Angina Does Not Identify Patients With Coronary Disease, Heart Failure, and a Reduced Left Ventricular Ejection Fraction Who Have Greater Prognostic Benefit From Surgical Revascularization: Insights From the STICH Trial

Brief title: The STICH Angina Analysis

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ABSTRACT:
Background: Patients with left ventricular (LV) systolic dysfunction, coronary artery disease (CAD), and angina are often thought to have a worse prognosis and a greater prognostic benefit from coronary artery bypass graft (CABG) surgery than those without angina.
Objectives: We investigated whether: 1) angina is associated with a worse prognosis; 2) angina identified patients who had a greater survival benefit from CABG; and 3) whether CABG improved angina in patients with LV systolic dysfunction and CAD.
Methods: We performed an analysis of the Surgical Treatment for Ischemic Heart Failure trial, in which 1,212 patients with an ejection fraction ≤35% and CAD were randomized to CABG or medical therapy. Multivariable Cox and logistic models were used to assess long-term clinical outcomes.
Results: At baseline, 770 patients (64%) reported angina. Amongst patients assigned to MED, all-cause mortality was similar in patients with and without angina (HR: 1.05; 95% CI: 0.79 to 1.38). The effect of CABG was similar whether the patient had angina (HR: 0.89; 95% CI: 0.71 to 1.13) or not (HR: 0.68; 95% CI: 0.50 to 0.94) (p interaction = 0.14). Patients assigned to CABG were more likely to report improvement in angina than those assigned to medical therapy alone (OR: 0.70; 95% CI: 0.55 to 0.90; $p < 0.01$).
Conclusions: Angina does not predict all-cause mortality in medically treated patients with LV systolic dysfunction and CAD, nor does it identify patients who have a greater survival benefit from CABG**.** However, CABG does improve angina to a greater extent than medical therapy alone.
(Comparison of Surgical and Medical Treatment for Congestive Heart Failure and Coronary Artery Disease [STICH]: NCT00023595**)**

<KW>Key words: Coronary Artery Bypass Grafting; Coronary Artery Disease; Heart Failure; Mortality

Abbreviations
BMI = body mass index
CABG = coronary artery bypass graft
CAD = coronary artery disease
CCS = Canadian Cardiovascular Society
CI = confidence interval
HR = hazard ratio
IQR = interquartile range
LVEF = left ventricular ejection fraction
MI = myocardial infarction
OR = odds ratio

Introduction

Coronary artery bypass grafting (CABG) is recommended in patients with angina (1), coronary artery disease (CAD), and left ventricular (LV) systolic dysfunction (2,3). However, compelling evidence that the presence or absence of angina should guide decisions about revascularization is lacking (4). Tests of myocardial viability or stress-induced ischemia have failed, so far, to identify a subset of patients with heart failure who have more to gain from CABG compared to medical therapy alone in randomized controlled trials (5,6).

Clinical guidelines identify angina as an important consideration when deciding whether patients with heart failure and reduced LV function should have CABG (7). Angina pectoris signals the presence of viable myocardium that is prone to ischemia and at risk of infarction, and may therefore confer an adverse outcome (8). Patients with heart failure and CAD who do not have angina might have less jeopardized myocardium at risk of ischemia, indicating a better prognosis, or have cardiac denervation rendering myocardial ischemia silent, or a substantial volume of myocardium affected by hibernation or replaced by scar, which could signal an adverse prognosis (9,10). Surprisingly, information on the prognostic significance of angina in patients with heart failure who are known to have CAD has not been reported. Accordingly, we conducted an analysis of the Surgical Treatment for Ischemic Heart Failure (STICH) trial data to address 3 questions: 1) Does the presence of angina influence outcomes in patients with heart failure and CAD managed without resort to revascularization? 2) Does angina identify patients who will experience a greater survival benefit from CABG? 3) Does CABG improve angina in this population?

Methods

Study population

The rationale and design of the STICH trial were published previously (11). STICH was a prospective, multicenter, randomized trial sponsored by the National Heart, Lung and Blood Institute (NHLBI) that recruited patients with CAD and an LV ejection fraction of 35% or less between 2002 and 2007 (NCT00023595) (4). For the present study, 1,212 participants enrolled in the surgical revascularization hypothesis were included. This part of the STICH trial assessed whether CABG combined with optimal medical therapy improved survival compared with optimal medical therapy alone. The inclusion and exclusion criteria and the requirements for ensuring high-quality surgical revascularization have been described (12). The NHLBI and the ethics committee at each recruiting institution approved the study protocol. All patients provided written informed consent. All authors have read and agreed to the paper as written.

Study outcomes

A blinded clinical events committee adjudicated all deaths using pre-specified criteria (4,11). Angina status was assessed using the Canadian Cardiovascular Society (CCS) classification at baseline and at each follow-up visit. Angina relief was primarily defined as an improvement of ≥1 CCS angina class.

Statistical analysis

Continuous variables are presented using the median (interquartile range) and compared using Wilcoxon rank-sum tests. Discrete variables are presented as counts (percentages), and compared using either Pearson's chi-square or the Fisher exact test, as appropriate. For time-to-event analysis, Kaplan–Meier survival estimates were used to estimate event rates over the long-term follow-up for patients who did and did not receive CABG surgery (13). Statistical

significance was determined at the 2-sided $\alpha = 0.05$ level. No adjustments were made for multiple comparisons, as this analysis should be considered exploratory, rather than definitive. Data analyses were performed with SAS software package (version 9.4, SAS Institute, Cary, North Carolina).

Modeling of outcomes

For each research question, a multivariable model was developed to adjust for known or expected confounding variables. For each model, candidate variables were pre-specified, using either clinical experience or previously reported risk factors (4,5,14). The primary analysis was on the basis of the intention-to-treat principle. We repeated the analyses according the treatments actually received (rather than assigned) to ascertain the influence of crossover outcomes.

The first analysis ascertained the relationship between angina and all-cause mortality (primary endpoint), and the composite of all-cause mortality or all-cause hospitalization (secondary endpoint) exclusively in patients assigned to medical therapy alone. The second analysis compared the effect of CABG versus medical therapy alone on all-cause mortality and the composite of all-cause mortality or hospitalization in patients with and without angina, and sought potential interactions between the presence of angina and randomly assigned group (see **Online Supplementary Methods**). For both analyses, adjustment for baseline risk factors was implemented by utilizing a multivariable Cox proportional hazards model to estimate the adjusted hazard ratio and its 95% confidence interval (CI) (15). In both models, the presence of angina was dichotomized as no angina (CCS = 0) versus angina (CCS = 1 or above). However, to assess the stability of our models across the spectrum of angina severity, we conducted alternate analyses after stratifying angina as absent (CCS = 0), mild (CCS = 1), and moderate or severe (CCS >1).

The third analysis investigated the relationship between randomization to CABG or medical therapy alone and the relief of angina. For the purpose of this analysis, we modeled a multivariable logistic regression in which the primary endpoint was defined as improvement of ≥1 CCS angina class from baseline to last available follow-up. The candidate independent predictors were identical to previous analyses, with the addition of change in beta-blocker and nitrate use from baseline and at follow-up. The robustness of the model was tested in a series of sensitivity analyses (see **Online Supplementary Methods**).

The authors reviewed the data, participated in the analyses, and wrote the manuscript, and assume responsibility for the completeness and accuracy of the data and the analyses, and for the fidelity of the study to the trial protocol.

Results

Study population

Of 1,212 patients enrolled, 770 patients (63.5%) reported angina at baseline (187 in CCS class I, 525 in CCS class II, and 58 in CCS class III/IV) and 442 patients (36.5%) reported having no angina. In each angina group, the proportion of patients assigned to CABG or medical therapy alone was similar (**Table 1**). Final follow-up status for all-cause mortality and all-cause hospitalization was ascertained for 1,207 patients (99.6%) over a median follow-up time of 56 months.

Baseline characteristics

The baseline characteristics and the burden of CAD of patients who did or did not report angina were similar, with some exceptions. Patients of Caucasian origin reported less angina. Patients who reported angina were younger, were more likely to have experienced a previous myocardial infarction (MI) and to be treated with long-acting nitrates, but were less likely to

have a history of atrial fibrillation, renal dysfunction, diabetes mellitus, stroke, or hyperlipidemia (**Table 1**). There was no significant difference in angina status at baseline between treatment arms (p = 0.52).

Angina and outcomes in patients assigned to medical therapy alone

Baseline characteristics of patients assigned to medical therapy alone with and without angina are compared in **Online Table 1**. Among patients assigned to medical therapy alone (n = 602), the presence or absence of angina at baseline was not associated with all-cause mortality (HR: 1.05; 95% CI: 0.79 to 1.38; p = 0.74, for absence of angina) (**Figure 1**, and **Online Table 2A**). However, after stratification, moderate to severe angina (CCS ≥2) as compared with no angina was associated with all-cause mortality (HR: 1.27; 95% CI: 1.04 to 1.57; p = 0.02) (**Online Table 2B**). Angina was not associated with a greater risk of the composite of all-cause mortality or hospitalization (HR: 1.05; 95% CI: 0.86 to 1.28; p = 0.64).

Influence of angina on the impact of CABG on all-cause death, hospitalizations, and cardiovascular endpoints

In patients with angina, all-cause mortality was similar among patients assigned to CABG or medical therapy alone (37.4% vs. 39.5%; adjusted HR: 0.89; 95% CI: 0.71 to 1.13; p = 0.34). In patients without angina, mortality was lower in patients assigned to CABG (32.7% vs. 42.7%; adjusted HR: 0.68; 95% CI: 0.50 to 0.94; p = 0.02) (**Table 2**, **Figure 2**). However, the interaction between the presence of angina and the effect of CABG versus medical therapy on survival was not significant (p = 0.14). The composite of all-cause mortality or hospitalizations was reduced to a similar extent in patients assigned to CABG, whether they had angina or not (HR: 0.78; 95% CI: 0.66 to 0.93, and HR: 0.80; 95% CI: 0.64 to 1.00, respectively) (**Table 2**).

Further stratifying patients according to severity of angina yielded similar results. Mortality rates in those assigned to CABG rather than to medical therapy alone, were similar for patients in CCS I (34.4% vs. 38.5%; HR: 0.83; 95% CI: 0.49 to 1.39; p = 0.47) and CCS >1 (39.9% vs. 38.4%; HR: 0.94; 95% CI: 0.73 to 1.23; p = 0.66) (**Online Table 3**). When crossovers from one treatment arm to another were considered, mortality was lower in patients with and without angina if they had CABG (HR: 0.67; 95% CI: 0.53 to 0.85, and HR: 0.63; 95% CI: 0.47 to 0.88, respectively) (**Online Figure 1, Online Table 4**). Data for other cardiovascular endpoints is presented in **Online Table 5**.

