Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix 1. PROMISE Trial Organization

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eAppendix 2. Statistical Methods

Application of Model

Using the final model, the predicted probability of Minimal Risk was computed for each subject in both the CCTA cohort and the functional testing cohort. For each cohort, the distribution of predicted probabilities was divided into deciles where the first decile included patients with lowest predicted probabilities of Minimal Risk (i.e., the patients least likely to be Minimal Risk), and the 10th decile included patients with the highest predicted probabilities (i.e., the patients most likely to be Minimal Risk). The frequency (%) of cardiovascular death or MI was reported for the combined CCTA and functional arms, since the results from the overall results comparing testing strategies in the PROMISE trial were neutral.[1] Criteria used for test results categories are shown in eTable 1. Following model building and for model application purposes, patients were excluded if they 1) had missing test results or uninterpretable test results (92 patients in the CCTA arm, 95 patients in the functional arm) or 2) were missing any of the 10 variables required to compute the probability of Minimal Risk in the final model (46 patients in the CCTA arm and 48 patients in the functional arm), aside from total and HDL cholesterol, which were imputed due to having >5% missingness.

Model Performance Comparisons

We compared the final Minimal Risk model to the predictive ability of 2 different scores currently used in clinical practice but not specifically designed for predicting Minimal Risk per our definition: 1) the Framingham Risk Score[2] and 2) the Combined Diamond–Forrester/ Coronary Artery Surgery Study (CASS) Score.[3] A logistic regression model was fit using the entire CCTA cohort and each of the 2 scores as predictors. The resulting c-statistics, as well as the corresponding receiver operating characteristic (ROC) curve for each model, including the PROMISE Minimal Risk model, were computed.

eTable 1. Complete Baseline Clinical Characteristics in the Full CCTA Analysis Population[a]

	Minimal Risk (N=1156)	**Other (N=3476)**	**All Subjects (N=4632)**	**p-value**
Age, mean ± SD, y[b]	57.7 ± 7.18	61.4 ± 8.30	60.5 ± 8.19	<.001
Female sex[b]	746 (64.5%)	1645 (47.3%)	2391 (51.6%)	<.0001
Racial or ethnic minority[b]	300 (26.2%)	747 (21.6%)	1047 (22.7%)	0.0014
Physician estimate of likelihood of obstructive disease[b]				
Very low/low (≤30%)	513 (44.4%)	1204 (34.7%)	1717 (37.1%)	<.001
Intermediate/high/very high (>30%)	642 (55.6%)	2265 (65.3%)	2907 (62.9%)	
Cardiac risk factor				
Hypertension[b]	665 (57.5%)	2326 (66.9%)	2991 (64.6%)	<.0001
Diabetes[b]	185 (16.0%)	784 (22.6%)	969 (20.9%)	<.0001
Metabolic Syndrome[b]	356 (30.8%)	1367 (39.3%)	1723 (37.2%)	<.0001
Dyslipidemia[b]	707 (61.2%)	2412 (69.4%)	3119 (67.3%)	<.0001
Family history of premature CAD[b]	348 (30.2%)	1166 (33.7%)	1514 (32.8%)	0.0311
Peripheral artery disease[b]	12 (1.0%)	65 (1.9%)	77 (1.7%)	0.0552
History of TIA	14 (1.2%)	52 (1.5%)	66 (1.4%)	0.4783
History of Stroke[b]	9 (0.8%)	77 (2.2%)	86 (1.9%)	0.0017
History of CVD[b]	27 (2.3%)	151 (4.3%)	178 (3.8%)	0.0021
History of CAS[b]	1 (0.1%)	23 (0.7%)	24 (0.5%)	0.0183
NYHA Class[b]				
Normal	1125 (97.6%)	3392 (98.1%)	4517 (98.0%)	0.3372
II or III	28 (2.4%)	64 (1.9%)	92 (2.0%)	
IV	0 (0.0%)	2 (0.1%)	2 (0.0%)	
Tobacco smoking[b]				<.001
Never	667 (57.7%)	1609 (46.3%)	2276 (49.1%)	
Ever	488 (42.3%)	1867 (53.7%)	2355 (50.9%)	
History of depression	246 (21.3%)	662 (19.0%)	908 (19.6%)	0.0972

