Optimized Prognostic Score for Coronary Computed Tomographic Angiography

Results From the CONFIRM Registry (COronary CT Angiography EvaluatioN For Clinical Outcomes: An InteRnational Multicenter Registry)

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Objectives   The aim of this study was to analyze the predictive value of coronary computed tomography angiography (CCTA) and to model and validate an optimized score for prognosis of 2-year survival on the basis of a patient population with suspected coronary artery disease (CAD).

Background   Coronary computed tomography angiography carries important prognostic information in addition to the detection of obstructive CAD. But it is still unclear how the results of CCTA should be interpreted in the context of clinical risk predictors.

Methods   The analysis is based on a test sample of 17,793 patients and a validation sample of 2,506 patients, all with suspected CAD, from the international CONFIRM (COronary CT Angiography EvaluatioN For Clinical Outcomes: An InteRnational Multicenter) registry. On the basis of CCTA data and clinical risk scores, an optimized score was modeled. The endpoint was all-cause mortality.

Results   During a median follow-up of 2.3 years, 347 patients died. The best CCTA parameter for prediction of mortality was the number of proximal segments with mixed or calcified plaques (C-index 0.64, p < 0.0001) and the number of proximal segments with a stenosis >50% (C-index 0.56, p = 0.002). In an optimized score including both parameters, CCTA significantly improved overall risk prediction beyond National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) score as best clinical score. According to this score, a proximal segment with either a mixed or calcified plaque or a stenosis >50% is equivalent to a 5-year increase in age or the risk of smoking.

Conclusions   In CCTA, both plaque burden and stenosis, particularly in proximal segments, carry incremental prognostic value. A prognostic score on the basis of this data can improve risk prediction beyond clinical risk scores.   (J Am Coll Cardiol 2013;62:468–76) © 2013 by the American College of Cardiology Foundation

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Coronary computed tomography angiography (CCTA) is commonly accepted as a clinically useful modality for the diagnosis and exclusion of obstructive coronary artery disease (CAD), particularly in patients with intermediate pre-test risk (1,2). It allows for, in addition to stenosis assessment, the noninvasive detection and further characterization of coronary plaques even in the absence of obstruction. Although the presence of obstructive CAD is the cornerstone for further medical and invasive therapy, multiple smaller studies (3–14) have revealed that nonobstructive plaques might have a significant influence on prognosis. Nevertheless, due to the small number of patients in these studies, only limited data exist concerning the best parameters to describe severity and extent of coronary atherosclerosis in the context of prognosis.

See page 477

The objective of this study was to analyze the predictive value of different parameters to assess the presence, extent, and type of coronary atherosclerotic plaque by computed tomography (CT) angiography and to model and validate an optimized prognostic score for 2-year survival in a large population of patients with suspected CAD from an international multicenter registry.

Methods

Study population. The CONFIRM (COronary CT Angiography EvaluatioN For Clinical Outcomes: An

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InteRnational Multicenter) registry is an international, multicenter, observational registry collecting clinical, procedural, and follow-up data of patients undergoing CCTA for clinically indicated reasons, currently comprising 31,807 patients from 17 participating sites in 7 countries (United States, Canada, Germany, Switzerland, Italy, Austria, and South Korea).

The CONFIRM registry contains 2 sections. Section 1 comprises 27,125 patients from 12 sites enrolled between January 2004 and May 2010 and was locked in October 2010. This section served as the test sample. Section 2 comprises 4,682 patients from 5 sites enrolled between July 2005 and October 2010 (database locked in May 2011) and served as validation sample. Institutional review board approval was obtained at each center.

Inclusion criteria for this analysis were: 1) patients with suspected but not proven CAD; 2) assessment of both luminal stenosis as well as presence and composition of plaque in CCTA; and 3) a follow-up of at least 90 days. The exclusion criterion of known CAD was defined as patient reported past myocardial infarction, coronary revascularization, or presence of any stents or grafts/graft stenosis as recorded by CT findings.

