

CLINICAL RESEARCH

The STICH Trial (Surgical Treatment for Ischemic Heart Failure)

Mode-of-Death Results

Peter Carson, MD,* John Wertheimer, MD,† Alan Miller, MD,‡ Christopher M. O'Connor, MD,§ Ileana L. Pina, MD,|| Craig Selzman, MD,¶ Carla Sueta, MD,# Lilin She, PhD,§ Deborah Greene, RN,§ Kerry L. Lee, PhD,§ Robert H. Jones, MD,§ Eric J. Velazquez, MD,§ for the STICH Investigators

Washington DC; Philadelphia, Pennsylvania; Jacksonville, Florida; Durham and Chapel Hill, North Carolina; Bronx, New York; and Salt Lake City, Utah

- Objectives** This study sought to assess the effect of the addition of coronary artery bypass grafting (CABG) to medical therapy on mode of death in heart failure.
- Background** Although CABG therapy is widely used in ischemic cardiomyopathy patients, there are no prospective clinical trial data on mode of death.
- Methods** The STICH (Surgical Treatment for Ischemic Heart Failure) trial compared the strategy of CABG plus medical therapy to medical therapy alone in 1,212 ischemic cardiomyopathy patients with reduced ejection fraction. A clinical events committee adjudicated deaths using pre-specified definitions for mode of death.
- Results** In the STICH trial, there were 462 deaths over a median follow-up of 56 months. The addition of CABG therapy tended to reduce cardiovascular deaths (hazard ratio [HR]: 0.83; 95% confidence interval [CI]: 0.68 to 1.03; $p = 0.09$) and significantly reduced the most common modes of death: sudden death (HR: 0.73; 95% CI: 0.54 to 0.99; $p = 0.041$) and fatal pump failure events (HR: 0.64; 95% CI: 0.41 to 1.00; $p = 0.05$). Time-dependent estimates indicate that the protective effect of CABG principally occurred after 24 months in both categories. Deaths post-cardiovascular procedures were increased in CABG patients (HR: 3.11; 95% CI: 1.47 to 6.60), but fatal myocardial infarction deaths were lower (HR: 0.07; 95% CI: 0.01 to 0.57). Noncardiovascular deaths were infrequent and did not differ between groups.
- Conclusions** In the STICH trial, the addition of CABG to medical therapy reduced the most common modes of death: sudden death and fatal pump failure events. The beneficial effects were principally seen after 2 years. Post-procedure deaths were increased in patients randomized to CABG, whereas myocardial infarction deaths were decreased. (J Am Coll Cardiol HF 2013;1:400–8) © 2013 by the American College of Cardiology Foundation

Chronic congestive heart failure with reduced ejection fraction is a progressive disease in which cardiac dysfunction

From the *Washington DC VA Medical Center, Washington DC; †Pennsylvania Heart and Vascular Group, Philadelphia, Pennsylvania; ‡University of Florida—Shands Jacksonville, Jacksonville, Florida; §Duke University Medical Center/Duke Clinical Research Institute, Durham, North Carolina; ||Montefiore Medical Center, Bronx, New York; ¶University of Utah School of Medicine, Salt Lake City, Utah; and the #University of North Carolina, Chapel Hill, North Carolina. This work supported by grants (U01HL69015 and U01HL69013) from the National, Heart, Lung, and Blood Institute. Dr. Miller is a consultant for St. Jude Medical, Biotronik, Biocontrol, and Pfizer. Dr. Velazquez has received research grants from Abbott Vascular and Icaria Pharmaceuticals; is on the advisory committee of Novartis; and is on the Speakers' Bureau of Gilead. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Michael R. Bristow, MD, PhD, acted as Guest Editor for this paper.

Manuscript received February 5, 2013; revised manuscript received April 17, 2013, accepted April 19, 2013.

is associated with increased hospitalization and shortened survival (1). Advances in medical therapy have improved outcomes, but the burden of disease remains excessive (2–7). In industrialized societies, coronary artery disease is the most common etiology of heart failure with reduced ejection fraction, and there has been great interest in the use of coronary revascularization to improve outcomes (8). The recently completed STICH (Surgical Treatment for Ischemic Heart Failure) study compared the addition of coronary artery bypass grafting (CABG) to medical therapy versus medical therapy alone (9). Although surgical therapy did not statistically reduce the primary outcome of all-cause mortality, there was significant benefit seen on secondary outcomes, including cardiovascular death, and composites of all-cause mortality or hospitalizations, whether for any cause

or for either cardiovascular or heart failure. These findings suggested a need to better understand the all-cause mortality events.

Mode-of-death analysis in heart failure trials has enhanced our understanding of fatal outcomes associated with this disease and suggested potential therapeutic approaches (10–12). Multiple lines of evidence have suggested potential benefit of CABG therapy on the most common modes of death in chronic heart failure: sudden death and pump failure (13–20).

The purpose of the current analysis was to determine the effect of CABG added to medical therapy on mode of death compared with medical therapy alone.

Methods

The current paper reports outcomes on 1,212 patients randomized in a comparison of CABG therapy plus medical therapy (610 patients) to medical therapy (602 patients) alone, with a median follow-up of 56 months. The study design, subject demographics, and main outcomes of the STICH trial have been previously described (21).

