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# Male Sex Associated with Increased Long-term Cardiovascular Mortality after Peripheral Vascular Surgery for Atherosclerosis Despite Optimal Medical Treatment

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**WHAT THIS PAPER ADDS**

Peripheral arterial disease is increasing in prevalence, and it appears that there are differences in the outcomes between sexes. This paper contradicts previous published data and is unique for two reasons: first, it looks at long-term outcomes on a much wider cohort than those previously reported, and, second, the important role of prophylactic medical therapy is taken into account.

**Background:** The cardiovascular burden and consequences of peripheral atherosclerosis appear to differ between men and women. Data regarding long-term outcomes, including the impact of medical prophylactic treatment, are insufficient. This study examined long-term outcomes according to sex following primary vascular surgery, adjusted for multiple variables as well as recommended medical prophylaxis.

**Methods:** All Danish patients who underwent peripheral vascular surgery from January 2000 to December 2007 were stratified into five procedural groups: (a) aorto-iliac bypass or thromboendarterectomy, (b) femoro—femoral crossover, (c) thromboendarterectomy of the femoral arteries, (d) infrainguinal bypass, or (e) axillo- uni-, and bifemoral bypass. Data were analyzed according to sex for differences in myocardial infarction, stroke, and death, individually and combined, after surgery.

**Results:** A total of 11,234 patients were included: 6,289 males and 4,945 females. The overall adjusted hazard ratio for male patients compared with female patients for death was 1.11 (95% CI 1.06—1.17), for MI was 1.16 (95% CI 1.04—1.29), for stroke was 0.99 (95% CI 0.89—1.11), and for any major adverse cardiovascular event was 1.10 (95% CI 1.05—1.16).

**Conclusions:** These findings show that, despite indication, severity, and concomitant medical treatment of peripheral artery disease, men have a higher risk of mortality and adverse cardiovascular events following surgery for peripheral arterial disease.



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**Keywords:** Mortality, Peripheral vascular disease, Outcomes, Sex

## INTRODUCTION

Peripheral artery disease (PAD) is associated with significant morbidity and mortality.[1—3] Its relatively high prevalence is of concern, particularly as the population ages and the incidence of diabetes mellitus and its complications among PAD patients persist.[4] Investigations into the influence of sex on PAD have recently intensified yet, as Hirsch and colleagues[5] point out, there are too many gaps in the evidence to properly define the differences in the natural history and outcomes following treatment of PAD between men and women.

This study looks at the long-term outcomes, specifically myocardial infarction (MI), stroke, and survival following vascular surgery for all patients with symptomatic PAD requiring surgical intervention. Taking age and several comorbidities into account, as well as secondary medical therapy, the aim was to discover differences in outcome between men and women in a national population following revascularization.

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## METHODS

### *Patient group*

A retrospective study of the national Danish Vascular Registry was performed, in which all patients having surgery for PAD between January 2000 and December 2007 were included. All operations were primary revascularization procedures. The Danish Vascular Registry (Karbase) has nationwide coverage and covers 99.2% of all vascular procedures performed at Danish hospitals (www.karbase.dk, annual report 2009). The registry includes data on 65 variables and has been thoroughly validated.[6] It is moreover cross-linked with the National Population Registry as well as the National Inpatient Registry, which is used for reimbursement. All individuals in Denmark have a unique and permanent civilian personal register (CPR) code, enabling complete follow up. All data were entered prospectively. Approval from the regional ethics committee was obtained prior to data retrieval.

### *Definition of variables of interest*

Patients were stratified according to the surgical procedure performed: (a) aorto-iliac bypass/thromboendarterectomy, (b) femoro-femoral crossover bypass, (c) thromboendarterectomy of the femoral arteries, (d) infrainguinal bypass, and (e) axillo- uni-, and bifemoral bypass. The indications for surgery were acute extremity ischemia, claudication, rest pain, and wound/gangrene of the foot/leg. For purposes of clarification, procedural codes in the Danish Vascular Registry are specified in terms of indication, that is specific codes for revascularization due to PAD or, similarly, codes for revascularization due to symptomatic aneurysmal disease or acute thrombosis.

