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Young Women with PAD are at High Risk of Cardiovascular Complications

CME

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ABSTRACT

Objectives: Prognostic research in patients with peripheral arterial disease (PAD) is scarce and determinants of outcome are mainly studied in males. The current management of PAD in women is based on evidence from, at best, mixed populations. We therefore assessed risk and prognostic factors in 313 men and 169 women from the Dutch Bypass Oral anticoagulants or Aspirin Study of whom long-term follow-up data were available.

Method: The primary composite outcome event was vascular death, myocardial infarction, stroke, or major amputation during 5 years of follow-up. Variables with a p-value <0.2 in the univariate analyses were added to the multivariate Cox proportional hazards model.

Results: Females were older (71 vs. 68 years; $p < 0.01$), had more advanced PAD (critical limb ischemia (CLI) 52.1 vs. 42.2%; $p = 0.04$), more often had peripheral bypass surgery as primary intervention (50.5 vs. 32.5%; $p < 0.01$), and had more often hypertension (48.5 vs. 33.2%; $p < 0.01$) than males. Males were more often smokers (63.6 vs. 53.3%; $p = 0.03$) and had more prior myocardial infarctions (18.5 vs. 10.1%; $p = 0.02$).

In total 170 events occurred, 74 (44%) in females and 96 (31%) in males. Overall, independent risk factors for the primary outcome event were age and critical limb ischemia. Independent risk factors in males were: age (HR: 1.06, 95% CI: 1.03–1.09), critical limb ischemia (HR: 1.7, 95% CI: 1.05–2.7), and diabetes mellitus (HR: 1.7, 95% CI: 1.01–2.8) and in females critical limb ischemia (HR: 3.5, 95% CI: 2.0–6.1), ABI≤0.9 (HR: 2.8, 95% CI: 1.2–6.1), and femorocrural bypass (HR: 1.9, 95% CI: 1.1–3.3). Although sex was not an independent risk factor in the overall analysis, women younger than 60 years had an increased risk for cardiovascular events compared to men of that age (HR: 4.9, 95% CI: 1.8–13.6), whereas no difference was seen above 60 years of age.

Conclusions: Risk factors for cardiovascular events in patients with PAD differ between men and women. To our knowledge, this is the first study that shows such a bad outcome in female patients younger than 60 years of age. More awareness leading to early diagnosis and optimal treatment might improve long-term clinical outcome in (young) women with PAD.

Patients with peripheral arterial disease (PAD) have greater functional impairments and higher risk of fatal and non-fatal cardiovascular events compared with patients with symptomatic atherosclerosis in other vascular beds such as coronary, carotid and cerebral arteries.[1,2] Yet, PAD is under-recognized by physicians, allied health-care professionals and the public.[1,2]

The prevalence of PAD is slightly greater in men than in women, particularly in the younger age groups. In patients with intermittent claudication (IC), the ratio of men to women ranges between 1:1 and 2:1. However, the prevalence of PAD in women increases rapidly beyond 40 years of age from 3 to 4.4% up to 15.5–29% at the age of 80 years and older.[3,4]

Long-term prognostic research in patients with PAD is scarce and outcome determinants have mainly been studied in males.[1,3–8] Due to a lower prevalence of PAD in young women compared with older women and men, even less is known about risk factors and prognostic factors of the long-term outcome in pre-menopausal women with PAD.[6–8]

The current management of PAD in women is based on evidence from, at best, mixed populations. As there are differences in etiology, presentation and outcome between men and women with atherosclerosis,[6–8] the management of PAD might have to be adjusted for women, in accordance with the sex-influenced management of coronary arterial disease.[9,10]

To determine whether sex and age-driven management of PAD is indicated, large prospective studies about the differences between men and women with PAD are required. We therefore assessed risk and prognostic factors of men and women with PAD in

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the long-term follow-up of the Dutch Bypass Oral anticoagulants or Aspirin (BOA) Study.[11]

Methods

Patients

The present longitudinal cohort study is derived from the Dutch BOA Study. Full details of this multicentre prospective randomized trial have been published elsewhere,[11] and are briefly summarized here. From 1995 until 1998, 2690 patients were included from 77 vascular centers throughout the Netherlands after infrainguinal bypass surgery. To study the effects of oral anticoagulants and aspirin in preventing bypass occlusion, lower limb amputation and ischemic events, these patients were randomly allocated to oral anticoagulation (target international normalized ratio (INR) 3.0–4.5) or to aspirin (100 mg carbasalate calcium daily).

For the long-term follow-up study we included all patients from the six sites that contributed most patients in the study (18%, $n = 482$). Based on the event rate in the Dutch BOA Study, the resulting sample size was sufficient to allow for the development of robust prediction models.

The Ethics Committee of the University Medical Centre Utrecht approved this follow-up study.