Effect of CABG and medical therapy on relief of angina

Eighty-five patients died in hospital after CABG or in the interval before the first follow-up outpatient visit at 4 months. Of the remaining 1,127 patients, an evaluation of angina was available in 1,089 (97%), with a median follow-up time of 52 months (**Online Figure 2**).

Of the 1,089 patients with information on angina available at follow-up, 494 (45.4%) reported an improvement in angina: 50% of those assigned to the CABG + medical therapy and 41% of those assigned to medical therapy alone. Patients reporting angina at baseline were less likely to have worsening CCS angina class if assigned to CABG rather than medical therapy alone (odds ratio: 0.70; 95% CI: 0.55 to 0.90; p < 0.01). The positive association between CABG and relief of angina persisted in all sensitivity analyses (**Table 3**).

Discussion

These analyses of the STICH trial are the first to investigate the impact of angina on outcomes in a randomized controlled study evaluating the benefits of CABG in patients with CAD, heart failure, and LV systolic dysfunction. Angina does not predict prognosis in medically treated patients with known CAD, nor does the presence or absence of angina identify patients

with LV dysfunction and CAD who have a greater benefit from CABG **(Central Illustration**). Although mortality was lower in patients assigned to CABG who did not have angina, the interaction between assigned treatment and angina at baseline was not significant. When crossovers were considered, the observed reduction in mortality with CABG was significant and of similar magnitude in patients with and without angina. Finally, as may be expected, CABG improves angina compared with medical therapy alone. These findings have important clinical implications, given the paucity of prior evidence to guide decision-making in patients with angina and LV systolic dysfunction.

Among patients with severe LV dysfunction, CABG is associated with an early risk of serious complications, including death (16). Findings from this study challenge the perceived benefit–risk balance for CABG in patients with and without angina. Although patients with heart failure and angina recalcitrant to pharmacological therapy should be considered for revascularization for symptom relief, this analysis suggests that insofar as subsequent prognosis is concerned, the presence or absence of angina should not be used as a discriminating factor to decide for or against revascularization as an initial treatment strategy. These findings conflict with the opinion expressed in several clinical practice guidelines, which infer that angina is both a marker of a poorer prognosis and of a greater likelihood of prognostic benefit from revascularization. The European Society of Cardiology recommends coronary revascularization when angina persists despite treatment with 2 anti-anginal drugs; revascularization is not recommended in patients without angina and viable myocardium (1,17). The American practice guidelines do not directly address the question of angina. Instead, the decision to proceed with either CABG or PCI in patients with CAD and LV systolic dysfunction should be on the basis of clinical judgment after a multidisciplinary consideration of the coronary anatomy (including

single vs. multiple coronary lesions), the presence of severe comorbid conditions, and the severity of LV systolic dysfunction (18,19).

By design, all patients in this study had CAD, which is well known to be associated with an adverse prognosis in patients with heart failure. Other analyses, in populations with less robust evidence of CAD, suggest that angina is associated with a worse outcome (14), but this may be because angina is a marker confirming the presence of CAD. The reasons why angina does not predict a mortality benefit from CABG are uncertain, and cannot be determined from the current study. Results of this analysis are consistent with previous findings from STICH and the Heart Failure Revascularization Trial (HEART) (20), suggesting that neither myocardial viability (5) nor reversible myocardial ischemia (6) helps predict which patients benefit from CABG.

There are no ongoing trials of CABG versus medical therapy in heart failure to confirm or refute our findings. The Study of Efficacy and Safety of Percutaneous Coronary Intervention to Improve Survival in Heart Failure (REVIVED-BCIS2) will address the effects of revascularization in heart failure, albeit by percutaneous coronary intervention (21), in patients with and without concomitant angina.

The findings of this analysis of the STICH trial should be applied to other types of patients with CAD with caution. CABG should be considered, whenever feasible, in patients with angina refractory to medical therapy, whether LV systolic function is reduced or not. However, the relationship between CAD, angina, and ischemic burden is complex, due, in part, to the great improvement in the contemporary medical therapy of heart failure and CAD. In the COURAGE (Clinical Outcomes Using Revascularization and Aggressive DruG Evaluation) (22), and BARI 2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes) trials (23,24),

both of which included very few patients with LV systolic dysfunction, the ischemic burden failed to predict the effect of revascularization on clinical endpoints. However, regardless of the presence of angina or ischemic burden, the severity of CAD (25) and the extent of myocardial dysfunction and scar do appear to influence the benefits of CABG.

Limitations

The present study is a retrospective analysis of a randomized trial, and unknown confounders and biases may have affected the complex relation between angina, CABG, and outcomes. To minimize this, we adjusted for key variables known to affect survival and performed sensitivity analyses. With few exceptions (20,26), there is no other prospective dataset besides the STICH trial, which assesses the effect of CABG on outcomes in patients with LV systolic dysfunction. This precludes any external validation of our findings with an independent trial population. Patients enrolled in the STICH trial were mostly men, white, and relatively young. Many patients and investigators may have elected to proceed to revascularization if the coronary anatomy was thought to be associated with a particularly adverse prognosis or was highly amenable to percutaneous coronary intervention, rather than enroll the patient in this study. This might be particularly true for patients with angina. For these reasons, extrapolation of our results to broader populations should be made with caution. The identification and classification of angina in patients enrolled in STICH was at the discretion of study-site investigators using established clinical guidelines. Even so, there may be local variability in the angina definitions employed; hence, our findings should be interpreted with caution in groups (women and older patients) (27) who present with atypical symptoms. Patients with markedly limiting angina (CCS class III or IV) were under-represented in the study. For this reason, it was

not possible to fully explore a dose-response effect across the complete spectrum of angina severity.

Conclusions

Our study suggests that among patients with CAD, heart failure, and LV systolic dysfunction, the presence of angina does not confer a markedly worse prognosis or the potential for a greater benefit from revascularization by CABG. However, CABG does improve angina compared with medical therapy alone. These findings may influence clinical practice by diminishing the relevance of the role of angina for treatment decisions and prognostication in patients with ischemic cardiomyopathy.

PERSPECTIVES

*Competency in Medical Knowledge***:** The occurrence of angina pectoris is not a predictor or mortality in medically treated patients with coronary artery disease (CAD) and left ventricular (LV) systolic dysfunction. Bypass surgery (CABG) is more effective than medical therapy in relieving angina and lowers mortality to a similar extent in those with and without angina.

Translational Outlook: Additional studies are needed to clarify the mechanisms underlying the interaction between angina, revascularization and clinical cardiovascular outcomes.

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FIGURE LEGENDS:

Central Illustration. The STICH Angina Substudy: The Interaction of Angina, Revascularization, and Outcomes in Patients With LV Systolic Dysfunction and Coronary Artery Disease

The presence of angina does not confer a markedly poorer prognosis in medically treated patient. By intention-to-treat, mortality rates are similar in patients assigned to CABG or to medical therapy, whether angina is present or not. Patients treated with CABG had greater improvement in CCS angina class compared to patients treated with medical therapy only, but the treatment effect diminishes over time. Angina, unless recalcitrant to medical therapy, does not appear useful in selecting patients with CAD, heart failure and LV systolic dysfunction for CABG. CABG = coronary artery bypass graft; CAD = coronary artery disease; CCS = Canadian Cardiology Society; LV = left ventricular.

Figure 1. Kaplan-Meier Estimates: Cumulative Incidence of All-Cause Mortality in Medically Treated Patients With and Without Angina

Amongst patients assigned to medical therapy, all-cause mortality was similar in patients with and without angina (HR: 1.05; 95% CI: 0.79 to 1.38).

Figure 2. Adjusted Cox Proportional Hazards Estimates of the Cumulative Risk of All-Cause Mortality According to Angina Status and Treatment Arm

The effect of CABG was similar whether the patient had angina (HR: 0.89; 95% CI: 0.71 to 1.13) or not (HR: 0.68; 95% CI: 0.50 to 0.94) (p interaction = 0.14). Analyses adjusted for LVEF, age, BMI (above or below 35), log of creatinine (0 to 0.4), peripheral vascular disease, mitral regurgitation, beta-blockers at baseline, atrial fibrillation/flutter. BMI = body mass index;

CABG = coronary artery bypass graft; CI = confidence interval; LVEF = left ventricular ejection fraction.

Table 1. Baseline Characteristics by Presence of Angina in the STICH Trial

Characteristics	Angina (n = 770)	No angina (n = 442)	p Value
Treatment Group			0.52
Medical therapy alone	377 (49.0%)	225 (50.9%)	
CABG + medical therapy	393 (51.0%)	217 (49.1%)	
Demographics			
Age, median (IQR), yrs	59 (53, 66)	61 (54-69)	<0.001
Sex, male, number (%)	671 (87.1%)	393 (88.9%)	0.37
BMI, median (IQR), kg/m^2	27 (24, 30)	27 (24-30)	0.76
Race or ethnic group, number (%)			<0.001
White	494 (64.2%)	333 (75.3%)	
Hispanic, Latino, or nonwhite	276 (35.8%)	109 (24.7%)	
Medical history, number (%)			
Previous myocardial infarction	633 (82.2%)	301 (68.1%)	<0.001
Diabetes mellitus	278 (36.1 %)	200 (45.2 %)	<0.01
Hypertension	454 (59.0 %)	274 (62.0 %)	0.30
Hyperlipidemia	436 (56.6 %)	294 (66.5 %)	<0.001
Previous coronary artery bypass surgery	24 (3.1 %)	12 (2.7 %)	0.69
Previous percutaneous coronary intervention	97 (12.6 %)	59 (13.3 %)	0.71

Chronic renal insufficiency*	44 (5.7 %)	50 (11.3 %)	<0.001
Previous stroke	48 (6.2 %)	44 (10.0 %)	0.02
Atrial flutter/fibrillation	83 (10.8%)	70 (15.8%)	0.01
Peripheral vascular disease	109 (14.2%)	75 (17.0%)	0.19
Presenting characteristics			
Systolic blood pressure, median (IQR), mm Hg	120 (110, 130)	120 (110-130)	0.002
CSS class, number (%)			
0	--	442 (100%)	
I	187 (24.3%)	--	
II	525 (68.2%)	--	
III	48 (6.2%)	--	
IV	10 (1.3%)	--	
NYHA class, number (%)			<0.001
I	261 (33.9%)	174 (39.6%)	
II	373 (48.4%)	181 (41.2%)	
III	112 (14.5%)	69 (15.7%)	
IV	24 (3.1%)	15 (3.4%)	
Hemoglobin, median (IQR), g/dl	14 (13, 15)	14 (13-15)	0.23
Creatinine, median (IQR), mg/dl	1.09 (0.94, 1.24)	1.10 (0.94-1.30)	0.04
Left ventricular ejection fraction, median	28 (22, 34)	27 (22-33)	0.06

(IQR), %			
Left ventricular end-systolic volume indexed	80 (61, 108)	83 (62-109)	0.44
Myocardial viability†	285 (78.1%)	202 (85.6%)	0.02
Mitral regurgitation, number (%)			0.11
none/trace (1+)	261 (33.9%)	174 (39.6%)	
mild (2+)	373 (48.4%)	181 (41.2%)	
moderate (3+)	112 (14.5%)	69 (15.7%)	
severe (4+)	24 (3.1%)	15 (3.4%)	
Angiographic information			
Duke CAD index, median (IQR)	65 (39, 77)	52 (39, 77)	0.29
Left main disease	19 (2.5%)	13 (2.9%)	0.62
1-vessel disease	76 (9.9%)	36 (8.1%)	0.32
2-vessel disease	230 (29.9%)	136 (30.8%)	0.74
3-vessel disease	463 (60.1%)	270 (61.1%)	0.74
Medications, number (%)			
Beta-blockers	662 (86.0%)	374 (84.6%)	0.52
Long-acting nitrates	484 (62.9%)	162 (36.7%)	<0.001

*Defined as creatinine >1.5: mg/dl.

