SUPPLEMENTAL METHODS

Patient Population

A total of 20,418 consecutive patients from 5 centers in the US, Canada and Israel who underwent SPECT-MPI between 2009 and 2014 were initially included in the study. Patients with large resting defect (rest TPD > 10%) were excluded (n=896) after identifying a significant interaction between large resting perfusion defect, early revascularization and ischemic TPD with respect to association with MACE (interaction p=0.028). Previous studies also determined that the association between ischemia, early revascularization, and all-cause mortality was not present in patients with large fixed defects.(2) Patients with a history of cardiac transplantation (n=93) or missing data (n=341) were also excluded leaving a final population of 19,088 patients. There was no interaction between history of CAD (defined as history of myocardial infarction [MI] or revascularization), early revascularization, ischemic TPD and MACE (p=0.271). Therefore, these patients were included in the analysis. The studied population was divided into 2 groups: patients who underwent early revascularization, defined as PCI or coronary artery bypass grafting (CABG) within 90 days after SPECT-MPI test [1], and those who were treated medically. Patients who underwent late revascularization were not excluded from the analysis.

Baseline demographic information included age, sex, family history of premature CAD, smoking status, previous PCI, previous CABG and past medical history of hypertension, hyperlipidemia, diabetes, or peripheral vascular disease. Presenting symptoms were classified as typical angina or non-typical using standard criteria.[2] Stress types were classified as exercise or pharmacologic. Patients who underwent low-level exercise in combination with pharmacologic stress were considered as pharmacologic stress. Resting ECGs and stress ECG response were interpreted by experienced cardiologists at the time of SPECT-MPI.

Clinical Outcomes

All-cause mortality was determined from the Social Security Death Index for US sites, the Ministry of Health National Death Database for Israel, and chart review including hospital and medical doctor's office (through the Open Architecture Clinical Information System) for Canada. Non-fatal events were adjudicated by experienced cardiologists at each site after considering all available clinical information including symptoms, ECG changes, cardiac biomarkers, imaging modalities such as echocardiography, stress test, SPECT-MPI, coronary computed tomography angiography and invasive angiography. Clinicians were encouraged to adjudicate outcomes based on standardized clinical criteria as previously defined.[3] Follow-up duration was determined based on the date of death or last date at which follow-up for events was available based on site-specific methods for ascertaining events and ranged from January 2015 to December 2017. Additional details of the ascertainment of events and follow-up duration are outlined in **Supplemental Table 1.**

Automated Quantification

All imaging data was quality control checked by experienced core laboratory technologists. After quality control, images were quantified with QPS/QGS (Cedars-Sinai Medical Center) for all patients sequentially in an automated batch mode which optimizes the computational resources required to process the image registry and records all quantitative data automatically for further analysis. The same software (QPS/QGS) was used for both camera systems, with utilization of specific normal limits for DSPECT and Discovery NM530c. Left ventricular ejection fraction (LVEF) was assessed on stress studies in either upright (D-SPECT) or supine (Discovery NM530c) positions.

REFERENCES

1. Hachamovitch R, Hayes SW, Friedman JD, Cohen I, Berman DS. Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. Circulation 2003;107:2900-7.

2. Gibbons RJ, Chatterjee K, Daley J et al. ACC/AHA/ACP Guidelines for the Management of Patients With Chronic Stable Angina. Circulation 1999;99:2829-2848.

3. Thygesen K, Alpert JS, Jaffe AS et al. Fourth Universal Definition of Myocardial Infarction (2018). J Am Coll Cardiol 2018;72:2231-2264.

SUPPLEMENTAL TABLES

Supplemental Table 1: Ascertainment of events and follow-up

Site	Number of Patients (%)	Follow-up (mean ± SD, years)	Last Date of follow-up	Ascertainment of death	Ascertainment of MACE
Assuta Medical Center	7363 (39.7)	4.0 ± 0.8	January 2015	Ministry of Health National Death Database	Electronic Medical Records
Brigham and Women's Hospital	2212 (11.9)	5.4 ± 1.7	December 2016	Social Security Death Index	Electronic Medical Records
Cedars-Sinai Medical Center	3234 (17.5)	5.4 ± 1.5	December 2017	Social Security Death Index	Electronic Medical Records
Oregon Heart and Vascular Institute	2536 (13.7)	6.5 ± 1.7	November 2017	Social Security Death Index	Electronic Medical Records
Ottawa Heart Institute	3189 (17.2)	3.4 ± 0.7	December 2017	Open Architecture Clinical Information System	Open Architecture Clinical Information System

Supplemental Table 1: Ascertainment of events and follow-up

Supplemental Table 2: Baseline population characteristics stratified by burden of ischemia.

Variable	Ischemic TPD 0 – 5% (n=15,930)	Ischemic TPD 5 – 10% (n=2,372)	Ischemic TPD >10% (n=786)	p-value
Site, no. (% of site cases)				<0.001
Assuta Medical Center	6010 (37.7)	1235 (52.1)	401 (51.0)	
Brigham and Women's Hospital	1867 (11.7)	286 (12.1)	108 (13.7)	
Cedars-Sinai Medical Center	3056 (19.2)	177 (7.5)	79 (10.1)	
Oregon Heart and Vascular Institute	2285 (14.3)	242 (10.2)	75 (9.5)	
Ottawa Heart Institute	2712 (17.0)	432 (18.2)	123 (15.7)	
Demographic characteristics				
Age (years), mean (SD)	63.3 (12.0)	66.9 (11.7)	17.3 (10.9)	<0.001
Male, no. (%)	8155 (51.2)	1808 (76.2)	662 (84.2)	<0.001
BMI (kg/m^2), mean (SD)	28.5 (6.0)	28.3 (6.7)	28.4 (6.1)	0.009
Cardiovascular risk factors no. (%)				
Peripheral Vascular Disease	1569 (9.9)	366 (15.4)	130 (16.5)	<0.001
Hypertension	9738 (61.1)	1624 (68.5)	583 (74.2)	<0.001
Diabetes Mellitus	3693 (23.2)	759 (32.0)	288 (36.6)	<0.001
Hyperlipidemia	9627 (60.4)	1654 (69.7)	597 (76.0)	<0.001
Family History of CAD	4497 (28.2)	603 (25.4)	193 (24.6)	0.002
Smoking	2972 (18.7)	503 (21.2)	152 (19.3)	0.013

