Supplementary Appendix

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

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Comparative Effectiveness of Revascularization Strategies

Supplementary Appendix

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Contents:

Imputation of Missing Variables

It was anticipated that the PCI study population and the CABG study population would differ substantially with respect to preprocedural characteristics. We therefore collected baseline variables available in both registries to make adjusted comparisons feasible. Variables common to both registries were identified from Versions 2.41 and 2.52 of the STS data specifications and Versions 2 and 3 of the ACCF CathPCI data specifications. Most variables were >99% complete in both groups. Exceptions were ejection fraction (missing 21% in PCI, 4% in CABG) and glomerular filtration rate (GFR) (missing 25% in PCI, 1% in CABG). Missing values of continuous risk factors were imputed by stratifying on treatment group and combinations of other related risk factors, and imputing stratum-specific medians. This approach was used for ejection fraction (stratification by sex, heart failure, prior myocardial infarction, and treatment group), GFR (stratification by age, race, gender, renal failure), and weight and height (stratification by gender and treatment group). Categorical variables had <1% missing data and were imputed to the most common category. Although a single imputation approach was used for our primary IPW analyses, additional analyses were performed using multiple imputation methodology, as described below.

Variables Included in the Propensity Model

Propensity scores to estimate the probability of receiving CABG were developed with logistic regression to adjust for between-group differences in baseline patient and hospital characteristics.[1] Patient-level covariates in the propensity model were: age, gender, race, height, BMI, smoking status, family history of coronary artery disease, GFR (defined as dialysis and/or GFR<=30), renal failure, hypertension, dyslipidemia, cerebrovascular disease, chronic lung disease, peripheral arterial disease, history of heart failure, prior PCI, prior myocardial infarction, angina prior to the procedure, ejection fraction, urgent procedure, number of diseased vessels, mitral insufficiency, mitral stenosis, aortic valve insufficiency and aortic stenosis. Hospital-level covariates were: hospital average annual PCI volume, hospital average annual CABG volume, academic hospital, and hospital location (rural/urban). For patients without renal failure, GFR was modeled as a linear trend between 30 and 90 and flat below 30 or above 90. Patients with renal failure were represented in the model by an indicator variable without further adjustment for GFR. The continuous variable ejection fraction was modeled as a linear trend. All other

continuous variables were modeled as a flexible polynomial with linear and quadratic components.

Sensitivity Analysis

Several sensitivity analyses were performed. First, to account for possible misspecification of the propensity model, survival curves were re-estimated using a regression-based approach that did not utilize propensity scores or inverse probability weighting (IPW). Briefly, we used the Cox proportional hazards model with time-varying hazard ratios to estimate the association between baseline covariates and subsequent survival separately within the PCI and CABG cohorts.[2] Covariates for each model were identical to the propensity model. Using these models, we estimated the average survival curves that would be predicted if all patients in the study were to undergo PCI and if all patients were to undergo CABG. Second, survival curves for PCI versus CABG were estimated using a double robust strategy of combining the IPW with regression-based estimation.[3] Finally, we used propensity matching to compare survival in a matched pairs cohort of CABG and PCI patients. Of the 103,549 PCIs and 86,244 CABGs in our data, 43,084 patients in each group had a match in the other group by at least 3 digits. The characteristics of the patients in the unadjusted, inverse probability weighted and matched pair groups are shown in Supplementary Appendix Table 1. Survival curves based on all of these alternative approaches were overlaid on those produced by the original IPW analysis and were found to be nearly identical (Supplementary Appendix Figure 2).

