Left ventricular volume change and long-term outcomes in ischaemic cardiomyopathy with or without surgical revascularisation: A post-hoc analysis of a randomised controlled trial

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Summary

Background Whether the association between post-therapeutic left ventricular volume change and long-term outcomes in ischaemic cardiomyopathy is influenced by the performance of coronary artery bypass grafting (CABG) remains unclear. We sought to perform a post-hoc analysis of the Surgical Treatment of Ischaemic Heart Failure (STICH) trial to investigate this association in patients treated with medical therapy (MED) with or without CABG.

Methods From July 24, 2002, to May 5, 2007, 1212 patients with ischaemic cardiomyopathy were enrolled in the STICH trial (NCT00023595) from 99 sites in 22 countries, and were randomly assigned to undergo CABG plus MED or MED alone. We completed a post-hoc analysis of this trial. Patients with paired left ventricular end-systolic volume index (ESVI) measured at baseline and 4-months were included in our analysis. The association between change in ESVI from baseline to 4-months and cardiovascular mortality or all-cause mortality was assessed in MED arm and CABG plus MED arm.

Findings 523 patients were included, with 291 (55.6%) assigned to MED arm and 232 (44.4%) to CABG plus MED arm. At a 4-month follow-up, ESVI reduction was more likely to occur among patients undergoing CABG plus MED. After a median follow-up of 10.3 years, for each 26% (1- standard deviation) decrement in ESVI, it was associated with a 22% lower risk of cardiovascular mortality (HR 0.78; 95% CI, 0.65-0.94) and 19% lower risk of all-cause mortality (HR 0.81; 95% CI, 0.69-0.95) in MED arm, whereas this association was not shown in CABG plus MED arm (cardiovascular mortality: HR 0.90; 95%CI, 0.74-1.10; all-cause mortality: HR 0.93; 95%CI, 0.79-1.09). A 16% reduction in ESVI was determined to be the most appropriate threshold of change in ESVI in the MED arm.

Interpretation In patients with ischaemic cardiomyopathy, left ventricular volume change was associated with long-term prognosis after medical therapy alone, whereas was likely not an optimal benchmark for evaluating the survival benefits associated with CABG. A more than 16% reduction in ESVI might assist in therapeutic efficacy assessment and prognostic evaluation in medically treated patients.

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Keywords: Ischaemic cardiomyopathy; Coronary artery bypass grafting; Left ventricular volume; STICH

Introduction

Ischaemic cardiomyopathy, defined as heart failure with reduced ejection fraction caused by severe coronary artery disease, has resulted in substantial mortality and disability worldwide.[1] Among patients with ischaemic cardiomyopathy, progressive enlargement of left ventricular volume due to infarct expansion, scar formation and decompensated cardiac hypertrophy following

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Research in context

Evidence before this study

We systematically searched PubMed, Embase, and the Cochrane Library, until March 15, 2022 by using keywords and medical subject heading (Mesh), including the following terms: ("ischaemic cardiomyopathy" OR "ischaemic heart failure" OR "ventricular dysfunction" OR "reduced ejection fraction") AND ("volume" OR "remodeling" OR "ventricular size" OR "ventricular function"). Full-text original research articles and reviews were included. The majority of studies in this area have focused on patients with mixed aetiologies of heart failure, whereas barely any studies have investigated the association between post-therapeutic left ventricular volume change and long-term outcomes in patients with ischaemic cardiomyopathy, and whether this association is influenced by the performance of coronary artery bypass grafting (CABG)

Added value of this study

By performing a post-hoc analysis of the Surgical Treatment of Ischaemic Heart Failure (STICH) trial, we found that left ventricular volume change was associated with long-term prognosis after medical therapy alone, whereas was likely not an optimal benchmark for evaluating the survival benefits associated with CABG. A more than 16% reduction in ESVI might assist in therapeutic efficacy evaluation, and could be considered a pragmatic prognostic indicator in medically treated patients.