	Minimal Risk (N=1156)	**Other (N=3476)**	**All Subjects (N=4632)**	**p-value**
Participate in physical activity	610 (52.8%)	1776 (51.2%)	2386 (51.6%)	0.3635
Risk burden				
Risk factors per patient				<.001
N	1156	3476	4632	
Mean ± SD	2.1 ± 0.99	2.5 ± 1.09	2.4 ± 1.08	
CAD equivalent[b]	215 (18.6%)	920 (26.5%)	1135 (24.5%)	<.001
Framingham Risk Score				<.001
N	1155	3469	4624	
Mean ± SD	14.9 ± 10.19	23.4 ± 15.57	21.3 ± 14.89	
Combined Diamond-Forrester/CASS, mean ± SD	47.2 ± 20.58	55.4 ± 21.25	53.3 ± 21.37	<.001
ASCVD Pooled Cohort Risk Score				<.001
N	1144	3438	4582	
Mean ± SD	9.5 ± 8.47	15.9 ± 11.90	14.3 ± 11.48	
Chest pain characterization				
Typical	120 (10.4%)	425 (12.2%)	545 (11.8%)	0.2120
Atypical	907 (78.5%)	2689 (77.4%)	3596 (77.6%)	
Non-Cardiac	129 (11.2%)	362 (10.4%)	491 (10.6%)	
Primary symptom[b]				
Chest Pain	906 (78.4%)	2506 (72.2%)	3412 (73.7%)	<.001
Dyspnea	122 (10.6%)	532 (15.3%)	654 (14.1%)	
Other	128 (11.1%)	435 (12.5%)	563 (12.2%)	
Primary symptom related to physical/mental stress[b]				
No	597 (51.6%)	1494 (43.0%)	2091 (45.2%)	<.001
Yes	430 (37.2%)	1606 (46.2%)	2036 (44.0%)	
Unknown	129 (11.2%)	373 (10.7%)	502 (10.8%)	

	Minimal Risk (N=1156)	**Other (N=3476)**	**All Subjects (N=4632)**	**p-value**
Primary symptom relieved by rest or nitroglycerin within 10 min[b]				
Always/Usually	340 (29.4%)	1178 (33.9%)	1518 (32.8%)	0.0146
Rarely/Never	269 (23.3%)	786 (22.6%)	1055 (22.8%)	
Unknown	547 (47.3%)	1509 (43.4%)	2056 (44.4%)	
Physical Exam				
BMI (kg/m^2)[b]				0.1387
N	1149	3441	4590	
Mean ± SD	30.3 ± 6.04	30.5 ± 6.02	30.5 ± 6.03	
Pulse (bpm)				0.7747
N	1153	3468	4621	
Mean ± SD	72.4 ± 11.66	72.3 ± 11.85	72.3 ± 11.80	
Normal (60-100 bpm)	1002 (86.9%)	2994 (86.3%)	3996 (86.5%)	0.6230
Abnormal	151 (13.1%)	474 (13.7%)	625 (13.5%)	
Diastolic BP				0.8011
N	1156	3469	4625	
Mean ± SD	78.7 ± 10.34	78.7 ± 10.15	78.7 ± 10.20	
Systolic BP[b]				<.001
N	1156	3469	4625	
Mean ± SD	128.7 ± 16.20	131.9 ± 16.55	131.1 ± 16.52	
Investigations				
GFR				0.1266
N	1142	3441	4583	
Median (25^{th}, 75^{th})	77.5 (67.4, 89.5)	77.1 (66.6, 89.0)	77.2 (66.9, 89.2)	
Mean ± SD	80.4 ± 18.49	79.3 ± 19.03	79.6 ± 18.90	
Min, Max	36.4, 179.5	33.5, 228.6	33.5, 228.6	
GFR Categorical				
<60	122 (10.7%)	461 (13.4%)	583 (12.7%)	0.0171

	Minimal Risk (N=1156)	Other (N=3476)	All Subjects (N=4632)	p-value
≥60	1020 (89.3%)	2980 (86.6%)	4000 (87.3%)	
Hemoglobin				0.0607
N	621	1830	2451	
Median (25^{th}, 75^{th})	14.1 (13.1, 14.9)	14.2 (13.2, 15.1)	14.2 (13.2, 15.0)	

[a]Values are expressed as number (percentage) unless otherwise indicated.
[b]Variables included in the multivariable analysis.
[#]CAD risk equivalent was defined as diabetes, peripheral vascular disease, or cerebrovascular disease.
Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; CAS, carotid artery stenosis; CASS, Coronary Artery Surgery Study; CCTA, coronary computed tomographic angiography; CVD, cerebrovascular disease; NYHA, New York Heart Association; TIA, transient ischemic attack.

