Burden of Medical Comorbidities and Benefit from Surgical Revascularization in Patients with Ischemic Cardiomyopathy

Insights from the STICH Trial

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ABSTRACT

Aims: The landmark *STICH* trial found that surgical revascularization compared to medical therapy alone improved survival in patients with heart failure (HF) of ischemic etiology and an ejection fraction (EF) ≤35%. However, the interaction between the burden of medical comorbidities and the benefit from surgical revascularization has not been previously described in patients with ischemic cardiomyopathy.

Methods: The *STICH* trial (ClinicalTrials.gov Number: **NCT00023595**) enrolled patients ≥18 years of age with coronary artery disease amenable to coronary artery bypass grafting (CABG) and an EF ≤35%. Eligible participants were randomly assigned 1:1 to receive medical therapy (MED) (602 patients) or MED/CABG (610 patient). A modified Charlson Comorbidity Index (CCI) based on the availability of data and study definitions was calculated by summing the weighted points for all comorbid conditions. Patients were divided into mild/moderate (CCI 1-4) and severe (CCI ≥5) comorbidity. Cox proportional hazards models were used to evaluate the association between CCI and outcomes. The interaction between severity of comorbidity and treatment effect was assessed with the log-rank test.

Results: The study population included 349 patients (29%) with a mild/moderate CCI score and 863 patients (71%) with a severe CCI score. Patients with a severe CCI score had greater functional limitations based on 6-minute walk test and impairments in health-related quality of life as assessed by the Kansas City Cardiomyopathy Questionnaire. A total of 161 patients (Kaplan-Meier [KM] rate = 50%) with a mild/moderate CCI score and 579 patients (KM rate = 69%) with a severe CCI score died over a median follow-up of 9.8 years. After adjusting for baseline confounders, patients with a severe CCI score were at higher risk for all-cause mortality

(Hazard Ratio [HR] 1.44, 95% confidence interval [CI] 1.19-1.74; p-value <0.001). There was no interaction between CCI score and treatment effect on survival (p-value = 0.756).

Conclusions: More than 70% of patients had a severe burden of medical comorbidities at baseline which was independently associated with increased risk of death. There was not a differential benefit of surgical revascularization with respect to survival based on severity of comorbidity.

Key Words: heart failure, ischemic cardiomyopathy, reduced ejection fraction, coronary artery bypass grafting, multimorbidity, survival

INTRODUCTION

Heart failure (HF) is a public health problem of pandemic proportions with an estimated 38 million patients worldwide (1-3). Cardiac and non-cardiac comorbidities are highly prevalent in HF and many coexisting medical conditions have been independently associated with increased risk of morbidity and mortality (4, 5). The Charlson Comorbidity Index (CCI) is a convenient bedside tool that allows physicians to assess a patient's burden of common cardiac and non-cardiac conditions and estimate the corresponding 10-year survival (6, 7).

The *Surgical Treatment for Ischemic Heart Failure (STICH)* trial(8-11) provides a unique opportunity to systematically describe the burden of cardiac and non-cardiac conditions (i.e. defined by CCI) as well as the impact of severity of comorbid illness on the relative efficacy and safety of medical therapy alone (i.e. MED) vs. medical therapy plus coronary artery bypass grafting (i.e. MED/CABG) in patients with ischemic cardiomyopathy and severe left ventricular (LV) dysfunction. Specifically, the objectives of this work are to 1.) describe the level of comorbidity using the CCI, 2.) study the association between the burden of comorbid conditions and survival, and 3.) evaluate the efficacy of MED vs. MED/CABG based on severity of comorbidity in HF patients of ischemic etiology with an ejection fraction (EF) $\leq$35%.

METHODS

Overview

The study design (8) and primary results (9-11) of the *STICH* trial (ClinicalTrials.gov Number: **NCT00023595**) have been previously reported. Briefly, *STICH* was an international, multicenter, randomized, active-controlled trial designed to assess the relative efficacy of three possible therapeutic options: medical therapy alone (i.e. MED), medical therapy plus CABG (i.e. MED/CABG), or medical therapy plus CABG and surgical ventricular reconstruction. The present analysis includes the 1212 patients enrolled in the hypothesis 1 component of the trial (i.e. MED vs. MED/CABG) at 99 centers in 22 countries between July 24, 2002 and May 5, 2007. Patients $\geq$18 years of age with coronary artery disease (CAD) that was amenable to CABG and an EF $\leq$35% within 3 months of trial entry were eligible for enrollment. Patients with a >50% left main coronary artery stenosis, Canadian Cardiovascular Society (CCS) grade III or IV angina (i.e. markedly limiting ordinary activity), a non-cardiac illness imposing substantial operative mortality or with a limited life-expectancy of <3 years, or conditions/circumstances limiting treatment adherence were excluded from participation.

Eligible participants were randomly assigned 1:1 to receive MED (602 patients) or MED/CABG (610 patient). A local cardiologist was responsible for managing background guideline-directed medical therapy for CAD and HF. Adherence to guideline recommendations was emphasized and monitored by a medical therapy committee. Cardiac surgery was performed by surgeons who were required to provide data on a minimum of 25 patients with an EF $\leq$40% in whom they had performed CABG with an operative mortality $\leq$5%. CABG was performed within 14 days of enrollment. All patients were asked to return for follow-up visits at the time of discharge or at 30 days, every 4 months for the first year, and every 6 months thereafter.

Charlson Comorbidity Index

The development and validation of the CCI has been previously described (6, 7). Briefly, the CCI accounts for 16 medical comorbidities and assigns each condition 1, 2, 3, or 6 points depending on the associated mortality risk. A modified CCI score (i.e. based on the availability of data and study definitions) was computed for each patient enrolled in the *STICH* trial by summing the weighted points for all comorbid conditions (**Supplemental Table 1**). A combined age-comorbidity score was subsequently calculated by adding 1 point for each decade of life over 40 years of age to account for the risk of comorbid death attributable to age. For example, a 60-year old patient with HF and a prior myocardial infarction would have a combined age-comorbidity score (i.e. hereafter referred to simply as the CCI) of 4 (i.e. HF = 1 point, myocardial infraction = 1 point, and age of 60 years = 2 points).

The predicted 10-year mortality based on the CCI was calculated (ref) as follows:

$$X = e^{0.9(CCI)}$$

$$\text{Mortality} = 1\text{-}0.983^{X}$$

Outcomes

The primary endpoint was all-cause mortality. Secondary endpoints included cardiovascular (CV) mortality and the composite of all-cause mortality and CV hospitalizations. Blinding was not pursued due to the nature of the surgical intervention, mode of death and CV hospitalizations for each patient were adjudicated by an independent clinical events committee who were unaware of treatment assignment.

Statistical Analysis

All categorical data were reported as a count (percentage) and continuous data as a mean (standard deviation [SD]) and/or median (25^{th}, 75^{th} percentiles). Patients were divided into mild/moderate (i.e. defined as CCI 1-4) and severe (i.e. defined as CCI $\geq$5) comorbid illness.

Baseline clinical characteristics including demographics, medical history, medication use, laboratory values, quality of life, and exercise testing were compared between groups. Comparisons for continuous variables were based on the Wilcoxon rank-sum test, while categorical variables were assessed using Pearson's chi-square test or Fisher's exact test as appropriate. Ten-year mortality is calculated in the CCI severity groups using the Kaplan-Meier method. The Kaplan-Meier estimates for each CCI score were plotted with 95% CIs in a figure, that included the predicted probability of mortality using the previously published CCI equation (6, 7).

