Supplemental Online Content

Sud M, Han L, Koh M, et al. Association between adherence to fractional flow reserve treatment thresholds and major adverse cardiac events in patients with coronary artery disease. *JAMA*. doi:10.1001/jama.2020.22708

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

eTable 1. Baseline Characteristics Before Propensity Score Weighting

	Ischemic Fractional Flow Reserve (≤ 0.80)			Non-ischemic Fractional Flow Reserve (> 0.80)		
Baseline Characteristics	**No PCI n=664**	**PCI n=2,029**	**Standardized Difference**	**No PCI n=5,603**	**PCI n=810**	**Standardized Difference**
Demographics						
Age, yrs, mean (SD)	66.0 ± 10.7	64.4 ± 10.6	0.146	66.1 ± 10.7	65.0 ± 10.3	0.100
Male, n (%)	478 (72.0%)	1,488 (73.3%)	0.030	3,372 (60.2%)	547 (67.5%)	0.153
Female, n (%)	186 (28.0%)	541 (26.7%)	0.030	2,231 (39.8%)	263 (32.5%)	0.153
Index Presentation						
Stable Coronary Artery Disease	439 (66.1%)	1,268 (62.5%)	0.076	3,625 (64.7%)	448 (55.3%)	0.193
Unstable Angina	104 (15.7%)	477 (23.5%)	0.199	1,220 (21.8%)	204 (25.2%)	0.081
Non-ST Elevation Myocardial Infarction	109 (16.4%)	265 (13.1%)	0.095	714 (12.7%)	151 (18.6%)	0.163
Pre-existing Comorbidities						
Myocardial Infarction	268 (40.4%)	816 (40.2%)	0.003	1,959 (35.0%)	334 (41.2%)	0.129
Percutaneous Coronary Intervention	182 (27.4%)	743 (36.6%)	0.198	1,916 (34.2%)	282 (34.8%)	0.013
Heart Failure	136 (20.5%)	219 (10.8%)	0.269	655 (11.7%)	76 (9.4%)	0.075
Diabetes	299 (45.0%)	750 (37.0%)	0.165	1,994 (35.6%)	296 (36.5%)	0.020
Cerebrovascular Disease	56 (8.4%)	167 (8.2%)	0.007	412 (7.4%)	62 (7.7%)	0.011
Peripheral Vascular Disease	52 (7.8%)	113 (5.6%)	0.091	315 (5.6%)	35 (4.3%)	0.060
Hypertension	539 (81.2%)	1,613 (79.5%)	0.042	4,419 (78.9%)	634 (78.3%)	0.015
Hyperlipidemia	508 (76.5%)	1,539 (75.9%)	0.015	4,241 (75.7%)	559 (69.0%)	0.150
Renal Disease	34 (5.1%)	38 (1.9%)	0.177	166 (3.0%)	23 (2.8%)	0.007
Dialysis	22 (3.3%)	30 (1.5%)	0.120	114 (2.0%)	12 (1.5%)	0.042
Chronic Obstructive Pulmonary Disease	91 (13.7%)	217 (10.7%)	0.092	630 (11.2%)	76 (9.4%)	0.061
Smoking						
Current	121 (18.2%)	433 (21.3%)	0.078	883 (15.8%)	140 (17.3%)	0.041

