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on behalf/for the CONFIRM Investigators

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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

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Background—Large multicenter studies validating the prognostic value of coronary computed tomographic angiography (CCTA) and left ventricular ejection fraction (LVEF) are lacking. We sought to confirm the independent and incremental prognostic value of coronary artery disease (CAD) severity measured using 64-slice CCTA over LVEF and clinical variables.

Methods and Results—A large international multicenter registry (CONFIRM Registry) was queried, and CCTA patients with LVEF data on CCTA were screened. Patients with a history of myocardial infarction, coronary revascularization, or cardiac transplantation were excluded. The National Cholesterol Education Program-Adult Treatment Panel III risk was calculated for each patient, and CCTA was evaluated for CAD severity (normal, nonobstructive, non–high-risk, or high-risk CAD) and LVEF <50%. Patients were followed for an end point of all-cause mortality; 27 125 patients underwent CCTA at 12 participating centers, with a total of 14 064 patients meeting the analysis criteria. Follow-up was available for 13 966 (99.3%) patients (mean follow-up of 22.5 months; 95% confidence interval, 22.3 to 22.7 months). All-cause mortality (271 deaths) occurred in 0.65% of patients without coronary atherosclerosis, 1.99% of patients with nonobstructive CAD, 2.90% of patients with non–high-risk CAD, and 4.95% for patients with high-risk CAD. Multivariable analysis confirmed that LVEF <50% (hazard ratio, 2.74; 95% confidence interval, 2.12 to 3.51) and CAD severity (hazard ratio, 1.58; 95% confidence interval, 1.42 to 1.76) were predictors of all-cause mortality, and CAD severity had incremental value over LVEF and clinical variables.

Conclusions—Our results demonstrate that CCTA measures of CAD severity and LVEF have independent prognostic value. Incorporation of CAD severity provides incremental value for predicting all-cause death over routine clinical predictors and LVEF in patients with suspected obstructive CAD. (*Circ Cardiovasc Imaging*. 2011;4:463-472.)

Key Words: computed tomography ■ coronary angiography ■ prognosis ■ all-cause mortality
■ left ventricular ejection fraction

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Prior studies have demonstrated superior operating characteristics for cardiac computed tomographic angiography (CCTA), and CCTA has had increasing acceptance into daily clinical practice for the diagnosis of obstructive coronary artery disease (CAD).^{1–5} Single-center studies suggest that CCTA has prognostic value for both all-cause mortality and major adverse cardiac events.^{6–12} However the validation of CCTA prognosis in large multicenter cohorts is lacking.

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Clinical Perspective on p 472

Previously, in a single-center study, the severity of CAD and left ventricular ejection fraction (LVEF) have been demonstrated to predict major adverse cardiac events and all-cause mortality.¹¹ The objective of the present study is to confirm the prognostic and incremental value of CAD severity and LVEF in a large international multicenter cohort of patients undergoing CCTA.

Methods

Centers with prospectively collected CCTA databases (previously published and unpublished data) using at least 64-slice CT were invited to contribute to a larger multicenter observational registry. Qualifying sites contributed baseline demographics, cardiac risk factors, CCTA findings, and outcomes such as all-cause mortality and major adverse cardiac events. Between February 2003 and December 2009, 27 125 consecutive patients underwent CCTA at 12 enrolling centers in 6 countries (Canada, Germany, Italy, Korea, Switzerland, and the United States) and were prospectively entered into an international multicenter Cardiac CT Registry (CONFIRM Registry).¹³ Each enrolling center contributed 499 to 4912 patients for analysis. CCTA patients with concomitant CT LVEF assessment were screened for study analysis. Patients with a history of myocardial infarction, coronary revascularization (coronary artery bypass and/or percutaneous coronary intervention), or cardiac transplantation were excluded from analysis. Follow-up procedures were approved by all study centers' institutional review boards.

Clinical Predictors

A medical history was recorded for all patients. Patients' pretest probability for obstructive CAD was calculated by using age, sex, and symptoms,^{11,14–16} and each patient's risk of future cardiac event was estimated using National Cholesterol Education Program-Adult Treatment Panel (NCEP-ATP) III guidelines.^{11,17}

CCTA Measures: CAD Severity and LVEF

Coronary CT angiography image acquisition and interpretation were performed as per clinical routine at each participating center.^{11,18–21} All scanners were single- or dual-source 64-slice CT scanners. Coronary diameter stenoses were graded using a 4-point score [normal, mild (<50%), moderate (50% to 69%), or severe (≥70%)].^{11,22} Patients were categorized as normal, nonobstructive CAD, non-high-risk obstructive (≥50% diameter stenosis) CAD, and high-risk CAD (defined as having a left main stenosis (≥50%), or 3-vessel disease (≥70%), or 2-vessel disease (≥70%) involving the proximal left anterior descending artery).^{11,23,24} LVEF was calculated using end-diastole and end-systole volumes and LVEF <50% was considered abnormal.^{11,25}

Patient Follow-Up

Patient follow-up for all-cause mortality was performed by each local institution by telephone interview, with validation of reported death through medical records whenever possible and/or a national death registry.