As a further sensitivity analysis, we estimated hazard ratios for CABG versus PCI using a series of covariate-adjusted Cox models. Although the proportional hazards assumption was not met for the treatment group variable (as evidenced by the crossing survival curves), the estimated hazard ratio may be interpreted as an "average" over the observed event times.[2] Model 1 included all of the hospital and patient-level covariates in the propensity model plus an indicator of treatment group (CABG versus PCI). Covariates other than treatment group were modeled with time-dependent hazard ratios in order to relax the proportional hazards assumption for these covariates. For Model 2, we removed hospital-level covariates and instead entered hospital ID as a stratification variable.[4] For Model 3, we accounted for missing data by using multiple imputation as implemented in the R (www.R-project.org) package Multivariate Imputation by Chained Equations (MICE).[5] The imputation model included covariates from Model 1 plus

mortality status (1=death, 0=censored), time to death or censoring (log-scale), and the interaction of mortality status and procedure date. Ten randomly imputed complete datasets were generated and analyzed individually using the methods described above. Regression coefficients from the 10 models were then combined using standard formulas.[6] Hazard ratios (HRs) for CABG versus PCI were similar to the IPW estimated 4-year risk ratios and were consistent for the 3 different versions of the Cox model (Model 1: HR 0.78 [95% CI: 0.75-0.80]; Model 2: 0.75 [95% CI: 0.73-0.78]; Model 3: 0.74 [95% CI: 0.72-0.76]). Based on Model 1 results, we employed the method of Lin et al[7] to assess whether an unmeasured binary risk factor could explain a hazard ratio of this magnitude (explained in the main text).

Supplementary Appendix Table 1

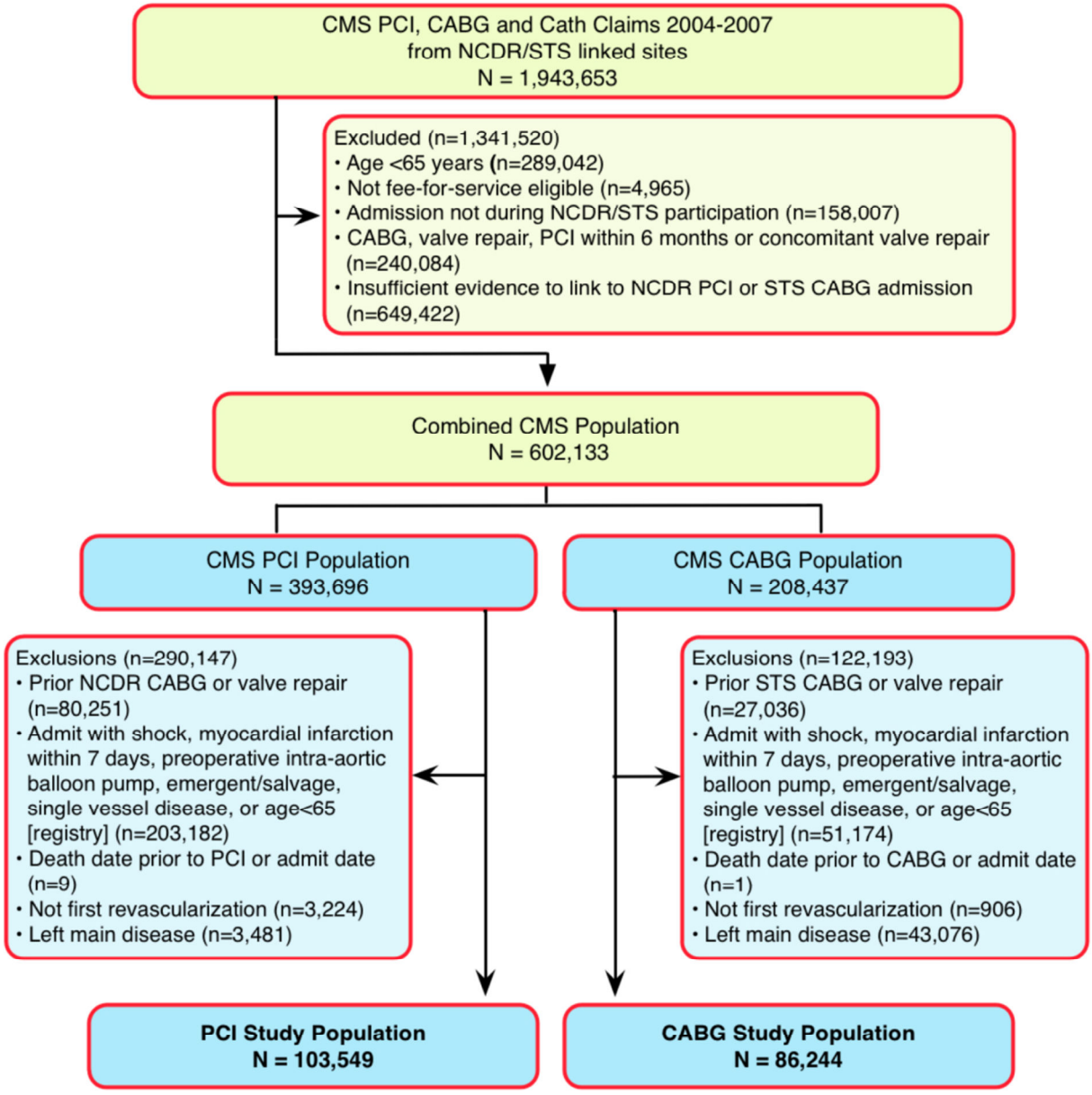
Unadjusted Inverse Probability Weighting Adjustment and Matched Pair Comparison

