared to either aspirin alone or placebo/control. Furthermore, though ranked the most effective agent, dual-antiplatelet therapy with aspirin and ticagrelor only significantly reduced SVGF relative to placebo/control, but not in comparison with any other interventions. Additionally, moderate-quality evidence showed that aspirin monotherapy was protective against SVGF relative to placebo/control. Besides the aforementioned comparisons, there were no significant differences found in any other treatment comparisons. These results (effect sizes and treatment rankings) were generally consistent across different units of analysis (base case versus per graft) and different durations of follow-up (longer [up to 8 years] versus shorter follow-up [up to 2 years]).

Our secondary objective was to conduct a NMA to assess the relative effects of antithrombotic agents on clinical outcomes. The present NMA could not demonstrate any significant differences in major cardiovascular adverse events (MI and mortality) and major bleeding amongst antithrombotic therapies.

5.2 Comparison to the Existing Literature

The current study is the first NMA to simultaneously evaluate the effect of various antithrombotic agents on SVGF; however, a number of pairwise meta-analyses comparing a subset of these agents had been previously published. Fremes *et al* and Henderson *et al* published the earliest meta-analyses in the late 1980s and early 1990s and found aspirin to be superior in reducing SVG occlusion among patients undergoing CABG over placebo.^{71 176} Our findings are consistent with these early meta-analyses. Additionally, an antiplatelet meta-analysis in 1994 demonstrated that the use of postoperative aspirin (75 to 325 mg/day) reduced the odds of any graft occlusion by 44% relative to control, although the proportion of occluded vein grafts was not reported.¹⁷⁷ In terms of duration of treatment, it has been suggested that the use of aspirin for longer than 1 year post CABG did not improve SVG patency.¹⁷⁸ Due to insufficient data, the current NMA could not confirm the benefits of long-term antithrombotic therapy use. In contrast to our results, Fremes *et al* and Henderson *et al* found a reduction in SVGF with anticoagulation. It is important to note that one of the three anticoagulation studies included in these meta-analyses (which was excluded from our analysis) provided an uninterrupted antiplatelet therapy with dipyridamole for seven days post CABG, an agent that is no longer used for SVGF prevention.¹⁷⁹ In 2013, Deo *et al* published a pairwise meta-analysis of five RCTs involving 1,419 SVGs and showed that the postoperative use of dual-antiplatelet therapy with aspirin and clopidogrel significantly reduced SVG occlusion compared with aspirin alone,⁷² which was congruent with the results observed in our NMA. In addition, the significant reduction remained when considering only patients undergoing CABG without CPB.⁷² Due to the lack of data, a sensitivity analysis including only OPCAB studies was not possible to confirm this reduction.

In terms of clinical outcomes, Fremes *et al* failed to demonstrate the survival benefits of aspirin monotherapy as well as anticoagulation, which was consistent with our study.⁷¹ Furthermore, a meta-analysis of 11 RCTs and observational studies involving 25,728 CABG patients showed that dual-antiplatelet therapy with aspirin and clopidogrel was associated with a significant reduced risk of 30-day mortality.⁷² Despite this association, a causative role of antithrombotic agents in reducing mortality in this population remains

unknown. A more recent meta-analysis examining the clinical effects of postoperative antithrombotic therapy in five RCTs (979 patients undergoing elective CABG) reported that there were no significant differences in mortality, MI, stroke, and major bleeding events between monotherapy with aspirin and dual-antiplatelet therapy with aspirin and clopidogrel.¹⁸⁰ Similar conclusions were also observed in our study. In summary, there have been no previously published NMAs of antithrombotic agents for SVG patency. However, the direct comparison findings within our NMA were generally in agreement with the previous pairwise meta-analyses in terms of SVGF and clinical outcomes.

5.2.1 Other comparisons

In this NMA, we did not observe any significant effect of vitamin-K antagonists on either SVGF or clinical outcomes. The low sample size may be mainly responsible for the non-significant results. Though increasing the power of the study is one solution to this statistical issue, warfarin has typically been used less frequently to prevent SVGF due to its association with increased bleeding and the need for regular testing of the INR.

Our NMA was also underpowered to detect significant differences in the incidence of SVGF or adverse events between monotherapy with clopidogrel¹⁶⁹ or dual-antiplatelet therapy with aspirin and ticagrelor¹⁷³ and other antithrombotic agents as currently there is only one published trial available for each comparison. It is hoped that the two trials (DACAB trial; ClinicalTrials.gov No. NCT02201771 and TICAB Trial; ClinicalTrials.gov No. NCT01755520) that are currently in progress can provide additional data on the use of dual-antiplatelet therapy with aspirin and ticagrelor among patients undergoing CABG.

5.3 Strengths and Limitations

The following are the main strengths of the current NMA: 1) its comprehensive systematic search that considered all available RCTs, published or unpublished, of antithrombotic therapies assessing the patency of SVGs as an outcome of interest. The eligibility criteria were pre-specified and stringent, which was purposefully done to reduce heterogeneity and risk of bias; 2) The use of a well-defined protocol. The protocol

was prepared to provide background information to the readers, to serve as a working outline, and most importantly, to enhance the integrity of the current study promoting transparency in scientific research;¹⁸¹ 3) The use of the GRADE approach to evaluate the quality of the evidence for individual trials and in aggregate. Understanding not only the magnitude and direction of treatment effects, but also the quality of evidence is important to avoid the over-reliance on statistical significance and treatment ranking; 4) Lastly, the use of NMA methodology for secondary analysis of existing studies. A NMA is useful to estimate network estimates with greater precision while simultaneously considering all relevant treatment options, even when some of the treatments have never been compared previously.

Despite these strengths, the results of this study should be interpreted in light of the following limitations. First, we encountered several challenges in evaluating the transitivity, homogeneity, and coherence assumptions of NMA. Although we felt it was appropriate to conclude that our networks did not transgress the transitivity assumption, the judgment was limited by the lack of global evidence and extent of clinical understanding of treatment-effect modification. Consequently, the choice of study-level effect modifiers was necessarily somewhat arbitrary, based on our best knowledge of clinical expectations rather than on empirical evidence (which does not yet exist). We also could not confirm whether it was appropriate to treat these covariates equally across outcomes and comparisons as potentially they could have different effects across different outcomes and comparisons. Even if there was sufficient pre-existing evidence to inform these relationships a priori, the assessment would still be limited if the effect modifiers were not measured or the information was not reported by each study report. These concerns are not unique to our NMA, and have been frequently discussed by authors and methodologists in previous NMA publications.^{141 182 183} Future research is therefore needed to better understand treatment-effect modification. Notably, this NMA used a qualitative approach to assess the transitivity assumption, which can be subjective. Another method has been recently proposed by Kabali and Ghazipura to evaluate the assumption using causal graphs and transport formulae.¹⁸³ However, a detailed description and application of this approach is beyond the scope of this NMA. Regarding coherence, our network is sparsely populated with only one closed loop provided by

direct comparison studies; therefore, we were not able to assess incoherence for the other parts of network. It is also important to note that lack of evidence of statistical incoherence does not necessarily mean evidence of coherence. There may be several factors contributing to the absence of this evidence in our NMA, such as the low power of tests for detecting local and global incoherence and the unexplained heterogeneity that may further reduce the power. In terms of the homogeneity assumption, although the statistical heterogeneity was found to be low or moderate, the power of the tests to quantify the extent of heterogeneity was limited by the relatively few studies and small sample size in the networks. Importantly, the inadequate data on baseline characteristics and the lack of patient-level data also preclude carrying out a full, comprehensive assessment of clinical and methodological heterogeneity and performing further analyses such as subgroup analysis or meta-regression to explore potential sources of heterogeneity or to adjust for the unbalanced distribution of effect modifiers. If factors influencing SVGF varied markedly across comparisons, the estimated treatment effects may be biased. While the results after we performed sensitivity analyses (to explore the impact of missing outcome data, differing duration of follow-up, and varied units of analysis) remained robust across different scenarios, it is important to highlight that the sensitivity analyses were also severely limited in power to detect differences.

Second, since our inclusion criteria for eligible RCTs was restricted to a single outcome (SVGf), the analyses of other clinically-relevant outcomes were very limited by the amount of data reported in the SVGf study reports. As expected, several interventions were compared in a relatively few studies and sample size. Hence, drawing definitive conclusions regarding the clinically-relevant impact on the ultimate outcomes of interest including MI and need for cardiac reintervention was not possible, which puts the current study at risk of type II error (failure in finding a significant result when in truth there is one). Most importantly, although the balance between health benefits and safety is an important aspect that influences the choice of intervention, assessing the balance of benefit and harms of antithrombotic therapies is not possible in this study due to limited data. Therefore, future research is needed to expand our knowledge and depth of understanding of the benefit:risk ratio. Third, although the chance is small, the possibility of drawing erroneous conclusions of statistical differences between comparisons cannot

be ruled out (type I error). Theoretically speaking, of 111 (direct, indirect, and network) statistical tests that we performed on four different endpoints using an alpha of 0.05, a total of six statistically significant differences (false positives) would be expected, and therefore our significant outcomes might be explained by chance alone.

Fourth, it is unknown whether different doses lead to clinically important differences in the patency of SVG. In this current study, we did not control for dose and our results may be confounded by it. Fifth, our NMA included studies which were published over a 38-year period, and thus, patient characteristics (i.e., risk factors and disease complexity), surgical techniques, advances in imaging, treatment regimens used in earlier studies may differ from those included in more recent studies (such as broad use of statins) and may not reflect the current clinical practice. Due to the small number of trials in each comparison, we are unable to perform a sensitivity analysis investigating the impact of year of publication (before and after year 2000). Sixth, substantial heterogeneity in the definition of SVGF exists in the included studies. Of those that reported clear definitions of SVGF, one study performed angiographic assessments in surviving patients only,¹⁵⁸ one study evaluated the patency of SVG post mortem,¹⁶⁰ and the remaining were unknown. Many studies also did not describe whether grafts or distal anastomoses were being counted. In addition, studies measured SVGF at different times and it is unclear whether these studies excluded perioperative (early) SVGF. Early SVGF is often a result of technical factors, regardless of the antithrombotic therapy received. The inclusion of early SVGF may underestimate the efficacy of antithrombotic agents themselves for SVG failure after CABG. Collectively, considerable heterogeneity in definitions of SVGF may therefore threaten internal validity. Furthermore, although the results from base case analysis and per graft analysis were similar, combining data from two different units of analysis may challenge the interpretation of the base case analysis. Seventh, follow-up period and length of treatment may be potential sources of heterogeneity. Many of these studies did not follow up patients for adequate number of years to allow for a fair indication of whether differences in SVGF would arise, and pooling studies with different lengths of treatment may reduce the relevance of the study findings. Eighth, women (11%) were underrepresented in all included studies, which may limit the generalizability of the results. Lastly, due to insufficient information, it is unclear whether studies

presented the data based on ITT analysis, an analysis that preserves the benefits of randomization in the presence of reasonable rate of missing data ensuring unbiased estimates.¹⁸⁴ The study findings therefore should be interpreted with caution due to the potential selection bias induced by the high rate of loss to angiographic follow-up (with patients having certain characteristics that are associated with treatment effects or side effects of treatment forgoing further angiographic follow-up), which occurred in most of the included studies, and by death as a competing event in SVGF analysis. The large loss to follow up indicates that our results remain unstable. Hence, the answers remain unknown, and demand future adequately controlled trials of sufficient duration to measure these outcomes.

5.4 Implications for Clinical Practice

Experts have recognized the importance of rating the quality of evidence in the process of making clinical decisions. According to the GRADE system, high quality of evidence is considered most desirable, followed by moderate quality of evidence since the observed treatment effect and our confidence in it are unlikely to alter as more studies emerge.¹⁸⁵ In this NMA, there are four comparisons with moderate quality of evidence on reducing SVGF but no comparison with high quality of evidence. The four comparisons are dual-antiplatelet therapy with aspirin and clopidogrel versus placebo/control, dual-antiplatelet therapy with aspirin and ticagrelor versus placebo/control, monotherapy with aspirin versus placebo/control, and dual-antiplatelet therapy with aspirin and clopidogrel versus monotherapy with aspirin; of these, all reached statistical significance. However, the first three comparisons included placebo/control, in which its use is not of interest. Indeed, it is unethical to give patients placebo when a strategy known to be efficacious exists and is recommended by clinical guidelines. Considering a placebo-controlled trial in the light of superiority evidence may therefore raise ethical concerns.^{186 187} This concern leaves us with the last comparison, which is dual-antiplatelet therapy with aspirin and clopidogrel versus monotherapy with aspirin, to discuss.

In the context of SVG patency, aspirin monotherapy is the current standard prophylactic treatment.⁶ However, there is growing evidence showing that the suboptimal performance

of aspirin alone is not uncommon among CABG patients.^{188 189} As briefly discussed in Chapter 1.3.3.2, this phenomenon is known as aspirin resistance, which affects 30 to 42% of patients undergoing CABG.^{188 189} Studies have shown that aspirin resistance was associated with an increased risk of cardiovascular adverse events and was more prevalent in patients with SVGF.^{67 190 191} Some argue that a higher (up to 325 mg daily) aspirin dose should be administered to prevent aspirin resistance.⁶ However, aspirin resistance is unlikely to be affected by higher doses of aspirin. Aspirin resistance is mainly caused by decreased bioavailability of some enteric-coated formulations and drug interactions with low-dose aspirin.^{192 193} Alternatively, the addition of clopidogrel to aspirin has been proposed to further reduce the risk of occlusion. Based on moderate-quality evidence, our study findings supported this hypothesis and showed that the use of dual-antiplatelet therapy with aspirin and clopidogrel reduced SVGF compared to aspirin alone. Although providing a recommendation with lower quality of evidence (Class IIb, Level of Evidence B-NR), the 2016 ACC/AHA guidelines on dual-antiplatelet therapy with aspirin and clopidogrel⁷⁰, also suggest that the addition of clopidogrel to aspirin (75 to 100 mg daily) for 12 postoperative months may improve the patency of SVGs. The findings of our NMA provide further support for this recommendation.

Furthermore, the beneficial effect of dual-antiplatelet with aspirin and clopidogrel on SVGF may have important impacts on the healthcare system as it may lead to a decrease in the rate of SVG-related repeat revascularization, which was found to be ~5.7% between 2004 and 2009 for SVG-related PCI and 1.3% at 10 year post initial CABG for re-do CABG, and a reduction in costs associated with these procedures.^{194 195} However, further studies are needed to ascertain whether the dual-antiplatelet therapy with aspirin and clopidogrel will lead to cost-effectiveness.

As important as it may seem, quality of evidence alone is not sufficient in making recommendations. There are many other aspects that should be considered including balance between beneficial and harmful effects, values and preferences, and cost-effectiveness, as they are also important factors that influence the choice of antithrombotic agents.¹⁸⁵ Due to insufficient information on clinical outcomes, we could not confirm whether the benefits related to SVGF of the dual-antiplatelet therapy with

aspirin and clopidogrel outweigh the harms or whether the beneficial effects will translate into long-term improvements in overall health.

It is important to note that though dual-antiplatelet therapy with aspirin and ticagrelor was the best-ranked treatment in preventing SVGF, treatment rankings derived from NMA cannot be interpreted clinically as SUCRA is not intended as a clinical ranking measure. Moreover, SUCRA does not account for the magnitude and uncertainty of differences in effect estimates between interventions, the quality of the network evidence, nor the contribution of each direct estimate to the network estimates. Consequently, it would be difficult to decide whether being the best is clinically and statistically different from being the second best as the difference may occur due to chance.¹⁹⁶

5.5 Implications for Research

The following are several important evidence gaps, which should be addressed by future research. First, SVGF is itself presumably a surrogate for more important clinical outcomes such as acute MI and death, however, there is little research evaluating the relationship between SVGF and these patient-important outcomes. Surrogate endpoints are useful in clinical trials to understand the mechanism of action of a drug and often used because trials can use smaller sample sizes and shorter follow-up periods to generate sufficiently powered results.¹⁹⁷ However, to appropriately use SVGF as a surrogate, the relationship between SVGF and the hard outcomes needs to be established. As practice patterns and patient demographics change, it is particularly important to understand its validity and reliability as a surrogate endpoint for describing the patterns. Second, many studies did not report data on cardiovascular adverse events as they were not designed to demonstrate the potential cardiovascular risk with antithrombotic agents. As a result, we were unable to adequately measure the clinical outcomes due to lack of statistical power owing to the few studies that reported on clinical outcomes. Therefore, well-designed studies (e.g., pragmatic RCTs) are needed to evaluate both SVGF and clinical outcomes to ascertain the balance between potential health benefits and safety. Third, research should focus on treatment-effect modification as identifying true effect modifiers is of clinical and research importance; it may help clinicians focus on the specific needs of

patients across different subgroups and may aid researchers in better evaluating the validity of NMA findings through transitivity and homogeneity assessment.

