Research Article

Sex Differences in the Outcomes of Peripheral Arterial Disease

Mohamad A. Hussain MD, Thomas F. Lindsay MDCM MSc, Muhammad Mamdani PharmD MA MPH, Xuesong Wang MSc, Subodh Verma MD PhD, Mohammed Al-Omran MD MSc

From the Divisions of Vascular Surgery (M.A.H., M.A-O.) and Cardiac Surgery (S.V.) of St. Michael's Hospital, Li Ka Shing Knowledge Institute of St. Michael's Hospital (M.M., S.V., M.A-O), Toronto, Ontario, Canada; the Department of Surgery, University of Toronto, Toronto, Ontario, Canada (M.A.H., T.F.L., S.V., and M.A-O.); the Division of Vascular Surgery, Peter Munk Cardiac Centre, University Health Network, Toronto, Ontario, Canada (T.F.L.); the Institute of Health Policy, Management, and Evaluation (M.M) and the Leslie Dan Faculty of Pharmacy (M.M.) of the University of Toronto; the Applied Health Research Centre, Toronto, Ontario, Canada (M.M.); the King Saud University-Li Ka Shing Collaborative Research Program, and the Department of Surgery, King Saud University, Riyadh, Kingdom of Saudi Arabia (M.M., S.V., M.A-O.); and the Institute for Clinical Evaluative Sciences, Toronto, Ontario, Canada (M.M., X.W.)

Address for correspondence:

Mohammed Al-Omran, MD, MSc, FRCSC

Professor and Head, Division of Vascular Surgery, St. Michael's Hospital, 30 Bond Street, Suite 7-074, Bond Wing, Toronto, Ontario, M5B 1W8, Canada. Tel: 416-864-6047; Fax: 416-864-6012; Email: AlomranM@smh.ca

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ABSTRACT

Background: The role of gender in the outcomes of patients with peripheral arterial disease (PAD) has been poorly studied. We sought to investigate differences in the long-term adverse cardiovascular (CV) and limb outcomes between male and female PAD patients.

Methods: A population-based cohort study with up to 7 years of follow-up was conducted using linked administrative databases in Ontario, Canada. Individuals aged 40 years or older who visited a vascular surgeon between 1 April 2004 and 31 March 2007 (index date), and carried a diagnosis of PAD comprised the study cohort. The primary outcome was a composite of death or hospitalization for stroke or myocardial infarction (MI). Secondary outcomes included lower limb amputation or revascularization. Cox proportional hazards modeling was used to compute unadjusted hazard ratios (HR), and HRs adjusted for baseline covariates.

Results: A total of 6,915 patients were studied. No significant differences in the risk of primary outcome were observed between men and women (adjusted HR, 0.99 [95% CI, 0.92 to 1.05]; p = 0.64), although women were less likely to undergo minor amputation (adjusted HR, 0.73 [95% CI, 0.62 to 0.85]; p <0.001) and bypass surgery (adjusted HR, 0.82 [95% CI, 0.71 to 0.94]; p = 0.004) relative to men, but more likely to have an acute MI (adjusted HR, 1.15, [95% CI, 1.00 to 1.31]; p = 0.048). There were no differences in the rates of major amputation or transluminal percutaneous angioplasty between men and women.

Conclusions: We identified no significant differences in the risk of major adverse CV events between women and men, although our findings suggest men with PAD may be at an increased risk of adverse limb events compared to women. Cardiovascular health campaigns should focus on both men and women with PAD to raise awareness of this disease.

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INTRODUCTION

Peripheral arterial disease (PAD) is the third most common cause of cardiovascular (CV) morbidity after coronary heart disease and stroke. Furthermore, there has been a rapid increase in the number of people impacted by PAD over the last decade, with approximately 202 million people living with the disease globally in 2010 (1). In addition, data from the Global Burden of Disease projects in 1990 and 2010 demonstrated that although men have an overall greater burden of PAD, women experienced a much more dramatic increase in PAD-related death and disability over the last 20 years compared to men (2). Despite this, PAD is not currently positioned as a focus in national cardiovascular health programs for men and women in Canada (3).