Adjudication process and definitions. A 7-member adjudication committee composed of 6 heart failure cardiologists and 1 cardiac surgeon reviewed deaths. Committee members reviewed source documents, and mode-of-death categorizations were assigned by majority vote during meetings. Deaths were considered cardiovascular unless a specific non-cardiovascular cause was present, or unknown if there was insufficient information for adjudication. The major cardiovascular mode of death subclassifications included the following definitions: *sudden death*—death that occurred suddenly and unexpectedly; *pump failure death*—new or worsening symptoms and/or signs of heart failure usually involving hospitalization; *myocardial infarction*—death due to an event with symptoms, electrocardiogram, cardiac marker/enzyme evidence, or autopsy data; *complication of cardiac procedure*—death occurring during or related to a cardiovascular procedure. The full adjudication definitions are in the [Online Appendix](#). The category labeled *unknown* consists of a small number of patients in whom documentation of the mode of death was insufficient for the committee to render a specific classification. The mortality analyses presented in this report are based strictly on classifications of the events committee except for supportive hospitalization data adjudicated by investigators for all-cause, cardiac, and heart failure categories. **Statistical analysis.** Baseline patient characteristics were descriptively summarized using medians with 25th and 75th percentiles for continuous variables, and frequencies and percentages for categorical variables. Comparisons of the distributions of continuous or ordinal baseline variables between patient groups were performed using the Wilcoxon rank sum test, and categorical variables were compared using the chi-square test or Fisher exact test.

Event-rate estimates in each treatment arm for different mode-of-death categories were calculated using the

Kaplan-Meier method (22) and statistically compared using the log-rank test (23). Relative risks, expressed as hazard ratios (HRs) with associated 95% confidence intervals (CIs), were derived using the Cox regression model (24). All treatment comparisons were performed with the treatment groups defined as randomized (i.e., intention to treat).

Results

Total mortality and demographics.

There were 462 deaths in the STICH trial reported during the follow-up period. From the baseline characteristics (Table 1), patients who died differed from the 750 subjects who did not in the following: they were older, with higher New York Heart Association (NYHA) functional class, worse renal function, and a worse Duke CAD score, lower left ventricular ejection fraction (LVEF), higher end-systolic volume index and end-diastolic volume index, and more mitral regurgitation. Among baseline medications, those who died tended to be less commonly treated with a beta-blocker, but were more commonly treated with amiodarone, loop diuretics, and insulin. Overall, 2.4% had an implantable cardioverter-defibrillator (ICD) at baseline. Baseline characteristics of patients who experienced the 2 major modes of death in the STICH trial, sudden death and pump failure, are also seen in Table 1: their characteristics differed little from those of the overall death group, although cardiac volumes were largest in the fatal pump failure group.

Mode of death. For committee-adjudicated fatal events, there were 351 deaths (29.0% of patients, 76.0% of overall deaths) categorized as cardiovascular, whereas 67 (5.5% of patients, 14.5% of deaths) were assessed as noncardiovascular. There were 44 deaths adjudicated as unknown (3.6% of patients, 9.5% of deaths) (Table 2).

Compared with medical therapy, the addition of CABG was associated with a nonsignificant decrease in cardiovascular mortality (HR: 0.83, 95% CI: 0.68 to 0.1.03; $p = 0.09$), but no difference was seen in the noncardiovascular and unknown categories.

Among the cardiovascular subclassification categories (Table 3), there were differences between the treatment groups in the following: sudden deaths were significantly reduced by CABG therapy, 74 CABG versus 99 medical therapy (HR: 0.73, 95% CI: 0.54 to 0.99; $p = 0.04$) with a similar effect on pump failure deaths, 33 versus 49 events, that was nominally significant (HR: 0.64, 95% CI: 0.41 to 1.00; $p = 0.05$). Fatal myocardial infarctions were infrequent, but also decreased by the addition of CABG therapy, 1 versus 13 (HR: 0.07, 95% CI: 0.01 to 0.57; $p < 0.01$), whereas cardiovascular procedure deaths were increased in the

Abbreviations and Acronyms

CABG = coronary artery bypass grafting

CEC = clinical events committee

CI = confidence interval

HR = hazard ratio

ICD = implantable cardioverter-defibrillator

LVEF = left ventricular ejection fraction

NYHA = New York Heart Association

Table 1 Baseline Characteristics of STICH Hypothesis 1 Patients by Mortality Status

Characteristics	Patients Survived (n = 750)	Patients Died (n = 462)			p Value†
		Sudden Deaths (n = 173)	Pump Failure Deaths (n = 82)	All-Cause Deaths* (n = 462)	
Age, yrs	59 (53-66)	59 (53-67)	61 (56-69)	62 (54-69)	<0.001
White race	66	64	78	72	0.017
Previous stroke	6	9	10	10	0.008
Renal insufficiency	5	9	17	12	<0.001
Atrial fibrillation	10	15	16	17	0.001
Current NYHA HF class					
I/II	13/53	9/52	9/46	10/49	
III/IV	32/2	35/5	40/5	37/5	0.003
Creatinine, mg/dl	1.1 (0.9-1.2)	1.1 (1.0-1.3)	1.2 (1.0-1.4)	1.1 (1.0-1.4)	<0.001
BUN, mg/dl	22 (16-35)	24 (16-37)	25 (19-43)	24 (17-39)	0.004
LVEF, %	28 (23-34)	25 (20-31)	24 (20-30)	25 (20-32)	<0.001
ESVI, ml/m ²	75 (57-97)	86 (67-111)	96 (70-128)	86 (65-118)	<0.001
EDVI, ml/m ²	108 (86-132)	120 (97-144)	127 (102-169)	120 (97-154)	<0.001
Mitral regurgitation					
Mild or less	85	81	65	76	
Moderate/severe	15	19	35	24	<0.001
Duke CAD Index (1-100)	52 (39-77)	65 (39-77)	65 (39-77)	65 (39-77)	0.018
Beta-blocker	87	88	79	83	0.046
Amiodarone	8	13	12	13	0.005
Diuretic (loop/thiazide)	61	69	77	72	<0.001
Diuretic (loop/thiazide or potassium sparing)	71	78	88	82	<0.001
Previous ICD	2	1	2	2	0.983

Values are median (interquartile range) or %. *All-cause deaths include sudden deaths, pump failure deaths, and deaths from other causes. †p Values are based on comparisons between patients who survived (n = 750) and patients who died (n = 462).

