Influence of Baseline Characteristics, Operative Conduct, and Postoperative Course on 30-Day Outcomes of Coronary Artery Bypass Grafting Among Patients With Left Ventricular Dysfunction

Results From the Surgical Treatment for Ischemic Heart Failure (STICH) Trial

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Background—Patients with severe left ventricular dysfunction, ischemic heart failure, and coronary artery disease suitable for coronary artery bypass grafting (CABG) are at higher risk for surgical morbidity and mortality. Paradoxically, those patients with the most severe coronary artery disease and ventricular dysfunction who derive the greatest clinical benefit from CABG are also at the greatest operative risk, which makes decision making regarding whether to proceed to surgery difficult in such patients. To better inform such decision making, we analyzed the Surgical Treatment for Ischemic Heart Failure (STICH) CABG population for detailed information on perioperative risk and outcomes.

Methods and Results—In both STICH trials (hypotheses), 2136 patients with a left ventricular ejection fraction of ≤35% and coronary artery disease were allocated to medical therapy, CABG plus medical therapy, or CABG with surgical ventricular reconstruction. Relationships of baseline characteristics and operative conduct with morbidity and mortality at 30 days were evaluated. There were a total of 1460 patients randomized to and receiving surgery, and 346 (≈25%) of these high-risk patients developed a severe complication within 30 days. Worsening renal insufficiency, cardiac arrest with cardiopulmonary resuscitation, and ventricular arrhythmias were the most frequent complications and those most commonly associated with death. Mortality at 30 days was 5.1% and was generally preceded by a serious complication (65 of 74 deaths). Left ventricular size, renal dysfunction, advanced age, and atrial fibrillation/flutter were significant preoperative predictors of mortality within 30 days. Cardiopulmonary bypass time was the only independent surgical variable predictive of 30-day mortality.

Conclusions—CABG can be performed with relatively low 30-day mortality in patients with left ventricular dysfunction. Serious postoperative complications occurred in nearly 1 in 4 patients and were associated with mortality.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00023595.

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Patients with severe left ventricular (LV) dysfunction, ischemic heart failure, and coronary artery disease (CAD) suitable to coronary artery bypass grafting (CABG) benefit from CABG.[1] Because these patients are at higher risk of surgical morbidity and mortality than patients with milder forms of LV dysfunction, clinicians remain hesitant to refer

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these patients for CABG. Paradoxically, there is evidence that higher-risk patients with LV dysfunction and CAD, such as those with a lower LV ejection fraction (LVEF), more LV dilatation, and multivessel disease benefit the most from CABG.[2] Thus, physicians and patients are left with challenging decisions. Will the potential benefits for a given individual outweigh the short- and long-term morbidity and mortality of the procedure? A number of well-accepted surgical risk scores exist to help guide clinicians and patients in making informed decisions regarding the risks of surgery.[3–6] However, although helpful, these scores have not been specifically devised for patients with severe LV dysfunction (LVEF≤35%).

The Surgical Treatment for Ischemic Heart Failure (STICH) trial evaluated the role of CABG versus medical treatment and of CABG versus CABG plus surgical ventricular reconstruction (SVR) in patients with CAD amenable to CABG and a LVEF≤35%.[7] In addition to providing information regarding the risk of early (within 30 days) postoperative mortality, STICH provides information on the risk of postoperative complications and their impact on outcomes. Once surgery has been successfully performed and the first critical postoperative period survived, little information exists to inform the healthcare team regarding the prognosis of an individual patient or the impact of complications on their postoperative course.[8] The STICH trial provides an opportunity to evaluate clinical and surgical characteristics that identify patients at risk for both early and late postoperative morbidity and mortality, information that can help influence decisions on how to proceed given a specific patient profile.

The objectives of the present analyses were to (1) evaluate the association of baseline patient characteristics and operative conduct on 30-day postoperative complications and mortality and (2) evaluate the incidence of postoperative complications and their association with 30-day mortality.

Methods

The overall objective of the STICH trial was to define the role of revascularization surgery in the management of patients with ischemic cardiomyopathy. STICH tested 2 hypotheses: (1) whether CABG is superior to optimal medical treatment alone in improving survival in patients with a LVEF≤35% and CAD amenable to CABG, and (2) whether the addition of SVR to CABG in patients with anterior wall akinesis or dyskinesis is superior to CABG alone. The STICH trial hypothesis 1 results found that, although CABG did not significantly reduce all-cause mortality in comparison with optimal medical therapy alone, it did reduce the combined prespecified secondary end point of all-cause mortality plus cardiovascular hospitalization.[9] The results of hypothesis 2 found that the addition of SVR to CABG alone did not improve mortality or freedom from cardiovascular hospitalization.[10]

The STICH trial was carefully planned to create a unique cohort of international CABG-eligible patients with CAD and a LVEF≤35% for whom preoperative, intraoperative, and postoperative data were prospectively acquired by using structured data forms with standardized descriptions of common operative and postoperative treatment decisions. Past performance of at least 25 CABG operations on patients with a LVEF of ≤0.40 with an operative mortality of ≤5% was required for certification of all STICH surgeons. STICH cardiologists and cardiac anesthesiologists experienced in managing operative and perioperative care of CABG patients helped coordinate preoperative and postoperative patient management decisions. All participating cardiac surgeons composed the STICH Surgical Committee that met regularly during the active recruitment and treatment phase of the study.[7]

The Duke University Medical Center Institutional Review Board and the institutional review board or ethics committee for each participating institution approved the study protocol, and all the patients provided written informed consent.

Patient Population

Between July 24, 2002, and May 5, 2007, 2136 patients were enrolled in the National Institutes of Health–funded STICH trial[11] and randomly assigned to treatment with medical therapy alone (n=602), medical therapy plus CABG (n=1033), and medical therapy plus CABG and SVR (n=501; Figure 1). Of 1534 STICH patients randomly assigned to surgery, 74 did not undergo surgery (11 patients died after randomization and before surgery). Among the 1460 patients who received CABG, there were 495 patients who underwent CABG with SVR and 965 patients who underwent CABG alone. Patients randomly assigned to medical therapy that ultimately received CABG during the follow-up period (n=65) were not considered for these analyses because detailed perioperative and postoperative data were not collected in these patients.