Statistical Analysis

Statistical analyses were performed using SAS (version 9.2, SAS Institute Inc, Cary, NC), and statistical significance was defined as $P < 0.05$. Continuous variables were presented as means and standard deviations, and categorical variables were presented as frequencies with percentages. To compare patient characteristics, the Wilcoxon rank sum test was used to compare continuous variables and the χ^2 test was used for categorical variables.

The prognostic value of CAD severity and LVEF was assessed for both univariable associations and multivariable associations, with all-cause mortality using Cox proportional hazard models. For the risk-adjusted analysis, the independent prognostic value of LVEF and CAD severity was assessed by controlling for clinical predictors (NCEP/ATP III) and creating adjusted survival curves. Model overfitting was considered, and the proportional hazards assumption was met. The incremental value of LVEF and CAD severity was calculated by defining the clinical predictor model followed by the addition of LVEF and CAD severity. Receiver-operator characteristic curves were constructed for the models of clinical predictors only, clinical+LVEF, and clinical+LVEF+CAD severity, respectively. The area under the receiver-operator characteristic curves (95% confidence intervals [CI]) was compared to evaluate the discrimination ability of LVEF over clinical predictors and CAD severity over clinical+LVEF to predict all-cause mortality using the method proposed by DeLong et al.²⁶ The improvement of reclassification using CAD severity and LVEF was assessed using a recently published method that estimated the net reclassification improvement (NRI).²⁷ For calculating the NRI, rescaled individual predicted risks from models with and without LVEF or with and without CAD severity were compared with the 10-year NCEP/ATPIII risk by the observed 4-year event rate.²⁸ This approach separately analyzed the reclassification of persons who had events and those who did not have events. Upward movement/improvement in reclassification occurred when patients with death were appropriately classified into a higher-risk group, and reclassification downward occurred when the test failed to identify a patient with an event. Among patients without death, reclassification upward was considered disadvantageous and reclassification downward was considered advantageous. Improvement in reclassification was estimated by taking the sum of differences in proportions of individuals reclassified upward minus the proportion reclassified downward for patients who had death and the proportion of individuals moving downward minus the proportion moving upward for those who did not have death. The statistical significance of the overall improvement was assessed with an asymptotic test.

A similar analysis was performed using a subgroup of 7015 CCTA patients with absolute LVEF measures to evaluate the incremental value of LVEF as a continuous variable. A secondary analysis was also performed that included patient symptoms (chest pain and dyspnea) in the multivariable analysis.

Results

The CONFIRM registry screened 27 125 CCTA patients at 12 participating centers. Of the 15 168 patients with clinical variables, CAD severity and LVEF assessment (normal versus abnormal LVEF), 1104 patients were excluded for a history of coronary revascularization and/or cardiac transplant. Of the 14 064 patients eligible for analysis, 7015 (50.2%) patients had absolute LVEF measurements; 98 (0.70%) patients were lost to follow-up. The final study population comprised 13 966 (99.3%) patients (mean age, 56.6±13.2 years; 50.9% men), with a median follow-up of 22.5 months (95% CI, 22.3 to 22.7) (Table 1).

Table 1. Patient Characteristics: All Patients and Patients With and Without Follow-Up

