Quality-of-Life Outcomes With Coronary Artery Bypass Graft Surgery in Ischemic Left Ventricular Dysfunction

A Randomized Trial

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Background: The STICH (Surgical Treatment for Ischemic Heart Failure) trial compared a strategy of routine coronary artery bypass grafting (CABG) with guideline-based medical therapy for patients with ischemic left ventricular dysfunction.

Objective: To describe treatment-related quality-of-life (QOL) outcomes, a major prespecified secondary end point in the STICH trial.

Design: Randomized trial. (ClinicalTrials.gov: NCT00023595)

Setting: 99 clinical sites in 22 countries.

Patients: 1212 patients with a left ventricular ejection fraction of 0.35 or less and coronary artery disease.

Intervention: Random assignment to medical therapy alone (602 patients) or medical therapy plus CABG (610 patients).

Measurements: A battery of QOL instruments at baseline (98.9% complete) and 4, 12, 24, and 36 months after randomization (collection rates were 80% to 89% of those eligible). The principal prespecified QOL measure was the Kansas City Cardiomyopathy Questionnaire, which assesses the effect of heart failure on patients' symptoms, physical function, social limitations, and QOL.

Results: The Kansas City Cardiomyopathy Questionnaire overall summary score was consistently higher (more favorable) in the CABG group than in the medical therapy group by 4.4 points (95% CI, 1.8 to 7.0 points) at 4 months, 5.8 points (CI, 3.1 to 8.6 points) at 12 months, 4.1 points (CI, 1.2 to 7.1 points) at 24 months, and 3.2 points (CI, 0.2 to 6.3 points) at 36 months. Sensitivity analyses to account for the effect of mortality on follow-up QOL measurement were consistent with the primary findings.

Limitation: Therapy was not masked.

Conclusion: In this cohort of symptomatic high-risk patients with ischemic left ventricular dysfunction and multivessel coronary artery disease, CABG plus medical therapy produced clinically important improvements in quality of life compared with medical therapy alone over 36 months.

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Clinical trials performed during the 1970s and 1980s defined several major coronary artery disease (CAD) subgroups for which coronary artery bypass grafting (CABG) provided incremental survival, angina relief, or both relative to medical therapy. These early trials formed the foundation for current practice patterns and guideline recommendations on the use of CABG (1–3). However, patients with severe left ventricular dysfunction (ejection fraction ≤0.35) were not represented. Thus, management decisions for these patients have largely relied on clinical judgment to extrapolate from those trials and a small group of observational studies (4, 5). The challenges in using this evidence to select treatment for contemporary patients is further complicated by the substantial improvement in medical therapies for both CAD and heart failure over those used in the earlier trials.

The STICH (Surgical Treatment for Ischemic Heart Failure) trial was funded by the National Heart, Lung, and Blood Institute in 2002 to provide a comprehensive evaluation of the incremental therapeutic benefits of routine CABG over contemporary guideline-based medical therapy in patients with severe systolic dysfunction due to CAD (6). A major prespecified secondary end point of the trial was health-related quality of life (QOL), which is an outcome that complements the major clinical end points by assessing the patient's experience of, and satisfaction with, the 2 therapeutic strategies compared (7, 8).

METHODS

Patient Population and Primary Clinical Results

To test the STICH trial's surgical revascularization hypothesis, we randomly assigned 1212 patients with site-defined left ventricular ejection fraction of 0.35 or less and CAD suitable for revascularization to CABG or medical therapy (6). Rationale, trial design, and complete inclusion and exclusion criteria have been described previously (7). Patients were enrolled at 99 clinical sites in 22 countries between July 2002 and May 2007. All patients provided

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Summary for Patients I-26

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Supplements

informed consent, and study protocol was approved by each site's institutional review board or ethics committee.