Former	196 (29.5%)	618 (30.5%)	0.021	1,767 (31.5%)	229 (28.3%)	0.071
Charlson Comorbidity Index, mean ± SD	1.8 ± 1.9	1.5 ± 1.6	0.212	1.4 ± 1.6	1.5 ± 1.5	0.036
Investigations						
Serum Creatinine						
≤1.36 mg/dL	533 (80.3%)	1,698 (83.7%)	0.089	4,708 (84.0%)	698 (86.2%)	0.060
1.37 to 2.04 mg/dL	59 (8.9%)	128 (6.3%)	0.097	316 (5.6%)	48 (5.9%)	0.012
>2.04 mg/dL	25 (3.8%)	36 (1.8%)	0.122	134 (2.4%)	9 (1.1%)	0.098
Missing	47 (7.1%)	167 (8.2%)	0.043	445 (7.9%)	55 (6.8%)	0.044
Left Ventricular Ejection Fraction						
≥50%	360 (54.2%)	1,000 (49.3%)	0.099	3,181 (56.8%)	383 (47.3%)	0.191
35-49%	98 (14.8%)	194 (9.6%)	0.160	549 (9.8%)	64 (7.9%)	0.067
<35%	49 (7.4%)	91 (4.5%)	0.040	247 (4.4%)	31 (3.8%)	0.030
Missing	157 (23.6%)	744 (36.6%)	0.280	1626 (30.0%)	332 (41.0%)	0.250
Symptom Status						
Canadian Cardiovascular Society Class[a]						
0 (least impaired)	134 (20.2%)	291 (14.3%)	0.150	869 (15.5%)	143 (17.7%)	0.060
1	87 (13.1%)	286 (14.1%)	0.030	741 (13.2%)	90 (11.1%)	0.060
2	166 (25.0%)	539 (26.6%)	0.040	1,531 (27.3%)	198 (24.4%)	0.070
3	88 (13.3%)	372 (18.3%)	0.140	870 (15.5%)	126 (15.6%)	<0.001
4 (most impaired)	189 (28.5%)	541 (26.7%)	0.060	1,592 (28.4%)	253 (31.2%)	0.120
Interventional Characteristics						
Fractional Flow Reserve, mean (SD)	0.75 (0.06)	0.74 (0.06)	0.150	0.89 (0.05)	0.87 (0.05)	0.400
Fractional Flow Reserve, median (IQR)	0.77 (0.73-0.79)	0.76 (0.72-0.78)	-	0.89 (0.85-0.93)	0.86 (0.83-0.91)	-
Vessels with stenosis ≥70%						
0	165 (24.8%)	514 (25.3%)	0.011	3,903 (69.7%)	307 (37.9%)	0.672
1	188 (28.3%)	1,040 (51.3%)	0.482	1,120 (20.0%)	353 (43.6%)	0.524
2	187 (28.2%)	382 (18.8%)	0.222	433 (7.7%)	115 (14.2%)	0.208
3	124 (18.7%)	93 (4.6%)	0.451	147 (2.6%)	35 (4.3%)	0.093

Fractional Flow Reserve Artery						
Left Anterior Descending	592 (89.2%)	1,608 (79.3%)	0.27	3,426 (61.1%)	520 (64.2%)	0.06
Right Coronary	45 (6.8%)	271 (13.4%)	0.22	1,210 (21.6%)	135 (16.7%)	0.13
Left Circumflex	27 (4.1%)	150 (7.4%)	0.14	967 (17.3%)	155 (19.1%)	0.05

Abbreviations: PCI – percutaneous coronary intervention, SD – standard deviation, IQR – interquartile range
a - the Canadian Cardiovascular Society classification is a score used to grade the severity of angina with 0 indicating least impaired (no angina) and 4 indicating most impaired (angina at rest)

eTable 2. Association Between Percutaneous Coronary Intervention and the Incidence of Non-fatal Outcomes After Propensity Score Weighting[a]

Outcome	Follow-up Time	Ischemic Fractional Flow Reserve (≤ 0.80)	Non-Ischemic Fractional Flow Reserve (> 0.80)
		sHR (95% CI)[b]	sHR (95% CI)
Myocardial Infarction	30 days	0.87 (0.44 to 1.72)	3.56 (1.70 to 7.46)
	1 year	1.17 (0.74 to 1.87)	2.05 (1.26 to 3.32)
	5 years	0.93 (0.65 to 1.34)	1.70 (1.21 to 2.39)
Unstable Angina	30 days	0.37 (0.18 to 0.74)	3.02 (1.26 to 7.25)
	1 year	0.68 (0.44 to 1.03)	2.40 (1.63 to 3.53)
	5 years	0.82 (0.59 to 1.15)	1.80 (1.36 to 2.38)
Urgent Coronary Revascularization[b]	30 days	0.13 (0.04 to 0.45)	0.97 (0.27 to 3.45)
	1 year	0.57 (0.33 to 0.97)	2.20 (1.29 to 3.75)
	5 years	0.72 (0.47 to 1.09)	1.78 (1.22 to 2.60)