BUN = blood urea nitrogen; CAD = coronary artery disease; EDVI = end-diastolic volume index; ESVI = end-systolic volume index; HF = heart failure; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association functional class; STICH = Surgical Treatment for Ischemic Heart Failure.

surgical group, 28 versus 9 (HR: 3.11, 95% CI: 1.47 to 6.60; p < 0.01). Fatal cardiovascular procedure events are listed in detail in Online Table A1. A forest plot of the major cardiovascular categories is seen in Figure 1. Within the noncardiovascular category, there were also no differences seen for any specific subclassification of event (Table 4). With unadjudicated data, CABG therapy significantly reduced all-cause hospitalizations as well as cardiac and heart failure subcategories (Table 5).

For the 2 most common subclassifications of mode of death, sudden and pump failure, time-to-event curves are shown by treatment group in Figures 2 and 3. For both modes of death, there was a later separation of the curves

with fewer events in the CABG group. Table 6 indicates a trend for benefit of CABG therapy within 6 months for sudden death, and significant benefit beyond 24 months for both modes of death.

Effect of functional class and ventricular function on mode of death. We further analyzed mode of death in subgroups by severity of LV dysfunction or NYHA functional class (Fig. 4). The addition of CABG continued to be directionally favorable, but the fewer events within each subgroup resulted in a loss of statistical significance in the sudden and pump failure subclassifications. Noncardiovascular deaths tended to be less frequent in those treated with medical therapy alone in the above-median

Table 2 CEC-Adjudicated Cause of Death

Mortality Distribution	Treatment			Hazard Ratio (95% CI)	p Value
	CABG (n = 610)	MED (n = 602)	Total (N = 1,212)		
All-cause death	218 (35.7)	244 (40.5)	462 (38.1)	0.86 (0.72-1.04)	0.12
Cardiovascular (CEC)	162 (26.6)	189 (31.4)	351 (29.0)	0.83 (0.68-1.03)	0.09
Noncardiovascular (CEC)	35 (5.7)	32 (5.3)	67 (5.5)	1.03 (0.64-1.67)	0.90
Unknown (CEC)	21 (3.4)	23 (3.8)	44 (3.6)	0.87 (0.48-1.58)	0.67

Values are n (%).

CABG = coronary artery bypass grafting; CEC = clinical events committee; CI = confidence interval; MED = medical therapy.

Mortality Distribution	Treatment		
	CABG (n = 610, 218)	MED (n = 602, 244)	Total (N = 1,212, 462)
Cardiovascular (CEC)	162 (26.6, 74.3)	189 (31.4, 77.5)	351 (29.0, 76.0)
Sudden	74 (12.1, 33.9)	99 (16.4, 40.6)	173 (14.3, 37.4)
Pump failure	33 (5.4, 15.1)	49 (8.1, 20.1)	82 (6.8, 17.7)
MI	1 (0.2, 0.5)	13 (2.2, 5.3)	14 (1.2, 3.0)
CVA	11 (1.8, 5.0)	12 (2.0, 4.9)	23 (1.9, 5.0)
Cardiac procedure	28 (4.6, 12.8)	9 (1.5, 3.7)	37 (3.1, 8.0)
Other cardiovascular	14 (2.3, 6.4)	7 (1.2, 2.9)	21 (1.7, 4.5)

Values are n (% of patients, % of deaths).
 CVA = cerebrovascular; MI = myocardial infarction; other abbreviations as in Table 2.

LVEF subgroup and in the NYHA functional class I/II subgroup, but no significant differences were seen.

Discussion

The STICH trial presents the opportunity to examine the effect of CABG added to medical therapy on mode of death. The results indicate that the majority of deaths were cardiovascular, with sudden and pump failure deaths being the 2 most common subclassifications. Using clinical events committee (CEC)-adjudicated data only, the addition of CABG therapy reduced cardiovascular deaths, although not significantly. Bypass surgery significantly reduced sudden deaths as well as deaths due to myocardial infarction, with a nominally significant effect on fatal pump failure events. Cardiovascular procedure deaths were increased, partially offsetting these findings. The benefits of bypass surgery on mode of death were supported by significant reductions in hospitalizations. Effects on the 2 major modes of death were principally seen after 2 years. Defining subgroups by median

LVEF or NYHA class did not alter the distribution of cardiovascular deaths or the direction of the CABG therapeutic result. These data represent the only prospective clinical trial experience evaluating the effect of CABG on mode of death in ischemic cardiomyopathy patients. It is also 1 of the larger databases using committee-adjudicated results to examine mode of death in CABG patients.

Mode of death in ischemic cardiomyopathy patients in the STICH trial. In the STICH trial, the majority of deaths adjudicated by the CEC were due to a cardiovascular cause, which is in agreement with other databases in heart failure with reduced ejection fraction (3-6,10,12,25,26). The number of cardiovascular deaths differs slightly in this paper compared with the main STICH trial paper (9) due to a difference in methodology in assignment for “unknown” deaths. For this analysis, deaths were adjudicated as unknown when the CEC believed that there were insufficient data to adjudicate. The main paper used a “best available” methodology, pre-specified before analyses, that combined committee-adjudicated cardiovascular deaths