A detailed description of the methods is published elsewhere (15). A structured interview was conducted before the investigation to collect information on symptoms attributable to cardiac disease and the presence of cardiovascular risk factors. Systemic arterial hypertension was defined as a documented history of blood pressure >140 mm Hg 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. A positive smoking history was defined as current smoking or cessation of smoking within 3 months of testing. Family history of premature coronary heart disease was defined as history of myocardial infarction of a first-degree relative below the age of 55 years for male and 65 years for female relatives. In addition blood cholesterol levels of the lipid test nearest to the index examination were recorded; the median time interval between CT exam and lipid test was 39 days in the test sample and 70 days in the validation sample. From these data, the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) (NCEP ATP III) score (16), the Framingham risk score (17), and the Morise clinical risk score (18) were calculated. **Image acquisition and analysis.** All CCTA investigations were performed on multiple-row detector CT scanners with at least 64 simultaneously acquired slices, and the imaging

Abbreviations and Acronyms

CAD = coronary artery disease

CCTA = coronary computed tomography angiography

CI = confidence interval

CT = computed tomography

IQR = interquartile range

NCEP ATP III = National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)

NRI = net reclassification improvement

protocol adhered to the Society of Cardiovascular Computed Tomography guidelines on appropriateness and performance of CCTA, as far as available at the time of scanning (2,19,20). Patient preparation, data acquisition, and analysis were according to the institutional policies of the local sites.

Coronary segments were scored visually for the presence and composition of coronary plaque and degree of luminal stenosis with a 16-segment coronary artery model (21). In each coronary artery segment, plaques were classified as noncalcified, mixed, or calcified. The presence of coronary calcification was determined visually in the contrast-enhanced dataset. Noncalcified plaque was defined as a tissue structure >1 mm^2 that could be clearly discriminated from the vessel lumen and surrounding tissue, with a density below the contrast-enhanced blood pool. Plaques meeting this definition and in addition showing calcified areas of any extent were classified as mixed plaques. The severity of luminal diameter stenosis was scored visually as none (0% luminal stenosis), mild (1% to 49% luminal stenosis), moderate (50% to 69% luminal stenosis), or severe ($\geq$70% luminal stenosis). For further analysis, the numbers of segments with a specific plaque composition or a specific luminal stenosis were summed up. The number of segments with any plaque or stenosis is equivalent to the segment involvement score proposed by Min et al. (7).

From each of these base scores optimized jeopardy scores were derived, assessing only proximal segments (proximal and mid right coronary artery, left main, proximal, and mid left anterior descendent, proximal circumflex, first obtuse marginal branch) and describing the result in 3 categories: no proximal segment affected; 1 proximal segment affected; $\geq$2 proximal segments affected.

With the best clinical risk score and the most predictive CCTA parameters the combined CONFIRM risk score was modeled.

Follow-up and study endpoint. The primary endpoint of the study was time to death from any cause. In U.S. sites, death status was ascertained by querying the Social Security Death Index. In non-U.S. sites, follow-up data were collected by mail or telephone contact with the patients or their families; events were verified by hospital records or contacts with the attending physician.

Statistical analysis. Categorical variables were expressed as frequencies and percentages; continuous variables were expressed as mean $\pm$ SD. All statistical evaluations are based on survival with the Kaplan-Meier method; hazard ratios (for difference between 75th and 25th percentile) and multivariable analyses were calculated with the Cox proportional hazard model. Significant contribution to a multivariable model was tested with Akaike's information criterion. C-indexes were calculated from time-to-event data as proposed by Harrell et al. (22). The incremental predictive value was assessed with the net reclassification improvement (NRI) according to Pencina et al. (23). For modeling the CONFIRM risk score, both internal validation by randomly

splitting the test sample and external validation on an independent dataset were performed; the modeling process is described in detail in a statistical supplement in the Online Appendix. Statistical significance was accepted for 2-sided p values <0.05. The statistical package R (version 2.10.1) (24) including the package rms (25) was used for statistical analysis.

Results

Study population, clinical characteristics, and follow-up. Of 27,125 patients in the test sample, 2,350 patients were excluded because of known CAD, 814 patients were excluded because of missing data on contrast enhanced coronary angiography (mainly because only calcium scoring was performed), 5,844 patients were excluded from sites not assessing plaque characterization, 1 patient was excluded because of missing information on age, and 323 patients were excluded because available follow-up was missing or <90 days. Hence, the study population for the test sample comprised 17,793 patients. Of 4,682 patients in the validation sample, 377 patients were excluded because of known CAD, 447 patients were excluded because of missing data on contrast enhanced coronary angiography, 1,334 patients were excluded from sites not assessing plaque characterization, 5 patients were excluded because of missing information on age, and 13 patients were excluded because available follow-up was missing or <90 days. Hence, the study population for the test sample comprised 2,506 patients.