Abbreviations: PCI – percutaneous coronary intervention, sHR –sub-distribution hazard ratio (using Fine and Gray regression), CI – confidence interval, RD – Risk Difference
a - The Fine and Gray regression model was used to calculate the sub-distribution hazard ratios of all non-fatal outcomes that treated death a competing risk event. Patients undergoing PCI were compared with no PCI (reference group). Lower sHR indicates better outcomes in favor of the PCI group.
b - urgent coronary revascularization was defined as unplanned hospitalization with percutaneous coronary intervention or coronary artery bypass grafting occurring during the same hospitalization

eTable 3. Outcomes of Patients Presenting With Ischemic Fractional Flow Reserve (≤ 0.80) and Without Myocardial Infarction After Propensity Score Weighting

Outcome[a]	Follow-up Time	No PCI (%) *Reference*	PCI (%)	RD (95% CI)[b]	HR (95% CI)[c]	sHR (95% CI)[d]
Primary Outcome						
MACE	30 days	5.3%	2.1%	-3.2% (-5.5% to -1.2%)	0.38 (0.22 to 0.65)	NA[e]
	1 year	13.7%	10.9%	-2.8% (-6.3% to 0.7%)	0.77 (0.57 to 1.04)	NA
	5 years	34.3%	29.5%	-4.8% (-12.5% to 2.0%)	0.78 (0.62 to 0.99)	NA
Secondary Outcomes						
Death	30 days	0.9%	0.4%	-0.5% (-1.4% to 0.4%)	0.46 (0.14 to 1.56)	NA
	1 year	3.3%	3.2%	-0.1% (-1.9% to 1.6%)	0.97 (0.56 to 1.68)	NA
	5 years	17.8%	14.8%	-3.0% (-10.2% to 3.0%)	0.78 (0.53 to 1.14)	NA
Myocardial Infarction	30 days	1.0%	0.6%	-0.4% (-1.4% to 0.5%)	0.62 (0.20 to 1.91)	0.63 (0.20 to 1.92)
	1 year	2.2%	2.8%	0.6% (-0.9% to 1.9%)	1.26 (0.68 to 2.34)	1.27 (0.68 to 2.35)
	5 years	8.0%	7.5%	-0.5% (-4.9% to 3.2%)	0.93 (0.60 to 1.45)	0.95 (0.61 to 1.47)
Unstable Angina	30 days	2.8%	1.1%	-1.7% (-3.4% to -0.3%)	0.39 (0.19 to 0.81)	0.39 (0.19 to 0.82)
	1 year	7.1%	5.1%	-2.0% (-4.6% to 0.5%)	0.70 (0.46 to 1.08)	0.71 (0.46 to 1.09)
	5 years	12.2%	10.6%	-1.6% (-5.6% to 2.2%)	0.81 (0.57 to 1.14)	0.81 (0.58 to 1.15)
Urgent Coronary Revascularization[f]	30 days	1.9%	0.2%	-1.7% (-3.0% to -0.6%)	0.11 (0.03 to 0.46)	0.11 (0.03 to 0.46)
	1 year	4.4%	2.2%	-2.2% (-4.2% to -0.1%)	0.50 (0.29 to 0.88)	0.50 (0.29 to 0.88)
	5 years	7.9%	5.9%	-2.0% (-5.9% to 1.4%)	0.70 (0.45 to 1.08)	0.70 (0.45 to 1.09)