†A total of 601 patients underwent viability assessment in the trial.

BMI = body mass index; CABG = coronary artery bypass grafting; CAD = coronary artery disease; CCS = Canadian Cardiovascular Society; IQR = interquartile range; NYHA = New York Heart Association

Table 2. Stratified Outcomes Analysis for Medical Therapy Alone Versus CABG by Presence of Angina at Baseline

Event	Medical Therapy Alone (n = 602)	CABG + Medical Therapy (n = 610)	Adjusted Hazard Ratio for CABG + Medical Therapy (95% CI) *†	p Value
No angina at baseline (n = 442)	(n = 225)	(n = 217)		
All-cause mortality			0.68 (0.50-0.94)	0.02
Number of events (crude event rate, %)	96 (42.7%)	71(32.7%)		
KM estimate of 5-yr event rate (%)	41.0%	31.9%		
Adjusted Cox proportional hazard estimates of cumulative risk of all-cause death at 5 yrs (%)	32.9%	25.0%		
All-cause mortality or all-cause hospitalization			0.80 (0.64-1.00)	0.05
Number of events (crude event rate, %)	172 (76.4%)	149 (68.7%)		
KM estimate of 5-yr event rate (%)	79.0%	68.1%		

Angina at baseline (n =770)	(n = 377)	(n = 393)		
All-cause mortality			0.89 (0.71-1.13)	0.34
Number of events (crude event rate, %)	149 (39.5%)	147 (37.4%)		
KM estimate of 5-year event rate (%)	39.8%	36.8%		
Adjusted Cox proportional hazard estimates of cumulative risk of all-cause death at 5 yrs (%)	37.2%	33.2%		
All-cause mortality or all-cause hospitalization			0.78 (0.66-0.93)	<0.001
Number of events (crude event rate, %)	270 (71.6%)	250 (63.6%)		
KM estimate of 5-year event rate (%)	72.2%	63.8%		

Of 1,212 patients randomized in STICH, 1,205 with known angina status at baseline were included in the multivariable statistical analysis. Implantation of a left ventricular assist device during follow-up was considered as equivalent to death (n = 1).

*All-cause death analysis was adjusted for LVEF, age, BMI (<35), log of creatinine (0 to 0.4), peripheral vascular disease, mitral regurgitation, beta-blocker at baseline, and atrial fibrillation/flutter. The p interaction for angina and treatment (medical therapy alone or CABG) = 0.14

†All-cause death plus all-cause hospitalization analyses were adjusted for treatment group (CABG vs. medical therapy alone), LVEF, age, white race, log of creatinine (< 0.4), hemoglobin, mitral regurgitation, and NYHA classification. The p interaction for angina and treatment (medical therapy alone or CABG) = 0.99.

The following values were assigned to baseline covariates for adjusted event rates: age = 60 years; LVEF = 28; BMI = 27; log2(creatinine) = 0.14; PVD = 0.15; mitral valve regurgitation (moderate/severe) = 0.18; beta-blocker = 0.85; and atrial fibrillation/flutter = 0.13.

KM = Kaplan-Meier; LVEF = left ventricular ejection fraction. Other abbreviations as in **Table 1**.

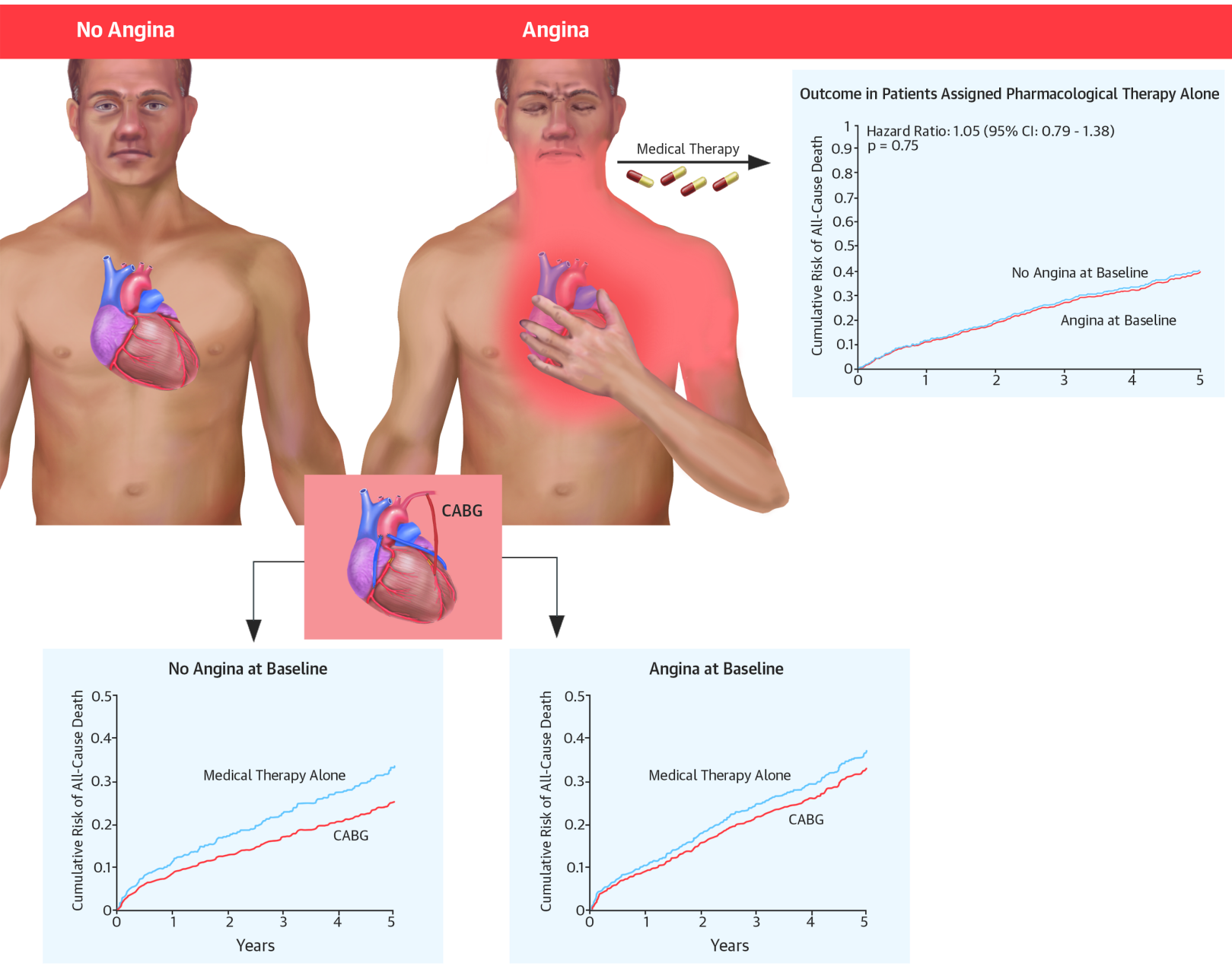
Table 3. Odds Ratios of Worsening Angina for Patients Treated with CABG Compared With Patients Treated with Medical Therapy Alone

Models	OR (95% CI)	p Value
Unadjusted data	0.70 (0.55-0.89)	< 0.01
Third principal model*	0.70 (0.55-0.90)	< 0.01
Sensitivity analyses		
1. Proportional odds model (angina as 3-level categorical variable)†	0.69 (0.55-0.87)	< 0.01
2. Third principal model + adjusted for antiangina medication post-randomization	0.78 (0.60-1.00)	0.05
3. Worst-case scenario	0.77 (0.61-0.98)	0.03

Of the 1,212 patients randomized in STICH, 1,089 with angina assessed at least once after randomization were included in the statistical model

*The model is the final adjusted binary logistic regression model. The model remained stable after internal validation (OR: 0.69; 95% CI: 0.54 to 0.89), and after crossover patients were taken into consideration (OR: 0.57; 95% CI: 0.45 to 0.74; $p < 0.01$).

