ORIGINAL RESEARCH

Severity of Remodeling, Myocardial Viability, and Survival in Ischemic LV Dysfunction After Surgical Revascularization

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ABSTRACT

OBJECTIVES This study sought to test the hypothesis that end-systolic volume (ESV), as a marker of severity of left ventricular (LV) remodeling, influences the relationship between myocardial viability and survival in patients with coronary artery disease and LV systolic dysfunction.

BACKGROUND Retrospective studies of ischemic LV dysfunction suggest that the severity of LV remodeling determines whether myocardial viability predicts improved survival with surgical compared with medical therapy, with coronary artery bypass grafting (CABG) only benefitting patients with viable myocardium who have smaller ESV. However, this has not been tested prospectively.

METHODS Interactions of end-systolic volume index (ESVI), myocardial viability, and treatment with respect to survival were assessed in patients in the prospective randomized STICH (Comparison of Surgical and Medical Treatment for Congestive Heart Failure and Coronary Artery Disease) trial of CABG versus medical therapy who underwent viability assessment (n = 601; age 61 ± 9 years; ejection fraction ≤35%), with a median follow-up of 5.1 years. Median ESVI was 84 ml/m^2. Viability was assessed by single-photon emission computed tomography or dobutamine echocardiography using pre-specified criteria.

RESULTS Mortality was highest among patients with larger ESVI and nonviability (p < 0.001), but no interaction was observed between ESVI, viability status, and treatment assignment (p = 0.491). Specifically, the effect of CABG versus medical therapy in patients with viable myocardium and ESVI ≤84 ml/m^2 (hazard ratio [HR]: 0.85; 95% confidence interval [CI]: 0.56 to 1.29) was no different than in patients with viability and ESVI >84 ml/m^2 (HR: 0.87; 95% CI: 0.57 to 1.31). Other ESVI thresholds yielded similar results, including ESVI ≤60 ml/m^2 (HR: 0.87; 95% CI: 0.44 to 1.74). ESVI and viability assessed as continuous rather than dichotomous variables yielded similar results (p = 0.562).

CONCLUSIONS Among patients with ischemic cardiomyopathy, those with greater LV ESVI and no substantial viability had worse prognosis. However, the effect of CABG relative to medical therapy was not differentially influenced by the combination of these 2 factors. Lower ESVI did not identify patients in whom myocardial viability predicted better outcome with CABG relative to medical therapy. (Comparison of Surgical and Medical Treatment for Congestive Heart Failure and Coronary Artery Disease [STICH]; NCT00023595) (J Am Coll Cardiol Img 2015;8:1121–9) © 2015 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

CABG = coronary artery bypass graft

CAD = coronary artery disease

EF = ejection fraction

ESV = end-systolic volume

ESVI = end-systolic volume index

FDG = ^{18}F-fluorodeoxyglucose

LV = left ventricular

PET = positron emission tomography

SPECT = single-photon emission computed tomography

Despite advances in diagnosis and treatment, heart failure remains a substantial cause of death and disability [1,2], driven importantly by the causal role of coronary artery disease (CAD) in the development of left ventricular (LV) dysfunction [3]. LV systolic dysfunction in the setting of CAD is not always an irreversible process because LV function may improve substantially with beta-blocker therapy, cardiac resynchronization, and revascularization [3-7]. LV function is most likely to improve with medical, device, or surgical therapies in patients with viable myocardium identified using noninvasive imaging [4,8-14]. Many previous studies, primarily retrospective and performed before the advent of beta-blockers for LV systolic dysfunction, suggested that myocardial viability also identified patients in whom survival is enhanced with revascularization compared with medical management [8,15,16]. In contradistinction, the prospective STICH (Comparison of Surgical and Medical Treatment for Congestive Heart Failure and Coronary Artery Disease) trial, which randomized patients with CAD and LV dysfunction to evidence-based medical therapy or coronary artery bypass graft (CABG) surgery plus medical therapy, demonstrated no interaction between myocardial viability and treatment strategy with respect to survival [17].

Previous retrospective studies of patients with ischemic LV dysfunction have suggested that the severity of LV remodeling affects the relation between myocardial viability and survival with CABG, such that patients with marked LV dilation (i.e., large end-systolic volume [ESV]) develop irreversible remodeling to the extent that viable myocardium, if present, does not contribute to improved LV function or improved survival with revascularization. According to this concept, the beneficial effect of CABG on LV functional recovery and survival would thus be limited to patients with viable myocardium and smaller ESV [18-21]. This theory is plausible but has not been tested prospectively with random allocation of treatment strategies. The current study investigated the impact of LV remodeling on the relationship between myocardial viability, treatment with revascularization versus medical management, and survival in patients enrolled in the STICH trial.