	All Patients (n=14 064)	Follow-Up Patients (n=13 966)	Patients Lost to Follow-Up (n=98)	P*
Mean follow-up, mo (95% CI)		22.5 (22.3 to 22.7)		
Age, y	56.6±13.2	56.6±13.2	50.6±11.9	<0.001
Men	7157 (50.9%)	7104 (50.9%)	53 (54.1%)	0.526
Body mass index, kg/m ² †	28.4±5.8	28.4±5.8	28.3±5.8	0.875
Pretest likelihood CAD (%)	32.4±28.0	35.5±29.4	24.5±26.8	<0.001
Reason for test				
Chest pain	9734 (69.2%)	9669 (69.2%)	65 (66.3%)	0.535
Nonanginal chest pain	4039 (28.7%)	4007 (28.7%)	32 (32.7%)	0.388
Atypical chest pain	3339 (23.7%)	3320 (23.8%)	19 (19.4%)	0.309
Typical chest pain	2356 (16.8%)	2342 (16.8%)	14 (14.3%)	0.512
Dyspnea	1141 (8.1%)	1126 (8.1%)	15 (15.3%)	0.011
Other	2991 (21.3%)	2973 (21.3%)	18 (18.4%)	0.439
Cardiac risk factors				
Smoker/ex-smoker	5876 (41.8%)	5822 (41.7%)	54 (55.1%)	0.007
Hypertension	7417 (52.7%)	7381 (52.8%)	36 (38.7%)	0.001
Dyslipidemia	7467 (53.1%)	7418 (53.1%)	49 (50.0%)	0.532
Diabetes	2092 (14.9%)	2083 (14.9%)	9 (9.2%)	0.112
Family history of CAD	6068 (43.1%)	6016 (43.1%)	52 (53.1%)	0.047
CCTA results				
Normal coronaries	5857 (41.6%)	5822 (41.7%)	35 (35.7%)	0.232
Nonobstructive CAD (<50%)	4508 (32.1%)	4465 (32.0%)	43 (43.9%)	0.012
Obstructive CAD (≥50%), non-high risk	1878 (13.4%)	1861 (13.3%)	17 (17.3%)	0.243
Obstructive CAD, high-risk CAD	1821 (12.9%)	1818 (13.0%)	3 (3.1%)	<0.001
NCEP/ATPIII score				
Low	3319 (23.6%)	3291 (21.7%)	28 (28.6%)	0.245
Intermediate	8160 (58.0%)	8110 (59.0%)	50 (51.0%)	0.159
High	2585 (18.4%)	2565 (19.3%)	20 (20.4%)	0.603
Abnormal LVEF, <50%	1895 (13.5%)	1887 (10.8%)	8 (8.2%)	0.122
LVEF‡	61.8±11.7	61.8±11.7	63.0±10.9	0.315
Radiation exposure, mSv	10.7±5.7	10.6±5.7	15.1±2.9	<0.001

CI indicates confidence interval; CAD, coronary artery disease; CCTA, coronary computed tomographic angiography; NCEP/ATP III, National Cholesterol Education Program/Adult Treatment Panel III; and LVEF, left ventricular ejection fraction.

Values given are mean±SD or n (%).

*Comparison of the patients with and without follow-up.

†Body mass index was only measured in 9384 (66.7%) patients (9286 with follow-up and 98 without follow-up).

‡Left ventricular volumes were not measured in 6958 patients, therefore LVEF in the remaining 7106 (50.5%) patients (7015 with follow-up and 91 patients without follow-up) was used for analysis.

Radiation exposure was only measured in 5010 (35.6%) patients (4919 with follow-up and 91 without follow-up).

All-Cause Mortality

At follow-up, all-cause mortality was observed in 271 patients (1.94%), with an annualized mortality rate for the entire study cohort of 1.06%. The absence of coronary atherosclerosis conferred an excellent prognosis, with only 38 (0.65%) deaths and an annual mortality rate of 0.36%. Patients with nonobstructive CAD had a death rate of 1.99% (n=89), which equates to an annualized mortality rate of 1.14%.

Death occurred in 90 of the 1818 patients (4.95%) with high-risk CAD compared with 54 (2.90%) of 1861 patients with non-high-risk CAD. The mean LVEF of patients who died was lower than that of those who survived (54.0±17.7% and

62.0±11.4%, respectively). Of the 1887 patients with abnormal LVEF, 87 (4.61%) died compared with 184 (1.52%) deaths in patients with normal LVEF. Patients with high-risk CAD had an annual death rate of 2.63% compared with 1.41% in patients with non-high-risk CAD.

Cox Models of Risk-Adjusted Outcomes

In univariate analysis, clinical parameters (age, chest pain, dyspnea, cardiac risk factors, body mass index, and NCEP/ATP III) and CT parameters (severity of CAD and abnormal LVEF) were significant predictors for all-cause mortality (Table 2). For the risk-adjusted analysis, the NCEP/ATP III

Table 2. Univariate Analysis of Clinical Characteristics for All-Cause Mortality

	No Death (n=13 695)	Death (n=271)	Hazard Ratio (95% CI)	P
Age, 10-y increase	56.4±13.1	68.6±12.7	2.16 (1.95 to 2.39)	<0.001
Male	6964 (50.8%)	142 (52.4%)	1.07 (0.84 to 1.35)	0.605
Body mass index, kg/m ²	28.4±5.8	26.5±6.1	0.93 (0.91 to 0.96)	<0.001
Chest pain	9502 (69.4%)	167 (61.6%)	0.67 (0.53 to 0.86)	0.001
Dyspnea	5589 (40.8%)	132 (48.7%)	1.32 (1.04 to 1.68)	0.021
Pretest likelihood for CAD			1.13 (0.89 to 1.42)	
Low	3665 (26.7%)	67 (24.7%)		0.315
Intermediate	9366 (68.4%)	184 (67.9%)		
High	671 (4.9%)	20 (7.4%)		
Cardiac risk factors				
Diabetes	2003 (14.6%)	80 (29.5%)	2.36 (1.82 to 3.07)	<0.001
Dyslipidemia	7305 (53.3%)	115 (42.3%)	0.64 (0.50 to 0.81)	<0.001
Hypertension	7192 (52.5%)	189 (69.7%)	2.05 (1.58 to 2.66)	<0.001
Family history of CAD	5920 (43.2%)	96 (35.4%)	0.71 (0.55 to 0.91)	0.007
Smoker/ex-smoker	5684 (41.5%)	141 (52.0%)	1.50 (1.18 to 1.90)	<0.001
NCEP/ATPIII risk			2.37 (1.95 to 2.86)	
Low	3273 (23.9%)	23 (8.5%)		<0.001
Intermediate	7967 (58.1%)	145 (53.5%)		
High	2462 (18.0%)	103 (38.0%)		
CAD severity			1.76 (1.59 to 1.95)	
No CAD	5787 (42.2%)	38 (14.0%)		<0.001
Nonobstructive	4380 (32.0%)	89 (32.8%)		
Obstructive	1807 (13.2%)	54 (19.9%)		
High risk	1728 (12.6%)	90 (33.2%)		
Abnormal LVEF <50%	1800 (13.1%)	87 (32.1%)	3.15 (2.44 to 4.07)	<0.001
LVEF (10% reduction)*	62.0±11.4	54.0±17.7	1.56 (1.42 to 1.72)	<0.001

