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Evidence for underprescription of and non-adherence to guideline-recommended cardiovascular medications among adults with peripheral artery disease: protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction: International guidelines strongly and consistently recommend that adults with peripheral artery disease (PAD) be prescribed antiplatelet, statin, and antihypertensive medications. However, it is unclear how often people with PAD are underprescribed these drugs, which patient and clinician characteristics predict underprescription of or non-adherence to guideline-recommended cardiovascular medications, and whether underprescription or non-adherence is associated with adverse health and health system outcomes.

Methods and analysis: We will search MEDLINE, EMBASE, and Evidence-Based Medicine Reviews from 2006 onwards. Two investigators will independently review abstracts and full-text studies. We will include studies that enrolled adults and reported the incidence and/or prevalence of underprescription of/non-adherence to guideline-recommended cardiovascular medications among people with PAD; adjusted risk factors for underprescription of or non-adherence to these medications; and adjusted associations between underprescription of/non-adherence to these medications and outcomes. Outcomes will include mortality, major adverse cardiac and limb events (including revascularization procedures and amputations), other reported morbidities, healthcare resource use, and costs. Two investigators will independently extract data and evaluate risk of bias. We will calculate summary estimates of the incidence and prevalence of underprescription/non-adherence across studies. We will also conduct subgroup meta-analyses and meta-regression to determine if estimates vary by country, characteristics of the patient and treating clinician, population- versus non-population-based design, and study risks of bias. Finally, we will calculate pooled adjusted risk factors for underprescription/non-adherence and adjusted associations between underprescription/non-adherence and outcomes. We will use GRADE to determine estimate certainty.

Ethics and dissemination: Ethics approval is not required. This systematic review will synthesize existing evidence regarding underprescription of and non-adherence to guideline-recommended cardiovascular medications in adults with PAD. This will be used to identify evidence-care gaps that may inform where knowledge translation interventions may be required to improve clinician prescribing and patient adherence to prescribed medications.

Protocol registration number: CRD42022362801

KEYWORDS

Peripheral artery disease, practice guideline, drug prescription, platelet aggregation inhibitors, antihypertensive agents, hydroxymethylglutaryl-CoA reductase inhibitors

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This systematic review will synthesize existing evidence regarding underprescription of and non-adherence to guideline-recommended cardiovascular medications in adults with peripheral artery disease
- Strengths of the study include our detailed description of rigorous study methods; our detailed search strategy; and our pre-planned meta-analyses. These meta-analyses will calculate summary estimates of the incidence and prevalence of underprescription/non-adherence to guideline-recommended cardiovascular medications in adults with peripheral artery disease and pooled adjusted risk factors for underprescription/non-adherence and adjusted associations between underprescription/non-adherence and outcomes using random-effects models.
- Potential limitations of the study include our potential reliance on studies using administrative health data, which may be at variable risk for misclassification bias; further, administration health data studies may have high specificity, but low sensitivity. Finally, evidence-based guidelines for peripheral artery disease vary somewhat by time and across countries; to account for this, we will report data for underprescription according to the clinical practice guideline setting and time during which it was published.

INTRODUCTION

The international incidence and prevalence of peripheral artery disease (PAD) is rising,[1] and people with PAD are typically older, current or past cigarette smokers, and have multiple comorbidities, including diabetes, coronary artery disease (CAD), and cerebrovascular disease (CVD).[2] The care of people with PAD is costly as they have a high annual incidence of visits to primary health care providers, emergency departments, and vascular specialists; hospital admissions; open and endovascular lower limb revascularization procedures; and minor (below-ankle) and major (above-ankle) lower limb amputation.[3] Those with chronic limb-threatening ischemia (CLTI), an advanced form of PAD manifested by ischemic rest pain, tissue loss, or toe or foot gangrene, suffer a substantial burden of disability and pain and >60% visit the emergency department annually.[4–7]

International clinical practice guidelines strongly and consistently recommend prescribing antiplatelet and statin (i.e., HMG-CoA reductase inhibitor) medications to people with PAD.[5,8–11] They also recommend prescribing antihypertensive medications (preferably angiotensin-targeted agents) to those with PAD and hypertension.[5,8–11] These recommendations mirror those for people with CAD and CVD because these drugs reduce risk of myocardial infarction, stroke, and death in randomized controlled trials (RCTs) that enrolled participants with PAD, CAD, and/or CVD.[5,8–11] RCTs that enrolled PAD patients have also reported that these medications reduce risk of lower limb revascularization, acute lower limb ischemia, and major lower limb amputation, an outcome rated by many people with PAD as worse than death.[12–15]

However, several cohort studies have reported that antiplatelet, statin, and antihypertensive medications may be underprescribed to adults with PAD, especially when

compared to those who have CAD or CVD.[16–25] In support of this, a 2007 study conducted in a Canadian tertiary care hospital reported that 69% of people with PAD were not prescribed a statin and 48% with PAD and hypertension were not prescribed an angiotensin-converting enzyme (ACE) inhibitor.[26] Further, a recent cross-sectional survey found that less than half of vascular surgeons (the specialists who most commonly manage patients with the most severe forms of PAD) routinely initiated or modified statin therapy and fewer than 10% prescribed angiotensin-targeted or other antihypertensive therapy.[27]

Objectives

No evidence synthesis has examined the frequency of underprescription of and non-adherence to guideline-recommended cardiovascular medications among adults with PAD, patient and clinician characteristics that predict underprescription of or non-adherence to these medications, and the association between underprescription of or non-adherence to these medications and adverse health and healthsystem outcomes. The primary objective of this systematic review is therefore to meta-analyze reported direct estimates of the incidence and prevalence of healthcare provider underprescription of and patient non-adherence to guideline-recommended medications in adults with PAD. Secondary objectives are to identify and summarize characteristics of the patient and treating clinician that predict underprescription of or non-adherence to guideline-recommended medications and determine whether underprescription and non-adherence is associated with increased mortality, major adverse cardiac and limb events (including revascularization procedures and major amputations), other morbidities, healthcare resource use, and costs. The work will be used to identify international evidence-care gaps for adults with PAD that may be used to inform where knowledge translation interventions may be

required to improve healthcare provider prescribing of guideline-recommend cardiovascular medications to people with PAD and patient adherence to these prescribed medications.

METHODS

Protocol, reporting, and registration

We pre-specified our methods following recommendations for conducting systematic reviews and meta-analyses of prognostic factor studies.[28–30] This protocol is reported according to the Preferred Reporting Items in Systematic Reviews and Meta-Analyses-Protocols (PRISMA-P) statement[31,32] (see Supplementary Data, Appendix A) and Sex and Gender Equity in Research (SAGER) guidelines[33] (see Supplementary Data, Appendix B). It is registered on PROSPERO, the international prospective register of systematic reviews (PROSPERO registration number: CRD42022362801).

Clinical questions

We formulated study clinical questions according to suggested frameworks for posing clinical questions for systematic reviews of prognostic factor studies.[29,30,34]

Primary clinical question

- In adults (age ≥18-years) with PAD, what is the pooled cumulative incidence, incidence rate, and point or period prevalence of underprescription of and non-adherence to guideline-recommended cardiovascular medications?

Secondary clinical question

1. In adults (age ≥18-years) with PAD, does the pooled underprescription of or non-adherence to guideline-recommended medications vary by country, characteristics of the treating clinician or patient, population-based design, or study risks of bias?

2. In adults (age ≥ 18-years) with PAD, which characteristics of the treating clinician and patient increase the pooled adjusted odds of underprescription of or non-adherence to guideline-recommended cardiovascular medications?
3. In adults (age ≥ 18-years) with PAD, is the underprescription of or non-adherence to guideline-recommended medications associated with an increased pooled adjusted odds of mortality, major adverse cardiac and limb events (including revascularization procedures and major amputations), other morbidities, healthcare resource use, and cost?

Definitions

We will define underprescription as not prescribing one or more guideline-recommended cardiovascular medications to adults with PAD. We will define medication non-adherence as not initially filling a prescription, failing to follow its medications instructions for use, and/or failure to refill and therefore continue a prescription despite the above being recommended by their healthcare provider.[35] We will define PAD as per the 2016 American College of Cardiology/American Heart Association (ACC/AHA) guideline as atherosclerotic disease of the lower limb arteries, including the aortoiliac, femoropopliteal, and infrapopliteal arterial segments, and excluding nonatherosclerotic disease of the lower extremity (e.g., fibromuscular dysplasia).[5] However, alternate definitions of PAD used by authors will also be accepted.

Clinical practice guideline-recommended cardiovascular medications for PAD will be defined as antiplatelets (e.g. aspirin, clopidogrel), statins, and antihypertensives (e.g. ACE-inhibitors, angiotensin receptor blockers, beta-blockers, calcium-channel blockers, thiazide diuretics) (for people with PAD and concurrent hypertension). These are medications that are consistent across multiple international evidence-based PAD clinical practice guidelines.[5,8–

11,36,37] Since there is some variation in specific recommendations, we will accept individual study authors' definition of underprescription where underprescription was defined as per a certain published guideline and setting (see **Table 1** for a comparison of medical therapy recommendations across PAD guidelines).

Antiplatelet therapy, antihypertensive drugs (for those with hypertension and PAD), and statins have been recommended in various ACC/AHA guidelines, including the 2005 PAD guideline.[36] Some discrepancies exist between the European guidelines, American guidelines, and the recently published Canadian guideline.[11,37] All three recommend antiplatelets for symptomatic PAD; however, they differ with regards to asymptomatic PAD. The European Society of Cardiology-European Society for Vascular Surgery (ESC-ESVS) and Canadian Cardiovascular Society (CCS) guidelines do not recommend antiplatelets in asymptomatic patients, while the ACC/AHA guideline does.[11] The recommendation to treat hypertension with an antihypertensive in people with PAD has been consistent across guidelines for years.[36] The most recent American, Canadian, and European guidelines recommended prescribing statins to all PAD patients. Medications that are consistently recommended across guidelines include antiplatelet therapy (e.g. aspirin, clopidogrel) for symptomatic PAD, antihypertensive therapy (e.g. ACE-inhibitors, ARBs, beta blockers, CCBs, thiazide diuretics) for PAD and concurrent hypertension, and statins in patients with an LDL cholesterol ≥2.5 mmol/L (100 mg/dL).[5,8–11]

Information sources

We will search MEDLINE; EMBASE; and Evidence-Based Medicine Reviews (which includes ACP Journal Club; the Cochrane Central Register of Controlled Trials, Database of Systematic Reviews, and Methodology Register Database; Database of Abstracts of Reviews of

Effects; Health Technology Assessment Database; and National Health Service Economic Evaluation Database) from January 1, 2006, without restrictions. We will start our search in 2006 as this is the year after publication of the first PAD treatment clinical practice guideline by ACC/AHA.[38] To identify additional citations, we will use the PubMed "related articles" feature and manually search bibliographies of included studies and relevant review articles identified during the search.

Search strategy

We created the MEDLINE and EMBASE search strategies with the assistance of an information-scientist/medical librarian (R.S.). Using a combination of Medical Subject Heading (MeSH) terms and keywords, search filters were constructed covering the themes *PAD* and *underprescription/non-adherence*. For *PAD*, we extracted disease-related keywords and MeSH subject headings used in a recent meta-analysis examining an exercise intervention for PAD.[39] For *underprescription/non-adherence*, we extracted keywords and MeSH subject headings used in a systematic review examining medication underuse in older adults.[40] We then used those terms to search for additional relevant studies in PubMed and extracted the MeSH terms that those studies were indexed under. After the MEDLINE search strategy was created, we submitted it to another information-scientist/medical librarian to peer-review it using the Peer-Review of Electronic Search Strategies (PRESS) guideline[41] (see **Table 2** for our PRESS'd MEDLINE search strategy). Subsequently, we searched for Emtree terms that were similar to the above MeSH terms in EMBASE and created a list of non-MeSH/non-Emtree keywords for PAD guideline-recommended medications and underprescription/non-adherence (**Table 2**).

