SUPPLEMENTAL MATERIAL

for

Clinical and Angiographic Risk Stratification and Differential Impact on Treatment Outcomes in the BARI 2D Trial

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A full listing of the BARI 2D Study Group can be found in the Supplementary Appendix, at NEJM.org. (N Engl J Med 2009;360:2503-15).

Appendix 1

Angiographic Risk Score:

The predicted probability of Death/MI/Stroke within three years of enrollment was derived from the logistic regression model for baseline angiographic variables.

$$P = \{ 1 + \exp [-2.833 + 0.010 (MJI) + 0.093 (\#\ lesions) + 0.55 (abnormal\ LVEF) + 0.40 (missing\ LVEF) + 0.27 (prior\ revascularization)] \}^{-1}$$

This model had a C-statistic = 0.634 indicating good, but not excellent, discrimination.

When an identical process was undertaken only including patients randomized to Medical therapy, the same four variables were selected for inclusion into the risk score. In addition, when a Cox regression model for Death/MI/Stroke based on all follow-up data was created, the same angiographic predictor variables were identified and similar coefficients were obtained.

As a point of reference, the mean myocardial jeopardy index (MJI) is presented according the number of disease vessels for the BARI 2D patient population.

Number of Diseased Vessels	Myocardial Jeopardy Index (MJI) Mean (Standard Deviation)
0/1 Vessel Disease	26.7 (16.8)
2 Vessel Disease	49.0 (18.5)
3 Vessel Disease	63.6 (22.3)

Patients with an estimated probability of death, MI or stroke by 3 years ≥ 17.1% (i.e. P from the above equation ≥ 0.171) were classified as having "high" angiographic risk.

Below are the calculated Angiographic Risk Scores for sample patients:

	Mild 2 Vessel Disease	3 Vessel Disease	3 Vessel Disease and Prior Revascularization	3 Vessel Disease and Low Ejection Fraction
Ejection Fraction	>50%	>50%	> 50%	<50%
Myocardial Jeopardy Index	30%	64%	64%	62%
Total Number of Lesions	3	7	7	6
Prior Revascularization	No	No	Yes	No
Angiographic Risk Score -- estimated risk of Death/MI/Stroke by 3-years	9.5%	18%	22%	25%

Framingham Clinical Risk Score for Patients with Coronary Heart Disease:

The predicted probability of coronary heart disease was derived from the logistic regression model developed as one of the Framingham risk scores by D'Agostino et. al. (1). There are separate models from males and females.

Males: $P = \{ 1 + \exp [4.995 - 0.3042 - 0.0145(\text{age in years}) - 0.6738(\log (\text{total cholesterol/HDL})] \}^{-1}$

Females: $P = \{ 1 + \exp [13.537 - 0.7829 - 0.0225(\text{age in years}) - 0.834(\log (\text{total cholesterol/HDL})] - 1.3713(\log(\text{systolic BP})) - 0.3669*(\text{current smoking}) \}^{-1}$

1. D'Agostino RB, Russell MW, Huse DM, Ellison RC, Silbershatz H, Wilson PWF, Hartz SC. Primary and subsequent coronary risk appraisal: New results from The Framingham Study. Am Heart J. 2000; 139:272-281.

Supplementary Table 1: Categorization of First MI and First Stroke Event per Patient including Fatal and Non-Fatal Events by Medical Therapy and Prompt Revascularization Treatment Assignment and Angiographic Risk

	Low Angiographic Risk		High Angiographic Risk	
	MED N = 815	**REV N= 771**	**MED N = 375**	**REV N = 404**
Myocardial Infarction Events				
PCI Stratum	N = 610	N=594	N=195	N=203
Any	54 (8.9%)	62 (10.4%)	34 (17.4%)	33 (16.3%)
Peri-procedural	9 (1.5%)	17 (2.9%)	2 (1.0%)	10 (4.9%)
Spontaneous	45 (7.4%)	45 (7.6%)	32 (16.4%)	23 (11.3%)
CABG Stratum	N = 205	N=177	N=180	N= 201
Any	20 (9.8%)	14 (7.9%)	43 (23.9%)	19 (9.5%)
Peri-procedural	1 (0.49%)	4 (2.3%)	5 (2.8%)	6 (3.0%)
Spontaneous	19 (9.3%)	10 (5.7%)	38 (21.1%)	13 (6.5%)
Stroke Events				
PCI Stratum	N = 610	N=594	N=195	N=203
Any	14 (2.3%)	20 (3.4%)	9 (4.6%)	4 (2.0%)
Peri-procedural	1 (0.2%)	2 (0.3%)	1 (0.5%)	1 (0.5%)
Spontaneous	13 (2.1%)	18 (3.0%)	8 (4.1%)	3 (1.5%)
CABG Stratum	N = 205	N=177	N=180	N= 201
Any	6 (2.9%)	3(1.7%)	6 (3.3%)	5 (2.5%)
Peri-procedural	1 (0.5%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Spontaneous	5 (2.4%)	3 (1.7%)	6 (3.3%)	4 (2.0%)

*MIs were classified by the BARI 2D Trial ECG Core Laboratory. Strokes were adjudicated by an independent classification committee.

