Differential effect of female gender on coronary artery disease and peripheral artery disease

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Background. Women are relatively protected against coronary artery disease (CAD). Whether female gender has a similar protective influence on the development of peripheral artery disease (PAD) has not been extensively investigated and was the main subject of our study.
Methods. We analysed 2707 consecutive patients (2008 men and 699 women) who underwent a first diagnostic coronary angiography for suspicion of CAD and 2367 consecutive patients (1426 men and 941 women) who underwent a first ankle arm index measurement because of suspicion of PAD.
Results. We found that a positive diagnosis for CAD and PAD was more common in men compared with women (80.7% vs 57.9%, p<0.0001 and 68.0% vs 60.7%, p<0.0001). Once CAD or PAD was established, severity of disease was similar for men and women, which pleads against a referral bias. Women had a reduced risk of CAD after adjustment for risk factors (odds ratio [OR] 0.32, 95% confidence interval [CI] 0.22-0.46, p<0.0001), but not of PAD (OR 0.82, 95% CI 0.66-1.03, p=NS). In patients with CAD and in those with PAD, women were older, more often had diabetes and hypertension, while men were more likely to be current smokers. Hypertension, smoking and diabetes were associated with CAD in both men and women. Current smoking was associated with PAD in men and women. Hypertension and diabetes were associated with PAD in women but not in men.
Conclusion. After adjustment for risk factors, the female protection for CAD seems to less present for PAD. (*Neth Heart J* 2002;10:500-5.)

Key words: coronary artery disease, peripheral artery disease, risk factors, men, women

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Coronary artery disease (CAD) and peripheral artery disease (PAD) are considered manifestations of the same disease, i.e. atherosclerosis, at different locations in the body. Although CAD has been the subject of extensive research, less is known about PAD. Diagnosis of atherosclerosis in the lower extremities is less life-threatening than atherosclerosis in coronary arteries. Nevertheless, the presence of PAD diagnosed by intermittent claudication or ankle arm index (AAI) is a powerful predictor for increased cardiovascular and overall mortality.[1-5] Whether the development of PAD and CAD is affected by the same risk factors and with a similar impact is unclear. Recent studies have shown that smoking, hypertension, and diabetes act as risk factors for both CAD and PAD.[6-8] However, there are also intriguing differences in risk factors for CAD and PAD. The well-established correlation between plasma lipids (total cholesterol, low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], and triglycerides) and CAD is less unequivocal in PAD. While both primary and secondary prevention studies have shown major clinical benefits of lipid-lowering therapy on reducing CAD risk,[9-11] such studies have not been performed for PAD. It is unknown whether the influence of cardiovascular risk factors on PAD is similar for men and women. The

lifetime risk of developing CAD is higher in men than in women at all ages.[12] This implies that women are relatively protected against CAD. Whether female gender has a similar protective influence on the development of PAD has not been extensively investigated.

Therefore, the main subject of our study was to evaluate the differential effect of female gender on CAD and PAD. In addition, we assessed whether the risk factors on the presence of CAD and PAD were different for men and women.

Methods

Study populations

We assessed two groups of patients: patients who underwent a first coronary angiogram due to suspicion of CAD between July 1981 and January 1998, and patients who had a first AAI measurement because of suspicion of PAD between July 1982 and January 1998 in the same hospital (the Oosterschelde Hospital in Goes, the Netherlands) with the same adherence area.

During the study period, 3095 consecutive patients underwent a first diagnostic coronary angiogram. Patients who were referred for coronary angiography for reasons other than suspicion of CAD (e.g. valve pathology, cardiomyopathy) were excluded from analysis (n=388), thus 2707 patients (2008 men and 699 women) were analysed. A total of 2414 consecutive patients had a first AAI measurement because of suspicion of PAD. Forty-seven patients could not be analysed because of missing values, leaving 2367 patients (1426 men and 941 women) for final analysis.

Coronary artery disease

The diagnosis of CAD was based on the result of a coronary angiogram. All coronary angiograms were performed according to the standard Judkins technique. The coronary angiograms were evaluated visually and independently by two experienced cardiologists. The extent of CAD was coded as one, two, three-vessel or left main disease, according to the number of coronary vessels with a ≥60% stenosis on visual examination, which was considered haemodynamically significant.[13-15] Patients with one or more vessels with a ≥60% stenosis were classified as CAD+, the other patients as CAD-.

