Supplemental Material

Supplement to Hoffmann U, Ferencik M, Udelson JE, et al. Prognostic value of noninvasive cardiovascular testing in patients with stable chest pain: insights from the PROMISE trial.

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Supplemental Table 1. Baseline characteristics of the population for prognostic analysis vs. the patients enrolled but not included.*

Variable	Patients included in the Prognostic Analysis (N=9118)	Excluded Patients (N=885)	P Value
Demographics			
Mean age — yr	60.7 ± 8.2	61.1 ± 8.9	0.742
Female sex — no. (%)	4796 (52.6%)	474 (53.6%)	0.585
Racial or ethnic minority — no. (%)	2006 (22.1%)	242 (27.5%)	<0.001
Cardiac risk factors			
Mean body mass index (kg/m^2)	30.4 ± 6.0	31.1 ± 7.1	0.214
Hypertension — no. (%)	5904 (64.8%)	597 (67.5%)	0.098
Diabetes — no. (%)	1940 (21.3%)	204 (23.1%)	0.213
Dyslipidemia — no. (%)	6169 (67.7%)	598 (67.6%)	0.995
Family history of premature CAD — no. (%)	2891 (31.8%)	311 (35.3%)	0.034
Peripheral or cerebrovascular disease — no. (%)	495 (5.4%)	57 (6.4%)	0.205
CAD equivalent — no. (%)	2293 (25.1%)	238 (26.9%)	0.254
History of heart failure — no. (%)	339 (3.7%)	26 (2.9%)	0.239
Metabolic syndrome — no. (%)	3441 (37.7%)	331 (37.4%)	0.843
Current or past tobacco use — no. (%)	4672 (51.3%)	432 (48.9%)	0.176
Sedentary lifestyle — no. (%)	4419 (48.6%)	447 (50.7%)	0.216
History of depression — no. (%)	1878 (20.6%)	180 (20.4%)	0.881
Risk factor burden			
No major risk factors — no. (%)	246 (2.7%)	17 (1.9%)	0.168
Mean number of risk factors per patient	2.4 ± 1.1	2.4 ± 1.0	0.149
Mean combined Diamond and Forrester and Coronary Artery Surgery Study risk score	53.2 ± 21.3	53.6 ± 22.5	0.378
Framingham risk score — no. (%)			
Low risk (<6%)	620 (6.8%)	66 (7.5%)	0.668
Intermediate risk (6-20%)	4672 (51.3%)	442 (50.1%)	
High risk (>20%)	3814 (41.9%)	374 (42.4%)	
ASCVD pooled cohort risk prediction (2013) — no. (%)			
Low risk (<7.5%)	2919 (32.3%)	285 (32.7%)	0.831
Elevated risk (≥7.5%)	6110 (67.7%)	587 (67.3%)	
Relevant medications — no. (%)			
Beta-blocker	2166 (24.8%)	233 (27.6%)	0.079
ACE inhibitor or ARB	3823 (43.8%)	371 (43.9%)	0.963
Statin	3994 (45.8%)	395 (46.7%)	0.591
Aspirin	3896 (44.7%)	384 (45.4%)	0.661
Primary presenting symptom and anginal type — no. (%)			
Chest pain	6630 (72.8%)	642 (72.6%)	0.931
Dyspnea on exertion	1369 (15.0%)	121 (13.7%)	0.287
Anginal type — site-reported			
Typical	1044 (11.4%)	122 (13.8%)	0.099
Atypical	7107 (77.9%)	666 (75.3%)	
Non-anginal	967 (10.6%)	97 (11.0%)	

* Plus-minus values are means ±SD. ACE indicates angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; and CAD, coronary artery disease.

Supplemental Table 2. Frequency of test findings and association with clinical events for anatomic and functional testing for a definition of nonobstructive coronary artery disease from 1-49%.