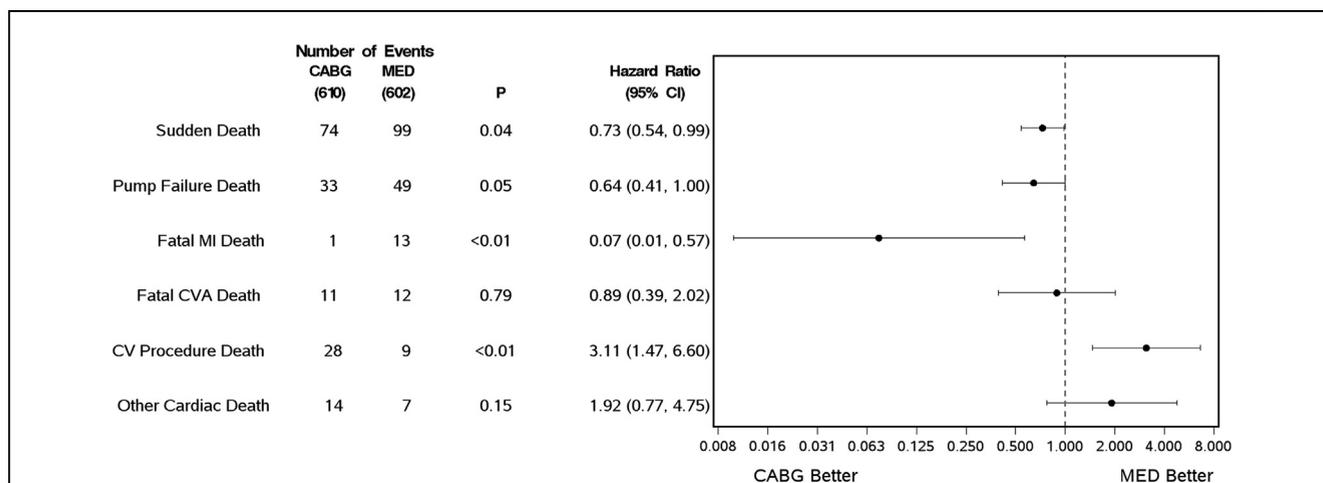


Figure 1 CV Modes of Death: HRs and CIs

CABG = coronary artery bypass grafting; CI = confidence interval; CV = cardiovascular; CVA = cerebrovascular accident; HR = hazard ratio; MED = medical therapy; MI = myocardial infarction.

Table 4 Cause of Death: Noncardiovascular Subclassifications

Mortality Distribution	Treatment		
	CABG (n = 610, 218)	MED (n = 602, 244)	Total (N = 1,212, 462)
Noncardiovascular (CEC)	35 (5.7, 16.1)	32 (5.3, 13.1)	67 (5.5, 14.5)
Infection	7 (1.1, 3.2)	5 (0.8, 2.0)	12 (1.0, 2.6)
Neurologic	0 (0.0, 0.0)	2 (0.3, 0.8)	2 (0.2, 0.4)
Pulmonary	2 (0.3, 0.9)	2 (0.3, 0.8)	4 (0.3, 0.9)
Renal	4 (0.7, 1.8)	0 (0.0, 0.0)	4 (0.3, 0.9)
Malignancy	17 (2.8, 7.8)	18 (3.0, 7.4)	35 (2.9, 7.6)
Other noncardiovascular	5 (0.8, 2.3)	5 (0.8, 2.0)	10 (0.8, 2.2)

Values are n (% of patients, % of deaths).
Abbreviations as in Table 2.

(excluding vascular deaths, n = 348) with those deaths the committee adjudicated as unknown, but the investigator assessed as cardiovascular (n = 21). Among all deaths classified by the site as cardiovascular, the event committee's adjudicated assessment was concordant with the site in 92% of cases (kappa coefficient = 0.67, 95% CI: 0.59 to 0.75; p < 0.001).

The treatment comparison with respect to cardiovascular death in the current paper remains directionally favorable for the addition of CABG therapy and has a similar effect size as that reported in the primary paper, but with a slightly wider confidence interval and hence a slightly larger p value due to fewer cardiovascular deaths. This directional effect is also consistent with the favorable effect of bypass surgery on the secondary outcome of all-cause mortality or cardiovascular hospitalization in the main paper (9).

Deaths assessed as noncardiovascular have been relatively infrequent (7% to 29%) in heart failure with reduced ejection fraction studies (3–6,10,12,25,26).

As noted in the preceding text, sudden deaths and fatal pump failure events were the most common specific subclassifications of death in the STICH trial, in comparable proportion to other recent heart failure trials (4,25–27). Myocardial infarction deaths were infrequent in the STICH trial as seen in other chronic heart failure trials, including those with an ischemic cohort (26,28).

Effect of surgical therapy on subclassification of mode of death in the STICH trial. Compared with medical therapy alone, the addition of CABG in the STICH trial significantly reduced sudden cardiac deaths. Previous reports have noted this finding, although those studies comprised

small numbers of patients (15) or were retrospective analyses (29,30). In the largest retrospective analysis, of the SOLVD (Studies of Left Ventricular Dysfunction) database, Veenhuyzen *et al.* (18) reported that patients with previous CABG were associated with a lower risk of sudden death than those without prior CABG, although it was noted that retrospective studies involving historical procedures must be interpreted cautiously (31).