	Unadjusted			Adjusted			Matched Pair		
	CABG (n=86,244)	**PCI (n=103,549)**	**P Value**	**CABG (n=86,244)**	**PCI (n=103,549)**	**P Value**	**CABG (n=43,084)**	**PCI (n=43,084)**	**P Value**
Demographics									
Age (years)	73.1±5.6	74.7±6.5	<0.0001	74.0±9.2	74.0±8.3	0.49	73.8±5.9	73.9±5.9	0.62
Male	68.6	57.8	<0.0001	62.3	62.8	0.17	63.7	63.5	0.68
Race									
White	90.1	89.5	<0.0001	89.7	89.9	0.27	89.7	89.8	0.69
African American	4.67	4.77	0.30	4.78	4.64	0.35	4.78	4.83	0.73
Other	5.24	5.73	<0.0001	5.51	5.42	0.54	5.51	5.38	0.39
Risk Factors									
Height (cm)	171±10	169±11	<0.001	170±15.7	170.1±14.3	0.20	170±11	170±11	0.59
BMI ($kg/m^{2)}$	28.7±5.8	28.7±5.9	0.78	28.8±8.6	28.7±7.9	0.97	28.8±5.8	28.8±5.8	0.77
Smoking Status									
Current Smoker	12.9	11.6	<0.0001	11.9	12.0	0.74	12.3	12.1	0.38
Former Smoker	44.0	42.5	<0.0001	43.0	43.3	0.45	43.1	43.4	0.38
Never	43.1	45.9	<0.0001	45.0	43.3	0.45	44.6	44.5	0.75
Family History of CAD	33.0	21.9	<0.001	26.6	26.8	0.62	26.2	26.8	0.067

