

Importance of Angina in Patients With Coronary Disease, Heart Failure, and Left Ventricular Systolic Dysfunction

Insights From STICH



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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 This study investigated: 1) whether angina was associated with a worse prognosis; 2) whether 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 STICH (Surgical Treatment for Ischemic Heart Failure) trial, in which 1,212 patients with an ejection fraction $\leq 35\%$ 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. Among patients assigned to medical therapy, all-cause mortality was similar in patients with and without angina (hazard ratio [HR]: 1.05; 95% confidence interval [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 (odds ratio: 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](https://clinicaltrials.gov/ct2/show/study/NCT00023595)) (J Am Coll Cardiol 2015;66:2092-100)
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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 than from medical therapy alone in randomized controlled trials (5,6).

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Clinical guidelines identify angina as an important consideration for the decision of 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, which might indicate a better prognosis, or have cardiac denervation that renders myocardial ischemia silent or have 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 STICH (Surgical Treatment for Ischemic Heart Failure) 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 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 who were enrolled in the surgical revascularization hypothesis part of the trial 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 previously (12). The National Heart, Lung, and Blood Institute 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 as median and interquartile range and were compared using Wilcoxon rank sum tests. Discrete variables are presented as counts (percentages) and were compared with either the Pearson 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, because this analysis should be considered exploratory rather than definitive. Data analyses were performed with the 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.

ABBREVIATIONS AND ACRONYMS

CABG = coronary artery bypass grafting

CAD = coronary artery disease

CCS = Canadian Cardiovascular Society

CI = confidence interval

HR = hazard ratio

LV = left ventricular

Health, Bethesda, Maryland. This work is solely the responsibility of the authors and does not necessarily represent the official views of the NHLBI or National Institutes of Health. Dr. Jolicœur is supported by research grants from les Fonds la Recherche du Québec en santé (FRQS), the Canadian Institutes for Health Research (CIHR), and la Fondation de l'Institut de Cardiologie de Montréal. Dr. Sun has served on an advisory committee for Sunshine Heart. Dr. Velazquez has received research grants from Alnylam Pharmaceuticals and GlaxoSmithKline; research funding from the NHLBI; served on the speakers bureau for Novartis; and has served on advisory committees for Novartis and Merck. Dr. Cleland has received research grants, has received speakers fees from, and served on advisory boards for Amgen, Servier, and Novartis. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

TABLE 1 Baseline Characteristics by Presence of Angina in the STICH Trial

	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, yrs	59 (53-66)	61 (54-69)	<0.001
Male	671 (87.1)	393 (88.9)	0.37
BMI, kg/m ²	27 (24-30)	27 (24-30)	0.76
Race or ethnic group			<0.001
White	494 (64.2)	333 (75.3)	
Hispanic, Latino, or nonwhite	276 (35.8)	109 (24.7)	
Medical history			
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, mm Hg	120 (110-130)	120 (110-130)	0.002
CCS class			
0	—	442 (100)	
I	187 (24.3)	—	
II	525 (68.2)	—	
III	48 (6.2)	—	
IV	10 (1.3)	—	
NYHA functional class			<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, g/dl	14 (13-15)	14 (13-15)	0.23
Creatinine, mg/dl	1.09 (0.94-1.24)	1.10 (0.94-1.30)	0.04
LVEF, %	28 (22-34)	27 (22-33)	0.06
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			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)	

Continued on the next page

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 to 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 (Online Appendix). For both analyses, adjustment for baseline risk factors was implemented using a multivariable Cox proportional hazards model to estimate the adjusted hazard ratio (HR) and its 95% confidence interval (CI) (15). In both models, the presence of angina was dichotomized as no angina (CCS = 0) versus angina (CCS = I 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 = I), or moderate or severe (CCS greater than I).

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 during follow-up. The robustness of the model was tested in a series of sensitivity analyses (Online Appendix).

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

RESULTS

STUDY POPULATION. Of 1,212 patients enrolled, 770 (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 (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 for 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 and were more likely to have experienced a previous myocardial infarction and to have been 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 ($p = 0.52$).