CI indicates confidence interval; CAD, coronary artery disease; NCEP/ATP III, National Cholesterol Education Program/Adult Treatment Panel III; and LVEF, left ventricular ejection fraction.

*Analysis of left ventricular volumes was performed in 7015 (50.23%) patients (6829 patients with no death and 186 patients with death).

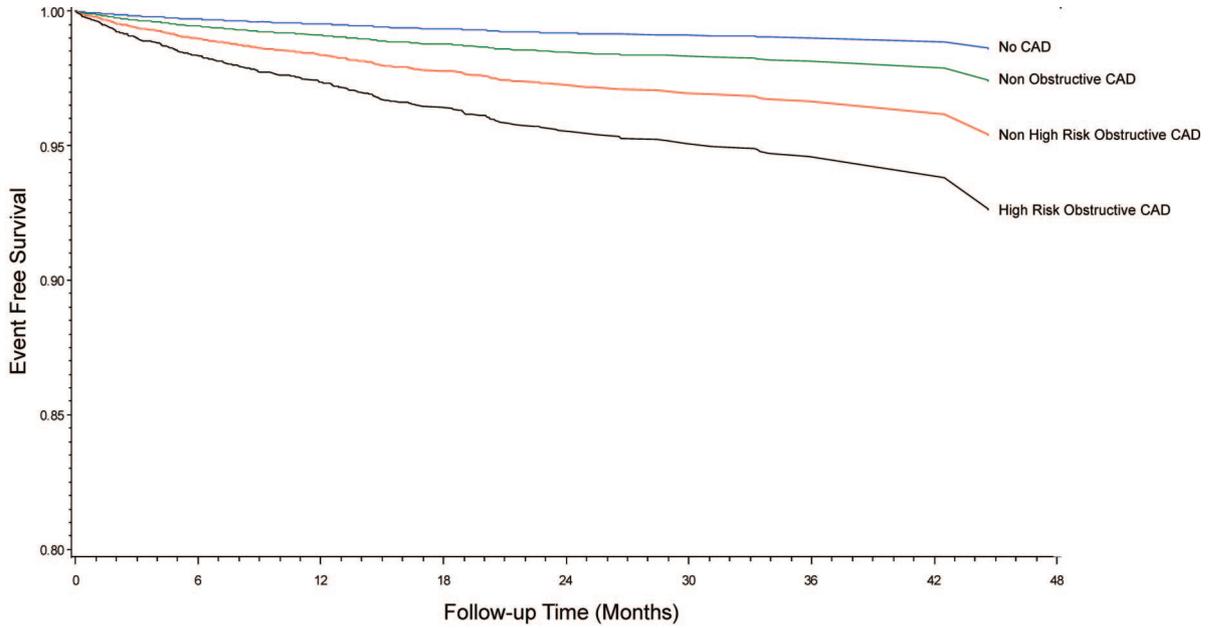
score was used as a clinical predictor to determine the incremental value of CCTA measures because it combined age, sex, and cardiac factors into a single measure. A multivariable Cox model of CAD severity and abnormal LVEF was tested, and CAD severity and abnormal LVEF remained independent predictors of all-cause mortality after adjusting for clinical characteristics (Figures 1 and 2 and Tables 3 and 4). Patient symptoms were included in a secondary analysis and showed that chest pain appeared to be protective (hazard ratio, 0.65; [0.51 to 0.83]) and that dyspnea did not have independent prognostic value (Table 5). The addition of symptoms to the Cox models did not alter the prognostic value of CCTA.

Receiver-operator characteristic curves were created for clinical predictors and the models with each CCTA measure, and the area under the curve was compared to assess the discrimination ability of each additional measure (Figure 3). The addition of each variable resulted in a significant improvement in the area under the curve ($P<0.001$).

