Gender Differences in Patients With Stable Chest Pain

Simran P. Sharma, MD[a,b], Olivier C. Manintveld, MD, PhD[b], Ricardo P.J. Budde, MD, PhD[a,b], Alexander Hirsch, MD, PhD[a,b], Mattie J. Lenzen, PhD[b], and Tjebbe W. Galema, MD, PhD[b,*]

This study sought to investigate gender differences in clinical presentation, presence, and extent of coronary artery disease (CAD), and all-cause mortality in patients with stable chest pain who underwent coronary computed tomography angiography (CCTA). Patients who visited the fast-track outpatient clinic of the Erasmus Medical Center and underwent CCTA were analyzed. Clinical characteristics of chest pain, CAD on CCTA, coronary artery calcium scores, and survival were collected retrospectively and compared between men and women. Logistic regression was used to identify independent risk factors for the presence of CAD and Cox regression for all-cause mortality. In 1,835 included patients, 966 (52.6%) were female. Men and women were similar in age (55 vs 56 years). Compared with men, women had a lower frequency of typical pain (22.8% vs 31.1%, p <0.001), lower prevalence of significant CAD (22.2% vs 38.1%, p <0.001), and lower coronary artery calcium scores (p <0.001). CAD was more prevalent in men than in women with typical pain (67.4% vs 35.9%, p <0.001) and also with nontypical pain (24.9% vs 18.1%, p = 0.002). After adjustment for baseline characteristic, male sex was associated with all-cause mortality (adjusted hazard ratio 1.87, 95% confidence interval 1.25 to 2.80, p = 0.002). The additional risk of mortality because of CAD was similar between men and women. Stratifying by typical and nontypical pain, women again had a better prognosis. Our study identifies gender-related differences in characteristics, CCTA-findings, and outcomes for women compared with men presenting for CCTA with chest pain. Women have less CAD and a better prognosis than men, the clinical implications of which require further study. **(Am J Cardiol 2022;171:84−90)**

In western countries, coronary artery disease (CAD) is the leading cause of mortality and morbidity in men and women. CAD accounts for 45% of the total deaths in Europe.[1] In the past, there was a widespread belief that CAD is a "man's disease." Consequently, in general, the CAD guidelines are based on research conducted primarily in men. Since 2006, the mean percentage of women enrolled in clinical trials has been 30%.[2] At present, the perception of CAD being a "man's disease" is gradually diminishing. It is now evident that women develop CAD, 5 to 10 years later than men.[2] In addition to the development of CAD at a more advanced age, women with CAD may present with different or less specific chest pain symptoms than men.[2,3] In addition, studies suggest that physicians pursue a less aggressive approach to CAD in women with chest pain than in men.[4,5] However, whether a gender-specific approach should be implemented in these patients remains unclear, as data-driven gender-specific guidelines for managing chest pain patients are still lacking. To investigate the gender differences in this patient population, we have analyzed patients referred to the fast-track outpatient clinic and who underwent coronary computed tomography angiography (CCTA) as a part of routine clinical management. The fast-track outpatient clinic provides rapid-access cardiology services to deal with the rising number of outpatients and meet the expectations of patients, such as short waiting time, direct evaluation of test results, and immediate therapy if needed.[6] The purpose of this single-center study was to investigate gender differences in clinical presentation, presence and extent of CAD, and survival in patients with stable chest pain referred for CCTA.

Methods

We performed a single-center retrospective cohort study including all consecutive adult patients (aged >18 years) with symptoms of stable chest pain, who visited the fast-track outpatient clinic between September 2006 and December 2016 and underwent a CCTA in the Erasmus Medical Center in The Netherlands. Data on the baseline characteristics (patient demographics, cardiovascular risk factors, co-morbidities, lipid profile), clinical characteristics of chest pain, coronary artery calcium (CAC) scores, and CAD on CCTA were obtained from our electronic patient system. The exclusion criteria were patients with a history of myocardial infarction, percutaneous coronary intervention and/or coronary artery bypass grafting, cases that lacked CCTA data, and duplicate cases. Duplicate cases were patients who visited the outpatient clinic twice. Of these patients, only the first visit was included in the analysis. The study was performed in line with the principles of

[a]Department of Radiology and Nuclear Medicine, Erasmus Medical Center, University Medical Centre, Rotterdam, The Netherlands; and [b]Department of Cardiology, Erasmus Medical Center, University Medical Centre, Rotterdam, The Netherlands. Manuscript received October 27, 2021; revised manuscript received and accepted January 26, 2022.