Supplementary Table 2: Five-Year Kaplan-Meier Event Rates for Medical Therapy versus Prompt Revascularization within Subgroups Defined by Framingham and Angiographic Risk

	DEATH					
	Low Angiographic Risk Score (n = 1163)			High Angiographic Risk Score (n = 380)		
PCI Stratum	**MED**	**REV**	**P-value ***	**MED**	**REV**	**P-value ***
Low Framingham Risk (n= 1075)	8.0%	7.8%	0.49	16.8%	13.3%	0.31
High Framingham Risk (n = 468)	9.7%	12.0%	0.58	15.5%	21.7%	0.68
	Low Angiographic Risk Score (n = 377)			High Angiographic Risk Score (n = 372)		
CABG Stratum	**MED**	**REV**	**P-value ***	**MED**	**REV**	**P-value ***
Low Framingham Risk (n= 454)	11.4%	7.5%	0.53	12.1%	13.2%	0.76
High Framingham Risk (n = 295)	25.7%	14.2%	0.24	22.7%	18.7%	0.68
	DEATH/MI/STROKE					
	Low Angiographic Risk Score (n = 1163)			High Angiographic Risk Score (n = 380)		
PCI Stratum	**MED**	**REV**	**P-value ***	**MED**	**REV**	**P-value ***
Low Framingham Risk (n= 1064)	18.5%	18.7%	0.26	27.6%	26.5%	0.85
High Framingham Risk (n = 479)	18.4%	24.4%	0.19	34.8%	34.2%	0.93
	Low Angiographic Risk Score (n = 377)			High Angiographic Risk Score (n = 372)		
CABG Stratum	**MED**	**REV**	**P-value ***	**MED**	**REV**	**P-value ***
Low Framingham Risk (n= 451)	19.9%	17.1%	0.58	28.3%	21.8%	0.17
High Framingham Risk (n = 298)	34.7%	23.5%	0.36	**47.3%**	**27.1%**	**0.010**
	CARDIAC DEATH/MI					
	Low Angiographic Risk Score (n = 1163)			High Angiographic Risk Score (n = 380)		
PCI Stratum	**MED**	**REV**	**P-value ***	**MED**	**REV**	**P-value ***
Low Framingham Risk (n= 1064)	12.4%	12.5%	0.33	19.1%	22.5%	0.52
High Framingham Risk (n = 479)	11.4%	11.9%	0.42	25.6%	28.2%	0.71
	Low Angiographic Risk Score (n = 377)			High Angiographic Risk Score (n = 372)		
CABG Stratum	**MED**	**REV**	**P-value ***	**MED**	**REV**	**P-value ***
Low Framingham Risk (n= 451)	12.3%	14.4%	0.96	23.7%	15.6%	0.11
High Framingham Risk (n = 298)	19.0%	13.5%	0.78	**37.9%**	**17.4%**	**0.011**

	MI					
	Low Angiographic Risk Score (n = 1163)			High Angiographic Risk Score (n = 380)		
PCI Stratum	**MED**	**REV**	**P-value ***	**MED**	**REV**	**P-value ***
Low Framingham Risk (n= 1075)	11.1%	10.9%	0.51	17.6%	14.3%	0.49
High Framingham Risk (n = 468)	9.8%	8.6%	0.70	24.5%	20.9%	0.95
	Low Angiographic Risk Score (n = 377)			High Angiographic Risk Score (n = 372)		
CABG Stratum	**MED**	**REV**	**P-value ***	**MED**	**REV**	**P-value ***
Low Framingham Risk (n= 454)	9.8%	9.8%	0.78	17.3%	11.1%	0.13
High Framingham Risk (n = 295)	13.0%	7.6%	0.49	**35.7%**	**9.9%**	**0.0010**
	STROKE					
	Low Angiographic Risk Score (n = 1163)			High Angiographic Risk Score (n = 380)		
PCI Stratum	**MED**	**REV**	**P-value ***	**MED**	**REV**	**P-value ***
Low Framingham Risk (n= 1075)	2.4%	3.5%	0.32	4.0%	2.8%	0.79
High Framingham Risk (n = 468)	2.0%	4.1%	0.57	**9.5%**	**0.0%**	**0.025**
	Low Angiographic Risk Score (n = 377)			High Angiographic Risk Score (n = 372)		
CABG Stratum	**MED**	**REV**	**P-value ***	**MED**	**REV**	**P-value ***
Low Framingham Risk (n= 454)	**4.3%**	**0.0%**	**0.043**	2.2%	2.8%	0.69
High Framingham Risk (n = 295)	0.0%	5.8%	0.063	5.8%	3.0%	0.42

CABG = coronary artery bypass grafting; MED = medical therapy; MI = myocardial infarction; PCI = percutaneous coronary intervention; REV = prompt revascularization

*p-value from the log rank test for MED versus REV within the subgroup defined by Framingham and Angiographic Risk

SUPPLEMENTARY FIGURE LEGENDS

Supplementary Figure 1: Lowess plot of the estimated probability of death/MI/stroke at 3-years (y-axis) among all BARI 2D patients according to the baseline angiographic risk score (x-axis). The vertical line indicates the dividing line between the lower 2 risk tertiles and the top risk tertile. Those patients with a predicted probability ≥17.1% of death/MI/stroke at 3-years were classified as being in the angiographic high-risk tertile.

