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Sex-based Prognostic Implications of Nonobstructive Coronary Artery Disease: Results from the International Multicenter CONFIRM Study[1]

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Purpose: To determine the clinical outcomes of women and men with nonobstructive coronary artery disease (CAD) with coronary computed tomographic (CT) angiography data in patients who were similar in terms of CAD risk factors, angina typicality, and CAD extent and distribution.

Materials and Methods: Institutional review board approval was obtained for all participating sites, with either informed consent or waiver of informed consent. In a prospective international multicenter cohort study of 27 125 patients undergoing coronary CT angiography at 12 centers, 18 158 patients with no CAD or nonobstructive (<50% stenosis) CAD were examined. Men and women were propensity matched for age, CAD risk factors, angina typicality, and CAD extent and distribution, which resulted in a final cohort of 11 462 subjects. Nonobstructive CAD presence and extent were related to incident major adverse cardiovascular events (MACE), which were inclusive of death and myocardial infarction and were estimated by using multivariable Cox proportional hazards models.

Results: At a mean follow-up ± standard deviation of 2.3 years ± 1.1, MACE occurred in 164 patients (0.6% annual event rate). After matching, women and men experienced identical annualized rates of myocardial infarction (0.2% vs 0.2%, $P = .72$), death (0.5% vs 0.5%, $P = .98$), and MACE (0.6% vs 0.6%, $P = .94$). In multivariable analysis, nonobstructive CAD was associated with similarly increased MACE for both women (hazard ratio: 1.96 [95% confidence interval {CI}: 1.17, 3.28], $P = .01$) and men (hazard ratio: 1.77 [95% CI: 1.07, 2.93], $P = .03$).

Conclusion: When matched for age, CAD risk factors, angina typicality, and nonobstructive CAD extent, women and men experience comparable rates of incident mortality and myocardial infarction.

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Prior investigators have identified substantial disparities in health outcomes according to patient sex in individuals with clinically significant coronary artery disease (CAD), with higher mortality in women compared with that in men with acute myocardial infarction (MI) (1–3). As compared with men, women are more likely to die of sudden death prior to arrival at the hospital (4). Further, women with symptomatic CAD require more frequent hospitalizations for both angina and heart failure and report lower quality of life scores, when compared with their male counterparts (5,6). These sex-based disparities in CAD outcomes persist, despite a lower incidence and extent of obstructive CAD and superior left ventricular function identified with invasive coronary angiography in women versus men (7–9). In keeping with these invasively derived findings, we observed with noninvasive coronary computed tomographic (CT) angiography a higher hazard ratio (HR) for mortality in women with three-vessel or left main obstructive CAD compared with men (10).

Recent pooled analyses of women from large randomized trials have suggested that women with nonobstructive CAD at invasive coronary angiography also have a worsened prognosis compared with those with normal coronary arteries (9), a finding that may be partially explained by the influence of revascularization rates on downstream outcomes. In addition, published data from the Women's Health Initiative document suggest that women with nonspecific or atypical chest pain exhibit a twofold greater risk for nonfatal MI (11). Furthermore, Women's Ischemia Syndrome Evaluation (WISE) data have demonstrated increased overall rates of mortality in women with chest pain and no obstructive CAD, suggesting that women may be at increased risk, despite atypical symptoms and the absence of obstructive disease (12).

Among stable patients suspected of having CAD, identification of nonobstructive CAD with coronary CT angiography enables prognostication of future all-cause mortality and major adverse cardiovascular events (MACE) (10). In other studies, investigators have attempted to look at the relative effect of nonobstructive disease identified with coronary CT angiography on downstream event rates (13); however, these have been limited by generally small sample sizes and, as a result, limited events. In addition, owing to the smaller sample sizes, more formal analyses inclusive of propensity matching of men and women have not been performed. We hypothesized that nonobstructive disease at coronary CT angiography confers similar prognosis in men and women when matched for preexisting CAD risk factors, symptom status, and extent of disease. To test our hypothesis, we assessed the clinical outcomes of women and men with nonobstructive CAD by using coronary CT angiography findings from a large international registry.