Abbreviations: MACE – major adverse cardiac events, PCI – percutaneous coronary intervention, HR –hazard ratio, sHR – sub-distribution hazard ratio, CI – confidence interval, RD – Risk Difference
a - Death treated as a competing risk for all non-fatal outcomes
b - risk differences were estimated from weighted cumulative incidence curves along with 95% confidence intervals generated in 2,000 bootstrap resamples
c - hazard ratios and 95% confidence intervals were estimated from weighted cause-specific proportional hazards models
d - sub-distribution hazard ratios and 95% confidence intervals were estimated from weighted Fine-Gray regression models

e - sub-distribution hazards were not estimated because outcomes included death as an event
f - urgent coronary revascularization was defined as unplanned hospitalization with percutaneous coronary intervention or coronary artery bypass grafting occurring during the same hospitalization

eTable 4. Outcomes of Patients Presenting With Non-ischemic Fractional Flow Reserve (> 0.80) and Without Myocardial Infarction After Propensity Score Weighting

Outcome[a]	Follow-up Time	No PCI (%) *Reference*	PCI (%)	RD (95% CI)[b]	HR (95% CI)[c]	sHR (95% CI)[d]
Primary Outcome						
MACE	30 days	1.0%	2.4%	1.4% (0.0% to 3.2%)	2.48 (1.23 to 4.98)	NA[e]
	1 year	5.5%	9.2%	3.7% (1.1% to 6.6%)	1.73 (1.24 to 2.40)	NA
	5 years	23.6%	30.2%	6.6% (1.1% to 12.8%)	1.30 (1.05 to 1.62)	NA
Secondary Outcomes						
Death	30 days	0.3%	0.0%	-0.3% (-0.5% to -0.1%)	0.15 (0.02 to 1.12)	NA
	1 year	1.9%	1.3%	-0.6% (-1.7% to 0.9%)	0.67 (0.27 to 1.68)	NA
	5 years	12.6%	11.3%	-1.3% (-5.6% to 3.6%)	0.81 (0.54 to 1.20)	NA
Myocardial Infarction	30 days	0.2%	1.6%	1.4% (0.2% to 2.9%)	7.25 (2.40 to 21.91)	7.25 (2.40 to 21.92)
	1 year	1.1%	2.8%	1.7% (0.0% to 3.5%)	2.48 (1.28 to 4.80)	2.48 (1.28 to 4.81)
	5 years	4.3%	7.4%	3.1% (0.4% to 6.4%)	1.83 (1.21 to 2.78)	1.85 (1.22 to 2.81)
Unstable Angina	30 days	0.4%	1.3%	0.9% (-0.2% to 2.3%)	2.88 (1.02 to 8.13)	2.88 (1.02 to 8.13)
	1 year	2.5%	5.8%	3.3% (1.3% to 5.7%)	2.42 (1.59 to 3.68)	2.42 (1.59 to 3.69)
	5 years	8.3%	14.1%	5.8% (1.8% to 10.5%)	1.76 (1.30 to 2.37)	1.78 (1.32 to 2.40)
Urgent Coronary Revascularization[f]	30 days	0.2%	0.2%	0.0% (-0.3% to 0.3%)	0.88 (0.19 to 4.19)	0.88 (0.19 to 4.19)
	1 year	1.0%	2.1%	1.1% (0.0% to 2.4%)	2.11 (1.14 to 3.92)	2.12 (1.14 to 3.93)
	5 years	4.0%	7.1%	3.1% (0.3% to 6.7%)	1.67 (1.10 to 2.52)	1.69 (1.12 to 2.56)

Abbreviations: MACE – major adverse cardiac events, PCI – percutaneous coronary intervention, HR –hazard ratio, sHR – sub-distribution hazard ratio, CI – confidence interval
a - Death treated as a competing risk for all non-fatal outcomes
b - risk differences were estimated from weighted cumulative incidence curves along with 95% confidence intervals generated in 2,000 bootstrap resamples
c - hazard ratios and 95% confidence intervals were estimated from weighted cause-specific proportional hazards models

d - sub-distribution hazard ratios and 95% confidence intervals were estimated from weighted Fine-Gray regression models
e - sub-distribution hazards were not estimated because outcomes included death as an event
f - urgent coronary revascularization was defined as unplanned hospitalization with percutaneous coronary intervention or coronary artery bypass grafting occurring during the same hospitalization

eTable 5. Outcomes of Patients Presenting With Ischemic and Non-ischemic Fractional Flow Reserve With a Multi-level Propensity Score Accounting for Hospital Site