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*Corresponding author: Tel: +31 010 703 56 69; fax 0107035513.
E-mail address: t.w.galema@erasmusmc.nl (T.W. Galema).

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the 1975 Declaration of Helsinki. Since this is a purely observational and retrospective study, the need for ethics committee approval was waived by the institutional review board (MEC 2021-0350). The described method of this study is similar to our previous study on chest pain patients of the fast-track outpatient clinic.[7]

The study end points included a confirmed diagnosis of significant CAD on CCTA, calcium scores, and all-cause mortality. The survival status of patients was determined on February 5, 2021, by contacting the municipal civil registry. Chest pain was classified as typical or nontypical by individual chart review by a single observer. Typical angina is defined by meeting the 3 criteria of the traditional clinical classification of suspected anginal symptoms: constricting discomfort in the front of the chest or the neck, jaw, shoulder, or arm; precipitated by physical exertion; relieved by rest or nitrates within 5 minutes. Nontypical angina consists of atypical and nonanginal chest pain, defined as meeting ≤2 of the criteria.[2,8] Significant CAD was defined as anatomical stenosis of ≥50% on CCTA in at least 1 vessel. CAC scores are presented in Agatston units. Percentiles were calculated using the CAC Score Reference Values web tool by the Multi-Ethnic Study of Atherosclerosis to adjust for age, gender, and race.[9] Hypertension was recorded if blood pressure was ≥140/90 mm Hg at the outpatient clinic visit or if it was mentioned in the medical history of the patient. Hypercholesterolemia was recorded if laboratory results showed a total cholesterol level >6.5 mmol/L or if it was mentioned in the medical history of the patient.

Continuous variables are expressed as mean ± SD or median (interquartile range), depending on the distribution, and were compared by Student's *t* test or Mann−Whitney *U* test. Normality was tested by the Shapiro-Wilk test. Categorical variables are expressed as frequencies with percentages and were compared by chi-square test or Fisher's exact test. Logistic regression was used to identify the independent risk factors of the presence of CAD. In the first model, only the variables male sex and typical chest pain were included. The significance of the differential associations between male sex and typical chest pain with the presence of CAD was tested using an interaction term. In the second model, other known risk factors were included in the multivariable logistic regression model: age, body mass index (BMI) >30 kg/m^2, creatinine >120 μmol/L, diabetes mellitus, male sex, typical chest pain, hypertension, hypercholesterolemia, smoking and the interaction term between male sex and typical chest pain. The third model contains all the risk factors included in model 2 and the log-transformed CAC score. The CAD consortium prediction model also suggests these variables to estimate the presence of CAD.[10] The Kaplan-Meier method was used to evaluate gender differences in the probability of survival. The survival estimates were compared by the log-rank test. Univariable Cox proportional hazard regression models were used to calculate hazard ratios. To determine independent predictors of mortality, 2 multivariable Cox proportional hazards regression models were used. In the first model, the variables male sex, presence of CAD, and the interaction term between the presence of CAD and male sex were entered in the model. In the second model, the variables age, male sex, the presence of CAD, hypertension, creatinine >120 μmol/L, BMI >30 kg/m^2, hypercholesterolemia, smoking, diabetes mellitus, and the interaction term between male sex and presence of CAD, were entered. A 2-tailed p <0.05 was considered to indicate statistical significance. All statistical analyses were performed using IBM SPSS Statistical Software (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0, IBM Corp, Armonk, New York).

Results

Of all 2,482 study cases, 45 were excluded because of previous myocardial infarction or percutaneous coronary intervention, 96 were excluded because of lack of data, 22 duplicates, and 484 patients did not undergo CCTA (e.g., because of inability to cooperate with scan protocols, renal impairment, refusal by the patient or decision of the physician). Of all women referred to the fast-track outpatient clinic, 20.1% did not undergo a CCTA versus 17.8% of all men (p = 0.31). The baseline characteristics of the final study population of 1,835 patients are listed in Table 1, stratified by gender. Of 1,835 patients enrolled, 966 (52.6%) were female. In this cohort, the mean age of men was similar to that of women. Women were more likely to have lung diseases, that is, chronic obstructive pulmonary disease or asthma. The cardiovascular risk factors of hypertension and BMI >30 kg/m^2 were more prevalent in women than in men. Women were more likely to have higher serum levels of cholesterol, lower levels of triglycerides, higher levels of high-density lipoprotein (HDL), and a lower cholesterol-to-HDL ratio. Women also more often had a creatinine >120 μmol/L. In contrast, women were less likely to be current or past smokers. Women were also less likely to have peripheral artery disease.