Data collection

During the Dutch BOA Study, follow-up visits took place at 3 and 6 months after surgery and every 6 months thereafter for prospective registration of outcome events. For the subsequent long-term follow-up of the BOA Study, outcome events and drug use of patients who were still alive at their last follow-up visit in April 1998 were collected until August 2009 in a stepwise manner. First, follow-up data were obtained from the study record and from the patients' attending vascular surgeon. Second, the patients' general practitioner was approached for similar information if data from the vascular surgeon were incomplete. Third, the patient was interviewed about the occurrence of outcome events if data remained incomplete at the general practitioner. In case the patient had died, relatives or acquaintances were approached for follow-up data. If the patient had moved, the last known residence was looked up at the municipality register to trace the patient's new home address. If the patient or their relatives or acquaintances did not respond, the registry office was contacted to inquire whether the patient had died and when.

To confirm a reported outcome event, clinical data specific for that event were gathered from the attended hospital and/or specialist (e.g., discharge letters, laboratory reports, 12-lead electrocardiogram, reports of Doppler or duplex scans, brain scan reports, operation reports and autopsy reports). All participating patients alive at time of our approach gave informed consent on completing our follow-up data.

Outcome events

The primary outcome event was the composite of vascular death, non-fatal myocardial infarction, non-fatal ischemic stroke or major lower limb amputation (whichever occurred first) within 5 years from inclusion. The definitions of outcome events are summarized in Appendix A. Each recorded outcome event was adjudicated and classified according to the pre-specified definitions by a panel consisting of a vascular surgeon, a clinical epidemiologist, a neurologist and a cardiologist. Discrepancies were resolved by discussion and documented in a logbook to ensure consistent adjudication of the outcome events.

Statistical analyses

Continuous variables were summarized as mean with standard deviation (SD), and discrete variables were summarized as frequency and percentage. Missing ankle brachial pressure index (ABI) data of 81 patients were imputed with single linear regression analysis.

All analyses were performed in three patient groups based on sex and age: 1) overall analyses (includes all patients), 2) patients under 60 years of age and 3) female patients.

Differences in dichotomous baseline variables between the different subgroups were analyzed with chi-square tests, and differences in continuous variables with Student's *t*-tests.

Cumulative risk of mortality and vascular events, and risk factors of the primary outcome event were calculated with a Cox proportional hazards model and numerically presented as adjusted hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) and presented graphically as Kaplan–Meier curves. Variables with a p-value <0.2 in the univariate analyses were added to the multivariate model in a forward stepwise manner.

Results

Overall analyses

Baseline variables

Demographic characteristics, medical history and intervention-related variables of all patients and stratified by sex are shown in Table 1. Of the 482 patients, 169 (35.1%) were female. Female patients were older (71 vs. 68 years; $p < 0.01$), had more advanced PAD (critical limb ischemia (CLI) 52.1 vs. 42.2%; $p = 0.04$), more

Table 1
Baseline variables.

	Overall N = 482	Men N = 313	Women N = 169	*P*-value
Demographic characteristics				
Age (mean ± SD)	68.8 ± 9.7	67.7 ± 9.7	70.7 ± 10.2	0.002
Male	313 (64.9%)	–	–	–
Female	169 (35.1%)	–	–	–
Medical History				
Diabetes mellitus	109 (22.6%)	65 (20.8%)	44 (26.0%)	0.210
Smoking	289 (60.0%)	199 (63.6%)	90 (53.3%)	0.032
Hypertension	186 (38.6%)	104 (33.2%)	82 (48.5%)	0.001
Hyperlipidemia	101 (21.0%)	65 (20.8%)	36 (21.3%)	0.907
Angina pectoris	80 (16.6%)	47 (15.0%)	33 (19.5%)	0.248
Myocardial infarction	75 (15.6%)	58 (18.5%)	17 (10.1%)	0.017
TIA/CVA	49 (10.2%)	27 (8.6%)	22 (13.0%)	0.155
Claudication				
AB index (mean ± SD)	0.55 ± 0.37	0.56 ± 0.37	0.52 ± 0.37	0.370
ABI ≤0.9	450 (93.4%)	292 (93.3%)	158 (93.5%)	1.000
ABI ≤0.6	288 (59.8%)	177 (56.5%)	111 (65.7%)	0.052
CLI	220 (45.6%)	132 (42.2%)	88 (52.1%)	0.044
Vascular intervention	213 (44.2%)	158 (50.5%)	55 (32.5%)	0.000
Trial Bypass				
Femorocrural/pedal bypass	107 (22.2%)	76 (24.3%)	31 (18.3%)	0.168
Venous bypass	313 (64.9%)	210 (67.1%)	103 (60.9%)	0.194
Trial Medication				
Aspirin	243 (50.4%)	151 (48.2%)	92 (54.4%)	0.195
Anticoagulants	239 (49.6%)	162 (51.8%)	77 (45.6%)	

Demographic characteristics, medical history and intervention-related variables of all patients and stratified by sex. Differences in dichotomous baseline variables between men and women were analyzed with chi-square tests, differences in continuous variables with Student *t*-tests.
AB index: ankle brachial pressure index, ABI ≤0.9: ankle brachial pressure index below 0.9; ABI ≤0.6: ankle brachial pressure index below 0.6; vascular intervention: previous vascular intervention at baseline; TIA/CVA: transient ischemic attack or cerebrovascular accident; CLI: critical limb ischemia.