Median age of the patients was 58 years (interquartile range [IQR]: 49 to 66 years) in the test sample and 57 years [IQR: 48 to 65 years] in the validation sample (p $<$ 0.0001). Sex distribution was similar in both groups, with 9,440 men (53%) in the test sample, and 1,319 men (53%) in the validation sample (p = 0.70). There were significant differences in risk profile and symptoms on presentation, as can be seen in Table 1. The pre-test risk was predominantly low when assessed by the NCEP ATP III and Framingham score and predominantly intermediate, according to the Morise score.

During a median follow-up of 2.3 years (IQR: 1.6 to 3.1 years) in the test sample, 317 patients died. This corresponds to an annual mortality rate of 0.75% (95% confidence interval [CI]: 0.67% to 0.82%). In the validation sample the median follow-up was 1.5 years (IQR: 1.0 to 2.8 years), and 30 patients died, resulting in an annual mortality rate of 0.63% (95% CI: 0.45% to 0.91%).

Predictive value of clinical risk scores. All 3 clinical risk scores correlated significantly with outcome. The best was NCEP ATP III (c-index 0.706), followed by the Framingham risk (c-index 0.623) and then the Morise (c-index 0.618) scores (see also Table 2). The difference between NCEP ATP III and Framingham was significant (p $<$ 0.0001); therefore all further analysis was based on NCEP ATP III.

Predictive value of CCTA. Patients had 2.1 $\pm$ 2.8 coronary segments affected by plaques, of which 0.3 $\pm$ 0.9 (17%)

Table 1	Clinical Characteristics and Risk Factors		
	Test Sample (n = 17,793)	Validation Sample (n = 2,506)	p Value
Age, yrs	58 (49–66)	57 (48–65)	<0.0001
Male	9,440 (53%)	1,319 (53%)	0.70
Hypertension	9,029 (51%)	1,432 (57%)	<0.0001
Diabetes	2,668 (15%)	402 (16%)	0.17
Total cholesterol, mg/dl	189 (162–217)	196 (166–226)	<0.0001
LDL cholesterol, mg/dl	115 (92–140)	114 (89–141)	0.36
HDL cholesterol, mg/dl	51 (42–61)	52 (43–64)	0.0003
Current smoker	3,634 (20%)	471 (19%)	0.059
Family history for CAD	6,174 (35%)	1,136 (45%)	<0.0001
Angina pectoris			<0.0001
Nonanginal chest pain	2,316 (13%)	390 (16%)	
Atypical angina	6,491 (37%)	476 (19%)	
Typical angina	3,024 (17%)	553 (22%)	
Dyspnea on exertion	5,919 (33%)	569 (23%)	<0.0001
NCEP ATP III risk	7.5 (2.5–16.4)	6.4 (2.0–16.6)	0.0013
Low risk (<10)	10,522 (59%)	1,523 (61%)	
Intermediate risk (10–20)	3,551 (20%)	433 (17%)	
High risk (>20)	3,720 (21%)	550 (22%)	
Framingham risk	9.8 (5.9–15.9)	9.8 (5.7–16.1)	0.49
Low risk (<10)	9,022 (51%)	1,263 (51%)	
Intermediate risk (10–20)	5,637 (32%)	790 (32%)	
High risk (>20)	2,951 (17%)	430 (17%)	
Morise score	11 (9–14)	11 (9–13)	0.015
Low risk (<9)	3,510 (20%)	486 (19%)	
Intermediate risk (9–15)	12,445 (70%)	1,794 (72%)	
High risk (>9)	1,838 (10%)	226 (9%)	

Values are median (interquartile range) or occurrences (%).

CAD = coronary artery disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein; NCEP ATP III = National Cholesterol Education Program Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III).

were noncalcified, 0.8 ± 1.6 (38%) were mixed, and 0.9 ± 1.7 (45%) were calcified. A mean of 0.5 ± 1.1 segments (22% of all segments with plaques) revealed a significant stenosis (>50% lumen reduction), and 0.2 ± 0.6 (7%) revealed a severe stenosis (>70% lumen reduction).