Median follow-up was 56 months. The primary intention-to-treat comparison showed that 35.7% of patients assigned to CABG and 40.5% of those assigned to medical therapy died (primary analysis: unadjusted hazard ratio for all-cause mortality, 0.86 [95% CI, 0.72 to 1.04]; $P = 0.123$; secondary analysis: adjusted hazard ratio for all-cause mortality, 0.82 [CI, 0.68 to 0.99]; $P = 0.039$). Patients assigned to CABG had lower rates of the 2 major secondary clinical end points: death from cardiovascular causes (hazard ratio, 0.81; $P = 0.050$) and the composite of all-cause mortality and hospitalization for cardiovascular causes (hazard ratio, 0.74; $P < 0.001$).

Context

A randomized, controlled trial of patients with high-risk coronary artery disease and heart failure previously reported no significant difference between medical therapy alone and medical therapy plus coronary artery bypass grafting when the outcome was death from any cause.

Contribution

This study from the same trial reports that medical therapy plus coronary artery bypass grafting is better than medical therapy alone when the outcome is quality of life.

Caution

The type of therapy was not concealed from patients or investigators.

Implication

This is the first study to examine how these therapies affect quality of life in patients who have coronary artery disease and heart failure.

—The Editors

Health-Related QOL Data Collection

We collected QOL data using structured interviews at baseline and 4, 12, 24, and 36 months after randomization. Site coordinators were specially trained by the Duke Clinical Research Institute Outcomes Research Group to conduct baseline interviews. The original research plan called for all patients to be enrolled in North America and all English- and Spanish-language follow-up QOL interviews to be completed via telephone by the Duke Clinical Research Institute. The few patients expected to require French-language interviews were to be interviewed by site coordinators. When enrollment was expanded outside of North America, the plan was modified to have those site coordinators do all QOL interviews in the patient's native language. For non–English-speaking participants, translations of the QOL instruments were obtained from the instrument developers or a translation service was used to create validated translations. The New York Heart Association (NYHA) class and Canadian Cardiovascular Society (CCS) angina class were collected on the clinical case report form at baseline and each follow-up interval.

QOL Measures

A battery of validated measures was used to provide a comprehensive but efficient assessment of QOL. The principal prespecified QOL measure was the Kansas City Cardiomyopathy Questionnaire (KCCQ), which is a 23-item instrument that measures the effect of heart failure symptoms on QOL (9). We used 3 scales from the Seattle Angina Questionnaire to assess the effect of angina symptoms on QOL outcomes (10), the Short Form-12 Survey to provide a brief overall generic measure of health status (11), and 5 individual scales from the Short Form-36 Health Survey to provide a more detailed assessment of areas of functioning and well-being from a generic perspective (12). Depressive symptoms were assessed using the Center for Epidemiologic Studies Depression Scale (13). The Cardiac Self-Efficacy Questionnaire was used to measure patient confidence in controlling disease symptoms and maintaining physical functioning (14). Finally, we used the EuroQol-5D, which is a generic instrument consisting of a 5-dimension single summary health status index and a self-rated visual analogue scale (0 to 100) of current health-related QOL (15).

Statistical Analysis

All primary comparisons were performed with the treatment group defined according to the intention-to-treat principle. Descriptive statistics included percentages for discrete variables and medians with 25th to 75th percentiles plus means with SDs for continuous variables. The chi-square test was used for discrete variable comparisons. Treatment comparisons of continuous variables were done by using a linear mixed model to account for repeated measures within a patient. The baseline QOL measure was used as one of the repeated measures. In PROC MIXED in SAS, version 9.2 (SAS Institute), the baseline, 4-, 12-, 24-, and 36-month measurements within a patient were fitted using maximum likelihood methods with unstructured covariance matrix (16). At each time point, estimated treatment differences, 95% CIs, and P values were obtained using the model estimates. Finally, the proportion of patients who achieved a clinically important improvement of 5 points or more in KCCQ overall summary scores were compared by treatment group using the chi-square test (17). All analyses were conducted using SAS, version 8 or higher.

