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ORIGINAL RESEARCH

Gender Differences in Health Status and Adverse Outcomes Among Patients With Peripheral Arterial Disease

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***Background*—**Few studies have examined gender differences in health status and cardiovascular outcomes in patients with peripheral artery disease (PAD). This study assessed (1) self-reported health status at PAD diagnosis and 12-months later, and explored (2) whether outcomes in women with PAD differ with regard to long-term major adverse events.

***Methods and Results*—**A total of 816 patients (285 women) with PAD were enrolled from 2 vascular clinics in the Netherlands. Baseline clinical data and subsequent adverse events were recorded and patients completed the Short Form-12 (SF-12, Physical Component Score [PCS] and Mental Component Score [MCS]) upon PAD diagnosis and 12-months later. Women had similar ages and clinical characteristics, but poorer socio-economic status and more depressive symptoms at initial diagnosis, as compared with men. Women also had poorer physical (PCS: 37±10 versus 40±10, *P*=0.004) and mental (MCS: 47±12 versus 49±11, *P*=0.005) health status at the time of presentation. At 12-months, women still reported a poorer overall PCS score (41±12 versus 46±11, *P*=0.006) and MCS score (42±14 versus 49±12, *P*=0.002). Female gender was an independent determinant of a poorer baseline and 12-month PCS and MCS scores. However, there were no significant differences by gender on either mortality (unadjusted hazard ratio [HR]=0.93, 95% CI 0.60;1.44, *P*=0.74) or major adverse events (unadjusted HR=0.90, 95% CI 0.63;1.29, *P*=0.57), after a median follow-up of 3.2 years.

***Conclusions*—**Women's physical and mental health status is compromised both at initial PAD diagnosis and at 12-month follow-up, despite experiencing a similar magnitude of change in their health scores throughout the first 12-months after diagnosis. **(*J Am Heart Assoc*. 2014;3:e000863 doi: 10.1161/JAHA.114.000863)**

Key Words: gender differences • health status • outcomes research • peripheral artery disease • women

In a recent scientific statement, the American Heart Association (AHA) released a "call to action" for more focused care and research that is sensitive to the specific concerns of women with peripheral artery disease (PAD).[1] Until recently, the majority of data on gender-based differences has been derived from coronary artery disease (CAD) where women have been shown to have poorer health status outcomes,[2] worse in-hospital/long-term mortality,[3,4] and increased mortality following cardiac revascularization procedures.[5] In contrast, major knowledge gaps exist in terms of gender-specific differences in the health status of PAD and cardiovascular mortality rates. Preliminary data suggest that women with PAD suffer more from depression,[6] experience more atypical lower-extremity symptoms, have a poorer overall health status (symptoms, functioning, quality of life),[7–15] and may be at increased risk for morbidity and mortality as compared with men.[16] Results from these studies have been derived from small cohorts, cross-sectional work, or studies that were not explicitly addressing gender differences in their primary objectives and analyses. With these factors in mind, the current longitudinal study was designed to assess gender-based differences in health status and long-term adverse prognosis, including exploring the explanatory role of depressive symptoms for these outcomes since women are known to have worse depressive symptoms than

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men with PAD, and depressive symptoms have provided part of the explanation for adverse outcomes in cardiovascular disorders.[6,17]

In light of the above, the current study aimed to (1) quantify self-reported symptomatic health status at PAD diagnosis and 12-months later, and (2) explore whether outcomes in women with PAD differ with regard to long-term major adverse events (followed for a median of 3.2 years). The underlying hypothesis was that women would have poorer outcomes, including a poorer self-reported health status, increased mortality, and an increased adverse event burden as compared with men.

Methods

Participants

Participants with newly diagnosed symptomatic PAD or with an exacerbation of existing PAD symptoms were consecutively enrolled from 2 vascular outpatient clinics of the St. Elisabeth Hospital (March 2006–November 2011) and Twee-Steden Hospital (March 2006–October 2008) in Tilburg, the Netherlands. Study entry criteria included having symptomatic PAD and an abnormal resting ankle–brachial index (ABI) ($\leq$0.90)[18] or an abnormal postexercise ABI (ABI decrease of 15% following exercise). Exclusion criteria included critical leg ischemia (we excluded patients in all Rutherford categories 4 to 6, which corresponds with the Fontaine III to IV classification),[19] significant cognitive impairment, severe psychiatric co-morbidities, life-threatening or debilitating conditions that prevented participation (eg, undergoing active cancer treatment), and insufficient knowledge of Dutch language and/or illiteracy. Patients with a noncompressible ABI ($\geq$1.30) were also excluded. The protocol was approved by the local ethics committees of the participating hospitals, and all participants provided written informed consent. Patients were invited to participate in the study by their treating vascular surgeon during their visit at one of the outpatient clinics following a vascular diagnostic work-up that confirmed the presence of PAD. All patients within the study completed a set of questionnaires collected by mail following recruitment as well as at 12-month follow-up. Demographic, risk factor, medication, and therapeutic information was obtained by abstracting patients' medical records.

Measures

Health status

The Dutch version of the Short Form-12 (SF-12) was administered to assess health status,[20,21] both at PAD diagnosis and 12-months later. This generic tool measures overall physical and mental health status and consists of 12 items with standard Likert scales. Physical Component Summary PCS and the Mental Component Summary MCS scores[22] are generated through a standardized scoring algorithm and were based on weights derived from Dutch population norms (score ranges between 0 and 100, mean score=50, SD=10), with higher scores indicating better functioning.[23] Reference values in the overall population in the Netherlands include a mean score of 51$\pm$8.9 and 52$\pm$8.4 for men on the MCS and PCS, respectively. Similarly, 49$\pm$9.6 and 49.38$\pm$9.7 represent the population averages for women.[23] The SF-12 has been demonstrated to be a valid and reliable instrument[20] and has been successfully utilized in PAD populations.[24,25]

Depressive symptoms

The 14-item self-report Hospital Anxiety and Depression Scale was used to measure self-reported depressive symptoms. Criterion scores of $\geq$8 for the depression subscale denote clinically relevant symptoms of depression.[26,27]

All-Cause Mortality and Adverse Events

The major adverse events studied included (1) all-cause mortality and (2) acute myocardial infarction (AMI) that was diagnosed by a cardiologist and required hospitalization, (3) stroke that was diagnosed by a neurologist and required hospitalization, and (4) any PAD-related lower-extremity amputation (eg, amputation of toes or part of the foot, below or above knee amputation, and through-knee amputation due to PAD, excluding traumatic amputations). Mortality was used both as a separate outcome of interest and also as a combined end point with the other major adverse events. Information on adverse events was documented from patients' medical records by a surgical fellow supervised by 2 vascular surgeons. For mortality, in-hospital mortality as well as mortality events outside the hospital were documented as patients' medical records are linked to the regional Social Security death index of the Tilburg community; deaths occurring outside the Tilburg community were reported by patients' general practitioners.