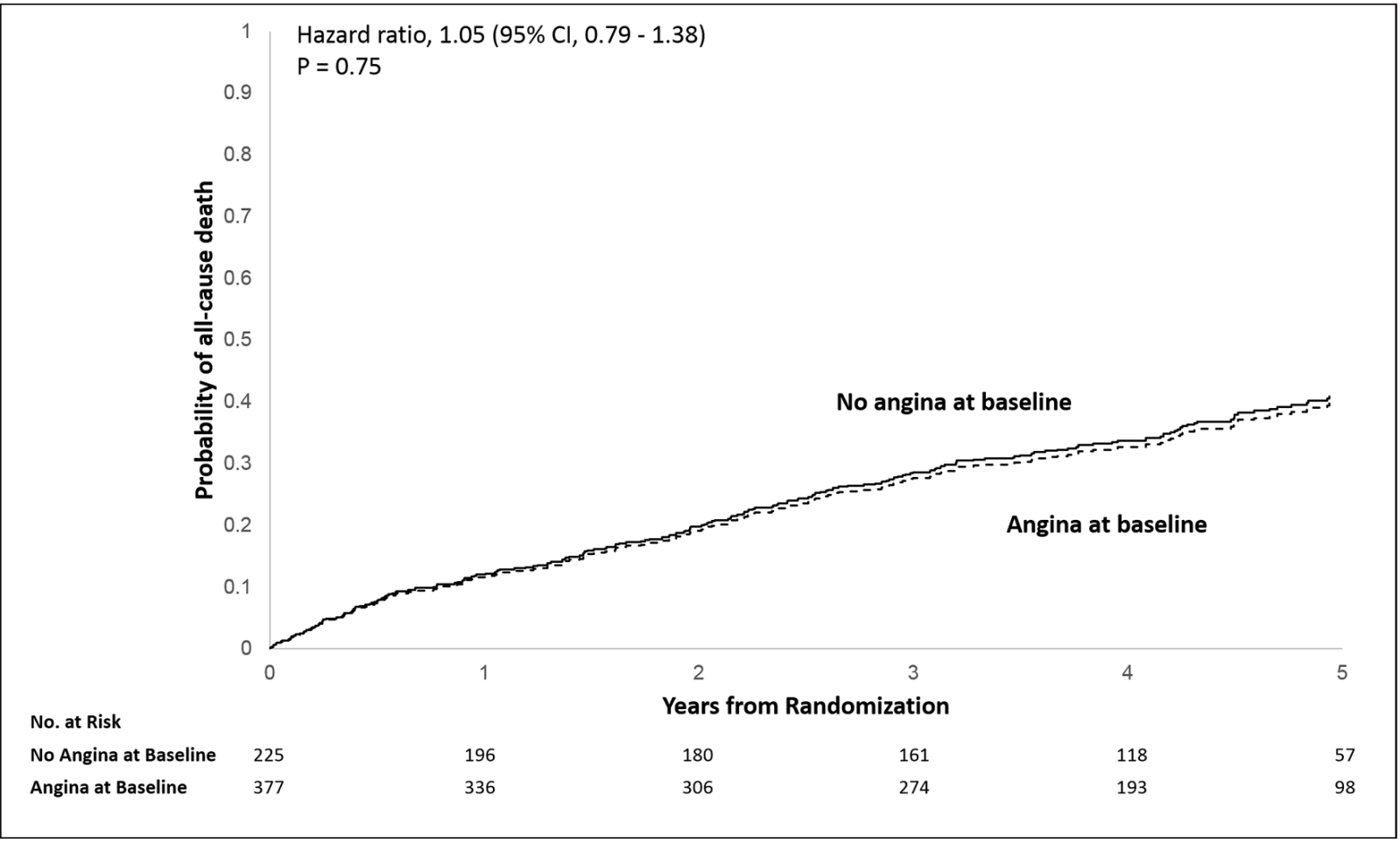
†Proportional odds model defines angina relief as an ordinal 3-level categorical variable with values representing worsening angina, stable angina, and angina relief. The odds ratio supplied is predicting the probability of angina relief averaging over worsening angina and stable angina.


No Angina
Angina
Medical Therapy
CABG

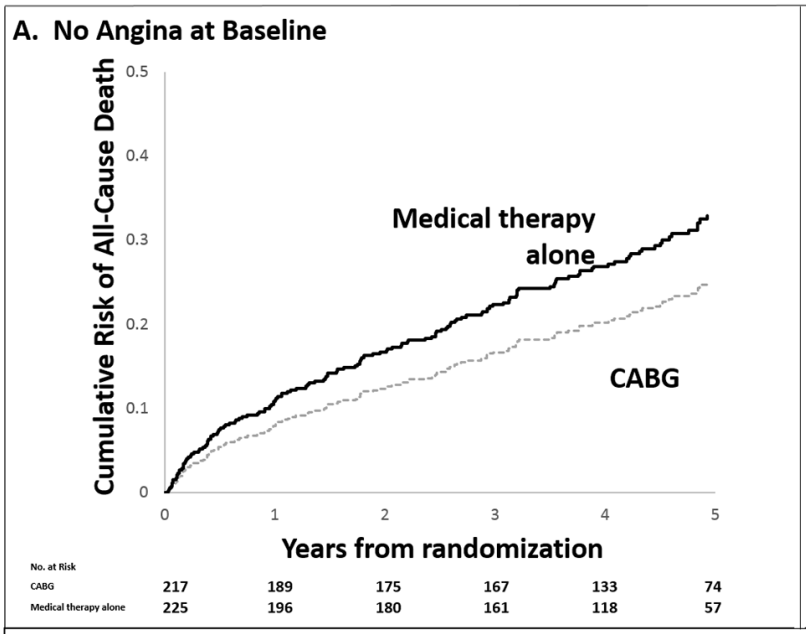
Outcome in Patients Assigned Pharmacological Therapy Alone
Hazard Ratio: 1.05 (95% CI: 0.79 - 1.38)
p = 0.75
Cumulative Risk of All-Cause Death
No Angina at Baseline
Angina at Baseline

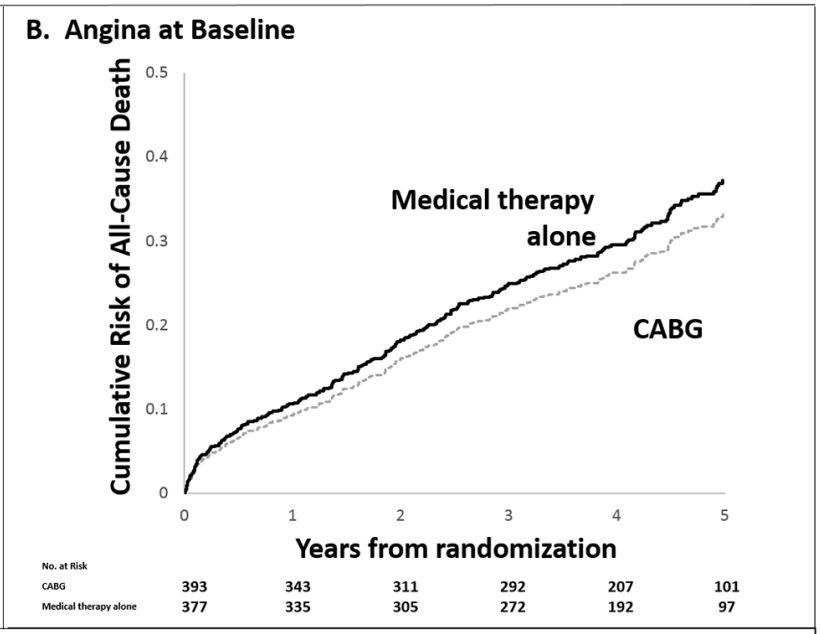
No Angina at Baseline
Cumulative Risk of All-Cause Death
Medical Therapy Alone
CABG
Years

Angina at Baseline
Cumulative Risk of All-Cause Death
Medical Therapy Alone
CABG
Years



No. at Risk						
No Angina at Baseline	225	196	180	161	118	57
Angina at Baseline	377	336	306	274	193	98





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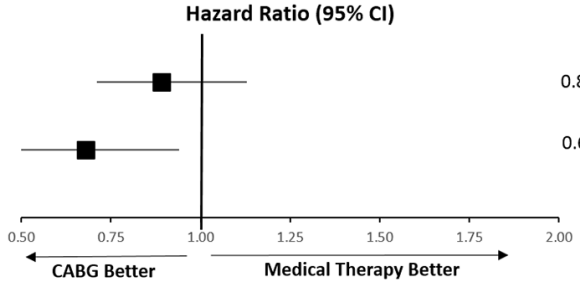
Subgroup	No.	Deaths	Hazard Ratio (95% CI)	P Value for Interaction
Angina at Baseline	770	296	0.89 (0.71, 1.13)	0.14
No Angina at Baseline	442	167	0.68 (0.50, 0.94)	



SUPPLEMENTARY METHODS

Modeling of outcomes for first and second analyses

For both the first and second analyses, the candidate independent predictors included demographics (age, sex, race, body mass index (BMI)), baseline characteristics (pulse pressure, systolic and diastolic blood pressure, hemoglobin, creatinine, LV ejection fraction (LVEF), NYHA functional class, CCS angina class), prior medical history (diabetes mellitus, atrial flutter/fibrillation, peripheral vascular disease, past MI, mitral regurgitation (as none/trace (1+) vs. mild (2+) vs. moderate (3+), vs. severe (4+)), and medication (beta-blockers, long-acting nitrates).

Multivariable models were assembled using a backward stepwise variable selection method with $p < 0.10$ cut-off used for inclusion in the final model. The Presence of Angina was forced into final models to assess its relationship with endpoints of interest after adjustment for other variables. The linearity assumption was evaluated by applying restricted cubic spline transformations to the continuous measures. The likelihood ratios for models with these transformations were compared with those in the linear models to assess the need for nonlinear terms. In case of nonlinearity, the plot of the restricted cubic spline transformation vs. the log hazard ratio (in the case of the Cox model) of the outcome was used to assist in identifying the appropriate transformations to apply. For survival analyses, the proportionality assumption was assessed by adding a time-dependent variable to the model. Whenever appropriate, the model's discrimination was evaluated by the c-index. The significance of multivariable regression coefficients was assessed with the Wald chi-square. Only patients with complete information were included in the models and no data imputation was performed.

Sensitivity analyses for third analysis

The robustness of the association between angina relief and revascularization was ascertained in 4 sensitivity analyses meant to explore: 1) a possible dose–response relationship between the variation of angina and the candidate predictors; 2) the possible confounding effect of the change in anti-angina medication following randomization; 3) the impact of missing data on angina status at follow-up (worst case scenario); and 4) the concerns around the variability of angina status collected repeatedly at follow-up. In the first sensitivity to explore the possibility of a dose–response relationship between variation of angina class and the candidate predictors, a proportional odds model(1) was implemented where the change in angina classes from baseline to follow-up was treated as a three level ordinal variable with values representing worsening angina, stable angina and angina relief. A second sensitivity analysis looked that the possible confounding effect of the change in anti-angina medication following randomization. In this instance, medication changes were treated as categorical variables, where a value of -1 was assigned to patients taken off the anti-angina medication during the study period, a value of 0 was assigned to patients whose medication status remained same throughout the study period, and a value of +1 was assigned to patients who started the medication during follow-up. The third sensitivity analysis explored the robustness of our data where patients with missing angina status at follow-up were categorized as deteriorating angina (no ≥ 1 CCS angina class improvement; worst case scenario). The fourth sensitivity analysis addressed the concerns around the variability of angina status collected repeatedly at follow-up. To this end, we conducted a repeated measures analysis using linear mixed models. To stabilize the model, we concentrated it on time frame between 4-60 months, which accounted for more than 90% of the CCS follow-up data collected. We chose the response variable for the model to be the change in CCS angina classification from baseline to each follow-up time point. This was treated as a continuous variable with values ranging from -4 to 4; negative values represents

improvement in CCS angina class from baseline. The final model assumed compound symmetry structure for the between and within subject correlation, was adjusted for baseline CCS angina classification and included the following effects: (1) a treatment effect (CABG vs. Medical Therapy, averaged over all time points); (2) a time effect (ranging from 4-60 months); and (3) a treatment by time interaction effect (is the treatment effect the same across all time points).