METHODS

PATIENT ENROLLMENT. Design and enrollment criteria for the STICH study and STICH viability substudy have been reported in detail [17,22,23]. The STICH study is a multicenter, nonblinded, randomized trial funded by the National Heart, Lung, and Blood Institute (NHLBI). The study of revascularization versus medical therapy was conducted at 99 sites in 22 countries. Patients with angiographic documentation of CAD amenable to surgical revascularization and LV ejection fraction (EF) ≤35% were eligible for enrollment. Exclusion criteria included left main coronary stenosis >50%, cardiogenic shock, myocardial infarction within 3 months, and need for aortic valve surgery. All participants provided written informed consent. Patients were randomized to receive medical therapy alone or medical therapy plus CABG. A "risk at randomization" score was calculated for each patient using a statistical model derived in an independent dataset from multiple variables with known power to predict 5-year risk of death without CABG [24]. Medical therapy was excellent, with ≥90% of patients receiving statins, beta-blockers, and either angiotensin-converting enzyme inhibitors or angiotensin receptor blockers at 1 year and 88% receiving aspirin (≥92% received either aspirin or warfarin) [23].

VIABILITY TESTING. Of the 1,212 enrolled patients, 601 underwent viability testing. Details regarding patient selection for imaging have been reported previously [17]. Viability was assessed using single-photon computed tomography (SPECT) in 471 patients or dobutamine echocardiography in 280 patients;

150 patients were studied by use of both techniques. For SPECT, 4 protocols for assessing myocardial viability were permitted at the enrolling sites, including thallium imaging using a rest-redistribution or stress-rest-reinjection protocol, rest-redistribution thallium imaging, or imaging with a technetium-99m tracer at rest after administration of nitroglycerin. For echocardiography, imaging was performed at rest and during staged infusions of dobutamine starting at 5 µg/kg/min and increasing to 10, 20, 30, and 40 µg/kg/min in 3- to 5-min intervals.

Independent NHLBI-funded core laboratories (22) blinded to patient details and treatment assignment coordinated data collection and analysis for the SPECT and dobutamine echocardiography studies. Thresholds of viable myocardium were pre-specified to classify patients in a binary fashion as being with or without substantial myocardial viability. Viability was also evaluated as a continuous variable. Core laboratory measurements were submitted to the Duke Clinical Research Institute, which performed all statistical analyses.

For SPECT, patients with viability were defined as those with ≥11 viable segments based on relative tracer activity using a 17-segment model. A myocardial segment was deemed viable if tracer activity was ≥50% of activity in the segment with maximal activity. For thallium rest-redistribution imaging, a segment with activity <50% of maximal myocardial activity on the redistribution images was also defined as viable if improvement in activity from rest to redistribution images was ≥12%.

For dobutamine echocardiography, patients with viability were defined as those with ≥5 segments with abnormal resting systolic function manifesting contractile reserve with dobutamine, using a 16-segment model. In the 150 patients studied with both techniques, based on the thresholds defined above, when both tests demonstrated viability, the sum of SPECT plus echocardiography scores was ≥16 viable segments; when both tests demonstrated nonviability, the sum was <16. This threshold was then applied to those with discordant results between the 2 tests; the SPECT viability and echocardiography viability scores were added together, and patients were considered to have viable myocardium when the total segment score was ≥16 (17).

LV FUNCTION AND ESVs. LVEF and ESV were measured by the independent investigators from core laboratories blinded to treatment allocation. As previously described (25), the best available method (based on study quality using a pre-determined hierarchical algorithm) was used to measure LVEF and volumes. The end-systolic volume index (ESVI) was computed by dividing ESV by body surface area.

PATIENT FOLLOW-UP. After trial enrollment, patients were followed every 4 months for the first year and every 6 months thereafter (17,23). The primary outcome was all-cause mortality. Secondary outcomes included cardiovascular mortality and all-cause mortality plus cardiovascular hospitalizations. All endpoints were adjudicated by an independent clinical events committee (22).

STATISTICAL METHODS. Baseline clinical characteristics of patients were descriptively summarized using means and SDs, unless otherwise specified. Group characteristics at baseline were compared using the Wilcoxon rank-sum test for continuous variables and the conventional chi-square test or Fisher exact test for categorical variables. Patients were initially subgrouped on the basis of median ESVI (84 ml/m²). The relationships of myocardial viability, ESVI, and treatment with the primary outcome of all-cause mortality were assessed using the Cox proportional hazards regression model and Kaplan-Meier mortality curves (26,27). Specifically, we examined whether the effect of CABG versus medical therapy on mortality differed depending on viability status and ESVI by assessing the interactions of these factors with treatment using the Cox model. We also produced Kaplan-Meier mortality curves for subgroups of patients defined by viability status and ESVI and descriptively summarized CABG mortality compared with medical mortality using hazard ratios (HRs) and 95% confidence intervals (CIs) generated from the Cox model and log-rank assessments of treatment differences. Sensitivity analyses of the interactions between myocardial viability, ESVI, and treatment were also performed using different thresholds of ESVI (>90, 61 to 90, and ≤60 ml/m²). Similar analyses to those described were performed for the secondary endpoints of cardiovascular death and death or cardiac hospitalization. In addition to treatment comparisons of CABG versus medical therapy as randomized (intention to treat), supplementary analyses compared the study arms as treated (accounting for treatment crossovers) and per protocol (28). Finally, Cox model analyses were performed treating viability status and ESVI as continuous rather than binary variables.