Prior PCI	2393 (15.0)	695 (29.3)	273 (34.7)	<0.001
Typical Angina	760 (5.0)	180 (7.6)	142 (18.1)	<0.001
Stress Test Type, no. (%)				<0.001
Exercise	8142 (51.1)	904 (38.1)	302 (38.4)	
Pharmacologic	7788 (48.9)	1468 (61.9)	484 (61.6)	
Stress ECG response, no. (%)				<0.001
Negative	14436 (90.6)	2110 (89.0)	564 (71.8)	
Positive	1494 (9.40	262 (11.1)	222 (28.2)	
Myocardial perfusion study				
Ejection Fraction (%), mean (SD)	63.4 (10.8)	58.8 (12.4)	55.1 (11.8)	<0.001
MACE, no. (%)	1348 (8.5)	356 (15.0)	132 (16.8)	<0.001
Early Revascularization, no. (%)	154 (1.0)	146 (6.2)	254 (32.3)	<0.001

Supplemental Table 2: Baseline population characteristics stratified by burden of ischemia. BMI - Body Mass Index, CABG - Coronary Artery Bypass Graft Surgery, CAD - Coronary Artery Disease, PCI - Percutaneous Coronary Intervention, SD - standard deviation, TPD – total perfusion deficit.

Supplemental Table 3: Univariable cox proportional hazard model of association with MACE

Variable	Unadjusted HR (95% CI)	p value
Age	2.23 (2.08 – 2.38)	< 0.001
Male Gender	1.39 (1.26 – 1.53)	< 0.001
Body Mass Index	0.76 (0.71 – 0.80)	< 0.001
Peripheral Vascular Disease	2.29 (2.02 – 2.60)	< 0.001
Hypertension	1.70 (1.53 – 1.89)	< 0.001
Diabetes Mellitus	1.87 (1.70 – 2.05)	< 0.001
Hyperlipidemia	1.23 (1.11 – 1.35)	< 0.001
Family History	0.69 (0.62 – 0.77)	< 0.001
Smoking	1.25 (1.10 – 1.41)	0.001
Prior PCI	1.79 (1.61 – 2.00)	< 0.001
Prior CABG	1.96 (1.71 – 2.26)	< 0.001
Non-Typical Angina	0.95 (0.78 – 1.15)	0.582
Ischemic TPD	2.15 (1.93 – 2.40)	< 0.001
Ejection Fraction	0.81 (0.76 – 0.85)	< 0.001
Early Revascularization	1.35 (1.02 - 1.78)	0.035
Ischemic TPD (Reference 0 – 5%)		
>5% – 10%	2.14 (1.90 – 2.41)	< 0.001
> 10%	2.33 (1.95 – 2.79)	< 0.001

ECG Response (Reference Negative)		
Positive	0.67 (0.57 – 0.80)	< 0.001

Supplemental Table 3: Univariable cox proportional hazard model of association with MACE. CABG – coronary artery bypass grafting, CI – confidence interval, HR – hazard ratio, MACE – major adverse cardiovascular events, PCI – percutaneous coronary intervention, TPD – total perfusion deficit.