eTable 2. Prospective Categorization of Noninvasive Imaging Test Results in the Anatomical and Functional Testing Arms of the Study

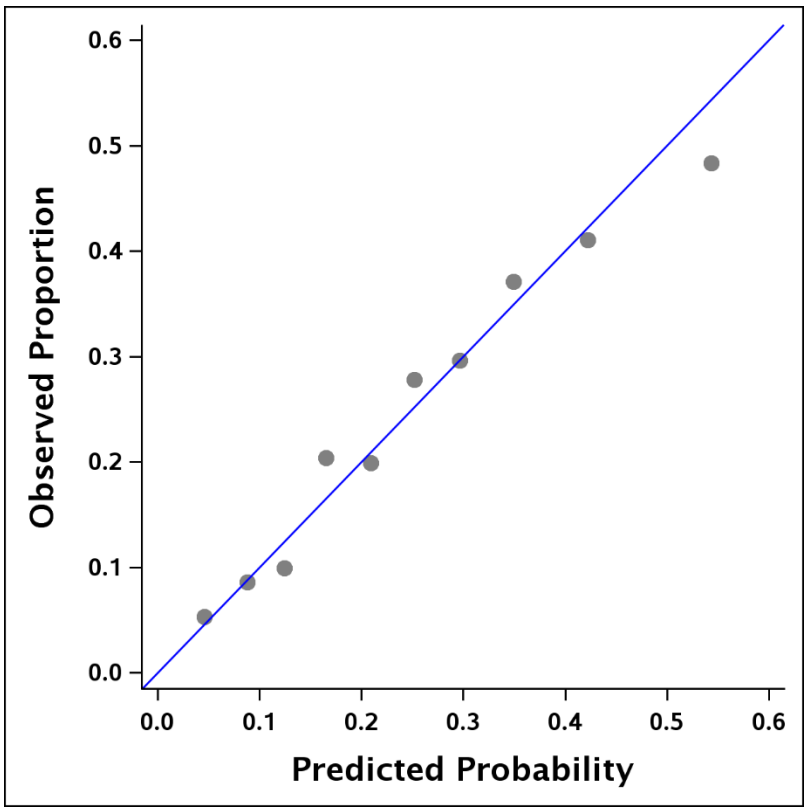
		Anatomic	Functional		
Test Strata		Coronary CTA	ETT	Stress MPI	Stress Echo
Abnormal	Severely abnormal	High-Risk CAD ≥2-vessel disease (≥70%) or ≥50% left main stenosis or ≥70% proximal LAD stenosis	Ischemic ECG ST changes consistent with ischemia during stress + either severe ventricular arrhythmia OR hypotension	Large territory inducible ischemia or mixed defect Septal/anterior/apical territory or other single territory with transient ischemic dilatation or 2 or more coronary territories with ischemia	Large territory inducible ischemia or mixed defect Wall motion abnormality or mixed abnormality (infarct and ischemia) Isolated septal/anterior/apical or other single territory +↓EF <35% during stress or 2 or more coronary territories
	Moderately abnormal	Obstructive CAD 50 to <70% proximal LAD stenosis, ≥70% stenosis in 1 major vessels/branch, 50 to <70% stenosis in any major vessel or vessels/branches*	Early positive TM Failure to reach stage 2, <3:00 min with ST changes OR symptoms reproduced OR any arrhythmia or hypotension	Inducible ischemia or mixed defect Perfusion abnormality in one coronary territory (lateral or inferior/posterior) OR Normal imaging but early positive TM Failure to reach stage 2, <3:00 min with ST changes OR symptoms reproduced OR any arrhythmia or hypotension	Inducible ischemia or mixed defect Wall motion abnormality or mixed abnormality (infarct and ischemia) in one coronary territory (lateral or inferior/posterior) OR Normal imaging but early positive TM Failure to reach stage 2, <3:00 min with ST changes OR symptoms reproduced

					OR any arrhythmia or hypotension
	Mildly abnormal	Nonobstructive CAD <50% stenosis or <50% left main stenosis	Late positive TM More than stage 2, >3:00 min, but failure to finish protocol or target heart rate achieved due to ST changes OR symptoms reproduced OR any arrhythmia or hypotension	Positive ECG Normal perfusion or fixed perfusion defect (Scar) OR Normal imaging but late positive TM More than stage 2, >3:00 min, but failure to finish protocol or target heart rate achieved due to ST changes OR symptoms reproduced OR any arrhythmia or hypotension	Positive ECG but normal wall motion or resting wall motion abnormality without inducible ischemia OR Normal imaging but late positive TM More than stage 2, >3:00 min, but failure to finish protocol or target heart rate achieved due to ST changes OR symptoms reproduced OR any arrhythmia or hypotension
Normal		Normal	Normal	Normal	Normal

*For secondary categorization, mildly abnormal was defined as <70% luminal narrowing.