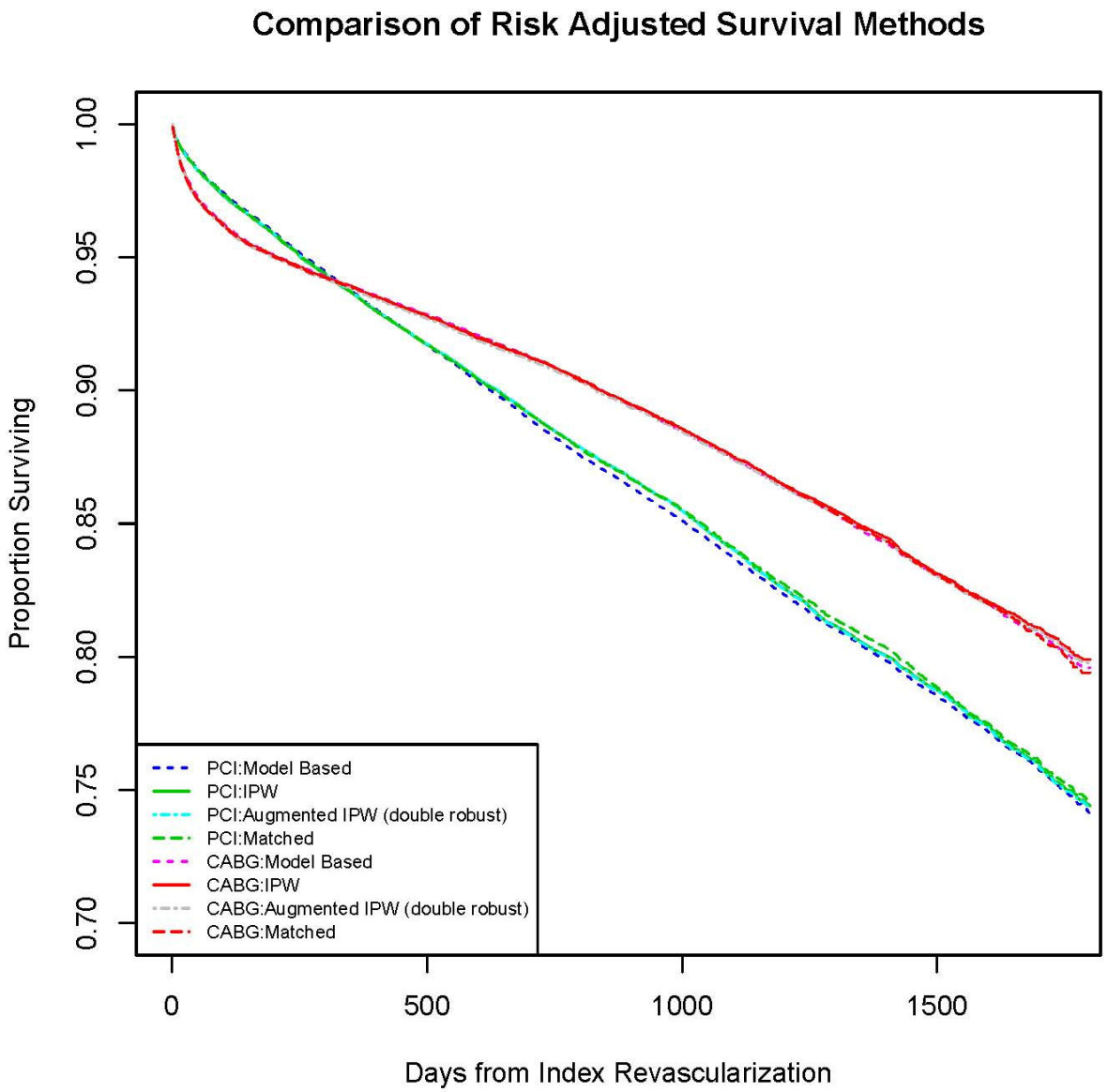
	Unadjusted			Adjusted			Matched Pair		
	CABG (n=86,244)	**PCI (n=103,549)**	**P Value**	**CABG (n=86,244)**	**PCI (n=103,549)**	**P Value**	**CABG (n=43,084)**	**PCI (n=43,084)**	**P Value**
Diabetes									
Insulin Requiring	10.2	9.8	0.0069	9.7	9.9	0.35	10.0	10.1	0.73
Not Insulin Requiring	28.4	24.6	<0.0001	26.8	25.9	0.56	26.6	26.4	0.44
No Diabetes	61.4	65.6	<0.0001	64.2	64.1	0.97	63.4	63.6	0.63
GFR (ml/min)	67.9±25.9	65.4±23.7	<0.0001	66.9 ±41.2	66.4 ±32	0.00063	66.9±24.3	66.5±24.0	0.58
Renal Failure	6.1	6.2	0.57	6.1	6.1	0.80	3.85	3.83	0.92
Hypertension	84.8	83.4	<0.0001	83.9	83.8	0.58	83.9	84.1	0.39
Dyslipidemia	77.7	74.9	<0.0001	75.9	76.0	0.61	75.8	75.8	0.87
Chronic Lung Disease	20.7	18.9	<0.0001	19.4	19.6	0.50	16.7	16.7	0.94
Cerebrovascular Disease	17.6	15.8	<0.0001	16.6	16.6	0.86	19.9	19.8	0.99
Peripheral Arterial Disease	17.9	15.3	<0.0001	16.4	16.4	0.97	16.4	16.6	0.45
Cardiac Status									
History of Heart Failure	11.5	10.2	<0.0001	11.2	10.8	0.067	10.8	11	0.30
Prior PCI	15.7	31.0	<0.0001	24.8	24.2	0.049	21.9	21.9	0.90
History of Myocardial Infarction	25.3	24.6	0.0001	24.5	24.7	0.51	24.1	24.2	0.88
Angina Prior to the Procedure									
No Angina	21.8	30.8	<0.0001	26.4	26.8	0.23	27.7	27.7	0.90
Stable Angina	49.6	22.6	<0.0001	34.6	34.9	0.46	33.9	34	0.64
Unstable Angina	28.6	46.6	<0.0001	39.0	38.3	0.066	38.4	38.3	0.73