All patients randomly assigned in STICH underwent baseline evaluations that included imaging of the LV at randomization. Descriptions of operative conduct and occurrence of perioperative complication events were recorded on the structured surgical treatment clinical report form by using explicit definitions (see online-only Data Supplement), and recorded at the time of hospital discharge post-CABG or at 30 days for patients who remained in the hospital for ≥30 days. Follow-up clinical assessment was performed at the time of hospital discharge or at 30 days post operation, and at 4-month intervals for the first year of follow-up, and thereafter at 6-month intervals over the remainder of the follow-up period. All postoperative in-hospital morbid events and complications that met a prespecified definition (online-only Data Supplement) and occurred within 30 days after the operation were tabulated.

The following postoperative complications were documented and considered major: return to the operating room (OR) for bleeding; return to the OR for any reason; mediastinitis; pulmonary edema requiring intubation; new-onset ventricular arrhythmia; cardiac arrest requiring cardiopulmonary resuscitation; worsening renal insufficiency (increase >2 mg/dL or 2× baseline creatinine or both); gastrointestinal complications; respiratory compromise; other major complications; acute myocardial infarction; and stroke. The following postoperative complications were documented and considered

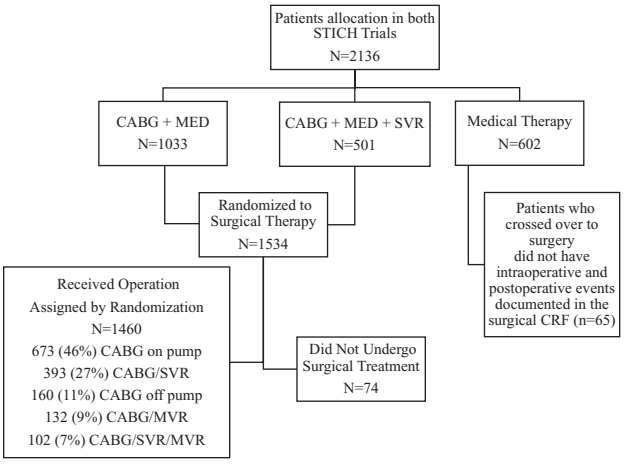

Figure 1. Consort diagram of patients enrolled in STICH that had CABG and the type of surgery performed. CABG indicates coronary artery bypass grafting; CRF, Case Report Form; MED, medical therapy; MVR, mitral valve repair/replacement; STICH, Surgical Treatment for Ischemic Heart Failure; and SVR, surgical ventricular reconstruction.

nonmajor: infection other than mediastinitis, new-onset atrial fibrillation, and delirium.

Statistical Analyses

Patient and operative conduct characteristics were summarized as number (percentage) for categorical variables and as median (25th, 75th percentile) for continuous variables. The characteristics of patients who did and did not develop major complications and who did and did not die within 30 days were summarized and compared with χ^2, Fisher's exact, or Wilcoxon rank-sum tests. Mortality rates in patients with different complications within the early postoperative interval are presented as Kaplan-Meier rates at 30 days. The Cox proportional hazards regression model was used in both univariable and multivariable analyses to identify baseline and perioperative factors associated with 30-day mortality. Time to death was censored at 30 days post operation in these analyses. The multivariable analysis used a backward elimination procedure to determine independently significant prognostic factors. For continuous variables, if needed, appropriate restricted cubic spline functions were used to assess linearity of the relationship of predictors with the log-hazard ratio in the Cox model. Candidate variables included baseline and intraoperative conduct characteristics. *P* values of <0.05 were considered statistically significant. All analyses were performed with SAS version 9.2 (SAS Institute, Inc, Cary, NC).

Results

Patient Outcomes

Of the 1460 patients who underwent CABG, 74 patients (5.1%) died within 30 days after surgery (of whom 65 [88%] died following at least 1 major complication). Five patients died in the OR, 45 died in an intensive care unit, 15 died in the step-down unit, and 9 died at home or in another facility. A total of 346 patients (23.7%) experienced at least 1 major complication. Of these 346 patients with at least 1 major complication, 65 (18.8%) died within 30 days of surgery. The remaining 1105 (75.7%) patients were alive without major complications at 30 days post operation. Patients without a major complication had <1% mortality, those with 1 major complication (14.3%) had 7% mortality, those with 2 major complications (5.8%) had 31% mortality, those with 3 major complications (1.6%) had 33% mortality, and those having ≥4 major complications (2.0%) had 59% mortality at 30 days.

Serious Postoperative Complications

The characteristics of patients who developed a serious postoperative complication in comparison with patients without serious complications are shown in Table 1. At enrollment, patients with postoperative complications were older, had more renal dysfunction defined as creatinine >1.5 mg/dL, previous CABG, more severe angina (Canadian Cardiovascular Society class), more symptomatic heart failure (New York Heart Association class), a higher Duke CAD score, more atrial fibrillation or flutter, a lower LVEF, a lower hemoglobin, and a lower 6-minute walk. Surgical characteristics of patients developing postoperative complications included prolonged aortic cross-clamp time, prolonged cardiopulmonary bypass pump time, and less use of cardioplegia. Surgical characteristics that marginally increased the risk of postoperative complications included SVR or mitral valve surgery. Notable characteristics not significantly associated with postoperative complications included diabetes mellitus, LV end-systolic volume index (LVESVI), and number of distal anastomoses.