Cohort	Analysis	MACE Follow-up Time	No PCI (%) *Reference*	PCI (%)	RD (95% CI)[a]	HR (95% CI)[b]
Ischemic Fractional Flow Reserve (≤ 0.80)	**Multi-level analysis for hospital site**	30 days	5.7%	2.8%	-2.9% (-5.4% to -1.1%)	0.48 (0.31 to 0.75)
		1 year	14.6%	11.8%	-2.8% (-6.5% to 0.1%)	0.79 (0.59 to 1.05)
		5 years	37.8%	31.3%	-6.5% (-15.4% to -0.1%)	0.81 (0.65 to 1.00)
Non-ischemic Fractional Flow Reserve (> 0.80)	**Multi-level analysis for hospital site**	30 days	1.5%	3.5%	2.0% (0.3% to 3.2%)	2.36 (1.37 to 4.05)
		1 year	6.5%	10.5%	4.0% (1.4% to 6.3%)	1.65 (1.22 to 2.21)
		5 years	24.3%	31.4%	7.1% (2.9% to 14.7%)	1.30 (1.06 to 1.60)

Abbreviations: MACE – major adverse cardiac events, PCI – percutaneous coronary intervention, HR –hazard ratio, RD – Risk Difference, CI – confidence interval
a - risk differences were estimated from weighted cumulative incidence curves along with 95% confidence intervals generated in 2,000 bootstrap resamples
b - hazard ratios and 95% confidence intervals were estimated from weighted cause-specific proportional hazards models

eTable 6. Outcomes of Patients Presenting With Ischemic and Non-ischemic Fractional Flow Reserve After Multiple Imputation for Missing Serum Creatinine and Left Ventricular Ejection Fraction[a]

Cohort	Analysis	MACE Follow-up Time	HR (95% CI)[b]
Ischemic Fractional Flow Reserve (≤ 0.80)	**Multiple Imputation of LVEF and Creatinine**	30 days	0.45 (0.29 to 0.72)
		1 year	0.73 (0.56 to 0.96)
		5 years	0.77 (0.63 to 0.94)
Non-ischemic Fractional Flow Reserve (> 0.80)	**Multiple Imputation of LVEF and Creatinine**	30 days	2.03 (1.22 to 3.37)
		1 year	1.71 (1.30 to 2.24)
		5 years	1.40 (1.17 to 1.68)

Abbreviations: MACE – major adverse cardiac events, PCI – percutaneous coronary intervention, HR –hazard ratio, CI – confidence interval
a – Multiple imputation was used to impute serum creatinine and left ventricular ejection fraction in 30 datasets. The propensity-weighted analysis was conducted in each dataset and the results were pooled.
b - hazard ratios and 95% confidence intervals were estimated from weighted cause-specific proportional hazards models

eTable 7. Outcomes of Patients Presenting With Ischemic and Non-ischemic Fractional Flow Reserve After Excluding Coronary Artery Bypass Grafting After Index Procedure

