



Extent of Coronary and Myocardial Disease and Benefit From Surgical Revascularization in LV Dysfunction

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ABSTRACT

BACKGROUND Patients with ischemic left ventricular dysfunction have higher operative risk with coronary artery bypass graft surgery (CABG). However, those whose early risk is surpassed by subsequent survival benefit have not been identified.

OBJECTIVES This study sought to examine the impact of anatomic variables associated with poor prognosis on the effect of CABG in ischemic cardiomyopathy.

METHODS All 1,212 patients in the STICH (Surgical Treatment of IsChemic Heart failure) surgical revascularization trial were included. Patients had coronary artery disease (CAD) and ejection fraction (EF) of $\leq 35\%$ and were randomized to receive CABG plus medical therapy or optimal medical therapy (OMT) alone. This study focused on 3 prognostic factors: presence of 3-vessel CAD, EF below the median (27%), and end-systolic volume index (ESVI) above the median (79 ml/m²). Patients were categorized as having 0 to 1 or 2 to 3 of these factors.

RESULTS Patients with 2 to 3 prognostic factors (n = 636) had reduced mortality with CABG compared with those who received OMT (hazard ratio [HR]: 0.71; 95% confidence interval [CI]: 0.56 to 0.89; p = 0.004); CABG had no such effect in patients with 0 to 1 factor (HR: 1.08; 95% CI: 0.81 to 1.44; p = 0.591). There was a significant interaction between the number of factors and the effect of CABG on mortality (p = 0.022). Although 30-day risk with CABG was higher, a net beneficial effect of CABG relative to OMT was observed at >2 years in patients with 2 to 3 factors (HR: 0.53; 95% CI: 0.37 to 0.75; p < 0.001) but not in those with 0 to 1 factor (HR: 0.88; 95% CI: 0.59 to 1.31; p = 0.535).

CONCLUSIONS Patients with more advanced ischemic cardiomyopathy receive greater benefit from CABG. This supports the indication for surgical revascularization in patients with more extensive CAD and worse myocardial dysfunction and remodeling. (Comparison of Surgical and Medical Treatment for Congestive Heart Failure and Coronary Artery Disease [STICH]; [NCT00023595](https://clinicaltrials.gov/ct2/show/study/NCT00023595)) (J Am Coll Cardiol 2014;64:553-61) © 2014 by the American College of Cardiology Foundation.

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**ABBREVIATIONS
AND ACRONYMS****CABG** = coronary artery bypass
graft surgery**CAD** = coronary artery disease**EF** = ejection fraction**ESVI** = end-systolic volume
index**LV** = left ventricular**NHLBI** = National Heart, Lung,
and Blood Institute**OMT** = optimal medical therapy**PCI** = percutaneous coronary
interventions

Unlike any other form of left ventricular (LV) dysfunction, patients with ischemic cardiomyopathy have the potential to improve their prognosis with revascularization. Recent randomized controlled trials have shown that revascularization with coronary artery bypass graft (CABG) surgery is superior to that with percutaneous coronary interventions (PCI) in patients with multivessel coronary artery disease (CAD) (1,2). However, the decision to pursue CABG is usually difficult in ischemic cardiomyopathy patients, particularly because the presence and severity of LV dysfunction impose a higher operative risk (3,4). The STICH (Surgical Treatment of IsChemic Heart failure) trial recently tested the hypothesis that surgical revascularization with CABG improves the survival of patients with ischemic LV dysfunction compared with that of patients receiving optimal medical therapy (OMT) without revascularization (5). During a median follow-up of 56 months, STICH demonstrated a trend toward better survival with CABG that did not reach statistical significance ($p = 0.12$) (5). Importantly, the treatment effect of CABG over medical therapy occurred in a clear time-dependent pattern, with an early (within 30 days) increased hazard related to the operative mortality and a late (≥ 2 years) survival benefit (Fig. 1).

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Several previous studies have shown that among patients with CAD, the number of vessels with angiographically detected stenoses, the LV ejection fraction (EF), and the LV end-systolic volume index (ESVI) are associated with prognosis (3,4,6-12). However, how these variables should be incorporated into the decision regarding revascularization in patients with ischemic cardiomyopathy is unclear. Hazard ratio (HR) analyses of pre-determined subgroups in STICH did not identify any variable with a statistically significant interaction with treatment allocation (see Fig. 3 Velazquez et al. [5]) and the lack of statistical significance for the primary endpoint in STICH has led to the concept that the indication for surgical revascularization in ischemic cardiomyopathy can be safely deferred until medical therapy fails or the

patient becomes unstable (13,14). However, previous analyses did not address whether the time-dependent survival relationship between the 2 treatment arms varies according to baseline risk.

Accordingly, the purpose of this study was to examine the impact of key anatomic variables used in routine clinical practice and known to be associated with prognosis on the time-dependent hazard of CABG relative to that of OMT in patients enrolled in the surgical revascularization hypothesis of the STICH trial. We hypothesized that this analysis could lead to the recognition of a group of patients whose early surgical risk is rapidly surpassed by subsequent survival benefit and in whom, therefore, the indication for CABG is more clearly supported.

METHODS

STUDY POPULATION. STICH was a prospective, multicenter, nonblinded, randomized trial sponsored by the National Heart, Lung, and Blood Institute (NHLBI) that recruited 2,136 patients with CAD and LV EF of $\leq 35\%$ between 2002 and 2007. The trial was designed to address 2 primary hypotheses: 1) that CABG combined with OMT improved survival compared with OMT alone (surgical revascularization hypothesis); and 2) that surgical ventricular reconstruction added to CABG improved survival free of cardiovascular hospitalization compared with CABG alone in patients with significant anterior wall akinesis (surgical ventricular reconstruction hypothesis). The trial design and results of the 2 primary hypotheses have been reported previously (5,15,16). For the purpose of this study, only the 1,212 patients included in the surgical revascularization arm were considered.