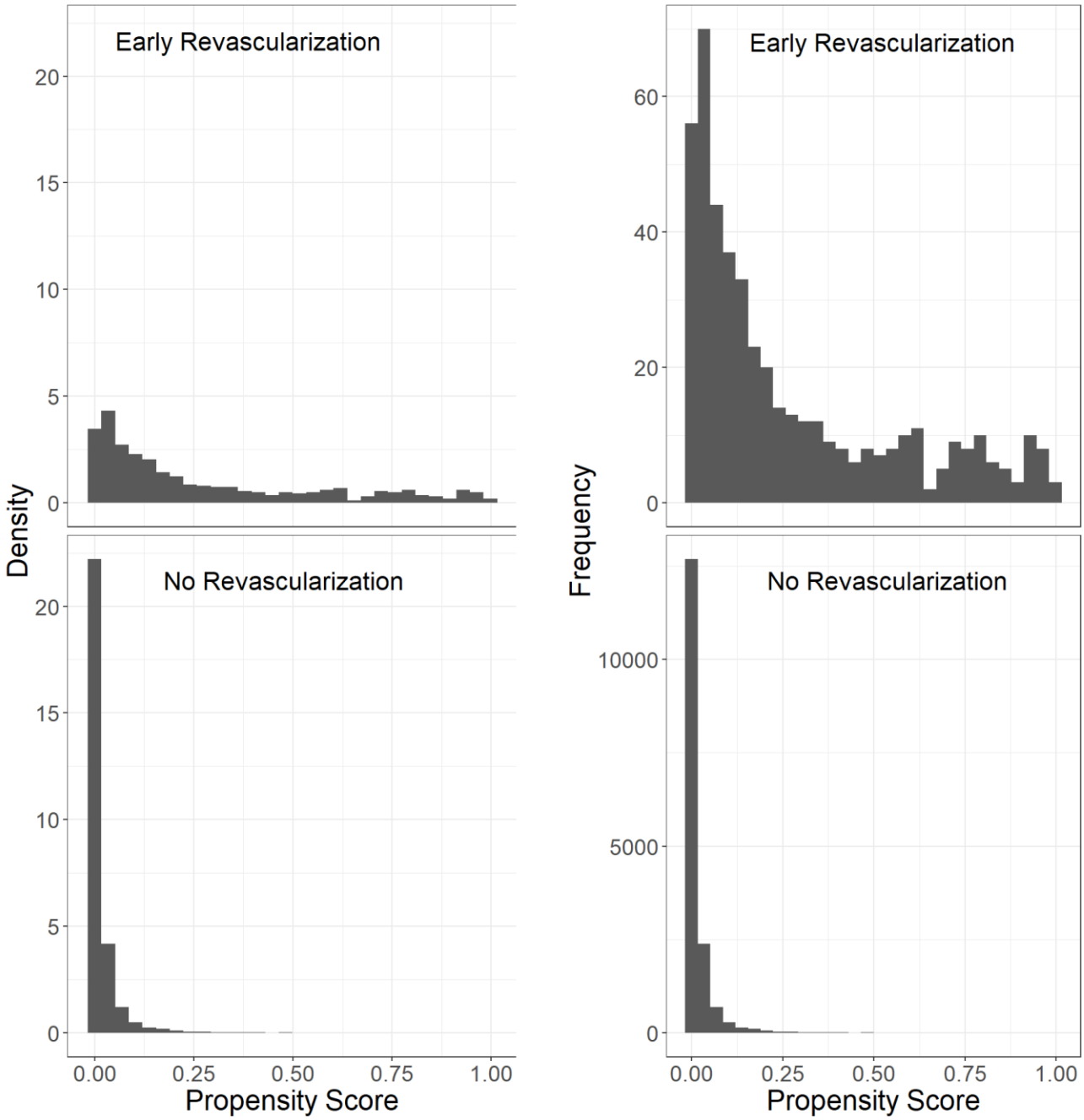
Supplemental Table 4: Components of the propensity score

Variable	Coding	OR (95% CI)	p value
Site	Site 1 / 5	0.52 (0.32 - 0.82)	< 0.001
	Site 2 / 5	1.28 (0.84 - 1.94)	
	Site 3 / 5	0.87 (0.57 - 1.33)	
	Site 4 / 5	0.74 (0.49 - 1.13)	
Age	72.81/56	0.94 (0.80 - 1.11)	0.058
Gender	Male/Female	1.34 (1.04 - 1.74)	0.024
Diabetes Mellitus	Yes/No	1.17 (0.95 - 1.45)	0.148
Hypertension	Yes/No	1.20 (0.95 - 1.51)	0.121
Hyperlipidemia	Yes/No	1.08 (0.86 - 1.36)	0.515
Family History of CAD	Yes/No	1.03 (0.82 - 1.29)	0.824
Smoking	Yes/No	0.81 (0.61 - 1.07)	0.135
Ejection Fraction	69.55/56.15	0.82 (0.69 - 0.97)	0.059
PVD	Yes/No	0.91 (0.66 - 1.26)	0.561
Ischemic TPD	3.65/0.31	8.35 (5.76 - 12.09)	< 0.001
Rest TPD	1.07/0	1.24 (1.06 - 1.46)	0.004
Angina Type	Non-typical/Typical	2.34 (1.77 - 3.08)	< 0.001
ECG Response	Positive/Negative	3.50 (2.76 - 4.43)	< 0.001
Stress Test Type	Others/Exercise	1.26 (1.00 - 1.58)	0.048
Prior CAD	Yes/No	0.71 (0.57 - 0.89)	0.003

Supplemental Table 4: Components of the propensity score. Coding denotes categories used for categorical variables or location of splines for continuous variables. CAD- coronary artery disease, PVD – peripheral vascular disease, TPD – total perfusion deficit.