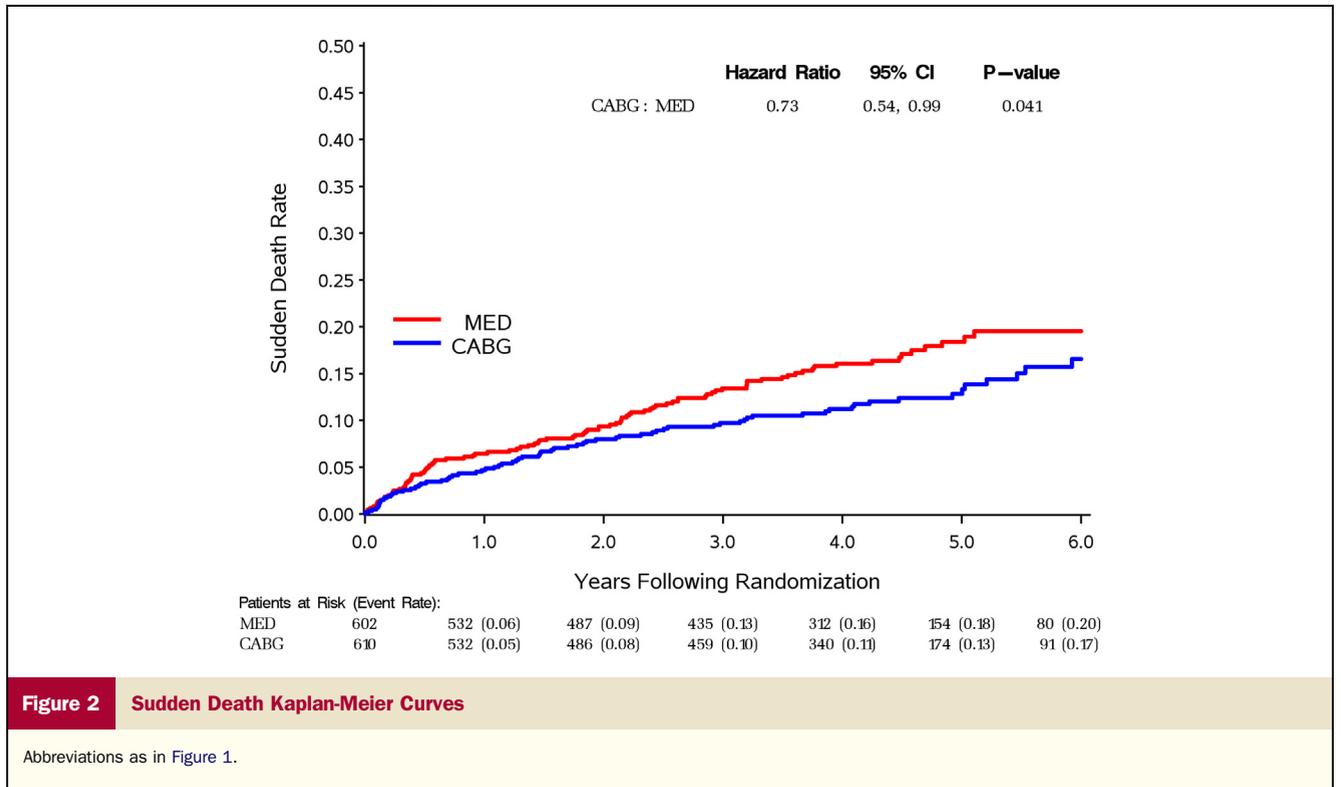
For the benefit seen in the prospective STICH trial, the pathophysiological benefit with CABG may be related to a reduction in severe ischemic events, including sudden coronary occlusions, which would reduce the substrate for the development of re-entrant ventricular arrhythmias. Although there are small event numbers, the reduction in myocardial infarction deaths in the STICH trial in the CABG treatment group provides support for reduction in fatal ischemic events as part of the sudden death benefit. Although myocardial infarction deaths were uncommon in the STICH trial and other chronic heart failure databases, coronary thromboses have been reported in sudden cardiac deaths in autopsy studies as well as angiography in sudden cardiac death survivors. In chronic heart failure, Uretsky *et al.* (32) reported coronary thromboses and undiagnosed myocardial infarctions in deaths adjudicated as sudden from the ATLAS (Assessment of Treatment with Lisinopril and Survival) study. The favorable effect on sudden death by bypass surgery may also be related to a salutary impact on heart failure progression, as indicated by a reduction in both fatal pump failure events.

There was a low use of ICDs in the STICH trial, which is common among international heart failure trials with enrollment predominantly outside of the United States and Western Europe (26,33). Whether widespread ICD use would have changed the reduction in sudden death seen with bypass surgery cannot be answered with currently available clinical trial data. The CABG Patch trial tested the addition of ICD therapy to bypass surgery patients, but interpretation of this relatively small trial is hampered by a low arrhythmic death rate (16,17). Conceptually, a trial containing both bypass surgery and ICDs would result in even lower arrhythmic event rates because these modalities influence different pathways to sudden deaths, and neither therapy could be expected to completely eliminate such

Table 5 Major Categories of Hospitalization: Site Adjudicated

Clinical Endpoint	CABG (n = 610)	MED (n = 602)	Hazard Ratio (95% CI)	p Value
Hospitalization (all cause)	290 (48)	340 (56)	0.77 (0.66–0.90)	0.001
Hospitalization (cardiac)	221 (36)	294 (49)	0.65 (0.55–0.78)	<0.001
Hospitalization (heart failure)	127 (21)	169 (28)	0.70 (0.56–0.88)	0.003

Values are n (%).
Abbreviations as in Table 2.



events as noted in the STICH trial for bypass surgery, in SCD-Heft for ICDs (34), and in CABG Patch for both therapies. It is of interest that the favorable effect of CABG

was more prominent after 24 months, which is consistent with a temporal relationship reported for the efficacy of ICD therapy and coronary revascularization in the MADIT-II