Cox proportional hazards regression models were used to evaluate the association between CCI as a categorical variable (i.e. mild/moderate = CCI 1-4 vs. severe = CCI $\geq$5) as well as continuous variable (i.e. calculated as the risk per additional CCI point) and outcomes. Multivariable Cox models were adjusted for following baseline covariates: sex, race, region, blood pressure, heart rate, Canadian Cardiovascular Society (CCS) angina class, New York Heart Association (NYHA) class, atrial fibrillation/flutter, hyperlipidemia, hypertension, prior CABG, prior percutaneous coronary intervention (PCI), number of diseased vessels, left main stenosis, proximal left anterior descending (LAD) stenosis, left ventricular EF (LVEF), left ventricular end-systolic volume index (LVESVI), moderate or severe mitral regurgitation, hemoglobin, sodium and estimated glomerular filtration rate (eGFR) as previously identified as being associated with clinical outcomes (12). The predicted probabilities (95% CI) for 10-year mortality were estimated from an unadjusted Cox model, that included CCI (as a continuous covariate). The interaction between severity of comorbidity as a categorical (i.e. mild/moderate = CCI 1-4, vs. severe = CCI $\geq$5) and continuous variable and randomized treatment (i.e. CABG/MED vs. MED) with respect to all-cause mortality was assessed with adjusted Cox

models that included the CCI severity-by-treatment interaction. Relationships are displayed with Kaplan-Meier plots stratified by treatment separately in the mild/moderate and severe comorbidity groups along with unadjusted hazard ratios (95% CI) and interaction p-value, KM 10-year rates, number of events, and forest plot and spline curves stratified by treatment showing comorbidity level as a continuous variable with 95% CI and interaction p-value.

P-values <0.05 from two-sided tests were considered statistically significant. Adjustments were not made for multiple comparisons. All analyses were performed using SAS 9.4 (SAS Institute Inc. Cary, North Carolina, USA).

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RESULTS

Study Population

A total of 1212 patients with CAD that was amenable to CABG and an EF ≤35% were included in the present analysis (**Table 1**). Study participants were a median of 60 (54, 67) years old and 88% were male. The median EF for the study population was 28% (22%, 34%). The median CCI score was 5 (4, 7) with a minimum of 1 and a maximum of 12. A total of 349 patients (29%) had a mild/moderate CCI score and 863 patients (71%) had a severe CCI score at baseline. At the time of randomization, 95% of patients reported no angina or CCS I/II angina and approximately 85% of patients reported New York Heart Association (NYHA) functional class II/III symptoms. Patients were well-treated with guideline-directed medical therapy for CAD and HF at baseline.

Patient Characteristics by Comorbidity Level

Patients with severe CCI score were more likely to self-identify as white and had greater functional limitations based on 6-minute walk test (6-MWT) and impairments in health-related quality of life as assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ) at baseline (**Table 1**). In contrast, there were no statistically significant differences between patients with mild/moderate vs. severe CCI scores in the rate of prior revascularization (i.e. percutaneous coronary intervention [PCI] or coronary artery bypass grafting [CABG]), LVEF and LV end-systolic volume index (LVESVI) measurements, coronary anatomy, CCS angina or NYHA functional class, or guideline-directed medical therapy for CAD or HF.

Comorbidity Severity and Clinical Outcomes

The 10-year mortality in the *STICH* population ranged from approximately 25% for patients with a CCI score of 1 and approached 100% for patients with a CCI score of 12 (**Figure**

1A). A total of 161 patients (50%) with a mild/moderate CCI score and 579 patients (69%) with a severe CCI score died over a median follow-up of 9.8 years (**Table 2**). In addition, the composite of all-cause mortality or CV hospitalization was reached in 254 patients (79%) with a mild/moderate CCI score and 731 patients (87%) with a severe CCI score over the same timeframe. The predicted 10-year mortality based on the CCI and the actual mortality for the *STICH* cohort are shown in **Figure 1B**. In general, the estimated 10-year mortality derived from the CCI tended to underestimate the risk of death for patients with a CCI score below 4 and overestimate the risk of death for patients with a CCI score above 4.

Patients with a severe CCI score were at higher risk for all-cause mortality (Hazard Ratio [HR] 1.44, 95% confidence interval [CI] 1.19-1.74; p-value <0.001), CV mortality (HR 1.35, 95% CI 1.09-1.68; p-value = 0.006), and all-cause mortality or CV hospitalization (HR 1.22, 95% CI 1.04-1.43; p-value = 0.012). The incremental risk of an adverse event per 1-point increase in CCI score was comparable for all-cause mortality (HR 1.12, 95% CI 1.06-1.18; p-value <0.001), CV mortality (HR 1.11, 95% CI 1.04-1.18; p-value <0.001), and all-cause mortality or CV hospitalization (HR 1.07, 95% CI 1.02-1.12; p-value = 0.003).

Efficacy of Surgical Revascularization by Comorbidity Level

There was no interaction between CCI score (i.e. mild/moderate vs. severe) and treatment effect (i.e. MED vs. MED/CABG) with respect to all-cause (**Figure 2A**) or CV mortality (**Figure 2B**) at 10 years in the intention-to-treat population. In contrast, although patients randomized to MED/CABG were less likely to reach the composite of all-cause mortality or CV hospitalization irrespective of CCI score, patients with a mild/moderate CCI score derived a more robust benefit from surgical revascularization over the same timeframe (**Figure 2C**). A sensitivity analysis did not reveal an interaction between CCI score and treatment effect with

respect to all-cause mortality, CV mortality, or the composite of all-cause mortality or CV hospitalization in the as-treated cohort (**Supplemental Figure 1**).

Figure 3 shows spline curves for all-cause mortality, CV mortality, and the composite of all-cause mortality or CV hospitalization at 1, 5, and 10 years for the intention-to-treat population. In general, the results of the interaction analyses with CCI score as a continuous variable were consistent with those observed with CCI score as a categorical variable (i.e. mild/moderate vs. severe). For example, there was no interaction between CCI score as a continuous variable and treatment effect (i.e. MED vs. MED/CABG) with respect to all-cause (p-value = 0.115) or CV mortality (p-value = 0.275). Similarly, patients with a CCI score in the mild/moderate range (i.e. 1-4) undergoing surgical revascularization experienced an earlier and more marked improvement in the composite of all-cause mortality or CV hospitalization compared to patients receiving medical therapy alone (p-value = 0.021).

DISCUSSION

This study found that more than 70% of the patients enrolled in the *STICH* trial had a severe burden of medical comorbidities at baseline. Patients with a severe level of comorbidity had greater functional limitations and impairments in health-related quality of life. In addition, these patients experienced an exceptionally poor prognosis with mortality approaching 70% at 10 years. After adjusting for potential confounders, all-cause mortality was almost 45% higher for patients with a severe CCI score and the incremental risk of death per 1-point increase in CCI score was in excess of 10%. However, patients with ischemic cardiomyopathy and a severe burden of medical comorbidities derived a comparable survival benefit from surgical revascularization over the duration of follow-up.