The following patient characteristics were obtained on admission: body mass index (BMI), creatinine (μmol/L), tobacco use at the time of surgery, hypertension (previous diagnosis and/or current antihypertensive medication), diabetes mellitus, and known pulmonary disease (previous diagnosis and/or medical treatment). Tobacco use was assessed by the admitting physician following direct interview with the patient: any current or history of use was considered positive. History of previous MI and stroke were collected from the National Inpatient Registry. A MI was defined according to the ICD-8 from 1976 through December 1993 as code 410, and from 1993 onwards according to the ICD-10 as codes I21—I22. Stroke was defined by ICD-8 codes 430—436, excluding transient ischemic attack, and ICD10 codes I60-I62.

Living status (deceased or alive) as per 15 February, June 2012, was obtained. Date of death was recorded for deceased patients. From the Danish National Inpatient Registry, diagnoses of patients and controls were gathered from the start of the registry in 1976 to 15 February 2012.

### *Prescription information*

Data regarding medical therapy was obtained from the Danish Registry of Medicinal Product Statistics and identified on the basis of Anatomical Therapeutical Chemical (ATC) classification system. Regular use was defined as two prescription fulfillments within 90 days after operative treatment. Medical therapy included the following antithrombotic agents: acetylsalicylic acid (B01AC06), clopidogrel (B01AC04), dipyridamole (B01AC07), and warfarin (B01AA03), or any combination thereof. Registered therapy also included statin treatment/HMG CoA reductase inhibitors (C10AA), diuretics (C03), calcium channel blockers (C08), angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARB) (C09), and beta blockers (C07).

### *Endpoints*

The primary end points were the first incidence of MI, stroke, or death, each as an individual end point, from the day of operation, and the combined endpoint, any major adverse cardiovascular event (MACE), that is either MI, stroke, or death, whichever occurred first.

### *Statistical analysis*

Data are presented as means with standard deviations (SD), which were compared using the two-sample *t* test, and proportions (percentages), which were compared using the chi-square test. Survival data were analyzed using the Kaplan—Meier method, while the log rank test was used to test for differences between groups. The Cox proportional hazards model was used to assess hazard ratios and 95% confidence intervals (CI), unadjusted and stratified by sex and then adjusted for the following: age, body mass index (BMI), diabetes mellitus, hypertension, tobacco use, creatinine, pulmonary disease, prior MI, prior stroke, and prophylactic medication, as described above. Missing data were as follows: creatinine, 6.0% ($n = 676$), body mass index, 24% ($n = 2,656$), hypertension, 2.1% ($n = 237$), diabetes mellitus, 1.1% ($n = 122$), tobacco, 3.3% ($n = 367$), and pulmonary disease, 1.5% ($n = 163$). Age and BMI were normally distributed, while creatinine values were first log-transformed in order to obtain normal distribution. Missing data are accounted for in the Cox proportional hazards model by either applying the median value for any missing continuous data, or creating a separate group for missing categorical data. Patients in each analysis were followed to an event, or censored, if death occurred (unless death was the endpoint analyzed). The two sided value of $p < .05$ was considered to be significant. Analysis was performed with STATA, version 13SE (STATA Corp., TX, USA) and SPSS, version 21 (SPSS Inc., Chicago, IL, USA).

