

Anti-thrombotic Therapy in Peripheral Artery Disease and the Role of Female Sex:
Assessing Outcomes, Representation, and Generalizability

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Preface

Shira A. Strauss (SAS) is the student. SAS was involved in all aspects of the thesis, from study design to data collection and from data analysis to manuscript writeup. Dr. Marc Carrier is the thesis supervisor. MC is a Senior Scientist in the Clinical Epidemiology Program at the Ottawa Hospital Research Institute, a Professor in the Faculty of Medicine at the University of Ottawa, and the Chief of the Division of Hematology in the Department of Medicine at The Ottawa Hospital. MC oversaw all aspects of protocol design, study execution, and data analysis, and reviewed and provided feedback on all thesis drafts. Dr. Daniel Kobewka (DK) and Dr. Prasad Jetty are Thesis Advisory Committee (TAC) members. DK is an Assistant Professor in the Faculty of Medicine at the University of Ottawa and a Staff Physician in the Department of General Internal Medicine at The Ottawa Hospital, with a special interest in vascular risk factor management. PJ is an Associate Professor in the Faculty of Medicine at the University of Ottawa, a Research Scientist at the Ottawa Hospital Research Institute, a vascular surgeon at The Ottawa Hospital, and the former Director of Research for the Ottawa Division of Vascular Surgery. DK and PJ contributed both clinical and research expertise in reviewing all phases of study design, study execution, and manuscript drafting. The specific roles of each author and their contributions to the chapters are listed at the beginning of each component article. Ethics approval was not required since none of the studies comprising the thesis involved primary data collection using living human participants or human biological materials.

Abstract

Peripheral artery disease (PAD) is associated with increased risk for arterial thromboembolic events, and antithrombotic therapy is fundamental to its treatment. Females with PAD have unique characteristics that impact their disease experience, but data is lacking on the differential effects of antithrombotic regimens in females with PAD. We developed a protocol and conducted two systematic reviews and meta-analyses to 1) assess the impact of female sex on cardiovascular, limb, and bleeding events in antithrombotic trials enrolling PAD patients, and 2) evaluate the representation of female PAD patients in antithrombotic trials, as well as trial generalizability. Females did not confer any benefit from dual antiplatelet therapy, dual pathway inhibition, or therapeutic oral anticoagulation over mono-antiplatelet therapy alone, however trial generalizability was limited by poor female enrolment and insufficient sex-based analyses. A more tailored approach to secondary prevention in females with PAD (beginning with improved study design) may yield better outcomes.

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Chapter 1: Introduction

Peripheral artery disease (PAD) is an arterial occlusive disease that can cause leg pain, tissue loss, and in severe cases, limb loss. PAD prevalence ranges from 5.6% to 28.7% worldwide,^{1,2} and it is associated with a significantly increased risk of arterial thrombotic events such as stroke, myocardial infarction (MI), and cardiovascular death.^{3,4} Antithrombotic therapy is thus a mainstay of treatment for patients with symptomatic PAD.⁵⁻⁸ Despite affecting males and females in at least roughly equal proportions, females with PAD are often underdiagnosed, undertreated, and in many cases, have poorer outcomes compared to their male counterparts.⁹⁻¹² The reasons for this are multifactorial, related to anatomical, physiological, psychological, and sociological differences between sexes and genders. Nevertheless, females are often under-represented in cardiovascular, and more specifically, PAD trials.¹³⁻¹⁵ As antithrombotic guidelines for the management of PAD quickly evolve, it is essential to determine whether females with PAD differ from males in their response to these medications, and whether they were adequately represented in the trials that shape current guidelines. The objectives of this thesis are to assess the risks and benefits of antithrombotic therapy among females with PAD, and to evaluate the representation of females with PAD in formative antithrombotic trials (and thus, the generalizability of these trials to society guidelines and the broader female PAD population).

Chapter 2. Background

2.1 Peripheral Artery Disease

Peripheral artery disease (PAD) is a vascular condition whereby atherosclerotic plaque builds up in the arteries, causing stenoses and/or occlusions that limit blood flow. PAD has a global prevalence of 5.6%-28.7%, affecting 237 million people over the age of 25 worldwide.^{1,2} It affects males and females in roughly equal proportions,^{2,16} with some recent studies indicating a slightly higher prevalence among females.^{2,17,18} Signs and symptoms of PAD range from asymptomatic to limb-threatening, often reflecting the degree of blood flow impairment.⁷ The classic symptom of PAD is claudication, described as a cramping pain in the calves (or thighs/buttocks, depending on the level of disease) that worsens with activity and resolves with rest.¹⁹ In its most severe form, PAD causes chronic limb-threatening ischemia (CLTI),

characterized by rest pain and tissue loss/gangrene. In both its milder and more severe forms, PAD has a significant impact on leg functioning, quality of life, and morbidity and mortality.^{20–24}

2.2 PAD and Arterial Thrombotic Risk

Patients with PAD are at increased risk for arterial thrombosis, both in the lower extremities as well as throughout the body. In 2009, a cohort study that followed >6000 elderly patients demonstrated that PAD was associated with an increased risk of cerebrovascular events (defined as stroke or carotid revascularization, hazard ratio [HR] 1.45; 95% confidence interval [CI] 1.06-1.98), cardiovascular events (defined as MI or coronary revascularization, HR 1.89; CI 1.56-2.28), and lower extremity peripheral vascular events (defined as lower extremity amputation or revascularization, HR 9.30; CI 6.31-13.71) over a five year period.³ PAD also was associated with a significantly increased risk of all-cause mortality (HR 1.76; CI 1.51-2.05), death due to cerebrovascular events (HR 2.75; CI 1.35-5.56), and death due to cardiovascular events (HR 2.07; CI 1.57-2.71).³ Clearly, PAD is not only a risk factor for limb ischemia and limb loss, but for MI, stroke, and mortality as well. To mitigate this risk and enhance secondary prevention, it is important to understand the multifactorial nature of PAD patients' risk profile.

PAD is a marker for atherosclerotic disease in other vascular beds, sharing a common set of risk factors with coronary artery disease (CAD) and cerebrovascular disease (CVD). This includes smoking, diabetes, advanced age, dyslipidemia, and hypertension.²⁵ However, the high prevalence of these risk factors *alone* does not account for PAD patients' increased cardiovascular risk. In 2008, a meta-analysis comprised of 16 population cohort studies demonstrated that, independent of their Framingham risk score (comprised of a patient's smoking status, age, cholesterol, blood pressure, and the presence of diabetes), patients with a low ankle brachial index (ABI<0.9, indicating PAD) had increased 10-year cardiovascular mortality risk compared to those with a normal ABI (HR 2.92; CI 2.31-3.70 for males and HR 2.97; CI 2.02-4.35 for females, respectively).⁴ Low ABI was also associated with increased risk of all-cause mortality (HR 2.34; CI 1.97-2.78 in males, HR 2.35; CI 1.76-3.13 in females) and major coronary events (HR 2.16; CI 1.76-2.66 in males, HR 2.49; CI 1.84-3.36 in females) after adjusting for Framingham risk score.⁴ Likewise, in a cohort study that followed 565 patients over 10 years, PAD patients *without* baseline cardiovascular disease demonstrated a three-fold increased risk of all-cause death, a six-fold increased risk of death due to cardiovascular disease,

and a four-fold increased risk of death due to coronary artery disease.²⁶ PAD has even proven to be a better predictor of adverse events than MI, as was illustrated by a recent cohort study of >100,000 patients that demonstrated a 30% higher risk of long-term cardiovascular mortality among patients with PAD alone as compared to those with MI alone.²⁷ It follows that prevention of arterial thrombotic events comprises the foundation of PAD treatment. This is achieved by controlling the aforementioned risk factors (e.g., smoking cessation, tight blood pressure/glucose/cholesterol targets, and exercise), and importantly, initiating antithrombotic therapy.^{5–8}

2.3 Females with PAD

There are various reasons to suspect that females with PAD might respond differently than their male counterparts to antithrombotic therapy. To begin, many studies have demonstrated important sex- and gender-based differences in other areas of PAD, such as clinical presentation, treatment, and outcomes. Historically, PAD was thought to predominantly affect males, however more recent studies have revealed that females have at least equal, and perhaps even higher, rates of PAD—especially among older patients.^{10,11,28,29} While overall prevalence is comparable between sexes, severity of disease may differ between them, as was demonstrated by a Swedish population-based study that showed females had a higher prevalence of asymptomatic PAD (12.6% vs. 9.4 %, $p=0.03$) and severe limb ischemia (1.5% vs. 0.8%, $p<0.008$) compared to males, but equal prevalence of PAD overall and intermittent claudication.²⁸ When it comes to signs and symptoms, females with PAD have exhibited greater impairment in their walking speed, walking distance, physical functioning, depression rates, and general health compared to males with PAD.^{29–31} Yet, females have demonstrated poor knowledge and awareness about PAD, its risk factors, and its associated cardiovascular morbidity and mortality, even when they are at high risk for cardiovascular disease themselves.³² It follows that females tend to be diagnosed with PAD at an older age and with more severe disease (based on ABI and clinical presentation) compared to males.^{33–35}

These differences are just a few factors that have undoubtedly impacted the treatment and outcomes of females with PAD. A Canadian cohort study of nearly 6000 patients with PAD demonstrated that females received suboptimal medical management overall and compared to males, with fewer females taking statins (45.6% vs. 49.1%, $p<0.001$), angiotensin converting

enzyme (ACE)-inhibitors (39.3% vs. 44.5%, $p<0.001$), and the combination of statin, ACEi, and antiplatelet agent (18.2% vs. 22.4%, $p<0.001$) compared to males.³⁶ Similarly, a cohort study based on the Reduction of Atherothrombosis for Continued Health (REACH) registry found that among >8000 PAD patients, male sex was independently associated with optimal risk factor control (defined as blood pressure, cholesterol, and glycemia at target as well as smoking cessation for >12 months).³⁷ This treatment gap is particularly alarming, given that females with PAD have a two- to four-fold increase in cardiovascular events compared to those without PAD;³⁸ females with ABI<0.90 trend towards higher rates of cardiovascular mortality, all-cause mortality, and major coronary events compared to males;¹² and females with PAD have demonstrated higher rates of hospitalization for acute MI compared to males (HR 1.15; CI 1.00-1.31).³⁹ Clearly, there is a pressing need to improve medical management among this high-risk and yet often neglected subset of PAD patients.

Differential treatment between males and females with PAD does not end at medical management. Studies have shown that females with PAD are less likely to undergo open arterial revascularization procedures³⁹⁻⁴¹ and less likely to be hospitalized for PAD or revascularization procedures compared to males.^{30,33,40} Yet, females are more often *emergently* hospitalized for PAD, and they demonstrate higher procedural mortality rates (after amputation, endovascular procedures, and open procedures) and greater likelihood of discharge to a nursing home.^{40,42,43} Those undergoing revascularization also tend to be older and have more advanced disease than their male counterparts.⁴²⁻⁴⁶ Perhaps this factors into the worse limb outcomes observed among females following open revascularization compared to males, with females demonstrating lower primary and secondary patency rates following both endarterectomy and bypass surgery.^{44,47} Of note, a large database study examining >300,000 hospitalizations involving at least one PAD procedure found that female gender increased the risk of postoperative bleeding by 33% (OR 1.33; CI 1.30-1.36).⁴² This effect was consistently observed across procedure types, whether endovascular or open revascularization or major amputation was performed ($p<0.05$ for each). Given that age, bleeding risk, cardiovascular events, and graft patency are all fundamental considerations when selecting an antithrombotic regimen, these studies highlight the importance of examining antithrombotic use specifically among females with PAD.

In addition to the reasons discussed above (e.g., poor knowledge of PAD among females, older age, and greater severity of disease at time of diagnosis, etc.), researchers have proposed various anatomic, physiologic, psychologic, and sociologic factors to explain the unique features of PAD in females and women (with the former term referring to sex, defined by biological characteristics, and the latter term referring to gender, defined by sociological characteristics that vary with space and time). From an anatomic perspective, female blood vessels are more narrow than males', with smaller diameters at the level of both inflow (e.g., aortic bifurcation, common iliac, external iliac and common femoral arteries)⁴⁸ and outflow (e.g., popliteal and crural arteries) vessels.⁴⁴ Physiologically, estrogen deficiency, complications related to pregnancy, and oral contraception (OCP) use have all been implicated in elevating PAD risk.^{17,49} Estrogen interacts with the vascular system in complex ways that both protect the vasculature and increase thrombotic risk. Its protective effects include decreasing inflammation (e.g., via reduced cytokine activity), promoting arterial vasodilation, and improving lipid profiles, which in turn, may slow the progression of atherosclerosis.^{50,51} From a thrombosis perspective, estrogen's role is less clear: some studies have demonstrated that hormone replacement therapy (HRT) increases fibrinolysis and decreases procoagulants,⁵² while others have paradoxically shown that HRT increases resistance to activated protein C, hereby promoting coagulation.^{53,54} Clinical data has also yielded conflicting results, with the Women's Health Initiative and the Heart and Estrogen/Progestin Replacement Study revealing increased venous thromboembolic risk and lack of cardiovascular benefit with HRT,^{55,56} while the Rotterdam study and a subsequent cohort study have demonstrated an association between HRT and reduced PAD rates in postmenopausal females.^{57,58} Considering the increased incidence of PAD among post-menopausal females, this data suggest that endogenous estrogen production may have an atheroprotective effect, but there is insufficient evidence to support a cardiovascular indication for HRT at this time.

Pregnancy-related complications and OCP use have demonstrated a more consistent association with increased rates of arterial occlusive disease.^{17,49} A retrospective cohort study based out of Ontario, Canada revealed that the risk of cardiovascular disease (adjusted HR 2.0; CI 1.7-2.2), and specifically, PAD (adjusted HR 3.0; CI 1.9-4.8) was increased among females with prior maternal placental syndrome, such as preeclampsia, gestational hypertension, placental abruption, or placental infarction, compared to those without.⁵⁹ Similarly, a meta-analysis examining over two million females across cohort and case-control studies showed that

the risk of cardiac, cerebrovascular, and peripheral artery disease approximately doubled in females with history of preeclampsia/eclampsia,⁶⁰ and subsequent cohort and case-control studies have lent further support to these findings.^{61,62} With respect to OCP use, its association with increased venous thromboembolic risk, as well as its multiplicative effect on the risk of stroke and MI when combined with other risk factors, has been well-established for roughly half a century.^{63,64} More recently, the RATIO study established an association between OCP use and PAD, demonstrating that first, second, and third generation OCPs all increased the odds of PAD (adjusted OR for any type of OCP 3.8; CI 2.4-5.8).⁶⁵ Whether the use of different antithrombotic regimens modifies the effect of these risk factors on PAD incidence and outcomes remains to be seen.

Psychologically, depression plays an important role in limb outcomes and quality of life for PAD patients, especially in females. Data from the Heart and Soul study on >1000 patients with coronary artery disease found that PAD increased the odds of depression (adjusted OR for sex and age, 1.79; CI 1.06-3.04) and that depressive symptoms were associated with a greater likelihood of PAD events (adjusted HR for sex and age, 2.09; 1.09-4.00).⁶⁶ Coincidentally, studies consistently report higher rates of depression among female as opposed to male PAD patients. Depression is associated with worse patency, worse leg symptoms, lower likelihood of discharge home, and increased major limb events among PAD patients post-lower extremity revascularization,^{66-69 66,68} Indeed, the Heart and Soul study's multivariate model indicated that depression was the greatest independent risk factor associated with PAD in females.⁷⁰ From a sociological perspective, researchers have postulated several explanations for why women with PAD present with symptoms later in life and with more advanced disease than men.³⁴ Some theories include that women are more likely to prioritize care for their families over themselves and to ignore symptoms when they are only mild/moderate.³⁴ Considering the complex interplay between these domains that shape PAD risk and outcomes in females, it is essential to adequately study this unique subpopulation in clinical trials.

2.4 Antithrombotic therapy

Antithrombotic therapy is an umbrella term for medications that prevent and/or treat thrombosis. The two most prescribed categories of antithrombotic therapy are antiplatelets and anticoagulants (note: thrombolytics represent a third category of antithrombotic therapy, but their

primary function is clot degradation rather than prevention, and their use is beyond the scope of this chapter). Antithrombotic therapies have different administration routes and mechanisms of action, all aimed at reducing thrombotic risk. Antiplatelet agents interfere with primary hemostasis by inhibiting specific steps in platelet activation, adhesion, and/or aggregation, while oral anticoagulants (OACs) target the coagulation cascade. A detailed description of the antithrombotic classes and mechanisms of action are outlined in Table 1.^{71,72} Importantly, in addition to differences in mechanisms of action, these agents differ in their metabolism (renal versus liver), dosing (daily versus twice daily), ability to elicit a patient response (related to diet, drug interactions, and genetics), need for routine blood testing to monitor for effect, bleeding risk, and availability of a reversal agent.⁷² Careful consideration of the patient, their comorbidities, their indication for antithrombotic therapy, and their bleeding risk must guide the choice of agent(s) and dosing.

Table 1. Characteristics of oral antithrombotic agents

Antithrombotic Agent	Targeted pathway	Class	Mechanism of Action	Example(s)
Antiplatelets	Primary hemostasis	Platelet activation inhibitors	COX-1 inhibitors	Aspirin
			P2Y ₁₂ receptor antagonists	Ticlopidine, Clopidogrel, Ticagrelor
			PAR-1 antagonists	Vorapaxar, Atopaxar
			P2Y ₁ receptor antagonists	A2P5P
			Thromboxane receptor antagonists	Terutroban
			Serotonin 2A antagonists	APD-791
		Platelet aggregation inhibitors	Glycoprotein (GP) Ia/IIa inhibitors	EMS16
			GP VI inhibitors	Monoclonal antibodies

			GP IIb/IIIa inhibitors	Tirofiban, Abciximab
			Phosphodiesterase III inhibitors	Cilostazol
			Adenosine uptake blockers	Dipyridamole
		Platelet adhesion inhibitors		C1q TNF-related protein 1, DZ-697b, RG12989
Anticoagulants	Coagulation cascade	Vitamin K antagonists	Prevent the activation of vitamin K-dependent clotting factors: factors II, VII, IX, and X and proteins C and S	Warfarin
		Direct Oral Anticoagulants (DOACs)	Thrombin (factor IIa) inhibitors	Dabigatran
			Factor Xa inhibitors	Rivaroxaban, Apixaban, Edoxaban

2.5 Antithrombotic Evidence in PAD

Oral antithrombotic therapy is a mainstay of secondary prevention in PAD patients, however the *choice* of oral antithrombotic therapy—whether antiplatelet agent, anticoagulation (at full or partial dosing), or a combination—remains controversial (Table 2). Although clinical equipoise persists, recent PAD guidelines agree that mono antiplatelet therapy (MAPT), at a minimum, is indicated for patients with symptomatic PAD.^{5–8} This recommendation is based on several pivotal studies. In 2002, The Antithrombotic Trialists’ (ATT) Collaboration published a meta-analysis revealing that, among 9214 symptomatic PAD patients across 42 trials, MAPT reduced the risk of serious vascular events, defined as non-fatal MI, non-fatal stroke, or vascular death, by nearly one quarter.⁷³ Since these findings were primarily driven by a trial examining picotamide versus placebo,⁷⁴ the Critical Leg Ischemia Prevention Study (CLIPS) group subsequently sought to determine whether aspirin demonstrated a similar effect. In a randomized

trial of 210 PAD patients (majority symptomatic), aspirin reduced the risk of major vascular events (including MI, stroke, and pulmonary embolus) by 64% compared to placebo, without increasing bleeding risk.⁷⁵ Shortly thereafter, an updated meta-analysis examined the effects of aspirin among 5269 PAD patients (both symptomatic and asymptomatic) across 18 randomized trials.⁷⁶ In this study, aspirin non-significantly reduced the risk of the primary composite outcome (defined as nonfatal MI, nonfatal stroke, and cardiovascular death, relative risk [RR] 0.88; CI 0.76-1.04) and significantly reduced the risk of nonfatal stroke (RR 0.66; CI 0.47-0.94). While aspirin did not demonstrate any significant effect on nonfatal MI, cardiovascular mortality, all-cause mortality, or bleeding, this may have been due to lack of power in the study rather than a true lack of benefit.⁷⁶ Taken together, these studies provide a foundation to support the use of MAPT among symptomatic PAD patients.

With evidence to support the use of MAPT in PAD, researchers looked to dual antiplatelet therapy (DAPT) for a similar effect. There are a number of large trials examining DAPT compared to MAPT in patients with cardiovascular disease, but it is their smaller PAD subgroup analyses, combined with dedicated PAD trials, that inform current guidelines.⁷⁷⁻⁸¹ The CHARISMA trial evaluated whether DAPT with clopidogrel and aspirin reduced the primary endpoint of MI, stroke, or cardiovascular death compared to aspirin alone in patients with atherosclerotic disease or atherothrombotic risk factors.⁸² Among the 3096 patients comprising the PAD subgroup (92% symptomatic), DAPT reduced the rate of MI (HR 0.63; CI 0.42-0.96) and hospitalization for ischemic events (HR 0.81; CI 0.68-0.95), but not composite MI, stroke, or cardiovascular death. DAPT also increased the odds of minor bleeding (Odds Ratio [OR] 1.99; CI 1.69-2.34), with no significant effect on severe, fatal or moderate bleeding.⁷⁷ In 2016, the TRA2P-TIMI 50 trial assessed the effect of vorapaxar in addition to baseline MAPT on the composite primary endpoint of cardiovascular death, MI, or stroke compared to MAPT alone in patients with a history of stroke, MI or symptomatic PAD.⁸³ Among the 3787 patients with qualifying PAD (i.e. claudication history and ABI<0.85 or prior limb revascularization), DAPT reduced rates of hospitalization for acute limb ischemia (ALI; HR 0.58; CI 0.39-0.86) and peripheral artery revascularization (HR 0.84; CI 0.73-0.97); however, it increased moderate/severe bleeding (HR 1.62; CI 1.21-2.18) and did not significantly affect the primary endpoint.⁷⁸ Shortly thereafter, the PEGASUS-TIMI 54 trial investigated long-term use of ticagrelor (at either 60 or 90 mg twice daily) plus aspirin compared to aspirin alone in patients

with prior MI.⁸⁴ Among the 1,143 PAD patients (~96% symptomatic) enrolled, ticagrelor (pooled doses) plus aspirin neither reduced the primary efficacy outcome (cardiovascular death, MI, or stroke), nor increased the rate of major bleeding compared to aspirin alone. However, ticagrelor did reduce the composite and individual endpoints of ALI and peripheral revascularization for ischemia (composite HR 0.65; CI 0.44-0.95, ALI HR 0.56; CI 0.23-1.37, peripheral revascularization HR 0.63; CI 0.43-0.93).⁷⁹ With insufficient evidence to support its benefits over its risks, there is currently no *blanket* recommendation for DAPT in PAD patients.

Two trials exclusive to PAD patients examined whether there is a role for DAPT in a more specific subset. The CASPAR trial randomized 851 patients undergoing below-knee arterial bypass surgery for PAD to DAPT with clopidogrel and aspirin or placebo and aspirin.⁸⁰ DAPT did not reduce the composite primary endpoint of bypass graft occlusion, surgical or endovascular revascularization on the index graft, above-ankle amputation of the index limb, or death in the overall population; however, among those who received a prosthetic (as opposed to venous) graft, DAPT *did* reduce the primary endpoint (HR 0.65; CI 0.45-0.95) as well as graft occlusions (HR 0.63; CI 0.42-0.93) and amputations (HR 0.48; CI 0.24-0.96). DAPT also reduced combined graft occlusion/graft intervention/ipsilateral above-ankle amputation (HR 0.62; CI 0.42-0.91) and amputation (HR 0.48; CI 0.24-0.96) in patients who received a prosthetic graft, but not overall or among those with a venous graft. There was no significant difference in the combined rate of cardiovascular death, MI, or stroke between treatment groups, and DAPT significantly increased total (16.7% vs 7.1%, $p<0.001$), mild (10.8% vs 5.0%, $p=0.002$), and moderate (3.8% vs 0.9%, $p=0.007$) bleeding events overall compared to MAPT.⁸⁰ This trial suggests a potential role for DAPT in patients undergoing lower extremity revascularization with a prosthetic bypass graft.

The MIRROR trial similarly evaluated the use of DAPT with clopidogrel plus aspirin compared to aspirin plus placebo, however it focused on symptomatic PAD patients undergoing endovascular therapy—specifically, angioplasty +/- stenting of a femoral and/or popliteal lesion.⁸¹ After six months, patients assigned to DAPT required fewer target lesion revascularizations (2/40 vs. 8/40, $p=0.040$) and fewer additional days in hospital related to the target lesion (0.13 ± 0.56 vs. 0.98 ± 2.29 , $p=0.026$) compared to those assigned to MAPT plus placebo.⁸¹ Notably, there was no difference between the two groups with respect to rates of total

occlusion, bleeding, cardiovascular events, mortality, change in ABI, or improvement in Rutherford category (a grading scale for PAD severity) at 6 months. Together, the CASPAR and MIRROR trials highlight the benefits of DAPT with respect to limb events, but not cardiovascular events, in select patients undergoing lower extremity revascularization. Its use in this population must be weighed against bleeding risk.

When it comes to the use of OACs in PAD at therapeutic (or “full”) doses, the bleeding risk outweighs the thrombotic benefit. The WAVE trial, published in 2007, enrolled a diverse PAD population, including those with symptomatic lower extremity arterial disease (ranging from intermittent claudication to CLTI), symptomatic and asymptomatic carotid artery disease, and subclavian artery disease.⁸⁵ This trial demonstrated that therapeutic OAC combined with antiplatelet therapy did not reduce the composite primary endpoint of MI, stroke, or cardiovascular death, but *did* increase the risk of life-threatening bleeding (RR 3.41; CI 1.84-6.35), compared to antiplatelet therapy alone. Several additional trials have examined therapeutic OAC use, focusing primarily on limb outcomes—such as graft patency—in patients at higher risk for adverse limb events—such as those who have undergone lower extremity revascularization.⁸⁶⁻⁹⁰ These trials have yielded mixed results. For example, the Dutch BOA trial, which randomized 2690 patients post-infrainguinal bypass surgery, found that therapeutic OAC (with a vitamin K antagonist) did *not* reduce graft occlusions or cardiovascular events (MI, stroke, vascular death, or amputation), but *did* increase major bleeding episodes (HR 1.96; CI 1.42-2.71) compared to aspirin alone.⁸⁶ However, when stratifying by graft type, those with vein grafts demonstrated lower rates of occlusion on OAC (HR 0.69; CI 0.54-0.88), while those with non-venous grafts demonstrated higher (HR 1.25; CI 1.03-1.55).⁸⁶ In contrast, a study from the Department of Veterans Affairs Cooperative study revealed that warfarin plus aspirin improved patency rates in patients with a 6-mm prosthetic femoral-popliteal bypass graft compared to aspirin alone (71.4% vs. 57.9%; $p=0.02$), but not in patients with venous, or 8-mm prosthetic, bypass grafts.⁸⁷ Similar to the Dutch BOA and WAVE trials, therapeutic OAC increased bleeding ($n=35$ vs. $n=15$; $p=0.02$), without protecting against cardiovascular events such as stroke, MI, or thromboembolic events compared to aspirin alone.⁸⁷ Considering these trials, current guidelines all recommend against the *routine* use of therapeutic OAC in PAD patients (in the absence of an alternate indication).