All of these parameters correlated significantly with outcome, except the number of segments with noncalcified plaques. After correction for clinical risk, the correlation with outcome remained significant only for the total number of segments with plaque (c-index 0.62, p < 0.0001). The predictive value could be significantly increased by focusing on proximal segments only (p = 0.0026 compared with the total number of segments with plaque) and further by only counting calcified or mixed plaque (p = 0.0030 for improvement). Although the number of all segments with stenosis >50% did not correlate significantly with outcome,

Table 2	Predictive Value of Clinical Risk Scores in the Test Group					
Score	No Death (n = 17,476)	Death (n = 317)	Hazard Ratio (95% CI)	Chi-Square	C-Index	p Value
NCEP ATP III risk	9.4 ± 7.7	15.5 ± 8.2	3.01 (2.62–3.45)	171	0.706	<0.001
Low risk (<10)	10,437 (60%)	85 (27%)				
Intermediate risk (10–20)	3,460 (20%)	91 (29%)				
High risk (>20)	3,579 (20%)	141 (44%)				
Framingham risk	12.5 ± 9.97	19.9 ± 16.6	1.54 (1.44–1.65)	118	0.623	<0.001
Low risk (<10)	8,920 (52%)	104 (33%)				
Intermediate risk (10–20)	5,543 (32%)	94 (30%)				
High risk (>20)	2,832 (16%)	119 (37%)				
Morise score	11.3 ± 3.25	12.7 ± 2.84	1.98 (1.67–2.36)	60	0.618	<0.001
Low risk (<9)	3,492 (20%)	18 (6%)				
Intermediate risk (9–15)	12,203 (70%)	242 (76%)				
High risk (>9)	1,781 (10%)	57 (18%)				

Values are mean ± SD or n (%), unless otherwise indicated.

CI = confidence interval.

Table 3	Predictive Value of Degree of Stenosis and Plaque Composition

| CT Parameter	No Death (n = 17,476)	Death (n = 317)	Hazard Ratio (95% CI)	Uncorrected		Corrected for Clinical Risk	
				C-Index	p Value	C-Index	p Value
Number of segments with any plaque or stenosis	2.1 ± 2.7	3.6 ± 2.87	1.22 (1.03–1.44)	0.683	<0.0001	0.621	<0.0001
Number of segments with stenosis >50%	0.45 ± 1.06	1.1 ± 1.58	1.17 (1.05–1.29)	0.643	<0.0001	0.524	0.29
Number of segments with stenosis >70%	0.15 ± 0.56	0.46 ± 0.99	1.26 (1.07–1.48)	0.603	<0.0001	0.535	0.18
Number of segments with noncalcified plaques	0.4 ± 0.86	0.31 ± 0.64	1.00 (0.84–1.19)	0.502	0.9	0.501	0.99
Number of segments with mixed plaques	0.77 ± 1.62	1.52 ± 1.9	1.06 (0.98–1.15)	0.619	<0.0001	0.516	0.60
Number of segments with calcified plaques	0.92 ± 1.72	1.77 ± 2.4	1.08 (1.01–1.15)	0.642	<0.0001	0.550	0.10
Number of segments with calcified or mixed plaques	1.69 ± 2.44	3.28 ± 2.68	1.41 (1.21–1.65)	0.696	<0.0001	0.618	<0.0001
Number of proximal segments with calcified or mixed plaques	0.32 ± 0.65	0.77 ± 0.87	1.39 (1.14–1.70)	0.696	<0.0001	0.643	<0.0001
Number of proximal segments with stenosis >50%	0.14 ± 0.43	0.41 ± 0.67	1.46 (1.15–1.87)	0.652	<0.0001	0.563	0.04

Values are mean ± SD, unless otherwise indicated.
CI = confidence interval; CT = computed tomography.

the number of proximal segments with stenosis >50% was a significant predictor (c-index 0.56, p = 0.003). Adjusted risk stratification is summarized in Table 3 and graphically displayed in Figure 1. Compared with NCEP ATP III score (c-index 0.706) risk prediction could be improved both by the number of proximal segments with mixed or calcified plaques (c-index 0.741 for the combined model, p < 0.0001 for improvement) and the number of proximal segments with stenosis >50% (c-index 0.734 for the combined model, p = 0.003 for improvement).