Gender based differences in the clinical presentation and outcomes of men and women with other vascular diseases such as coronary heart disease are well documented (4–6), and several national initiatives have been established to tackle these differences in health care. Differences in the etiology and clinical presentation of men and women with PAD have also been suggested (7). However, long-term data on sex-based differences in the CV and limb outcomes of PAD patients are limited. Previous population-based studies have focused primarily on post-operative in-hospital outcomes of men and women with PAD, and their findings have been conflicting (8–10). To that end, a Scientific Statement from the American Heart Association published in 2012 indicated, “Cardiovascular mortality, all-cause mortality, and major coronary rates by gender (in patients with PAD) have not been well defined in population-based studies. (11).”

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To address this gap in knowledge, we conducted a large population-based cohort study to examine differences in major adverse CV and limb event rates between men and women with PAD over the long-term.

METHODS

Setting. We designed a retrospective population-based cohort study of men and women with PAD using linked healthcare administrative databases in the province of Ontario, Canada over a 10-year period – from 1 April 2004 to 31 March 2013. Over 13 million residents of Ontario have access to universal healthcare services funded by the Ministry of Health and Long Term Care.

Data sources. We used the following linked Ontario administrative datasets to conduct this study: the Canadian Institute for Health Information Discharge Abstract Database (captures all hospital admission information including diagnoses and procedures), the Ontario Health Insurance Plan Database (data from all inpatient and outpatient physician billing claims), the Registered Persons Database (demographic and vital statistics data), the National Ambulatory Care Reporting System (data from outpatient surgeries and emergency department visits), the Institute for Clinical Evaluate Sciences Physicians Database (demographic and specialty information about all physicians practicing in Ontario), and the Ontario Drug Benefit database (data from medication prescriptions dispensed to Ontario residents aged 65 years or older). These databases have shown to be of high quality (12); they have been validated for identifying a variety of diagnoses and procedures (13–16), and they are routinely used for population-based outcome studies (17–19).

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Patients. All men and women who were seen by a vascular surgeon in Ontario between 1 April 2004 and 31 March 2007, and carried a diagnosis of PAD within 3 years prior to that visit were considered eligible for this study. PAD diagnosis was defined by using a previously validated model-based billing code algorithm that has shown to be accurate in identifying PAD patients in the non-invasive vascular lab and the community (20). Details of the billing code algorithm, and the *International Statistical Classification of Diseases*, 9th and 10th edition codes used to identify PAD patients can be found in **Appendix 1**. To restrict the analysis to patients with atherosclerotic disease, we excluded those who were <40 years old.

Outcome measures and follow-up. The primary outcome was a composite of death or hospitalization for acute myocardial infarction (MI) or stroke. Each individual component outcome of the primary outcome was examined as a secondary outcome. We also examined the following limb outcomes as secondary outcomes: major amputation (level of ankle, below-knee or above-knee), minor amputation (toe or through-foot), peripheral arterial bypass surgery, and percutaneous translumnial angioplasty (PTA). Hospitalization for congestive heart failure, carotid endarterectomy, abdominal aortic aneurysm repair, coronary revascularization, and initiation of dialysis were measured as tertiary outcomes. Follow-up was initiated on the day a PAD patient had a clinical encounter with a vascular surgeon (cohort entry date). Patients were followed until they experienced the primary endpoint, reached the maximum follow-up period of 7 years, or end of the study (31 March 2013).

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Covariates. We controlled for confounding factors that might influence the effect of gender on adverse cardiovascular outcomes by utilizing various linked administrative datasets. These factors included: patient age, income level, medical comorbidities and overall comorbidity burden, medication usage, and health services utilization (including hospitalizations, emergency department visits and outpatient physician visits). Income level was estimated by linking the patient's home postal code to Statistics Canada population census data in order to obtain the median household income quintile (21). Overall comorbidity burden was estimated using the Charlson comorbidity index with a 5-year look-back window in the datasets. This comorbidity index has been validated to predict the probability of death from comorbid disease in patients with PAD and aortic disease (22). In general, the risk of death from an increase of one Charlson comorbidity score is equivalent to the risk of death from an additional decade of age (22). In addition, we also controlled for patient ambulatory care grouping using the Comprehensive Ambulatory Care Classification System (CACS), which is a national grouping methodology for ambulatory care patient data. CACS places patient visits into groups that are clinically and resource homogeneous, and can be used to further predict patient comorbidity burden and healthcare resource utilization (23). We controlled for baseline medication usage by determining the medication prescriptions dispensed to patients using the Ontario Drug Benefit database (12).