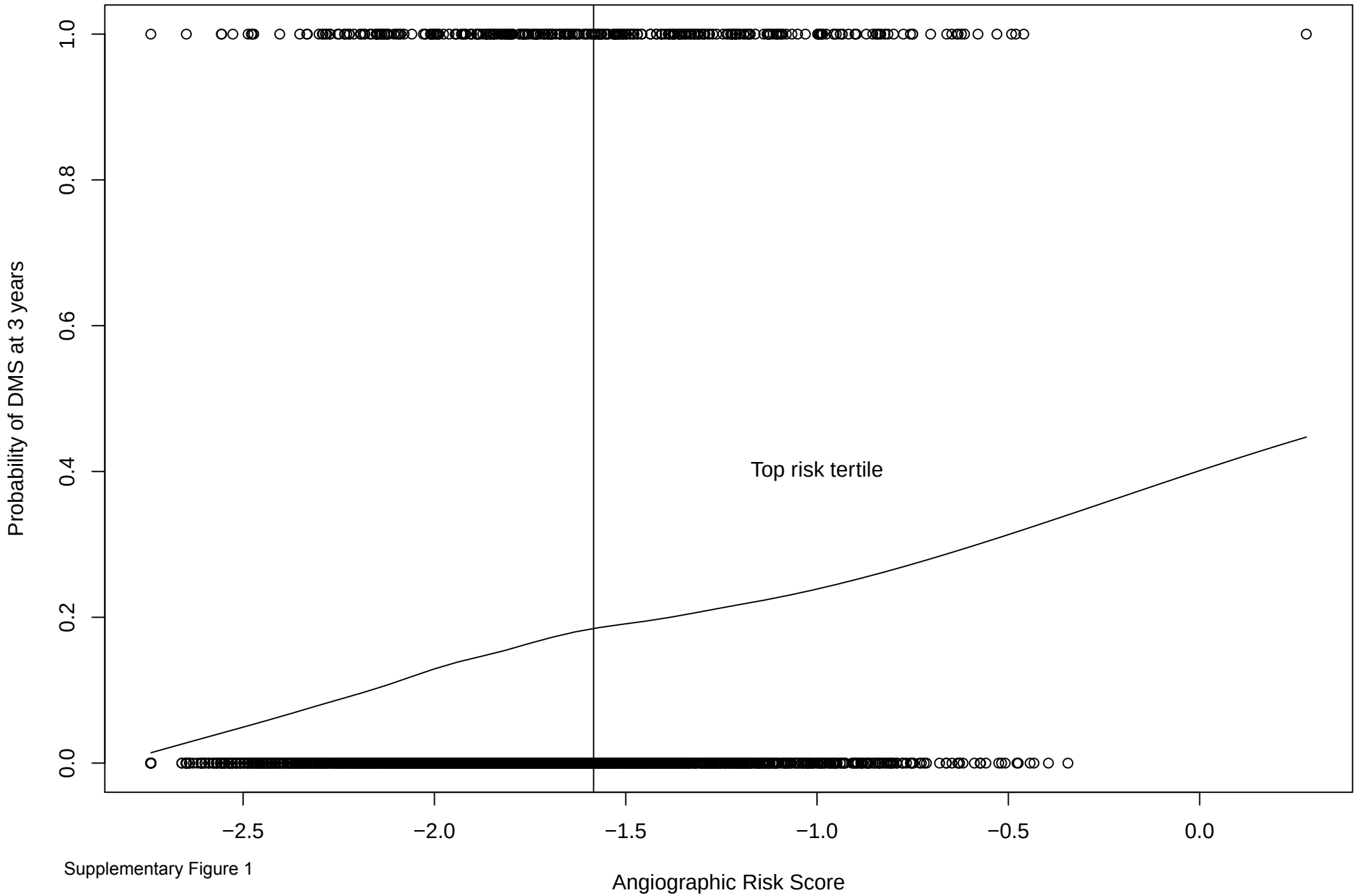
Supplementary Figure 2: Mortality by angiographic risk score category and intended revascularization. Each figure shows the cumulative Kaplan-Meier event rates for death for patients randomized to medical therapy (MED blue) and prompt revascularization (REV red) with the log-rank p-value. Patients are stratified according to intended revascularization stratum and angiographic risk score. Panel a) PCI stratum, low angiographic risk, b) PCI stratum, high angiographic risk, c) CABG stratum low angiographic risk, d) CABG stratum, high angiographic risk

Supplementary Figure 3: Cardiac death or MI by angiographic risk score category and intended revascularization. Each figure shows the cumulative Kaplan-Meier event rates for the composite outcome cardiac death/MI for patients randomized to medical therapy (MED blue) and prompt revascularization (REV red) with the log-rank p-value. Patients are stratified according to intended revascularization stratum and angiographic risk score. Panel a) PCI stratum, low angiographic risk, b) PCI stratum, high angiographic risk, c) CABG stratum low angiographic risk, d) CABG stratum, high angiographic risk.