In addition to the above, there are several trials that examined the role for therapeutic OAC in specific settings (e.g., high-risk revascularization procedures, endovascular procedures, etc.), as well as its performance compared to DAPT. One such trial, published in 1998, randomized 56 patients with infrainguinal bypass grafts at high risk for failure to warfarin plus aspirin or aspirin alone.⁸⁹ This trial found that the addition of warfarin to aspirin improved immediate postoperative patency (97.3% vs. 85.2%; $p=0.07$), immediate (100% vs. 88.9%; $p=0.04$) and 3-year (81% vs. 31%; $p=0.02$) limb salvage rates, and 3-year primary (74% vs. 51%; $p=0.04$), primary-assisted (77% vs 56%; $p=0.05$), and secondary (81% vs. 56%; $p=0.01$) graft patency rates compared to aspirin alone. There was an increased rate of postoperative wound hematoma with warfarin (32% vs 4%; $p=0.004$), but no difference in packed red cells transfused, intracranial or gastrointestinal bleeds, or cardiovascular events (e.g. MI or perioperative death) between groups.⁸⁹ More recently, a 2012 trial comparing warfarin plus clopidogrel to DAPT (clopidogrel and aspirin) in patients undergoing femoropopliteal bypass surgery found that warfarin and clopidogrel improved long-term graft patency ($p=0.026$) and freedom from severe PAD leading to amputation ($p=0.044$).⁹⁰ Notably, rates of overall bleeding and life-threatening bleeding/bleeding requiring hospitalization and/or transfusion were comparable between the two groups.⁹⁰ Finally, the ePAD trial—one of the few to examine the use of a DOAC (at therapeutic dosing) in patients undergoing femoropopliteal endovascular therapy—found that edoxaban and aspirin neither reduced 6-month restenosis/reocclusion rates, nor increased bleeding rates, compared to DAPT.⁸⁸ These conflicting results suggest that there may be a place for full-dose (i.e., therapeutic dosing) OAC in PAD patients with high-risk grafts and low risk of bleeding, but this role is limited.

In contrast to full-dose OAC, there is a growing body of evidence to support the routine use of very low dose OAC (in combination with aspirin) in patients with symptomatic PAD. In fact, the emergence of dual pathway inhibition (DPI)—typically defined as the combination of very low dose rivaroxaban (2.5 mg BID) plus aspirin—has influenced PAD antithrombotic guidelines arguably more than any other development in the past five years. The concept of DPI, as its name would suggest, is to employ different pathways to prevent thrombotic events, while limiting the added bleeding risk with a reduced dose of OAC. The two main trials that sparked the “DPI revolution” in vascular surgery are the COMPASS and VOYAGER trials. The COMPASS trial randomized 27,395 patients with stable atherosclerotic (coronary and/or

peripheral artery) disease to three arms: rivaroxaban (5 mg BID), DPI (rivaroxaban 2.5 mg BID plus aspirin 100 mg daily) or aspirin (100 mg daily).⁹¹ The trial was terminated early after DPI demonstrated a clear and consistent benefit over MAPT with respect to the primary composite outcome of cardiovascular death, stroke or MI (HR 0.76; CI 0.66-0.86).⁹¹ DPI also outperformed MAPT with respect to composite stroke, MI, acute limb ischemia, or death from coronary artery disease (HR 0.72; CI 0.63-0.83), as well as all-cause mortality, cardiovascular death, stroke, and hospitalization for cardiovascular causes ($p < 0.05$ for each). DPI did increase major (HR 1.70; CI 1.40-2.05) and minor (HR 1.70; CI 1.52-1.90) bleeding, but not fatal (HR 1.49; CI 0.67-3.33) or intracranial (HR 1.16; CI 0.67-2.00) bleeding. The subgroup analysis of 7470 PAD patients revealed an even more profound effect—DPI reduced both the composite cardiovascular outcome (cardiovascular death, MI, or stroke; HR 0.72; CI 0.57-0.90), as well as the composite limb outcome (development of acute or chronic limb ischemia or major amputation due to vascular causes; HR 0.54; CI 0.35-0.82).⁹² In the wake of this trial, DPI was approved by the US food and drug administration (FDA) for patients with coronary and peripheral artery disease and patients with PAD post-lower extremity revascularization.⁹³ Canadian regulatory bodies followed suit, with the CADTH Canadian Drug Expert Committee endorsing the use and reimbursement of DPI in patients with concomitant coronary and peripheral artery disease in November 2018.⁹⁴

The VOYAGER trial, published shortly after COMPASS, lent further support to the use of DPI in PAD by randomizing over 6000 patients to DPI or aspirin plus placebo following lower extremity revascularization.⁹⁵ Consistent with the aforementioned studies, VOYAGER demonstrated that DPI reduced the composite risk of acute limb ischemia, major amputation for vascular causes, MI, stroke, or cardiovascular death (HR 0.85; CI 0.76-0.96).⁹⁵ DPI was also found to be safe, without increasing the principal safety outcome of TIMI major bleeding (HR 1.43; CI 0.97-2.10), intracranial hemorrhage (HR 0.78; CI 0.38-1.61) or fatal bleeding (HR 1.02; CI 0.33-2.15). Together, the COMPASS and VOYAGER trials have significantly influenced antithrombotic therapy in cardiovascular disease, with DPI becoming ubiquitous across international society guidelines.^{5,8,96,97} As the landscape of antithrombotic therapy in PAD rapidly evolves, it is prudent to consider whether specific subpopulations of PAD patients might respond differently to these medications, and whether those subpopulations are adequately represented in the trials that shape current guidelines.

Table 2. Antithrombotic recommendations across recent major guidelines on the management of lower extremity PAD.

Guideline	Recommendation
2016 AHA/ACC Guideline on the management of patients with lower extremity peripheral artery disease ⁷	“In asymptomatic patients with PAD ($ABI \leq 0.90$), antiplatelet therapy is reasonable to reduce the risk of MI, stroke, or vascular death”
	“Antiplatelet therapy with aspirin alone or clopidogrel alone is recommended to reduce MI, stroke, and vascular death in patients with symptomatic PAD”
	“The effectiveness of dual antiplatelet therapy to reduce the risk of cardiovascular ischemic events in patients with symptomatic PAD is not well established”
	“Dual antiplatelet therapy may be reasonable to reduce the risk of limb-related events in patients with symptomatic PAD after lower extremity revascularization”
	“The usefulness of anticoagulation to improve patency after lower extremity autogenous vein or prosthetic bypass is uncertain”
	“Anticoagulation should not be used to reduce the risk of cardiovascular ischemic events in patients with PAD”
2017 ESC Guidelines on the diagnosis and treatment of peripheral arterial disease, in collaboration with the European Society for Vascular Surgery ⁶	“Single antiplatelet therapy is indicated only if lower extremity arterial disease (LEAD) patients are symptomatic or have undergone revascularization. Clopidogrel is the preferred antiplatelet drug in LEAD patients”
	“Chronic anticoagulation therapy is given only if there is a concomitant indication and may be combined with single antiplatelet therapy when there is a recent revascularization procedure”
Global Vascular Guidelines on the Management of Chronic Limb-	“Treat all patients with CLTI with an antiplatelet agent”
	“Consider low-dose aspirin and rivaroxaban, 2.5 mg twice daily, to reduce adverse cardiovascular events and lower extremity ischemic events in patients with CLTI.”

Threatening Ischemia (CLTI) ⁵	“Do not use systemic vitamin K antagonists for the treatment of lower extremity atherosclerosis in patients with CLTI.”
Canadian Cardiovascular Society 2022 Guidelines for Peripheral Arterial Disease ⁸	“We recommend against routine antithrombotic therapy (antiplatelet or anticoagulant) for patients with isolated asymptomatic lower extremity PAD”
	“We recommend treatment with rivaroxaban 2.5 mg twice daily in combination with aspirin (80-100 mg daily) for management of patients with symptomatic lower extremity PAD who are at high risk for ischemic events (high-risk comorbidities such as polyvascular disease, diabetes, history of heart failure, or renal insufficiency) and/or high-risk limb presentation post peripheral revascularization, (limb amputation, rest pain, ischemic ulcers) and at low bleeding risk”
	“We recommend combination treatment with rivaroxaban 2.5 mg twice daily and aspirin or single antiplatelet therapy for patients with symptomatic lower extremity PAD and low bleeding risk in the absence of high-risk limb presentation or high-risk comorbidities”
	“We recommend single antiplatelet therapy with either aspirin (75-325 mg) or clopidogrel (75 mg) be considered for patients with symptomatic lower extremity PAD at high bleeding risk who remain eligible for antithrombotic therapy”
	“We suggest that clopidogrel (75 mg daily) should be the preferred agent when single antiplatelet therapy is deemed to be the optimal antithrombotic choice”
	“We suggest that dual antiplatelet therapy (aspirin and clopidogrel or aspirin and ticagrelor) be used for patients with symptomatic lower extremity PAD at high risk for vascular events, at low bleeding risk, and who have contraindications to rivaroxaban”
	“We recommend against the additional use of full-dose anticoagulation with antiplatelet therapy for the purpose of decreasing MACE and MALE events in patient with stable lower extremity PAD”

2.6 Female Representation in Cardiovascular Trials

Unfortunately, despite increasing recognition that PAD affects both sexes approximately equally, females are consistently underrepresented in cardiovascular—and more specifically, PAD—trials. In 2010, a review of 77 randomized trials examined female enrollment rates across

vascular studies on aortic aneurysm repair, carotid revascularization, and lower extremity revascularization.¹³ Compared to their estimated population procedural incidence, females were underrepresented across all three categories of procedural trials (e.g., females comprised 41.3% of lower extremity revascularizations on a population level, but only 22.4% of trial subjects). Three years later, a systematic review assessing underrepresentation of PAD in modern cardiovascular trials further elucidated the systematic exclusion of females, revealing that females comprised less than one third of cardiovascular trial participants.¹⁴ Unfortunately, this trend has not improved with time, with females continuing to be underrepresented across vascular trials through present day.¹⁵

The paucity of sex- and gender-based PAD research is not a new issue. In fact, ten years ago the American Heart Association published a scientific statement entitled “A Call to Action: Women and Peripheral Artery Disease”, which highlighted the unique features of PAD in females, urged researchers to actively recruit female participants in trials and explore the aetiologies underlying these differences, and stressed the need to increase awareness about PAD among females at risk.¹² So pressing is the need to integrate sex and gender analyses into research, that leading research institutes and medical regulatory bodies, including the National Institutes of Health (NIH), the Canadian Institutes of Health Research (CIHR), and the FDA, require that this be considered in all research proposals.^{98–100} Understanding sex- and gender-based differences is key to informing medical decisions, raising awareness among populations at risk, and determining whether trial findings can be extrapolated to a broader population.

2.7 Study Rationale and Objectives

To summarize, PAD is a major risk factor for arterial thromboses throughout the body, increasing the risk of stroke, MI, limb loss, and cardiovascular death. Antithrombotic therapy is therefore a cornerstone of symptomatic PAD management, and as new antithrombotic regimens emerge, guidelines are rapidly evolving. Yet, despite PAD affecting both males and females in roughly equal proportions, there are notable differences in their manifestations of this disease, which may necessitate a more tailored approach to their treatment. Furthermore, there may be underrepresentation of females within antithrombotic vascular trials, making it unclear whether trial findings, and in turn, practice guidelines, can be extrapolated to this unique subgroup. Indeed, many systematic and structured reviews assessing antithrombotic regimens in PAD

patients have been conducted over the past few years, but none of these has looked specifically at the female subset.^{101–110} Thus, the purpose of this thesis is two-fold:

1. To assess the impact of female sex on cardiovascular (CV), limb, and bleeding event rates in antithrombotic trials enrolling PAD patients. This will be achieved by examining female-specific rates of CV, limb, and bleeding events in trials enrolling PAD patients, and by analyzing the effect of female sex on CV and limb events *among PAD patients* (i.e. the PAD *subgroup* in trials with more heterogenous atherosclerotic populations) on various antithrombotic regimens.
2. To evaluate the representation of female PAD patients in antithrombotic trials, as well as the generalizability of antithrombotic trial findings to female PAD patients

2.8 Chapter Descriptions

The thesis objectives will be addressed in the following chapters:

- Chapter 3 outlines the protocol for a systematic review and meta-analysis examining female-specific efficacy (cardiovascular and limb events) and safety (namely, bleeding) outcomes in trials evaluating different antithrombotic regimens and enrolling PAD participants
- Chapter 4 addresses the first thesis objective by reporting the results of the systematic review and meta-analysis outlined in chapter 3
- Chapter 5 addresses the second thesis objective through a systematic review and meta-analysis that assesses the proportion of females enrolled, inclusion/exclusion criteria that limits female enrolment (e.g. pregnancy), the presence of sex-based analyses, and the proportion to prevalence ratio (PPR, which measures the representation of a subpopulation in a trial relative to their disease burden in the general population) in trials examining antithrombotic therapy in participants with PAD
- Chapter 6 is a discussion chapter that summarizes and unites the three component articles of the thesis, relates them to the current state of vascular research, and offers future directions for improving the analysis of females in PAD research

2.9 Chapter 1 & 2 References

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Chapter 3: Antithrombotic Regimens in Females with Symptomatic Lower Extremity Peripheral Arterial Disease

Protocol for a Systematic Review and Meta-Analysis

Chapter Overview

Chapter 3 outlines a protocol for a systematic review and meta-analysis aimed at addressing thesis objective 1 on female-specific efficacy and safety outcomes on different antithrombotic regimens in randomized trials enrolling PAD participants. This protocol aims to bridge a gap in the literature by incorporating all trials to date comparing dual antiplatelet (DAPT), dual pathway inhibition (DPI) or oral anticoagulation (OAC) with or without mono-antiplatelet therapy (MAPT) to MAPT alone *and* looking specifically at outcomes in females.

Author Contributions

All four authors substantially contributed to the design of this protocol. SAS drafted the protocol and is responsible for the design, execution, and writeup of the study. PJ, DK, and MC provided invaluable input in designing the study and will be overseeing the completion of this project. All four authors have provided approval of the version that was published and agreed to be accountable for all aspects of the work, including its accuracy and integrity. SAS was the guarantor of the review.

Manuscript Status

This manuscript has been published in BMJ Open. The published article is presented in Appendix A.

**Antithrombotic Regimens in Females with Symptomatic Lower Extremity
Peripheral Arterial Disease**
Protocol for a Systematic Review and Meta-Analysis

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Word Count: 2841

ABSTRACT

Introduction: Patients with peripheral arterial disease (PAD) are at increased risk for systemic arterial thromboembolic events. Females represent a unique subset of PAD patients, who differ from males in important ways: they have smaller-diameter vessels, undergo lower extremity bypass less frequently, and experience higher rates of graft occlusion, amputation, and mortality than males. Females also trend towards higher rates of major coronary events and cardiovascular mortality. Current guidelines recommend mono-antiplatelet therapy (MAPT) for secondary prevention in patients with symptomatic PAD. However, indications for more intensive anti-thrombotic therapy in this cohort—especially among females, who are frequently underrepresented in randomized controlled trials (RCTs)—remain unclear. As newer antithrombotic therapies emerge, some RCTs have demonstrated differential effects in females versus males. A systematic review is needed to quantify the rates of arterial thromboembolic and bleeding events with different antithrombotic regimens in females with symptomatic PAD.

Methods and Analysis: We will search Medline, Embase, and the Cochrane Central Register of Controlled trials for published RCTs that include females with symptomatic PAD and compare full dose anticoagulation +/- antiplatelet therapy, dual pathway inhibition, or dual antiplatelet therapy to MAPT. Title, abstract, and full-text screening will be conducted in duplicate by three reviewers. Authors will be contacted to obtain sex-stratified outcomes as needed. Risk of bias will be assessed using the Cochrane Risk of Bias tool. Data will be extracted by independent reviewers and confirmed by a second reviewer. Quantitative synthesis will be conducted using Review Manager 5 for applicable outcomes data. Planned subgroup analysis by PAD severity, vascular intervention, and indication for antithrombotics will be conducted where data permits.

Ethics and Dissemination: Ethics approval is waived as the study does not involve primary data collection. This review will be submitted for publication in a peer-reviewed journal and for presentation at national and international scientific meetings.

Strengths and Limitations:

- This protocol was reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines
- This review offers a broad search strategy to capture all studies that might include the population of interest, including as a subset of a larger sample
- This review addresses an important gap in the literature by targeting female-specific vascular outcomes
- This review will not be limited by language or date specifications
- Depending on the availability of sex-stratified data, quantitative synthesis
- may not be possible for all outcomes of interest

INTRODUCTION

Rationale:

Lower extremity peripheral arterial disease (PAD) is common, affecting approximately 800,000 Canadians and over 200 million people worldwide.^{1,2} Patients with large-vessel PAD are at increased risk for arterial thromboembolic events compared to those without, with a 5.9-fold increased risk of death from all cardiovascular (CV) causes and a 6.6-fold increased risk of death from coronary heart disease.³ Among patients with severe, untreated PAD, one-year mortality and amputation rates reach 22%.⁴ While previous demographic data have yielded mixed findings about the distribution of PAD across sexes,^{5–9} more recent studies have revealed the prevalence to be at least equal, if not higher, in females compared to males.¹⁰ Despite similar distributions of the disease, females with PAD differ from males in a number of important ways,^{10–12} including higher functional impairment, lower likelihood of undergoing lower extremity bypass, and potentially, higher bleeding risk.^{13–19} Among females who do undergo lower extremity bypass, rates of graft occlusion, amputation, and mortality are higher than in males.^{16,20} Females with PAD also trend towards higher rates of CV mortality and major coronary events as compared to their male counterparts.¹⁰ Smaller diameter vessels, older age at presentation, hormonal differences, and greater number of comorbidities may explain the discrepancy in treatment, risks, and outcomes between the sexes.^{11,19}

To mitigate the risk of arterial thromboembolic events, antithrombotic therapy has become a fundamental component of the management of symptomatic PAD.^{21,22} Antithrombotic therapy refers to antiplatelet agents and/or anticoagulants, which target different steps in the coagulation cascade. Antiplatelet agents interfere with platelet activation, adhesion, and aggregation through various mechanisms, such as thromboxane A1 inhibition (aspirin), ADP receptor antagonism (P2Y₁₂ inhibitors such as clopidogrel), and glycoprotein IIb/IIIa inhibition (e.g. abciximab).²³ In contrast, anticoagulants primarily affect secondary hemostasis by targeting components of the coagulation cascade. For example, vitamin K antagonists, such as warfarin, impair the activity of vitamin K-dependent clotting factors,²³ and direct oral anticoagulants (DOACs), such as dabigatran and rivaroxaban, inhibit factor IIa (thrombin) and factor Xa, respectively.^{24,25} Finally, dual pathway inhibition (DPI), which combines very low dose anticoagulation (typically rivaroxaban) with antiplatelet therapy (typically aspirin), is thought to

synergistically reduce thromboembolic risk by inhibiting platelet activation *and* attenuating thrombin generation.²⁶ Careful consideration of the patient's comorbidities, characteristics, intrinsic thrombogenicity, and indication for—as well as response to—antithrombotic therapy must guide selection of the appropriate regimen.

The benefits of antiplatelet therapy are well-documented in the Antithrombotic Trialists Collaboration meta-analysis, which demonstrated a significant reduction in nonfatal stroke, nonfatal myocardial infarction (MI), and CV death with anti-platelet therapy in patients at high risk for vascular occlusive events ($p=0.004$).²⁷ However, with more intensive antithrombotic therapy, there is ambiguity surrounding which PAD populations benefit most. The CHARISMA trial, which compared dual antiplatelet therapy (DAPT) to aspirin alone, revealed no reduced risk in the PAD subgroup with respect to the composite outcome: CV death, MI, or stroke.²⁸ Likewise, in the CASPAR trial, DAPT did not significantly reduce the composite outcome of index-graft occlusion or revascularization, ipsilateral above-ankle amputation, or death compared to aspirin alone in patients with recent below-knee bypass for PAD.²⁹ However, in another CHARISMA subgroup analysis that combined patients with prior MI, stroke, or symptomatic PAD, DAPT significantly reduced rates of the composite outcome in patients with atherosclerotic disease in multiple vascular beds.³⁰ In PAD patients undergoing lower extremity endovascular revascularization, a number of trials have compared DAPT to mono antiplatelet therapy (MAPT), with no clear consensus about its benefits.^{31–33}

There are also several trials that examined the use of full dose anticoagulation in PAD patients. One demonstrated that anticoagulation in addition to antiplatelet therapy did not reduce rates of MI, stroke, or CV death in patients with symptomatic PAD;³⁴ one demonstrated that anticoagulation did not reduce rates of graft occlusion compared to aspirin in patients who underwent infrainguinal bypass grafting;³⁵ one demonstrated that anticoagulation increased graft patency at the cost of increased perioperative hematoma in high risk patients undergoing vein bypass grafting;³⁶ and a few additional studies examining different anticoagulation versus antiplatelet comparisons in PAD patients offered no conclusive evidence.³⁷ The question of whether particularly high risk PAD patients—such as those undergoing bypass therapy with a specific type of graft—may benefit from the addition of full dose anticoagulation remains.

Recently, DPI has emerged as an antithrombotic option in patients at high risk for CV events. In particular, very low dose (2.5 mg BID) rivaroxaban in combination with aspirin gained popularity after publication of the COMPASS trial, which demonstrated a reduction in major adverse cardiac events (CV death, stroke, and MI) with DPI compared to aspirin alone in patients with stable CV disease.³⁸ This study led to its approval in Canada for secondary prevention in patients with coronary artery disease or symptomatic, high-risk PAD.³⁹ The VOYAGER trial followed, demonstrating a reduction in the composite outcome of acute limb ischemia, major amputation for vascular causes, MI, ischemic stroke, or CV death with the addition of very low dose rivaroxaban to aspirin in PAD patients with recent lower extremity revascularization.⁴⁰ While no heterogeneity was observed in the efficacy of DPI between sexes, sex-stratified analyses revealed that neither the primary efficacy nor safety outcome was statistically significant in females. Since the trial was not powered to detect a difference in the female subgroup, it can be difficult to interpret the clinical significance of these findings. Pooling the data from similar trials may uncover interesting trends according to sex and inform clinical practice guidelines, which are currently in evolution.⁴¹

The existing data have led to uncertainty about optimal antithrombotic therapy in patients with PAD; however, the ambiguity is even more pronounced within the female sub-population. Despite differences between males and females with PAD,^{10–17} females are consistently under-represented in vascular trials.^{42,43} Females have also demonstrated different responses than males to vascular interventions in other vascular beds—for example, males with asymptomatic carotid stenosis derived benefit from carotid endarterectomy while females did not.⁴⁴ Yet, sex is not currently factored into decision-making algorithms for antithrombotic therapy for PAD in clinical practice guidelines.^{22,41,45} In 2012, the American Heart Association released a statement that highlighted the differences between males and females with PAD and stressed the need for sex-specific CV research. This study aims to respond to that call by systematically reviewing the literature on rates of arterial thromboembolic and bleeding events with different antithrombotic regimens in females with symptomatic PAD.

Objective: To systematically review the literature reporting efficacy and safety outcomes of various anti-thrombotic regimens with respect to arterial thromboembolic and bleeding events in females with symptomatic PAD.

METHODS

Protocol and Registration:

This protocol was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) guidelines (See Appendix B for PRISMA-P Reporting Checklist).⁴⁶ The protocol was registered with the PROSPERO International Prospective Register of Systematic Reviews (ID# CRD42020196933). If changes to the protocol are required, we will report deviations from the original protocol and rationale with transparency.

Eligibility criteria:

Inclusion and exclusion criteria are presented in Table 1.

Table 1. Eligibility criteria

	Inclusion	Exclusion
Study Design	• Randomized controlled trials • If the number of RCTs meeting inclusion criteria proves limited, we will broaden the search strategy to include prospective and retrospective cohort studies	• Cross sectional • Case-control • Case series with <10 patients • Case reports
Population*	• Females with symptomatic PAD, defined as atherosclerotic disease of the lower extremities causing intermittent claudication, rest pain, or tissue loss and/or necessitating endovascular or open surgical revascularization and/or amputation • Diagnosis of PAD will be at the discretion of each trial, whether by clinical assessment, self report, or objective diagnostic criteria (including ankle brachial index, duplex ultrasound, computed tomography, magnetic resonance imaging, or angiography) • Sex-stratified outcomes must be published or available upon request to the authors	• Males • Asymptomatic PAD • Trials focused specifically on the management of acute limb ischemia
Intervention and Comparator**	• Full dose oral anticoagulation (+/- antiplatelet therapy) vs. MAPT	• MAPT vs. MAPT • DAPT vs. DAPT • Anticoagulant vs. anticoagulant • MAPT vs. placebo

	• DPI (Very low dose oral anticoagulation + antiplatelet therapy) vs. MAPT • DAPT vs. MAPT	• DAPT vs. placebo • Very low dose anticoagulation alone vs. MAPT
Other	There will be no limitation with respect to language/date of publication.	Trials focusing on intraoperative/intra-procedural administration of anticoagulant therapy (eg. heparin administered <i>only</i> during surgery and not extending into the postoperative period), or on the acute management of acute limb ischemia (e.g. thrombolytic therapy or therapies lasting <30 days), will be excluded.

*In the event that a trial includes participants with PAD as a subgroup of the main trial, and sex-stratified outcomes are available for the overall trial but not within the PAD subgroup, then the sex-stratified outcomes from the main trial will be discussed in the narrative and quantitative synthesis (where applicable) and the population analyzed will be clearly stated.

**There will be no limitation with respect to class/dosing of antithrombotic agents.

Information Sources:

We will search Medline, Embase, and the Cochrane Central Register of Controlled trials. The information sources will be supplemented by searching registered clinical trials on ClinicalTrials.gov and the International Standard Randomised Controlled Trials Number (ISRCTN) database. Grey literature will be excluded. We will also scan the reference list of systematic reviews of similar scope and included trials to ensure that all relevant studies are captured. If sex-stratified outcomes are not reported for studies that otherwise meet inclusion criteria, authors will be contacted to request sex-stratified data.

Search Strategy:

The search strategy will be designed with collaborative input from a librarian experienced in systematic review searches. A combination of Medical Subject Headings (MeSH) and keyword terms related to the population and interventions of interest will be used. The search strategy will begin with Medline (see Appendix C) and will be translated according to the requirements of each electronic database. A search filter for RCTs will be applied.

Study Records:

Data Management

Results from the literature search will be uploaded to Covidence online software.⁴⁷ Duplicate articles will be identified and removed by the Covidence screen for duplicates and by the review authors. We will extract data from the final studies included in the narrative summary and quantitative synthesis—and perform statistical analysis—using Review Manager (RevMan) 5.

Selection Process

All titles, abstracts, and full text screening will be performed in duplicate by three independent reviewers. Studies that are disputed during the abstract review phase will be brought to full text review. Disputes about full-text articles will be resolved through discussion between the reviewers and input from the study supervisors (PJ, DK, and MC) where required.

Data collection process

Data will be extracted from the studies by a team of independent reviewers and stored in a shared Excel document. Reviewers will undertake data collection in duplicate for the first few studies to ensure uniform data collection. Following this, data from each study will be collected independently and confirmed by a second reviewer. Any disputes will be resolved through discussion or input from the study supervisors.

Data items

The following data items will be extracted:

- 1) General study data: title, authors, year/journal/country/language of publication, sample size, recruitment period, study design, timing of randomization to treatment, consideration for the potential impact of sex on the trial (i.e. was the impact of sex analyzed and how)
- 2) Population: baseline demographics (such as age, relevant comorbidities and medications), total number and proportion of females, total number and proportion of symptomatic PAD patients (as well subcategories for severity of ischemia or type of revascularization where applicable), compliance with assigned treatment (and crossover rate in each arm)
- 3) Intervention: type, dosing, and frequency of antithrombotic, duration of therapy

- 4) Comparator: type, dosing, and frequency of antithrombotic, duration of therapy
- 5) Outcomes: primary, secondary, and safety outcomes, length of follow up
- 6) Outcome measures: reported effect measures for all outcomes, including p-values, standard deviations, and confidence intervals, time-to-event where applicable, analysis type (i.e. intention to treat versus per protocol)
- 7) Funding: Type and source where applicable

Outcomes and Prioritization:

Primary Efficacy Outcome

There will be two co-primary efficacy outcomes: a primary limb and a primary CV outcome. The primary limb outcome will be major (i.e. above ankle) amputation. The primary CV outcome will be a composite of CV death, MI, and stroke.

Secondary Efficacy Outcomes

Secondary outcomes will include the individual components of the primary CV outcome, acute limb ischemia, surgical or endovascular intervention not planned at the time of randomization, and all-cause mortality, as well as primary, primary-assisted, and secondary patency.

