

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Analysis of the relationship between sex and prescriptions for guideline-recommended therapy in peripheral arterial disease, in relation to 1-year all-cause mortality. A primary care cohort study.
AUTHORS	Benson, Ruth; Okoth, Kelvin; Keerthy, Deepiksana; Gokhale, Krishna; Adderley, Nicola; Nirantharakumar, Krishnarajah; Lasserson, Daniel

VERSION 1 – REVIEW

REVIEWER	Sandeep Bahia East Kent Hospitals University NHS Foundation Trust, Vascular Surgery
REVIEW RETURNED	30-Sep-2021

GENERAL COMMENTS	<p>A very relevant area of research to a highly comorbid cohort and very well written. Better prescribing of evidence based risk-modifying medication is a key area for improving outcomes in this patient group.</p> <p>Some significant reservations:</p> <p>(1) The database used only has 6.2% of UK population represented; what are the reasons for this, is there some bias in terms of patients recorded on the database? does it suggest more proactive practice in some regions, which will skew the data?</p> <p>(2) There is a significant proportion of patients who will not have a formal diagnosis of PAD - would their relative freedom (or otherwise) from mortality dilute the assumptions and conclusions reached?</p> <p>(3) The decision-making algorithm that may have been part of the process in prescribing or otherwise for patients with PAD could have a significant bearing on the conclusions inferred, and indeed patients may be formally anticoagulated. The rationale for this decision-making is intrinsic to drawing valid conclusions.</p> <p>(4) What do we think might account for the drop in PAD over time? Again is this a function of the quality of data?</p>
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REVIEWER	Kajenny Srivaratharajah McMaster University Faculty of Health Sciences, Medicine
REVIEW RETURNED	05-Oct-2021

GENERAL COMMENTS	This paper discusses contemporary UK data on peripheral arterial disease (PAD) and sex-disparities – a topic that is under-recognized and understudied. The authors present population data on prevalence and incidence of peripheral arterial disease (PAD) and
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	<p>sex-based differences in use of guideline-based therapy in PAD. A retrospective analysis is carried out on a large prospective primary care database in the UK. Results show that annual incidence and prevalence is lower in women compared to men; however, all-cause mortality is similar across the groups. Between 2010 and 2017, the authors suggest that all-cause mortality in this population remained stable but mortality rates are increasing amongst women whilst decreasing amongst men. Despite this, rates of guideline directed therapy in both men and women is suboptimal, with women less likely to be prescribed statin therapy or antiplatelet therapy.</p> <p>In the abstract on page 2, Results section, line 29- the authors state “However once fully adjusted for this...” Please clarify or reword this sentence. ? Adjusted for age and sex or other covariates.</p> <p>In the Introduction on page 3, first paragraph, last sentence (line 23)- please check to ensure this reference is correct. I suspect the authors are referring to both reference 5 and 13 as reference 5 does not mention excess non-cardiovascular mortality.</p> <p>In the Introduction on page 3, paragraph 3, line 40- the following sentence needs to be reworded. “Prospective studies and registry data have documented significantly poorer clinical outcomes in women being treated for symptomatic arterial disease such as acute stroke, heart attack, critical limb ischaemia and ruptured abdominal aortic aneurysm, with hypotheses focusing older age at presentation, and less focus on the care provided in the years prior to needing surgery(9–12).”</p> <p>Suggestion- “Prospective studies and registry data have documented significantly poorer clinical outcomes in women being treated for symptomatic arterial disease such as acute stroke, heart attack, critical limb ischaemia and ruptured abdominal aortic aneurysm, with hypotheses citing older age at presentation and less care provided in the years preceding surgery (9–12).”</p> <p>On the same page (3), line 49, Please check reference 11 as this appears to be incorrect: References cited page 20 lists “Davarian S, Kalantari KK, Rezasoltani A et al. Effect and persistency of botulinum toxin iontophoresis in the treatment of palmar hyperhidrosis. <i>Australas J Dermatol</i>[Internet]. 2008 May [cited 2013 Jul 24];49(2):75–9. Available from:http://www.ncbi.nlm.nih.gov/pubmed/18412805” as reference 11.</p> <p>In Table 1, page 11 lines 10-13: consider listing BMI categories of obesity by class eg. BMI 30-35 Obese Class I and BMI> 35 Obese Class 2. It then follows that “Women were more likely to live in areas of greatest deprivation (16.2% versus 15.1%), be classified as severely obese (10% versus 7.8% with Class II obesity) or hypertensive...” on page 9 line 50-55.</p> <p>Table 1 also suggests less anticoagulant prescription in women compared to men. Given the results of COMPASS trial (Anand et al. Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial. <i>Lancet</i>. 2018;391(10117):P219-229), it may be relevant to expand upon this in the results and discussion.</p>
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	Supplementary data suggests coding for non-statin lipid therapy is available in the database. Are the authors able to look at sex-disparities in non-statin lipid lowering therapy such as PCSK-9 inhibitor use or aggregate data on lipid lowering therapy and how this may or may not differ between men and women.
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Mr. Sandeep Bahia, East Kent Hospitals University NHS Foundation Trust