Peripheral artery disease

All patients underwent a noninvasive vascular laboratory evaluation involving segmental Doppler waveform analysis and AAI measurement at rest and after exercise. A standardised treadmill exercise test was performed on a 10° incline for 5 minutes at 2 mph. A Doppler stethoscope and a standard mercury manometer were used to assess systolic pressure of the right brachial artery and of both posterior tibial arteries (or any other available ankle artery) in rapid succession. The AAI for each leg was calculated as the ratio of the ankle systolic pressure to the right brachial systolic pressure. The diagnosis of PAD was based upon AAI measurement. The mean AAI was defined as the average value of the left and right AAI. Peripheral artery disease (PAD+) was defined either as an AAI at rest or exercise of <0.90 and/or a drop in ankle pressure after exercise >20% compared with baseline or a drop of >20 mmHg, as is described previously.[16-19] The other patients were classified as PAD-.

Lipids and apolipoproteins

Of the patients who were evaluated for CAD, plasma lipids were determined after overnight fasting. Only lipid profiles measured before lipid-lowering medication were used for analysis. Total cholesterol and triglyceride concentrations were measured enzymatically (Vitros analyser, Johnson & Johnson). HDL-C fractions were prepared by precipitation from plasma of the apolipoprotein B containing lipoproteins with the use of dextran sulphate and $MgCl_2$. Plasma LDL-C was calculated using the Friedewald formula (total cholesterol–HDL-C–0.45 × triglycerides).[20]

Risk factors

Information on body mass index (BMI), current smoking, diabetes mellitus, hypertension and family history of CAD in the population evaluated for CAD was obtained by questionnaire. Self-reported height and weight were used to calculate BMI (kg/m^2). Patients were asked whether they were currently smoking. Patients who had stopped smoking <6 months were also considered current smokers. History of diabetes was assessed by a positive response to the question whether they had diabetes or high blood sugar. Patients were diagnosed as hypertensive when they were taking antihypertensive drugs or were on an antihypertensive diet. Family history of CAD was considered positive if a first-degree relative had premature documented CHD (men <65 years of age, women <60 years of age). All patients who underwent AAI measurements were interviewed by a trained nurse who recorded information about smoking, diabetes and hypertension.

Statistical analysis

Continuous variables of men and women were compared with a Student's t-test. Binary logistic regression was used to analyse the effect of gender on CAD and PAD. Categorical variables were compared by chi-square tests. Continuous variables are presented as mean value ± standard deviation. A p value <0.05 was considered statistically significant.

Results

Coronary artery disease

Table 1 shows the characteristics of the 2707 patients (2008 [74%] men and 699 [26%] women) who underwent a first coronary angiography on suspicion of

Table 1. Baseline characteristics of patient population suspected of coronary artery disease.

	CAD- (n=682)			CAD+ (n=2025)			CAD- vs CAD+	CAD- vs CAD+
	Men	Women	p value	Men	Women	p value	Men	Women
N	388 (19.3%)	294 (42.1%)	<0.0001	1620 (80.7%)	405 (57.9%)	<0.0001	<0.0001	<0.0001
Age (years)	52.8±9.9	57.6±9.4	<0.0001	60.0±9.5	63.6±9.2	<0.0001	<0.0001	<0.0001
Severity of disease								
One vessel	-	-	-	673 (41.5%)	175 (43.2%)	0.832	-	-
Two vessel	-	-	-	437 (27.0%)	111 (27.4%)		-	-
Three vessel	-	-	-	420 (25.5%)	96 (23.7%)		-	-
Left main	-	-	-	90 (5.6%)	23 (5.7%)		-	-
Risk factors								
BMI (kg/m^2)	26.7±3.5	26.0±4.5	0.067	26.5±3.7	26.5±4.3	0.844	0.500	0.245
Current smoking	166 (43.2%)	47 (16.5%)	<0.0001	844 (52.8%)	108 (27.3%)	<0.0001	0.001	0.001
Diabetes mellitus	18 (4.7%)	20 (7.1%)	0.237	149 (9.4%)	56 (14.1%)	0.008	0.003	0.004
Hypertension	85 (21.9%)	93 (31.6%)	0.004	452 (28.0%)	178 (44.0%)	<0.0001	0.016	0.001
Family history of CAD	85 (21.9%)	75 (25.5%)	0.271	410 (25.3%)	134 (33.1%)	0.002	0.163	0.031
TC (mmol/L)	6.11±1.27	6.55±1.30	<0.0001	6.53±1.20	7.09±1.45	<0.0001	<0.0001	<0.0001
HDL-C (mmol/L)	1.14±0.32	1.07±0.30	<0.0001	1.29±0.30	1.42±0.38	<0.0001	0.010	0.002
LDL-C (mmol/L)	4.00±1.15	4.28±1.15	0.067	4.25±1.07	4.77±1.41	<0.0001	0.007	0.001
Triglycerides (mmol/L)	1.85±0.91	2.21±1.34	0.362	1.74±0.95	2.04±1.14	0.104	<0.0001	0.023