Implications of all the available evidence

This study provides a comprehensive depiction into the association between left ventricular volume change, surgical revascularisation and long-term outcomes in patients with ischaemic cardiomyopathy. Our findings have the potential to provide mechanistic insights into how medical therapy or surgical revascularization might affect prognosis, and could be factored into the therapeutic-decision making in clinical practice.

myocardial infarction,[2] as measured by a higher left ventricular end-systolic volume index (ESVI), has been identified as a strong prognostic predictor.[3,4]

Left ventricular volume change, which is considered an early signal of pharmacological efficacy on long-term outcomes,[5,6] can be achieved in patients with ischaemic cardiomyopathy after appropriate medical therapy or revascularisation.[7,8] Whether the association between post-therapeutic left ventricular volume change and long-term outcomes in ischaemic cardiomyopathy is influenced by the performance of coronary artery bypass grafting (CABG) remains unclear.

The Surgical Treatment for Ischaemic Heart Failure (STICH)[9] trial was a multicentre randomised controlled trial that investigated the role of CABG plus optimal medical therapy (MED) compared with MED alone in patients with ischaemic cardiomyopathy. By performing a post-hoc analysis of the STICH trial, we sought to (i) investigate the change in ESVI from baseline to 4-month follow-up in patients with ischaemic cardiomyopathy undergoing MED with or without CABG; (ii) study the association between change in ESVI with long-term outcomes and the effect of CABG on this association; and (iii) determine the most appropriate clinical threshold of change in ESVI.

Methods

The present study is a post-hoc analysis of the STICH[9] and the STICH extension study (STICHES) (ClinicalTrials.gov registration number NCT00023595).[10] The STICH trial was approved by the institutional review committees at each multicentre and written informed consent was obtained from all participants. The de-identified dataset was obtained from the National Heart, Lung, and Blood Institute's Biologic Specimen and Data Repository Information Coordinating Centre (BioLINCC) via an approved proposal by the institutional review board of our hospital. Our study complies with the Declaration of Helsinki.

Study population

The study designs and main results of the STICH trial have been published previously.[11] From July 24, 2002, to May 5, 2007, a total of 1212 patients with ischaemic cardiomyopathy [defined as coronary artery disease and left ventricular ejection fraction (LVEF) less than 35%] were enrolled from 99 sites in 22 countries. The inclusion criteria of LVEF less than 35% were determined based on any available imaging assessment performed within 3 months prior to randomisation. For hypothesis 1 of the STICH trial, 1212 patients were included and randomised to optimal medical therapy alone (602 patients) or medical therapy plus CABG (610 patients), and were followed up for a median of 9.8 years.

Among all 1212 patients enrolled in hypothesis 1 of the STICH trial, the following patients were excluded: 1) patients who died within 4-month from the randomisation (n=78); 2) patients without baseline ESVI measured by any imaging modalities including echocardiography, cardiac magnetic resonance or single-photon emission-computed tomography radionuclide imaging (n=234); 3) patients who did not have ESVI measured at 4 months (n=317); 4) patients who did not have paired ESVI measured at baseline and 4-month using the same imaging modality (n=54); 5) patients underwent concomitant surgical ventricular reconstruction (n=6), leaving 523 patients eligible for our study (Supplementary Figure S1).

Imaging data

All 523 included patients have paired imaging data measured at baseline and 4-month follow-up using the same imaging modality. All imaging data were objectively assessed by respective Core Laboratory (Mayo Clinic for echocardiography, University of Southern California for cardiac magnetic resonance, and Northwestern University and Cedars-Sinai Medical Centre for radionuclide) based on standardised methods without knowledge of the patients' treatment assignment or any clinical data.[12,13] The imaging modality was used according to the preferential hierarchy reported by Oh et al.[12] We first used the echocardiography data in all patients when available. If the echocardiography data were not available, we then used the cardiac magnetic resonance data, and last to the radionuclide data. Imaging quality was not considered in our imaging priority algorithm. Using this approach, 478 patients with echocardiography data, 11 patients with cardiac magnetic resonance data and 34 patients with radionuclide data were included in our analyses. Left ventricular volume change was represented by percent change in ESVI from baseline to 4-month.