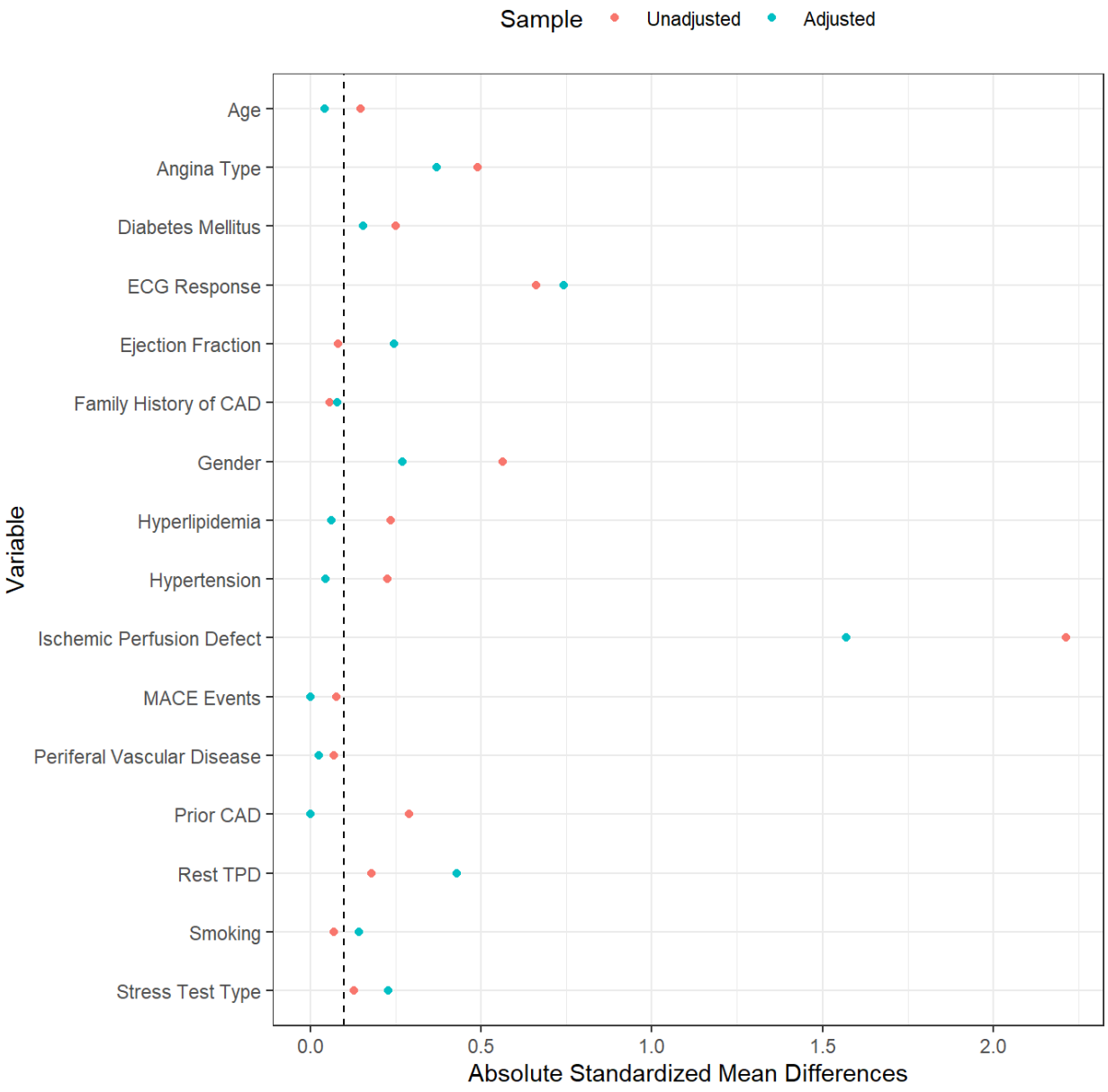
SUPPLEMENTAL FIGURES

Supplemental Figure 1:



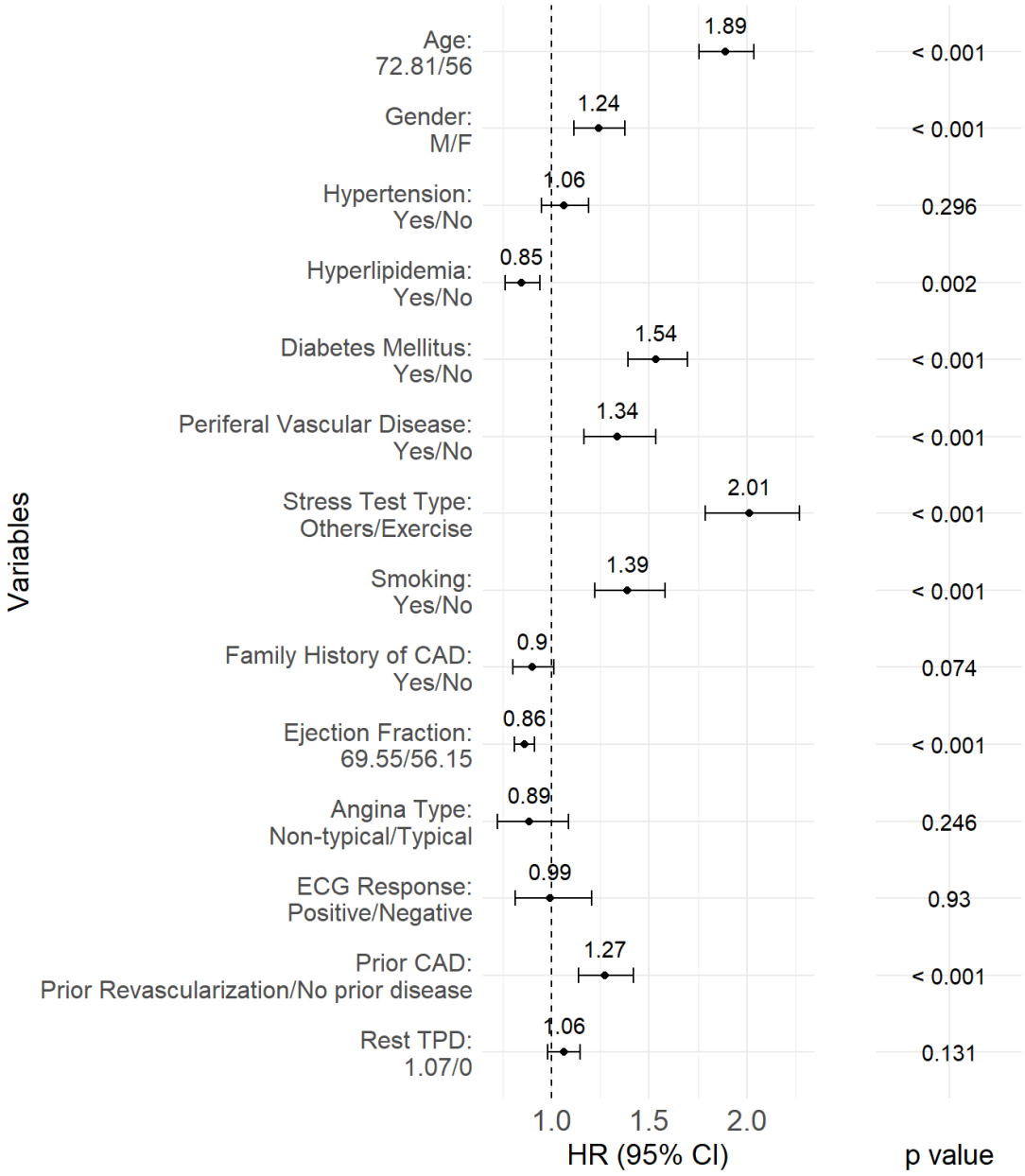
Supplemental Figure 1: Distribution of propensity scores as density and frequency in patients managed with early revascularization or no revascularization.

