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

David de Launay,[1] Maude Paquet,[2] Aidan M Kirkham,[2] Ian D Graham,[3,4] Dean A Fergusson ,[5] Sudhir K Nagpal,[6,7] Risa Shorr,[8] Jeremy M Grimshaw,[9] Derek J Roberts [10]

To cite: de Launay D, Paquet M, Kirkham AM, *et al*. 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. *BMJ Open* 2024;**14**:e076795. doi:10.1136/bmjopen-2023-076795

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2023-076795).

Received 16 June 2023
Accepted 16 February 2024

For numbered affiliations see end of article.

Correspondence to
Dr Derek J Roberts;
Derek.Roberts01@gmail.com

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 are 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 revascularisation procedures and amputations), other reported morbidities, healthcare resource use and costs. Two investigators will independently extract data and evaluate study 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-based 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 Grading of Recommendations, Assessment, Development and Evaluation to determine estimate certainty.

Ethics and dissemination Ethics approval is not required as we are studying published data. This systematic review will synthesise existing evidence regarding clinician underprescription of and patient non-adherence to guideline-recommended cardiovascular medications

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 preplanned meta-analyses, stratified meta-analyses and meta-regressions.

⇒ Two investigators will also independently evaluate the risk of bias of the included studies using the Joanna Brigg's Institute critical appraisal checklist of studies reporting prevalence data and the Quality in Prognosis Studies tool. For those studies that used administrative data, we will also 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 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.

in adults with PAD. Results 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.
PROSPERO registration number CRD42022362801.

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 healthcare providers, emergency departments and vascular specialists; hospital admissions; open and endovascular lower limb revascularisation procedures and minor (below-ankle) and major (above-ankle) lower limb amputations.[3] Those with chronic limb-threatening ischaemia (CLTI), an advanced form of PAD manifested by ischaemic 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 [ie, 3-hydroxy-3-methylglutaryl coenzyme A (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 are 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 randomised 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 revascularisation, acute lower limb ischaemia 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 with 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 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 associations 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-analyse 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 summarise 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 revascularisation 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 methodological guidance documents to examine the independent prognostic value of these predictors over and above (ie, adjusted for) other prognostic factors.[28] Results of the work will be used to identify international evidence-care gaps for adults with PAD and 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 prespecified 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 statement[31 32] (see online supplemental appendix A) and Sex and Gender Equity in Research (SAGER) guidelines[33] (see online supplemental 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 26 June 2023 while the

planned end date (submission of the manuscript for peer-review) is 1 November 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 are 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

- 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?
- 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?
- In adults (age ≥18 years) with PAD, is clinician underprescription of or patient non-adherence to guideline-recommended medications associated with an increased pooled adjusted odds of mortality, major adverse cardiac and limb events (including revascularisation 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 medication instructions for use and/or failure to refill the prescription and therefore continue taking it despite 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 (eg, 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 (eg, aspirin, clopidogrel), statins and antihypertensives [eg, ACE-inhibitors, angiotensin receptor blockers (ARBs), beta-blockers, calcium-channel blockers (CCBs), 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 35 36] 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 online supplemental 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 regard to asymptomatic PAD. The European Society of Cardiology-European Society for Vascular Surgery and Canadian Cardiovascular Society 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 recommend prescribing statins to all PAD patients. Medications that are consistently recommended across guidelines include antiplatelet therapy (eg, aspirin, clopidogrel) for symptomatic PAD, antihypertensive therapy (eg, 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 1 January 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 (RS). 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 box 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 (box 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 (DdL and MP) 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 (DJR). 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):
  - 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.
  - ORs, risk ratios (RRs) or HRs [and surrounding standard errors (SEs) or 95% confidence intervals (CIs)] adjusted for the presence of other clinician (eg, specialty, years of training) and patient (eg, age, rural vs urban residence) risk and confounding factors and relating one or more potential risk factor of interest to the clinician underprescription of or patient non-adherence to guideline-recommended medications for PAD.
  - ORs, RRs, HRs or other measures (and surrounding SEs or 95% CIs) describing differences in mortality, major adverse cardiac and limb events (including revascularisation procedures and major amputations), other morbidities, healthcare resource use and costs associated with clinician underprescription of or patient non-adherence to guideline-recommended medication for PAD and adjusted for the presence of other risk factors or confounding factors.