Statistical analysis. We used standardized differences to compare male and female patients' baseline demographic and clinical characteristics. Standardized differences of less than 0.1 generally indicate good balance (24).

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We preformed time-to-event analyses using multivariable Cox proportional hazards regression (PROC PHREG in SAS, version 9.4 [SAS Institute, Cary, North Carolina]) to compare outcomes of men and women with PAD, with men as the reference group. We generated unadjusted hazard ratios (HRs), and HRs adjusted for baseline demographic and clinical variables. We tested the proportional hazards assumption by visually inspecting log-log survival curves, and by examining the statistical significance of time-dependent covariates. We also generated unadjusted Kaplan-Meier curves with 95% confidence intervals (CIs) to demonstrate the cumulative incidence of primary and secondary outcomes.

Statistical significance was set at the 0.05 level, and all *p* values are two-tailed. All statistical analyses were conducted using SAS, version 9.4.

RESULTS

Cohort identification and follow-up. A total of 6,915 patients with PAD were included in our analysis. Of these patients, 2,461 (36%) were women. Median follow-up for the cohort was 5.4 years (interquartile range, 1.8 to 7 years).

Baseline characteristics (Table 1). Women with PAD were more likely to be older (72 versus 69 years old for men), and they were more likely to be prescribed a calcium channel blocker at baseline. Men with PAD were more likely to have a history of coronary artery disease or diabetes mellitus, and they tended to have a higher Charlson comorbidity score, indicating a greater comorbidity burden. Men were also prescribed oral antihyperglycemic agents and statins at higher rates then women. Analysis of baseline income quintile, health services utilization and

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clinical encounters based on 17 unique ambulatory care groupings revealed no significant differences between men and women.

Primary outcome. The primary outcome (composite of death or admission to hospital for either acute MI or stroke) occurred in 2,860 (64%) male and 1,644 (67%) female PAD patients. Women experienced the primary outcome at a higher rate in the unadjusted model (unadjusted HR, 1.06 [95% CI, 1.002 to 1.13]; $p = 0.044$), although there was no significant difference in the risk of primary outcome among men and women after controlling for baseline covariates (adjusted HR, 0.99 [95% CI, 0.92 to 1.05]; $p = 0.64$) (**Table 2**). The cumulative incidence of the primary outcome over follow-up is presented in **Figure 1.**

Secondary and tertiary outcomes. With respect to secondary outcomes (**Table 2)**, women were less likely to undergo minor amputation (adjusted HR, 0.73 [95% CI, 0.62 to 0.85]; $p < 0.0001$), and arterial bypass surgery (adjusted HR, 0.82 [95% CI, 0.71 to 0.94]; $p = 0.004$) than men, but more likely to be hospitalized for acute MI (adjusted HR, 1.15, [95% CI, 1.00 to 1.31]; $p = 0.048$). There were no differences in the rates of major amputation, PTA, stroke, or death between men and women. The cumulative incidences of secondary limb outcomes are presented in **Figure 2** and **Figure 3**. In addition, there were no significant differences in any of the tertiary outcomes between men and women in the adjusted models.

INTERPRETATION

In this large population-based cohort study, we found no statistically significant differences between women and men with respect to a composite risk of acute MI, stroke, or death.

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Secondary analyses revealed that female gender is associated with a higher risk of hospitalization due to MI, but a lower risk of minor amputation and arterial bypass surgery.

Although prior studies have examined sex-related differences in the outcomes of PAD patients following peripheral arterial procedures, their findings have been conflicting. Jackson and colleagues recently reported data on 12,379 patients (41% female) that underwent peripheral vascular interventions. Although women experienced more procedure-related complications in this study, the rates of MI, stroke, death, and amputation did not differ among women and men (8). This study however was limited to in-hospital post-procedure follow-up. In contrast, Vouyouka and colleagues analyzed population-based data from 372,692 (44% female) PAD-related surgical hospitalizations, and reported a higher risk of postoperative complications, major amputations and mortality among women even after adjusting for baseline covariates (9). This study was also limited by a lack of longitudinal follow-up post-discharge, and only enrolled patients undergoing peripheral arterial revascularization or amputation procedures. Recent data from the US Nationwide Inpatient Sample suggests that women who undergo interventions for PAD have higher in-hospital mortality than men, although the rates for both men and women have declined over time, likely due to improvements in technology and medical therapy (10). No other clinical outcomes besides mortality were measured in this study due to a limitation of the administrative databases.