Study outcomes

The study outcomes included cardiovascular mortality and all-cause mortality. The causes of death were adjudicated by an independent blinded committee using prespecified definitions.

Statistical analysis

All statistical analyses were performed under the intention-to-treat principle. Baseline characteristics of patients in the MED and CABG arms were compared. To evaluate the potential selection bias, we compared the baseline characteristics of the final included and excluded patients (patients who died before the 4-month follow-up were not counted). Continuous variables were presented as the median (25th, 75th, percentiles) or mean (standard deviation) and were compared by Wilcoxon rank-sum test or Student t-test. Categorical data were presented as numbers with percentages and were analysed by Pearsons' chi-square or Fisher's exact tests, if appropriate. Change in ESVI from baseline to 4-month were evaluated by the paired t-test. Sankey diagrams were created using the open access SankeyMATIC website. The correlation between change in ESVI, change in LVEF, and baseline ESVI was assessed using the Spearman correlation test. The association between change in ESVI and all-cause mortality was assessed by univariable and multivariable cox proportional hazards models, and the proportional hazards assumption was assessed to ensure it was met. Fine and Gray competing risk regression and cumulative incidence functions were used for the risk of cardiovascular mortality, with death from other causes as a competing risk.[14] The adjusted covariates were selected based on previously published studies and clinically relevant experience. Different models were examined to investigate the effects of different confounders on the association between change in ESVI and outcomes. Model 1 was adjusted for key demographics including age and sex; Model 2 was adjusted for age, sex, baseline ESVI and baseline LVEF. Model 3 was adjusted for the variables in Model 2 plus baseline comorbidities including diabetes mellitus, atrial fibrillation, renal insufficiency and stroke. The results were presented as hazard ratios (HRs) and 95% confidence intervals (CIs). The visualised relationship between change in ESVI on a continuous scale with HRs of cardiovascular or all-cause mortality was plotted using a multivariable adjusted Cox model with restricted cubic splines. The number of knots was chosen according to the Akaike's information criterion for best fit: three knots were placed at the default locations (10th, 50th, and 90th percentiles of its distribution). By using the X-tile software (Version 3.6.1, Yale University School of medicine), the most appropriate clinical cut-off value of ESVI reduction was determined according to the highest chi-square value (the lowest log-rank *P* value) defined by the Kaplan-Meier survival analysis.[15] Cumulative event rates were estimated using the Kaplan-Meier method and compared by the log-rank test. Subgroup analyses were performed based on pre-specified clinically accepted thresholds of baseline ESVI ($\leq$ 60 mL/m^2; 60-90 mL/m^2; and $>$ 90 mL/m^2).[16] For sensitivity analyses, we then analysed the data based only on 478 patients with paired echocardiographic measurements to test the robustness of our results. We also tested the consistency of our results under the per-protocol principle. All tests were two-sided, and *P* values less than 0.05 were considered significant. All statistical analyses were performed using R, version 3.6.3 (R Foundation for Statistical Computing, http://www.R-project.org) and STATA, version 14.0 (StataCorp, College Station, TX).

Role of the funding source

The funding source did not have any involvement in study design, data collection, data analysis, data interpretation, the writing of the report, or the decision to submit the paper. All authors confirm that they had full access to all the data in the study and accept the responsibility to submit for publication.