Data management and selection process

The titles and abstracts of citations identified during the search will be imported into Rayyan Systematic Review Software (https://www.rayyan.ai/).[42] Two investigators (D.D., M.P.) will use Rayyan to remove duplicates, independently review titles and abstracts of articles identified by the search, and select any article deemed potentially-relevant by either investigator for full-text review. These two investigators will subsequently review the full-text of all potentially-relevant citations and select studies for inclusion in the systematic review. Disagreements regarding study inclusion will be resolved via consensus or arbitration by the senior investigator (D.J.R.). Chance-corrected agreement between investigators regarding full-text inclusion will be calculated using a kappa statistic.[43]

Eligibility criteria and outcomes

We will use the following inclusion criteria:[30,34]

- The study included adults (age ≥ 18-years) with PAD
- The study reported one or more of the following outcomes (or these outcomes could be calculated from the data provided):
    1. Cumulative incidence, incidence rate, or point or period prevalence of underprescription of or non-adherence to guideline-recommended medications in adults with PAD
    2. Odds ratios (ORs), risk ratios (RRs), or hazard ratios (HRs) [and surrounding standard errors or 95% confidence intervals (CIs)] adjusted for the presence of other clinician (e.g., specialty, years of training) and patient (e.g., age, rural versus urban residence) risk and confounding factors and relating one or more

potential risk factor of interest to the underprescription of or non-adherence to guideline-recommended medications for PAD;

OR

3. ORs, RRs, HRs or other measures (and surrounding standard errors or 95% CIs) describing differences in mortality, major adverse cardiac and limb events (including revascularization procedures and major amputations), other morbidities, healthcare resource use, and costs associated with underprescription of or non-adherence to guideline-recommended medication for PAD and adjusted for the presence of other risk factors or confounding factors.

- The study design was observational (i.e., cohort, case-control, or cross-sectional, including studies nested within RCTs[44,45]).

We will exclude studies that were: 1) grey literature; 2) published only as an abstract; 3) only enrolled patients before the year 2006; 4) only reported unadjusted risk factors for underprescription or non-adherence or unadjusted associations between underprescription or non-adherence and outcomes; or 5) did not distinguish between underprescription and non-adherence (e.g., reported underuse without a description).

Data items and collection process

Two investigators will independently extract data in duplicate using a data extraction tool piloted on a random sample of five included studies. We will extract the following data from included studies: 1) design, data source, and study setting [country, whether the country was

high- or middle/low-income, rural versus urban setting (as defined by authors), and low versus high socioeconomic status (as defined by authors)]; 2) patient recruitment period; 3) definition of PAD; 4) sample size; 5) included patient characteristics, including number and percentages of patient sex, race, and socioeconomic status and patients with CAD, CVD, and PAD; pulmonary disease; diabetes; chronic kidney disease; cancer; and a past or present smoking history; 6) included clinician characteristics, including number and percentages of their sex, practice type (e.g., primary community care versus tertiary care center), clinician training (medicine, nursing), and clinician subspecialty (general practice, nurse practitioner, vascular surgery, general internal medicine, cardiology, and other); 7) reported cumulative incidence, incidence rate, and point or period prevalence of underprescription of or non-adherence to guideline-recommended medications; 8) reported adjusted risk factors for underprescription of or non-adherence to guideline-recommended medications (and their surrounding 95% CIs); 9) reported adjusted associations between underprescription of or non-adherence to guideline-recommended medications and mortality, major adverse cardiac and limb events (including revascularization procedures and major amputations), other morbidities, healthcare resource use, and cost (and their surrounding 95% CIs or standard deviations); and 10) which other prognostic or confounding factors were adjusted for in the above adjusted analyses. Where reported comparisons between the frequency of prescription of guideline-recommended medications to patients with PAD instead of CAD or CVD, these will also be extracted as well. Three investigators will independently extract data when they are only presented visually (e.g., a bar graph) and then their results will be averaged.

Risk of bias assessment

Two investigators will independently evaluate the risk of bias of studies reporting incidence and prevalence estimates using the Joanna Briggs Institute's critical appraisal checklist of studies reporting prevalence data.[29] The Joanna Briggs checklist includes questions about whether the sample frame was appropriate to address the target population, participants were sampled in an appropriate way, sample size was adequate, study participants (i.e., both patients and treating clinicians) and setting was described in detail, the data analysis was conducted with sufficient coverage of the identified sample, valid methods were used for the identification of the condition, the condition was measured in a standard and reliable way, and the statistical analyses were appropriate.[29] Those studies that reported risk factors for underprescription of or non-adherence to guideline-recommended medications for PAD or associations between underprescription and outcomes will also be independently evaluated by two investigators using the Quality in Prognosis Studies tool.[46,47] This tool includes questions regarding study participation and attrition; potential risk factor and outcome description and measurement; confounding measurement and account; and methods and reporting of statistical analyses.[46,47] For those studies that used administrative data, we will also examine whether the study authors considered the accuracy (sensitivity and specificity) of the codes used to define variables. Disagreements regarding risk of bias assessments will be resolved by consensus or arbitration by the senior investigator.

Qualitative data synthesis

We will perform a narrative synthesis of the included studies and their reported data before considering meta-analyses.[48] We will first tabulate characteristics of the included

studies, including their design, data source, setting, recruitment period, included treating clinicians and patients, and reported outcomes. This tabulation will help us identify potentially duplicate data and where meta-analyses may be appropriate.

Quantitative data synthesis and statistical analyses

Where it was not reported, we will calculate the cumulative incidence, incidence rate, and point or period prevalence of underprescription of or non-adherence to guideline-recommended medications for PAD. Cumulative incidence will be calculated using the following formula:

$$\text{Cumulative incidence} = \frac{\text{Number of new cases of underprescription of or non} - \text{adherence to guideline recommended medication for PAD}}{\text{Total population at risk}}$$

where the total population at risk will be defined as the number of adults with PAD. Incidence rate will be determined using the formula:

$$\text{Incidence rate} = \frac{\text{Number of new cases of underprescription of or non} - \text{adherence to guideline recommended medication for PAD}}{\text{Total person} - \text{time at risk}}$$

Point or period prevalence will be determined using the formula:

$$\text{Point or period prevalence} = \frac{\text{Number of existing cases of underprescription of or non} - \text{adherence to guideline recommended medication for PAD at a point in time or over a period of time}}{\text{Total defined population at that time or over that period of time}}$$

The standard error and 95% confidence interval of these proportions will be determined using the Clopper-Pearson exact binomial method.

Where we identify multiple studies that provide non-overlapping or non-duplicated data estimates of underprescription of or non-adherence to guideline-recommended medications for PAD, incidence or prevalence estimates will be pooled using DerSimonian and Laird random-effects models.[49] These pooled analyses will be done according to setting and clinical practice guideline source. As suggested by Barendregt *et al*., we will first transform these proportional estimates using a double arcsine transformation prior to meta-analyses.[29,50] The data will then be back-transformed to incidence and prevalence estimates after meta-analyses.[29]

We will use the OR (for dichotomous outcomes) or standardized mean difference (for continuous outcomes) as the summary measures of choice for pooled risk factor and outcome analyses. Similar adjusted risk factor estimates and outcome associations will be pooled using DerSimonian and Laird random-effects models.[49] Where the OR was not reported, we will pool RRs or HRs instead. When adjusted estimates were calculated from the same data source across several studies, we will include the estimate derived from the largest study. As a sensitivity analysis, we will also recalculate the estimate using that derived from the potentially overlapping study that reported the most adjusted estimates as studies may have variably adjusted their estimates for potentially confounding factors.

We will inspect forest plots, calculate I^2 inconsistency statistics, and conduct tests of homogeneity to assess for inter-study heterogeneity in the above estimates.[51–53] We will consider I^2 statistics >25%, >50%, and >75% to represent low, moderate, and high degrees of heterogeneity, respectively.[52] In the presence of at least low inter-study heterogeneity in our pooled estimates of incidence and prevalence, we will conduct subgroup meta-analyses and

meta-regression. We will use the following predictor variables to explore heterogeneity in these stratified meta-analyses and meta-regressions: country; percentages of patient sex, race, and socioeconomic status and patients with CAD, CVD, PAD, pulmonary disease, diabetes, chronic kidney disease, cancer, and a past or present smoking history; percentages of clinicians' sex, practice type (e.g., primary community care versus tertiary care center), clinician training (medicine, nursing), and clinician subspecialty (general practice, nurse practitioner, vascular surgery, general internal medicine, cardiology other); and population-based design versus not.

We will evaluate for evidence of small study effects potentially due to publication bias by visually inspecting funnel plots of incidence and prevalence of underprescription and using Egger's tests.[54] We will use the study sample size instead of the inverse of the standard error on the y-axis as this may perform more favourably in these analyses.[29,55] Statistical analyses will be performed by a trained meta-analyst using Stata version 13.0 (Stata Corp., College Station, Texas, USA).

Certainty in the cumulative evidence

We will use Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) to assess certainty in the estimates of associations between the reported risk factors and underprescription or non-adherence and between underprescription/non-adherence and outcomes.[56] We will first assess the risk of bias, imprecision, inconsistency, indirectness, and publication bias associated with the evidence for the reported risk factors.[57–61] Estimate certainty will then be adjudicated as high (further research is very unlikely to change the estimate), moderate (further research could have an important impact, which may change the

estimate), or low (further research is very likely to have an important impact, which is likely to change the estimate).

PATIENT AND PUBLIC INVOLVEMENT

There is no patient involvement in the development of this systematic review.

ETHICS AND DISSEMINATION

No ethics approval is required for this study as it includes previously published data. International clinical practice guidelines have consistently recommended that a number of cardiovascular medications be prescribed to adults with PAD to prevent morbidity, mortality, lower limb revascularization, and minor and major amputation. This study seeks to determine how often these medications are underprescribed to these patients and how often these patients do not adhere to them after prescription. We also seek to compare the frequency with which these medications are prescribed to those with PAD instead of CAD or CVD, identify patient and treating clinician characteristics that predict underprescription of or non-adherence to these guideline-recommended medications in adults with PAD, and estimate outcomes associated with underprescription of or non-adherence to these medications in people with PAD. Finally, as sex-based differences in PAD mortality have been observed,[62] we will also examine whether the above varies by patient sex.

This proposed systematic review has both strengths and limitations. The strengths of our approach include the rigorous methodology employed. A limitation is likely a reliance on studies using administrative health data, which may be at variable risk for misclassification bias. An additional concern with administrative data studies is that their measurement of complications has been suggested to have high specificity, but low sensitivity.[63] A final important limitation is the slight inconsistencies that exist between evidence-based guidelines for PAD across time and countries. To account for this, we will report data for underprescription according to the clinical practice guideline setting and time during which it was published.

The aim of this systematic review will be to identify evidence-care gaps for PAD, compare these gaps across different countries and settings, and identify those patients at highest

risk for underprescription and non-adherence and physicians/physician characteristics related to underprescribing and non-adherence. We will also seek to quantify the importance of these gaps, notably how underprescription of or non-adherence to these medications influences PAD patient outcomes and the burden on the healthcare system. If our study identifies that an important gap between clinical practice guideline recommendations and healthcare provider and patient behaviors, it may justify design and testing of knowledge translation interventions to improve prescription of guideline-recommended cardiovascular medications to adults with PAD and possibly patient adherence to these medications after prescription.

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AUTHORS CONTRIBUTIONS

DdL and DJR contributed to the conceptualization of the study and drafted the initial manuscript. DdL, MP, DJR, and RS created and revised the search strategy. DdL, MP, AMK, IDG, DF, SKN, RS, JMG, and DJR contributed to the design of the study methods. DdL drafted the manuscript. DdL, MP, AMK, IDG, DF, SKN, RS, JMG, and DJR revised the manuscript for important intellectual content. DdL, MP, AMK, IDG, DF, SKN, RS, JMG, and DJR approved the final version of the manuscript and agreed to submit it for publication.

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COMPETING INTERESTS

The authors have no conflicts of interest to declare.

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WORD COUNT

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Table 1. Comparison of antiplatelet, antihypertensive, and statin guidance across international guidelines for PAD.

