

SUPPLEMENTAL MATERIAL

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Risk Reclassification

Net reclassification index (NRI) for independent prognostic value of coronary flow reserve (CFR) or maximal myocardial blood flow (MBF):

Pre-risk model included age, sex, hypertension, diabetes, dyslipidemia, dialysis, tobacco use, body mass index, prior history of coronary artery disease, left ventricular ejection fraction, and summed stress score as an estimate of the amount of myocardial scar and/or ischemia.

Post-risk models, in addition, also included CFR or maximal MBF to assess NRIs for independent prognostic value of CFR or maximal MBF respectively.

The addition of CFR to the pre-risk model resulted in categorical NRI of 5.2% (95% CI: 1.1–9.5 %) across clinically meaningful risk categories of <1%, 1% to 3%, and >3% annual rate of cardiovascular death. The continuous NRI was 38.9% (95% CI: 25.9–53.1 %). The addition of maximal MBF to the pre-risk model resulted in categorical NRI of 1.4% (95% CI: -1.8–4.5 %) across risk categories of <1%, 1% to 3%, and >3% annual rate of cardiovascular death. The continuous NRI was 25.6% (95% CI: 12.7–38.2 %).

NRI for incremental prognostic value of maximal MBF over CFR:

Pre-risk model included age, sex, hypertension, diabetes, dyslipidemia, dialysis, tobacco use, body mass index, prior history of coronary artery disease, left ventricular ejection fraction, and summed stress score as an estimate of the amount of myocardial scar and/or ischemia, and CFR as binary (impaired or not).

Post-risk model included clinical risk factors described above and a categorical variable with 4 categories: both CFR and maximal MBF impaired, only CFR impaired, only maximal MBF impaired and neither impaired.

The addition of maximal MBF to the pre-risk model with CFR resulted in categorical NRI of 0.7% (95% CI: -1.7–3.4 %) across risk categories of <1%, 1% to 3%, and >3% annual rate of cardiovascular death. The continuous NRI was -12.0% (95% CI: -24.9–2.5 %).

Supplementary Table 1. Baseline Patient and Imaging Characteristics by Cardiovascular Death

Variable	CV Death (n = 392)	No CV Death (n = 3637)	All Patients (n=4029)
Demographics			
Age, y	75 (65-82)	65 (56-74)	66 (57-75)
Male	246 (63.0)	1749 (48.1)	1995 (49.5)
Race			
White	266 (67.9)	2346 (64.5)	2612 (64.8)
Black	55 (14.0)	601 (16.5)	656 (16.3)
Other/Unknown	71 (18.1)	690 (19.0)	761 (18.9)
Cardiovascular Risk Factors			
Hypertension	353 (90.1)	2978 (81.9)	3331 (82.7)
Diabetes	183 (46.7)	1266 (34.8)	1449 (36.0)
Dyslipidemia	282 (71.9)	2468 (67.9)	2750 (68.3)
Body Mass Index, kg/m ²	27.0 (23.5-31.2)	29.1 (25.2-34.6)	28.9 (25.1-34.3)
Body Mass Index \geq 30	123 (31.4)	1644 (45.2)	1767 (43.9)
Family history of CAD	80 (20.4)	948 (26.1)	1028 (25.5)
Tobacco use	37 (9.4)	353 (9.7)	390 (9.7)
Dialysis	32 (8.2)	156 (4.3)	188 (4.7)
Cardiovascular History			
Known CAD	261 (66.6)	1392 (38.3)	1653 (41.0)
Prior MI	193 (49.2)	939 (25.8)	1132 (28.1)
Prior PCI	121 (30.9)	768 (21.1)	889 (22.1)
Prior CABG	113 (28.8)	448 (12.3)	561 (13.9)
Early Revascularization (\leq 90 d post PET)	43 (11.1)	364 (10.0)	407 (10.1)
Late Revascularization ($>$ 90 d post PET)	34 (8.6)	216 (5.9)	250 (6.2)
Heart Failure	73 (18.6)	182 (5.0)	255 (6.3)
Peripheral Vascular Disease	56 (14.3)	214 (5.9)	270 (6.7)
Cerebrovascular Disease	37 (9.4)	233 (6.4)	270 (6.7)
Medications			
Aspirin	270 (68.9)	2254 (62.0)	2524 (62.6)
Beta-blockers	305 (77.8)	2302 (63.3)	2607 (64.7)
Lipid Lowering	286 (73.0)	2298 (63.2)	2584 (64.1)
ACE Inhibitors	170 (43.4)	1408 (38.7)	1578 (39.2)
Insulin	108 (27.6)	580 (15.9)	688 (17.1)
Indications			
Chest pain	112 (28.6)	1701 (46.8)	1813 (45.0)
Dyspnea	170 (43.4)	1009 (27.7)	1179 (29.3)
Pre-operative	62 (15.8)	510 (14.0)	572 (14.2)
Stress Agent			