Ankle-Brachial Index

The vascular laboratory assessment procedures have been described previously.[28] In brief, a handheld Doppler ultrasonic instrument was used to obtain systolic blood pressure readings in the right and left brachial arteries, right and left dorsalis pedis arteries, and right and left posterior tibial arteries. The ABI at rest and after walking on a treadmill (distance limited 1000 m) was obtained with the lower resting ABI used in all analyses. In all patients, the pain-free walking distance and the ABI index were measured as indices of

severity of PAD, whereby the ABI is defined as the ratio of the ankle systolic blood pressure to the brachial artery systolic blood pressure and has a normal resting value of ≈1.0.[29] A value of <0.90 has been shown to be highly sensitive to detect PAD.[30]

Sociodemographics and Clinical Variables

Age and gender were abstracted from medical records, and information on sociodemographics was self-reported by the patients. These included marital status (not having a partner versus having a partner), high school education or more (less than high school education versus high school education or more), and work status (active versus non-active working status). Clinical variables for patients were obtained from medical records at baseline and included the following: cardiovascular risk factors (current smoking, hypercholesterolemia, hypertension, diabetes mellitus, chronic heart failure), cardiovascular history (previous AMI, angina, coronary artery bypass grafting, percutaneous coronary intervention, stroke, and transient ischemic attack), co-morbidities (renal dysfunction, chronic obstructive pulmonary disease, body mass index [kg/m^2], prior documented back pain, prior documented knee/hip osteoarthritis, and depression) and PAD clinical factors (resting and postexercise ABI and pain-free walking distance [PFWD]). Medications that patients were taking upon enrollment were abstracted from their medical charts.

Statistical Analysis

Baseline characteristics were examined for the total sample and compared between genders. In addition, baseline and 12-month follow-up health status scores were examined for the total population and stratified by gender. The Student *t* tests and Wilcoxon tests were used for continuous variables and χ^2 tests or Fisher's exact tests were used for categorical variables, as appropriate.

For the health status analyses, 6 sets of median regression models examined the relationship between gender, and (1) baseline SF-12 health status scores (baseline PCS and MCS), (2) 12-month SF-12 health status scores (12-month PCS and MCS), and (3) SF-12 health status change scores (12-month PCS/MCS scores minus baseline PCS/MCS scores). Median regression was performed due to nonlinear distributions of health status scores. The following variables were sequentially entered into the models: demographics (gender, age), socio-demographics (marital status, educational level), and cardiovascular risk factors and cardiovascular history (diabetes, current smoking, prior stroke, prior AMI, heart failure, and renal dysfunction). In 3 exploratory steps, depression was included into the model first, and obesity (body mass index ≥30 versus <30), chronic obstructive pulmonary disease, back pain, knee/hip osteoarthritis, PFWD, and ABI thereafter. Interaction terms between gender and age, and between gender and depressive symptoms for SF-12 scores were evaluated, but not included in the final models, as these terms were not significant in any of the analyses.

Missing SF-12 items were assumed to be missing at random and handled by multiple imputation (mean of 5 iterations) if ≥75% of all items were complete at baseline and 12-months. The pooled estimates and 95% CI for the 5 imputed datasets were used. A comparison of baseline characteristics was conducted for those who were included in the SF-12 analyses (0% to 25% missing) versus those who were eligible for inclusion but who were not in the SF-12 analyses (>25% missing). Baseline characteristics were similar between these groups; however, patients not in the analyses were more likely to be women (Cramér's V=0.079) or smokers (Cramér's V=0.083) as compared with those who were included in the SF-12 analyses (all effect sizes were very small).

Two sets of Cox proportional hazards models were constructed to examine the relationship between gender and (1) all-cause mortality and (2) major adverse events outcomes (ie, all-cause mortality, AMI, stroke, and lower-extremity amputation). As our study was mainly powered to evaluate unadjusted associations between gender and health status outcomes, the following 2 multivariable Cox models (1 for all-cause mortality and 1 for major adverse events) were only conducted for exploratory and hypothesis-generating reasons. Both models were sequentially built including the following variables: demographics (gender, age), and cardiovascular risk factors and cardiovascular history (diabetes mellitus, current smoking, prior stroke, prior AMI, heart failure, and renal dysfunction). Socio-economic factors (marital status, educational level) and depression were only added as an exploratory last step. We assessed an interaction term between gender and age for all-cause mortality and major adverse cardiac event outcomes, but in both analyses the interaction term was not significant (P=0.72, P=0.49, respectively) and thus was excluded from the final model. All tests were 2-tailed and a P<0.05 was considered statistically significant. All analyses were performed using SPSS 17.0 for Windows (PASW Inc, Chicago, IL) and SAS Software version 9.2. (SAS Institute Inc, Cary, NC).

Results

Patient Characteristics

Baseline characteristics of the total sample (N=816) were stratified by gender and are listed in Table 1. The mean age of the total cohort was 65 years and 285 (35%) were women.