SUPPLEMENTARY RESULTS

Effect of crossover on outcomes

A total of 55 patients assigned to CABG were treated with medical therapy alone, and 65 patients assigned to medical therapy alone underwent CABG. Due to these crossovers, an additional 29 patients with angina initially assigned to medical therapy underwent CABG. Likewise, an additional 11 patients with no angina initially assigned to CABG were treated with medical therapy alone. There was no significant difference in presence and severity of angina at baseline and treatment arm (p=0.15). In Patients who did not report angina at baseline, those who underwent CABG as compared with those who received medical therapy alone, had a significantly lower rate of all-cause death (Kaplan-Meier of 7-year event rates: 39.3% vs. 67.4%; adjusted hazard ratio, 0.64; 95% CI, 0.47 to 0.88; $p < 0.01$). Similarly, in patients who reported angina at baseline, those who underwent CABG as compared with those who received medical therapy alone, had similar Kaplan-Meier rates of all-cause death (51.7% vs. 56.7%); but after adjustment for covariates those patients receiving CABG had significantly lower risk of all-cause death (adjusted hazard ratio, 0.67; 95% CI, 0.53 to 0.85; $p < 0.001$) (Supplementary Figure 1, and Supplementary Table 3).

Sensitivity analyses for the effect of CABG and medical therapy on relief of angina

A repeated measures analysis on CCS angina class collected at follow-up visits between 4 and 60 months post randomization, found a significant time by treatment effect. However, further exploration found that while the treatment effect diminished over time, patients receiving CABG consistently displayed a greater improvement in CCS angina classification compared to patients receiving Medical Therapy Only (Supplementary Figure 3)

REFERENCES

1. McCullagh P. Regression Models for Ordinal Data. Journal of the Royal Statistical Society Series B (Methodological) 1980;42:109-142.

FIGURE LEGENDS:

Supplementary Figure 1. Effect of Crossovers on Adjusted Cox Proportional Hazards Estimates of the Cumulative Risk of All-Cause Death According to Angina Status and Treatment Arm

Footnotes: Adjusted for LVEF, age, BMI (<35), log of creatinine (0 to 0.4), peripheral vascular disease, mitral regurgitation, beta-blockers at baseline, atrial fibrillation/flutter (p interaction = 0.74)

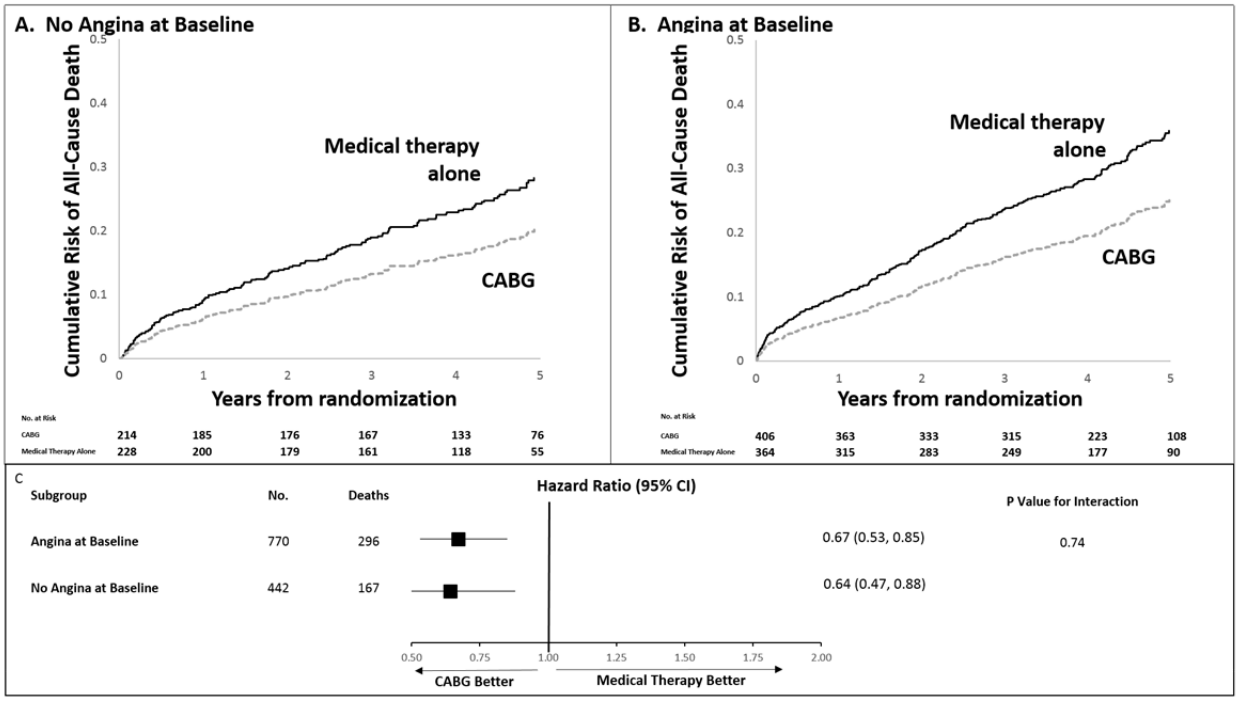
Supplementary Figure 2. Variation in Angina Classes During Follow-Up

Footnotes: a) patients assigned to medical therapy alone; b) patients assigned to CABG. Figures display only patients who presented angina at baseline. The X axis is actually not proportional in time despite the current representation due to the varying schedule of visits at follow-up.

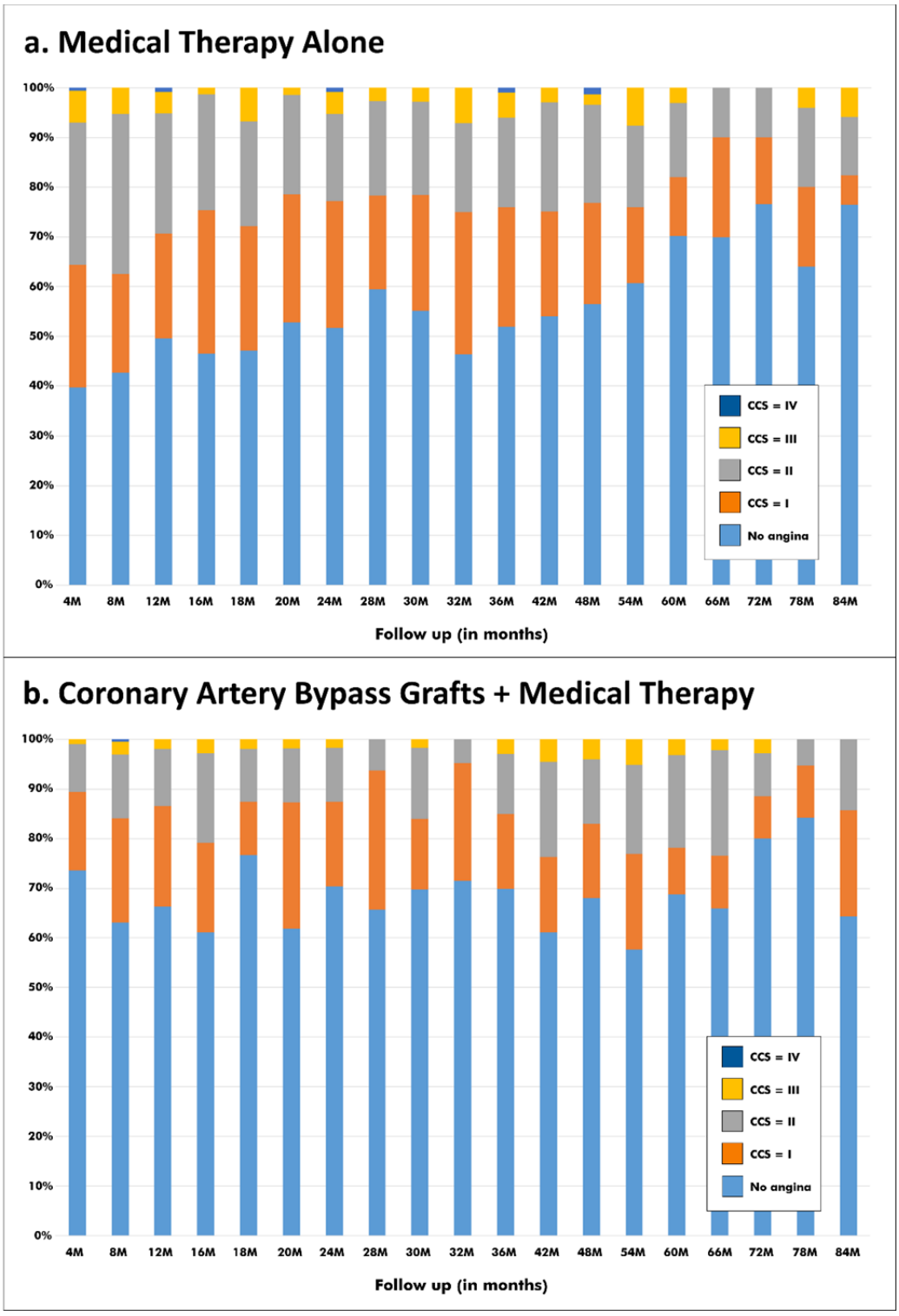
Supplementary Figure 3. Patients Assigned to CABG Experienced a Larger Decreases in Angina Class at Follow-Up Compared to Medical Therapy

Footnotes: The mixed model analysis found that a significant treatment by time interaction effect in which the relieving effect of CABG on angina changes over time to becomes less significant (the difference in changes in CCS angina class between CABG and Medical Therapy gets closer to zero) as follow-up time increases. However, at all time points, CABG consistently provided a larger decrease in change in CCS angina class compared to Medical Therapy.