Variable	CV Death (n = 392)	No CV Death (n = 3637)	All Patients (n=4029)
Adenosine	24 (6.2)	213 (5.9)	237 (5.9)
Dipyridamole	201 (51.5)	1279 (35.3)	1480 (36.9)
Dobutamine	17 (4.4)	143 (3.9)	160 (4.0)
Regadenoson	148 (37.9)	1991 (54.9)	2139 (53.3)
Radiotracer			
N-13 Ammonia	18 (4.6)	533 (14.7)	551 (13.7)
Rubidium-82	374 (95.4)	3104 (85.3)	3478 (86.3)
Hemodynamic Parameters			
HR, bpm			
Rest	71 (63-80)	69 (61-78)	69 (61-78)
Stress	78 (70-90)	85 (75-96)	85 (74-96)
Systolic BP, mm Hg			
Rest	138 (122-163)	145 (128-164)	144 (127-164)
Stress	127 (109-151)	134 (117-154)	134 (117-154)
Diastolic BP, mm Hg			
Rest	69 (59-79)	73 (65-81)	72 (64-81)
Stress	61 (54-73)	65 (58-74)	65 (58-74)
Rate Pressure Product, mm Hg*bpm	9792 (8311-11830)	9987 (8448-11859)	9965 (8436-11859)
Imaging Parameters			
Rest LVEF, %	46 (32-57)	58 (49-66)	57 (47-65)
LVEF \geq 50, %	170 (43.5)	2670 (73.6)	2840 (70.7)
Scar, %	2.9 (0-14.7)	0 (0-1.5)	0 (0-2.9)
Ischemia, %	2.9 (0-10.3)	0 (0-5.9)	0 (0-5.9)
Scar + Ischemia, %	8.8 (0-29.4)	0 (0-10.3)	0 (0-11.8)
CFR	1.37 (1.12-1.68)	1.77 (1.39-2.25)	1.72 (1.35-2.20)
Maximal MBF, ml \cdot g ⁻¹ \cdot min ⁻¹	1.28 (0.94-1.84)	1.79 (1.28-2.43)	1.75 (1.24-2.39)
Resting MBF, ml \cdot g ⁻¹ \cdot min ⁻¹	0.93 (0.74-1.24)	0.99 (0.78-1.28)	0.98 (0.78-1.28)

Continuous variables are presented as median [25th–75th percentile]; Categorical variables are presented as n (%). BP, blood pressure; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CFR, coronary flow reserve; CV, cardiovascular; HR, heart rate; LVEF, left ventricular ejection fraction; MBF, myocardial blood flow; MI, myocardial infarction; PCI, percutaneous coronary intervention; SBP, systolic blood pressure

