



Sex-Specific Associations Between Coronary Artery Plaque Extent and Risk of Major Adverse Cardiovascular Events

The CONFIRM Long-Term Registry

Joshua Schulman-Marcus, MD,^a Bráin ó Hartaigh, PhD,^a Heidi Gransar, MS,^b Fay Lin, MD,^a Valentina Valenti, MD,^a Iksung Cho, MD,^a Daniel Berman, MD,^b Tracy Callister, MD,^c Augustin DeLago, MD,^d Martin Hadamitzky, MD,^e Joerg Hausleiter, MD,^e Mouaz Al-Mallah, MD,^f Matthew Budoff, MD,^g Philipp Kaufmann, MD,^h Stephan Achenbach, MD,ⁱ Gilbert Raff, MD,^j Kavitha Chinnaiyan, MD,^j Filippo Cademartiri, MD,^k Erica Maffei, MD,^k Todd Villines, MD,^l Yong-Jin Kim, MD,^m Jonathon Leipsic, MD,ⁿ Gudrun Feuchtner, MD,^o Ronen Rubinshtein, MD,^p Gianluca Pontone, MD,^q Daniele Andreini, MD,^q Hugo Marques, MD,^r Leslee Shaw, MD,^s James K. Min, MD^a

ABSTRACT

OBJECTIVES The purpose of this study was to examine sex-specific associations, if any, between per-vessel coronary artery disease (CAD) extent and the risk of major adverse cardiovascular events (MACE) over a 5-year study duration.

BACKGROUND The presence and extent of CAD diagnosed by coronary computed tomography angiography (CTA) is associated with increased short-term mortality and MACE. Nevertheless, some uncertainty remains regarding the influence of sex on these findings.

METHODS 5,632 patients (mean age 60.2 ± 11.8 years, 36.5% women) from the CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter) registry were followed for 5 years. Obstructive CAD was defined as $\geq 50\%$ luminal stenosis in a coronary vessel. Using Cox proportional hazards models, we calculated the hazard ratio (HR) for incident MACE among women and men, defined as death or myocardial infarction.

RESULTS Obstructive CAD was more prevalent in men (42% vs. 26%; $p < 0.001$), whereas women were more likely to have normal coronary arteries (43% vs. 27%; $p < 0.001$). There were a total of 798 incident MACE events. After adjustment, there was a strong association between increased MACE risk and nonobstructive CAD (HR: 2.16 for women, 2.56 for men; $p < 0.001$ for both), obstructive 1-vessel CAD (HR: 3.69 and 2.66; $p < 0.001$), 2-vessel CAD (HR: 3.92 and 3.55; $p < 0.001$), and 3-vessel/left main CAD (HR: 5.94 and 4.44; $p < 0.001$). Further exploratory analyses of atherosclerotic burden did not identify sex-specific patterns predictive of MACE.

CONCLUSIONS In a large prospective coronary CTA cohort followed long-term, we did not observe an interaction of sex for the association between MACE risk and increased per-vessel extent of obstructive CAD. These findings highlight the persistent prognostic significance of anatomic CAD subsets as detected by coronary CTA for the risk of MACE in both women and men. (J Am Coll Cardiol Img 2016;9:364-72) © 2016 by the American College of Cardiology Foundation.

From the ^aDalio Institute of Cardiovascular Imaging, Weill Cornell Medical College and New York Presbyterian Hospital, New York, New York; ^bDepartment of Imaging, Cedars-Sinai Medical Center, Los Angeles, California; ^cTennessee Heart and Vascular Institute, Hendersonville, Tennessee; ^dCapital Cardiology Associates, Albany, New York; ^eDivision of Cardiology, Deutsches Herzzentrum München, Munich, Germany; ^fResearch Center, King Abdul Aziz Cardiac Center, National Guard Health Affairs, Riyadh, Saudi Arabia; ^gDepartment of Medicine, Harbor UCLA Medical Center, Los Angeles, California; ^hUniversity Hospital, Zurich, Switzerland; ⁱDepartment of Medicine, University of Erlangen, Erlangen, Germany; ^jWilliam Beaumont Hospital, Royal Oak, Michigan; ^kCardiovascular Imaging Unit, Giovanni XXIII Hospital, Monastier, Treviso, Italy; ^lDepartment of Medicine, Walter Reed Medical Center, Washington, DC; ^mSeoul National University Hospital, Seoul, South Korea; ⁿDepartment of Medicine and Radiology, University of British Columbia, Vancouver, British Columbia, Canada; ^oDepartment of Radiology, Medical University of Innsbruck, Innsbruck, Austria; ^pDepartment of Cardiology at the Lady Davis Carmel Medical Center, The Ruth and Bruce Rappaport School of Medicine, Technion-Israel Institute of Technology, Haifa, Israel; ^qDepartment of Clinical Sciences and Community Health, University of Milan, Centro Cardiologico Monzino, IRCCS, Milan, Italy; ^rDepartment of Surgery,

Sex disparities in coronary artery disease (CAD) outcomes are well documented (1-4). Although women tend to have a lower prevalence of obstructive CAD, prior evidence indicates that women are more likely to be admitted for angina pectoris and experience worsened outcomes after myocardial infarction (MI) (5). Likewise, women with symptomatic CAD are more likely to suffer worse clinical outcomes, a finding present even among women with apparently normal or nonobstructive coronary arteries as evaluated by invasive coronary angiography (6,7). In light of the considerable burden of CAD in women, further improvements in risk stratification are essential for guiding preventive strategies and public health initiatives.