Table 1. Baseline/12-Month Demographics for the Total Sample and Stratified by Gender

	Total Sample (n=816)	Men (n=531, 65%)	Women (n=285, 35%)	*P* Value
Socio-demographics				
Age (mean years, SD, range)	65.3 (9.8, 37 to 92)	65.3 (9.6)	65.2 (10.2)	0.91
No partner (n, %)	175 (25.1)	75 (16.8)	100 (39.7)	<0.0001
<High school education (n, %)	177 (25.6)	96 (21.5)	81 (32.9)	0.001
Non-active work status (n, %)	501 (74.4)	328 (73.9)	173 (75.5)	0.64
Cardiovascular risk factors				
Current smoker (n, %)	406 (49.8)	259 (48.8)	147 (51.6)	0.45
Hypercholesterolemia (n, %)	548 (67.2)	358 (67.4)	190 (66.7)	0.83
Hypertension (n, %)	488 (59.8)	306 (57.6)	182 (63.9)	0.08
Diabetes mellitus (n, %)	196 (24.0)	128 (24.1)	68 (23.9)	0.94
Chronic heart failure (n, %)	41 (5.0)	27 (5.1)	14 (4.9)	0.91
Cardiovascular history				
Myocardial infarction (n, %)	151 (18.5)	103 (19.4)	48 (16.8)	0.37
Angina (n, %)	124 (15.2)	86 (16.2)	38 (13.3)	0.28
Coronary artery bypass graft (n, %)	90 (11.0)	66 (12.4)	24 (8.4)	0.08
Percutaneous coronary intervention (n, %)	74 (9.1)	50 (9.4)	24 (8.4)	0.64
Stroke (n, %)	66 (8.1)	49 (9.2)	17 (6.0)	0.10
Transient ischemic attack (n, %)	76 (9.3)	53 (10.0)	23 (8.1)	0.37
Co-morbidities				
Renal dysfunction (n, %)	73 (8.9)	56 (10.5)	17 (6.0)	0.029
COPD (n, %)	142 (17.4)	91 (17.1)	51 (17.9)	0.79
Body mass index (mean, SD)	26.8 (5.0)	26.8 (4.4)	26.7 (6.0)	0.82
Back pain (n, %)	126 (15.4)	76 (14.3)	50 (17.5)	0.22
Knee/hip osteoarthritis (n, %)	169 (20.7)	116 (21.8)	53 (18.6)	0.28
Depressive symptoms (n, %)	186 (27.0)	103 (23.4)	83 (33.2)	0.005
PAD clinical factors				
Resting ABI (mean, SD)	65.7 (16.9)	66.1 (17.1)	65.0 (16.5)	0.35
Postexercise ABI (median, SD)	36.0 (19.5)	35.0 (19.4)	36.5 (19.8)	0.17
PFWD (meters, median, SD)	80.0 (140.5)	80.0 (143.4)	70.0 (133.5)	<0.0001
Medications				
Aspirin (n, %)	647 (79.3)	427 (80.4)	220 (77.2)	0.28
Statin (n, %)	672 (82.4)	431 (81.2)	241 (84.6)	0.23
Anticoagulants (n, %)	139 (17.0)	86 (16.2)	53 (18.6)	0.38
β-Blocker (n, %)	345 (42.3)	222 (41.8)	123 (43.2)	0.71
Calcium channel blocker (n, %)	186 (22.8)	128 (24.1)	58 (20.4)	0.22
ACE inhibitor (n, %)	257 (31.5)	179 (33.7)	78 (27.4)	0.06
Diuretics (n, %)	206 (25.2)	128 (24.1)	78 (27.4)	0.31
Nitrate (n, %)	77 (9.4)	48 (9.0)	29 (10.2)	0.60
Antiarrhythmics (n, %)	21 (2.6)	12 (2.3)	9 (3.2)	0.44
Antidepressants (n, %)	48 (5.9)	23 (4.3)	25 (8.8)	0.010
Anxiolytics (n, %)	34 (4.2)	12 (2.3)	22 (7.7)	<0.0001
Hypnotics (n, %)	37 (4.5)	18 (3.4)	19 (6.7)	0.032

Continued

Table 1. Continued

	Total Sample (n=816)	Men (n=531, 65%)	Women (n=285, 35%)	*P* Value
Functional performance at 12-months				
12-month ABI (mean, SD)	68.4 (21.2)	68.2 (21.0)	68.7 (21.8)	0.79
Difference 12-month ABI (mean, SD)	2.9 (19.9)	2.6 (19.2)	3.6 (21.3)	0.58
12-month PFWD (meters, median, SD)	320 (355.8)	350.0 (353.3)	280.0 (357.2)	0.008
Difference 12-month PFWD (meters, median, SD)	220.0 (352.8)	240.0 (355.4)	190.0 (344.5)	0.11

ABI indicates ankle-brachial index; ACE, angiotensin-converting enzyme; COPD, chronic obstructive pulmonary disease; PAD, peripheral artery disease; PFWD, pain-free walking distance.

Both men and women were similar in terms of age, cardiovascular risk factors, medical history, and ABI values (resting and postexercise); however, women were less likely to be partnered, have completed high school education or more, or suffer from renal dysfunction as compared with men. In addition, women also had a significantly shorter PFWD. Women also had higher rates of depressive symptoms and were more likely to be on antidepressants, anxiolytics, and hypnotics as compared with men (Table 1).

In regards to functional performance status at 12-months, there was no difference between sexes in ABI values and/or the change in ABI from baseline. In addition, although women had a lower 12-month PFWD than men, there was no statistically significant difference from baseline to 12-months (Table 1).

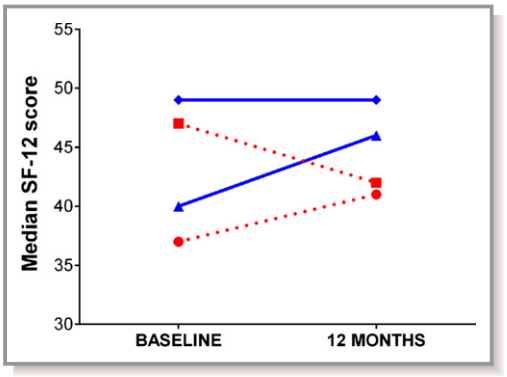

Figure 1. Median PCS and MCS SF-12 summary scores at baseline and 12-month follow-up stratified by gender (red circle, PCS women; red square, MCS women; blue triangle, PCS men; blue diamond, MCS men). MCS indicates mental component score; PCS, physical component score; SF-12, short form-12.

Health Status Analyses

In the total sample, median physical health status (PCS) improved from 39±10 at baseline (mean=39±9) to 43±11 (mean=41±9) at 12-month follow-up (median difference 2.6±10; *P*<0.0001) (mean difference=1.84±10). Conversely, median mental health scores (MCS) did not improve over 12-months (48±11 at baseline [mean=45±10] and 47±13 [mean=42±10] at 12-months, median difference −0.6±10, *P*=0.12) (mean difference=−2.96±11).