5.6 Conclusions

A NMA of RCTs was conducted to simultaneously assess the relative effects of various oral antithrombotic agents on SVGF and clinical outcomes among patients undergoing CABG. Based on very low to moderate quality of evidence, no significant differences in the incidence of major bleeding, mortality, and myocardial infarction post CABG across antithrombotic comparisons were found, owing to low number of events and small sample size. Compared to placebo/control, three active medications (aspirin monotherapy, dual-antiplatelet therapy with aspirin and clopidogrel, and dual-antiplatelet therapy with aspirin and ticagrelor) significantly reduced SVGF. Importantly, based on moderate-quality evidence, dual-antiplatelet therapy with aspirin and clopidogrel was the only intervention that improved the SVG patency compared to aspirin monotherapy. Our results may, therefore, help clarify whether the current guidelines should be revisited to more compellingly recommend the use of dual-antiplatelet therapy with aspirin and clopidogrel in patients undergoing CABG. Certainly, optimal antithrombotic therapy options should be individualized based on a multidisciplinary evaluation that incorporates considerations of comorbidity burden, perception of risks, and patient values and preferences informed by the evidence and its remaining uncertainties.

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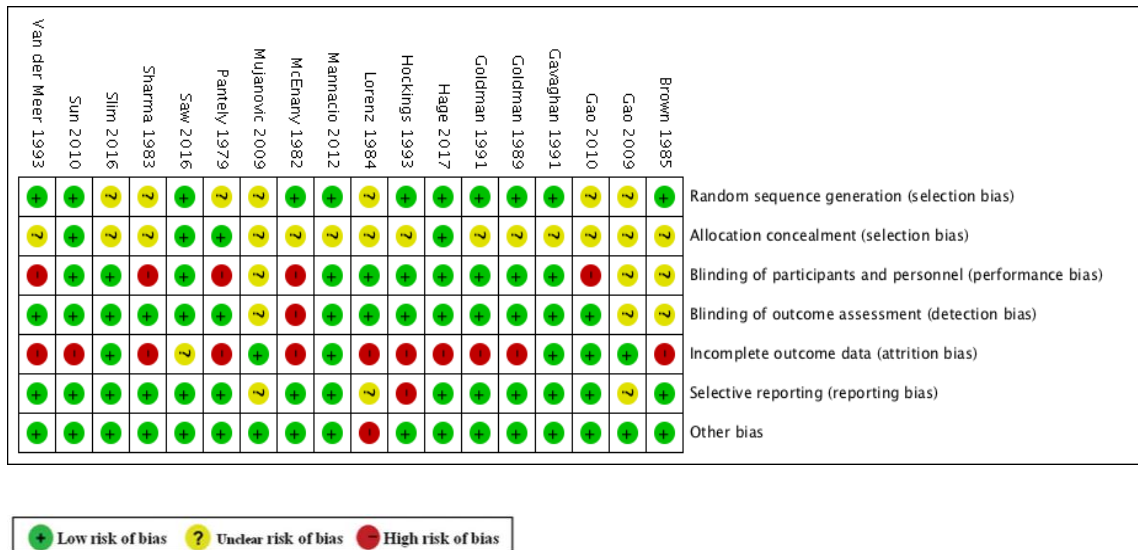
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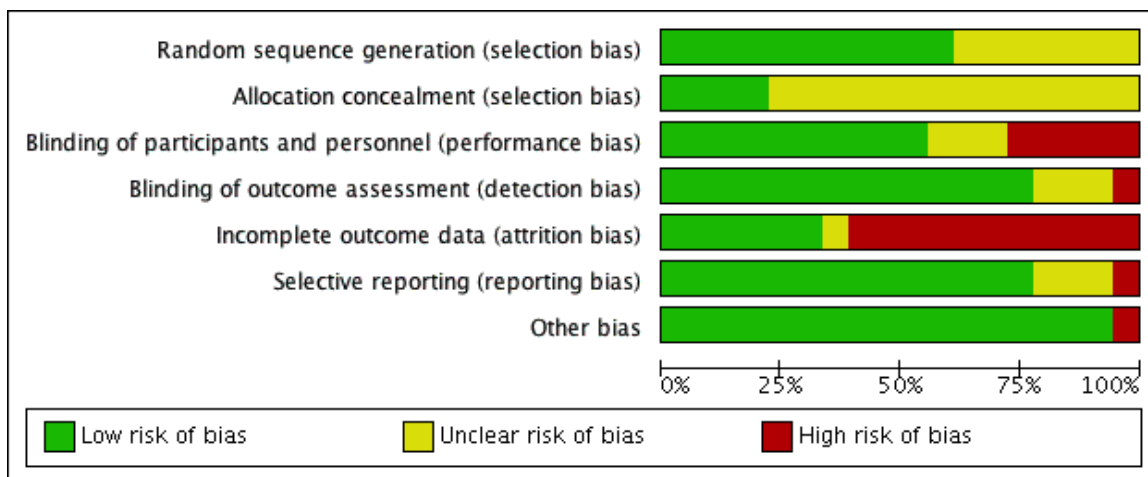
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Appendices

Appendix A: eFigures

eFigure 1. Risk of bias assessments for SVGF



eFigure 2. The overall risk of bias graph for SVGF

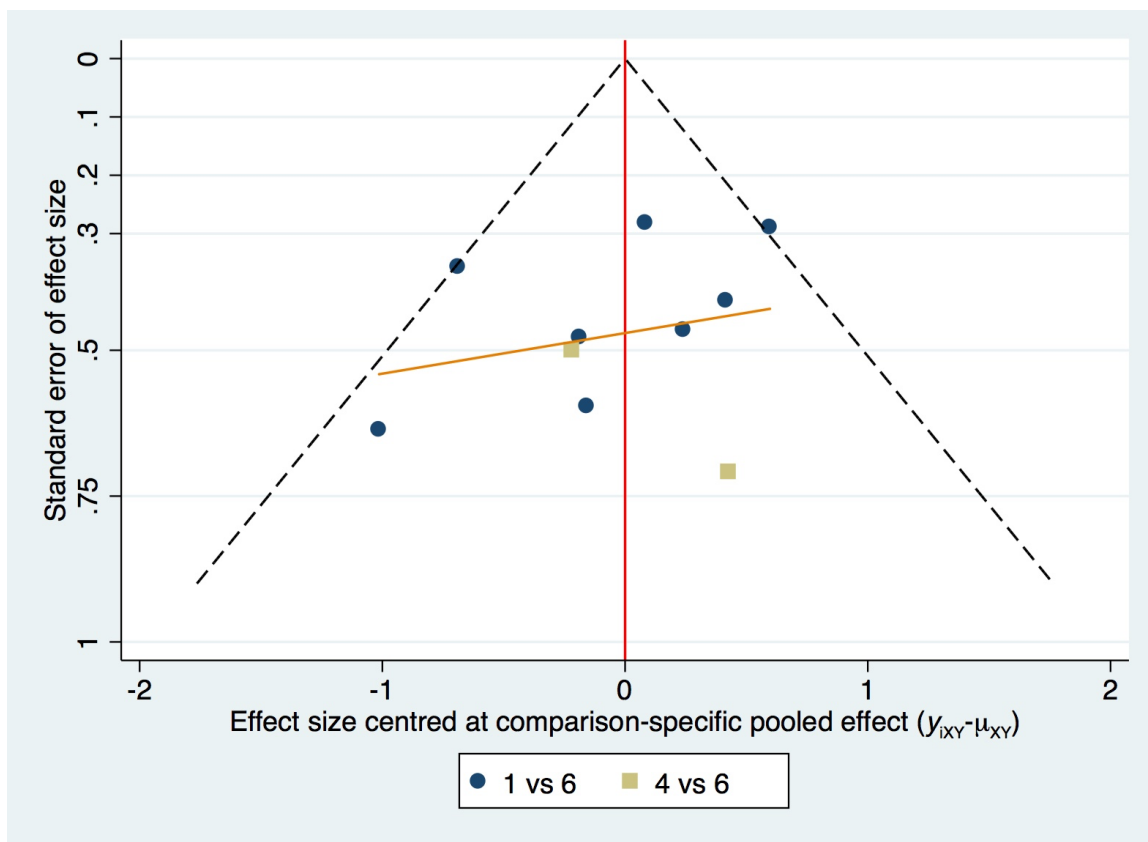
eFigure 3. Summary of direct and network estimates for major bleeding (A), mortality (B), and MI (C)

A Major Bleeding					
Control	3.75 (0.42-33.28)	6.70 (0.75-59.62)	3.75 (0.04-341.19)	2.84 (0.25-32.26)	
2.62 (0.11-64.98)	Aspirin	1.79 (0.95-3.35)	1.00 (0.02-51.80)	0.76 (0.26-2.20)	
9.98 (0.53-188.92)	2.26 (0.56-9.12)	Vit K A	0.56 (0.01-30.44)	0.42 (0.12-1.46)	
--	Not estimable	--	Aspirin & Ticagrelor	0.76 (0.01-45.19)	
--	0.76 (0.25-2.31)	--	--	Aspirin & Clopidogrel	
B Mortality					
Control	1.77 (0.52-5.99)	1.04 (0.23-4.72)	0.57 (0.02-18.18)	1.19 (0.21-6.71)	
1.54 (0.36-6.66)	Aspirin	0.59 (0.19-1.87)	0.32 (0.01-8.23)	0.67 (0.20-2.30)	
3.44 (0.14-85.97)	0.65 (0.10-4.10)	Vit K A	0.55 (0.02-17.09)	1.14 (0.21-6.17)	
--	0.32 (0.01-8.23)	--	Aspirin & Ticagrelor	2.07 (0.07-66.02)	
--	0.67 (0.20-2.30)	--	--	Aspirin & Clopidogrel	
C Myocardial Infarction					
Control	0.53 (0.13-2.10)	0.49 (0.12-2.00)	0.53 (0.01-34.71)	0.38 (0.07-2.12)	
0.97 (0.03-27)	Aspirin	0.92 (0.52-1.62)	1.00 (0.02-51.80)	0.71 (0.25-2.02)	
0.21 (0.02-1.89)	0.97 (0.55-1.71)	Vit K A	1.09 (0.02-58.80)	0.77 (0.23-2.54)	
--	Not estimable	--	Aspirin & Ticagrelor	0.71 (0.01-42.04)	
--	0.69 (0.23-2.04)	--	--	Aspirin & Clopidogrel	

Top diagonal (network estimates): column- versus row-defining treatment
Bottom (direct estimates): row- versus column-defining treatment

Estimates are presented as OR and its 95% CI.

eFigure 4. Comparison-adjusted funnel plot of placebo-controlled trials for SVGF



Treatment 1: Aspirin, 4: Vitamin K antagonists, 6: Control. The yellow line is the linear regression of the comparison-specific differences (i.e., the difference between the individual study-level effect size and the summary effect estimate for each comparison, x-axis) on the standard error of the summary estimate of each study (y-axis)

Appendix B: eTables

eTable 1: Ovid MEDLINE search strategy

#	Searches (November 13, 2016)	Results
1	exp Coronary Artery Bypass/	50665
2	((aortocoronary or aorto-coronary or coronary) adj2 (bypass or by-pass or graft* or saphenous or radial or vein or venous or internal mammar*)).mp.	68443
3	(CABG or "coronary artery bypass").mp.	62608
4	1 or 2 or 3	69629
5	fibrinolytic agents/ or aspirin/ or ticlopidine/	73496
6	platelet aggregation inhibitors/ or aspirin/ or aspirin, dipyridamole drug combination/ or dipyridamole/ or prasugrel hydrochloride/ or ticlopidine/	72898
7	anticoagulants/ or acenocoumarol/ or phenprocoumon/ or warfarin/ or antithrombins/ or exp factor xa inhibitors/	79011
8	(antithrombotic* or anti-thrombotic* or anticoagula* or anti-coagula* or antiplatelet* or anti-platelet*).mp.	139797
9	((platelet or thromboxane or adenosine diphosphate receptor or ADP receptor or thienopyridine or cyclo-oxygenase or cyclooxygenase or cyclic GMP phosphodiesterase type V enzyme or vitamin K or vitamin-K or direct thrombin or direct factor Xa) adj1 (antagonist* or inhibitor*)).mp.	28064
10	(aspirin or acetylsalicylic acid or acylpyrin or aloxiprimuma or colfarit or dispril or easprin or ecotrin or endosprin or magnecyl or micristin or polopirin or polopiryna or solprin or solupsan or zorprin).mp.	65552
11	exp Dipyridamole/	7772
12	(dipyridamole or persantine or antistenocardin or cerebrovase or cleridium or curantil or curantyl or dipyramidole or kurantil or miosen or novo-dipiradol or persantin or persantine).mp.	10587
13	(clopidogrel or Plavix or clopilet or grepid or iscover or zopya or zylagren or zylit).mp.	12243
14	Prasugrel Hydrochloride/ or (prasugrel or effient or efient).mp.	1814
15	(ticagrelor or brilinta or briliq or possia).mp.	1480
16	(indobufen or ibustrin).mp.	171
17	(warfarin or adoisine or athrombin or befarin or carfin or circuvit or coumadan or coumadin or coumadine or coumafene or coumaphene or dagonal or farin or jantoven or aldocumar or kumatox or maforan or marevan or orgarin or panwarfarin or panwarfin or prothromadin or sofarin or tintorane or uniwarfin or wafarin or waran or warfarine or warfilone or warnerin or marevan or tedicumar or warfant).mp.	7024
18	(acenocoumarol or acenocoumarin or acenocoumarine or acenocoumarole or acenocoumarolum or acenocoumarol or acenocoumarolo or acenocumerol or acenokumarin or acitrom or neo sintrom or neosintrom or neositron or nicoumalone or nicumalon or nitrovarfarin or nitrowarfarin or sincoumar or sincumar or sinkumar or sinthrom or sinthrome or sintrom or sintroma or sintron or syncoumar or syncumar or syntrom or synthrom or trombostop or zotil or mini sintrom or mini-sintrom or minisintrom).mp.	1674
19	(phenprocoumon or falithrom or falithrome or fenprocoumon or liquamar or marcoumar or marcumar or phenprocouman or phenprocoumalol or phenprocoumarol or phenprocoumon or phenprocoumom or phenprocumarol or phenprogramma).mp.	1272
20	(Ticlopidine or agulan or anagregal or antigreg or aplaket or cartrilet or cempidine or clotidone or crodin or declot or desitic or goclid or licodin or nufaclapide or panaldine or siclot or tacron or ticard or ticdine or ticlid or ticlidil or ticlodine or ticlodix or ticlodone or ticlomed or ticlon or ticuring or tikleen or tiklid or tiklyd or tikol or tilodone or tiodin or tipidin or tipidine or tyklid or viladil).mp.	10455
21	(Rivaroxaban or xarelto).mp.	3088