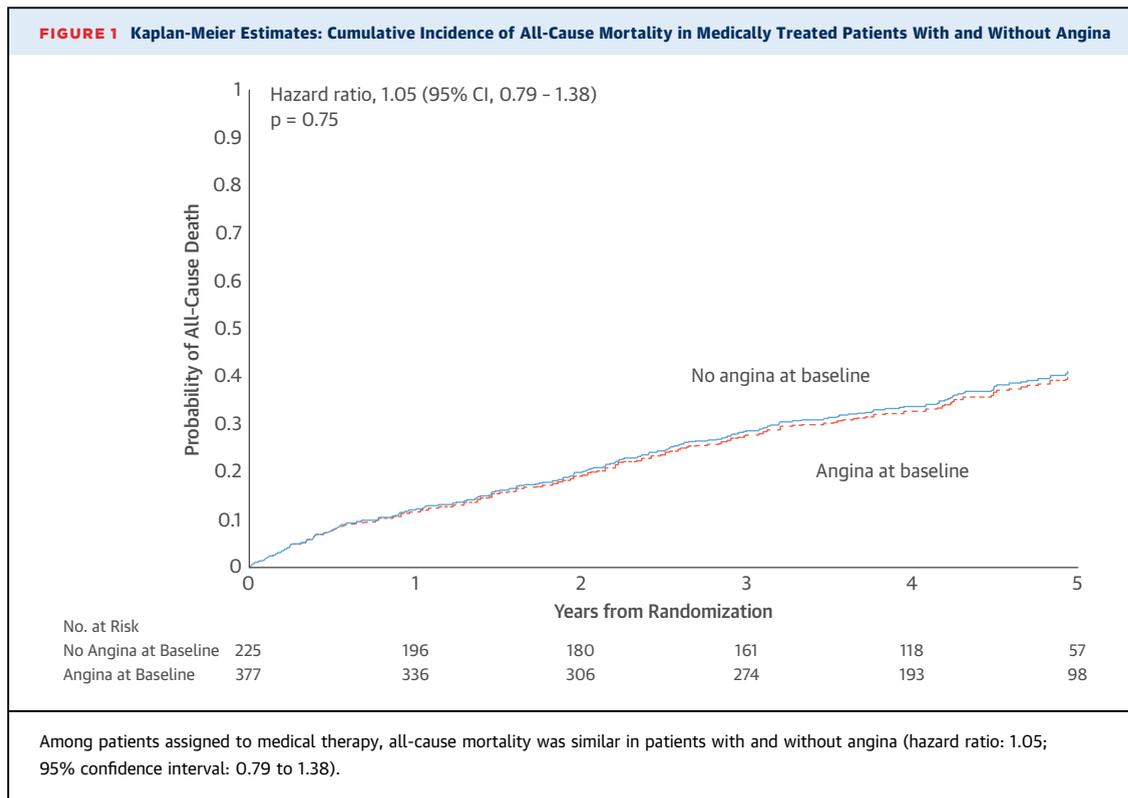
ANGINA AND OUTCOMES IN PATIENTS ASSIGNED TO MEDICAL THERAPY ALONE. Baseline characteristics of patients assigned to medical therapy alone with and without angina are compared in Online Table 1. Among patients assigned to medical therapy alone ($n = 602$), the presence or absence of angina at baseline 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, Online Table 2A). However, after stratification, moderate to severe angina (CCS II or greater) compared with no angina was associated with greater all-cause mortality, but only after adjusting for other variables (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; $p = 0.64$).

TABLE 1 Continued

	Angina (n = 770)	No Angina (n = 442)	p Value
Angiographic information			
Duke CAD index	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			
Beta-blockers	662 (86.0)	374 (84.6)	0.52
Long-acting nitrates	484 (62.9)	162 (36.7)	<0.001

Values are n (%) or median (interquartile range). For SPECT, patients with viability were defined as those with ≥ 11 viable segments (out of 16) on the basis of relative tracer activity. For dobutamine echocardiography, patients with viability were defined as those with ≥ 5 segments (out of 17) with abnormal resting systolic function but manifesting contractile reserve during dobutamine administration. *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; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; STICH = Surgical Treatment for Ischemic Heart Failure.