Test Results	Anatomic Testing (N=4516)				Functional Testing (N=4602)			
	Results Frequency— no./N (%)	Event Rate— no./N (%)	Hazard Ratio (95% CI)	P Value	Results Frequency— no./N (%)	Event Rate— no./N (%)	Hazard Ratio (95% CI)	P Value
All-cause death/MI/UA								
Severely Abnormal	632/4516 (14.0)	56/632 (8.9)	8.55 (4.62–15.83)	<0.0001	365/4602 (7.9)	35/365 (9.6)	3.88 (2.58–5.85)	<0.0001
Moderately Abnormal	449/4516 (9.9)	21/449 (4.7)	4.82 (2.42–9.63)	<0.0001	217/4602 (4.7)	13/217 (6.0)	2.65 (1.46–4.83)	0.0014
Mildly Abnormal	1930/4516 (42.7)	46/1930 (2.4)	2.38 (1.30–4.38)	0.0051	432/4602 (9.4)	9/432 (2.1)	0.94 (0.47–1.89)	0.8666
Normal	1505/4516 (33.3)	14/1505 (0.9)	REF		3588/4602 (78.0)	75/3588 (2.1)	REF	
CV death/MI/UA								
Severely Abnormal	632/4516 (14.0)	50/632 (7.9)	14.11 (6.50–30.65)	<0.0001	365/4602 (7.9)	31/365 (8.5)	4.59 (2.93–7.19)	<0.0001
Moderately Abnormal	449/4516 (9.9)	19/449 (4.2)	7.97 (3.44–18.47)	<0.0001	217/4602 (4.7)	13/217 (6.0)	3.50 (1.89–6.48)	<0.0001
Mildly Abnormal	1930/4516 (42.7)	32/1930 (1.7)	2.99 (1.37–6.56)	0.0061	432/4602 (9.4)	8/432 (1.9)	1.11 (0.53–2.34)	0.7834
Normal	1505/4516 (33.3)	8/1505 (0.5)	REF		3588/4602 (78.0)	56/3588 (1.6)	REF	
CV death/MI								
Severely Abnormal	632/4516 (14.0)	20/632 (3.2)	4.85 (1.96–12.04)	0.0007	365/4602 (7.9)	14/365 (3.9)	2.13 (1.16–3.91)	0.0141
Moderately Abnormal	449/4516 (9.9)	9/449 (2.0)	3.65 (1.33–10.04)	0.0122	217/4602 (4.7)	5/217 (2.3)	1.53 (0.60–3.90)	0.3681
Mildly Abnormal	1930/4516 (42.7)	24/1930 (1.2)	2.23 (0.94–5.27)	0.0671	432/4602 (9.4)	5/432 (1.2)	0.81 (0.32–2.04)	0.6542
Normal	1505/4516 (33.3)	7/1505 (0.5)	REF		3588/4602 (78.0)	48/3588 (1.3)	REF	

CV indicates cardiovascular; MI, myocardial infarction; and UA, unstable angina.

Supplemental Table 3. Test findings and clinical events in 4602 patients randomized to the functional arm of PROMISE according to the functional test performed.

	Exercise Treadmill N=467 (10.1%)		Stress Echocardiography N=1019 (22.1%)		Stress Nuclear Perfusion N=3116 (67.8%)	
	No. of Patients	No. of Events	No. of Patients	No. of Events	No. of patients	No. of Events
All cause death/MI/UA						
Severely Abnormal	0	0	66	4	299	31
Moderately Abnormal	59	2	16	0	142	11
Mildly Abnormal	77	1	57	2	298	6
Normal	331	3	880	14	2377	58
CV death/MI/UA						
Severely Abnormal	0	0	66	4	299	27
Moderately Abnormal	59	2	16	0	142	11
Mildly Abnormal	77	0	57	2	298	6
Normal	331	3	880	7	2377	46
CV death/MI						
Severely Abnormal	0	0	66	2	299	12
Moderately Abnormal	59	0	16	0	142	5
Mildly Abnormal	77	0	57	0	298	5
Normal	331	2	880	6	2377	40

CV indicates cardiovascular; MI, myocardial infarction; and UA, unstable angina.

Supplemental Table 4. Frequency of test findings and association with clinical events for anatomic and functional testing in patients prespecified to receive stress nuclear perfusion imaging.