The most frequent postoperative complications (Table 2) were worsening renal insufficiency (8.4%), new-onset ventricular arrhythmias (7.1%), cardiac arrest requiring cardiopulmonary resuscitation (4.7%), return to the OR for bleeding (3.8%), return to the OR for other reasons (3.6%), and pulmonary edema requiring intubation (3.1%). The complications most frequently associated with death were renal insufficiency (37 deaths), cardiac arrest requiring cardiopulmonary resuscitation (35 deaths), new-onset ventricular arrhythmia (31 deaths), and pulmonary edema requiring intubation (18 deaths). Acute myocardial infarction was infrequent (0.8%) but resulted in a high death rate (42%). Stroke was also infrequent (1.6%) and was not associated with as great a risk (17%) as most other major complications. Finally, the incidence of mediastinitis was low (1.7%) and associated with a relatively low mortality rate (8%) in comparison with other major complications.

Early (30 Days) Postoperative Mortality

The baseline preoperative characteristics of patients who died within 30 days post operation differed in a number of respects in comparison with those who survived (Table 3). Patients who died were older and had renal dysfunction, atrial fibrillation or flutter, more symptomatic heart failure, more mitral regurgitation, a lower LVEF, and a lower hemoglobin. In addition, they had a greater LVESVI and more peripheral vascular disease. Differences between the groups in less frequently occurring characteristics such as a history of stroke (12.2% versus 6.3%) did not reach statistical significance. The only operative characteristic associated with 30-day mortality was bypass time. Type of cardioplegia was not associated with mortality.

Univariable Relationship of Baseline and Surgical Characteristics (Conduct) With Mortality at 30 Days

The univariable relationships that were strongly predictive of 30-day mortality (Table 4) were creatinine, age, LVESVI, New York Heart Association class, hemoglobin, the presence of baseline atrial fibrillation or flutter, previous CABG, and bypass pump time >120 minutes.

Multivariable Model of Baseline and Operative Conduct and 30-Day Mortality

The multivariable model (C statistic of 0.83) identified creatinine and LVESVI as the 2 most powerful baseline and operative conduct characteristics for predicting 30-day mortality (Table 5). Mortality risk increased linearly with creatinine >1 mg⁄dL and appeared to level off at 1.6 mg⁄dL (Figure 2), although the number of patients with more elevated creatinine values was limited. Other strong (*P*<0.01) characteristics identified included age and moderate or severe mitral regurgitation. Other predictive characteristics were current angina, atrial fibrillation or flutter, hemoglobin, the preoperative use of both statins and aspirin, clopidogrel, or warfarin (reduced risk), cardiopulmonary bypass time >120 minutes, mitral valve procedure (reduced risk), body mass index, peripheral vascular disease, and a high Duke CAD index.

Discussion

This is the largest international cohort of CABG-eligible patients with CAD and low LVEF (≤35%) for whom

Table 1. Baseline and Surgical Characteristics and Complications

	n	No Major Complications	n	One or More Major Complications	*P* Value*
Age at randomization	1114	60.2 (53.3, 67.5)	346	65.1 (57.5, 71.3)	<0.0001
Female	1114	148 (13.3)	346	52 (15.0)	0.4100
Myocardial infarction	1114	918 (82.4)	346	294 (85.0)	0.2670
Hyperlipidemia	1111	756 (68.0)	346	229 (66.2)	0.5181
Hypertension	1114	645 (57.9)	346	224 (64.7)	0.0236
Diabetes mellitus	1114	397 (35.6)	346	137 (39.6)	0.1818
Peripheral vascular disease	1114	156 (14.0)	346	59 (17.1)	0.1622
Chronic renal insufficiency	1113	57 (5.1)	346	61 (17.6)	<0.0001
Body mass index, kg/m^2	1114	27.0 (24.4, 30.1)	346	27.2 (23.9, 30.5)	0.8051
Creatinine, mg/dL	1114	1.05 (0.90, 1.20)	346	1.16 (1.00, 1.40)	<0.0001
Hemoglobin, g/dL	1114	13.8 (12.7, 14.9)	346	13.6 (12.4, 14.7)	0.0127
Stroke	1114	66 (5.9)	346	31 (9.0)	0.0477
Previous PCI	1114	174 (15.6)	346	68 (19.7)	0.0780
Previous CABG	1114	22 (2.0)	346	16 (4.6)	0.0069
Current Canadian Cardiovascular Society Angina Class	1114		346		0.0073
None		313 (28.1)		108 (31.2)	
I		113 (10.1)		31 (9.0)	
II		317 (28.5)		70 (20.2)	
III		313 (28.1)		107 (30.9)	
IV		58 (5.2)		30 (8.7)	
Current NYHA heart failure class	1114		346		<0.0001
I		111 (10.0)		25 (7.2)	
II		546 (49.0)		131 (37.9)	
III		420 (37.7)		160 (46.2)	
IV		37 (3.3)		30 (8.7)	
Number of diseased vessels (≥75% stenosis)	1114		346		0.0650
None		24 (2.2)		5 (1.4)	
One		223 (20.0)		55 (15.9)	
Two		454 (40.8)		132 (38.2)	
Three		413 (37.1)		154 (44.5)	
Left main stenosis ≥50%	1114	147 (13.2)	346	58 (16.8)	0.0952
Proximal LAD stenosis ≥75%	1113	805 (72.3)	346	253 (73.1)	0.7725
Duke CAD index (0–100)	1114	65 (39, 77)	346	65 (43, 91)	0.0078
LVEF	1114	28 (23, 34)	346	26 (22, 33)	0.0068
LVESVI	1114	78 (59, 97)	346	81 (61, 104)	0.0705
Distance walked at baseline, meters	835	357 (280, 420)	234	331 (240, 399)	0.0005
Atrial fibrillation/flutter	1114	112 (10.1)	346	58 (16.8)	0.0007
Statin and at least 1 of ASA, clopidogrel, or warfarin	1114	768 (68.9)	346	217 (62.7)	0.0309
Mitral regurgitation	1111		340		0.0679
None or trace		417 (37.5)		110 (32.4)	
Mild (≤2+)		515 (46.4)		162 (47.6)	
Moderate (3+)		150 (13.5)		51 (15.0)	
Severe (4+)		29 (2.6)		17 (5.0)	
Number of distal anastomoses	1111	3 (2, 4)	343	3 (2, 4)	0.4778
Number of distal anastomoses, n (%)	1111		343		0.4504
0–1		101 (9.1)		32 (9.3)	
2–3		685 (61.7)		199 (58.0)	
≥4		325 (29.3)		112 (32.7)	

