Circulation
Heart Failure
JOURNAL OF THE AMERICAN HEART ASSOCIATION

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Circ Heart Fail 2013;6;443-450; originally published online March 20, 2013;
DOI: 10.1161/CIRCHEARTFAILURE.112.000130
Circulation: Heart Failure is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 1941-3289. Online ISSN: 1941-3297

Influence of Crossover on Mortality in a Randomized Study of Revascularization in Patients With Systolic Heart Failure and Coronary Artery Disease

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Background—To assess the influence of therapy crossovers on treatment comparisons and mortality at 5 years in patients with ischemic heart disease and heart failure randomly assigned to medical therapy alone (MED) or to MED and coronary artery bypass graft (CABG) surgery in the Surgical Treatment for Ischemic Heart Failure (STICH) trial.

Methods and Results—The influence of early crossover (within the first year after randomization) on 5-year mortality was assessed using time-dependent multivariable Cox models. CABG was performed in 65/602 patients (10.8%) assigned to MED, and 55/610 patients (9.0%) assigned to CABG received MED only. Common reasons for crossover from MED to CABG were progressive symptoms or acute decompensation. MED-assigned patients who underwent CABG had lower 5-year mortality than those who received MED only (25% vs 42%; hazard ratio, 0.50; 95% confidence interval, 0.30–0.85; P=0.008).The main reason for crossover from CABG to MED was patient/family decision. Five patients did not undergo their assigned CABG within a year but died before receiving surgery without status change. They were deemed crossover to MED. The CABG-to-MED crossover population had higher 5-year mortality compared with those treated with CABG per-protocol (59% vs 33%; hazard ratio, 2.01; 95% confidence interval, 1.36–2.96; P<0.001). CABG was associated with lower mortality compared with MED in per-protocol and several time-dependent analyses (all P<0.05).

Conclusions—CABG reduced mortality in both the per-protocol and crossover STICH patient populations. Crossover from assigned therapy, therefore, diminished the impact of CABG on survival in STICH when analyzed by intention to treat.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00023595. **(*Circ Heart Fail.* 2013;6:443-450.)**

Key Words: coronary bypass surgery ■ heart failure ■ medical therapy

Patient enrollment into trials evaluating the effect of a major surgical procedure is challenging. Doctors, patients, and patient families often have strong views on the merits of specific treatments that may change treatment choice in response to changing circumstances. The characteristics of patients selected for trials influence their enrollment. Even with careful study design and conduct, a substantial proportion of patients may deviate from their assigned treatment after randomization.[1,2]

Clinical Perspective on p 450

The surgical revascularization hypothesis of the Surgical Treatment for Ischemic Heart Failure (STICH) trial compared a strategy of guideline-indicated medical therapy alone (MED) with a similar strategy combined with coronary artery bypass graft (CABG) surgery in 1212 patients with left ventricular systolic dysfunction and coronary artery disease (CAD).[3] STICH is a National Institutes of Health–funded, international multicenter trial conducted at 96 hospitals with documented expertise in the treatment of patients with heart failure. On the basis of a median follow-up of 56 months, intention-to-treat

Received October 18, 2012; accepted March 6, 2013.

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The online-only Data Supplement is available at http://circheartfailure.ahajournals.org/lookup/suppl/doi:101161/CIRCHEARTFAILURE.112.000130/DC1.

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Circ Heart Fail **is available at http://circheartfailure.ahajournals.org** **DOI: 10.1161/CIRCHEARTFAILURE.112.000130**

(ITT) analysis demonstrated a trend toward reduced all-cause mortality in those assigned to CABG (hazard ratio [HR], 0.86; 95% confidence interval [CI], 0.72–1.04; P=0.123) but an a priori as-treated comparison suggested a survival benefit for CABG (HR, 0.70; 95% CI, 0.58–0.84; P<0.001).[3] The STICH Extension Study (STICHES) will follow patients for 5 additional years and will provide definitive information in due course. In the interim, physicians and surgeons must use the best available evidence to advise patients about the need for coronary angiography and revascularization. Because the difference between the ITT and the as-treated analyses is caused by the patients not following their assigned treatment (crossovers), we analyzed all crossover events specifically for their reasons of crossover. We here report these reasons and the subsequent outcome after crossover and the effect of those crossovers on the primary ITT analysis in the STICH trial.

Methods

Trial Design Provision for Crossover

In the STICH trial, the informed consent process used standardized videos, written information, and discussions with investigators to inform patients that consenting to the study meant they were willing to accept either MED or MED with CABG. Patients who declined to participate were free to choose their preferred treatment strategy. Patients who did consent were also informed that they were able to withdraw consent at any time.

The STICH protocol specified that pharmacological treatments should be optimized early after randomization for all patients.[4] For patients assigned to CABG, the operation should be done within 14 days of randomization. Randomization was accomplished using a telephone-based interactive voice response system. As set by the trial's protocol, the reasons for crossover were recorded only in the first year and the clinical information requested from the sites within the first year was free text and not prestructured responses guided by prespecified definitions. The rationale for this protocol set-up was the expected imbalance in early mortality between the MED and the CABG cohorts. The current report, therefore, addresses all crossover events that occurred in the first year (77.4% of all crossovers).

Detection and Documentation of Treatment Crossover

An early report was obtained in all patients at hospital discharge or 30 days after randomization. Subsequent follow-up clinical data were collected at 4, 8, and 12 months and at 6-month intervals thereafter for the study duration. Patients assigned to CABG who did not receive surgery within 1 year after randomization were defined as crossover from CABG to MED. Patients who were assigned to MED who had CABG within 1 year after randomization were defined as an early crossover from MED to CABG. For each early crossover event, free-text narrative documents were collected by the investigative teams. Categorization of crossover reasons was performed on the basis of these documents. No attempt was made to identify the reasons for late crossover after 1 year from MED to CABG and such events were not considered in this analysis.