22	(Dabigatran or pradax or pradaxa or prazaxa or rendix).mp.	3543
23	(Apixaban or eliques or eliquis).mp.	1903
24	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23	256464
25	4 and 24	4778
26	("randomized controlled trial" or "controlled clinical trial").pt.	559642
27	(random* or placebo* or single-blind* or double-blind* or triple-blind* or "single blind*" or "double blind*" or "triple blind*").ti,ab.	1051974
28	clinical trials as topic.sh.	189460
29	26 or 27 or 28	353315
30	exp animals/ not humans.sh.	4668056
31	29 not 30	1237283
32	25 and 31	1211
33	("graft paten*" or "graft occlu*" or "occlu* graft*" or "graft fail*" or "fail* graft*" or "patency rate*" or paten* or "total occlu*").mp.	27036
34	("string sign" or stenosis or Fitzgibbon or "TIMI flow").mp	175704
35	("cardiac revasculari\$ation" or revasculari\$ation or "repeat CABG" or "repeat coronary artery bypass" or "redo CABG" or "redo coronary artery bypass" or "re-do CABG" or "re-do coronary artery bypass" or PCI or "percutaneous coronary intervention").mp.	33226
36	33 or 34 or 35	300192
37	32 and 36	494

eTable 2: Ovid EMBASE search strategy

#	Searches (November 13, 2016)	Results
1	exp Coronary Artery Bypass/	66277
2	((aortocoronary or aorto-coronary or coronary) adj2 (bypass or by-pass or graft* or saphenous or radial or vein or venous or internal mammar*)).mp.	92637
3	(CABG or "coronary artery bypass").mp.	90465
4	1 or 2 or 3	98265
5	antithrombocytic agent/	36964
6	acetylsalicylic acid plus clopidogrel/	406
7	exp prasugrel/ or exp antithrombocytic agent/ or exp ticlopidine/ or exp acetylsalicylic acid/ or exp dipyridamole/ or exp ticagrelor/ or exp clopidogrel/ or exp anticoagulant agent/	605804
8	(antithrombotic* or anti-thrombotic* or anticoagula* or anti-coagula* or antiplatelet* or anti-platelet*).mp.	225540
9	((platelet or thromboxane or adenosine diphosphate receptor or ADP receptor or thienopyridine or cyclo-oxygenase or cyclooxygenase or cyclic GMP phosphodiesterase type V enzyme or vitamin K or vitamin-K or direct thrombin or direct factor Xa) adj1 (antagonist* or inhibitor*)).mp.	18919
10	(aspirin or acetylsalicylic acid or acylpyrin or aloxiprimuma or colfarit or dispril or easprin or ecotrin or endosprin or magneacyl or micristin or polopirin or polopiryna or solprin or solupsan or zorprin).mp.	198403
11	(dipyridamole or persantine or antistenocardin or cerebrovase or cleridium or curantil or curantyl or dipyrimidole or kurantil or miosen or novo-dipiradol or persantin or persantine).mp.	24832
12	(clopidogrel or Plavix or clopilet or grepid or iscover or zopya or zylagren or zylit).mp.	48978
13	(prasugrel or effient or efient).mp.	6079
14	(ticagrelor or brilinta or briliq or possia).mp.	4772
15	(indobufen or ibustrin).mp.	492
16	(warfarin or adoisine or athrombin or befarin or carfin or circuvit or coumadan or coumadin or coumadine or coumafene or coumaphene or dagonal or farin or jantoven or aldocumar or kumatox or maforan or marevan or orfarin or panwarfarin or panwarfin or prothromadin or sofarin or tintorane or uniwarfin or wafarin or waran or warfarine or warfilone or warnerin or marevan or tedicumar or warfant).mp.	80901
17	(acenocoumarol or acenocoumarin or acenocoumarine or acenocoumarole or acenocoumarolum or acenocoumarol or acenocoumarolo or acenocumerol or acenokumarin or acitrom or neo sintrom or neosintrom or neositron or nicoumalone or nicumalon or nitrovarfarin or nitrowarfarin or sincoumar or sincumar or sinkumar or sinthrom or sinthrome or sintrom or sintroma or sintron or syncoumar or syncumar or syntrom or synthrom or trombostop or zotil or mini sintrom or mini-sintrom or minisintrom).mp.	5736
18	(phenprocoumon or falithrom or falithrome or fenprocoumon or liquamar or marcoumar or marcumar or phenprocouman or phenprocoumalol or phenprocoumarol or phenprocoumon or phenprocoumom or phenprocoumarol or phenprogramma).mp.	13870
19	(Ticlopidine or agulan or anagregal or antigreg or aplaket or cartrilet or cenpidine or clotidone or crodin or declot or desitic or goclid or licodin or nufaclapide or panaldine or siclot or tacron or ticard or ticdine or ticlid or ticlidil or ticlodine or ticlodix or ticlodone or ticlomed or ticlon or ticuring or tikleen or tiklid or tiklyd or tikol or tilodene or tiodin or tipidin or tipidine or tyklid or viladil).mp.	4922
20	(Rivaroxaban or xarelto).mp.	9305
21	(Dabigatran or pradax or pradaxa or prazaxa or rendix).mp.	10004
22	(Apixaban or eliques or eliquis).mp.	5968
23	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22	660898
24	4 and 23	15137

25	("randomized controlled trial" or "controlled clinical trial").pt.	0
26	(random* or placebo* or single-blind* or double-blind* or triple-blind* or "single blind*" or "double blind*" or "triple blind*").ti,ab.	1281645
27	25 or 26	1281645
28	24 and 27	2402
29	("graft paten*" or "graft occlu*" or "occlu* graft*" or "graft fail*" or "fail* graft*" or "patency rate*" or paten* or "total occlu*").mp.	171788
30	("string sign" or stenosis or Fitzgibbon or "TIMI flow").mp.	265679
31	("cardiac revasculari\$ation" or revasculari\$ation or "repeat CABG" or "repeat coronary artery bypass" or "redo CABG" or "redo coronary artery bypass" or "re-do CABG" or "re-do coronary artery bypass" or PCI or "percutaneous coronary intervention").mp	75778
32	29 or 30 or 31	483433
33	28 and 32	1114

eTable 3: CINAHL search strategy

#	Searches (November 13, 2016)	Results
1	(MH "Coronary Artery Bypass+")	7115
2	"coronary artery bypass" or "coronary bypass" or "aortocoronary bypass" or "aortocoronary saphenous" or "aortocoronary vein" or "saphenous vein graft*" or CABG	8615
3	S1 OR S2	8657
4	(MH "Platelet Aggregation Inhibitors+")	10826
5	Antiplatelet* or anti-platelet*	2779
6	(MH "Anticoagulants+")	14670
7	Anticoagulant* or anti-coagulant*	11709
8	"platelet antagonist*" or "platelet inhibitor*" or "thromboxane antagonist*" or "thromboxane inhibitor*" or "adenosine diphosphate receptor antagonist*" or "adenosine diphosphate receptor inhibitor*" or "ADP receptor antagonist*" or "ADP receptor inhibitor*" or "thienopyridine antagonist*" or "thienopyridine inhibitor*" or "cyclo-oxygenase antagonist*" or "cyclo-oxygenase inhibitor*" or "cyclooxygenase antagonist*" or "cyclooxygenase inhibitor*" or "cyclic GMP phosphodiesterase type V enzyme antagonist*" or "cyclic GMP phosphodiesterase type V enzyme inhibitor*" or "vitamin K antagonist*" or "vitamin K inhibitor*" or "vitamin-K antagonist*" or "vitamin-K inhibitor*" or "direct thrombin antagonist*" or "direct thrombin inhibitor*" or "direct factor Xa antagonist*" or "direct factor Xa inhibitor*"	779
9	(MH "Aspirin")	6415
10	aspirin or acetylsalicylic acid or acylpyrin or aloxiprimuma or colfarit or dispril or easprin or ecotrin or endosprin or magneacyl or micristin or polopirin or polopiryna or solprin or solupsan or zorprin	8489
11	dipyridamole or persantine or antistenocardin or cerebrovase or cleridium or curantil or curantyl or dipyrnidole or kurantil or miosen or novo-dipiradol or persantin or persantine	544
12	clopidogrel or Plavix or clopilet or grepid or iscover or zopya or zylagren or zylit	2327
13	prasugrel or effient or efient	304
14	ticagrelor or brilinta or brilique or possia	265
15	indobufen or ibustrin	6
16	warfarin or adoisine or athrombin or befarin or carfin or circuvit or coumadan or coumadin or coumadine or coumafene or coumaphene or dagonal or farin or jantoven or aldocumar or kumatox or maforan or marevan or orfarin or panwarfarin or panwarfin or prothromadin or sofarin or tintorane or uniwarfin or wafarin or waran or warfarine or warfilone or warnerin or marevan or tedicumar or warfant	5257
17	acenocoumarol or acenocoumarin or acenocoumarine or acenocoumarole or acenocoumarolum or acenocoumarol or acenocoumarolo or acenocumerol or acenokumarin or acitrom or neo sintrom or neosintrom or neositron or nicoumalone or nicumalon or nitrovarfarin or nitrowarfarin or sincoumar or sincumar or sinkumar or sinthrom or sinthrome or sintrom or sintroma or sintron or syncoumar or syncumar or syntrom or synthrom or trombostop or zotil or mini sintrom or mini-sintrom or minisintrom	42
18	phenprocoumon or falithrom or falithrome or fenprocoumon or liquamar or marcoumar or marcumar or phenprocouman or phenprocoumalol or phenprocoumarol or phenprocoumon or phenprocoumom or phenprocumarol or phenprogramma	29
19	Rivaroxaban or xarelto	525
20	Dabigatran or pradax or pradaxa or prazaxa or rendix	722
21	Apixaban or eliques or eliquis	292
22	S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21	28599
23	random* or placebo* or "single-blind*" or "double-blind*" or "triple-blind*" or "single blind*" or "double blind*" or "triple blind*"	186004
24	("graft paten*" or "graft occlu*" or "occlu* graft*" or "graft fail*" or "fail* graft*" or	7088

	"patency rate*" or paten* or "total occlu*").mp.	
25	("string sign" or stenosis or Fitzgibbon or "TIMI flow").mp.	12034
26	("cardiac revasculari\$ation" or revasculari\$ation or "repeat CABG" or "repeat coronary artery bypass" or "redo CABG" or "redo coronary artery bypass" or "re-do CABG" or "re-do coronary artery bypass" or PCI or "percutaneous coronary intervention").mp	4806
27	S24 OR S25 OR S26	22912
28	S3 AND S22 AND S23 AND S27	42

eTable 4: Web of Science search strategy

#	Searches (November 13, 2016)	Results
1	“coronary artery bypass” or “coronary bypass” or “aortocoronary bypass” or “aortocoronary saphenous” or “aortocoronary vein” or “saphenous vein graft*” or CABG	45358
2	Antithrombotic* or anti-thrombotic*	17850
3	Antiplatelet* or anti-platelet* or anticoagula* or anti-coagula*	96184
4	“platelet antagonist*” or “platelet inhibitor*” or “thromboxane antagonist*” or “thromboxane inhibitor*” or “adenosine diphosphate receptor antagonist*” or “adenosine diphosphate receptor inhibitor*” or “ADP receptor antagonist*” or “ADP receptor inhibitor*” or “thienopyridine antagonist*” or “thienopyridine inhibitor*” or “cyclo-oxygenase antagonist*” or “cyclo-oxygenase inhibitor*” or “cyclooxygenase antagonist*” or “cyclooxygenase inhibitor*” or “cyclic GMP phosphodiesterase type V enzyme antagonist*” or “cyclic GMP phosphodiesterase type V enzyme inhibitor*” or “vitamin K antagonist*” or “vitamin K inhibitor*” or “vitamin-K antagonist*” or “vitamin-K inhibitor*” or “direct thrombin antagonist*” or “direct thrombin inhibitor*” or “direct factor Xa antagonist*” or “direct factor Xa inhibitor*”	6260
5	aspirin or acetylsalicylic acid or acylpyrin or aloxiprimuma or colfarit or dispril or easprin or ecotrin or endosprin or magnecycl or micristin or polopirin or polopiryna or solprin or solupsan or zorprin	56834
6	dipyridamole or persantine or antistenocardin or cerebrovase or cleridium or curantil or curantyl or dipyrnidole or kurantil or miosen or novo-dipiradol or persantin or persantine	8316
7	clopidogrel or Plavix or clopilet or grepid or iscover or zopya or zylagren or zylit	14390
8	prasugrel or effient or efient	2177
9	ticagrelor or brilinta or brilique or possia	1538
10	indobufen or ibustrin	194
11	warfarin or adoisine or athrombin or befarin or carfin or circuvit or coumadan or coumadin or coumadine or coumafene or coumaphene or dagonal or farin or jantoven or aldocumar or kumatox or maforan or marevan or orfarin or panwarfarin or panwarfin or prothromadin or sofarin or tintorane or uniwarfin or wafarin or waran or warfarine or warfilone or warnerin or marevan or tedicumar or warfant	25997
12	acenocoumarol or acenocoumarin or acenocoumarine or acenocoumarole or acenocoumarolum or acenocoumarol or acenocoumarolo or acenocumerol or acenokumarin or acitrom or neo sintrom or neosintrom or neositron or nicoumalone or nicumalon or nitrovarfarin or nitrowarfarin or sincoumar or sincumar or sinkumar or sinthrom or sinthrome or sintrom or sintroma or sintron or syncoumar or syncumar or syntrom or synthrom or trombostop or zotil or mini sintrom or mini-sintrom or minisintrom	1047
13	phenprocoumon or falithrom or falithrome or fenprocoumon or liquamar or marcoumar or marcumar or phenprocouman or phenprocoumalol or phenprocoumarol or phenprocoumon or phenprocoumom or phenprocoumarol or phenprogramma	957
14	Rivaroxaban or xarelto	3512
15	Dabigatran or pradax or pradaxa or prazaxa or rendix	4340
16	Apixaban or eliques or eliquis	1887
17	#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16	174560
18	#1 AND #17	2835
19	controlled trial* OR clinical trial* OR comparative stud* OR OR prospective stud* OR random* OR placebo* OR (single blind*) OR (double blind*)	2430123
20	#18 AND #19	1214
21	"graft paten*" or "graft occlu*" or "occlu* graft*" or "graft fail*" or "fail* graft*" or "patency rate*" or paten* or "total occlu*"	105834
22	"string sign" or stenosis or Fitzgibbon or "TIMI flow"	127165
23	"cardiac revasculari\$ation" or revasculari\$ation or "repeat CABG" or "repeat coronary	85164

	artery bypass" or "redo CABG" or "redo coronary artery bypass" or "re-do CABG" or "re-do coronary artery bypass" or PCI or "percutaneous coronary intervention"	
24	#21 OR #22 OR #23	295412
25	#21 AND #20	705

eTable 5: Cochrane Library search strategy

#	Searches (October 31, 2016)	Results
1	MeSH descriptor: [Coronary Artery Bypass] explode all trees	5397
2	“coronary artery bypass” or “coronary bypass” or “aortocoronary bypass” or “aortocoronary saphenous” or “aortocoronary vein” or “saphenous vein graft*” or CABG:ti,ab,kw	9174
3	#1 OR #2	9194
4	MeSH descriptor: [Anticoagulants] explode all trees	4532
5	MeSH descriptor: [Platelet Aggregation Inhibitors]	3505
6	Anticoagula* or anti-coagula*:ti,ab,kw	9419
7	Antiplatelet* or anti-platelet*:ti,ab,kw	3542
8	MeSH descriptor: [Aspirin]	4816
9	aspirin or acetylsalicylic acid or acylpyrin or aloxiprimuma or colfarit or dispril or easprin or ecotrin or endosprin or magnecyl or micristin or polopirin or polopiryna or solprin or solupsan or zorprin:ti,ab,kw	11585
10	dipyridamole or persantine or antistenocardin or cerebrovase or cleridium or curantil or curantyl or dipyramidole or kurantil or miosen or novo-dipiradol or persantin or persantine:ti,ab,kw	1179
11	clopidogrel or Plavix or clopilet or grepid or iscover or zopya or zylagren or zylit:ti,ab,kw	3135
12	prasugrel or effient or efient:ti,ab,kw	480
13	ticagrelor or brilinta or brilique or possia:ti,ab,kw	417
14	indobufen or ibustrin:ti,ab,kw	85
15	warfarin or adoisine or athrombin or befarin or carfin or circuvit or coumadan or coumadin or coumadine or coumafene or coumaphene or dagonal or farin or jantoven or aldocumar or kumatox or maforan or marevan or orfarin or panwarfarin or panwarfin or prothromadin or sofarin or tintorane or uniwarfin or wafarin or waran or warfarine or warfilone or warnerin or marevan or tedicumar or warfant:ti,ab,kw	3116
16	acenocoumarol or acenocoumarin or acenocoumarine or acenocoumarole or acenocoumarolum or acenocoumarol or acenocoumarolo or acenocumerol or acenokumarin or acitrom or neo sintrom or neosintrom or neositron or nicoumalone or nicumalon or nitrovarfarin or nitrowarfarin or sincoumar or sincumar or sinkumar or sinthrom or sinthrome or sintrom or sintroma or sintron or syncoumar or syncumar or syntrom or synthrom or trombostop or zotil or mini sintrom or mini-sintrom or minisintrom:ti,ab,kw	224
17	phenprocoumon or falithrom or falithrome or fenprocoumon or liquamar or marcoumar or marcumar or phenprocouman or phenprocoumalol or phenprocoumarol or phenprocoumon or phenprocoumom or phenprocumarol or phenprogramma:ti,ab,kw	189
18	Rivaroxaban or xarelto:ti,ab,kw	547
19	Dabigatran or pradax or pradaxa or prazaxa or rendix:ti,ab,kw	430
20	Apixaban or eliques or eliquis:ti,ab,kw	316
21	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20	24362
22	#3 AND #21	1088
23	"controlled trial*" or "clinical trial*" or "comparative stud*" or "prospective stud*" or random* or placebo* or "single blind*" or "double blind*" or “triple blind*” or "single-blind*" or "double-blind*" or "triple-blind*":ti,ab,kw	704157
24	#23 AND #22	952
25	"graft paten*" or "graft occlu*" or "occlu* graft*" or "graft fail*" or "fail* graft*" or "patency rate" or paten* or "total occlu*":ti,ab,kw	5963
26	"string sign" or stenosis or Fitzgibbon or "TIMI flow":ti,ab,kw	7223
27	"cardiac revasculari\$ation" or revasculari\$ation or "repeat CABG" or "repeat coronary artery bypass" or "redo CABG" or "redo coronary artery bypass" or "re-do CABG" or "re-do coronary artery bypass" or PCI or "percutaneous coronary	6052

	intervention":ti,ab,kw	
28	#27 or #28 or #29	17746
29	#24 AND #30	432

eTable 6: Grey literature search strategy

Sources (August 29, 2016)
ClinicalTrials.gov
International Clinical Trials Registry Platform (ICTRP): Australian (ANZCTR), India (CTRI), UK (EU-CTR), Chinese (ChiCTR), Dutch (NTR), German (DRKS), Japanese (UMIN CTR), Korean (CRiS), Persian (IRCT), Portuguese (ReBec), Spanish (PRCEC), Pan African (PACTR), Sri Lanka (SLCTR), Thai (TCTR)
Other clinical trial registries: AstraZeneca, Bayer, Bristol-Myers Squibb
USA Food and Drug Administration (FDA)
Electronic Theses Online Service
Gray Matters (https://www.cadth.ca/resources/finding-evidence/gray-matters)

