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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

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Objectives We examined mortality in relation to coronary artery disease (CAD) as assessed by ≥64-detector row coronary computed tomography angiography (CCTA).

Background Although CCTA has demonstrated high diagnostic performance for detection and exclusion of obstructive CAD, the prognostic findings of CAD by CCTA have not, to date, been examined for age- and sex-specific outcomes.

Methods We evaluated a consecutive cohort of 24,775 patients undergoing ≥64-detector row CCTA between 2005 and 2009 without known CAD who met inclusion criteria. In these patients, CAD by CCTA was defined as none (0% stenosis), mild (1% to 49% stenosis), moderate (50% to 69% stenosis), or severe (≥70% stenosis). CAD severity was judged on a per-patient, per-vessel, and per-segment basis. Time to mortality was estimated using multivariable Cox proportional hazards models.

Results At a 2.3 ± 1.1-year follow-up, 404 deaths had occurred. In risk-adjusted analysis, both per-patient obstructive (hazard ratio [HR]: 2.60; 95% confidence interval [CI]: 1.94 to 3.49; $p < 0.0001$) and nonobstructive (HR: 1.60; 95% CI: 1.18 to 2.16; $p = 0.002$) CAD conferred increased risk of mortality compared with patients without evident CAD. Incident mortality was associated with a dose-response relationship to the number of coronary vessels exhibiting obstructive CAD, with increasing risk observed for nonobstructive (HR: 1.62; 95% CI: 1.20 to 2.19; $p = 0.002$), obstructive 1-vessel (HR: 2.00; 95% CI: 1.43 to 2.82; $p < 0.0001$), 2-vessel (HR: 2.92; 95% CI: 2.00 to 4.25; $p < 0.0001$), or 3-vessel or left main (HR: 3.70; 95% CI: 2.58 to 5.29; $p < 0.0001$) CAD. Importantly, the absence of CAD by CCTA was associated with a low rate of incident death (annualized death rate: 0.28%). When stratified by age <65 years versus ≥65 years, younger patients experienced higher hazards for death for 2-vessel (HR: 4.00; 95% CI: 2.16 to 7.40; $p < 0.0001$ vs. HR: 2.46; 95% CI: 1.51 to 4.02; $p = 0.0003$) and 3-vessel (HR: 6.19; 95% CI: 3.43 to 11.2; $p < 0.0001$ vs. HR: 3.10; 95% CI: 1.95 to 4.92; $p < 0.0001$) CAD. The relative hazard for 3-vessel CAD (HR: 4.21; 95% CI: 2.47 to 7.18; $p < 0.0001$ vs. HR: 3.27; 95% CI: 1.96 to 5.45; $p < 0.0001$) was higher for women as compared with men.

Conclusions Among individuals without known CAD, nonobstructive and obstructive CAD by CCTA are associated with higher rates of mortality, with risk profiles differing for age and sex. Importantly, absence of CAD is associated with a very favorable prognosis. (J Am Coll Cardiol 2011;58:849–60) © 2011 by the American College of Cardiology Foundation

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Abbreviations and Acronyms

CAD = coronary artery disease

CCTA = coronary computed tomography angiography

CI = confidence interval

CT = computed tomography

D-F = Diamond-Forrester

HR = hazard ratio

LAD = left anterior descending artery

LCx = left circumflex artery

LM = left main artery

RCA = right coronary artery

Coronary computed tomography angiography (CCTA) is a recently introduced noninvasive imaging modality that permits accurate detection and exclusion of coronary artery disease (CAD) (1–3). Prior studies have examined the prognostic significance of CAD detection by CCTA, but have been generally limited to single centers and small cohorts (4–14). Given the enormous evidence base on prognosis with other cardiac imaging modalities, the development of "real world" effectiveness data that are acquired across diverse healthcare settings and populations is a requisite criterion to guide appropriate application of CCTA. Fundamental to the use of CCTA is its ability to risk stratify younger and older women and men. To date, however, age- and sex-specific outcomes of CCTA-identified CAD have been absent or exploratory (15). To that end, we examined the predictive value of nonobstructive and obstructive CAD from a large cohort of 23,854 patients without known CAD for intermediate-term mortality risk and further investigated the relationship of mortality risk to CAD as stratified by age and sex.

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Methods

Patients. CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry) enrolled consecutive adults ≥18 years of age between 2005 and 2009 who underwent ≥64-detector row CCTA for suspected CAD at 12 centers (Cedars Sinai Medical Center, Los Angeles, California; Harbor UCLA Medical Center, Los Angeles, California; Tennessee Heart and Vascular Institute, Hendersonville, Tennessee; Capital Cardiology Associates, Albany, New York; University of Munich, Munich, Germany; Ottawa Heart Institute, Ontario, Canada; Henry Ford Medical Center, Detroit, Michigan; Yonsei Medical Center, Seoul, Korea, University Hospital, Zurich, Switzerland; William Beaumont Hospital, Royal Oak, Michigan; Walter Reed Army Medical Center, Washington, DC; and University Hospital of Parma, Parma, Italy). Institutional review board approval was obtained at each center. Individuals with known CAD, as defined by prior myocardial infarction or coronary revascularization, were excluded from the present study analysis.

All patients were in normal sinus rhythm and were capable of the breath hold needed for CCTA. Patients with heart rates >70 beats/min were given oral or intravenous metoprolol as per local site protocol. All centers used intravenous metoprolol at the time of CCTA performance to lower heart rates below 70 beats/min. If the patient's heart rate did not drop below 70 beats/min, then CCTA was performed at the lowest heart rate.

Before the initiation of the scan, we prospectively collected information on the presence of categorical cardiac risk factors in each individual. Systemic arterial hypertension was defined as a documented history of high blood pressure or treatment with antihypertensive medications. Diabetes mellitus was defined by diagnosis of diabetes made previously by a physician and/or use of insulin or oral hypoglycemic agents. Dyslipidemia was defined as known but untreated dyslipidemia or current treatment with lipid-lowering medications. A positive smoking history was defined as current smoking or cessation of smoking within 3 months of testing. Family history of coronary heart disease was determined by patient query. Symptom presentation was classified into 1 of 4 categories: typical chest pain, atypical chest pain, noncardiac pain, or dyspnea (16).