Categorization of Crossover Reasons

Three authors (T.D., J.R., and R.J.) used a 2-step Delphi process to develop 4 categories of MED-to-CABG crossover reasons and 4 categories of reasons for CABG-to-MED crossovers based on the perceived susceptibility of the early crossover event to reflect possible bias of the enrolling investigators. The 4 categories created for MED-to-CABG crossover were (1) progressive symptoms (ie, worsening of angina or of heart failure or of the combination), (2) acute decompensation (ie, heart failure, myocardial infarction or angina; cardiac arrest or ventricular arrhythmias; or endocarditis), (3) clinician decision despite stable symptoms, (4) patient/family decision. The least to most susceptible to investigator bias categories of reasons created for CABG-to-MED crossover were (1) patient/family decision, (2) died before operation, (3) clinical decision, (4) research staff/provider miscommunication.

Documentation of Risk at Randomization

A risk at randomization (RAR) index was calculated for each patient enrolled in the study.[5] This predicted risk of 5-year mortality, assuming MED-only treatment, was based on prognostic factors identified from a multivariable Cox model analysis developed in a completely independent database of patients, namely STICH-eligible patients in the Duke Databank for Cardiovascular Diseases.[5] In the present report, the 1212 patients of the surgical revascularization hypothesis of the STICH trial were clustered into 1 of 3 tertile RAR groupings (RAR, 1–6; 7–16; 17–32) to assess the influence of baseline risk on crossover occurrence. In addition, the 5-year mortality rates of the 1092 patients who received their assigned randomized treatment of MED (n=537) or CABG (n=555) per-protocol and the 5-year mortality of the MED-to-CABG crossovers and the CABG-to-MED crossovers were tabulated by RAR grouping to help define the relationship of baseline risk to treatment effect on mortality.

Statistical Methods

HRs and associated 95% CIs for comparing CABG versus MED with respect to all-cause mortality were calculated using the Cox regression model with CABG as a time-dependent variable expanding on our previously presented analysis in the primary report.[4] A total of 5 different methods to account for death before CABG and for early crossover to CABG of patients assigned to MED were considered. A 0/1 time-dependent covariate was created to reflect the CABG-free interval after randomization and used with the Cox model to indicate whether and when a patient received CABG, thereby allowing an assessment of the CABG treatment effect from multiple different clinical scenarios. One of the modeling strategies initially set the time-dependent covariate to 0 for all 1212 H1 patients (no CABG) and changed the covariate value to 1 (indicating CABG was performed) on the day the operation occurred. This approach can be viewed as an as-treated analysis, and survival time prior to CABG (in the patients who undergo CABG) is thus credited to medical therapy. A second and closely related strategy assigned a value of 1 at the time of randomization to all patients randomized to CABG who actually underwent the operation. Two additional analyses were performed in which patients randomized to CABG but who died early before receiving CABG (within 30 days or within 60 days of randomization respectively) were credited to CABG (ie, early deaths among patients randomized to CABG that occurred before CABG was performed were attributed to the CABG arm). A fifth analysis was done by assigning 1 to all patients randomized to CABG at the time of randomization regardless of whether or not CABG was ever performed. In this latter analysis, all patients randomized to CABG were thus counted with the CABG patients regardless of whether they received CABG, whereas the CABG variable was set to 0 for MED-assigned patients at the time of randomization and only changed to 1 on the day of CABG as a crossover operation. This family of models provides a range of assessments of the treatment effects of CABG depending on various different ways of accounting for patients randomized to MED who crossed over to CABG and of delay or failure to undergo a timely CABG operation in patients randomized to the CABG arm.

Kaplan–Meier estimates of mortality as a function of time from randomization were calculated to characterize the mortality patterns of patients who adhered to their randomized treatment assignment, as well as the patients who crossed over from their treatment assignment during the first year following randomization. All analyses were performed using SAS statistical software, version 9.2 (SAS Institute, Cary, NC).

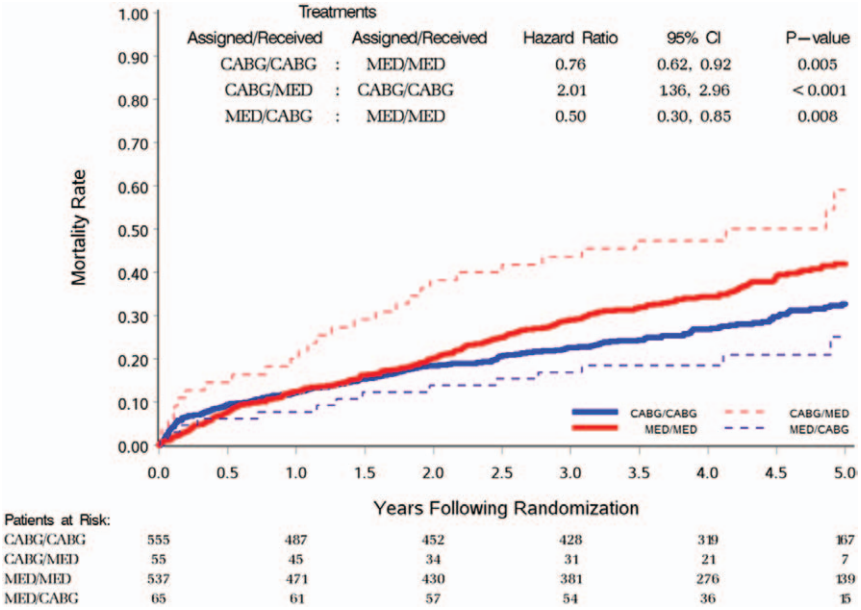

Figure 1. Kaplan–Meier analysis of patients assigned to coronary artery bypass graft (CABG; blue lines) or medical therapy alone (MED; red lines) either adhering (per-protocol) or not adhering (crossover) to their randomly assigned treatment.

Results

Of 602 patients assigned to MED, 537 (89%) remained in their assigned group and 65 crossed over to CABG within the first year after randomization. There were 35 additional MED patients who received CABG later during follow-up. Of 610 patients assigned to CABG, 555 (91%) received CABG within the first year after randomization at a median of 10 days (interquartile range, 5–16 days). The 55 CABG-assigned patients who did not receive CABG within 1 year of randomization were considered to have crossed over to MED.