Supplementary Figure 4: MI by angiographic risk score category and intended revascularization. Each figure shows the cumulative Kaplan-Meier event rates for MI for patients randomized to medical therapy (MED blue) and prompt revascularization (REV red) with the log-rank p-value. Patients are stratified according to intended revascularization stratum and angiographic risk score. Panel a) PCI stratum, low angiographic risk, b) PCI stratum, high angiographic risk, c) CABG stratum low angiographic risk, d) CABG stratum, high angiographic risk.

Supplementary Figure 5: Stroke by angiographic risk score category and intended revascularization. Each figure shows the cumulative Kaplan-Meier event rates for Stroke for patients randomized to medical therapy (MED blue) and prompt revascularization (REV red) with the log-rank p-value. Patients are stratified according to intended revascularization stratum and angiographic risk score. Panel a) PCI stratum, low angiographic risk, b) PCI stratum, high angiographic risk, c) CABG stratum low angiographic risk, d) CABG stratum, high angiographic risk.

Supplementary Figure 6: The HR of death/MI/stroke for MED therapy vs. prompt revascularization by angiographic, Framingham risk and EuroSCORE stratified by intended revascularization. The number of patients and the 5-Year Kaplan-Meier event rates for patients randomized to MED and REV in each of the subgroups are reported. The hazard ratio for MED versus REV (diamond) and its 95% confidence interval is plotted using a log scale. The vertical line represents a HR of 1 (no randomized treatment effect). The interaction p-value is a test of equality of the HR's among the levels of the subgroup variable. The left panel shows results for patients randomized in the PCI stratum and the right shows results for patients in the CABG stratum.

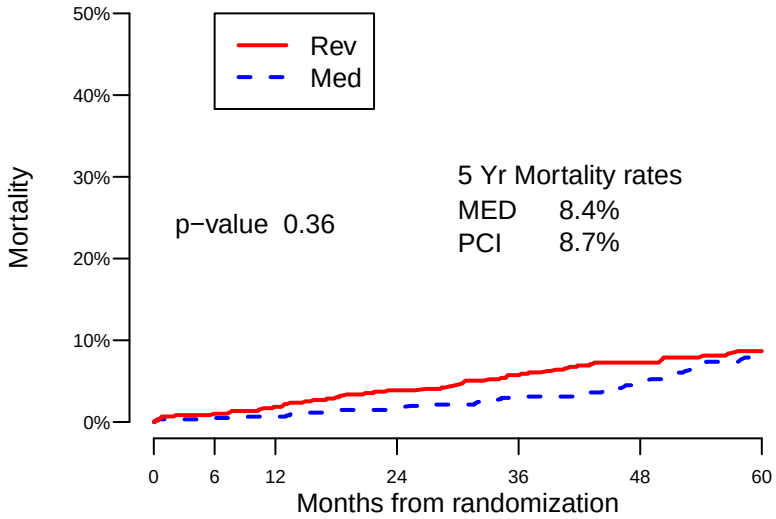


Supplementary Figure 1

Mortality
by Angiographic Risk and Intended Revascularization Stratum

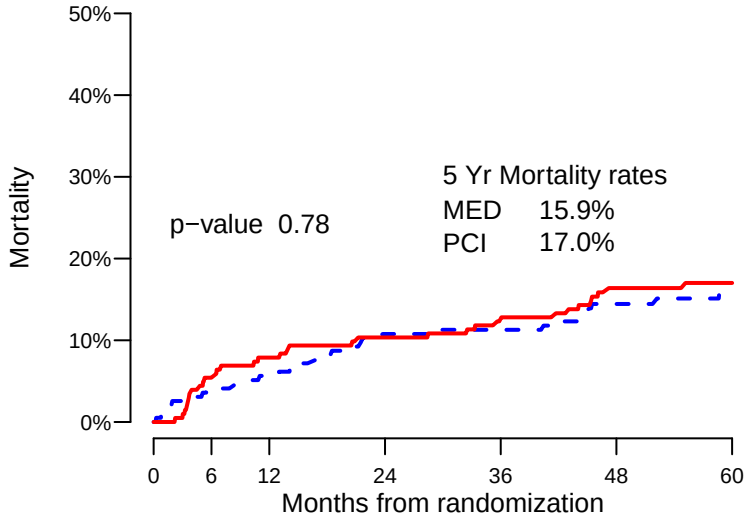
A. PCI Stratum

Low Risk (n = 1204)



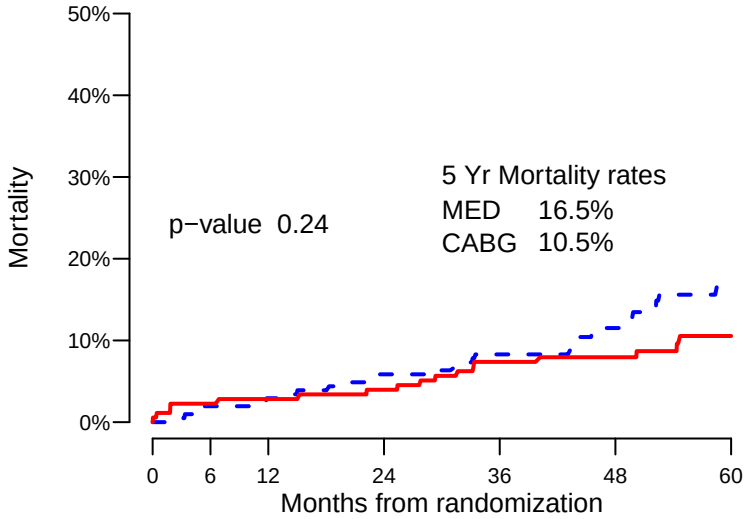
B. PCI stratum

High Risk (n = 398)