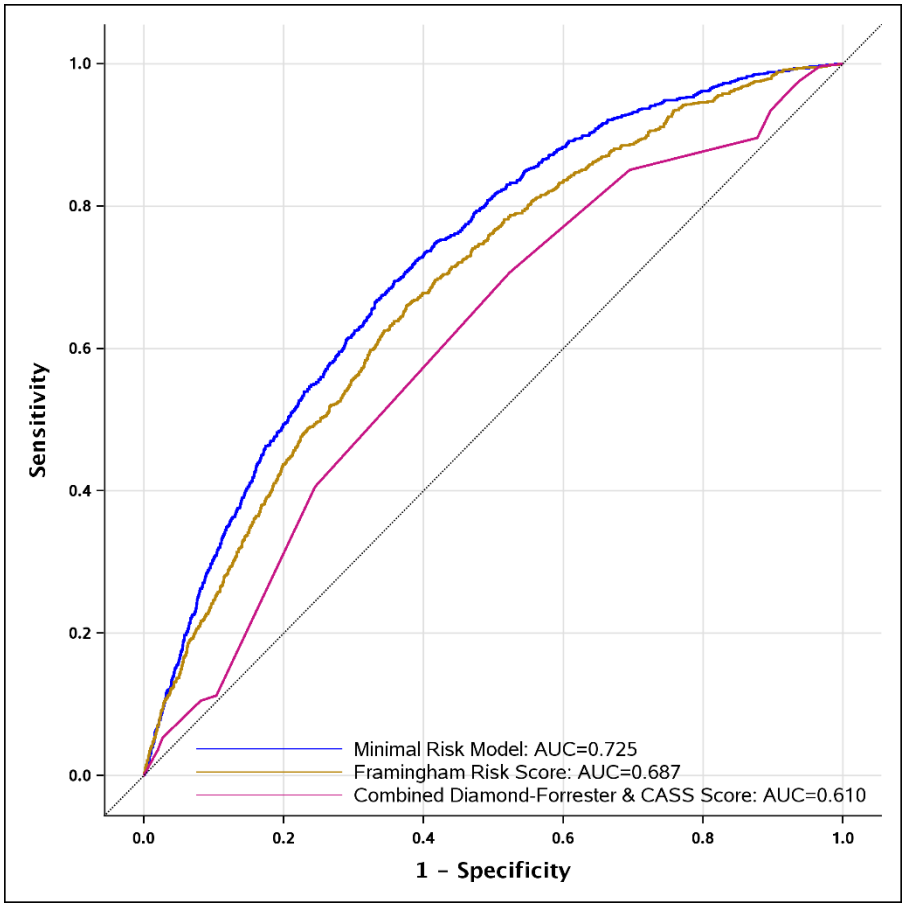
Abbreviations: CAD, coronary artery disease; CTA, computed tomographic angiography; ECG, electrocardiogram; ETT, exercise treadmill test; LAD, left anterior descending artery; MPI, myocardial perfusion imaging; TM, treadmill.

eFigure 1. Model Calibration in the CCTA Validation Cohort



Observed proportion of Minimal Risk subjects (y-axis) by decile of predicted values (x-axis). Excellent calibration is demonstrated graphically and by the Hosmer–Lemeshow calibration statistic (chi-square=5.91, P=0.66).

eFigure 2. Comparison of Risk Scores for the Prediction of Minimal Risk



The PROMISE Minimal Risk score (area under the curve [AUC] =0.725; 95% CI, 0.709-0.741) better categorizes patients as Minimal Risk compared to both the Framingham (AUC=0.687; 95% CI, 0.670-0.704) and combined Diamond-Forrester/Coronary Artery Surgery Study Scores (AUC=0.610; 95% CI, 0.592-0.628).

eReferences

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3. Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: executive summary: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation.* 2012;126(25):3097-3137.