## RESULTS

A total of 11,234 patients were included in the study period. There were 6,289 (56.0%) male and 4,945 (44%) female patients. The mean age was 67.8 (SD, 10.5) years for male patients and 70.8 (SD, 10.7) years for females. See Table 1 for further patient demographics as well as indications for surgery and 30 day mortality. Table 2 presents the number

**Table 1.** Baseline patient characteristics and indications for surgery.

| | Male patients ($n$ = 6,289) | Female patients ($n$ = 4,945) | $p$ |
|---|---|---|---|
| Age (years) | 67.8 ± 10.5 | 70.8 ± 10.7 | <.001[a] |
| BMI (kg/m$^2$) | 25.4 ± 4.2 | 23.7 ± 4.7 | <.001[a] |
| Creatinine (μmol/L) | 109 ± 81 | 89 ± 56 | <.001[a] |
| Smoking, $n$ (%) | 5,454 (86.7) | 3,934 (79.6) | <.001[b] |
| Hypertension, $n$ (%) | 2,940 (46.7) | 2,637 (53.3) | <.001[b] |
| Diabetes mellitus, $n$ (%) | 1,604 (25.5) | 877 (17.7) | <.001[b] |
| Pulmonary disease, $n$ (%) | 997 (15.9) | 856 (17.3) | .04[b] |
| Previous MI, $n$ (%) | 1,265 (20.1) | 677 (13.7) | <.001[b] |
| Previous stroke, $n$ (%) | 856 (13.6) | 589 (11.9) | .008[b] |
| Acute ischemia, $n$ (%) | 487 (7.7) | 328 (6.6) | <.001[b] |
| Claudication, $n$ (%) | 2,217 (35.3) | 1,698 (34.3) | <.001[b] |
| Rest pain, $n$ (%) | 1,311 (20.8) | 1,270 (25.7) | <.001[b] |
| Gangrene, $n$ (%) | 2,274 (36.1) | 1,649 (33.3) | <.001[b] |
| 30 day mortality, $n$ (%) | 232 (3.7) | 180 (3.6) | .89[b] |

*Note*. Values are mean ± standard deviation. BMI = body mass index; MI = myocardial infarction.
[a] Two-sample $t$ test.
[b] Chi-square test.

**Table 2.** Number of procedures performed per year based on sex.

| | Total | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 |
|---|---|---|---|---|---|---|---|---|---|
| Patients, $n$ | 11,234 | 1,508 | 1,444 | 1,323 | 1,401 | 1,436 | 1,403 | 1,397 | 1,322 |
| Men, n (%) | 6,289 (56.0) | 832 (55.2) | 803 (55.6) | 723 (54.6) | 796 (56.8) | 813 (56.6) | 766 (54.6) | 807 (57.8) | 749 (56.7) |
| Women, $n$ (%) | 4945 (44.0) | 676 (44.8) | 641 (44.4) | 600 (45.4) | 605 (43.2) | 623 (43.4) | 637 (45.4) | 590 (42.2) | 573 (43.3) |

of operations performed in the period under analysis. The number of procedures performed fell gradually from 1,508 in 2000 to 1,322 in 2007.

Data regarding medication are given in Table 3. There were no significant differences in the use of statins or beta blockers, while differences between men and women were noted for antithrombotics, as well as calcium channel blockers, ACE inhibitors/ARBs, and diuretics.

Maximum follow up was 12.3 years. The overall mean follow up (to death) was 5.2 years (SD, 3.3) for men and 5.4 years (SD, 3.3) for women. Mean follow up durations for the individual procedures, as estimated from Kaplan-Meier curves are given in Table 4.

**Table 3.** Pre-operative medication for male and female patients.

| | Male patients ($n$ = 6,289) | Female patients ($n$ = 4,945) | $p$[a] |
|---|---|---|---|
| Statin, $n$ (%) | 3,917 (62.3) | 3,067 (62.0) | .77 |
| Antithrombotic, $n$ (%) | 4,976 (79.1) | 4,011 (81.1) | <.001 |
| Beta blocker, $n$ (%) | 2,216 (35.2) | 1,745 (35.3) | .954 |
| CCB, $n$ (%) | 2,168 (34.5) | 2,004 (40.5) | < .001 |
| ACE inhibitor/ARB, $n$ (%) | 3,342 (53.1) | 2,480 (50.2) | < .002 |
| Diuretic, $n$ (%) | 3,383 (53.8) | 3,184 (64.4) | <.001 |

ACE = angiotensin converting enzyme; ARB = angiotensin II receptor blocker; CCB = calcium channel blockers.
[a] Chi-square test.