INFLUENCE OF ANGINA ON THE IMPACT OF CABG ON ALL-CAUSE DEATH, HOSPITALIZATIONS, AND CARDIOVASCULAR ENDPOINTS. Among 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; $p = 0.34$). Among patients without angina, mortality was lower for 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 stratification of 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 greater than I (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 are presented in Online Table 5.

EFFECT OF CABG AND MEDICAL THERAPY ON RELIEF OF ANGINA. Eighty-five patients died in the

hospital after CABG or in the interval before the first follow-up outpatient visit at 4 months. Among the remaining 1,127 patients, an evaluation of angina was available in 1,089 (97%), with a median follow-up 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 plus 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 to 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

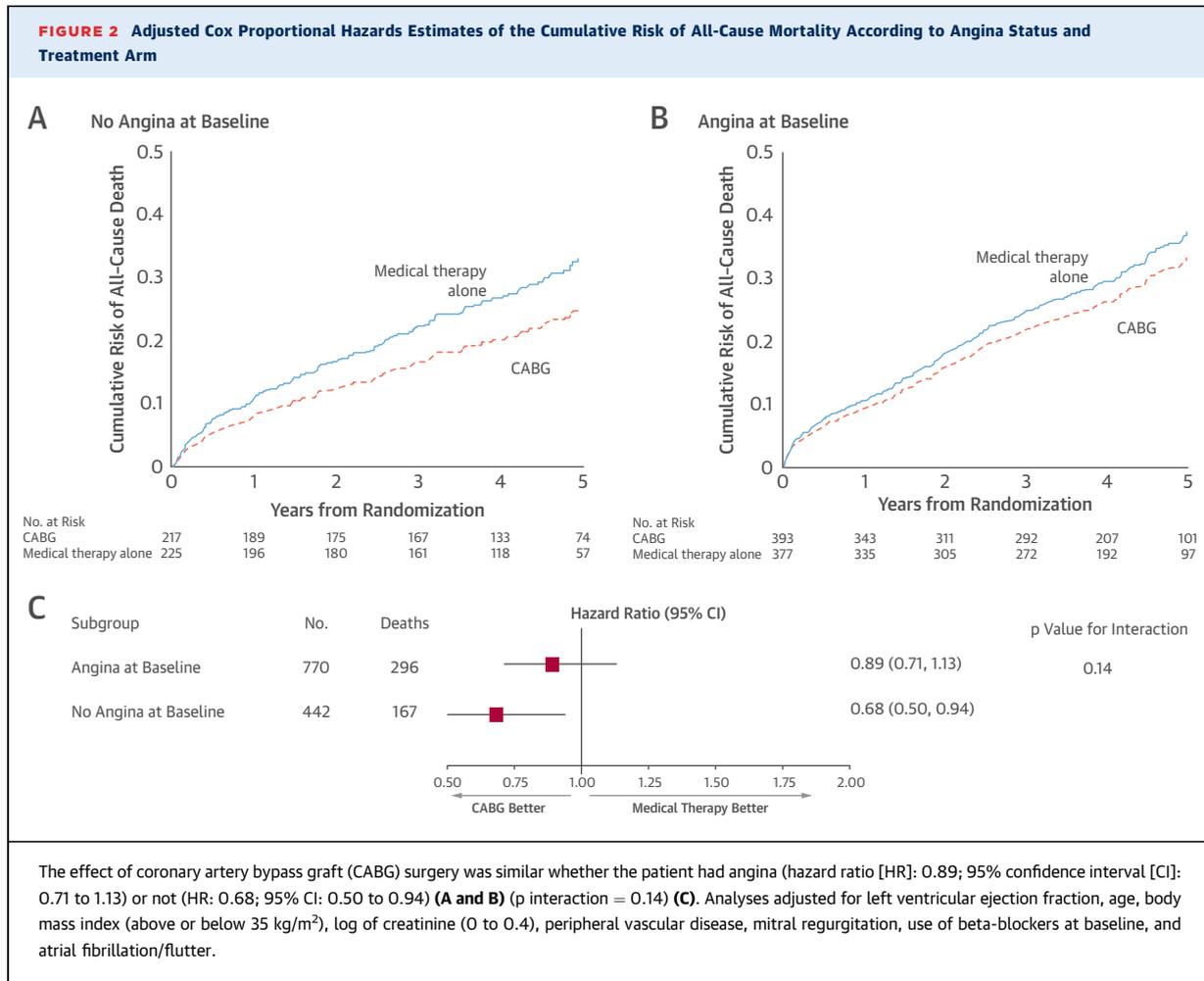
These analyses of the STICH trial are the first to investigate the impact of angina on outcomes in a randomized controlled study evaluating the benefits of CABG in patients with CAD, heart failure, and LV systolic dysfunction. Angina does not predict prognosis in medically treated patients with known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