TC=total cholesterol.

CAD. In the total population 682 (25.2%) patients were diagnosed as CAD- and 2025 (74.8%) as CAD+. CAD+ was more prevalent in men than in women (80.7% vs 57.9%, p<0.0001). Women with CAD were older than women without CAD (57.6±9.4 vs 63.6±9.2 years, p<0.0001) and CAD+ men were older than CAD- men (52.8±9.9 vs 60.0±9.5 years, p<0.0001). In both the CAD- and the CAD+ population, women were older than men. In CAD+ patients the severity of disease as assessed by the number of stenotic vessels was similar for men and women (p=0.832). In both groups (CAD+ and CAD-), current smoking was more common in men than in women and diabetes was more prevalent in women than in men. The lipid profile of women showed a higher total cholesterol and HDL-C level compared with men. In patients with CAD, women more often had a positive family history of CAD and a higher LDL-C level than men. In patients without CAD, LDL-C was not significantly different among women and men (table 1). Current smoking, diabetes and hypertension were significantly associated with the presence of CAD in both men and women. In women but not in men a positive family history of CAD was predictive for the presence of CAD. BMI was not associated with CAD in men or women. High levels of total cholesterol, LDL-C and triglycerides and low levels of HDL-C were predictive for CAD in both men and women (table 1). We observed that female gender was associated with a reduced risk on CAD (odds ratio (OR) 0.33, 95% confidence interval (CI) 0.27-0.40, p<0.0001) (table 3). This protective effect of female gender remained significant after adjustment for age, current smoking, diabetes, hypertension, family history, total cholesterol, HDL-C, LDL-C and triglycerides (OR 0.32, 95% CI 0.22-0.46, p<0.0001).

Peripheral artery disease

From July 1982 until January 1998, 2367 patients (1426 [60%] men, 941 [40%] women) underwent a first AAI measurement because of suspicion of PAD (table 2). The excess of male patients in this population was less than in the population evaluated for CAD (60% vs 74%, p<0.0001). PAD was present in 1540 (65.1%) patients. A higher percentage of men was diagnosed as PAD+ (68.0% in men vs 60.7%, in women, p<0.0001). The severity of disease as assessed by mean AAI was similar for men and women in the PAD+ group (76.4±.20.0 vs 74.7±.20.9 years, p=NS). Men and women without PAD were of similar age (64.1±14.1 vs 64.3±17.1 years, p=0.871), but in patients with PAD, women were significantly older than men (66.3±13.5 vs 69.1±17.7 years, p=0.001). PAD+ men and PAD+ women were older than PAD- men and PAD- women. In both the PAD- and PAD+ populations, current smoking was more prevalent in men and hypertension more common in women. In the PAD+ population women more often had diabetes

Table 2. Baseline characteristics of patient population suspected for peripheral artery disease.

