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.

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.

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