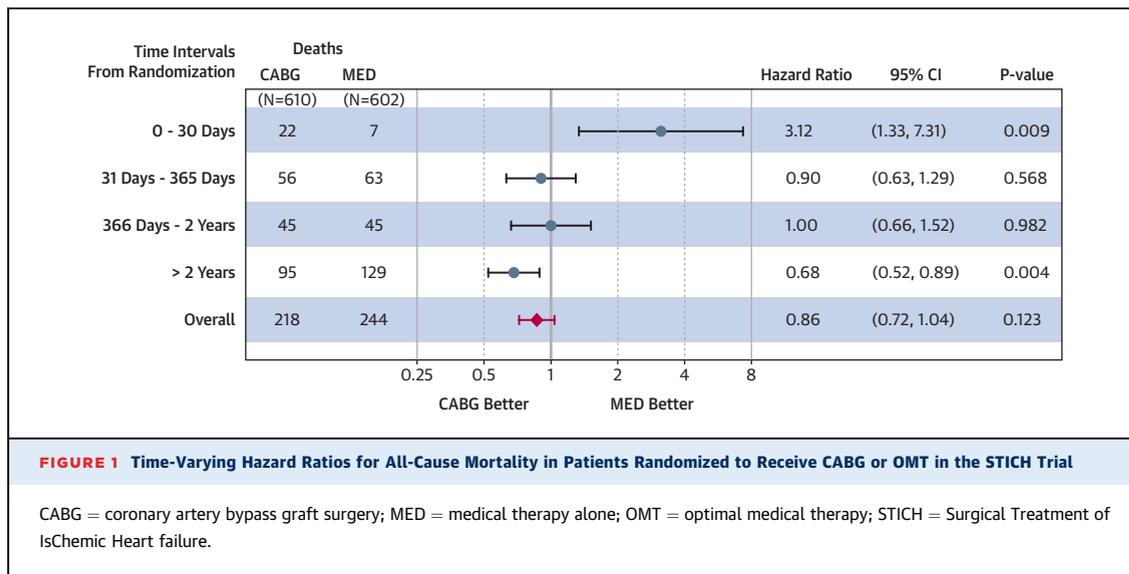
All patients had angiographic documentation of CAD that favored a diagnosis of CABG and EF of $\leq 35\%$. Patients with left main coronary stenosis of $>50\%$, cardiogenic shock, myocardial infarction within 3 previous months, or who demonstrated a need for aortic valve surgery were excluded. Patients were randomly assigned to receive CABG with medical therapy or medical therapy alone. PCI was not considered among the revascularization strategies in the STICH protocol. According to the original design of the trial (15), PCI during follow-up was regarded as downstream medical care associated with either

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of the treatment strategies, and PCI was performed as a subsequent procedure in only 37 of the 602 patients (6%) randomized to medical therapy alone and in 26 of the 610 patients (4%) randomized to CABG (p = NS). The NHLBI and ethics committee at each recruiting institution approved the study protocol. All patients provided written informed consent for participation in the trial.

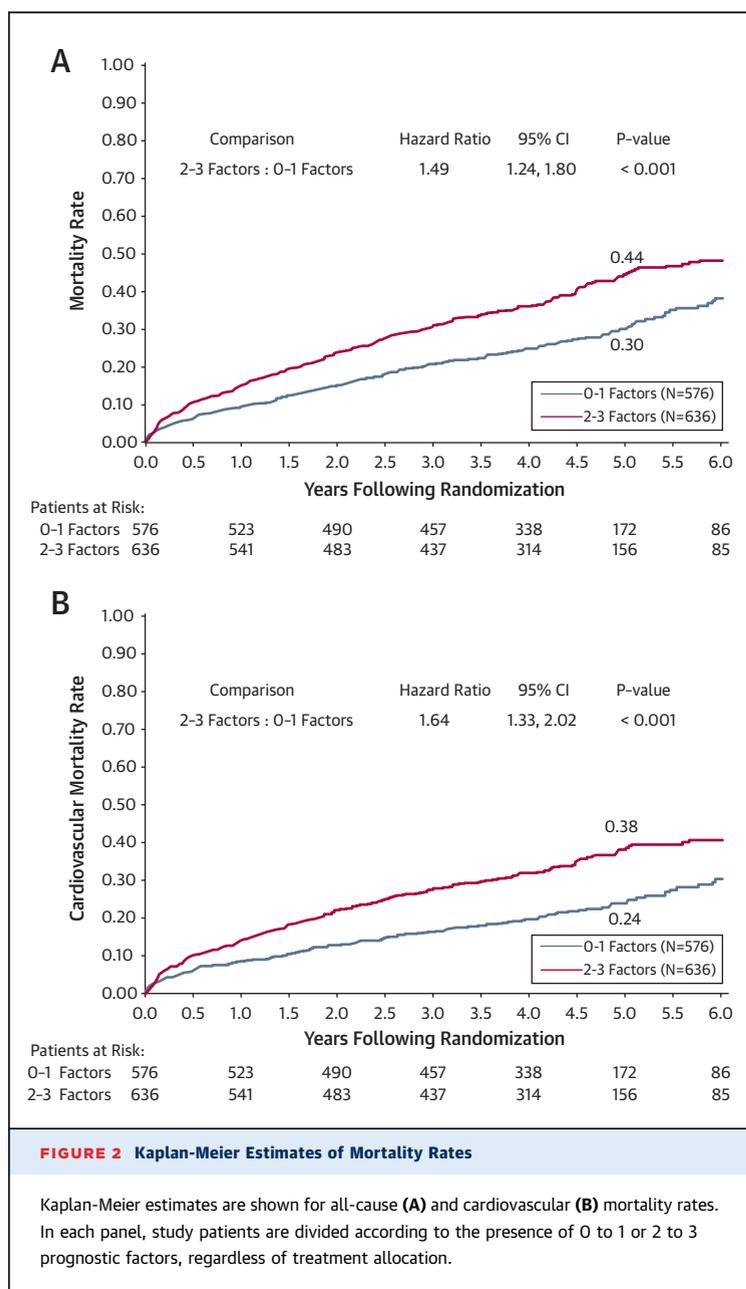
For the purpose of this study, attention was focused on 3 variables known to be prognostically important: 1) presence of 3-vessel CAD (defined as ≥50% stenosis); 2) baseline LV EF; and 3) baseline LV ESVI. These variables were selected prospectively for the purpose of this analysis on the basis of their known prognostic significance. Assessment of coronary anatomy was made by the investigators at each recruiting center and relayed to the Data Coordinating Center at Duke University, using specifically designed data collection forms. LV EF and LV ESVI were measured by core laboratories independently funded by NHLBI and blinded to all clinical and outcome information. As previously published, the best available method (on the basis of study quality using a pre-determined hierarchical algorithm) was used for LV EF and LV ESVI measurements (17). Patients were divided in a binary fashion according to the presence or absence of 3-vessel disease, LV EF below or above the median value, and LV ESVI below or above the median value. In addition, each patient was categorized by the number of prognostic factors defined by these variables, namely: 1) presence of 3-vessel CAD; 2) LV EF below the median value; and 3) LV ESVI above the median value. The presence of 3-vessel CAD was selected on the basis of the results