Our study has several strengths that provide unique insight into the influence of gender in PAD patients. First, unlike prior studies, the index event in our study cohort was not a surgical intervention for PAD, but rather a clinical encounter with a vascular surgeon and a prior

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diagnosis of PAD. This approach allowed us to include inpatient and outpatient PAD patients with varying levels of disease severity in our cohort. Prior studies have only focused on patients with advanced PAD (critical limb ischemia or debilitating intermittent claudication) who undergo peripheral arterial interventions (8–10,25,26). Findings from our study may be more generalizable as we included a broader range of patients in our study. Second, our study provides robust long-term data (median follow-up, 5.4 years), whereas prior population-based studies have largely focused on in-hospital outcomes in this population. Third, we adjusted for several factors that may confound the relationship between gender and PAD outcomes, such as: socioeconomic status, healthcare service utilization, ambulatory care grouping, and overall comorbidity burden. These factors play an important role in access to care, and have not been measured in prior studies examining sex-related differences in PAD. Finally, our study provides unique insight into the characteristics of PAD patients that have not been previously described. For instance, we found that ~50% men and women with PAD belonged to the lowest two income quintiles. Given socioeconomic class is closely associated with health status (27), our data indicates further investigation is warranted to determine the impact of lower socioeconomic status on the health outcomes of PAD patients.

Our results also show that women with PAD tend to be older than men, which is consistent with data from other studies (8–10,25). This may be because women are more likely to experience atypical symptoms that are not characteristic of a classical history of intermittent claudication, thus leading to a delay in PAD diagnosis (28,29). Furthermore, women with PAD have more advanced disease at the time of presentation, as evidenced by a greater incidence of critical limb ischemia (30,31) and faster functional decline (32). Although these clinical findings can be

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explained by advanced age, other factors such as an enhanced pro-inflammatory state (33), impaired microvascular function (34) and greater burden of femoropopliteal lesions (35) observed in women with PAD may also contribute to more advanced disease compared to men.

Although women were at an increased risk for acute MI, stroke, or death in the unadjusted analysis, we found no differences among women and men after adjusting for age and other covariates. This further indicates the importance of early diagnosis and treatment of women with PAD, as gender-related differences in the rate of primary outcome are neutralized once unbalanced baseline characteristics such as advanced age are taken into account. We did however find two key differences between men and women with PAD in our secondary analyses that merit discussion. First, we found that women were less likely to undergo minor amputation and arterial bypass surgery compared to men. This may be because men were observed to have to a greater comorbidity burden at baseline, including a prior history of diabetes mellitus, which is a significant risk factor for advanced atherosclerosis and amputation (19). Second, we found women with PAD were at an increased risk for acute MI in the adjusted analysis. Given women with PAD in our study were on average 3 years older than men, this finding is consistent with previous research that indicates women experience an acute MI at an older age than men (36). We found no significant differences among women and men with respect to the adjusted rates of stroke, death, major amputation, PTA, or any of the tertiary outcomes.

Study Limitations. Our study has several limitations. First, as with all observational studies, the possibility remains that our results are biased by unmeasured differences between men and women. However, this seems unlikely as we measured several demographic and clinical

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covariates at baseline, and we also adjusted our analyses for variables that may confound the relationship between gender and PAD outcomes. Second, inaccurate coding is a possible source of bias in population-based studies. To mitigate this risk, we used codes that have already been validated in our databases to identify PAD patients and their outcomes. The validated model-based billing code algorithm has good accuracy (86% sensitivity, 83% specificity, 91% positive predictive value [PPV], 74% negative predictive value) in identifying patients with PAD (20). Coding for the major CV and limb outcomes of interest have also been validated in our databases through reabstraction studies, including: acute MI (83% sensitivity, 87% PPV), stroke (81% accuracy), arterial bypass surgery (87% sensitivity, 88% PPV), and major amputation (98% sensitivity, 96% PPV) (37). Finally, our databases did not allow us to determine the severity of PAD symptoms among our cohort. However, by including PAD patients who had a clinical encounter with a vascular surgeon, we are confident that our cohort represents a broad PAD population with varying severity of disease that is managed by vascular specialists.