Results

Baseline characteristics of patients

Among the 1212 patients enrolled in hypothesis 1 of the STICH trial, 523 patients with paired ESVI at baseline and 4-month met our inclusion criteria. The baseline

characteristics and clinical outcomes of the 523 included patients were generally similar to the 611 excluded patients, except for diabetes mellitus, hypertension and CABG treatment arm assignment (Supplementary Table S1). Among the 523 included patients, 291 (55.6%) were assigned to the MED arm and 232 (44.4%) to the CABG arm. No significant difference was observed in the baseline characteristics between patients assigned to the MED or CABG arms (Table 1).

Effect of MED or CABG on left ventricular volume change

As shown in Figure 1A, ESVI significantly reduced from baseline to 4-month in the CABG arm (85.0 ± 28.6 mL/m^2 to 81.1 ± 32.9 mL/m^2, P = 0.011), but not in the MED arm (85.0 ± 31.2 mL/m^2 to 83.8 ± 33.9 mL/m^2, P = 0.301). As shown by the Sankey diagrams delineating the dynamic change of ESVI from baseline to 4-month, the reduction in left ventricular volume is more likely to occur among patients undergoing CABG, compared with medically treated patients (Figure 1B). The distribution of change in ESVI in the MED arm and the CABG arm was shown in Supplementary Figure S2. The change in ESVI for every individual patient was shown in Supplementary Figure S3.

Left ventricular volume change and outcomes

After a median follow-up of 10.3 years, 133 cardiovascular mortalities occurred in the MED arm and 86 occurred in the CABG arm. As presented in Figure 2A, restricted cubic splines delineated the patterns of change in ESVI and cardiovascular mortality in all patients, MED arm and CABG arm. The decrement in ESVI was progressively associated with a lower risk of cardiovascular mortality in the overall cohort, and in the MED arm, but not in the CABG arm. For all-cause mortality, 181 occurred in the MED arm and 131 occurred in the CABG arm. Similar patterns between percent change in ESVI and all-cause mortality were presented in Figure 2B.

Variable	Overall (n = 523)	MED (n = 291)	CABG (n = 232)	P value
Age, years	60.6 ± 9.3	60.4 ± 9.5	60.7 ± 9.2	0.730
Sex, female	63 (12.1)	35 (12.0)	28 (12.1)	0.988
BSA, m^2	1.9 ± 0.2	1.9 ± 0.2	1.9 ± 0.2	0.518
NYHA class ≥ grade 3	175 (33.5)	97 (33.3)	78 (33.6)	0.945
Diabetes mellitus	181 (34.6)	101 (34.7)	80 (34.5)	0.957
Hypertension	292 (55.8)	167 (57.4)	125 (53.9)	0.422
Atrial fibrillation	64 (12.2)	37 (12.7)	27 (11.6)	0.709
Renal insufficiency	32 (6.1)	17 (5.8)	15 (6.5)	0.758
Stroke	39 (7.5)	22 (7.6)	17 (7.3)	0.920
Baseline LVEF, %	28.3 ± 8.4	28.5 ± 8.6	28.1 ± 8.1	0.590
Baseline EDVI, mL/m^2	116.6 ± 32.4	116.7 ± 33.7	116.6 ± 30.7	0.975
Baseline ESVI, mL/m^2	85.0 ± 30.0	85.0 ± 31.2	85.0 ± 28.6	0.994
LVEF at 4-month, %	29.8 ± 9.9	30.0 ± 9.6	29.6 ± 10.4	0.651
ESVI at 4-month, mL/m^2	82.6 ± 33.5	83.8 ± 33.9	81.1 ± 32.9	0.368
ESVI < 60 mL/m^2 at 4-month	144 (27.5)	77 (26.5)	67 (28.9)	0.538
Change in LVEF at 4-month, %	1.5 ± 9.0	1.5 ± 8.6	1.5 ± 9.5	0.999
Change in ESVI at 4-month, mL/m^2	-2.4 ± 21.7	-1.2 ± 20.3	-3.9 ± 23.3	0.162
Three-vessel disease	180 (34.4)	101 (34.7)	79 (34.1)	0.875
Proximal LAD stenosis	354 (67.7)	198 (68.0)	156 (67.2)	0.846
Medications at Baseline				
Beta-blocker	465 (88.9)	260 (89.4)	205 (88.4)	0.722
Aspirin	440 (84.1)	250 (85.9)	190 (81.9)	0.212
Statin	436 (83.4)	243 (83.5)	193 (83.2)	0.923
ACEI/ARB	475 (90.8)	260 (89.4)	215 (92.7)	0.191
Clinical Outcomes				
Cardiovascular mortality	219 (41.9)	133 (45.7)	86 (37.1)	0.047
All-cause mortality	312 (59.7)	181 (62.2)	131 (56.5)	0.184