from the CASS (Coronary Artery Surgery Study) trial showing that this variable identifies a population of patients that may preferentially benefit from CABG (18). The thresholds for EF and ESVI were selected post-hoc on the basis of the median values of the

TABLE 1 Comparison of Baseline Characteristics of Patients With Different Numbers of Prognostic Factors According to 3-Vessel Disease, Low LVEF, and High ESVI

Variable	Patients With 0-1 Prognostic Factor (n = 576)	Patients With 2-3 Prognostic Factors (n = 636)	p Value
Age, yrs	60 ± 9	60 ± 9	0.961
Females	90 (16)	58 (9)	<0.001
White patients, %	390 (68)	437 (69)	0.708
Body mass index, kg/m ²	27 ± 5	27 ± 5	0.683
History of myocardial infarction	436 (76)	498 (78)	0.281
Atrial flutter or fibrillation	58 (10)	95 (15)	0.011
Previous CABG	10 (2)	26 (4)	0.016
Previous PCI	68 (12)	88 (14)	0.292
Advanced angina*	33 (6)	25 (4)	0.143
Advanced heart failure†	179 (31)	268 (42)	<0.001
3-vessel CAD	289 (50)	445 (70)	<0.001
Moderate or severe mitral regurgitation	83 (14)	137 (22)	0.001
LV EF, %	34 ± 7	23 ± 5	NA
ESVI, ml/m ²	61 ± 16	104 ± 30	NA
EDVI, ml/m ²	92 ± 24	139 ± 37	NA
Patients randomized to CABG	274 (48)	336 (53)	0.067

Values are mean ± SD or n (%). *Canadian Cardiac Society class III or IV. †New York Heart Association functional class III or IV.
CABG = coronary artery bypass grafting; CAD = coronary artery disease; EDVI = end-diastolic volume index; EF = ejection fraction; ESVI = end-systolic volume index; LV = left ventricle/ventricular; LVEF = left ventricular ejection fraction; NA = not applicable; PCI = percutaneous coronary intervention.



STICH population; no multiple views or comparisons with other thresholds were performed. For the purpose of data analysis, patients were grouped into those having 0 to 1 and those having 2 to 3 prognostic factors.

FOLLOW-UP AND OUTCOMES. After enrollment, patients were followed every 4 months for the first year and every 6 months thereafter. Adherence to guideline-directed medical therapy was high throughout the study period, without significant differences between the treatment groups (5). As for

the primary STICH trial analysis, the primary outcome was death from any cause, and the secondary endpoint was death from cardiovascular causes. Definitions of the trial endpoints have been previously reported (5). An independent clinical events committee adjudicated all endpoints. Median follow-up was 56 months (maximum, 8.3 years).

STATISTICAL ANALYSES. Demographic and baseline variables were summarized by using means and standard deviations for continuous variables and by number (n) and percentage (%) for categorical variables. Comparisons for continuous and ordinal variables between patient groups were performed with the Wilcoxon rank-sum test. The chi-square test or Fisher exact test was used to compare categorical variables.

Event rate estimates in each patient group were calculated using the Kaplan-Meier method and presented graphically (19). The significance of differences in mortality between patient groups was assessed using the log-rank test (20). Relative risks, expressed as HRs with associated 95% CIs, were derived using the Cox regression model (21). The interaction of prognostic factors and randomized treatment with respect to mortality was also assessed using the Cox model.

To examine the time-dependent nature of the randomized treatment effect, time-varying HRs and 95% CIs comparing CABG with medical therapy were calculated for discrete time periods after randomization (i.e., ≤ 30 days; 31 to 365 days; 366 days to 2 years; and > 2 years). These time points were selected prospectively for the purpose of this study. This analysis also was performed separately by patient groups (e.g., patients with 0 to 1 prognostic factor and patients with 2 to 3 prognostic factors).

