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Authors

Schulman-Marcus, Joshua
Hartaigh, Bríain Ó
Gransar, Heidi
et al.

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Sex-Specific Associations Between Coronary Artery Plaque Extent and Risk of Major Adverse Cardiovascular Events: from the CONFIRM Long-Term Registry

Joshua Schulman-Marcus, MD[#(a)], **Bríain 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, PhD**[(s)], and **James K. Min, MD**[(a)]

[(a)]Dalio Institute of Cardiovascular Imaging, Weill Cornell Medical College and New York Presbyterian Hospital, New York, NY [(b)]Department of Imaging, Cedars-Sinai Medical Center, Los Angeles, CA [(c)]Tennessee Heart and Vascular Institute, Hendersonville, TN [(d)]Capital Cardiology Associates, Albany, NY [(e)]Division of Cardiology, Deutsches Herzzentrum Munchen, Munich, Germany [(f)]Research Center, King Abdul Aziz Cardiac Center, National Guard Health Affairs, Riyadh, Saudi Arabia [(g)]Department of Medicine, Harbor UCLA Medical Center, Los Angeles, CA [(h)]University Hospital, Zurich, Switzerland [(i)]Department of Medicine, University of Erlangen, Erlangen, Germany [(j)]William Beaumont Hospital, Royal Oaks, MI [(k)]Cardiovascular Imaging Unit, Giovanni XXIII Hospital, Monastier, Treviso, Italy [(l)]Department of Medicine, Walter Reed Medical Center, Washington, DC, USA [(m)]Seoul National University Hospital, Seoul, South Korea [(n)]Department of Medicine and Radiology, University of British Columbia, Vancouver, BC, Canada [(o)]Department of Radiology, Medical University of Innsbruck, Innsbruck, Austria [(p)]Department of Cardiology at the Lady Davis Carmel Medical Center, The Ruth and Bruce Rappaport School of Medicine, Technion-Israel Institute of Technology, Haifa, Israel [(q)]Department of Clinical Sciences and Community Health, University of Milan, Centro Cardiologico Monzino, IRCCS, Milan, Italy [(r)]Department of Surgery, Curry Cabral Hospital, Lisbon, Portugal [(s)]Division of Cardiology, Emory University School of Medicine, Atlanta, GA

[#] These authors contributed equally to this work.

Abstract

Objective—To examine sex-specific associations, if any, between per-vessel CAD extent and the risk of major adverse cardiovascular events (MACE) over a five-year study duration.

Address for correspondence: James K. Min, MD, FACC, FSCCT, 413 East 69th Street, Suite 108, Dalio Institute of Cardiovascular Imaging, Weill Cornell Medical College and the New York-Presbyterian Hospital, New York, NY 10021, Phone: 646-962-6268, jkm2001@med.cornell.edu.

All other authors have no relevant disclosures.

Background—The presence and extent of coronary artery disease (CAD) diagnosed by coronary computed tomography angiography (CCTA) is associated with increased short-term mortality and MACE. Nevertheless, some uncertainty remains regarding the influence of gender on these findings.

Methods—5,632 patients (mean age 60.2 + 11.8 years, 36.5% female) from the CONFIRM (COronary CT Angiography EvaluatioN For Clinical Outcomes: An InteRnational Multicenter) registry were followed over the course of 5 years. Obstructive CAD was defined as ≥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 (MI).

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 non-obstructive CAD (HR 2.16 for women, 2.56 for men, p<0.001 for both), obstructive one-vessel CAD (HR 3.69 and 2.66, p<0.001), two-vessel CAD (HR 3.92 and 3.55, p<0.001) and three-vessel/left-main CAD (HR 5.94 and 4.44, p<0.001). Further exploratory analyses of atherosclerotic burden did not identify gender-specific patterns predictive of MACE.

Conclusion—In a large prospective CCTA cohort followed long-term, we did not observe an interaction of gender 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 CCTA for the risk of MACE in both women and men.

