PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	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
AUTHORS	de Launay, David; Paquet, Maude; Kirkham, Aidan; Graham, Ian; Fergusson, Dean; Nagpal, Sudhir; Shorr, Risa; Grimshaw, Jeremy; Roberts, Derek

VERSION 1 – REVIEW

REVIEWER	Gupta, Pankaj University Hospitals Of Leicester NHS Trust, Chemical Pathology & Metabolic Med
REVIEW RETURNED	13-Aug-2023

GENERAL COMMENTS	The authors have undertaken a lot of work but unfortunately the study has major flaws. The high nonresponse rate, in my opinion, makes it unlikely that confounding factors can be adequately adjusted - as there is not enough statistical power to do so. Further, it is no clear how the composite of patient perception was constructed and whether this was validated. The results are also not novel and do not advance the field in my opinion. Discontinuation due to patients experiencing side effects with platelets or statins (the two drugs that appear to have reached adjusted statistical significance) is also a significant limitation I wish the authors all the best and use this experience to design better and larger studies.

REVIEWER	Farmer, Caroline University of Exeter, Evidence Synthesis &Modelling for Health Improvement
REVIEW RETURNED	15-Dec-2023

GENERAL COMMENTS	I'm really pleased to have had the opportunity to review the protocol for your review on under-prescription and non-adherence to guideline recommendations in PAD. This is a beautifully written protocol and you are clearly planning to use rigorous methods. I also think that the topic is relevant to readers of BMJ Open and will likely have a decent readership, as it will appeal to those interested in PAD and those interested in clinical guidelines and their implementation. I had a few minor comments on the submission, which are largely just suggestions for minor alterations to the text within the journal format.

	Abstract: Would it be possible to clarify (as you did elsewhere in the protocol) that it's *clinician* under-prescribing and *patient* non-adherence? Also in the ethics section of the abstract, you could choose to clarify that it's published data that you're including, as from the abstract it might have been that you found disease registry data. Strengths and limitations bullets: These as written are not how I interpret the aim of these in the BMJ Open protocol guidance. I think these might need a re-write to highlight the strengths and limitations of the methods that you've chosen (rather than strengths of your description of the methods in the protocol, for example). Introduction: One thing you don't mention in the introduction is around whether the guideline recommendations you're going to compare against are mandated recommendations or (to use the NICE-lingo) 'consider' recommendations. I guess that puts a slightly different spin on things, particularly for clinician behaviour. Relatedly, I think that your last research question is a particular strength of your review as it means (potentially and data providing) that you might be able to comment on whether physician's choice is having a negative impact or not. Also in your introduction it might be worth introducing why you're choosing to look only at adjusted data. This obviously makes sense when you want to understand the *reasons* for the outcomes, but potentially worth spelling out. While unadjusted data won't explain the reasons, it could potentially highlight those groups who are particularly affected by under-prescription/non-adherence, which might in itself be useful (e.g. there may be complex reasons why a particular ethnic group is less likely to adhere to medication, but knowing that they do may still open the door to further research). Your approach is fine if that's your priority, i just wondered if it was worth making that clear. Methods: I would suggest summarising the list of items to be extracted in a box or table? The text goes on a bit and the reader might have a tendency to skip over and miss the next couple of sentences in that paragraph. Also i might have missed it, but did you specify in the methods that you were going to match outcome data with the relevant guideline and time point? That's mentioned in the limitations section but i couldn't see it in the methods. Apologies if i missed it. That's really all. All the best with the review! I imagine there will be some tricky points. I look forward to reading your published findings!

VERSION 1 – AUTHOR RESPONSE

Reviewer 1: Dr. Pankaj Gupta, University Hospitals of Leicester NHS Trust

Comments to the Author:
1. The authors have undertaken a lot of work but unfortunately the study has major flaws. The high nonresponse rate, in my opinion, makes it unlikely that confounding factors can be adequately

adjusted – as there is not enough statistical power to do so. Further, it is no clear how the composite of patient perception was constructed and whether this was validated. The results are also not novel and do not advance the field in my opinion. Discontinuation due to patients experiencing side effects with platelets or statins (the two drugs that appear to have reached adjusted statistical significance) is also a significant limitation.

I wish the authors all the best and use this experience to design better and larger studies.

We thank Dr. Gupta for the kind review of our manuscript and apologize for any confusion regarding our study methods. We do not plan to measure response/nonresponse or patient perception. The proposed systematic review will synthesize existing evidence regarding clinician underprescription of and patient non-adherence to guideline-recommended cardiovascular medications in adults with peripheral artery disease. We would respectfully argue that our work is novel as results will be used to identify evidence-care gaps that may inform where implementation interventions may be required to improve clinician prescribing and patient adherence to prescribed medications. They will also identify which populations of patients with peripheral artery disease are at greatest risk for underprescribing and nonadherence of guideline-recommended medications and the "real-world" (i.e., not-randomized controlled trial) consequences of underprescibing and nonadherence to these medications. In direct response to the above suggestion, we have carefully reviewed the revised version of our submitted systematic review and meta-analysis to ensure that the methods are clearly reported.

Reviewer 2: Dr. Caroline Farmer, University of Exeter

Comments to the Author:
1. I'm really pleased to have had the opportunity to review the protocol for your review on under-prescription and non-adherence to guideline recommendations in PAD. This is a beautifully written protocol and you are clearly planning to use rigorous methods. I also think that the topic is relevant to readers of BMJ Open and will likely have a decent readership, as it will appeal to those interested in PAD and those interested in clinical guidelines and their implementation. I had a few minor comments on the submission, which are largely just suggestions for minor alterations to the text within the journal format.