Guideline, evidence grading	Antiplatelet	Antihypertensives	Statins
ACC/AHA 2005[38] **Class I:** Benefit >>> Risk. Procedure/ Treatment SHOULD be performed/ administered **Class IIa:** Benefit >> Risk. Additional studies with focused objectives needed. IT IS REASONABLE to perform procedure/ administer treatment **Class IIb:** Benefit ≥ Risk. Additional studies with broad objectives needed; Additional registry data would be helpful. Procedure/ treatment MAY BE CONSIDERED. **Class III:** Risk ≥ Benefit. No additional studies needed. Procedure/ treatment should not be performed/administered SINCE IT IS NOT HELPFUL AND MAY BE HARMFUL **Level A:** Multiple (3-5) population risk strata evaluated. General consistency of direction and magnitude of effect. **Level B:** Limited (2-3) population risk strata evaluated. **Level C:** Very limited (1-2) population risk strata evaluated.	**Class I** 1. Antiplatelet therapy is indicated to reduce the risk of MI, stroke, or vascular death in individuals with atherosclerotic lower extremity PAD. (**Level A**). 2. Aspirin, in daily doses of 75 to 325 mg, is recommended as safe and effective antiplatelet therapy to reduce the risk of MI, stroke, or vascular death in individuals with atherosclerotic lower extremity PAD. (**Level A**) 3. Clopidogrel (75 mg per day) is recommended as an effective alternative antiplatelet therapy to aspirin to reduce the risk of MI, stroke, or vascular death in individuals with atherosclerotic lower extremity PAD. (**Level B**) **Class III** Oral anticoagulation therapy with warfarin is not indicated to reduce the risk of adverse cardiovascular ischemic events in individuals with atherosclerotic lower extremity PAD. (**Level C**)	**Class I** 1. Antihypertensive therapy should be administered to hypertensive patients with lower extremity PAD to achieve a goal of less than 140 mm Hg systolic over 90mm Hg diastolic (nondiabetics) or less than 130 mmHg systolic over 80 mm Hg diastolic (diabetics and individuals with chronic renal disease) to reduce the risk of MI, stroke, congestive heart failure, and cardiovascular death. (**Level A**) 2. Beta-adrenergic blocking drugs are effective antihypertensive agents and are not contraindicated inpatients with PAD. (**Level A**) **Class IIa** The use of angiotensin-converting enzyme inhibitors is reasonable for symptomatic patients with lower extremity PAD to reduce the risk of adverse cardio-vascular events. (**Level B**) **Class IIb** Angiotensin-converting enzyme inhibitors may be considered for patients with asymptomatic lower extremity PAD to reduce the risk of adverse cardio-vascular events. (**Level C**)	**Class I** Treatment with a hydroxymethyl glutaryl (HMG)coenzyme-A reductase inhibitor (statin) medication is indicated for all patients with PAD to achieve a target LDL cholesterol level of less than 100 mg per dL. (**Level B**) **Class IIa** 1. Treatment with an HMG coenzyme-A reductase inhibitor (statin) medication to achieve a target LDL cholesterol level of less than 70 mg per dL is reasonable for patients with lower extremity PAD at very high risk of ischemic events. (**Level B**) 2. Treatment with a fibric acid derivative can be useful for patients with PAD and low HDL cholesterol, normal LDL cholesterol, and elevated triglycerides. (**Level C**)
ACC/AHA 2016[5] **Class I:** Benefit >>> Risk (STRONG) **Class IIa:** Benefit >> Risk (MODERATE) **Class IIb:** Benefit ≥ Risk	**Class I** Antiplatelet therapy with aspirin alone (range 75–325 mg per day) or clopidogrel alone (75 mg per day) is recommended to reduce MI, stroke, and vascular death in patients	**Class I** Antihypertensive therapy should be administered to patients with hypertension and PAD to reduce the risk of MI, stroke, heart failure, and cardiovascular death. (**Level A**)	**Class I** 1. Treatment with a statin medication is indicated for all patients with PAD. (**Level A**)

(WEAK) **Class 3: No benefit.** Benefit = Risk (MODERATE) **Class 3: Harm.** Risk > Benefit (STRONG) **Level A:** High-quality evidence from more than 1 RCT; meta-analyses of high quality RCTs; one or more RCTs corroborated by registry studies **Level B-R:** Moderate-quality evidence from 1 or more RCTs; meta-analyses of moderate-quality RCTs **Level B-NR:** Moderate-quality evidence from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies; meta-analyses of such studies **Level C-LD:** Randomized or nonrandomized observational or registry studies with limitations of design or execution; meta-analyses of such studies; physiological or mechanistic studies in human subjects **Level C-EO:** Consensus of expert opinion based on clinical experience	with symptomatic PAD. (**Level A**) **Class IIa** In asymptomatic patients with PAD (ABI ≤0.90), antiplatelet therapy is reasonable to reduce the risk of MI, stroke, or vascular death. (**Level C-EO**) **Class IIb** 1. In asymptomatic patients with borderline ABI (0.91–0.99), the usefulness of antiplatelet therapy to reduce the risk of MI, stroke, or vascular death is uncertain. (**Level B-R**) 2. The effectiveness of dual antiplatelet therapy (DAPT) (aspirin and clopidogrel) to reduce the risk of cardiovascular ischemic events in patients with symptomatic PAD is not well established. (**Level B-R**) 3. DAPT (aspirin and clopidogrel) may be reasonable to reduce the risk of limb-related events in patients with symptomatic PAD after lower extremity revascularization. (**Level C-LD**) 4. The overall clinical benefit of vorapaxar added to existing antiplatelet therapy in patients with symptomatic PAD is uncertain. (**Level B-R**)	**Class IIa** The use of angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers can be effective to reduce the risk of cardiovascular ischemic events in patients with PAD. (**Level A**)	
CCS Consensus Conference 2005[64] **Quality of Evidence** **I:** Evidence obtained from at least one properly randomized controlled trial or one large epidemiological study. **II:** Evidence based on at least one non-	**Grade 1A** Medical therapies to reduce cardiovascular events in PAD: Antiplatelets **Grade 1A** Lifelong antiplatelet therapy with aspirin (75 to 325 mg/d) or clopidogrel (75 mg/day) in patients with or without clinically manifest coronary or	**Grade 1A** Medical therapies to reduce cardiovascular events in PAD: ACE inhibitors. There is evidence that ACE inhibitors may be effective irrespective of their blood pressure lowering effect, and therefore this class of drugs is a reasonable first	**Grade 1A** Medical therapies to reduce cardiovascular events in PAD: Statins

randomized cohort comparison or multi-centre study, chronological series or extra ordinarily results from large non-randomized studies. **III:** Opinions of respective authorities, based on clinical experience, descriptive studies or reports of expert committees. **Classification and Recommendations** **A:** Evidence sufficient for universal use (usually based on randomized clinical trials). **B:** Evidence acceptable for widespread use, evidence less robust, but based on randomized clinical trials. **C:** Evidence not based on randomized clinical trials.	cerebrovascular disease. **Grade 1B** Aspirin or Clopidogrel recommended over ticlopidine **Grade 1B** Cilostazol is recommended for patients with disabling intermittent claudication who do not respond to conservative measures (risk factor modification and exercise therapy) and who are not candidates for surgical or catheter-based intervention **Grade 2B** Pentoxyfilline is not recommended **Grade 2B** Anticoagulant therapy (vitamin K antagonists) is not recommended	choice if blood pressure lowering is required. **No Grade assigned** Blood Pressure Lowering The evidence of the effectiveness of BP lowering in other vascular subgroups (…) taken together with the emerging data of its effectiveness in PAD patients allows us to advocate for aggressive BP lowering in this high-risk subgroup.	
CCS The Use of Antiplatelet Therapy in the Outpatient Setting 2011[65] **Class I:** Evidence and/or general agreement that a given diagnostic procedure/treatment is beneficial, useful, and effective **Class IIa:** Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the treatment with the weight of evidence in favour **Class IIb:** Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the treatment with the	**Class I** For patients with symptomatic PAD with overt CAD or cerebrovascular disease, antiplatelet therapy as indicated for the CAD and/or cerebrovascular status is recommended (**Level A**). **Class IIa** 1. For patients allergic or intolerant to ASA, use of clopi- dogrel is suggested (**Level B**). 2. For all infrainguinal reconstructions, low-dose ASA (75- 162 mg daily) should be given (**Level B**). 3. Long-term antiplatelet therapy with ASA 75-162 mg daily should be given to patients who undergo lower-extremity balloon angioplasty with or without stenting for	**N/A**	**N/A**

usefulness/ efficacy less well established **Class III:** Evidence that the treatment is not useful and in some cases may be harmful **Level A:** Data derived from multiple randomized clinical trials or meta-analyses **Level B:** Data derived from a single randomized clinical trial or large nonrandomized studies **Level C:** Consensus of opinion by experts and/or small studies, retrospective studies, and registries	chronic symptomatic PAD (**Level C**). **Class IIb** 1. For patients with symptomatic PAD without overt CAD or cerebrovascular disease, low-dose ASA (75-162 mg daily) or clopidogrel 75 mg daily is recommended, provid- ing the risk for bleeding is low (**Level B**). The choice of drug may depend on patient preference and cost considerations. 2. For patients with intermittent claudication, using clopidogrel 75 mg daily in addition to ASA 75-162 mg daily is not recommended unless the patient is judged to be at high vascular risk along with a low risk of bleeding (**Level B**). 3. For patients with asymptomatic PAD with an ABI < 0.9, low-dose ASA (75-162 mg daily) may be considered for those at high risk because of associated atherosclerotic risk factors in the absence of risk factors for bleeding (**Level C**). 4. In those with infrainguinal grafts and a high risk of thrombosis or limb loss, combination therapy with a vitamin K antagonist and ASA may be of benefit (**Level C**). 5. Low-dose ASA (75-162 mg daily) may be considered for all patients with an AAA, particularly those with clinical or subclinical PAD (**Level C**). **Class III** 1. For patients with symptomatic PAD with an indication for oral anticoagulation such as		

	atrial fibrillation, venous thromboembolism, heart failure, or mechanical valves, antiplatelet therapy should not be added to oral anticoagulation (**Level A**). 2. For patients with symptomatic PAD without compelling indications for oral anticoagulation such as atrial fibrillation or venous thromboembolism, oral anticoagulation should not be added to antiplatelet therapy (**Level B**). 3. Anticoagulation with heparin or vitamin K antagonists should be avoided in this setting (**Level B**). 4. For patients with intermittent claudication, dipyridamole should not be used in addition to ASA (**Level C**).		
CCS 2022 (PAD Guideline)[37] **Strength of Recommendation:** **Strong:** guideline panel is confident that the desirable effects of an intervention outweigh its undesirable effects (strong recommendation for an intervention) or that the undesirable effects of an intervention outweigh its desirable effects (strong recommendation against an intervention). **Weak:** the desirable effects probably outweigh the undesirable effects (weak recommendation for an intervention) or undesirable effects probably outweigh the desirable effects (weak recommendation against an intervention)	1. We recommend against routine antithrombotic therapy (antiplatelet or anticoagulant) for patients with isolated asymptomatic lower extremity PAD (**Strong Recommendation; High-Quality Evidence**). 2. 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 (**Strong Recommendation; High-**	1. We suggest that the approach to initiation and titration of antihypertensive agents should follow the Hypertension Canada guidelines (**Weak Recommendation; Low-Quality Evidence**). 2. We suggest treating hypertension to a target of less than 140/90 mm Hg in patients with PAD without compelling indications for specific agents or targets (**Weak Recommendation; Low-Quality Evidence**). 3. We recommend that PAD patients with hypertension be treated with ACE inhibitors or ARBs as the first choice in the absence of contraindications (**Strong Recommendation; Moderate-Quality Evidence**).	1. We recommend that patients with PAD qualify as statin-indicated patients and should receive lipid-modifying therapy for the reduction of death, CV death, nonfatal MI, nonfatal stroke (MACE), and MALE concordant with the recommendations in the 2021 Canadian Cardiovascular Society (CCS) guide- lines for the management of dyslipidemia (**Strong Recommendation; High-Quality Evidence**). a. Maximally tolerated dose of statin therapy b. Statin add-on therapies (ezetimibe and/or PCSK-9 inhibitors) if receiving maximally tolerated dose of statin therapy and the low-density lipoprotein cholesterol is ≥ 1.8 mmol/L, non-high-density lipoprotein cholesterol ≥ 2.4 mmol/L or apolipoprotein B100 ≥ 0.7 mg/dL.

but appreciable uncertainty exists. **Quality of Evidence:** **High:** We are very confident that the true effect lies close to that of the estimate of the effect. **Moderate:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different **Low:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect**.** **Very Low:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect	**Quality Evidence**). 3. 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 (**Strong Recommendation; High-Quality Evidence**). 4. 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 (**Strong Recommendation; High-Quality Evidence**). 5. We suggest that clopidogrel (75 mg daily) should be the preferred agent when single antiplatelet therapy is deemed to be the optimal antithrombotic choice (**Weak Recommendation; Moderate-Quality Evidence**). 6. We suggest that dual antiplatelet therapy(DAPT; 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 (**Weak Recommendation; Moderate-Quality Evidence**). 7. We recommend against the additional use of full-dose anticoagulation with antiplatelet therapy for the purpose of decreasing		2. We recommend that patients with PAD, who, despite maximally tolerated dose of statin therapy have a triglyceride level of 1.5-5.6 mmol/L, should be considered for use of icosapent ethyl for the reduction CV death, nonfatal MI, and nonfatal stroke concordant with the recommendations in the 2021 CCS guidelines for the management of dyslipidemia (**Strong Recommendation; Moderate-Quality Evidence**).