Cohort	Exclusion	MACE Follow-up Time	No PCI (%) *Reference*	PCI (%)	RD (95% CI)[a]	HR (95% CI)[b]
Ischemic Fractional Flow Reserve (≤ 0.80)	**CABG within 1 month of FFR Excluded**	30 days	4.4%	3.1%	-1.3% (-2.9% to 0.4%)	0.70 (0.45 to 1.10)
		1 year	18.7%	13.3%	-5.4% (-8.5% to -2.2%)	0.68 (0.54 to 0.84)
		5 years	37.4%	34.3%	-3.1% (-8.9% to 3.0%)	0.80 (0.68 to 0.95)
	CABG within 3 months of FFR Excluded	30 days	5.0%	2.9%	-2.1% (-3.9% to -0.1%)	0.59 (0.38 to 0.92)
		1 year	16.8%	12.6%	-4.2% (-7.3% to -0.9%)	0.73 (0.57 to 0.93)
		5 years	40.0%	33.8%	-6.2% (-13.6% to 0.6%)	0.76 (0.64 to 0.92)
Non-ischemic Fractional Flow Reserve (> 0.80)	**CABG within 1 month of FFR Excluded**	30 days	1.5%	3.0%	1.5% (0.3% to 3.0%)	2.02 (1.22 to 3.34)
		1 year	6.9%	10.8%	3.9% (1.3% to 6.7%)	1.61 (1.23 to 2.10)
		5 years	27.8%	39.3%	11.5% (4.7% to 18.1%)	1.36 (1.14 to 1.61)
	CABG within 3 months of FFR Excluded	30 days	1.5%	3.0%	1.5% (0.3% to 3.0%)	2.02 (1.22 to 3.36)
		1 year	6.7%	10.8%	4.1% (1.6% to 6.8%)	1.66 (1.27 to 2.17)
		5 years	27.7%	39.6%	11.9% (5.3% to 18.5%)	1.38 (1.16 to 1.64)

Abbreviations: MACE – major adverse cardiac events, PCI – percutaneous coronary intervention, HR –hazard ratio, CI – confidence interval, RD – Risk Difference, FFR – Fractional Flow Reserve, CABG – coronary artery bypass grafting

a - risk differences were estimated from weighted cumulative incidence curves along with 95% confidence intervals generated in 2,000 bootstrap resamples

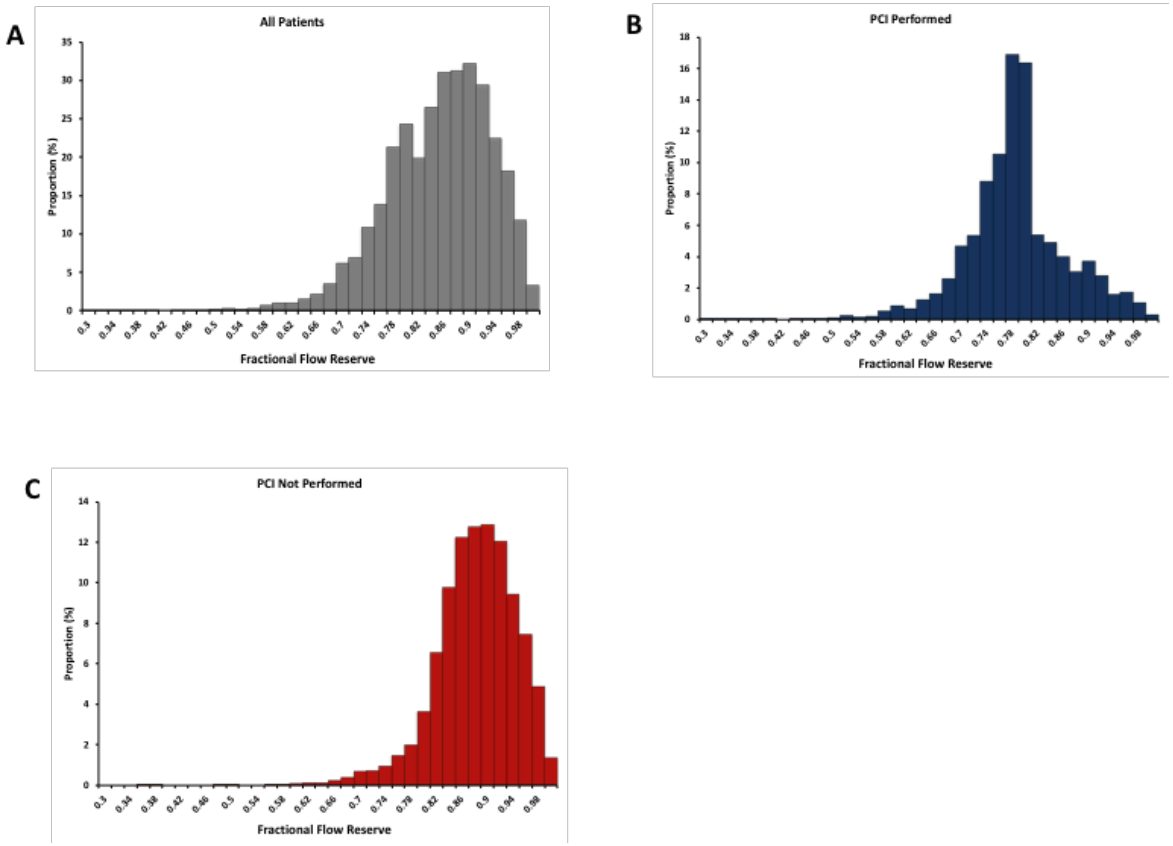
b - hazard ratios and 95% confidence intervals were estimated from weighted cause-specific proportional hazards models