Women, as compared with men, had poorer median physical (PCS: 37±10 versus 40±10, *P*=0.004) (mean=38±9 versus 40±9) and mental (MCS: 47±12 versus 49±11, *P*=0.005) (mean=43±10 versus 46±10) baseline health status scores upon being diagnosed with PAD (Figure 1).

At 12-month follow-up, women still reported a poorer overall median PCS score (41±12 versus 46±11, *P*=0.006) (mean=40±9 versus 42±9) and MCS score (42±14 versus 49±12, *P*=0.002) (mean=41±10 versus 43±10). Women and men had similar improvement in their physical function over 12-months (3.2±11 versus 2.4±10) (mean=1.93±10 versus 1.79±10) and neither group experienced an improvement in their mental health status (−1.2±12 versus −0.6±8.8) (mean=−2.94±10 versus −2.97±10).

In terms of baseline PCS scores, there was a significant effect of female gender in the unadjusted model (female β=−2.76, 95% CI −5.06;−0.46, *P*=0.019). When adjusting for clinical factors (female β=−2.70; 95% CI −5.23;−0.16, *P*=0.037) (adjusted step 4), depression (adjusted step 5) (female β=−2.17, 95% CI −4.28;−0.06, *P*=0.044), and other exploratory factors (obesity [body mass index ≥30 versus <30], COPD, back pain, knee/hip osteoarthritis, adjusted step 6) (female β=−2.13; 95% CI −4.17;−0.09, *P*=0.041), the association between female gender and lower physical health status persisted (full-model results are presented in Table 2; sequential modeling results in Table 3).

In terms of baseline MCS scores, there was a trend towards women reporting a poorer mental health status at initial PAD diagnosis as observed in the unadjusted model (female β=−2.29, 95% CI −4.98;0.40, *P*=0.10), which became significant after adjustment for age (female β=−2.95 95% CI −5.53;−0.37, *P*=0.025). After full adjustment, there was no statistically significant effect of female gender in this model (female β=−1.08, 95% CI −3.45;1.29, *P*=0.37) (Tables 2 and 3).

Table 2. Full Adjusted Model for the Association Between Gender and Baseline Health Status

	SF-12 PCS at Baseline			SF-12 MCS at Baseline		
	Estimate	95% CI	*P* Value	Estimate	95% CI	*P* Value
Full model						
Female gender	−2.70	−5.23; −0.16	0.037	−1.08	−3.45; 1.29	0.37
Age	0.15	0.00 to 0.31	0.052	0.12	0.00 to 0.23	0.045
No partner	−1.47	−4.10;1.17	0.28	−3.74	−6.58;−0.90	0.010
<High school education	−2.71	−5.32;−0.11	0.042	−2.31	−5.02; 0.41	0.10
Diabetes	−2.54	−5.15;0.07	0.06	−3.27	−6.25; −0.29	0.031
Smoking	1.59	−0.63;3.81	0.16	−0.74	−3.16; 1.69	0.56
Prior stroke	−4.35	−7.89;−0.80	0.016	−2.42	−6.99; 2.15	0.30
Prior AMI	−2.04	−4.81;0.73	0.15	1.24	−1.88; 4.37	0.44
Heart failure	−6.35	−11.94;−0.75	0.027	−5.88	−13.08; 1.32	0.11
Renal dysfunction	−3.92	−7.61;−0.23	0.039	−3.52	−7.47;0.42	0.09

Regression coefficients (B) and 95% CIs are presented. AMI indicates acute myocardial infarction; MCS, mental component summary score; PCS, physical component summary score.

In terms of physical health status at 12-month follow-up, women tend to report a poorer physical health status (unadjusted female β=−3.89, 95% CI −7.21; −0.58, *P*=0.023). This effect persisted when adjusting for age (female β=−3.90; 95% CI −6.75; −1.06, *P*=0.007), after adding depression to the model (adjusted step 5) (female β=−3.35; 95% CI −6.34; −0.37, *P*=0.028), as well as PFWD and ABI (female β=−2.69; 95% CI −5.24; −0.15, *P*=0.039).

Table 3. Unadjusted and Adjusted Association Between Gender and Baseline Health Status

	SF-12 PCS at Baseline			SF-12 MCS at Baseline		
	Estimate	95% CI	*P* Value	Estimate	95% CI	*P* Value
Unadjusted						
Female gender	−2.76	−5.06; −0.46	0.019	−2.29	−4.98; 0.40	0.10
Adjusted step 1*						
Female gender	−2.25	−4.81; 0.31	0.09	−2.95	−5.53; −0.37	0.025
Adjusted step 2†						
Female gender	9.83	−4.95; 24.62	0.19	−3.69	−19.40; 12.01	0.66
Adjusted step 3‡						
Female gender	−1.47	−4.00; 1.06	0.26	−0.40	−3.18; 2.38	0.79
Adjusted step 4§						
Female gender	−2.70	−5.23; −0.16	0.037	−1.08	−3.45; 1.29	0.37
Adjusted step 5‖						
Female gender	−2.17	−4.28; −0.06	0.044	−1.33	−3.22; 0.56	0.17
Adjusted step 6¶						
Female gender	−2.13	−4.17; −0.09	0.041	−1.78	−3.82; 0.27	0.09
Adjusted step 7#						
Female gender	−1.76	−3.67; −0.15	0.07	−1.36	−3.21; −0.48	0.14

Regression coefficients and 95% CIs are presented. MCS indicates mental component score, PCS, physical component score. The following covariates are sequentially included in the adjusted models: *adjusted model 1, gender and age; †adjusted model 2, model 1 and gender × age; ‡adjusted model 3, model 1 and socio-demographics (no partner and <high school education); §adjusted model 4, model 3, and clinical factors (diabetes, current smoking, prior stroke, prior acute myocardial infarction heart failure, and renal dysfunction). The exploratory adjusted models include the following covariates: ‖exploratory adjusted model 5, model 4 and depression; ¶exploratory adjusted model 6, model 5 and co-morbidities (body mass index ≥30 kg/m^2, chronic obstructive pulmonary disease, back pain, and hip/knee osteoarthritis); #exploratory adjusted model 7, model 6, pain-free walking distance and ankle brachial index.