Initial Test Results	Anatomical Testing (N=3050)				Functional Testing (N=3136)			
	Frequency n/N(%)	Event Rate n/N(%)	Hazard Ratio (95% CI)	P-value	Frequency n/N(%)	Event Rate n/N(%)	Hazard Ratio (95% CI)	P-value
All cause death/MI/UA								
Severely Abnormal	199/3050 (6.52)	21/199 (10.55)	14.49 (5.67, 37.04)	<.0001	299/3136 (9.53)	31/299 (10.37)	4.34 (2.77, 6.78)	<.0001
Moderately Abnormal	191/3050 (6.26)	16/191 (8.38)	12.07 (4.63, 31.48)	<.0001	146/3136 (4.66)	12/146 (8.22)	3.14 (1.67, 5.91)	0.0004
Mildly Abnormal	1699/3050 (55.70)	52/1699 (3.06)	4.33 (1.84, 10.21)	0.0008	298/3136 (9.50)	6/298 (2.01)	0.81 (0.35, 1.89)	0.6277
Normal	961/3050 (31.51)	6/961 (0.62)	REF		2393/3136 (76.31)	55/2393 (2.30)	REF	
CV death/MI/UA								
Severely Abnormal	199/3050 (6.52)	19/199 (9.55)	19.59 (6.45, 59.50)	<.0001	299/3136 (9.53)	27/299 (9.03)	4.80 (2.95, 7.80)	<.0001
Moderately Abnormal	191/3050 (6.26)	13/191 (6.81)	14.81 (4.73, 46.39)	<.0001	146/3136 (4.66)	12/146 (8.22)	4.04 (2.11, 7.72)	<.0001
Mildly Abnormal	1699/3050 (55.70)	40/1699 (2.35)	5.03 (1.78, 14.22)	0.0023	298/3136 (9.50)	6/298 (2.01)	1.03 (0.44, 2.42)	0.9450
Normal	961/3050 (31.51)	4/961 (0.42)	REF		2393/3136 (76.31)	44/2393 (1.84)	REF	
CV death/MI								
Severely Abnormal	199/3050 (6.52)	8/199 (4.02)	6.90 (1.74, 27.34)	0.0060	299/3136 (9.53)	12/299 (4.01)	2.21 (1.15, 4.26)	0.0179
Moderately Abnormal	191/3050 (6.26)	4/191 (2.09)	4.36 (0.95, 20.11)	0.0588	146/3136 (4.66)	5/146 (3.42)	1.86 (0.72, 4.77)	0.1982
Mildly Abnormal	1699/3050 (55.70)	27/1699 (1.59)	3.51 (1.04, 11.83)	0.0429	298/3136 (9.50)	5/298 (1.68)	0.98 (0.39, 2.51)	0.9740
Normal	961/3050 (31.51)	3/961 (0.31)	REF		2393/3136 (76.31)	38/2393 (1.59)	REF	

CV indicates cardiovascular; MI, myocardial infarction; and UA, unstable angina.