	MACE and MALE events in patients with stable lower extremity PAD (**Strong Recommendation; High-Quality Evidence**).		
ESC 2011[8] **Class I:** Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective. **Class II:** Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure. **Class IIa:** Weight of evidence/opinion is in favour of usefulness/efficacy. **Class IIb:** Usefulness/efficacy is less well established by evidence/opinion. **Class III:** Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful. **Level A:** Data derived from multiple randomized clinical trials or meta-analyses. **Level B:** Data derived from a single randomized clinical trial or large non-randomized studies. **Level C:** Consensus of opinion of the experts and/ or small studies, retrospective studies, registries.	**Class I** Antiplatelet therapy is recommended in patients with symptomatic PAD. (**Level C**)	**Class I** All patients with PAD should have their blood pressure controlled to ≤140/90 mmHg. (**Level A**) **Class IIa** ß-Blockers are not contraindicated in patients with LEAD, and should be considered in the case of concomitant coronary artery disease and/or heart failure (**Level B**)	**Class I** All patients with PAD should have their LDL cholesterol lowered to <2.5 mmol/L (100 mg/dL), and optimally to <1.8 mmol/L (70 mg/dL), or ≥ 50% when the target level cannot be reached. (**Level C**)
ESC-ESVS 2017[10] **Class I:** Evidence and/or general	**Class I** 1. Antiplatelet therapy is recommended in patients with symptomatic PADs.	**Class I** In patients with PADs and hypertension, it is recommended to control	**Class I** 1. Statins are recommended in all patients with PADs. (**Level**

agreement that a given treatment or procedure is beneficial, useful, effective. **Class II:** Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure. **Class IIa:** Weight of evidence/opinion is in favour of usefulness/efficacy. **Class IIb:** Usefulness/efficacy is less well established by evidence/opinion. **Class III:** Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful. **Level A:** Data derived from multiple randomized clinical trials or meta-analyses. **Level B:** Data derived from a single randomized clinical trial or large non-randomized studies. **Level C:** Consensus of opinion of the experts and/ or small studies, retrospective studies, registries.	(Level C) 2. Long-term SAPT is recommended in symptomatic patients. (**Level A**) **Class IIb** In patients requiring antiplatelet therapy, clopidogrel may be preferred over aspirin. (**Level B**) **Class III** Because of a lack of proven benefit, antiplatelet therapy is not routinely indicated in patients with isolated asymptomatic LEAD. (**Level A**)	blood pressure at <140/90 mmHg. (**Level A**) **Class IIa** ACEIs or ARBs should be considered as first-line therapyc in patients with PADs and hypertension. (**Level B**)	**A**) 2. In patients with PADs, it is recommended to reduce LDL-C to < 1.8 mmol/L (70 mg/dL) or decrease it by >_50% if baseline values are 1.8–3.5 mmol/L (70–135 mg/dL). (**Level C**)
NICE 2012[9]	Offer all people with peripheral arterial disease information, advice, support and treatment regarding the secondary prevention of cardiovascular disease, in line with published NICE guidance on: - smoking cessation - diet, weight management and exercise - lipid modification and statin therapy - the prevention, diagnosis and management of diabetes - the prevention, diagnosis and management of high blood pressure - antiplatelet therapy		

ACC: American College of Cardiology, AHA: American Heart Association, CCS: Canadian Cardiovascular Society, ESC: European Society of Cardiology, ESVS: European Society for Vascular Surgery, NICE: National Institute for Health and Care Excellence, COR: class of recommendation, ABI: ankle-brachial index, ACEi: ace-inhibitor, ARB: angiotensin II receptor blocker, BP: blood pressure, CAD: coronary artery disease, DAPT: dual-antiplatelet therapy, HDL: high-density-lipoprotein, LDL: low-density-lipoprotein, MI: myocardial infarction, PAD: peripheral artery

disease, LEAD: lower extremity artery disease, SAPT: single-antiplatelet therapy, MACE: major adverse cardiovascular events, MALE: major adverse limb events

Table 2. PRESS'd search strategies.

Ovid MEDLINE

1 Arterial Occlusive Diseases/
2 Arteriolosclerosis/
3 Arteriosclerosis/
4 Arteriosclerosis Obliterans/
5 Intermittent Claudication/
6 Intermittent Claudic*.tw,kf.
7 arteriosclero*.tw,kf.
8 exp Peripheral Vascular Diseases/
9 (limb adj2 isch?em*).tw,kf.
10 (periph* adj2 arter* adj2 disease*).tw,kf.
11 or/1-10
12 (under utili* or underutili*).tw,kf.
13 "under use*".tw,kf.
14 underusage.tw,kf.
15 underuse*.tw,kf.
16 under usage.tw,kf.
17 underprescri*.tw,kf.
18 under prescri*.tw,kf.
19 (under treat* or undertreat*).tw,kf.
20 ((inadequate or deficien* or insufficien* or substandard or suboptimal) adj3 (treatment or management or control or therap*)).tw,kf.
21 Health Services Accessibility/ or "Delivery of Health Care"/ or Practice Patterns, Physicians'/
22 Guideline Adherence/ or Prescriptions/ or Drug Prescriptions/ or Drug Utilization/
23 Medication Adherence/ or "Treatment Adherence and Compliance"/
24 ((prescription or prescribing) adj2 (rate* or practice*)).tw,kf.
25 adheren*.tw,kf.
26 ((treatment or practice) adj2 pattern*).tw,kf.
27 (noncomplian* or nonadheren*).tw,kf.
28 ((treatment or prescribing or therapy) adj3 complian*).tw,kf. or complian*.ti.
29 or/12-28
30 11 and 29
31 limit 30 to yr="2006 -Current"
32 exp animals/ not humans/
33 31 not 32
34 33 use medall

Ovid EMBASE

35 exp peripheral occlusive artery disease/
36 intermittent claudication/ or Intermittent Claudic*.tw.
37 (limb adj2 isch?em*).tw.
38 (periph* adj2 arter* adj2 disease*).tw.
39 arteriolosclerosis/ or arteriosclerosis/ or arteriosclero*.tw.
40 or/35-39
41 (under utili* or underutili*).tw.
42 "under use*".tw.
43 underusage.tw.
44 underuse*.tw.
45 under usage.tw.
46 underprescri*.tw.
47 under prescri*.tw.
48 (under treat* or undertreat*).tw.
49 ((inadequate or deficien* or insufficien* or substandard or suboptimal) adj3 (treatment or management or control or therap*)).tw.
50 *health care access/ or unmet medical need/

51	*health care delivery/
52	*clinical practice/
53	((treatment or practice) adj2 pattern*).tw.
54	((prescription or prescribing) adj2 (rate* or practice*)).tw.
55	protocol compliance/
56	drug utilization/
57	*"drug use"/ or *prescription/
58	((treatment or prescribing or therapy) adj3 adheren*).tw. or adheren*.ti.
59	((treatment or prescribing or therapy) adj3 complian*).tw. or complian*.ti.
60	(noncomplian* or nonadheren*).tw.
61	or/41-60
62	40 and 61
63	(exp animal/ or nonhuman/) not exp human/
64	62 not 63
65	limit 64 to yr="2006 -Current"
66	65 use emczd
67	34 or 66

Evidence for Underprescription of and Non-Adherence to Guideline-Recommended Cardiovascular Medications in Adults with Peripheral Artery Disease: Protocol for a Systematic Review and Meta-Analysis

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	✓
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Title Page
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	Not applicable
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	CRD42022362801
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Will be provided
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Will be provided
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	Grant Information
Sponsor	5b	Provide name for the review funder and/or sponsor	Grant Information
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	Grant Information
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Introduction

Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Methods - clinical questions
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Methods - eligibility criteria and outcomes
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Methods - information sources
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Table 2. MEDLINE search strategy (PRESS'd)
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Methods - data management and selection process
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Methods - data management and selection process
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Methods - data items and collection process
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Methods - data items and collection process
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Methods - eligibility criteria and outcomes
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Methods - risk of bias assessment

Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Methods - quantitative data synthesis and statistical analyses
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	Methods - quantitative data synthesis and statistical analyses
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Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Methods - risk of bias assessment
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Evidence for Underprescription of and Non-Adherence to Guideline-Recommended Cardiovascular Medications in Adults with Peripheral Artery Disease: Protocol for a Systematic Review and Meta-Analysis

Sex and Gender Equity in Research (SAGER) checklist

✓	Checklist item	Reported on section
General		
Yes	The terms sex/gender used appropriately	Introduction, methods
Title		
N/A	Title specifies the sex/gender of participants if only one included	N/A
Abstract		
N/A	Abstract specifies the sex/gender of participants if only one included	N/A
N/A	Study population described with sex/gender breakdown*	N/A
Introduction		
Yes	If relevant, previous studies that show presence or lack of sex/gender differences or similarities are cited	Introduction
Yes	Mention of whether sex/gender might be an important variant and if differences might be expected	Introduction
N/A	The demographics of the study population with regard to sex/gender (eg, disease prevalence among male/female study participants) are outlined*	N/A
Methods		
Yes	Method of definition of sex/gender (eg, self-report, genetic testing)	Methods
Yes	Description of how sex/gender was considered in the design, whether authors ensured adequate representation of male and female study participants, justification of the reasons for any exclusion of male or female participants, or explanation if not considered. Justification of other sex/gender-specific interventions of study designs (eg, mandating contraception for women).* Explicit reporting of the scientific rationale for contraception requirements and exclusions for pregnancy and lactation should be required*	Methods
Results (N/A – protocol paper)		
Discussion		
Yes	Potential implications of sex/gender on the study results and analyses, including the extent to which the findings can be generalized to all sexes/genders in a population	Yes

N/A	If a sex/gender analysis not done, a rationale is given and implications of the lack of such analysis on the interpretation of the results are discussed	N/A

Adapted from SAGER guidelines. Sex and Gender Equity in Research: rationale for the SAGER guidelines and recommended use. Research Integrity and Peer Review 1, Article number: 2 (2016) https://researchintegrityjournal.biomedcentral.com/articles/10.1186/s41073-016-0007-6.
* These points extend beyond the original SAGER table

Source: https://ease.org.uk/wp-content/uploads/2023/01/EASE-SAGER-Checklist-2022.pdf

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Evidence for Underprescription of and Non-Adherence to Guideline-Recommended Cardiovascular Medications in Adults with Peripheral Artery Disease: Protocol for a Systematic Review and Meta-Analysis

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BMJ Open

Evidence for clinician underprescription of and patient non-adherence to guideline-recommended cardiovascular medications among adults with peripheral artery disease: protocol for a systematic review and meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2023-076795.R1
Article Type:	Protocol
Date Submitted by the Author:	14-Feb-2024
Complete List of Authors:	de Launay, David; Queen's University, Department of Surgery Paquet, Maude; University of Ottawa, Division of Vascular and Endovascular Surgery, Department of Surgery Kirkham, Aidan; University of Ottawa, Division of Vascular and Endovascular Surgery, Department of Surgery Graham, Ian; Ottawa Hospital Research Institute, Clinical Epidemiology Program; University of Ottawa, Department of Clinical Epidemiology Fergusson, Dean; Ottawa Hospital Research Institute, Clinical Epidemiology Nagpal, Sudhir; University of Ottawa, Department of Surgery; The Ottawa Hospital Shorr , Risa; Ottawa Hospital, Learning Services Grimshaw, Jeremy; Ottawa Health Research Institute, Clinical Epidemiology Program Roberts, Derek; Ottawa Health Research Institute, Division of Vascular and Endovascular Surgery, Department of Surgery
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Health services research
Keywords:	Vascular medicine < INTERNAL MEDICINE, Risk Factors, Systematic Review, Vascular surgery < SURGERY, VASCULAR MEDICINE, VASCULAR SURGERY

Evidence for clinician underprescription of and patient non-adherence to guideline-recommended cardiovascular medications among adults with peripheral artery disease: protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction: International guidelines recommend that adults with peripheral artery disease (PAD) be prescribed antiplatelet, statin, and antihypertensive medications. However, it is unclear how often people with PAD are underprescribed these drugs, which characteristics predict clinician underprescription of and patient non-adherence to guideline-recommended cardiovascular medications, and whether underprescription and non-adherence is associated with adverse health and health system outcomes.