Scan protocol and image reconstruction. The CCTA scans were performed on a variety of different scanner platforms (Lightspeed VCT, GE Healthcare, Milwaukee, Wisconsin; Somatom Definition CT, Siemens, Erlangen, Germany; Somatom Definition Flash CT, Siemens). Im-

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aging of a test bolus of contrast was performed at 2 mm superior to the take-off of the left main coronary artery for precise timing of contrast injection. During the CCTA acquisition, 80 to 140 ml of iodinated contrast (Isovue 370, Bracco Diagnostics, Princeton, New Jersey; Omnipaque, GE Healthcare, Princeton, New Jersey; Visipaque, GE Healthcare, Princeton, New Jersey; or Imeron 350; Bracco Atlana Pharma, Konstanz, Germany) was injected, followed by a 50-ml saline flush. Contrast timing was performed to optimize uniform contrast enhancement of the coronary arteries. The scan parameters were as follows: 64 × 0.625/0.750-mm collimation, tube voltage 100 or 120 mV, effective 400 to 650 mA. Dose reduction strategies—including electrocardiogram-gated tube current modulation, reduced tube voltage, and prospective axial triggering—were used whenever feasible. Estimated radiation dose for CCTA ranged from 3 to 18 mSv.

Helical or axial scan data were obtained with retrospective or prospective electrocardiogram gating, respectively. Images were reconstructed immediately after completion of the scan to identify motion-free coronary artery images. Optimal phase reconstruction was assessed by comparison of different phases, if available, and the phase with the least amount of coronary artery motion was chosen for analysis. Multiple phases were utilized for image interpretation if minimal coronary artery motion was different for different arteries. CCTAs were evaluated by an array of post-processing imaging techniques, including axial, multiplanar reformat, maximum-intensity projection, and short-axis cross-sectional views. 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 non-evaluable segment was scored similarly to the most proximal segment that was evaluable.

Noninvasive coronary artery analysis by CCTA. All scans were analyzed by Level III–equivalent cardiologists with experience interpreting several thousand CCTA scans. Interpretation of CCTA was uniform across all study sites, with coronary segments visually scored for the presence of coronary plaque using a 16-segment coronary artery model in an intent-to-diagnose fashion. In each coronary artery segment, coronary atherosclerosis was defined as tissue structures >1 mm^2 that existed either within the coronary artery lumen or adjacent to the coronary artery lumen that could be discriminated from surrounding pericardial tissue, epicardial fat, or the vessel lumen itself. Coronary atherosclerotic lesions were quantified for stenosis by visual estimation. Luminal-diameter stenosis severity was scored as none (0% luminal stenosis), mild (1% to 49% luminal stenosis), moderate (50% to 69% luminal stenosis), or severe (≥70% luminal stenosis). Percent obstruction of coronary artery lumen was based on a comparison of the luminal diameter of the segment exhibiting obstruction to the luminal diameter of the most normal-appearing site immediately proximal to the plaque. In instances in which plaque was highly calcified, 2-dimensional oblique images were also visualized without maximal-intensity projection (i.e., 0.625- to 0.75-mm isotropic voxel resolution) or multiplanar reformats with cross-sectional views to minimize partial-volume averaging artifact of calcium.

Plaque severity was graded on a per-patient, per-vessel, and per-segment level. Per-patient maximal plaque severity was defined by the maximal intraluminal stenosis in any of the coronary segments at the ≥50% stenosis or ≥70% stenosis threshold.

For purposes of classification for per-vessel analyses, we considered 4 arterial territories: left main artery (LM), left anterior descending artery (LAD), left circumflex artery (LCx), and right coronary artery (RCA). Obstructive CAD in the diagonal branches, obtuse marginal branches, and posterolateral branches was considered as part of the LAD, LCx, and RCA system, respectively. The posterior descending artery was considered as part of the RCA or LCx system, depending on the coronary artery dominance. A ≥50% stenosis in the LM was considered obstructive in all models. Per-vessel CAD severity was defined by ≥50% stenosis or ≥70% stenosis in 0, 1, 2, or 3 coronary artery vessels.

Per-segment analysis was judged for individual coronary artery segments that included a 16-segment model, as we have previously described (4). Similarly, the incremental hazards of CAD for increasing numbers of segments were calculated as clinical coronary artery plaque scores, as we have previously described (4). 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. We further examined risk in association with any severe proximal stenosis in the LAD, LCx, or RCA vessels. Finally, we examined risk for any plaque within the LM.

Follow-up. The primary endpoint was time to death from all causes. Follow-up procedures were approved by all study centers' institutional review boards. Death status for non-U.S. centers was gathered by clinical visits, telephone contacts, and questionnaires sent by mail, with verification of all reported events by hospital records or direct contact with a patient's attending physician. Death status for U.S. centers was ascertained either by query of the Social Security Death Index or by scripted interview by experienced physician and/or nurse study investigators.

Statistical analysis. SPSS version 12.0 (SPSS Inc., Chicago, Illinois) and SAS version 9.2 (SAS Institute, Cary, North Carolina) were used for all statistical analyses.

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Table 1 Demographics of the Entire Registry and Study Cohort

	Entire Registry (n = 27,125)	Study Cohort (n = 23,854)	Excluded Patients (n = 3,271)	p Value
Age, yrs	58 ± 13	57 ± 13	60 ± 13	<0.0001
Male	14,997 (55)	12,922 (54)	2,075 (64)	<0.0001
Diabetes	4,067 (15)	3,451 (15)	616 (19)	0.0002
Family history of premature CAD	9,849 (37)	8,624 (37)	1,225 (38)	0.1614
Hyperlipidemia	14,906 (56)	12,807 (54)	2,099 (64)	<0.0001
Hypertension	13,582 (51)	11,646 (49)	1,936 (59)	<0.0001
Current smoker	4,994 (19)	4,251 (18)	743 (23)	<0.0001
History of PAD/CVD	485 (4)	369 (4)	116 (8)	<0.0001
Chest pain†				<0.0001
Typical angina	3,556 (16)	3,152 (15)	404 (21)	
Atypical angina	8,860 (39)	8.343 (40)	517 (27)	
Noncardiac	2,699 (12)	2,483 (12)	216 (11)	
Asymptomatic	7,796 (34)	7,009 (33)	787 (41)	
Pre-test CAD likelihood†				<0.0001
Low	6,477 (28)	6,060 (29)	417 (22)	
Intermediate	14,137 (62)	12,978 (62)	1,159 (61)	
High	2,153 (9)	1,824 (9)	329 (17)	

Values are mean ± SD or n (%). *p value for differences in percentages for study cohort versus excluded patients. †Typicality of chest pain and pre-test likelihood of CAD missing in 518 patients.
CAD = coronary artery disease; CVD = cardiovascular disease; PAD = peripheral arterial disease.