Supplemental Figure 2:



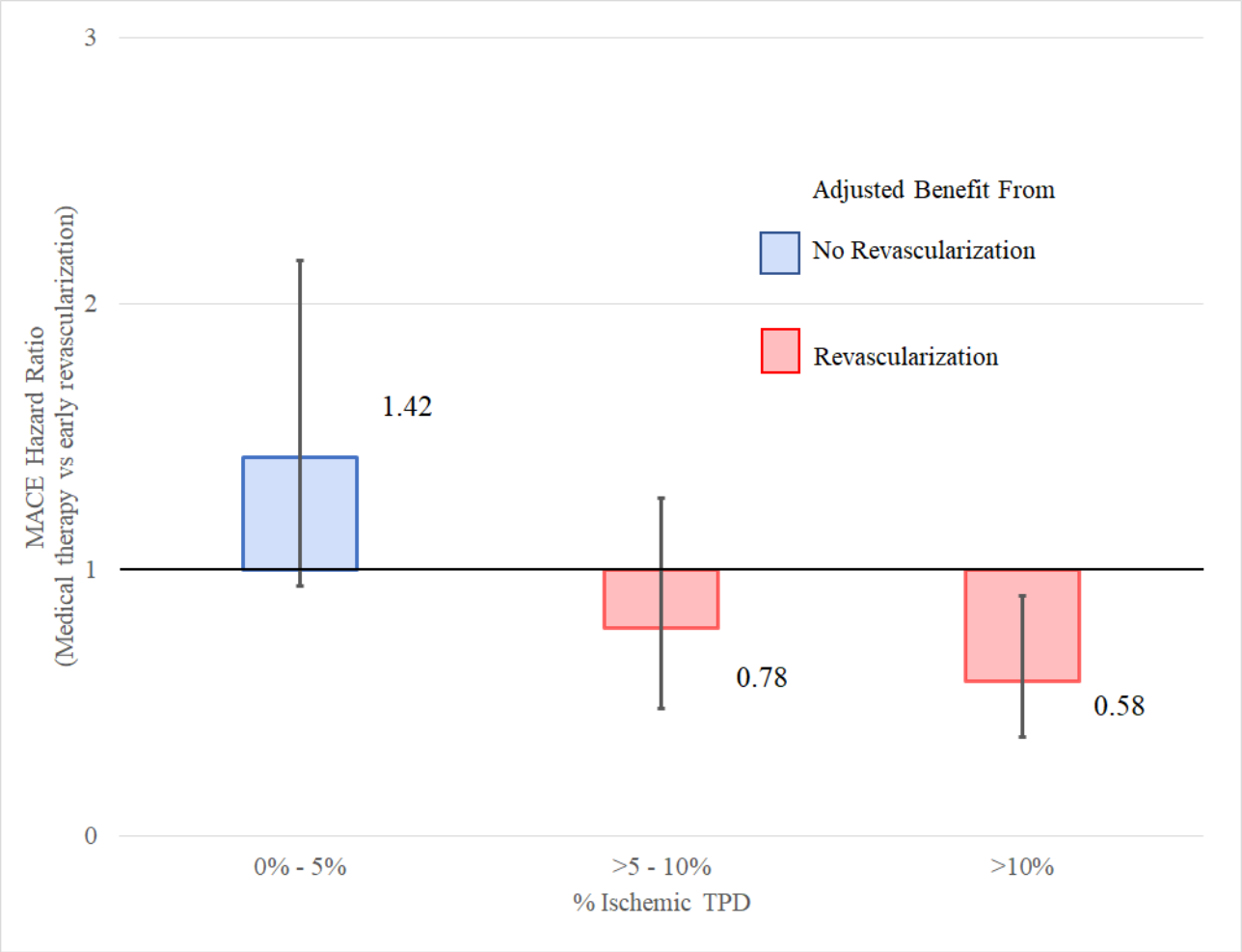
Supplemental Figure 2: Absolute standardized mean differences between patients managed with early revascularization before and after adjusting for the propensity score.