Methods and analysis: We will search MEDLINE, EMBASE, and Evidence-Based Medicine Reviews from 2006 onwards. Two investigators will independently review abstracts and full-text studies. We will include studies that enrolled adults and reported the incidence and/or prevalence of clinician underprescription of or patient non-adherence to guideline-recommended cardiovascular medications among people with PAD; adjusted risk factors for underprescription of/non-adherence to these medications; and adjusted associations between underprescription/non-adherence to these medications and outcomes. Outcomes will include mortality, major adverse cardiac and limb events (including revascularization procedures and amputations), other reported morbidities, healthcare resource use, and costs. Two investigators will independently extract data and evaluate risk of bias. We will calculate summary estimates of the incidence and prevalence of clinician underprescription/patient non-adherence across studies. We will also conduct subgroup meta-analyses and meta-regression to determine if estimates vary by country, characteristics of the patients and treating clinicians, population- versus non-population-based design, and study risks of bias. Finally, we will calculate pooled adjusted risk factors for underprescription/non-adherence and adjusted associations between

underprescription/non-adherence and outcomes. We will use GRADE to determine estimate certainty.

Ethics and dissemination: Ethics approval is not required as we are studying published data. This systematic review will synthesize existing evidence regarding clinician underprescription of and patient non-adherence to guideline-recommended cardiovascular medications in adults with PAD. This will be used to identify evidence-care gaps and inform where interventions may be required to improve clinician prescribing and patient adherence to prescribed medications.

Protocol registration number: CRD42022362801

KEYWORDS

Peripheral artery disease, practice guideline, drug prescription, platelet aggregation inhibitors, antihypertensive agents, hydroxymethylglutaryl-CoA reductase inhibitors

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Strengths of this study include the creation of a detailed protocol in accordance with rigorous systematic review conduct and reporting and Sex and Gender Equity in Research guidelines; development of a piloted and peer-reviewed search strategy; and our extensive pre-planned meta-analyses, stratified meta-analyses, and meta-regressions.
- Two investigators will also independently evaluate risk of risk of the included studies using the Joanna Brigg's Institute critical appraisal checklist of studies reporting prevalence data, the Quality in Prognosis Studies tool, and, for those studies that used administrative data, we will examine whether study authors considered the accuracy of codes used to define study variables.
- Finally, we will use Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) to assess certainty in the estimates of associations between the reported risk factors and clinician underprescription and patient non-adherence and between underprescription and non-adherence and outcomes.
- Limitations of the study include our potential reliance on studies using administrative health data, which may put our meta-analyses at variable risk for misclassification bias.
- Further, evidence-based guidelines for peripheral artery disease vary somewhat by time and across countries; to account for this, we will report data for underprescription according to the clinical practice guideline setting and time during which it was published.

INTRODUCTION

The international incidence and prevalence of peripheral artery disease (PAD) is rising,[1] and people with PAD are typically older, current or past cigarette smokers, and have multiple comorbidities, including diabetes, coronary artery disease (CAD), and cerebrovascular disease (CVD).[2] The care of people with PAD is costly as they have a high annual incidence of visits to primary health care providers, emergency departments, and vascular specialists; hospital admissions; open and endovascular lower limb revascularization procedures; and minor (below-ankle) and major (above-ankle) lower limb amputations.[3] Those with chronic limb-threatening ischemia (CLTI), an advanced form of PAD manifested by ischemic rest pain, tissue loss, or toe or foot gangrene, suffer a substantial burden of disability and pain and >60% visit the emergency department annually.[4–7]

International clinical practice guidelines strongly and consistently *recommend* that people with PAD be prescribed antiplatelet and statin (i.e., HMG-CoA reductase inhibitor) medications because class-1 evidence supports that the benefit of these medications greatly outweighs their risks.[5,8–11] They also strongly *recommend* that all those with PAD and hypertension be prescribed antihypertensive medications (and many guidelines *suggest* that these should preferably be angiotensin-targeted agents).[5,8–11] These recommendations mirror those for people with CAD and CVD because antiplatelets, statins, and antihypertensives reduce risk of myocardial infarction, stroke, and death in large, well-designed and -conducted randomized controlled trials (RCTs) that enrolled participants with PAD, CAD, and/or CVD.[5,8–11] RCTs that enrolled PAD patients have also reported that these medications reduce risk of lower limb revascularization, acute lower limb ischemia, and major lower limb amputation, an outcome rated by many people with PAD as worse than death.[12–15]

However, several cohort studies have reported that antiplatelet, statin, and antihypertensive medications may be underprescribed to adults with PAD, especially when compared to those who have CAD or CVD.[16–25] In support of this, a 2007 study conducted in a Canadian tertiary care hospital reported that 69% of people with PAD were not prescribed a statin and 48% with PAD and hypertension were not prescribed an angiotensin-converting enzyme (ACE) inhibitor.[26] Further, a recent cross-sectional survey found that less than half of vascular surgeons (the specialists who most commonly medically and surgically manage patients with the most severe forms of PAD) routinely initiated or modified statin therapy and fewer than 10% prescribed angiotensin-targeted or other antihypertensive therapy.[27]

Objectives

No evidence synthesis has examined the frequency of clinician underprescription of and patient non-adherence to guideline-recommended cardiovascular medications among adults with PAD, patient and clinician characteristics that predict underprescription of and non-adherence to these medications, and the association between underprescription of and non-adherence to these medications and adverse health and healthsystem outcomes. The primary objective of this systematic review is therefore to meta-analyze reported direct estimates of the incidence and prevalence of healthcare provider underprescription of and patient non-adherence to guideline-recommended medications in adults with PAD. Secondary objectives are to identify and summarize characteristics of the patient and treating clinician that predict clinician underprescription of and patient non-adherence to guideline-recommended medications in multivariable, adjusted analyses and determine whether underprescription and non-adherence is associated with an increased adjusted risk of mortality, major adverse cardiac and limb events

(including revascularization procedures and major amputations), other morbidities, healthcare resource use, and costs. We will include adjusted instead of unadjusted predictor estimates because these are recommended by rigorous systematic review methodologic guidance documents to examine the independent prognostic value of these predictors over and above (i.e., adjusted for) other prognostic factors.[28] The work will be used to identify international evidence-care gaps for adults with PAD that may be used to inform where implementation interventions may be required to improve healthcare provider prescribing of guideline-recommend cardiovascular medications to people with PAD and patient adherence to these prescribed medications.

METHODS

Protocol, reporting, and registration

We pre-specified our methods following recommendations for conducting systematic reviews and meta-analyses of prognostic factor studies.[28–30] This protocol is reported according to the Preferred Reporting Items in Systematic Reviews and Meta-Analyses-Protocols (PRISMA-P) statement[31,32] (see Supplementary Data, Appendix A) and Sex and Gender Equity in Research (SAGER) guidelines[33] (see Supplementary Data, Appendix B). It is registered on PROSPERO, the international prospective register of systematic reviews (PROSPERO registration number: CRD42022362801). The start date of the study was June 26, 2023 while the planned end date (submission of the manuscript for peer-review) is November 1, 2024.

Clinical questions

We formulated study clinical questions according to suggested frameworks for posing clinical questions for systematic reviews of prognostic factor studies.[29,30,34]

Primary clinical question

- In adults (age ≥18-years) with PAD, what is the pooled cumulative incidence, incidence rate, and point or period prevalence of clinician underprescription of and patient non-adherence to guideline-recommended cardiovascular medications?

Secondary clinical question

1. In adults (age ≥18-years) with PAD, does the pooled clinician underprescription of and patient non-adherence to guideline-recommended medications vary by country, characteristics of the treating clinician or patient, population-based design, or study risks of bias?
2. In adults (age ≥ 18-years) with PAD, which characteristics of the treating clinician and patient increase the pooled adjusted odds of underprescription of or non-adherence to guideline-recommended cardiovascular medications?
3. In adults (age ≥ 18-years) with PAD, is the underprescription of or non-adherence to guideline-recommended medications associated with an increased pooled adjusted odds of mortality, major adverse cardiac and limb events (including revascularization procedures and major amputations), other morbidities, healthcare resource use, and cost?

Definitions

We will define underprescription as not prescribing one or more guideline-recommended cardiovascular medications to adults with PAD. We will define patient medication non-adherence as not initially filling a prescription, failing to follow its medications instructions for use, and/or failure to refill and therefore continue a prescription despite the above being recommended by their healthcare provider.[35] We will define PAD as per the 2016 American College of Cardiology/American Heart Association (ACC/AHA) guideline as atherosclerotic disease of the lower limb arteries, including the aortoiliac, femoropopliteal, and infrapopliteal arterial segments, and excluding nonatherosclerotic disease of the lower extremity (e.g.,

fibromuscular dysplasia).[5] However, alternate definitions of PAD used by study authors will also be accepted.

Clinical practice guideline-recommended cardiovascular medications for PAD will be defined as antiplatelets (e.g. aspirin, clopidogrel), statins, and antihypertensives (e.g. ACE-inhibitors, angiotensin receptor blockers, beta-blockers, calcium-channel blockers, thiazide diuretics) (for people with PAD and concurrent hypertension). These are medications that are consistently recommended across multiple international evidence-based PAD clinical practice guidelines.[5,8–11,36,37] Since there is some variation in specific recommendations, we will accept individual study authors' definition of underprescription where underprescription was defined as per a certain published guideline and setting (see Supplementary Data, Appendix C for a comparison of medical therapy recommendations across PAD guidelines).

Antiplatelet therapy, antihypertensive drugs (for those with hypertension and PAD), and statins have been recommended in various ACC/AHA guidelines, including the 2005 PAD guideline.[36] Some discrepancies exist between the European guidelines, American guidelines, and the recently published Canadian guideline.[11,37] All three recommend antiplatelets for symptomatic PAD; however, they differ with regards to asymptomatic PAD. The European Society of Cardiology-European Society for Vascular Surgery (ESC-ESVS) and Canadian Cardiovascular Society (CCS) guidelines do not recommend antiplatelets in asymptomatic patients, while the ACC/AHA guideline does.[11] The recommendation to treat hypertension with an antihypertensive in people with PAD has been consistent across guidelines for years.[36] The most recent American, Canadian, and European guidelines recommended prescribing statins to all PAD patients. Medications that are consistently recommended across guidelines include antiplatelet therapy (e.g. aspirin, clopidogrel) for symptomatic PAD, antihypertensive therapy

(e.g. ACE-inhibitors, ARBs, beta blockers, CCBs, thiazide diuretics) for PAD and concurrent hypertension, and statins in patients with an LDL cholesterol ≥2.5 mmol/L/≥100 mg/dL.[5,8–11]

Information sources

We will search MEDLINE; EMBASE; and Evidence-Based Medicine Reviews (which includes ACP Journal Club; the Cochrane Central Register of Controlled Trials, Database of Systematic Reviews, and Methodology Register Database; Database of Abstracts of Reviews of Effects; Health Technology Assessment Database; and National Health Service Economic Evaluation Database) from January 1, 2006, without restrictions. We will start our search in 2006 as this is the year after publication of the first PAD treatment clinical practice guideline by ACC/AHA.[38] To identify additional citations, we will use the PubMed "related articles" feature and manually search bibliographies of included studies and relevant review articles identified during the search.

Search strategy

We created the MEDLINE and EMBASE search strategies with the assistance of an information-scientist/medical librarian (R.S.). Using a combination of Medical Subject Heading (MeSH) terms and keywords, search filters were constructed covering the themes *PAD* and *underprescription/non-adherence*. For *PAD*, we extracted disease-related keywords and MeSH subject headings used in a recent meta-analysis examining an exercise intervention for PAD.[39] For *underprescription/non-adherence*, we extracted keywords and MeSH subject headings used in a systematic review examining medication underuse in older adults.[40] We then used those terms to search for additional relevant studies in PubMed and extracted the MeSH terms that

those studies were indexed under. After the MEDLINE search strategy was created, we submitted it to another information-scientist/medical librarian to peer-review it using the Peer-Review of Electronic Search Strategies (PRESS) guideline[41] (see **Table 1** for our PRESS'd MEDLINE search strategy). Subsequently, we searched for Emtree terms that were similar to the above MeSH terms in EMBASE and created a list of non-MeSH/non-Emtree keywords for PAD guideline-recommended medications and underprescription/non-adherence (**Table 1**).