Key terms used for grey literature:

CABG: coronary artery bypass, coronary bypass, CABG

Antithrombotic agents: antithrombotic, antiplatelet, anticoagulation, aspirin, acetylsalicylic acid, clopidogrel, Plavix, prasugrel, effient, ticagrelor, brilinta, indobufen, Ibustrin, dipyridamole, persantine, warfarin, Coumadin, jantoven, acenocoumarol, sinthrome, phenprocoumon, marcumar, ticlopidine, Ticlid, rivaroxaban, Xarelto, apixaban, eliquis, dabigatran, pradaxa.

eTable 7: List of selected excluded studies (after full-text retrieval)

No.	Reference	Reason for Exclusion
1	ClinicalTrials.gov: NCT02201771; Compare the Efficacy of Different Antiplatelet Therapy Strategy After Coronary Artery Bypass Graft Surgery (DACAB-1)	Ongoing Trial
2	ClinicalTrials.gov: NCT01560780; Prasugrel for Prevention of Early Saphenous Vein Graft Thrombosis –	Ongoing Trial
3	ClinicalTrials.gov: NCT01598337; The Effect of Antiplatelets Therapy on Saphenous Vein Coronary Artery Bypass Graft Patency	Ongoing Trial
4	ClinicalTrials.gov: NCT00330772; Preoperative Aspirin and Postoperative Antiplatelets in Coronary Artery Bypass Grafting: The PAPA CABG Study (PAPA CABG)	Ongoing Trial
5	ClinicalTrials.gov: NCT01268917; The Effect of Preoperative Aspirin on Graft Patency and Cardiac Events in Off-pump Coronary Artery Bypass	Ongoing Trial
6	ClinicalTrials.gov: NCT02352402; The Effect of Ticagrelor on Saphenous Vein Graft Patency in Patients Undergoing Coronary Artery Bypass Grafting Surgery (POPular CABG)	Ongoing Trial
7	de Waha A, Sandner S, von Scheidt M.... A randomized, parallel group, double-blind study of ticagrelor compared with aspirin for prevention of vascular events in patients undergoing coronary artery bypass graft operation: Rationale and design of the Ticagrelor in CABG (TiCAB) trial: An Investigator-Initiated trial. <i>Am Heart J.</i> 2016 Sep;179:69-76.	Ongoing Trial
8	Rafiq S, Johansson PI, Kofoed KF, Lund JT, Olsen PS, Bentsen S, Steinbrüchel DA. Thrombelastographic hypercoagulability and antiplatelet therapy after coronary artery bypass surgery (TEG-CABG trial): a randomized controlled trial. <i>Platelets.</i> 2017 Feb 22:1-8	Highly selected group of patients (patients with hypercoagulable states)
9	Kolluri R, Plessa AL, Sanders MC, Singh NK, Lucore C. A randomized study of the safety and efficacy of fondaparinux versus placebo in the prevention of venous thromboembolism after coronary artery bypass graft surgery. <i>Am Heart J.</i> 2016 Jan;171(1):1-6.	Wrong intervention (heparin and fondaparinux) and wrong outcome
10	El Messaoudi S, Wouters CW, van Swieten HA, Effect of dipyridamole on myocardial reperfusion injury: A double-blind randomized controlled trial in patients undergoing elective coronary artery bypass surgery. <i>Clin Pharmacol Ther.</i> 2016 Apr;99(4):381-9	Wrong intervention (dipyridamole) and Wrong outcome
11	Paikin JS, Hirsh J, Ginsberg JS, Weitz JI, Chan NC, Whitlock RP, Pare G, Johnston M, Eikelboom JW. Multiple daily doses of acetyl-salicylic acid (ASA) overcome reduced platelet response to once-daily ASA after coronary artery bypass graft surgery: a pilot randomized controlled trial.	Wrong outcome (did not assess VGF; did not report repeat revascularization) and only assess aspirin
12	Thopte OS, Patil SP, Deshmukh RS. A study of aspirin plus clopidogrel versus aspirin alone on saphenous vein graft patency after coronary artery bypass graft surgery-an angiographic follow-up after three months. <i>Indian Heart Journal.</i> 2014;66:S22.	Results are not reported (published)
13	Ebrahimi R, Bakaeen FG, Uberoi A... Effect of clopidogrel use post coronary artery bypass surgery on graft patency. <i>Ann Thorac Surg.</i>	Wrong study design (subgroup)

- 2014 Jan;97(1):15-21 analysis of RCT)
- 14 Gasparovic H, Petricevic M, Kopjar T, Djuric Z, Svetina L, Biocina B. Impact of dual-antiplatelet therapy on outcomes among aspirin-resistant patients following coronary artery bypass grafting. *Am J Cardiol.* 2014 May 15;113(10):1660-7 Wrong outcome (did not assess VGF nor repeat revascularization)
 - 15 Wang X, Gong X, Zhu T, Zhang Q, Zhang Y, Wang X, Yang Z, Li C. Clopidogrel improves aspirin response after off-pump coronary artery bypass surgery. *J Biomed Res.* 2014 Mar;28(2):108-13 Wrong outcome (did not assess VGF; did not report repeat revascularization)
Duplication: Wang XZ, Gong XX, Zhu TT, Li CJ, Yang ZJ. [Effect of aspirin plus clopidogrel therapy on aspirin resistance after off-pump coronary artery bypass surgery]. *Zhongguo Yi Xue Ke Xue Yuan Xue Bao.* 2013 Oct;35(5):495-502.
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 - 18 Veeger NJ, Zijlstra F, Hillege HL, van der Meer J, CABADAS Research Group of the Interuniversity Cardiology Institute of The Netherlands. Fourteen-year follow-up from CABADAS: vitamin K antagonists or dipyridamole not superior to aspirin. *The Annals of thoracic surgery.* 2010 Nov 30;90(5):1515-21. Wrong outcome (unclear definition of repeat revascularization)
 - 19 Tetik S, Ak K, Isbir S, Eksioglu-Demiralp E, Arsan S, Iqbal O, Yardimci T. Clopidogrel provides significantly greater inhibition of platelet activity than aspirin when combined with atorvastatin after coronary artery bypass grafting: a prospective randomized study. *Clinical and Applied Thrombosis/Hemostasis.* 2010 Apr;16(2):189-98. Wrong outcome
 - 20 Kayacioglu I, Gunay R, Saskin H...The role of clopidogrel and acetylsalicylic acid in the prevention of early-phase graft occlusion due to reactive thrombocytosis after coronary artery bypass operation. *Heart Surg Forum.* 2008;11:E152–157. Did not measured graft patency in all participants, but only in those who have positive exercise tests
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- Duplication: Lim E, Cornelissen J, Routledge T... Biological efficacy of low versus medium dose aspirin after coronary surgery: results from a randomized trial [NCT00262275]. BMC medicine. 2006 May 22;4(1):12.
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- 26 Hashimoto K, Onoguchi K, Sasaki T... Strategy for balancing anticoagulation and hemostasis in aortocoronary bypass surgery: blood conservation and graft patency. Jpn Circ J. 1999 Mar;63(3):165-9. Wrong intervention
- 27 Post Coronary Artery Bypass Graft Trial Investigators. The effect of aggressive lowering of low-density lipoprotein cholesterol levels and low-dose anticoagulation on obstructive changes in saphenous-vein coronary-artery bypass grafts. N Engl J Med. 1997 Jan 16;336(3):153-62. Wrong patient population (randomization occurred 1-11 years post-CABG)
- 28 van der Meer J, Brutel de la Rivière A, van Gilst WH... Effects of low dose aspirin (50 mg/day), low dose aspirin plus dipyridamole, and oral anticoagulant agents after internal mammary artery bypass grafting: patency and clinical outcome at 1 year. CABADAS Research Group of the Interuniversity Cardiology Institute of The Netherlands. Prevention of Coronary Artery Bypass Graft Occlusion by Aspirin, Dipyridamole and Acenocoumarol/Phenprocoumon Study. J Am Coll Cardiol. 1994 Nov 1;24(5):1181-8. Wrong outcome (IMA patency) and Wrong study design (Subgroup analysis of CABADAS trial)
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- 30 Goldman S, Copeland J, Moritz T... Long-term graft patency (3 years) after coronary artery surgery. Effects of aspirin: results of a VA Cooperative study. Circulation. 1994 Mar 1;89(3):1138-43. Double counting
- 31 Rajah SM, Nair U, Rees M... Effects of antiplatelet therapy with indobufen or aspirin-dipyridamole on graft patency one year after coronary artery bypass grafting. The Journal of Thoracic and Cardiovascular Surgery. 1994 Apr 1;107(4):1146-53. Wrong intervention (indobufen and dipyridamole)
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- 34 Agnew TM, French JK, Neutze JM, Whitlock RM, Brandt PW, Kerr AR, Webber BJ, Rutherford JD. The role of dipyridamole in addition to low dose aspirin in the prevention of occlusion of coronary artery Wrong intervention (dipyridamole)

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- 37 Ollivier JP. [Permeability of aortocoronary bypass after 6 months. A multicenter French study]. *Arch Mal Coeur Vaiss*. 1991 Apr;84(4):537-42. Wrong intervention (dipyridamole) and Study not in English
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- 39 Goldman S, Copeland J, Moritz T, Henderson W, Zadina K, Ovitt T, Kern KB, Sethi G, Sharma GV, Khuri S, et al. Internal mammary artery and saphenous vein graft patency. Effects of aspirin. *Circulation*. 1990 Nov;82(5 Suppl):IV237-42. Wrong outcome (IMA patency) and Wrong study design (subgroup analysis of RCT)
- 40 Pfisterer M, Burkart F, Jockers G, Meyer B, Regenass S, Burckhardt D, Schmitt HE, Müller-Brand J, Skarvan K, Stulz P, Hasse J. Prevention of aortocoronary vein bypass graft occlusion: Which antithrombotic treatment and for how long?. *Thrombosis Research*. 1990 Jan 1;57:11-21. Wrong intervention (OAC 12 mth vs OAC 3 mth)
- First Duplication: Pfisterer M, Jockers G, Regenass S, ... [How long should antithrombotic therapy be continued following aortocoronary bypass surgery?]. *Schweiz Med Wochenschr*. 1989 Oct 28;119(43):1518-20.
- Second Duplication: Pfisterer 1989. Duration of thrombolytic treatment after coronary artery bypass surgery. *Schweiz Med Wochenschr*
- Third Duplication: Pfisterer M, Jockers G, Meier B, ... [Anticoagulants vs. low-dose aggregation inhibitors in the prevention of perioperative occlusion of aortocoronary bypass grafts. Preliminary results of a prospective randomized study]. *Helv Chir Acta*. 1987 Feb;53(4):497-500.
- Fourth Duplication: Pfisterer M, Burkart F, Jockers G, ... Trial of low-dose aspirin plus dipyridamole versus anticoagulants for prevention of aortocoronary vein graft occlusion. *Lancet*. 1989 Jul 1;2(8653):1-7.
- 41 Sanz G, Pajaron A, Alegría E, Coello I, Cardona M, Fournier JA, Gómez-Recio M, Ruano J, Hidalgo R, Medina A. Prevention of early aortocoronary bypass occlusion by low-dose aspirin and dipyridamole. Grupo Espanol para el Seguimiento del Injerto Coronario (GESIC). *Circulation*. 1990 Sep 1;82(3):765-73. Wrong patient population (in all patients, dipyridamole was used before study medications were administered)
- Duplication: Sanz G. Does low-dose aspirin prevent aortocoronary vein bypass graft occlusion?. *Thrombosis research*. 1990 Jan 1;57:23-6.
- 42 Sethi GK, Copeland JG, Goldman S, Moritz T, Zadina K, Henderson WG. Implications of preoperative administration of aspirin in patients undergoing coronary artery bypass grafting. *Journal of the American College of Cardiology*. 1990 Jan 1;15(1):15-20. Wrong study design (subgroup analysis of Goldman 1988's

- RCT), Wrong intervention and Wrong outcome
- Wrong intervention (heparin)
- 43 Weber MA, Hasford J, Tailens C, ... Low-dose aspirin versus anticoagulants for prevention of coronary graft occlusion. *Am J Cardiol.* 1990 Dec 15;66(20):1464-8
Duplication: Weber Meister. *Br. J clin. Pharmac.* 1984, 17, 703-11
- 44 Pirk J, Rohn V, Peregrin J. The effect of ibustrin on early aortocoronary bypass patency. *Cor Vasa.* 1990;32(3):258-62. Wrong intervention (dipyridamole)
- 45 Guiteras P, Altimiras J, Arís A, Augé JM, Bassons T, Bonal J, Caralps JM, Castellarnau C, Crexells C, Masotti M, et al. Prevention of aortocoronary vein-graft attrition with low-dose aspirin and triflusal, both associated with dipyridamole: a randomized, double-blind, placebo-controlled trial. *Eur Heart J.* 1989 Feb;10(2):159-67. Wrong intervention (dipyridamole)
- 46 Gershlick AH, Lyons JP, Wright JE, ... Long term clinical outcome of coronary surgery and assessment of the benefit obtained with postoperative aspirin and dipyridamole. *Br Heart J.* 1988 Aug;60(2):111-6. Wrong intervention (dipyridamole)
- 47 Thaulow E, Frøysaker T, Dale J, Vatne K. Failure of combined acetylsalicylic acid and dipyridamole to prevent occlusion of aortocoronary venous bypass graft. *Scand J Thorac Cardiovasc Surg.* 1987;21(3):215-20. Wrong intervention (dipyridamole)
- 48 Limet R, David JL, Magotteaux P, Larock MP, Rigo P. Prevention of aorta-coronary bypass graft occlusion. Beneficial effect of ticlopidine on early and late patency rates of venous coronary bypass grafts: a double-blind study. *J Thorac Cardiovasc Surg.* 1987 Nov;94(5):773-83
- 49 Pirk J, Vojáček J, Kovác J. Improvement of aortocoronary bypass patency by antiplatelet drug administration. Preliminary communication. *Cor Vasa.* 1986;28(3):177-80. Wrong intervention (dipyridamole)
Duplication: Pirk J, Vojáček J, Kovác J, Improved patency of the aortocoronary bypass by antithrombotic drugs. *Ann Thorac Surg.* 1986 Sep;42(3):312-4.
- 50 Brooks N, Wright J, Sturridge M, Pepper J, Magee P, Walesby R, Layton C, Honey M, Balcon R. Randomised placebo controlled trial of aspirin and dipyridamole in the prevention of coronary vein graft occlusion. *Br Heart J.* 1985 Feb;53(2):201-7. Wrong intervention (dipyridamole)
- 51 Rothlin ME, Pfluger N, Speiser K, Platelet inhibitors versus anticoagulants for prevention of aorto-coronary bypass graft occlusion. *Eur Heart J.* 1985 Feb;6(2):168-75. Wrong intervention (ticlopidine)
- 52 Rajah SM, Salter MC, Donaldson DR, ... Acetylsalicylic acid and dipyridamole improve the early patency of aorta-coronary bypass grafts. A double-blind, placebo-controlled, randomized trial. *J Thorac Cardiovasc Surg.* 1985 Sep;90(3):373-7. Wrong intervention (dipyridamole)
- 53 Chesebro JH, Fuster V, Elveback LR, Clements IP, Smith HC, Holmes DR Jr, Bardsley WT, Pluth JR, Wallace RB, Puga FJ, et al. Effect of dipyridamole and aspirin on late vein-graft patency after coronary bypass operations. *N Engl J Med.* 1984 Jan 26;310(4):209-14. Wrong intervention (dipyridamole)
- 54 Chevigné M, David JL, Rigo P, Limet R. Effect of ticlopidine on saphenous vein bypass patency rates: a double-blind study. *Ann Thorac Surg.* 1984 May;37(5):371-8. Wrong intervention (ticlopidine)
- 55 Chesebro JH, Clements IP, Fuster V... A platelet-inhibitor-drug trial in coronary-artery bypass operations: benefit of perioperative Wrong intervention