Combined score. An optimized score was modeled, combining clinical risk assessment and CCTA parameters that comprised 3 parameters: the NCEP ATP III score, the number of proximal segments with stenosis >50%, and the number of proximal segments with either calcified or mixed plaques. This model could significantly improve prediction beyond the NCEP ATP III score both in the test sample (NRI 49%,

p < 0.0001) and in the validation sample (NRI 60%, p = 0.0011). The model is summarized in Table 4, the incremental predictive value is visualized in Figure 2, and a detailed description of the modeling process is provided as a statistical supplement in the Online Appendix. An online calculator for the CONFIRM prognostic score is available (26).

To be comparable with the NCEP APT III score, which assesses the risk for cardiac death or myocardial infarction instead of overall mortality as used in this study, cutoffs of 0.8% and 1.6% annual mortality rate between low and intermediate risk and between intermediate and high risk were used, respectively. With these values, the annual mortality rate ranged from 0.32% (95% CI: 0.26% to 0.39%) for low risk to 1.3% (95% CI: 1.1% to 1.6%) for intermediate risk to 2.4% (95% CI: 2.0% to 2.9%) for high risk in the test sample and from 0.29% (95% CI: 0.15% to 0.56%) for low risk to 1.1% (95% CI: 0.64% to 2.0%) for
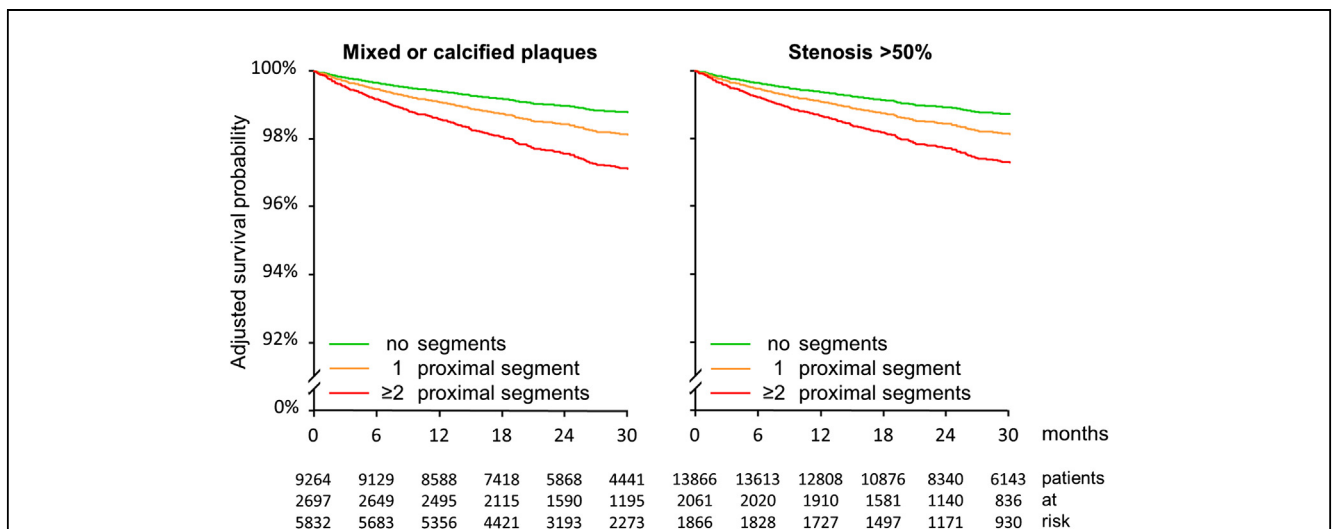
Figure 1	Kaplan-Meier Plot

Survival probability dependent on proximal segments with calcified or mixed plaque **(left)** and proximal stenosis >50% **(right)**, corrected for National Cholesterol Education Program Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III) score.