Comments to the Author:

A very relevant area of research to a highly comorbid cohort and very well written. Better prescribing of evidence based risk-modifying medication is a key area for improving outcomes in this patient group.

Some significant reservations:

(1) The database used only has 6.2% of UK population represented; what are the reasons for this, is there some bias in terms of patients recorded on the database? does it suggest more proactive practice in some regions, which will skew the data?

There are 3 primary care databases for UK based practices, of which THIN is one. None of the databases cover the whole of the UK, (over 6000 in the UK) and all contain a mix of 1000-2000 practices with regards to region and size. We cannot comment on bias in the database, but all three practices are used regularly across a range of specialties and publications to analyse real world health data and are all highly cited. We have used THIN as it is the database the team have licenced access to.

(2) There is a significant proportion of patients who will not have a formal diagnosis of PAD - would their relative freedom (or otherwise) from mortality dilute the assumptions and conclusions reached?

A great question – we can only use the data available from the electronic healthcare record. If a patient has not had a diagnosis of PAD recorded, they will not be included. Whether this dilutes the assumptions, or actually provides bias towards supporting our assumption (using the assumption that those without a diagnosis are the least symptomatic), we cannot tell. It is a criticism shared by all healthcare databases.

(3) The decision-making algorithm that may have been part of the process in prescribing or otherwise for patients with PAD could have a significant bearing on the conclusions inferred, and indeed patients may be formally anticoagulated. The rationale for this decision-making is intrinsic to drawing valid conclusions.

We completely agree, and this has been explicitly stated in the paper's limitations. This is always a limitation in analysing data for medication prescription adherence. The best place to analyse it is in a study with this as its primary outcome. We hope that by publishing this work, we can demonstrate the need for looking at why discussions with female and male patients do not always lead to guideline based practice and pave the way for more qualitative research.

(4) What do we think might account for the drop in PAD over time? Again is this a function of the quality of data?

The data goes through quality assurance processes regularly. Therefore we believe it to be a true result, and reflects similar patterns seen internationally.

Reviewer: 2

Dr. Kajenny Srivaratharajah, McMaster University Faculty of Health Sciences

Comments to the Author:

This paper discusses contemporary UK data on peripheral arterial disease (PAD) and sex-disparities – a topic that is under-recognized and understudied. The authors present population data on prevalence and incidence of peripheral arterial disease (PAD) and sex-based differences in use of guideline-based therapy in PAD. A retrospective analysis is carried out on a large prospective primary care database in the UK. Results show that annual incidence and prevalence is lower in women compared to men; however, all-cause mortality is similar across the groups. Between 2010 and 2017, the authors suggest that all-cause mortality in this population remained stable but mortality rates are increasing amongst women whilst decreasing amongst men. Despite this, rates of guideline directed therapy in both men and women is suboptimal, with women less likely to be prescribed statin therapy or antiplatelet therapy.