### Mortality

Overall, there were a total of 6,407 deaths in the follow up period: 2,800 among women and 3,607 among men. Kaplan—Meier curves (Fig. 1, upper left) shows that mortality is significantly increased in male patients (log-rank $p$ = .04). The overall hazard ratio for men undergoing surgery for peripheral atherosclerotic disease, as compared to women, for death was 1.05 (95% CI 1.00—1.11) and 1.11 (95% CI 1.06—1.17) after adjustment.

### Myocardial infarction

There were 1,496 MIs: among 588 women and 908 men. Kaplan—Meier curves (Fig 1, upper right) showed a significantly increased incidence of MI in male patients (log-rank $p$ = .001). The overall hazard ratio for men, as compared to

**Table 4.** Mean survival times, given in years, based on Kaplan—Meier estimates for sex and procedure.

| | Male patients ($n$ = 6,289) | Female patients ($n$ = 4,945) | Log rank $p$ |
|---|---|---|---|
| Overall | 6.6 ± 0.06 | 6.8 ± 0.07 | .04 |
| Aorto-iliac procedures | 8.2 ± 0.13 | 8.3 ± 0.13 | .55 |
| Femoral artery procedures | 7.2 ± 0.16 | 6.7 ± 0.20 | .12 |
| Femoro—femoral crossover bypass | 6.7 ± 0.16 | 6.9 ± 0.16 | .63 |
| Infrainguinal bypass | 5.9 ± 0.08 | 6.1 ± 0.10 | .29 |
| Axillo-femoral bypass | 3.3 ± 0.36 | 4.9 ± 0.34 | .01 |