Table 4	Incremental Predictive Value of Proximal Plaque in CCTA				
Model				**Net Reclassification From Clinical Risk**	
Parameter	**Coefficient**	**p Value**		**Test Sample**	**Validation Sample**
Model 1: Clinical risk				Base model	Base model
NCEP ATP III risk	0.207	<0.0001			
Model 2: Clinical risk + CT parameters				49% (p < 0.0001)	60% (p = 0.0011)
NCEP ATP III risk	0.144	<0.0001			
Proximal mixed or calcified plaque	0.407	0.0003			
Proximal stenosis >50%	0.398	0.0001			

National Cholesterol Education Program Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III) (NCEP ATP III) risk is formatted to represent 1 score point in the published point system. The first 2 proximal segments with calcified or mixed plaques and the first 2 proximal segments with a stenosis >50% are each equivalent to 2.8 points (16). For further details please refer to the statistical supplement in the Online Appendix.

intermediate risk to 1.6% (95% CI: 0.84% to 3.1%) for high risk in the validation sample. With these risk categories, 32% of the patients in the test sample and 33% of the patients in the validation sample could be reclassified with regard to their cardiovascular risk. In the test sample 3,909 patients (22.0%) were assigned to a lower risk, and 1,774 patients (10.0%) were assigned to a higher risk. Similar percentages were found in the validation sample, as described in Figure 3 in more detail.

Discussion

It is well known from single-center studies that, in addition to the degree of stenosis, the extent of coronary atherosclerosis as documented by CCTA is an important prognostic factor. Ostrom et al. (10) demonstrated a correlation between mortality and the number of involved vessels both for nonobstructive and obstructive lesions. Min et al. (7) found that a segment involvement score counting segments that exhibited plaque, irrespective of stenosis severity, had a particularly good correlation with survival. Our analysis of 20,299 patients from the international CONFIRM registry reaffirms the predictive value

of segmental plaque burden above and beyond the degree of stenosis.

Multiple studies both on invasive angiography and on CCTA have shown that diseased proximal segments are prognostically more relevant than distal ones, and a number of jeopardy scores with varying complexity have been proposed to account for this fact (7,27,28). In our patient population, we identified 7 coronary segments as being important for prognosis: the left main, proximal, mid-left anterior descending, proximal circumflex and the first obtuse marginal branch, and the proximal and mid-right coronary artery. By focusing only on the presence of atherosclerotic plaques in these segments the predictive value of CCTA could be improved significantly.

With regard to plaque composition, we found that exclusively noncalcified plaques had no significant correlation with mortality. Furthermore, a predictive model considering only mixed or calcified plaques was significantly better than a model considering all plaques. This result is surprising, because non-calcified plaque components are often considered more vulnerable to future rupture and hence future myocardial infarction and death (29,30). A possible explanation for this finding could be that CCTA is
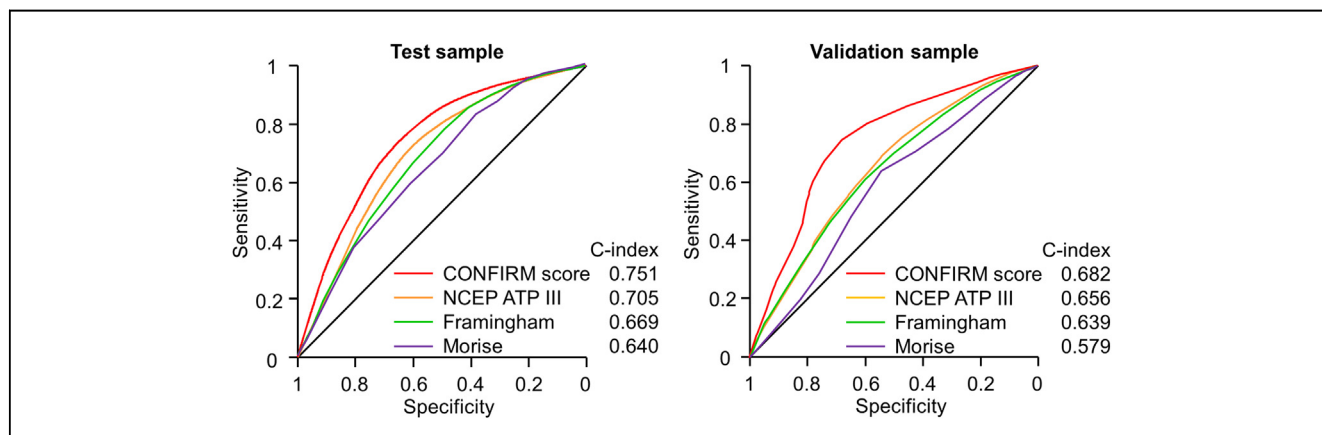
Figure 2   ROC Curve for All-Cause Mortality