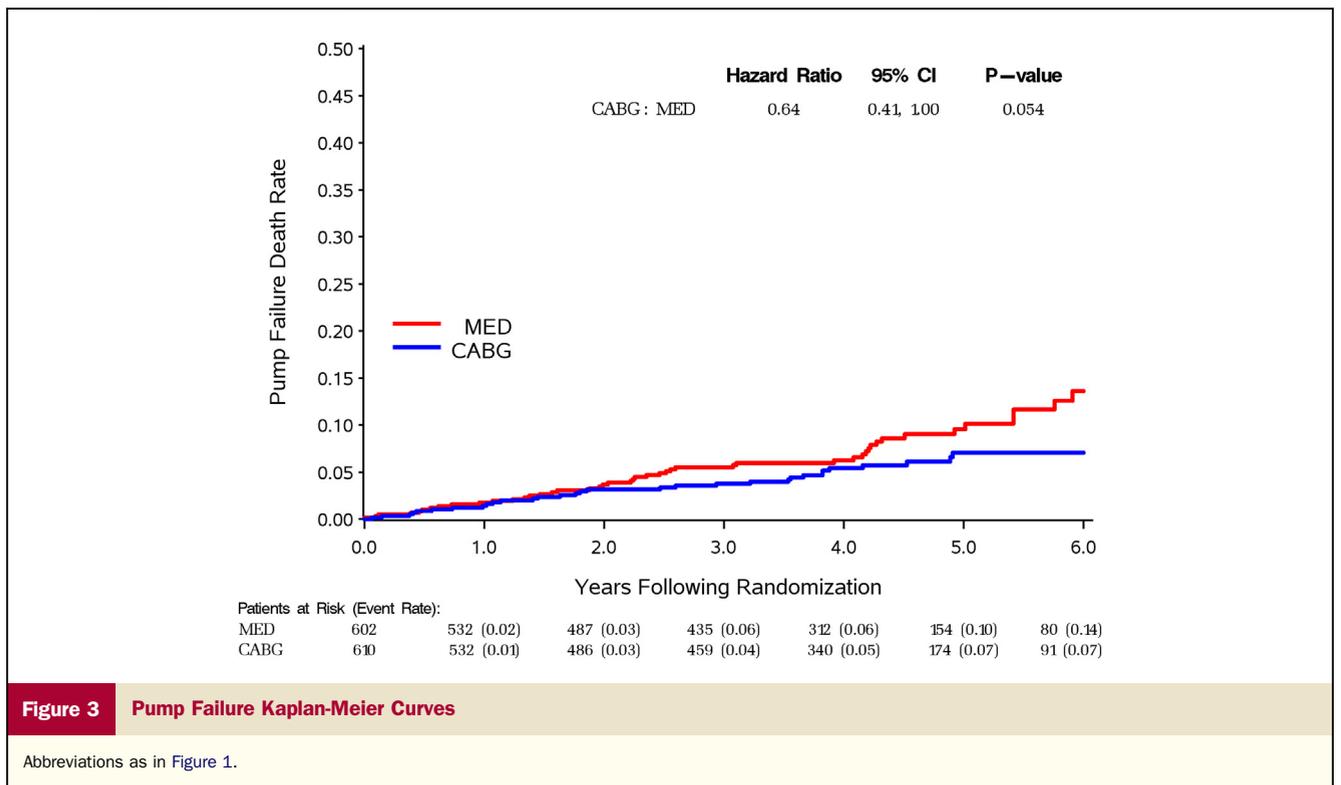


Table 6 Sudden Deaths and Pump Failure Deaths by Treatment Group

Events	Time Intervals Following Randomization (Months)	Number of Events		Hazard Ratio (CABG/MED)	95% CI of Hazard Ratio	p Value
		CABG (n = 610)	MED (n = 602)			
Sudden death	0-6	19	26	0.74	(0.41-1.34)	0.321
	6-24	26	28	0.93	(0.55-1.59)	0.801
	>24	29	45	0.60	(0.38-0.96)	0.032
	Overall	74	99	0.73	(0.54-0.99)	0.041
Pump failure death	0-6	5	6	0.84	(0.26-2.76)	0.778
	6-24	12	13	0.93	(0.42-2.03)	0.848
	>24	16	30	0.49	(0.27-0.90)	0.021
	Overall	33	49	0.64	(0.41-1.00)	0.054

Abbreviations as in Table 2.

(Multicenter Automatic Defibrillator Implantation Trial II) database (35). Furthermore, a continued late benefit on mortality has been noted previously in CABG trials (13,14).

Surgical therapy also reduced pump failure deaths, although this effect was only marginally significant due to a low number of events. It is interesting that this finding was present, considering the concept of “competing risk”: a favorable effect on sudden death could increase patients at risk for fatal pump failure events. There are no other prospective data on the CABG effect on pump failure deaths, and the SOLVD retrospective analysis described in the preceding text did not show a favorable association of previous bypass surgery with pump failure deaths (18). The explanation for benefit on pump failure outcomes is not certain. Previous data on ventricular function indicated an association with revascularization for viable myocardium (19,20)

although the substudy in the STICH trial did not indicate benefit associated with this pathway for CABG therapy (36). However, the favorable effect on pump failure deaths is consistent with the secondary outcome in the STICH trial of all-cause mortality or heart failure hospitalizations (9).

Myocardial infarction deaths were also decreased by CABG therapy in the STICH trial, although this was a small number of fatal events. As indicated in the preceding text, these data are concordant with the reduction in sudden death in that at least some of these events may represent severe ischemia or coronary thrombosis.

Cardiac procedure deaths were increased in the surgical group compared with medical therapy, a finding that would not be surprising in a population of patients with predominantly NYHA functional class II/III heart failure and depressed ejection fraction.