Advances in Knowledge

- The extent and pattern of coronary artery disease (CAD) may vary between men and women; however, when matched for cardiac risk factors, symptom status, and extent of nonobstructive disease identified with coronary CT angiography, men and women exhibit the same rates of major adverse cardiac events.
- Nonobstructive CAD confers an increased risk of myocardial infarction and death in both men and women across varied stratifications of cardiovascular risk and symptom status (hazard ratio [HR] for women: 1.77 [95% confidence interval {CI}: 1.07, 2.93]; HR for men: 1.96 [95% CI: 1.17, 3.28]).
- Women without atherosclerosis at coronary CT angiography have a similar excellent clinical prognosis to that of men, irrespective of the type or presence of symptoms (annualized event rate of 0.3% vs 0.3% [not significant]).
- When stratified by the presence or absence of symptoms and by angina typicality, there were no observed differences in the relationship between nonobstructive disease and mortality for women versus men (not significant).

Implication for Patient Care

- Our data suggest that men and women with comparable risk and disease extent have a comparable prognosis, regardless of symptom nature and status, and should likely be treated accordingly.

Materials and Methods

Eligibility Criteria

The design of the Coronary CT Angiography Evaluation For Clinical Outcomes: An International Multicenter, or CONFIRM, registry has been described in detail (14). Institutional review board

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Abbreviations:
CAD = coronary artery disease
CI = confidence interval
HR = hazard ratio
MACE = major adverse cardiovascular events
MI = myocardial infarction
SIS = segment involvement score
WISE = Women's Ischemia Syndrome Evaluation

Author contributions:
Guarantors of integrity of entire study, J.L., T.Q.C., H.J.C., J.K.M.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; literature research, J.L., C.M.T., L.J.S., A.A., A.T., M.J.B., F.C., T.Q.C., H.J.C., G.M.F., P.A.K., T.C.V., J.K.M.; clinical studies, J.L., C.M.T., L.J.S., A.T., D.S.B., J.H., M.A.M., F.C., T.Q.C., H.J.C., R.C.C., G.M.F., P.A.K., E.M., G.L.R., T.C.V., J.K.M.; experimental studies, J.L., M.J.B., G.L.R., T.C.V., J.K.M.; statistical analysis, J.L., H.G., L.J.S., A.T., K.H., T.Q.C., A.L.D., J.K.M.; and manuscript editing, J.L., C.M.T., L.J.S., A.A., A.T., K.H., D.S.B., S.A., M.A.M., M.J.B., F.C., H.J.C., B.J.W.C., R.C.C., A.L.D., G.M.F., K.M.C., E.M., G.L.R., T.C.V., M.J.G., J.K.M.

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Conflicts of interest are listed at the end of this article.

approval was obtained for all participating sites, with either informed consent or waiver of informed consent. As a prospective, observational, multicenter registry, adults at least 18 years of age were prospectively enrolled at each of the 12 enrolling centers between 2005 and 2009. Enrolled patients included prospective referrals of those undergoing at least 64–detector row coronary CT angiography. All centers had institutional review board approval for patient enrollment, including follow-up methods. For this analysis, only those patients without known CAD and with either no or mild disease (defined as stenosis of up to 50% of the artery diameter) at coronary CT angiography were included. Among 27 125 consecutive patients referred to the participating centers for coronary CT angiography, 8967 were excluded for having known disease or for having obstructive disease identified with coronary CT angiography, leaving a total of 18 158 subjects identified in the remaining group with a stenosis grading of none (n = 10 101) or mild (>0% but <50% stenosis, n = 8057) at coronary CT angiography. Men and women were then matched in 1:1 fashion on the basis of preexisting CAD risk factors, angina typicality, and nonobstructive CAD extent by the number of segments with coronary lesions. The final matched cohort comprised 11 462 patients.