Box 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/

Continued

Box 1 Continued

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

- The study design was observational (ie, 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 clinician underprescription and patient non-adherence (eg, 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 1 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 (eg, 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 (ie, both

Table 1 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 income 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 (eg, primary community care vs tertiary care centre) 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 revascularisation 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.

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 SE and 95% CI of these proportions will be determined using the Clopper-Pearson exact binomial method. As evidence-based guidelines for PAD 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 clinician underprescription of or patient 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 (standardised) 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 interstudy 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 interstudy 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 (eg, primary community care vs tertiary care centre), 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 SE 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 V.13.0 (StataCorp).

Certainty in the cumulative evidence

We will use Grading of Recommendations, Assessment, Development and Evaluation 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 revascularisation 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 preplanned 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 exists between clinical practice guideline recommendations and healthcare provider and patient behaviours, 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.

Author affiliations
[1]Department of Surgery, Queen's University, Kingston, Ontario, Canada
[2]Division of Vascular and Endovascular Surgery, Department of Surgery, University of Ottawa, Ottawa, Ontario, Canada
[3]Clinical Epidemiology Program, Ottawa Hospital Research Institute, Ottawa, Ontario, Canada
[4]Department of Clinical Epidemiology, University of Ottawa, Ottawa, Ontario, Canada
[5]Clinical Epidemiology, Ottawa Hospital Research Institute, Ottawa, Ontario, Canada
[6]Department of Surgery, University of Ottawa, Ottawa, Ontario, Canada
[7]The Ottawa Hospital, Ottawa, Ontario, Canada
[8]Learning Services, Ottawa Hospital, Ottawa, Ontario, Canada
[9]Clinical Epidemiology Program, Ottawa Health Research Institute, Ottawa, Ontario, Canada
[10]Division of Vascular and Endovascular Surgery, Department of Surgery, Ottawa Health Research Institute, Ottawa, Ontario, Canada

Twitter Derek J Roberts @DerekRoberts01

Contributors DdL and DJR contributed to the conceptualisation of the study and drafted the initial manuscript. DdL, MP, DJR and RS created and revised the search strategy. DdL, MP, AK, IDG, DAF, SKN, RS, JG and DJR contributed to the design of the study methods. DdL drafted the manuscript. DdL, MP, AK, IDG, DAF, SKN, RS, JG and DJR revised the manuscript for important intellectual content. DdL, MP, AK, IDG, DAF, SKN, RS, JG and DJR approved the final version of the manuscript and agreed to submit it for publication. All authors meet the ICMJE criteria for authorship.

Funding This study is supported by funding from Physician Services' Incorporated and a Research Program Award from the University of Ottawa, Department of Surgery. IDG is a recipient of a Canadian Institutes of Health Research Foundation Grant (FDN# 143237). The Division of Vascular and Endovascular Surgery, Department of Surgery, University of Ottawa in Ottawa, Ontario, Canada provided funds for open access publication, but otherwise had no input on manuscript writing, decision to submit manuscript or any other involvement.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
Dean A Fergusson http://orcid.org/0000-0002-3389-2485
Derek J Roberts http://orcid.org/0000-0001-6111-6291