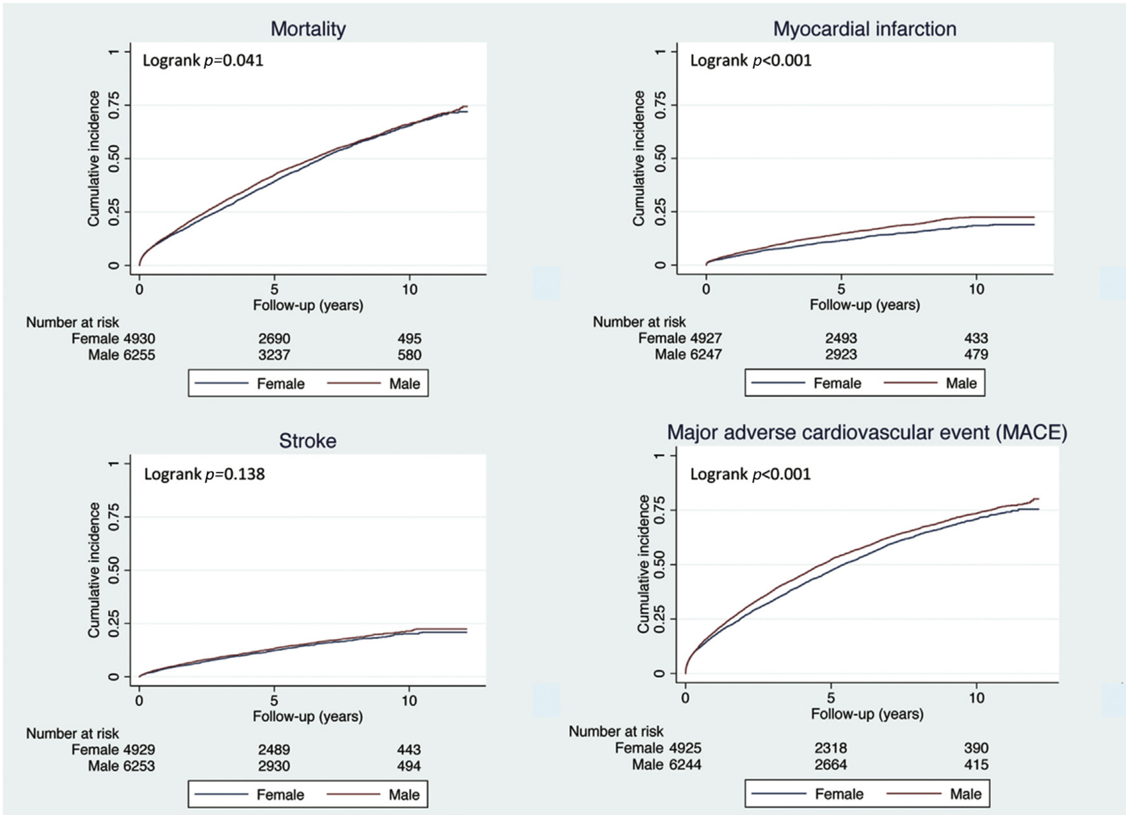


**Figure 1.** Kaplan—Meier curves comparing death (upper left), myocardial infarction (MI) (upper right), stroke (lower left), and MACE (major adverse cardiovascular event) (lower right) between male and female patients surgically treated for peripheral arterial disease.

women, for MI was 1.27 (95% CI 1.15—1.42) and 1.16 (95% CI 1.04—1.29) after adjustment.

## *Stroke*

There were 1,446 strokes among 621 women and 825 men. Kaplan-Meier curves (Fig. 1, lower left) showed no significant difference in the incidence of stroke between men and women operated on for PAD (log-rank $p = .14$). The overall adjusted hazard ratio for men, as compared to women, for stroke was 1.08 (95% CI 0.98—1.20) and 0.99 (95% CI 0.89—1.11) after adjustment.

## *MACE*

For the combined endpoint MACE, there were 7,195 events among 3,092 women and 4,103 men. Kaplan—Meier curves (Fig. 1, lower right) showed a significantly increased incidence of MACE in male patients (log-rank $p = .001$). The overall adjusted hazard ratio for men, compared with women, for MACE was 1.11 (95% CI 1.06—1.17) and 1.10 (95% CI 1.05—1.16) after adjustment.

The adjusted hazard ratios for the four endpoints are provided in Fig. 2, while specific data per procedure between men and women are detailed in Table 5. Finally, the 30 day mortality for all procedures and patients are included in Table 1.

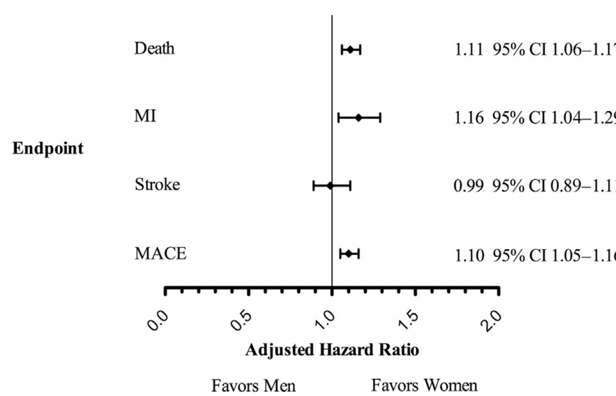


**Figure 2.** Forest plot showing the adjusted hazard ratios (HR) for death, myocardial infarction (MI), stroke, and MACE (major adverse cardiovascular event) between male and female patients operated on for peripheral arterial disease. The 95% confidence intervals (CI) are provided to the right of each endpoint.