It is notable that more than 70% of study participants had a CCI score in the severe range. However, this finding likely underestimates the real-world burden of medical comorbidities in patients with ischemic cardiomyopathy and severe LV systolic dysfunction as the *STICH* protocol excluded participants with a non-cardiac illness imposing substantial operative mortality or with a limited life-expectancy (8). There is a growing appreciation of the clinical impact of multimorbidity on the *patient journey* in HF (4). This assertion is supported by the fact that patients with a severe CCI score had worse functional capacity (i.e. 6-MWT) and health-related quality of life (i.e. KCCQ). These differences were not only statistically significant but also consistent with the generally accepted minimal clinically important difference for these assessments (13, 14). Interestingly, despite differences in age and comorbidity profile between patients with mild/moderate and severe CCI scores, there was very little difference in underlying cardiac substrate including coronary anatomy, echocardiographic parameters of remodeling, and symptom status (i.e. CCS angina and/or NYHA functional class). In addition, patients with a

severe CCI score were equally likely to be treated with evidence-based medications for CAD and HF despite the fact that certain non-cardiac comorbidities may lead to real or perceived barriers to optimal implementation of guideline-directed medical therapies (15, 16).

The CCI was initially developed as a method for quantifying the degree of comorbidity and assessing prognosis in longitudinal cohort studies (6, 7). Although a reliable and accurate research tool, there is a more limited experience with the CCI in a HF population and its clinical utility is not well-established. Of note, this study found a relatively linear relationship between CCI score and all-cause mortality at 10 years with the incremental risk of death an estimated 12% per 1-point increase in CCI score independent of traditional prognostic indicators. In addition, since the CCI incorporates age and cardiac and non-cardiac comorbidities, the risk of CV and non-CV mortality tended to rise proportionally with increasing CCI score and it was found to be equally useful when estimating all-cause and CV-specific mortality in this patient population. Thus, the CCI may supplement clinical judgment and play a meaningful role when discussing life-expectancy and prognosis with HF patients. However, it should be noted that the CCI was originally developed in a relatively low-risk cohort. As a result, the previously published regression equation did not perform well in the high-risk *STICH* population and tended to underestimate the risk of death in patients with a low/moderate CCI score and overestimate the risk of death in patients with a severe CCI score. This finding suggests that additional research is required to prospectively validate the prognostic potential of the CCI in patients with HF in order to provide reliable and accurate estimates of survival based on comorbidity burden.

More importantly, in an era of personalized medicine it is relevant to consider the impact of severity of comorbidity on the relative efficacy and safety of surgical revascularization in patients with ischemic cardiomyopathy and severe LV systolic dysfunction. In general, patients

undergoing major cardiovascular surgery are exposed to perioperative/post-operative complications with the expectation that by correcting the underlying cardiac pathology this upfront risk will eventually be offset by a long-term reduction in CV morbidity and mortality. This generalization is consistent with the primary results of the *STICH* trial which demonstrated that although mortality was initially higher in patients randomized to surgical revascularization, the survival curves crossed over after the 2-year mark and a statistically significant benefit emerged over a median follow-up of 9.8 years (9-11). In contrast, this study found that among patients with a mild/moderate CCI, the Kaplan-Meier plots for all-cause mortality for MED vs. MED/CABG did not exhibit this crossover phenomenon but rather paralleled one another initially before demonstrating a potentially earlier and more pronounced survival benefit with surgical revascularization. In addition, although patients randomized to MED/CABG were at lower risk for the composite of all-cause mortality or CV hospitalization irrespective of CCI score, patients with a mild/moderate CCI score derived a more robust benefit from surgical revascularization driven by a reduction in CV hospitalizations. Thus, among patients with HF of ischemic etiology who are young and relatively free of comorbid conditions, surgical revascularization poses minimal upfront risk and these patients experience an early and dramatic improvement in all-cause and CV-specific morbidity and mortality compared to medical therapy alone. However, it cannot be overemphasized that this study found no interaction between comorbidity level and all-cause and CV mortality at 10 years suggesting that elderly patients with a severe burden of medical comorbidities should not be denied surgical revascularization based on these factors alone. The decision to refer a patient with ischemic cardiomyopathy and severe LV systolic dysfunction for CABG should be individualized and take into account age (17), comorbidity profile, coronary anatomy (i.e. single- vs. triple-vessel CAD) (18),

echocardiographic parameters of remodeling (i.e. LVEF and LVESVI) (19), and functional capacity (20).

There are several limitations of the data that should be acknowledged. First, patients with a non-cardiac illness imposing substantial operative mortality or with a limited life-expectancy were excluded from enrollment potentially restricting the generalizability of the data to an otherwise unselected real-world population of patients with ischemic cardiomyopathy and severe LV systolic dysfunction. Second, the *STICH* protocol did not require reporting of several medical comorbidities (i.e. liver disease and acute immunodeficiency syndrome) included in the CCI. Third, although more than 70% of patients had a severe level of comorbidity there were very few patients with a CCI >8 (i.e. ~6%) and the possibility that there was heterogeneity in treatment effect (i.e. MED vs. MED/CABG) cannot be excluded for this subset of the population. Fourth, early crossover occurred in approximately 20% of patients enrolled in the *STICH* trial and a differential crossover rate between patients with a mild/moderate vs. severe CCI may have biased the results towards the null hypothesis and impended the ability to detect an interaction between comorbidity severity and treatment effect (21). However, a sensitivity analysis was performed and found no interaction between CCI severity and treatment effect in the as-treated cohort. Finally, due to the nature of surgical revascularization, physicians and patients were necessarily unblinded to treatment assignment although outcomes were adjudicated by a blinded and independent clinical events committee.

In conclusion, more than 70% of patients with ischemic cardiomyopathy and severe LV systolic dysfunction had a severe burden of medical comorbidities. Multimorbidity was associated with greater functional limitations and impairments in health-related quality of life and decreased survival. There was not a differential response to MED vs. MED/CABG with

respect to all-cause and CV-specific mortality based on severity of comorbidity among patients with ischemic cardiomyopathy and severe LV systolic dysfunction. Additional research is required to identify patient and procedural factors that may define patient groups who may derive a more robust or more limited response to surgical revascularization compared to medical therapy alone.

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Table 1. Baseline patient characteristics by level of comorbidity. All values reported as N (%) and median (25^{th}, 75^{th}percentiles).

	All Patients (N=1212)	Mild/Moderate (N=349)	Severe (N=863)	p-value
Demographics				
Age (years)	60 (54, 67)	53 (48, 57)	63 (57, 70)	<0.001
Female sex	148 (12%)	35 (10%)	113 (13%)	0.140
Race				<0.001
White	827 (68%)	206 (59%)	621 (72%)	
Black	31 (3%)	4 (1%)	27 (3%)	
Asian	209 (17%)	88 (25%)	121 (14%)	
Other	145 (12%)	51 (15%)	94 (11%)	
Vitals/Physical Examination				
BMI (kg/m^2)	27 (24, 30)	26 (24, 29)	27 (24, 30)	0.057
HR (bpm)	74 (66, 82)	74 (68, 82)	73 (65, 80)	0.050
SBP (mmHg)	120 (110, 130)	120 (110, 130)	120 (110, 130)	0.002
CCS angina class				0.115
0	442 (37%)	112 (32%)	330 (38%)	
I	187 (15%)	53 (15%)	134 (16%)	
II	525 (43%)	171 (49%)	354 (41%)	
III	48 (4%)	11 (3%)	37 (4%)	
IV	10 (1%)	2 (1%)	8 (1%)	
NYHA class				0.069
I	139 (12%)	44 (13%)	95 (11%)	
II	626 (52%)	195 (56%)	431 (50%)	
III	412 (34%)	104 (30%)	308 (36%)	
IV	35 (3%)	6 (2%)	29 (3%)	
Laboratory Values				
Hg (g/dL)	13.9 (12.7, 14.9)	14.3 (13.3, 15.2)	13.7 (12.5, 14.8)	<0.001
sCr (mg/dL)	1.1 (0.9, 1.3)	1.0 (0.9, 1.2)	1.1 (1.0, 1.3)	<0.001
eGFR ($mL/min/1.73\ m^2$)	77 (61, 96)	90 (74, 107)	71 (57, 89)	<0.001
Sodium (mEq/L)	140 (137, 142)	139 (137, 142)	140 (137, 142)	0.381
BUN (mg/dL)	23 (16, 37)	21 (16, 32)	23 (17, 38)	0.049
Baseline Assessments				
LVEF	28 (22, 34)	28 (23, 34)	27 (22, 34)	0.443
ESVI (mL/m^2)	78 (61, 99)	78 (61, 99)	78 (61, 99)	0.873
6-MWT (m)	320 (200, 400)	340 (240, 410)	310 (180, 390)	<0.001
KCCQ	62 (44, 79)	64 (50, 81)	60 (43, 78)	0.007
Medical Comorbidities				