All mortality comparisons of the randomized treatment arms were performed according to intention-to-treat principle (as randomized). Secondary analyses included comparisons by treatment received (e.g., CABG or medical therapy, regardless of randomization), and according to protocol (i.e., excluding the patients who crossed over to the other treatment arm). All 462 deaths (38.1% of the STICH population) reported at the time of database closure were included in the analysis.

RESULTS

STUDY POPULATION. Of the 1,212 patients included in the STICH revascularization hypothesis trial, 734 had 3-vessel CAD. The median LV EF was 26.7%, and the median ESVI was 78.6 ml/m². There were 576

patients with 0 to 1 prognostic factor and 636 patients with 2 to 3 prognostic factors, as defined above. **Table 1** shows the distribution of baseline characteristics in the patient groups defined according to the number of prognostic variables. As expected, compared with patients with 0 to 1 prognostic factor, those with 2 to 3 factors had a greater prevalence of characteristics associated with poor prognosis, including greater proportion of atrial flutter or fibrillation, previous CABG, moderate or severe mitral regurgitation, and more common presentation of advanced heart failure. Accordingly, patients with 2 to 3 prognostic factors had significantly higher overall mortality and higher rates of cardiovascular mortality than those with 0 to 1 prognostic factor, when treatment allocation was not considered (**Fig. 2**).

EFFECT OF SURGICAL REVASCUARIZATION ON SURVIVAL ACCORDING TO KEY ANATOMIC VARIABLES.

Patients with 3-vessel CAD received a significant benefit with CABG compared with those receiving medical therapy alone in terms of overall mortality ($p = 0.046$) and cardiovascular deaths ($p = 0.030$). In contrast, no such effect was observed among patients without 3-vessel CAD ($p = 0.906$ and $p = 0.554$ for overall and cardiovascular mortality, respectively) (**Online Figs. 1 and 2**). Similarly, patients with LV EF below the median value had reduced overall mortality ($p = 0.021$) and cardiovascular mortality ($p = 0.043$) with CABG compared with patients receiving medical therapy, an effect not found among patients with EF above the median value ($p = 0.970$ and $p = 0.288$ for overall and cardiovascular mortality, respectively) (**Online Figs. 3 and 4**). Patients with LV ESVI higher than the median value had a marginal reduction in overall mortality ($p = 0.055$) with CABG compared with those receiving medical therapy and no significant benefit in terms of cardiovascular mortality ($p = 0.177$), whereas no significant differences were noted between the 2 treatment arms among patients with ESVI below the median ($p = 0.596$ and $p = 0.064$ for overall and cardiovascular mortality, respectively) (**Online Figs. 5 and 6**). Finally, when patients with 2 to 3 prognostic factors were analyzed as a group, there was a highly significant mortality reduction with CABG compared with that observed with medical therapy alone (HR: 0.71; CI: 0.56 to 0.89; $p = 0.004$); no such therapeutic effect of CABG was found among patients with 0 to 1 prognostic factor (HR: 1.08; CI: 0.81 to 1.44; $p = 0.591$). A statistically significant interaction ($p = 0.022$) was observed between the number of prognostic factors and the treatment effect of CABG on mortality (**Fig. 3**). Analysis of the Kaplan-Meier mortality rates according to