CONCLUSIONS

Our results suggest that although women with PAD tend to be older than men, no gender-based differences exist in the long-term risk of acute MI, stroke, or death in PAD patients after controlling for baseline risk factors. Men with PAD tend to have a higher comorbidity burden, and they may be at an increased risk for adverse limb events compared to women. Our results highlight the need to target both men and women in cardiovascular health campaigns to promote early diagnosis and management of PAD.

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FIGURE LEGENDS

Figure 1. Observed incidence of the primary outcome (acute myocardial infarction, stroke, or death). The error bars represent 95% confidence intervals.

Figure 2. Observed incidence of minor amputation (top) and major amputation (bottom). The error bars represent 95% confidence intervals.

Figure 3. Observed incidence of arterial bypass surgery (top) and percutaneous transluminal angioplasty (bottom). The error bars represent 95% confidence intervals.

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Table 1. Baseline demographic and clinical characteristics

Characteristic	Men (n = 4,454)	Women (n = 2,461)	Standardized difference*
Mean age ± SD, y	68.7 ± 10.6	71.6 ± 11.5	0.27
Charlson comorbidity, n (%)			
0	219 (4.9)	133 (5.4)	-
1	953 (21.4)	619 (25.2)	-
≥2	2,735 (61.4)	1,384 (56.2)	0.11
Neighbourhood income quintile, n (%)			
1 (Lowest)	1,149 (25.8)	641 (26.0)	-
2	986 (22.1)	593 (24.1)	-
3	833 (18.7)	432 (17.6)	-
4	759 (17.0)	423 (17.2)	-
5 (Highest)	705 (15.8)	353 (14.3)	-
Ambulatory care group, n (%)			
Nervous system diseases	122 (2.7)	61 (2.5)	-
Eye diseases	7 (0.2)	5 (0.2)	-
Ear, nose, mouth and throat diseases	34 (0.8)	23 (0.9)	-
Respiratory diseases	113 (2.5)	77 (3.1)	-
Circulatory system diseases	885 (19.9)	525 (21.3)	-
Digestive system diseases	135 (3.0)	108 (4.4)	-
Hepatobillary and pancreatic diseases	24 (0.5)	6 (0.2)	-
Musculoskeletal and connective tissue diseases	181 (4.1)	117 (4.8)	-
Skin, subcutaneous tissue, and breast diseases	418 (9.4)	239 (9.7)	-
Endocrine, nutritional, and metabolic diseases	325 (7.3)	126 (5.1)	-
Kidney and genitourinary tract diseases	297 (6.7)	148 (6.0)	-
Haematological diseases	26 (0.6)	17 (0.7)	-
Oncological diseases	37 (0.8)	7 (0.3)	-
Systematic infections	34 (0.8)	8 (0.3)	-
Mental diseases	18 (0.4)	13 (0.5)	-
Examination and other health factors	384 (8.6)	191 (7.8)	-
Trauma, coma and toxic effects	258 (5.8)	147 (6.0)	-
Health service utilization			
Mean outpatient physician visits in past year ± SD	17.0 ± 11.1	16.6 ± 10.2	-
Mean emergency department visits in past 3 years ± SD	3.9 ± 5.3	4.0 ± 5.1	-
Mean hospital admissions in past 3 years ± SD	2.8 ± 2.3	2.8 ± 2.2	-
Medications, n (%)†			
Oral antihyperglycemic	798 (28.4)	382 (21.9)	0.15
Insulin	505 (18.0)	263 (15.1)	-
Statin	1,715 (61.0)	949 (54.5)	0.13
Beta-blocker	1,403 (49.9)	838 (48.1)	-
Calcium channel blocker	1,086 (38.6)	831 (47.7)	0.18
ACE inhibitor or ARB	1,999 (71.1)	1,206 (69.2)	-
Diuretic	1,017 (36.2)	701 (40.2)	-