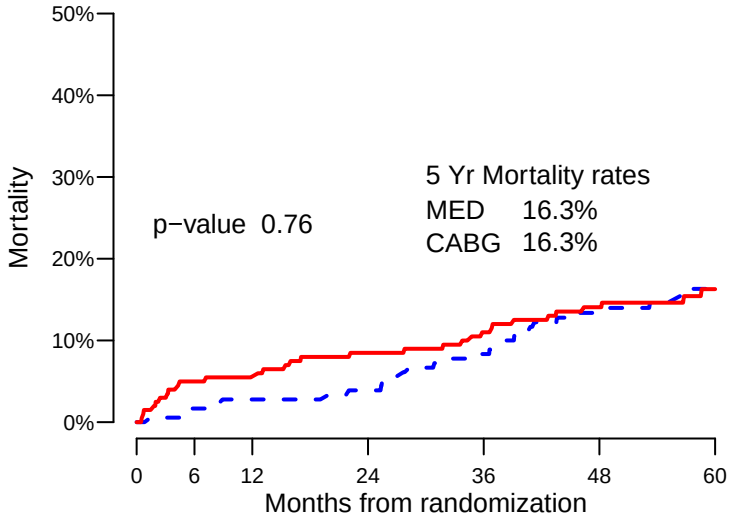
C. CABG stratum

Low Risk (n = 382)



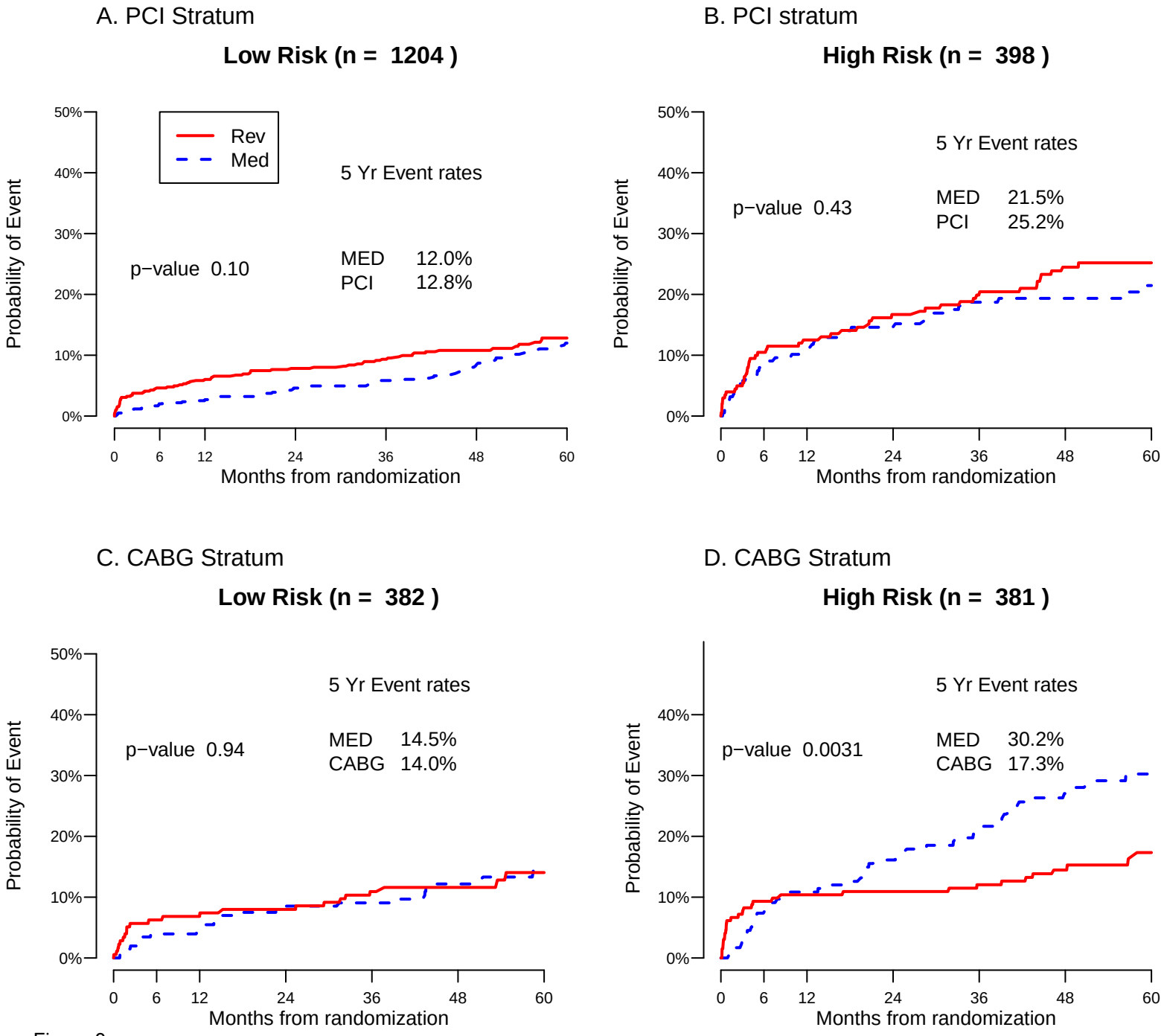
D. CABG stratum

High Risk (n = 381)