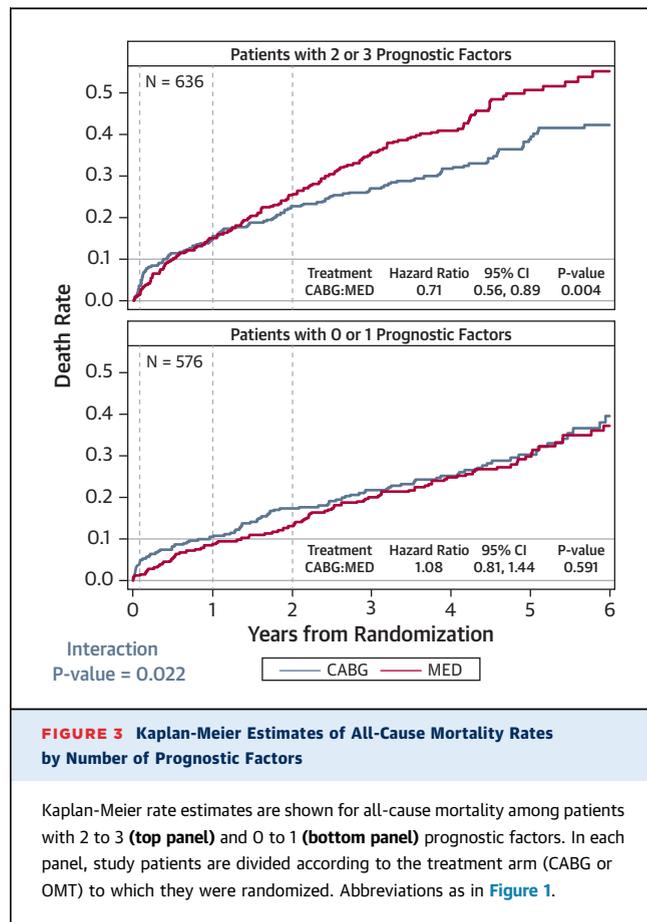
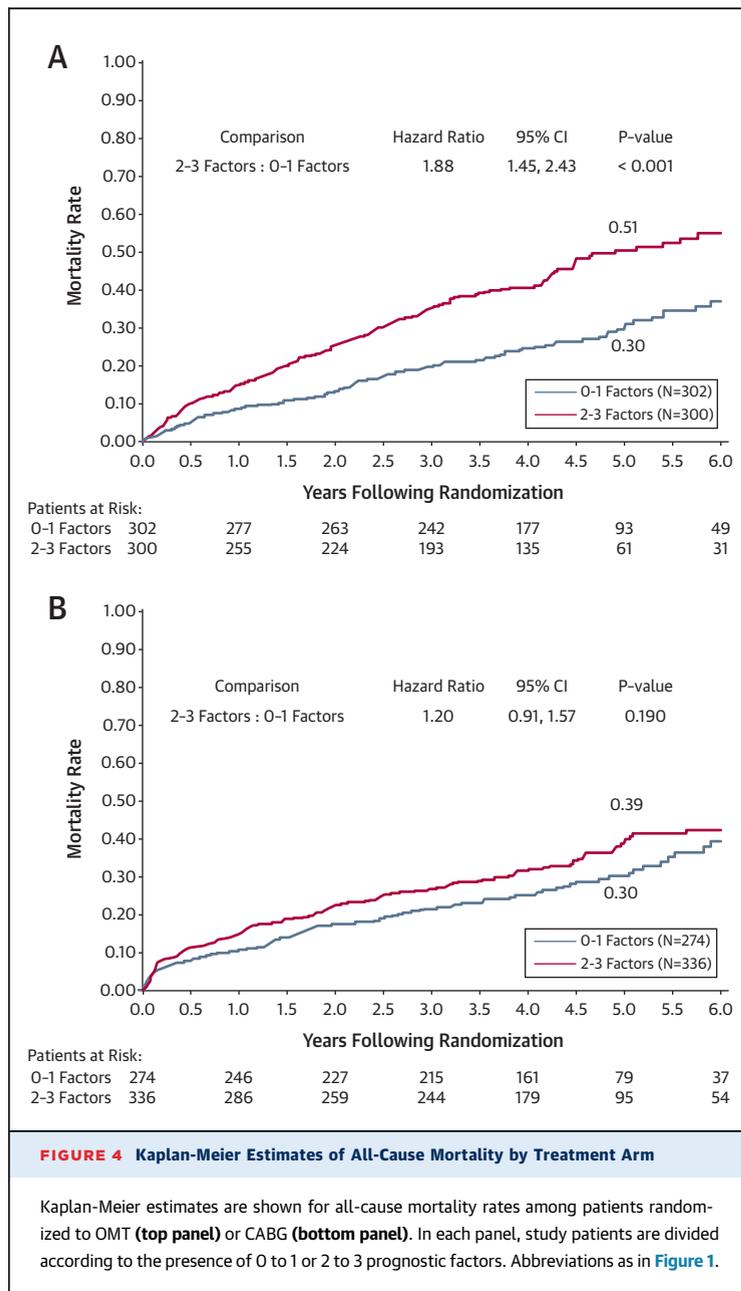


FIGURE 3 Kaplan-Meier Estimates of All-Cause Mortality Rates by Number of Prognostic Factors

Kaplan-Meier rate estimates are shown for all-cause mortality among patients with 2 to 3 (**top panel**) and 0 to 1 (**bottom panel**) prognostic factors. In each panel, study patients are divided according to the treatment arm (CABG or OMT) to which they were randomized. Abbreviations as in **Figure 1**.

treatment allocation among patients with 2 to 3 prognostic factors revealed that the curves crossed (indicating the elimination of the higher surgical risk) at approximately 6 to 15 months after randomization (**Fig. 3**, top panel). This was also true for patients with only 1 prognostic factor (**Online Figs. 1, 3, and 5**). Patients with 2 to 3 factors also had reduced cardiovascular mortality with CABG compared with those receiving medical therapy (HR: 0.72; CI: 0.56 to 0.94; $p = 0.014$), with no such effect observed among patients with 0 to 1 factor (HR: 0.89; CI: 0.64 to 1.25; $p = 0.502$).

Of note, among patients randomized to medical therapy alone, there was a significantly higher mortality in patients with 2 to 3 prognostic factors than in those with 0 to 1 factor ($p < 0.001$). However, such a difference was not observed among patients randomized to CABG ($p = 0.190$), hence indicating that the treatment effect of surgical revascularization markedly blunted the higher mortality risk conveyed by the presence of anatomic findings associated with poor prognosis (**Fig. 4**).



TIME-DEPENDENT MORTALITY HAZARD OF CABG VERSUS MEDICAL THERAPY ACCORDING TO KEY ANATOMIC VARIABLES. Patients with 3-vessel CAD, those with LV EF below the median, and those with LV ESVI above the median had a clear time-dependent overall and cardiovascular mortality hazard with surgical revascularization, with an early higher risk (within 30 days) with CABG and a clear benefit at ≥ 2 years (Online Figs. 7 to 12). This time-dependent hazard was different among the subgroups of patients without these anatomic

characteristics, in that their mortality benefit with CABG was not statistically significant at ≥ 2 years (except for reduced cardiovascular mortality in patients without 3-vessel CAD and in those with LV ESVI above the median) (Online Figs. 8 and 12).

Of note, when the anatomic characteristics were combined, patients with 2 to 3 prognostic factors showed a trend toward higher overall mortality ($p = 0.087$) and statistically significant higher cardiovascular mortality ($p = 0.048$) with CABG within 30 days and a markedly significant benefit of CABG at ≥ 2 years in terms of overall mortality ($p < 0.001$) and cardiovascular deaths ($p = 0.003$) than those randomized to medical therapy alone. The overall HR was 0.71 (95% CI: 0.56 to 0.89; $p = 0.004$) for all-cause mortality and 0.72 (95% CI: 0.56 to 0.94; $p = 0.014$) for cardiovascular deaths. In contrast, patients with 0 to 1 prognostic factor had a significantly higher early mortality hazard with CABG than those receiving medical therapy alone ($p = 0.047$ for both overall and cardiovascular mortality), without survival benefit at any time point (overall HR: 1.08; 95% CI: 0.81 to 1.44; $p = 0.591$ for all-cause mortality and 0.89; 95% CI: 0.64 to 1.25; $p = 0.502$ for cardiovascular deaths) (Fig. 5). In patients randomized to CABG, the early mortality (within 30 days of randomization) among patients with 2 to 3 prognostic factors (3.57%) was similar to that in patients with 0 to 1 prognostic factor (3.65%).