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Any anti-hypertensive	2,470 (87.9)	1,545 (88.7)	-
Clopidogrel	348 (12.4)	198 (11.4)	-
Acetylsalicylic acid	604 (21.5)	365 (21.0)	-
Warfarin	719 (25.6)	372 (21.4)	-
Comorbid conditions, n (%)			
Congestive heart failure	721 (16.2)	388 (15.8)	-
Stroke	180 (4.0)	98 (4.0)	-
Acute myocardial infarction	564 (12.7)	250 (10.2)	-
Coronary artery disease	1,173 (26.3)	495 (20.1)	0.15
Chronic obstructive pulmonary disease	359 (8.1)	240 (9.8)	-
Chronic kidney disease	871 (19.6)	403 (16.4)	-
Diabetes mellitus	1,694 (38.0)	776 (31.5)	0.14

Note: SD = standardized deviation; ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker.
*Standardized difference of >0.1 indicates significant difference.
†Medication usage is reported only for those aged 66 years or older.

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Table 2. Outcomes of men and women with peripheral arterial disease

Outcome	Men* (n = 4,454)	Women* (n = 2,461)	Unadjusted HR (95% CI)	*p* value	Adjusted HR (95% CI)	*p* value
Primary outcome†	2860 (64.2)	1644 (66.8)	1.06 (1.00-1.13)	0.044	0.99 (0.92-1.05)	0.6
Secondary outcomes						
Acute MI	618 (13.9)	360 (14.6)	1.07 (0.94-1.22)	0.3	1.15 (1.00-1.31)	0.048
Stroke	229 (5.1)	140 (5.7)	1.13 (0.92-1.40)	0.3	1.02 (0.82-1.27)	0.9
Death	2562 (57.5)	1468 (59.7)	1.06 (0.99-1.13)	0.092	0.96 (0.90-1.03)	0.2
Major amputation	764 (17.2)	375 (15.2)	0.89 (0.79-1.01)	0.064	0.95 (0.84-1.08)	0.4
Minor amputation	583 (13.1)	211 (8.6)	0.65 (0.55-0.76)	<0.0001	0.73 (0.62-0.85)	<0.0001
Arterial bypass surgery	685 (15.4)	311 (12.6)	0.82 (0.72-0.94)	0.004	0.82 (0.71-0.94)	0.004
PTA	609 (13.7)	330 (13.4)	0.99 (0.87-1.14)	0.9	1.04 (0.90-1.19)	0.6
Tertiary outcomes						
Congestive heart failure	1144 (25.7)	623 (25.3)	1.01 (0.92-1.11)	0.9	1.01 (0.91-1.12)	0.9
Carotid endarterectomy	82 (1.8)	34 (1.4)	0.76 (0.51-1.14)	0.2	0.77 (0.50-1.12)	0.2
AAA repair	271 (6.1)	126 (5.1)	0.85 (0.69-1.05)	0.1	0.92 (0.74-1.15)	0.5
Coronary revascularization	442 (9.9)	187 (7.6)	0.77 (0.65-0.91)	0.002	0.85 (0.71-1.02)	0.076
Initiation of dialysis	749 (16.8)	322 (13.1)	0.77 (0.68-0.88)	0.0001	0.89 (0.78-1.03)	0.1

Note: HR = hazard ratio; CI = confidence interval; MI = myocardial infarction; PTA = percutaneous transluminal angioplasty; AAA = abdominal aortic aneurysm.
*Values are presented as n (%).
†A composite of death or hospitalization with acute myocardial infarction or stroke.

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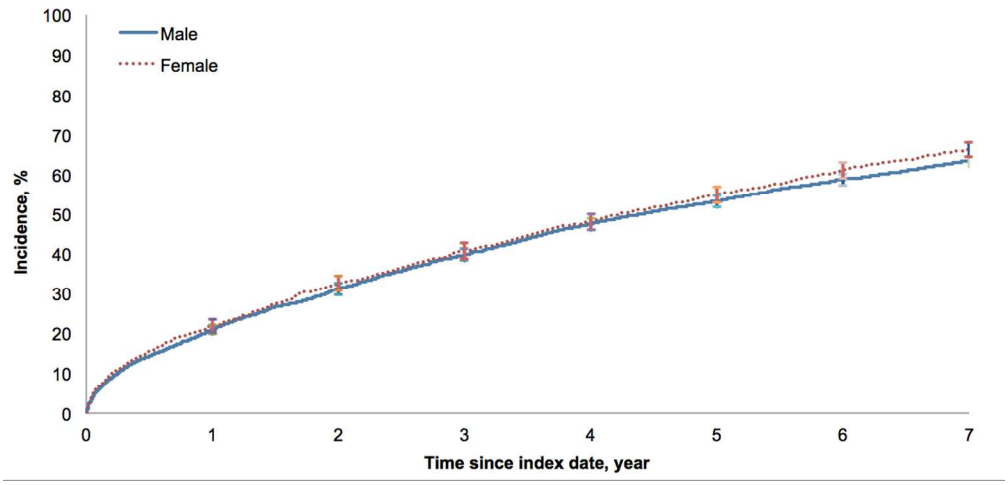