- dipyridamole and aspirin therapy on early postoperative vein-graft patency. *N Engl J Med.* 1982 Jul 8;307(2):73-8. (dipyridamole)
- 56 Mayer JE Jr, Lindsay WG, Castaneda W, Nicoloff DM. Influence of aspirin and dipyridamole on patency of coronary artery bypass grafts. *Ann Thorac Surg.* 1981 Mar;31(3):204-10. Wrong intervention (dipyridamole)
- 57 Dale J. Prevention of closure of aorto-coronary venous bypass grafts. *Scand J Haematol Suppl.* 1981;38:131-41. Protocol (No results)
- 58 Gohlke H, Gohlke-Bärwolf C, Stürzenhofecker P...Improved graft patency with anticoagulant therapy after aortocoronary bypass surgery: a prospective, randomized study. *Circulation.* 1981 Aug;64(2 Pt 2):II22-7 Wrong patient population (in all patients, dipyridamole was administered)
- Duplication: Gohlke H, Gohlke-Bärwolf C, Stürzenhofecker P, Görnandt L, Ritter B, Reichelt M, Buchwalsky R, Schmuziger M, Roskamm H. [Improved flow through aortocoronary venous bypasses after anticoagulant therapy. A prospective randomized study]. *Schweiz Med Wochenschr.* 1981 Nov 7;111(45):1722-4.
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- 60 Thaneeru P.; Gamel A.E.; Harding S.; Galvin S.; Hamilton F.; Kirk M.; Devlin G. IMPACT: Improving Coronary Graft Patency with Postoperative Aspirin and Clopidogrel Versus Aspirin and Ticagrelor. 2017. (conference abstract) Abstract (cannot extract relevant information)
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eTable 8. Characteristics of included studies in the systematic review and network meta-analysis

Study, Year	Location	Overall sample size	No. of eligible arms	Antithrombotic status prior random; antifibrinolytic use; heparin use	Patency assessment method (unit of analysis)	Time from random to patency assessment	Overall loss of patency follow-up	CABG type; setting
Pantely, 1979	US	47	2	NR; NR; NR	Angiography (per patient+per graft)	6 mth	21.3%	CCAB; Elective + Urgent
McEnany, 1982	US	216	3	NR; NR; NR	Angiography (per patient+per graft)	21.5 mth (range: 1 to 47 mth)	48.6%	NR; Elective + Urgent
Sharma, 1983	US	116	2	NR; NR; NR	Angiography (per patient+per graft)	12 mth	19.0%	CCAB; NR
Lorenz, 1984	DE	60	2	NR; NR; Yes during operation	Cineangiography (per patient+per graft)	4 mth	23.3%	CCAB; NR
Brown, 1985	US	98	2	NR; NR; NR	Angiography (per patient+per graft)	12 mth	16.3%	CCAB; Elective
Goldman, 1988	US	307	2	Stopped ASA ≥ 7 d pre-study entry; NR; NR	Angiography (per patient+per graft)	9 d (range: 6 to 60 d)	20.7%	NR; Elective
Goldman, 1989*	US	307	2	Stopped ASA ≥ 7 d pre-study entry; NR; NR	Angiography (per patient+per graft)	367 d (range: 62 to 527 d)	33.5%	NR; Elective
Goldman, 1991	US	489	2	Stopped ASA ≥ 5 d pre-CABG; NR; NR	Angiography (per patient+per graft)	8 d (range: 4 to 58 d)	28.2%	CCAB; Elective
Gavaghan 1991	AU	237	2	Stopped ASA or other antiplatelet agents ≥ 7 d pre-CABG; NR; Yes during operation	Angiography (per patient+per graft)	363 d (range: 222 to 430 d)	7.6%	CCAB; NR
Van der Meer, 1993	NL, DE, CH	635	2	Stopped antiplatelet ≥ 14 d pre-CABG or OAC ≥ 5 d pre-CABG; NR; Yes during	Angiography (per patient+per graft)	371 d	15.9%	CCAB; Elective

operation								
Hockings, 1993	AU	140	2	Stopped aspirin or platelet active drug ≥ 7 d pre-CABG; NR; NR	Angiography (per patient)	6 mth	27.1%	NR; Elective
Mujanovic, 2009	NO	20	2	All patients were on aspirin pre-CABG; NR; Yes during operation	Angiography (per graft)	3 mth	0%	OPCAB; Elective
Gao, 2009	CN	197	2	Stopped antiplatelet $\geq 5-7$ d pre-CABG; NR	64-Multislice CT Angiography (per graft)	12 mth	0%	CCAB + OPCAB; Elective + Urgent
Kulik, 2010	CA	113	2	Aspirin was not withheld pre-CABG; NR; NR	Angiography (per patient + per graft)	12 mth	18.6%	CCAB + OPCAB; Elective
Hage, 2017*	CA	113	2	Aspirin was not withheld pre-CABG; NR; NR	CT Angiography (per graft)	8 y	41.6%	CCAB + OPCAB; Elective
Gao, 2010	CN	249	2	Stopped clopidogrel or aspirin ≥ 7 d pre-CABG; NR; NR	Multislice CT Angiography (per graft)	3 mth	10.0%	CCAB + OPCAB; Elective
Sun, 2010	CA	99	2	NR; Y; NR	Cardiac CT angiography (per patient)	50 d	22.0%	CCAB; Elective
Mannacio, 2012	IT	300	2	Stopped antiplatelet ≥ 15 d pre-CABG; Yes during peri-op, but not during first 15 d post-op; Yes during peri-op but not during first 15 d post-op	64-slice multidetector CT angiography (per graft)	12 mth	4%	OPCAB; Elective
Saw, 2016	CA	70	2	All patients were on aspirin pre-CABG; NR; NR	320-detector or 128-slice dual source CT scanner (per graft)	12 mth	24.3%	NR; Elective + Urgent

Slim, 2016	NR	20	2	NR; NR; NR	128-slice dual-source scanner (per graft)	12 mth	0%	CCAB + OPCAB; Elective
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*Long-term follow-up of the originally published study. ASA: aspirin. CA: Canada. CH: Switzerland. CCAB: On-pump CABG. CN: China. CT: computed tomography. d: day(s). DE: Germany. DK: Denmark. IT: Italy. mth: month(s). NL: Netherlands. NO: Norway. NR: Not reported. OAC: oral anticoagulation. OD: once daily. OPCAB: Off-pump CABG. Random: randomization. Vit K A: Vitamin K Antagonists. y: year.

eTable 9. Demographic and clinical characteristics of patients enrolled in the included studies

Study, Year	Time of drug initiation post-CABG	Treatment duration	Relevant study arms	Age (y)	Male (%)	DM (%)	HTN (%)	Prior MI (%)	No. of any graft/vein per patient
Pantely, 1979	+3 d	6 mth	Vit K A: warfarin (INR target: NR)	56±8	69.2	-	-	-	2.85/2.85
			Control: No study medication	52±8	83.3	-	-	-	2.54/2.54
McEnany, 1982	+3 to 4 d	12 mth	Vit K A: warfarin (INR target: 1.5-2)	-	92.9	19.6	16.1	69.6	1.91/1.91
			Aspirin: 600 mg BID	-	82.0	14.0	26.0	58.0	2.03/2.03
			Control: Matching placebo	-	87.3	12.7	20.0	63.6	2.00/2.00
Sharma, 1983	+3 to 5 d	12 mth	Aspirin: 325 mg TID	-	100	23.4	25.0	57.8	2.20/2.20
			Control: No study medication	-	100	19.2	23.1	67.3	2.20/2.20
Lorenz, 1984	+24 h	4 mth	Aspirin: 100 mg OD	55±10	82.8	-	-	58.6	2.69/2.69
			Control: Matching placebo	55±6	90.3	-	-	77.4	3.35/3.35
Brown, 1985	+67 ± 27 h	12 mth	Aspirin: 325 mg TID	-	-	-	-	-	3.10/3.10
			Control: Matching placebo	-	-	-	-	-	3.30/3.30
Goldman, 1988	-12 h	<2 mth	Aspirin: 325 mg OD	58±8	100	-	47.4	55.8	-/3.20
			Control: Matching placebo	58±7	100	-	49.0	56.9	
Goldman, 1989*	-12 h	12 mth	Aspirin: 325 mg OD	59±8	100	-	45.2	52.9	-/3.20
			Control: Matching placebo	58±8	100	-	49.5	57.0	

Goldman, 1991	-12 h	0 h	Aspirin: 325 mg OD	60±8	100	-	56.0	62.0	-/2.60
			Control: Matching placebo	60±7	100	-	50.0	60.0	-/2.60
Gavaghan 1991	+1 h	12 mth	Aspirin: 324 mg OD	56±8	86.6	0.0	45.0	56.7	-/3.40
			Control: Matching placebo	56±7	83.6	0.0	39.0	60.9	-/3.60
Van der Meer, 1993	-12 h; 24 h	12 mth	Vit K A: 4 mg Acenocoumarol or 6 mg Phenprocoumon (INR Target: 2.8-4.8)	58±8	88.0	10.1	40.1	52.1	-/3.10
			Aspirin: 50 mg OD	58±8	87.0	8.1	34.0	56.0	-/2.80
Hockings, 1993	-7 d	6 mth	Aspirin: 100 mg OD	60±9	94.0	6.0	50.0	-	3.14/2.56
			Control: Matching placebo	60±9	92.3	5.8	30.8	-	3.48/2.79
Mujanovic, 2009	Immediately post-op	3 mth	Aspirin & Clopidogrel: 100 and 75 mg OD, respectively	58±8.5	-	-	-	-	2.9±0.99/1.9
			Aspirin: 100 mg OD	60±8.5	-	-	-	-	2.7±0.48/1.7
Gao, 2009	+1 d	Unclear	Aspirin & Clopidogrel: 100 and 75 mg OD, respectively	61±10	82.1	60.0	62.1	58.9	2.66±0.75/ 1.71±0.94
			Clopidogrel: 75 mg OD	62±9.9	83.3	50.0	64.7	48.0	2.49±0.72/ 1.51±0.85
Kulik, 2010	0 d	12 mth	Aspirin & Clopidogrel: 162 and 75 mg OD, respectively	65±7.5	91.1	25.0	48.2	-	3.6±0.8/2.30
			Aspirin: 162 mg OD and matching placebo	68±7.4	87.7	33.3	52.6	-	3.4±0.6/2.24
Hage 2017*	0 d	12 mth	Aspirin & Clopidogrel: 162 and 75 mg OD, respectively	72±7.7	92.2	33.3	64.7	-	3.6±0.8/2.30 [‡]
			Aspirin: 162 mg OD and matching placebo	75±7.6	87.5	45.8	83.3	-	3.4±0.6/2.24 [‡]
Gao, 2010	≤ +48 h	3 mth	Aspirin & Clopidogrel: 100 and 75 mg OD, respectively	58±8.3	82.3	39.8	61.9	49.6	3.18/2.14

			Aspirin: 100 mg OD	60±7.9	83.8	40.5	56.8	44.1	3.11/2.09
Sun, 2010	+6 to 7 h	1 mth	Aspirin & Clopidogrel: 81 and 75 mg OD, respectively	66±9.4	93.9	36.7	69.4	46.9	4.04/2.35
			Aspirin: 81 mg OD	65±9.3	86.0	34.0	70.0	32.0	3.94/2.30
Mannacio, 2012	+28 ± 12 h	12 mth	Aspirin & Clopidogrel: 100 and 75 mg OD, respectively	59±7.7	73.3	0.0	47.3	38.0	3.1±0.6/1.78
			Aspirin: 100 mg OD	59±8.3	75.3	0.0	45.3	34.7	3.2±0.6/1.87
Saw, 2016	+58 to 59 h	3 mth	Aspirin & Ticagrelor: 81 mg OD and 90 mg BID, respectively	62±7.5	85.7	31.4	74.3	14.3	3.49/1.14
			Aspirin: 81 mg OD and matching placebo	63±9.7	88.6	28.6	80.0	20.0	3.71/1.69
Slim, 2016	+6 h	8 mth	Aspirin & Clopidogrel: 81 and 75 mg OD, respectively	-	-	41.7	100	-	3.00/2.00
			Aspirin: 81 mg OD and matching placebo	-	-	62.5	87.5	-	3.38/2.38

*Long-term follow-up of the originally published study. INR: International Normalized Ratio. #from a secondary source.⁷²

eTable 10. Pairwise meta-analyses of antithrombotic agents

Intervention, by outcome	Comparator	No. of RCTs	No. of events/Total		OR (95% CI)	I ² (%)
			Intervention	Comparator		
SVGF (Base case analysis)						
Aspirin	Control	8	138/599	182/583	0.62 (0.43-0.90)	41
Vit K A	Control	2	15/47	25/61	0.68 (0.30-1.51)	0
Vit K A	Aspirin	2	79/291	88/310	0.94 (0.66-1.35)	0
ASA/Clo	Aspirin	6	56/546	83/539	0.60 (0.42-0.88)	0
ASA/Clo	Clopidogrel	1	5/145	9/141	NE	NA
ASA/Tic	Aspirin	1	4/39	12/53	NE	NA
SVGF (Per graft analysis)						
Aspirin	Control	8	130/1243	194/1236	0.63 (0.49-0.80)	0
Vit K A	Control	2	15/84	26/111	0.72 (0.33-1.59)	17
Vit K A	Aspirin	2	85/637	100/643	0.84 (0.62-1.15)	0
ASA/Clo	Aspirin	6	58/618	81/574	0.61 (0.42-0.88)	0
ASA/Clo	Clopidogrel	1	5/145	9/141	NE	NA
ASA/Tic	Aspirin	1	4/39	12/53	NE	NA
Major bleeding						
Aspirin	Control	2	1/198	0/187	2.62 (0.11-64.98)	NA
Vit K A	Control	1	4/68	0/71	NE	NA
Vit K A	Aspirin	2	29/375	16/380	2.26 (0.56-9.12)	30
ASA/Clo	Aspirin	4	6/262	8/256	0.76 (0.25-2.31)	0
ASA/Clo	Clopidogrel	0	NR	NR	NR	NA
ASA/Tic	Aspirin	1	0/35	0/35	NE	NA
Mortality						
Aspirin	Control	4	5/309	3/290	1.54 (0.36-6.66)	0
Vit K A	Control	2	1/81	0/101	3.44 (0.14-85.97)	NA
Vit K A	Aspirin	2	4/375	8/380	0.65 (0.10-4.10)	32
ASA/Clo	Aspirin	4	4/374	6/373	0.67 (0.20-2.30)	0
ASA/Clo	Clopidogrel	0	NR	NR	NR	NA
ASA/Tic	Aspirin	1	0/35	1/35	NE	NA
Myocardial infarction						
Aspirin	Control	3	4/374	5/362	0.97 (0.03-27)	70
Vit K A	Control	1	1/68	5/77	NE	NA
Vit K A	Aspirin	2	25/375	26/380	0.97 (0.55-1.71)	0
ASA/Clo	Aspirin	5	6/386	8/381	0.69 (0.23-2.04)	0
ASA/Clo	Clopidogrel	0	NR	NR	NR	NA
ASA/Tic	Aspirin	1	0/35	0/35	NE	NA
Cerebrovascular accident						
Aspirin	Control	2	1/223	1/226	1.09 (0.07-17.89)	NA
Vit K A	Control	0	NR	NR	NR	NA
Vit K A	Aspirin	1	3/307	1/309	NE	NA
ASA/Clo	Aspirin	3	5/250	8/248	0.60 (0.19-1.87)	0
ASA/Clo	Clopidogrel	0	NR	NR	NR	NA
ASA/Tic	Aspirin	1	0/35	0/35	NE	NA
Repeat revascularization						
Aspirin	Control	0	NR	NR	NR	NA
Vit K A	Control	0	NR	NR	NR	NA
Vit K A	Aspirin	0	NR	NR	NR	NA
ASA/Clo	Aspirin	2	7/201	9/198	0.72 (0.25-2.05)	0
ASA/Clo	Clopidogrel	0	NR	NR	NR	NA
ASA/Tic	Aspirin	1	0/35	1/35	NE	NA