Receiver operator characteristics (ROC) of Morise; Framingham; and National Cholesterol Education Program Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III) (NCEP ATP III) clinical scores and the optimized score (additionally including proximal segments with calcified or mixed plaque and proximal segments with stenosis >50%). Test sample on the **left**, and validation sample on the **right**. CONFIRM = COronary CT Angiography EvaluatioN For Clinical Outcomes: An InteRnational Multicenter registry.
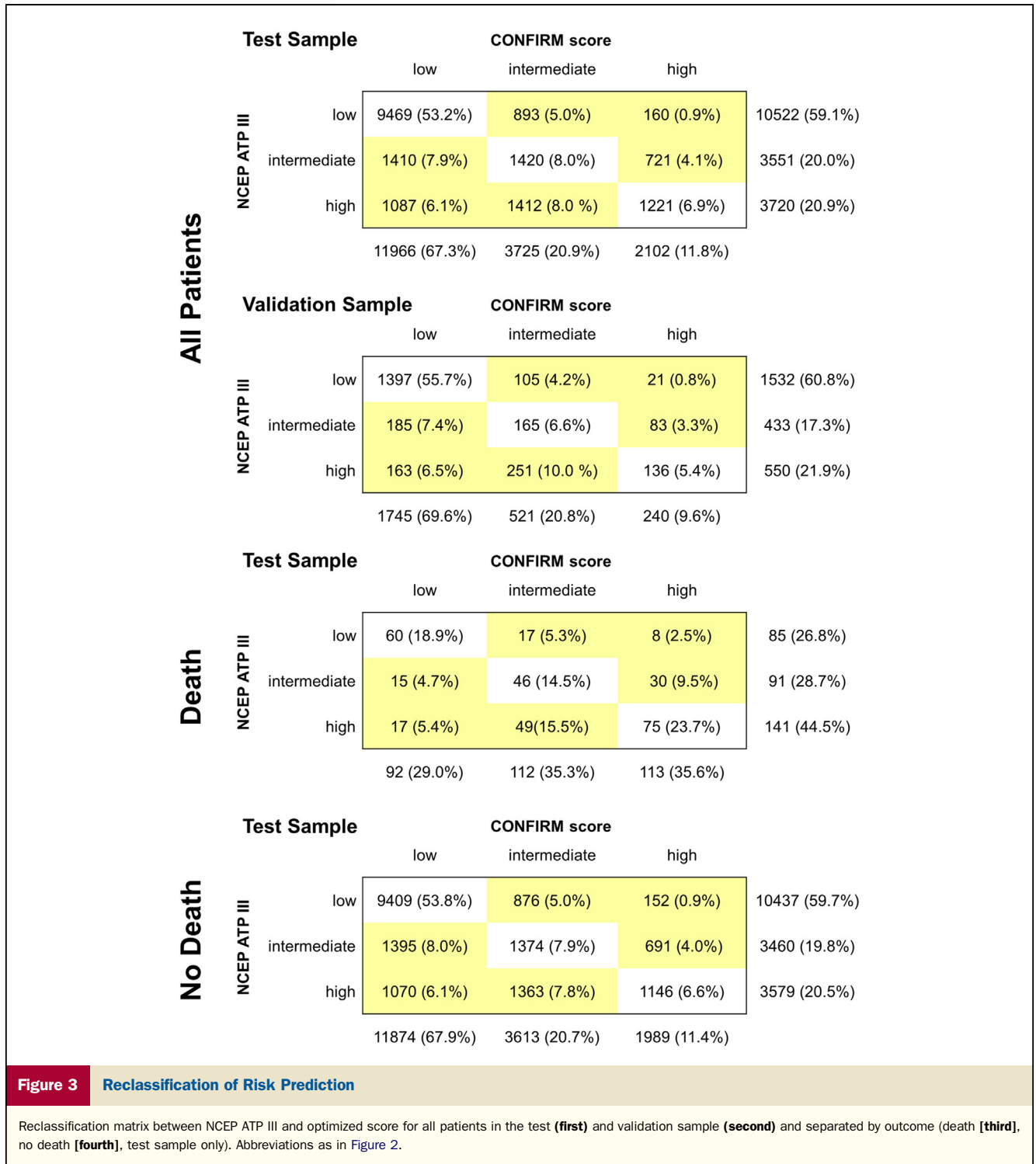
Figure 3   Reclassification of Risk Prediction

Reclassification matrix between NCEP ATP III and optimized score for all patients in the test **(first)** and validation sample **(second)** and separated by outcome (death **[third]**, no death **[fourth]**, test sample only). Abbreviations as in Figure 2.

not able to identify the rupture-prone plaques and that vulnerable plaques are only a small fraction of all noncalcified plaques identified by CCTA. Taking into account the size of this study population, this finding deserves further analysis beyond the scope of the present report.