CAD Risk Factor and Angina Typicality Ascertainment

Prior to coronary CT angiography, demographic data and a focused history of CAD risk factors and the nature of chest pain were obtained from each patient. Chest pain was categorized according to the classic criteria for angina pectoris (15). Patients with typical angina experienced substernal, jaw, and/or arm pressure–like pain that consistently occurred with exertion and consistently resolved within 15 minutes of rest and/or use of nitroglycerin. Patients with atypical angina experienced two of three of these characteristics. Patients with nonanginal chest pain experienced one or none of these characteristics. Asymptomatic patients had no chest pain. At each site, symptom category was prospectively ascertained through written questionnaire or interview by a physician or allied health professional.

Clinical history was ascertained through patient interview and clinical questionnaire. A prior diagnosis of CAD was defined as a documented MI or coronary revascularization. Hypertension, diabetes mellitus, and hyperlipidemia were defined as previous diagnoses of these diseases or treatment with medications targeted at managing them. Current cigarette smokers or those who quit smoking within 3 months of testing were established to have a positive smoking history. A clinically significant family history of CAD was defined as that occurring in a prior relative less than 65 years of age in women and less than 55 years of age in men.

Coronary CT Angiography Image Acquisition and Interpretation Procedures

We used standardized protocols, defined by the Society of Cardiovascular Computed Tomography, for image acquisition (16). Coronary CT angiography was performed by using multiple scanner platforms (Light Speed VCT, GE Healthcare, Milwaukee, Wis; Somatom Definition CT, Siemens, Erlangen, Germany; and Somatom Definition Flash CT, Siemens). Timing bolus or automated bolus tracking at the proximal ascending aorta was used to determine the time from contrast material injection to optimal coronary artery enhancement. Contrast material (80–140 mL) was injected, and whole-volume image acquisition was completed in a single breath hold. The scanning parameters were 64 × 0.625-mm or 64 × 0.750-mm collimation and tube voltage of 100 or 120 kVp, and the tube current was assigned on the basis of body size and scanner platform.

Helical or axial scanning data were obtained with retrospective or prospective electrocardiogram gating, respectively. Acquired image data were initially reconstructed in mid-diastole (always) and end-systole (when available), and images from the phase with the least amount of coronary artery motion were chosen for analysis. Reconstructed data were evaluated by highly experienced readers (level III equivalent and/or board certified in coronary CT angiography) (J.L., with 8 years of experience; M.A.M., with 8 years of experience; D.S.B., with 12 years of experience; M.J.B., with 15 years of experience; F.C., with 9 years of experience; T.Q.C., with 12 years of experience; a nonauthor, with 9 years of experience; A.J.D., with 11 years of experience; B.J.W.C., with 9 years of experience; M.H., with 8 years of experience; J.H., with 9 years of experience; G.M.F., with 9 years of experience; R.C.C., with 10 years of experience; T.C.V., with 9 years of experience; K.M.C., with 7 years of experience; and G.L.R., 9 years of experience) by using all necessary postprocessing techniques to determine the presence of CAD in any visible segment at least 2 mm in diameter. In all individuals, irrespective of image quality, every arterial segment was scored in an intent-to-diagnose fashion. If a coronary artery segment was uninterpretable despite these multiple techniques, the segment that could not be evaluated was scored similarly to the most proximal segment that could be evaluated.

All participating sites used standardized anatomic segmental analysis for the coronary CT angiography interpretation. For this analysis, each of the 16 segments was coded for the presence of no stenosis and mild stenosis (defined as >0% but <50%). Patients defined as having a stenosis of at least 50% were not included in this series. As a measure of overall coronary artery plaque extent and distribution, the segment involvement score (SIS) was calculated as the total number of coronary artery segments that exhibited plaque (minimum score = 0, maximum score = 16) (17). All sites performed the coronary CT angiography interpretations prospectively at the time of image acquisition.

Follow-up Methods

The methods for follow-up have been described previously (14). Participants

were followed up with the primary end point of MI and death. For participating U.S. centers, the national death index was queried for all patients. In non-U.S. sites, all patients, their relatives, or primary care physicians were interviewed to ascertain vital status. As there is substantial misclassification of cause of death, we base our analysis on all-cause mortality (18), and MI ascertainment and adjudication were performed at sites by means of direct interview, telephone contact, or review of medical records. For the purposes of this analysis, only death and MI were considered as events. Coronary revascularization (≤90 days) was censored (72 patients) to eliminate the risk of sex-based treatment bias affecting the clinical event rate.