eTable 8. Outcomes in Patients Presenting With Ischemic and Non-ischemic Fractional Flow Reserve Stratified by the Number of Diseased Coronary Artery Disease Vessels

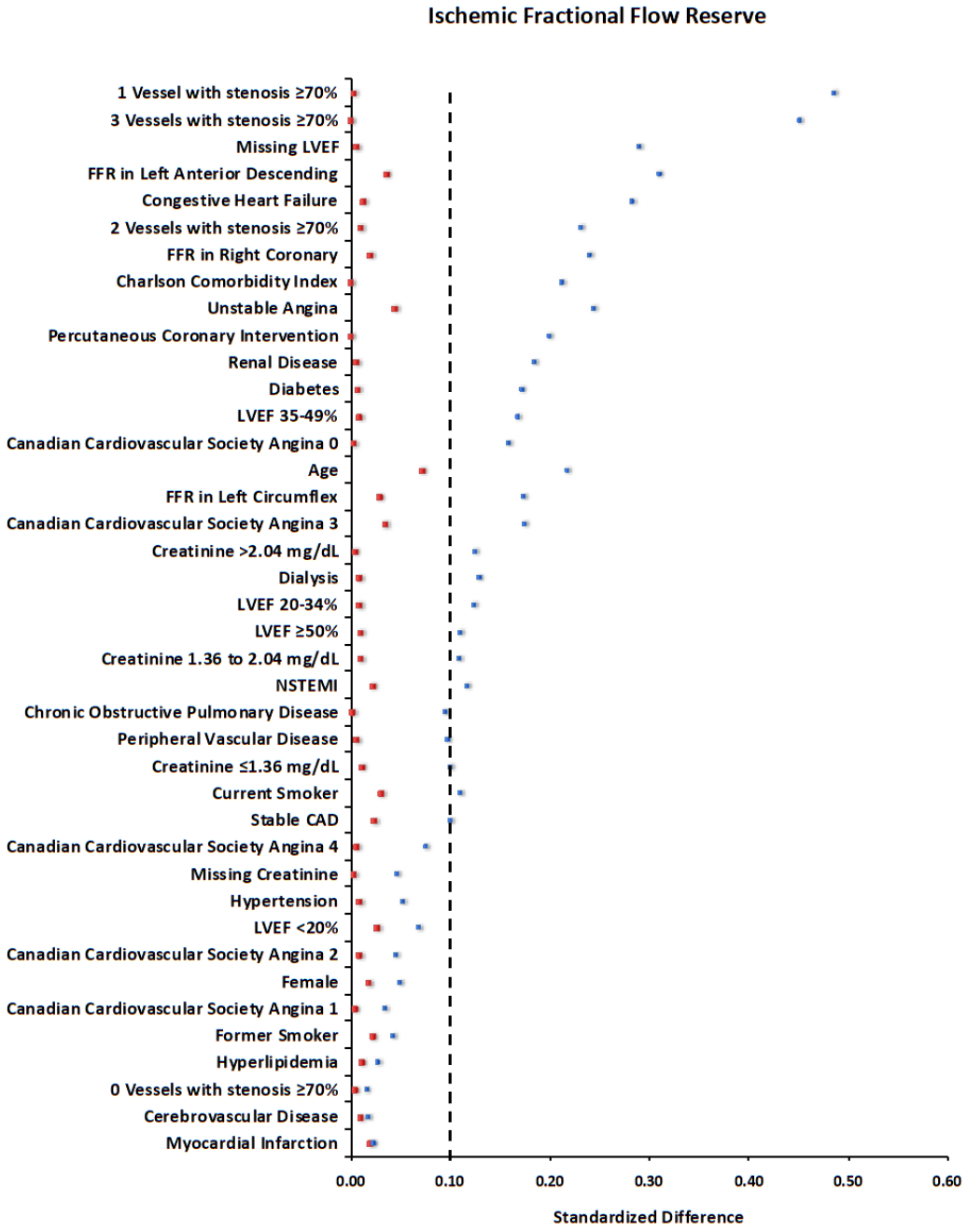
Cohort	Diseased Vessels with Stenosis ≥70%	MACE Follow-up Time	No PCI (%) *Reference*	PCI (%)	RD (95% CI)[a]	HR (95% CI)[b]
Ischemic Fractional Flow Reserve (≤ 0.80)	0 or 1-vessel	30 days	3.8%	2.0%	-1.8% (-4.4% to 0.4%)	0.52 (0.27 to 1.02)
		1 year	10.7%	8.8%	-1.9% (-5.8% to 1.8%)	0.81 (0.55 to 1.19)
		5 years	35.7%	26.8%	-8.9% (-20.7% to 1.3%)	0.78 (0.60 to 1.02)
	2- or 3-vessel	30 days	11.4%	5.0%	-6.4% (-11.6% to -1.7%)	0.44 (0.24 to 0.78)
		1 year	24.1%	18.6%	-5.5% (-12.2% to 1.6%)	0.72 (0.51 to 1.02)
		5 years	49.2%	44.2%	-5.0% (-15.7% to 6.1%)	0.80 (0.61 to 1.04)
Non-ischemic Fractional Flow Reserve (> 0.80)	0 or 1-vessel	30 days	0.8%	2.9%	2.1% (0.8% to 3.5%)	3.56 (2.00 to 6.34)
		1 year	5.0%	9.6%	4.6% (2.1% to 7.4%)	2.00 (1.46 to 2.74)
		5 years	21.6%	30.2%	8.6% (3.5% to 13.8%)	1.45 (1.18 to 1.77)
	2- or 3-vessel	30 days	6.4%	5.9%	-0.5% (-5.5% to 3.9%)	0.92 (0.36 to 2.33)
		1 year	17.4%	23.8%	6.4% (-5.6% to 13.9%)	1.40 (0.88 to 2.23)
		5 years	42.9%	38.7%	-4.2% (-20.6% to 8.1%)	1.01 (0.70 to 1.46)