	All Patients (N=1212)	Mild/Moderate (N=349)	Severe (N=863)	p-value
Prior PCI	156 (13%)	35 (10%)	121 (14%)	0.060
Prior CABG	36 (3%)	10 (3%)	26 (3%)	0.891
Moderate or severe MR	220 (18.2%)	60 (17.2%)	160 (18.6%)	0.584
PVD	184 (15%)	6 (2%)	178 (21%)	<0.001
MI	934 (77%)	225 (65%)	709 (82%)	<0.001
CVA	92 (8%)	2 (1%)	90 (10%)	<0.001
HL	730 (60%)	188 (54%)	542 (63%)	0.004
HTN	728 (60%)	183 (52%)	545 (63%)	<0.001
DM	478 (39%)	46 (13%)	432 (50%)	<0.001
Afib/aflutter	153 (13%)	30 (9%)	123 (14%)	0.007
CKD	94 (8%)	3 (1%)	91 (11%)	<0.001
Cancer	14 (1%)	0 (0%)	14 (2%)	0.014
Depression	76 (6%)	4 (1%)	72 (8%)	<0.001
Current Smoking	252 (21%)	39 (11%)	213 (25%)	<0.001
Baseline Medications				
ACEI	996 (82%)	290 (83%)	706 (82%)	0.596
ARB	115 (10%)	23 (7%)	92 (11%)	0.029
β-Blocker	1036 (86%)	298 (85%)	738 (86%)	0.954
MRA	556 (46%)	173 (50%)	383 (44%)	0.101
Loop Diuretic	791 (65%)	214 (61%)	577 (67%)	0.063
Digoxin	245 (20%)	75 (22%)	170 (20%)	0.482
Aspirin	1002 (83%)	286 (82%)	716 (83%)	0.672
Clopidogrel	208 (17%)	64 (18%)	144 (17%)	0.490
Warfarin	127 (11%)	24 (7%)	103 (12%)	0.009
Statin	983 (81%)	284 (81%)	699 (81%)	0.879
Nitrate	646 (53%)	177 (51%)	469 (54%)	0.243
Antiarrhythmic	128 (11%)	41 (12%)	87 (10%)	0.393
Insulin	197 (16%)	8 (2%)	189 (22%)	<0.001
Oral Diabetic agent	286 (24%)	38 (11%)	248 (29%)	<0.001
Coronary Anatomy				
Number of diseased vessels (75%)				0.268
0	25 (2%)	8 (2%)	17 (2%)	
1	282 (23%)	83 (24%)	199 (23%)	
2	462 (38%)	145 (42%)	317 (37%)	
3	442 (37%)	113 (32%)	329 (38%)	
LM stenosis $\geq$ 50%	32 (3%)	5 (1%)	27 (3%)	0.095
Proximal LAD stenosis $\geq$ 75%	826 (68%)	244 (70%)	582 (68%)	0.417

Abbreviations: BMI = body mass index; HR = heart rate; SBP = systolic blood pressure; CCS = Canadian Cardiovascular Society; NYHA = New York Heart Association; Hg = hemoglobin; sCr = serum creatinine; eGFR = estimated glomerular filtration rate; BUN = blood urea nitrogen; LVEF = left ventricular ejection fraction; ESVI = end-systolic volume index; 6-MWT = 6-minute walk test; KCCQ = Kansas City Cardiomyopathy Questionnaire; PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting; MR = mitral regurgitation; PVD = peripheral vascular disease; MI = myocardial infarction; CVA = cerebral vascular accident; HL = hyperlipidemia; HTN = hypertension; DM = diabetes mellitus; afib/flutter = atrial fibrillation/flutter; CKD = chronic kidney disease; ACEI = angiotensin converting-enzyme inhibitor; ARB = angiotensin receptor blocker; MRA = mineralocorticoid receptor antagonist; LM = left main; LAD = left anterior descending.

Table 2. Hazard ratio for categorized and continuous CCI for primary and secondary endpoints.

	Number of events (KM 10-year rate)		Categorized CCI				Continuous CCI			
Event	Mild/ Moderate	Severe	Unadjusted HR (95% CI) for severe comorbidity	p-value	Adjusted HR (95% CI) for severe comorbidity*	p-value	Unadjusted HR (95% CI) for 1 point increase	p-value	Adjusted HR (95% CI) for 1 point increase*	p-value
All-cause mortality	161 (49.7%)	579 (69.3%)	1.73 (1.45, 2.06)	<0.001	1.44 (1.19, 1.74)	<0.001	1.17 (1.13, 1.22)	<0.001	1.12 (1.06, 1.18)	<0.001
CV mortality	130 (42.2%)	408 (53.6%)	1.49 (1.23, 1.82)	<0.001	1.35 (1.09, 1.68)	0.006	1.12 (1.07, 1.18)	<0.001	1.11 (1.04, 1.18)	<0.001
All-cause mortality or CV hospitalization	254 (79.1%)	731 (86.5%)	1.45 (1.25, 1.67)	<0.001	1.22 (1.04, 1.43)	0.012	1.12 (1.09, 1.16)	<0.001	1.07 (1.02, 1.12)	0.003

* Adjusted for sex, race, region, blood pressure, heart rate, CCS angina class, NYHA class, atrial fibrillation/flutter, hyperlipidemia, hypertension, prior CABG, prior PCI, number of diseased vessels, left main stenosis, proximal LAD stenosis, LVEF, and LVESVI, moderate or severe mitral regurgitation, hemoglobin, sodium, eGFR, and randomized treatment

Abbreviations: CV = cardiovascular; KM = Kaplan-Meier; CCI = Charlson Comorbidity Index; HR = hazard ratio; CI = confidence interval; CCS = Canadian Cardiovascular Society; NYHA = New York Heart Association; CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention; LAD = left anterior descending; LVEF = left ventricular ejection fraction; LVESVI = left ventricular systolic volume index; eGFR = estimated glomerular filtration rate.

Figure 1A. Observed probability of 10-year all-cause mortality according to CCI.