SEE PAGE 373

Coronary computed tomography angiography (CTA) is a noninvasive imaging modality that enables accurate detection and exclusion of CAD. Prior epidemiological studies have demonstrated that the presence and extent of anatomic CAD are associated with a heightened risk of death as well as major adverse cardiovascular events (MACE) within a 2-year follow-up period (8-13). A chief limitation, however, is the lack of certainty regarding the influence of sex on these findings. One study reported that non-obstructive CAD was associated with increased mortality risk in women but not in men (8). A subsequent propensity-matched study derived from similar data documented an equivalent risk of mortality and MI for nonobstructive CAD between sexes (13); however, the latter study failed to examine the sex-specific relationship between obstructive CAD and MACE. Further still, most of the available published reports have been unable to account for the risk beyond 3 years. Thus, an additional question is whether sex-specific differences in risk persist or attenuate over a longer duration of follow-up. Using data from a large prospective coronary CTA registry, we therefore set out to determine the sex-specific relationships, if any, between the extent of CAD and risk of MACE over a 5-year study period.

METHODS

STUDY POPULATION. Study patients were identified from the CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter) registry, a dynamic, international, multicenter, observational cohort study that prospectively collects clinical, procedural, and follow-up data on patients undergoing ≥ 64 -detector row coronary CTA. The rationale, design, site-specific patient characteristics, and follow-up durations have been described previously (14). In brief, this study screened 12,086 patients with 5-year follow-up data who underwent coronary CTA at 17 centers in 9 countries (Austria, Canada, Germany, Israel, Italy, Portugal, South Korea, Switzerland, and the United States) between 2002 and 2009. Individuals with known CAD at the time of coronary CTA, as defined by prior MI or coronary revascularization or cardiac transplantation, were excluded (n = 1,593). Patients with incomplete follow-up of all clinical events (n = 4,585), with adverse events on the day of the coronary CTA (n = 50), with missing plaque severity data (n = 224), or those who were missing age and sex information (n = 2) were also omitted. Thus, the analytic sample comprised 5,632 patients. Each study site received institutional review board approval for all registry procedures, including follow-up methodologies, and each participant provided written informed consent.

CLINICAL DATA COLLECTION. Standardized data collection methods were used at the participating study sites. Data were systematically collected for each consecutive patient while applying consistent definitions for suspected cardiac symptoms, risk factors, and angiographic CAD extent and severity. Patient information was gathered for traditional cardiac risk factors, including hypertension, diabetes, dyslipidemia, current smoking, and a family history of premature CAD. Patients who were treated for hypertension, diabetes, or dyslipidemia, or who otherwise had a prior diagnosis for these conditions

ABBREVIATIONS AND ACRONYMS

ACEI/ARB = angiotensin-converting enzyme/angiotensin receptor blocker
CTA = computed tomographic angiography
CP = calcified plaque
HR = hazard ratio
LM = left main
MACE = major adverse clinical events
MI = myocardial infarction
NCP = noncalcified plaque
PCP = partially calcified plaque

Curry Cabral Hospital, Lisbon, Portugal; and the [§]Division of Cardiology, Emory University School of Medicine, Atlanta, Georgia. Research reported in this publication was supported by the Heart Lung and Blood Institute of the National Institutes of Health under award number R01 HL115150, and funded, in part, by a generous gift from the Dalio Institute of Cardiovascular Imaging and the Michael Wolk Foundation. Dr. Min has received the following grants, NIH/NIHLBI R01HL111141, NIH/NIHLBI R01HL115150, NIH/NIHLBI R01HL118019, NIH/NIHLBI, U01HL105907, NPRP09-370-3-089. Dr. Min has served as a consultant with HeartFlow; has served on the scientific advisory board of Arineta; has partial ownership in MDDX and Autoplaq; and has received research support from GE Healthcare. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Schulman-Marcus and Ó Hartaigh contributed equally to this work. John Mahmarian, MD, served as Guest Editor for this article.

Manuscript received February 15, 2016; revised manuscript received February 19, 2016, accepted February 22, 2016.

TABLE 1 Study Demographics

	Overall (n = 5,632)	Women (n = 2,056)	Men (n = 3,576)	p Value
Age, yrs	60.2 ± 11.8	62.4 ± 11.4	58.9 ± 11.8	<0.001
Cardiac risk factors				
Hypertension	3,079 (54.9)	1,234 (60.3)	1,845 (51.9)	<0.001
Hyperlipidemia	3,031 (54.1)	1,133 (55.3)	1,898 (53.3)	0.15
Diabetes	961 (17.1)	358 (17.5)	603 (16.9)	0.61
Current smoker	1,193 (21.4)	306 (15.0)	887 (25.0)	<0.001
Family history of premature CAD	1,662 (29.9)	674 (33.2)	988 (28.0)	<0.001
Chest pain				<0.001
Typical	739 (14.8)	292 (15.8)	447 (14.1)	
Atypical	1,625 (32.4)	651 (35.3)	974 (30.8)	
Noncardiac	664 (13.3)	298 (16.2)	366 (11.6)	
Asymptomatic	1,983 (39.6)	603 (32.7)	1,380 (43.6)	
Dyspnea	734 (16.8)	328 (20.2)	406 (14.7)	<0.001
Baseline medication use				
ASA	1,443 (32.6)	491 (30.5)	952 (33.8)	0.02
Beta blocker	1,289 (29.1)	498 (30.9)	791 (28.1)	0.05
ACEI/ARB	1,273 (28.8)	439 (27.3)	834 (29.6)	0.1
Statin	1,603 (36.0)	588 (36.3)	1,015 (35.9)	0.78
Extent of CAD by coronary CTA				
Normal	1,844 (32.7)	878 (42.7)	966 (27.0)	<0.001
Nonobstructive CAD	1,690 (30.0)	611 (29.7)	1,079 (30.2)	0.72
1-vessel obstructive CAD	1,094 (19.4)	318 (15.5)	776 (21.7)	<0.001
2-vessel obstructive CAD	544 (9.7)	135 (6.6)	409 (11.4)	<0.001
3-vessel/LM obstructive CAD	460 (8.2)	114 (5.5)	346 (9.7)	<0.001
Early revascularization (<90 days)	1,243 (22.1)	345 (16.8)	898 (25.1)	<0.001