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

Event	Medical Therapy Alone (n = 602)	CABG Plus Medical Therapy (n = 610)	Adjusted HR (95% CI) for CABG Plus Medical Therapy*†	p Value
No angina at baseline (n = 442), n				
All-cause mortality	225	217	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				
All-cause mortality	377	393	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-yr 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 (yrs), BMI (<35 kg/m²), log of creatinine (0 to 0.4 mg/dl), peripheral vascular disease, mitral regurgitation, beta-blocker use at baseline, and atrial fibrillation/flutter. The p interaction for angina and treatment (medical therapy alone or CABG) was 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 (g/dl) mitral regurgitation, and NYHA classification. The p interaction for angina and treatment (medical therapy alone or CABG) was 0.99. The following values were assigned to baseline covariates for adjusted event rates: age = 60 yrs; LVEF = 28%; BMI = 27 kg/m²; log2(creatinine) = 0.14; peripheral vascular disease = 0.15; mitral valve regurgitation (moderate/severe) = 0.18; beta-blocker = 0.85; and atrial fibrillation/flutter = 0.13.

CI = confidence interval; HR = hazard ratio; KM = Kaplan-Meier; other abbreviations as in Table 1.



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 improved 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.

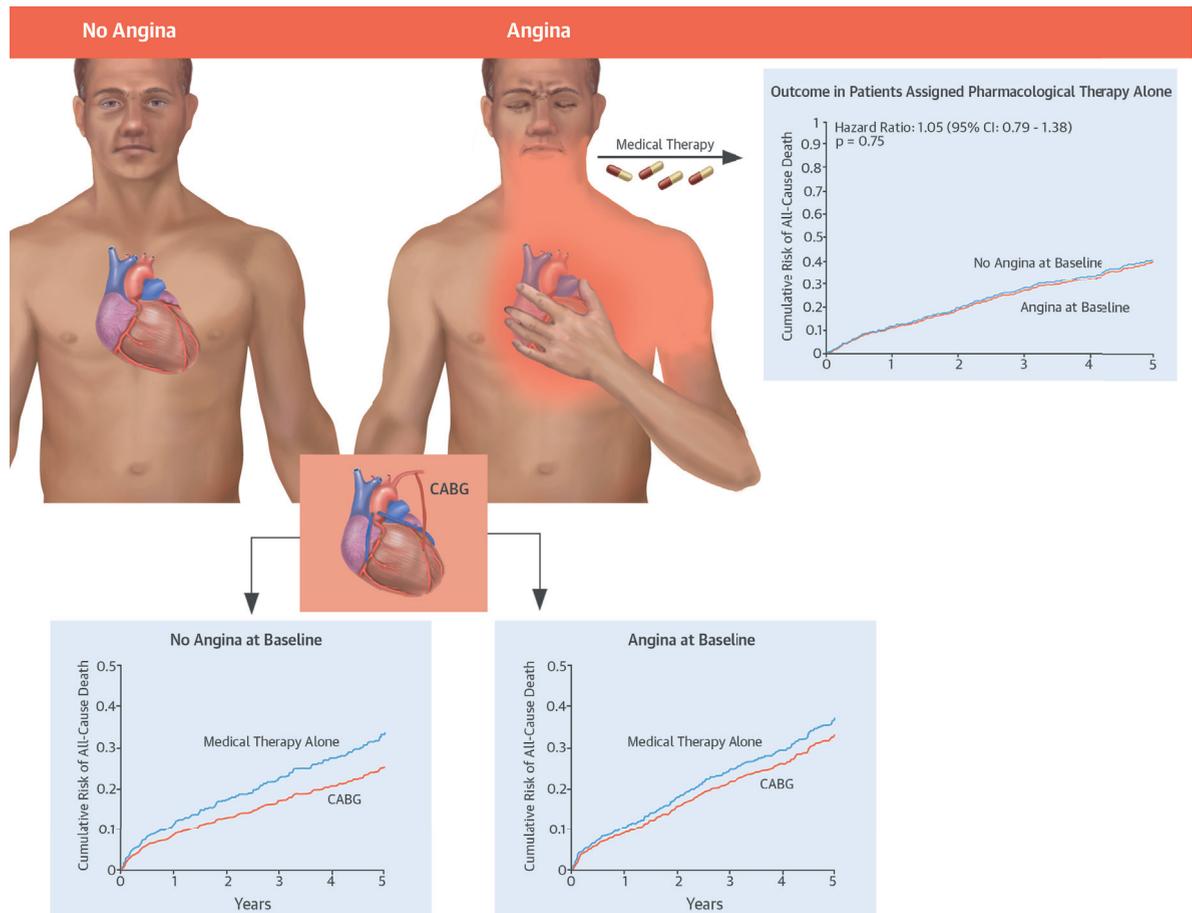
Among patients with severe LV dysfunction, CABG is associated with an early risk of serious complications, including death (16). Findings from this study challenge the perceived benefit-risk balance for CABG in patients with and without angina. Although revascularization should be considered for symptom relief for patients with heart failure and angina recalcitrant to pharmacological therapy, 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

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 with adjustment for anti-anginal 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. OR = odds ratio; other abbreviations as in Tables 1 and 2.

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

Jolicœur, E.M. *et al.* J Am Coll Cardiol. 2015; 66(19):2092-100.