(*Continued*)

Table 1. Continued

	n	No Major Complications	n	One or More Major Complications	*P* Value*
More distal anastomoses than conduits	1114	258 (23.2)	346	78 (22.5)	0.8119
Arterial conduits ≥1, n (%)	1114	1019 (91.5)	346	308 (89.0)	0.1657
On pump surgery	1114	983 (88.2)	346	317 (91.6)	0.0789
Mitral valve procedure	1114	164 (14.7)	346	70 (20.2)	0.0147
SVR procedure	1114	362 (32.5)	346	133 (38.4)	0.0413
Surgery was not elective	1114	130 (11.7)	346	51 (14.7)	0.1301
Cardioplegia	1110		346		0.0039
None		177 (15.9)		41 (11.8)	
Crystalloid		254 (22.9)		62 (17.9)	
Blood		646 (58.2)		223 (64.5)	
Both		33 (3.0)		20 (5.8)	
Bypass pump time, min	1114	95 (65, 127)	346	112 (75, 158)	<0.0001
Cardiopulmonary bypass time >120 min	1114	321 (28.8)	346	151 (43.6)	<0.0001
Aorta cross-clamp time, min	1114	58 (36, 83)	346	67 (41, 95)	0.0001

The entries in this table are median (25th, 75th percentiles) for continuous variables and n (%) for categorical variables. ASA indicates aspirin; CABG, coronary artery bypass grafting; CAD, coronary artery disease; LAD, left anterior descending; LVEF, left ventricular ejection fraction; LVESVI, left ventricular end-systolic volume index; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; and SVR, surgical ventricular reconstruction.

*Wilcoxon rank-sum tests used for continuous variables and χ^2 tests used for categorical variables.

preoperative, intraoperative, and postoperative data were prospectively acquired permitting the analysis of variables associated with 30-day postoperative mortality and morbidity. Major postoperative complications were relatively frequent (23.7% of all cases) and correlated with death in 88% of fatal cases. Not surprisingly, clinical and operative characteristics predictive of postoperative complication and 30-day mortality were similar, with 1 notable exception. Increased LVESVI was not significantly associated with the risk of postoperative complications, but was 1 of the 2 characteristics most predictive of 30-day mortality. The only operative conduct characteristic predictive of 30-day mortality was prolonged cardiopulmonary bypass time, which likely reflects a more difficult or complicated operative procedure.[12–14]

Postoperative Complications

When a complication occurred, it was frequently followed by at least another complication (137 of 346 patients), and mortality increased markedly as more complications occurred.[15] Preoperative renal dysfunction, indices of LV dysfunction

Table 2. Perioperative Complications

Complications	n (%)	Deaths	30-day Kaplan-Meier Mortality Rate, %
Major complication			
Worsening renal insufficiency (increase >2 mg/dL and 2× baseline creatinine)	123 (8.4)	37	30
Cardiac arrest requiring CPR	69 (4.7)	35	51
New-onset ventricular arrhythmia	103 (7.1)	31	30
Pulmonary edema requiring intubation	45 (3.1)	18	40
Other major complication	21 (1.4)	9	43
Return to OR for other reason	53 (3.6)	9	17
Return to OR for bleeding	56 (3.8)	7	12
Acute MI	12 (0.8)	5	42
Stroke	24 (1.6)	4	17
Respiratory compromise	31 (2.1)	4	13
GI complication	14 (1.0)	2	14
Mediastinitis	25 (1.7)	2	8
Complications not considered major			
New-onset atrial fibrillation/flutter	329 (22.5)	26	8
Other infection	132 (9.0)	13	10
Delirium	65 (4.5)	7	11

CPR indicates cardiopulmonary resuscitation; GI, gastrointestinal; MI, myocardial infarction; and OR, operating room.

Table 3. Baseline and Surgical Characteristics and 30-Day Mortality

	n	Alive at 30 Days	n	30-Day Death	*P* Value*
Age at randomization	1386	60.8 (53.9, 68.1)	74	66.1 (59.9, 71.7)	0.0002
Female	1386	190 (13.7)	74	10 (13.5)	0.9621
Myocardial infarction	1386	1146 (82.7)	74	66 (89.2)	0.1465
Hyperlipidemia	1383	941 (68.0)	74	44 (59.5)	0.1244
Hypertension	1386	817 (58.9)	74	52 (70.3)	0.0532
Diabetes mellitus	1386	502 (36.2)	74	32 (43.2)	0.2216
Peripheral vascular disease	1386	194 (14.0)	74	21 (28.4)	0.0007
Chronic renal insufficiency	1385	102 (7.4)	74	16 (21.6)	<0.0001
Body mass index, kg/m^2	1386	27.0 (24.3, 30.1)	74	27.3 (23.4, 30.5)	0.9595
Creatinine, mg/dL	1386	1.08 (0.92, 1.24)	74	1.30 (1.05, 1.50)	<0.0001
Hemoglobin, g/dL	1386	13.8 (12.7, 14.9)	74	13.1 (12.2, 14.6)	0.0369
Stroke	1386	88 (6.3)	74	9 (12.2)	0.0869
Previous PCI	1386	231 (16.7)	74	11 (14.9)	0.6847
Previous CABG	1386	31 (2.2)	74	7 (9.5)	0.0023
Current Canadian Cardiovascular Society Angina Class	1386		74		0.0302
None		406 (29.3)		15 (20.3)	
I		139 (10.0)		5 (6.8)	
II		368 (26.6)		19 (25.7)	
III		395 (28.5)		25 (33.8)	
IV		78 (5.6)		10 (13.5)	
Current NYHA heart failure class	1386		74		0.0001
I		134 (9.7)		2 (2.7)	
II		647 (46.7)		30 (40.5)	
III		549 (39.6)		31 (41.9)	
IV		56 (4.0)		11 (14.9)	
Number of diseased vessels (≥75% stenosis)	1386		74		0.1796
None		29 (2.1)		0 (0)	
One		269 (19.4)		9 (12.2)	
Two		550 (39.7)		36 (48.6)	
Three		538 (38.8)		29 (39.2)	
Left main stenosis ≥50%	1386	194 (14.0)	74	11 (14.9)	0.8342
Proximal LAD stenosis ≥75%	1385	996 (71.9)	74	62 (83.8)	0.0258
Duke CAD Index (0–100)	1386	65 (39, 77)	74	65 (52, 91)	0.0312
LVEF	1386	28 (23, 34)	74	25 (20, 30)	0.0002
LVESVI	1386	78 (59, 98)	74	94 (71, 110)	<0.0001
Distance walked at baseline, meters	1022	350 (274, 420)	47	310 (224, 450)	0.3178
Atrial fibrillation/flutter	1386	151 (10.9)	74	19 (25.7)	0.0001
Statin and at least one ASA, clopidogrel, or warfarin	1386	945 (68.2)	74	40 (54.1)	0.0115
Mitral regurgitation	1378		73		0.0004
None or trace		513 (37.2)		14 (19.2)	
Mild (≤2+)		639 (46.4)		38 (52.1)	
Moderate (3+)		187 (13.6)		14 (19.2)	
Severe (4+)		39 (2.8)		7 (9.6)	
Total number of distal anastomoses	1381	3 (2, 4)	73	3 (2, 4)	0.6633
Number of distal anastomoses, n (%)	1381		73		0.5555
0–1		124 (9.0)		9 (12.3)	
2–3		843 (61.0)		41 (56.2)	
≥4		414 (30.0)		23 (31.5)	