RESULTS

Among the 601 patients undergoing viability testing, the median ESVI was 84 ml/m². Myocardial viability was present in 487 patients (81%) (17). Patients with viable myocardium had higher LVEF (27.5 ± 8.3% vs. 22.9 ± 8.8%; p < 0.001) and lower ESVI

TABLE 1 Baseline Characteristics of Patients With Myocardial Viability

	Patients With LV ESVI ≤84 ml/m² (n = 267)	Patients with LV ESVI >84 ml/m² (n = 220)	p Value
Age, yrs	61 ± 10	60 ± 9	0.077
Prior myocardial infarction	208 (78)	165 (75)	0.452
Diabetes	115 (43)	83 (38)	0.232
Prior stroke	25 (9)	17 (8)	0.522
Hypertension	175 (66)	137 (62)	0.454
Hyperlipidemia	177 (67)	149 (68)	0.782
Current smoker	53 (20)	55 (25)	0.173
Chronic renal insufficiency	19 (7)	14 (6)	0.734
Atrial flutter/fibrillation	42 (16)	32 (15)	0.717
Peripheral vascular disease	45 (17)	30 (14)	0.328
RAR score*	12 ± 9	13 ± 8	0.140
Previous CABG	5 (2)	7 (3)	0.354
Bypass graft status			
≥1 stenosed or occluded	4 (80)	7 (100)	
≥1 occluded	4 (80)	6 (86)	
Previous PCI	43 (16)	34 (16)	0.845
CAD distribution			
No. of diseased vessels ≥75%			0.162
0	6 (2)	3 (1)	
1	77 (29)	47 (22)	
2	91 (34)	88 (40)	
3	93 (35)	81 (37)	
Proximal LAD stenosis ≥75%	170 (64)	139 (64)	0.964
Left main stenosis (≥50%)	8 (3)	4 (2)	0.408
Highest NYHA functional class within 3 months			0.002
I	14 (5)	10 (5)	
II	114 (43)	68 (31)	
III	110 (41)	101 (46)	
IV	29 (11)	41 (19)	
Medications at baseline			
Beta-blocker	235 (88)	202 (92)	0.169
ACE inhibitor	223 (84)	189 (86)	0.467
ARB	21 (8)	19 (9)	0.758
ACE inhibitor or ARB	242 (91)	204 (93)	0.408
Statin	227 (85)	178 (81)	0.228
Aspirin	227 (85)	187 (85)	0.995
Blood pressure, mm Hg			
Systolic	123 ± 19	119 ± 16	0.029
Diastolic	75 ± 11	75 ± 11	0.564
Heart rate, beats/min	72 ± 11	75 ± 13	0.074
LV ejection fraction, %	33 ± 8	23 ± 6	<0.001
LV EDVI, ml/m²	94 ± 21	145 ± 31	<0.001
LV ESVI, ml/m²	63 ± 15	111 ± 24	–
Hemoglobin, g/dl	14 ± 2	14 ± 2	0.195
Creatinine, mg/dl	1.2 ± 1.0	1.1 ± 0.3	0.573
BUN, mg/dl	30 ± 21	29 ± 19	0.540

Values are mean ± SD or n (%). *The RAR score ranges from 1 to 32, with higher numbers indicating a higher predicted rate of death. Among patients receiving medical therapy, a score of 1 predicts a rate of 18% and a score of 32 predicts a rate of 99% over 5 years.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BUN = blood urea nitrogen; CABG = coronary artery bypass graft; CAD = coronary artery disease; EDVI = end-diastolic volume index; ESVI = end-systolic volume index; LAD = left anterior descending coronary artery; LV = left ventricular; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; RAR = risk at randomization.

(84.5 ± 30.9 ml/m² vs. 107.7 ± 43.5 ml/m²; $p < 0.001$) than those without myocardial viability. ESVI did not differ between patients undergoing CABG versus medical therapy (88.7 ± 33.9 ml/m² vs. 89.1 ± 35.7 ml/m²; $p = 0.820$). Baseline characteristics of patients with viable myocardium, comparing those with ESVI above and below the median value, are presented in Table 1, and characteristics of patients without viable myocardium are presented in Table 2. Among patients with myocardial viability, those with ESVI >84 ml/m² had more severe symptoms, lower LVEF, and higher LV end-diastolic volume index but otherwise did not differ from those with lower ESVI.