All reported P values were 2-sided. No adjustment was made in significance levels for multiple comparisons. Benchmarks for clinically significant changes in QOL scores for individual patients were used informally to assess the magnitude of the mean difference between the 2 groups. However, a QOL difference between groups at or exceeding the benchmark was not used as a formal decision rule to define clinical significance.

Subgroup Analysis

Regional effects were tested as interactions between the 5 regions used in the clinical analyses (Asia, Australia and New Zealand, Europe, North America, and South America) and the KCCQ overall summary score. Other interactions tested from those prespecified in the clinical analysis plan included age, sex, race, current NYHA class, left ventricular ejection fraction, baseline diabetes, CCS angina class, and myocardium viability.

Sensitivity Analysis

Some QOL data were missing because a small proportion of living patients did not complete a scheduled QOL assessment and a larger proportion of patients died before 1 or more of the scheduled assessments could be done. Almost all cases of missing data among living patients were attributed to administrative reasons rather than their state of health (**Supplement 1**, available at www.annals.org), which supports the assumption of missing at random and the use of multiple imputation techniques.

The STICH trial had a high overall mortality rate and a treatment-related mortality difference, as noted previously. These deaths produced a nonrandom group of survivors who provided the follow-up QOL data. No consensus exists in the statistical literature about how best to analyze intermediate end points, such as QOL, when death prevents complete data collection. The primary concern this issue raises in a treatment comparison is that a therapy more effective at preventing death may also preserve more patients with poor QOL than the comparison therapy. Thus, when comparing QOL in such a situation using all survivors, the therapy with the worse survival might have an artifactual improvement in QOL measurements. Rubin has proposed that because QOL data that are "censored due to death" do not exist even in theory and should be regarded as undefined, the most meaningful analysis is to compare QOL for patients in the 2 treatment groups who would have survived with either therapy (18). To accomplish this, we performed a survival average causal effect (SACE) analysis (18–21). The SACE estimates of QOL are calculated from weighted averages of the QOL data multiplied by survival probability estimates (from survival models developed in the parent STICH study cohort) specific to the study group. The 95% CIs for the SACE were calculated using 200 repetitions of a nonparametric bootstrap procedure (22). These sensitivity analyses are helpful as supplements to the primary analysis but have their own difficulties, not the least of which are the important but untestable assumptions they require.

Finally, to evaluate the possible effects of treatment crossovers on QOL results, we performed as-treated and per-protocol analyses.

Table 1. **Baseline Characteristics***

Characteristic	Medical Therapy (n = 602)	CABG + Medical Therapy (n = 610)
Median age (IQR), y†	59 (53–67)	60 (54–68)
Female	75 (12)	73 (12)
Race/ethnicity†		
White	402 (67)	389 (64)
Hispanic, Latino, or non-White	200 (33)	221 (36)
Median BMI (IQR), kg/m^2	27 (24–30)	27 (24–30)
Medical history		
Previous myocardial infarction	472 (78)	462 (76)
Diabetes	238 (40)	240 (39)
Previous stroke	41 (7)	51 (8)
Previous CABG	14 (2)	22 (4)
Current smoker	122 (20)	130 (21)
Current CCS angina class		
0–1	316 (52)	313 (52)
2–4	286 (48)	297 (48)
Current NYHA class		
I	74 (12)	65 (11)
II–IV	528 (88)	545 (89)

BMI = body mass index; CABG = coronary artery bypass grafting; CCS = Canadian Cardiovascular Society; IQR = interquartile range; NYHA = New York Heart Association.
* Modified from reference 6. Values are reported as numbers (percentages) unless otherwise indicated.
† Self-reported.

Role of the Funding Source

This study was conducted in collaboration with and support from the National Heart, Lung, and Blood Institute. The authors designed the study, collected and analyzed the data, wrote all versions of the article, and are fully responsible for its contents. Dr. Mark had full access to all of the data in the study and had final responsibility for the decision to submit for publication.

