Cardiac Imaging

CME

Prognostic Assessment of Coronary Artery Bypass Patients With 64-Slice Computed Tomography Angiography

Anatomical Information Is Incremental to Clinical Risk Prediction

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CME Objective for This Article: At the conclusion of this activity, the learner should be able to understand the potential ability of coronary computed tomography angiography to provide risk stratification and prognostic information in coronary artery bypass graft patients.

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Prognostic Assessment of Coronary Artery Bypass Patients With 64-Slice Computed Tomography Angiography

Anatomical Information Is Incremental to Clinical Risk Prediction

Objectives	We sought to determine the incremental prognostic value of 64 multi-slice coronary computed tomography angiography (CCTA) in coronary artery bypass graft (CABG) patients.
Background	Prognostication in CABG patients can be difficult. Anatomical assessment of native coronary artery disease and graft patency might provide useful information, but the utility of CCTA in the assessment of CABG patients is unknown.
Methods	Six hundred fifty-seven CABG patients with all-cause mortality follow-up were identified from a multicenter CCTA registry, of 10,628 patients from 5 CCTA centers. Clinical risk was profiled with modified logistic and additive EuroSCOREs (European Systems for Cardiac Operative Risk Evaluations). The CCTA defined coronary anatomy. Patients were classified by unprotected coronary territory (UCT) or a summary of native vessel disease and graft patency: the coronary artery protection score (CAPS).
Results	Forty-four deaths occurred during a mean follow-up of 20 months. Left ventricular ejection fraction, creatinine, age, severity of native vessel disease, UCT, CAPS, and EuroSCOREs were univariate predictors of mortality ($p < 0.001$). In multivariate analysis with additive EuroSCORE, UCT ($p = 0.004$) and CAPS were predictive of events ($p < 0.001$). In comparison with additive EuroSCORE, CAPS score was associated with a 27% net reclassification index.
Conclusions	Coronary computed tomography angiography provides incremental anatomical data to clinical risk assessment to help determine the prognosis of patients after CABG. The CAPS evaluation with CCTA might help identify those patients at highest risk. (J Am Coll Cardiol 2011;58:2389–95) © 2011 by the American College of Cardiology Foundation

Coronary computed tomography angiography (CCTA) is an emerging technique, with the potential ability to risk-stratify coronary artery bypass (CABG) patients on the basis

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of native vessel anatomy and graft patency (1–4). The utility of risk stratification of CABG patients on the basis of anatomy has been shown with invasive angiography but has not been well-studied with CCTA (5). A noninvasive anatomical test might be desirable, acknowledging that complications from invasive coronary angiography are higher in the CABG population (6).

There are limited data demonstrating the prognostic utility of CCTA in CABG patients. With a multicenter CCTA registry, we sought to evaluate the incremental prognostic value of CCTA to predict all-cause death in CABG patients.

Methods

From February 2004 to June 2010, 10,628 consecutive patients underwent CCTA at 5 centers and were prospectively entered into a multicenter cardiac CCTA registry. The CCTA patients with a history of CABG and coronary and graft CCTA data were selected for study analysis. The study was approved by the Human Research Ethics Board at each participating center, and all patients provided written informed consent.

Clinical predictors. Modified additive and logistical European Systems for Cardiac Operative Risk Evaluation (EuroSCORE) were used. Acute pre-operative markers of operative and anesthetic risk were not consistently available (such as pre-operative state, acute endocarditis,

neurological dysfunction, pulmonary hypertension, ventricular septal rupture, or additional surgery other than CABG) and therefore were omitted. With the additive EuroSCORE, patients were categorized as low (0 to 2), intermediate (>2 to 5), or high risk (>5); and for the logistic EuroSCORE, patients were categorized as low (0 to 3), intermediate (>3 to 10), high (>10 to 20), and very high risk (>20) (7–9).