Supplemental Figure 3:



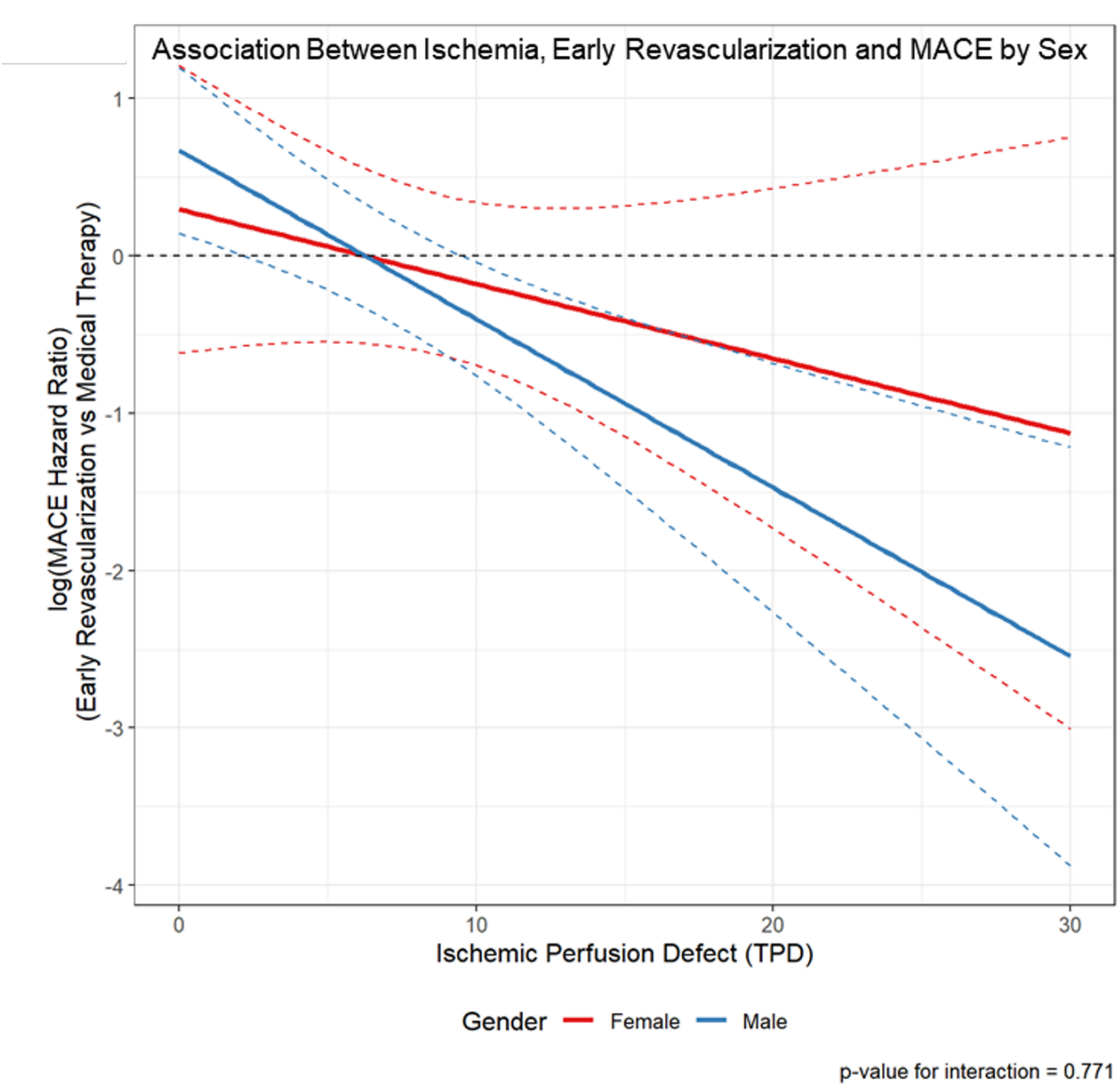
Supplemental Figure 3: Multivariable Cox Proportional Hazards model showing associations of non-perfusion variables with major adverse cardiovascular events (MACE). Values below age and ejection fraction are the 25th and 75th percentile, with the hazard ratio reflecting difference in risk between them. CAD – coronary artery disease. CI – confidence interval. HR – hazard ratio.

Supplemental Figure 4:



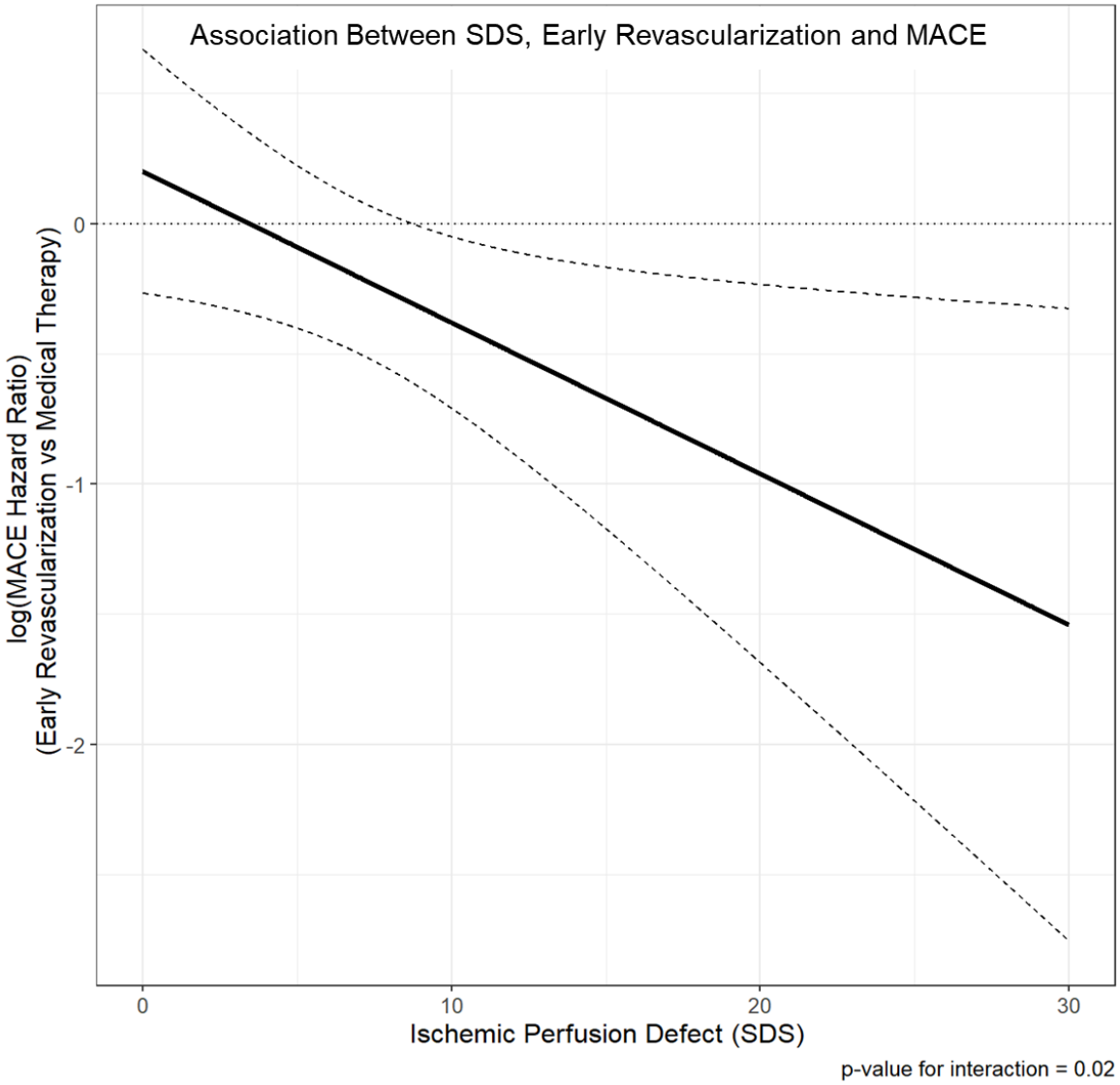
Supplemental Figure 4: Interaction between ischemic total perfusion deficit (TPD) as a categorical variable and treatment, adjusted for propensity score and baseline characteristics. Major adverse cardiovascular event (MACE) includes all-cause mortality, non-fatal myocardial infarction, and admission for unstable angina. In patients with >10% ischemic TPD, there is reduction in MACE associated with early revascularization.

Supplemental Figure 5:



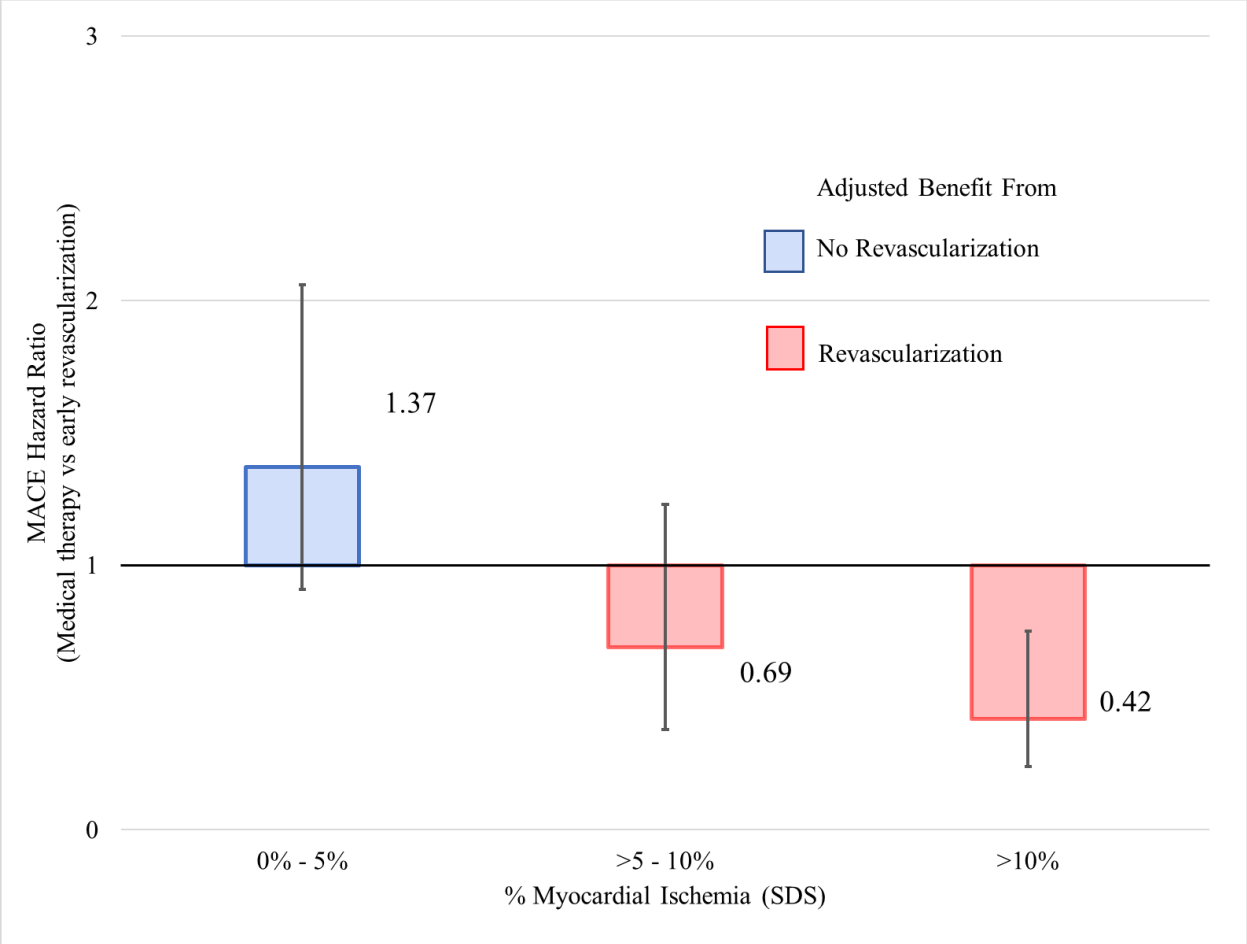
Supplemental Figure 5: Association between ischemic total perfusion defect (TPD) and major adverse cardiovascular events (MACE) in men and women, managed with early revascularization (red) or no revascularization (blue).