Figure 1 shows the Kaplan–Meier (K–M) curves for the per-protocol and the crossover cohorts. Patients who were assigned to and received CABG in the first year had a lower 5-year mortality than MED patients who remained in their assigned group (HR, 0.76; 95% CI, 0.62–0.92; *P*=0.005). The 65 patients who were assigned to MED but received CABG had a lower 5-year mortality (14 deaths; K–M, 5-year rate 25%) than the 537 patients (208 deaths; K–M, 5-year rate 42%) randomized to MED who remained in their assigned group (HR, 0.50; 95% CI, 0.30–0.85; *P*=0.008). In contrast, the 55 patients assigned to CABG who did not receive surgery within 1 year of randomization had a higher 5-year mortality (29 deaths; K–M, 5-year rate 59%) than the 555 patients (167 deaths; K–M, 5-year rate 33%) who were randomized to and received CABG within 1 year (HR, 2.01; 95% CI, 1.36–2.96; *P*<0.001). To address the question why the CABG-to-MED crossovers had the worst and the MED-to-CABG crossovers had the best outcomes, we analyzed in detail the reasons for crossover (Figure 2) and the influence of individual risks as assessed by the RAR score (Table 1).

The adjudicated reasons for early crossover from MED to CABG are shown in Figure 2A and from CABG to MED in Figure 2B. Patients were grouped according to their RAR score as low (1–6), intermediate (7–16), and high risk (17–32). The main reason for crossover from MED to CABG was acute decompensation or progressive worsening of status/symptoms (44 of 65 patients). The most common reason for crossover from CABG to MED was a decision change by the patients or their families (37 of 55 patients). The clinical investigator responsible for the care of each patient made the decision to cross over from CABG to MED in only 11 cases. In 5 patients, the reason for crossover was deemed to be death before operation because no unavoidable reason for the interval between randomization and death was described in the free-text documents. Only 2 of these deaths occurred before the 14-day interval after randomization specified by protocol as the acceptable interval between randomization and CABG. Appendix I in the online-only Data Supplement provides a listing of all 120 early crossover patients with extraction of phrases from free-text documents provided by STICH investigators that best reflect the rationale for crossover of each patient.

Table 1 shows the relationship between risk at baseline (RAR score groups as in Figure 2) and 5-year mortality rates for patients who received their assigned therapy (per-protocol), as well as for those having crossed over. Five-year mortality rates rose as baseline risk increased, but in each case, mortality rates were lower in patients receiving CABG. On the basis of the information in Table 1 and Figure 2, no pattern indicative of outcome in the 2 crossover populations could be identified.

Table 2 shows the baseline risk spectrum of the per-protocol and the crossover patients. Patients assigned to MED who crossed over to CABG had more severe symptoms of angina (*P*=0.004), heart failure (*P*=0.003), and a lower 6-minute walk distance (*P*=0.024) compared with the patients assigned to MED who did not cross over. In contrast, patients assigned to CABG that crossed over to MED included more patients with previous bypass surgery (*P*=0.01), more prior percutaneous coronary intervention (*P*=0.056), and larger left ventricular end systolic volume index (*P*=0.036) compared with the patients assigned to CABG who did not cross over. However, none of these differences explain the outcome because the majority of patients crossing from CABG to MED did so on the basis of a family or patient decision, and the crossover patients did not differ in their level of risk (as assessed by the RAR score) from the per-protocol patients at the time of randomization.

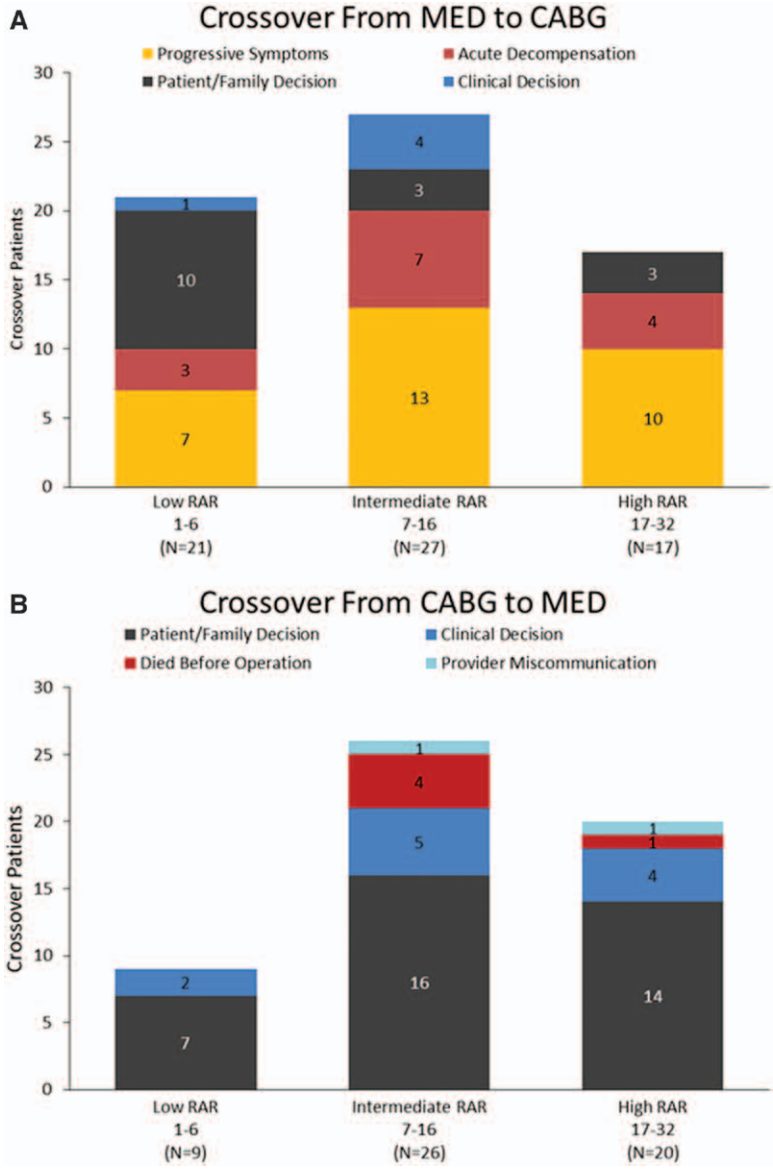

Figure 2. Crossover by reason (as adjudicated by a committee) with increasing risk at randomization (RAR) indices. The reasons for crossover are shown for medical therapy alone (MED)-to-coronary artery bypass graft (CABG) crossovers (**A**) and CABG-to-MED crossovers (**B**).