Observed incidence of the primary outcome (acute myocardial infarction, stroke, or death). The error bars represent 95% confidence intervals.
244x116mm (144 x 144 DPI)

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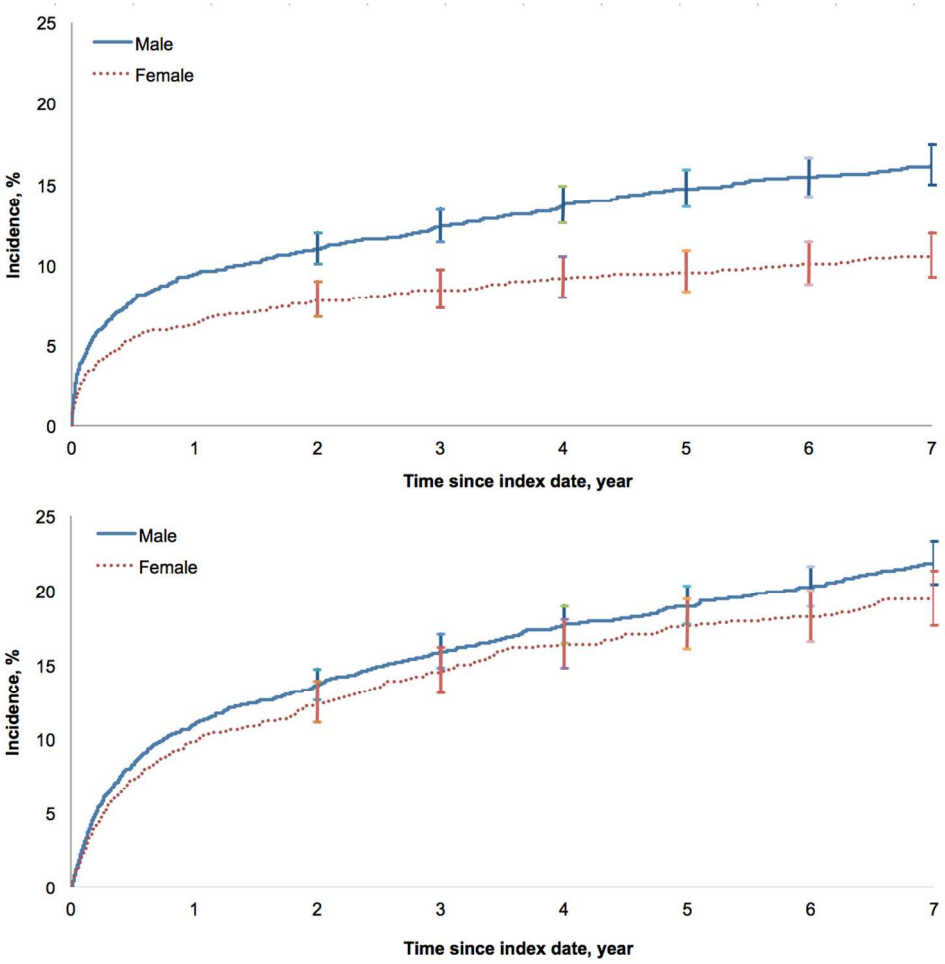
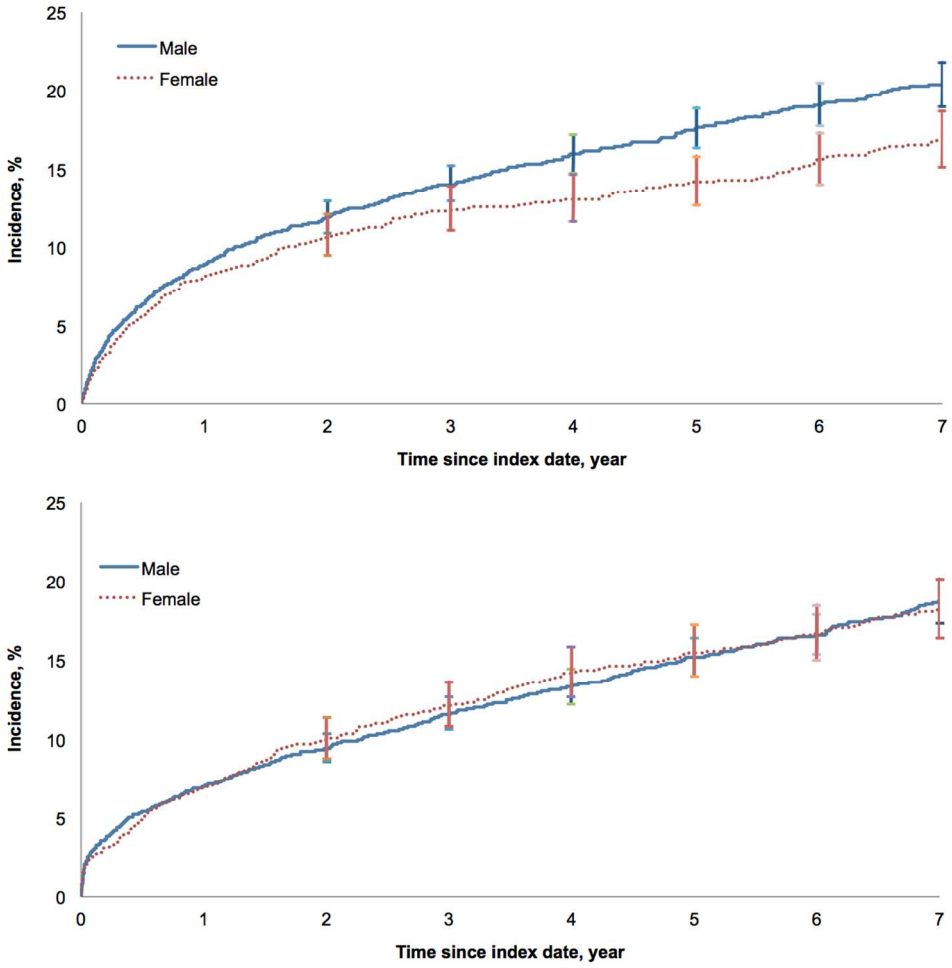