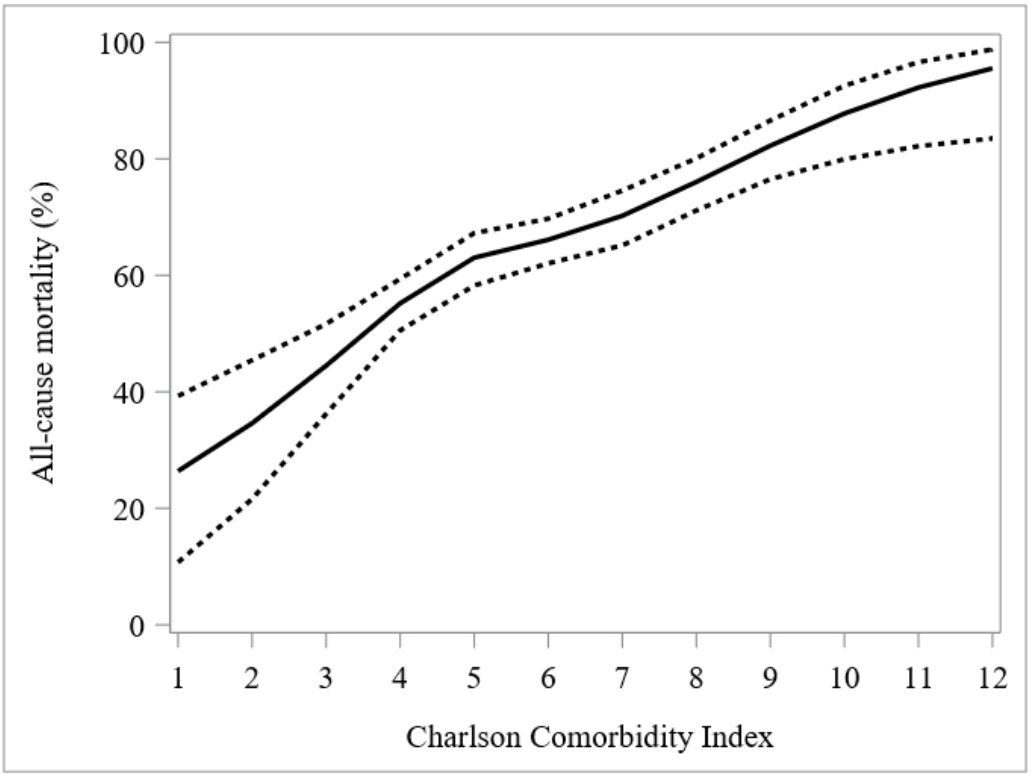


Figure 1B. Predicted and observed 10-year mortality by CCI score.

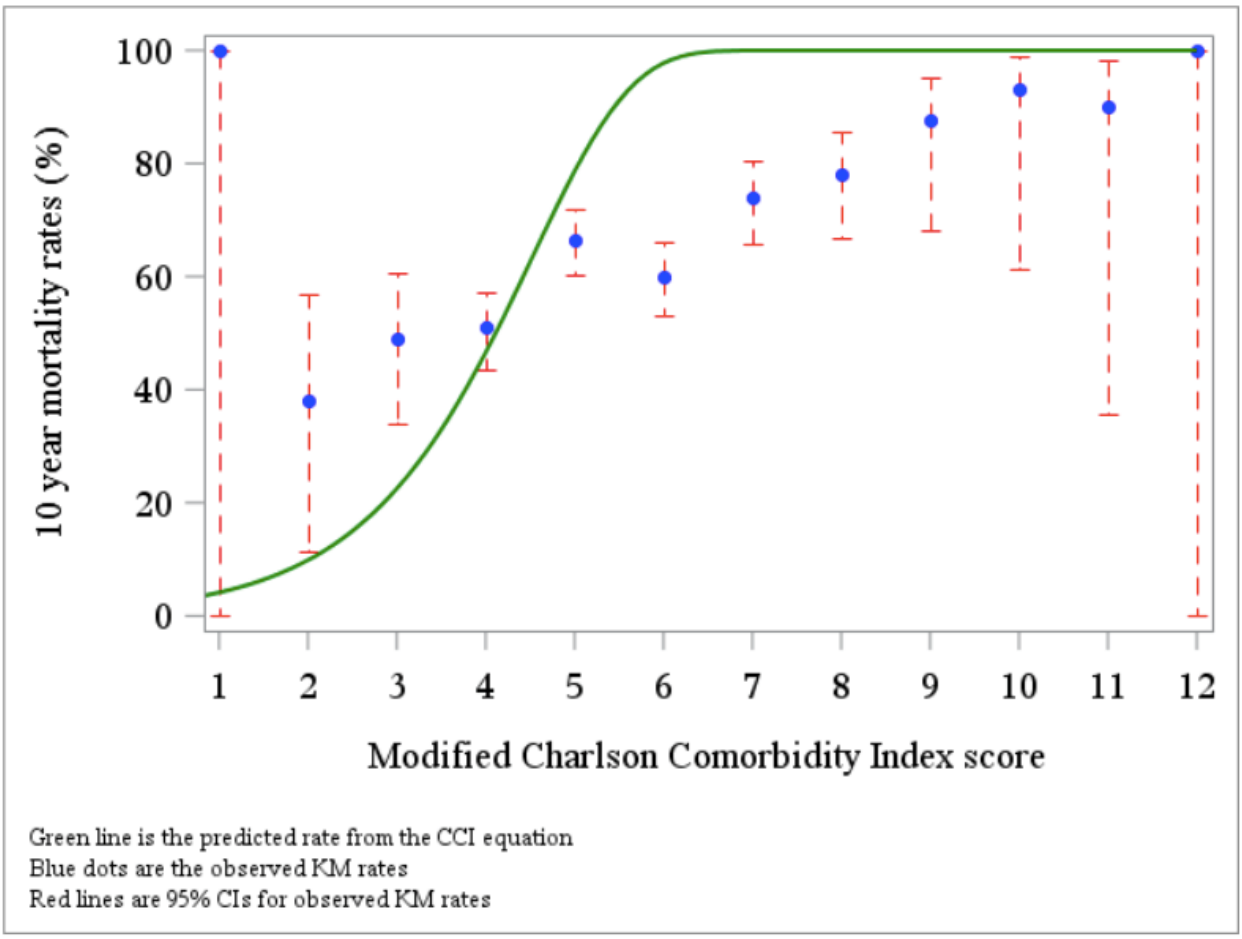
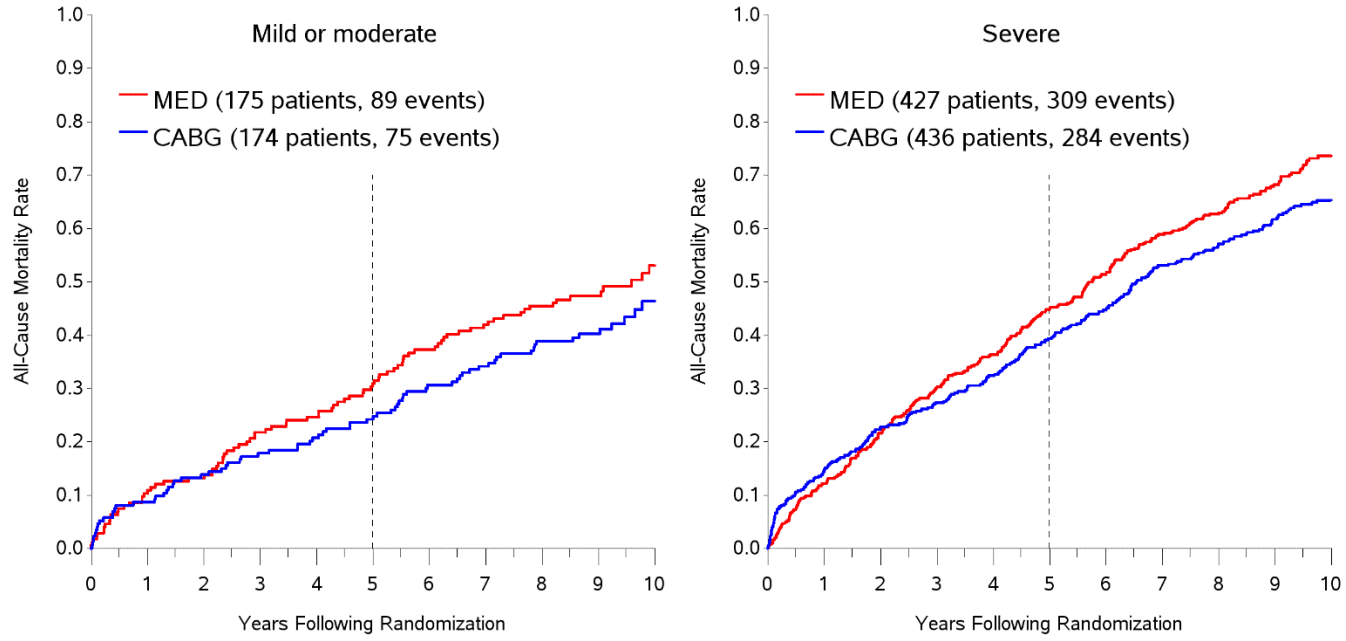
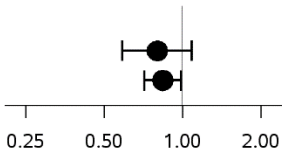