Table 4. Full Adjusted Model for the Association Between Gender and 12-Month Health Status

	SF-12 PCS at 12 Months			SF-12 MCS at 12 Months		
	Estimate	95% CI	*P* Value	Estimate	95% CI	*P* Value
Full model						
Female gender	−3.41	−6.88; 0.07	0.06	−4.10	−7.84; −0.36	0.032
Age	−0.11	−0.28; 0.05	0.20	0.10	−0.07; 0.26	0.24
No partner	−2.60	−7.11; 1.90	0.27	−1.29	−6.02; 3.43	0.59
<High school education	−3.13	−6.70; 0.43	0.09	−3.76	−7.35; −0.17	0.040
Diabetes	−5.81	−10.12; −1.51	0.008	−5.25	−9.12; −1.38	0.008
Smoking	1.19	−2.07; 4.46	0.49	0.77	−2.42; 3.97	0.64
Prior stroke	−3.54	−9.17; 2.09	0.22	−0.12	−6.85; 6.61	0.97
Prior AMI	−1.89	−5.29; 1.52	0.28	0.49	−3.28; 4.26	0.80
Heart failure	0.57	−9.70; 10.84	0.76	−3.81	−15.25; 7.64	0.51
Renal dysfunction	−7.88	−13.61; −2.16	0.008	−5.06	−9.71; −2.14	0.033

Regression coefficients (B) and 95% CIs are presented. AMI indicates acute myocardial infarction; MCS, mental component summary score; PCS, physical component summary score.

There was no effect of gender within the intermediate adjusted steps for PCS scores at 12-month follow-up (fully adjusted model presented in Table 4; sequential analyses in Table 5).

With regard to patients' mental health status at 12-month follow-up, women reported a poorer mental health status (unadjusted female β=−4.66; 95% CI −8.55; −0.77, *P*=0.019) and also following adjustment for age (female

Table 5. Unadjusted and Adjusted Association Between Gender and 12-Month Health Status

	SF-12 PCS at 12-Months			SF-12 MCS at 12-Months		
	Estimate	95% CI	*P* Value	Estimate	95% CI	*P* Value
Unadjusted						
Female gender	−3.89	−7.21; −0.58	0.023	−4.66	−8.55; −0.77	0.019
Adjusted step 1*						
Female gender	−3.90	−6.75; −1.06	0.007	−4.99	−9.07; −0.91	0.017
Adjusted step 2†						
Female gender	−9.53	−30.03; 10.97	0.36	−17.30	−50.73; 16.14	0.31
Adjusted step 3‡						
Female gender	−2.32	−5.95; 1.31	0.22	−2.82	−6.75; 1.11	0.16
Adjusted step 4§						
Female gender	−3.41	−6.88; 0.07	0.06	−4.10	−7.84; −0.36	0.032
Adjusted step 5‖						
Female gender	−3.35	−6.34; −0.37	0.028	−2.21	−5.47; 1.05	0.19
Adjusted step 6¶						
Female gender	−2.26	−5.05; 0.54	0.11	−2.44	−5.52; 0.65	0.12
Adjusted step 7#						
Female gender	−2.69	−5.24; −0.15	0.039	−1.04	−4.35; 2.26	0.53

Regression coefficients and 95% CIs are presented. MCS indicates mental component score; PCS, physical component score. The following covariates are sequentially included in the adjusted models: *adjusted model 1; gender and age; †adjusted model 2, model 1 and gender × age; ‡adjusted model 3, model 1 and socio-demographics (no partner and <high school education); §adjusted model 4, model 3 and clinical factors (diabetes, current smoking, prior stroke, prior acute myocardial infarction, heart failure, and renal dysfunction). The exploratory adjusted models include the following covariates: ‖exploratory adjusted model 5, model 4 and depression; ¶exploratory adjusted model 6, model 5 and co-morbidities (body mass index ≥30 kg/m^2, chronic obstructive pulmonary disease, back pain, and hip/knee osteoarthritis); #exploratory adjusted model 7, model 6, pain-free walking distance and ankle brachial index.

β=−4.99, 95% CI −9.07; −0.91, *P*=0.017) and clinical factors (female β=−4.10; 95% CI −7.84; −0.36, *P*=0.032) (adjusted step 4 in the fully adjusted model).

Lastly, women's 12-month change scores for physical and mental health status did not differ significantly from that of men's, neither in the unadjusted models for PCS (female β=0.44, 95% CI −1.66; 2.54, *P*=0.68) and MCS (female β=0.35, 95% CI −1.69;2.39, *P*=0.74), nor in the fully adjusted models for PCS (female β=−0.18, 95% CI −2.44; 2.08, *P*=0.88) and MCS (female β=−0.78, 95% CI −2.98; 1.43, *P*=0.49) (Table 6 full-model results; sequential model results are shown in Table 7).

Adverse Event Analyses

The study cohort had a median follow-up time of 3.2 years (interquartile range=1.7 to 4.5 years). During follow-up, a total of 92 (11%) deaths occurred (30 women [11%] versus 62 men [12%]) and 138 patients (17%) experienced a first adverse event (mortality, AMI, stroke, lower-extremity amputation) (45 women [16%] versus 93 men [18%]). The Kaplan–Meier curves for all-cause mortality revealed no significant gender differences in survival time (*P*=0.74, Figure 2). Similarly, for the onset of a first adverse event (mortality, AMI, stroke, lower-extremity amputation) there was no difference between men and women (*P*=0.57, Figure 3).

No difference in all-cause mortality was observed between men and women in the unadjusted (hazard ratio [HR] for women=0.93, 95% CI 0.60;1.44, *P*=0.74) and the final adjusted model (HR=0.86, 95% CI 0.55; 1.34, *P*=0.50) (Table 8). Older age (HR=1.05, 95% CI 1.02; 1.08, *P*<0.001), current smoking (HR=1.57, 95% CI 1.00; 2.45, *P*=0.048), heart failure (HR=3.27, 95% CI 1.80; 5.92, *P*<0.001), and renal dysfunction (HR=1.90 95% CI 1.07; 3.39, *P*=0.030) were independently associated with mortality in the final adjusted model (full model results are presented in Table 9).

