


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,

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.

	Inclusion	Exclusion
Study design	<ul style="list-style-type: none"> ▶ 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. 	<ul style="list-style-type: none"> ▶ Cross-sectional. ▶ Case-control. ▶ Case series with <10 patients. ▶ Case reports.
Population*	<ul style="list-style-type: none"> ▶ 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. 	<ul style="list-style-type: none"> ▶ Males. ▶ Asymptomatic PAD. ▶ Trials focused specifically on the management of acute limb ischaemia.
Intervention and comparator†	<ul style="list-style-type: none"> ▶ Full dose oral anticoagulation (±antiplatelet therapy) versus MAPT. ▶ DPI (very low dose oral anticoagulation+antiplatelet therapy) versus MAPT. ▶ DAPT versus MAPT. 	<ul style="list-style-type: none"> ▶ 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/intraprocedural 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 20 g/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 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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