Analyses of the data according to treatment received (e.g., CABG or medical therapy regardless of randomization) and protocol (i.e., excluding the patients who crossed over to the other treatment arm) showed results similar to those of the primary intention-to-treat analysis (Online Figs. 13 and 14).

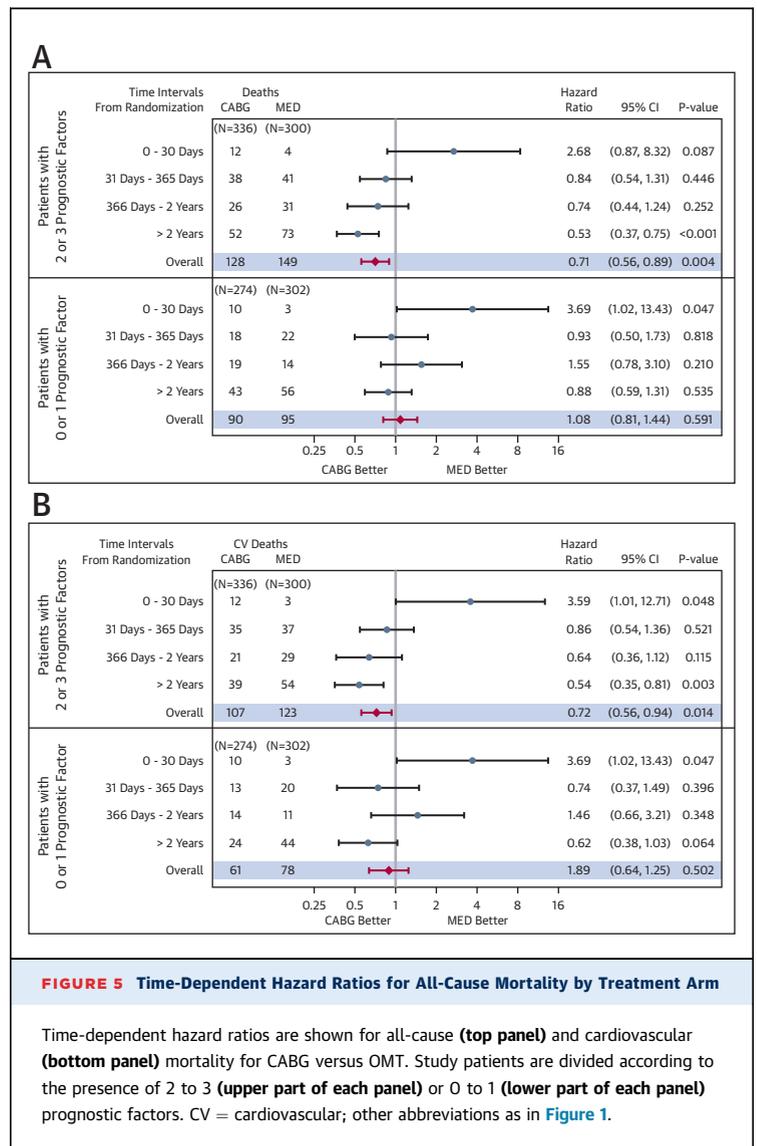
DISCUSSION

The decision of whether to proceed with surgical revascularization in a patient with ischemic cardiomyopathy is an increasingly common one, given the rising prevalence of this condition (22). Unfortunately, it is also a difficult one because of the complexity and variability of the clinical presentations and, until recently, because of the paucity of data from randomized clinical trials. The recently completed STICH trial showed a trend ($p = 0.12$) toward better overall survival with CABG than medical therapy alone and a statistically significant benefit in the secondary endpoints of cardiovascular mortality and death from any cause plus cardiac hospitalization (5). As expected, on the basis of clinical experience, the mortality curves for the 2 treatment arms crossed during the follow-up period due

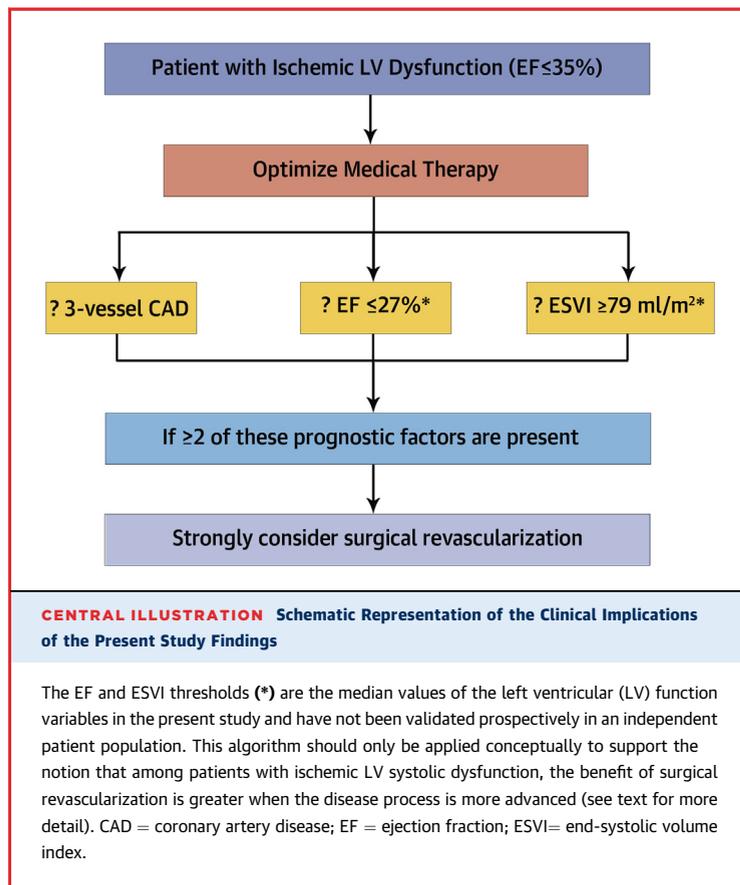
to the increased early but decreased late mortality observed with CABG. This increased early risk of death with surgery partly negates the overall benefit of CABG and, most importantly, may be limited to certain subgroups of patients. Identification of those patients whose early surgical risk is clearly offset by the long-term benefit of revascularization could lead to the selection of a specific group of patients in whom deferring surgery may not be the most appropriate choice.