Statistical Analysis

Continuous variables were compared by using two-sample *t* tests or the Wilcoxon rank-sum test if nonnormally distributed. Categorical variables were compared by using the Pearson χ^2 test or the Fisher exact for small cell counts less than six. Survival curves were visualized by using Kaplan-Meier curves and were compared by using log-rank tests. Annual event rates were derived by dividing the number of events by person-years. Predictors of MACE, MI, and death were assessed by using Cox regression modeling, after verifying the assumption of proportional hazards with Schoenfeld residuals. Men and women were matched for risk factors (age, hypertension, high cholesterol, diabetes, smoking, family history, chest pain symptom presence, and log SIS, where the SIS was log-transformed toward normality and then back-transformed into original units for purposes of reporting; matching was done by using the 1:1 Mahalanobis nearest-neighbor algorithm within a caliper of 0.01) and evaluated by using standardized differences (19,20). A post hoc analysis with our observed MACE event rates show 80% power to detect a minimum HR of 1.5 with 11 462 patients and 1.7 in men or women subgroups. All data were analyzed by using Stata version 11.2 software *(www.statacorp.com)*. A *P* value less than .05 was considered to indicate a significant difference.

Table 1

Baseline Clinical Characteristics, Demographics, and Pretest Clinical Risk Assessment of the Study Population (Unmatched Cohort)

Parameter	All (*n* = 18 158)	Women (*n* = 8808)	Men (*n* = 9350)	*P* Value
Age (y)*	55.6 ± 12.5	57.4 ± 12.3	53.8 ± 12.5	<.0001
Asymptomatic patients	5530 (30.4)	2180 (24.8)	3350 (35.8)	<.001
Hypertension	8296 (45.7)	4372 (49.6)	3924 (42.0)	<.001
Hyperlipidemia	9232 (50.8)	4577 (52.0)	4655 (49.8)	.003
Diabetes	2182 (12.0)	1135 (12.9)	1047 (11.2)	<.001
Current smoker	3001 (16.5)	1253 (14.2)	1748 (18.7)	<.001
Family history	6209 (34.2)	3256 (37.0)	2953 (31.6)	<.001
Log (SIS + 1)*	0.52 ± 0.66	0.41 ± 0.61	0.63 ± 0.69	<.001
Pretest likelihood of CAD				.001
<15%	7417 (40.8)	3717 (42.2)	3700 (39.6)	.95
15%–85%	7423 (40.9)	3776 (42.9)	3647 (39.0)	.07
>85%	1257 (6.9)	570 (6.5)	687 (7.3)	<.001

Note.—Data are numbers of patients, unless indicated otherwise. Numbers in parentheses are percentages.

* Data are means ± standard deviations.

Results

Baseline Clinical Characteristics of the Study Population

Tables 1 and 2 provide clinical characteristics, demographics, and pretest clinical risk assessment of the overall cohort and the final propensity-matched cohort. The propensity score resulted in successfully matching 5731 (65.1%) of the 8808 women to 5731 men (mean caliper difference, 0.006 ± 0.004). The standardized differences were all less than 0.1, indicating acceptable matching. Within the propensity-matched cohort of 11 462 subjects, there were 164 cases (1.4%) of MI and death, with 37 experiencing MI, 120 deaths, and seven cases of both MI and death.