	PAD- (n=827)			PAD+ (n=1540)			PAD- vs PAD+	PAD- vs PAD+
	Men	Women	p value	Men	Women	p value	Men	Women
N	457 (32.0%)	370 (39.3%)	<0.0001	969 (68.0%)	571(60.7%)	<0.0001	<0.0001	<0.0001
Age (years)	64.1±14.1	64.3±17.1	0.871	66.3±13.5	69.1±17.7	0.001	0.007	<0.0001
Mean AAI	110.5±10.8	110.5±11.0	0.958	76.4±20.0	74.7±20.9	0.133	<0.0001	<0.0001
Risk factors								
Current smoking	121 (37.0%)	36 (14.8%)	<0.0001	408 (57.8%)	102 (28.3%)	<0.0001	<0.0001	<0.0001
Diabetes mellitus	50 (15.3%)	29 (12.0%)	0.253	101(14.1%)	83 (23.1%)	0.001	0.676	0.001
Hypertension	75 (23.0%)	74 (30.6%)	0.042	193 (27.3%)	170 (47.2%)	<0.0001	0.140	<0.0001

AAI=ankle arm index.

than men (table 2). In men and women current smoking was associated with the presence of PAD. Hypertension and diabetes were associated with PAD in women but not in men (table 2).

Female gender was associated with a reduced risk of PAD (OR 0.73, 95% CI 0.61-0.86, p=0.003) (table 3). However, when current smoking was entered into the logistic regression model, gender was no longer significantly associated with PAD (OR 0.84, 95% CI 0.69-1.07, p=NS), which did not change after further adjustment for age (OR 0.82, 95% CI 0.66-1.03, p=NS).

Discussion

The main finding of our study was that after adjustment for risk factors, female gender was significantly associated with a reduced risk of CAD but that this was less significant with PAD. Once CAD or PAD was established, the severity of disease was similar for men and women, which pleads against the possibility of a referral bias.

Influence of gender on CAD versus PAD

To our knowledge there are no previous studies investigating the influence of gender on CAD versus PAD, although some studies indirectly addressed this issue. Several autopsy studies[21,22] have documented the extent and severity of atherosclerosis in different arterial beds for men and women. The World Health Organisation[22] reported that the percent surface area involved with total atherosclerosis in the abdominal aorta rises with age and is similar for men and women. This study reports that the surface area involved with atherosclerosis in the coronary arteries is greater in men than in women, although after the age of 50 years (after the menopause) a steep increase is seen in women. The Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study[21] showed similar raised atherosclerotic lesions in the aorta of women and men, but less raised lesions in the right coronary artery of women compared with men. In a population of patients with familial hypercholesterolaemia, the onset of CAD was significantly later in life in men than in women.[23] In contrast, the age of onset of PAD was similar for men and women. These data all suggest that protection in females against coronary atherosclerosis is less in the peripheral arteries, which is in agreement with our findings. The Rotterdam study,[24] a population-based study, evaluated the prevalence of PAD and intermittent claudication in 3052 men and 4663 women ≥55 years. This study showed that mean AAI by age and distribution of AAI were similar for men and women, thereby indicating no impact of gender

Table 3. Relative risk of female gender on the presence of CAD and PAD.

	CAD		PAD	
	Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
Female gender	0.33 (0.27-0.40)	<0.0001	0.73 (0.61-0.86)	0.003
Female gender, smoking	0.38 (0.31-0.46)	<0.0001	0.84 (0.69-1.07)	0.1651
Female gender, smoking, diabetes	0.38 (0.31-0.46)	<0.0001	0.85 (0.68-1.06)	0.1479
Female gender, smoking, diabetes, age	0.30 (0.24-0.37)	<0.0001	0.82 (0.66-1.03)	0.0896
Female gender, smoking, diabetes, age, plasma lipids (TC, HDL-C, LDL-C,TG)	0.32 (0.22-0.46)	<0.0001		

TC=total cholesterol; TG=triglycerides.

on the development of PAD. An interesting finding was that men with PAD more often had symptoms of claudication than women. If men are more likely to have symptoms associated with PAD than women, the probability of referral for evaluation of PAD is likely to increase. This would explain the higher percentage of male patients compared with female patients with a positive test in our PAD population.

Possible mechanisms of the differential influence of gender on CAD and PAD

In addition to previous studies,[21-23] our study indicates that female gender is less protective against the development of PAD than the development of CAD. The background for this finding is unknown, but several explanations are possible.