Figure 2. Kaplan-Meier curves for treatment effect (i.e. MED vs. MED/CABG) by CCI category (i.e. mild/moderate vs. severe) for (A) all-cause mortality, (B) CV mortality, and (C) all-cause mortality or CV hospitalization.

A



Comorbidity	N	Events	Hazard Ratio	95% CI	10 Year Rates MED Group	10 Year Rates CABG Group
Mild or moderate	349	164	0.80	0.59, 1.09	53.0%	46.3%
Severe	863	593	0.84	0.72, 0.99	73.5%	65.2%

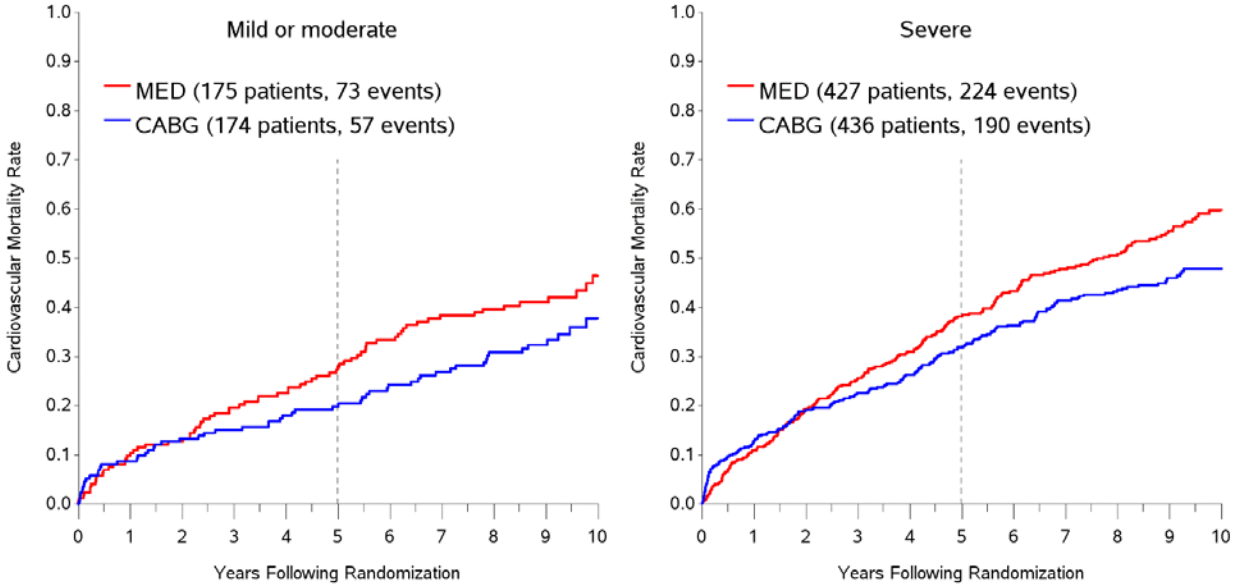


Interaction
P-value = 0.756

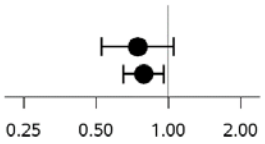
CABG Group Better

MED Group Better

B



Comorbidity	N	Events	Hazard Ratio	95% CI	10 Year Rates MED Group	10 Year Rates CABG Group
Mild or moderate	349	130	0.75	0.53, 1.06	46.4%	37.7%
Severe	863	414	0.79	0.65, 0.96	59.7%	47.8%

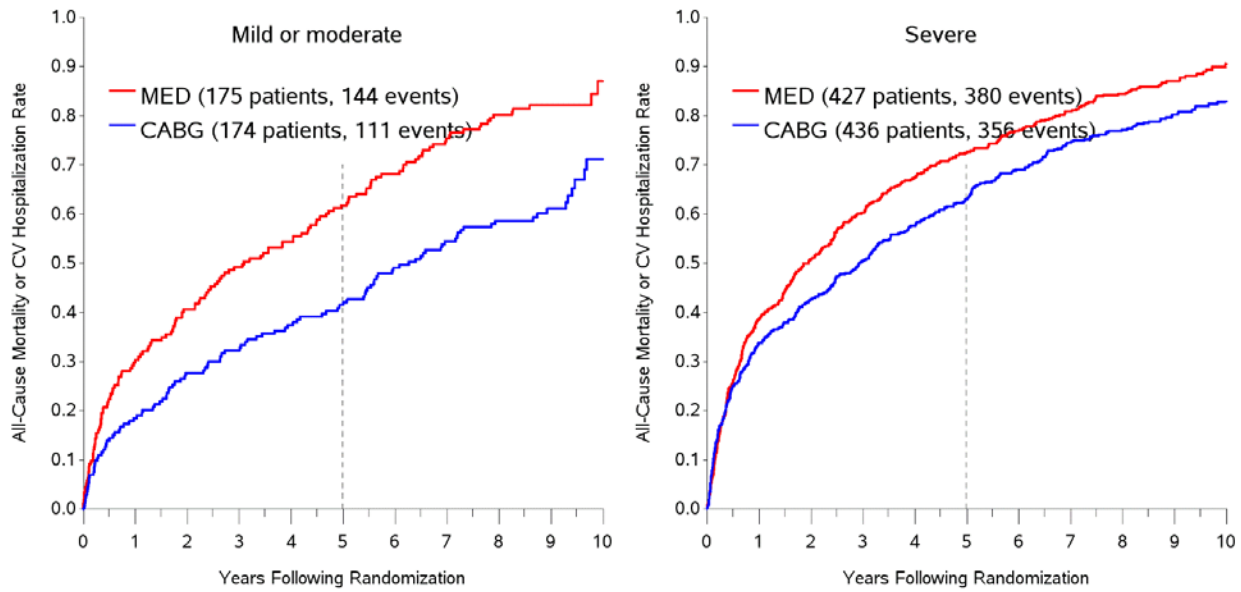


Interaction
P-value = 0.775

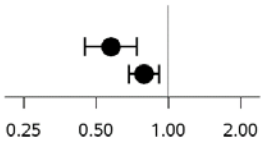
CABG Group Better

MED Group Better

C



Comorbidity	N	Events	Hazard Ratio	95% CI	10 Year Rates MED Group	10 Year Rates CABG Group
Mild or moderate	349	255	0.58	0.45, 0.74	87.0%	71.1%
Severe	863	736	0.79	0.69, 0.92	90.5%	82.8%