REFERENCES

1 Criqui MH, Aboyans V. Epidemiology of peripheral artery disease. *Circ Res* 2015;116:1509–26.
2 Nehler MR, Duval S, Diao L, *et al*. Epidemiology of peripheral arterial disease and critical limb ischemia in an insured national population. *J Vasc Surg* 2014;60:686–95.
3 Chase MR, Friedman HS, Navaratnam P, *et al*. Comparative assessment of medical resource use and costs associated with patients with symptomatic peripheral artery disease in the United States. *J Manag Care Spec Pharm* 2016;22:667–75.
4 Roberts DJ, Nagpal SK, Forster AJ, *et al*. Disability, pain, and wound-specific concerns self-reported by adults at risk of limb loss: a cross-sectional study using the world health organization disability assessment schedule 2.0. *PLoS One* 2021;16:e0253288.
5 Gerhard-Herman MD, Gornik HL, Barrett C, *et al*. 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: a report of the American college of cardiology/American heart association task force on clinical practice guidelines. *Circulation* 2017;135:e726–79.
6 Conte MS, Bradbury AW, Kolh P, *et al*. Global vascular guidelines on the management of chronic limb-threatening ischemia. *J Vasc Surg* 2019;69:3S–125S.
7 Roberts DJ, Nagpal SK, Kubelik D, *et al*. Association between neuraxial anaesthesia or general anaesthesia for lower limb revascularisation surgery in adults and clinical outcomes: population based comparative effectiveness study. *BMJ* 2020;371:m4104.
8 Tendera M, Aboyans V, *et al*, European Stroke Organisation. ESC guidelines on the diagnosis and treatment of peripheral artery diseases: document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries. *Eur Heart J* 2011;32:2851–906.
9 National Institute for Health and Care Excellence. Peripheral arterial disease: diagnosis and management (CG147). 2012. Available: www.nice.org.uk/guidance/cg147
10 Aboyans V, Ricco J-B, Bartelink M-L, *et al*. 2017 ESC guidelines on the diagnosis and treatment of peripheral arterial diseases, in collaboration with the European society for vascular surgery (ESVS): document covering atherosclerotic disease of Extracranial carotid and vertebral, mesenteric, renal. *Eur Heart J* 2018;39:763–816.
11 Kithcart AP, Beckman JA. ACC/AHA versus ESC guidelines for diagnosis and management of peripheral artery disease: JACC guideline comparison. *J Am Coll Cardiol* 2018;72:2789–801.
12 Wong PF, Chong LY, Mikhailidis DP, *et al*. Antiplatelet agents for intermittent claudication. *Cochrane Database Syst Rev* 2011:CD001272.
13 Pastori D, Farcomeni A, Milanese A, *et al*. Statins and major adverse limb events in patients with peripheral artery disease: a systematic review and meta-analysis. *Thromb Haemost* 2020;120:866–75.
14 Kokkinidis DG, Arfaras-Melainis A, Giannopoulos S, *et al*. Statin therapy for reduction of cardiovascular and limb-related events in critical limb ischemia: a systematic review and meta-analysis. *Vasc Med* 2020;25:106–17.
15 Katsanos K, Spiliopoulos S, Saha P, *et al*. Comparative efficacy and safety of different antiplatelet agents for prevention of major cardiovascular events and leg amputations in patients with peripheral arterial disease: a systematic review and network meta-analysis. *PLoS One* 2015;10:e0135692.
16 Yao X, Shah ND, Gersh BJ, *et al*. Assessment of trends in Statin therapy for secondary prevention of atherosclerotic cardiovascular disease in US adults from 2007 to 2016. *JAMA Netw Open* 2020;3:e2025505.
17 Armstrong EJ, Chen DC, Westin GG, *et al*. Adherence to guideline-recommended therapy is associated with decreased major adverse cardiovascular events and major adverse limb events among patients with peripheral arterial disease. *J Am Heart Assoc* 2014;3:e000697.
18 Arya S, Khakharia A, Binney ZO, *et al*. Association of statin dose with amputation and survival in patients with peripheral artery disease. *Circulation* 2018;137:1435–46.