Values are mean ± SD or n (%).
ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ASA = acetylsalicylic acid; CAD = coronary artery disease; CTA = computed tomography angiography; LM = left main.

were categorized as having that risk factor. Family history of premature CAD was defined as a primary relative with a diagnosis early in life (i.e., mother <65 years of age or father <55 years of age). Chest pain was defined and categorized by the interviewing physician as nonanginal, atypical angina, or typical angina pectoris. The presence of excessive dyspnea as a reason for referral was also noted. The baseline use of cardiac medications (aspirin, beta blockers, angiotensin-converting enzyme/angiotensin receptor blocker, statin) were also collected.

CORONARY CTA PERFORMANCE AND INTERPRETATION. Standardized protocols for image acquisition, as defined by the Society of Cardiovascular Computed Tomography, were used at all participating sites (15). Specific details of coronary CTA procedures have been defined in detail elsewhere (14). Each site applied the standard anatomic segmental analysis for image interpretation. Plaque composition was defined as noncalcified, partially calcified, or calcified. All segments were coded for the presence and severity of coronary stenosis and were scored as

normal (0% luminal stenosis), mild-moderate (1% to 49% luminal stenosis), moderate (50% to 69% luminal stenosis), or severe (\geq 70% luminal stenosis). For the primary analysis, CAD extent was defined by \geq 50% stenosis in 0, 1, 2, or 3 coronary artery vessels. As reported in prior studies (8,9,16), given its prognostic significance, left main disease (50% luminal stenosis) was grouped with 3-vessel obstructive CAD.

Limited exploratory analyses of plaque composition and per-segment severity were also performed using previously reported methods (8). A segment involvement score was calculated as the total number of coronary artery segments exhibiting plaque, irrespective of the degree of luminal stenosis within each segment (minimum = 0; maximum = 16). A segment stenosis score was used as a measure of overall coronary artery plaque extent. Each individual coronary segment was graded as having no to severe plaque (i.e., scores from 0 to 3) based on extent of obstruction of coronary luminal diameter. Then the extent scores of all 16 individual segments were summed to yield a total score ranging from 0 to 48.

STUDY OUTCOME. Patients were followed prospectively for 5 years. The primary outcome measure for the present study was MACE, which included a combination of all-cause mortality and nonfatal MI. Secondary exploratory outcomes were all-cause mortality and nonfatal MI. Cause of death was not obtained in the CONFIRM registry. Late revascularization was not included as an outcome owing to insufficient data. Follow-up procedures were approved by all study centers' institutional review boards. All-cause mortality was adjudicated by trained study personnel or by querying of national medical databases. Other events were collected through a combination of direct questioning of patients using a scripted interview and examination of the patients' medical records as previously described (14). Acute MI was further ascertained using biomarker quantification during patients' hospital stays.

STATISTICAL METHODS. Demographic characteristics were summarized according to sex, with categorical variables presented as counts with proportions and continuous variables as mean ± SD, unless specified otherwise. Categorical variables were compared with the chi-square test, whereas continuous variables were compared with Student unpaired *t* test or Wilcoxon nonparametric tests where appropriate. Kaplan-Meier curves with log-rank tests were used to assess the sex-specific relationship between CAD extent and MACE. Next, we attempted to select the most relevant candidate risk factors for

multivariate adjustment using a stepwise Cox regression procedure, reporting hazard ratios (HRs) with 95% confidence intervals (CIs). Initially, we modeled associations between each clinical risk factor and MACE, selecting a subset of covariates with a p value <0.25 in univariate analyses. We then used a backward multivariate regression model with a covariant retention threshold set at a p value of <0.10. We chose a less-conservative p value of 0.10 to permit inclusion of covariates that are traditionally associated with cardiovascular risk but were not deemed significant at the conventional threshold p value of <0.05. Categorical variables were retained if 1 component was significant. As a sensitivity check, and to conform to prior studies reported from the CONFIRM registry (9), patients who underwent early revascularization procedures ≤90 days previous were excluded from all survival analyses (n = 1,245). Variables retained in the final Cox model were also used as covariates during exploratory analyses of various plaque characteristics. For the purpose of this study, we also tested for an interaction between sex and each of the coronary CTA characteristics with the study outcomes. A 2-tailed p value <0.05 was considered statistically significant. All statistical analyses were conducted using STATA version 12 (StataCorp, College Station, Texas).

RESULTS

BASELINE CHARACTERISTICS. Of 5,632 patients included in the study, 2,056 (36.5%) were women. The mean age of the cohort was 60.2 ± 11.8 years; women were significantly older than men (mean 62.4 vs. 58.9, p < 0.001). Demographic data are displayed in Table 1. Men were more likely to be smokers, whereas women were more likely to have hypertension, a family history of premature CAD, symptoms of chest pain, and excessive dyspnea (p < 0.001 for all). With regard to the extent of visualized atherosclerosis, men had an increased number of vessels with obstructive CAD, whereas women were more likely to have normal coronary arteries (p < 0.001 for all). There were a total of 371 deaths and 484 MIs in the cohort; 798 first MACE events were used for analyses. No sex-specific differences in the number of deaths or MIs were observed.