Re-exploration for bleeding						
Aspirin	Control	4	34/506	9/485	3.59 (1.67-7.73)	0
Vit K A	Control	0	NR	NR	NR	NA
Vit K A	Aspirin	1	18/307	10/309	NE	NA
ASA/Clo	Aspirin	1	0/49	1/50	NE	NA
ASA/Clo	Clopidogrel	0	NR	NR	NR	NA
ASA/Tic	Aspirin	0	NR	NR	NR	NA
Minor bleeding						
Aspirin	Control	0	NR	NR	NR	NA
Vit K A	Control	0	NR	NR	NR	NA
Vit K A	Aspirin	0	NR	NR	NR	NA
ASA/Clo	Aspirin	4	10/262	11/256	0.89 (0.36-2.18)	0
ASA/Clo	Clopidogrel	0	NR	NR	NR	NA
ASA/Tic	Aspirin	1	11/35	1/35	NE	NA
MACCE						
Aspirin	Control	0	NR	NR	NR	NA
Vit K A	Control	0	NR	NR	NR	NA
Vit K A	Aspirin	1	52/307	43/309	NE	NA
ASA/Clo	Aspirin	3	6/330	8/332	0.75 (0.25-2.25)	0
ASA/Clo	Clopidogrel	0	NR	NR	NR	NA
ASA/Tic	Aspirin	0	NR	NR	NR	NA

Not estimable because of zero events in both arms or insufficient data (<2 studies). ASA: Aspirin. ASA/Clo: Dual-antiplatelet with aspirin and clopidogrel. ASA/Tic: Dual-antiplatelet therapy with aspirin and ticagrelor. Control: Placebo/control. MACCE: Major adverse cardiac and cerebrovascular event. NE: Not estimable. NR: Not reported. NA: Not applicable. SVGF: Saphenous vein graft failure. Vit K A: Vitamin K Antagonists.

eTable 11. Summary of direct, indirect, and network estimates for primary and secondary outcomes

Treatment, by outcome	Comparator	Direct OR (95% CI)	Indirect OR (95% CI)	NMA OR (95% CI)
SVGF (Base case analysis)				
ASA/Clo	Control	-	0.40 (0.24-0.69)	0.40 (0.24-0.69)
ASA/Tic	Control	-	0.25 (0.07-0.94)	0.25 (0.07-0.94)
Vit K A	Control	0.68 (0.30-1.51)	0.58 (0.28-1.21)	0.63 (0.37-1.06)
Aspirin	Control	0.62 (0.43-0.90)	0.79 (0.19-3.41)	0.64 (0.47-0.88)
Clopidogrel	Control	-	0.77 (0.21-2.86)	0.77 (0.21-2.86)
ASA/Clo	Aspirin	0.60 (0.42-0.88)	Not estimable	0.63 (0.41-0.97)
ASA/Tic	Aspirin	0.39 (0.12-1.32)	Not estimable	0.39 (0.11-1.42)
Vit K A	Aspirin	0.94 (0.66-1.35)	1.49 (0.42-5.21)	0.98 (0.61-1.57)
ASA/Clo	Clopidogrel	0.52 (0.17-1.60)	Not estimable	0.52 (0.16-1.73)
ASA/Tic	Clopidogrel	-	0.32 (0.05-1.98)	0.32 (0.05-1.98)
Vit K A	Clopidogrel	-	0.81 (0.21-3.15)	0.81 (0.21-3.15)
Aspirin	Clopidogrel	-	0.83 (0.23-2.96)	0.83 (0.23-2.96)
ASA/Clo	Vit K A	-	0.64 (0.34-1.22)	0.64 (0.34-1.22)
ASA/Tic	Vit K A	-	0.40 (0.10-1.57)	0.40 (0.10-1.57)
ASA/Clo	ASA/Tic	-	1.62 (0.41-6.31)	1.62 (0.41-6.31)
The estimated common between-study variance (τ^2) = $0.216^2 = 0.047$				
SVGF (Per graft analysis)				
ASA/Clo	Control	-	0.39 (0.25,0.61)	0.39 (0.25,0.61)
ASA/Tic	Control	-	0.25 (0.07-0.87)	0.25 (0.07-0.87)
Vit K A	Control	0.72 (0.33-1.59)	0.53 (0.35-0.81)	0.57 (0.40-0.82)
Aspirin	Control	0.63 (0.49-0.80)	1.04 (0.37-2.96)	0.65 (0.51-0.82)
Clopidogrel	Control	-	0.75 (0.22-2.49)	0.75 (0.22-2.49)
ASA/Clo	Aspirin	0.61 (0.42-0.88)	Not estimable	0.61 (0.42-0.88)
ASA/Tic	Aspirin	0.39 (0.12-1.32)	Not estimable	0.39 (0.12-1.32)
Vit K A	Aspirin	0.84 (0.62-1.15)	1.47 (0.56-3.86)	0.89 (0.66-1.20)
ASA/Clo	Clopidogrel	0.52 (0.17-1.60)	Not estimable	0.52 (0.17-1.60)
ASA/Tic	Clopidogrel	-	0.34 (0.06-1.84)	0.34 (0.06-1.84)
Vit K A	Clopidogrel	-	0.77 (0.23-2.59)	0.77 (0.23-2.59)
Aspirin	Clopidogrel	-	0.86 (0.27-2.81)	0.86 (0.27-2.81)
ASA/Clo	Vit K A	-	0.68 (0.42-1.11)	0.68 (0.42-1.11)
ASA/Tic	Vit K A	-	0.44 (0.13-1.54)	0.44 (0.13-1.54)
ASA/Clo	ASA/Tic	-	1.56 (0.43-5.56)	1.56 (0.43-5.56)
The estimated common between-study variance (τ^2) = $(3.61 \times 10^{-10})^2 = 1.30 \times 10^{-19}$				
Major bleeding (no Clopidogrel monotherapy)				
ASA/Clo	Control	-	2.84 (0.25-32.26)	2.84 (0.25-32.26)
ASA/Tic	Control	-	3.75 (0.04-341.19)	3.75 (0.04-341.19)
Vit K A	Control	9.98 (0.53-188.92)	2.50 (0.13-48.51)	6.70 (0.75-59.62)
Aspirin	Control	2.62 (0.11-64.98)	Not estimable	3.75 (0.42-33.28)
ASA/Clo	Aspirin	0.76 (0.25-2.31)	Not estimable	0.76 (0.26-2.20)
ASA/Tic	Aspirin	Not estimable	Not estimable	1.00 (0.02-51.80)
Vit K A	Aspirin	2.26 (0.56-9.12)	Not estimable	1.79 (0.95-3.35)
ASA/Clo	Vit K A	-	0.42 (0.12-1.46)	0.42 (0.12-1.46)

ASA/Tic	Vit K A	-	0.56 (0.01-30.44)	0.56 (0.01-30.44)
ASA/Clo	ASA/Tic	-	0.76 (0.01-45.19)	0.76 (0.01-45.19)

The estimated common between-study variance (τ^2) = $(2.32 \times 10^{-11})^2 = 5.38 \times 10^{-22}$

Mortality (no Clopidogrel monotherapy)

ASA/Clo	Control	-	1.19 (0.21-6.71)	1.19 (0.21-6.71)
ASA/Tic	Control	-	0.57 (0.02-18.18)	0.57 (0.02-18.18)
Vit K A	Control	3.44 (0.14-85.97)	0.53 (0.08-3.57)	1.04 (0.23-4.72)
Aspirin	Control	1.54 (0.36-6.66)	Not estimable	1.77 (0.52-5.99)
ASA/Clo	Aspirin	0.67 (0.20-2.30)	Not estimable	0.67 (0.20-2.30)
ASA/Tic	Aspirin	0.32 (0.01-8.23)	Not estimable	0.32 (0.01-8.23)
Vit K A	Aspirin	0.65 (0.10-4.10)	Not estimable	0.59 (0.19-1.87)
ASA/Clo	Vit K A	-	1.14 (0.21-6.17)	1.14 (0.21-6.17)
ASA/Tic	Vit K A	-	0.55 (0.02-17.09)	0.55 (0.02-17.09)
ASA/Clo	ASA/Tic	-	2.07 (0.07-66.02)	2.07 (0.07-66.02)

The estimated common between-study variance (τ^2) = $(4.40 \times 10^{-9})^2 = 1.93 \times 10^{-17}$

Myocardial Infarction (no Clopidogrel monotherapy)

ASA/Clo	Control	-	0.38 (0.07-2.12)	0.38 (0.07-2.12)
ASA/Tic	Control	-	0.53 (0.01-34.71)	0.53 (0.01-34.71)
Vit K A	Control	0.21 (0.02-1.89)	1.74 (0.19-15.92)	0.49 (0.12-2.00)
Aspirin	Control	0.97 (0.03-27)	Not estimable	0.52 (0.13-2.10)
ASA/Clo	Aspirin	0.69 (0.23-2.04)	Not estimable	0.71 (0.25-2.02)
ASA/Tic	Aspirin	NA	Not estimable	1.00 (0.02-51.80)
Vit K A	Aspirin	0.97 (0.55-1.71)	Not estimable	0.92 (0.52-1.62)
ASA/Clo	Vit K A	-	0.77 (0.23-2.54)	0.77 (0.23-2.54)
ASA/Tic	Vit K A	-	1.09 (0.02-58.80)	1.09 (0.02-58.80)
ASA/Clo	ASA/Tic	-	0.71 (0.01-42.40)	0.71 (0.01-42.40)

The estimated common between-study variance (τ^2) = $(1.04 \times 10^{-7})^2 = 1.08 \times 10^{-14}$

Not estimable because of zero events in all study arms or because a second direct comparison needed to contribute to that specific indirect comparison is not available. Bold estimates indicate statistically significant differences. ASA/Clo: Dual-antiplatelet with aspirin and clopidogrel. ASA/Tic: Dual-antiplatelet therapy with aspirin and ticagrelor. Control: Placebo/control. Vit K A: Vitamin K Antagonists.

eTable 12. Treatment rankings according to SUCRA curves

Treatment by outcome	SUCRA
SVGf (Base case analysis)	
ASA/Tic	89.3
ASA/Clo	79.9
Vit K A	45.6
Aspirin	43.5
Clopidogrel	33.3
Control	8.4
SVGf (Per graft analysis)	
ASA/Tic	89.7
ASA/Clo	81.1
Vit K A	52.0
Aspirin	37.7
Clopidogrel	32.8
Control	6.7
Major Bleeding (no Clopidogrel monotherapy)	
Control	83.3
ASA/Clo	59.6
Aspirin	47.3
ASA/Tic	45.9
Vit K A	13.9
Mortality (no Clopidogrel monotherapy)	
ASA/Tic	66.4
Control	56.5
Vit K A	55.9
ASA/Clo	49.1
ASA	22.1
Myocardial Infarction (no Clopidogrel monotherapy)	
ASA/Clo	71.4
Vit K A	57.7
ASA/Tic	50.7
Aspirin	48.9
Control	21.3

ASA/Clo: Dual-antiplatelet with aspirin and clopidogrel. ASA/Tic: Dual-antiplatelet therapy with aspirin and ticagrelor. Control: Placebo/control. SUCRA: Surface Under the Cumulative Ranking. Vit K A: Vitamin K Antagonists. Larger SUCRA values indicates better interventions.

eTable 13. Contribution percentage (%) of direct evidence to the entire network

Outcome	ASA/Clo vs ASA	ASA/Tic vs ASA	Vit K A vs ASA	Aspirin vs Control	ASA/Clo vs Clo	Vit K A vs Control
SVGF (base case analysis)	27.7	17.3	16.4	16.2	17.3	5.1
Major bleeding	31.3	NE	33.7	16.7	NA	18.3
Mortality	24.0	23.9	20.5	23.3	NA	8.3
MI	30.9	NE	37.4	9.9	NA	21.8

NE: not estimated because of zero events in all arms. NA: not applicable because outcome data were not reported. ASA/Clo: Dual-antiplatelet with aspirin and clopidogrel. ASA/Tic: Dual-antiplatelet therapy with aspirin and ticagrelor. Clo: Clopidogrel monotherapy. Control: Placebo/control. Vit K A: Vitamin K Antagonists.

eTable 14. Local inconsistency tests assuming a common loop-specific heterogeneity estimated using the method of moments.

Closed loop of evidence	Inconsistency factor (IF, 95% CI)	Loop heterogeneity, τ^2
SVGF (Base case analysis)		
Aspirin-Vit K A-Control	0.25 (0.00-1.42)	0.098
SVGF (Per graft analysis)		
Aspirin-Vit K A-Control	0.30 (0.00-1.12)	0.000
Major Bleeding		
Aspirin-Vit K A-Control	0.85 (0.00-5.25)	0.000
Mortality		
Aspirin-Vit K A-Control	1.48 (0.00-5.22)	0.000
Myocardial Infarction		
Aspirin-Vit K A-Control	3.33 (0.00-7.06)	0.000

Control: Placebo/control. Vit K A: Vitamin-K Antagonists. If the 95% CI excludes zero, incoherence is detected statistically.

eTable 15. Global inconsistency using the design-by-treatment interaction model

Outcomes of interest	Chi-square	Global inconsistency, p-value
SVGf (Base case analysis)	0.86 (df=3)	0.8341
SVGf (Per graft analysis)	1.72 (df=3)	0.6323
Major bleeding	1.49 (df=2)	0.4759
Mortality	1.92 (df=3)	0.5899
Myocardial infarction	3.31 (df=2)	0.1910

eTable 16. Quality of direct evidence assessment

Comparison	No. of RCTs	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	OR (95% CI)	Quality of evidence
Vein graft failure (Base case analysis)								
Aspirin vs Control	8	Not Serious ¹	Not Serious ²	Serious ³	Not Serious ⁴	Unclear ⁵	0.62 (0.43-0.90)	Moderate
Vit K A vs Control	2	Serious ⁶	Not Serious ²	Serious ³	Serious ⁷	Unclear ⁵	0.68 (0.30-1.51)	Very Low
Vit K A vs Aspirin	2	Serious ⁸	Not Serious ²	Serious ³	Serious ⁷	Unclear ⁵	0.94 (0.66-1.35)	Very Low
ASA/Clo vs Aspirin	6	Not Serious ⁹	Not Serious ²	Serious ³	Not Serious ⁴	Unclear ⁵	0.60 (0.42-0.88)	Moderate
ASA/Clo vs Clo	1	Not Serious	NA ¹⁰	Serious ³	Serious ⁷	Unclear ⁵	0.52 (0.17-1.60)	Low
ASA/Tic vs Aspirin	1	Not Serious	NA ¹⁰	Serious ³	Serious ⁷	Unclear ⁵	0.39 (0.12-1.32)	Low
Major bleeding								
Aspirin vs Control	2	Not Serious	NA ¹⁰	Serious ³	Serious ⁷	NA ¹¹	2.62 (0.11-65)	Low
Vit K A vs Control	1	Serious ¹²	NA ¹⁰	Not Serious	Serious ⁷	NA ¹¹	9.98 (0.53-189)	Low
Vit K A vs Aspirin	2	Serious ¹²	Not Serious ²	Serious ³	Serious ⁷	NA ¹¹	2.26 (0.56-9.12)	Very Low
ASA/Clo vs Aspirin	4	Not Serious	Not Serious ²	Serious ³	Serious ⁷	NA ¹¹	0.76 (0.25-2.31)	Low
ASA/Tic vs Aspirin	1	Not Serious	NA ¹⁰	Not Serious	Serious ¹³	NA ¹¹	Not estimable	Moderate
All-cause mortality								

Aspirin vs Control	4	Not Serious	Not Serious ²	Serious ³	Serious ⁷	NA ¹¹	1.54 (0.36-6.66)	Low
Vit K A vs Control	2	Serious ¹²	NA ¹⁰	Not Serious	Serious ⁷	NA ¹¹	3.44 (0.14-86)	Low
Vit K A vs Aspirin	2	Serious ¹²	Not Serious ²	Serious ³	Serious ⁷	NA ¹¹	0.65 (0.10-4.10)	Very Low
ASA/Clo vs Aspirin	4	Not Serious	Not Serious ²	Serious ³	Serious ⁷	NA ¹¹	0.67 (0.20-2.30)	Low
ASA/Tic vs Aspirin	1	Not Serious	NA ¹⁰	Not Serious	Serious ⁷	NA ¹¹	0.32 (0.01-8.23)	Moderate
All myocardial infarction								
Aspirin vs Control	3	Not Serious	Not Serious ²	Serious ³	Serious ⁷	NA ¹¹	0.97 (0.03-27)	Low
Vit K A vs Control	1	Serious ¹²	NA ¹⁰	Not Serious	Serious ⁷	NA ¹¹	0.21 (0.02-1.89)	Low
Vit K A vs Aspirin	2	Serious ¹²	Not Serious ²	Serious ³	Serious ⁷	NA ¹¹	0.97 (0.55-1.71)	Very Low
ASA/Clo vs Aspirin	5	Not Serious	Not Serious ²	Serious ³	Serious ⁷	NA ¹¹	0.69 (0.23-2.04)	Low
ASA/Tic vs Aspirin	1	Not Serious	NA ¹⁰	Not Serious	Serious ¹³	NA ¹¹	Not estimable	Moderate

NA: Not applicable

¹Eight studies have incomplete patency data (range: 16% to 48.6%). Of these, three studies reported comparable missing rates and similar reasons for missing outcome across arms. Of six studies that reported in sufficient detail, adequate generation of a randomized sequence was performed in all of the studies and blinding was likely effective in all of them. No studies adequately described allocation concealment.