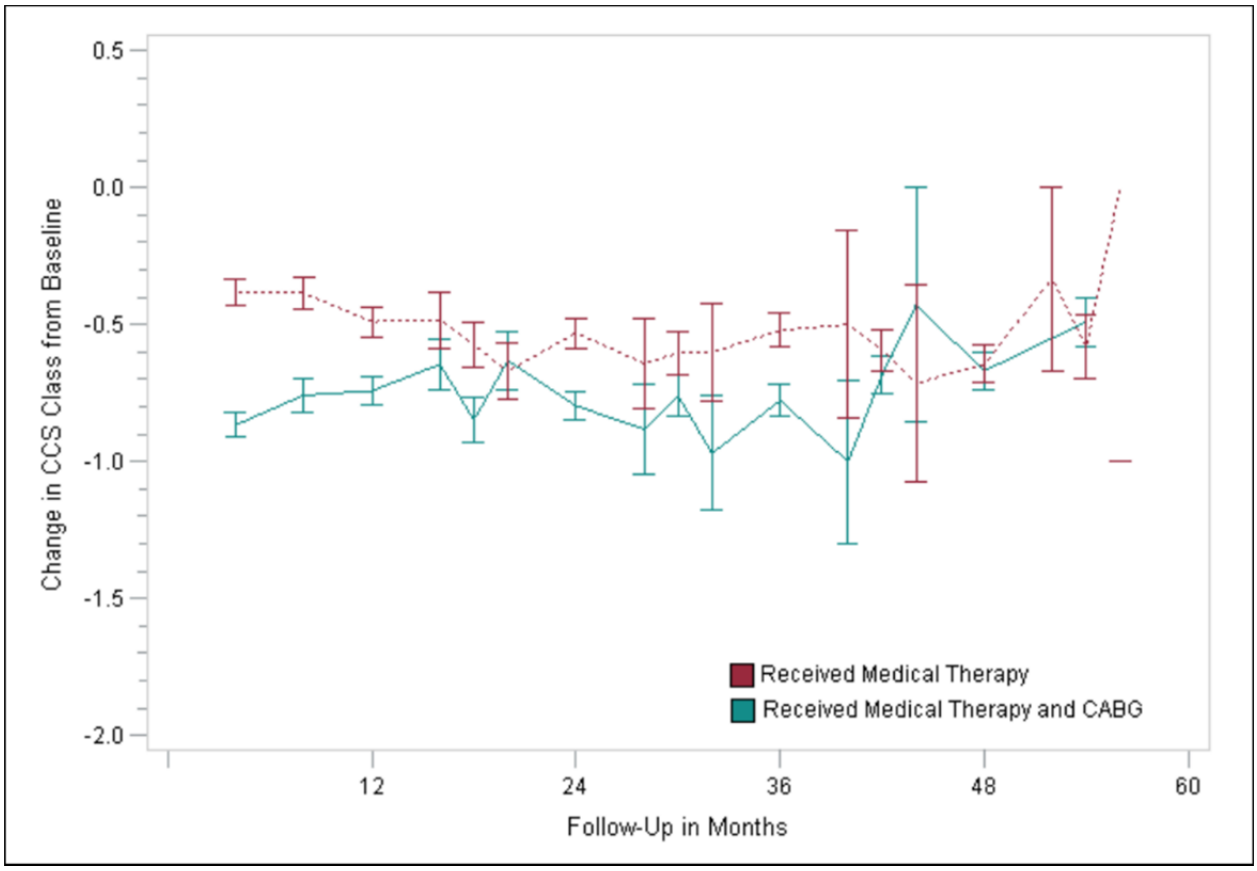
Supplementary Figure 1. Effect of Crossovers on Adjusted Cox Proportional Hazards Estimates of the Cumulative Risk of All-Cause Death According to Angina Status and Treatment Arm



Supplementary Figure 2. Variation in Angina Classes During Follow-Up



Supplementary Figure 3. Patients Assigned to CABG Experienced a Larger Decreases in Angina Class at Follow-Up Compared to Medical Therapy.



Supplementary Table 1. Baseline Characteristics by Presence of Angina for Patients Assigned to Medical Therapy Alone

Characteristic	All Patients (N=602)	No Angina (N=225)	Angina (N=377)	p-Value
Age, yrs, median (IQR)	59 (53, 67)	60 (54, 69)	58 (53, 66)	<0.01
Sex				0.07
Male	527 (87.5%)	204 (90.7%)	323 (85.7%)	
Female	75 (12.5%)	21 (9.3%)	54 (14.3%)	
Race				<0.001
non-white	182 (30.2%)	50 (22.2%)	132 (35.0%)	
white	420 (69.8%)	175 (77.8%)	245 (65.0%)	
Body Mass Index (kg/m2), median (IQR)	27 (24, 30)	26 (24, 29)	27 (24, 30)	0.12
LVEF, median (IQR)	28 (22, 34)	27 (21, 34)	28 (23, 34)	0.17
Creatinine (mg/dL), median (IQR)	1.10 (0.93, 1.27)	1.10 (0.93, 1.30)	1.09 (0.93, 1.25)	0.27
Creatinine Clearance [Cockcroft Gault] (mL/min), median (IQR)	76.36 (61.10, 95.55)	74.39 (58.62, 93.17)	78.10 (63.06, 97.66)	0.06
Hemoglobin (g/dL), median (IQR)	14 (13, 15)	14 (13, 15)	14 (13, 15)	0.18
Diastolic blood pressure, median (IQR)	80 (70, 80)	72 (65, 80)	80 (70, 80)	<0.01
Systolic blood pressure, median (IQR)	120 (110, 130)	120 (110, 130)	120 (110, 130)	0.03
Pulse pressure (mmHg), median (IQR)	45 (40, 50)	42 (36, 54)	45 (40, 50)	0.76
Atrial fibrillation or flutter				<0.01
No	525 (87.2%)	184 (81.8%)	341 (90.5%)	
Yes	77 (12.8%)	41 (18.2%)	36 (9.5%)	
Peripheral vascular disease				0.73
No	507 (84.2%)	188 (83.6%)	319 (84.6%)	
Yes	95 (15.8%)	37 (16.4%)	58 (15.4%)	
Myocardial infarction				<0.001
No	130 (21.6%)	69 (30.7%)	61 (16.2%)	
Yes	472 (78.4%)	156 (69.3%)	316 (83.8%)	
Mitral regurgitation				0.36
None or trace	222 (37.1%)	89 (40.1%)	133 (35.3%)	
Mild <= 2+	261 (43.6%)	89 (40.1%)	172 (45.6%)	
Moderate 3+	98 (16.4%)	35 (15.8%)	63 (16.7%)	
Severe 4+	18 (3.0%)	9 (4.1%)	9 (2.4%)	
Current NYHA heart failure class				<0.001
I	74 (12.3%)	41 (18.2%)	33 (8.8%)	
II	307 (51.0%)	104 (46.2%)	203 (53.8%)	
III	205 (34.1%)	69 (30.7%)	136 (36.1%)	
IV	16 (2.7%)	11 (4.9%)	5 (1.3%)	
Duke CAD Index (0-100), median (IQR)	65 (39, 77)	52 (39, 77)	65 (39, 77)	0.03

Characteristic	All Patients (N=602)	No Angina (N=225)	Angina (N=377)	p-Value
Nitrate at baseline				<0.001
No	293 (48.7%)	148 (65.8%)	145 (38.5%)	
Yes	309 (51.3%)	77 (34.2%)	232 (61.5%)	
Beta blocker at baseline				0.94
No	73 (12.1%)	27 (12.0%)	46 (12.2%)	
Yes	529 (87.9%)	198 (88.0%)	331 (87.8%)	

Patients who reported angina at baseline had higher diastolic blood pressure, higher rates of prior MI, higher NYHA heart failure classification and were more likely to be taking nitrates compared to patients who did not report angina.

BMI, body mass index; CAD, coronary artery disease; CCS, Canadian Cardiovascular Society; mmHg, millimeters of mercury; IQR, interquartile range; mmHg, millimeters of mercury; NYHA, New York Heart Association; No, number; Yrs, years.

Supplementary Table 2A. Predictors of All-Cause Death for Patients Assigned to Medical Therapy Alone with angina dichotomized as Yes vs. No

	All Cause Death		
Patient Characteristic	**χ2**	**HR (95% CI)**	**P-Value**
LVEF (per 5%)	14.95	0.86 (0.79-0.93)	<0.001
Log of Creatinine (doubling)	7.36	1.53 (1.12-2.07)	<0.01
Baseline Diastolic BP [70 to 85mmHg] (per 10 mmHg)	7.22	1.49 (1.11-1.99)	<0.01
Hemoglobin ≤ 14 g/dL (per 1 g/dL)	6.37	0.86 (0.76-0.97)	0.01
Mitral Regurgitation (Severe+Moderate vs. None+Mild)	5.9	1.46 (1.08-1.97)	0.02
Age ≤ 55 (per 5 years)	4.85	0.80 (0.66-0.98)	0.03
Baseline Diastolic BP [< 70 mmHg] (per 10 mmHg)	3.97	0.74 (0.55-0.995)	0.04
Age > 55 (per 5 years)	3.57	1.10 (0.996-1.21)	0.05
Atrial Fibrillation / Flutter	3.17	1.38 (0.97-1.98)	0.07
Hemoglobin > 14 g/dL (per 1 g/dL)	0.64	1.06 (0.92-1.24)	0.42
Baseline Diastolic BP [> 85mmHg] (per 10 mmHg)	0.44	0.86 (0.55-1.35)	0.51
Angina (Yes vs. No)	0.1	1.05 (0.79-1.38)	0.74

LVEF, left ventricular ejection fraction

Supplementary Table 2B. Predictors of All-Cause Death for Patients Assigned to Medical Therapy Alone, with Angina Stratified as Absent, Mild, or Moderate to Severe

	All Cause Death		
Patient Characteristic	**χ2**	**HR (95% CI)**	**P-Value**
LVEF (per 5%)	23.85	0.87 (0.82, 0.92)	<0.001
Log of Creatinine [0 to 0.4] (doubling)	15.52	3.17 (1.79, 5.63)	<0.001
Age > 55 (per 5 years)	9.69	1.12 (1.04, 1.20)	<0.01
Mitral Regurgitation (Severe+Moderate vs. None+Mild)	8.95	1.40 (1.12, 1.75)	<0.01
Beta Blocker at Baseline	5.63	0.74 (0.58, 0.95)	0.02
Moderate to severe Angina (CCS > 1 vs. CCS = 0)	5.34	1.27 (1.04, 1.57)	0.02
Atrial Fibrillation/Flutter	4.87	1.34 (1.03, 1.73)	0.03
Peripheral Vascular Disease	4.54	1.30 (1.02, 1.65)	0.03
Body Mass Index ≤ 35 (per 1 unit)	4.13	0.98 (0.95, 0.999)	0.04
Treatment (CABG vs. Medical Therapy Only)	3.73	0.83 (0.69, 1.00)	0.05
Age ≤ 55 (per 5 years)	2.16	0.88 (0.75, 1.03)	0.11
Mild Angina (CCS = 1 vs. CCS = 0)	0.14	1.06 (0.79, 1.41)	0.71

LVEF, left ventricular ejection fraction

Supplementary Table 3. Survival Analysis for Medical Therapy Alone vs. CABG, with Angina

Event	Medical therapy alone (n=770)	CABG + Medical therapy (n=442)	Adjusted Hazard Ratio for CABG + Medical Therapy (95% CI)	P-Value
No Angina at Baseline (n=442)	(n = 225)	(n = 217)		
All-cause death			0.68 (0.50, 0.94)	0.02
No. of events (Crude event rate, %)	96 (42.7%)	71 (32.7%)		
Kaplan-Meier estimate of 5-year event rate (%)	41.0%	31.9%		
All-cause death or all-cause hospitalization			0.80 (0.64, 1.00)	0.05
No. of events (Crude event rate, %)	172 (76.4%)	149 (68.7%)		
Kaplan-Meier estimate of 5-year event rate (%)	79.0%	68.1%		
Angina at Baseline (CCS = 1) (n =187)	(n = 91)	(n = 96)		
All-cause death			0.83 (0.49, 1.39)	0.47
No. of events (Crude event rate, %)	35 (38.5%)	33 (34.4%)		
Kaplan-Meier estimate of 5-year event rate (%)	37.1%	34.0%		
All-cause death or all-cause hospitalization			0.59 (0.40, 0.86)	<0.01
No. of events (Crude event rate, %)	69 (%)	64 (%)		
Kaplan-Meier estimate of 5-year event rate (%)	77.0%	62.3%		
Angina at Baseline (CCS > 1)(n =583)	(n = 286)	(n = 297)		
All-cause death			0.94 (0.73, 1.23)	0.66
No. of events (Crude event rate, %)	114 (39.9%)	114 (38.4%)		
Kaplan-Meier estimate of 5-year event rate (%)	40.9%	37.9%		
All-cause death or all-cause hospitalization			0.84 (0.69, 1.03)	0.09
No. of events (Crude event rate, %)	201 (70.3%)	186 (62.6%)		
Kaplan-Meier estimate of 5-year event rate (%)	70.7%	64.6%		

Stratified as Absent, Mild, or Moderate to Severe

P interaction for angina*treatment (medical therapy alone or CABG) p = 0.26 for all-cause death; p = 0.91 for all-cause death and all-cause hospitalization.