Prognostic Implications of Nonobstructive CAD versus Normal Coronary Arteries after Propensity Matching

The annual mortality rate was 0.5% (95% confidence interval [CI]: 0.4%, 0.6%) overall and 0.3% (95% CI: 0.2%, 0.4%) and 0.9% (95% CI: 0.7%, 1.1%) for patients with no CAD and nonobstructive CAD, respectively, at coronary CT angiography ($P < .0001$). The risk-adjusted HR for the prediction of mortality in patients with nonobstructive CAD as compared with no CAD was 1.58 (95% CI: 1.06, 2.37) ($P = .03$). The annual MI rate was 0.2% (95% CI: 0.1%, 0.2%) overall and 0.08% (95% CI: 0.04%, 0.1%) and 0.3% (95% CI: 0.2%, 0.5%) for patients with no CAD and nonobstructive CAD, respectively ($P < .0001$). The risk-adjusted HR for MI in patients with nonobstructive CAD as compared with no CAD was 3.24 (95% CI: 1.56, 6.73) ($P = .002$). The annual MACE (MI and death) rate was 0.6% (95% CI: 0.5%, 0.7%) overall and 0.3% (95% CI: 0.3%, 0.4%) and 1.1% (95% CI: 0.9%, 1.4%) for patients with no CAD and nonobstructive CAD, respectively ($P < .0001$). The risk-adjusted HR for MACE in patients with nonobstructive CAD as compared with no CAD was 1.84 (95% CI: 1.28, 2.63) ($P = .001$) (Fig 1).

Sex-stratified Prognostic Implications for MACE (MI and Death) in Nonobstructive CAD versus Absence of CAD after Propensity Matching

Annual rates of MACE (MI and death) based on normal arteries and nonobstructive CAD were similar for women (0.3% [95% CI: 0.2%, 0.5%] and 1.2% [95% CI: 0.9%, 1.5%], respectively) and men (0.3% [95% CI: 0.2%,

Table 2

Baseline Clinical Characteristics, Demographics, and Pretest Clinical Risk Assessment of the Study Population (Matched Cohort with Standardized Differences)

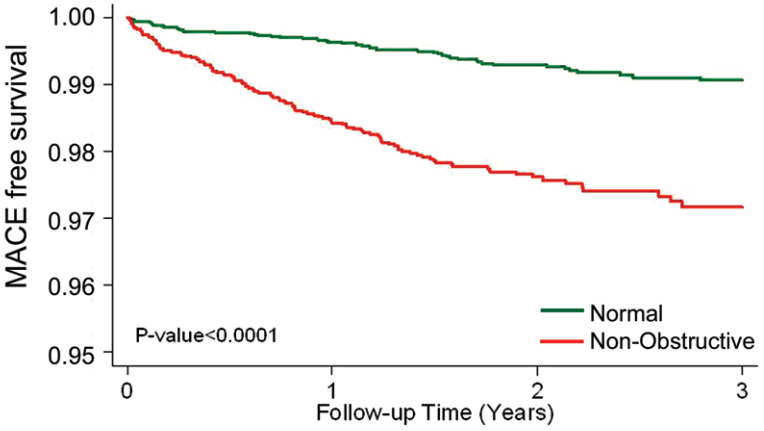
Parameter	All (n = 11 462)	Women (n = 5731)	Men (n = 5731)	Standardized Differences	P Value
Age (y)*†	55.1 ± 12.3	55.5 ± 12.5	54.7 ± 12.0	0.06	.0001
Asymptomatic patients†	3849 (33.6)	1934 (33.7)	1915 (33.4)	0.007	.71
Hypertension†	5197 (45.3)	2603 (45.4)	2594 (45.3)	0.003	.87
Hyperlipidemia†	5867 (51.2)	2984 (52.1)	2883 (50.3)	0.04	.06
Diabetes†	1372 (12.0)	723 (12.6)	649 (11.3)	0.04	.03
Current smoker†	2052 (17.9)	1044 (18.2)	1008 (17.6)	0.02	.38
Family history†	3829 (33.4)	1952 (34.1)	1877 (32.8)	0.03	.14
No. of involved segments*†	0.60 ± 0.89	0.62 ± 0.91	0.59 ± 0.86	0.03	.35

Note.—Data are numbers of patients, unless indicated otherwise. Numbers in parentheses are percentages.

* Data are means ± standard deviations.

† Matching factors.

Figure 1



Number at risk

Normal	6759	6248	3852	1857
Non-Obstructive	4703	4294	2203	908

Figure 1: Graph demonstrates 3-year Kaplan-Meier event-free survival for no CAD versus nonobstructive disease in the propensity-matched cohort.