²Low heterogeneity ($I^2 < 75\%$).

³At least one study used aspirin at doses higher than those that are currently used (75-100 mg/day) and/or SVGF is a surrogate outcome as well as the short duration of treatment and follow-up for SVGF are not very applicable to the real-world situation.

⁴The 95% confidence interval is narrow, does not cross the clinical decision threshold, and OIS is met.

⁵As per protocol, the funnel plot or Egger's test was not performed because of insufficient information (<10 studies).

⁶No blinding in one study and incomplete blinding in another study. Both studies have incomplete patency data (range: 21% to 48.6%), and the proportion of missing data was not balanced between arms in one study.

⁷The confidence interval crosses the clinical decision threshold with small number of events and sample size.

⁸Both studies failed to blind patients and personnel and had incomplete patency data (range: 15.9% to 48.6%). The proportion of missing data was not balanced between arms in one study.

⁹Of six studies, one study did not blind patient and personnel and missing data (41.6%) was not balanced in another study.

¹⁰Unable to assess because there are <2 studies available with non-zero events in both arms.

¹¹This NMA was designed to include studies that evaluated SVGF. Many studies reporting only clinical outcomes were excluded as a result of the design. Therefore, it is not possible to explore the impact of publication bias for clinical outcomes.

¹²All studies failed to blind patients and personnel completely.

¹³Small number of events and sample size.

eTable 17. Quality of network evidence assessment

Comparison	Direct Evidence		Indirect Evidence		Network Meta-Analysis*	
	OR (95% CI)	Quality of Evidence	OR (95% CI)	Quality of Evidence	OR (95% CI)	Quality of Evidence
SVGF (Base case analysis)						
ASA/Clo vs Control	-	-	0.40 (0.24-0.69)	Moderate ^{1,3,5}	0.40 (0.24-0.69)	Moderate
ASA/Tic vs Control	-	-	0.25 (0.07-0.94)	Moderate ^{1,3,6}	0.25 (0.07-0.94)	Moderate
Vit K A vs Control	0.68 (0.30-1.51)	Very Low	0.58 (0.28-1.21)	Very Low ^{2,8}	0.63 (0.37-1.06)	Very Low
Aspirin vs Control	0.62 (0.43-0.90)	Moderate	0.79 (0.19-3.41)	Very Low ^{2,10}	0.64 (0.47-0.88)	Moderate
Clopidogrel vs Control	-	-	0.77 (0.21-2.86)	Very Low ^{1,2,5}	0.77 (0.21-2.86)	Very Low
ASA/Clo vs Aspirin	0.60 (0.42-0.88)	Moderate	Not estimable	Not estimable	0.63 (0.41-0.97)	Moderate
ASA/Tic vs Aspirin	0.39 (0.12-1.32)	Low	Not estimable	Not estimable	0.39 (0.11-1.42)	Low
Vit K A vs Aspirin	0.94 (0.66-1.35)	Very Low	1.49 (0.42-5.21)	Very Low ^{2,4,7}	0.98 (0.61-1.57)	Very Low
ASA/Clo vs Clopidogrel	0.52 (0.17-1.60)	Low	Not estimable	Not estimable	0.52 (0.16-1.73)	Low
ASA/Tic vs Clopidogrel	-	-	0.32 (0.05-1.98)	Very Low ^{1,2,7}	0.32 (0.05-1.98)	Very Low
Vit K A vs Clopidogrel	-	-	0.81 (0.21-3.15)	Very Low ^{1,2,7}	0.81 (0.21-3.15)	Very Low
Aspirin vs Clopidogrel	-	-	0.83 (0.23-2.96)	Low ^{2,7}	0.83 (0.23-2.96)	Low
ASA/Clo vs Vit K A	-	-	0.64 (0.34-1.22)	Very Low ^{1,2,5}	0.64 (0.34-1.22)	Very Low
ASA/Tic vs Vit K A	-	-	0.40 (0.10-1.57)	Very Low ^{1,2,6}	0.40 (0.10-1.57)	Very Low
ASA/Clo vs ASA/Tic	-	-	1.62 (0.41-6.31)	Very Low ^{2,5}	1.62 (0.41-6.31)	Very Low
Major Bleeding						
ASA/Clo vs Control	-	-	2.84 (0.25-32.26)	Very Low ^{1,2,6}	2.84 (0.25-32)	Very Low
ASA/Tic vs Control	-	-	3.75 (0.04-341.19)	Very Low ^{1,2,8}	3.75 (0.04-341)	Very Low
Vit K A vs Control	9.98 (0.53-189)	Low	2.50 (0.13-48.51)	Very Low ^{1,2,8}	6.70 (0.75-60)	Low
Aspirin vs Control	2.62 (0.11-65)	Low	Not estimable	Not estimable	3.75 (0.42-33)	Low
ASA/Clo vs Aspirin	0.76 (0.25-2.31)	Low	Not estimable	Not estimable	0.76 (0.26-2.20)	Low
ASA/Tic vs Aspirin	NA	Moderate	Not estimable	Not estimable	1.00 (0.02-52)	Moderate
Vit K A vs Aspirin	2.26 (0.56-9.12)	Very Low	Not estimable	Not estimable	1.79 (0.95-3.35)	Very Low
ASA/Clo vs Vit K A	-	-	0.42 (0.12-1.46)	Very Low ^{1,2,6}	0.42 (0.12-1.46)	Very Low
ASA/Tic vs Vit K A	-	-	0.56 (0.01-30.44)	Very Low ^{1,2,9}	0.56 (0.01-30)	Very Low
ASA/Clo vs ASA/Tic	-	-	0.76 (0.01-45.19)	Very Low ^{2,4,8}	0.76 (0.01-45)	Very Low
Mortality						
ASA/Clo vs Control	-	-	1.19 (0.21-6.71)	Very Low ^{1,2,6}	1.19 (0.21-6.71)	Very Low
ASA/Tic vs Control	-	-	0.57 (0.02-18.18)	Very Low ^{1,2,5}	0.57 (0.02-18)	Very Low

Vit K A vs Control	3.44 (0.14-86)	Low	0.53 (0.08-3.57)	Very Low ^{1,2,8}	1.04 (0.23-4.72)	Low
Aspirin vs Control	1.54 (0.36-6.66)	Low	Not estimable	Not estimable	1.77 (0.52-5.99)	Low
ASA/Clo vs Aspirin	0.67 (0.20-2.30)	Low	Not estimable	Not estimable	0.67 (0.20-2.30)	Low
ASA/Tic vs Aspirin	0.32 (0.01-8.23)	Moderate	Not estimable	Not estimable	0.32 (0.01-8.23)	Moderate
Vit K A vs Aspirin	0.65 (0.10-4.10)	Very Low	Not estimable	Not estimable	0.59 (0.19-1.87)	Very Low
ASA/Clo vs Vit K A	-	-	1.14 (0.21-6.17)	Very Low ^{1,2,8}	1.14 (0.21-6.17)	Very Low
ASA/Tic vs Vit K A	-	-	0.55 (0.02-17.09)	Very Low ^{1,2,5}	0.55 (0.02-17)	Very Low
ASA/Clo vs ASA/Tic	-	-	2.07 (0.07-66.02)	Very Low ^{2,4,8}	2.07 (0.07-66)	Very Low
Myocardial Infarction						
ASA/Clo vs Control	-	-	0.38 (0.07-2.12)	Very Low ^{1,2,6}	0.38 (0.07-2.12)	Very Low
ASA/Tic vs Control	-	-	0.53 (0.01-34.71)	Very Low ^{1,2,8}	0.53 (0.01-35)	Very Low
Vit K A vs Control	0.21 (0.02-1.89)	Low	1.74 (0.19-15.92)	Very Low ^{1,2,8}	0.49 (0.12-2.00)	Low
Aspirin vs Control	0.97 (0.03-27)	Low	Not estimable	Not estimable	0.52 (0.13-2.10)	Low
ASA/Clo vs Aspirin	0.69 (0.23-2.04)	Low	Not estimable	Not estimable	0.71 (0.25-2.02)	Low
ASA/Tic vs Aspirin	NA	Moderate	Not estimable	Not estimable	1.00 (0.02-52)	Moderate
Vit K A vs Aspirin	0.97 (0.55-1.71)	Very Low	Not estimable	Not estimable	0.92 (0.52-1.62)	Very Low
ASA/Clo vs Vit K A	-	-	0.77 (0.23-2.54)	Very Low ^{1,2,6}	0.77 (0.23-2.54)	Very Low
ASA/Tic vs Vit K A	-	-	1.09 (0.02-58.80)	Very Low ^{1,2,9}	1.09 (0.02-59)	Very Low
ASA/Clo vs ASA/Tic	-	-	0.71 (0.01-42.40)	Very Low ^{2,4,8}	0.71 (0.01-42)	Very Low

ASA/Clo: Dual-antiplatelet with aspirin and clopidogrel. ASA/Tic: Dual-antiplatelet therapy with aspirin and ticagrelor. Control: Placebo/control. Vit K A: Vitamin-K Antagonists. Not estimable because a second direct comparison needed to contribute to that specific indirect comparison is not available. Indirect estimates were obtained using the node-splitting approach.

* $\tau_{NMA}^2 < 50\%$ quantiles of the empirical distribution (i.e., low heterogeneity) and lack of evidence of incoherence.

¹. Probable intransitivity (more CCAB patients and/or earlier drug administration in one of the direct comparisons).

². Imprecision (wide 95% CI)

³. Effect size is < 0.5 and statistically significant.

⁴. Probable intransitivity (more elective patients and/or earlier drug administration in one of the direct comparisons).

5. The rating of the direct comparison with a stronger contribution is moderate.
6. The rating of the direct comparison with a stronger contribution is low.
7. Both direct comparisons have equal contributions to the indirect evidence, but the rating of the one with a larger sample size is moderate.
8. Both direct comparisons have equal contributions to the indirect evidence, but the rating of the one with a larger sample size is low.
9. Both direct comparisons have equal contributions to the indirect evidence, but the rating of the one with a larger sample size is very low.
10. The rating of the direct comparison with a stronger contribution is very low.

eTable 18. Imputation analysis: SVGF

Treatment	Comparator	Pairwise OR (95% CI)	NMA OR (95% CI)	
			Base Case	All missing failure
ASA/Clo	Control	-	0.40 (0.24-0.69)	0.53 (0.36-0.80)
ASA/Tic	Control	-	0.25 (0.07-0.94)	0.28 (0.08-0.99)
Vit K A	Control	0.68 (0.30-1.51)	0.63 (0.37-1.06)	0.80 (0.54-1.17)
Aspirin	Control	0.62 (0.43-0.90)	0.64 (0.47-0.88)	0.71 (0.55-0.92)
Clopidogrel	Control	-	0.77 (0.21-2.86)	1.02 (0.30-3.43)
ASA/Clo	Aspirin	0.60 (0.42-0.88)	0.63 (0.41-0.97)	0.75 (0.55-1.02)
ASA/Tic	Aspirin	0.39 (0.12-1.32)	0.39 (0.11-1.42)	0.39 (0.11-1.35)
Vit K A	Aspirin	0.94 (0.66-1.35)	0.98 (0.61-1.57)	1.12 (0.80-1.56)
ASA/Clo	Clopidogrel	0.52 (0.17-1.60)	0.52 (0.16-1.73)	0.52 (0.17-1.65)
ASA/Tic	Clopidogrel	-	0.32 (0.05-1.98)	0.27 (0.05-1.52)
Vit K A	Clopidogrel	-	0.81 (0.21-3.15)	0.78 (0.23-2.69)
Aspirin	Clopidogrel	-	0.83 (0.23-2.96)	0.70 (0.21-2.30)
ASA/Clo	Vit K A	-	0.64 (0.34-1.22)	0.67 (0.42-1.05)
ASA/Tic	Vit K A	-	0.40 (0.10-1.57)	0.35 (0.10-1.26)
ASA/Clo	ASA/Tic	-	1.62 (0.41-6.31)	1.92 (0.53-6.90)

ASA/Clo: Dual-antiplatelet with aspirin and clopidogrel. ASA/Tic: Dual-antiplatelet therapy with aspirin and ticagrelor. Control: Placebo/control. Vit K A: Vitamin-K Antagonists.

eTable 19. SUCRA values for SVGF after accounting for loss to follow-up

Treatment by outcome	Base case	All Missing Failure
	SUCRA	SUCRA
ASA/Tic	89.3	92.6
ASA/Clo	79.9	79.1
Vit K A	45.6	37.2
Aspirin	43.5	51.4
Clopidogrel	33.3	26.2
Control	8.4	13.4

ASA/Clo: Dual-antiplatelet with aspirin and clopidogrel. ASA/Tic: Dual-antiplatelet therapy with aspirin and ticagrelor. Control: Placebo/control. SUCRA: Surface Under the Cumulative Ranking. Vit K A: Vitamin-K Antagonists.