To assess the influence of time of crossover on outcome, we performed various Cox multivariable statistical models using CABG as a time-dependent variable. The results are graphically illustrated in Figure 3. Relative to the time of randomization, the figure depicts when the time-dependent covariate in the multivariable model was set or changed for a given patient to reflect the period of follow-up in which the patient was counted as a CABG patient. In the first analysis

Table 1. Influence of Risk at Randomization on Difference in 5-Year Mortality Rate of 1212 Patients Randomized to MED (n=602) or CABG (n=610) Treatment

			RAR Tertile Groups		
Patient Population	Parameters	Treatment Group	Low (1–6)	Intermediate (7–16)	High (17–32)
Patients received randomized treatment per-protocol	Number of patients	All (n=1092)	n=349	n=376	n=367
	Kaplan–Meier estimates of 5-year death rate*	MED	34% (±4%)	41% (±4%)	50% (±4%)
		CABG	21% (±3%)	30% (±4%)	46% (±4%)
Crossover patients	Number of patients	All (n=120)	n=30	n=53	n=37
	Kaplan–Meier estimates of 5-year death rate*	Crossover to MED	22% (±14%)	69% (±11%)	56% (±11%)
		Crossover to CABG	10% (±6%)	29% (±12%)	37% (±12%)

*Kaplan–Meier rates are reported in the format of death rate (±SE). CABG indicates coronary artery bypass graft; MED, medical therapy alone; and RAR, risk at randomization.

Table 2. Patient Characteristics According to Management

	Randomized to MED			Randomized to CABG		
	Rec. MED (Per-Protocol) (n=537)	Rec. CABG (Crossover) (n=65)	*P* Value	Rec. MED (Crossover) (n=55)	Rec. CABG (Per-Protocol) (n=555)	*P* Value
Age, y	59 (54, 67)	57 (51, 65)	0.170	61 (57, 69)	60 (54, 68)	0.237
Women, %	11.9	16.9	0.249	10.9	12.1	0.800
White, %	70.2	66.2	0.502	61.8	67.2	0.419
Black or other, %	29.8	33.8		38.2	32.8	
Body mass index, median, kg/m^2	27 (24, 30)	26 (24, 29)	0.842	26 (24, 29)	27 (24, 30)	0.226
Medical history, %						
Myocardial infarction	78.4	78.5	0.991	74.5	75.9	0.829
Hyperlipidemia	61.5	62.5	0.871	47.3	60.3	0.061
Hypertension	62.6	52.3	0.108	50.9	59.5	0.219
Diabetes mellitus	40.8	29.2	0.072	40.0	39.3	0.917
Current smoker	19.2	29.2	0.058	27.3	20.7	0.258
Previous percutaneous coronary intervention	12.3	12.3	0.997	21.8	12.6	0.056
Chronic renal insufficiency	7.8	4.6	0.460	14.5	7.4	0.071
Stroke	6.7	7.7	0.793	5.5	8.6	0.609
PVD	14.2	29.2	0.002	10.9	15.0	0.418
Previous CABG	2.6	0.0	0.383	10.9	2.9	0.010
Current CCS angina class, %			0.001			0.255
No angina	39.5	20.0		29.1	36.2	
I	15.5	12.3		16.4	15.7	
II	41.2	60.0		47.3	43.1	
III/IV	4.0	7.7		7.2	5.0	
Current NYHA heart failure class			0.003			0.069
I, %	13.0	6.2		9.1	10.8	
II, %	52.3	40.0		41.8	53.3	
III/IV, %	34.6	53.9		49.1	35.9	
Systolic blood pressure, median (IQR) mm Hg	120 (110, 130)	120 (110, 130)	0.224	120 (110, 140)	120 (110, 130)	0.836
Pulse, median (IQR) beats per min	72 (65, 80)	74 (68, 80)	0.858	72 (65, 84)	74 (66, 82)	0.502
Able to perform 6-min walk, %	89.2	92.2	0.455	72.2	84.7	0.019
6-min walk distance, median (IQR) ft	1139 (878, 1348)	984 (738, 1247)	0.024	984 (853, 1290)	1148 (875, 1325)	0.356
No. diseased vessels (≥75%), %			0.648			0.859
<1	26.1	29.3		26.0	24.2	
2	38.4	35.4		37.0	38.4	
3	35.6	35.4		37.0	37.5	
Proximal LAD≥75%	68.7	70.8	0.735	61.1	68.1	0.295
LVEF (site-reported), median (IQR)	27 (22, 30)	30 (25, 33)	0.003	27 (24, 31)	27 (22, 31)	0.993
LVEF (core laboratory+site), median (IQR)	28 (21, 34)	27 (23, 32)	0.579	25 (19, 33)	27 (22, 33)	0.306
LVESVI (core laboratory+site), median (IQR)	79 (58, 108)	78 (64, 95)	0.888	92 (73, 111)	78 (61, 101)	0.036
Mitral regurgitation (site-reported)			0.333			0.446
None or trace, %	38.0	29.2		27.3	35.7	
Mild, %	42.5	52.3		49.1	47.9	
Moderate (3+), %	16.7	13.8		18.2	13.2	
Severe (4+), %	2.8	4.6		5.5	3.2	
RAR score, median (IQR)	11 (5, 20)	10 (5, 17)	0.588	12 (7, 20)	11 (5, 19)	0.136

Data shown are median and interquartile range or proportions as a percentage. CABG indicates coronary artery bypass graft; CCS, Canadian Cardiovascular Society; IQR, interquartile range; LAD, left anterior descending; LVEF, left ventricular ejection fraction; LVESVI, left ventricular end systolic volume index; MED, medical therapy alone; NYHA, New York Heart Association; PVD, peripheral vascular disease; and RAR, risk at randomization.