CCTA measures (coronary artery disease severity and left ventricular ejection fraction). Native coronary and bypass graft CCTA image acquisition and interpretation were performed with single or dual source 64-slice computed tomography scanners. Coronary and graft diameter stenoses were graded with a 4-point score (normal, mild [<50%], moderate [50% to 69%], severe [≥70%]).

Patients were categorized as having 1, 2, or 3 coronary artery disease (CAD) according to the occurrence of severe disease (≥70%) in the right coronary, left anterior descending, and left circumflex territories. Left main disease was classified as 2-vessel disease for patients with a right dominant circulation and 3-vessel disease for those with a left dominant circulation. Branch vessel disease was apportioned to the parent artery. Revascularization was classified in terms of the territories supplied by grafts (right coronary, left anterior descending, or left circumflex). Bypass grafts to branch vessels were assigned to the parent artery. A coronary territory was protected if the native artery supplying the territory did not have severe disease or if the territory was supplied by a nonstenotic graft (5).

Two models of CAD severity were assessed: unprotected coronary territories (UCT), and coronary artery protection score (CAPS) (5,10). The UCT documented the number of vascular territories that were at risk, whereas CAPS combined the severity of both native and graft disease (Table 1).

Patient follow-up. Patient follow-up was performed by each local institution by telephone and/or a national death registry. Centers in the United States used the Social Security Death Index (11).

Statistical analysis. The statistical software SAS (version 9.2, SAS Institute, Inc., Cary, North Carolina) and PASW (Statistics version 18, SPSS, Chicago, Illinois) were used for all statistical analyses, and statistical significance was defined as $p < 0.05$. Continuous variables were expressed as means and SDs, and categorical variables were presented as frequencies with percentages. Wilcoxon rank-sum test was used to compare continuous variables, and Fisher exact test or chi-square test was used for categorical variables. In 29% of patients, left ventricular ejection fraction data were not recorded at CCTA and completed by multiple imputation procedures assuming missing at random in accordance with the registry protocol.

The prognostic value of CAPS was assessed for both univariable and multivariable associations with all-cause mortality. Unadjusted comparisons of all-cause mortality were performed on survival analysis log-rank tests. An-

nual event rates were calculated by dividing the Kaplan-Meier event rates by mean years of follow-up. Risk adjusted analyses were performed with Cox proportional hazard models to determine the independent prognostic value of CAPS by controlling for clinical predictors (additive EuroSCORE) and creating adjusted survival curves. Model overfitting was considered, and the proportional hazards assumption was met. The incremental value of CAPS was calculated by defining the clinical predictors model followed by the addition of CAPS. The area under receiver-operator characteristic curves (95% confidence intervals [CIs]) was compared to evaluate the discrimination ability of CAPS over clinical predictors (12). The net reclassification improvement (NRI) assessed the improvement of reclassification with CAPS (13). For calculating the NRI, rescaled individual predicted risks from models with and without CAPS were compared with established EuroSCOREs risk thresholds (7,14,15).

Abbreviations and Acronyms
CABG = coronary artery bypass graft
CAPS = coronary artery protection score
CCTA = coronary computed tomography angiography
CI = confidence interval
EuroSCORE = European Systems for Cardiac Operative Risk Evaluation
NRI = net reclassification improvement
UCT = unprotected coronary territory

Results

Clinical characteristics. From the 10,628 patients undergoing CCTA, diagnostic data were available for 667 patients with previous CABG surgery. Follow-up was complete on 657 patients (98.5%). The mean follow-up period was 20 ± 10 months (Table 2). The majority of patients had moderate- to high-risk EuroSCORES (Table 3).