eTable 20. Sensitivity analyses: SVGF

Treatment	Comparator	Pairwise OR (95% CI)	NMA OR (95% CI)		
			Base Case	Closer to 1-year follow-up	Without OPCAB studies
ASA/Clo	Control	-	0.40 (0.24-0.69)	0.38 (0.22-0.66)	0.50 (0.26-0.96)
ASA/Tic	Control	-	0.25 (0.07-0.94)	0.24 (0.06-0.93)	0.25 (0.06-0.97)
Vit K A	Control	0.68 (0.30-1.51)	0.63 (0.37-1.06)	0.58 (0.32-1.04)	0.63 (0.36-1.09)
Aspirin	Control	0.62 (0.43-0.90)	0.64 (0.47-0.88)	0.62 (0.44-0.86)	0.64 (0.46-0.89)
Clopidogrel	Control	-	0.77 (0.21-2.86)	0.72 (0.19-2.75)	0.95 (0.24-3.80)
ASA/Clo	Aspirin	0.60 (0.42-0.88)	0.63 (0.41-0.97)	0.62 (0.39-0.96)	0.78 (0.44-1.39)
ASA/Tic	Aspirin	0.39 (0.12-1.32)	0.39 (0.11-1.42)	0.39 (0.11-1.44)	0.39 (0.10-1.46)
Vit K A	Aspirin	0.94 (0.66-1.35)	0.98 (0.61-1.57)	0.93 (0.55-1.57)	0.98 (0.59-1.63)
ASA/Clo	Clopidogrel	0.52 (0.17-1.60)	0.52 (0.16-1.73)	0.52 (0.16-1.76)	0.52 (0.15-1.78)
ASA/Tic	Clopidogrel	-	0.32 (0.05-1.98)	0.33 (0.05-2.09)	0.26 (0.04-1.74)
Vit K A	Clopidogrel	-	0.81 (0.21-3.15)	0.79 (0.20-3.21)	0.66 (0.16-2.80)
Aspirin	Clopidogrel	-	0.83 (0.23-2.96)	0.85 (0.23-3.10)	0.67 (0.17-2.61)
ASA/Clo	Vit K A	-	0.64 (0.34-1.22)	0.66 (0.33-1.32)	0.79 (0.37-1.71)
ASA/Tic	Vit K A	-	0.40 (0.10-1.57)	0.42 (0.10-1.71)	0.40 (0.10-1.63)
ASA/Clo	ASA/Tic	-	1.62 (0.41-6.31)	1.58 (0.40-6.26)	1.99 (0.47-8.41)

ASA/Clo: Dual-antiplatelet with aspirin and clopidogrel. ASA/Tic: Dual-antiplatelet therapy with aspirin and ticagrelor. Control: Placebo/control. OPCAB: Off-pump CABG. Vit K A: Vitamin-K Antagonists.

eTable 21. Description of outcomes used in RCTs included in the present NMA

Study, by outcome	Description of outcome
VEIN GRAFT FAILURE	
Pantely 1979	Measured at six postoperative months using coronary angiography and expressed per patient. A graft was defined as occluded if the contrast agent failed to flow through it and into the grafted artery.
McEnany 1982	Measured at 21.5 postoperative months using coronary angiography and expressed per graft and per patient, including post-mortem.
Sharma 1983	Measured at 12 postoperative months. Expressed per patient. Vein grafts were “opacified by selective cannulation or aortic root angiography.”
Lorenz 1984	Measured at four postoperative months using coronary angiography and expressed per patient. Contrast was selectively injected into each vein graft bypass.
Brown 1985	Measured at 12 postoperative months. Expressed per patient. Grafts (distal anastomoses) fully visualized to supply the distal artery during selective injection were called “patent”; otherwise they were considered occluded.
Goldman 1989	Measured at 367 postoperative days. Expressed per patient. A single vein graft was defined as occluded if the contrast agent failed to flow through it and into the grafted artery. Each distal anastomotic site is counted as a single graft
Goldman 1991	Measured at eight postoperative days. Expressed per patient. A graft was defined as occluded if the contrast agent failed to flow through it and into the grafted artery. Each distal anastomotic site is counted as a single graft
Gavaghan 1991	Measured at 363 postoperative days using angiography with the transfemoral Judkin's technique. Vein graft occlusion (or patency) rates were expressed per patient (with one or more distal anastomoses occluded). A graft was defined as occluded if the contrast agent failed to flow through it and into the grafted artery.
Van der Meer 1993	Measured at 371 postoperative days. Expressed per patient. A graft was defined as occluded “if the contrast agent failed to flow through the graft, or one or more distal anastomoses were occluded. A distal anastomosis was defined as occluded if contrast did not flow from the proximal graft into the grafted native artery.”
Hockings 1993	Measured at six postoperative months using invasive angiography. Expressed per patient.
Mujanovic 2009	Measured at three postoperative months using angiography. Fitzgibbons method of classification was used. Expressed per graft.
Gao 2009	Measured at 12 postoperative months using 64-Multislice Computed Tomography Angiography (MSCTA) and expressed per graft.
Kulik 2010	Measured at 12 postoperative months using angiography and expressed per patient.
Hage 2017	Measured at eight postoperative years using CCTA and expressed per graft in surviving patients.
Gao 2010	Measured at three postoperative months using multislice computed tomography angiography (MSCTA) and expressed per graft. A graft

Sun 2010	was considered occluded if a conduit did not fill with contrast at all. Measured at 50 postoperative days using cardiac CT angiography and expressed Per patient. “Stenosed grafts without diffuse luminal narrowing were considered to be patent”
Mannacio 2012	Measured at 12 postoperative months using 64-slice multidetector CT angiography. The quality of the anastomosis and conduits was graded according to Fitzgibbon.
Saw 2016	Measured at 12 postoperative months using 320-detector or 128-slice dual source CT scanner. A graft was defined as occluded if there was lack of contrast flow in the graft segment from the proximal anastomosis
Slim 2016	Measured at 12 postoperative months using a 128-slice dual-source scanner (failure is defined as stenosis $\geq 50\%$) and expressed per graft.
MAJOR BLEEDING	
McEnany 1982	No definition
Gavaghan 1991	GI bleeding
Van der Meer 1993	If life threatening or fatal and if blood transfusion or surgery was necessary
Kulik 2010	As per CURE trial definition
Hage 2017	A follow-up Case Report Form was designed to collect long-term clinical data and was sent to patients via mail.
Sun 2010	Intracranial hemorrhage... bleeding causing death, or bleeding requiring transfusion of >1 unit of RBC
Mannacio 2012	Defined according to the CURE trial
Saw 2016	Bleeding events were defined as per PLATO study. Major bleeding was defined as “bleeding that led to clinically significant disability, or bleeding with haemoglobin drop ≥ 3.0 g/dL but <5.0 g/dL or requiring 2-3 units of transfusion”
Slim 2016	Bleeding events were defined as per TIMI study
MORTALITY	
Pantely 1979	All cause mortality at 6 months
McEnany 1982	Mortality at 34 months
Sharma 1983	All cause mortality at 12 months
Brown 1985	All cause mortality at 12 months
Gavaghan 1991	All cause mortality at 12 months
Van der Meer 1993	All cause mortality at 12 months
Mujanovic	No definition at 3 months
Kulik 2010	All cause mortality at 12 months
Hage 2017	Cardiac Mortality. A follow-up Case Report Form was designed to collect long-term clinical data and was sent to patients via mail.
Gao 2010	All cause mortality at 3 months
Sun 2010	All cause mortality at 1 month
Mannacio 2012	Cardiac death at 12 months
Saw 2016	Cardiovascular death defined as “any death from cardiovascular or cerebrovascular cause, and any death without another known cause at 12 months”
MYOCARDIAL INFARCTION (MI)	
McEnany 1982	Fatal and non-fatal MI at 24 months
Goldman 1991	Assessed during postoperative catheterization (60 days)

Gavaghan 1991	Peri-operative new Q wave infarction
Van der Meer 1993	Diagnosed according to strict ECG criteria... at 12 months
Kulik 2010	Assessed at 12 months
Hage 2017	Collected at 8 years. A follow-up Case Report Form was designed to collect long-term clinical data and was sent to patients via mail.
Sun 2010	30-day MI defined as “creatin kinase-MB >10 times the upper limit of normal or >5 times the upper limit of normal with new Q waves >30 msec in 2 contiguous leads on electrocardiogram of a new wall abnormality”
Mannacio 2012	Assessed at 12 months. According to the joint ESC/ACCF/AHA/WHF definition
Saw 2016	Assessed at 12 months. In accordance with the universal definition ¹⁹⁸ . MI with CABG was defined as “>5 times normal reference elevation of troponin-I within 72 h after CABG...”
Slim 2016	Unknown. Assessed at 12 months
Cerebrovascular Accidents (CVA)	
Brown 1985	CVA at 12 months
Goldman 1991	CVA during postoperative catheterization (60 days)
Van der Meer 1993	Ischemic stroke at 12 months
Kulik 2010	CVA at 12 months
Hage 2017	Ischemic stroke at 8 years. A follow-up Case Report Form was designed to collect long-term clinical data and was sent to patients via mail.
Sun 2010	Stroke at 30 days
Mannacio 2012	Stroke at 12 months
Saw 2016	Assessed at 12 months. Stroke defined as “focal loss of neurological function caused by an ischaemic or haemorrhagic event...lasting \geq 24 h or leading to death”
CARDIAC RE-INTERVENTION	
Veeger 2010	Need for repeat revascularization at 14 years
Kulik 2010	Need for coronary intervention at 12 months
Hage 2017	Coronary reintervention (PCI) at 8 years. A follow-up Case Report Form was designed to collect long-term clinical data and was sent to patients via mail.
Mannacio 2012	Repeat revascularization (PCI or repeat CABG) at 12 months
Saw 2016	Repeat Revascularization (PCI or repeat CABG) at 12 months
HEART FAILURE	
Van der Meer 1993	Assessed at 12 months
SURGICAL RE-EXPLORATION FOR BLEEDING	
Goldman 1988	Re-operation
Goldman 1991	Re-operation
Gavaghan 1991	Re-operation
Van der Meer 1993	Re-operation for bleeding
Hockings 1993	Re-operation for bleeding
Sun 2010	Re-operation
MACCE	

Van der Meer 1993	MI, stroke, TIA, DVT, PE, major bleeding, death at 12 months
Kulik 2010	Cardiovascular death, MI, CVA, hospitalization for coronary ischemia, need for coronary intervention at 12 months
Gao 2010	Cardiovascular mortality, MI, and need for revascularization at 3 months
Mannacio 2012	Cardiac death, MI, repeat revascularization (PCI or repeat CABG), stroke at 12 months
ADMISSION DUE TO CARDIOVASCULAR CAUSE	
Kulik 2010	Hospitalization for coronary ischemia at 12 months
MINOR BLEEDING	
Kulik 2010	As per CURE trial definition
Hage 2017	Data collected at 8 years. A follow-up Case Report Form was designed to collect long-term clinical data and was sent to patients via mail.
Sun 2010	“Bleeding requiring modification of antithrombotic drug regimens or transfusion of 1 unit of RBC”
Mannacio 2012	Defined according to the CURE trial
Saw 2016	“Bleeding that led to clinically significant disability, or bleeding with haemoglobin drop ≥ 3.0 g/dL but <5.0 g/dL or requiring 2-3 units of transfusion”
Slim 2016	Defined according to the TIMI trial

DVT: deep vein thrombosis. GI: Gastrointestinal. PE: pulmonary embolism. PLATO: Platelet Inhibition and Patient Outcomes. RBC: red blood cells. TIMI: Thrombolysis in Myocardial Infarction. CURE: Clopidogrel in Unstable Angina to Prevent Recurrent Events.

eTable 22. Matrix indicating which outcomes that were and were not reported in included studies

Study ID	SVGf	Major Bleed	Mortality	CVA	MI	Cardiac re-intervention	Heart Failure	Surgical re-exploration	Minor bleeding	Admission to hospital
Pantely, 1979	√ (PP)		√							
McEnany, 1982	√ (PP)	√	√		√					
Sharma, 1983	√ (PP)		√							
Lorenz, 1984	√ (PP)									
Brown, 1985	√ (PP)		√	√						
Goldman, 1988	√ (PP)							√		
Goldman, 1989	√ (PP)									
Goldman, 1991	√ (PP)			√	√			√		
Gavaghan 1991	√ (PP)	√	√		√			√		
Van der Meer, 1993	√ (PP)	√	√	√	√		√	√		
Hockings, 1993	√ (PP)							√		
Mujanovic, 2009	√ (PG)									
Gao, 2009	√ (PG)									
Kulik, 2010	√ (PP)	√	√	√	√	√			√	√
Hage, 2017	√ (PG)	√	√	√	√	√			√	
Gao, 2010	√ (PG)		√		√					
Sun, 2010	√ (PP)	√	√	√	√			√	√	
Mannacio, 2012	√ (PG)	√	√	√	√	√			√	
Saw, 2016	√ (PG)	√	√	√	√	√			√	
Slim, 2016	√ PG)	√			√				√	

√: Reported. PP: per patient. PG: per graft.

eTable 23. Study-specific and comparison-specific risk of bias: SVGF

Comparison	No of studies	Study ID	Study-specific risk of bias	Comparison-specific risk of bias
Aspirin vs Control	8	McEnany 1982, Sharma 1983, Lorenz 1984, Brown 1985, Goldman 1989, Goldman 1991, Gavaghan 1991, Hockings 1993	High, High, High, Uncertain, Uncertain , Uncertain , Low , High	Moderate (not serious)
Vit K A vs Control	2	Pantely 1979, McEnany 1982	High, High	High (serious)
Vit K A vs Aspirin	2	McEnany 1982, Van der Meer 1993	High, High	High (Serious)
ASA/Clo vs Aspirin	6	Mujanovic 2009, Hage 2017, Gao 2010, Sun 2010, Mannacio 2012, Slim 2016	Low, Uncertain, Uncertain, Uncertain, Low , Low	Low (serious)
ASA/Clo vs Clo	1	Gao 2009	Low	Low (serious)
ASA/Tic vs Aspirin	1	Saw 2016	Low	Low (serious)

Bold texts indicate studies with larger sample sizes. ASA/Clo: Dual-antiplatelet with aspirin and clopidogrel. ASA/Tic: Dual-antiplatelet therapy with aspirin and ticagrelor. Clo: Clopidogrel monotherapy. Control: Placebo/control. Vit K A: Vitamin-K Antagonists.

Study-specific risk of bias assessment: low (if low risk of bias in all domains); uncertain (if high risk of bias in 1 domain); and high (if high risk of bias in ≥ 2 domains).

Comparison-specific risk of bias assessment: low (if all studies with larger sample size are at low risk of bias); moderate (if studies with larger sample size are either at low or unclear risk of bias and no studies with high risk of bias); high (if ≥ 1 studies with larger sample size are at high risk of bias).

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Travel Award, April 2017

Conference Presentations: (Presenter in Bold)

Solo K, Martin J, Bagur R. *Pre-operative Use of Aspirin in Patients Undergoing Coronary Artery Bypass Grafting: A Systematic Review and Meta-Analysis*, [Poster]. Canadian Agency for Drugs & Technologies in Health (CADTH) Symposium 2017. Ottawa, Ontario. April 23 - 25 2017.

Solo K, Bagur R. *The Effect of Embolic Protection Devices During Transcatheter Aortic Valve Implantation*, [Poster]. Western Science Research Conference 2016. London, Ontario. March 19, 2016.

Lownie S, Lopez-Ojeda P, Munoz C, Solo K, Salehi F, Johnson P, Pandey S, Pelz D. *Safety Evaluation of Primary Carotid Stenting: Embolic Detection using Procedural TCD and Correlation with DWI*. [Poster]. 84th AANS Annual Scientific Meeting. Chicago, Illinois. April 30 – May 4, 2016.

Publications:

Solo K, Martin J, Lavi S, Kabali C, John-Baptiste A, Nevis IF, Choudhury T, Mamas MA, Bagur R. Antithrombotic Therapy in Patients Undergoing Coronary Artery Bypass Grafting: A Protocol for a Systematic Review and Network Meta-Analysis. (submitted)

Solo K, Lavi S, Choudhury T, Martin J, Kwok CS, Kotronias RA, Nishina N, Ayan D, Mamas MA, Bagur R. Pre-operative Use of Aspirin in Patients Undergoing Coronary Artery Bypass Grafting: A Systematic Review and Meta-Analysis. (submitted)

Puka K*, Rab F*, Singh S*, **Solo K***, Thavam T*, Wilk P. Correlates of Unmet Healthcare Needs in Individuals with Cardiovascular Related Chronic Diseases (submitted)

Chow JTY, Hutnik CML, **Solo K**, Malvankar-Mehta MS. When Is Evidence Enough Evidence? A Systematic Review and Meta-Analysis of the Trabectome as a Solo Procedure in Patients with Primary Open-Angle Glaucoma. *J Ophthalmol.* 2017;2017:2965725.

Spence JD, **Solo K**. Resistant Atherosclerosis: The Need for Monitoring of Plaque Burden. *Stroke.* 2017;48(6):1624-1629.

Bagur R, **Solo K**, Alghofaili S, Nombela-Franco L, Kwok CS, Hayman S, Siemieniuk RA, Foroutan F, Spencer FA, Vandvik PO, Schäufele TG, Mamas MA. Cerebral Embolic Protection Devices During Transcatheter Aortic Valve Implantation: Systematic Review and Meta-Analysis. *Stroke.* 2017;48(5):1306-1315.

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