Absolute LVEF was available for 7015 (50.2%) patients, and a subanalysis was performed using LVEF as a continuous variable. These results also confirmed the independent and incremental prognostic value of LVEF (Table 5).

Incremental Prognostic Value of CAD Severity and LVEF

The incremental prognostic value of abnormal LVEF and CAD severity over clinical predictors was evaluated. The patient classification was significantly improved when LVEF was added to a model containing clinical variables only (NRI, 22.5%; $P<0.001$). A total of 50 (18.5%) patients who had an event were appropriately reclassified upward, and a total of 35 (12.9%) patients who had an event were reclassified downward. Similar calculations for patients who did not have an event revealed a total of 3248 (23.7%) patients who were correctly reclassified downward and a total of 917 (6.7%) patients who were reclassified upward. Also, when CAD severity was added to a model containing clinical variables and LVEF, a total of 53

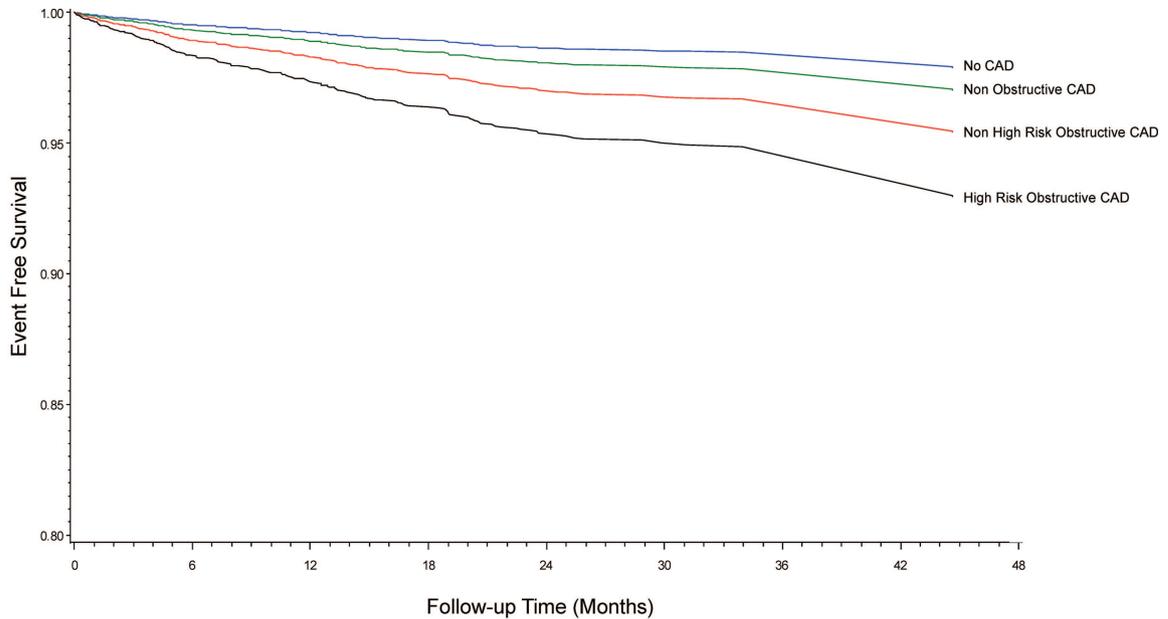


	5822	5598	5204	3952	2553	1470	694	155	40
ive CAD	4655	4250	3917	2821	1544	735	308	128	31
k Obstructive CAD	1861	1818	1719	1284	703	320	93	34	15
structive CAD	1818	1741	1643	1418	1138	928	547	44	9

Figure 1. Cox risk-adjusted all-cause mortality-free survival by coronary artery disease (CAD) severity for patients without coronary atherosclerosis (blue line), nonobstructive CAD (green line), non-high-risk CAD (red line), and high-risk CAD (black line); $P < 0.001$.

(19.6%) patients who had an event were reclassified upward, and a total of 29 (10.7%) patients who had an event were reclassified downward. For patients who did not have an event, a total of 2954 (21.6%) patients were

reclassified downward and a total of 1732 (12.6%) patients were reclassified upward. The CAD severity model yielded an NRI of 17.8% ($P < 0.001$) when added to the model of clinical+LVEF (Figure 4).



	2747	2570	2279	1785	1342	1024	562	83
e CAD	2167	2014	1783	1234	709	429	176	63
Obstructive CAD	739	714	645	449	213	115	52	11
uctive CAD	1362	1305	1224	1089	925	847	520	29

Figure 2. Cox risk-adjusted all-cause mortality-free survival by coronary artery disease (CAD) severity in a subgroup of 7015 patients with absolute left ventricular ejection fraction measures for patients without coronary atherosclerosis (blue line), nonobstructive CAD (green line), non-high-risk CAD (red line), and high-risk CAD (black line); $P < 0.001$.