## DISCUSSION

These findings show that survival, stroke, and MI following open surgery for PAD are worse for men than women. This appears true for both central aorto-iliac procedures, as well as peripheral in situ bypass procedures. There are no significant differences in 30 day mortality between women and men. Although there is a gradual decline in the number of open surgical procedures, as given in Table 2, the

**Table 5.** Adjusted hazard ratios for all endpoints per procedure.

| | Death, HR (95% CI) | MI, HR (95% CI) | Stroke, HR (95% CI) | MACE, HR (95% CI) |
|---|---|---|---|---|
| All procedures | 1.11 (1.06—1.17) | 1.16 (1.04—1.29) | 0.99 (0.89—1.11) | 1.10 (1.05—1.16) |
| Aorto-iliac procedures | 1.16 (1.03—1.34) | 1.15 (0.87—1.52) | 1.07 (0.82—1.40) | 1.16 (1.03—1.31) |
| Femoral artery procedures | 1.16 (0.98—1.37) | 1.37 (0.99—1.89) | 0.86 (0.68—1.38) | 1.15 (0.99—1.34) |
| Femoro-femoral crossover | 1.07 (0.93—1.23) | 1.16 (0.84—1.59) | 0.84 (0.63—1.13) | 1.06 (0.93—1.21) |
| Infrainguinal bypass | 1.11 (1.03—1.19) | 1.08 (0.93—1.25) | 1.02 (0.87—1.19) | 1.09 (1.01—1.17) |
| Axillo-femoral bypass | 1.18 (0.82—1.72) | 0.66 (0.25—1.73) | 1.96 (0.88—4.32) | 1.34 (0.94—1.90) |

*Note.* Female patients are the reference value of 1.0. Multifactorial adjusted for age, surgical indication, body mass index, diabetes mellitus, hypertension, tobacco use, creatinine, pulmonary disease, previous MI, previous stroke, and the following medical treatment: statins, ACE inhibitors/ARBs, CCBs, beta blockers, and antithrombotic therapy. ACE = angiotensin converting enzyme; ARB = angiotensin II receptor blocker; CCB = calcium channel blocker; HR = hazard ratio; MACE = major adverse cardiovascular event; MI = myocardial infarction.

percentage of patients based on sex appears relatively unchanged. It is also interesting to note in Table 4 that long-term survival is greater for both sexes following aorto-iliac bypass surgery compared with femoro-femoral cross-over bypass surgery. Although these procedures treat a similar anatomic segment, the greater survival following aortic surgery probably reflects and confirms the pre-operative considerations of the patient’s tolerance to the procedure, as well as long-term prognosis.

There are several issues regarding PAD and sex. First, PAD is increasing worldwide, while it appears that women are bearing the burden; the age dependent prevalence of PAD among women is perhaps lower than for men, yet the total population burden is greater.[4,7–9]

Second, symptoms and quality of life may be affected differently between the sexes. According to a Swedish study, it appears that asymptomatic PAD is higher among women, while the inherent cardiovascular morbidity and mortality is by no means mitigated.[10] Women also tend to have more “atypical” symptoms, just as functional decline is greater for women than it is for men.[11,12] How these affect eventual treatment and outcomes is not clear but could potentially play a role, perhaps similar to hypothesized explanations for prognostic differences between men and women following MI.[13]

Third, outcomes following treatments may differ, yet working out if or why this is so poses both practical and interpretive challenges. Magnant et al.[14] reported lower primary and secondary infrainguinal bypass patencies among female patients, but this has been contradicted by other studies.[15] Belkin et al.[16] found a lower peri-operative mortality among women undergoing in-situ bypass operations, further supported by Hultgren et al.,[17] who found that female sex was not an important risk factor for either amputation or survival. These issues are often complicated by confounders such as age and various comorbidities such as diabetes, which, in themselves may be impacted by sex.