On the basis of the current study, we identified the 2 parameters "number of proximal segments with mixed or calcified plaques" and "number of proximal segments with stenosis >50%" as the best CCTA parameter improving outcome predicting beyond clinical risk scores.

Putting these parameters in context with the clinical risk factors as assessed by the NCEP ATP III score, which was the best clinical risk predictor in our cohort, we found that both a proximal segment with mixed or calcified plaques and

a proximal segment with stenosis >50% are equivalent to 2.8 score points in the published point model of the NCEP ATP III score (16), which is in the same range as an increase in age of 5 years or the average risk of smoking.

These results confirm the incremental prognostic value of CCTA beyond clinical risk factors and allow for a quantification of the risk associated with proximal plaque in CCTA. This risk is not only significant but also substantial and in the same ranges as relevant clinical risk factors like hypertension or smoking. Thus CCTA can describe the vascular age and the associated risk for mortality.

Assessing the prognosis of a typical patient undergoing CCTA having a low to intermediate risk for CAD is difficult. Most of the established risk scores like the Framingham risk score are tested on asymptomatic individuals and aim for the long-term prediction of symptomatic CAD. Both criteria are not met in the patient group of interest. Even the Morise score, which is designed for the risk of all-cause mortality in symptomatic patients, had a limited predictive value in our study population. Obviously, this score, which was validated on a patient population with a higher annual mortality (1.1% vs. 0.75% in our study), cannot be applied to a low- to intermediate-risk population without restrictions.

It is our opinion, on the basis of the largest patient population currently available, that the proposed combined score now clearly improves risk prediction beyond established clinical risk scores and allows for a robust risk assessment of patients with suspected CAD undergoing CCTA.

This might facilitate a more targeted prevention regimen for CAD. Patients at high risk according to the new score have an annual mortality risk of >1.0%, and an intensified preventive regimen including both lifestyle change and medication seems logical. In low-risk patients, there might be the possibility for reducing preventive efforts. However, we have limited information on medication during follow-up in our study, and this option must be validated by prospective outcome studies.

An analysis of invasive angiographies and revascularizations during follow-up is beyond the scope of this study and is covered by a companion paper (31).

Study limitations. This is an observational multicenter study. Pre-test risk differs significantly between sites. This might confound the results of the study. However, the risk score performed significantly in all sites (Online Appendix), demonstrating the broad applicability of the results. There is only limited information with regard to lifestyle modification and medical and interventional therapy during follow-up, so that a correction for its confounding influence was not possible. This is an inherent limitation of the study design and can only be circumvented by prospective outcome trials. Nevertheless, the results of this study are based on the largest currently available pooled patient population, and they can serve as a robust base for the design and initiation of such trials.

The weak correlation between noncalcified plaques and outcome might be caused by the heterogeneity of the study population and the equipment used. Detection of noncalcified plaques is not always easy, particularly with suboptimal image quality, and might be influenced by filters used for image presentation, which vary considerably between vendors. In addition, advanced reconstruction algorithms were not widely available at the time the scans of this study were performed.

Conclusions

In patients undergoing CCTA, both atherosclerotic plaque burden and obstructive coronary disease—particularly in the proximal segments—carry incremental prognostic value beyond clinical risk factors. The increase in mortality risk associated with the presence of proximal CAD manifestation in CCTA is comparable with the risk of clinical risk factors like smoking or an increase in "vascular" age of 5 years. A predictive score combining CCTA parameters with clinical information significantly improves prediction compared with well-established clinical risk scores and allows for a reclassification of approximately one-third of the patients with regard to their mortality risk.

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Key Words: coronary artery disease ■ coronary CT angiography ■ prognosis.

► **APPENDIX**

For supplementary material, please see the online version of this article.