Table 3. Cox Models of CCTA Measures and All-Cause Mortality

Models	Hazard Ratio (95% CI)	P Value
Clinical variables		
NCEP/ATPIII risk	2.36 (1.95 to 2.86)	<0.001
Clinical+LVEF <50%		
NCEP/ATPIII risk	2.25 (1.86 to 2.73)	<0.001
LVEF <50%	2.91 (2.25 to 3.76)	<0.001
Clinical+LVEF <50%+CAD severity		
NCEP/ATPIII risk	1.87 (1.53 to 2.29)	<0.001
LVEF <50%	2.72 (2.10 to 3.51)	<0.001
CAD severity		
No CAD	1.0	...
Nonobstructive CAD (<50%)	2.75 (1.88 to 4.04)	<0.001
Obstructive CAD (\geq 50%), non-high risk	3.30 (2.17 to 5.04)	<0.001
Obstructive CAD, high risk	4.96 (3.36 to 7.31)	<0.001

CCTA indicates coronary computed tomographic angiography; CI, confidence interval; NCEP/ATP III, National Cholesterol Education Program/Adult Treatment Panel III; LVEF, left ventricular ejection fraction; and CAD, coronary artery disease.

Homogeneity of Results

The homogeneity of the results was evaluated across different sites. Overall, there is no significant heterogeneity identified. For the risk-adjusted analysis, CAD severity and abnormal LVEF remained independent predictors of all-cause mortality after adjusting for clinical characteristics. The direction of hazard ratios for CAD severity and abnormal LVEF was consistent across different sites.

Table 4. Cox Models of CCTA Measures and All-Cause Mortality for Patients With LVEF Analyzed as a Continuous Variable

Models	Hazard Ratio (95% CI)	P Value
Clinical variables		
NCEP/ATPIII risk	2.37 (1.89 to 2.97)	<0.001
Clinical+LVEF		
NCEP/ATPIII risk	2.27 (1.81 to 2.85)	<0.001
LVEF (10% reduction)	1.52 (1.38 to 1.68)	<0.001
Clinical+LVEF+CAD		
NCEP/ATPIII risk	2.04 (1.61 to 2.59)	<0.001
LVEF (10% reduction)*	1.50 (1.36 to 1.65)	<0.001
CAD severity		
No CAD	1.0	...
Nonobstructive CAD (<50%)	2.57 (1.65 to 4.00)	<0.001
Obstructive CAD (\geq 50%), non-high risk	2.79 (1.65 to 4.71)	<0.001
Obstructive CAD, high risk	2.84 (1.83 to 4.39)	<0.001

CCTA indicates coronary computed tomographic angiography; CI, confidence interval; NCEP/ATP III, National Cholesterol Education Program/Adult Treatment Panel III; LVEF, left ventricular ejection fraction; and CAD, coronary artery disease.

*Analysis of left ventricular volumes was performed in 7015 (50.23%) patients (6829 patients with no death and 186 patients with death).

Table 5. Cox Models of Symptoms and CCTA Measures and All-Cause Mortality

Models	Hazard Ratio (95% CI)	P Value
Clinical variables (including symptoms)		
NCEP/ATPIII risk	2.39 (1.97 to 2.89)	<0.001
Chest pain	0.65 (0.51 to 0.83)	<0.001
Clinical variables (including symptoms)		
NCEP/ATPIII risk	2.34 (1.93 to 2.83)	<0.001
Chest pain	0.61 (0.47 to 0.78)	<0.001
Dyspnea	1.28 (1.00 to 1.64)	0.052
Clinical+LVEF <50%		
NCEP/ATPIII risk	2.27 (1.88 to 2.74)	<0.001
Chest pain	0.65 (0.51 to 0.84)	<0.001
LVEF <50%	2.89 (2.24 to 3.73)	<0.001
Clinical+LVEF <50%+CAD		
NCEP/ATPIII risk	1.88 (1.54 to 2.30)	<0.001
Chest pain	0.65 (0.51 to 0.83)	<0.001
LVEF <50%	2.71 (2.09 to 3.50)	<0.001
CAD severity		
No CAD	1.0	...
Nonobstructive CAD (<50%)	2.64 (1.80 to 3.87)	<0.001
Obstructive CAD (\geq 50%), non-high risk	3.24 (2.12 to 4.94)	<0.001
Obstructive CAD, high risk	4.93 (3.35 to 7.27)	<0.001

CCTA indicates coronary computed tomographic angiography; CI, confidence interval; NCEP/ATP III, National Cholesterol Education Program/Adult Treatment Panel III; LVEF, left ventricular ejection fraction; and CAD, coronary artery disease.

Discussion

In the present analysis of the international multicenter CONFIRM Registry, we observed an additive prognostic value of CCTA-measured LVEF and CAD severity for the prediction of all-cause mortality. Both CAD severity and abnormal LVEF had incremental prognostic value over baseline clinical variables alone, and the CAD severity was incremental to LVEF+clinical variables.