Clinical characteristics associated with mortality. At follow-up, all-cause mortality was observed in 44 patients (6.7%) with an annualized mortality rate of 3.8%. Death occurred in 35 of the 322 patients (10.9%) with triple-vessel CAD, compared with 3 (1.9%) of 160 patients with single-vessel CAD (Table 4). Patients with all 3 coronary territories protected had a crude mortality rate of 3.9%. In contrast,

Table 1	CAPS Scoring System	
Extent of Native CAD and Degree of Revascularization		**CAPS**
Single-vessel disease ± 1 protected territory		1
2-vessel disease + 2 protected territories		2
2-vessel disease + 1 protected territory		3
2-vessel disease + 0 protected territory		4
3-vessel disease + 3 protected territories		5
3-vessel disease + 2 protected territories		6
3-vessel disease + 1 protected territory		7
3-vessel disease + 0 protected territory		8

CAD = coronary artery disease; CAPS = coronary artery protection score.

Table 2	Clinical Characteristics (N = 657)	
Age, yrs		68 (61–75)
Male		76.6%
Diabetes		34.1%
Hypertension		76.1%
Family history of coronary artery disease		51.9%
Hyperlipidemia		90.9%
History of smoking		48.9%
History of PVD/CVD		41.2%
Creatinine (μmol/l)		83 ± 50
Prior MI		45.2%
LVEF		62.0 (50–70)
BMI >30 kg/m^2		35.2%
Chest pain		74.4%
Dyspnoea		57.1%

Values are median (25th to 75th percentile), %, or mean ± SD. Symptoms were not recorded in 29% of individuals; percentages represent the frequency of symptoms in those with available data.
BMI = body mass index; CVD = cerebrovascular disease; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PVD = peripheral vascular disease.

Table 3	Clinical Variables (N = 657)	
Additive EuroSCORE		
Low		188 (28.6)
Moderate		113 (17.2)
High		356 (54.2)
Logistic EuroSCORE		
Low		60 (9.1)
Moderate		329 (50.1)
High		207 (31.5)
Severe		61 (9.3)
Grafts to LAD		584 (88.9)
Grafts to LCx		375 (57.1)
Grafts to RCA		408 (62.1)
Left internal mammary artery		485 (73.8)
Other arterial graft		97 (14.6)
Saphenous vein graft		427 (65.0)
Total contrast volume		116 ± 20
Effective dose (mSv)		19.9 ± 8.5

Values are n (%) or mean ± SD.
EuroSCORE = European Systems for Cardiac Operative Risk Evaluation; LAD = left anterior descending artery; LCx = left circumflex artery; RCA = right coronary artery.

patients with 3-vessel CAD and 0 protected coronary territories experienced a crude mortality rate of 17.4%.

In the univariable Cox proportional hazard models, increased hazard ratios for death were associated with advanced age, left ventricular ejection fraction, creatinine, severity of native vessel disease, UCT, and CAPS (Tables 4 and 5). Both the additive and logistic EuroSCOREs were predictive of all-cause mortality (Table 5).

Cox models of risk-adjusted outcomes. The EuroSCORE was used to determine the incremental value of CCTA. In multivariate analyses with the EuroSCORE, UCT (p = 0.004) and CAPS (p < 0.001) were independent predictors of all-cause mortality (Fig. 1, Table 6).

Receiver-operator characteristic curves were created for the additive EuroSCORE, UCT, and CAPS. Area under the curve was 0.64 (95% CI: 0.56 to 0.71) for additive EuroSCORE; 0.68 (95% CI: 0.60 to 0.76) for UCT + additive EuroSCORE (p = 0.08); and 0.75 (95% CI: 0.68 to 0.81) for CAPS + additive EuroSCORE (p < 0.001) (Fig. 2, Table 6). For this reason, CAPS was used in the NRI calculation. The NRI was performed and demonstrated that, after clinical risk stratification with additive EuroSCORE, CAPS was able to reclassify 27.2% (p = 0.003) of patients (Table 7).