Safety Outcomes:

The primary safety outcome will be major bleeding as defined by each trial. The secondary safety outcome will be minor bleeding as defined by each trial. In trials that do not differentiate between major and minor bleeding, we will employ either the Thrombolysis In Myocardial Infarction (TIMI) hemorrhage criteria or the International Society on Thrombosis and Hemostasis (ISTH) criteria (depending on the bleeding outcomes that were reported in the trial) to determine whether bleeding events should be classified as major or minor. TIMI classifies major bleeding as bleeding associated with any one of the following: “is fatal, leads to hypotension requiring treatment with intravenous inotropic agents, requires surgical intervention for ongoing bleeding, necessitates the transfusion of four or more units of blood over a 48-hour period, or is a symptomatic intracranial hemorrhage.”⁴⁸ ISTH defines major bleeding in non-surgical patients as, “fatal bleeding, and/or symptomatic bleeding in a critical area or

organ...and/or bleeding causing a fall in hemoglobin level of 20g/L (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells.”⁴⁹

Risk of bias in individual studies:

Risk of bias will be assessed by one reviewer and verified by a second reviewer using the risk of bias tool (ROB 2) for randomized trials from the Cochrane Handbook for Systematic Reviews.^{50(p8)} Using this tool, we will assess bias across several domains: randomization, deviation from intended intervention, missing outcome data, outcome measurement, and selective reporting. Results of the overall risk of bias assessment will be reported in a narrative summary and individual risk within each domain across all studies will be reported in a table. Sensitivity analysis will be performed excluding trials that demonstrate a low level of quality where applicable.

Data synthesis:

We will assess patient population, study design, comparator arms, and event rates for data synthesis. We will use I^2 to assess for statistical heterogeneity between studies. A narrative synthesis will be reported instead of a meta-analysis if there is insufficient data to conduct a quantitative analysis. Pooled estimates will be calculated, and meta-analysis will be performed using RevMan 5 software. Treatment effect will be measured using odds ratio (OR), risk difference (RD), or hazard ratio (HR) (depending on which measure is most commonly reported across included studies), to compare the effect of the antithrombotic intervention versus the MAPT control in females with symptomatic PAD. A random effects model will be employed to determine weights for meta-analysis.

The following pre-planned subgroup analysis will be performed where data permits:

- Stratification by severity of symptoms: intermittent claudication vs. critical limb ischemia
- Stratification by indication for therapy: PAD alone vs. PAD plus coronary artery disease
- Stratification by type of intervention: conservative vs. open revascularization (i.e. bypass) vs. endovascular revascularization (i.e. angioplasty and/or stenting) vs. amputation

We will conduct a sensitivity analysis excluding trials with high risk of bias or small number of participants. We will also conduct a sensitivity analysis excluding older trials if medical regimens beyond the assigned intervention and control arms vastly differ from more modern trials (e.g. use of statin therapy). Meta-bias will be assessed by repeating the primary efficacy and safety outcomes using a fixed effects model and by creating a funnel plot if the number of included studies exceeds ten. If fewer than ten studies are included in the final analysis, we will not evaluate for publication bias given its limited power in the setting of a small number of studies.

Confidence in Cumulative Evidence:

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework will be employed to assess the quality of all reported outcomes.⁴⁶

Patient and Public Involvement: Patients or the public WERE NOT involved in the design, or conduct, or reporting, or dissemination plans of our research.

ETHICS AND DISSEMINATION: Ethics approval is waived as the study does not involve primary data collection. This review will be submitted for publication in a peer-reviewed journal and for presentation at national and international scientific meetings.

ACKNOWLEDGMENTS: The authors would like to acknowledge Sarah Visintini, Berkman Library, University of Ottawa Heart Institute (UOHI), for her assistance in designing our search strategy, and the PSI Foundation for their funding in support of medical trainee research.

CONFLICTS OF INTEREST: None to disclose.

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Chapter 4: Antithrombotic Therapy Among Females with Peripheral Artery Disease

A Systematic Review and Meta-Analysis of Female-Specific Outcomes

Chapter Overview

This chapter reports the results of the systematic review and meta-analysis outlined in chapter 3. It addresses thesis objective #1 by outlining female-specific efficacy and safety outcomes in antithrombotic trials enrolling participants with PAD and comparing dual antiplatelet therapy (DAPT), dual pathway inhibition (DPI) or oral anticoagulation (OAC) with or without mono-antiplatelet therapy (MAPT) to MAPT alone.

Manuscript Status

This study was presented at the Society for Vascular Surgery (SVS) Vascular Annual Meeting in August 2021 and the Canadian Society for Vascular Surgery (CSVV) Annual Meeting in September 2021 (corresponding abstract can be found in appendix D).

Author Contributions

SAS drafted the manuscript and was responsible for the design, execution, and writeup of the study. SAS, CS, and CH were heavily involved in the data collection and analysis. PJ, DK, DJ, and MC provided invaluable input in designing the study, overseeing the data collection and analysis, and reviewing/editing all versions of the manuscript.

Antithrombotic Therapy Among Females with Peripheral Artery Disease: A Systematic Review and Meta-Analysis of Female-Specific Outcomes

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Word Count: 6254

Abstract:

Background. Antithrombotic therapy is essential for both secondary and tertiary prevention in patients with peripheral artery disease (PAD); yet, despite equal prevalence of PAD among the sexes, little is known about the impact of antithrombotic therapy in females with PAD. The purpose of this study is to explore the effects of dual antiplatelet therapy (DAPT), dual pathway inhibition (DPI), and oral anticoagulation (OAC) compared to mono-antiplatelet therapy (MAPT) on limb, cardiovascular (CV), and bleeding events in females with PAD.

Methods. We searched MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials for randomized controlled trials (RCTs) including females with PAD that compared DAPT, DPI or OAC (+/- MAPT) to MAPT. Cochrane risk of bias tool was employed. Meta-analyses of CV, limb, and bleeding events in females were performed for trials reporting sex-stratified outcomes using random-effects models.

Results. The literature search identified a total of 9202 studies, of which eight RCTs met inclusion criteria and six offered sex-stratified outcomes for female-specific meta-analyses. Meta-analyses of DAPT versus MAPT among females (n=2 trials) revealed that DAPT did not reduce composite CV death, myocardial infarction (MI), or stroke (pooled hazard ratio [HR] 0.68; 95% CI 0.68-1.04), but *did* increase major bleeding (pooled HR 1.42; 95% confidence interval [CI] 1.08-1.86). Likewise, meta-analyses of DPI versus MAPT among females (n=2 trials) showed no difference in composite CV and limb events (pooled odds ratio [OR] 0.85; 95% CI 0.65-1.10) with DPI, and increased odds of major bleeding (pooled OR 2.11; 95% CI 1.42-3.13). The OAC trials (n=2) found no interaction between sex and their primary CV, limb or bleeding outcomes; meta-analysis of female-specific safety events revealed that OAC (+/- MAPT) increased the risk of major bleeding (pooled RR 3.24; 95% CI 1.98-5.31) compared to MAPT alone.

Conclusions. Females did not confer any benefit from DAPT, DPI, or OAC over MAPT in antithrombotic trials enrolling PAD patients. Further research is needed to determine whether these findings are generalizable to females with PAD, and to elucidate pathophysiological differences in the antithrombotic mechanisms in females compared to males with PAD.

Background:

Peripheral artery disease (PAD) is a blood flow-limiting condition that affects over 230 million people worldwide.¹ PAD usually results from atherosclerotic plaque buildup in the arteries, and it most commonly refers to disease in the lower extremities.¹ Depending on the degree of flow limitation, patients with PAD may be asymptomatic or experience a range of signs and symptoms, from claudication (typically described as exertional leg cramping that resolves with rest) to chronic limb-threatening ischemia (CLTI, defined by rest pain and/or tissue loss).² Beyond its effects on the limbs, PAD is an important surrogate marker for cardiovascular disease throughout the body, with high rates of concomitant coronary artery disease (CAD) and cerebrovascular disease (CVD) among PAD patients.^{3,4} Furthermore, while PAD *alone* increases the risk of cardiovascular (CV) events, such as CV death, stroke, and myocardial infarction (MI),^{5–7} PAD *in combination* with CAD is particularly concerning, with CV event rates reaching 72.8 per 1000 person-years (compared to 34.7 and 42.2 with PAD alone and CAD alone, respectively).⁸ With this in mind, antithrombotic therapy for both secondary and tertiary prevention represents a cornerstone of PAD treatment.^{2,9–11}

Antithrombotic therapy comes in many different forms, including mono-antiplatelet therapy (MAPT), dual antiplatelet therapy (DAPT), oral anticoagulation (OAC), and most recently, dual pathway inhibition (DPI, defined as very low dose rivaroxaban [i.e., 2.5 mg BID] combined with daily aspirin). PAD guidelines have markedly evolved in recent years as new agents, combination therapies, and randomized controlled trials (RCTs) unfold; yet, clinical equipoise surrounding the optimal therapy in PAD patients persists.^{2,9–11} Indeed, while guidelines generally agree that antiplatelet therapy—at a minimum—is warranted in symptomatic PAD patients, there is no “one-size-fits-all” approach. Clinicians must consider an individual’s, or a particular subgroup’s, risk profile before applying current guidelines to their care.

Unfortunately, despite a roughly equal¹²—and according to recent studies, *higher*—prevalence of PAD among females compared to males,^{13–15} females are one subgroup that remains consistently under-represented in CV trials.^{16–18} This is particularly problematic because females possess unique characteristics—such as narrower vascular anatomy, natural fluctuations in estrogen/hormone levels, exposure to prothrombotic drugs/states (e.g. oral contraception and pregnancy), more advanced disease at time of presentation, etc.—that may influence their

vascular disease course and response to treatment.^{19–24} The need for dedicated female PAD research is so pronounced that the American Heart Association, in collaboration with the Vascular Disease foundation, published a scientific statement in 2012 urging clinicians and researchers to consider these important sex differences in their clinical and academic work.²⁵ Nevertheless, while many systematic and structured reviews have explored the use of antithrombotic therapy in PAD patients, none has looked at female-specific outcomes.^{26–33} The purpose of this systematic review and meta-analysis is to assess female-specific outcomes in antithrombotic trials enrolling PAD patients, and thus explore whether PAD guidelines reflect the findings in this unique subgroup.

Methods:

Information Sources and Search Strategy

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.³⁴ The PRISMA checklist is available in Appendix A. The protocol was registered with PROSPERO International Prospective Register of Systematic Reviews in August 2020 (PROSPERO 2020 ID# CRD42020196933) and the methods have been published previously,³⁵ with changes to the original protocol noted herein. In brief, Medline, Embase, and the Cochrane Central Register of Controlled trials were searched from inception to August 2020 for randomized controlled trials (RCTs) enrolling participants with PAD and comparing antithrombotic regimens. The search was supplemented by reviewing the reference list of relevant studies for applicable trials. Grey literature and non-English studies were excluded. The complete search strategy is available in Appendix B.

Selection Criteria

RCTs enrolling female participants with PAD and comparing either DAPT, DPI, or OAC (+/- MAPT) to MAPT alone were included (see Table 1 for complete eligibility criteria). Trials were required to report *any* form of sex-based analysis to be eligible for the narrative summary, and specifically sex-stratified outcomes to be included in the meta-analysis of outcomes in females (or to have sex-stratified outcomes available upon request of the authors).

Table 1. Eligibility criteria

	Inclusion	Exclusion
Study Design	• Randomized controlled trials • Sex-stratified outcomes published or available upon request, or alternative sex-based analysis reported	• Cross sectional • Case-control • Case series with <10 patients • Case reports
Population*	• Females with PAD, defined as atherosclerotic disease of the lower extremities[†] • Diagnosis of PAD was at the discretion of each trial (e.g. via clinical assessment, self-report, or objective diagnostic criteria such as ankle brachial index)	• Trials exclusively enrolling males • Trials focused on the management of acute limb ischemia
Intervention and Comparator [‡]	• Full dose OAC (+/- MAPT) vs. MAPT • DPI vs. MAPT • DAPT vs. MAPT	• MAPT vs. MAPT or placebo • DAPT vs. DAPT or placebo • Anticoagulant vs. anticoagulant, DAPT or placebo • Very low dose anticoagulation alone vs. MAPT • Triple antiplatelet therapy vs. MAPT, DAPT or placebo • Intravenous or subcutaneous anticoagulation • Venous thromboembolism prophylaxis dosing
Outcomes	• Major adverse CV events (MACE) including CV death, stroke, and myocardial infarction (MI) • Major adverse limb events (MALE) including amputation, acute limb ischemia (ALI), and peripheral revascularization (revasc) • Safety events including major bleeding and all-cause death	
Other	• English language • No limitation with respect to date of publication	• Trials focused on acute limb ischemia (e.g. thrombolytic therapy or therapies lasting <30 days)

* For trials that included participants with PAD as a subgroup of the main trial, sex-stratified outcomes from the main trial were used for the meta-analysis of outcomes in females, and the PAD-specific sex-based analysis was discussed in the narrative synthesis (if available).

[†] Trials were included if they exclusively enrolled PAD patients *or* if they published data specific to the PAD subset (either within the main study or a related publication from the same trial)

[‡] There was no limitation with respect to class of oral antithrombotic agent. To be considered uniform baseline therapy, ≥80% of participants in the arm of interest had to be taking the antithrombotic agent in question.

Selection Process, Data Collection, and Data Items

All studies identified through the literature search were uploaded to COVIDENCE. Duplicates were excluded by the reviewers and COVIDENCE's automated tool. All title, abstract, and full-text review, as well as data extraction and risk of bias assessment, were performed independently and in duplicate by three study authors (SAS, CS, and CH). Disputes were resolved by consensus. Data items were identified a priori and included study and population characteristics, intervention and comparator details, and efficacy and safety outcomes as defined above. Outcomes data were sought for the female subgroup, where available. Risk of bias was performed using RevMan V.5 software in accordance with the Cochrane risk of bias tool (ROB 2) for randomised trials.³⁶

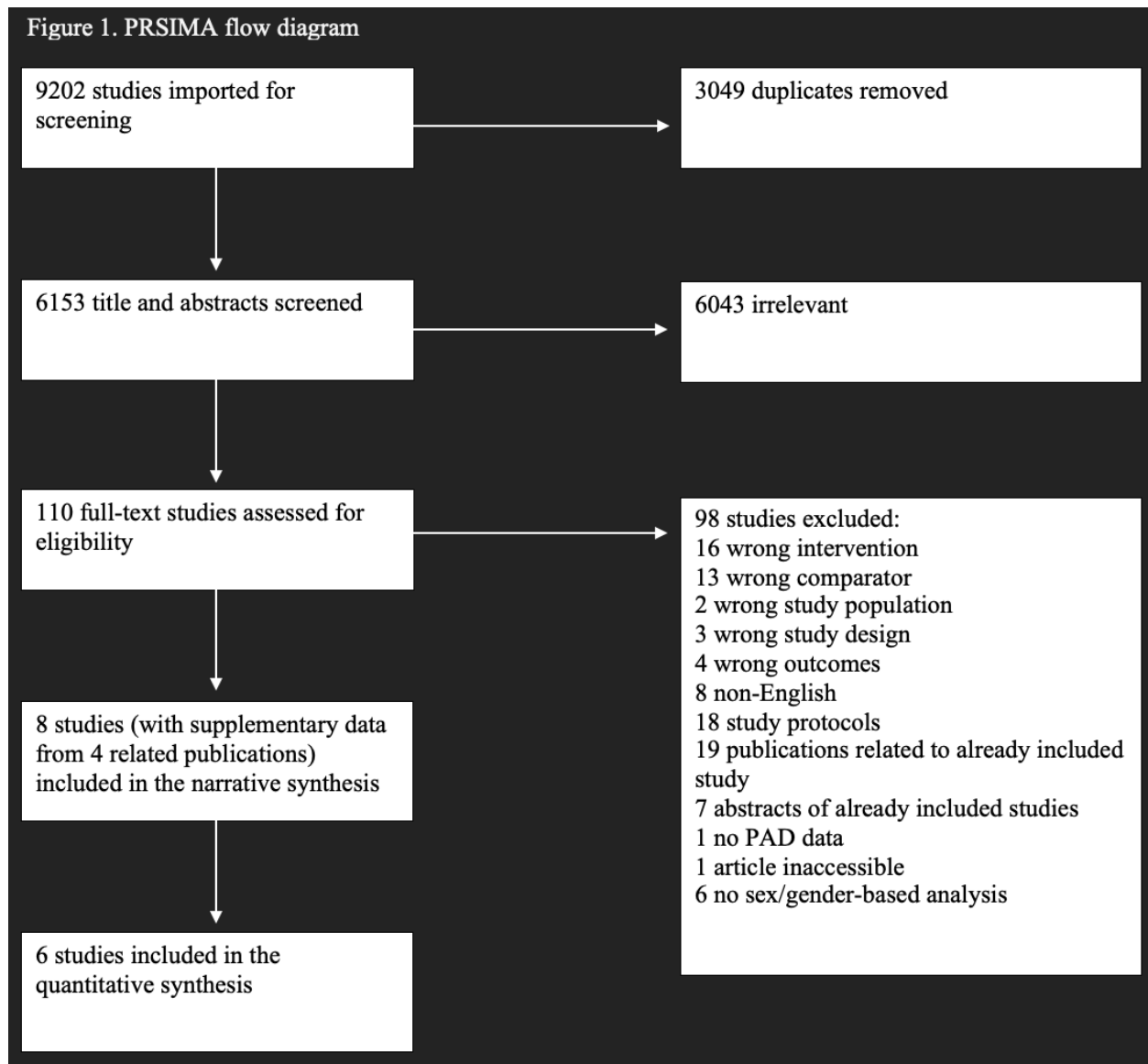
Data Synthesis

Study results were grouped according to intervention (DAPT, DPI or OAC) for both the qualitative and quantitative analyses. The narrative synthesis was reported with a focus on outcomes in the PAD subset and the effect of sex on these outcomes (as well as female-specific outcomes among PAD participants, where available). In the absence of a sex-based analysis *specific* to the PAD subgroup, findings from the main trial sex-based analysis were reported. Meta-analyses of female-specific outcomes from the main trial populations were performed using RevMan V.5 software. We used a random effects model to determine study weights and I^2 to assess for between-study statistical heterogeneity. There was insufficient data to conduct subgroup analyses based on severity of symptoms, indication for therapy (e.g., PAD vs. coronary artery disease) or prior intervention (i.e., prior endovascular or open revascularization or amputation). Likewise, a sensitivity analysis excluding trials with high risk of bias was not conducted due to insufficient data, and evaluation for publication bias was not performed given its limited power in the setting of a small (i.e., <10) number of studies.

Results:

The literature search identified a total of 9202 studies (Figure 1). After removing 3049 duplicates, 6153 title and abstracts were reviewed in duplicate. Ultimately, 110 studies underwent full-text review. Among these, eight studies^{37–44} (with supplementary data from five

related publications^{45–49}) met eligibility criteria for inclusion in the narrative synthesis, and six^{42–46,48} had female-specific outcomes data available for meta-analysis.



Included studies

This review included eight RCTs whose characteristics are listed in Table 2. Half of the included studies exclusively enrolled PAD participants,^{39,42–44} while the other half represented dedicated analyses of the PAD subgroup from a larger RCT with broader inclusion criteria.^{37,38,40,41} These eight RCTs reported on a total of 23,511 females (with PAD and/or atherosclerosis in alternate vascular beds) and 27,637 participants with PAD (both sexes).

Among the PAD participants, 7798 (28.2%) were female. Unpublished sex-stratified data (ideally from PAD participants) was sought for all eight RCTs, and was provided for one trial only (courtesy of the Dutch-BOA authors, Appendix E⁴³). Supplemental data were obtained from the main trial publications^{45–48} (i.e., the original trial with broader inclusion criteria) and related publications that reported on specific subgroups of interest.⁴⁸ All included RCTs were multicentre, ranging from 77⁴³ to 1161³⁷ participating sites and spanning up to 34 countries.⁴²

Table 2. Characteristics of the eight included RCTs (and four related studies providing supplemental data)

Trial	Main trial or PAD subgroup	Author, Year	Population	Females n (%)	Total PAD subjects n (%)	Intervention	Comparator	1° outcome
DAPT vs. MAPT								
CASPAR ³⁹	Main	Belch, 2010	Undergoing unilateral below-knee arterial bypass for PAD	207 (24)	851 (100)	Clopidogrel 75 mg daily + ASA 75-100 mg daily	ASA 75-100 mg daily	Index bypass occlusion, endovascular revascularization, above-ankle amputation, or death
PEGASUS-TIMI 54 ^{37,45}	Main	Bonaca, 2015	>50 years old with recent (1-3 years prior) MI + ≥ 1 of: age ≥ 65 , DM requiring meds, 2 nd prior spontaneous MI, multivessel CAD, CKD	5060 (24)	1143 (5)	Ticagrelor 90 or 60 mg BID + ASA 75-100 mg daily	ASA 75-100 mg daily	Composite CV death, MI, or stroke
	PAD subgroup	Bonaca, 2016	PEGASUS-TIMI 54 ⁴⁵ trial participants with PAD, defined as ABI ≤ 0.90 , history of peripheral revascularization, or history of claudication	254 (22)	1143 (100)	Ticagrelor 90 or 60 mg BID + ASA 75-100 mg daily	ASA 75-100 mg daily	Composite CV death, MI, or stroke
TRA2°P-TIMI 50 ^{38,46}	Main	Morrow, 2012	Atherosclerosis history (spontaneous MI, ischemic stroke within previous 2 wks-12 months, or PAD [intermittent claudication + ABI	6326 (24)	6136 (23)	Vorapaxar 2.5 mg daily + baseline antiplatelet therapy	Placebo + Baseline antiplatelet therapy	Composite CV death, MI, stroke, or recurrent ischemia leading to urgent coronary revascularization

			<0.85 or previous revascularization)					
	PAD subgroup	Qamar, 2020	TRA2P-TIMI 50 trial participants with PAD (ABI ≤ 0.90 or > 1.3 , carotid stenosis $\geq 50\%$, prior carotid intervention or peripheral artery revascularization, claudication, and/or prior amputation for limb ischemia)	1756 (29)	6136 (100)	Vorapaxar 2.5 mg daily + baseline antiplatelet therapy	Placebo + Baseline antiplatelet therapy	Primary CV efficacy outcome was MACE (composite of CV death, MI or stroke). Primary limb efficacy outcome was MALE (composite of hospitalization for ALI, urgent peripheral revascularization, or major amputation due to limb ischemia)
CHARISMA ^{40,47}	Main	Bhatt, 2006	≥ 45 years old +: multiple atherothrombotic risk factors or documented CAD, CVD, or symptomatic PAD	4644 (30)	3531 (23)	Clopidogrel 75 mg daily + ASA 75-162 mg daily	Placebo + ASA 75-162 mg daily	Composite stroke, MI or CV death (including hemorrhage)
	PAD subgroup	Cacoub, 2009	CHARISMA ⁴⁷ trial participants with symptomatic (intermittent claudication [IC] with ABI ≤ 0.85 or history of IC with prior revascularization or amputation) and asymptomatic (ABI < 0.90 with risk factors) PAD	930 (30)	3096 (100)	Clopidogrel 75 mg daily + ASA 75-162 mg daily	Placebo + ASA 75-162 mg daily	Composite stroke, MI or CV death (including hemorrhage)
DPI vs MAPT								
β COMPASS ^{41,48}	Main	Liang, 2020	≥ 65 years old + CAD, PAD or both OR < 65 years old + CAD, PAD or both AND documentation of atherosclerosis involving ≥ 2 vascular beds OR ≥ 2 additional risk factors (current smoking, DM, eGFR < 60 ml/min, heart failure, or nonlacunar ischemic	4048 (22)	4996 (27)	Rivaroxaban 2.5 mg BID + ASA 100 mg once daily	Placebo BID + ASA 100 mg once daily	Composite CV death, stroke or MI

			stroke $\geq$ 1 month earlier)					
	PAD subgroup	Anand, 2018	COMPASS ^{48,50} trial participants with ABI<0.90; prior aortofemoral bypass surgery, limb bypass surgery, percutaneous transluminal angioplasty revascularization of the iliac or infrainguinal arteries; limb or foot amputation for PAD; intermittent claudication + peripheral artery stenosis $\geq$ 50%; carotid revascularization or asymptomatic carotid artery stenosis $\geq$ 50%	1425 (29)	4996 (100)	Rivaroxaban 2.5 mg BID + ASA 100 mg once daily	Placebo BID + ASA 100 mg once daily	Composite CV death, stroke or MI
VOYAGER ⁴²	Main	Bonaca, 2009	>50 years old with recent (i.e. prior 10d) successful revascularization for symptomatic PAD	1704 (26)	6564 (100)	Rivaroxaban 2.5 mg BID + 100 mg ASA daily	Placebo + 100 mg ASA daily	composite of ALI, major vascular amputation, MI, ischemic stroke, or CV death
OAC +/- MAPT vs MAPT								
DUTCH BOA ^{43,49}	Main	Eikelboom, 2000	Patients requiring infrainguinal bypass graft for obstructive PAD	952 (36)	2690 (100)	Phenprocoumon or acenocoumarol daily (target INR 3-4.5)	carbasalate calcium 100 mg daily (metabolizes to aspirin 80 mg)	Graft occlusion
WAVE ⁴⁴	Main	Anand, 2007	Age 35-85 years old with symptomatic lower extremity PAD, symptomatic carotid disease, asymptomatic carotid disease, or subclavian artery occlusive disease	570 (26)	2161 (100)	Warfarin or acenocoumarol daily (target INR 2-3) + baseline MAPT (ASA, clopidogrel or ticlopidine)	Baseline MAPT (ASA, clopidogrel or ticlopidine)	Composite CV death, MI, stroke, severe ischemia requiring urgent intervention of the coronary or peripheral artery circulation

DAPT= dual antiplatelet therapy, MAPT= mono-antiplatelet therapy, DPI= dual pathway inhibition, AC= anticoagulation, ASA= acetylsalicylic acid, MI= myocardial infarction, CV=cardiovascular, CAD= coronary artery disease, ALI= acute limb ischemia, CVD= cerebrovascular disease, CKD= chronic kidney disease, PCI= percutaneous coronary intervention, EVT= endovascular therapy

^β Only rivaroxaban 2.5 BID + ASA and ASA arms included

Four of the included trials compared DAPT to MAPT.³⁷⁻⁴⁰ Among these, only the CASPAR trial exclusively enrolled PAD patients.³⁹ The remaining three trials—TRA2°P-TIMI 50, PEGASUS-TIMI 54, and CHARISMA—enrolled patients with more generalized atherosclerotic disease (and/or risk factors), and conducted post-hoc analyses on patients with symptomatic and asymptomatic PAD.^{37,38,40} Females constituted 22-30% of participants with PAD across the four trials. The total CV, limb, and safety outcomes among PAD participants are summarized in Table 3.

The CASPAR trial found that DAPT with aspirin and clopidogrel compared to aspirin alone had no effect on CV, limb, or safety outcomes in patients undergoing below-knee arterial bypass surgery (Table 3). The trial authors did not report sex-stratified outcomes; however, multivariate analyses of potential risk factors revealed that gender had no effect on the primary composite endpoint (bypass graft occlusion, surgical or endovascular revascularization on the index bypass graft or para-anastomotic region, above-ankle amputation, or death).³⁹ Similarly, the CHARISMA trial compared aspirin and clopidogrel to aspirin and placebo, and found no difference in the rate of composite CV death, stroke or MI; above-ankle amputation; major bleeding; CV death; stroke; all-cause death; or peripheral revascularization within the PAD subgroup (Table 3).⁴⁰ The only outcome that significantly improved with DAPT among PAD participants was MI (hazard ratio [HR] 0.63; 95% confidence interval [CI] 0.42-0.96). Unfortunately, no sex-based analysis was conducted specifically for the PAD subgroup. The main CHARISMA trial, however, reported sex-stratified outcomes graphically, illustrating that DAPT did not significantly affect the primary endpoint (CV death, stroke or MI) in either sex, though it did trend towards improving rates in males and worsening rates in females.⁴⁷ Numeric values were not reported, which precluded pooling of this female-specific data in the meta-analysis.