	Unadjusted			Adjusted			Matched Pair		
	CABG (n=86,244)	**PCI (n=103,549)**	**P Value**	**CABG (n=86,244)**	**PCI (n=103,549)**	**P Value**	**CABG (n=43,084)**	**PCI (n=43,084)**	**P Value**
Ejection Fraction	52.9±12.2	55.5±11.4	<0.0001	54.4±17.6	54.4±16.2	0.58	54.2±11.6	54.3±11.9	<.0001
Vessels Diseased (3 vs 2)	80.3	32.1	<0.0001	53.2	53.8	0.043	62.7	62.6	0.88
Procedure Status Urgent	68.6	57.8	<0.0001	62.3	62.8	0.17	35.6	35.5	0.82
Valve Assessment									
Mitral Valve Insufficiency	2.56	1.44	<0.0001	1.95	1.95	0.72	1.88	1.9	0.76
Mitral Valve Stenosis	0.37	0.68	<0.0001	0.58	0.56	0.55	0.50	0.51	0.85
Aortic Valve Insufficiency	0.73	0.53	<0.0001	0.66	0.65	0.84	0.64	0.65	0.83
Aortic Valve Stenosis	1.98	2.16	0.0049	2.05	2.12	0.44	2.04	2.08	0.74
Hospital Variables									
Average CABG Volume/Year	215±161	191±144	<0.0001	201±224	201±202	0.87	201±151	201±151	0.053
Average PCI Volume/Year	512±371	530±379	<0.0001	516±547	518±496	0.65	513±367	513±365	0.27
Academic Institution	27.9	28.0	0.74	28.4	27.7	0.034	27.6	28	0.22
Rural (vs. Urban)	5.23	3.73	<0.0001	4.43	4.53	0.52	4.51	4.47	0.82