Categorical variables are presented as frequencies and continuous variables as mean ± SD. Variables were compared with chi-square statistic for categorical variables and by Student unpaired *t* test for continuous variables. Time to death from all causes and death rates were calculated using univariable Cox proportional hazards models. In each case, the proportional hazards assumption was met. Adjusted models were also devised including multivariable stepwise models adjusting for baseline demographics, cardiac risk factors, typicality of angina, and pre-test likelihood of obstructive CAD. Adjusted models were also developed to test first-order interactions related to age, sex, and study site. A hazard ratio (HR) and 95% confidence interval (CI) were calculated from the Cox models. A 2-tailed $p < 0.05$ was considered statistically significant.

Results

Clinical characteristics of the study cohort. Amongst 27,125 consecutive patients undergoing CCTA at 12 centers for whom per-segment CAD data were available, 2,350 patients with a history of myocardial infarction, coronary revascularization, and cardiac transplant were excluded. The final analysis cohort consisted of 24,775 patients. Follow-up was obtained for 23,854 patients (96.3%), with 921 patients

Table 2 Clinical Characteristics of Study Group Stratified by Normal, Nonobstructive, and Obstructive CAD by CCTA

	Normal (n = 10,146)	Nonobstructive CAD (n = 8,114)	Obstructive CAD (n = 5,594)	p Value for Trend
Male	4,528 (44.73)	4,849 (60.00)	3,545 (63.70)	<0.0001
Diabetes	985 (9.80)	1,202 (14.94)	1,264 (22.79)	<0.0001
Hypertension	4,187 (41.75)	4,139 (51.81)	3,320 (59.98)	<0.0001
Dyslipidemia	4,611 (45.99)	4,647 (57.84)	3,549 (64.03)	<0.0001
Family history of premature CAD	3,417 (34.330	2,810 (35.32)	2,397 (43.53)	<0.0001
Current smoking	1,742 (17.34)	1,269 (15.83)	1,240 (22.35)	<0.0001
Chest pain typicality*				<0.0001
Typical	1,332 (14.17)	820 (12.01)	1,000 (21.03)	
Atypical	4,236 (45.05)	2,512 (36.78)	1,595 (33.55)	
Noncardiac	1,059 (11.26)	733 (10.73)	691 (14.54)	
Asymptomatic	2,776 (29.52)	2,765 (40.48)	1,468 (30.88)	
Pre-test CAD likelihood				<0.0001
Low	3,249 (34.78)	1,923 (28.31)	888 (18.78)	
Intermediate	5,618 (60.14)	4,293 (63.21)	3,067 (64.86)	
High	474 (5.07)	576 (8.48)	774 (16.37)	

Values are n (%). *Chest pain typicality and pre-test likelihood of CAD missing in 2,867 patients.
CAD = coronary artery disease; CCTA = coronary computed tomography angiography.

Table 3 Clinical Characteristics Associated With Mortality

Variable	Univariate HR (95% CI)	p Value
Age	1.09 (1.08–1.10)	<0.0001
Male	1.05 (0.87–1.28)	0.6021
Diabetes	2.13 (1.71–2.65)	<0.0001
Hypertension	1.93 (1.57–2.37)	<0.0001
Hyperlipidemia	0.71 (0.59–0.87)	0.0007
Current smoking	1.47 (1.17–1.85)	0.0009
Family history of premature CAD	1.11 (0.90–1.36)	0.3401
Pre-test CAD likelihood	1.20 (0.996–1.45)	0.0547

CAD = coronary artery disease; CI = confidence interval; HR = hazard ratio.

lost to follow-up. The study cohort was middle-aged (age 57 ± 13 years, 54% male) with a high prevalence of cardiovascular risk factors and symptoms. They presented with typical or atypical angina in the majority of cases, with the majority of individuals having intermediate or high pre-test likelihood of obstructive CAD. Excluded patients had a higher pre-test likelihood of CAD (Table 1).

Clinical characteristics associated with CAD and mortality. Survival was examined after a mean follow-up of 2.3 ± 1.1 years (median 2.1 years; interquartile range: 1.5 to 3.1 years), at which point 404 deaths were recorded. Increasing severity of CAD was associated with male sex, diabetes, hypertension, dyslipidemia, family history of CAD, current smoking, typical angina, and high pre-test likelihood of CAD ($p < 0.0001$ for all) (Table 2). In univariable Cox proportional hazards models, increased hazard for death was associated with advanced age, diabetes, hypertension, untreated dyslipidemia, and current smoking, but not family history of CAD or pre-test CAD likelihood (Table 3).

CCTA findings among those who lived versus died. As compared with patients who were alive at follow-up, patients who died had significantly more severe coronary artery stenoses in the majority of coronary segments (Table 4).

Impact of per-patient, per-vessel, and per-segment CAD severity by CCTA on death from all causes. In both univariable as well as multivariable Cox regression analysis considering age and CAD risk factors, all-cause mortality was predicted by maximal per-patient nonobstructive and obstructive CAD, whether using a definition of obstructive CAD as 1% to 49% or 1% to 69% stenosis (Table 5, Fig. 1).

By both univariable and multivariable Cox models, per-vessel assessment of obstructive CAD demonstrated a dose-response relationship for increased hazards for death for 1-vessel, 2-vessel, 3-vessel, or LM CAD (Table 5, Fig. 2). Similarly, in both univariable and multivariable Cox regression analysis, on a per-segment basis, higher rates of mortality were associated with greater numbers of segments with plaque, with stenosis-adjusted segments with plaque, with any severe proximal stenosis, and with any plaque within the LM (Table 5).