Keywords

CT coronary angiography; Gender differences; CAD

Introduction

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 that is present even among women with apparently normal or non-obstructive 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.

Coronary computed tomography angiography (CCTA) 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 two-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 non-obstructive 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 literature has been unable to account for the risk beyond three years. Thus, an additional question is whether sex-specific differences in risk persist or attenuate over a longer-term duration of follow-up. Using data from a large prospective CCTA registry, we therefore set out to determine the sex-specific relationships, if any, between the extent of CAD and risk of MACE over a five-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 CCTA. The rationale, design, site-specific patient characteristics, and follow-up durations have been described previously.(14) In brief, this study screened a total of 12,086 patients with five year follow-up data who underwent CCTA at 17 centers in 9 countries (Austria, Canada, Germany, Israel, Italy, Portugal, South Korea, Switzerland, and United States) between 2002 and 2009. Individuals with known CAD at the time of CCTA, 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 CCTA (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 employed at 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 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 non-anginal, 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 (ACEi/ARB), statin) were also collected.

CCTA Performance and Interpretation

Standardized protocols for image acquisition, as defined by the Society of Cardiovascular Computed Tomography, were employed at all participating sites.(15) Specific details of CCTA 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), or moderate (50-69% luminal stenosis) or severe (≥70% luminal stenosis). For the primary analysis, CAD extent was defined by ≥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 three-vessel obstructive coronary artery disease.

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 over the course of 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 non-fatal myocardial infarction. 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' IRB. 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 ± standard deviation, unless specified otherwise. Categorical variables were compared with the chi-squared test, while continuous variables were compared with Student's unpaired t-test or Wilcoxon non-parametric tests where appropriate. Kaplan Meier curves with log-rank test 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 (HR) with 95% confidence intervals (95% CI). 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

employed 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 so as 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 one 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 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 CCTA characteristics with the study outcomes. A two-tailed p-value <0.05 was considered statistically significant. All statistical analyses were conducted using STATA version 12 (College Station, TX).

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 regards to the extent of visualized atherosclerosis, men had increased number of vessels with obstructive CAD, while 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, ACEi/ARB 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 0.71-1.04, 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 towards 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 CCTA) 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 CCTA and heightened risk of MACE over a five year time period among women and men. Similar findings were observed for the secondary outcome of nonfatal MI in both sexes, while 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 CCTA for both women and men.

The current study observations are fitting with previous observations – that is, while obstructive CAD detected by CCTA 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 and colleagues found that while increased mortality risk was noted in both men and women with non-obstructive, 1-vessel, and 2-vessel obstructive disease, in women 3-vessel/LM obstructive disease was associated with an even higher mortality risk as compared with men (HR 4.21 compared to 3.27).(8) In a smaller single-center cohort of 1,127 patients (57% women), Shaw and colleagues also observed that while higher obstructive CAD burden by CCTA was associated with increased mortality in both sexes, women with 3-vessel obstructive/LM disease had a higher risk of death compared with men.(16) These findings concord with prior registry data demonstrating higher rates of in-hospital mortality in women with obstructive CAD.(17) Our study extends the prior literature by observing the attenuation of the aforementioned sex-specific differences in MACE over a longer duration of time. However, our study emphasizes the core finding of the prior literature that the extent of obstructive CAD detected by CCTA, regardless of sex, is the most significant predictor of increased MACE risk.

The present study findings are also in line with those of Leipsic and colleagues who observed an association between increased risk of MACE and non-obstructive CAD by

CCTA and no significant disparity between women and men.(13) 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 non-obstructive CAD by CCTA for age and CAD risk factors. Following this approach, the annual death, MI, or MACE rates for both women and men with non-obstructive CAD were equivalent. This analysis stands in contrast to other CCTA and retrospective invasive studies suggesting a unique adverse prognosis for non-obstructive CAD by CCTA in women as compared with men.(1,6,7,18) Our study re-enforces the findings of Leipsic and colleagues by observing a similar attenuation in sex-specific MACE risk for non-obstructive CAD over a longer time frame and with a larger number of events available for analysis. Further still, the present study highlights that non-obstructive 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 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, while 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 CCTA, and whether these are associated with a higher risk of clinical events.