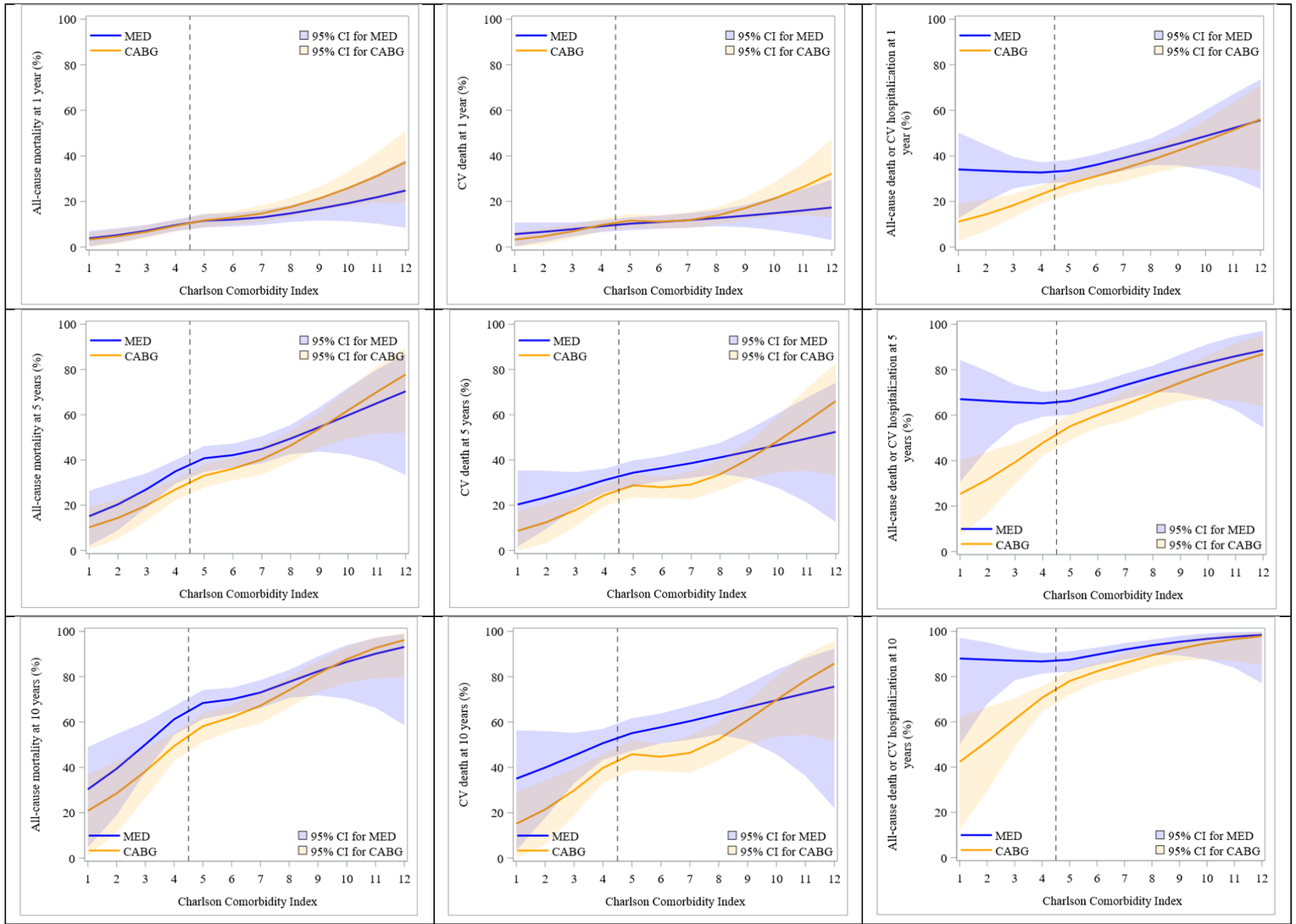


Interaction
P-value = 0.041

CABG Group Better

MED Group Better

Figure 3. Spline curves for treatment effect (i.e. MED vs. MED/CABG) by CCI as a continuous variable for all-cause mortality, CV mortality, and all-cause mortality or CV hospitalization at 1, 5, and 10 years.



Interaction: unadjusted p=0.115	Interaction: unadjusted p=0.275	Interaction: unadjusted p=0.021

Supplemental Table 1. Clinical variables and study definitions used to calculate modified CCI.

Clinical Variables	Points	STICH
Age		
≤40	0	
41-50	1	✓
51-60	2	
61-70	3	
>70	4	
Myocardial Infarction	1	✓
Heart Failure	1	All
Peripheral Vascular Disease	1	✓
Cerebrovascular Disease	1	✓
Dementia	1	NA[1,2]
Chronic Obstructive Pulmonary Disease	1	✓[3]
Connective Tissue Disease	1	NA
Peptic Ulcer Disease	1	NA
Diabetes Mellitus	1-2	✓[4]
Chronic Kidney Disease	2	✓[5]
Hemiplegia	2	NA[1]
Leukemia	2	✓[6,7]
Malignant Lymphoma	2	
Solid Tumor	2-6	
Liver Disease	1-3	NA[7]
AIDS	6	NA[7]

[1]Patients were excluded if they were unable to provide informed consent or had medical conditions/circumstances likely to lead to poor treatment adherence

[2]Depression was substituted for dementia when available

[3]Active smoking was considered to be a chronic obstructive pulmonary disease equivalent

[4]Patients with concomitant diabetes on oral hypoglycemic were assigned 1 point while insulin-dependent diabetics were assigned 2 points

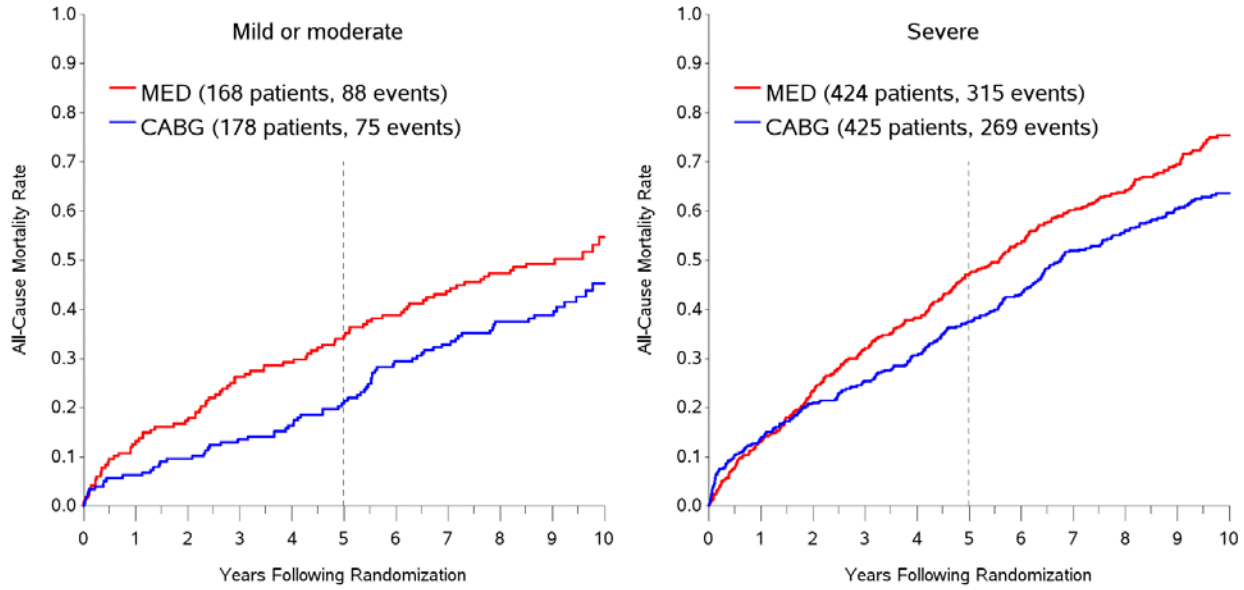
[5]Defined as a serum creatinine >1.5 mg/dL