Sixty-six deaths (0.65%) occurred in patients without evident CAD by CCTA (n = 10,146; 43%), resulting in a mean annualized death rate of 0.28%. In additional analyses of patients undergoing CCTA followed for ≥4 years (n = 1,816) without evidence by CCTA (n = 1,009), annualized death rates were 0.22%.

Age- and sex-stratified impact of CCTA-visualized CAD on death from all causes. Individuals <65 years of age had lower pre-test probability of CAD than those ≥65 years of

Table 4 Coronary Artery Stenosis Severity by Segment For Individuals Who Lived Versus Died

	Alive (n = 23,450)			Dead (n = 404)			p Value	
Coronary Segment	n	% With CAD	Stenosis Score	n	% With CAD	Stenosis Score	Stenosis Score	% With CAD
LM	3,257	14	0.16 ± 0.43	107	27	0.34 ± 0.61	<0.0001	<0.0001
LAD								
Proximal	9,539	41	0.55 ± 0.76	259	68	1.11 ± 1.00	<0.0001	<0.0001
Mid	7,407	33	0.49 ± 0.80	195	51	0.90 ± 1.06	<0.0001	<0.0001
Distal	1,811	9	0.12 ± 0.43	59	18	0.24 ± 0.60	<0.0001	<0.001
Diagonal artery 1	2,560	12	0.18 ± 0.55	77	22	0.37 ± 0.81	<0.0001	<0.0001
Diagonal artery 2	799	5	0.08 ± 0.35	15	8	0.16 ± 0.59	0.0016	0.1034
LCx								
Proximal	4,459	20	0.26 ± 0.59	158	41	0.65 ± 0.94	<0.0001	<0.0001
Distal	1,763	9	0.12 ± 0.45	66	21	0.33 ± 0.74	<0.0001	<0.0001
Obtuse marginal 1	1,768	8	0.12 ± 0.47	55	16	0.29 ± 0.74	<0.0001	<0.0001
Obtuse marginal 2	468	5	0.08 ± 0.37	16	12	0.19 ± 0.60	0.0002	0.0012
Right coronary artery								
Proximal	5,424	24	0.32 ± 0.65	181	48	0.78 ± 0.99	<0.0001	<0.0001
Mid	4,157	19	0.27 ± 0.65	143	40	0.66 ± 0.96	<0.0001	<0.0001
Distal	2,159	11	0.15 ± 0.48	61	21	0.27 ± 0.62	<0.0001	<0.0001
Right PL artery	123	1	0.02 ± 0.18	5	8	0.10 ± 0.35	0.0006	<0.0001
Left PL artery	277	2	0.03 ± 0.25	9	5	0.05 ± 0.22	0.4342	0.0389
Posterior descending artery	956	5	0.07 ± 0.35	48	14	0.23 ± 0.63	<0.0001	<0.0001

CAD = coronary artery disease; LAD = left anterior descending artery; LCx = left circumflex artery; LM = left main artery; PL = posterolateral.

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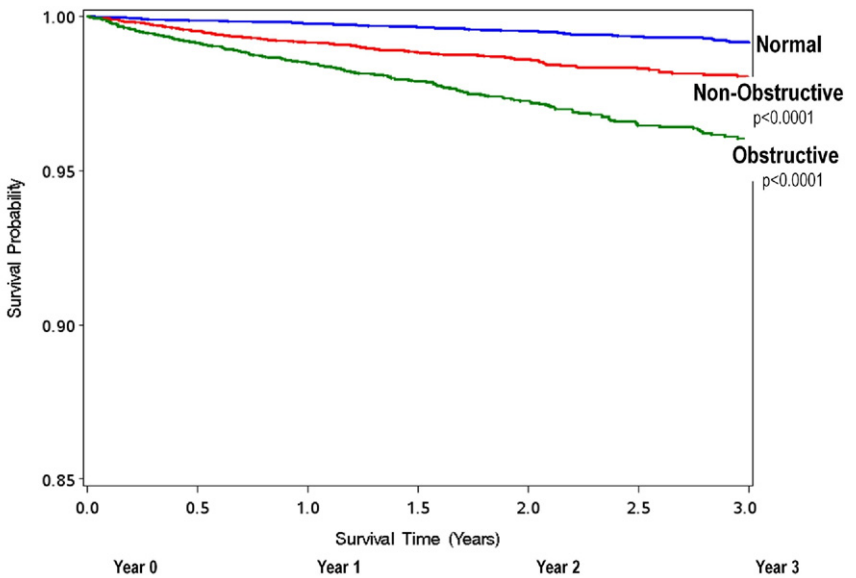
Table 5 Univariable and Adjusted Hazard Ratios for All-Cause Mortality by Per-Patient, Per-Vessel, and Per-Segment Analysis by Obstructive CAD at the 50% and 70% Stenosis Level

	Obstructive CAD (Defined at 50% Level)				Obstructive CAD (Defined at 70% Level)			
CCTA Result	Univariable HR (95% CI)	p Value	Risk-Adjusted HR (95% CI)	p Value	Univariable HR (95% CI)	p Value	Risk-Adjusted HR (95% CI)	p Value
Per-patient analysis								
Normal	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Nonobstructive CAD	2.88 (2.15–3.86)	<0.0001	1.60 (1.18–2.16)	0.0023	3.29 (2.50–4.34)	<0.0001	1.76 (1.32–2.34)	0.0001
Obstructive CAD	6.05 (4.58–7.99)	<0.0001	2.60 (1.94–3.49)	<0.0001	8.11 (6.00–11.0)	<0.0001	3.13 (2.27–4.31)	<0.0001
Per-vessel analysis								
Normal	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Nonobstructive	2.88 (2.15–3.86)	<0.0001	1.62 (1.20–2.19)	0.0018	3.30 (2.50–4.34)	<0.0001	1.77 (1.33–2.36)	<0.0001
1-vessel obstructive	4.12 (2.96–5.72)	<0.0001	2.00 (1.43–2.82)	<0.0001	5.67 (3.97–8.10)	<0.0001	2.35 (1.62–3.42)	<0.0001
2-vessel obstructive	6.93 (4.82–9.96)	<0.0001	2.92 (2.00–4.25)	<0.0001	11.40 (7.56–17.2)	<0.0001	3.94 (2.57–6.04)	<0.0001
3-vessel or left main obstructive	10.52 (7.50–14.7)	<0.0001	3.70 (2.58–5.29)	<0.0001	15.52 (10.1–23.9)	<0.0001	5.27 (3.36–8.27)	<0.0001
Per-segment analysis								
Segment involvement score (per segment involved)	1.22 (1.18–1.25)	<0.0001	1.10 (1.06–1.13)	<0.0001	NA	NA	NA	NA
Segment stenosis score (per segment severity)	1.12 (1.11–1.14)	<0.0001	1.06 (1.05–1.08)	<0.0001	NA	NA	NA	NA
Any severe proximal stenosis	4.01 (3.12–5.17)	<0.0001	2.15 (1.66–2.78)	<0.0001	NA	NA	NA	NA
Any left main stenosis	2.51 (2.01–3.13)	<0.0001	1.45 (1.15–1.82)	0.0015	NA	NA	NA	NA