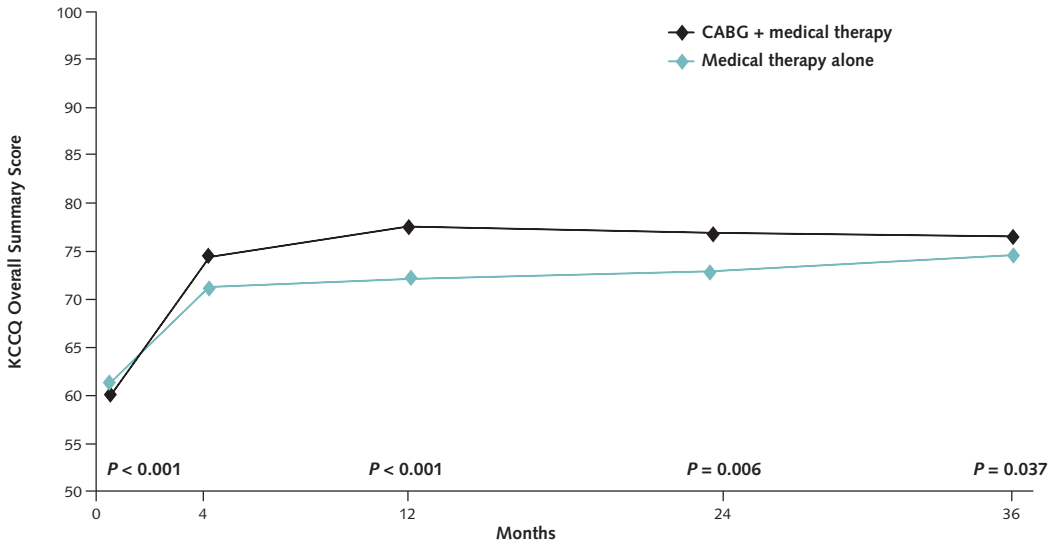
RESULTS

Baseline Characteristics and QOL Data Collection Rates

Of the 1212 patients, 610 were randomly assigned to CABG and 602 to medical therapy alone. The baseline characteristics were well-balanced between the 2 treatment groups (**Table 1**) (6). Overall, the median age of the patients was 60 years and 12.2% were female. Seventy-seven percent (77.1%) had a history of myocardial infarction. Thirty-seven percent (36.9%) had either NYHA class III or IV heart failure symptoms, 51.7% had class II, and 11.5% had class I. Thirty-six percent (36.5%) of patients had no angina at the time of randomization, 15.4% had class I, and 43.3% had class II. Median ejection fraction was 0.27, and 74.7% had multivessel CAD (≥75% diameter stenosis).

We collected baseline QOL data on 1199 (98.9%) of the 1212 patients randomly assigned. Of 4293 patient contacts expected during the 36-month follow-up, 3644 QOL questionnaires were collected, which represented 80.1% to 89.3% of patients eligible at each assessment interval (**Supplement 1**). During follow-up, 0.6% of patients declined to complete forms and 4.2% of forms collected were incomplete. The rate of missing QOL assessments did not differ by treatment group at baseline or any follow-up interval.

Figure 1. **KCCQ overall summary scale.**



CABG + medical therapy, *n*					
Questionnaire data	607	520	476	418	412
Dead	0	49	79	122	149
Missing	3	41	55	70	49
CABG	0	478	443	397	387
Medical therapy alone, *n*					
Questionnaire data	592	537	473	417	391
Dead	2	29	71	115	167
Missing	8	36	58	70	44
CABG	0	40	53	67	69

Higher scores indicate more favorable quality of life, fewer symptoms, and better functioning. Data are shown by intention to treat. Values below the *x*-axis are the numbers of patients with questionnaire data, patients who died, patients with missing questionnaire data, and patients with provided questionnaire data who had received CABG surgery at each follow-up assessment. CABG = coronary artery bypass grafting; KCCQ = Kansas City Cardiomyopathy Questionnaire.