Similar results were found for the association with adverse events whereby men and women did not differ in both the unadjusted (HR for women=0.90, 95% CI 0.63; 1.29, *P*=0.57) and final adjusted model (HR=0.85, 95% CI 0.59; 1.23, *P*=0.39). Again, older age (HR=1.06, 95% CI 1.04; 1.08, *P*≤0.001), current smoking (HR=1.59, 95% CI 1.10; 2.30, *P*=0.013), prior AMI (HR=1.72, 95% CI 1.18; 2.52, *P*=0.005), and heart failure (HR=2.04, 95% CI 1.19; 3.49, *P*=0.010) were independently associated with experiencing a first adverse event in the final adjusted model (Table 9). Adding marital status, educational level, and depression to the models did not significantly alter the results of the event analyses (Table 10).

Discussion

This study is the first of which we are aware to prospectively compare women's and men's outcomes following their diagnosis of PAD in a real-world setting. Since little is known about the existence of potential gender disparities in PAD, the AHA issued a scientific statement prioritizing a research agenda for this important topic.[1] Our study showed that there were differences at both presentation and follow-up in terms of health status, with women generally reporting worse scores as compared with men. Demographic and clinical factors were not always able to explain these differences in

Table 6. Full Adjusted Model for the Association Between Gender and Health Status Change Scores

	SF-12 PCS Change Scores			SF-12 MCS Changes Scores		
	Estimate	95% CI	*P* Value	Estimate	95% CI	*P* Value
Full model						
Female gender	−0.18	−2.44; 2.08	0.88	−0.78	−2.98; 1.43	0.49
Age	−0.16	−0.28; −0.04	0.011	0.01	−0.09; 0.10	0.89
No partner	−0.13	−2.57; 2.31	0.86	1.79	−0.50; 4.08	0.13
<High school education	−1.09	−3.05; 0.87	0.28	−0.16	−2.22; 1.90	0.85
Diabetes	−1.33	−4.18; 1.53	0.36	0.26	−2.07; 2.59	0.82
Smoking	1.07	−1.12; 3.26	0.34	0.70	−0.86; 2.27	0.39
Prior stroke	0.84	−3.98; 5.67	0.73	3.26	−1.84; 8.36	0.21
Prior AMI	0.07	−2.26; 2.39	0.96	−0.51	−3.12; 2.10	0.70
Heart failure	6.06	0.39; 11.73	0.045	0.01	−5.33; 5.35	0.96
Renal dysfunction	−3.67	−7.77; 0.44	0.08	−3.83	−8.69; 1.04	0.14

Regression coefficients (B) and 95% CIs are presented. AMI indicates acute myocardial infarction; MCS, mental component summary score; PCS, physical component summary score.

Table 7. Unadjusted and Adjusted Association Between Gender and Health Status Change Scores

	SF-12 PCS Change Scores			SF-12 MCS Change Scores		
	Estimate	95% CI	*P* Value	Estimate	95% CI	*P* Value
Unadjusted						
Female gender	0.44	−1.66; 2.54	0.68	0.35	−1.69; 2.39	0.74
Adjusted step 1*						
Female gender	−0.74	−3.46; 1.97	0.59	0.26	−1.63; 2.14	0.79
Adjusted step 2†						
Female gender	−4.25	−21.22; 12.72	0.63	−9.57	−21.62; 2.48	0.12
Adjusted step 3‡						
Female gender	0.09	−2.85; 3.03	0.82	−0.77	−2.66; 1.13	0.44
Adjusted step 4§						
Female gender	−0.18	−2.44; 2.08	0.88	−0.78	−2.98; 1.43	0.49
Adjusted step 5‖						
Female gender	−0.16	−2.48; 2.15	0.89	−0.57	−2.79; 1.65	0.62
Adjusted step 6¶						
Female gender	−0.53	−3.35; 2.30	0.71	0.30	−2.14; 2.74	0.81
Adjusted step 7#						
Female gender	0.67	−2.00; 3.35	0.62	0.66	−1.62; 2.94	0.56

Regression coefficients and 95% CIs are presented. MCS indicates mental component score; PCS, physical component score. The following covariates are sequentially included in the adjusted models: *adjusted model 1, gender and age; †adjusted model 2, model 1 and gender × age; ‡adjusted model 3, model 1 and socio-demographics (no partner and <high school education); §adjusted model 4, model 3 and clinical factors (diabetes, current smoking, prior stroke, prior acute myocardial infarction, heart failure, and renal dysfunction). The exploratory adjusted models include the following covariates: ‖exploratory adjusted model 5, model 4 and depression; ¶exploratory adjusted model 6, model 5 and co-morbidities (body mass index ≥30 kg/m^2, chronic obstructive pulmonary disease, back pain, and hip/knee osteoarthritis); #exploratory adjusted model 7, model 6, pain-free walking distance and ankle brachial index.

our multivariable models. More objective performance measures and changes over 12-months in those measures such as the ABI did not show any differences between men and women, although women had a slightly lower threshold to report pain when doing the treadmill exercise test (women had lower PFWD scores as compared with men). The magnitude of change in women's health status scores over

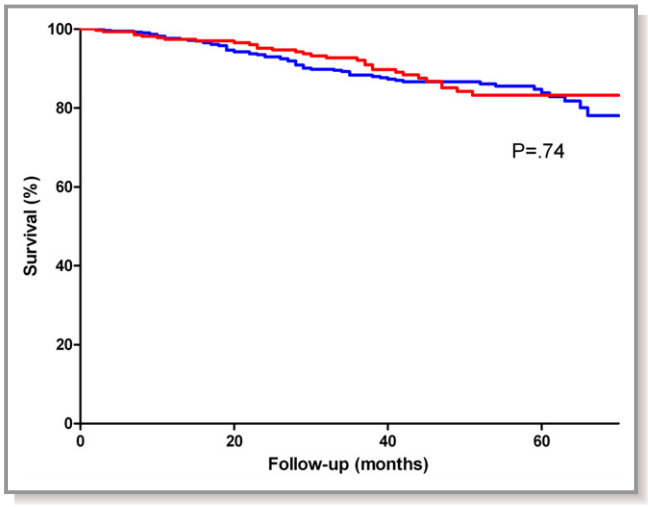

Figure 2. Kaplan–Meier survival curve for all-cause 3.2 year (interquartile range 1.7 to 4.5 years) mortality stratified by gender. The *P*-value for the log rank test for women versus men is provided (women, red line; men, blue line).