19 Berger JS, Ladapo JA. Underuse of prevention and lifestyle counseling in patients with peripheral artery disease. *J Am Coll Cardiol* 2017;69:2293–300.
20 Chen DC, Armstrong EJ, Singh GD, *et al*. Adherence to guideline-recommended therapies among patients with diverse manifestations of vascular disease. *Vasc Health Risk Manag* 2015;11:185–92.
21 Hoeks SE, Scholte op Reimer WJM, van Gestel YRBM, *et al*. Medication underuse during long-term follow-up in patients with peripheral arterial disease. *Circ Cardiovasc Qual Outcomes* 2009;2:338–43.
22 O'Donnell TFX, Deery SE, Darling JD, *et al*. Adherence to lipid management guidelines is associated with lower mortality and major adverse limb events in patients undergoing revascularization for chronic limb-threatening ischemia. *J Vasc Surg* 2017;66:572–8.
23 Pande RL, Perlstein TS, Beckman JA, *et al*. Secondary prevention and mortality in peripheral artery disease: national health and nutrition examination study, 1999 to 2004. *Circulation* 2011;124:17–23.
24 Saxon JT, Safley DM, Mena-Hurtado C, *et al*. Adherence to guideline-recommended therapy-including supervised exercise therapy referral-across peripheral artery disease specialty clinics: insights from the International PORTRAIT registry. *J Am Heart Assoc* 2020;9:e012541.
25 Subherwal S, Patel MR, Kober L, *et al*. Missed opportunities: despite improvement in use of cardioprotective medications among patients with lower-extremity peripheral artery disease, underuse remains. *Circulation* 2012;126:1345–54.
26 Kundhal KK, Chin SL, Harrison L, *et al*. Patterns of medical therapy in patients with peripheral artery disease in a tertiary care centre in Canada. *Can J Cardiol* 2007;23:357–61.
27 Li B, Salata K, de Mestral C, *et al*. Perceptions of Canadian vascular surgeons toward pharmacologic risk reduction in patients with peripheral artery disease: 2018 update. *Ann Vasc Surg* 2019;58:166–73.
28 Riley RD, Moons KGM, Snell KIE, *et al*. A guide to systematic review and meta-analysis of prognostic factor studies. *BMJ* 2019;364:k4597.
29 Mueller M, D'Addario M, Egger M, *et al*. Methods to systematically review and meta-analyse observational studies: a systematic scoping review of recommendations. *BMC Med Res Methodol* 2018;18:44.
30 Munn Z, Moola S, Lisy K, *et al*. Methodological guidance for systematic reviews of observational epidemiological studies reporting prevalence and cumulative incidence data. *Int J Evid Based Healthc* 2015;13:147–53.
31 Moher D, Shamseer L, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1.
32 Shamseer L, Moher D, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;350:g7647.
33 Heidari S, Babor TF, De Castro P, *et al*. Sex and gender equity in research: rationale for the SAGER guidelines and recommended use. *Res Integr Peer Rev* 2016;1:2.
34 Moons KGM, de Groot JAH, Bouwmeester W, *et al*. Critical appraisal and data extraction for systematic reviews of prediction modelling studies: the CHARMS checklist. *PLoS Med* 2014;11:e1001744.
35 Baroletti S, Dell'Orfano H. Medication adherence in cardiovascular disease. *Circulation* 2010;121:1455–8.
36 Morcos R, Louka B, Tseng A, *et al*. The evolving treatment of peripheral arterial disease through guideline-directed recommendations. *J Clin Med* 2018;7:9.
37 Abramson BL, Al-Omran M, Anand SS, *et al*. Canadian cardiovascular society 2022 guidelines for peripheral arterial disease. *Can J Cardiol* 2022;38:560–87.
38 Hirsch AT, Haskal ZJ, Hertzer NR, *et al*. ACC/AHA 2005 practice guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for vascular surgery/society for vascular sur. *Circulation* 2006;113:e463–654.
39 Golledge J, Singh TP, Alahakoon C, *et al*. Meta-analysis of clinical trials examining the benefit of structured home exercise in patients with peripheral artery disease. *Br J Surg* 2019;106:319–31.