PEGASUS-TIMI 54 was a large trial comparing aspirin and either 60 or 90 mg of ticagrelor twice daily to aspirin alone in patients with recent MI and atherosclerotic risk factors. Among the PAD subgroup (both sexes), DAPT (with pooled ticagrelor dosing or 90 mg BID) neither increased bleeding rates nor decreased CV or limb events (Table 3), with the exception of

one outcome: revascularization (HR 0.63; 95% CI 0.43-0.93).³⁷ TRA2°P-TIMI 50, the most recent and largest of the four trials, compared vorapaxar to placebo on a background of baseline antiplatelet therapy (MAPT for the majority of participants). Within the PAD subgroup (both sexes), the addition of vorapaxar significantly reduced the primary composite outcome of CV death, stroke, and MI (HR 0.85; 95% CI 0.73-0.99), as well as limb events such as peripheral revascularization (HR 0.79; 95% CI 0.68-0.91) and acute limb ischemic (ALI) requiring hospitalization (HR 0.57; 95% CI 0.75-1.07).³⁸ These benefits came at the cost of increased major bleeding (HR 1.39; 95% CI 1.12-1.71). While neither PEGASUS-TIMI 54 nor TRA2°P-TIMI 50 conducted a sex-based analysis *specific* to their PAD subgroups, both reported no heterogeneity in the effect of ticagrelor (at either dose) or vorapaxar, respectively, on the risk of the primary composite endpoint (stroke, CV death or MI) or the primary safety endpoint (major or moderate to severe bleeding) according to sex within their *main* trial populations.^{45,46}

Table 3. CV, limb and safety outcomes among PAD participants in trials comparing DAPT vs. MAPT, DPI vs. MAPT, and OAC vs. MAPT, respectively.

	Composite CV death, stroke and MI	Major amputation	Major Bleeding	MI	CV death	Stroke	All-cause death	ALI	Revasc
DAPT vs. MAPT									
CASPAR	HR 1.09 [95% CI 0.65-1.82], p=0.75	HR 0.69 [95% CI 0.44-1.09], p=0.11	*RR 1.78 [95% CI 0.60-5.28], p=0.30	HR 0.81 [95% CI 0.32-2.06], p=0.66	HR 1.49 [95% CI 0.73-3.01], p=0.27	HR 1.02 [95% CI 0.41-2.57], p=0.96	HR 1.44 [95% CI 0.77-2.68]	NR	HR 0.89 (0.65-1.23)
TRA2°P-TIMI 50	HR 0.85 [95% CI 0.73-0.99], p=0.03	HR 0.90 [95% CI 0.59-1.38], p=0.62	HR 1.39 [95% CI 1.12-1.71], p=0.003	HR 0.90 [95% CI 0.73-1.10], p=0.30	HR 0.85 [95% CI 0.68-1.08], p=0.18	HR 0.77 [95% CI 0.53-1.11], p=0.17	HR 0.90 [95% CI 0.75-1.07], p=0.23	HR 0.57 [95% CI 0.39-0.84], p=0.005	HR 0.79 [95% CI 0.68-0.91], p<0.001
PEGASUS-TIMI 54 (Pooled ticagrelor dosing vs. placebo,	HR 0.75 [95% CI 0.55-1.01]	*RR 0.55 [95% CI 0.03-8.71], p=0.67	HR 1.32 [95% CI 0.41-4.29]	90 mg BID vs. placebo: HR 0.87 [95% CI 0.53-	90 mg BID vs. placebo: HR 0.83 [95% CI 0.50-	90 mg BID vs. placebo: HR 0.63 [95% CI 0.29-	90 mg BID vs. placebo: HR 0.88 [95% CI 0.58-	HR 0.56 [95% CI 0.23-1.37]	HR 0.63 [95% CI 0.43-0.93]

unless otherwise specified)				1.44], p=0.59	1.38], p=0.46	1.38], p=0.25	1.32], p=0.53		
CHARISMA	HR 0.85 [95% CI 0.66-1.08], p=0.18	*RR 0.71 [95% CI 0.34-1.48], p=0.36	HR 0.97 [95% CI 0.56-1.66], p=0.901	HR 0.63 [95% CI 0.42-0.96], p=0.03	HR 0.92 [95% CI 0.65-1.28], p=0.61	HR 0.79 [95% CI 0.51-1.21], p=0.28	HR 0.89 [95% CI 0.68-1.16], p=0.39	NR	*RR 0.74 [95% CI 0.53-1.03], p=0.07
DPI vs. MAPT									
COMPASS	HR 0.72 [95% CI 0.57-0.90], p=0.0047	HR 0.30 [95% CI 0.11-0.80], p=0.011	HR 1.61 [95% CI 1.12-2.31], p=0.0089	HR 0.76 [95% CI 0.53-1.09]	HR 0.82 [95% CI 0.59-1.14]	HR 0.54 [95% CI 0.33-0.87]	HR 0.91 [95% CI 0.72-1.16]	HR 0.56 [95% CI 0.32-0.99], p=0.042	NR
VOYAGER	NR	HR 0.80 [95% CI 0.56-1.15]	HR 1.43 [95% CI 0.97-2.10], p=0.07	HR 0.75 [95% CI 0.56-1.00]	HR 0.85 [95% CI 0.68-1.08], p=0.18	HR 0.92 [95% CI 0.68-1.25]	HR 0.90 [95% CI 0.75-1.07], p=0.23	HR 0.64 [95% CI 0.51-0.80]	HR 0.88 [95% CI 0.79-0.99], p=0.03
OAC +/- MAPT vs MAPT									
Dutch BOA	NR	HR 0.90 [95% CI 0.69-1.19]	HR 1.96 [95% CI 1.42-2.71]	HR 0.69 [95% CI 0.42-1.10]	HR 0.94 [95% CI 0.74-1.18]	HR 0.74 [95% CI 0.48-1.14]	HR 1.02 [95% CI 0.85-1.24]	NR	HR 0.95 [95% CI 0.84-1.09]
WAVE	RR 0.92 [95% CI 0.73-1.16], p=0.48	*RR 0.67 [95% CI 0.27-1.63], p=0.37	^a RR 3.21 [95% CI 2.02-5.08], p<0.001	RR 0.82 [95% CI 0.57-1.18], p=0.28	RR 1.04 [95% CI 0.74-1.46], p=0.84	RR 1.01 [95% CI 0.65-1.59], p=0.96	RR 1.04 [95% CI 0.79-1.38], p=0.76	RR 0.96 [95% CI 0.63-1.47], p=0.86	*RR 0.90 [95% CI 0.58-1.41], p=0.64

CV death= cardiovascular death; MI= myocardial infarction; ALI= acute limb ischemia; Revasc= lower extremity revascularization; HR= hazard ratio, CI= confidence interval, NR= not reported, RR= relative risk

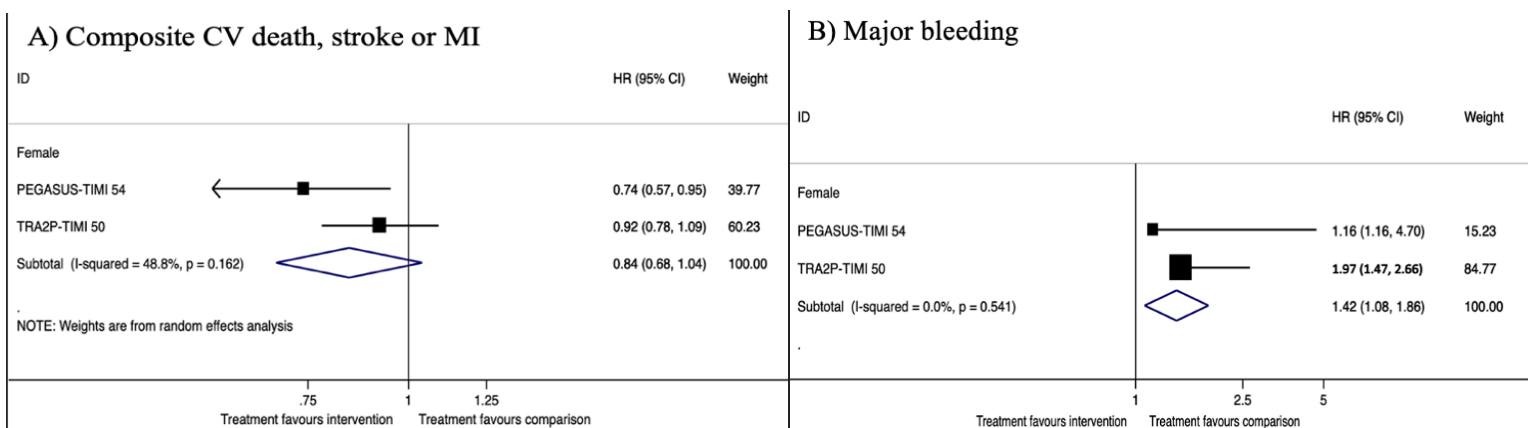
*RR, CI, and p-values calculated from absolute totals provided

^aMajor bleeding defined as life threatening or moderate

DAPT vs. MAPT Meta-analysis

No PAD-specific, sex-stratified data were available for the trials comparing DAPT to MAPT; however, sex-stratified data were available for the primary CV outcome (composite CV death, MI or stroke) and safety outcome (bleeding) within the *overall* populations of the PEGASUS-TIMI 54 and TRA2°P-TIMI 50 trials (which included, but were not restricted to, PAD participants). Among the pooled female subgroups of the overall trials, DAPT increased major bleeding (pooled HR 1.42; 95% CI 1.08-1.86; I^2 : 49%; figure 2A) without significantly reducing the composite rate of CV death, stroke or MI compared to MAPT (pooled HR 0.68; 95% CI 0.68-1.04; I^2 : 0%; figure 2B).

Figure 2. Female-specific outcomes in DAPT vs MAPT trials. DAPT did not reduce rates of composite CV death, stroke or MI (A) but did increase rates of major bleeding (B) among females in trials comparing DAPT vs. MAPT.



DPI vs. MAPT: Qualitative Review

Two of the included trials compared DPI to MAPT.^{41,42} The COMPASS trial, originally published in 2017, randomized patients with stable atherosclerotic vascular disease to one of three arms: rivaroxaban alone (5 mg BID), rivaroxaban (2.5 mg BID) plus aspirin, or aspirin alone.⁵⁰ For the purpose of this systematic review, only the latter two arms—comparing DPI and MAPT—were included. Within the PAD subgroup, DPI significantly reduced rates of composite CV death, stroke and MI (HR 0.72; 95% CI 0.57-0.90); major amputation (HR 0.30; 95% CI 0.11-0.90); stroke (HR 0.54; 95% CI 0.33-0.87); and ALI (HR 0.56; 95% CI 0.32-0.99) compared to MAPT (Table 3).⁴¹ These benefits came at the cost of increased major (HR 1.61; 95% CI 1.12-2.31) and minor (HR 1.43; 95% CI 1.15-1.77) bleeding. There was no sex-based

analysis reported for the PAD subgroup; however, a detailed analysis on the effect of sex in the main trial population (participants with chronic CAD and/or PAD) found that the benefits of DPI over aspirin alone were consistent in both women and men.⁴⁸ Specifically, females receiving DPI experienced lower rates of composite CV death, stroke or MI (HR 0.72; 95% CI 0.54-0.97); composite CV death, ischemic stroke, MI, ALI or vascular amputation (HR 0.73; 95% CI 0.55-0.97); and stroke (HR 0.39; 95% CI 0.22-0.71), as well as higher rates of major bleeding (HR 2.22; 95% CI 1.42-3.46), compared to females receiving MAPT. No interactions were observed between sex and any of the outcomes assessed; however, females on DPI—unlike their male counterparts—did not see a reduction in CV death or death from any cause ($p>0.05$ for each).⁴⁸

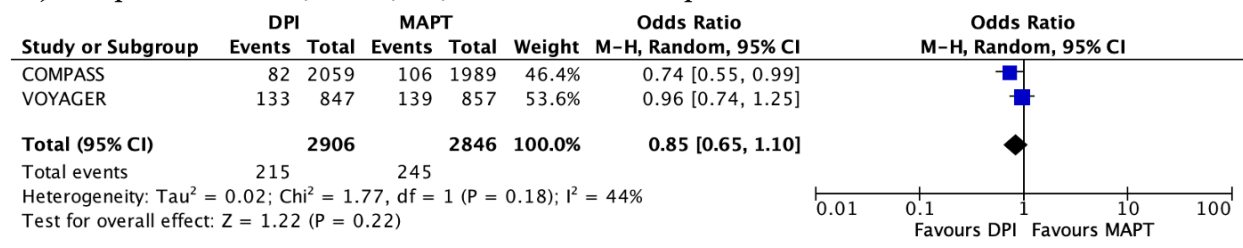
The VOYAGER trial, published three years after COMPASS, similarly examined the effects of DPI compared to MAPT but in a narrower population, consisting of patients who underwent recent successful lower extremity revascularization for symptoms of PAD.⁴² VOYAGER demonstrated that after three years, DPI significantly reduced the primary composite efficacy outcome of ALI, major amputation for vascular causes, MI, ischemic stroke, or CV death compared to MAPT (HR 0.85; 95% CI 0.76-0.96). The trial did not report the composite outcome of CV death, stroke or MI, but it did report no benefit to DPI over MAPT for each of the individual components (table 3). DPI *did* shine in many of the limb outcomes, reducing the rates of ALI (HR 0.67; 95% CI 0.55-0.82), unplanned index-limb revascularization (HR 0.88; 95% CI 0.79-0.99), and hospitalization for coronary or peripheral events of a thrombotic nature (HR 0.72; 95% CI 0.62-0.85) compared to MAPT. Interestingly, DPI significantly increased the rate of ISTH major bleeding (HR 1.42; 95% CI 1.10-1.84), but not TIMI or BARC major bleeding ($p=0.07$ and $p=0.10$, respectively). VOYAGER found no heterogeneity in the effect of DPI compared to MAPT on the primary efficacy or safety (TIMI major bleeding) outcomes across major subgroups, including sex. Nevertheless, it is worth noting that sex stratification revealed no benefit to DPI over MAPT in women for the primary efficacy outcome (HR 0.97; 95% CI 0.76-1.23), in contrast to the significant effect observed in men (HR 0.82; 95% CI 0.71, 0.94).

DPI vs. MAPT Meta-analysis

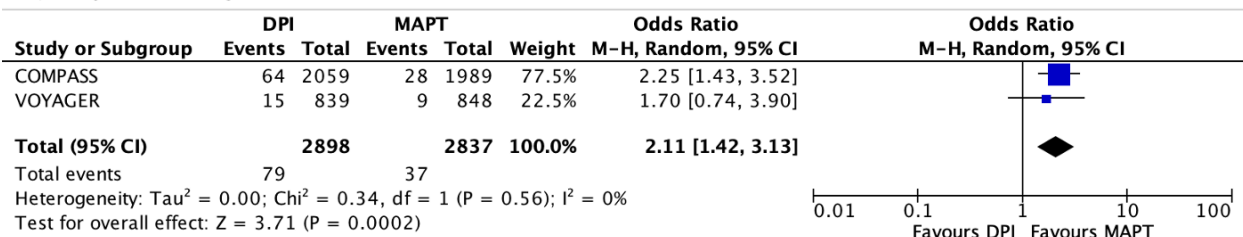
Female-specific outcomes data were available from VOYAGER and the main population (not PAD-specific) of COMPASS.^{42,48} Among the females enrolled in these trials, DPI conferred no benefit over MAPT for the composite outcome of CV death, stroke, MI, ALI or vascular amputation (pooled odds ratio [OR] 0.85; 95% CI 0.65-1.10; I^2 : 44%; figure 3A), but did increase the odds of major bleeding (pooled OR 2.11; 95% CI 1.42-3.13; I^2 : 0%; figure 3B).

Figure 3. Forest plots of female-specific outcomes in DPI vs MAPT trials. DPI did not reduce the odds of composite CV death, stroke, MI, ALI or vascular amputation (A) but did increase odds of major bleeding (B) among females in trials comparing DPI vs. MAPT.

A) Composite CV death, stroke, MI, ALI or vascular amputation



B) Major bleeding



OAC (+/- MAPT) vs. MAPT: Qualitative Review

Two trials, both specific to PAD, examined the use of OAC compared to MAPT. The Dutch Bypass Oral Anticoagulants or Aspirin (Dutch BOA) study randomized patients to OAC with a vitamin K antagonist (target international normalised ratio [INR]= 3.0-4.5) or MAPT (metabolized to aspirin 80 mg daily) within five days of infrainguinal bypass grafting for obstructive arterial disease.⁴³ Overall, OAC reduced the risk of ischemic stroke over MAPT (HR 0.50; 95% CI 0.28-0.90), but did not confer any benefit for the other CV or limb outcomes, including graft occlusion; composite vascular death, non-fatal MI, non-fatal stroke or amputation; all-cause death; CV death; MI; all-cause stroke; amputation; or vascular intervention

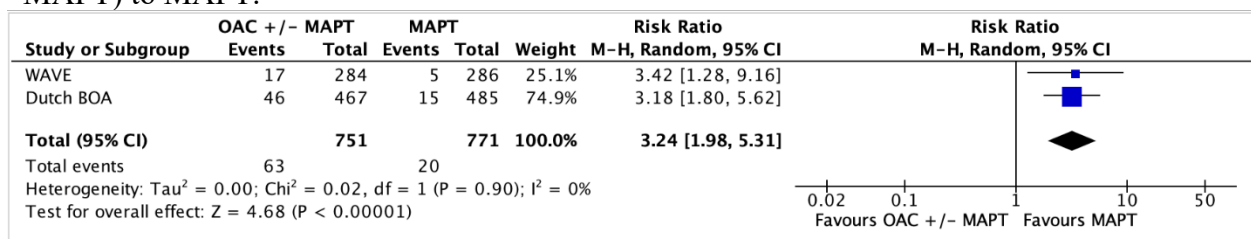
($p > 0.05$ for each; Table 3). The stroke benefit came at the cost of increased risk of hemorrhagic stroke (HR 3.48; 95% CI 1.14-10.6) and overall hemorrhage (including intracranial) with OAC compared to MAPT (HR 1.96; 95% CI 1.42-2.71). Using a Cox proportional-hazards model to adjust for differences in prognostic variables (including sex), the authors concluded that this adjustment did not alter the results.⁴³ In addition, unpublished sex-stratified data (provided by the authors, Appendix E) revealed no difference between OAC and MAPT among females with respect to any of the following CV or limb outcomes: composite CV death, stroke, MI or amputation (relative risk [RR] 0.87; 95% CI 0.68-1.11); amputation (RR 0.86; 95% CI 0.58-1.26); CV death (RR 0.80; 95% CI 0.56-1.15); all-cause death (RR 0.96; 95% CI 0.71-1.29); MI (RR 0.58; 95% CI 0.27-1.24); stroke (RR 0.84; 95% CI 0.41-1.73); graft occlusion (RR 1.02; 95% CI 0.83-1.26); or vascular intervention (RR 1.09; 95% CI 0.91-1.31).⁵¹ The only significant effect of OAC compared to MAPT in females was an adverse one, with OAC increasing major bleeding (RR 3.18; 95% CI 1.80-5.62).

The Warfarin Antiplatelet Vascular Evaluation (WAVE) trial, published seven years after Dutch BOA, similarly examined the effect of OAC on CV, limb, and bleeding outcomes, albeit with a few notable differences: 1) the study population was broader, enrolling participants with symptomatic PAD as well as symptomatic and asymptomatic carotid stenosis, 2) all trial participants—regardless of assigned intervention group—were maintained on baseline antiplatelet therapy (majority aspirin), and 3) participants in the OAC arm received warfarin with a lower target INR of 2.0-3.0.⁴⁴ Like its predecessor, the WAVE trial demonstrated no benefit to OAC plus MAPT over MAPT alone with respect to the CV or limb outcomes, including composite CV death, stroke, MI; amputation; MI; stroke; CV death; all-cause death; ALI; or revascularization ($p > 0.05$ for each; Table 3). Once again, this lack of benefit was compounded by an increased risk of bleeding with OAC, including moderate or life-threatening (RR 3.21; 95% CI 2.02-5.08). Subgroup analyses revealed no interaction between sex and the primary efficacy (composite CV death, stroke or MI) or safety (life-threatening or moderate bleeding) endpoints (p -value for interaction= 0.91 and 0.78, respectively); in females, OAC plus MAPT demonstrated an increased risk of bleeding (RR 3.42; 95% CI 1.28-9.16) and no effect on composite CV death, stroke, or MI (RR 0.94; 95% CI 0.58-1.53).⁴⁴

OAC (+/- MAPT) vs. MAPT Meta-analysis

Female-specific data were available for efficacy and safety outcomes from both the Dutch BOA and WAVE trials;^{44,51} however, due to heterogeneity in the outcomes assessed, only major bleeding was amenable to quantitative synthesis. In trials comparing OAC (+/- MAPT) to MAPT in patients with PAD, OAC significantly increased major bleeding risk among females (pooled RR 3.24; 95% CI 1.98-5.31; I^2 : 0%; figure 4).

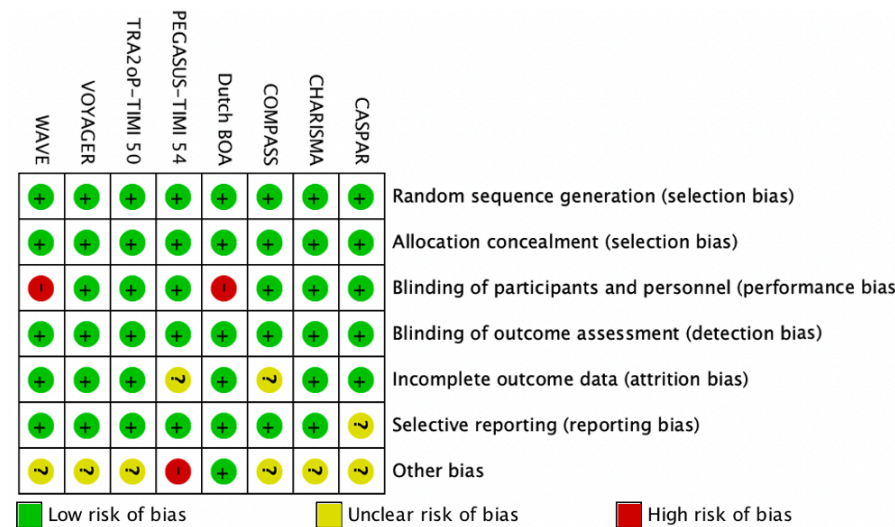
Figure 4. Forest plot of female-specific outcomes in OAC (+/- MAPT) vs MAPT trials. OAC (+/- MAPT) increased the risk of major bleeding among females with in trials comparing OAC (+/- MAPT) to MAPT.



Risk of Bias

Risk of bias assessment for the eight RCTs is summarized in figure 5, and detailed justifications for each judgement are provided in Appendix F. In brief, all studies were deemed to be at low risk of bias for random sequence generation (selection bias), allocation concealment (selection bias), and blinding of outcomes assessment (detection bias).^{39,41–47} Three trials were deemed to be at high risk of bias overall due to a high-risk judgment in one domain.^{43–45} Both the Dutch BOA and WAVE trials posed a high risk of performance bias due to the need for INR monitoring in the intervention group, thus precluding participant blinding.^{43,44} In contrast, PEGASUS-TIMI 54 introduced a high risk of bias by permitting modification to the assigned study medication in patients who developed an indication for adenosine diphosphate (ADP) receptor blockade.⁴⁵ In such patients, the protocol allowed for the addition of clopidogrel to the placebo arm (i.e., the original MAPT arm), effectively blurring the comparison of DAPT to MAPT.

Figure 5. Risk of bias summary



Discussion:

This systematic review examined the role of DAPT, DPI, and OAC (+/- MAPT) compared to MAPT among 23,511 *females* with either PAD, atherosclerotic disease (i.e., including coronary or cerebrovascular disease), and/or atherosclerotic risk factors, and 27,637 participants with PAD (of whom 28.2% were female). The main findings can be summarized as follows:

- No significant interaction was demonstrated between sex and the primary CV, limb, and/or safety outcomes in any of the included trials
- Meta-analyses of female-specific outcomes revealed that DAPT did not confer any benefit over MAPT with respect to composite CV death, stroke, or MI; nor did DPI confer benefit over MAPT for composite CV death, stroke, MI, ALI, or amputation
- Meta-analyses of safety outcomes revealed that DAPT, DPI, and OAC (+/- MAPT) all increased major bleeding in females compared to MAPT
- While heterogeneity precluded pooling of the CV and limb outcomes in the OAC (+/- MAPT) vs. MAPT trials, sex-stratified data from each revealed that OAC did not reduce composite CV death, stroke, or MI or composite CV death, stroke, MI or amputation
- There was no high heterogeneity among the meta-analyses conducted, as measured by I^2
- Female-specific limb outcomes were scarcely reported across all trials

Our findings on the effects of DAPT and therapeutic OAC compared to MAPT in females (namely, their lack of cardiovascular/limb benefit and increased bleeding risk) align well with previous systematic reviews and current PAD guidelines.⁵² Indeed, all four major European and North American guidelines published in the past six years (representing the American Heart Association [AHA], European Society for Vascular Surgery [ESVS], Society for Vascular Surgery [SVS], and Canadian Society for Vascular Surgery [CSVS], among others) agree that MAPT, at a minimum, is indicated for patients with symptomatic PAD, while DAPT and OAC have limited (if any) and controversial roles.^{2,9–11}

Our female-specific findings deviate from current guidelines with respect to the benefit—or rather, lack thereof—of DPI. Since the COMPASS and VOYAGER trials (published in 2017 and 2020, respectively) demonstrated a net clinical benefit to DPI over MAPT in participants with PAD (and/or CAD, in the case of the COMPASS trial),^{42,50} cardiovascular guidelines have endorsed the use of DPI in patients with higher-risk PAD (such as those with CLTI or polyvascular disease). Yet, while neither COMPASS nor VOYAGER found heterogeneity in the efficacy or safety of DPI compared to MAPT across sexes,^{42,50} this meta-analysis revealed that, in contrast to males, females did not see a reduction in composite ALI, amputation, MI, stroke, or CV death with DPI over MAPT. This lack of effect was driven by the VOYAGER trial, which showed a significant benefit in males (HR 0.82; 95% CI 0.71-0.94) but not females (HR 0.97; 95% CI 0.76-1.23).⁴² There are a number of explanations—some related to research methodology, others to pathophysiology—that may account for this difference. From a methodological perspective, females may not have demonstrated a significant benefit because the study was not powered to detect this difference in females. In addition, there may have been confounding by other known (e.g., concomitant clopidogrel use) and unknown variables in the female-specific analysis due to loss of the randomization node (as is inherent to post-hoc analyses that do not control for baseline risk factors).

Alternatively, perhaps these methodological issues better account for the *lack* of sex-based differences seen in the *other* trials, rather than the differences that *were* observed in VOYAGER. Previous studies have elucidated features of platelet functioning and antithrombotic therapy, as well as both risk and protective factors for thrombosis and bleeding, that are unique to females (though it remains unclear whether the balance of these features favors or disadvantages

females).⁵⁴ For example, fluctuations in hormone levels related to pregnancy, oral contraception, menopause, and hormone replacement therapy have been associated with increased thrombotic risk, while endogenous estrogen has been shown to protect against atherosclerosis, inhibit platelet aggregation, and reduce platelet reactivity (corresponding with prolonged bleeding times observed in premenopausal females compared to males).^{54–58} Yet, females have also demonstrated greater residual platelet aggregation after high-dose aspirin (325 mg daily) compared to men treated with a lower dose of aspirin (81 mg daily).⁵⁹ These differences may account for the reduced CV benefit (though not statistically significant) observed with DAPT over MAPT in females compared to males, as was evidenced by a meta-analysis of 79 613 patients (30% female) with CAD.⁶⁰ Clinical differences in bleeding outcomes have also unfolded through large observational studies from the Global Registry of Acute Coronary Events (GRACE) and the CRUSADE National Quality Improvement Initiative Registry (each consisting of over 20,000 CAD patients), which demonstrated that female sex was associated with higher rates of in-hospital bleeding, due in part to excessive dosing of antithrombotic therapy.^{61,62} This elevated bleeding risk may further blunt the net clinical benefit of antithrombotic therapy in females compared to males.