We thank Dr. Farmer for the kind review of our manuscript. Your comments are greatly appreciated and have improved our manuscript and its reported methods.

2. Abstract: Would it be possible to clarify (as you did elsewhere in the protocol) that it's *clinician* underprescribing and *patient* non-adherence? Also in the ethics section of the abstract, you could choose to clarify that it's published data that you're including, as from the abstract it might have been that you found disease registry data.

Thank you for the suggestion. In direct response, we have clarified throughout the Abstract that it is clinician underprescribing and patient nonadherence. We also clarify in the Ethics section of the Abstract that it is published data (e.g., rather than disease registry data) that we are including. The Abstract now reads:

"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" (page 3-4)

3. Strengths and limitations bullets: These as written are now how I interpret the aim of these in the BMJ Open protocol guidance. I think these might need a re-write to highlight the strengths and limitations of the methods that you've chosen (rather than the strengths of your description of the methods in the protocol, for example).

We agree with Dr. Farmer. We have therefore revised the Strengths and limitations section of the manuscript such that we now list five short bullet points that all relate specifically to the strengths and limitations of the methods. We have removed any summary of the novelty, aims, results, or expected impact of the study as suggested by the Editor and Dr. Farmer. The Strengths and limitations section now reads:

"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." (page 5)

4. Introduction: One thing you don't mention in the introduction is around whether the guideline recommendations you're going to compare against are mandated recommendations or (to use the NICE-lingo) "consider" recommendations. I guess that puts a slightly different spin on things, particularly for clinician behavior. Relatedly, I think your last research question is a particular strength of your review as it means (potentially and data providing) that you might be able to comment on whether physician's choice or not.

We agree. International clinical practice guidelines strongly and consistently recommend that people with peripheral artery disease be prescribed antiplatelet and statin (i.e., HMG-CoA reductase inhibitor) medications because class-1 evidence supports that the benefit of these medications benefits greatly outweighs their risks. They also strongly recommend that all those with peripheral artery disease and hypertension be prescribed antihypertensive medications (and many guidelines suggest that these should preferably be angiotensin-targeted agents). We also highlight the recommendations and strength of these recommendations across published guidelines in Supplementary Data, Appendix C of the manuscript in detail, which confirms that all of these medications are recommended by these guidelines instead of suggested or interventions that should be considered. The revised second paragraph of the Introduction section of the manuscript, revised in direct response to the above suggestions, now reads:

"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]" (page 6)

5. Also in your introduction it might be worth introducing why you're choosing to look only at adjusted data. This obviously makes sense when you want to understand the "reasons" for the outcomes, but potentially worth spelling out. While unadjusted data won't explain the reasons, it could potentially highlight those groups who are particularly affected by under-prescription/non-adherence, which might in itself be useful (e.g., there may be complex reasons why a particular ethnic group is less likely to adhere to medication, but knowing that they do may still open the door to further research). Your approach is fine if that's your priority, I just wondered if it was worth making that clear.

For estimates of incidence and prevalence, we plan to pool the unadjusted estimates together, including in our primary (unstratified) and secondary (stratified analyses). This will provide estimates of clinician underprescription and patient non-adherence overall, by individual medication (aspirin, statin, and antihypertensives), and by certain predictors in stratified meta-analyses and meta-regression. These pre-specified predictors will include patient sex, race, and socioeconomic status; CAD, CVD, PAD, pulmonary disease, diabetes, chronic kidney disease, cancer, and a past or present smoking history; clinicians' sex, practice type (e.g., primary community care versus tertiary care center), training (medicine, nursing), and subspecialty (general practice, nurse practitioner, vascular surgery, general internal medicine, cardiology other); and population-based design versus not.

However, when meta-analyzing associations between risk factors for underprescription of/non-adherence and underprescription/non-adherence and outcomes, we will only use adjusted data. This is because adjusted estimates are recommended by systematic review of prognostic studies methodologic guidance documents in order to examine the independent prognostic value over and above (i.e., adjusted for) other prognostic factors.[1] In order to make this more clear in the manuscript, we have therefore described this rationale in the Introduction section of the manuscript as suggested by Dr. Farmer. The relevant sentence describing this now reads:

“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]” (page 8)

6. Methods: I would suggest summarizing the list of items to be extracted in a box or table? The text goes on a bit and the reader may have a tendency to skip over and miss the next couple of sentences in that paragraph. Also I might have missed it, but did you specify in the methods that you were going to match outcome data with the relevant guideline and time point? That’s mentioned in the limitations section but I couldn’t see it in the methods. Apologies if I missed it.

Thank you for the suggestion. In direct response, we have created a Table (Table 2 in the revised manuscript) that summarizes the data items to be extracted in detail. We also added the following sentence to the Methods section of the manuscript as suggested: “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.” (page 17)

7. That’s really all. All the best with the review! I imagine there will be some tricky points. I look forward to reading your published findings!

VERSION 2 – REVIEW

REVIEWER	Farmer, Caroline University of Exeter, Evidence Synthesis &Modelling for Health Improvement
REVIEW RETURNED	16-Feb-2024

GENERAL COMMENTS	Dear authors, many thanks for your consideration and response to my review. I'm satisfied that you've addressed the minor suggestions I had on the protocol and it looks great. All the best with your review!