The presence of angina does not confer a markedly poorer prognosis in medically treated patients. By intention-to-treat analysis, mortality rates are similar in patients assigned to coronary artery bypass graft surgery (CABG) or to medical therapy whether angina is present or not. Patients treated with CABG have greater improvement in Canadian Cardiology Society angina class than 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 coronary artery disease, heart failure, and LV systolic dysfunction for CABG. LV = left ventricular; STICH = Surgical Treatment for Ischemic Heart Failure.

strategy. These findings conflict with the opinion expressed in several clinical practice guidelines, which infer that angina is a marker of both a poorer prognosis and a greater likelihood of prognostic benefit from revascularization. The European Society of Cardiology recommends coronary revascularization when angina persists despite treatment with 2 antianginal 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

percutaneous coronary intervention in patients with CAD and LV systolic dysfunction should be based on 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 have suggested that angina is associated with a worse

outcome (14), but this may be because angina is a marker that confirms 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), which suggests 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. REVIVED-BCIS2 (Study of Efficacy and Safety of Percutaneous Coronary Intervention to Improve Survival in Heart Failure) 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, in part because of 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, when the severity of CAD (25) and the extent of myocardial dysfunction are both taken into account, they do appear to influence the benefits of CABG.

STUDY LIMITATIONS. The present study was 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 that 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 used; 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 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 in treatment decisions and prognostication in patients with ischemic cardiomyopathy.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The occurrence of angina pectoris is not a predictor of mortality in medically treated patients with coronary artery disease and left ventricular systolic dysfunction. Bypass surgery (CABG) is more effective than medical therapy in relieving angina and may lower 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. Further studies to confirm or refute a reduction in mortality with coronary revascularization in patients with heart failure are necessary.

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APPENDIX For an expanded Methods section, please see the online version of this article.