(*Continued*)

Table 3. Continued

	n	Alive at 30 Days	n	30-Day Death	*P* Value*
More distal anastomoses than conduits	1386	323 (23.3)	74	13 (17.6)	0.2533
Arterial conduits ≥1, n (%)	1386	1264 (91.2)	74	63 (85.1)	0.0774
On pump surgery	1386	1231 (88.8)	74	69 (93.2)	0.2350
Mitral valve procedure	1386	219 (15.8)	74	15 (20.3)	0.3072
SVR procedure	1386	466 (33.6)	74	29 (39.2)	0.3243
Surgery was not elective	1386	170 (12.3)	74	11 (14.9)	0.5086
Cardioplegia	1382		74		0.7758
None		204 (14.8)		14 (18.9)	
Crystalloid		301 (21.8)		15 (20.3)	
Blood		826 (59.8)		43 (58.1)	
Both		51 (3.7)		2 (2.7)	
Bypass pump time, min	1386	97 (66, 131)	74	125 (90, 176)	<0.0001
Cardiopulmonary bypass time >120 min	1386	434 (31.3)	74	38 (51.4)	0.0003
Aorta cross-clamp time, min	1386	60 (37, 86)	74	72 (32, 92)	0.1413

The entries in this table are median (25th, 75th percentiles) for continuous variables and n (%) for categorical variables. ASA indicates aspirin; CABG, coronary artery bypass grafting; CAD, coronary artery disease; LAD, left anterior descending; LVEF, left ventricular ejection fraction; LVESVI, left ventricular end-systolic volume index; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; and SVR, surgical ventricular reconstruction.

*Fisher's exact tests used for stroke and previous CABG. χ^2 tests used for the remaining categorical variables, and Wilcoxon rank-sum tests used for continuous variables.

including LVEF, and exertional tolerance, such as New York Heart Association class and distance walked, were the patient characteristics most closely associated with the development of major postoperative complications. Although it would appear that particular caution should be exercised when considering CABG in these patients, these are precisely the clinical characteristics that identify those patients who may have the most to gain from CABG.[2] Strategies to optimize pre- and perioperative renal[16] and cardiac function as well as myocardial protection[17–19] may be particularly important factors to consider in the management of these complex patients.[20]

Postoperative 30-Day Mortality

Worsening renal function (37 of 74 deaths), cardiac arrest requiring cardiopulmonary resuscitation (35 of 74 deaths), the development of ventricular arrhythmias (31 of 74 deaths), and pulmonary edema requiring intubation (18 of 74 deaths), were the postoperative complications most frequently associated with death. Worsening renal function probably reflects numerous risk factors and probably also contributes to the development of pulmonary edema requiring intubation. These complications are all generally associated with poor or worsening LV function, which may also be reflective of a complicated, difficult, and prolonged operation.

Myocardial infarction, stroke, and mediastinitis were reasonably infrequent and associated with a relatively small number of deaths, 5, 4, and 2, respectively. The low major adverse event rate of these 3 complications may help explain the low 30-day postoperative mortality seen in the STICH trial.[21]

Patients undergoing CABG with impaired LV function are among the most challenging patients undergoing coronary surgery.[22] Commonly, the EuroSCORE, Society of Thoracic Surgeons, and New York state risk scores are used to assess the risk in patients undergoing CABG.[3–6] These risk scores do not specifically and thoroughly address the patient with severe LV dysfunction. However, as with commonly used risk scores, STICH identified advanced age, renal dysfunction, low LVEF, and the presence of more advanced atherosclerosis, whether a higher Duke CAD severity score or the presence of peripheral vascular disease, as important risk factors. Again, although Duke CAD severity score identified patients at higher risk, previous analyses of STICH have also identified these patients to be among those that benefit most by CABG.[2] As opposed to commonly used risk scores, sex was not predictive of 30-day mortality in STICH.