Prognostic Value of CCTA

Several single-center studies have examined the prognostic value of CCTA and the incremental value of LVEF above CAD severity.⁶⁻¹¹ Our results expand on previous literature by confirming that measures of CCTA (CAD severity and abnormal LVEF) have prognostic value in a large international multicenter registry. The variety of sites included in the analysis ensures that these measures are clinically useful across different ethnicities and different institutions with potentially different CCTA reading thresholds. Similarly, the different centers used different CT platforms and postprocessing software, suggesting that assessments of LVEF and CAD severity were independent of vendor.

With the increasing use of prospective ECG-triggered image acquisition to minimize patient radiation exposure, LVEF may not be routinely available with all CCTA.

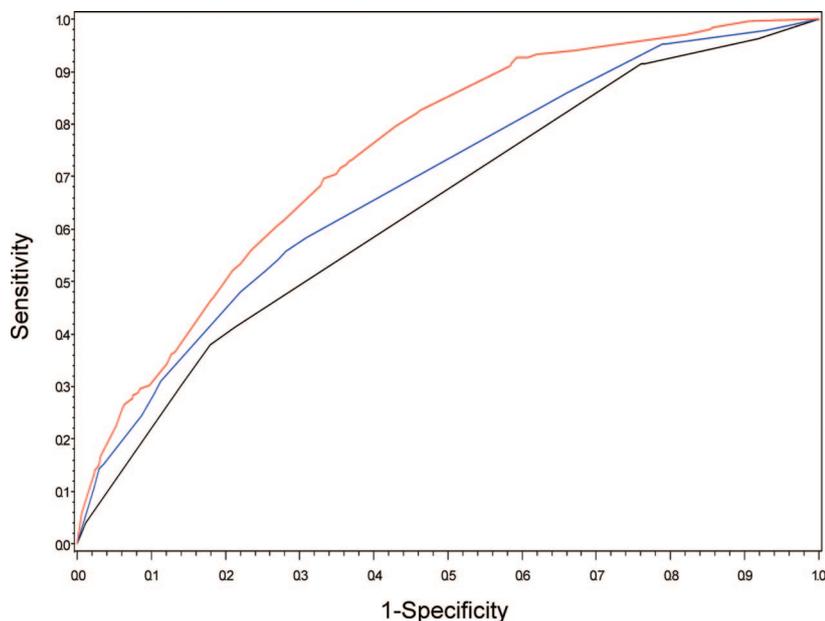


Figure 3. Receiver-operator characteristic curves show the incremental value of coronary artery disease (CAD) severity (**red line**) (area under the curve [AUC], 0.75; 95% confidence interval [CI], 0.72 to 0.77; $P < 0.001$) over left ventricular ejection fraction (LVEF) $< 50\%$ (**blue line**) (AUC, 0.68; 95% CI, 0.65 to 0.71; $P < 0.001$) over clinical predictors (**black line**) (AUC, 0.64; 95% CI, 0.61 to 0.67).

However, based on our results, the assessment of LVEF should be considered if the end-systolic and end-diastolic datasets are available.

Compared with existing modalities (echocardiography, radionuclide angiography, and cardiac MRI) commonly used to assess LVEF, the temporal resolution of contemporary multislice CT scanners is suboptimal.² This limitation may result in the underestimation of end-systolic LV volumes and potentially the underestimation of LVEF. However, recent comparisons of LVEF by CCTA to MRI have shown tight agreement, and our results suggest that the measurement of LVEF with CT remains of high clinical value.^{29–32} The authors recognize that LVEF assessment is commonly available before CCTA. To ensure that CAD severity had incremental prognostic value over LVEF, the sequence of analysis was modified to reflect this scenario. This new model demonstrated that LVEF had incremental value over clinical predictors, and the CAD severity was incremental to LVEF and clinical variables combined with an NRI of 17.8% ($P < 0.001$).

There is mounting enthusiasm for characterization of coronary atherosclerosis and its potential prognostic value over CAD severity and LVEF. Because the coronary calcium scores and plaque characterization were not uniformly available for our study cohort, the incremental values of these measures were not examined.

Prognostic Value of Symptoms

Because patient symptoms may have prognostic value, chest pain and dyspnea were individually evaluated in the multivariable analysis. Dyspnea did not have incremental value over NCEP/ATPIII risk+chest pain. Conversely, chest pain appeared to be protective and was associated with improved survival. Though this finding appears counterintuitive, patient symptoms may have biased patient treatment (medical therapy, revascularization, and downstream investigations). Importantly, inclusion of

chest pain in the multivariable analysis did not change the prognostic power of CCTA.