Several limitations of this study need to be emphasized. Although CONFIRM represents the largest consecutive cohort of patients undergoing CCTA, 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 confidence intervals observed for some of the risk estimates reported in this study. A further and important limitation is that data were not collected on post-CCTA 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 CCTA with long-term outcomes data available.

In conclusion, the present study emphasized the clear prognostic significance of per-vessel obstructive CAD extent as detected by CCTA over a five-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 CCTA.

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Abbreviations

ACEi/ARB	angiotensin-converting enzyme/angiotensin receptor blocker
CCTA	coronary computed tomographic angiography
CP	calcified plaque
CONFIRM	Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter)
HR	hazard ratio
LM	left main
MACE	major adverse clinical events
MI	myocardial infarction
NCP	noncalcified plaque
PCP	partially calcified plaque

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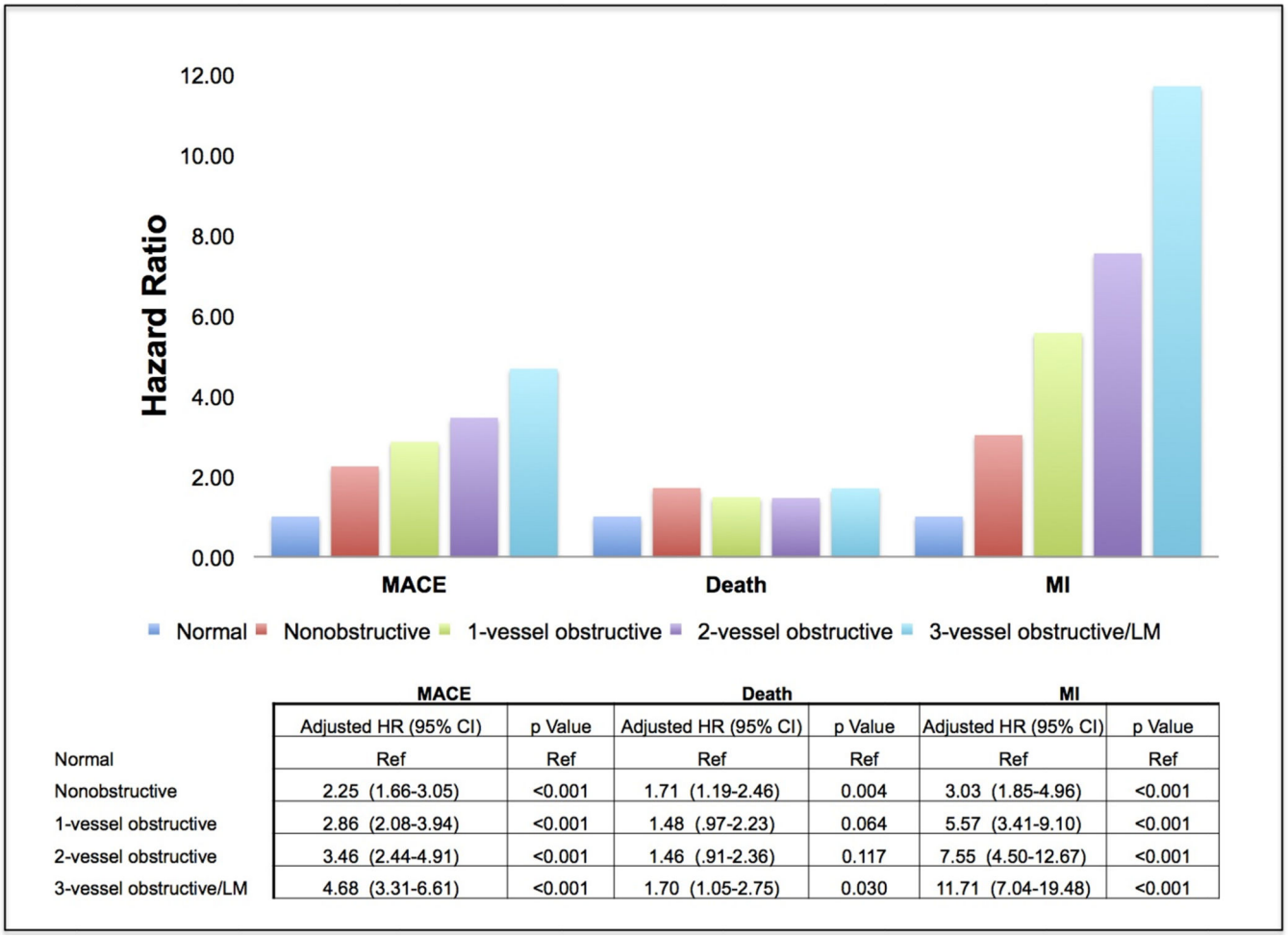
Perspectives