For the entire group, there was no interaction between ESVI, viability status, and treatment assignment to CABG versus medical therapy with respect to survival ($p = 0.491$). Among the 487 patients with viable myocardium (Figure 1), no interaction was observed between ESVI and treatment assignment with respect to survival ($p = 0.962$). Specifically, the effect of CABG compared with medical therapy in patients with ESVI ≤84 ml/m² (HR: 0.85; 95% CI: 0.56 to 1.29) was not different than that of patients with ESVI >84 ml/m² (HR: 0.87; 95% CI: 0.57 to 1.31). Among patients with viability treated surgically, post-operative mortality was higher in those with high ESVI compared with low ESVI (37.7% vs. 25.8% at 5 years) (Figure 1), but this trend was not significant (HR: 1.30; 95% CI: 0.85 to 2.00).

An additional analysis separated the patients with myocardial viability into 3 subgroups of ESVI (>90, 61 to 90, and ≤60 ml/m²). There was no difference in the effect of CABG compared with medical therapy on 5-year mortality across the range of ESVI (Figure 2), including the subgroup with the lowest ESVI (interaction p value = 0.955).

Similarly, in patients with nonviable myocardium, the effect of CABG compared with medical therapy did not differ significantly between patients with ESVI ≤84 ml/m² (HR: 1.30; 95% CI: 0.34 to 5.00) and those with ESVI >84 ml/m² (HR: 0.67; 95% CI: 0.38 to 1.20), although the number of patients with nonviable myocardium was small, particularly among those with lower values of ESVI.

MYOCARDIAL VIABILITY AND ESVI AS CONTINUOUS VARIABLES. Analyses in which both myocardial viability scores and ESVI were assessed as continuous rather than dichotomous variables did not demonstrate significant interactions of viability, ESVI, and treatment with CABG versus medical therapy on mortality ($p = 0.562$). Mortality rates across the continuum of magnitude of viable myocardium are shown in Figure 3A, and rates across the continuum of ESVI are shown in Figure 3B. Specifically, patients with greater

degrees of myocardial viability and lower values of ESVI did not manifest a significant differential benefit of CABG over medical therapy compared with patients with less viability and/or larger values of ESVI.

SECONDARY ENDPOINTS. Analysis of secondary endpoints paralleled that of the primary analysis, showing no significant interactions of myocardial viability, ESVI, treatment, and outcome. With respect to cardiovascular mortality, the effect of CABG compared with medical therapy in patients with myocardial viability did not differ significantly between patients with ESVI ≤84 ml/m² (HR: 0.65; 95% CI: 0.39 to 1.08) and those with ESVI >84 ml/m² (HR: 0.88; 95% CI: 0.56 to 1.37; interaction p value = 0.387). Similarly, with the composite endpoint of mortality plus cardiovascular hospitalizations in patients with myocardial viability, the effect of CABG compared with medical therapy did not differ between patients with ESVI ≤84 ml/m² (HR: 0.68; 95% CI: 0.50 to 0.92) and those with ESVI >84 ml/m² (HR: 0.67; 95% CI: 0.49 to 0.92; interaction p value = 0.942).

ANALYSIS OF TREATMENT RECEIVED. Analysis of actual treatment received provided similar results to the intention-to-treat analysis for both primary and secondary endpoints. For example, for the primary endpoint of all-cause mortality among patients with myocardial viability, the effect of CABG compared with medical therapy did not differ between patients with ESVI ≤84 ml/m² (HR: 0.77; 95% CI: 0.51 to 1.16) and those with ESVI >84 ml/m² (HR: 0.82; 95% CI: 0.54 to 1.24; interaction p value = 0.873).