Quality-of-Life Outcomes

On the basis of the KCCQ overall summary score, which was the prespecified primary QOL outcome measure, both treatment groups experienced improved heart failure–specific QOL over the initial 4 months of treatment (**Figure 1** and **Table 2**). At 4 months, the CABG group improved more than the medical therapy group (by 4.4 points [95% CI, 1.8 to 7.0 points]; adjusted $P < 0.001$) (**Table 2**). The difference favoring CABG was larger at 12 months (5.8 points [CI, 3.1 to 8.6 points]; adjusted $P < 0.001$) and persisted at 24 months (4.1 points [CI, 1.2 to 7.1 points]; adjusted $P = 0.006$) and 36 months (3.2 points CI, 0.2 to 6.3 points; adjusted $P = 0.037$). The 4 components of the KCCQ overall summary score showed similar patterns and magnitudes of differences (**Supplement 2**, available at www.annals.org). When we compared the proportion of patients in each group who had a clinically important improvement in the KCCQ overall summary score (≥5 points) relative to baseline, more patients in the CABG group met this criterion: 9 more patients per 100 at 4 months ($P = 0.002$), 11 more per 100 at 12 months ($P < 0.001$), 10 more per 100 at 24 months ($P = 0.005$), and 7 more per 100 at 36 months ($P = 0.046$). This corresponds to a number needed to treat of 9 to 14 patients treated with CABG plus medical therapy instead of medical therapy alone to produce 1 extra patient with a clinically meaningful improvement in QOL.

The Seattle Angina Questionnaire angina frequency scale showed higher (more favorable) scores for CABG at 4 months (9.4 points; $P < 0.001$), 12 months (9.2 points; $P < 0.001$), 24 months (6.7 points; $P < 0.001$), and 36 months (4.3 points; $P = 0.010$) (**Figure 2** and **Supplement 3**, available at www.annals.org). The Seattle Angina Questionnaire QOL subscale showed a very similar pattern (**Supplement 3**).

Psychological well-being (Short Form-36 Health Survey Mental Health Inventory 5) was better in the CABG group at 4 months, had the largest relative improvement at 12 and 24 months, and did not differ between groups at 36 months (**Supplement 4**, available at www.annals.org). The Short Form-36 Health Survey vitality and social func-

Table 2. **KCCQ Overall Summary Score***

KCCQ Overall Summary Score†	CABG + Medical Therapy (n = 610)	Medical Therapy Alone (n = 602)	Adjusted Difference Between CABG and Medical Therapy (95% CI)	Adjusted P Value
Baseline				
Patients, *n*	607	592	–	–
Median (IQR)	62 (44–77)	62 (45–80)	–	–
Mean (SD)	60.3 (22.3)	61.3 (23.2)	–	–
4 mo				
Patients, *n*	520	537	–	–
Median (IQR)	79 (62–92)	74 (57–89)	–	–
Mean (SD)	74.3 (21.0)	71.2 (21.3)	4.4 (1.8–7.0)	<0.001
12 mo				
Patients, *n*	476	473	–	–
Median (IQR)	85 (65–94)	78 (57–92)	–	–
Mean (SD)	77.5 (20.4)	72.2 (22.7)	5.8 (3.1–8.6)	<0.001
24 mo				
Patients, *n*	418	417	–	–
Median (IQR)	83 (65–93)	80 (59–92)	–	–
Mean (SD)	76.9 (20.1)	72.9 (23.4)	4.1 (1.2–7.1)	0.006
36 mo				
Patients, *n*	412	391	–	–
Median (IQR)	83 (65–93)	80 (60–92)	–	–
Mean (SD)	76.6 (20.9)	74.5 (21.4)	3.2 (0.2–6.3)	0.037
All follow-up				
Patients, *n*	1826	1818	–	–
Median (IQR)	82.0 (64–93)	78 (58–92)	–	–
Mean (SD)	76.2 ± 20.6	72.5 ± 22.2	4.4 (2.0–6.8)	<0.001