Supplementary Figure 2

Cardiac Death or MI
by Angiographic Risk and Intended Revascularization Stratum

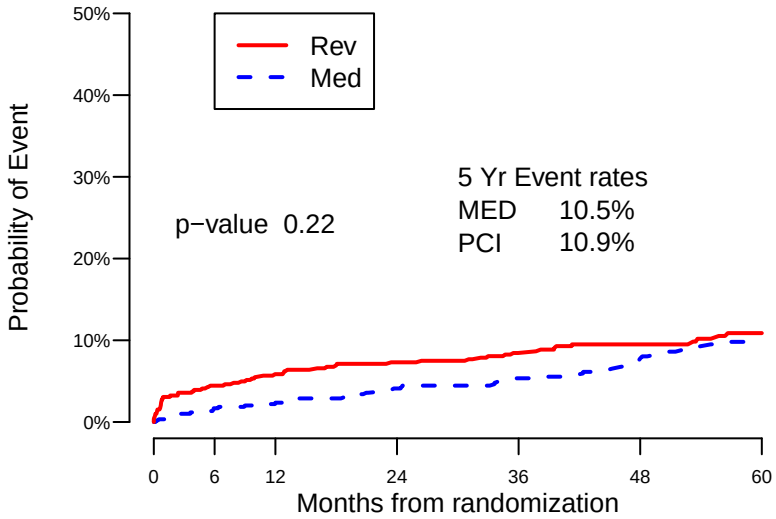


Supplementary Figure 3

MI
by Angiographic Risk and Intended Revascularization Stratum

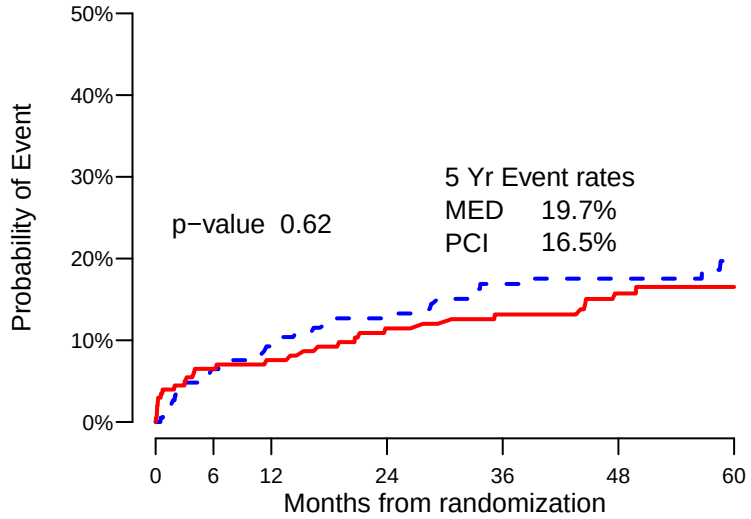
A. PCI Stratum

Low Risk (n = 1204)



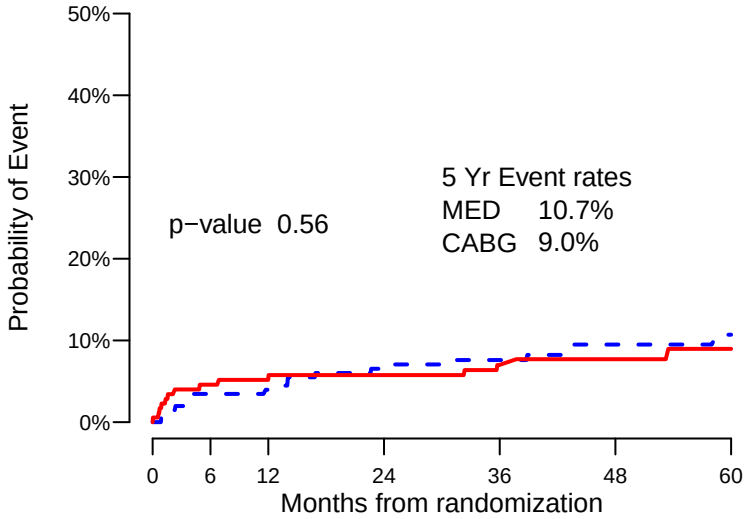
B. PCI stratum

High Risk (n = 398)