Analysis of CABG as a Time-dependent Covariate[a] in a Cox Multivariable Model

Analysis		Timing of Introduction of CABG as Model Covariate (CABG , MED)		Hazard Ratio CABG:MED	95% Hazard Ratio Confidence Limit (lower, upper)	P Value
	Treatment Groups (Assigned/Received)	From randomization to the time of CABG received	From the time of CABG received to the end of follow-up			
1[b]	CABG/CABG			0.74	(0.62, 0.89)	0.001
	CABG/MED					
	MED/MED					
	MED/CABG					
2[c]	CABG/CABG			0.75	(0.62, 0.90)	0.002
	CABG/MED					
	MED/MED					
	MED/CABG					
3[d]	CABG/CABG			0.77	(0.64, 0.93)	0.005
	CABG/MED					
	MED/MED					
	MED/CABG					
4[e]	CABG/CABG			0.77	(0.64, 0.93)	0.005
	CABG/MED					
	MED/MED					
	MED/CABG					
5[f]	CABG/CABG			0.83	(0.69, 1.00)	0.044
	CABG/MED					
	MED/MED					
	MED/CABG					

Figure 3. Time-dependent covariate Cox multivariable analysis of coronary artery bypass graft (CABG) versus medical therapy alone (MED). a, A numeric (0, 1) time-dependent covariate was created in the Cox model to indicate whether and when a patient received CABG, with the format of 1=CABG and 0=MED. This variable allows an assessment of the CABG treatment effect to begin at the time that a patient actually received CABG. b, Analysis 1 has the CABG variable initially set to 1 for all patients who were assigned to CABG and actually received CABG. For patients assigned to MED who crossed over to CABG, the CABG variable is started as 0 and set to 1 at the time of the crossover. For all other patients (ie, those assigned to MED who received MED, and assigned to CABG but did not receive CABG), the time-dependent CABG variable remains as 0 in the Cox model. c, Analysis 2 is the same as analysis 1 except that early deaths in patients randomized to CABG are handled differently. In this analysis, patients who were assigned to CABG but died within 30 days after randomization without receiving CABG are counted as CABG=1. These patients are not counted as MED patients (as in analysis 1) even though they never received CABG. Thus, these early deaths are credited to the CABG arm. d, Analysis 3 is the same as analysis 2 except that patients who died within 60 days after randomization before receiving CABG are all counted as CABG=1. e, Analysis 4 has the CABG variable started as 0 (MED) for all 1212 hypothesis 1 patients. For patients who received CABG treatment, the CABG variable is set to 1 on the day of surgery. f, Analysis 5 has the CABG variable started as 1 for all patients who were randomized to CABG regardless of whether they ever received the CABG. For all the other patients (ie, MED patients), the CABG variable is started as 0 and switched to 1 at the time of CABG for any patients who crossed over from MED to CABG.

depicted in the figure, patients randomized to receive CABG were included in the CABG group from the time they were randomized as long as they had CABG at some time within the following year. Patients randomized to MED were all initially included in the MED group, but those who crossed over to CABG within the first year were shifted to the CABG cohort on the date of surgery. This strategy produced the lowest CABG: MED HR (0.74) and the smallest *P* value (*P*=0.001). Analysis strategy 5 in Figure 1 represents a scenario in which all patients randomized to CABG, including patients who died before surgery and all other CABG-to-MED crossovers, were counted in the CABG group. Among patients randomized to MED, the MED-to-CABG crossovers were counted with the CABG group once they received surgery. Even in this analysis, which may be considered the least biased toward surgery and which differed from the primary outcome report only by treating the MED/CABG crossovers differently, the HR was 0.83 (95% CI, 0.69–1.00) and still significant (*P*=0.044). The other analysis scenarios depicted in Figure 1 considered different time frames of counting patients in one or the other group. They produced results that were intermediate between those of analyses 1 and 5, all showing a significant favorable effect of CABG.

Discussion

CAD is the most common cause of heart failure associated with left ventricular systolic dysfunction.[3] Effective treatment of CAD should retard or reverse the progression of left ventricular systolic dysfunction and heart failure. Medical treatments, such as β-blockers[6] and ACE inhibitors,[7] seem to be effective for both heart failure and CAD. However, interventions directed solely at CAD, including aspirin[8,9] and statins,[10,11] have met with little success when applied to patients enrolled in trials on the basis of heart failure. Historically, trials of coronary revascularization have excluded patients who had either heart failure or substantial left ventricular systolic dysfunction.

Recently, the STICH trial failed to show a statistically significant reduction in the primary end point of all-cause mortality by ITT analysis.[3] However, there were a number

of treatment crossovers during patient follow-up in the trial, and the as-treated analysis demonstrated that patients who received CABG had a lower mortality than patients treated with MED only. Furthermore, CABG showed a significant improvement compared with MED for secondary end points, such as survival free of cardiac hospitalization.[3] These observations suggest that CABG may reduce mortality but that crossovers between assigned groups during the trial diluted the effect of the intervention.

The National Institutes of Health–funded Coronary Artery Surgery Study (CASS) compared survival of 780 patients with left ventricular ejection fraction of ≥0.35 randomized to MED or CABG.[2] During 10 years of follow-up of the cohort randomized to MED, CABG was performed in 6% of patients within 6 months of randomization[2] compared with the 11% crossover of STICH patients randomized to MED who had CABG within 1 year. Of the CASS patients assigned to CABG, 11% remained on MED only at 6 months after randomization[2] compared with 9% of CABG-assigned patients in STICH who remained on MED 1 year after randomization. Therefore, the rate of crossover in STICH was comparable to that of CASS despite the management challenges imposed in STICH by the patients with more severe LV dysfunction. Moreover, in response to comments of others about outcomes of MED-to-CABG crossovers in CASS stating the introduction of moribund patients into the surgical group would bias results against operation, Fisher et al[12] countered by pointing out that in the CASS trial, MED-to-CABG crossovers had a lower mortality rate than the original patients who remained compliant with the CABG treatment assignment. This concordance in outcome of crossover events between MED-to-CABG crossover cohorts of CASS and STICH patients most likely reflects the entry criteria at baseline that required knowledge of the coronary anatomy at the time of randomization. Because patients in both clinical trials were known by investigators responsible for their clinical care, appropriate evaluation and treatment could be expedited in response to deterioration of clinical status of the patient.