CABG = coronary artery bypass grafting; IQR = interquartile range; KCCQ = Kansas City Cardiomyopathy Questionnaire.
* By intention to treat.
† Mean of the physical limitations, total symptom, quality-of-life, and social limitation scores. Scale, 0–100; higher scores represent better outcomes.

tion scales showed a similar pattern. At baseline, 43.2% of patients were depressed as measured by the Center for Epidemiologic Studies Depression Scale (**Supplement 5**, available at www.annals.org). No statistically significant difference in depression between groups was observed at 4 months (26.6% in the CABG group vs. 27.5% in the medical therapy group; $P = 0.78$) or 12 months (25.0% vs. 26.9%; $P = 0.55$), but depression increased in the medical therapy group at 24 months (24.1% vs. 31.1%; $P = 0.027$) and this difference persisted to 36 months (22.4% vs. 29.5%; $P = 0.031$). The EuroQol-5D visual analogue scale showed improvement for the CABG group compared with the medical therapy group starting at 4 months, peaking at 12 and 24 months, and then diminishing by 36 months (**Supplement 6**, available at www.annals.org). The EuroQol-5D summary health index (**Supplement 6**) and the 2 summary SF-12 generic health status measures (**Supplement 4**) showed marginal treatment differences.

NYHA and CCS Angina Class

The percentage in each treatment group with NYHA class I heart failure symptoms at baseline was similar (10.7% in the CABG group vs. 12.3% in the medical therapy group; $P = 0.37$) (**Supplement 7**, available at www.annals.org). More patients had NYHA class I in the CABG group at 4 months (40.4% vs. 28.8%; $P < 0.001$), 12 months (41.8% vs. 34.2%; $P < 0.001$), 24 months (40.7% vs. 30.7%; $P = 0.004$), 36 months (37.2% vs. 32.3%; $P = 0.192$), and 48 months (34.9% vs. 31.4%; $P = 0.43$). The percentage of patients with CCS angina class I was similar in both treatment groups at baseline (51.3% vs. 52.5%; $P = 0.68$) (**Supplement 7**), but the CABG group had more patients with CCS angina class I at 4 months (93.2% vs. 75.9%; $P < 0.001$), 12 months (89.5% vs. 79.0%; $P < 0.001$), 24 months (91.5% vs. 84.6%; $P = 0.003$), 36 months (89.2% vs. 82.3%; $P = 0.012$), and 48 months (87.2% vs. 84.0%; $P = 0.32$).

Subgroup Analysis

No overall interaction between geographic region and treatment benefit from CABG was seen. No statistically significant interactions were found between treatment assignment and prespecified baseline characteristics with respect to the KCCQ overall summary score (**Supplement 8**, available at www.annals.org).

Sensitivity Analysis

To account for potential biases introduced by the loss of QOL data due to death, we estimated the SACE for the

KCCQ at each follow-up point. The results (**Table 3**) were not materially different from the primary study analysis.

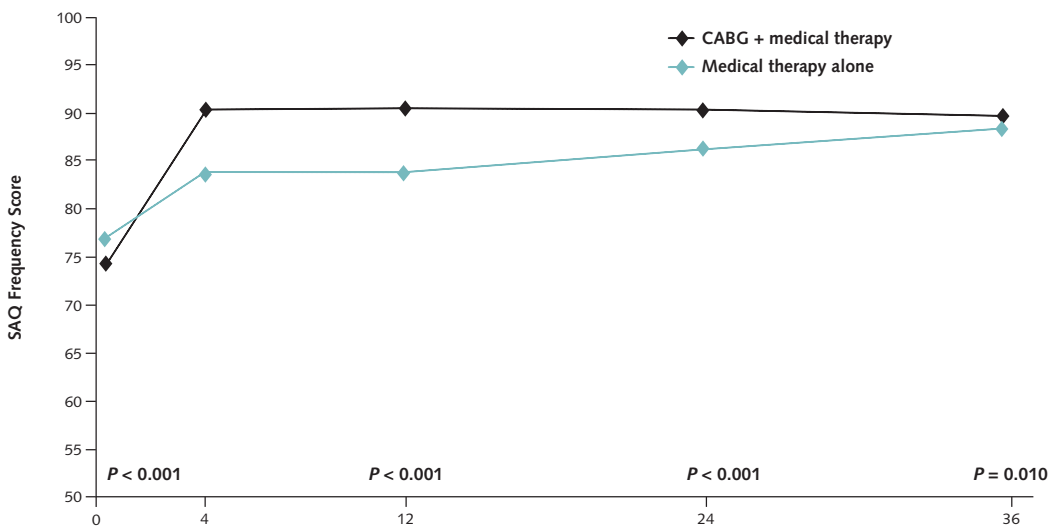
Neither the treatment received nor the per-protocol analyses produced important differences from the primary analysis (**Supplement 9**, available at www.annals.org).