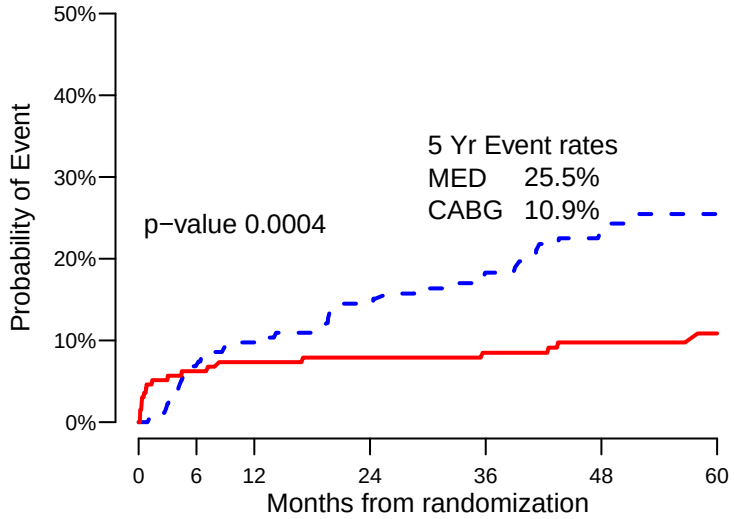
C. CABG stratum

Low Risk (n = 382)



D. CABG stratum

High Risk (n = 381)

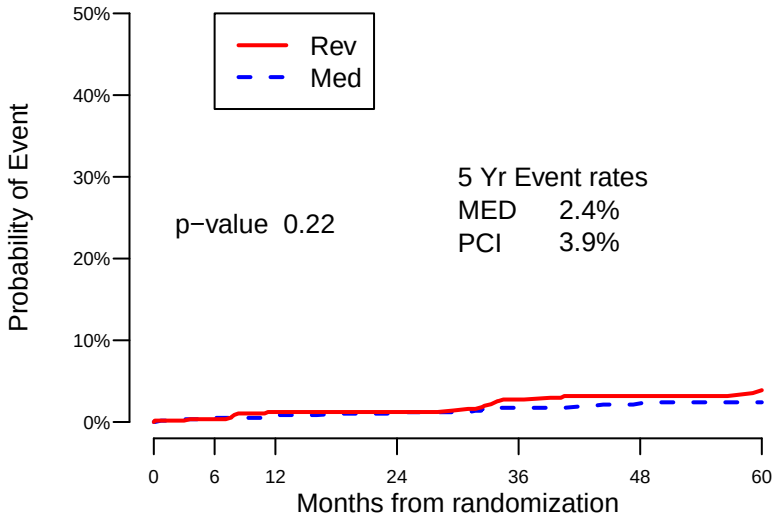


Supplementary Figure 4

Stroke
by Angiographic Risk and Intended Revascularization Stratum

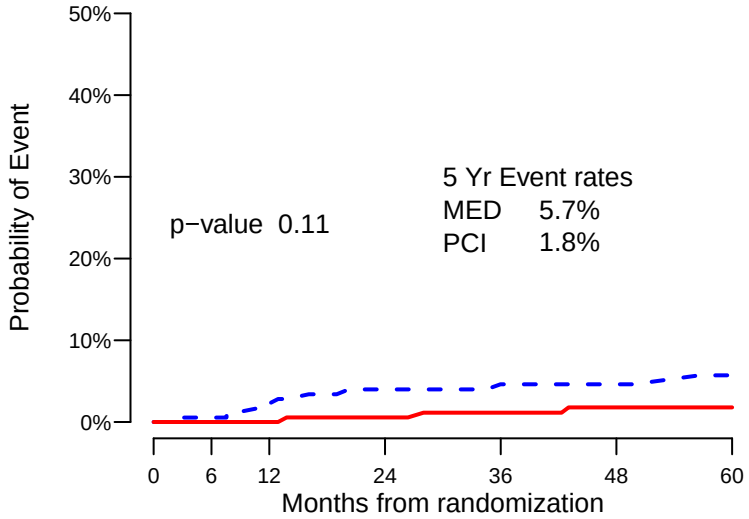
A. PCI Stratum

Low Risk (n = 1204)



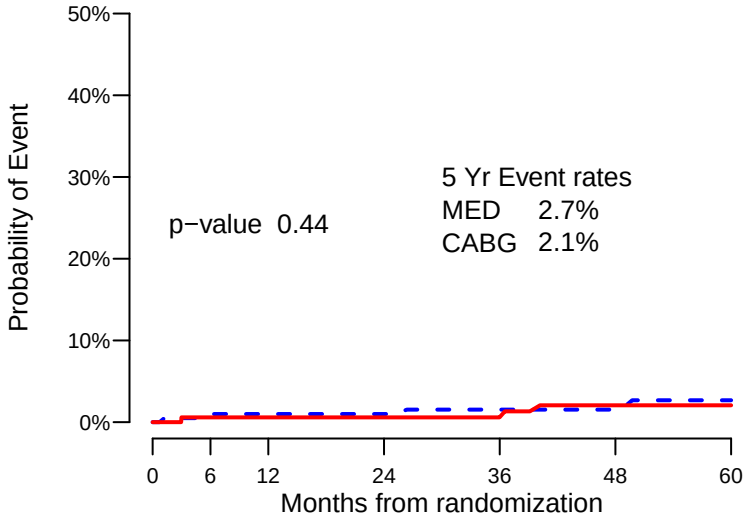
B. PCI stratum

High Risk (n = 398)