Management of patients with long-term medical conditions, such as heart failure, requires continuing evaluation and adjustment of treatment according to changing circumstances. This is also true in clinical trials. Randomization reflects a decision at a particular time to implement a certain strategy, but if the patient's condition changes from baseline after randomization, the management strategy must also change to reflect the usual standard of care for patient safety. In this respect, crossover remains part of the original design of STICH. We found that crossover events could not be pinpointed to a specific subset of patients who in retrospect might have been inappropriate for randomization on initial evaluation. Table 2 demonstrates the baseline clinical profiles to reflect a broad spectrum of risk of the crossover patients. The few patients (1.8%) who did cross from CABG to MED because the responsible clinician felt CABG was no longer in the patient's best interest had similar baseline RAR scores to patients crossing over from MED to CABG. Thus, as there was no way to identify patients easily who were treated medically that would eventually decompensate and require CABG without a demonstrable increased mortality, the results of STICH should not be interpreted as suggesting that a delay to proceeding with CABG is warranted in routine clinical practice. However, in common with many other clinical trials, the median age of patients in STICH was substantially lower than in epidemiological cohorts of patients with heart failure and coronary disease. The results of STICH should, therefore, be extrapolated with care to older patients with heart failure and multiple comorbidities where operative risk may be increased.

The STICH study was powered to show a 25% reduction in mortality with CABG compared with pharmacological therapy using an ITT analysis allowing for crossover rates of up to 20% for the duration of the study. For the comparison of treatment outcomes with early crossing of survival curves where technically the proportional hazards assumption is violated, the time-dependent Cox regression analyses that incorporate treatment crossovers, along with Kaplan–Meier analysis of the long-term outcomes, can be helpful in guiding physician and patient decisions about accepting the higher early risk of CABG with the hope of longer survival once patients are safely through the period of operative risk. While it is true that for patients meeting the STICH inclusion criteria, the initial risk of CABG will always be higher than an additional day of MED treatment, the longer-term benefits of CABG reflected in these analyses appear to offset the early risk, making CABG an attractive option in these patients.

The role of this report is, therefore, to provide data on survival of all 1212 STICH surgical revascularization hypothesis patients as individuals who also can be considered to be part of 1 of 4 observational cohorts—those who were and those who were not compliant with their randomized treatment assignment. This type of analysis introduces bias into the analysis. Here, it is important to realize that the bias was by definition not in the per-protocol patients. They were compliant with their assigned treatment. Any potential bias resided in the crossover patients and that bias can never be understood without placing the early crossover events in the context of data available only in this current article. The current article, therefore, complements our primary publication and in no way contradicts the conclusion of the primary report.[3] Nevertheless, without the message of this article in the literature, the full message of the STICH surgical revascularization hypothesis cohort would never be complete.

Conclusion

CABG reduced mortality in both the per-protocol and the crossover STICH patient populations. The crossover events from randomly assigned therapy, therefore, diminished the impact of CABG on survival in STICH when analyzed by ITT. Until the 10-year outcomes (STICHES) are available, STICH-like patients should be informed about the 5-year outcome results of the STICH surgical revascularization hypothesis patients before making their own treatment decision.

Sources of Funding

The Surgical Treatment for Ischemic Heart Failure trial was supported by grants U01HL69015 and U01HL69013.

Disclosures

Dr Doenst received fees for consulting from B. Braun, St. Jude Medical and Edwards and research grants from B. Braun and the German Research Foundation (DFG); Dr Ohman received consulting fees from AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Gilead Sciences, Janssen Pharmaceuticals, Liposcience, Merck, Pozen Inc, Roche, Sanofi Aventis, The Medicines Company, and research grants from Daiichi Sankyo, Eli Lilly & Company, Gilead Sciences; Dr Velazquez received consulting fees from Gilead and Novartis and research grants from Abbott Vascular and Ikaria.

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CLINICAL PERSPECTIVE

The international, multicenter Surgical Treatment for Ischemic Heart Failure (STICH) trial had identified a 14% relative risk reduction in mortality of coronary artery bypass graft versus medical therapy alone. However, this risk reduction was not statistically significant. We illustrate in this article that crossover events within the first year of randomization diluted the difference between the 2 treatment options because all medical therapy alone patients had higher 5-year mortality than all coronary artery bypass graft patients. Importantly, we analyzed the reasons for such crossover events and were unable to identify predictable patterns or risk profiles that characterized the crossover patients. In other words, we provide strong support for the conclusion that crossover events were random and not associated with the patients perceived risk at the time of randomization or thereafter. This information should, therefore, be helpful for advising all patients with systolic heart failure and coronary artery disease amenable for bypass surgery with respect to treatment options until definitive information on all-cause mortality is available by the STICH Extension Study.