The second most powerful predictor of 30-day mortality in STICH was LVESVI. Mortality risk increased linearly with increasing values of LVESVI (Figure 2). This measurement not only reflects reduced LVEF, but reflects the degree of LV remodeling that is itself an independent predictor of poor outcome.[23] Well-established surgical risk scores have identified LVEF as a very powerful predictor of surgical and 30-day mortality, but, because of the lack of availability, LVESVI has not been included in these scores. In STICH patients, LVESVI was a stronger predictor of 30-day mortality than LVEF as a significant independent predictor of 30-day mortality. Postinfarct studies have also found LVESVI to be a more important predictor of outcome than LVEF.[24] Thus, in considering the surgical risk of death in patients with LV dysfunction, LVESVI should be carefully evaluated because it appears to carry more prognostic significance for risk than does LVEF and also predicts a better outcome with CABG than with medical therapy alone.[2]

The only operative conduct characteristic predictive of 30-day mortality was prolonged cardiopulmonary bypass time. As mitral valve surgery was associated with reduced mortality, and SVR was not independently associated with increased mortality, it would appear likely that the increased

Table 4. Univariable Association Between Baseline and Surgical Characteristics and 30-Day Mortality

Characteristic	HR (95% CI)	χ^2	*P* Value
Age, HR for 10-y increase	1.60 (1.25–2.05)	13.63	0.0002
Female	0.99 (0.51–1.93)	<0.01	0.9732
Myocardial infarction	1.71 (0.82–3.56)	2.06	0.1512
Hyperlipidemia	0.70 (0.44–1.11)	2.36	0.1244
Hypertension	1.61 (0.98–2.66)	3.55	0.0597
Diabetes mellitus	1.33 (0.84–2.11)	1.48	0.2233
Peripheral vascular disease	2.35 (1.42–3.90)	10.99	0.0009
Chronic renal insufficiency	3.22 (1.85–5.60)	17.14	<0.0001
BMI, HR for 1 kg/m^2 increase		10.39	0.0155
≤ 25	0.83 (0.74–0.93)		
25–30	1.19 (1.02–1.37)		
Creatinine, HR for 0.1 mg/dL increase		35.94	<0.0001
≤1.0	0.68 (0.52–0.89)		
1.0–1.4	1.65 (1.38–1.97)		
Hemoglobin, HR for 1 g/dL increase		13.11	0.0044
<12.5	1.21 (0.82–1.78)		
12.5–15.5	0.64 (0.48–0.84)		
>15.5	2.08 (1.32–3.29)		
Stroke	2.00 (1.00–4.02)	3.80	0.0511
Previous PCI	0.87 (0.46–1.66)	0.17	0.6774
Previous CABG	4.16 (1.91–9.07)	12.89	0.0003
Current angina	1.62 (0.92–2.85)	2.75	0.0971
Current NYHA HF class, HR for 1 category increase	1.80 (1.30–2.49)	12.73	0.0004
Number of diseased vessels (≥75% stenosis)	1.21 (0.90–1.63)	1.54	0.2153
Left main stenosis ≥ 50%	1.07 (0.56–2.03)	0.04	0.8412
Proximal LAD stenosis ≥ 75%	1.99 (1.07–3.69)	4.76	0.0292
Duke CAD Index, HR for 10 U increase		7.88	0.0194
≤ 53	1.81 (1.16–2.82)		
> 53	0.95 (0.80–1.14)		
Ejection fraction, HR for 10% increase	0.58 (0.44–0.77)	14.11	0.0002
ESVI, HR for 100 mL/m^2 increase	3.19 (1.90–5.34)	19.34	<0.0001
Atrial fibrillation/flutter	2.70 (1.60–4.55)	13.92	0.0002
Statin and at least one ASA, clopidogrel, or warfarin	0.56 (0.36–0.89)	6.13	0.0133
Moderate or severe mitral regurgitation	1.99 (1.20–3.31)	7.17	0.0074
Total number of distal anastomoses	1.01 (0.82–1.25)	0.01	0.9036
More distal anastomoses than conduits	0.71 (0.39–1.29)	1.29	0.2569
Arterial conduits ≥ 1	0.56 (0.30–1.07)	3.11	0.0777
CABG with CPB	1.71 (0.69–4.25)	1.35	0.2450
Mitral valve procedure	1.34 (0.76–2.36)	1.03	0.3111
SVR procedure	1.26 (0.79–2.02)	0.97	0.3250
Surgery was not elective	1.24 (0.65–2.35)	0.43	0.5142
Cardioplegia (reference is none)		1.12	0.7730
Crystalloid	0.73 (0.35–1.52)		
Blood	0.76 (0.42–1.39)		
Both	0.58 (0.13–2.55)		
Cardiopulmonary bypass time > 120 min	2.27 (1.44–3.58)	12.38	0.0004

ASA indicates aspirin; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CI, confidence interval; CPB, cardiopulmonary bypass; LAD, left anterior descending; ESVI, end-systolic volume index; HF, heart failure; HR, hazard ratio; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; and SVR, surgical ventricular reconstruction.

Table 5. Multivariable Association Between Baseline and Surgical Characteristics and 30-Day Mortality (C statistic=0.826)

Variable	HR (95% CI)	*P* Value
Creatinine, HR for 0.1 mg/dL increase		<0.0001
≤1.0	0.67 (0.51–0.89)	
1.0–1.4	1.52 (1.26–1.82)	
ESVI, HR for 100 mL/m^2 increase	2.73 (1.50–4.98)	0.0010
Age, HR for 10-y increase	1.47 (1.12–1.93)	0.0052
Moderate or severe mitral regurgitation	2.35 (1.27–4.34)	0.0065
Current angina	2.08 (1.17–3.70)	0.0126
Atrial fibrillation/flutter	1.97 (1.14–3.39)	0.0153
Hemoglobin, HR for 1 g/dL increase		0.0178
<12.5	1.41 (0.91–2.19)	
12.5–15.5	0.68 (0.51–0.90)	
>15.5	1.88 (1.19–2.96)	
Cardiopulmonary bypass time >120 min	1.83 (1.10–3.04)	0.0199
Body mass index, HR for 1 kg/m^2 increase		0.0202
0–25	0.86 (0.76–0.97)	
25–30	1.21 (1.04–1.41)	
Mitral valve procedure	0.43 (0.20–0.90)	0.0251
Peripheral vascular disease	1.84 (1.07–3.18)	0.0278
Statin and at least 1 ASA, clopidogrel, or warfarin	0.58 (0.36–0.95)	0.0285
Duke CAD Index, HR for 10-point increase to 53	1.46 (1.00–2.13)	0.0485

ASA indicates aspirin; CAD, coronary artery disease; CI, confidence interval; ESVI, end-systolic volume index; and HR, hazard ratio.