Supplementary Figure 1. Risk Reclassification

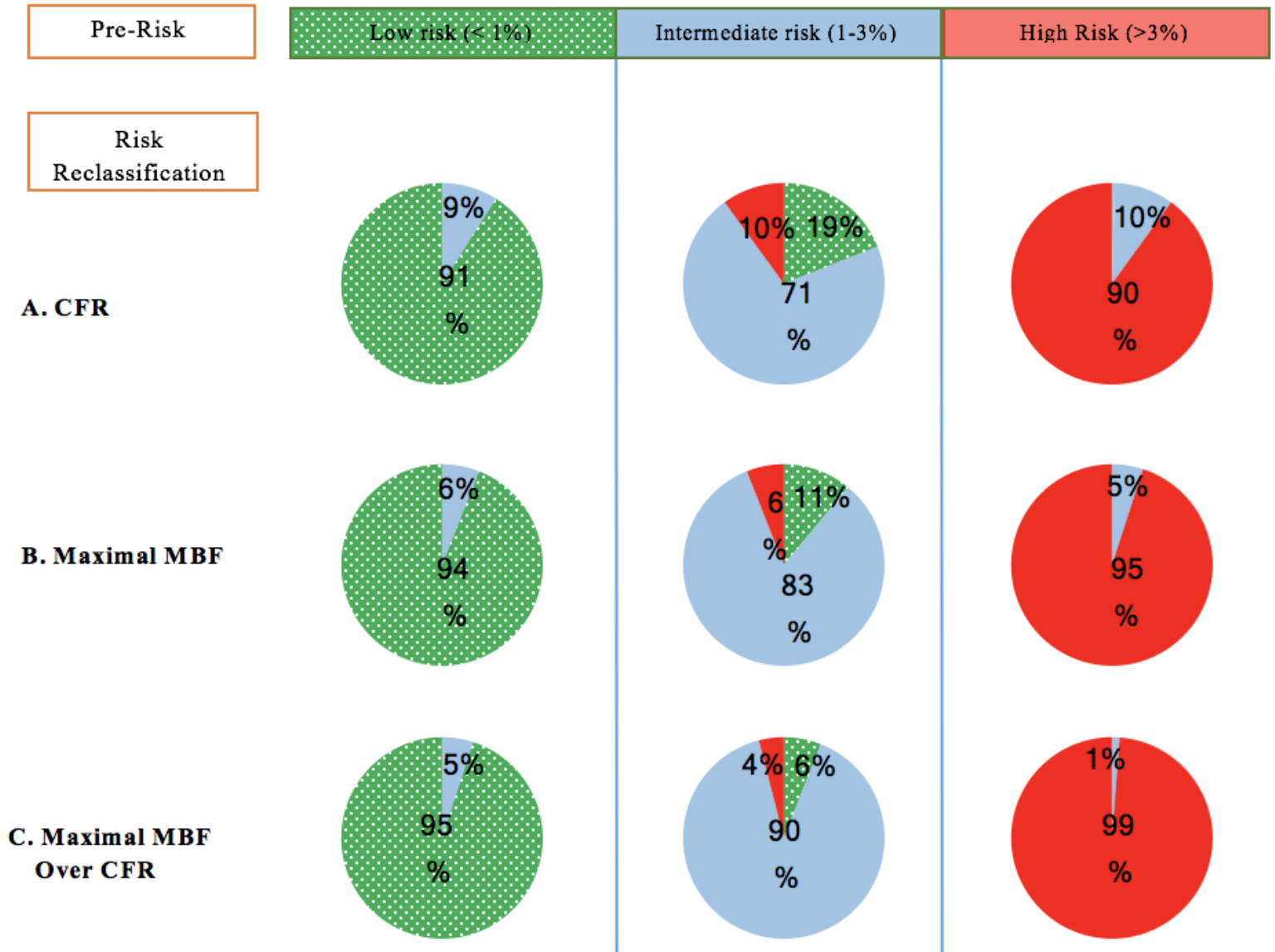


Figure shows risk reclassification at 2-year follow-up using threshold annual rates of cardiac mortality of 1% and 3% based on the American College of Cardiology/American Heart Association guidelines for the management of patients with stable ischemic heart disease. Pie charts indicate percentage of patients who are reclassified to another risk category. Risk categories are color-coded: low risk: patterned green; intermediate risk: solid light blue; high risk: solid dark red.