Observed incidence of minor amputation (top) and major amputation (bottom). The error bars represent 95% confidence intervals.
239x235mm (144 x 144 DPI)



Observed incidence of arterial bypass surgery (top) and percutaneous transluminal angioplasty (bottom).
The error bars represent 95% confidence intervals.
239x234mm (144 x 144 DPI)

APPENDIX 1

Diagnosis and Procedure Codes Used to Identify Peripheral Arterial Disease Patients*

Variable	ICD-9	ICD- 10
Diagnosis codes		
ASO extremities with gangrene	440.24	I70.2
ASO extremities with IC	440.21	I70.2
ASO extremities with ulceration	440.23	I70.2
ASO extremities, unspecified	440.20	I70.2
ASO extremities with rest pain	440.22	I70.2
PVD, unspecified	443.9	I73.9
Generalized and unspecified ASO	440.9	I7.09
Procedure codes		
Amputation of toe		CCI: 1WK93 Records with the following ICD-10 diagnosis codes excluded: C40, D16, D48.0, D48.1, D48.2, Q65-Q79, S70 – S99, T20 – T32
Angiography, extremity, bilateral, radiological		CCI: 3KG10 + variable code: BL (bilateral legs)
MRA lower extremity with or without contrast		CCI: 3KG40
Angiography, extremity, unilateral, radiological		CCI: 3KG10 + variable code: LL (left leg), or RL (right leg)
CT angiogram- abdominal aorta and lower extremity runoff		CCI: 3KG20
Non-invasive physiologic studies of lower extremity arteries		CCI: 3KG30

*Codes were used in combination with a model-based billing code algorithm validated by Fan and colleagues (20) to identify patients with peripheral arterial disease.
ICD = International Statistical Classification of Diseases; ASO = atherosclerosis; CCI = Canadian Classification of Health Interventions; MRA = magnetic resonance angiography; CT = computed tomography.

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