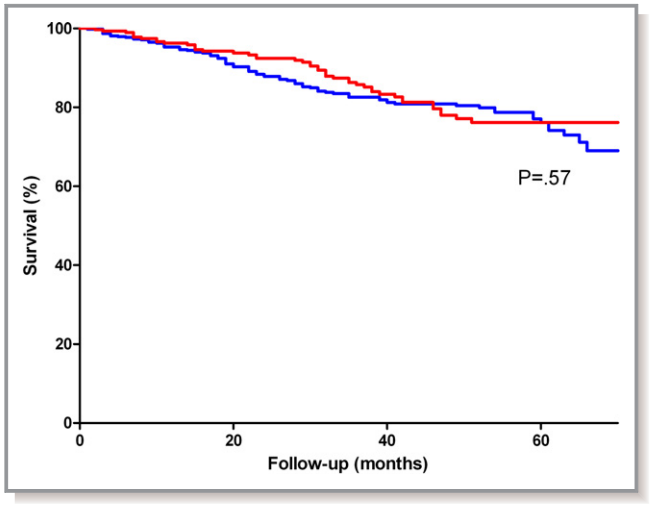

Figure 3. Kaplan–Meier survival curve for experiencing a first cardiovascular event (all-cause mortality, AMI, stroke, and lower-extremity amputation) stratified by gender. The *P*-value for the log rank test for women versus men is provided (women, red line; men, blue line). AMI indicates acute myocardial infarction.

Table 8. Unadjusted and Adjusted Cox Proportional Regression Model Between Gender for Mortality and All-Cause Adverse Events (Mortality, AMI, Stroke, and Lower-Extremity Amputation)

	Mortality			Adverse Events		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Unadjusted						
Female gender	0.93	0.60; 1.44	0.74	0.90	0.63; 1.29	0.57
Adjusted 1						
Female gender	0.90	0.58; 1.39	0.63	0.87	0.61; 1.24	0.43
Adjusted 2						
Female gender	0.86	0.55; 1.34	0.50	0.85	0.59; 1.23	0.39

Hazard ratios (HR) and 95% CIs are presented. AMI indicates acute myocardial infarction.

12-months was also not different from that of men, suggesting that both men and women improved equally following PAD diagnosis and management. Importantly, health status change scores for both men and women failed to reach the threshold for what is defined as a clinically relevant difference (a clinically relevant difference is defined as a score of ≥5 to 10 for a 0.5 to 1.0 SD change, respectively) for the SF-12. In addition, all mean health status scores at all time points and across genders were far below the norm of what is noted in the general Dutch population.[8,23,31–34] This underscores the need for more effective PAD management strategies to alleviate the health status burden of PAD patients in both men and women. Although multivariable regression analyses adjusting for a broad range of potentially confounding characteristics attenuated differences that were found, the nature of the association remained the same. With regard to our secondary aim, we were able to demonstrate that survival/cardiovascular morbidity outcomes 3 years following initial PAD diagnosis do not seem to differ between genders, which was surprising considering the poorer prognostic outcomes in women with CAD.[4,35,36] These findings may open opportunities to start looking into gender-based interventions to improve health status, which have been shown to be effective in CAD populations, including group-based psychosocial interventions (ie, relaxation training techniques, self-monitoring, and cognitive restructuring),

Table 9. Unadjusted and Fully Adjusted Multivariable Cox Proportional Regression Model for Mortality and All Cause Adverse Events (Mortality: AMI, Stroke, and Lower-Extremity Amputation)

	Mortality			Adverse Events		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Unadjusted						
Female gender	0.93	0.60; 1.44	0.74	0.90	0.63; 1.29	0.57
Adjusted step 1						
Female gender	0.90	0.58; 1.39	0.63	0.87	0.61; 1.24	0.43
Age	1.05	1.03; 1.08	<0.001	1.06	1.04; 1.08	<0.001
Adjusted step 2						
Female gender	0.86	0.55; 1.34	0.50	0.85	0.59; 1.23	0.39
Age	1.05	1.02; 1.08	<0.001	1.06	1.04; 1.08	<0.001
Diabetes	0.92	0.56; 1.49	0.72	0.98	0.67; 1.45	0.94
Current smoking	1.57	1.00; 2.45	0.048	1.59	1.10; 2.30	0.013
Prior stroke	0.74	0.32; 1.72	0.48	0.95	0.52; 1.75	0.87
Prior AMI	1.30	0.81; 2.10	0.28	1.72	1.18; 2.52	0.005
Heart failure	3.27	1.80; 5.92	<0.001	2.04	1.19; 3.49	0.010
Renal dysfunction	1.90	1.07; 3.39	0.030	1.53	0.93; 2.52	0.10

Hazard ratios (HR) and 95% CIs are presented. AMI indicates acute myocardial infarction.

Table 10. Exploratory Multivariable Cox Proportional Model for Mortality and All Cause Adverse Events (Death, AMI, Stroke, and Amputation)

	Mortality			Adverse Events		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Unadjusted						
Female gender	0.93	0.60; 1.44	0.74	0.90	0.63; 1.29	0.57
Adjusted step 1						
Female gender	0.90	0.58; 1.39	0.63	0.87	0.61; 1.24	0.43
Age	1.05	1.03; 1.08	<0.001	1.06	1.04; 1.08	<0.001
Adjusted step 2						
Female gender	0.86	0.55; 1.34	0.50	0.85	0.59; 1.23	0.39
Age	1.05	1.02; 1.08	<0.001	1.06	1.04; 1.08	<0.001
Diabetes	0.92	0.56; 1.49	0.72	0.98	0.67; 1.45	0.94
Current smoking	1.57	1.00; 2.45	0.048	1.59	1.10; 2.30	0.013
Prior stroke	0.74	0.32; 1.72	0.48	0.95	0.52; 1.75	0.87
Prior AMI	1.30	0.81; 2.10	0.28	1.72	1.18; 2.52	0.005
Heart failure	3.27	1.80; 5.92	<0.001	2.04	1.19; 3.49	0.010
Renal dysfunction	1.90	1.07; 3.39	0.030	1.53	0.93; 2.52	0.10
Adjusted step 3						
Female gender	0.72	0.41; 1.25	0.24	0.70	0.45; 1.10	0.12
Age	1.04	1.01; 1.07	0.004	1.06	1.03; 1.08	<0.001
Diabetes	0.90	0.51; 1.58	0.72	0.99	0.63; 1.55	0.96
Current smoking	1.42	0.85; 2.36	0.18	1.54	1.02; 2.33	0.041
Prior stroke	0.93	0.40; 2.20	0.88	1.06	0.56; 2.02	0.85
Prior AMI	1.22	0.69; 2.15	0.50	1.56	1.01; 2.43	0.047
Heart failure	2.76	1.36; 5.58	0.005	1.77	0.95; 3.32	0.07
Renal dysfunction	2.03	1.06; 3.88	0.034	1.58	0.90; 2.77	0.11
No partner	1.67	0.97; 2.87	0.06	1.55	0.90; 2.77	0.050
Lower education	1.12	0.66; 1.88	0.68	0.96	0.63; 1.47	0.86
Depression	1.60	0.97; 2.63	0.06	1.60	1.06; 2.41	0.026