This is a succinct review, thank you.

In the abstract on page 2, Results section, line 29- the authors state “However once fully adjusted for this...” Please clarify or reword this sentence. ? Adjusted for age and sex or other covariates.

This has been updated:

‘Once fully adjusted for and medical therapy, all-cause mortality was similar between women and men (aHR 0.95, 95% CI 0.87-1.03, p = 0.198 for all patients, aHR 1.01, 95% CI 0.88- 1.16, p = 0.860 for those with CVD).’

In the Introduction on page 3, first paragraph, last sentence (line 23)- please check to ensure this reference is correct. I suspect the authors are referring to both reference 5 and 13 as reference 5 does not mention excess non-cardiovascular mortality.

Thank you for picking this up – the reference has been updated.

In the Introduction on page 3, paragraph 3, line 40- the following sentence needs to be reworded.

“Prospective studies and registry data have documented significantly poorer clinical outcomes in women being treated for symptomatic arterial disease such as acute stroke, heart attack, critical limb ischaemia and ruptured abdominal aortic aneurysm, with hypotheses focusing older age at presentation, and less focus on the care provided in the years prior to needing surgery(9–12).”

Suggestion- “Prospective studies and registry data have documented significantly poorer clinical outcomes in women being treated for symptomatic arterial disease such as acute stroke, heart attack, critical limb ischaemia and ruptured abdominal aortic aneurysm, with hypotheses citing older age at presentation and less care provided in the years preceding surgery (9–12).”

Thanks, your suggestion has been incorporated.

On the same page (3), line 49, Please check reference 11 as this appears to be incorrect: References cited page 20 lists “Davarian S, Kalantari KK, Rezasoltani A et al. Effect and persistency of botulinum toxin iontophoresis in the treatment of palmar hyperhidrosis. *Australas J Dermatol*[Internet]. 2008 May [cited 2013 Jul 24];49(2):75–9. Available from:<http://www.ncbi.nlm.nih.gov/pubmed/18412805>” as reference 11.

Again, thank you. This reference has been removed.

In Table 1, page 11 lines 10-13: consider listing BMI categories of obesity by class eg. BMI 30-35 Obese Class I and BMI> 35 Obese Class 2. It then follows that “Women were more likely to live in

areas of greatest deprivation (16.2% versus 15.1%), be classified as severely obese (10% versus 7.8% with Class II obesity) or hypertensive...,” on page 9 line 50-55.

Thank you for these suggestions, they have been incorporated into the text.

Table 1 also suggests less anticoagulant prescription in women compared to men. Given the results of COMPASS trial (Anand et al. Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial. *Lancet*. 2018;391(10117):P219-229), it may be relevant to expand upon this in the results and discussion.

A great question. We wonder, as we don't have data for combined DOAC and Aspirin prescriptions, if that message may be something for a future analysis which does record if patients happened to be on both and the relation to outcomes in this PAD subgroup.

Supplementary data suggests coding for non-statin lipid therapy is available in the database. Are the authors able to look at sex-disparities in non-statin lipid lowering therapy such as PCSK-9 inhibitor use or aggregate data on lipid lowering therapy and how this may or may not differ between men and women.

Thanks for this, and for highlighting a limitation of the guidelines – the guidelines only refer to statins, therefore we have used statins in our analysis. I fully accept that this leaves a (very small) number of patients on lipid lowering therapy out of the analysis and the limitations have been updated to make this clear. An analysis including alternatives, with lipid targets would be a great research theme.

VERSION 2 – REVIEW

REVIEWER	Sandeep Bahia East Kent Hospitals University NHS Foundation Trust, Vascular Surgery
REVIEW RETURNED	05-Dec-2021
GENERAL COMMENTS	Comments and responses noted, thank you
REVIEWER	Kajenny Srivaratharajah McMaster University Faculty of Health Sciences, Medicine
REVIEW RETURNED	11-Dec-2021
GENERAL COMMENTS	Reviewer's comments and suggestions have been adequately addressed.