Table 4	Univariable Analysis: Clinical Characteristics			
Variables	Alive (n = 613)	All Death (n = 44)	Hazard Ratio (95% CI)	p Value
Age, yrs	68.0 (61, 75)	71.0 (65, 77)	1.04 (1.01–1.08)	0.008
Male	468 (76.3%)	35 (79.5%)	1.20 (0.58–2.50)	0.622
Diabetes	205 (33.6%)	19 (43.2%)	1.49 (0.82–2.70)	0.193
Hypertension	465 (75.9%)	35 (79.5%)	1.23 (0.59–2.55)	0.585
Family history of coronary artery disease	320 (52.2%)	21 (47.7)	0.85 (0.47–1.54)	0.590
Hyperlipidemia	557 (90.9%)	40 (91.0%)	1.14 (0.41–3.18)	0.809
History of smoking	294 (48.0%)	27 (61.4%)	1.71 (0.93–3.13)	0.085
History of PVD/CVD	250 (40.8%)	21 (47.7%)	1.52 (0.84–2.77)	0.171
Creatinine μmol/l	81.1 ± 51.4	114.0 ± 104.8	1.01 (1.00–1.01)	<0.001
BMI ≥30 kg/m^2	219 (35.7%)	13 (29.5%)	0.77 (0.41–1.48)	0.438
Prior MI	272 (44.4%)	25 (56.8%)	1.52 (0.84–2.75)	0.168
LVEF (10% decrease)	59.7 ± 14.6%	51.6 ± 20.1%	1.39 (1.17–1.66)	<0.001
Additive EuroSCORE			1.83 (1.21–2.78)	0.004
Low	185 (29.9%)	5 (11.4%)		
Intermediate	105 (17.1%)	8 (18.2%)		
High	325 (53.0%)	31 (70.5%)		
Logistic EuroSCORE			1.91 (1.32–2.76)	0.001
Low	60 (9.8%)	0		
Intermediate	310 (50.6%)	19 (43.2%)		
High	190 (31.0%)	17 (36.8%)		
Severe	53 (8.6%)	8 (18.2%)		

Values are median (25th, 75th percentile), n (%), or mean ± SD.
Abbreviations as in Table 2.

Table 5	Univariable Analysis: CCTA Variables			
Variables	Alive (n = 613)	All Death (n = 44)	Hazard Ratio (95% CI)	p Value
Native vessel disease			2.63 (1.55–4.46)	<0.001
1	157 (25.6%)	3 (6.8%)		
2	169 (27.6%)	6 (13.6%)		
3	287 (46.8%)	35 (79.5%)		
Unprotected territory			1.73 (1.27–2.36)	<0.001
0	269 (43.9%)	11 (25.0%)		
1	215 (35.1%)	16 (36.4%)		
2	110 (18.0%)	13 (29.5%)		
3	19 (3.0%)	4 (9.0%)		
CAPS			1.40 (1.20–1.63)	<0.001
1	157 (25.6%)	3 (6.8%)		
2	75 (12.2%)	1 (2.3%)		
3	67 (10.9%)	3 (6.8%)		
4	27 (4.4%)	2 (4.5%)		
5	75 (12.2%)	7 (15.9%)		
6	110 (17.9%)	13 (29.5%)		
7	83 (13.5%)	11 (25%)		
8	19 (3.1%)	4 (9.1%)		

CAPS = coronary artery protection score; CCTA = coronary computed tomography angiography; CI = confidence interval.

Discussion

Our analysis demonstrates the usefulness of CCTA to determine prognosis in the CABG population. The CAPS, as assessed by CCTA, is incremental to clinical predictors. The study extends our current understanding of the role of CCTA and highlights the utility of this technique in the CABG population.

We also assessed the prognostic utility of UCT and determined that it did have incremental value over the EuroSCORE in predicting all-cause mortality (p = 0.004) (10). The UCT, however, appeared less predictive than CAPS. It should be noted, however, that in earlier descriptions of UCT different outcomes (all-cause mortality vs. nonfatal MI and cardiac death) were used (10).

To understand the value of CAPS, the NRI was calculated. The NRI demonstrated that, after clinical evaluation, CAPS was able to appropriately reclassify 27.2% of patients.