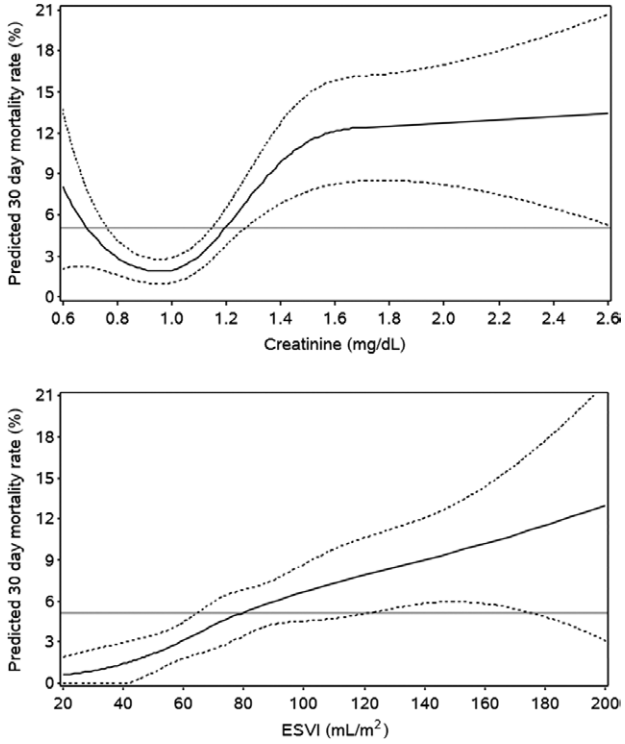

Figure 2. Relationship between creatinine and LVESVI vs 30-day mortality and the 95% confidence interval (dotted lines). LVESVI indicates left ventricular end-systolic volume index.

risk associated with cardiopulmonary bypass time is reflective of a more difficult and complex revascularization procedure rather than concomitant surgical procedures. Consistent with this hypothesis is the lack of association between mortality and aortic cross-clamp time found in this and other analyses.[12]

Mitral valve surgery at the time of CABG was the only surgical characteristic associated with improved 30-day survival. It is unclear why this was associated with improved survival, but it may result from a beneficial effect on patients with significant mitral regurgitation and heart failure.[25,26] In STICH, mitral valve repair (221 of 234 mitral valve surgeries) was the overwhelming form of mitral valve surgery performed, such that differential results for mitral valve repair versus replacement cannot be evaluated. The finding of reduced risk with mitral valve surgery in the present analysis is also consistent with the long-term benefits demonstrated in STICH when mitral valve repair is performed at the time of CABG in patients with moderate to severe mitral regurgitation.[27] These findings also differ from those of a recent trial of 300 patients with moderate ischemic mitral regurgitation randomly assigned to receive CABG plus mitral repair or CABG only.[28] In those patients, who had significantly better LV function than in STICH, no significant difference was found in LVESVI, survival, or quality of life at 12 months, but there was a 30% lower prevalence of moderate or severe mitral regurgitation, suggesting that mitral valve repair may have greater benefit in patients with more severe LV dysfunction, or that the benefit of mitral valve repair may not be seen until these patients have been followed for a longer period of time.

Clinical Implications

This analysis of the STICH trial data has identified a number of patient characteristics that predict an increased risk of 30-day postoperative complications and mortality risk. Paradoxically some of these risk factors, such as LVESVI, LVEF, and more extensive CAD, also predict which patients will improve most with CABG. The presence of moderate to severe mitral regurgitation also predicts patients at greater risk, but again, mitral regurgitation repair appears to have a marked beneficial effect, both short and long term and should be performed when appropriate. Other factors that increase risk and that are difficult to modify, such as renal dysfunction, advanced age, and the presence of atrial fibrillation or flutter, among others, may encourage surgeons to perhaps choose operative procedures that limit cardiopulmonary bypass time.

Limitations

The results of these analyses need to be viewed within the context of the STICH trial where these procedures were performed by surgical teams with proven excellent results in such high-risk patients. Also, patients in STICH were relatively young (with a median age of 61 years) when enrolled and mortality may be higher than that reported in STICH for older more fragile patients and those with other comorbidities. Finally, this STICH analysis did not consider patients that crossed over from medical therapy to CABG. Although the addition of these 65 patients may have altered the results somewhat because these crossover patients had a particularly

good outcome,[29] it is probable that their inclusion would have had limited impact on our findings.

These analyses identified patient and operative characteristics associated with increased risk of serious postoperative complications and mortality, but did not evaluate interventions that could reduce these risks. Also, other variables known to be important in assessing postoperative risk, such as pulmonary hypertension, that were not prospectively collected and not considered in these analyses may be as important in identifying risk as those considered in the present analyses.

Conclusions

The STICH trial demonstrated that CABG can be performed with relatively low 30-day mortality in patients with severe LV dysfunction and ischemic heart failure. Despite this low mortality, serious complications are relatively common in these high-risk patients and occur before death in the majority of patients dying within 30 days of surgery. Greater renal dysfunction, LVESVI, advanced age, and preoperative atrial fibrillation or flutter are the strongest baseline characteristics predictive of a poor survival. Prolonged cardiopulmonary bypass time is the single operative characteristic independently predictive of poor early outcome.

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Disclosures

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Influence of Baseline Characteristics, Operative Conduct, and Postoperative Course on 30-Day Outcomes of Coronary Artery Bypass Grafting Among Patients With Left Ventricular Dysfunction: Results From the Surgical Treatment for Ischemic Heart Failure (STICH) Trial

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SUPPLEMENTAL MATERIAL

Supplemental Methods: CRF instructions to sites for patients randomized to CABG or CABG + SVR treatment

Mediastinitis: Any wound disruption exposing the sternum or requiring a secondary operation or stabilization of the sternum prior to discharge.