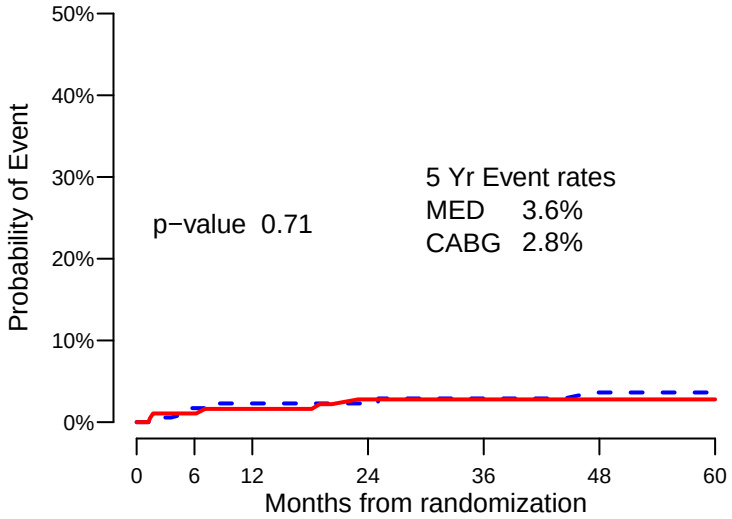
C. CABG stratum

Low Risk (n = 382)



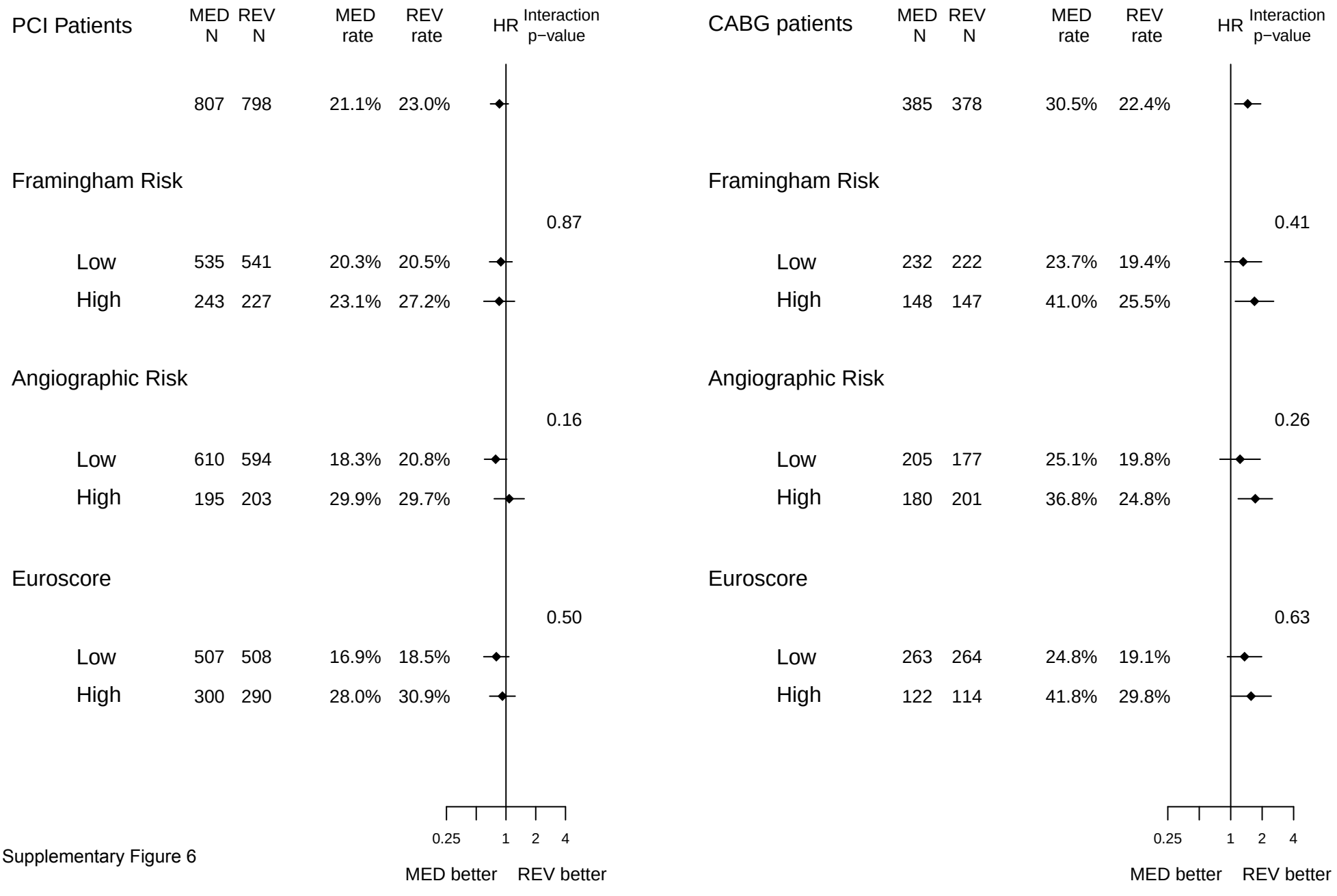
D. CABG stratum

High Risk (n = 381)



Supplementary Figure 5

Hazard ratio for Death/MI/Stroke
by Angiographic Risk, Framingham Risk and EuroScore



Supplementary Figure 6