Overall, the annualized mortality in the study cohort was 3.8%. Higher levels of annualized mortality rates were seen with accumulating severity of native vessel disease and CAPS score (Fig. 1). The use of CAPS as a

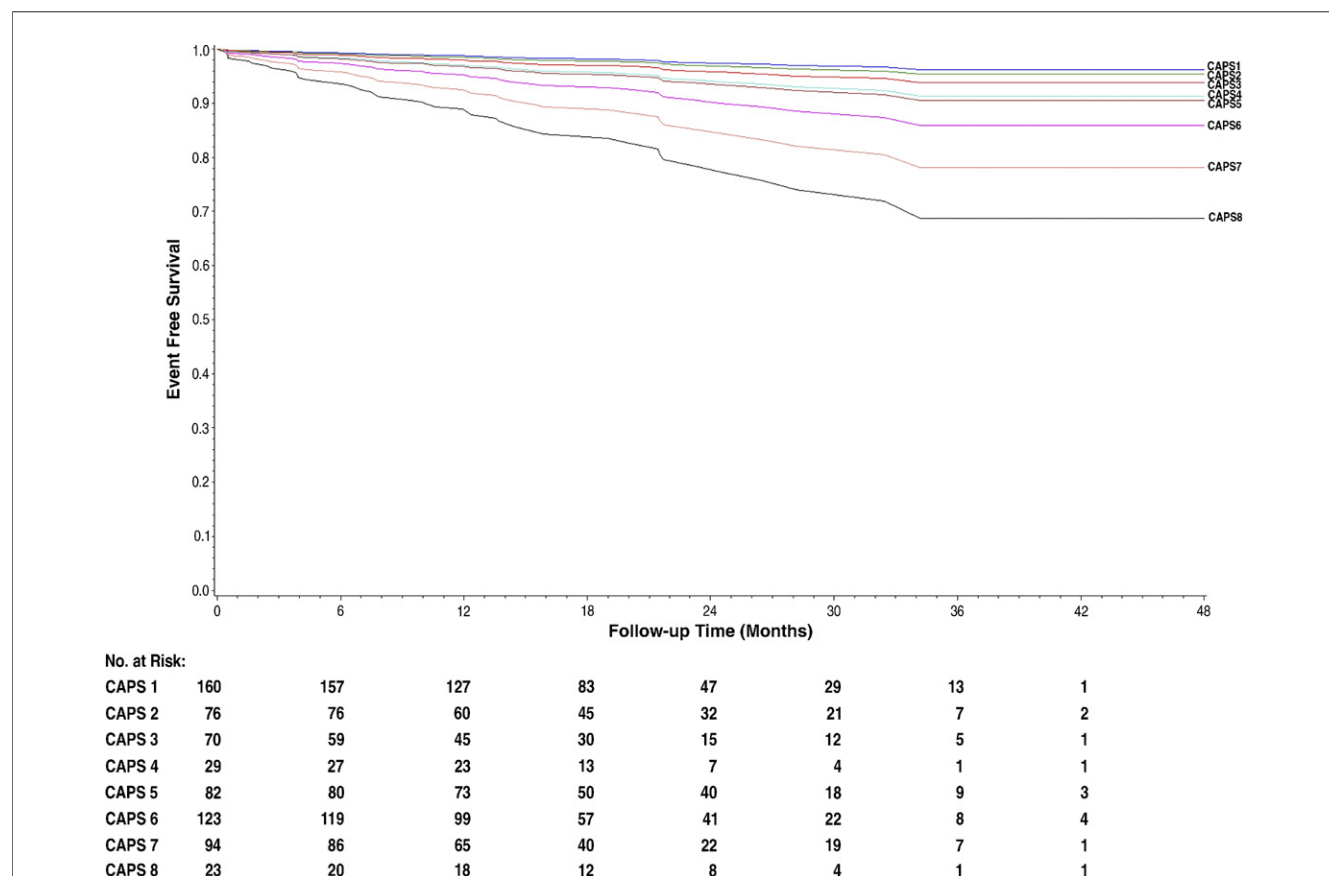| No. at Risk:								
CAPS 1	160	157	127	83	47	29	13	1
CAPS 2	76	76	60	45	32	21	7	2
CAPS 3	70	59	45	30	15	12	5	1
CAPS 4	29	27	23	13	7	4	1	1
CAPS 5	82	80	73	50	40	18	9	3
CAPS 6	123	119	99	57	41	22	8	4
CAPS 7	94	86	65	40	22	19	7	1
CAPS 8	23	20	18	12	8	4	1	1