NA = not applicable; other abbreviations as in Table 3.

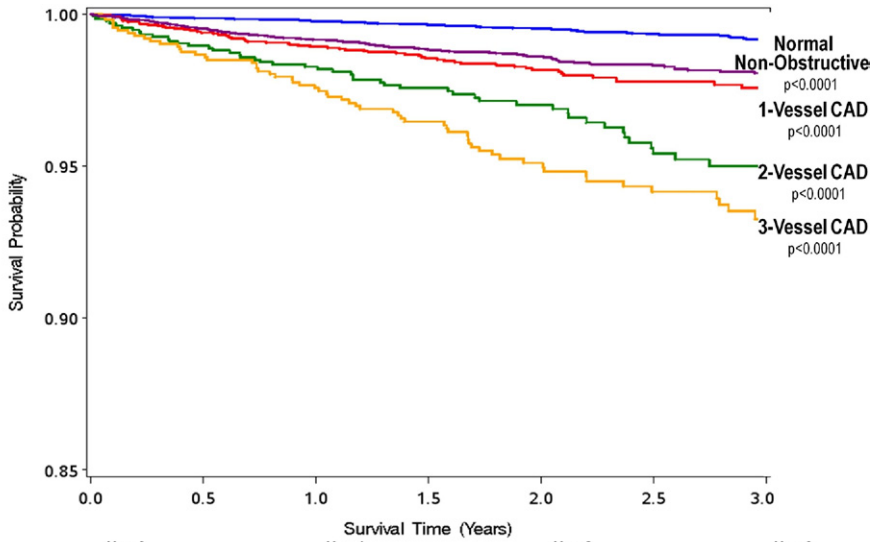
age (pre-test probability low 34% vs. 16%; intermediate 60% vs. 67%, high 6% vs. 17%, chi-square $p < 0.0001$). As compared with individuals without CAD within respective age groups, patients <65 years of age experienced higher hazards for mortality if 2- or 3-vessel/LM obstructive CAD was present than patients ≥65 years of age, with similar rates of death for nonobstructive and 1-vessel obstructive CAD (Table 6, Fig. 3).



At Risk	Year 0	Year 1	Year 2	Year 3
Normal	10146	9357	5800	2907
Non-Obstructive (1-49%)	8114	7437	4081	1930
Obstructive (≥50%)	5594	5135	3153	1430

Figure 1 Unadjusted All-Cause 3-Year Kaplan-Meier Survival by the Maximal Per-Patient Presence of None, Nonobstructive, and Obstructive CAD

Patients with nonobstructive coronary artery disease (CAD) had an intermediate prognosis that resides between patients with no evident CAD and those with obstructive CAD.



At Risk	Year 0	Year 1	Year 2	Year 3
Normal	10146	9357	5800	2907
Non-Obstructive	8114	7437	4081	1930
1-Vessel	3118	2873	1747	782
2-Vessel	1346	1228	742	324
3-Vessel/Left Main	1130	1034	664	324

Figure 2 **Unadjusted All-Cause 3-Year Kaplan-Meier Survival by the Presence, Extent, and Severity of CAD by CCTA**

Note the dose-response relationship of mortality to increasing numbers of vessels with obstructive coronary artery disease (CAD).
CCTA = coronary computed tomography angiography.

Female patients referred to CCTA had higher pre-test probability of CAD than men. Differences in pre-test likelihood for obstructive CAD existed by sex, with male and female patients presenting with low (pre-test probability low 35% vs. 24%, intermediate 56% vs. 68%, and high 9% vs. 9%; $p < 0.0001$). As compared with individuals without CAD within respective sexes, women experienced higher hazards for mortality for 3-vessel or LM obstructive CAD than males, with similar rates of death for nonobstructive, 1-vessel, and 2-vessel obstructive CAD (Table 7, Fig. 4).

When stratified by both age and sex, differences in multivariable risk-adjusted hazards for mortality were observed for nonobstructive and 1-, 2-, and 3-vessel or LM obstructive CAD (Table 8). Tests for interactions of age and CAD ($p = 0.21$) and sex and CAD ($p = 0.76$) did not reveal significant relationships.

Discussion

These results of the CONFIRM registry represent the first prospective international multicenter data to relate CCTA-determined extent and severity of CAD to all-cause mortality and demonstrate the independent prognostic value of both obstructive as well as nonobstructive CAD by CCTA. Importantly, this study had adequate sample size and was adequately powered (beta >0.90, alpha <0.001) to permit differential risk stratification of individuals as categorized by age group and sex. The findings of this study should be considered widely generalizable, given the high number of

Table 6 **Adjusted Hazard Ratios for All-Cause Mortality for Patients <65 Versus ≥65 Years of Age**

	Age <65 Yrs			Age ≥65 Yrs		
Variable	HR	95% CI	p Value	HR	95% CI	p Value
Normal	1	Reference	Reference	1	Reference	Reference
Nonobstructive	1.57	0.98–2.51	0.0594	1.63	1.08–2.47	0.0212
1-vessel disease	2.12	1.22–3.69	0.0080	1.96	1.25–3.07	0.0036
2-vessel disease	4.00	2.16–7.40	<0.0001	2.46	1.51–4.02	0.0003
3-vessel disease or left main disease	6.19	3.43–11.2	<0.0001	3.10	1.95–4.92	<0.0001

Abbreviations as in Table 3.