DISCUSSION

Compared with guideline-based medical therapy alone, routine CABG plus medical therapy produced clinically relevant improvements in health-related QOL—pertaining to heart failure, angina, and overall health—in patients with ischemic left ventricular dysfunction. Treatment differences were evident as soon as 4 months after randomization (9 additional patients with ≥5-point improvement in QOL score per 100 treated with CABG), peaked in magnitude at 12 to 24 months (10 to 11 additional patients with clinically important improvement per 100 treated), and were still evident at 36 months (7 additional patients with clinically relevant improvement per 100 treated). To our knowledge, the STICH trial is the first randomized comparison of these 2 therapies using contemporary versions of both therapies and the first to include a comprehensive assessment of health-related QOL. The pattern of QOL treatment benefits for CABG was seen in the principal QOL measure (the KCCQ, which reflects heart failure–related QOL outcomes) and various secondary QOL outcome measures reflecting angina symptoms, physical and social functioning, and general well-being. Overall, these data describe a consistent and coherent benefit in QOL from CABG over medical therapy alone from the patient's perspective. Clinician-derived measures of symptom relief and functional status were consistent with the patient-derived QOL data; 35% to 42% of surgically treated patients achieved freedom from heart failure symptoms (NYHA class I), whereas about 90% of CABG patients were free of angina (CCS class I) during follow-up.

The STICH trial is the first large-scale randomized trial to evaluate the QOL benefits of CABG in patients with ischemic cardiomyopathy. Earlier trials of CABG in other populations with CAD found that angina relief was more frequent with CABG through 5 years (23, 24). At 10 years, however, CABG and medical therapy had a similar proportion of patients without angina. The STICH population differs from all prior large revascularization trial populations in having both angina and heart failure symptoms and an ejection fraction of 0.35 or less.

Figure 2. **SAQ angina frequency scale.**



CABG + medical therapy, *n*					
Questionnaire data	594	506	459	404	395
Dead	0	49	79	122	149
Missing	16	55	72	84	66
Medical therapy alone, *n*					
Questionnaire data	584	522	458	403	372
Dead	2	29	71	115	167
Missing	16	51	73	84	63

Higher scores reflect lower incidence of angina symptoms. Values below the *x*-axis are the numbers of patients with questionnaire data, patients who died, and patients with missing questionnaire data at each follow-up assessment. CABG = coronary artery bypass grafting; SAQ = Seattle Angina Questionnaire.

Table 3. **Effect of CABG Plus Medical Therapy Versus Medical Therapy Alone on the KCCQ Overall Summary Score***

Time Point	Estimated Difference Between CABG and Medical Therapy With the Adjusted Model (95% CI)†	Estimated Difference Between CABG and Medical Therapy With Survival Average Causal Effect (95% CI)‡
4 mo	4.4 (1.8 to 7.0)	3.1 (0.4 to 5.7)
12 mo	5.8 (3.1 to 8.6)	5.4 (2.7 to 8.0)
24 mo	4.1 (1.2 to 7.1)	4.0 (1.0 to 7.0)
36 mo	3.2 (0.2 to 6.3)	2.1 (−0.8 to 5.0)