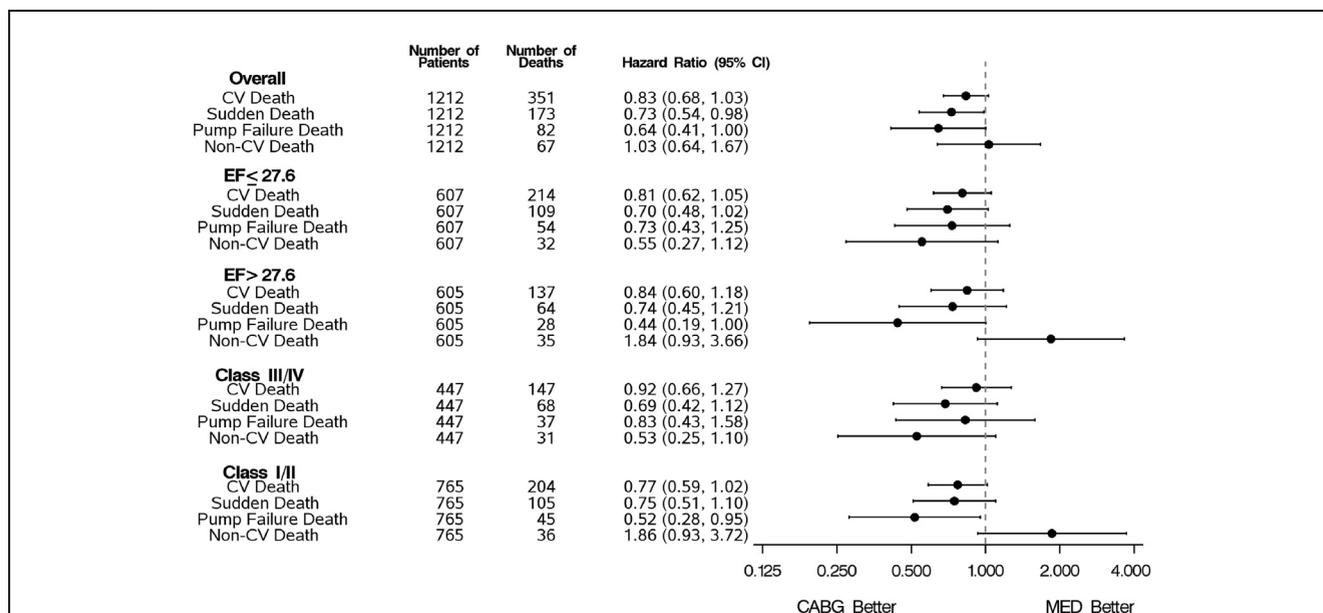


Figure 4 CV, Sudden Death, Pump Failure, and Non-CV Deaths

Data are by treatment group for LVEF and NYHA subgroups. EF = ejection fraction; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; other abbreviations as in Figure 1.

Effect of CABG therapy on mode of death for patients stratified by ejection fraction and NYHA class. In this analysis, patients with more impaired ventricular function and worse NYHA functional class had higher event rates, but the proportion of sudden and pump failure deaths or the direction of therapeutic effect did not change. There are no previous prospective data assessing the effect of bypass surgery on cause-specific outcomes in ischemic cardiomyopathy patients stratified by either ventricular function or heart failure severity. The CASS (Coronary Artery Surgery Study) (13) did indicate a relationship of ventricular function to risk for sudden death as well as an association with CABG therapy in a multivariable model, but it did not include patients with LVEF <34%, and there was no assessment of response to bypass surgery by NYHA functional class. The retrospective SOLVD analysis reported a consistent reduction of LVEF on sudden death rate in CABG patients.

Study limitations. Interpreting the results of secondary endpoints and subgroup analyses in clinical trials in which the primary outcome has not been met needs to be done with caution (37). However, the mode-of-death results are concordant directionally and in degree with the favorable effects previously reported on composite outcomes involving hospitalizations and in STICH (9) on major nonfatal hospitalization categories.

The adjudication of clinical endpoints is dependent upon the availability, accuracy, and quality of clinical information that is available from sites. The adjudication process in the STICH trial involved standardized definitions used in other heart failure trials, as well as the participation of experienced physicians. In the case of international clinical trials, there are limitations on availability of clinical material, and there may be some loss of information due to translation or patient follow-up. However, the STICH trial had excellent follow-up with missing status on only 5 patients (9). All clinical trials in heart failure must deal with the difficulties of sudden death events in that such events, thought to be predominantly arrhythmic, usually lack evidence of exact causality, and therefore, this categorization always contains an inherent uncertainty. Deaths assessed as unknown by the clinical event committee remained a separate category in this analysis; alternative approaches include classifying these as cardiovascular.

Conclusions

In the STICH trial, CABG therapy reduced the most common modes of death, sudden and pump failure. Fatal myocardial infarctions were also reduced, but the beneficial effects of bypass surgery on cardiovascular mortality were offset by an increase in post-procedure deaths. Non-cardiovascular deaths were relatively infrequent and did not differ between treatment groups. The beneficial effects on the 2 major modes of death were principally seen after 2 years. The durability of these findings is currently being tested in the STICH Extension study.

Acknowledgments

The authors wish to thank Vanessa Moore for her assistance in preparation of the manuscript, Thomas Barfield for administrative activities in the STICH trial, and James Hill, MD, and the publications committee for their review of the manuscript.

Reprint requests and correspondence: Dr. Peter Carson, Washington VA Medical Center, 50 Irving Street NW, Washington DC 20422. E-mail: peter.carson@va.gov.