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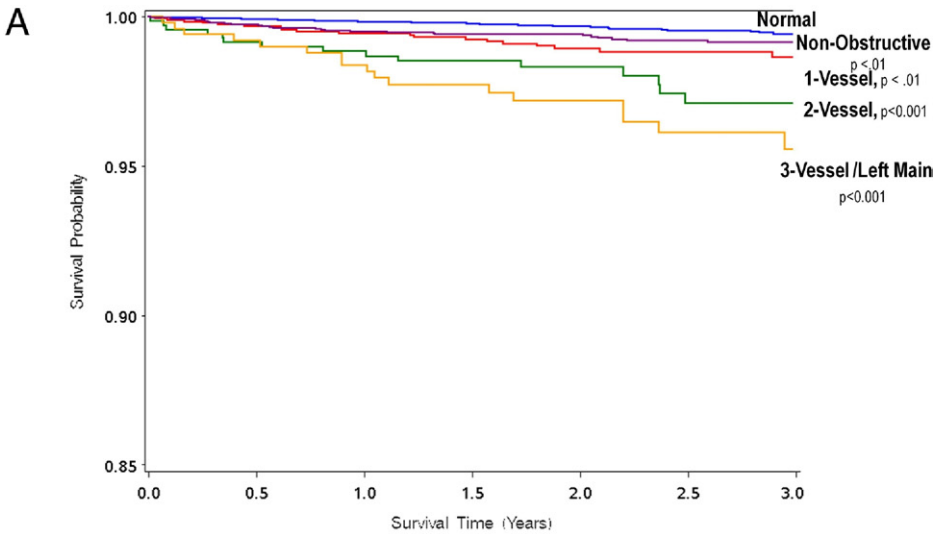
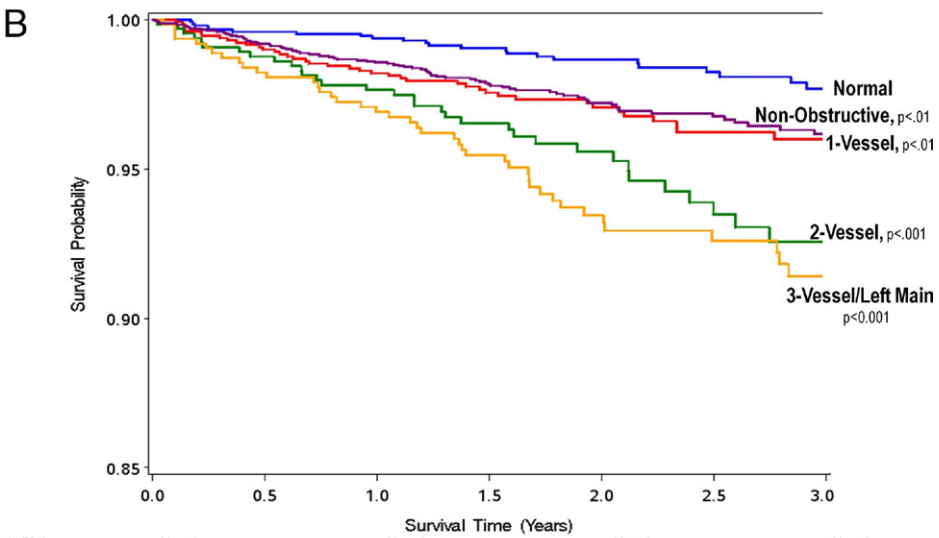


At Risk	Year 0	Year 1	Year 2	Year 3
Normal	8646	8010	4693	2474
Non-Obstructive	5103	4717	2606	1287
1-Vessel	1807	1693	1049	481
2-Vessel	692	640	419	180
3-Vessel/Left Main	501	466	306	151



At Risk	Year 0	Year 1	Year 2	Year 3
Normal	1500	1347	837	433
Non-Obstructive	3011	2720	1475	643
1-Vessel	1311	1180	698	301
2-Vessel	654	588	323	144
3-Vessel/Left Main	629	568	358	173

Figure 3 **Unadjusted All-Cause 3-Year Kaplan-Meier Survival by Presence, Extent, and Severity of CAD by CCTA as Stratified by Age <65 or ≥65 Years**

Although rates of mortality in relationship to CAD extent are lower in patients age <65 years **(A)**, patients age <65 years with 2- and 3-vessel CAD experience a higher relative rate of mortality referenced to patients age <65 years with no CAD in comparison with patients age ≥65 years with 2- and 3-vessel CAD referenced to patients age ≥65 years with no CAD **(B)**. Abbreviations as in Figure 2.

Table 7 Adjusted Hazard Ratios for All-Cause Mortality for Female Versus Male Patients

	Female			Male		
CAD Severity	HR	95% CI	p Value	HR	95% CI	p Value
Normal	1.00	Reference	Reference	1	Reference	Reference
Nonobstructive	1.67	1.10–2.54	0.0160	1.52	0.97–2.40	0.0689
1-vessel disease	1.83	1.11–3.01	0.0176	2.05	1.25–3.35	0.0043
2-vessel disease	2.88	1.63–5.07	0.0003	2.81	1.65–4.77	0.0001
3-vessel/left main disease	4.21	2.47–7.18	<0.0001	3.27	1.96–5.45	<0.0001

Abbreviations as in Table 3.

enrolled subjects; the inclusion of numerous clinical sites within North America, Europe, and Asia; and the uniformity of study results across sites.

Despite increasing adoption of CCTA for clinical use in individuals with suspected CAD, limited "real world" effectiveness evidence still exists to support the prognostic significance of CAD findings as detected by current-generation ≥64-detector row CCTA. Furthermore, prior studies to date that have examined the ability of CCTA findings to stratify risk have been generally limited to single centers with relatively small sample sizes. We previously reported the predictive value of CCTA measures of CAD extent and severity in a 2-center study of 5,330 consecutive patients, but data were limited in that population to vessel-based analyses, and the prognostic potential of segment-based as well as nonobstructive CAD detection by CCTA could not be examined (5). In a separate analysis, we reported the prognostic significance of CCTA-identified CAD findings in 1,256 consecutive patients with suspected CAD for the prediction of major adverse cardiac events (8). Although we noted a 16- to 17-fold increased risk in myocardial events in patients with obstructive CAD, the observed event rates were low (0.6% to 1.8%) and the follow-up duration shorter than in the present study. In this regard, the current data extend prior studies by examining CCTA findings of CAD in a large consecutive cohort comprising multiple international sites that was evaluated by current-generation computed tomography (CT) technology for measures of both obstructive and nonobstructive CAD. That CCTA can effectively risk stratify individuals without known CAD should be invaluable for guiding the development of clinical practice guidelines and appropriate use criteria.