SUPPLEMENTAL MATERIAL

Appendix 1. STICH Hypothesis 1 Treatment Crossovers/Reasons

Index Number*	RAR Score	Treatment Received	Crossover Reason Classification	Randomized Treatment	Reason for Crossover
M-AD1	10	CABG	Group 1: Acute decompensation	MED	Heart failure, ventricular tachycardia
M-AD2	3	CABG	Group 1: Acute decompensation	MED	Myocardial infarction with ICD discharge
M-AD3	26	CABG	Group 1: Acute decompensation	MED	Recurrent syncope, decompensation
M-AD4	10	CABG	Group 1: Acute decompensation	MED	ICD for recurrent ventricular tachycardia
M-AD5	31	CABG	Group 1: Acute decompensation	MED	Unstable heart failure with pulmonary edema
M-AD6	15	CABG	Group 1: Acute decompensation	MED	Tricuspid endocarditis
M-AD7	8	CABG	Group 1: Acute decompensation	MED	Heart failure requiring intra-aortic balloon pump
M-AD8	10	CABG	Group 1: Acute decompensation	MED	Pulmonary edema
M-AD9	1	CABG	Group 1: Acute decompensation	MED	Ventricular fibrillation, cardiac arrest
M-AD10	17	CABG	Group 1: Acute decompensation	MED	Worsening heart failure
M-AD11	16	CABG	Group 1: Acute decompensation	MED	Myocardial infarction after randomization
M-AD12	15	CABG	Group 1: Acute decompensation	MED	Cardiac arrest three months after randomization
M-AD13	19	CABG	Group 1: Acute decompensation	MED	Non-ST myocardial infarction
M-AD14	4	CABG	Group 1: Acute decompensation	MED	Angina, pulmonary edema
M-PS1	12	CABG	Group 2: Progressive symptoms	MED	Angina on medical therapy
M-PS2	22	CABG	Group 2: Progressive symptoms	MED	Unstable angina, syncope
M-PS3	12	CABG	Group 2: Progressive symptoms	MED	Angina, left ventricular failure
M-PS4	16	CABG	Group 2: Progressive symptoms	MED	Angina on aggressive medical therapy
M-PS5	20	CABG	Group 2: Progressive symptoms	MED	Increasing heart failure, Class III
M-PS6	21	CABG	Group 2: Progressive symptoms	MED	Angina, homeless patient
M-PS7	27	CABG	Group 2: Progressive symptoms	MED	Increasing dyspnea and angina on medical therapy
M-PS8	22	CABG	Group 2: Progressive symptoms	MED	Severe angina and dyspnea with any activity
M-PS9	20	CABG	Group 2: Progressive symptoms	MED	Increasing angina
M-PS10	23	CABG	Group 2: Progressive symptoms	MED	Rest dyspnea and angina
M-PS11	7	CABG	Group 2: Progressive symptoms	MED	Progressive dyspnea, shortness of breath
M-PS12	16	CABG	Group 2: Progressive symptoms	MED	Unstable angina
M-PS13	30	CABG	Group 2: Progressive symptoms	MED	Severe mitral regurgitation
M-PS14	20	CABG	Group 2: Progressive symptoms	MED	Increasing heart failure requiring hospital admission
M-PS15	15	CABG	Group 2: Progressive symptoms	MED	Persistent ischemia after PCI
M-PS16	10	CABG	Group 2: Progressive symptoms	MED	Pulmonary edema
M-PS17	8	CABG	Group 2: Progressive symptoms	MED	CCS III/IV angina
M-PS18	21	CABG	Group 2: Progressive symptoms	MED	Syncope, Class IV angina
M-PS19	12	CABG	Group 2: Progressive symptoms	MED	Unstable angina with untreatable symptoms
M-PS20	6	CABG	Group 2: Progressive symptoms	MED	Heart failure decompensation
M-PS21	3	CABG	Group 2: Progressive symptoms	MED	Angina, 3 mm ST depression on exercise test
M-PS22	9	CABG	Group 2: Progressive symptoms	MED	Class III/IV angina
M-PS23	15	CABG	Group 2: Progressive symptoms	MED	Class II/IV angina
M-PS24	3	CABG	Group 2: Progressive symptoms	MED	Early positive ETT

Index Number*	RAR Score	Treatment Received	Crossover Reason Classification	Randomized Treatment	Reason for Crossover
M-PS25	8	CABG	Group 2: Progressive symptoms	MED	Severe pain episodes
M-PS26	1	CABG	Group 2: Progressive symptoms	MED	Severe dyspnea, orthopnea
M-PS27	1	CABG	Group 2: Progressive symptoms	MED	Unstable angina
M-PS28	6	CABG	Group 2: Progressive symptoms	MED	Unstable angina
M-PS29	12	CABG	Group 2: Progressive symptoms	MED	Limited in daily activities
M-PS30	2	CABG	Group 2: Progressive symptoms	MED	Class IV angina on medical therapy
M-PF1	24	CABG	Group 3: Patient/family decision	MED	Family advised patient with three prior MIs
M-PF2	4	CABG	Group 3: Patient/family decision	MED	Patient insisted on CABG
M-PF3	4	CABG	Group 3: Patient/family decision	MED	Patient's wife insisted on CABG
M-PF4	1	CABG	Group 3: Patient/family decision	MED	Patient changed mind and chose CABG
M-PF5	17	CABG	Group 3: Patient/family decision	MED	Patient insisted on CABG after randomization
M-PF6	3	CABG	Group 3: Patient/family decision	MED	Relatives insisted on CABG
M-PF7	5	CABG	Group 3: Patient/family decision	MED	Patient/family decision after randomization
M-PF8	5	CABG	Group 3: Patient/family decision	MED	Relatives insisted on CABG
M-PF9	22	CABG	Group 3: Patient/family decision	MED	Patient changed mind and insisted on CABG
M-PF10	14	CABG	Group 3: Patient/family decision	MED	Patient changed mind
M-PF11	7	CABG	Group 3: Patient/family decision	MED	Patient changed mind four days after randomization
M-PF12	9	CABG	Group 3: Patient/family decision	MED	Relatives insisted on CABG
M-PF13	6	CABG	Group 3: Patient/family decision	MED	Relatives insisted on CABG
M-PF14	1	CABG	Group 3: Patient/family decision	MED	Relatives insisted on CABG
M-PF15	1	CABG	Group 3: Patient/family decision	MED	Patient changed mind
M-PF16	3	CABG	Group 3: Patient/family decision	MED	Change suggested by doctor friend
M-CD1	14	CABG	Group 4: Clinical decision	MED	Reversible ischemia on MRI
M-CD2	5	CABG	Group 4: Clinical decision	MED	Physician changed mind (3-vessel disease, ≤50% LM)
M-CD3	11	CABG	Group 4: Clinical decision	MED	Physician opinion difference (3-vessel and 33% LM)
M-CD4	9	CABG	Group 4: Clinical decision	MED	Physician opinion difference
M-CD5	13	CABG	Group 4: Clinical decision	MED	Physician opinion difference
C-DW1	10	MED	Group 1: Died waiting for operation	CABG	Patient requested home visit before CABG
C-DW2	11	MED	Group 1: Died waiting for operation	CABG	Died before CABG could have been scheduled
C-DW3	22	MED	Group 1: Died waiting for operation	CABG	Logistic reasons required a two-month delay of CABG
C-DW4	9	MED	Group 1: Died waiting for operation	CABG	Died two days after randomization
C-DW5	12	MED	Group 1: Died waiting for operation	CABG	Died during Christmas - 1 day before scheduled CABG
C-PF1	10	MED	Group 3: Patient/family decision	CABG	Family unsupportive of CABG
C-PF2	29	MED	Group 3: Patient/family decision	CABG	Patient changed mind
C-PF3	23	MED	Group 3: Patient/family decision	CABG	Patient changed mind
C-PF4	12	MED	Group 3: Patient/family decision	CABG	Died at home on medical therapy
C-PF5	14	MED	Group 3: Patient/family decision	CABG	Financial constraints, symptoms not severe
C-PF6	20	MED	Group 3: Patient/family decision	CABG	Patient concern for risk of operation
C-PF7	8	MED	Group 3: Patient/family decision	CABG	Reconsidered risk as too high
C-PF8	3	MED	Group 3: Patient/family decision	CABG	Patient changed mind