CABG = coronary artery bypass grafting; KCCQ = Kansas City Cardiomyopathy Questionnaire.
* Positive values indicate better health status with CABG.
† A linear mixed model was used to account for repeated measures in the same patient.
‡ Calculated from weighted averages of the quality-of-life data multiplied by survival probability estimates specific to the study group, with 95% CI calculated using 200 repetitions of a nonparametric bootstrap procedure. These estimates represent the differences in quality-of-life outcomes in the subpopulation of patients who would have survived with either treatment.

The primary limitation to our study comes from the uncertainty created by missing outcome data. In a clinical trial, QOL outcome data may be missing for various reasons, and those missing data may result in a biased estimate of treatment effect (25). In this study, we had missing data in patients who were still alive, mostly due to administrative issues, when the data were theoretically obtainable (**Supplement 1**), and missing data due to patient death (26). Although in the former situation, an assumption of missing at random is often reasonable and use of multiple imputation methods to fill in the missing values can improve precision and reduce bias, death due to the disease or treatments being studied creates nonrandom withdrawals in the QOL data. In that situation, the data are not missing but rather are undefined (18, 19, 27). We used SACE analysis to examine the potential biases caused by loss of QOL data due to death (18–20). Conceptually, the SACE estimates the QOL results that would have been expected in the subset of patients who would have survived in either treatment group. These counterfactual analyses (**Table 3**) provide important reassurances that our primary results are robust to the effect of QOL data loss due to death.

Two other important caveats should be considered during interpretation of our results. First, no masking of therapy was possible in the STICH trial and patient or clinician knowledge of treatment assignment could have created expectations for recovery in patients independent of the treatment effects themselves. However, we believe that this is unlikely to be the full explanation for our findings, given that the largest effects were seen in the disease-specific measures that were expected a priori to show the most sensitivity to treatment and the treatment effect was sustained for up to 3 years. A potential related concern is possible bias introduced by the site coordinators who did QOL interviews and were aware of treatment assignment. To mitigate this potential problem, we required all site coordinators involved in QOL data collection to have formal training in structured interviewing techniques by the QOL coordinating center. This training emphasized the importance of strict adherence to wording and ordering questions, avoiding nonverbal cues, and using neutral probes when required. Second, our data showed that the magnitude of QOL benefits for CABG at 36 months was consistently smaller than at 12 or 24 months. Our analysis showed that this was not due to crossovers from medical therapy to CABG in the first year, and the small number of crossovers that occurred later also does not seem responsible (data not shown). The NYHA class and CCS angina class data collected at 48 months show no residual treatment benefit for CABG and suggest that the pattern of attenuation of benefits we observed for many QOL measures between 24 and 36 months is completed by 48 months. The cause of this attenuation is not evident.

In conclusion, we found that CABG provided clinically important QOL improvements relative to medical therapy alone for up to 36 months in patients with ischemic left ventricular dysfunction.

From Outcomes Research Group, Duke Clinical Research Institute, Duke University Medical Center, Duke University, Durham, North Carolina; Medical University of Silesia, Katowice, Poland; Queen Elizabeth II Health Sciences Centre, Dalhousie University, Halifax, Nova Scotia, Canada; Saint Luke's Mid America Heart Institute/University of Missouri–Kansas City, Kansas City, Missouri; All India Institute of Medical Sciences, Delhi, India; Baylor Soltero Cardiovascular Research Center, Dallas, Texas; SAL Hospital, Ahmedabad, India; and National Heart, Lung, and Blood Institute, Bethesda, Maryland.

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Reproducible Research Statement: *Study protocol and statistical code*: Not available. *Data set*: Will be made available for public access via the National Heart, Lung, and Blood Institute according to National Institutes of Health policy (see www.nhlbi.nih.gov/research/funding/human-subjects/set-preparation-guidelines.htm).

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