Supplementary Table 4. As Treated Analysis: Effect of Crossovers on the Stratified Survival Analysis for CABG vs. Medical Therapy alone by Presence of Angina at Baseline

Event	Medical therapy alone (n=592)	CABG + Medical therapy (n=620)	Adjusted Hazard Ratio for CABG + Medical Therapy (95% CI)	p-Value
No Angina at Baseline	(n = 236)	(n = 206)		
All-cause death			0.64 (0.47, 0.88)	<0.01
No. of events (Crude event rate, %)	99 (41.9%)	68 (33.0%)		
Kaplan-Meier estimate of 5-year event rate (%)	41.9%	30.9%		
Adjusted Cox proportional hazard estimates of cumulative risk of all-cause death at 5 years (%)	28.2%	20.1%		
Angina at Baseline	(n = 348)	(n = 422)		
All-cause death			0.67 (0.53, 0.85)	<0.001
No. of events (crude event rate, %)	161 (46.3%)	135 (32.0%)		
Kaplan-Meier estimate of 5-year event rate (%)	44.7%	32.6%		
Adjusted Cox proportional hazard estimates of cumulative risk of all-cause death at 5 years (%)	35.9%	25.1%		

All-cause death analysis was adjusted for LVEF, age, BMI (<35), log of creatinine (0 to 0.4), peripheral vascular disease, mitral regurgitation, beta blocker at baseline, atrial fibrillation / flutter. P interaction for angina and treatment (medical therapy alone or CABG), p = 0.74

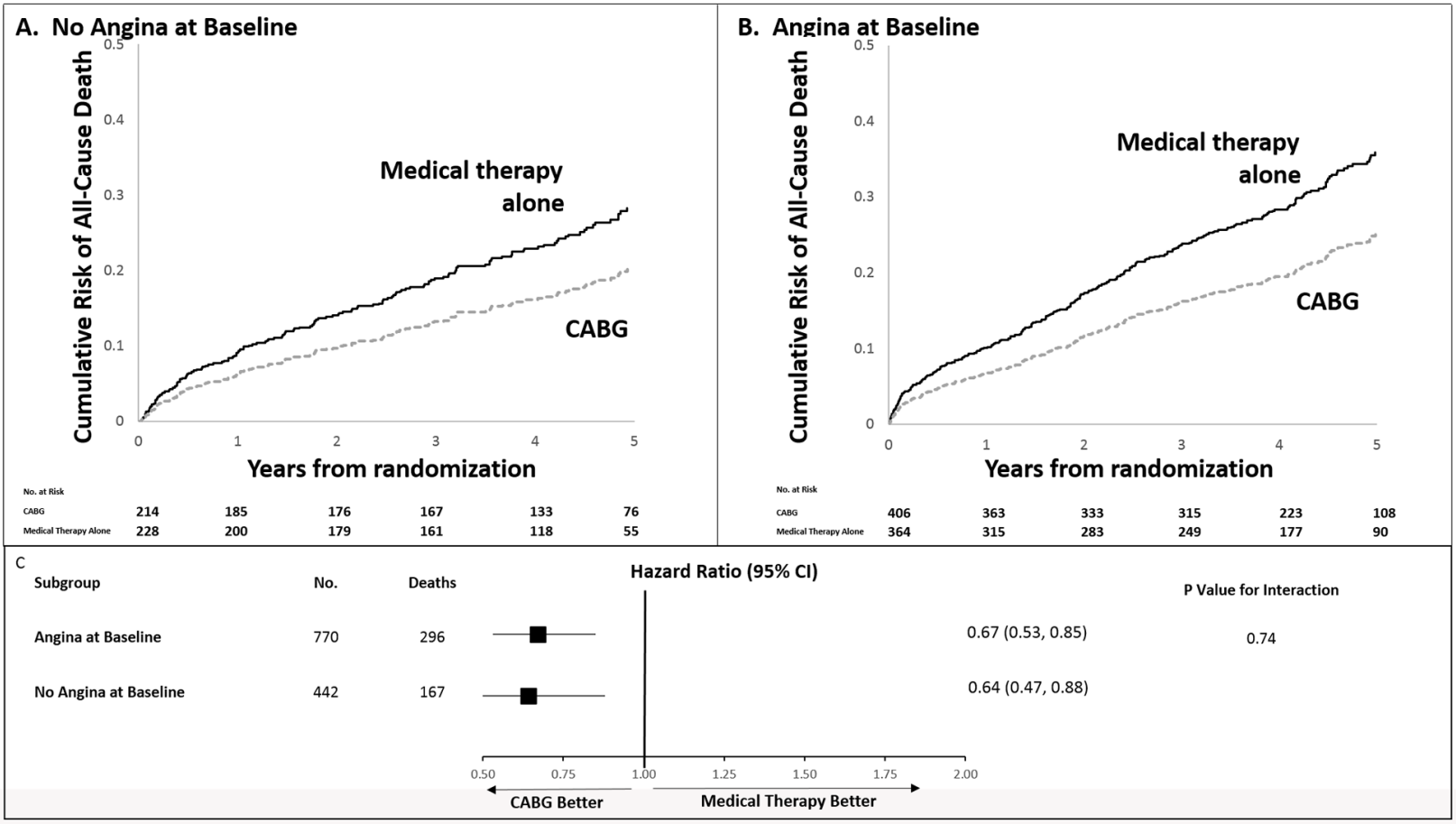
BMI, body mass index; CABG, coronary artery bypass grafting; KM, Kaplan Meier; LVEF, left ventricle ejection fraction; No, number; NYHA, New York Heart Association

Supplementary Table 5. Cardiovascular endpoints for Medical Therapy Alone vs. CABG by Presence of Angina at Baseline

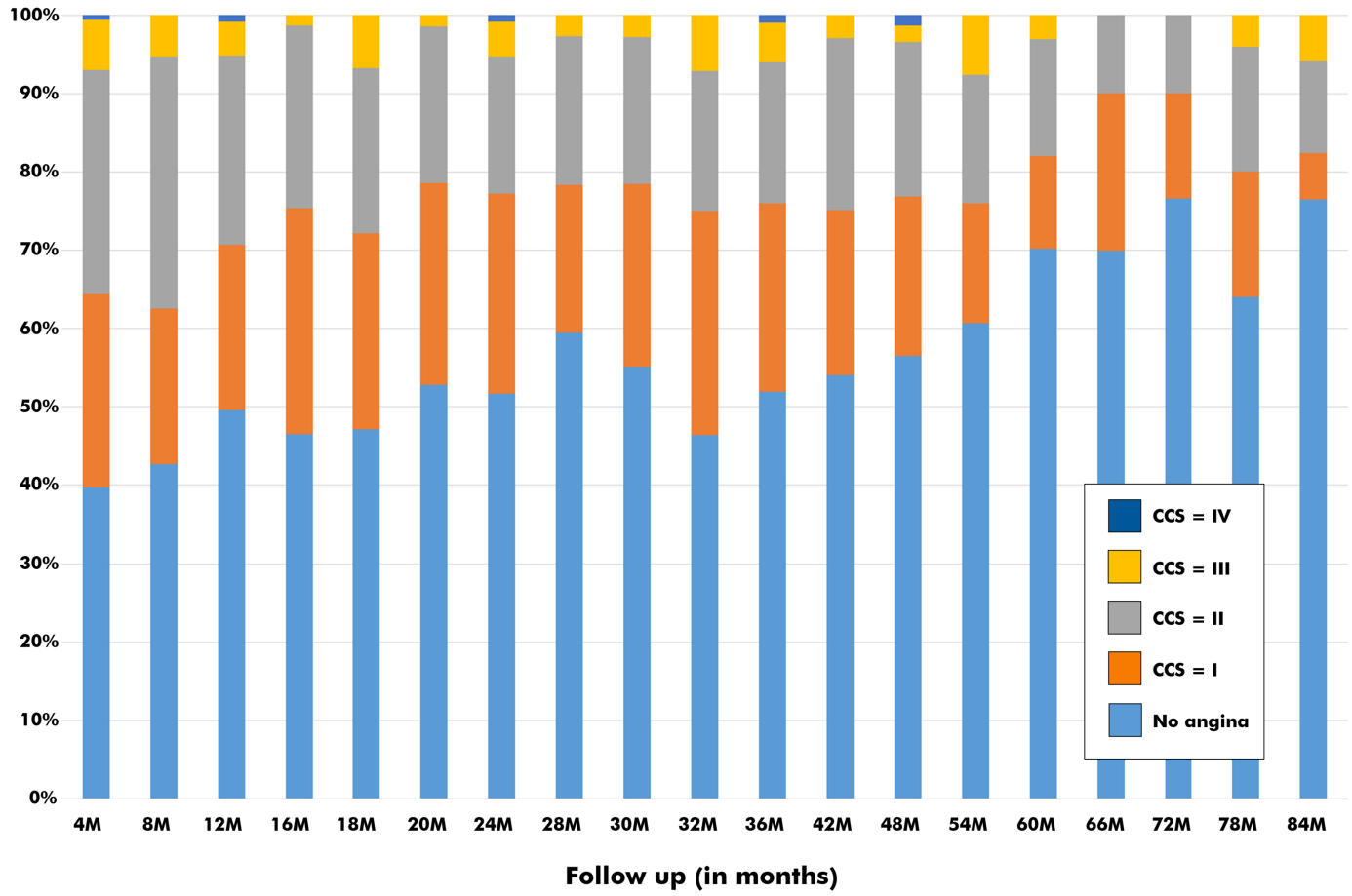
	No Angina at Baseline (n=442)			Angina at Baseline (n =770)			
Events No. (Crude event rate, %)	**Medical therapy alone (n=225)**	**CABG + Medical therapy (n=217)**	**HR for CABG + Medical Therapy (95% CI)****	**Medical therapy alone (n=377)**	**CABG + Medical therapy (n=393)**	**HR for CABG + Medical Therapy (95% CI)****	*p* interaction
Cardiovascular death	80 (35.6%)	53 (24.4%)	0.64 (0.45-0.91)	121 (32.1%)	115 (29.2%)	0.92 (0.71-1.19)	0.10
Cardiovascular hospitalization	110 (48.9%)	81 (37.3%)	0.68 (0.51-0.91)	172 (45.6%)	130 (33.1%)	0.66 (0.52-0.83)	0.90
Revascularization*	35 (15.6%)	9 (4.1%)	0.52 (0.22-1.24)	93 (24.7%)	18 (4.6%)	0.16 (0.10-0.27)	0.39
Myocardial infarction*	15 (6.7%)	9 (4.1%)	0.52 (0.22-1.24)	27 (7.2%)	21 (5.3%)	0.71 (0.40-1.27)	0.54