Data management and selection process

The titles and abstracts of citations identified during the search will be imported into Rayyan Systematic Review Software (https://www.rayyan.ai/).[42] Two investigators (D.D., M.P.) will use Rayyan to remove duplicates, independently review titles and abstracts of articles identified by the search, and select any article deemed potentially-relevant by either investigator for full-text review. These two investigators will subsequently review the full-text of all potentially-relevant citations and select studies for inclusion in the systematic review. Disagreements regarding study inclusion will be resolved via consensus or arbitration by the senior investigator (D.J.R.). Chance-corrected agreement between investigators regarding full-text inclusion will be calculated using a kappa statistic.[43]

Eligibility criteria and outcomes

We will use the following inclusion criteria:[30,34]

- The study included adults (age ≥ 18-years) with PAD
- The study reported one or more of the following outcomes (or these outcomes could be calculated from the data provided):

1. Cumulative incidence, incidence rate, or point or period prevalence of clinician underprescription of or patient non-adherence to guideline-recommended medications in adults with PAD
2. Odds ratios (ORs), risk ratios (RRs), or hazard ratios (HRs) [and surrounding standard errors or 95% confidence intervals (CIs)] adjusted for the presence of other clinician (e.g., specialty, years of training) and patient (e.g., age, rural versus urban residence) risk and confounding factors and relating one or more potential risk factor of interest to the underprescription of or non-adherence to guideline-recommended medications for PAD;

   OR
3. ORs, RRs, HRs or other measures (and surrounding standard errors or 95% CIs) describing differences in mortality, major adverse cardiac and limb events (including revascularization procedures and major amputations), other morbidities, healthcare resource use, and costs associated with underprescription of or non-adherence to guideline-recommended medication for PAD and adjusted for the presence of other risk factors or confounding factors.

- The study design was observational (i.e., cohort, case-control, or cross-sectional, including studies nested within RCTs[44,45]).

We will exclude studies that were: 1) grey literature; 2) published only as an abstract; 3) only enrolled patients before the year 2006; 4) only reported unadjusted risk factors for underprescription or non-adherence or unadjusted associations between underprescription or

non-adherence and outcomes; or 5) did not distinguish between underprescription and non-adherence (e.g., reported underuse without a description).

Data items and collection process

Two investigators will independently extract data in duplicate using a data extraction tool piloted on a random sample of five included studies (see **Table 2** for data items to be extracted). Where reported comparisons between the frequency of prescription of guideline-recommended medications to patients with PAD instead of CAD or CVD, these will also be extracted as well. Three investigators will independently extract data when they are only presented visually (e.g., a bar graph) and then their results will be averaged.

Risk of bias assessment

Two investigators will independently evaluate the risk of bias of studies reporting incidence and prevalence estimates using the Joanna Briggs Institute's critical appraisal checklist of studies reporting prevalence data.[29] The Joanna Briggs checklist includes questions about whether the sample frame was appropriate to address the target population, participants were sampled in an appropriate way, sample size was adequate, study participants (i.e., both patients and treating clinicians) and setting was described in detail, the data analysis was conducted with sufficient coverage of the identified sample, valid methods were used for the identification of the condition, the condition was measured in a standard and reliable way, and the statistical analyses were appropriate.[29] Those studies that reported risk factors for clinician underprescription of or patient non-adherence to guideline-recommended medications for PAD or associations between underprescription and outcomes will also be independently evaluated by two

investigators using the Quality in Prognosis Studies tool.[46,47] This tool includes questions regarding study participation and attrition; potential risk factor and outcome description and measurement; confounding measurement and account; and methods and reporting of statistical analyses.[46,47] For those studies that used administrative data, we will also examine whether the study authors considered the accuracy (sensitivity and specificity) of the codes used to define variables. Disagreements regarding risk of bias assessments will be resolved by consensus or arbitration by the senior investigator.

Qualitative data synthesis

We will perform a narrative synthesis of the included studies and their reported data before considering meta-analyses.[48] We will first tabulate characteristics of the included studies, including their design, data source, setting, recruitment period, included treating clinicians and patients, and reported outcomes. This tabulation will help us identify potentially duplicate data and where meta-analyses may be appropriate.

Quantitative data synthesis and statistical analyses

Where it was not reported, we will calculate the cumulative incidence, incidence rate, and point or period prevalence of clinician underprescription of and patient non-adherence to guideline-recommended medications for PAD. Cumulative incidence will be calculated using the following formula:

$$\text{Cumulative incidence} = \frac{\text{Number of new cases of underprescription of or non} - \text{adherence to guideline recommended medication for PAD}}{\text{Total population at risk}}$$

where the total population at risk will be defined as the number of adults with PAD. Incidence rate will be determined using the formula:

$$\text{Incidence rate} = \frac{\text{Number of new cases of underprescription of or non} - \text{adherence to guideline recommended medication for PAD}}{\text{Total person} - \text{time at risk}}$$

Point or period prevalence will be determined using the formula:

$$\text{Point or period prevalence} = \frac{\text{Number of existing cases of underprescription of or non} - \text{adherence to guideline recommended medication for PAD at a point in time or over a period of time}}{\text{Total defined population at that time or over that period of time}}$$

The standard error and 95% confidence interval of these proportions will be determined using the Clopper-Pearson exact binomial method. As evidence-based guidelines for peripheral artery disease vary somewhat by time and across countries, we will report estimates of clinician underprescription according to the clinical practice guideline setting and time during which it was published.

Where we identify multiple studies that provide non-overlapping or non-duplicated data estimates of underprescription of or non-adherence to guideline-recommended medications for PAD, incidence or prevalence estimates will be pooled using DerSimonian and Laird random-effects models.[49] These pooled analyses will be done according to setting and clinical practice guideline source. As suggested by Barendregt *et al*., we will first transform these proportional

estimates using a double arcsine transformation prior to meta-analyses.[29,50] The data will then be back-transformed to incidence and prevalence estimates after meta-analyses.[29]

We will use the OR (for dichotomous outcomes) or standardized mean difference (for continuous outcomes) as the summary measures of choice for pooled risk factor and outcome analyses. Similar adjusted risk factor estimates and outcome associations will be pooled using DerSimonian and Laird random-effects models.[49] Where the OR was not reported, we will pool RRs or HRs instead. When adjusted estimates were calculated from the same data source across several studies, we will include the estimate derived from the largest study. As a sensitivity analysis, we will also recalculate the estimate using that derived from the potentially overlapping study that reported the most adjusted estimates as studies may have variably adjusted their estimates for potentially confounding factors.

We will inspect forest plots, calculate I^2 inconsistency statistics, and conduct tests of homogeneity to assess for inter-study heterogeneity in the above estimates.[51–53] We will consider I^2 statistics >25%, >50%, and >75% to represent low, moderate, and high degrees of heterogeneity, respectively.[52] In the presence of at least low inter-study heterogeneity in our pooled estimates of incidence and prevalence, we will conduct subgroup meta-analyses and meta-regression. We will use the following predictor variables to explore heterogeneity in these stratified meta-analyses and meta-regressions: country; percentages of patient sex, race, and socioeconomic status and patients with CAD, CVD, PAD, pulmonary disease, diabetes, chronic kidney disease, cancer, and a past or present smoking history; percentages of clinicians' sex, practice type (e.g., primary community care versus tertiary care center), clinician training (medicine, nursing), and clinician subspecialty (general practice, nurse practitioner, vascular surgery, general internal medicine, cardiology other); and population-based design versus not.

We will evaluate for evidence of small study effects potentially due to publication bias by visually inspecting funnel plots of incidence and prevalence of underprescription and using Egger's tests.[54] We will use the study sample size instead of the inverse of the standard error on the y-axis as this may perform more favourably in these analyses.[29,55] Statistical analyses will be performed by a trained meta-analyst using Stata version 13.0 (Stata Corp., College Station, Texas, USA).

Certainty in the cumulative evidence

We will use Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) to assess certainty in the estimates of associations between the reported risk factors and clinician underprescription and patient non-adherence and between underprescription/non-adherence and outcomes.[56] We will first assess the risk of bias, imprecision, inconsistency, indirectness, and publication bias associated with the evidence for the reported risk factors.[57–61] Estimate certainty will then be adjudicated as high (further research is very unlikely to change the estimate), moderate (further research could have an important impact, which may change the estimate), or low (further research is very likely to have an important impact, which is likely to change the estimate).

PATIENT AND PUBLIC INVOLVEMENT

There is no patient involvement in the development of this systematic review.

ETHICS AND DISSEMINATION

No ethics approval is required for this study as it includes previously published data. International clinical practice guidelines have strongly and consistently recommended that antiplatelets, statins, and antihypertensives be prescribed to adults with PAD to prevent morbidity, mortality, lower limb revascularization, and major amputation. This study seeks to determine how often these medications are underprescribed by clinicians to these patients and how often patients do not adhere to them after prescription. We also seek to compare the frequency with which these medications are prescribed to those with PAD instead of CAD or CVD, identify patient and treating clinician characteristics that predict underprescription of and non-adherence to these guideline-recommended medications in adults with PAD, and estimate outcomes associated with underprescription of and non-adherence to these medications in people with PAD. Finally, as sex-based differences in PAD mortality have been observed,[62] we will also examine whether the above varies by patient sex.

This proposed systematic review has both strengths and limitations. The strengths of our study include the creation of a detailed protocol in accordance with rigorous systematic review conduct and reporting and SAGER guidelines; the piloted and peer-reviewed search strategy; and our extensive pre-planned meta-analyses, stratified meta-analyses, and meta-regressions. A limitation is likely a reliance on studies using administrative health data, which may put our meta-analyses at variable risk for misclassification bias. An additional concern with administrative data studies is that their measurement of complications has been suggested to have high specificity, but low sensitivity.[63] A final important limitation is the slight inconsistencies that exist between evidence-based guidelines for PAD across time and countries.

To account for this, we will report data for underprescription according to the clinical practice guideline setting and time during which it was published.

The aim of this systematic review will be to identify evidence-care gaps for PAD, compare these gaps across different countries and settings, and identify those patients at highest risk for clinician underprescription and patient non-adherence and physician characteristics related to underprescribing and non-adherence. We will also seek to quantify the importance of these gaps, notably how underprescription of and non-adherence to these medications influences PAD patient outcomes and the burden on the healthcare system. If our study identifies that an important gap between clinical practice guideline recommendations and healthcare provider and patient behaviors, it may justify design and testing of implementation strategies to improve prescription of guideline-recommended cardiovascular medications to adults with PAD and possibly patient adherence to these medications after prescription.

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AUTHORS CONTRIBUTIONS

DdL and DJR contributed to the conceptualization of the study and drafted the initial manuscript. DdL, MP, DJR, and RS created and revised the search strategy. DdL, MP, AMK, IDG, DF, SKN, RS, JMG, and DJR contributed to the design of the study methods. DdL drafted the manuscript. DdL, MP, AMK, IDG, DF, SKN, RS, JMG, and DJR revised the manuscript for important intellectual content. DdL, MP, AMK, IDG, DF, SKN, RS, JMG, and DJR approved the final version of the manuscript and agreed to submit it for publication.

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COMPETING INTERESTS

The authors have no conflicts of interest to declare.

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WORD COUNT

3448 / 4000

Table 1. PRESS'd search strategies.