Competency in Medical Knowledge

Greater per-vessel extent of obstructive CAD as detected by CCTA is associated with greater MACE risk over a five-year duration. As there was no observed interaction for this association, this holds true of CAD detected in both women and men.

Translational Outlook

While 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 CCTA, and whether these are associated with a higher risk of clinical events.



	MACE		Death		MI	
	Adjusted HR (95% CI)	p Value	Adjusted HR (95% CI)	p Value	Adjusted HR (95% CI)	p Value
Normal	Ref	Ref	Ref	Ref	Ref	Ref
Nonobstructive	2.25 (1.66-3.05)	<0.001	1.71 (1.19-2.46)	0.004	3.03 (1.85-4.96)	<0.001
1-vessel obstructive	2.86 (2.08-3.94)	<0.001	1.48 (.97-2.23)	0.064	5.57 (3.41-9.10)	<0.001
2-vessel obstructive	3.46 (2.44-4.91)	<0.001	1.46 (.91-2.36)	0.117	7.55 (4.50-12.67)	<0.001
3-vessel obstructive/LM	4.68 (3.31-6.61)	<0.001	1.70 (1.05-2.75)	0.030	11.71 (7.04-19.48)	<0.001

Figure 1. Multivariate Cox Regression Model for Risk of MACE

Increasing number of vessels with obstructive CAD associated with a monotonic rise in MACE risk.