Considering these potent biological sex differences in light of the trials that did *not* demonstrate a clinical difference between females and males in this systematic review, the aforementioned methodological issues may offer some clarity. It has been shown that females generally present with more advanced cardiovascular disease and at older ages compared to males.^{63–66} Thus, clinical trials that enroll females with inherently higher thrombotic risk than their male counterparts may overestimate the benefit of antithrombotic therapy in females relative to males (since their benefit may be comparatively less than males with a more similar risk profile). This holds true when examining the COMPASS trial, for example. The sex-based analysis of the COMPASS trial revealed that females were significantly older and had higher cholesterol levels, rates of PAD, diabetes, hypertension, previous stroke, heart failure, and renal dysfunction compared to males; whereas males had higher rates of smoking, previous MI and CAD.⁴⁸ Perhaps this imbalance in risk factors led to an exaggerated benefit in females, accounting for the significant composite CV benefit seen with DPI compared to MAPT in both sexes. Lending support to this hypothesis, this sex-based analysis demonstrated that, after stratifying patients according to low vs. high REACH scores (which estimate CV risk), males

with high REACH scores demonstrated a greater and significant CV benefit with DPI over MAPT (HR 0.71; 95% CI 0.58-0.86) compared to females with high REACH scores who, in turn, did not significantly benefit from DPI (HR 0.77; 95% CI 0.53-1.12).⁴⁸

This systematic review and meta-analysis had a number of limitations. First and foremost, there were limited PAD- and female-specific outcomes data available. While there are various antithrombotic trials in patients with CV disease, many did not screen for the presence of PAD, did not conduct a PAD subgroup analysis, or did not conduct a sex-based analysis.⁶⁷⁻⁷⁵ Had more PAD-specific studies/data been available, we could have performed a meta-regression to examine the effect of female sex on CV, limb, and bleeding outcomes in PAD patients, while bypassing the paucity of sex-stratified data. However, without an adequate number of studies (ideally, 10 per comparison), this analysis cannot lead to meaningful conclusions and was therefore not performed. Furthermore, among the trials that did conduct a sex-based analysis, few reported sex-stratified outcomes, fewer reported sex-stratified outcomes *among PAD participants*, and others reported CV and limb outcomes that were too different to pool. This not only limited the power of this study, but also increased heterogeneity between the study populations that were included in the meta-analysis (since some studies only reported sex stratified data from their main, non-PAD-specific, trial populations). With this in mind, the study results must be interpreted with caution, as further sex-specific PAD research is required to determine the generalizability of these findings.

This study highlights the importance of examining female-specific outcomes within this high-risk population. To facilitate more robust analyses, future trials should focus on standardizing outcomes (i.e., establishing a uniform definition for major adverse cardiac events and major adverse limb events), enrolling PAD participants, and planning sex-based analyses a-priori (including stratifying outcomes by sex) so that they can be powered appropriately and adjusted for baseline risk factors. Further research is needed to determine whether female enrolment in PAD trials adequately reflects their burden of disease, to assess the generalizability of these trial findings to females with PAD, and to identify therapeutic pathways tailored to females that target their unique physiology and risk factors.

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Chapter 5: Analyzing Antithrombotic Trials: The Representation of, and Generalizability to, Females with PAD

A Systematic Review

Chapter Overview

This chapter addresses thesis objective #2 by reporting a systematic review and meta-analysis that examines female representation (based on the proportion of females enrolled and the participant to prevalence ratio, which assesses the representation of a subgroup in a trial relative to their disease burden in the general population) in antithrombotic trials of PAD participants, as well as generalizability of the trial findings to females with PAD in the general population (based on exclusion criteria that limited female enrolment, the presence of sex-based analyses, and the methods by which female sex was collected/reported)

Manuscript Status

This study was presented at the Society for Vascular Surgery (SVS) Vascular Annual Meeting in August 2021 and the Canadian Society for Vascular Surgery (CSVV) Annual Meeting in September 2021 (corresponding abstract can be found in appendix D).

Author Contributions

SAS drafted the manuscript and was responsible for the design, execution, and writeup of the study. SAS, CS, and CH were heavily involved in the data collection and analysis. PJ, DK, DJ, and MC provided invaluable input in designing the study, overseeing the data collection and analysis, and reviewing/editing all versions of the manuscript.

Antithrombotic Therapy Among Females with Peripheral Artery Disease: A Systematic Review and Meta-Analysis of Female-Specific Outcomes

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Abstract:

Background. Sex differences may alter the experience of females with peripheral artery disease (PAD) compared to males. Adequate female enrolment and the presence of a sex-based analysis help to inform whether trial findings are generalizable to females with PAD. The purpose of this study was to evaluate female representation in PAD trials comparing oral antithrombotic regimens, and to assess trial generalizability to females with PAD.

Methods. We conducted a systematic review of MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials for randomized controlled trials comparing dual antiplatelet therapy (DAPT), dual pathway inhibition (DPI), or oral anticoagulation (OAC) +/- mono-antiplatelet therapy (MAPT) to MAPT in participants with PAD. We assessed female representation by calculating the proportion of females with PAD as well as the participation-to-prevalence ratio (PPR). We evaluated trial generalizability based on the presence and type of sex-based analyses and the use of exclusion criteria that limited female enrolment.

Results. The literature search generated 9202 studies, of which 14 met inclusion criteria. Females comprised less than half of trial participants across all studies (excluding one that did not report total females), with female enrollment ranging from 0.7% to 47.5% of PAD participants. The PPR was 0.41, indicating underrepresentation of females with PAD in antithrombotic trials. The majority of studies (n=10 studies, 71.4%) had inclusion/exclusion criteria that exclusively affected females, such as pregnancy. A minority of trials (n= 4 studies, 28.6%) reported sex-based analyses, most commonly in the form of sex-stratification.

Conclusions. Females with PAD are under-represented in trials comparing oral antithrombotic regimens, and caution should be exercised when generalizing trial findings to females with PAD.

Background:

Atherosclerotic cardiovascular disease, including peripheral artery disease (PAD), was historically viewed primarily as a male disease.^{1,2} Clinical research reflected this concept, with females being grossly underrepresented in clinical trials and in some cases, even systematically excluded.^{3–7} More recent epidemiologic studies have challenged the notion of PAD as a male disease, demonstrating that PAD prevalence is likely *at least* equal among the sexes, and perhaps even higher among females.^{8–11} Despite similar disease prevalence, however, there are notable sex differences that affect females' disease experience as well as their access, and potentially, response, to treatment. For example, studies have demonstrated that females with PAD experience worse leg pain and poorer functioning,¹² are more often undiagnosed,¹¹ and are more likely to be admitted to hospital for acute myocardial infarction,¹³ compared to their male counterparts. At the same time, females are less likely to be offered surgical intervention for PAD,¹⁴ and they have unique biological characteristics, such as a higher proportion of body fat composition, delayed gastric emptying time, and menstrual cycle-related blood volume fluctuations, that may impact their metabolism of pharmacotherapy.¹⁵ The differential treatment of females in formative clinical trials—namely, their underrepresentation—has left gaps in our knowledge about the risks and benefits of various therapies, and consequently limited the extrapolation of trial findings to a broader population.^{9,16}

Underscoring the importance of sex and gender differences, multiple leading research institutions have introduced guidelines on the enrollment of, and data analysis as it pertains to, females in clinical trials. Dating back to 1987, the Food and Drug Administration (FDA) issued industry guidance on the inclusion of both sexes of animals in preclinical drug safety studies, followed by the 1988 recommendation that efficacy and safety data be analyzed according to sex.¹⁷ The National Institute of Health (NIH) followed suit: in accordance with the Revitalization Act of 1993, it mandated that all NIH-funded clinical research projects not only *include* women, but also assess whether study outcomes differ for them.¹⁸ Likewise, Canadian Institutes of Health Research (CIHR) adopted the Government of Canada's Health Portfolio Sex- and Gender-Based Analysis Policy and the Tri-Council Policy Statement on Ethical Conduct for Research Involving Humans, which require that research applicants structure sex and gender into their research design and practice where appropriate.¹⁹ Despite these efforts, the American Heart Association

and the Vascular Disease Foundation identified a paucity of research on PAD in women in their 2012 “Call to Action”, urging researchers and clinicians to further explore the basis for sex differences in PAD and to educate female patients on their PAD risk.¹⁶ While campaigns such as the American Heart Association’s “Go Red for Women” have aimed to bridge this gap within cardiovascular research,²⁰ this prudence must extend to the rapidly evolving realm of PAD research as well.

Antithrombotic therapy represents one such area of PAD research that has dramatically changed over the past 15 years. Since the FDA approved the first direct oral anticoagulant (DOAC) in 2010,²¹ a variety of new antithrombotic agents, as well as dosing and combination regimens (such as dual pathway inhibition [DPI], which combines very low dose rivaroxaban twice per day [BID] with daily aspirin) have emerged.²² As vascular guidelines are updated to reflect evolving data,^{23,24} it is important to consider whether females were adequately represented in the formative trials, and whether the trial outcomes can be appropriately extrapolated to the broader female PAD population. The purpose of this study was thus two-fold: to evaluate the representation of females with PAD in trials comparing oral antithrombotic regimens, and to assess the generalizability of these trial findings to females with PAD.

Methods:

Information Sources, Search Strategy and Selection Criteria

The same information sources and search strategy were employed for this study as in the previous chapter (see “Chapter 3. Methods” for full details). Briefly, Medline, Embase, and the Cochrane Central Register of Controlled trials were queried from inception to August 2020 for randomized controlled trials (RCTs) enrolling participants with PAD and comparing dual antiplatelet therapy (DAPT), DPI, or oral anticoagulation (OAC) (with or without mono-antiplatelet therapy [MAPT]) to MAPT alone. The selection criteria were also replicated from the previous chapter, albeit with the following exceptions: 1) trials were included in this analysis *regardless* of whether or not they reported sex-stratified outcomes and/or a sex-based analysis, and 2) trials that did not exclusively enroll PAD participants were excluded *unless* a separate, published PAD subgroup analysis was available (in which case the subgroup analysis, as opposed to the main trial publication, was included). The reason for the deviations from the original protocol for this analysis are that 1) the *absence* of a sex-based analysis is important

when assessing the generalizability of a study's findings to a particular sex, and 2) the representation of females *with PAD* can be more accurately assessed when the overall study population is specific to PAD (as opposed to a trial enrolling a more heterogeneous cardiovascular population, which may not consistently assess for, or report, the presence of PAD). As noted in the previous chapter, all title, abstract and full-text review, as well as data extraction, were performed independently and in duplicate by three study authors (SAS, CS, and CH), with disputes resolved by consensus.

Data Items

Data items collected included study and population characteristics (e.g. trial location, year of publication, definition of PAD, etc.), intervention and comparator details, and efficacy and safety outcomes. Female-specific data was collected including number of females and number of pregnant, postmenopausal, and surgically sterile females enrolled, as well as *how* sex was reported (i.e. whether it was investigator-reported or patient-reported). In addition, data pertaining to female representation (such as proportion of females) and generalizability to females (such as exclusion criteria that disproportionately affects females) were collected, as outlined in detail below. Of note, while sex and gender represent *distinct* entities (with sex referring to an individual's biological characteristics and gender referring to their self-proclaimed identity as a woman, man, or other, as defined within their social/cultural context and experience), these terms may be conflated in the included trials. With this in mind, this study will exclusively use the terms "female", "sex", and "sex-based analysis" to describe the trial populations and analyses, unless a trial has explicitly and accurately defined its use of the terms "woman", "gender", and/or "gender-based analysis" to reflect non-biological characteristics (in which case this study will clearly outline how the population was characterized by the trial authors).

Female Representation

The representation of female patients with PAD was determined by calculating the proportion of females enrolled in the PAD trials, as well as by calculating the participation to prevalence ratio (PPR). PPR is a tool that assesses whether the percent enrollment of a subgroup

(in this case, females) in a trial accurately represents the burden of disease (in this case, PAD) among that subgroup in the general population. It is calculated by dividing the proportion of the subgroup in the trial by the proportion of that subgroup in the general disease population. A PPR between 0.8 to 1.2 indicates adequate representation of the subgroup in the trial, with a PPR less than 0.8 indicating under-representation and a PPR greater than 1.2 indicating over-representation.^{5,25,26} For our PPR calculations, we obtained global epidemiologic data from the Global Burden of Disease Database,²⁷ a public database updated in 2019 by the Institute for Health Metrics and Evaluation (IHME). The IHME is an independent population health research center based out of the University of Washington, which makes their epidemiologic research freely available “so that policymakers have the evidence they need to make informed decisions about how to allocate resources to best improve population health.”²⁸ We used this data to calculate individual PPRs for each trial, as well as a cumulative PPR to assess the representation of females with PAD in antithrombotic trials in general. Recognizing that the prevalence of female sex among PAD patients varies regionally,²⁹ we obtained epidemiologic data from the countries where each trial was conducted (as well as international data for international multi-site trials), and weighted them according to the trial size when tallying the denominator for the cumulative PPR calculation (see appendix G for the detailed PPR calculation).

Generalizability to Females with PAD

The generalizability of the trial findings to females with PAD was assessed qualitatively by examining inclusion and exclusion criteria that disproportionately affected females or limited their recruitment/enrollment (e.g. pregnancy, oral contraceptive use, etc.), as well as by searching for the presence and type of sex-based analyses.

Results:

The literature search identified a total of 9202 studies. After removing 3049 duplicates, 6153 title and abstracts were reviewed in duplicate. Ultimately, 110 studies underwent full-text review, of which 14 studies met inclusion criteria (Figure 1). Among the included studies, eight studies compared DAPT to MAPT, two studies compared DPI to MAPT, and four studies compared OAC +/- MAPT to MAPT alone (Table 1). The majority of studies (n=10, 71.4%) were randomized controlled trials (RCTs) that exclusively enrolled participants with PAD; the

remaining four studies were PAD subgroup analyses from RCTs that originally enrolled a more heterogeneous atherosclerotic population.

Figure 1. PRISMA flow diagram

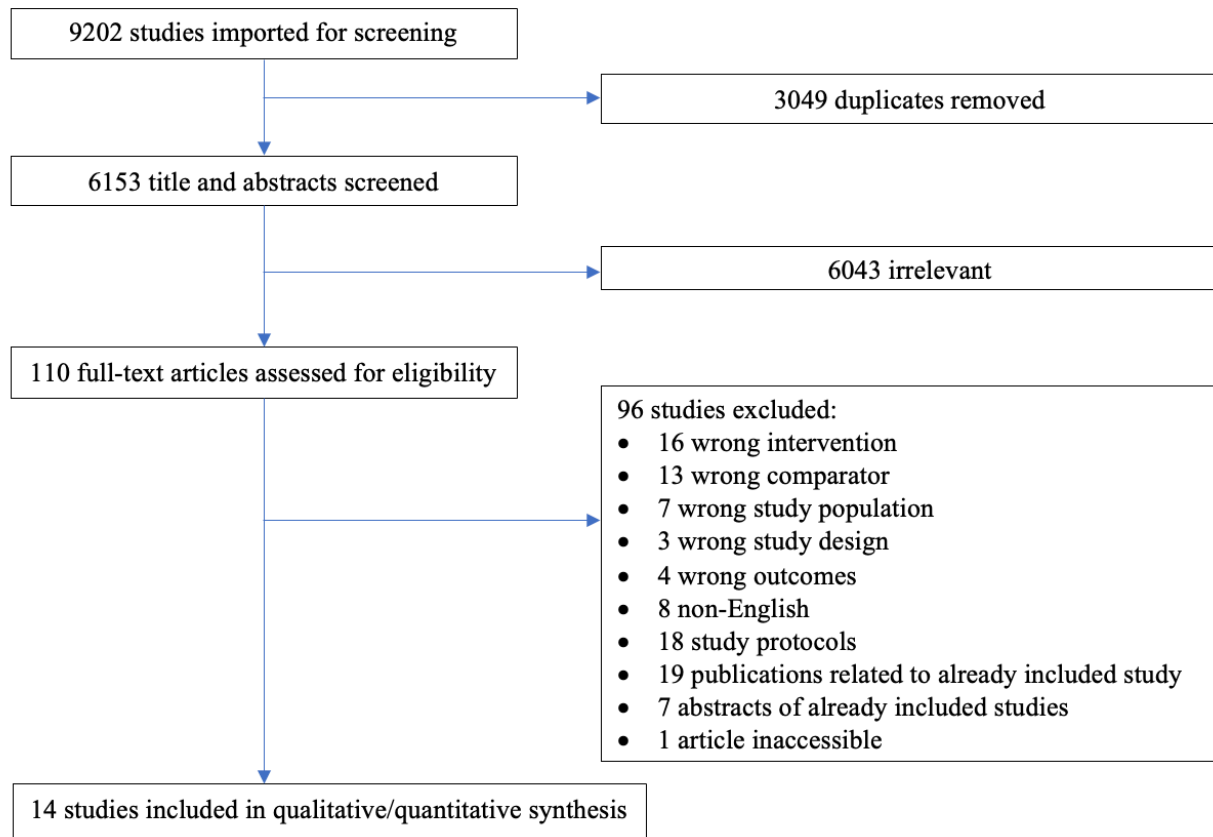


Table 1. Characteristics of the 14 included studies.

Trial or Title	Main trial (PAD-specific) or PAD subgroup	Author, Year, Country	Population	Intervention	Comparator	1° outcome
DAPT vs. MAPT						
“Effects of aspirin and dipyridamole on ePTFE graft patency ³⁰	Main	Green, 1982, USA	Undergoing infrainguinal bypass [for PAD]	Dipyridamole 75 mg + ASA 325 mg TID	Placebo + ASA 325 mg TID	1-year graft patency rate
CRAMPS ³¹	Main	Gresele, 2000, Italy	Intermittent claudicants age 19-74 with stable stage II claudication (Fontaine); initial claudication distance of 50-200 m	Cloricromene 100 mg BID + 160 mg ASA	Placebo BID + 160 mg ASA	Initial claudication distance at 26 weeks

			on treadmill test and absolute claudication distance <500 m; and resting ABI <0.85 in the symptomatic leg			
CHARISMA ³²	PAD subgroup	Cacoub, 2009, International	CHARISMA ³³ trial participants (≥45 years old +: multiple atherothrombotic risk factors or documented CAD, CVD, or PAD) with symptomatic (intermittent claudication [IC] with ABI≤0.85 or history of IC with prior revascularization or amputation) and asymptomatic (ABI<0.90 with risk factors) PAD	Clopidogrel 75 mg daily + ASA 75-162 mg daily	Placebo + ASA 75-162 mg daily	Composite stroke, MI or CV death (including hemorrhage)
CASPAR ³⁴	Main	Belch, 2010, International (Europe/Australia)	Undergoing unilateral below-knee arterial bypass for PAD	Clopidogrel 75 mg daily + ASA 75-100 mg daily	ASA 75-100 mg daily	Index bypass occlusion, endovascular revascularization, above-ankle amputation, or death
MIRROR ³⁵	Main	Tepe, 2012, Germany	Age 35-85 years and ≥1 of: intermittent claudication with objective evidence of PAD (e.g. ABI < 0.9); ischemic rest pain of the lower limbs; ischemic non-healing ulcers or focal gangrene; previous limb amputations due to PAD; previous lower extremity arterial surgery or angioplasty for PAD; blue toe syndrome; other significant PAD (e.g. subclavian stenosis, prior carotid endarterectomy, asymptomatic carotid stenosis >50%, etc.).	Clopidogrel 75 mg daily + ASA 100 mg daily	Placebo + ASA 500 mg daily	Concentration of platelet activation markers using the Chandler-Loop vessel model
PEGASUS-TIMI 54 ³⁶	PAD subgroup	Bonaca, 2016, International	PEGASUS-TIMI 54 ³⁷ trial participants (>50 years old with recent MI + ≥1 of: age ≥65, DM requiring meds, 2 nd prior spontaneous MI, multivessel CAD, CKD) with PAD, defined as ABI≤0.90, history of peripheral revascularization, or history of claudication	Ticagrelor 90 or 60 mg BID + ASA 75-100 mg daily	ASA 75-100 mg daily	Composite CV death, MI, or stroke
CABBAGE ³⁸	Main	Soga, 2017, Japan	Patients ≥20 years old with critical limb ischemia and infrapopliteal disease undergoing endovascular therapy	Cilostazol 200 mg daily + ASA 100 mg daily	Cilostazol 200 mg daily + ASA 100 mg daily	3-month angiographic restenosis rate
TRA2°P-TIMI 50 ³⁹	PAD subgroup	Qamar, 2020, International	TRA2P-TIMI 50 trial participants ⁴⁰ (atherosclerosis history) with PAD (ABI ≤0.90 or >1.3, carotid stenosis ≥50%, prior carotid intervention or peripheral artery revascularization, claudication, and/or prior amputation for limb ischemia)	Vorapaxar 2.5 mg daily + baseline antiplatelet therapy	Placebo + Baseline antiplatelet therapy	Primary CV efficacy outcome was MACE (composite of CV death, MI or stroke). Primary limb efficacy outcome was MALE (composite of hospitalization for ALI, urgent peripheral revascularization, or major amputation due to limb ischemia)

DPI vs. MAPT						
^β COMPASS ⁴¹	PAD subgroup	Anand, 2018, International	COMPASS ⁴² trial participants (≥65 years old with CAD, PAD or both and atherosclerosis in ≥2 vascular beds or ≥2 additional risk factors) with ABI<0.90; prior aortofemoral bypass surgery, limb bypass surgery, percutaneous transluminal angioplasty revascularization of the iliac or infrainguinal arteries; limb or foot amputation for PAD; intermittent claudication + peripheral artery stenosis ≥50%; carotid revascularization or asymptomatic carotid artery stenosis ≥50%	Rivaroxaban 2.5 mg BID + ASA 100 mg once daily	Placebo BID + ASA 100 mg once daily	Composite CV death, stroke or MI
VOYAGER ⁴³	Main	Bonaca, 2009, International	>50 years old with recent (i.e. prior 10d) successful revascularization for symptomatic PAD	Rivaroxaban 2.5 mg BID + ASA 100 mg daily	Placebo + ASA 100 mg daily	composite of ALI, major vascular amputation, MI, ischemic stroke, or CV death
OAC +/- MAPT vs. MAPT						
Warfarin improves the outcome of infrainguinal vein bypass grafting at high risk of failure ⁴⁴	Main	Sarac, 1998, USA	Patients undergoing infrainguinal arterial bypass grafting (for PAD) with autogenous vein at high risk for graft occlusion (e.g. suboptimal venous conduit, poor arterial runoff, or redo infrainguinal bypass grafting)	Warfarin daily (target INR 2-3) + ASA 325 mg daily	ASA 325 mg daily	Graft patency, limb salvage, and operative mortality
DUTCH BOA ⁴⁵	Main	Eikelboom, 2000, Netherlands	Patients requiring infrainguinal bypass graft for obstructive PAD	Phenprocoumon or acenocoumarol daily (target INR 3-4.5)	carbasalate calcium 100 mg daily (metabolizes to aspirin 80 mg)	Graft occlusion
VA Cooperative ⁴⁶	Main	Johnson, 2002, USA	Patients scheduled for elective axillofemoral, femoral-femoral, femoral-popliteal, or femoral-distal bypass surgery	Warfarin daily (target INR 1.4-2.8) + ASA 325 mg daily	ASA 325 mg daily	Assisted primary patency
WAVE ⁴⁷	Main	Anand, 2007, International	Age 35-85 years old with symptomatic lower extremity PAD, symptomatic carotid disease, asymptomatic carotid disease, or subclavian artery occlusive disease	Warfarin or acenocoumarol daily (target INR 2-3) + baseline MAPT (ASA, clopidogrel or ticlopidine)	Baseline MAPT (ASA, clopidogrel or ticlopidine)	Composite CV death, MI, stroke, severe ischemia requiring urgent intervention of the coronary or peripheral artery circulation

DAPT= dual antiplatelet therapy, MAPT= mono-antiplatelet therapy, DPI= dual pathway inhibition, AC= anticoagulation, ASA= acetylsalicylic acid, ABI= ankle brachial index, MI= myocardial infarction, CV=cardiovascular, CAD= coronary artery disease, ALI= acute limb ischemia, CVD= cerebrovascular disease, CKD= chronic kidney disease, PCI= percutaneous coronary intervention, EVT= endovascular therapy

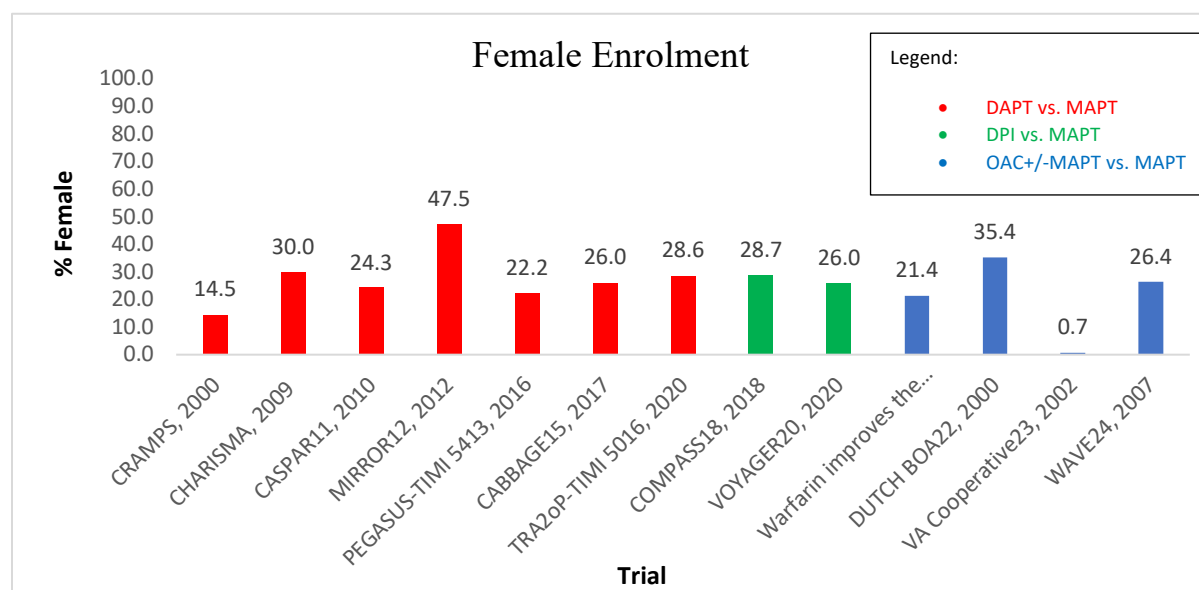
^α Only Dipyridamole + ASA and ASA arms included

^β Only rivaroxaban 2.5 BID + ASA and ASA arms included

Female Representation

The proportion of females enrolled was available for all studies except one, which was notably the oldest trial (published in 1982).³⁰ Females comprised less than half of trial participants in each of the 13 remaining studies, and female enrollment ranged from 0.7% to 47.5% (Figure & Table 2).^{35,46} The proportion of female participants was similar across trials comparing DAPT to MAPT (28.0%), DPI to MAPT (27.2%), and OAC +/- MAPT to MAPT (26.8%). None of the studies specified the proportion of females who were fertile, pregnant, surgically sterile, or postmenopausal (though these characteristics did factor into the inclusion/exclusion criteria of some studies, as will be detailed in the following section on generalizability). Furthermore, none of the studies specified *how* sex was reported (i.e. whether by the study investigators or by the trial participants), nor did they clearly define terms such as “female” or “woman” to indicate whether they were referring to participants’ sex or gender. Individual PPRs calculated for each trial ranged from 0.01 to 0.77 (Table 2),^{35,46} indicating under-representation of females across all trials relative to their prevalence in the PAD population. Likewise, the cumulative PPR (weighted according to trial size and adjusted to geographic location) was 0.41, lending further support that females are underrepresented within PAD cohorts enrolled in antithrombotic trials.

Figure 2. Proportion of females enrolled in studies comparing antithrombotic agents in PAD participants.