0.5%] and 1.1% [95% CI: 0.8%, 1.4%], respectively). For women, propensity-matched HR for nonobstructive CAD versus no CAD was 1.96 (95% CI: 1.17, 3.28) (P = .01) and for men was 1.77 (95% CI: 1.07, 2.93) (P = .03) (Table E1 [online]). For women, propensity-matched HR for risk of MI in nonobstructive CAD versus no CAD was 3.04 (95% CI: 1.13, 8.17) (P = .03) and for men was 3.54 (95% CI: 1.18, 10.58) (P = .02) (Table E1 [online]).

Sex-based Relationship of Coronary CT Angiography Findings and Mortality

No differences in mortality were observed between men and women in the setting of normal coronary CT angiography findings (HR = 1.09 [range, 0.6–2.0], P = .78; annual event rate = 0.3% [95% CI: 0.2%, 0.4%] in both, P = .87) or in the presence of nonobstructive disease (HR = 1.01 [range, 0.7–1.6], P = .95) (annual event rate = 0.9% [95% CI: 0.7%, 1.2%] and 0.8% [95% CI: 0.6%, 1.1%] in women and men, respectively; P = .89) (Fig 2). Men exhibit an increasing risk with higher SIS: 1–2 segments, HR = 2.71 (range, 1.61–4.57), $P < .001$; 3–6 segments, HR = 3.99 (range, 2.24–7.09), $P < .001$; and more than six segments, HR = 6.16 (range, 2.15–17.66), P = .001. Women exhibit similarly elevated hazard for death when stratified by SIS: 1–2 segments, HR = 2.80 (range, 1.65–4.76), $P < .001$; 3–6 segments, HR = 4.22 (range, 2.41–7.40), $P < .001$; and more than six segments, HR = 4.72 (range, 1.65–13.54), P = .004.

Sex-based Relationship of Coronary CT Angiography Findings and All-Cause Mortality and MI Stratified by Symptom Status and Type

When stratified by the presence or absence of symptoms and angina typicality, there were no observed differences in the relationship between nonobstructive disease and mortality for women versus men (not significant) (Tables E2 and E3 [online]).

Effect of Plaque Morphology on All-Cause Mortality and MI Stratified by Sex

In a subgroup of patients with noncalcified plaque (Table E3 [online]), the risk of MACE prognosis in men was not significantly different compared with women (unadjusted HR = 1.96 [95% CI: 0.90, 4.28], P = .09; risk-adjusted HR = 1.91 [95% CI: 0.87, 4.20], P = .11). This similar relationship between