CLINICAL CHARACTERISTICS ASSOCIATED WITH MACE. The results of the multivariate model construction procedures are reported in Table 2. All variables were entered into the backward regression except for female sex (p = 0.68) and family history (p = 0.32). Of candidate risk factors, age, hypertension, diabetes, tobacco use, angiotensin-converting enzyme/

TABLE 2 Predictors of MACE

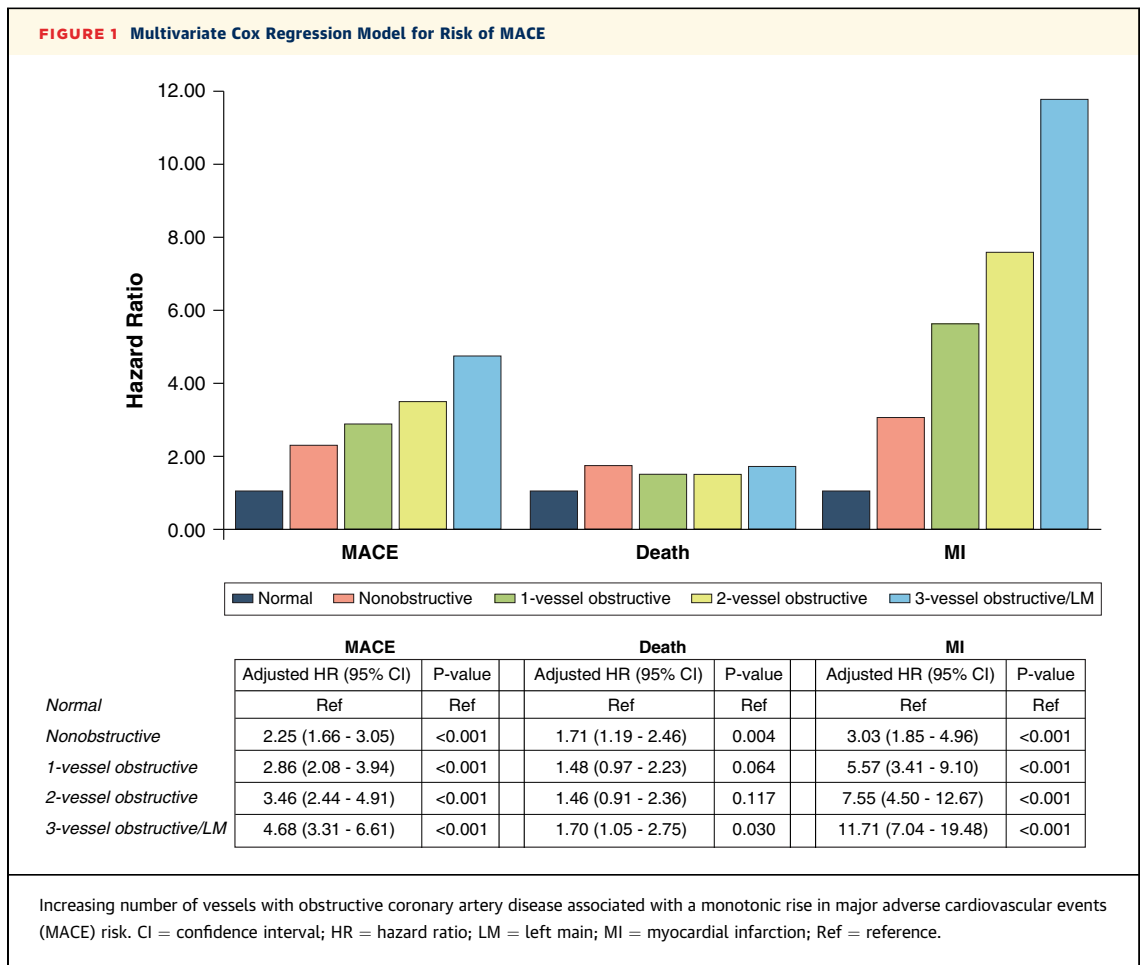
	Univariate		Multivariate*	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Age	1.04 (1.03-1.05)	<0.001	1.03 (1.02-1.04)	<0.001
Women	0.97 (0.84-1.12)	0.68		
Hypertension	1.51 (1.31-1.75)	<0.001	1.24 (1.02-1.51)	0.035
Hyperlipidemia	0.93 (0.81-1.07)	0.32		
Diabetes	1.92 (1.64-2.25)	<0.001	1.42 (1.16-1.74)	0.001
Smoking	1.20 (1.03-1.41)	0.03	1.48 (1.21-1.82)	<0.001
Family history of premature CAD	0.90 (0.77-1.06)	0.21		
Typical angina	1.52 (1.25-1.85)	<0.001	1.30 (1.01-1.66)	0.038
Atypical angina	0.98 (0.83-1.16)	0.82	0.99 (0.79-1.24)	0.904
Noncardiac chest pain	0.84 (0.67-1.05)	0.12	1.12 (0.85-1.66)	0.396
Dyspnea	1.50 (1.22-1.84)	<0.001		
Aspirin	1.63 (1.37-1.94)	<0.001		
Beta blocker	1.25 (1.04-1.50)	0.02		
ACE/ARB	1.58 (1.32-1.88)	<0.001	1.26 (1.04-1.52)	0.017
Statin	1.36 (1.14-1.62)	<0.001		
Nonobstructive disease	0.95 (0.81-1.10)	0.47	2.25 (1.66-3.05)	<0.001
1-vessel obstructive disease	1.65 (1.40-1.93)	<0.001	2.86 (2.08-3.94)	<0.001
2-vessel obstructive disease	1.73 (1.41-2.11)	<0.001	3.46 (2.44-4.91)	<0.001
3-vessel obstructive disease	2.42 (1.99-2.95)	<0.001	4.68 (3.31-6.61)	<0.001
Early revascularization	2.41 (2.07-2.80)	<0.001		