First, it could be that PAD and CAD are essentially manifestations of the same disease with similar risk factors, although these risk factors have a differential impact on CAD and PAD. We found that, when we adjusted for smoking, gender was no longer significantly associated with PAD, although gender remained of influence on CAD. Therefore, smoking could be a dominant risk factor for the development of PAD (but not of CAD) which overrules the influence of gender. Smoking has been documented as a stronger risk factor for PAD than CAD.[6,25-27] The Edinburgh Atherosclerosis Study, a cross-sectional survey of 1592 men and women, compared the incidence of risk factors in those subjects who developed PAD and those who developed CAD. A recent report of this study[25] demonstrated that the only risk factor with a different impact between CAD and PAD was smoking. The adjusted relative risks of PAD associated with moderate smoking were 1.70 (95% CI 0.72-3.99) and 2.72 (95% CI 1.13-6.53) for heavy smoking. Similarly, the adjusted risks of CAD were 1.22 (95% CI 0.72-2.07) and 1.61 72 (95% CI 0.91-2.85).

Secondly, it could be that CAD and PAD are essentially the same disease with similar risk factors but that the impact of these risk factors is different for men and women. Although the association between CAD and current smoking, diabetes, hypertension, total cholesterol, HDL-C, LDL-C and triglycerides has been well established for both men and women,[28-30] fewer studies have investigated the predictive value of these risk factors for PAD. The majority of these studies[6,8,31] have included both men and women. To our knowledge, only one study[32] investigated the association between risk factors and PAD by gender. In this study by Fowkes et al.,[32] cigarette smoking and diabetes showed a similar correlation with AAI in men and women. Plasma fibrinogen, blood viscosity and plasma viscosity had a stronger correlation with lower AAI in men than in women.

Finally, a unique characteristic of female gender is the influence of oestrogens on the vascular system. Endogenous oestrogens affect the atherosclerotic process through a variety of mechanisms. Oestrogens modify risk factors in lowering total cholesterol and LDL-C,[33-35] lipoprotein(a)[36] and homocysteine[37,38] In addition, oestrogens have acute vasodilatory effects on the vessel wall and an atheroprotective effect involving inhibition of smooth-muscle cell proliferation.[39] Based on our data it is not possible to evaluate whether oestrogens have a similar effect on coronary arteries and on peripheral arteries. It could be clinically important to further investigate this in future studies, as it would provide information whether or not it would be useful to perform studies with hormone replacement therapy in PAD. One previous study[40] evaluated the influence of hormone replacement therapy on PAD in 2196 post-menopausal women. In this study the use of hormone replacement therapy for >1 year was associated with a 52% decreased risk of PAD after adjustment for other risk factors. However, this study was retrospective and observational, and the authors could not exclude that their findings were based on selection bias.

Considerations and limitations of the study

Several studies have reported a gender-related bias in the referral for diagnostic procedures for CAD.[41,42] In these studies it was found that women were referred to coronary angiography less often and in a later stage of disease. In the current populations we found that women and men had a similar severity of disease as assessed by the number of stenotic vessels for CAD and mean AAI for PAD. Consequently, we consider a pre-test referral bias favouring either men or women unlikely. Because the study hospital is the only one in the region, we do know whether all patients with either CAD or PAD were referred to this institution.

There are several limitations to our study. Our results apply to a selected population of patients who were referred to a specialist (cardiologist for CAD, vascular surgeon for PAD) and it is not certain whether they can be applied to the general population. Information about risk factors for PAD and for CAD were not obtained in exactly the same manner. Therefore, this could account for some of the differences seen in risk factors between the CAD and PAD populations. Unfortunately, there were not enough patients with lipid measurements in the population evaluated for PAD we could use for analysis. This can be seen as a reflection of the initial lack of interest in lipid metabolism by vascular surgeons. At present, all patients referred to the vascular surgeon for PAD in our institution have a complete lipid profile evaluation and in future studies we hope to use these data. Also, we did not have complete data of the hormonal status of the women in this study.

In conclusion, the protection females have against CAD seems to be present less for PAD. It would be of interest to further investigate the background of this observation as it could have clinical implications on the management of patients with PAD. ■

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