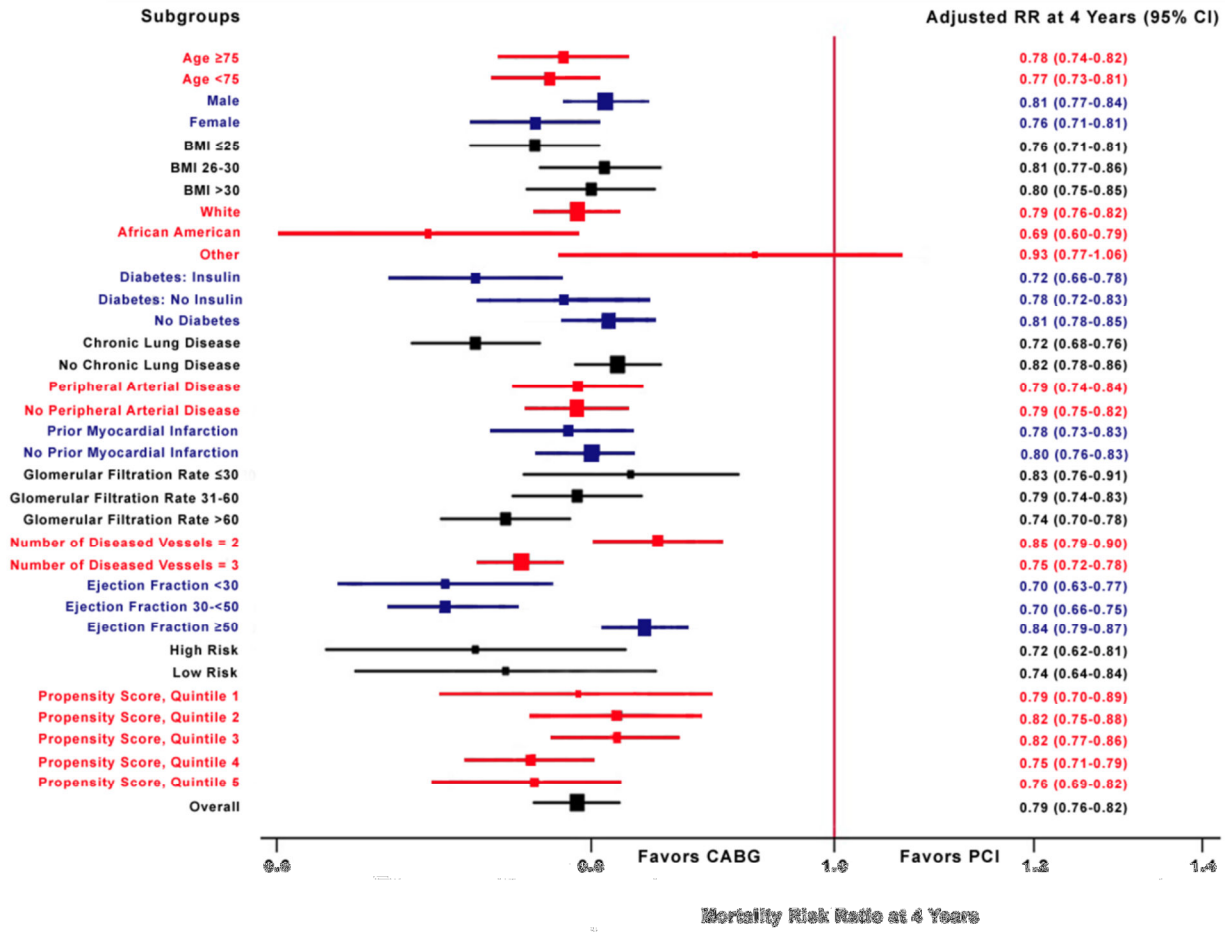
Numbers are in percentages or mean ± standard deviation. Abbreviations: CAD, coronary artery disease; GFR, glomerular filtration rate; CABG coronary artery bypass graft; PCI, percutaneous coronary intervention.



Supplementary Appendix Figure 1: Patient Selection Flow Diagram



Supplementary Appendix Figure 2: Survival in the PCI and CABG populations using different analytic methods: covariate-adjusted model, inverse probability weighted (IPW) analysis, augmented IPW double-robust analysis and propensity score matching analysis.



Supplementary Appendix Figure 3: Forest plot of hazard ratios for mortality by subgroup

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