The results of this study demonstrate that patients with more advanced forms of ischemic cardiomyopathy (as expressed by the presence of 3-vessel disease and more severe LV systolic dysfunction and remodeling) are those who receive the greatest benefit from surgical revascularization. Thus, among the 1,212 patients enrolled in the STICH revascularization hypothesis trial, those with $\geq 50\%$ stenosis in all 3 major coronary arteries, LV EF below the median value, and LV ESVI above the median value showed a clear time-dependent benefit of CABG compared with those receiving medical therapy alone. This resulted in an overall statistically significant benefit of CABG over the entire follow-up period despite the higher early (within 30 days) mortality with surgery compared with that with medical therapy. Importantly, as the number of prognostic factors defined by these variables increases, the time-dependent pattern of the benefit of CABG relative to medical therapy (e.g., diminished early surgical risk and enhanced late benefit) becomes more pronounced.

These findings have important clinical implications for patients with ischemic cardiomyopathy that may influence the paradigm used by clinicians for their decision regarding surgical revascularization (Central Illustration). Although more extensive CAD and worse LV dysfunction and remodeling may be intuitively thought to be associated with increased operative mortality, instinctively leading to the avoidance of CABG, our findings do not confirm that view: the early mortality with CABG in patients with 2 to 3 prognostic factors was similar to that observed among patients with 0 to 1 prognostic factor. Instead, the present study results indicate that those characteristics are found among patients who derive the greatest benefit from revascularization and, hence, are those in whom CABG may not be delayed. Patients with a higher number of prognostic factors benefit from surgical revascularization because their early and late mortality with medical therapy alone is extremely high. Consequently, the risk of CABG in patients with more advanced forms of ischemic cardiomyopathy is counterbalanced by the even higher mortality



observed with medical therapy alone. In fact, our findings support the notion that surgical revascularization blunts the higher mortality conveyed by the presence of anatomic prognostic factors when patients are treated with medical therapy alone. As a result, the analysis favors the indication for surgical revascularization in patients who present with worse CAD and more severe LV dysfunction and remodeling. Importantly, although PCI may appear to be an alternative for some patients, recent randomized trials have demonstrated the superiority of surgical revascularization in patients with extensive disease or diabetes (1,2). Nevertheless, it must be acknowledged that CABG in STICH was performed by experienced surgeons with a previously documented



operative mortality rate of $\leq 5\%$ in similar patients; hence, these findings may not be applicable to centers with a higher surgical death rate.

STUDY LIMITATIONS. First, these observations are on the basis of a retrospective nonprespecified analysis of the STICH trial and therefore do not necessarily have the same level of credibility as those that can be derived from prospectively defined subgroups of patients entered into a clinical trial. Nonetheless, the allocation to CABG or medical therapy alone was prospectively decided by randomization. Accordingly, the number of patients undergoing CABG was approximately one-half in each of the subgroups, ruling out any potential biased association between allocation to surgical revascularization and presence of 3-vessel CAD, lower EF, or higher ESVI. Second, the STICH trial was designed with statistical power to detect differences in overall survival with CABG over that with medical therapy alone in all CAD patients with EF $\leq 35\%$. Therefore, categorizing patients according to those anatomic variables obviously resulted in a reduced number of patients in each subgroup with a consequently diminished statistical power. Crossover of patients from 1 treatment arm to the

other also may have affected the results of our study, which was based on an intention-to-treat analysis. The impact of crossovers in the STICH trial has been carefully analyzed in a separate study (23). Importantly, however, the “as treated” and “per protocol” analyses (both of which considered crossover patients) showed results similar to those of the primary intention-to-treat analysis. Finally, because the median follow-up of the STICH trial was 56 months, we cannot establish whether the benefit of CABG observed after 2 years in certain subsets of patients extends beyond this period of follow-up. The STICH ES (STICH Extension Study) is presently being conducted to confirm the longer-term effects of surgical revascularization in these patients.

It must be emphasized that the LV EF and LV ESVI values used to separate patients into subgroups were determined on the basis of the distribution of these variables in this particular study population. Because these thresholds have not been validated prospectively in an independent patient population, our findings should not be considered dogmatic postulates of specific values to be used when making decisions for individual patients. Instead, these results should be applied conceptually to support the notion that among patients with LV systolic failure due to ischemic heart disease, the benefit of surgical revascularization is greater when the disease process is more advanced.

Taken in conjunction with the neutral results of the myocardial viability (24) and myocardial ischemia (25) substudies, the present study results indicate that compared with functional imaging, assessment of the anatomical extent of the disease is a better predictor of benefit from CABG in patients with ischemic cardiomyopathy. This concept is consistent with that reported in a recent analysis by the COURAGE trial investigators (26) in which the anatomic burden was a more consistent predictor of outcome than the assessment of the ischemic burden in patients with EF of $\geq 30\%$.