Chest pain symptoms were different between men and women. Women more often presented with nontypical chest pain than men (Table 1).

CAD was more prevalent in men than in women (38.1% vs 22.2%, p <0.001) and CAC scores were higher (23 [0 to 19] vs 0 [0 to 42], p <0.001). Men with typical chest pain showed CAD more often than women with typical chest pain. Median CAC scores were higher in men with typical chest pain than women with typical chest pain. In the case of nontypical chest pain, women were older than men, and men again had more CAD and higher median CAC scores than women. (Table 2) Model 2 of the multivariable logistic regression analysis showed that the male sex (odds ratio 1.85, 95% confidence interval [CI] 1.39 to 2.46, p <0.001) and typical chest pain (odds ratio 2.46, 95% CI 1.74 to 3.49, p <0.001) were factors independently associated with the presence of CAD. However, if CAC score was also added to the multivariable model (model 3), male sex was no longer independently associated with the presence of CAD. There was a significant interaction between male sex and typical chest pain in relation to the presence of CAD in all models (Table 3).

During a median follow-up time of 10 (7 to 12) years, 207 patients (11.3%) died (all-cause mortality). The survival status of 1,810 patients (98.6%) was known. Overall

Table 1
Baseline characteristics

Variable	Total (n = 1835)	Female (n = 966)	Male (n = 869)	P value
Age (years)	56 ± 10.5	56 ± 10.2	55 ± 10.7	0.137
BMI > 30 kg/m^2	566 (30.8%)	359 (37.2%)	207 (23.8%)	<0.001
Creatinine > 120 μmol/L	294 (16.0%)	226 (23.4%)	68 (7.8%)	<0.001
COPD/asthma	192 (10.5%)	114 (11.8%)	78 (9.0%)	0.048
Atrial fibrillation/atrial flutter	16 (0.9%)	5 (0.5%)	11 (1.3%)	0.085
History of ischemic stroke/TIA	25 (1.4%)	15 (1.6%)	10 (1.2%)	0.46
History of peripheral artery disease	8 (0.4%)	1 (0.1%)	7 (0.8%)	0.031
Cardiovascular risk factors				
Hypertension	829 (45.2%)	466 (48.2%)	363 (41.8%)	0.005
Hypercholesterolemia	821 (44.8%)	432 (44.9%)	389 (44.8%)	0.99
Ever smoker	529 (28.9%)	217 (22.5%)	312 (35.9%)	<0.001
Diabetes mellitus	289 (15.8%)	163 (16.9%)	126 (14.5%)	0.161
Lipid profile				
Cholesterol (mmol/L)	5.2 [4.4-6.0]	5.2 [4.5-6.1]	5.1 [4.4-5.9]	0.009
Triglycerides (mmol/L)	1.3 [0.9-1.9]	1.2 [0.9-1.7]	1.4 [1.0-2.1]	<0.001
HDL-cholesterol (mmol/L)	1.4 [1.1-1.7]	1.5 [1.3-1.8]	1.2 [1.0-1.5]	<0.001
LDL-cholesterol (mmol/L)	3.3 [2.6-4.0]	3.3 [2.6-4.0]	3.4 [2.6-4.1]	0.05
Cholesterol/HDL ratio	3.4 [2.8-4.2]	3.1 [2.6-3.8]	3.8 [3.0-4.7]	<0.001
Angina classification				
Typical	490 (26.7%)	220 (22.8%)	270 (31.1%)	<0.001
Non-typical	1345 (73.3%)	746 (77.2%)	599 (68.9%)	<0.001

Data are presented as mean ± standard deviation (SD), median (25th-75th percentile), or frequencies (percentage).
BMI = body mass index; COPD = chronic obstructive pulmonary disease; TIA = transient ischemic attack.

mortality was higher in men than in women (log-rank p <0.001), with estimated mortality at 10 years of 14.5% in men and 8.7% in women. This better long-term survival in women was present both in patients with and without typical chest pain (log-rank p = 0.024 and p = 0.016, respectively) (Figure 1). Estimated all-cause mortality from the Kaplan-Meier curves in women compared with men in patients with typical chest pain were 4.6% versus 5.7% at 5 years and 10.1% versus. 17.7% at 10 years, and in women compared with men in patients with nontypical chest pain were 3.2% versus 4.9% at 5 years and 6.4% versus 9.3% at 10 years (Figure 1) Figure 1. shows the Kaplan-Meier curves in women and men stratified by the presence of CAD. Mortality was significantly worse in men than women in patients without CAD (log-rank p = 0.048). In patients with CAD, there was a trend toward a worse prognosis in men (p = 0.089). However, hazard ratios for men versus women were comparable in patients with and without CAD: hazard ratio 1.43, 95% CI 0.95 to 2.15, p = 0.091 and hazard ratio 1.48, 95% CI 1.00 to 2.19, p = 0.049 (Figure 1).