40 Meid AD, Lampert A, Burnett A, *et al*. The impact of pharmaceutical care interventions for medication Underuse in older people: a systematic review and meta-analysis. *Br J Clin Pharmacol* 2015;80:768–76.
41 McGowan J, Sampson M, Salzwedel DM, *et al*. PRESS peer review of electronic search strategies: 2015 guideline statement. *J Clin Epidemiol* 2016;75:40–6.
42 Ouzzani M, Hammady H, Fedorowicz Z, *et al*. Rayyan-a web and mobile app for systematic reviews. *Syst Rev* 2016;5:210.
43 Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977;33:159–74.
44 Porta M, ed. *A Dictionary of Epidemiology*. 2014.
45 Dekkers OM, Egger M, Altman DG, *et al*. Distinguishing case series from cohort studies. *Ann Intern Med* 2012;156:37–40.
46 Hayden JA, Côté P, Bombardier C. Evaluation of the quality of prognosis studies in systematic reviews. *Ann Intern Med* 2006;144:427–37.
47 Hayden JA, van der Windt DA, Cartwright JL, *et al*. Assessing bias in studies of prognostic factors. *Ann Intern Med* 2013;158:280–6.
48 Popay J, Roberts H, Sowden A, *et al*. Guidance on the conduct of narrative synthesis in systematic reviews. Lancaster, UK Lancaster University; 2006.
49 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177–88.
50 Barendregt JJ, Doi SA, Lee YY, *et al*. Meta-analysis of prevalence. *J Epidemiol Community Health* 2013;67:974–8.
51 Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21:1539–58.
52 Higgins JPT, Thompson SG, Deeks JJ, *et al*. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557–60.
53 Egger M, Davey-Smith G, Altman D, eds. *Systematic reviews in health care: meta-analysis in context*. BMJ Books, 2001.
54 Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994;50:1088–101.
55 Hunter JP, Saratzis A, Sutton AJ, *et al*. In meta-analyses of proportion studies, funnel plots were found to be an inaccurate method of assessing publication bias. *J Clin Epidemiol* 2014;67:897–903.
56 Foroutan F, Guyatt G, Zuk V, *et al*. GRADE guidelines 28: use of GRADE for the assessment of evidence about prognostic factors: rating certainty in identification of groups of patients with different absolute risks. *J Clin Epidemiol* 2020;121:62–70.
57 Guyatt GH, Oxman AD, Vist G, *et al*. GRADE guidelines: 4. rating the quality of evidence-study limitations (risk of bias). *J Clin Epidemiol* 2011;64:407–15.
58 Guyatt GH, Oxman AD, Montori V, *et al*. GRADE guidelines: 5. rating the quality of evidence-publication bias. *J Clin Epidemiol* 2011;64:1277–82.
59 Guyatt GH, Oxman AD, Kunz R, *et al*. GRADE guidelines 6. rating the quality of evidence-imprecision. *J Clin Epidemiol* 2011;64:1283–93.
60 Guyatt GH, Oxman AD, Kunz R, *et al*. GRADE guidelines: 7. rating the quality of evidence-inconsistency. *J Clin Epidemiol* 2011;64:1294–302.
61 Guyatt GH, Oxman AD, Kunz R, *et al*. GRADE guidelines: 8. rating the quality of evidence-Indirectness. *J Clin Epidemiol* 2011;64:1303–10.
62 Parvar SL, Thiyagarajah A, Nerlekar N, *et al*. A systematic review and meta-analysis of gender differences in long-term mortality and cardiovascular events in peripheral artery disease. *J Vasc Surg* 2021;73:1456–65.
63 Romano PS, Mull HJ, Rivard PE, *et al*. Validity of selected AHRQ patient safety indicators based on VA national surgical quality improvement program data. *Health Serv Res* 2009;44:182–204.