Hazard ratios (HR) and 95% CIs are presented. AMI indicates acute myocardial infarction.

telephone-derived collaborative care, and centralized depression care via telephone or internet.[37–39]

Symptomatic Health Status

Findings from our study are in line with previous research suggesting that women with PAD have a worse health status and health-related quality of life as compared with men,[9,13–15,40] and contrasts with those that have found no differences by gender.[41–44] Using the SF-36, previous authors have demonstrated that physical functioning and general health were both significantly lower for women,[14] which was consequently associated with greater mood disturbance than in men with PAD.[13] In addition, female gender adversely impacts durability or quality of life following revascularization for claudication or critical limb ischemia.[40] Furthermore, young women (<50 years) with PAD scored lower than age-matched healthy controls on all health-related quality of life domains on the Research and Development 36-Item Health Survey (RAND-36) in a cross-sectional population-based study.[15] Finally, a mixed cohort of patients with PAD at various disease stages confirmed that women experience worse physical health, greater disability, as well as poorer overall health status many years after diagnosis.[9] These preliminary studies were limited either in terms of their small sample size, their (cross-sectional) design, or did not explicitly focus on gender in their main objectives.[9] Accordingly, our study has extended the literature with results on prospectively

captured health status information in a large, homogeneous PAD population before they started treatment, demonstrating that women with PAD have a compromised health status both around prognosis and 12-months after follow-up. The reason for this gender disparity is likely to be multifactorial and requires further evaluation.

Mechanisms for Poorer Health Status in Women

The potential mechanisms contributing to the observed gender disparity in health outcomes may include differences in socio-demographics, clinical characteristics, and psychosocial factors. As age and cardiovascular risk profiles were similar between genders in this specific cohort, and were included as covariates in the models, it seems unlikely that these explain the observed differences in health status. Furthermore, there was no difference noted in disease severity with which patients presented at diagnosis (as assessed by the ABI), which contradicts prior assertions that differences in disease severity may explain poorer health-related quality of life for women.[40]

In terms of socio-demographic factors, women reported a lower educational attainment compared with men, which may make them more vulnerable in dealing with the many challenges that a diagnosis and management of PAD brings forth, potentially translating into poorer health status scores. Secondly, women were less likely to have a partner, which may decrease the "protective effect" that marriage is associated with.[45] In particular, lack of social support has been shown to be a potent risk factor for women with CAD[46,47] due to a greater propensity to engage in unhealthy behaviors and thus may be an important factor on women's health status in this PAD cohort. These surrogate markers of socio-economics (education, relationship status) should remain the focus of future research, as they have been able to explain many disparities in outcomes among cardiovascular populations.[46,47]

At initial diagnosis, women were also more likely than men to present with depressive symptoms, thus severely impacting their well-being. This finding has been previously demonstrated at diagnosis and long-term follow-up, specifically, younger women with PAD are known to be at a higher risk of depression than other gender age groups.[6] Depressive symptoms or "mood states" as well as a greater degree of bodily pain may be associated with substantially compromised functional status[48] as well as a poorer prognosis,[49] which ultimately has adverse effects on patients' health status.[50,51] When we adjusted for depression scores, after including other relevant demographic, socio-economic, and cardiovascular risk factors, we found further attenuation in the association between gender and health status for physical health status at baseline. Future investigations should explore this in a formal mediation analysis.

Mortality and Adverse Events

To complement our analyses on gender differences and health status outcomes in PAD, we additionally explored the association between gender and adverse events. Cardiovascular mortality, all-cause mortality, and major adverse coronary event rates by gender have not been well examined in PAD population-based studies. The few data available suggest that the relationship between ABI values, mortality (total, cardiovascular), and major coronary events are in fact similar between genders.[16] In the recent AHA statement, 16 population-based studies were pooled to examine these associations, which revealed that the relationship between ABI values and total mortality, cardiovascular mortality, and major cardiovascular events are similar in women and men.[1] Furthermore, the gender effects on survival following lower-extremity PAD revascularization have been inconsistent.[1,52,53] In our study, with real-world patients recently diagnosed with PAD, we failed to observe significant gender differences in survival or experiencing a first adverse event over time; however, future, more adequately powered studies should continue to evaluate this effect as these findings appear to be counterintuitive against findings in CAD, where clear evidence for poorer prognostic outcomes in women is available.[4,35,36]

Limitations

Some limitations of this study are apparent. First, only two institutions were included in this study and therefore results may only be generalizable to this type of setting. As a result minority patient populations were, for example, not well represented, and therefore, future replications of our work including more diverse populations are certainly needed. Second, although we adjusted for clinically important confounders in both the SF-12 regression models and Cox regression models, the possibility of residual confounding remains. Last, we did not utilize a disease-specific health status instrument, which may have been more sensitive to detected differences in the clinical manifestations of PAD to patients. This should be the focus of future research.

Conclusions

In conclusion, this study has extended findings from earlier studies demonstrating that women report a poorer physical and mental health status both at initial diagnosis (baseline) and 12-month follow-up.[9,13–15,40] Second, women seem to have a similar prognosis as examined for all-cause mortality or the experience of a first adverse event as compared with men. Future studies should focus on re-examining these effects using more sensitive disease-specific health status

instruments and further exploring the role for socio-economic, clinical, and psychological factors in diverse settings of patients that may help explain these differences.

Data Access and Responsibility

Drs Smolderen and van Zitteren had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Disclosures

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