Supplemental Figure 6:



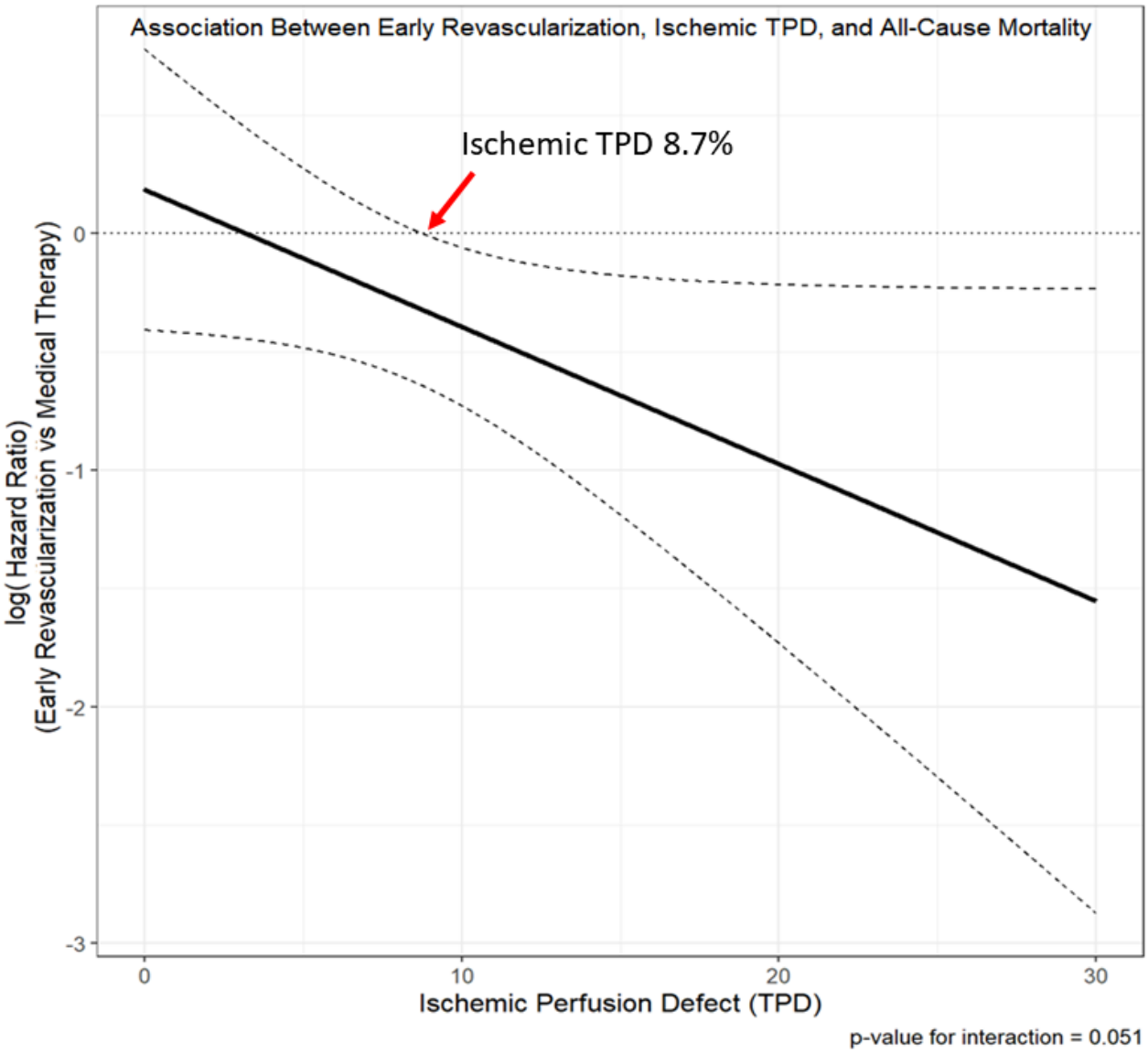
Supplemental Figure 6: Association between ischemia quantified using summed difference score (SDS) and major adverse cardiovascular events (MACE). Ischemia was modeled as a continuous variable.

Supplemental Figure 7:



Supplemental Figure 7: Association between ischemia quantified using summed difference score (SDS) and major adverse cardiovascular events (MACE). Ischemia was modeled as a categorical variable.

Supplemental Figure 8:



Supplemental Figure 8: Association between ischemic total perfusion defect (TPD) and all-cause mortality in patients managed with early revascularization.