Index Number*	RAR Score	Treatment Received	Crossover Reason Classification	Randomized Treatment	Reason for Crossover
C-PF9	13	MED	Group 3: Patient/family decision	CABG	Family physician said no
C-PF10	31	MED	Group 3: Patient/family decision	CABG	Patient changed mind
C-PF11	31	MED	Group 3: Patient/family decision	CABG	Patient refused CABG
C-PF12	27	MED	Group 3: Patient/family decision	CABG	Feeling too good for CABG
C-PF13	7	MED	Group 3: Patient/family decision	CABG	Patient had PCI at non-STICH center
C-PF14	4	MED	Group 3: Patient/family decision	CABG	Patient decided risk too high
C-PF15	32	MED	Group 3: Patient/family decision	CABG	Patient became fearful
C-PF16	3	MED	Group 3: Patient/family decision	CABG	Fearful of planned redo CABG
C-PF17	14	MED	Group 3: Patient/family decision	CABG	Withdrew near time of operation
C-PF18	32	MED	Group 3: Patient/family decision	CABG	Patient's wife not supportive of CABG
C-PF19	32	MED	Group 3: Patient/family decision	CABG	Virus delayed/canceled CABG
C-PF20	22	MED	Group 3: Patient/family decision	CABG	Patient declined
C-PF21	13	MED	Group 3: Patient/family decision	CABG	Patient declined
C-PF22	20	MED	Group 3: Patient/family decision	CABG	Patient declined
C-PF23	11	MED	Group 3: Patient/family decision	CABG	Prostate cancer found
C-PF24	9	MED	Group 3: Patient/family decision	CABG	Patient declined CABG
C-PF25	7	MED	Group 3: Patient/family decision	CABG	URI delayed CABG, never performed
C-PF26	4	MED	Group 3: Patient/family decision	CABG	Patient feared CABG
C-PF27	19	MED	Group 3: Patient/family decision	CABG	Patient withdrew consent for redo CABG
C-PF28	11	MED	Group 3: Patient/family decision	CABG	Treated with cardiac pacing instead
C-PF29	9	MED	Group 3: Patient/family decision	CABG	Patient feared risk
C-PF30	30	MED	Group 3: Patient/family decision	CABG	Patient refused CABG
C-PF31	14	MED	Group 3: Patient/family decision	CABG	Patient refused CABG
C-PF32	7	MED	Group 3: Patient/family decision	CABG	Patient refused CABG and received PCI
C-PF33	7	MED	Group 3: Patient/family decision	CABG	Declined redo CABG
C-PF34	6	MED	Group 3: Patient/family decision	CABG	Declined redo CABG
C-PF35	2	MED	Group 3: Patient/family decision	CABG	Non-STICH physicians offered PCI
C-PF36	18	MED	Group 3: Patient/family decision	CABG	Patient's insurance carrier denied coverage
C-PF37	5	MED	Group 3: Patient/family decision	CABG	Declined as operation date neared
C-CD1	6	MED	Group 4: Clinical decision	CABG	While CABG waitlisted, patient had 1-vessel PCI
C-CD2	32	MED	Group 4: Clinical decision	CABG	Veins found to be too small for CABG conduit
C-CD3	10	MED	Group 4: Clinical decision	CABG	Lung cancer found, no CABG
C-CD4	21	MED	Group 4: Clinical decision	CABG	Poor lung function, PCI not CABG performed
C-CD5	9	MED	Group 4: Clinical decision	CABG	Veins inadequate for conduit
C-CD6	1	MED	Group 4: Clinical decision	CABG	Coronary "lesion" was spasm
C-CD7	14	MED	Group 4: Clinical decision	CABG	Surgeons reassessed risk
C-CD8	9	MED	Group 4: Clinical decision	CABG	Risk reassessed as too high - EF 0.11, not 0.24
C-CD9	19	MED	Group 4: Clinical decision	CABG	Risk reassessed as too high - EF 11% with MR
C-CD10	7	MED	Group 4: Clinical decision	CABG	Arrhythmia ablation instead of CABG chosen
C-CD11	17	MED	Group 4: Clinical decision	CABG	Non-viable test result after randomization
C-PM1	9	MED	Group 5: Provider miscommunication	CABG	Research to clinical staff

Index Number*	RAR Score	Treatment Received	Crossover Reason Classification	Randomized Treatment	Reason for Crossover
C-PM2	18	MED	Group 5: Provider miscommunication	CABG	Cardiology to research staff

*coded version to protect patient ID numbers