DISCUSSION

The current report extends the analysis of the prospective STICH myocardial viability study (17) to examine the interaction of ESVI, as a marker of severity of LV remodeling, with extent of myocardial viability and treatment with CABG versus medical therapy with respect to survival in patients with CAD and LV systolic dysfunction. The results indicate that, even after accounting for ESVI, specifically in patients with lower values of ESVI, there was no significant interaction between viability and treatment assignment with respect to survival.
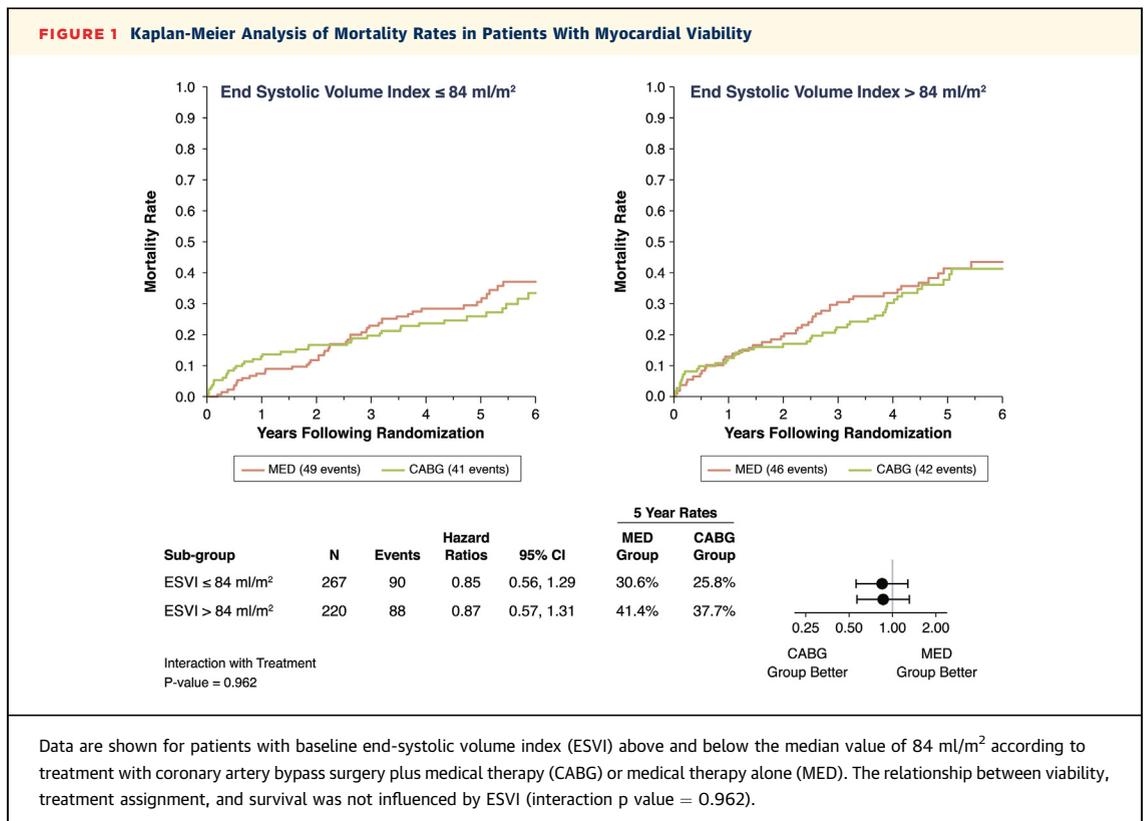
The current study was inspired by previous reports suggesting that improvement in LV function after CABG occurs in patients with myocardial viability who have less severe LV remodeling, whereas functional recovery is less likely, despite viable myocardium, in patients with severe LV remodeling. Yamaguchi et al. (18) studied 20 patients undergoing CABG with LVEF <30% and reported improvement in LV function in those with ESVI <100 ml/m² but not in those with

larger ESVI. Three other studies assessing the impact of ESV on recovery of LV function after revascularization did not index ESV for body size. Bax et al. (19) studied patients with mean LVEF of 29% and observed

TABLE 2 Baseline Characteristics of Patients Without Myocardial Viability

	Patients with LV ESVI ≤84 ml/m² (n = 37)	Patients with LV ESVI >84 ml/m² (n = 77)	p Value
Age, yrs	64 ± 8	60 ± 9	0.019
Prior myocardial infarction	34 (92)	74 (96)	0.388
Diabetes	11 (30)	15 (20)	0.222
Prior stroke	3 (8)	8 (10)	1.000
Hypertension	23 (62)	28 (36)	0.010
Hyperlipidemia	30 (81)	47 (62)	0.039
Current smoker	4 (11)	14 (18)	0.312
Chronic renal insufficiency	3 (8)	7 (9)	1.000
Atrial flutter/fibrillation	3 (8)	13 (17)	0.207
Peripheral vascular disease	1 (3)	15 (20)	0.016
RAR score*	10 ± 9	14 ± 9	0.039
Previous CABG	1 (3)	3 (4)	1.000
Bypass graft status			
≥1 stenosed or occluded	1 (100)	3 (100)	
≥1 occluded	1 (100)	3 (100)	
Previous PCI	12 (32)	15 (20)	0.128
CAD distribution			
No. of diseased vessels ≥75%			0.835
0	0 (0)	3 (4)	
1	8 (22)	20 (26)	
2	17 (46)	25 (33)	
3	12 (32)	29 (38)	
Proximal LAD stenosis ≥75%	27 (73)	53 (69)	0.651
Left main stenosis (≥50%)	1 (3)	1 (1)	0.546
Highest NYHA functional class within 3 months			0.349
I	2 (5)	1 (1)	
II	10 (27)	20 (26)	
III	21 (57)	43 (56)	
IV	4 (11)	13 (17)	
Medications at baseline			
Beta-blocker	30 (81)	67 (87)	0.405
ACE inhibitor	32 (87)	70 (91)	0.521
ARB	2 (5)	4 (5)	1.000
ACE inhibitor or ARB	34 (92)	74 (96)	0.388
Statin	36 (97)	67 (87)	0.100
Aspirin	31 (84)	68 (88)	0.559
Blood pressure, mm Hg			
Systolic	118 ± 14	113 ± 14	0.050
Diastolic	75 ± 9	73 ± 9	0.385
Heart rate, beats/min	71 ± 11	75 ± 16	0.190
LV ejection fraction	31 ± 9	20 ± 6	<0.001
LV EDVI, ml/m²	94 ± 23	172 ± 44	<0.001
LV ESVI, ml/m²	63 ± 14	129 ± 36	–
Hemoglobin, g/dl	14 ± 2	14 ± 1	0.401
Creatinine, mg/dl	1.1 ± 0.3	1.2 ± 0.4	0.074
BUN, mg/dl	26 ± 18	28 ± 18	0.498