In the multivariable Cox regression analysis, male sex and the presence of CAD were independently associated with all-cause mortality. The additional risk of mortality because of the presence of CAD is similar between men and women (p = 0.45) (Table 3).

Table 2
Coronary computed tomography angiography results

Variable	Total (n = 1835)	Female (n = 966)	Male (n = 869)	P value
CAD	545 (29.7%)	214 (22.2%)	331 (38.1%)	<0.001
CAC percentile*	35 [00-82]	0 [0-83]	49 [0-81]	0.002
CAC score†	3 [00-99]	0 [0-42]	23 [0-198]	<0.001
Typical chest pain	490 (27.2%)	220 (22.8%)	270 (31.1%)	<0.001
- Age (years)	58 ± 10.5	57 ± 10.7	59 ± 10.4	0.067
- CAD	261 (53.3%)	79 (35.9%)	182 (67.4%)	<0.001
- CAC score‡	51 [0-351]	6 [0-127]	127 [12-540]	<0.001
Nontypical chest pain	1345 (73.3%)	746 (77.2%)	599 (68.9%)	<0.001
- Age (years)	55 ± 10.3	56 ± 10.1	54 ± 10.6	0.001
- CAD	284 (21.1%)	135 (18.1%)	149 (24.9%)	0.002
- CAC score§	0 [0-53]	0 [0-30]	4 [0-98]	<0.001

Data are presented as mean ± standard deviation, median (25th-75th percentile), or frequencies (percentage); CAC score is presented in Agatston units.
* Of 1,675 patients (missing CAC percentiles due to unknown race)
† Of 1,740 patients.
‡ Out of 450 patients.
§ Of 1290 patients.
CAC = coronary artery calcium; CAD = coronary artery disease.

Table 3
Multivariable models for the presence of coronary artery disease and mortality

Multivariable logistic regression models for the presence of CAD			
	Odds ratio	95% CI	P value
Model 1 (n = 1835)*			
Male sex	1.50	1.15-1.95	0.003
Typical chest pain	2.54	1.82-3.54	<0.001
Male sex × typical chest pain	2.46	1.56-3.89	<0.001
Model 2 (n = 1,826)*			
Male sex	1.85	1.39-2.46	<0.001
Typical chest pain	2.46	1.74-3.49	<0.001
Male sex × typical chest pain	2.00	1.24-3.24	0.005
Model 3 (n = 1,733)*			
Male sex	1.14	0.82-1.59	0.44
Typical chest pain	2.08	1.38-3.13	<0.001
Male sex × typical chest pain	1.86	1.06-3.26	0.031
Multivariable Cox proportional hazard models for all-cause mortality			
	Hazard ratio	95% CI	P value
Model 1 (n = 1,810)†			
Male sex	1.48	1.00-1.2.20	0.049
Presence of CAD	2.23	1.44-3.46	<0.001
Male sex × presence of CAD	0.96	0.55-1.70	0.90
Model 2 (n = 1,801)†			
Male sex	1.87	1.25-2.80	0.002
Presence of CAD	1.65	1.06-2.59	0.028
Male sex × presence of CAD	0.80	0.45-1.42	0.45

* Model 1 included male sex, typical chest pain, and interaction term; model 2 was also adjusted for age, BMI > 30 kg/m^2, creatinine > 120 μmol/L, diabetes, hypertension, hypercholesterolemia, and smoking; model 3 included model 2 and natural logarithm of CAC score+1.

† Model 1 included male sex, presence of CAD, and interaction term; model 2 was also adjusted for age, BMI > 30 kg/m^2, creatinine > 120 μmol/L, diabetes, hypertension, hypercholesterolemia, and smoking.

CAD = coronary artery disease; CI = confidence interval.