REFERENCES

1. Jessup M, Brozena S. Heart failure. *N Engl J Med* 2003;348:2007-18.
2. The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med* 1987;316:1429-35.
3. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991;325:293-302.
4. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomized trial. *Lancet* 1999;353:9-13.
5. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet* 1999;353:2001-7.
6. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med* 1999;341:709-17.
7. Jhund PS, Macintyre K, Simpson CR, et al. Long-term trends in first hospitalization for heart failure and subsequent survival between 1986 and 2003: a population study of 5.1 million people. *Circulation* 2009;119:515-23.
8. Gheorghiadu M, Sopko G, De Luca L, et al. Navigating the crossroads of coronary artery disease and heart failure. *Circulation* 2006;114:1202-13.
9. Velazquez EJ, Lee KL, Deja MA, et al. Coronary-artery bypass surgery in patients with left ventricular dysfunction. *N Engl J Med* 2011;364:1607-16.
10. Cohn JN, Johnson G, Ziesche S, et al. Enalapril vs. hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. *N Engl J Med* 1991;325:303-10.
11. O'Connor CM, Carson PE, Belkin RN, et al. Effect of amlodipine on mode of death in severe chronic heart failure: the PRAISE trial. *Am J Cardiol* 1998;82:881-8.
12. Carson P, Anand I, O'Connor C, et al. Mode of death in advanced heart failure: the Comparison of Medical, Pacing, and Defibrillation Therapies in Heart Failure (COMPANION) trial. *J Am Coll Cardiol* 2005;46:2329-34.
13. Coronary Artery Surgery Study (CASS): a randomized trial of coronary artery bypass surgery: survival data. *Circulation* 1983;68:939-50.
14. Passamani E, Davis KB, Gillespie MJ, Killip T. A randomized trial of coronary artery bypass surgery: survival of patients with a low ejection fraction. *N Engl J Med* 1985;312:1665-71.
15. Holmes DR Jr., Davis KB, Mock MB, et al. The effect of medical and surgical therapy on subsequent sudden cardiac death in patients with coronary artery disease: a report from the Coronary Artery Surgery Study. *Circulation* 1986;73:1254-63.
16. Bigger JT Jr. Prophylactic use of implanted cardiac defibrillators in patients at high risk for ventricular arrhythmias after coronary-artery bypass graft surgery. *N Engl J Med* 1997;337:1569-75.
17. Bigger JT Jr., Whang W, Rottman JN, et al. Mechanisms of death in the CABG Patch trial: a randomized trial of implantable cardiac defibrillator prophylaxis in patients at high risk of death after coronary artery bypass graft surgery. *Circulation* 1999;99:1416-21.
18. Veenhuyzen GD, Singh SN, McAreavey D, et al. Prior coronary artery bypass surgery and risk of death among patients with ischemic left ventricular dysfunction. *Circulation* 2001;104:1489-93.
19. Allman KC, Shaw LJ, Hachamovitch R, et al. Myocardial viability testing and impact of revascularization on prognosis in patients with

- coronary artery disease and left ventricular dysfunction: a meta-analysis. *J Am Coll Cardiol* 2002;39:1151-8.
20. Elefteriades JA, Tolis G Jr., Levi E, et al. Coronary artery bypass grafting in severe left ventricular dysfunction: excellent survival with improved ejection fraction and functional state. *J Am Coll Cardiol* 1993;22:1411-7.
 21. Velazquez EJ, Lee KL, O'Connor CM, et al. The rationale and design of the Surgical Treatment for Ischemic Heart Failure (STICH) trial. *J Thorac Cardiovasc Surg* 2007;134:1540-7.
 22. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457-81.
 23. Kalbfleisch JD, Prentice RL. *The Statistical Analysis of Failure Time Data*. 2nd edition. New York, NY: John Wiley & Sons, 2002.
 24. Cox DR. Regression models and life-tables (with discussion). *J R Stat Soc Series B Stat Methodol* 1972;34:187-220.
 25. Solomon SD, Wang D, Finn P, et al. Effect of candesartan on cause-specific mortality in heart failure patients: the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) program. *Circulation* 2004;110:2180-3.
 26. Kjekshus J, Apetrei E, Barrios V, et al. Rosuvastatin in older patients with systolic heart failure. *N Engl J Med* 2007;357:2248-61.
 27. Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med* 2001;345:1667-75.
 28. O'Connor CM, Gottlieb S, Bourque JM, et al., BEST Investigators. Impact of nonfatal myocardial infarction on outcomes in patients with advanced heart failure and the effect of bucindolol therapy. *Am J Cardiol* 2005;95:558-64.
 29. Pigott JD, Kouchoukos NT, Oberman A, et al. Late results of surgical and medical therapy for patients with coronary artery disease and depressed left ventricular function. *J Am Coll Cardiol* 1985;5:1036-45.
 30. Hammermeister KE, DeRouen TA, Murray JA, et al. Effect of aortocoronary saphenous vein bypass grafting on death and sudden death: comparison of nonrandomized medically and surgically treated cohorts with comparable coronary disease and left ventricular function. *Am J Cardiol* 1977;39:925-34.
 31. Weintraub WS. Revascularization versus implantable cardioverter-defibrillators to prevent sudden death in patients with severe left ventricular dysfunction. *Circulation* 2001;104:1457-8.
 32. Uretsky BF, Thygesen K, Armstrong PW, et al. Acute coronary findings at autopsy in heart failure patients with sudden death: results from the Assessment of Treatment with Lisinopril and Survival (ATLAS) trial. *Circulation* 2000;102:611-6.
 33. Zannad F, McMurray JJV, Krum H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med* 2011;364:11-21.
 34. Packer DL, Prutkin JM, Hellkamp AS, et al. Impact of implantable cardioverter-defibrillator, amiodarone, and placebo on the mode of death in stable patients with heart failure: analysis from the Sudden Cardiac Death in Heart Failure Trial. *Circulation* 2009;120:2170-6.
 35. Goldenberg I, Moss AJ, McNitt S, et al. Time dependence of defibrillator benefit after coronary revascularization in the Multicenter Automatic Defibrillator Implantation Trial (MADIT)-II. *J Am Coll Cardiol* 2006;47:1811-7.
 36. Bonow RO, Maurer G, Lee KL, et al. Myocardial viability and survival in ischemic left ventricular dysfunction. *N Engl J Med* 2011;364:1617-25.
 37. Freemantle N. Interpreting the results of secondary endpoints in subgroup analyses in clinical trials: should we lock the crazy aunt in the attic? *BMJ* 2001;322:989-91.

Key Words: heart failure ■ mode of death ■ surgical.

 **APPENDIX**

For the full adjudication definitions and a supplementary table, please see the online version of this paper.