Values are mean ± SD or n (%). *The RAR score ranges from 1 to 32, with higher numbers indicating a higher predicted rate of death. Among patients receiving medical therapy, a score of 1 predicts a rate of 18% and a score of 32 predicts a rate of 99% over 5 years.

Abbreviations as in **Table 1**.

FIGURE 1 Kaplan-Meier Analysis of Mortality Rates in Patients With Myocardial Viability

Data are shown for patients with baseline end-systolic volume index (ESVI) above and below the median value of 84 ml/m² according to treatment with coronary artery bypass surgery plus medical therapy (CABG) or medical therapy alone (MED). The relationship between viability, treatment assignment, and survival was not influenced by ESVI (interaction p value = 0.962).

improvement in EF after CABG in patients with smaller ESV and myocardial viability (assessed using ^{18}F-fluorodeoxyglucose [FDG] SPECT). The same investigators subsequently reported comparable results using dobutamine echocardiography to assess viability (20), in which the likelihood of recovery of LVEF decreased proportionally with the increase in ESV despite the presence of viable myocardium. Similarly, Mandegar et al. (21) reported changes in LV function after CABG in 85 patients with EF ≤35% (mean 27%), all of whom manifested myocardial viability by dobutamine echocardiography; patients with ≥6 viable segments manifested improvement in EF postoperatively, whereas patients with <6 viable segments did not increase EF if there was high ESV. Of these 4 studies, only Bax et al. (19) reported postoperative survival data, in which patients with viable myocardium and small ESV had lower mortality rates after CABG than those with viable myocardium and high ESV (similar to trends we observed in **Figures 1 to 3** in the current study). None of these 4 studies included a comparison cohort of patients treated with medical therapy alone.