Trial Generalizability to Females with PAD

Among the 14 included studies, 10 (71.4%) had inclusion and/or exclusion criteria that limited female enrolment, including pregnancy or intention to become pregnant, breastfeeding, or the requirement to use an “acceptable” form of contraception for those of child-bearing potential (Table 2). Several of the OAC +/- MAPT vs. MAPT trials did not explicitly highlight conditions unique to females in their exclusion criteria; however, by excluding participants with contraindications to the trial medications, they indirectly excluded pregnant participants (since pregnancy is a contraindication to warfarin and coumarin derivatives).^{44–46} A minority of trials (n= 4 studies, 28.6%) reported sex-based analyses, most commonly in the form of sex-stratification (Table 2). While none of the four PAD subgroup analyses (originally from a larger parent study) examined the effect of sex on their study outcomes, it is worth noting that their parent trials did perform sex-based analyses (albeit not unique to the PAD population).^{33,37,40,42,48}

Table 2. Female Representation and Study Characteristics Impacting Generalizability to Females

	Trial Name or Title, Year of Publication	Female Proportion of PAD cohort (%)	Exclusion Criteria Limiting Female Enrollment	PPR	Presence of Sex-Based Analysis?	Type of Sex-Based Analysis
DAPT vs. MAPT	^a Effects of aspirin and dipyridamole on ePTFE graft patency ³⁰ , 1982	[not reported]/32 (--)	No exclusion criteria reported	N/A	No	N/A
	CRAMPS ³¹ , 2000	23/159 (14.5)	Pregnancy	0.21	No	N/A
	CHARISMA ³² , 2009	930/3096 (30.0)	None	0.45	No	N/A Note: original trial (not PAD-specific) did report sex-stratified data
	CASPAR ³⁴ , 2010	207/851 (24.3)	None	0.36	Yes	Multivariate analysis

	MIRROR ³⁵ , 2012	38/80 (47.5)	Childbearing potential or existing pregnancy	0.77	No	N/A
	PEGASUS-TIMI 54 ³⁶ , 2016	254/1143 (22.2)	Pregnancy, lactation, females of child-bearing potential who are not willing to use a medically accepted method of contraception that is considered reliable in the judgment of the investigator	0.33	No	N/A Note: original trial (not PAD-specific) did report sex-stratified data
	CABBAGE ³⁸ , 2017	13/50 (26.0)	None	0.34	No	N/A
	TRA2°P-TIMI 50 ³⁹ , 2020	1756/6136 (24.3)	Pregnant or intending to become pregnant, breastfeeding, women of childbearing potential who are sexually active and do not agree to use contraception	0.43	No	N/A Note: original trial (not PAD-specific) did report sex-stratified data
DPI vs. MAPT	βCOMPASS ⁴¹ , 2018	1435/4996 (28.7)	Subjects who are pregnant, breastfeeding, or are of childbearing potential and sexually active and not practicing an effective method of birth control	0.43	No	N/A Note: original trial (not PAD-specific) did report sex-stratified data
	VOYAGER ⁴³ , 2020	1704/6564 (26)	Pregnancy, women of reproductive potential who do not agree to use adequate contraception when sexually active	0.39	Yes	Sex stratification
OAC +/- MAPT vs. MAPT	Warfarin improves the outcome of infrainguinal vein bypass grafting at high risk of failure ⁴⁴ , 1998	12/56 (21.4)	Contraindication anticoagulation therapy (though not explicitly stated, warfarin is contraindicated in pregnancy)	0.38	No	N/A
	DUTCH BOA ⁴⁵ , 2000	952/2690 (35.4)	Contraindication to one of the trial medications (though not explicitly stated, coumarin derivatives are contraindicated in pregnancy)	0.58	Yes	Sex stratification and cox proportional hazards models
	VA Cooperative ⁴⁶ , 2002	6/831 (0.7)	Contraindication to one of the trial medications (though not explicitly stated, warfarin is contraindicated in	0.01	No	N/A

			pregnancy); note also that study was conducted at veteran affairs hospitals			
	WAVE ⁴⁷ , 2007	570/2161 (26.4)	Pregnancy or planning to become pregnant	0.39	Yes	Sex stratification

^α Only Dipyridamole + ASA and ASA arms included

^β Only rivaroxaban 2.5 BID + ASA and ASA arms included

Discussion:

This systematic review revealed that females with PAD are underrepresented in antithrombotic trials relative to their disease burden in the broader PAD population. This pattern was consistent across trials comparing DAPT to MAPT, DPI to MAPT, and OAC with or without MAPT to MAPT alone. Inclusion/exclusion criteria targeting female subgroups (such as pregnancy) were present in the majority of trials and may have impacted the disproportionate enrolment rates between the sexes. Combined with a lack of sex-based analyses within the PAD cohorts of these trials, these findings raise doubt about the generalizability of trial outcomes and their ability to inform clinical practice guidelines.

Our findings echo those of other studies examining female representation in cardiovascular trials, albeit with some variability depending on the disease process.^{3,5,6,49} Female under-enrolment appears to be the norm for vascular surgery trials, as was demonstrated by a review of 52 RCTs on aortic aneurysm repair, carotid revascularization, or lower extremity revascularization, which identified that women were disproportionately underrepresented across all procedure categories.³ Likewise, a 2020 systematic review on the participation of women and older participants in RCTs of lipid-lowering therapies found that women were consistently under-represented relative to their disease burden in trials of diabetes (PPR 0.74), heart failure (PPR 0.27), stable coronary heart disease (PPR 0.48), and acute coronary syndrome (PPR 0.51).⁵ In contrast, a recent study that examined FDA reviews for 36 cardiovascular drug approvals found that females were adequately represented relative to their disease burden in trials examining atrial fibrillation, hypertension, and pulmonary arterial hypertension (PPR 0.8-1.1, 0.9, and 1.4, respectively), but under-represented in heart failure, coronary artery disease, and acute coronary syndrome/myocardial infarction trials (PPR 0.5-0.6, 0.6, and 0.6, respectively).⁶ Notably, four of these drugs described gender differences in efficacy or safety in their drug

labeling. This not only underscores the importance of diversifying trial participants so that subgroup nuances are identified, but also demonstrates a method to communicate these findings to the public (i.e., by including it in the drug labeling) and empower them to make informed healthcare decisions.

Several factors may account for the discrepancies in female enrolment in the antithrombotic trials included in our review. As previously mentioned, prohibitive inclusion/exclusion criteria often discriminate against females, though not necessarily with derogatory intent. For example, pregnancy or criteria related to pregnancy (such as lactation or refusal to use contraception in a female of child-bearing potential) are often cited in exclusion criteria,⁵ as it would be unethical to subject females or their offspring to potentially harmful or teratogenic medications. This is particularly relevant when studying anti-thrombotics, since early data has raised concerns about rates of miscarriage and fetal/neonatal abnormalities with DOAC use in pregnancy, and several studies have demonstrated increased risk of fetal malformations with the use of vitamin K antagonists.^{50,51} In addition, females of child-bearing age are not the only age group excluded from pivotal RCTs; indeed, older participants are frequently underrepresented in cardiovascular trials.^{3,5,52} Since females with PAD tend to present to medical attention at older ages than males,^{2,14,53,54} exclusion of older participants likely compounds females' disproportionate enrolment in these trials. Restricting trial participation to older age groups may help address both of these barriers to female enrolment in future RCTs. Alternatively, strategies such as matching (by sex or other important risk factors) can be used when enrolling participants, and when unavoidable discrepancies in enrolment are anticipated, the study design can help account for this (e.g., using a crossover study design, or incorporating a prespecified sex-based analysis so that the trial is adequately powered to detect important differences).⁵⁵

Unfortunately, in addition to low female enrolment, this review identified a lack of sex-based analyses among the included trials. When exploring the reasons for this, it is important to consider that four of the 15 studies were subgroup analyses of the PAD subset within an originally larger and more heterogeneous trial.^{32,36,39,41} Thus, statistical power would have been reduced with every further subgroup analysis performed on the PAD participants and may not have provided meaningful information. Furthermore, these *sub*-subgroup analyses would be

subject to confounding by both known and unknown variables due to loss of the randomization node in the post-hoc analyses. It is notable that all four of these trials did incorporate sex-based analyses in their original, main trial populations,^{33,37,40,48} suggesting that the study authors may have deliberately omitted a sex-based analysis from the PAD subgroup for good reason (i.e., due to the potential for bias in a post-hoc subgroup analysis that has lost its randomization).

There are a number of limitations to this study. As discussed above, since we included studies that focused on the PAD *subgroup* of an originally larger trial, as opposed to limiting this review to trials that were exclusive to PAD participants, sex-based analyses may not have been practical or meaningful for all studies even if they *had* been available. Nevertheless, given that these pivotal RCTs influenced vascular guidelines and the management of PAD patients, we felt that it was important to capture them in this study. Another limitation was the availability (or rather, lack thereof,) of reliable and up-to-date epidemiologic data on PAD. For the sake of consistency when calculating PPRs, we opted to use the IHME database when calculating the burden of PAD among females in different parts of the world. As per the IHME, their 2019 global health data has largely been collected from partners,⁵⁶ who estimated PAD prevalence using different methods and/or classified the disease differently.⁵⁷ For example, some data sources, such as one particularly large population-based study out of China, evaluated PAD prevalence using population-based screening methods such as an ankle brachial index,⁵⁸ which would capture a high rate of asymptomatic disease, while other data sources, such as one particularly large population-based study out of Sweden, focused primarily on clinical diagnoses such as critical limb ischemia.¹⁰ This is an important distinction, considering that females have a higher incidence of asymptomatic PAD compared to males^{59,60} and that most vascular guidelines do not recommend routine antithrombotic therapy in patients with asymptomatic PAD.^{24,61} Thus, it could be argued that the PPR for antithrombotic trials should be calculated based on the prevalence of females with *symptomatic* PAD in the global population, in which case the PPRs in this study would likely be an underestimate. Future studies may opt to query a variety of different databases to increase their confidence in the estimates of PAD prevalence (especially symptomatic PAD), and calculate/interpret their PPRs accordingly.

Finally, it is important to distinguish between sex and gender and to highlight that these terms are often conflated in cardiovascular research (including in the trials that comprised this

review). Sex reflects biological characteristics, such as anatomy, hormones, and genetics, whereas gender is a social construct that may be self-ascribed (meaning that a person who is biologically male may choose to identify as a man, woman, or other, and vice versa).⁶² While both sex and gender can impact health outcomes, they do so in different ways. In the context of PAD and antithrombotic therapy, certain medications may increase the risk of menorrhagia or hemorrhagic ovarian cysts, which are important female sex characteristics to consider when designing these clinical trials.⁶³ In contrast, the effects of gender on PAD experience and outcomes are not as clearly defined, but are likely influenced by the complex interplay between gender, environment, and other social categories such as race and socioeconomic status.² These differences illuminate potential pitfalls for trials that fail to define their use of sex and gender and neglect to report how male/female classification was assigned during data collection. As awareness of gender identity—and its distinction from biological sex—increases, PAD research can benefit from routinely and clearly accounting for sex and gender in trial structure and analysis.

Conclusions:

Females with PAD comprise a small proportion of antithrombotic trial participants, and they are under-represented in these trials relative to their PAD disease burden. Eligibility criteria disproportionately affects female enrollment in antithrombotic PAD trials, and sex-based analyses are lacking. These findings suggest that antithrombotic trial outcomes may not be generalizable to the broader female PAD population, and that the effects of both sex and gender on trial outcomes should be considered carefully when shaping clinical practice guidelines.

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Chapter 6: Discussion

6.1 Discussion Introduction

The purpose of this thesis was to assess female-specific efficacy and safety outcomes with different antithrombotic regimens in trials enrolling patients with PAD, to explore the representation of females with PAD in antithrombotic trials, and consequently, to determine the generalizability of antithrombotic trial findings to the broader female PAD population. This discussion chapter will summarize the findings of the three thesis component articles; contextualize these findings within the current state of CV research; and finally, highlight special considerations for females with PAD in the design of future trials.

6.2 Summary of Findings

While many comprehensive systematic and narrative review studies have explored the risks and benefits of antithrombotic regimens in PAD patients, none has looked specifically at the female subset. In chapter three, we outlined a protocol for a systematic review and meta-analysis that would focus on clinical efficacy and safety outcomes, such as arterial thrombotic events (including MI, stroke, CV death, and ischemic limb events) and bleeding, in randomized controlled trials enrolling females with PAD. The review would explore three comparisons of interest: DAPT versus MAPT, DPI versus MAPT, and OAC +/- MAPT versus MAPT).

Chapter four reported the findings of said systematic review and meta-analysis. In trials enrolling PAD patients and comparing antithrombotic regimens, females experienced increased rates of bleeding with DAPT (pooled HR 1.42; 95% CI 1.08-1.86), DPI (pooled OR 2.11; 95% CI 1.42-3.13), and OAC +/- MAPT (pooled RR 3.24; 95% CI 1.98-5.31) compared to MAPT alone. Further, DAPT did not reduce rates of composite CV death, MI or stroke (pooled HR 0.68; 95% CI 0.68-1.04;), nor did DPI reduce composite CV or limb events (pooled OR 0.85; 95% CI 0.65-1.10) compared to MAPT. CV and limb efficacy data could not be pooled for the OAC +/- MAPT versus MAPT trials due to heterogeneity in the reported outcomes; however, each trial found that females did not confer any benefit from OAC +/- MAPT over MAPT alone with respect to CV and/or limb events. We therefore concluded that, among females enrolled in

antithrombotic CV trials (including PAD participants), DAPT, DPI, and OAC +/- MAPT offer no benefit over MAPT alone and may introduce harm.

In the following chapter, we conducted a systematic review that employed the same literature search strategy as outlined in chapters three and four, albeit with two notable differences: 1) this systematic review included only studies that were exclusive to PAD participants, and 2) it focused on female representation by examining the proportion of females enrolled (and the method of recording female sex), the participant to prevalence ratio (PPR), inclusion criteria that disproportionately limited female enrolment, and the presence of a sex-based analysis. This study revealed that females comprised 28.0%, 27.2%, and 26.8% of participants in trials comparing DAPT and MAPT, DPI and MAPT, and OAC +/- MAPT and MAPT, respectively. No trials reported *how* female sex was tallied, and a minority of trials (n=4, 28.6%) reported a sex-based analysis. The vast majority of trials (n=10, 71.4%) listed exclusion criteria that disproportionately affected females (e.g., pregnancy), and the PPR across all trials was 0.41, indicating underrepresentation of females with PAD relative to their disease burden in the broader population. Taken together, the component articles outlined in chapters three through five suggest that, while females with PAD may not benefit from more intensive antithrombotic therapy compared to MAPT alone, generalizability of antithrombotic trial findings is significantly limited by lack of female enrollment, female representation, and sex-based analyses within these trials.

6.3 Impact of Female Sex and Gender on PAD and Current State of the Literature

There are many reasons to explore the potential impact of female sex and gender on therapy outcomes in patients with PAD, and to consider the proper tools for eliciting these differences in randomized trials. Covering all of these factors is beyond the scope of this thesis; however, we will briefly summarize select biological and social factors that may affect females' experience with PAD and its treatment, and highlight barriers to uncovering these differences in the design and execution of trials.

From a biological standpoint, there are hormonal, anatomic, genetic, pregnancy-related, and metabolic factors unique to females that may influence their course of PAD and their response to treatment.^{1,2} Estrogen—and its differential effects on the vascular system when produced

endogenously versus exogenously—is one of the most important factors, and unsurprisingly, it represents a focal point of CV research.^{3–7} Estrogen interacts with the vascular system in various and complex ways, including altering cholesterol levels (increasing high- and decreasing low-density lipoprotein), reducing inflammation, modulating vasodilation and constriction, and paradoxically enhancing *both* pro- and anti-coagulant pathways.^{1,3} Yet, despite evidence of an association between decreasing endogenous estrogen levels seen in menopause and increasing endothelial dysfunction (and subsequent development of atherosclerosis and PAD),¹ large trials such as the Women’s Health Initiative⁸ and the Heart and Estrogen/Progestin Replacement Study^{5,7} have found no reduction in CV events such as MI, stroke, or PAD in postmenopausal females on hormone replacement therapy (and in some instances, they revealed *increased* rates of thromboembolic events).^{4,5,7–9} This is relevant to antithrombotic trials not only because estrogen levels may affect the outcomes of interest (e.g., rates of MI, stroke, and limb ischemia), but also because hormone therapy is a primary *treatment* option for several antithrombotic side effects, such as abnormal uterine bleeding and hemorrhagic ovarian cysts. While these particular side effects are rarely listed as outcomes of interest in ground-breaking antithrombotic trials, they plague anywhere from 4% to 66% of females on anticoagulation and adversely affect their quality of life, adherence to therapy, and clinical outcomes.^{10–12}

Our analysis discussed in chapter four revealed that, in contrast to current guidelines and the overall COMPASS and VOYAGER trial findings,^{13–17} females with atherosclerosis (and specifically, PAD) did not benefit from DPI over MAPT alone and actually faced greater risk. Considering the complex interplay between estrogen and the aging vascular system, as well as the elderly populations that were studied in both of these trials (mean age=late 60s for each), it is possible that declining endogenous estrogen levels and/or high rates of exogenous hormone replacement therapy blunted the benefits, or confounded the risks, of DPI in this largely postmenopausal female population. This underscores the importance of studying sex differences in clinical outcomes, as well as the biological basis that might account for them. Furthermore, it is notable that the risk of abnormal uterine bleeding differs between anticoagulants, and that treatment options that avoid estrogen are available for abnormal uterine bleeding as well.^{10,18} By factoring these considerations into randomized trials, maintaining a high index of suspicion for outcomes that are *triggered* and *treated* by estrogen, and structuring sex-specific analyses into trial design, researchers can help empower females and their healthcare providers to make

informed decisions about selecting the appropriate antithrombotic therapy, as well as treatments for its side effects.

Though not the primary focus of this thesis, gender—characterized by social factors that shape one’s identity as a man, woman, or other—may also impact PAD experience. As a social construct, gender classifications vary with time and place (in contrast to sex, which refers to biological differences that generally do not change).^{19,20} While there is now increasing awareness about the distinction between sex and gender, these definitions were historically often conflated in medical literature, with gender frequently used as a misnomer for sex. The fluidity in gender’s definitions and the inconsistency in its use have made gender particularly challenging to study as it relates to PAD. Researchers have speculated that social characteristics, such as women’s tendency to focus on their family’s needs over their own, or to brush aside mild symptoms until they reach a severity that can no longer be ignored, may account for unique aspects of women’s PAD experience, including their older age and more advanced stage of disease at the time of presentation.^{21,22} These remain *theories*, however, and before we can confidently draw associations between gender and PAD outcomes (let alone infer the reasons behind them), we must first learn to accurately collect data on sex and gender. Researchers need to be explicit and clear in their questions and definitions, while remaining respectful and inclusive when collecting responses (for example, gender should not be limited to a binary set of “woman” or “man,” and participants should not be assumed to identify with the sex that they were assigned at birth). These distinctions are particularly important in the field of vascular surgery, where biological sex impacts clinical decision-making (for example, screening recommendations and thresholds for repair for abdominal aortic aneurysms), and conflating one’s sex and gender could compromise that patient’s care.¹⁹

Finally, our findings in chapter five, which highlighted the under-enrolment of females with PAD in antithrombotic trials, unfortunately accurately reflect the current state of vascular research. Previous studies have exposed the ubiquity of female exclusion and under-representation in trials throughout the vascular system (from the carotids to the legs),²³ and the American Heart Association has urgently called on researchers to bridge the sex and gender gap in PAD, and more broadly—CV, research.^{24,25} While initiatives such as the “Go Red for Women” campaign have helped fund this type of research and raise public awareness about CV

disease in females, reforms are still needed to improve the way that sex and gender are studied in PAD research, incorporated into practice guidelines, and considered in clinical decision-making. This can happen both at the micro level (e.g., by integrating sex/gender issues into study design) and the macro level (e.g., by promoting *cultural* changes in vascular research, bringing females onto editorial boards and into leadership positions, and amplifying the voices of females suffering from the disease we strive to treat).

6.4 Future Directions

This thesis established that the benefits of DAPT, DPI, and/or OAC +/- MAPT in females with atherosclerosis and/or PAD do not outweigh their risks compared to MAPT alone, despite current PAD guidelines increasingly advocating for the use of DPI. However, given the under-representation of females within these trials relative to their PAD burden, as well as the lack of sex-based analyses and the presence of discriminatory inclusion criteria, these findings must be interpreted with caution and cannot confidently be generalized to the broader female PAD population. With this in mind, there are changes that can be incorporated more specifically into trial design, as well as more broadly into the culture of vascular research and clinical care.

Beginning with trial design, improvements can be made with respect to female recruitment/enrolment, incorporation of prespecified sex- and gender-based analyses, and consideration of risk factors and adverse outcomes that are unique to females. To improve female recruitment and enrolment, researchers can match participants by sex during the enrolment process; design female-specific trials; or restrict enrolment to older age groups so that concerns about female fertility and drug interactions weigh less on the trial demographics. Researchers could also invest in publicizing their trials in female-centered spaces (such as women's gyms or women's health clinics) to enhance trial recruitment and encourage dialogue about PAD. When designing the trials, researchers should take care to pre-specify sex-based analyses so that they can power the trial accordingly and draw meaningful conclusions. During the data collection process, they should consider female-specific factors that may impact their outcomes of interest, such as use of hormone replacement therapy or oral contraception, or history of pregnancy-related complications (such as preeclampsia, gestational hypertension, placental infarction, etc.), which are associated with an increased risk of CV events later in life.²⁶

Finally, when selecting outcomes of interest, researchers should consider female-specific consequences of the intervention being studied, which may pose safety concerns and/or impairments to quality of life (such as abnormal uterine bleeding). Since abnormal uterine bleeding may not present as overtly as gastrointestinal or intracranial bleeding, it is insufficient to expect these events to be captured in a blanket “bleeding” safety outcome; rather, participants should be explicitly educated about the risk of abnormal uterine bleeding while on antithrombotic therapy and when to report it, and researchers should have a low threshold to monitor hemoglobin and ferritin levels in this at-risk population.

In order to sustain changes that improve the representation and analysis of females in research and its translation to clinical care, systemic changes in the field of vascular surgery and CV research are needed as well. This starts with enhancing female representation within vascular leadership and on vascular editorial boards, and extends to funding research on vascular disease in females, upholding research regulations that mandate adequate female representation and sex-based analyses, enhancing awareness about PAD in females among primary care providers and the public, and engaging females with PAD in their care. It is noteworthy that two of North America’s leading vascular practice groups—the Society for Vascular Surgery (est. 1947) and the Canadian Society for Vascular Surgery (est. 1979)—have had only one and two female presidents, respectively, since their inceptions. Nevertheless, progress is being made: in June of 2022, the outgoing editor-in-chief and senior editor of the *Journal of Vascular Surgery* (arguably the field’s most prominent journal) proudly announced in their farewell address, “We have considerably transformed our editorial policies, increased the diversity of our editorial boards and included more than 25% more women and underrepresented minorities.”²⁷ Furthermore, major research institutes, such as the Canadian Institutes of Health Research (CIHR) and the National Institute of Health (NIH), adhere to government policies that mandate sex- and gender-based analyses and are dedicated to educating medical researchers on its importance.^{28,29}

Yet, there is still progress to be made. Previous studies have demonstrated a lack of awareness of PAD among both females at risk for CV disease as well as primary care providers.^{30,31} Fostering relationships between vascular specialists and primary care providers (for example, by incorporating vascular education into family medicine residency training and continuing medical education seminars) can help improve primary care physicians’ knowledge

on vascular disease and lower their threshold to test for PAD (especially in females, who may present atypically). This, in turn, can help increase diagnosis and awareness among the general public, and connect patients with specialized care when they need it. Finally, it is important to engage patients in their care and to elicit feedback from participants in clinical trials. Focus groups comprised of females with PAD can provide a platform for patients to speak about the symptoms and medication side effects that they find most bothersome. With a better understanding of what matters most to patients, researchers can identify treatments that not only are effective and safe, but also offer higher rates of compliance.

6.5 Conclusions

Antithrombotic therapy is fundamental to the treatment of patients with PAD, however there is limited data on female-specific outcomes and female representation in antithrombotic trials. We found that females did not benefit from more intensive antithrombotic therapy (whether DAPT, DPI, or OAC +/- MAPT) compared to MAPT alone in trials evaluating participants with PAD. Low female enrolment, female under-representation relative to their PAD burden, and lack of sex-based analyses limited the generalizability of these findings to the care of the broader female PAD population.

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Appendices

Appendix A. BMJ Open

Open access

Protocol

BMJ Open Antithrombotic regimens in females with symptomatic lower extremity peripheral arterial disease: protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction Patients with peripheral arterial disease (PAD) are at increased risk for systemic arterial thromboembolic events. Females represent a unique subset of patients with PAD, who differ from males in important ways: they have smaller diameter vessels, undergo lower extremity bypass less frequently and experience higher rates of graft occlusion, amputation and mortality than males. Females also trend towards higher rates of major coronary events and cardiovascular mortality. Current guidelines recommend monoantiplatelet therapy (MAPT) for secondary prevention in patients with symptomatic PAD. However, indications for more intensive antithrombotic therapy in this cohort—especially among females who are frequently under-represented in randomised controlled trials (RCTs)—remain unclear. As newer antithrombotic therapies emerge, some RCTs have demonstrated differential effects in females versus males. A systematic review is needed to quantify the rates of arterial thromboembolic and bleeding events with different antithrombotic regimens in females with symptomatic PAD.

Methods and analysis We will search MEDLINE, Embase and the Cochrane Central Register of Controlled trials for published RCTs that include females with symptomatic PAD and compare full dose anticoagulation+antiplatelet therapy, dual pathway inhibition or dual antiplatelet therapy with MAPT. Title, abstract and full-text screening will be conducted in duplicate by three reviewers. Authors will be contacted to obtain sex-stratified outcomes as needed. Risk of bias will be assessed using the Cochrane Risk of Bias tool. Data will be extracted by independent reviewers and confirmed by a second reviewer. Quantitative synthesis will be conducted using Review Manager (RevMan) V.5 for applicable outcomes data. Planned subgroup analysis by PAD severity, vascular intervention and indication for antithrombotics will be conducted where data permits.

Ethics and dissemination Ethics approval is waived as the study does not involve primary data collection. This review will be submitted for publication in a peer-reviewed journal and for presentation at national and international scientific meetings.

Trial registration number This protocol was registered with the PROSPERO International Prospective Register of Systematic Reviews (ID# CRD42020196933).

Strengths and limitations of this study

- This protocol was reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols guidelines.
- This review offers a broad search strategy to capture all studies that might include the population of interest, including as a subset of a larger sample.
- This review addresses an important gap in the literature by targeting female-specific vascular outcomes.
- This review will not be limited by language or date specifications.
- Depending on the availability of sex-stratified data, quantitative synthesis may not be possible for all outcomes of interest.

INTRODUCTION

Rationale

Lower extremity peripheral arterial disease (PAD) is common, affecting approximately 800 000 Canadians and over 200 million people worldwide.^{1,2} Patients with large-vessel PAD are at increased risk for arterial thromboembolic events compared with those without, with a 5.9-fold increased risk of death from all cardiovascular (CV) causes and a 6.6-fold increased risk of death from coronary heart disease.³ Among patients with severe, untreated PAD, 1-year mortality and amputation rates reach 22%.⁴ While previous demographic data have yielded mixed findings about the distribution of PAD across sexes,^{5–9} more recent studies have revealed the prevalence to be at least equal, if not higher, in females compared with males.¹⁰ Despite similar distributions of the disease, females with PAD differ from males in a number of important ways,^{10–12} including higher functional impairment, lower likelihood of undergoing lower extremity bypass and, potentially, higher bleeding risk.^{13–19} Among females who do undergo lower extremity bypass, rates of graft occlusion,

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amputation and mortality are higher than in males.^{16 20} Females with PAD also trend towards higher rates of CV mortality and major coronary events as compared with their male counterparts.¹⁰ Smaller diameter vessels, older age at presentation, hormonal differences and greater number of comorbidities may explain the discrepancy in treatment, risks and outcomes between the sexes.^{11 19}

To mitigate the risk of arterial thromboembolic events, antithrombotic therapy has become a fundamental component of the management of symptomatic PAD.^{21 22} Antithrombotic therapy refers to antiplatelet agents and/or anticoagulants, which target different steps in the coagulation cascade. Antiplatelet agents interfere with platelet activation, adhesion and aggregation through various mechanisms, such as thromboxane A1 inhibition (aspirin), ADP receptor antagonism (P2Y₁₂ inhibitors such as clopidogrel) and glycoprotein IIb/IIIa inhibition (eg, abciximab).²³ In contrast, anticoagulants primarily affect secondary haemostasis by targeting components of the coagulation cascade. For example, vitamin K antagonists, such as warfarin, impair the activity of vitamin K dependent clotting factors,²³ and direct oral anticoagulants, such as dabigatran and rivaroxaban, inhibit factor IIa (thrombin) and factor Xa, respectively.^{24 25} Finally, dual pathway inhibition (DPI), which combines very low dose anticoagulation (typically rivaroxaban) with antiplatelet therapy (typically aspirin), is thought to synergistically reduce thromboembolic risk by inhibiting platelet activation and attenuating thrombin generation.²⁶ Careful consideration of the patient's comorbidities, characteristics, intrinsic thrombogenicity and indication for—as well as response to—antithrombotic therapy must guide selection of the appropriate regimen.