Finally, there is an issue of whether patients with PAD receive recommended optimal medical therapy. Guidelines regarding medical treatment for PAD are well described and include statins, antiplatelet medication, and antihypertensive therapy.[18–20] Previous studies have indicated that many patients do not receive this “optimal medical therapy”, particularly patient groups such as women and elderly people, although this gap may be closing.[21]

With these issues in mind, it is important to consider what the findings reveal, particularly when recalling the size of the study population and the number of adjustments made in the analysis. It was found that men fare worse than women when undergoing treatment for peripheral arterial disease. This is true for the overall results, but also for many of the subgroups as seen in Table 5. The hazard ratios are also supported by the average survivals given in Table 4, which, in general, show greater survival for female patients. Some of this is driven by the large difference shown in the axillo-femoral procedures, despite the comparatively fewer patients in this subgroup. These patients often have considerable comorbidities, limiting their therapeutic options, and it is therefore interesting to note that it is here where a large difference appears between male and female patients. Why this is so cannot immediately be explained from the data.

As mentioned above, the findings stand in contrast to several other studies, where women either fared similarly or worse than men in terms of cardiovascular mortality[14,22–24] Magnant et al.,[14] showed worse three year survivals (54% vs. 72%) for women than men following infrainguinal bypass surgery. Egorova et al.[22] likewise showed worse mortality rates for women following interventional treatment for PAD, particularly after open surgery. Many although not all studies were from a single institution. The patients here are a national cohort and bear the characteristics of typical PAD patients: high levels of hypertension and tobacco use, as well as substantial numbers of previous MIs and strokes. The percentage of smokers is notably greater among men, which perhaps plays an underlying role in the differences in cardiovascular outcomes. Prophylactic medical therapy is respectable in the group, although not optimal. Actual compliance is obviously difficult to ascertain, gauged by fulfillment of two prescriptions within 90 days following operative treatment. There may be unobserved compliance differences between men and women that could also partially explain the results obtained. As to why women have better outcomes among Danish patients cannot be exacted from the data presented, although it is interesting that these findings are to some degree comparable to those reported by Hultgren et al. in their study among Swedish patients.[17] Another recent study from Sweden reported a better adjusted prognosis for women than men following acute MI, which, in their discussion, may be related to the social and political milieu.[25] Speculations aside, these data do contradict the possible proposition that there is an inherent or possible biological basis that women should fare worse in the treatment of PAD.

There are several limitations to the study. It is retrospective, and therefore there are certain inherent biases at play. The data are dependent on reliable data recording. As mentioned above, the national Danish vascular surgery database has been validated on two occasions and should minimize this risk. Selection bias is also a concern. The large data pool and patient demographic similarities should mitigate some of this bias. There is also a question of data generalizability. The study is nationwide, but some patients were not included. Patients who underwent endovascular treatment, for example, were not included. There is no question that the number of endovascular procedures is increasing, further evidenced by the decline in the number of open surgical procedures in Table 2. Whether there is a difference in the offering of endovascular treatment for men or women cannot be ascertained from these data, but this lack of accounting may affect the conclusions. It is important to note, however, that the ratio between men and women did not change in the period under analysis. The decision not to include endovascular procedures was deliberate, however, mostly out of a concern for further confounding. True, newer therapies, such as drug eluting balloons/stents could potentially affect long-term patency and other outcomes in patients, even though the underlying cardiovascular risk profile is unchanged, but this is unknown. Evolving treatment is an issue for any retrospective analysis.

To that end, it is important to reiterate that any vascular therapy should take several factors into account when addressing outcomes, including patency, amputation rates, and quality of life. The authors chose to look at the long-term cardiovascular burden in patients with PAD to see if there is a difference between men and women, despite revascularization and best medical therapy.

## CONCLUSION

These findings show that, despite indication, severity, and concomitant medical treatment of peripheral artery disease, men have a higher risk of mortality and adverse cardiovascular events following surgical treatment.

## CONFLICT OF INTEREST

None.

## FUNDING

None.

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