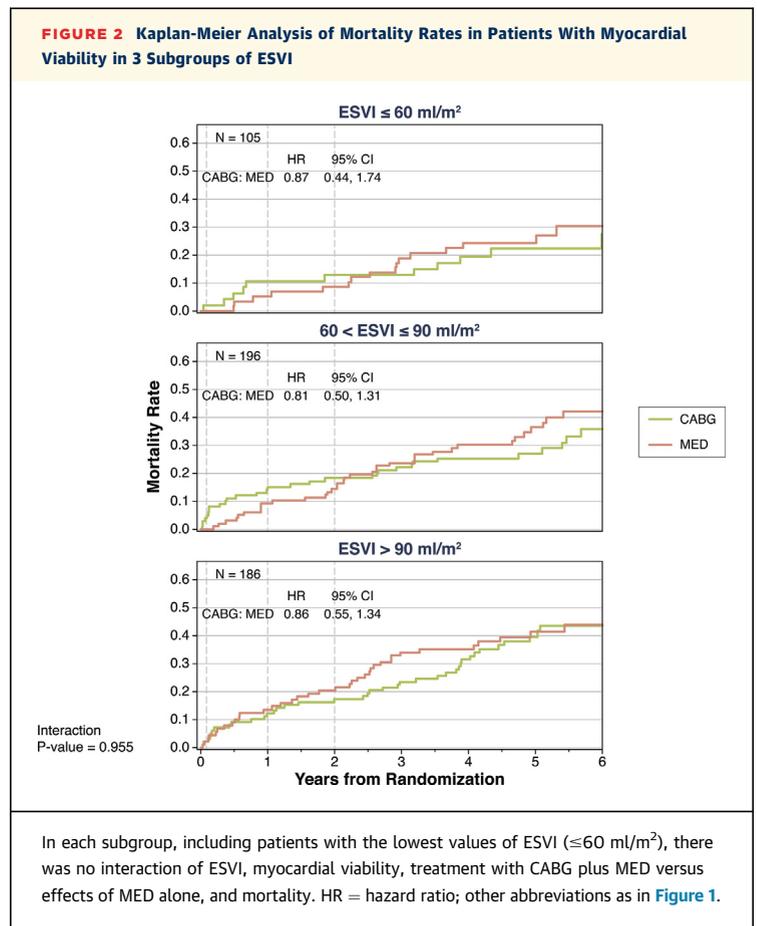
Previous studies and meta-analyses indicating improved survival with CABG compared with medical therapy in patients with LV systolic dysfunction and viable myocardium are limited by retrospective design and lack of adjustment for key baseline comorbidities (9,15,16). Factors influencing recommendations for revascularization in each patient were not considered; hence, the subsequent analyses ignore the biases inherent in therapeutic decisions made by each treating physician. Moreover, the medical therapies used are often not reported, and when reported, would be considered suboptimal by current standards. Specifically, beta-blockers were underused or not used at all. Treatment with beta-blockers has the potential to improve survival in patients with ischemic LV dysfunction (6) and to improve LV function in those with myocardial viability (10-12). Although patients in the STICH trial had lower mean LVEF than patients with myocardial viability treated medically in prior reports (9,15-17), patients with viable myocardium randomized to medical therapy in STICH had substantially lower annual mortality rates than patients with viability treated medically in the previous studies. This appears to reflect the adherence to guideline-driven medical therapy in the majority of patients in this prospective trial (29).
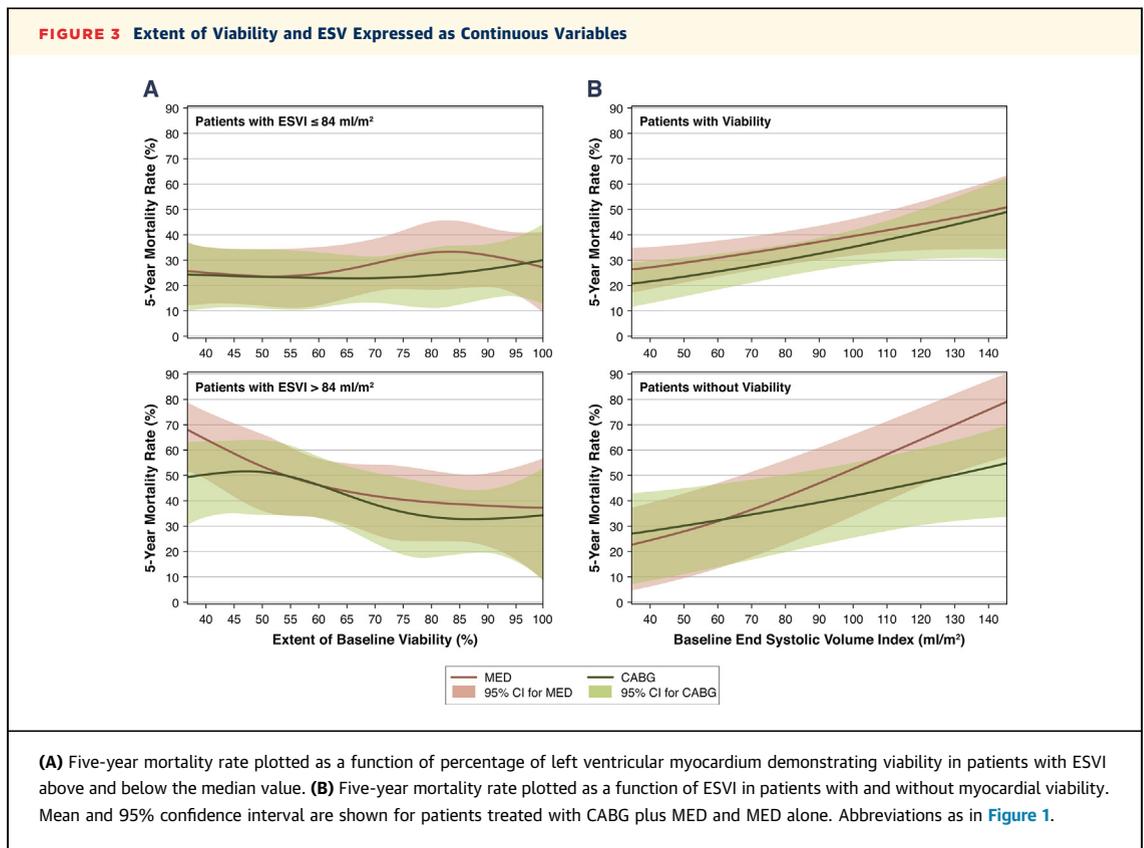
When myocardial viability was assessed as a continuous variable in the current analysis (**Figure 3**),