CONCLUSIONS

Our findings support the indication for surgical revascularization in patients with ischemic cardiomyopathy who present with more extensive CAD and worse myocardial dysfunction and remodeling.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Among patients with left ventricular (LV) systolic failure due to ischemic heart disease, the benefit of surgical revascularization is greater when the disease process is more advanced.

COMPETENCY IN PATIENT CARE: Patients with ischemic cardiomyopathy should be made aware that assessment of the anatomical extent of the disease is important to estimate the benefit of coronary artery bypass surgery (CABG) over medical therapy.

TRANSLATIONAL OUTLOOK 1: Because the median follow-up of the STICH trial was 56 months, the benefit of CABG beyond this period of follow-up is uncertain. The STICH Extension Study (STICHES) is presently being conducted to confirm the longer-term effects of surgical revascularization in these patients.

TRANSLATIONAL OUTLOOK 2: Taken in conjunction with the neutral results of the myocardial viability and myocardial ischemia STICH substudies, it appears that, compared to functional imaging, assessment of the anatomical extent of the disease is a better predictor of benefit from CABG, a concept consistent with that reported in a recent report from the COURAGE trial. Hence, evaluation of the added value of functional imaging to that provided by anatomic assessment of the disease should be undertaken.

REFERENCES

1. Serruys PW, Morice MC, Kappetein AP, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med* 2009;360:961-72.
2. Farkouh ME, Domanski M, Sleeper LA, et al. Strategies for multivessel revascularization in patients with diabetes. *N Engl J Med* 2012;367:2375-84.
3. Herlitz J, Karlson BW, Sjolund H, et al. Long term prognosis after CABG in relation to preoperative left ventricular ejection fraction. *Int J Cardiol* 2000;72:163-71.
4. Topkara VK, Cheema FH, Kesavaramanujam S, et al. Coronary artery bypass grafting in patients with low ejection fraction. *Circulation* 2005;112 Suppl 1:344-50.
5. 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.
6. Felker GM, Shaw LK, O'Connor CM. A standardized definition of ischemic cardiomyopathy for use in clinical research. *J Am Coll Cardiol* 2002;39:210-8.
7. Dzavik V, Ghali WA, Norris C, et al. Long-term survival in 11,661 patients with multivessel coronary artery disease in the era of stenting: a report from the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) investigators. *Am Heart J* 2001;142:119-26.
8. Smith PK, Califf RM, Tuttle RH, et al. Selection of surgical or percutaneous coronary intervention provides differential longevity benefit. *Ann Thorac Surg* 2006;82:1420-9.
9. White HD, Norris RM, Brown MA, Brandt PW, Whitlock RM, Wild CJ. Left ventricular end-systolic volume as the major determinant of survival after recovery from myocardial infarction. *Circulation* 1987;76:44-51.
10. Bolognese L, Neskovic AN, Parodi G, et al. Left ventricular remodeling after primary coronary angioplasty: patterns of left ventricular dilation and long-term prognostic implications. *Circulation* 2002;106:2351-7.
11. Wong M, Staszewsky L, Latini R, et al. Severity of left ventricular remodeling defines outcomes and response to therapy in heart failure. *J Am Coll Cardiol* 2004;43:2022-7.
12. Solomon SD, Skali H, Anavekar NS, et al. Changes in ventricular size and function in patients with valsartan, captopril, or both after myocardial infarction. *Circulation* 2005;111:3411-9.
13. Fang JC. Underestimating medical therapy for coronary artery disease...again. *N Engl J Med* 2011;364:1671-3.
14. Elamm C, Fang JC. The world post-STICH: is this a "game changer?" A non-invasive cardiologist's perspective—revascularization is the treatment of choice only in patients who fail medical therapy. *Prog Cardiovasc Dis* 2013;55:466-9.
15. 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.
16. Jones RH, Velazquez EJ, Michler RE, et al. Coronary bypass surgery with or without surgical ventricular reconstruction. *N Engl J Med* 2009;360:1705-17.
17. Oh JK, Velazquez EJ, Menicanti L, et al. Influence of baseline left ventricular function on the clinical outcome of surgical ventricular reconstruction in patients with ischaemic cardiomyopathy. *Eur Heart J* 2013;34:39-47.
18. 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.
19. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Statist Assn* 1958;53:457-81.
20. Kalbfleisch JD, Prentice RL. *The Statistical Analysis of Failure Time Data*. 2nd edition. New York: John Wiley & Sons, Inc., 2002.
21. Cox DR. Regression models and life-tables (with discussion). *J Royal Statist Soc B* 1972;34:187-220.
22. Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics—2012 update: a report from the American Heart Association. *Circulation* 2012;125:e2-220.
23. Doenst T, Cleland JGF, Rouleau JL, et al. Influence of crossover on mortality in a randomized study of revascularization in patients with systolic heart failure and coronary artery disease. *Circ Heart Fail* 2013;6:443-50.
24. 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.
25. Panza JA, Holly TA, Asch FM, et al. Inducible myocardial ischemia and outcomes in patients with coronary artery disease and left ventricular dysfunction. *J Am Coll Cardiol* 2013;61:1860-70.
26. Mancini GBJ, Hartigan PM, Shaw LJ, et al. Predicting outcome in the COURAGE trial. Coronary anatomy versus ischemia. *J Am Coll Cardiol Intv* 2014;7:195-201.

KEY WORDS coronary artery disease, heart failure, left ventricular dysfunction, myocardial ischemia, outcomes

APPENDIX For supplemental figures, please see the online version of this article.