*HRs shown only for variables retained.
 ACE = angiotensin-converting enzyme; CI = confidence interval; HR = hazard ratio; MACE = major adverse cardiovascular events; other abbreviations as in Table 1.

angiotensin receptor blocker use, angina typicality, and per-vessel CAD severity were retained as important predictors of MACE. Sex was not a significant predictor of MACE when forced into the final multivariate model (HR: 0.86; 95% CI: 0.71 to 1.04; p = 0.12). All variables remained significantly associated with MACE in the multivariate Cox proportional hazards model with the exception of some angina variants.

CAD EXTENT AND MACE. In multivariate regression analyses, an increasing number of vessels with obstructive CAD was associated with increased MACE risk in a dose-response relationship (Figure 1). As displayed in Figure 2, increased per-vessel CAD extent was associated with MACE risk over time in both women and men (p < 0.001 by log-rank test for both). After adjustment, increasing per-vessel CAD extent was significantly associated with increased MACE risk in a manner similar to the overall cohort in both women and men (Table 3) (p for interaction = 0.98).

In exploratory analyses of secondary outcomes, there was no clear stepwise relationship between the number of diseased vessels and all-cause mortality in either sex (p for interaction = 0.58). Notably, in both women and men, the adjusted point estimates trended toward increased hazard of death



for both nonobstructive and obstructive disease. Conversely, in both women and men, there appeared to be a stepwise relationship between the secondary outcome of nonfatal MI and number of diseased vessels after adjustment for covariates (p for interaction = 0.93). These findings were not materially different when patients with early revascularization (≤ 90 days after the index coronary CTA) were removed as a sensitivity check (data not shown).

SEX-SPECIFIC PLAQUE PATTERNS AND MACE. In exploratory analyses of other per-patient and per-segment measures, men had a higher prevalence of atherosclerotic plaque and obstructive CAD (Table 4). After adjustment, all measures of increased atherosclerotic severity and extent were associated with increased MACE risk in women and men. There were no significant sex-specific interactions, with the exception that increased segments of calcified plaque were associated with increased MACE risk in women but not in men (p for interaction = 0.004).

DISCUSSION

In the present study, we observed a strong and independent association between increased extent of per-vessel obstructive CAD by coronary CTA and heightened risk of MACE over a 5-year period among women and men. Similar findings were observed for the secondary outcome of nonfatal MI in both sexes, whereas increased mortality risk was more uniform across the spectrum of anatomic CAD. These findings highlight the persistent prognostic significance of increased CAD extent as detected by coronary CTA for both women and men.

The current study observations are fitting with previous observations; that is, although obstructive CAD detected by coronary CTA is less common in women than in men, its presence is associated with equal if not worse adverse outcomes. In an analysis of 24,775 patients followed over a mean of 2.3 years, Min et al. (8) found that although increased mortality risk was noted in both men and women with

nonobstructive, 1-vessel, and 2-vessel obstructive disease, in women 3-vessel/left main obstructive disease was associated with an even higher mortality risk compared with men (HR: 4.21 compared with 3.27). In a smaller single-center cohort of 1,127 patients (57% women), Shaw et al. (16) also observed that although higher obstructive CAD burden by coronary CTA was associated with increased mortality in both sexes, women with 3-vessel obstructive/left main disease had a higher risk of death compared with men. These findings are in concord with prior registry data demonstrating higher rates of in-hospital mortality in women with obstructive CAD (17). Our study extends the prior published reports by observing the attenuation of the aforementioned sex-specific differences in MACE over a longer duration. However, our study emphasizes the core finding of the prior published reports that the extent of obstructive CAD detected by coronary CTA, regardless of sex, is the most significant predictor of increased MACE risk.

The present study findings are also in line with those of Leipsic et al. (13), who observed an association between increased risk of MACE and non-obstructive CAD by coronary CTA and no significant disparity between women and men. In that study, over the course of 2.3 years, the authors made use of propensity analysis to match patients with normal coronary arteries and nonobstructive CAD by coronary CTA for age and CAD risk factors. Following this approach, the annual death, MI, or MACE rates for both women and men with nonobstructive CAD were equivalent. This analysis stands in contrast to other coronary CTA and retrospective invasive studies suggesting a unique adverse prognosis for nonobstructive CAD by coronary CTA in women compared with men (1,6,7,18). Our study re-enforces the findings of Leipsic et al. (13) by observing a similar attenuation in sex-specific MACE risk for nonobstructive CAD over a longer time frame and with a larger number of events available for analysis. Further still, the present study highlights that nonobstructive CAD is associated with increased risk of MACE in men as well as women (19), and its presence in the former category should not be overlooked.