Figure 1   Risk-Adjusted Survival Curve for CAPS

Risk-adjusted (for additive European Systems for Cardiac Operative Risk Evaluation) survival for coronary artery protection score (CAPS) (CAPS 1 to 8). Numbers of patients at risk depicted at 6 monthly intervals.

Table 6	Cox Models of CCTA Measures		
Models	Hazard Ratio (95% CI)	p Value	Global Chi-Square Statistic
Clinical variable	2.23 (1.45–3.45)	<0.001	
Additive EuroSCORE			
Clinical + CCTA data			
Additive EuroSCORE	2.04 (1.31–.16)	0.002	
UCT	1.35 (0.98–1.84)	0.004	21.5
0	1.00	—	
1	1.86 (0.86–4.01)	0.116	
2	2.63 (1.17–5.92)	0.020	
3	3.95 (1.25–12.50)	0.020	
Clinical + CCTA data			
Additive EuroSCORE	2.05 (1.33–3.15)	0.001	
CAPS	1.35 (1.17–1.56)	<0.001	30.5
1	1.00	—	
2	0.74 (0.08–7.16)	0.797	
3	3.11 (0.63–15.45)	0.166	
4	4.46 (0.74–26.77)	0.102	
5	5.33 (1.37–20.82)	0.016	
6	6.26 (1.78–22.0)	0.004	
7	6.21 (1.73–22.32)	0.005	
8	8.76 (1.96–39.20)	0.005	

Model fitting reported by global chi-square statistic.

UCT = unprotected coronary territory; other abbreviations as in Table 3 and 4.

measure of native CAD and graft patency highlights important differences in prognosis between different anatomical subgroups and emphasizes that prognosis in CABG patients does vary. Such results suggest that certain populations of CABG patients might require closer clinical surveillance.

Study limitations. Because cardiac death was not available at all sites, all-cause mortality was used as the outcome variable. Although the authors recognize that noncardiac deaths might have been included in the analysis, 87% of all CABG patient deaths are cardiac (16). The time interval between CABG surgery and CCTA was not available and therefore could not be factored into the analysis. Many of the pre-operative findings and markers of anesthetic risk were absent; therefore, our modified EuroSCORE calculation might have under-estimated its true prognostic value. The registry could not distinguish between the various grafts used; therefore, we were unable to examine the influence of different arterial and venous grafts on prognosis. Not all CCTA studies will be diagnostic in CABG patients. Because the database did not identify nonevaluable CCTA studies, the results of this study should only apply to diagnostic CCTA studies. The mean radiation exposure was nearly 20 mSv; however, recent technological advances have reduced radiation exposure significantly, and therefore it is unlikely this value represents current CCTA practice.