*Endpoint not adjudicated; **unadjusted analysis

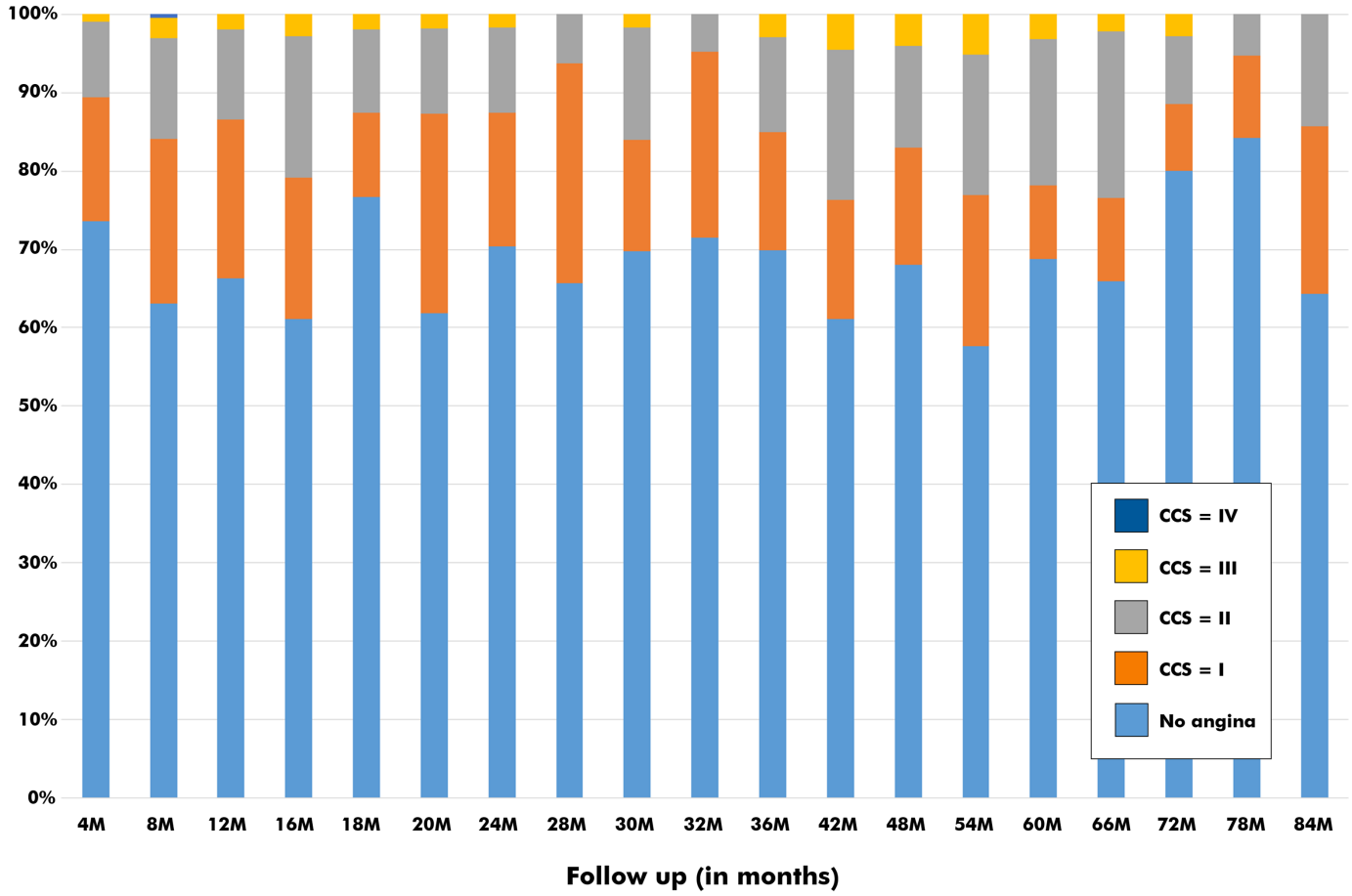
CABG, coronary artery bypass graft; CI, confidence interval; HR, Hazards ratio; No, number of events

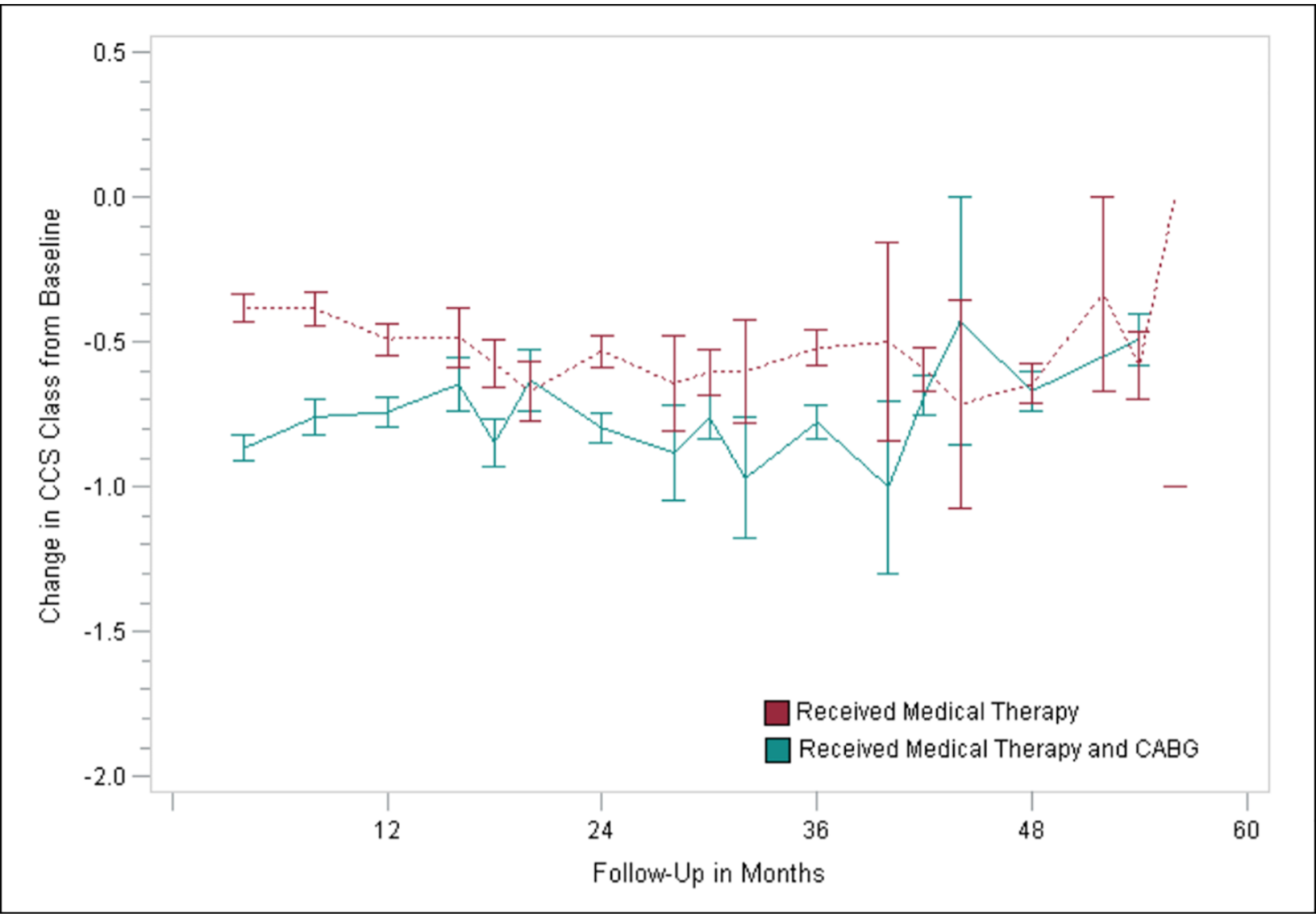

A. No Angina at Baseline
Cumulative Risk of All-Cause Death
0.5
0.4
0.3
0.2
0.1
0
Medical therapy alone
CABG
0
1
2
3
4
5
Years from randomization
No. at Risk
CABG 214 185 176 167 133 76
Medical Therapy Alone 228 200 179 161 118 55
B. Angina at Baseline
Cumulative Risk of All-Cause Death
0.5
0.4
0.3
0.2
0.1
0
Medical therapy alone
CABG
0
1
2
3
4
5
Years from randomization
No. at Risk
CABG 406 363 333 315 223 108
Medical Therapy Alone 364 315 283 249 177 90
C
Subgroup
No.
Deaths
Hazard Ratio (95% CI)
P Value for Interaction
Angina at Baseline 770 296 0.67 (0.53, 0.85) 0.74
No Angina at Baseline 442 167 0.64 (0.47, 0.88)
0.50
0.75
1.00
1.25
1.50
1.75
2.00
CABG Better
Medical Therapy Better

a. Medical Therapy Alone



b. Coronary Artery Bypass Grafts + Medical Therapy




0.5
0.0
-0.5
-1.0
-1.5
-2.0
Change in CCS Class from Baseline
12
24
36
48
60
Follow-Up in Months
Received Medical Therapy
Received Medical Therapy and CABG

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Article entitled: Importance of Angina in Patients with Left Ventricular Systolic Dysfunction and Coronary Artery Disease: Insights from the STICH Trial

Manuscript number: JACC052615-1764

Corresponding Author: Dr. Jolicoeur

Corresponding author's printed name: E. Marc Jolicoeur

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Manuscript number: JACC052615-1764

Corresponding Author: Dr. Jolicoeur

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