there was no differential effect of CABG over medical therapy with increasing extent of viable myocardium. These findings are supported by the previous retrospective study of Tarakji et al. (30), who reported survival with medical therapy versus revascularization in 765 patients with LVEF ≤35% (mean 23%). Across the continuum of magnitude of compromised viable myocardium assessed by FDG positron emission tomography (PET), there was no differential effect of CABG with increasing extent of myocardial viability. A subsequent study from the same institution (31) in 648 patients with CAD and LV systolic dysfunction (mean EF 31%) studied with FDG PET did report reduced mortality with early revascularization compared with medical therapy as a function of increasing extent of hibernating myocardium. However, in that study, early revascularization was defined as revascularization within 92 days of PET, yet the survival analysis began at 92 days, excluding all deaths before 92 days from the analysis. Thus, early post-operative mortality, the time period of greatest hazard for CABG relative to medical therapy (23,32), was not accounted for in the survival curves. The STICH trial results also demonstrate a differential benefit of CABG over medical therapy once patients survived the first several months, and it is the higher early mortality risk of CABG that produced the overall balance between surgical and medical outcomes (23,32). In the current analysis, in which early post-operative mortality was included in the mortality analysis, no interaction between myocardial viability, ESVI, and survival with CABG or medical therapy was observed across the spectra of myocardial viability and ESVI (**Figure 3**).

STUDY LIMITATIONS. Viability assessment with SPECT and dobutamine echocardiography does not incorporate the particular advantages of metabolic imaging with PET or assessment of myocardial fibrosis with cardiac magnetic resonance (31,33,34). However, in a meta-analysis and other reviews, SPECT and dobutamine echocardiography have had similar prognostic potential to that of PET (9,15,16), a small randomized study of PET versus SPECT for viability assessment failed to show improved event-free survival in patients assigned to PET (35), and a randomized study of PET-guided care versus usual care failed to demonstrate improved outcome with the PET strategy (36). The STICH protocol was designed in 2000 (22) before the advent of cardiac magnetic resonance for viability assessment (8), using imaging protocols identical to those in previous nonrandomized studies reporting survival advantages of CABG over medical therapy in patients with viable myocardium (9). As noted previously, patients with viability data represent roughly 50% of all patients enrolled in the STICH trial, and viability testing was not performed on a randomly selected subset but depended on test availability and judgment of the recruiting investigator. However, previous analyses did not reveal an interaction between performance of a viability test and treatment assignment (17), which was prospective and randomized. The majority of patients studied were deemed to have viable myocardium based on our pre-specified criteria. Although this limits the interpretation of outcomes in patients with nonviable myocardium, it provides sufficient patient numbers in those with myocardial viability to assess the interaction of ESVI with outcomes in patients with viable myocardium. In addition, assessment of viability as a continuous variable (**Figure 3**) supports the primary analysis in which viability was assessed as a dichotomous variable. The STICH results pertain only to patients eligible for enrollment in the STICH trial (LVEF ≤35%), and the interaction of ESVI, myocardial viability, and survival with CABG compared with medical therapy may differ in patients with less severe LV dysfunction.

FIGURE 2 Kaplan-Meier Analysis of Mortality Rates in Patients With Myocardial Viability in 3 Subgroups of ESVI

In each subgroup, including patients with the lowest values of ESVI (≤60 ml/m²), there was no interaction of ESVI, myocardial viability, treatment with CABG plus MED versus effects of MED alone, and mortality. HR = hazard ratio; other abbreviations as in **Figure 1**.

FIGURE 3   Extent of Viability and ESV Expressed as Continuous Variables

(A) Five-year mortality rate plotted as a function of percentage of left ventricular myocardium demonstrating viability in patients with ESVI above and below the median value. **(B)** Five-year mortality rate plotted as a function of ESVI in patients with and without myocardial viability. Mean and 95% confidence interval are shown for patients treated with CABG plus MED and MED alone. Abbreviations as in **Figure 1**.

The lack of significant interaction between myocardial viability and survival with surgical versus medical management of patients with severe ischemic LV dysfunction is reflected in the current recommendations for revascularization in the 2013 American College of Cardiology/American Heart Association guideline for the management of heart failure (37), which indicates that, in the absence of angina, CABG may be considered, with the intent of improving survival in patients with ischemic heart disease with severe LV systolic dysfunction (EF <35%) whether or not viable myocardium is present (class IIb, level of evidence B). In contrast, other guidelines continue to recommend that decisions for revascularization be driven by evidence of myocardial viability (38,39). The current data should stimulate further discussion of the role of viability testing in determining appropriate candidacy for revascularization.

CONCLUSIONS

The current findings indicated that patients with ischemic LV dysfunction and extensive LV remodeling (manifested by greater ESVI) had a worse prognosis than those with lower ESVI. However, the effect of CABG when added to evidence-based medical therapy was not differentially influenced by the combination of ESVI and extent of myocardial viability. Lower ESVI did not identify patients in whom the presence of viable myocardium predicted a better outcome with CABG relative to medical therapy alone.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Among patients with coronary artery disease and LV systolic dysfunction, lower LV end-systolic volume index does not identify patients in whom myocardial viability predicts better outcome with surgical relative to medical treatment.

TRANSLATIONAL OUTLOOK: Future research should determine whether end-systolic volume and myocardial viability interact to affect improvement in LV function with surgical versus medical treatment and determine the relation between improvement in function and survival.

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