Limitations

All-cause mortality was used as the primary outcome measure, and the specific causes of death for each patient were not available. Although a previous study demonstrated that 41% of all deaths were related to cardiac causes,¹¹ the proportion of deaths that may have been attributable to cardiac or cardiovascular events is unknown. Because the NCEP/ATP III is traditionally used to predict future cardiovascular events and not all-cause mortality, the authors recognize the potential limitations of NCEP/ATP III for predicting all-cause mortality. Such limitations could result in overestimating the prognostic value of CCTA. Similarly, the ability of CT measures to predict cardiac and cardiovascular events (myocardial infarction and cardiac death) in the COMFIRM Registry cannot be verified. Body mass index, a potential measure with prognostic value, was not reported by all centers and therefore could not be used in the multivariable analysis. Such exclusion could result in the overestimation of CCTA's prognostic value.

The availability of fasting lipid profiles was not uniformly available at all centers. For patients with available fasting lipid profile results, the NCEP was calculated. Because some patients were already being treated with a statin, the fasting lipid profile may not represent their true risk. Because the NCEP/ATP III model was created in a statin-naïve population, patients receiving statin therapy were presumed to have dyslipidemia and were considered to have elevated total cholesterol values and normal HDL. As well, changes in medical therapy as a result of CCTA results were not documented. However, aggressive risk factor modification may reduce cardiovascular events, biasing the results against CCTA.

Not all centers collected information regarding early revascularization. The authors also recognize that patients

10-year Probability of Event after LVEF<50% included

10-year Probability of Event by Clinical	Case	<10%	10%-20%	>20%	Total
	Non-Case				
<10%	101 3034	16 202	3 178	120 3414	
10%-20%	18 940	48 3927	31 555	97 5422	
>20%	0 0	16 2143	38 2716	54 4859	
Total	119 3974	80 6272	72 3449	271 13695	

Steps in calculations
 Patients experiencing death: 50 patients were reclassified upwards and 34 patients were reclassified downwards; Net % classified=(50-34)/271=5.9%
 Patients not experiencing death: 3083 patients were reclassified downwards and 935 patients were reclassified upwards; Net % classified=(3083-935)/13695=15.7%
 NRI=(5.9%+15.7%)=21.6% (p<0.001)

10-year Probability of Event after CAD severity included

10-year Probability of Event by Clinical and LVEF<50%	Case	<10%	10%-20%	>20%	Total
	Non-Case				
<10%	103 3610	14 285	2 79	119 3974	
10%-20%	17 2309	28 2668	35 1295	80 6272	
>20%	0 21	10 920	62 2508	72 3449	
Total	120 5940	52 3873	99 3882	271 13695	

Steps in calculations
 Patients experiencing death: 51 patients were reclassified upwards and 27 patients were reclassified downwards; Net % classified=(51-27)/271=8.9%
 Patients not experiencing death: 3250 patients were reclassified downwards and 1659 patients were reclassified upwards; Net% classified=(3250-1659)/13695=11.6%
 NRI=(8.9%+11.6%)=20.5% (p<0.001)

Figure 4. Calculations of net reclassification improvement (NRI) evaluating the incremental value of left ventricular ejection fraction (LVEF) to a model with clinical variables only and coronary artery disease (CAD) severity to a model with clinical variables and LVEF.

diagnosed with obstructive CAD are more likely to undergo revascularization, which may improve patient survival. This could lead to lower mortality rates in the cohort, resulting in the underestimation of the true prognostic value of CCTA.

Not all participating centers reported absolute percent LVEF; thus LVEF could not be analyzed as a continuous variable for the entire cohort. Because data regarding “abnormal LVEF” (<50%) was available at most centers, LVEF was analyzed as a categorical variable. However, a subanalysis of 7015 patients with absolute LVEF measurements confirmed the findings in the larger cohort.

Conclusions

Our results demonstrate that CCTA measures of CAD severity and LVEF have independent prognostic value. CAD severity has incremental value over LVEF+clinical variables for predicting all-cause death.

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CLINICAL PERSPECTIVE

The prognostic value of cardiac computed tomographic angiography has been demonstrated in single center studies; however, large multicenter studies validating the prognostic value of CCTA and LVEF are lacking. Using a large international multicenter registry (CONFIRM Registry) of 27 125 patients, we sought to confirm the independent and incremental prognostic value of coronary artery disease (CAD) severity measured using 64-slice CT over left ventricular ejection fraction (LVEF) and clinical variables. Multivariable analysis of 14 064 patients, confirmed that LVEF <50% (hazard ratio, 2.74 [2.12 to 3.51]) and CAD severity (hazard ratio, 1.58; 95% confidence interval, 1.42 to 1.76) were predictors of all-cause mortality and CAD severity had incremental value over LVEF and clinical variables. Our results demonstrate that CCTA measures of CAD severity and LVEF have independent prognostic value. Incorporation of CAD severity provides incremental value for predicting all-cause death over routine clinical predictors and LVEF in patients with suspected obstructive CAD.