Supplemental Table 5. Sensitivity analysis of the association of the definition of normal functional testing with and without consideration of the cardiovascular risk factors (Framingham Risk Score).
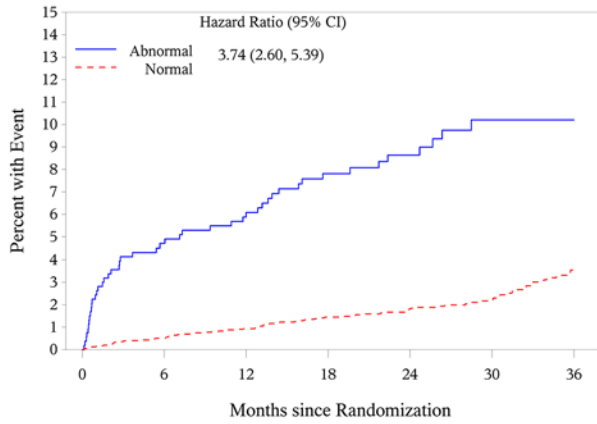
Initial Test Results	Functional Testing – original definition (N=4602)				Functional Testing – New mildly abnormal definition (N=4602)			
	Frequency n/N (%)	Event Rate n/N (%)	Hazard Ratio (95% CI)	P-value	Frequency n/N (%)	Event Rate n/N (%)	Hazard Ratio (95% CI)	P-value
All cause death/MI/UA								
Severely Abnormal	365/4602 (7.93)	35/365 (9.59)	3.88 (2.58, 5.85)	<.0001	365/4602 (7.93)	35/365 (9.59)	6.01 (2.68, 13.51)	<.0001
Moderately Abnormal	217/4602 (4.72)	13/217 (5.99)	2.65 (1.46, 4.83)	0.0014	217/4602 (4.72)	13/217 (5.99)	4.14 (1.64, 10.45)	0.0026
Mildly Abnormal	432/4602 (9.39)	9/432 (2.08)	0.94 (0.47, 1.89)	0.8666	3146/4602 (68.36)	76/3146 (2.42)	1.61 (0.75, 3.45)	0.2219
Normal	3588/4602 (77.97)	75/3588 (2.09)	REF		874/4602 (18.99)	8/874 (0.92)	REF	
CV death/MI/UA								
Severely Abnormal	365/4602 (7.93)	31/365 (8.49)	4.59 (2.93, 7.19)	<.0001	365/4602 (7.93)	31/365 (8.49)	6.05 (2.54, 14.41)	<.0001
Moderately Abnormal	217/4602 (4.72)	13/217 (5.99)	3.50 (1.89, 6.48)	<.0001	217/4602 (4.72)	13/217 (5.99)	4.63 (1.76, 12.24)	0.0020
Mildly Abnormal	432/4602 (9.39)	8/432 (1.85)	1.11 (0.53, 2.34)	0.7834	3146/4602 (68.36)	57/3146 (1.81)	1.38 (0.61, 3.15)	0.4433
Normal	3588/4602 (77.97)	56/3588 (1.56)	REF		874/4602 (18.99)	7/874 (0.80)	REF	
CV death/MI								
Severely Abnormal	365/4602 (7.93)	14/365 (3.84)	2.13 (1.16, 3.91)	0.0141	365/4602 (7.93)	14/365 (3.84)	2.22 (0.83, 5.88)	0.1103
Moderately Abnormal	217/4602 (4.72)	5/217 (2.30)	1.53 (0.60, 3.90)	0.3681	217/4602 (4.72)	5/217 (2.30)	1.60 (0.47, 5.38)	0.4490
Mildly Abnormal	432/4602 (9.39)	5/432 (1.16)	0.81 (0.32, 2.04)	0.6542	3146/4602 (68.36)	46/3146 (1.46)	1.02 (0.43, 2.39)	0.9678
Normal	3588/4602 (77.97)	48/3588 (1.34)	REF		874/4602 (18.99)	7/874 (0.80)	REF	

CV indicates cardiovascular; MI, myocardial infarction; and UA, unstable angina.

Supplemental Figure 1. Kaplan-Meier curves demonstrating cumulative event rates based on the presence of myocardial ischemia and obstructive CAD for anatomic testing (A) and functional testing (B).
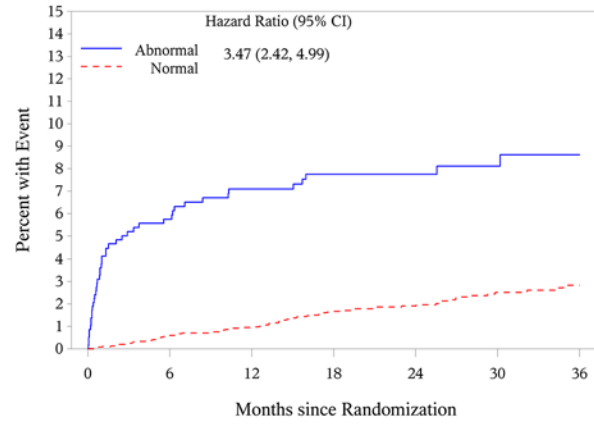

A. Anatomic Testing

Hazard Ratio (95% CI)

Abnormal — 3.74 (2.60, 5.39)
Normal - - -

Percent with Event / Months since Randomization

# at Risk	Baseline (0)	6 Mo.	12 Mo.	18 Mo.	24 Mo.	30 Mo.	36 Mo.
Abnormal	534	496	466	378	279	169	81
Normal	3966	3811	3556	2908	2190	1430	755

B. Functional Testing

Hazard Ratio (95% CI)

Abnormal — 3.47 (2.42, 4.99)
Normal - - -

Percent with Event / Months since Randomization

# at Risk	Baseline (0)	6 Mo.	12 Mo.	18 Mo.	24 Mo.	30 Mo.	36 Mo.
Abnormal	582	503	455	386	280	186	102
Normal	4020	3751	3428	2773	1992	1261	690