Conclusions

This study suggests that CCTA has independent and incremental prognostic value in CABG patients in predict-
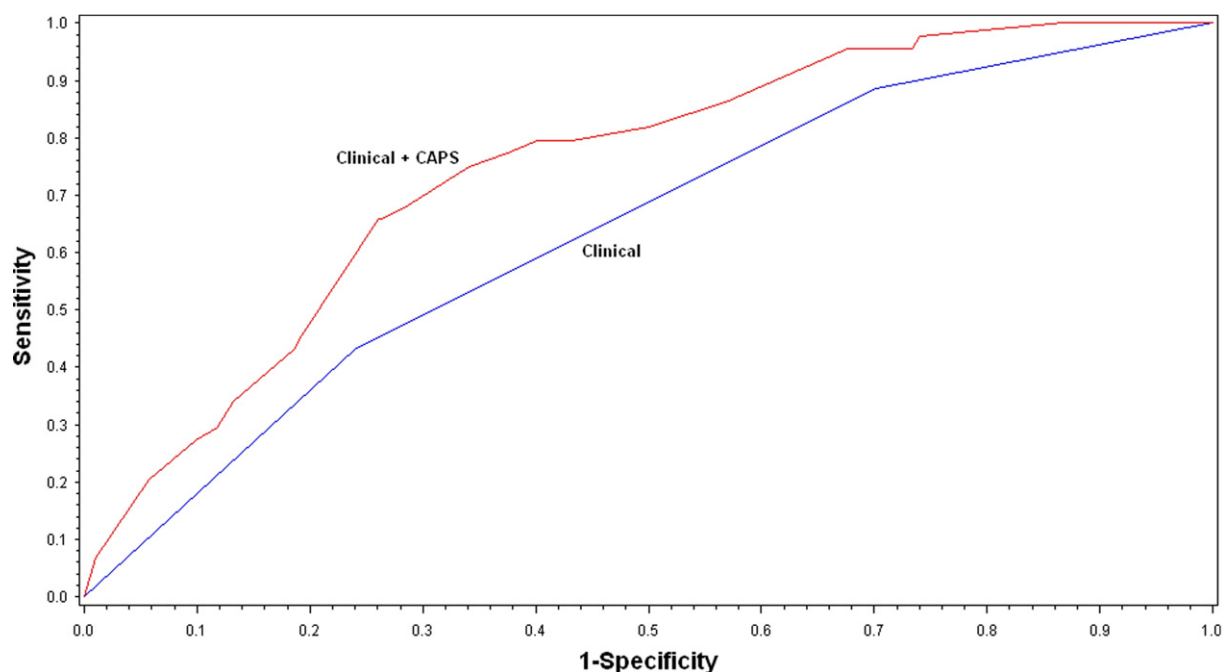

Figure 2   **Receiver-Operator Characteristic Curves for Multivariate Models**

Additive European Systems for Cardiac Operative Risk Evaluation + coronary artery protection score **(red line)** area under the curve 0.75 (95% confidence interval: 0.68 to 0.81) versus Additive European Systems for Cardiac Operative Risk Evaluation **(blue line)** 0.64 (95% confidence interval: 0.56 to 0.71) (global chi-square = 30.5, p < 0.001).

Table 7	**Evaluating the Incremental Value of CAPS to a Model With Clinical Variables Only (Additive EuroSCORE)**			
5-Year Probability of Event by Clinical Variables	**5-Year Probability of Event After CAPS Included**			
	<10%	**10%–20%**	**>20%**	**Total**
10%				
Case	11	4	0	15
Non-case	73	41	0	114
10%–20%				
Case	3	6	6	15
Non-case	105	49	81	235
>20%				
Case	0	2	12	14
Non-case	30	84	150	264
Total				
Case	14	12	18	44
Non-case	208	174	231	613

Net reclassification improvement calculation: 48 month follow-up data rescaled to 5 years, allowing comparison with published 5 year outcomes using additive EuroSCOREs. Patients experiencing death: 10 patients were reclassified upwards and 5 patients were reclassified downward. Net percentage classified = (10–5)/44 = 11.4%. Patients not experiencing death: 219 patients reclassified downward, and 122 patients reclassified upward; net percentage classified = (219–122)/613 = 15.8%. Net reclassification improvement = (11.4% + 15.8%) = 27.2% (p = 0.003).

CAPS = coronary artery protection score; EuroSCORE = European Systems for Cardiac Operative Risk Evaluation.

ing all-cause mortality. Patients with a low CAPS have much better outcomes than those with a high CAPS score. Incremental to the clinical predictors, CCTA-derived CAPS appropriately reclassified 27.2% of patients. Further studies are required to understand the role of CCTA in managing patients after CABG.

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