One notable finding in our study was that although the pre-test likelihood of obstructive CAD—as estimated by the Diamond-Forrester (D-F) tabular method—was highly predictive of the presence of obstructive CAD by CCTA, it did not demonstrate predictive value for incident death in this large cohort of patients with suspected CAD. At present, clinicians commonly use D-F pre-test estimations of likelihood of obstructive CAD as a metric to determine whether patients would benefit from noninvasive testing. Because global clinical risk scores are currently lacking for symptomatic stable individuals with suspected CAD, many have also adopted use of the D-F method for "risk" assessment (17,18). The current data suggest that use of the D-F method is insufficient for this purpose and should not be used solely as a judge of risk.

We also identified a utility of nonobstructive CAD detection for risk stratification of individuals at heightened risk of incident death. Indeed, individuals with nonobstructive CAD (HR: 1.62; 95% CI: 1.08 to 2.43) by CCTA experienced a mortality risk that was similar to that of those with obstructive 1-vessel CAD (HR: 1.75; 95% CI: 1.12 to 2.72). These data corroborate our prior studies using older generation electron beam CT technology, where the presence of nonobstructive CAD conferred similar risk as 1-vessel obstructive CAD. These findings have important implications, as patients with nonobstructive CAD comprise the majority of patients who experience myocardial events and for whom functional stress testing aimed at detecting flow-limiting coronary artery stenoses would be expectedly negative (19). Given a robust evidence base demonstrating the highly salutatory effect of primary prevention of CAD events in at-risk individuals, future studies should be performed to determine the effect of aggressive medical therapy and lifestyle modification for individuals with CCTA-identified nonobstructive CAD.

We recently reported the results of an exploratory analysis of 1,127 consecutive patients with suspected CAD undergoing 16-detector row CCTA identified to have only obstructive CAD. In this study, 490 patients were identified as having nonobstructive CAD (as defined by maximal <50% luminal diameter stenosis at the per-patient level) (15). In 4-year follow-up, the number of coronary segments exhibiting nonobstructive CAD was predictive of incident death in women but not in men. This study expands on these prior published results by using a study cohort of sufficient magnitude to examine the presence of nonobstructive CAD at the per-patient level. The present data corroborate the prior data, revealing a prognostic value for per-patient nonobstructive CAD detection in women but not in men. Further, the current study extends prior study results by demonstration that 1-vessel obstructive CAD also confers heightened risk of death in women but not in men. Numerous possibilities exist to explain these findings. Women in our study had lower rates of both obstructive and nonobstructive CAD in contrast to their male

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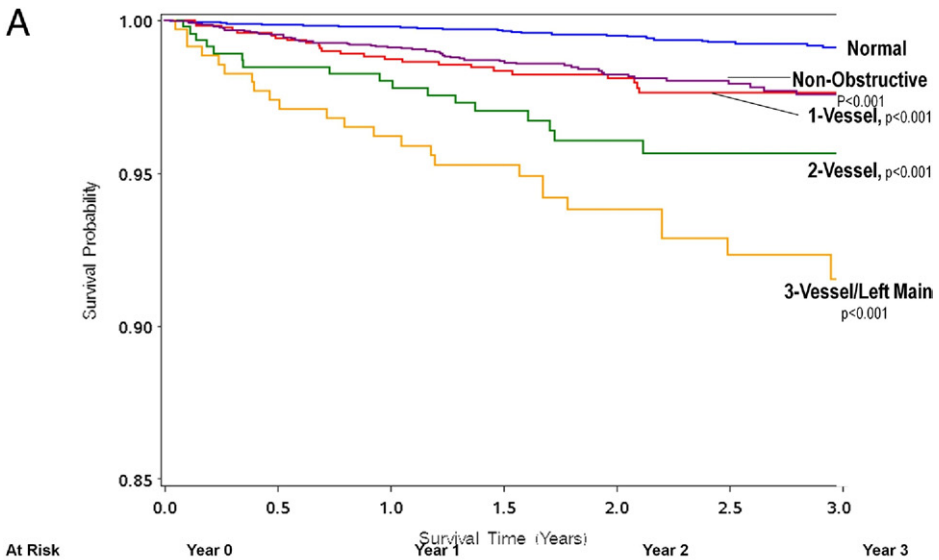
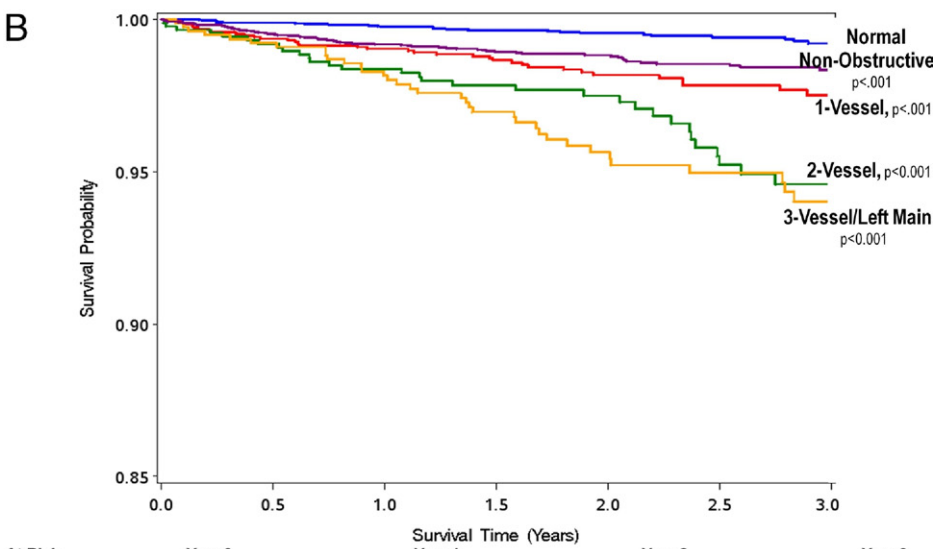