Although this study did not identify sex differences in MACE risk for several measures of CAD severity and extent, it must be emphasized that our findings do not exclude sex differences in the pathophysiology and functional importance of atherosclerosis. For example, an intriguing study of early atherosclerosis using intravascular ultrasound reported that women have lower measures of

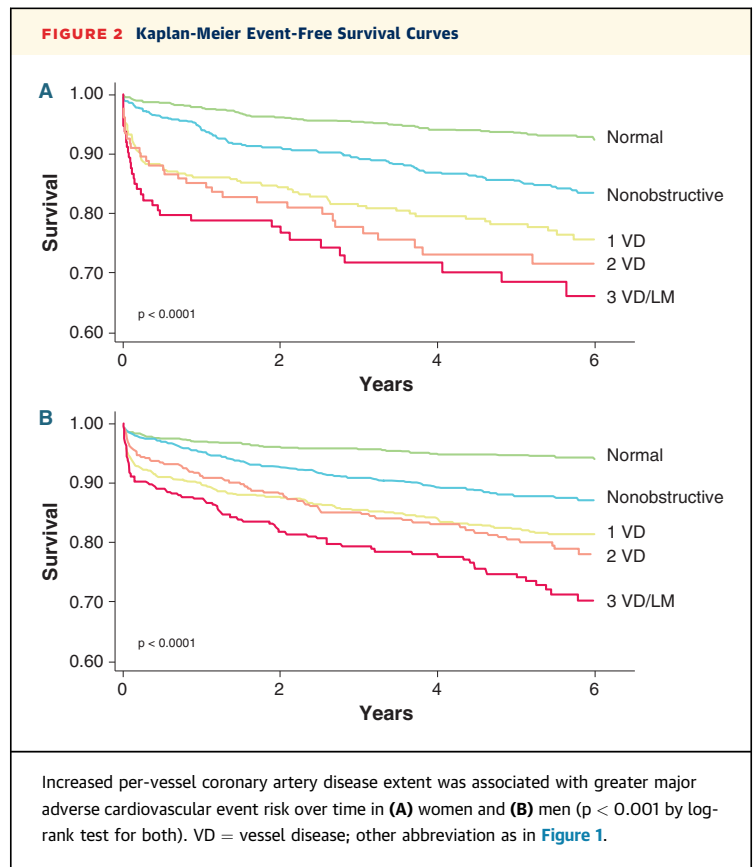


TABLE 3 Adjusted Hazards of MACE and MACE Components by CAD Extent, Stratified by Sex

	Women		Men	
	Adjusted HR (95% CI)	p Value	Adjusted HR (95% CI)	p Value
Total MACE				
Normal	Ref	Ref	Ref	Ref
Nonobstructive	2.16 (1.41-3.29)	<0.001	2.56 (1.62-4.04)	<0.001
1-vessel obstructive	3.69 (2.35-5.78)	<0.001	2.66 (1.66-4.26)	<0.001
2-vessel obstructive	3.92 (2.24-6.85)	<0.001	3.55 (2.17-5.79)	<0.001
3-vessel obstructive/LM	5.94 (3.47-10.17)	<0.001	4.44 (2.73-7.22)	<0.001
Death				
Normal	Ref	Ref	Ref	Ref
Nonobstructive	1.89 (1.14-3.16)	0.013	1.74 (1.02-2.97)	0.042
1-vessel obstructive	1.96 (1.07-3.58)	0.028	1.33 (0.75-2.38)	0.314
2-vessel obstructive	2.06 (0.95-4.45)	0.066	1.35 (0.71-2.56)	0.346
3-vessel obstructive/LM	1.66 (0.70-3.98)	0.253	1.76 (0.94-3.29)	0.064
MI				
Normal	Ref	Ref	Ref	Ref
Nonobstructive	2.38 (1.22-4.61)	0.011	4.58 (2.02-10.35)	<0.001
1-vessel obstructive	5.96 (3.11-11.40)	<0.001	6.79 (3.01-15.32)	<0.001
2-vessel obstructive	6.26 (2.86-13.69)	<0.001	10.42 (4.57-23.80)	<0.001
3-vessel obstructive/LM	14.04 (6.89-28.61)	<0.001	13.57 (5.96-30.89)	<0.001

MI = myocardial infarction; Ref = reference; other abbreviations as in Tables 1 and 2.