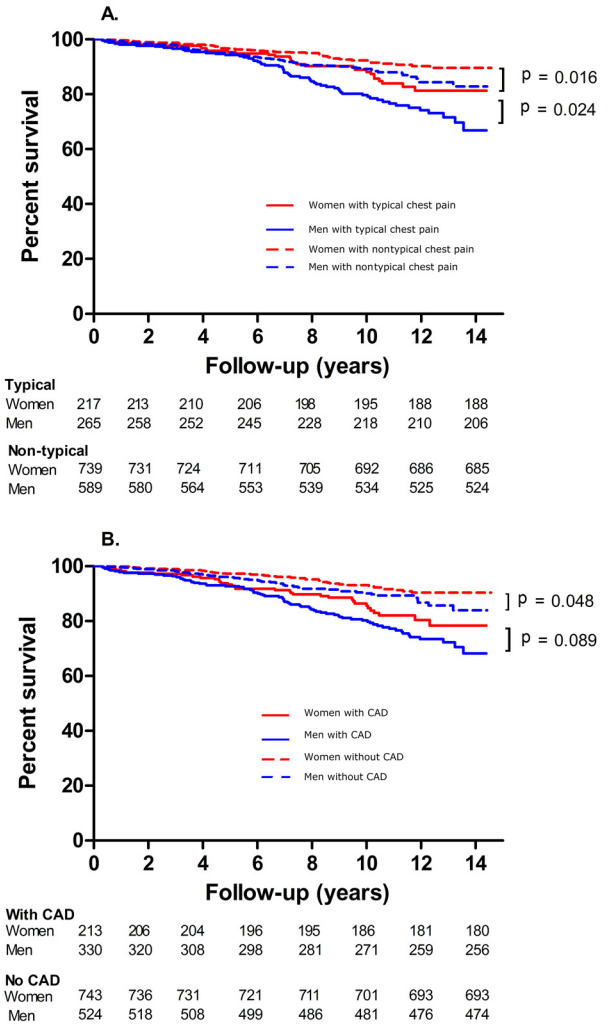

Figure 1. (*A*) Kaplan-Meier long-term survival estimates of women versus men stratified according to typical or nontypical chest pain. (*B*) Kaplan-Meier long-term survival estimates of women versus men stratified according to the presence or absence of coronary artery disease.

Discussion

In our study, comprising of a consecutive cohort of patients (men and women equally represented) with stable chest pain who were referred for CCTA, women presented more often with nontypical chest pain than men and had a lower prevalence of confirmed CAD with subsequently lower mortality.

This observation agrees with several other studies,[5,11–13] including a secondary analysis of the ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) randomized clinical trial. In this study, women had a greater burden of angina symptoms than men, although having less extensive CAD,[14] which was similar to the lower CAC scores and prevalence of CAD in women as shown in our study, and the survival benefit of women as compared with men. In contrast to other studies identifying CAD in women, the women in our study were not older than men at baseline.[11–13,15–17] The relatively young age of our study population and the fact that women develop CAD on average 7 to 10 years later than men partly explains the low rates of CAD in our female chest pain population.[18] These findings are relevant as it is important to know whether or not a gender-specific approach should be implemented in patients with chest pain because data-driven gender-specific guidelines for managing chest pain patients are still lacking.[2,3]

Similar to current literature, our study showed that women presented with nontypical chest pain more often than men.[2,3,5,15] In addition, having typical symptoms more often resulted in a confirmed diagnosis for CAD in both men and women. Of all women with typical chest pain, 35.9% were diagnosed with CAD, whereas in women presenting with nontypical chest pain only 18.1% had CAD. In men with typical chest pain, 67.4% were diagnosed with CAD, whereas 24.9% of those with nontypical chest pain had confirmed CAD. The results of our study do not only show that the risk of CAD is twice as high for men than women in patients with typical chest pain, but also that in both men and women, typical chest pain is more often followed by the presence of CAD than nontypical chest pain. This finding is consistent with the results of a prospective study on patients with diagnosed coronary heart disease.[16] This study showed more similarities in symptoms than differences in men and women with evident coronary heart disease.