Ovid MEDLINE	
1	Arterial Occlusive Diseases/
2	Arteriolosclerosis/
3	Arteriosclerosis/
4	Arteriosclerosis Obliterans/
5	Intermittent Claudication/
6	Intermittent Claudic*.tw,kf.
7	arteriosclero*.tw,kf.
8	exp Peripheral Vascular Diseases/
9	(limb adj2 isch?em*).tw,kf.
10	(periph* adj2 arter* adj2 disease*).tw,kf.
11	or/1-10
12	(under utili* or underutili*).tw,kf.
13	"under use*".tw,kf.
14	underusage.tw,kf.
15	underuse*.tw,kf.
16	under usage.tw,kf.
17	underprescri*.tw,kf.
18	under prescri*.tw,kf.
19	(under treat* or undertreat*).tw,kf.
20	((inadequate or deficien* or insufficien* or substandard or suboptimal) adj3 (treatment or management or control or therap*)).tw,kf.
21	Health Services Accessibility/ or "Delivery of Health Care"/ or Practice Patterns, Physicians'/
22	Guideline Adherence/ or Prescriptions/ or Drug Prescriptions/ or Drug Utilization/
23	Medication Adherence/ or "Treatment Adherence and Compliance"/
24	((prescription or prescribing) adj2 (rate* or practice*)).tw,kf.
25	adheren*.tw,kf.
26	((treatment or practice) adj2 pattern*).tw,kf.
27	(noncomplian* or nonadheren*).tw,kf.
28	((treatment or prescribing or therapy) adj3 complian*).tw,kf. or complian*.ti.
29	or/12-28
30	11 and 29
31	limit 30 to yr="2006 -Current"
32	exp animals/ not humans/
33	31 not 32
34	33 use medall
Ovid EMBASE	
35	exp peripheral occlusive artery disease/
36	intermittent claudication/ or Intermittent Claudic*.tw.
37	(limb adj2 isch?em*).tw.
38	(periph* adj2 arter* adj2 disease*).tw.
39	arteriolosclerosis/ or arteriosclerosis/ or arteriosclero*.tw.
40	or/35-39
41	(under utili* or underutili*).tw.
42	"under use*".tw.
43	underusage.tw.
44	underuse*.tw.
45	under usage.tw.
46	underprescri*.tw.
47	under prescri*.tw.
48	(under treat* or undertreat*).tw.
49	((inadequate or deficien* or insufficien* or substandard or suboptimal) adj3 (treatment or management or control or therap*)).tw.
50	*health care access/ or unmet medical need/

51	*health care delivery/
52	*clinical practice/
53	((treatment or practice) adj2 pattern*).tw.
54	((prescription or prescribing) adj2 (rate* or practice*)).tw.
55	protocol compliance/
56	drug utilization/
57	*"drug use"/ or *prescription/
58	((treatment or prescribing or therapy) adj3 adheren*).tw. or adheren*.ti.
59	((treatment or prescribing or therapy) adj3 complian*).tw. or complian*.ti.
60	(noncomplian* or nonadheren*).tw.
61	or/41-60
62	40 and 61
63	(exp animal/ or nonhuman/) not exp human/
64	62 not 63
65	limit 64 to yr="2006 -Current"
66	65 use emczd
67	34 or 66

Table 2. Data items to be extracted from included studies.

Data item theme	Items to be extracted
Study characteristics	Design Data source Study setting [country, whether the country was high- or middle/low income, and rural- versus urban-setting (as defined by study authors)] Patient recruitment period Definition of PAD Sample size
Included patient characteristics	Number and percentages of: Patient sex, race, and socioeconomic status Patients with CAD, CVD, and PAD; pulmonary disease; diabetes; chronic kidney disease; cancer; and a past or present smoking history
Included clinician characteristics	Number and percentages of their: Sex Practice type (e.g., primary community care versus tertiary care center) Clinician training (medicine, nursing) Clinician subspecialty (general practice, nurse practitioner, vascular surgery, general internal medicine, cardiology, and other)
Occurrence rate estimates	Reported cumulative incidence, incidence rate, and point or period prevalence of clinician underprescription of or patient non-adherence to guideline-recommended cardiovascular medications
Reported adjusted risk factors	Reported adjusted risk factors for clinician underprescription of or patient non-adherence to guideline-recommended cardiovascular medications (and their surrounding 95% CIs)
Reported adjusted outcome associations	Reported adjusted associations between clinician underprescription of or patient non-adherence to guideline-recommended cardiovascular medications and mortality, major adverse cardiac and limb events (including revascularization procedures and major amputations), other morbidities, healthcare resource use, and costs (and their surrounding 95% CIs)
Model covariates	Which other prognostic or confounding factors were adjusted for in the above analyses

CAD: coronary artery disease, CI: confidence interval, CVD: cerebrovascular disease, PAD: peripheral artery disease.

Evidence for Underprescription of and Non-Adherence to Guideline-Recommended Cardiovascular Medications in Adults with Peripheral Artery Disease: Protocol for a Systematic Review and Meta-Analysis

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	✓
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Title Page, Page 1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	Not applicable
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	CRD42022362801, Page 4 and 9
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Page 2
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Page 31
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	Page 31
Sponsor	5b	Provide name for the review funder and/or sponsor	Page 31
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	Page 31
INTRODUCTION			

Rationale	6	Describe the rationale for the review in the context of what is already known	Introduction, Page 6-7
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Introduction, Page 7-8
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Methods, Page 13-15
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Methods, Page 12
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Methods, Page 12-13
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Methods, Page 13
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Methods, Page 13
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Methods, Page 15
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Methods, Page 15
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Methods, Page 13-15
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Methods, Page 15-16
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Methods, Page 16-19

	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	Methods, Page 17-19
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Methods, Page 17-19
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	N/A
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Methods, Page 19
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Methods, Page 19

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

Evidence for Underprescription of and Non-Adherence to Guideline-Recommended Cardiovascular Medications in Adults with Peripheral Artery Disease: Protocol for a Systematic Review and Meta-Analysis

Sex and Gender Equity in Research (SAGER) checklist

✓	Checklist item	Reported on section
General		
Yes	The terms sex/gender used appropriately	Introduction, methods
Title		
N/A	Title specifies the sex/gender of participants if only one included	N/A
Abstract		
N/A	Abstract specifies the sex/gender of participants if only one included	N/A
N/A	Study population described with sex/gender breakdown*	N/A
Introduction		
Yes	If relevant, previous studies that show presence or lack of sex/gender differences or similarities are cited	Introduction
Yes	Mention of whether sex/gender might be an important variant and if differences might be expected	Introduction
N/A	The demographics of the study population with regard to sex/gender (eg, disease prevalence among male/female study participants) are outlined*	N/A
Methods		
Yes	Method of definition of sex/gender (eg, self-report, genetic testing)	Methods
Yes	Description of how sex/gender was considered in the design, whether authors ensured adequate representation of male and female study participants, justification of the reasons for any exclusion of male or female participants, or explanation if not considered. Justification of other sex/gender-specific interventions of study designs (eg, mandating contraception for women).* Explicit reporting of the scientific rationale for contraception requirements and exclusions for pregnancy and lactation should be required*	Methods
Results (N/A – protocol paper)		
Discussion		
Yes	Potential implications of sex/gender on the study results and analyses, including the extent to which the findings can be generalized to all sexes/genders in a population	Yes

N/A	If a sex/gender analysis not done, a rationale is given and implications of the lack of such analysis on the interpretation of the results are discussed	N/A

Adapted from SAGER guidelines. Sex and Gender Equity in Research: rationale for the SAGER guidelines and recommended use. Research Integrity and Peer Review 1, Article number: 2 (2016) https://researchintegrityjournal.biomedcentral.com/articles/10.1186/s41073-016-0007-6.
* These points extend beyond the original SAGER table

Source: https://ease.org.uk/wp-content/uploads/2023/01/EASE-SAGER-Checklist-2022.pdf

Appendix C. Comparison of antiplatelet, antihypertensive, and statin guidance across international guidelines for PAD.

Guideline, evidence grading	Antiplatelet	Antihypertensives	Statins
ACC/AHA 2005[1] **Class I:** Benefit >>> Risk. Procedure/ Treatment SHOULD be performed/ administered **Class IIa:** Benefit >> Risk. Additional studies with focused objectives needed. IT IS REASONABLE to perform procedure/ administer treatment **Class IIb:** Benefit ≥ Risk. Additional studies with broad objectives needed; Additional registry data would be helpful. Procedure/ treatment MAY BE CONSIDERED. **Class III:** Risk ≥ Benefit. No additional studies needed. Procedure/ treatment should not be performed/administered SINCE IT IS NOT HELPFUL AND MAY BE HARMFUL **Level A:** Multiple (3-5) population risk strata evaluated. General consistency of direction and magnitude of effect. **Level B:** Limited (2-3) population risk strata evaluated. **Level C:** Very limited (1-2) population risk strata evaluated.	**Class I** 1. Antiplatelet therapy is indicated to reduce the risk of MI, stroke, or vascular death in individuals with atherosclerotic lower extremity PAD. (**Level A**). 2. Aspirin, in daily doses of 75 to 325 mg, is recommended as safe and effective antiplatelet therapy to reduce the risk of MI, stroke, or vascular death in individuals with atherosclerotic lower extremity PAD. (**Level A**) 3. Clopidogrel (75 mg per day) is recommended as an effective alternative antiplatelet therapy to aspirin to reduce the risk of MI, stroke, or vascular death in individuals with atherosclerotic lower extremity PAD. (**Level B**) **Class III** Oral anticoagulation therapy with warfarin is not indicated to reduce the risk of adverse cardiovascular ischemic events in individuals with atherosclerotic lower extremity PAD. (**Level C**)	**Class I** 1. Antihypertensive therapy should be administered to hypertensive patients with lower extremity PAD to achieve a goal of less than 140 mm Hg systolic over 90mm Hg diastolic (nondiabetics) or less than 130 mmHg systolic over 80 mm Hg diastolic (diabetics and individuals with chronic renal disease) to reduce the risk of MI, stroke, congestive heart failure, and cardiovascular death. (**Level A**) 2. Beta-adrenergic blocking drugs are effective antihypertensive agents and are not contraindicated inpatients with PAD. (**Level A**) **Class IIa** The use of angiotensin-converting enzyme inhibitors is reasonable for symptomatic patients with lower extremity PAD to reduce the risk of adverse cardio-vascular events. (**Level B**) **Class IIb** Angiotensin-converting enzyme inhibitors may be considered for patients with asymptomatic lower extremity PAD to reduce the risk of adverse cardio-vascular events. (**Level C**)	**Class I** Treatment with a hydroxymethyl glutaryl (HMG)coenzyme-A reductase inhibitor (statin) medication is indicated for all patients with PAD to achieve a target LDL cholesterol level of less than 100 mg per dL. (**Level B**) **Class IIa** 1. Treatment with an HMG coenzyme-A reductase inhibitor (statin) medication to achieve a target LDL cholesterol level of less than 70 mg per dL is reasonable for patients with lower extremity PAD at very high risk of ischemic events. (**Level B**) 2. Treatment with a fibric acid derivative can be useful for patients with PAD and low HDL cholesterol, normal LDL cholesterol, and elevated triglycerides. (**Level C**)
ACC/AHA 2016[2] **Class I:** Benefit >>> Risk (STRONG) **Class IIa:** Benefit >> Risk (MODERATE) **Class IIb:** Benefit ≥ Risk	**Class I** Antiplatelet therapy with aspirin alone (range 75–325 mg per day) or clopidogrel alone (75 mg per day) is recommended to reduce MI, stroke, and vascular death in patients	**Class I** Antihypertensive therapy should be administered to patients with hypertension and PAD to reduce the risk of MI, stroke, heart failure, and cardiovascular death. (**Level A**)	**Class I** 1. Treatment with a statin medication is indicated for all patients with PAD. (**Level A**)