TABLE 4 Plaque Patterns and Adjusted Risk of MACE, Stratified by Sex

	Demographics			Adjusted HR* (95% CI)			
	Women	Men	p Value	Women	p Value	Men	p Value
Per patient							
CACS			<0.001				
None	766 (55.3)	760 (37.1)		1.00	1.00	1.00	1.00
1-400	470 (33.9)	901 (44.0)		1.76 (1.11-2.78)	0.02	1.93 (1.18-3.16)	0.01
≥400	149 (10.8)	388 (18.9)		2.86 (1.65-4.95)	<0.001	2.41 (1.41-4.13)	0.001
Maximal CAD stenosis severity			<0.001				
No plaque	878 (42.7)	966 (27.0)		1.00	1.00	1.00	1.00
Mild (1%-49%)	611 (29.7)	1,079 (30.2)		2.14 (1.40-3.26)	<0.001	2.56 (1.62-4.03)	<0.001
Moderate (50%-69%)	215 (10.5)	538 (15.0)		3.64 (2.25-5.88)	<0.001	2.62 (1.61-4.28)	<0.001
Severe (≥70%)	352 (17.1)	993 (27.8)		4.50 (2.89-7.01)	<0.001	3.74 (2.38-5.87)	<0.001
Location of any obstructive CAD							
RCA	258 (13.0)	726 (21.1)	<0.001	1.99 (1.39-2.84)	<0.001	1.62 (1.27-2.07)	<0.001
LAD artery	436 (21.5)	1,176 (33.2)	<0.001	2.54 (1.86-3.47)	<0.001	1.45 (1.15-1.83)	0.002
LCX artery	184 (9.5)	631 (18.6)	<0.001	2.58 (1.78-3.74)	<0.001	1.83 (1.43-2.33)	<0.001
LM	32 (1.6)	95 (2.8)	0.006	1.99 (0.92-4.30)	0.08	1.21 (0.70-2.09)	0.49
Per segment							
CAD severity and extent							
Log segment involvement score	0.8 (0.0-1.4)	1.1 (0.0-1.8)	<0.001	2.04 (1.68-2.49)	<0.001	1.59 (1.36-1.87)	<0.001
Log segment stenosis score	0.9 (0.0-1.6)	1.3 (0.0-2.1)	<0.001	1.88 (1.60-2.21)	<0.001	1.53 (1.34-1.74)	<0.001
No. of segments with NCP			<0.001				
0	1,668 (82.8)	2,535 (74.5)		1.00	1.00	1.00	1.00
1	205 (10.2)	415 (12.2)		1.14 (0.75-1.74)	0.53	1.09 (0.79-1.52)	0.59
2	72 (3.6)	195 (5.7)		1.21 (0.62-2.39)	0.58	1.34 (0.89-2.01)	0.17
≥3	69 (3.4)	257 (7.6)		1.12 (0.54-2.30)	0.77	1.02 (0.69-1.49)	0.93
No. of segments with PCP			<0.001				
0	1,632 (81.0)	2,289 (67.3)		1.00	1.00	1.00	1.00
1	189 (9.4)	401 (11.8)		1.24 (0.81-1.90)	0.32	1.02 (0.73-1.42)	0.93
2	76 (3.8)	259 (7.6)		1.45 (0.81-2.60)	0.21	1.13 (0.78-1.65)	0.51
≥3	117 (5.8)	453 (13.3)		2.09 (1.35-3.25)	0.001	1.12 (0.83-1.50)	0.46
No. of segments with CP†			<0.001				
0	1,526 (75.8)	2,148 (63.1)		1.00	1.00	1.00	1.00
1	199 (9.9)	436 (12.8)		1.52 (0.99-2.36)	0.06	0.94 (0.67-1.34)	0.74
2	94 (4.7)	265 (7.8)		1.76 (1.02-3.05)	0.04	0.93 (0.62-1.39)	0.72
≥3	195 (9.7)	553 (16.2)		2.39 (1.66-3.45)	<0.001	1.11 (0.84-1.47)	0.47

Values are n (%) or median (interquartile range), unless otherwise indicated. *Adjusted for age, hypertension, diabetes, smoking, symptoms, and use of ACEI/ARB. †p for interaction = 0.004.

CACS = coronary artery calcium score; CP = calcified plaque; IQR = interquartile range; LAD = left anterior descending; LCX = left circumflex; NCP = noncalcified plaque; PCP = partially calcified plaque; RCA = right coronary artery; other abbreviations as in [Tables 1 to 3](#).

microvascular dysfunction, whereas men tend to have a higher burden of atheroma and endothelial dysfunction in epicardial arteries (20). In addition, prior research has shown that women with non-obstructive CAD but who present with chest pain and apparently normal invasive angiograms have increased rates of microvascular dysfunction, which is associated with a higher burden of clinical outcomes (18). Differing mechanisms of plaque disruption in acute MI have been noted between men and women (3). Finally, although rigorous and clinically relevant, the measures of CAD extent used in the present study are relatively crude. Given these considerations, further studies are needed to distinguish

whether there are sex-specific plaque characteristics detected by coronary CTA, and whether these are associated with a higher risk of clinical events.

STUDY LIMITATIONS. Although CONFIRM represents the largest consecutive cohort of patients undergoing coronary CTA, as a registry it is subject to potential selection and referral bias. Many of the patients with long-term follow-up had incomplete outcomes data regarding MI and were excluded from this study. Thus, in spite of a lengthy follow-up and a relatively high number of events, the analyses relative to several sex-specific subgroups may have been underpowered, which likely explains the wide 95% CIs

observed for some of the risk estimates reported in this study. A further and important limitation is that data were not collected on post-coronary CTA modifications of pharmacotherapy or behavior. Studies in other cohorts have demonstrated variable changes in post-test medical therapy by degree of anatomic CAD (21,22). It is unknown whether such treatment choices are affected by sex, and this is a matter worthy of further study. Data were also unavailable regarding any stress testing, and so the functional significance of stenoses was unknown. Other clinically relevant outcomes (e.g., cause-specific mortality, stroke) were not collected. In light of these limitations, however, this study is the largest consecutive cohort of patients undergoing coronary CTA with long-term outcomes data available.

CONCLUSIONS

The present study emphasized the clear prognostic significance of per-vessel obstructive CAD extent as detected by coronary CTA over a 5-year period. During this time, there were no distinct sex-specific differences in the risk of MACE. Though our findings await confirmation through forthcoming studies, as an initial step preventive strategies should be

encouraged for men and women who present with any atherosclerosis as detected by coronary CTA.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. James K. Min, Dalio Institute of Cardiovascular Imaging, Weill Cornell Medical College and the New York-Presbyterian Hospital, 413 East 69th Street, Suite 108, New York, New York 10021. E-mail: jkm2001@med.cornell.edu.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Greater per-vessel extent of obstructive CAD as detected by coronary CTA is associated with greater MACE risk over a 5-year duration. Because there was no observed interaction for this association, this holds true of CAD detected in both women and men.

TRANSLATIONAL OUTLOOK: Although rigorous and clinically relevant, the measures of CAD extent used in the present study are relatively crude. Further studies are needed to distinguish whether there are sex-specific plaque characteristics detected by coronary CTA and whether these are associated with a higher risk of clinical events.