At Risk	Year 0	Year 1	Year 2	Year 3
Normal	5594	5179	3143	1545
Non-Obstructive	3232	2955	1564	650
1-Vessel	1214	1119	680	298
2-Vessel	459	433	253	113
3-Vessel/Left Main	347	317	218	107



At Risk	Year 0	Year 1	Year 2	Year 3
Normal	4528	4160	2648	1357
Non-Obstructive	4849	4457	2513	1280
1-Vessel	1887	1743	1064	484
2-Vessel	881	790	489	211
3-Vessel/Left Main	777	712	444	217

Figure 4 **Unadjusted All-Cause 3-Year Kaplan-Meier Survival by Presence, Extent, and Severity of CAD by CCTA as Stratified by Sex**

Although rates of mortality in relationship to CAD extent are lower in women, women with 3-vessel CAD experience a higher relative rate of mortality referenced to women with no CAD **(A)** in comparison with men with 3-vessel CAD referenced to men with no CAD **(B)**. Abbreviations as in Figure 2.

counterparts, despite higher estimated pre-test probability. This generally lower prevalence of disease in women has been historically associated with lower rates of invasive coronary angiographic evaluation and often leads to "exclusion" of cardiac causes of symptoms in women, despite a higher rate of hospitalization for angina as compared with men (20,21). It remains possible in this open-label study that the identification of nonobstructive

Table 8 Multivariable Adjusted Hazard Ratios for All-Cause Mortality as Stratified by Age and Sex

	Age <65 Yrs				Age ≥65 Yrs			
	Male		Female		Male		Female	
CAD Severity	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Normal	0.70	0.36–1.36	1.00	Reference	5.53	2.74–11.2	3.72	1.97–7.02
Nonobstructive	1.65	0.93–2.91	1.59	0.79–3.21	7.79	4.72–12.9	8.08	4.86–13.4
1-vessel disease	2.46	1.26–4.82	2.23	0.95–2.23	10.54	6.13–18.1	8.28	4.60–14.9
2-vessel disease	4.16	1.97–8.82	6.59	2.65–16.3	14.73	8.20–26.5	11.96	6.10–23.5
3-vessel/left main disease	6.80	3.35–13.8	10.59	4.50–24.9	16.25	9.38–28.2	18.68	10.0–34.7

Abbreviations as in Table 3.

disease in women led clinicians to pursue alternative noncardiac diagnoses for symptoms, and lack of aggressive treatment for these CAD findings resulted in heightened risk of incident death. Future studies should carefully evaluate this potential explanation and should determine the effect of primary prevention with aggressive medical therapy in this cohort.

In the present study, we also observed differential risk stratification of CCTA-identified CAD findings by age groups. Although risk of all-cause death increased in a generally linear fashion for patients ≥65 years of age for extent and severity of CAD, patients <65 years of age experienced a more abrupt increase in risk of death associated with 2- and 3-vessel or LM CAD over nonobstructive or 1-vessel CAD. Although numerous explanations exist to account for these findings, it may be that younger patients with greater extent and severity of CAD represent a cohort with more aggressive forms of atherosclerosis than their older counterparts, thus resulting in a higher risk than for older patients with more insidious atherosclerosis.

Finally, we observed a very low rate of death for individuals without evident CAD by CCTA. This low rate of death validates the favorable prognosis that has been uniformly observed in prior smaller registries and emphasizes a clinical value of CCTA for identification of individuals in whom no further additional testing and/or therapy is necessary or indicated (4–14). Using older generation electron beam CT technology, Ostrom et al. (22) demonstrated that this very low death rate continues to persist for up to 7 years from the time of the CCTA, and the present results are in direct accordance with those findings. Similarly, the long-term ≥4-year prognosis of patients in the present registry without evident CAD by CCTA was extremely favorable, with a 0.22% annualized death rate. These results may inform clinicians on the need for repeat testing in patients with normal CCTA and suggest a "warranty" period of a normal CCTA to last at least 4 years.

Study limitations. Although this study addresses many of the shortcomings of prior analyses examining the prognostic value of CCTA, it is not without limitations. For the present analysis, the major endpoint was all-cause mortality. Other "softer" endpoints—including myocardial infarction, unstable angina, or CAD-related hospitalization—were not included in this initial analysis. Although use of all-cause death mitigates ascertainment bias, it will nevertheless be important to perform future studies examining the risk of major adverse cardiac events in relation to CCTA findings. Further, referral bias due to excluded patients and treatment of individuals based on CCTA findings of CAD are unknown in this open-label multicenter registry. Whether percutaneous or surgical coronary revascularization, enhanced medical therapy, or lifestyle modifications occurred after CCTA performance is unknown. We have previously demonstrated that CAD risk factor control is improved in direct relation to the extent and severity of CCTA CAD findings, but whether this affects mortality has not been explored. For proper evaluation of this issue, large-scale trials with prescribed treatment algorithms will be necessary. In addition, our analysis entailed the evaluation of CAD by semiquantitative visual analysis rather than by volumetric quantification of plaque. At the time of initiation of the study (and to date), no automated validated software existed for automatic quantification of plaque or stenosis severity. Instead, this multicenter study used experienced level III CCTA imagers and used a uniform grading system that is most commonly used in daily clinical practice. Finally, this study examined only patients without history of known CAD. As such, whether these findings can be extrapolated to those with prior myocardial infarction or coronary revascularization needs to be tested in future studies.

Conclusions

In the large, prospective, international, multicenter CONFIRM registry, extent and severity of CAD by CCTA successfully identifies individuals at heightened risk for all-cause mortality. Presence of both obstructive and nonobstructive CAD by CCTA on a per-patient, per-vessel, and per-segment basis portends worsened prognosis, with differential risk noted between sex and age groups. Importantly, individuals without evident CAD by CCTA are at very low risk of death.

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Key Words: atherosclerosis ■ computed tomography ■ coronary disease ■ nonobstructive ■ prognosis.