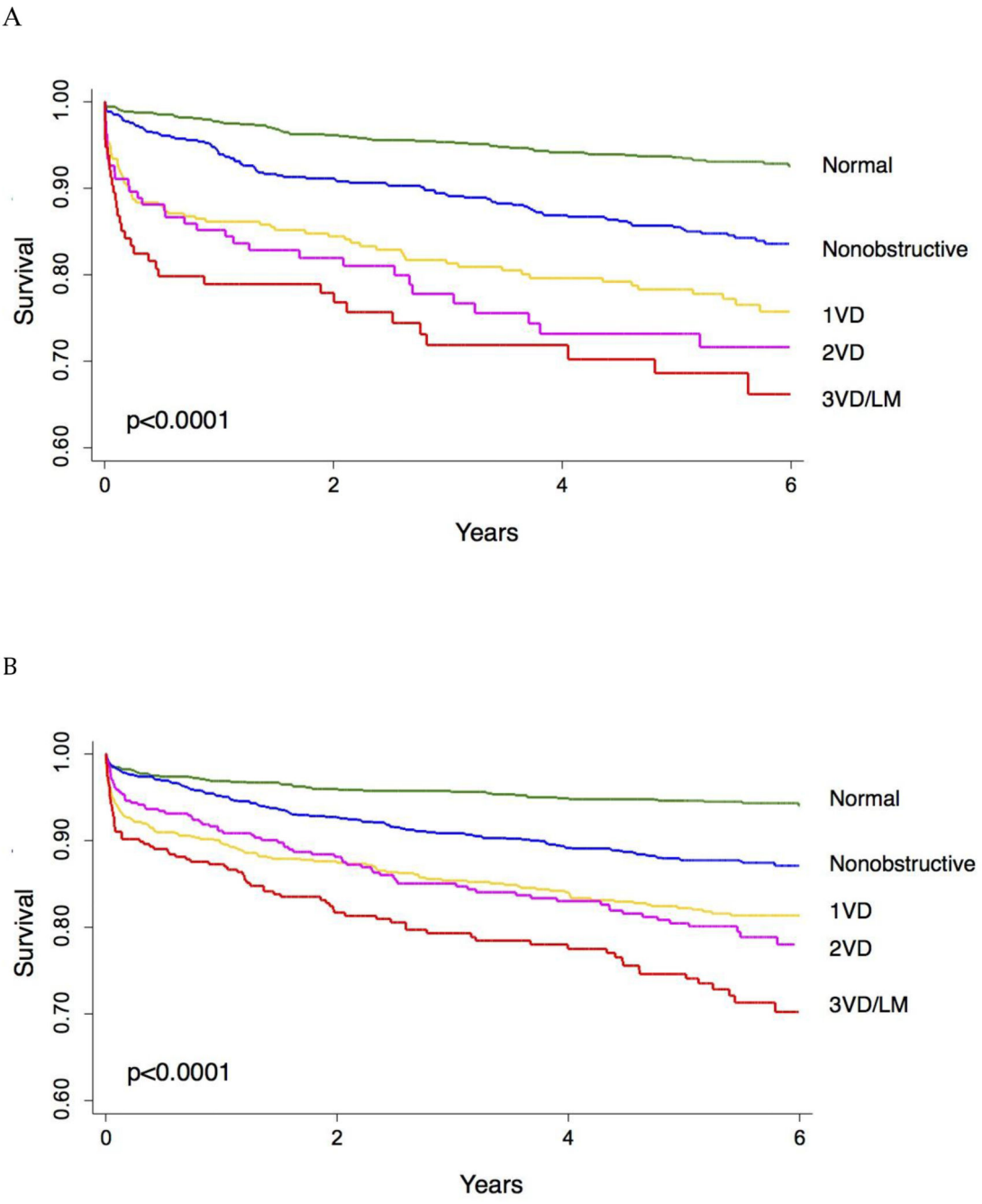


Figure 2. Kaplan Meier Event-Free Survival Curves

Increased per-vessel CAD extent was associated with greater MACE risk over time in (a) women and (b) men ($p<0.001$ by log-rank test for both).

Table 1

Study Demographics

	Overall (n=5632)	Women (n=2056)	Men (n=3576)	p-value
Age, years ± SD	60.2±11.8	62.4±11.4	58.9±11.8	<0.001
Cardiac risk factors, n (%)				
Hypertension	3079 (54.9)	1234 (60.3)	1845 (51.9)	<0.001
Hyperlipidemia	3031 (54.1)	1133 (55.3)	1898 (53.3)	0.15
Diabetes	961 (17.1)	358 (17.5)	603 (16.9)	0.61
Current smoker, n (%)	1193 (21.4)	306 (15.0)	887 (25.0)	<0.001
Family history of premature CAD	1662 (29.9)	674 (33.2)	988 (28.0)	<0.001
Chest Pain, n (%)				<0.001
Typical	739 (14.8)	292 (15.8)	447 (14.1)	
Atypical	1625 (32.4)	651 (35.3)	974 (30.8)	
Non-cardiac	664 (13.3)	298 (16.2)	366 (11.6)	
Asymptomatic	1983 (39.6)	603 (32.7)	1380 (43.6)	
Dyspnea, n (%)	734 (16.8)	328 (20.2)	406 (14.7)	<0.001
Baseline medication use				
ASA	1443 (32.6)	491 (30.5)	952 (33.8)	0.02
Beta blocker	1289 (29.1)	498 (30.9)	791 (28.1)	0.05
ACE inhibitor/ARB	1273 (28.8)	439 (27.3)	834 (29.6)	0.1
Statin	1603 (36.0)	588 (36.3)	1015 (35.9)	0.78
Extent of CAD by CCTA				
Normal	1844 (32.7)	878 (42.7)	966 (27.0)	<0.001
Non-obstructive CAD	1690 (30.0)	611 (29.7)	1079 (30.2)	0.72
1-vessel obstructive CAD	1094 (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 (<90d)	1243 (22.1)	345 (16.8)	898 (25.1)	<0.001