[6]Cancer (excluding skin cancer) within the last 5 years

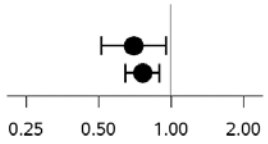
[7]Patients were excluded if they had a non-cardiac illness with a life expectancy of less than 3 years

Supplemental Figure 1. Kaplan-Meier curves for treatment effect (i.e. MED vs. MED/CABG) within CCI category (i.e. mild/moderate vs. severe) for (A) all-cause mortality, (B) CV mortality, and (C) all-cause mortality or CV hospitalization for the as-treated cohort.

A



Comorbidity	N	Events	Hazard Ratio	95% CI	10 Year Rates MED Group	10 Year Rates CABG Group
Mild or moderate	346	163	0.70	0.51, 0.95	54.7%	45.2%
Severe	849	584	0.76	0.65, 0.90	75.3%	63.6%

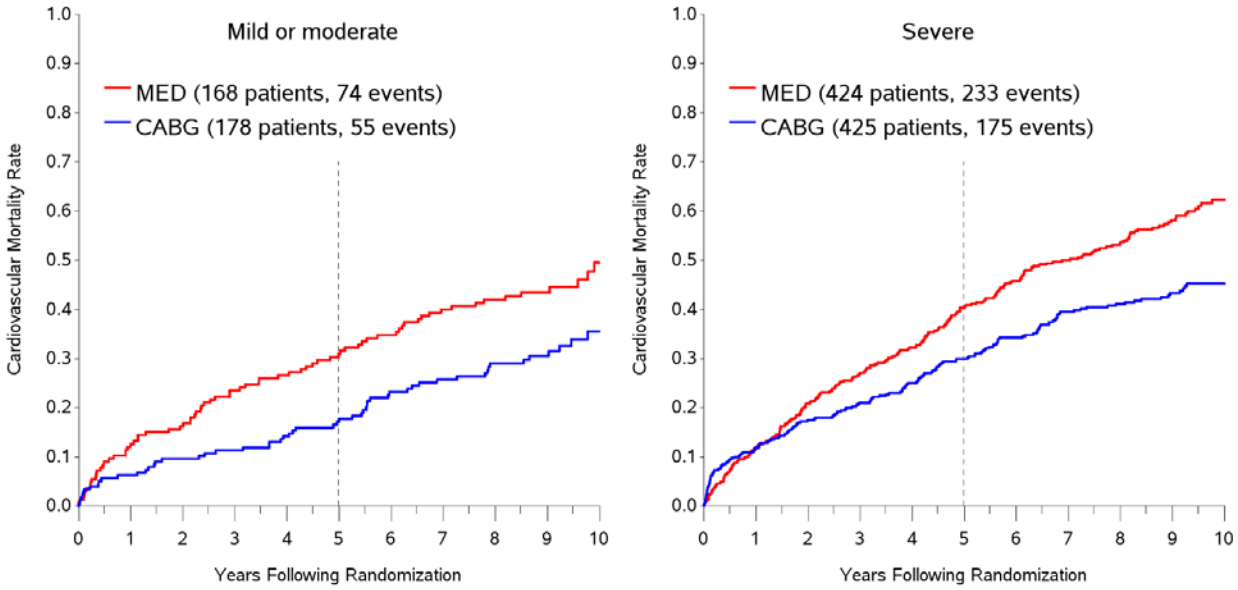


Interaction
P-value = 0.603

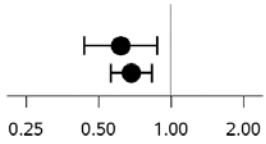
CABG Group Better

MED Group Better

B



Comorbidity	N	Events	Hazard Ratio	95% CI	10 Year Rates MED Group	10 Year Rates CABG Group
Mild or moderate	346	129	0.62	0.44, 0.88	49.5%	35.4%
Severe	849	408	0.68	0.56, 0.83	62.3%	45.1%

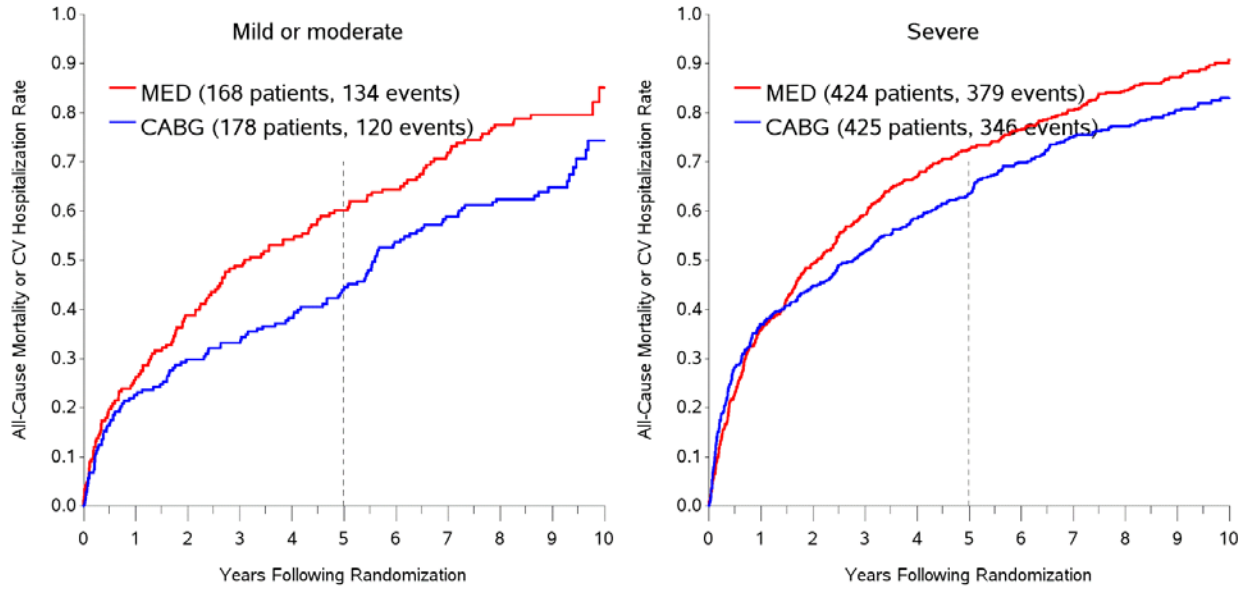


Interaction
P-value = 0.608

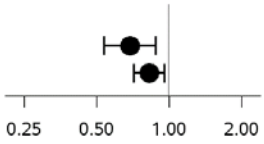
CABG Group Better

MED Group Better

C



Comorbidity	N	Events	Hazard Ratio	95% CI	10 Year Rates MED Group	10 Year Rates CABG Group
Mild or moderate	346	254	0.69	0.54, 0.88	85.1%	74.2%
Severe	849	725	0.83	0.72, 0.96	90.6%	82.9%



Interaction
P-value = 0.240

CABG Group Better

MED Group Better