The benefits of antiplatelet therapy are well documented in the Antithrombotic Trialists' Collaboration meta-analysis, which demonstrated a significant reduction in non-fatal stroke, non-fatal myocardial infarction (MI) and CV death with antiplatelet therapy in patients at high risk for vascular occlusive events ($p=0.004$).²⁷ However, with more intensive antithrombotic therapy, there is ambiguity surrounding which PAD populations benefit most. The CHARISMA trial, which compared dual antiplatelet therapy (DAPT) with aspirin alone, revealed no reduced risk in the PAD subgroup with respect to the composite outcome: CV death, MI or stroke.²⁸ Likewise, in the CASPAR trial, DAPT did not significantly reduce the composite outcome of index graft occlusion or revascularisation, ipsilateral above-ankle amputation or death compared with aspirin alone in patients with recent below-knee bypass for PAD.²⁹ However, in another CHARISMA subgroup analysis that combined patients with prior MI, stroke or symptomatic PAD, DAPT significantly reduced rates of the composite outcome in patients with atherosclerotic disease in multiple vascular beds.³⁰ In PAD patients undergoing lower extremity endovascular revascularisation, a number of trials have compared DAPT with monoantiplatelet therapy (MAPT), with no clear consensus about its benefits.^{31–33}

There are also several trials that examined the use of full dose anticoagulation in patients with PAD. One demonstrated that anticoagulation in addition to antiplatelet therapy did not reduce rates of MI, stroke or CV death in patients with symptomatic PAD³⁴; one demonstrated that anticoagulation did not reduce rates of graft occlusion compared with aspirin in patients who underwent infrainguinal bypass grafting³⁵; one demonstrated that anticoagulation increased graft patency at the cost of increased perioperative haematoma in high-risk patients undergoing vein bypass grafting³⁶; and a few additional studies examining different anticoagulation versus antiplatelet comparisons in PAD patients offered no conclusive evidence.³⁷ The question of whether particularly high-risk PAD patients—such as those undergoing bypass therapy with a specific type of graft—may benefit from the addition of full dose anticoagulation remains.

Recently, DPI has emerged as an antithrombotic option in patients at high risk for CV events. In particular, very low dose (2.5 mg two times per day) rivaroxaban in combination with aspirin gained popularity after publication of the COMPASS trial, which demonstrated a reduction in major adverse cardiac events (CV death, stroke and MI) with DPI compared with aspirin alone in patients with stable CV disease.³⁸ This study led to its approval in Canada for secondary prevention in patients with coronary artery disease or symptomatic, high-risk PAD.³⁹ The VOYAGER trial followed, demonstrating a reduction in the composite outcome of acute limb ischaemia, major amputation for vascular causes, MI, ischaemic stroke or CV death with the addition of very low dose rivaroxaban to aspirin in PAD patients with recent lower extremity revascularisation.⁴⁰ While no heterogeneity was observed in the efficacy of DPI between sexes, sex-stratified analyses revealed that neither the primary efficacy nor safety outcome was statistically significant in females. Since the trial was not powered to detect a difference in the female subgroup, it can be difficult to interpret the clinical significance of these findings. Pooling the data from similar trials may uncover interesting trends according to sex and inform clinical practice guidelines, which are currently in evolution.⁴¹

The existing data have led to uncertainty about optimal antithrombotic therapy in patients with PAD; however, the ambiguity is even more pronounced within the female subpopulation. Despite differences between males and females with PAD,^{10–17} females are consistently under-represented in vascular trials.^{42 43} Females have also demonstrated different responses than males to vascular interventions in other vascular beds; for example, males with asymptomatic carotid stenosis derived benefit from carotid endarterectomy while females did not.⁴⁴ Yet, sex is not currently factored into decision-making algorithms for antithrombotic therapy for PAD in clinical practice guidelines.^{22 41 45} In 2012, the American Heart Association released a statement that highlighted the differences between males and females with PAD and stressed the need for sex-specific CV research.¹⁰ This study aims to

respond to that call by systematically reviewing the literature on rates of arterial thromboembolic and bleeding events with different antithrombotic regimens in females with symptomatic PAD.

Objective

To systematically review the literature reporting efficacy and safety outcomes of various antithrombotic regimens with respect to arterial thromboembolic and bleeding events in females with symptomatic PAD.

METHODS

Protocol and registration

This protocol was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) guidelines (see online supplemental appendix A for PRISMA-P Reporting Checklist).⁴⁶ The protocol was registered with the PROSPERO International Prospective Register of

Systematic Reviews (ID# CRD42020196933). If changes to the protocol are required, we will report deviations from the original protocol and rationale with transparency.

Eligibility criteria

Inclusion and exclusion criteria are presented in table 1.

Information sources

We will search MEDLINE, Embase and the Cochrane Central Register of Controlled trials. The information sources will be supplemented by searching registered clinical trials on ClinicalTrials.gov and the International Standard Randomised Controlled Trials Number database. Grey literature will be excluded. We will also scan the reference list of systematic reviews of similar scope and included trials to ensure that all relevant studies are captured. If sex-stratified outcomes are not reported for studies that otherwise meet inclusion criteria, authors will be contacted to request sex-stratified data.

Table 1 Eligibility criteria

	Inclusion	Exclusion
Study design	▶ Randomised controlled trials. ▶ If the number of RCTs meeting inclusion criteria proves limited, we will broaden the search strategy to include prospective and retrospective cohort studies.	▶ Cross-sectional. ▶ Case-control. ▶ Case series with <10 patients. ▶ Case reports.
Population*	▶ Females with symptomatic PAD, defined as atherosclerotic disease of the lower extremities causing intermittent claudication, rest pain or tissue loss and/or necessitating endovascular or open surgical revascularisation and/or amputation. ▶ Diagnosis of PAD will be at the discretion of each trial, whether by clinical assessment, self-report or objective diagnostic criteria (including ankle brachial index, duplex ultrasound, CT, MRI or angiography). ▶ Sex-stratified outcomes must be published or available on request to the authors.	▶ Males. ▶ Asymptomatic PAD. ▶ Trials focused specifically on the management of acute limb ischaemia.
Intervention and comparator†	▶ Full dose oral anticoagulation (±antiplatelet therapy) versus MAPT. ▶ DPI (very low dose oral anticoagulation+antiplatelet therapy) versus MAPT. ▶ DAPT versus MAPT.	▶ MAPT versus MAPT. ▶ DAPT versus DAPT. ▶ Anticoagulant versus anticoagulant. ▶ MAPT versus placebo. ▶ DAPT versus placebo. ▶ Very low dose anticoagulation alone versus MAPT.
Other	There will be no limitation with respect to language/date of publication.	Trials focusing on intraoperative/intraoperative administration of anticoagulant therapy (eg, heparin administered <i>only</i> during surgery and not extending into the postoperative period), or on the acute management of acute limb ischaemia (eg, thrombolytic therapy or therapies lasting <30 days), will be excluded.

*In the event that a trial includes participants with PAD as a subgroup of the main trial, and sex-stratified outcomes are available for the overall trial but not within the PAD subgroup, then the sex-stratified outcomes from the main trial will be discussed in the narrative and quantitative synthesis (where applicable) and the population analysed will be clearly stated.

†There will be no limitation with respect to class/dosing of antithrombotic agents.

DAPT, dual antiplatelet therapy; DPI, dual pathway inhibition; MAPT, monoantiplatelet therapy; PAD, peripheral arterial disease; RCTs, randomised controlled trials.

Search strategy

The search strategy will be designed with collaborative input from a librarian experienced in systematic review searches. A combination of Medical Subject Headings and keyword terms related to the population and interventions of interest will be used. The search strategy will begin with MEDLINE (see online supplemental appendix B) and will be translated according to the requirements of each electronic database. A search filter for RCTs will be applied.

Study records

Data management

Results from the literature search will be uploaded to Covidence online software.⁴⁷ Duplicate articles will be identified and removed by the Covidence screen for duplicates and by the review authors. We will extract data from the final studies included in the narrative summary and quantitative synthesis—and perform statistical analysis—using RevMan 5.

Selection process

All titles, abstracts and full-text screening will be performed in duplicate by three independent reviewers. Studies that are disputed during the abstract review phase will be brought to full-text review. Disputes about full-text articles will be resolved through discussion between the reviewers and input from the study supervisors (PJ, DK and MC) where required.

Data collection process

Data will be extracted from the studies by a team of independent reviewers and stored in a shared Excel document. Reviewers will undertake data collection in duplicate for the first few studies to ensure uniform data collection. Following this, data from each study will be collected independently and confirmed by a second reviewer. Any disputes will be resolved through discussion or input from the study supervisors.

Data items

The following data items will be extracted:

1. General study data: title, authors, year/journal/country/language of publication, sample size, recruitment period, study design, timing of randomisation to treatment, consideration for the potential impact of sex on the trial (ie, was the impact of sex analysed and how).
2. Population: baseline demographics (such as age, relevant comorbidities and medications), total number and proportion of females, total number and proportion of patients with symptomatic PAD (as well subcategories for severity of ischaemia or type of revascularisation where applicable), compliance with assigned treatment (and crossover rate in each arm).
3. Intervention: type, dosing, and frequency of anti-thrombotic, duration of therapy.
4. Comparator: type, dosing and frequency of antithrombotic, duration of therapy.

5. Outcomes: primary, secondary and safety outcomes, length of follow-up.
6. Outcome measures: reported effect measures for all outcomes, including p values, SD and CIs, time-to-event where applicable, analysis type (ie, intention to treat vs per protocol).
7. Funding: type and source where applicable.

Outcomes and prioritisation

Primary efficacy outcome

There will be two coprimary efficacy outcomes: a primary limb and a primary CV outcome. The primary limb outcome will be major (ie, above ankle) amputation. The primary CV outcome will be a composite of CV death, MI and stroke.

Secondary efficacy outcomes

Secondary outcomes will include the individual components of the primary CV outcome, acute limb ischaemia, surgical or endovascular intervention not planned at the time of randomisation and all-cause mortality, as well as primary, primary-assisted and secondary patency.

Safety outcomes

The primary safety outcome will be major bleeding as defined by each trial. The secondary safety outcome will be minor bleeding as defined by each trial. In trials that do not differentiate between major and minor bleeding, we will employ either the thrombolysis in myocardial infarction (TIMI) haemorrhage criteria or the International Society on Thrombosis and Hemostasis (ISTH) criteria (depending on the bleeding outcomes that were reported in the trial) to determine whether bleeding events should be classified as major or minor. TIMI classifies major bleeding as bleeding associated with any one of the following: 'is fatal, leads to hypotension requiring treatment with intravenous inotropic agents, requires surgical intervention for ongoing bleeding, necessitates the transfusion of four or more units of blood over a 48-hour period, or is a symptomatic intracranial hemorrhage'.⁴⁸ ISTH defines major bleeding in non-surgical patients as 'fatal bleeding, and/or symptomatic bleeding in a critical area or organ...and/or bleeding causing a fall in hemoglobin level of 20g/L (1.24mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells'.⁴⁹

Risk of bias in individual studies

Risk of bias will be assessed by one reviewer and verified by a second reviewer using the risk of bias tool (ROB 2) for randomised trials from the Cochrane Handbook for Systematic Reviews (p. 8).⁵⁰ Using this tool, we will assess bias across several domains: randomisation, deviation from intended intervention, missing outcome data, outcome measurement and selective reporting. Results of the overall risk of bias assessment will be reported in a narrative summary and individual risk within each domain across all studies will be reported in a table.

Sensitivity analysis will be performed excluding trials that demonstrate a low level of quality where applicable.

Data synthesis

We will assess patient population, study design, comparator arms and event rates for data synthesis. We will use I^2 to assess for statistical heterogeneity between studies. A narrative synthesis will be reported instead of a meta-analysis if there is insufficient data to conduct a quantitative analysis. Pooled estimates will be calculated, and meta-analysis will be performed using RevMan V.5 software. Treatment effect will be measured using OR, risk difference or HR (depending on which measure is most commonly reported across included studies) to compare the effect of the antithrombotic intervention versus the MAPT control in females with symptomatic PAD. A random effects model will be employed to determine weights for meta-analysis.

The following preplanned subgroup analysis will be performed where data permits:

- ▶ Stratification by severity of symptoms: intermittent claudication versus critical limb ischaemia.
- ▶ Stratification by indication for therapy: PAD alone versus PAD plus coronary artery disease.
- ▶ Stratification by type of intervention: conservative versus open revascularisation (ie, bypass) versus endovascular revascularisation (ie, angioplasty and/or stenting) versus amputation.

We will conduct a sensitivity analysis excluding trials with high risk of bias or small number of participants. We will also conduct a sensitivity analysis excluding older trials if medical regimens beyond the assigned intervention and control arms vastly differ from more modern trials (eg, use of statin therapy). Meta-bias will be assessed by repeating the primary efficacy and safety outcomes using a fixed effects model and by creating a funnel plot if the number of included studies exceeds 10. If fewer than 10 studies are included in the final analysis, we will not evaluate for publication bias given its limited power in the setting of a small number of studies.

Confidence in cumulative evidence

The Grading of Recommendations Assessment, Development, and Evaluation framework will be employed to assess the quality of all reported outcomes.⁴⁶

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

ETHICS AND DISSEMINATION

Ethics approval is waived as the study does not involve primary data collection. This review will be submitted for publication in a peer-reviewed journal and for presentation at national and international scientific meetings.

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Contributors All four authors substantially contributed to the design of this protocol. SAS drafted the protocol and is responsible for the design, execution and writeup of the study. PJ, DK and MC provided invaluable input in designing the study and will be overseeing the completion of this project. All four authors have provided approval of the version to be published and agree to be accountable for all aspects of the work, including its accuracy and integrity. SAS is the guarantor of the review.

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Appendix B. 2020 PRISMA Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	
	13c	Describe any methods used to tabulate or visually display results of	

Section and Topic	Item #	Checklist item	Location where item is reported
		individual studies and syntheses.	
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	
Study characteristics	17	Cite each included study and present its characteristics.	
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	
	23b	Discuss any limitations of the evidence included in the review.	
	23c	Discuss any limitations of the review processes used.	
	23d	Discuss implications of the results for practice, policy, and future	

Section and Topic	Item #	Checklist item	Location where item is reported
		research.	
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	
Competing interests	26	Declare any competing interests of review authors.	
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	

Appendix C. Medline Search Strategy

7/3/2020

Ovid: Abstract Reference

Database(s): **Ovid MEDLINE(R) ALL** 1946 to July 02, 2020

Search Strategy:

#	Searches	Results
1	arterial occlusive diseases/ or exp atherosclerosis/ or intermittent claudication/ or peripheral vascular diseases/ or peripheral arterial disease/	86295
2	(peripheral arter* adj3 (disease or occlusion or stenosis)).tw.	15686
3	claudica*.tw.	10640
4	vascular surgical procedures/ or vascular grafting/ or exp blood vessel prosthesis implantation/	54746
5	(endovascular or angioplasty or stent*).tw.	161298
6	(peripheral or lower extremity or limb or leg).tw.	784140
7	5 and 6	12894
8	(bypass adj3 (graft or surgery or infrainguinal)).tw.	41500
9	(peripheral vascular adj3 disease).tw.	8930
10	(limb adj3 (ischemi* or infarct*)).tw.	9072
11	1 or 2 or 3 or 4 or 7 or 8 or 9 or 10	197769
12	exp anticoagulants/ or exp antithrombins/ or exp platelet aggregation inhibitors/	329880
13	(aspirin or clopidogrel or ticlopidine or ticagrelor or prasugrel or cangrelor or abiciximab or eptifibatide or tirofiban or dipyridamole or cilostazol or vorapaxar or atopaxar).tw.	67241
14	(warfarin or heparin or dabigatran or edoxaban or rivaroxaban or apixaban or argatroban or enoxaparin or dalteparin or tinzaparin or fondaparinux or nadroparin or bemiparin or pamaparin or reviparin).tw.	104668
15	oral anticoagula*.tw.	17552
16	(antithrombotic or anti-thrombotic or anticoagula* or anti-coagula*).tw.	107846
17	(anti-platelet or antiplatelet).tw.	30406
18	(thromboxane inhibit* or (glycoprotein adj3 inhibit*) or phosphodiesterase inhibit* or (protease-activated adj3 inhibit*)).tw.	12366
19	(thrombin inhibit* or factor Xa inhibit* or vitamin K antagonis*).tw.	7292
20	12 or 13 or 14 or 15 or 16 or 17 or 18 or 19	441534
21	11 and 20	13994
22	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt.	601060
23	randomized controlled trial/	508810
24	exp Randomized Controlled Trials as Topic/	137324
25	"Randomized Controlled Trial (topic)"/	0
26	randomization/	103118
27	Controlled Clinical Trial/	93744
28	exp Controlled Clinical Trials as Topic/	142630
29	"Controlled Clinical Trial (topic)"/	0
30	Random Allocation/	103118
31	Double-Blind Method/	158511
32	Double Blind Procedure/	0
33	Double-Blind Studies/	158511
34	Single-Blind Method/	28741
35	Single Blind Procedure/	0
36	Placebos/	34944
37	Placebo/	0
38	Control Groups/	1677
39	Control Group/	1677
40	(random* or sham or placebo*).ti,ab,hw,kf,kw.	1500152
41	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	236870
42	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	1025
43	(control* adj3 (study or studies or trial* or group*)).ti,ab,hw,kf,kw.	985241
44	allocated.ti,ab,hw.	65742
45	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf,kw.	34648
46	((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	8317
47	(pragmatic study or pragmatic studies).ti,ab,hw,kf,kw.	405
48	((pragmatic or practical) adj3 trial*).ti,ab,hw,kf,kw.	5115
49	(phase adj3 (III or "3") adj3 (study or studies or trial*)).ti,hw,kf,kw.	28204
50	or/22-49	2142190
51	21 and 50	3349

Appendix D. Abstract published in the Journal of Vascular Surgery

Citation: Strauss SA, Seo C, Huynh H, Jetty P, Kobewka D, Roberts D, Carrier M. Antithrombotic Therapy in Females with Peripheral Artery Disease: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. J Vasc Surg 2021;74(5):e435-e437.

945 years, and 48.0% were female. A total of 52% were categorized as frail by modified frailty index-5 score and 50% were weak by grip strength measurement (65% convergence; $P = .37$). Frail patients had a longer transfer time (mean, 11.6 vs 9.9 seconds; $P = .19$). A median of 37 coded factors based on visually present patient appearance and movement were coded. Patients who were considered frail more often used their arms to push up from sitting position (69.2% vs 25.0%; $P = .04$), have a medical device visible (eg, portable oxygen, orthotic shoe, insulin pump) (58.5% vs 0%; $P = .04$), have a walking assistive device present (eg, wheelchair, cane) (23.1% vs 0%; $P = .22$), and display postural instability during transfer (50% vs 8.3%; $P = .07$). There appeared to be no difference in the presence of no-lace shoes (46.2% vs 41.7%; $P = .82$).

Conclusions: Our pilot study reveals that visual factors of patient appearance and movement correlate with objective measures of operative risk. These factors may underlie unstructured frameworks used by vascular surgeons. Future work will build on this work by exploring surgeons' blind spots, biases, and the relative value of objective measures in assessing patient risk for vascular procedures through case simulations.



Fig.

Author Disclosures: M. S. Anderson: Nothing to disclose; M. E. Byrnes: Nothing to disclose; M. A. Corriere: AIM Specialty Health, Inc.: Consulting Fees (eg, advisory boards); M. P. Goldman: Nothing to disclose; D. Keith: Nothing to disclose; C. Y. Kim: Nothing to disclose.

IP261.



Antithrombotic Therapy in Females With Peripheral Artery Disease: A Systematic Review and Meta-analysis of Randomized Controlled Trials

Shira A. Strauss, Chau Huynh, Chanhee Seo, Prasad Jetty, Daniel Kobewka, Derek J. Roberts, Marc Carrier, University of Ottawa, Ottawa, Canada

Objective: Females with peripheral artery disease (PAD) may respond to antithrombotic therapy differently than males. We sought to summarize female-specific risks of arterial thromboembolism and bleeding

across randomized controlled trials (RCTs) comparing antithrombotic regimens in PAD patients and to assess generalizability of these trials to female PAD patients.

Methods: We searched MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials for RCTs that included females and compared mono-antiplatelet therapy (MAPT) with therapeutic anticoagulation (AC), dual pathway inhibition (DPI: low-dose rivaroxaban [2.5 mg BID] combined with antiplatelet therapy), or dual antiplatelet therapy (DAPT). Trials lacking sex-based analyses were excluded from female-specific outcome assessments but included in generalizability analyses. Risk of bias was assessed using the Cochrane tool. Meta-analysis of cardiovascular (CV), limb, and bleeding events was performed using a random-effects model. Trial generalizability was evaluated through assessment of female participation, sex-based analyses, and participation-to-prevalence ratio (the proportion of females enrolled relative to their PAD burden).

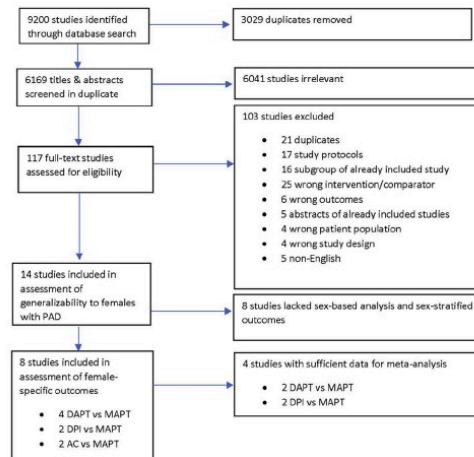


Fig. PRISMA flow diagram.

Table. Characteristics of the eight randomized controlled trials (RCTs) included in the analysis of female-specific outcomes

Trial, author, year	Population (brief description)	Females, n (%)	PAD subjects, n (%)	Intervention (daily unless specified)	Comparator	1° outcome
DAPT vs MAPT						
CASPAR, Belch, 2010	Below-knee arterial bypass for PAD	207 (24)	851 (100)	Clopidogrel + ASA	ASA	Index bypass occlusion, endovascular revascularization, above-ankle amputation, or death
PEGASUS-TIMI 54, Bonaca, 2015 ^a	Recent MI + ≥ 1 of: age ≥ 65 , DM requiring meds, 2nd prior spontaneous MI, multivessel CAD, CKD	3399 (24)	1143 (5)	Ticagrelor 90 mg BID + ASA	ASA	Composite CV death, MI, or stroke
TRA2P-TIMI 50, Morrow, 2012	Atherosclerosis hx (MI, ischemic stroke, or PAD; intermittent claudication + ABI < 0.85 or previous revascularization)	6326 (24)	6136 (23)	Vorapaxar + baseline MAPT	Placebo + Baseline MAPT	Composite CV death, MI, stroke, or recurrent ischemia leading to urgent coronary revascularization

(Continued on next page)

Table. Continued.

Trial, author, year	Population (brief description)	Females, n (%)	PAD subjects, n (%)	Intervention (daily unless specified)	Comparator	1° outcome
MATCH, Diener, 2004	Recent ischemic stroke/TIA + ≥1 of: previous ischemic stroke or MI, angina, DM, or symptomatic PAD within previous 3 years	2821 (37)	776 (10)	ASA + Clopidogrel	Placebo + Clopidogrel	Composite ischemic stroke, MI, vascular death, or rehospitalization for acute ischemic event
DPI vs MAPT						
COMPASS ^b , Eikelboom, 2017 & Liang, 2020	CAD (MI in last 20 years, multivessel CAD with symptoms, multivessel PCI or CABG) or symptomatic PAD. Additional criteria for CAD patients <65	4048 (22)	4996 (27)	Rivaroxaban 2.5 mg BID + ASA	Placebo BID + ASA	Composite CV death, stroke, or MI
VOYAGER, Bonaca, 2020	Recent (≤10 days) successful revascularization for symptomatic PAD	1704 (26)	6564 (100)	Rivaroxaban 2.5 mg BID + ASA	Placebo BID + ASA	Composite ALI, major vascular amputation, MI, ischemic stroke, or CV death
AC ± MAPT vs MAPT						
DUTCH BOA, Eikelboom, 2000	Infrainguinal bypass graft for obstructive PAD	952 (36)	2690 (100)	Vitamin K antagonist (target INR 3-4.5)	ASA ^c	Graft occlusion
WAVE, Anand, 2007	Symptomatic lower extremity PAD or carotid disease, asymptomatic carotid disease, or subclavian artery occlusive disease	570 (26)	2161 (100)	Vitamin K antagonist (target INR 2-3) + baseline MAPT	Baseline MAPT	Composite CV death, MI, stroke, severe ischemia requiring urgent intervention of the coronary or peripheral artery circulation

ABI, Ankle-brachial index; AC, anticoagulation; ALI, acute limb ischemia; ASA, American Society of Anesthesiologists class; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CKD, chronic kidney disease; CV, cardiovascular; DM, diabetes mellitus; DPI, dual pathway inhibition; INR, international normalized ratio; MAPT, monoantithrombotic therapy; MI, myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; TIA, transient ischemic attack.

Trials reported on a total of 20,027 females. For trials with PAD subgroups, main trial data were reported.

^aOnly ticagrelor 90 mg BID + ASA and ASA arms included.

^bOnly rivaroxaban 2.5 mg BID + ASA and ASA arms included.

^cCarbasalate calcium 100 mg daily metabolized to aspirin 80 mg.

Results: Among 6169 abstracts reviewed, we included 14 RCTs, of which 8 provided sex-based analyses (Fig). Trial characteristics are listed in the Table. Meta-analyses comparing DAPT vs MAPT (n = 2 trials) in females revealed no difference in composite CV outcomes (stroke/death/myocardial infarction) (hazard ratio = 0.84; 95% confidence interval [CI] = 0.68-1.04), but increased bleeding (hazard ratio = 1.42; 95% CI = 1.08-1.86) in females on DAPT compared with MAPT. Meta-analysis of DPI vs MAPT showed increased major bleeding (odds ratio = 2.11; 95% CI = 1.42-3.13) with DPI in females, but no difference in a composite of stroke/death/MI/acute limb ischemia/vascular amputation (odds ratio = 0.85; 95% CI = 0.65-1.10). Of the AC trials, one did not report female-specific events but noted no effect of sex on graft occlusion. The second reported no interaction between sex and composite CV outcomes or bleeding; AC increased significant bleeding in both sexes but did not affect composite CV outcomes. Among the 14 trials assessed for generalizability, 5 (35.6%) included a sex-based analysis specific to PAD participants. Females comprised 28.0%, 27.2%, and 26.8% of PAD participants in the DAPT, DPI, and AC vs MAPT trials, respectively. The participation-to-prevalence ratio was 0.41, indicating under-representation of females with PAD across antithrombotic trials.

Conclusions: Antithrombotic trials including PAD patients showed increased bleeding but no difference in thromboembolic events on DAPT, DPI, and AC compared with MAPT in females. Limited

sex-stratified PAD data and female under-representation within PAD cohorts restricted generalizability of the trial findings. Future research on antithrombotic therapy in PAD patients should prioritize female enrollment and sex-stratified analyses.