Other infection: All other types of major postoperative infections (except mediastinitis), such as pneumonia, pyelonephritis, septicemia, and infections at the vein-harvest site.

New onset atrial flutter/fibrillation (AF): New onset AF in a patient that was previously in normal sinus rhythm (regardless of history of AF) at randomization lasting at least 24 hours and/or requiring electrical or chemical cardioversion.

New onset ventricular arrhythmia: Ventricular tachycardia sustained for >30 seconds or ventricular tachycardia requiring anti-arrhythmic or cardioversion.

Worsening renal insufficiency: An insufficiency resulting in an increase of >2 mg/dL and 2x baseline creatinine level or a new requirement for dialysis.

Delirium: State of mental confusion and excitement characterized by disorientation for time and place, usually with illusions and hallucinations.

Acute MI: A myocardial infarction characterized by at least 2 of the following criteria:

- Prolonged (>20 min) typical chest pain not relieved by rest and/or nitrates.

- Enzyme level elevation defined as troponin T or I ≥3x ULN or CK-MB ≥2x normal in medically treated patients, CK-MB ≥3x normal in patients after PCI, or CK-MB ≥5x normal in patients after CABG.
- At least 2 serial ECGs with changes and/or serially in ST-T and/or Q waves that are 0.03 seconds in width and/or one third or more of the total QRS complex in 2 or more contiguous leads.

Stroke: A new central neurological deficit (i.e., extremity weakness or loss of motion, loss of consciousness, loss of speech, field cuts) of sudden onset that is not reversible within 24 hours and not due to a readily identifiable cause (i.e. brain tumor, or trauma) persisting >72 hours after onset or leading to death.

Complications, which were available to check by investigators in the clinical report form, had pre-specified definitions, but also an open category "other." All complications filled in category "other" are listed in Supplemental Table 1. After reviewing this list based on clinical judgment, two authors/investigators, who are experienced cardiac surgeons, made the decision to create new categories: GI complications, respiratory compromise, other major, and other non-major.

Supplemental Table 1

All postoperative in-hospital morbid events and complications that met a pre-specified definition that occurred within 30 days after operation were tabulated. Definitions follow.

Major Complications Derived from Case Report Form (CRF) Text
Gastrointestinal
Peripheral, abdominal embolism (suspected)
Small bowel ischemia
Acute pancreatitis
GI bleeding
Cholestasis
Ileus
Upper GI bleed

Hospitalized for GI distress
Gastric bleeding
Mesenteric ischemia
GI bleeding duodenal
Lower digestive tract hemorrhage
Acute gastritis

Respiratory compromise

- Respiratory insufficiency
- Left bronchus obturation requiring bronchoscopy and aspiration
- Intensive respiratory therapy
- Tracheostomy
- Pneumothorax
- Pneumothorax [left pleural effusion]
- Respiratory distress
- Pneumonia with reintubation
- Desaturation to below 90% oxygen saturation on room air
- Respiratory arrest
- Pneumothorax
- Re-intubation
- Tracheotomy
- Reintubation for bronchospasm
- Reintubation for low oxygen saturation
- Respiratory failure
- Pneumonia with intubation
- Intubation
- Nitric oxide inhalation (patient died at ICU being intubated)
- Pleural effusion
- Reintubation for chronic obstructive pulmonary disease

Other major complications

- Defibrillation
- Pulmonary embolus
- Tamponade
- Multi-organ failure (MOF)
- Severe bleeding
- ECMO
- Cardiogenic shock
- Heart failure
- Right femoral thrombectomy Grade IV medical limits
- Low cardiac output – heart failure
- Hypotension traced back to ACU
- Sepsis
- Seizures
- Liver failure
- Systemic inflammatory response syndrome
- Septic shock
- ECMO
- Stroke
- Dialysis

Not considered major and not included as a complication in the models

- Left pleural effusion
- Large left pleural effusion
- Pleural effusion
- Pleural effusion
- Pleural effusion and puncture
- Electrocardioversion
- IABP placed electively at preinduction of anesthesia
- IABP
- Pneumocystydiosis
- Recurrent atrial fibrillation
- Anemia, requested 3 blood units
- Postoperative anemia requiring transfusion
- Anemia, requested 2 blood transfusion
- 2 units of PRBCS and 1 unit of FFP
- Blood transfusion
- Oliguria
- Intraventricular conduction delay
- Cardioversion for atrial flutter/fibrillation
- Hyperamylasemia
- Perianal abscess
- Leg edema
- Ventricular fibrillation/cardiac arrest before enrollment to STICH
- Psychotic syndrome
- Hydrothorax
- Pneumonia
- Pericardial fluid
- Thoracentesis
- Unstable sternum
- Hypotension
- Anaphylactic reaction postoperatively
- Hematuria
- Depression
- RFA radiofrequency ablation was performed because of macro re-entry atrial tachycardia
- Low output syndrome
- Coagulopathy
- Anterior compartment syndrome of left lower extremity requiring fasciotomy and muscle debridement
- Hemodynamic instability at the time of chest opening (beginning of the procedure) resulted in low cardiac output of the wheezing from cardiopulmonary bypass at the end of the procedure
- Allergic reaction against plasma transfusion
- Transient ischemic attack
- Transient ischemic attack
- Pericardial effusion syndrome post cardiotomy
- Transient sinus pause
- Hyperthermia
- Chronic renal insufficiency
- Cerebrovascular accident – stroke or TIA
- Hyperkalemia
- Hyperamylasemia
- Tinnitis

- Low hematocrit
- Left ventricular thrombus
- Peripheral artery occlusion
- Fever
- Arrhythmia
- High chest tube output
- Temporary pacemaker for heart rate
- Non-functioning ICD re-implant