Figure 2

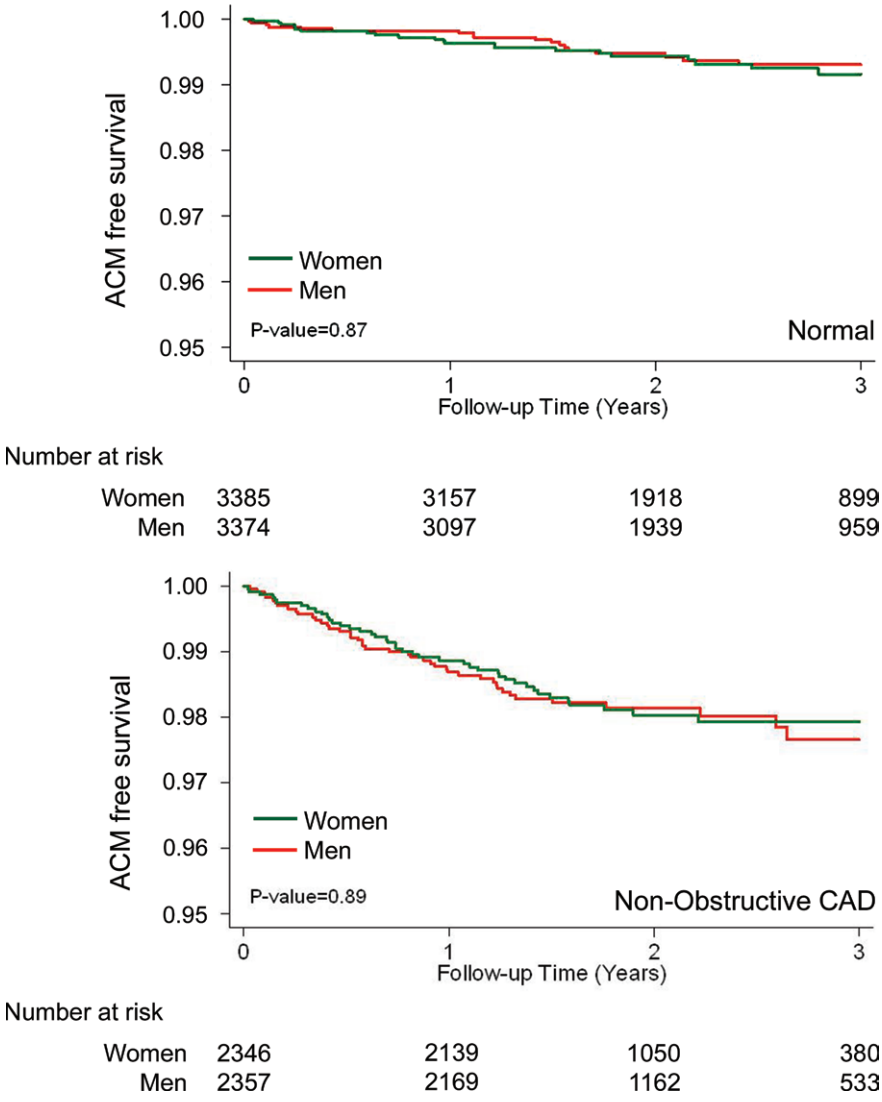


Figure 2: Graphs demonstrate Kaplan-Meier event-free survival curves in a matched population, matched on the basis of age, symptoms, risk factors, and log SIS. *ACM* = all-cause mortality.

men and women holds true for calcified plaque (unadjusted HR = 0.74 [95% CI: 0.46, 1.22], P = .24; risk-adjusted HR = 0.84 [95% CI: 0.51, 1.38], P = .49) and partially noncalcified plaque (unadjusted HR = 0.80 [95% CI: 0.45, 1.80], P = .43; risk-adjusted HR = 0.70 [95% CI: 0.40, 1.25], P = .23).

Discussion

In the present study, we aimed to examine whether the extent of epicardial nonobstructive CAD would serve as a potentially important variable for prediction of prognosis according to sex. In our prospective multicenter international study, we observed a prognostic importance for all patients with nonobstructive CAD wherein rates of incident mortality and MI were heightened for patients with CAD as compared with patients without. Yet, among women and men who were similar according to age, CAD risk factors, and nonobstructive CAD extent, we did not observe a differential effect of nonobstructive CAD on adverse prognosis when examining mortality, MI, or both. Of equal importance, the absence of CAD at coronary CT angiography conferred an excellent prognosis for both women and men and did not differ according to sex. Importantly, in our analysis, we attempted to advance our understanding of the prognostic importance of nonobstructive disease in men and women through propensity matching of subjects on the basis of CAD risk, symptoms, and extent of disease in an attempt to isolate sex as the only distinguishing variable. In addition, in our analysis, we explored a historically large number of subjects and events in an attempt to better understand the effect of sex on clinical outcomes after coronary CT angiography.

Our data build on those of prior studies in which investigators attempted to address the question of the effect of sex on prognosis. Some of these prior studies have been conflicting in their results. Min and colleagues showed comparable clinical outcomes between men and women but did not focus on nonobstructive disease and were limited to all-cause mortality as an end point, without data on MI (10). Shaw et al published results that conflicted with our data and suggested that men and women have disparate clinical outcomes (13). Importantly, however, the aforementioned study was an analysis of a small cohort with limited events and was methodologically different than our study, without matching of men and women, and did not focus on nonobstructive disease. Through our careful matching of men and women, we feel we are able to explore the potential effect of sex on prognosis, as all other potential drivers of events have been accounted for, leaving only differences in patient sex.