REFERENCES

1. Shaw LJ, Bugiardini R, Merz CN. Women and ischemic heart disease: evolving knowledge. *J Am Coll Cardiol* 2009;54:1561-75.
2. Hochman JS, Tamis JE, Thompson TD, et al. Sex, clinical presentation, and outcome in patients with acute coronary syndromes. Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes IIb Investigators. *N Engl J Med* 1999;341:226-32.
3. Della Rocca DG, Pepine CJ. What causes myocardial infarction in women without obstructive coronary artery disease? *Circulation* 2011;124:1404-6.
4. Vaccarino V, Parsons L, Peterson ED, Rogers WJ, Kiefe CI, Canto J. Sex differences in mortality after acute myocardial infarction: changes from 1994 to 2006. *Arch Intern Med* 2009;169:1767-74.
5. Johnson BD, Shaw LJ, Pepine CJ, et al. Persistent chest pain predicts cardiovascular events in women without obstructive coronary artery disease: results from the NIH-NHLBI-sponsored Women's Ischaemia Syndrome Evaluation (WISE) study. *Eur Heart J* 2006;27:1408-15.
6. Gulati M, Cooper-DeHoff RM, McClure C, et al. Adverse cardiovascular outcomes in women with nonobstructive coronary artery disease: a report from the Women's Ischemia Syndrome Evaluation Study and the St James Women Take Heart Project. *Arch Intern Med* 2009;169:843-50.
7. Sedlak TL, Lee M, Izadnegahdar M, Merz CN, Gao M, Humphries KH. Sex differences in clinical outcomes in patients with stable angina and no obstructive coronary artery disease. *Am Heart J* 2013;166:38-44.
8. Min JK, Dunning A, Lin FY, et al. Age- and sex-related differences in all-cause mortality risk based on coronary computed tomography angiography findings results from the International Multicenter CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry) of 23,854 patients without known coronary artery disease. *J Am Coll Cardiol* 2011;58:849-60.
9. Nakazato R, Arsanjani R, Achenbach S, et al. Age-related risk of major adverse cardiac event risk and coronary artery disease extent and severity by coronary CT angiography: results from 15 187 patients from the International Multisite CONFIRM Study. *Eur Heart J Cardiovasc Imaging* 2014;15:586-94.
10. Chow BJ, Small G, Yam Y, et al. Incremental prognostic value of cardiac computed tomography in coronary artery disease using CONFIRM: Coronary computed tomography angiography evaluation for clinical outcomes: an International Multicenter registry. *Circ Cardiovasc Imaging* 2011;4:463-72.
11. Hadamitzky M, Achenbach S, Al-Mallah M, et al. Optimized prognostic score for coronary computed tomographic angiography: results from the CONFIRM registry (Coronary CT Angiography Evaluation For Clinical Outcomes: An International Multicenter Registry). *J Am Coll Cardiol* 2013;62:468-76.
12. Leipsic J, Taylor CM, Grunau G, et al. Cardiovascular risk among stable individuals suspected of having coronary artery disease with no modifiable risk factors: results from an international multicenter study of 5262 patients. *Radiology* 2013;267:718-26.
13. Leipsic J, Taylor CM, Gransar H, et al. Sex-based prognostic implications of nonobstructive coronary artery disease: results from the International Multicenter CONFIRM Study. *Radiology* 2014;273:393-400.
14. Min JK, Dunning A, Lin FY, et al. Rationale and design of the CONFIRM (COronary CT Angiography Evaluation For Clinical Outcomes: An International Multicenter) Registry. *J Cardiovasc Comput Tomogr* 2011;5:84-92.
15. Abbara S, Arbab-Zadeh A, Callister TQ, et al. SCCT guidelines for performance of coronary computed tomographic angiography: a report of the Society of Cardiovascular Computed Tomography Guidelines Committee. *J Cardiovasc Comput Tomogr* 2009;3:190-204.
16. Shaw LJ, Min JK, Narula J, et al. Sex differences in mortality associated with computed tomographic angiographic measurements of obstructive and nonobstructive coronary artery disease: an exploratory analysis. *Circ Cardiovasc Imaging* 2010;3:473-81.
17. Shaw LJ, Shaw RE, Merz CNB, et al. Impact of ethnicity and gender differences on angiographic coronary artery disease prevalence and in-hospital

mortality in the American College of Cardiology-National Cardiovascular Data Registry. *Circulation* 2008;117:1787-801.

18. Bairey Merz CN, Shaw LJ, Reis SE, et al. Insights from the NHLBI-Sponsored Women's Ischemia Syndrome Evaluation (WISE) Study: part II: gender differences in presentation, diagnosis, and outcome with regard to gender-based pathophysiology of atherosclerosis and macrovascular and microvascular cor. *J Am Coll Cardiol* 2006;47: S21-9.

19. Maddox TM, Stanislawski MA, Grunwald GK, et al. Nonobstructive coronary artery disease and risk of myocardial infarction. *JAMA* 2014;312:1754-63.

20. Han SH, Bae JH, Holmes DR Jr., et al. Sex differences in atheroma burden and endothelial function in patients with early coronary atherosclerosis. *Eur Heart J* 2008;29:1359-69.

21. Hulten E, Bittencourt MS, Singh A, et al. Coronary artery disease detected by coronary computed tomographic angiography is associated with intensification of preventive medical therapy

and lower low-density lipoprotein cholesterol. *Circ Cardiovasc Imaging* 2014;7:629-38.

22. Pursnani A, Celeng C, Schlett CL, et al. Use of coronary computed tomographic angiography findings to modify statin and aspirin prescription in patients with acute chest pain. *Am J Cardiol* 2016; 117:319-24.

KEY WORDS CAD, CT coronary angiography, sex differences