Although the relatively young age of the women in our study may explain the lower rates of CAD, it remains relevant to explore what mechanisms contribute to the causes of chest pain in our female chest pain population, which has a similar age as the male population. Although having higher rates of hypertension, renal insufficiency, and obesity, women had a better lipid profile (including triglycerides, HDL, and cholesterol ratio) than men. As there is an evident relation between lipid abnormalities and CAD, the better overall lipid profile in the women of our study could explain the protection against CAD of the female gender.[19,20]

Furthermore, protection against CAD in our relatively young female population is associated with sex hormone levels, as the incidence and severity of cardiovascular disease increases in postmenopausal women. The prevalence of CAD is greater in young women who have had an oophorectomy than those with intact ovaries.[21] The premenopausal protection against cardiovascular disease is believed to be related, at least in part, to the main circulating female hormone, estrogen (E2), because endogenous levels of E2 and the expression of E2 receptors differ considerably between genders. The likely protective mechanisms of E2 against cardiovascular disease are related to increasing angiogenesis and vasodilation and decreasing reactive oxygen species, oxidative stress, and fibrosis.[22] It could be important to further investigate the subject of female cardio-protection in future studies, as it would provide insight into the pathophysiology of CAD in women.

When seeking an explanation of the less prevalent CAD in the female patients with chest pain in our study, sex hormone levels and the mechanism of microvascular angina and endothelial dysfunction should be considered. Microvascular angina is based on functional abnormalities of the coronary microcirculation during stress, including abnormal dilator responses and an increased response to vasoconstrictors. Endothelial dysfunction is likely to be one of the underlying causes.[23] Patients with chest pain and nonobstructive CAD have a high prevalence of coronary microvascular abnormalities.[24] The findings of this study can be explained by microvascular causes including microvascular spasm being very prevalent in female patients with nontypical angina. Moreover, women with such chest pain may also have an epicardial spasm, which can only be proved with invasive provocative testing.[25]

Gender differences do not only appear in the extent of CAD. Previous studies have consistently shown that women have a lower prevalence and less severity of CAC than men.[26–28] Similarly, in this study, CAC scores were lower in women than in men. Even women with typical chest pain had lower CAC scores than men with typical chest pain. CAC is part of the development of atherosclerosis. The presence of CAC is a direct marker of coronary plaque burden and is associated with a higher risk of adverse cardiovascular outcomes.[26,29] This again supports the idea that the women in our study are relatively more protected from atherosclerosis than the men and that the men in our study are more at risk for adverse cardiovascular outcomes than the women.

The higher risk of adverse outcomes for men is also represented in our study, as long-term survival was better in women. In both typical chest pain and nontypical chest pain cases, women fare better than men. When stratified by the presence of CAD, the hazard ratio of men versus women was comparable for patients with or without CAD. These results suggest that women with chest pain, regardless of the type of pain, and confirmed CAD, do not need to be treated differently from men. On the contrary, some studies report less aggressive pharmacological therapy and lower use of revascularization in women.[30,31]

Moreover, studies suggest that women with suspected CAD are less likely to be referred for diagnostic procedures than men.[4,32] However, in our study, there was an equal representation of men and women who visited the fast-track outpatient clinic and were referred for CCTA. This emphasizes the nondiscriminatory design of the fast-track outpatient clinic, and consequently, this study.

Several limitations to our study should be considered when interpreting the present results. First, inherent to the retrospective observational study design, we cannot prove causality. Secondly, we only have data on all-cause mortality. To study the outcomes of chest pain, analyzing disease-specific mortality would have been interesting. Nonetheless, all-cause mortality is a hard end point free from bias. Next to lack of information on cardiovascular deaths, we do not have information on other cardiovascular events like nonfatal myocardial infarction or revascularization. Furthermore, the generalizability of these study results may be limited, as the study population consists of patients with chest pain who are referred for CCTA according to the practice pattern of 1 center. The strengths of our study include the large sample size and the long follow-up period.

In conclusion, women present more often with nontypical chest pain and have a lower prevalence of CAD, and lower CAC scores, which translated into subsequent better survival rates than men. However, differences and similarities were present in this study. For both men and women, typical chest pain more often resulted in the presence of CAD than nontypical chest pain. Further study is required to investigate the clinical implications of less CAD and a better prognosis in women than in men.

Authors' Contributions

Conceptualization, methodology, formal analysis, writing - review & editing, supervision: Tjebbe W. Galema, Olivier C. Manintveld, Mattie J. Lenzen.

Methodology, formal analysis, writing - review & editing, supervision: Alexander Hirsch, Ricardo P.J. Budde.

Methodology, formal analysis, writing − original draft: Simran P. Sharma.

All authors gave final approval and agreed to be accountable for all aspects of this work, ensuring integrity and accuracy.

Disclosures

The authors have no conflicts of interest to declare.

Supplementary materials

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