(WEAK) **Class 3: No benefit.** Benefit = Risk (MODERATE) **Class 3: Harm.** Risk > Benefit (STRONG) **Level A:** High-quality evidence from more than 1 RCT; meta-analyses of high quality RCTs; one or more RCTs corroborated by registry studies **Level B-R:** Moderate-quality evidence from 1 or more RCTs; meta-analyses of moderate-quality RCTs **Level B-NR:** Moderate-quality evidence from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies; meta-analyses of such studies **Level C-LD:** Randomized or nonrandomized observational or registry studies with limitations of design or execution; meta-analyses of such studies; physiological or mechanistic studies in human subjects **Level C-EO:** Consensus of expert opinion based on clinical experience	with symptomatic PAD. (**Level A**) **Class IIa** In asymptomatic patients with PAD (ABI ≤0.90), antiplatelet therapy is reasonable to reduce the risk of MI, stroke, or vascular death. (**Level C-EO**) **Class IIb** 1. In asymptomatic patients with borderline ABI (0.91–0.99), the usefulness of antiplatelet therapy to reduce the risk of MI, stroke, or vascular death is uncertain. (**Level B-R**) 2. The effectiveness of dual antiplatelet therapy (DAPT) (aspirin and clopidogrel) to reduce the risk of cardiovascular ischemic events in patients with symptomatic PAD is not well established. (**Level B-R**) 3. DAPT (aspirin and clopidogrel) may be reasonable to reduce the risk of limb-related events in patients with symptomatic PAD after lower extremity revascularization. (**Level C-LD**) 4. The overall clinical benefit of vorapaxar added to existing antiplatelet therapy in patients with symptomatic PAD is uncertain. (**Level B-R**)	**Class IIa** The use of angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers can be effective to reduce the risk of cardiovascular ischemic events in patients with PAD. (**Level A**)	
CCS Consensus Conference 2005[3] **Quality of Evidence** **I:** Evidence obtained from at least one properly randomized controlled trial or one large epidemiological study. **II:** Evidence based on at least one non-	**Grade 1A** Medical therapies to reduce cardiovascular events in PAD: Antiplatelets **Grade 1A** Lifelong antiplatelet therapy with aspirin (75 to 325 mg/d) or clopidogrel (75 mg/day) in patients with or without clinically	**Grade 1A** Medical therapies to reduce cardiovascular events in PAD: ACE inhibitors. There is evidence that ACE inhibitors may be effective irrespective of their blood pressure lowering effect, and therefore this class of drugs is a reasonable first	**Grade 1A** Medical therapies to reduce cardiovascular events in PAD: Statins

randomized cohort comparison or multi-centre study, chronological series or extra ordinarily results from large non-randomized studies. **III:** Opinions of respective authorities, based on clinical experience, descriptive studies or reports of expert committees. **Classification and Recommendations** **A:** Evidence sufficient for universal use (usually based on randomized clinical trials). **B:** Evidence acceptable for widespread use, evidence less robust, but based on randomized clinical trials. **C:** Evidence not based on randomized clinical trials.	manifest coronary or cerebrovascular disease. **Grade 1B** Aspirin or Clopidogrel recommended over ticlopidine **Grade 1B** Cilostazol is recommended for patients with disabling intermittent claudication who do not respond to conservative measures (risk factor modification and exercise therapy) and who are not candidates for surgical or catheter-based intervention **Grade 2B** Pentoxyfilline is not recommended **Grade 2B** Anticoagulant therapy (vitamin K antagonists) is not recommended	choice if blood pressure lowering is required. **No Grade assigned** Blood Pressure Lowering The evidence of the effectiveness of BP lowering in other vascular subgroups (…) taken together with the emerging data of its effectiveness in PAD patients allows us to advocate for aggressive BP lowering in this high-risk subgroup.	
CCS The Use of Antiplatelet Therapy in the Outpatient Setting 2011[4] **Class I:** Evidence and/or general agreement that a given diagnostic procedure/treatment is beneficial, useful, and effective **Class IIa:** Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the treatment with the weight of evidence in favour **Class IIb:** Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the treatment with the	**Class I** For patients with symptomatic PAD with overt CAD or cerebrovascular disease, antiplatelet therapy as indicated for the CAD and/or cerebrovascular status is recommended (**Level A**). **Class IIa** 1. For patients allergic or intolerant to ASA, use of clopi- dogrel is suggested (**Level B**). 2. For all infrainguinal reconstructions, low-dose ASA (75- 162 mg daily) should be given (**Level B**). 3. Long-term antiplatelet therapy with ASA 75-162 mg daily should be given to patients who undergo lower-extremity balloon angioplasty with or without stenting for	**N/A**	**N/A**

usefulness/ efficacy less well established **Class III:** Evidence that the treatment is not useful and in some cases may be harmful **Level A:** Data derived from multiple randomized clinical trials or meta-analyses **Level B:** Data derived from a single randomized clinical trial or large nonrandomized studies **Level C:** Consensus of opinion by experts and/or small studies, retrospective studies, and registries	chronic symptomatic PAD (**Level C**). **Class IIb** 1. For patients with symptomatic PAD without overt CAD or cerebrovascular disease, low-dose ASA (75-162 mg daily) or clopidogrel 75 mg daily is recommended, provid- ing the risk for bleeding is low (**Level B**). The choice of drug may depend on patient preference and cost considerations. 2. For patients with intermittent claudication, using clopidogrel 75 mg daily in addition to ASA 75-162 mg daily is not recommended unless the patient is judged to be at high vascular risk along with a low risk of bleeding (**Level B**). 3. For patients with asymptomatic PAD with an ABI < 0.9, low-dose ASA (75-162 mg daily) may be considered for those at high risk because of associated atherosclerotic risk factors in the absence of risk factors for bleeding (**Level C**). 4. In those with infrainguinal grafts and a high risk of thrombosis or limb loss, combination therapy with a vitamin K antagonist and ASA may be of benefit (**Level C**). 5. Low-dose ASA (75-162 mg daily) may be considered for all patients with an AAA, particularly those with clinical or subclinical PAD (**Level C**). **Class III** 1. For patients with symptomatic PAD with an indication for oral anticoagulation such as		

	atrial fibrillation, venous thromboembolism, heart failure, or mechanical valves, antiplatelet therapy should not be added to oral anticoagulation (**Level A**). 2. For patients with symptomatic PAD without compelling indications for oral anticoagulation such as atrial fibrillation or venous thromboembolism, oral anticoagulation should not be added to antiplatelet therapy (**Level B**). 3. Anticoagulation with heparin or vitamin K antagonists should be avoided in this setting (**Level B**). 4. For patients with intermittent claudication, dipyridamole should not be used in addition to ASA (**Level C**).		
CCS 2022 (PAD Guideline)[5] **Strength of Recommendation:** **Strong:** guideline panel is confident that the desirable effects of an intervention outweigh its undesirable effects (strong recommendation for an intervention) or that the undesirable effects of an intervention outweigh its desirable effects (strong recommendation against an intervention). **Weak:** the desirable effects probably outweigh the undesirable effects (weak recommendation for an intervention) or undesirable effects probably outweigh the desirable effects (weak recommendation against an intervention)	1. We recommend against routine antithrombotic therapy (antiplatelet or anticoagulant) for patients with isolated asymptomatic lower extremity PAD (**Strong Recommendation; High-Quality Evidence**). 2. 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 (**Strong**	1. We suggest that the approach to initiation and titration of antihypertensive agents should follow the Hypertension Canada guidelines (**Weak Recommendation; Low-Quality Evidence**). 2. We suggest treating hypertension to a target of less than 140/90 mm Hg in patients with PAD without compelling indications for specific agents or targets (**Weak Recommendation; Low-Quality Evidence**). 3. We recommend that PAD patients with hypertension be treated with ACE inhibitors or ARBs as the first choice in the absence of contraindications (**Strong Recommendation; Moderate-Quality Evidence**).	1. We recommend that patients with PAD qualify as statin-indicated patients and should receive lipid-modifying therapy for the reduction of death, CV death, nonfatal MI, nonfatal stroke (MACE), and MALE concordant with the recommendations in the 2021 Canadian Cardiovascular Society (CCS) guide- lines for the management of dyslipidemia (**Strong Recommendation; High-Quality Evidence**). a. Maximally tolerated dose of statin therapy b. Statin add-on therapies (ezetimibe and/or PCSK-9 inhibitors) if receiving maximally tolerated dose of statin therapy and the low-density lipoprotein cholesterol is ≥ 1.8 mmol/L, non-high-density lipoprotein cholesterol ≥ 2.4 mmol/L or apolipoprotein B100 ≥ 0.7 mg/dL.

but appreciable uncertainty exists. **Quality of Evidence:** **High:** We are very confident that the true effect lies close to that of the estimate of the effect. **Moderate:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different **Low:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect**.** **Very Low:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect	**Recommendation; High-Quality Evidence**). 3. 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 (**Strong Recommendation; High-Quality Evidence**). 4. 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 (**Strong Recommendation; High-Quality Evidence**). 5. We suggest that clopidogrel (75 mg daily) should be the preferred agent when single antiplatelet therapy is deemed to be the optimal antithrombotic choice (**Weak Recommendation; Moderate-Quality Evidence**). 6. We suggest that dual antiplatelet therapy(DAPT; 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 (**Weak Recommendation; Moderate-Quality Evidence**). 7. We recommend against the additional use of full-dose anticoagulation with antiplatelet therapy for the		2. We recommend that patients with PAD, who, despite maximally tolerated dose of statin therapy have a triglyceride level of 1.5-5.6 mmol/L, should be considered for use of icosapent ethyl for the reduction CV death, nonfatal MI, and nonfatal stroke concordant with the recommendations in the 2021 CCS guidelines for the management of dyslipidemia (**Strong Recommendation; Moderate-Quality Evidence**).

	purpose of decreasing MACE and MALE events in patients with stable lower extremity PAD (**Strong Recommendation; High-Quality Evidence**).		
ESC 2011[6] **Class I:** Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective. **Class II:** Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure. **Class IIa:** Weight of evidence/opinion is in favour of usefulness/efficacy. **Class IIb:** Usefulness/efficacy is less well established by evidence/opinion. **Class III:** Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful. **Level A:** Data derived from multiple randomized clinical trials or meta-analyses. **Level B:** Data derived from a single randomized clinical trial or large non-randomized studies. **Level C:** Consensus of opinion of the experts and/ or small studies, retrospective studies, registries.	**Class I** Antiplatelet therapy is recommended in patients with symptomatic PAD. (**Level C**)	**Class I** All patients with PAD should have their blood pressure controlled to ≤140/90 mmHg. (**Level A**) **Class IIa** ß-Blockers are not contraindicated in patients with LEAD, and should be considered in the case of concomitant coronary artery disease and/or heart failure (**Level B**)	**Class I** All patients with PAD should have their LDL cholesterol lowered to <2.5 mmol/L (100 mg/dL), and optimally to <1.8 mmol/L (70 mg/dL), or ≥ 50% when the target level cannot be reached. (**Level C**)
ESC-ESVS 2017[7]	**Class I** 1. Antiplatelet therapy is recommended in patients	**Class I** In patients with PADs and hypertension, it is	**Class I** 1. Statins are recommended in all

Class I: Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective. **Class II:** Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure. **Class IIa:** Weight of evidence/opinion is in favour of usefulness/efficacy. **Class IIb:** Usefulness/efficacy is less well established by evidence/opinion. **Class III:** Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful. **Level A:** Data derived from multiple randomized clinical trials or meta-analyses. **Level B:** Data derived from a single randomized clinical trial or large non-randomized studies. **Level C:** Consensus of opinion of the experts and/ or small studies, retrospective studies, registries.	with symptomatic PADs. (Level C) 2. Long-term SAPT is recommended in symptomatic patients. (**Level A**) **Class IIb** In patients requiring antiplatelet therapy, clopidogrel may be preferred over aspirin. (**Level B**) **Class III** Because of a lack of proven benefit, antiplatelet therapy is not routinely indicated in patients with isolated asymptomatic LEAD. (**Level A**)	recommended to control blood pressure at <140/90 mmHg. (**Level A**) **Class IIa** ACEIs or ARBs should be considered as first-line therapyc in patients with PADs and hypertension. (**Level B**)	patients with PADs. (**Level A**) 2. In patients with PADs, it is recommended to reduce LDL-C to < 1.8 mmol/L (70 mg/dL) or decrease it by >_50% if baseline values are 1.8–3.5 mmol/L (70–135 mg/dL). (**Level C**)
NICE 2012[8]	Offer all people with peripheral arterial disease information, advice, support and treatment regarding the secondary prevention of cardiovascular disease, in line with published NICE guidance on: - smoking cessation - diet, weight management and exercise - lipid modification and statin therapy - the prevention, diagnosis and management of diabetes - the prevention, diagnosis and management of high blood pressure - antiplatelet therapy		

ACC: American College of Cardiology, AHA: American Heart Association, CCS: Canadian Cardiovascular Society, ESC: European Society of Cardiology, ESVS: European Society for Vascular Surgery, NICE: National Institute for Health and Care Excellence, COR: class of recommendation, ABI: ankle-brachial index, ACEi: ace-inhibitor, ARB:

angiotensin II receptor blocker, BP: blood pressure, CAD: coronary artery disease, DAPT: dual-antiplatelet therapy, HDL: high-density-lipoprotein, LDL: low-density-lipoprotein, MI: myocardial infarction, PAD: peripheral artery disease, LEAD: lower extremity artery disease, SAPT: single-antiplatelet therapy, MACE: major adverse cardiovascular events, MALE: major adverse limb events

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