Pre-Risk models includes: age, sex, hypertension, diabetes, dyslipidemia, dialysis, tobacco use, body mass index, known coronary artery disease, left ventricular ejection fraction and amount of myocardial scar and ischemia. Pre-risk model for risk-reclassification by addition of maximal MBF over CFR also includes CFR as binary variable (impaired versus not impaired). *Post-risk models* include CFR (A), maximal MBF (B) or a combination of both (C) as a 4-level categorical variable (both impaired/only CFR impaired/only maximal MBF impaired/neither impaired). CFR, coronary flow reserve; MBF, myocardial blood flow

Supplementary Figure 2. Competing Risk Analysis

Group	Unadjusted			Adjusted		
	Forest Plot	HR (95% CI)	p-value	Forest Plot	HR (95% CI)	p-value
Independent Prognostic Value						
CFR		3.19 (2.56-3.98)	<0.001		1.70 (1.34-2.15)	<0.001
Maximal MBF		2.20 (1.85-2.61)	<0.001		1.32 (1.08-1.61)	0.01
Incremental Prognostic Value						
CFR		2.27 (1.74-2.97)	<0.001		1.64 (1.25-2.16)	<0.001
Maximal MBF		1.50 (1.23-1.82)	<0.001		1.06 (0.85-1.32)	0.6

Figure shows independent and incremental prognostic value of CFR and maximal MBF using competing risk analysis. Non-CV death was modeled as a competing risk for CV death using Fine and Gray competing risk model. Hazard ratios are expressed per unit decrease in CFR or maximal MBF. Adjusted Cox model includes the following covariates: age, sex, hypertension, diabetes, dyslipidemia, dialysis, body mass index, known coronary artery disease, left ventricular ejection fraction, amount of myocardial scar/ischemia, revascularization post-PET, rate-pressure-product, type of radiotracer or stress agent. CFR, coronary flow reserve; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MBF, myocardial blood flow; PET, positron emission tomography

Supplementary Figure 3. All-Cause Mortality









Group	Unadjusted			Adjusted		
	Forest Plot	HR (95% CI)	p-value	Forest Plot	HR (95% CI)	p-value
Independent Prognostic Value						
CFR		2.40 (2.14-2.69)	<0.001		1.73 (1.52-1.97)	<0.001
Maximal MBF		1.63 (1.50-1.77)	<0.001		1.28 (1.15-1.41)	<0.001
Incremental Prognostic Value						
CFR		2.07 (1.80-2.37)	<0.001		1.72 (1.48-2.01)	<0.001
Maximal MBF		1.19 (1.08-1.31)	<0.001		1.00 (0.89-1.13)	0.9

Figure shows independent and incremental prognostic value of CFR and maximal MBF for predicting all-cause mortality. Hazard ratios are expressed per unit decrease in CFR or maximal MBF. Adjusted Cox model includes the following covariates: age, sex, hypertension, diabetes, dyslipidemia, dialysis, body mass index, known coronary artery disease, left ventricular ejection fraction, amount of myocardial scar/ischemia, revascularization post-PET, rate-pressure-product, type of radiotracer or stress agent. CFR, coronary flow reserve; CI, confidence interval; HR, hazard ratio; MBF, myocardial blood flow; PET, positron emission tomography

Supplementary Figure 4. Incremental Prognostic Value of Maximal Myocardial Blood Flow by Severity of Coronary Flow Reserve Impairment

Group	CV Deaths	Total patients	<u>Unadjusted</u>			<u>Adjusted</u>		
			Forest Plot	HR (95% CI)	p-value	Forest Plot	HR (95% CI)	p-value
Mild to Moderately Impaired CFR (1.5-2)	107	1222		1.57 (1.17-2.09)	0.003		1.11 (0.78-1.57)	0.6
Severely Impaired CFR (<1.5)	242	1430		1.65 (1.30-2.10)	<0.001		1.09 (0.81-1.46)	0.6

Figure shows incremental prognostic value of maximal MBF in mild to moderately (1.5-2) and severely impaired CFR (<1.5). Hazard ratios are expressed per unit decrease in maximal MBF. Adjusted Cox model includes the following covariates: age, sex, hypertension, diabetes, dyslipidemia, dialysis, body mass index, known coronary artery disease, left ventricular ejection fraction, amount of myocardial scar/ischemia, revascularization post-PET, rate-pressure-product, type of radiotracer or stress agent. CFR, coronary flow reserve; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; PET, positron emission tomography