Author Disclosures: M. Carrier: Nothing to disclose; C. Huynh: Nothing to disclose; P. Jetty: Nothing to disclose; D. Kobewka: Nothing to disclose; D. J. Roberts: Nothing to disclose; C. Seo: Nothing to disclose; S. A. Strauss: Nothing to disclose.

IP263.



Quality Assessment of Online Resources for Thoracic Outlet Syndrome Patients

Wesley Clothier, Zachary Harbin, Preston Tolbert, John Treffalls, Qi Yan, Mark Davies, University of Texas Health Science Center, San Antonio, Tex

Objective: This study seeks to evaluate the quality and readability of patient resources that appear in the top search results for thoracic outlet syndrome (TOS).

Methods: Searches were performed for "TOS" and "Thoracic Outlet Syndrome" on Google, Yahoo, Bing, Yippy, and Dogpile. Websites were screened for exclusion and evaluated by two reviewers for accountability.

Appendix E. Supplemental Data Provided by the DUTCH BOA Authors

```

CROSSTABS
  /TABLES=compositeoutcome amputation vasculardeath allcausedeath myocinf s
stroke occlusion vascint bleeding
  BY medication BY sex
  /FORMAT=AVALUE TABLES
  /CELLS=COUNT COLUMN
  /COUNT ROUND CELL.

```

Crosstabs

Case Processing Summary						
	Cases					
	Valid		Missing		Total	
	N	Percent	N	Percent	N	Percent
compositeoutcome vasc death, mi, stroke or amputation * medication * sex sex	2650	100,0%	0	0,0%	2650	100,0%
amputation amputation * medication * sex sex	2650	100,0%	0	0,0%	2650	100,0%
vasculardeath vascular death * medication * sex sex	2650	100,0%	0	0,0%	2650	100,0%
allcausedeath all cause death * medication * sex sex	2650	100,0%	0	0,0%	2650	100,0%
myocinf myocardial infarction * medication * sex sex	2650	100,0%	0	0,0%	2650	100,0%
stroke stroke * medication * sex sex	2650	100,0%	0	0,0%	2650	100,0%
occlusion occlusion * medication * sex sex	2650	100,0%	0	0,0%	2650	100,0%
vascint vascular intervention * medication * sex sex	2650	100,0%	0	0,0%	2650	100,0%
bleeding bleeding * medication * sex sex	2650	100,0%	0	0,0%	2650	100,0%

compositeoutcome vasc death, mi, stroke or amputation * medication * sex sex Crosstabulation

sex sex				medication		Total
				0 aspirin	1 oral anticoagulants	
0 male	compositeoutcome vasc death, mi, stroke or amputation	0 no	Count	676	705	1381
			% within medication	80,6%	82,1%	81,3%
		1 yes	Count	163	154	317
			% within medication	19,4%	17,9%	18,7%
		Total	Count	839	859	1698
			% within medication	100,0%	100,0%	100,0%
1 female	compositeoutcome vasc death, mi, stroke or amputation	0 no	Count	373	373	746
			% within medication	76,9%	79,9%	78,4%
		1 yes	Count	112	94	206
			% within medication	23,1%	20,1%	21,6%
		Total	Count	485	467	952
			% within medication	100,0%	100,0%	100,0%
Total	compositeoutcome vasc death, mi, stroke or amputation	0 no	Count	1049	1078	2127
			% within medication	79,2%	81,3%	80,3%
		1 yes	Count	275	248	523
			% within medication	20,8%	18,7%	19,7%
		Total	Count	1324	1326	2650
			% within medication	100,0%	100,0%	100,0%

amputation amputation * medication * sex sex Crosstabulation

sex sex				medication		Total
				0 aspirin	1 oral anticoagulants	
0 male	amputation amputation	0 no	Count	780	801	1581
			% within medication	93,0%	93,2%	93,1%
		1 yes	Count	59	58	117
			% within medication	7,0%	6,8%	6,9%
		Total	Count	839	859	1698
			% within medication	100,0%	100,0%	100,0%
1 female	amputation amputation	0 no	Count	434	425	859
			% within medication	89,5%	91,0%	90,2%
		1 yes	Count	51	42	93
			% within medication	10,5%	9,0%	9,8%
		Total	Count	485	467	952
			% within medication	100,0%	100,0%	100,0%
Total	amputation amputation	0 no	Count	1214	1226	2440
			% within medication	91,7%	92,5%	92,1%
		1 yes	Count	110	100	210
			% within medication	8,3%	7,5%	7,9%
		Total	Count	1324	1326	2650
			% within medication	100,0%	100,0%	100,0%

vasculardeath vascular death * medication * sex sex Crosstabulation

sex sex				medication		Total
				0 aspirin	1 oral anticoagulants	
0 male	vasculardeath vascular death	0 no	Count	755	770	1525
			% within medication	90,0%	89,6%	89,8%
		1 yes	Count	84	89	173
			% within medication	10,0%	10,4%	10,2%
	Total		Count	839	859	1698
			% within medication	100,0%	100,0%	100,0%
1 female	vasculardeath vascular death	0 no	Count	423	419	842
			% within medication	87,2%	89,7%	88,4%
		1 yes	Count	62	48	110
			% within medication	12,8%	10,3%	11,6%
	Total		Count	485	467	952
			% within medication	100,0%	100,0%	100,0%
Total	vasculardeath vascular death	0 no	Count	1178	1189	2367
			% within medication	89,0%	89,7%	89,3%
		1 yes	Count	146	137	283
			% within medication	11,0%	10,3%	10,7%
	Total		Count	1324	1326	2650
			% within medication	100,0%	100,0%	100,0%

allcausedeath all cause death * medication * sex sex Crosstabulation

sex sex				medication		Total
				0 aspirin	1 oral anticoagulants	
0 male	allcausedeath all cause death	0 no	Count	711	719	1430
			% within medication	84,7%	83,7%	84,2%
		1 yes	Count	128	140	268
			% within medication	15,3%	16,3%	15,8%
	Total		Count	839	859	1698
			% within medication	100,0%	100,0%	100,0%
1 female	allcausedeath all cause death	0 no	Count	408	396	804
			% within medication	84,1%	84,8%	84,5%
		1 yes	Count	77	71	148
			% within medication	15,9%	15,2%	15,5%
	Total		Count	485	467	952
			% within medication	100,0%	100,0%	100,0%
Total	allcausedeath all cause death	0 no	Count	1119	1115	2234
			% within medication	84,5%	84,1%	84,3%
		1 yes	Count	205	211	416
			% within medication	15,5%	15,9%	15,7%
	Total		Count	1324	1326	2650
			% within medication	100,0%	100,0%	100,0%

myocinf myocardial infarction * medication * sex sex Crosstabulation

sex sex				medication		Total
				0 aspirin	1 oral anticoagulants	
0 male	myocinf myocardial infarction	0 no	Count	815	840	1655
			% within medication	97,1%	97,8%	97,5%
		1 yes	Count	24	19	43
			% within medication	2,9%	2,2%	2,5%
		Total	Count	839	859	1698
			% within medication	100,0%	100,0%	100,0%
1 female	myocinf myocardial infarction	0 no	Count	467	457	924
			% within medication	96,3%	97,9%	97,1%
		1 yes	Count	18	10	28
			% within medication	3,7%	2,1%	2,9%
		Total	Count	485	467	952
			% within medication	100,0%	100,0%	100,0%
Total	myocinf myocardial infarction	0 no	Count	1282	1297	2579
			% within medication	96,8%	97,8%	97,3%
		1 yes	Count	42	29	71
			% within medication	3,2%	2,2%	2,7%
		Total	Count	1324	1326	2650
			% within medication	100,0%	100,0%	100,0%

stroke stroke * medication * sex sex Crosstabulation

sex sex				medication		Total
				0 aspirin	1 oral anticoagulants	
0 male	stroke stroke	0 no	Count	808	837	1645
			% within medication	96,3%	97,4%	96,9%
		1 yes	Count	31	22	53
			% within medication	3,7%	2,6%	3,1%
		Total	Count	839	859	1698
			% within medication	100,0%	100,0%	100,0%
1 female	stroke stroke	0 no	Count	469	454	923
			% within medication	96,7%	97,2%	97,0%
		1 yes	Count	16	13	29
			% within medication	3,3%	2,8%	3,0%
		Total	Count	485	467	952
			% within medication	100,0%	100,0%	100,0%
Total	stroke stroke	0 no	Count	1277	1291	2568
			% within medication	96,5%	97,4%	96,9%
		1 yes	Count	47	35	82
			% within medication	3,5%	2,6%	3,1%
		Total	Count	1324	1326	2650
			% within medication	100,0%	100,0%	100,0%

occlusion occlusion * medication * sex sex Crosstabulation

sex sex				medication		Total
				0 aspirin	1 oral anticoagulants	
0 male	occlusion occlusion	0 no	Count	644	676	1320
			% within medication	76,8%	78,7%	77,7%
		1 yes	Count	195	183	378
			% within medication	23,2%	21,3%	22,3%
	Total		Count	839	859	1698
			% within medication	100,0%	100,0%	100,0%
1 female	occlusion occlusion	0 no	Count	358	342	700
			% within medication	73,8%	73,2%	73,5%
		1 yes	Count	127	125	252
			% within medication	26,2%	26,8%	26,5%
	Total		Count	485	467	952
			% within medication	100,0%	100,0%	100,0%
Total	occlusion occlusion	0 no	Count	1002	1018	2020
			% within medication	75,7%	76,8%	76,2%
		1 yes	Count	322	308	630
			% within medication	24,3%	23,2%	23,8%
	Total		Count	1324	1326	2650
			% within medication	100,0%	100,0%	100,0%

vascint vascular intervention * medication * sex sex Crosstabulation

sex sex				medication		Total
				0 aspirin	1 oral anticoagulants	
0 male	vascint vascular intervention	0 no	Count	547	592	1139
			% within medication	65,2%	68,9%	67,1%
		1 yes	Count	292	267	559
			% within medication	34,8%	31,1%	32,9%
		Total	Count	839	859	1698
			% within medication	100,0%	100,0%	100,0%
1 female	vascint vascular intervention	0 no	Count	331	305	636
			% within medication	68,2%	65,3%	66,8%
		1 yes	Count	154	162	316
			% within medication	31,8%	34,7%	33,2%
		Total	Count	485	467	952
			% within medication	100,0%	100,0%	100,0%
Total	vascint vascular intervention	0 no	Count	878	897	1775
			% within medication	66,3%	67,6%	67,0%
		1 yes	Count	446	429	875
			% within medication	33,7%	32,4%	33,0%
		Total	Count	1324	1326	2650
			% within medication	100,0%	100,0%	100,0%

bleeding bleeding * medication * sex sex Crosstabulation

sex sex				medication		Total
				0 aspirin	1 oral anticoagulants	
0 male	bleeding bleeding	0 no	Count	798	797	1595
			% within medication	95,1%	92,8%	93,9%
		1 yes	Count	41	62	103
			% within medication	4,9%	7,2%	6,1%
		Total	Count	839	859	1698
			% within medication	100,0%	100,0%	100,0%
1 female	bleeding bleeding	0 no	Count	470	421	891
			% within medication	96,9%	90,1%	93,6%
		1 yes	Count	15	46	61
			% within medication	3,1%	9,9%	6,4%
		Total	Count	485	467	952
			% within medication	100,0%	100,0%	100,0%
Total	bleeding bleeding	0 no	Count	1268	1218	2486
			% within medication	95,8%	91,9%	93,8%
		1 yes	Count	56	108	164
			% within medication	4,2%	8,1%	6,2%
		Total	Count	1324	1326	2650
			% within medication	100,0%	100,0%	100,0%

MEANS TABLES=age BY medication BY sex
/CELLS=MEAN COUNT STDDEV.

Means

Case Processing Summary

	Cases					
	Included		Excluded		Total	
	N	Percent	N	Percent	N	Percent
age age (years) * medication * sex sex	2650	100,0%	0	0,0%	2650	100,0%

Report

age age (years)

medication	sex sex	Mean	N	Std. Deviation
0 aspirin	0 male	67,51	839	9,565
	1 female	70,59	485	10,515
	Total	68,64	1324	10,030
1 oral anticoagulants	0 male	67,17	859	9,936
	1 female	71,62	467	9,535
	Total	68,74	1326	10,021
Total	0 male	67,34	1698	9,753
	1 female	71,10	952	10,054
	Total	68,69	2650	10,024

Appendix F. Risk of Bias Justification

i. CASPAR

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Study-drug assignment was performed centrally by an interactive voice-response system using a pre-established randomization scheme, stratified according to the graft type (venous or prosthetic, with the latter class including any composite graft in which prosthetic material was used). Within each stratum, patients were randomized to clopidogrel or placebo in a 1:1 ratio."
Allocation concealment (selection bias)	Low risk	"Patients were considered to be randomized as soon as the treatment allocation was given via the interactive voice-response system. Study drug was initiated on the day of randomization."
Blinding of participants and personnel (performance bias)	Low risk	"CASPAR was a prospective, multicenter, randomized, double-blind, placebo-controlled study"
Blinding of outcome assessment (detection bias)	Low risk	"All occurrences of the primary endpoint were adjudicated on a blinded basis by the Clinical Endpoints Committee."
Incomplete outcome data (attrition bias)	Low risk	Treatment was permanently discontinued by 88 patients (21.0%) in the placebo group and 107 patients (25.2%) in the clopidogrel group. However, none of the results below changed when the analyses were carried out on the on-treatment group alone."
Selective reporting (reporting bias)	Unclear risk	Secondary outcomes listed on clinicaltrials.gov ("1st occurrence of any component of following cluster of events : index bypass graft occlusion, any revascularization procedure or amputation. Change in ABPI.") differ from secondary outcomes listed in methods section ("first occurrence of any individual component of the primary endpoint, and the first occurrence of the following during follow-up: CV death, or myocardial infarction, or stroke, or any amputation above the ankle")
Other bias	Unclear risk	"We are grateful to Sanofi-Aventis and Bristol-Myers Squibb for their help with the funding and completion of this study. Editorial support was funded by Sanofi-Aventis and provided by Alpha-Plus Medical Communications Ltd. "

ii. PEGASUS-TIMI 54

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was performed with the use of a central computerized telephone or Web-based system, and assignment was double-blinded."
Allocation concealment (selection bias)	Low risk	"Each pack will be labeled with a unique pack ID number that will be used to assign the treatment to the patient but will not indicate treatment allocation to the investigator or patient." – Protocol
Blinding of participants and personnel (performance bias)	Low risk	"assignment was double-blinded."
Blinding of outcome assessment (detection bias)	Low risk	"A central clinical-events committee, whose members were unaware of the treatment assignments, adjudicated all efficacy end points and bleeding episodes."
Incomplete outcome data (attrition bias)	Unclear risk	"The proportions of patients in each group who discontinued treatment prematurely over the duration of the trial were 32.0% in the group that received 90 mg of ticagrelor twice daily, 28.7% in the group that received 60 mg of ticagrelor twice daily, and 21.4% in the placebo group (P<0.001 for the comparison of each ticagrelor dose vs. placebo). The majority of premature discontinuations in the two ticagrelor groups were due to adverse events."
Selective reporting (reporting bias)	Low risk	Outcomes established a priori and protocol published
Other bias	High risk	"During the study if a patient has an event that requires ADP receptor blockade, the patient can receive modified study medication to ensure that they receive active ADP receptor blockade. This modification will include the addition of clopidogrel capsules that will either be placebo (in patients already allocated to active ticagrelor) or active (in patients already allocated to placebo ticagrelor)." – Protocol --> This introduces bias by introducing DAPT to patients who otherwise would be receiving MAPT. To eliminate this source of bias, investigators could have limited enrolment to patients requiring ADP receptor blockade and randomized them to either DAPT with ASA + ticag or DAPT with ASA + plavix "The trial was designed as a collaboration among the Thrombolysis in Myocardial Infarction (TIMI) Study Group, the executive and steering committees, and AstraZeneca, the trial sponsor [...] The raw database was provided to the TIMI Study Group, which conducted all the data analyses independently of the sponsor."

iii. TRA2°P-TIMI 50

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A Central Randomization Service will provide randomized treatment assignment across the study through an IVRS, using a randomization scheme provided by the sponsor." – Protocol
Allocation concealment (selection bias)	Low risk	"Upon enrollment, subjects will receive randomized allocation of treatment with SCH 530348 bisulfate 2.5 mg or matching placebo in a 1:1 ratio [...] After a subject qualifies for the study, the study center will contact the IVRS and receive a subject randomization number (subject number) and subject treatment kit assignment. The IVRS will assign the subject randomization number according to the subject's sequential entry into the study (this will be the subject's identification number throughout the study)." – Protocol
Blinding of participants and personnel (performance bias)	Low risk	"Vorapaxar and placebo were administered orally in a blinded fashion once daily until the end of follow-up."
Blinding of outcome assessment (detection bias)	Low risk	"A clinical-events committee whose members were unaware of the study-group assignments adjudicated all components of the primary and major secondary efficacy end points and bleeding episodes."
Incomplete outcome data (attrition bias)	Low risk	"Of the 26,449 subjects enrolled, 32 (0.1%) were lost to follow-up, and 532 (2.0%) withdrew consent for follow-up at a median of 9 months from randomization. Of the remaining 25,885 subjects who completed follow-up according to the protocol, 98.2% had ascertainment for end point events through their final study contact [...] Other than the DSMB-directed discontinuation of study drug in stroke patients, premature discontinuation of treatment because of an adverse event, the patient's preference, or for other reasons was 24% in the vorapaxar group (9.6% per year) and 22% (8.8% per year) with placebo." – Appendix
Selective reporting (reporting bias)	Low risk	"The protocol-defined primary efficacy end point was a composite of cardiovascular death, myocardial infarction, stroke, or recurrent ischemia leading to urgent coronary revascularization[...] Before the database was locked and during blinded treatment, the investigators reviewed data from the newly completed Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRACER) trial (ClinicalTrials.gov number, NCT00527943). On the basis of data from that trial, the steering committee amended the main data-analysis plan to reorder the hierarchy of efficacy analyses, defining as the primary end point the composite of cardiovascular death, myocardial infarction, or stroke."
Other bias	Unclear risk	"The trial was sponsored by Merck and was designed by the TIMI Study Group in conjunction with the steering committee and trial sponsor. [...] The raw database was provided to the TIMI Study Group, which carried out the data analyses independently of the sponsor, prepared this report, and made the decision to submit the manuscript for publication."

iv. CHARISMA

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"After providing written informed consent, patients were randomly assigned either to clopidogrel (75 mg per day) plus low-dose aspirin (75 to 162 mg per day) or to placebo plus low dose aspirin. Study drug assignment was performed centrally by an interactive voice-response system on the basis of a preestablished randomization scheme, stratified according to site."
Allocation concealment (selection bias)	Low risk	"Study drug assignment was performed centrally by an interactive voice-response system on the basis of a preestablished randomization scheme, stratified according to site."
Blinding of participants and personnel (performance bias)	Low risk	"The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial was a prospective, multicenter, randomized, double-blind, placebo-controlled study"
Blinding of outcome assessment (detection bias)	Low risk	"All primary trial end points were adjudicated by the clinical events committee, whose members were unaware of patients' treatment assignments."
Incomplete outcome data (attrition bias)	Low risk	"Follow-up with respect to the primary efficacy end point (the first occurrence of myocardial infarction, stroke, or death from cardiovascular causes) was complete in 99.5 percent of the patients randomly assigned to receive clopidogrel and aspirin and 99.6 percent of those randomly assigned to receive placebo and aspirin."
Selective reporting (reporting bias)	Low risk	Outcomes a-priori outcomes outlined in protocol were reported in manuscript
Other bias	Unclear risk	"The trial was designed by Dr. Topol, who was responsible for obtaining funding and executing the trial, and it was planned and conducted by the executive committee, with extensive review of the data for its interpretation." "Funding for the CHARISMA trial was provided by Sanofi-Aventis and Bristol-Myers Squibb. The sponsor and cosponsor had advisory input in the design of the study, had nonvoting input in the executive committee, and were responsible for auditing at individual study sites. The executive committee bears complete responsibility for the analysis of the results, the veracity and completeness of the reporting, and the writing of the manuscript; the sponsors did have the opportunity to review the manuscript." "Treatment was permanently discontinued by 20.4 percent of the patients in the clopidogrel group, as compared with 18.2 percent in the placebo group (P<0.001)."

v. COMPASS

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk 	"A computer-generated randomisation schedule was generated by the Population Health Research Institute." – COMPASS PAD (DOI: 10.1016/S0140-6736(17)32409-1)
Allocation concealment (selection bias)	Low risk 	"Each treatment group was double dummy, and the patient, investigators, and central study staff were masked to treatment allocation." – COMPASS PAD (DOI: 10.1016/S0140-6736(17)32409-1)
Blinding of participants and personnel (performance bias)	Low risk 	"Each treatment group was double dummy, and the patient, investigators, and central study staff were masked to treatment allocation." – COMPASS PAD (DOI: 10.1016/S0140-6736(17)32409-1)
Blinding of outcome assessment (detection bias)	Low risk 	"Each treatment group was double dummy, and the patient, investigators, and central study staff were masked to treatment allocation." – COMPASS PAD (DOI: 10.1016/S0140-6736(17)32409-1)
Incomplete outcome data (attrition bias)	Unclear risk 	"At the first formal interim analysis for efficacy (50% of planned events), the independent data and safety monitoring board recommended early termination of the randomized comparison of rivaroxaban with or without aspirin versus aspirin alone on February 6, 2017, having observed a consistent difference in the primary efficacy outcome in favor of rivaroxaban plus aspirin ($z = -4.592$)." – Original COMPASS trial (DOI: 10.1056/NEJMoa1709118) "At the completion of follow-up, 15.9% of women and 16.7% of men in" – Liang
Selective reporting (reporting bias)	Low risk 	"Peripheral artery disease outcomes were prespecified and included: acute limb ischaemia, chronic limb ischaemia, and amputation." – COMPASS PAD (DOI: 10.1016/S0140-6736(17)32409-1) All other study outcomes were established a-priori in the published protocol
Other bias	Unclear risk 	"Eligible participants (except those who underwent randomization 4 to 14 days after coronary-artery bypass graft [CABG] surgery) entered a run-in phase during which they received a rivaroxaban- matched placebo twice daily and aspirin at a dose of 100 mg once daily. The purpose of the run-in phase was to identify participants who were unwilling or unable to adhere to the trial regimen, who had adverse events, or who were otherwise not suitable for randomization." "The trial sponsor is Bayer." – Original COMPASS trial (DOI: 10.1056/NEJMoa1709118)

vi. VOYAGER

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk 	"randomization was performed with a centralized computerized system and was stratified according to the type of index procedure (endovascular [including hybrid] vs. surgical) and according to clopidogrel use or nonuse within the group of patients who underwent an endovascular procedure" "Treatments will be balanced within a country for each stratum by block randomization" –protocol
Allocation concealment (selection bias)	Low risk 	"Randomization and study treatment will commence as soon as possible but no later than 7 days after the qualifying revascularization" –protocol
Blinding of participants and personnel (performance bias)	Low risk 	"Neither the investigators nor the patients were aware of the treatment assignments."
Blinding of outcome assessment (detection bias)	Low risk 	"An independent academic clinical events committee adjudicated all deaths, potential ischemic cardiovascular and limb events, and bleeding events in a blinded manner."
Incomplete outcome data (attrition bias)	Low risk 	"Ascertainment of the primary outcome was complete for 98.8% of potential patient-years of follow up"
Selective reporting (reporting bias)	Low risk 	All reported outcomes established a-priori and protocol published
Other bias	Unclear risk 	"It was designed and overseen by a collaborative group that included [...] Bayer and Janssen Pharmaceuticals. Bayer participated in the trial design, trial oversight, site selection, and the drafting of the manuscript."

vii. DUTCH BOA

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomisation was done by telephone at the central trial office with computer-generated blocked sequences of numbers based on different block lengths, stratified by centre."
Allocation concealment (selection bias)	Low risk	"Randomisation was done by telephone at the central trial office with computer-generated blocked sequences of numbers based on different block lengths, stratified by centre. Treatment was to be started within 5 days after surgery."
Blinding of participants and personnel (performance bias)	High risk	"To avoid the ethical and practical difficulties of sham monitoring of blood coagulation in the aspirin group, treatment assignment was open."
Blinding of outcome assessment (detection bias)	Low risk	"Events were adjudicated and classified by two members of an independent panel of neurologists, cardiologists, vascular internists, and vascular surgeons who were unaware of treatment status. Discrepancies were resolved by a third reviewer. If three different classifications were made, consensus was reached by discussion. During the trial, no investigator had any knowledge of the event rates in relation to treatment status."
Incomplete outcome data (attrition bias)	Low risk	2.17% vs 2.96% of patients in each arm withdrew or were lost to follow up (comparable rates)
Selective reporting (reporting bias)	Low risk	all outcomes listed in methods are reported in results
Other bias	Low risk	–

viii. WAVE

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk 	"A central 24-hour computerized randomization service was used to assign the patient to either the combination of oral anticoagulation and antiplatelet therapy (1080 patients) or antiplatelet therapy alone (1081 patients). A permuted-block randomization stratified according to clinical center was used."
Allocation concealment (selection bias)	Low risk 	"Patients will be considered randomized as soon as the treatment allocation is given over the phone" –WAVE trial protocol
Blinding of participants and personnel (performance bias)	High risk 	"randomized, open-label, clinical trial" --> would be unethical to blind ppl as only OAC group required to monitor INR
Blinding of outcome assessment (detection bias)	Low risk 	"All outcomes were determined by the members of a central adjudication committee who used standard definitions and were unaware of treatment allocation."
Incomplete outcome data (attrition bias)	Low risk 	"Complete data at the end of the study were available for 2159 of the patients randomly assigned to treatment (99.9%)"
Selective reporting (reporting bias)	Low risk 	All outcomes were established a-priori in the published protocol
Other bias	Unclear risk 	If a stable INR between 2.0 and 3.0 was achieved during the run-in phase, the patient agreed to continue and adhered to therapy, and no side effects had occurred, a central 24-hour computerized randomization service was used to assign the patient to either the combination of oral anticoagulation and antiplatelet therapy (1080 patients) or antiplatelet therapy alone (1081 patients)." --> excluding patients who experienced side effects on their assigned treatment during the run-in phase likely introduced bias, but unclear in which direction. "None of the corporate sponsors had any role in the design or conduct of the trial, analysis of the data, or preparation of the manuscript." --> low risk of bias due to sponsorship

Appendix G. Detailed PPR calculation

females with PAD enrolled/ total PAD participants enrolled:

International trials: $(207 + 254 + 1756 + 930 + 1435 + 1704 + 570) / (851 + 1143 + 6136 + 3096 + 4996 + 6564 + 2161) = 6856/24947$

US trials: $(6 + 12) / (831 + 56) = 18/887$

Italy: 23/159

Japan: 13/50

Germany: 38/80

Netherlands: 952/2690

Total participants: $24947 + 887 + 159 + 50 + 80 + 2690 = 28,813$

Weighted international: $24947/28813 = 0.8658$

Weighted US: $887/28813 = 0.0308$

Weighted Italy: $159/28813 = 0.0055$

Weighted Japan: $50/28813 = 0.0017$

Weighted Germany: $80/28813 = 0.0028$

Weighted Netherlands: $2690/28813 = 0.0934$

PPR Numerator: $(6856 + 18 + 23 + 13 + 38 + 952) / 28813$
 $= 7900/28813 = 0.2742$

PPR Denominator: $[(76,093,176.22/113,443,016.70)*(24947/28813)] +$
 $[(7,058,553.57/12,461,374.83)*(887/28813) + [(1,908,498.39/2,810,306.19)*(159/28813)] +$
 $[(3,725,980.88/4,865,501.38)*(50/28813)] + [(2,248,565.16/3,631,855.36)*(80/28813)] +$
 $[(395582.73/654478.36)*(2690/28813)]$
 $= 0.58076 + 0.01744 + 0.00375 + 0.00133 + 0.00172 + 0.05643$
 $= 0.66142$

PPR= $(7900/28813) / 0.66142 = 0.2742/0.6614 = 0.4145$