Abbreviations: MACE – major adverse cardiac events, PCI – percutaneous coronary intervention, HR –hazard ratio, CI – confidence interval, RD – Risk Difference, FFR – Fractional Flow Reserve
a - risk differences were estimated from weighted cumulative incidence curves along with 95% confidence intervals generated in 2,000 bootstrap resamples
b - hazard ratios and 95% confidence intervals were estimated from weighted cause-specific proportional hazards models

eFigure 1. Distribution of Fractional Flow Reserve Measurements. Histograms depict the proportion of patients with fractional flow reserve measurements among **(A)** the entire cohort (median 0.86, IQR: 0.79 – 0.91), **(B)** in patients undergoing PCI (median 0.78, IQR: 0.74 – 0.82) and **(C)** patients who did not have PCI (median 0.88, IQR 0.84 – 0.92).



eFigure 2. Standardized Differences Before and After Propensity Weighting in Patients With Ischemic FFR. The standardized differences for each confounder before (blue) and after (red) propensity score weighting are depicted in descending order. Ideally, a standardized difference of less than 0.1 is desirable, and indicates good balance.



eFigure 3. Standardized Differences Before and After Propensity Weighting in Patients With Non-ischemic FFR. The standardized differences for each confounder before (blue) and after (red) propensity score weighting are depicted in descending order. Ideally, a standardized difference of less than 0.1 is desirable, and indicates good balance.