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
Female gender	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	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		
Non-obstructive 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		

*Hazard ratios shown only for variables retained.

Table 3

Adjusted hazards of MACE and MACE Components by CAD Extent, stratified by gender

	Women		Men	
	Adjusted HR (95% CI)	p Value	Adjusted HR (95% CI)	p Value
Total MACE				
Normal	Ref	Ref	Ref	Ref
Non-obstructive	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
Non-obstructive	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
Non-obstructive	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

Table 4

Plaque patterns and Adjusted Risk of MACE, stratified by gender

	Demographics			Adjusted HR* (95% CI)			
	Women	Men	p-value	Women	p-value	Men	p-value
Per-patient							
Coronary artery calcium score (%)			<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, n (%)			<0.001				
No plaque	878 (42.7)	966 (27.0)		1.00	1.00	1.00	1.00
Mild (1%-49%)	611 (29.7)	1079 (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, n (%)							
Right coronary artery	258 (13.0)	726 (21.1)	<0.001	1.99(1.39-2.84)	<0.001	1.62(1.27-2.07)	<0.001
Left anterior descending artery	436 (21.5)	1176(33.2)	<0.001	2.54(1.86-3.47)	<0.001	1.45 (1.15-1.83)	0.002
Left circumflex 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
Left main	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, median (IQR)							
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. Segments with NCP, n (%)			<0.001				
0-segments	1668 (82.8)	2535 (74.5)		1.00	1.00	1.00	1.00
1-segments	205 (10.2)	415 (12.2)		1.14 (0.75-1.74)	0.53	1.09 (0.79-1.52)	0.59
2-segments	72 (3.6)	195 (5.7)		1.21 (0.62-2.39)	0.58	1.34 (0.89-2.01)	0.17
≥3-segments	69 (3.4)	257 (7.6)		1.12 (0.54-2.30)	0.77	1.02 (0.69-1.49)	0.93
No. Segments with PCP, n (%)			<0.001				
0-segments	1632 (81.0)	2289 (67.3)		1.00	1.00	1.00	1.00
1-segments	189 (9.4)	401 (11.8)		1.24 (0.81-1.90)	0.32	1.02 (0.73-1.42)	0.93
2-segments	76 (3.8)	259 (7.6)		1.45 (0.81-2.60)	0.21	1.13 (0.78-1.65)	0.51

	Demographics			Adjusted HR* (95% CI)			
≥3-segments	117 (5.8)	453 (13.3)		2.09 (1.35-3.25)	0.001	1.12 (0.83-1.50)	0.46
No. Segments with CP, n (%)†			<0.001				
0-segments	1526 (75.8)	2148 (63.1)		1.00	1.00	1.00	1.00
1-segments	199 (9.9)	436 (12.8)		1.52 (0.99-2.36)	0.06	0.94 (0.67-1.34)	0.74
2-segments	94 (4.7)	265 (7.8)		1.76 (1.02-3.05)	0.04	0.93 (0.62-1.39)	0.72
≥3-segments	195 (9.7)	553 (16.2)		2.39 (1.66-3.45)	<0.001	1.11 (0.84-1.47)	0.47

Abbreviations: NCP=Noncalcified plaque, PCP = Partially calcified plaque, CP = calcified plaque

*Adjusted for age, hypertension, diabetes, smoking, symptoms, and use of ACE inhibitor/ARB.

†p for interaction 0.004