Over the past 2 decades, there has been growing evidence that the pathophysiology of CAD in women and men may be different (7–9,11,12). Microvascular dysfunction has been implicated as a potential cause of these differences, with microvascular dysfunction said to be more common in women than in men, with resultant higher event rates and a greater burden of chest pain

and symptoms, despite the absence of obstructive disease at invasive angiography. It has also been suggested that these differences may result in paradoxical frequent (atypical) symptoms and adverse clinical outcomes (11,12). There are a number of theories as to why microvascular dysfunction may be more common in women, including vascular inflammation, risk factor clustering, vascular remodeling, and hormonal alterations (11,12,20). To date, however, the mechanisms of these adverse prognostic findings have not yet been elucidated.

In this regard, our data may clarify prior study findings in which CAD was examined in invasive catheter angiography studies, wherein the prognosis of nonobstructive CAD has been reported as differing between men and women (8,9,11,12). In the WISE studies, investigators have reported that approximately one-half of symptomatic women without obstructive CAD at catheter angiography have microvascular coronary dysfunction that results in ischemia and that microvascular dysfunction is associated with adverse cardiovascular prognosis (8,9,11,12). Our data strengthen the WISE conclusions that extent and distribution of epicardial nonobstructive CAD may not be a significant contributor to sex-based differences in adverse clinical outcomes, as was observed in women and men who were similar in age, CAD risk factors, and coronary CT angiography–identified CAD extent. In fact, when matched for important characteristics, differences in MI and death did not exist.

Importantly, the adverse prognosis associated with microvascular dysfunction in the WISE cohorts has been documented even in the setting of normal invasive coronary angiography findings, whereas we observed a similarly excellent prognosis among both women and men with normal coronary arteries at coronary CT angiography. This apparent discordance between the data presented herein and past publications likely reflects differences in the technique used for coronary artery assessment. It is well established that coronary CT angiography is more sensitive than catheter angiography for the detection of mild CAD, particularly in the absence of luminal encroachment (21). Unlike invasive angiography, CT is able to not only allow traditional angiographic measurement of stenosis severity, but also demonstrate atherosclerotic plaque and coronary arterial wall features in a fashion similar to that of intravascular ultrasonography (21–23). In this regard, we observed an excellent prognosis for both sexes in the setting of normal coronary CT angiography findings—a result that was independent of symptom status—suggesting a prognostic utility of normal coronary CT angiography findings that can be used to clarify risk in a sex-neutral manner. Additionally, our data suggest that while the cause of the different patterns and severity of chest pain and the apparent discordance between the severity of coronary disease and symptoms in women remain unclear, normal coronary angiography findings without atherosclerosis confer a similar prognosis in men and women, regardless of symptom status.

This study is not without limitations. First, it was composed of individuals undergoing clinically indicated coronary CT angiography studies and was observational in nature. As a result, inherent biases associated with selection and ascertainment cannot be excluded. Thus, our study findings, while provocative, cannot allow for cause-and-effect conclusions. Second, direct comparisons of the present study findings cannot be made with those of prior investigations, such as those observed in the WISE study. In our study, we specifically examined patients undergoing noninvasive testing—given the higher number of individuals suspected of having CAD who were undergoing this type of work-up—whereas prior studies have primarily focused on individuals undergoing invasive evaluation, yielding a population that may differ in disease extent and pathophysiology. Third, while our propensity matching was extensive and careful, there remained differences in age between the sexes in our analysis. Importantly, women were older, which if anything would result in a bias toward worsened outcomes as compared with the men, but they in fact had very similar downstream event rates to those of men, despite being older. Finally, downstream treatment decisions—including medication use and lifestyle modifications—are unknown, and, thus, the possibility of sex-based treatment biases cannot be excluded.

In conclusion, when matched for age, CAD risk factors, angina typicality, and nonobstructive epicardial CAD extent, women and men experience comparable rates of incident mortality, MI, and MACE. The absence of any coronary atherosclerosis at coronary CT angiography afforded a remarkably low annual mortality (0.3%) and MI (0.08%) rate, irrespective of sex.

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