***Table 1*: Baseline characteristics and clinical outcomes of patients in MED and CABG arm.**
Continuous variables were presented as the mean ± standard deviation. Categorical data were presented as numbers (percentages).
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BSA, body surface area; CABG, coronary artery bypass grafting; EDVI, end-diastolic volume index; ESVI, end-systolic volume index; LAD, left anterior descending; LVEF, left ventricular ejection fraction; MED, optimal medical therapy; NYHA, New York Heart Association.

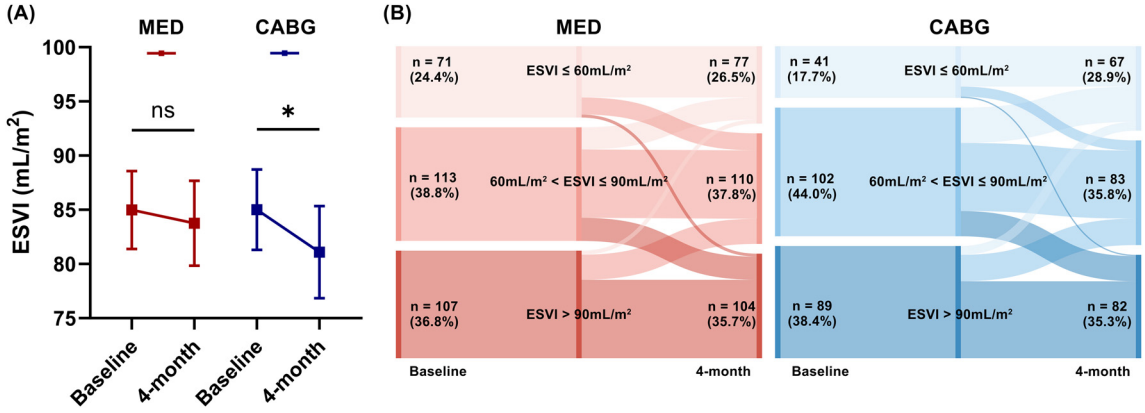

Figure 1. Change in ESVI from baseline to 4-month follow-up. (A) The overall change in ESVI from baseline to 4-month follow-up in the MED arm and CABG arm. Mean values along with 95% confidence intervals were noted. **(B)** Sankey diagrams depicting the change in ESVI in MED arm and CABG arm. Compared with medically treated patients, left ventricular volume reduction is more likely to occur among patients undergoing CABG.

*indicates $P < 0.05$ from a paired t-test.

CABG, coronary artery bypass grafting; ESVI, end-systolic volume index; MED, optimal medical therapy.

After full adjustment, per 26.0% (1- standard deviation) decrement in ESVI, as a continuous variable, was significantly associated with a 17% lower risk of cardiovascular mortality in the overall cohort (HR 0.83, 95% CI, 0.72-0.95), and a 22% lower risk in MED arm (HR 0.78; 95% CI, 0.65-0.94), but this association was not observed in CABG arm (HR 0.90; 95% CI, 0.74-1.10). Similarly, per 26.0% (1-standard deviation) decrement in ESVI was significantly associated with a 14% lower risk of all-cause mortality in the overall cohort (HR

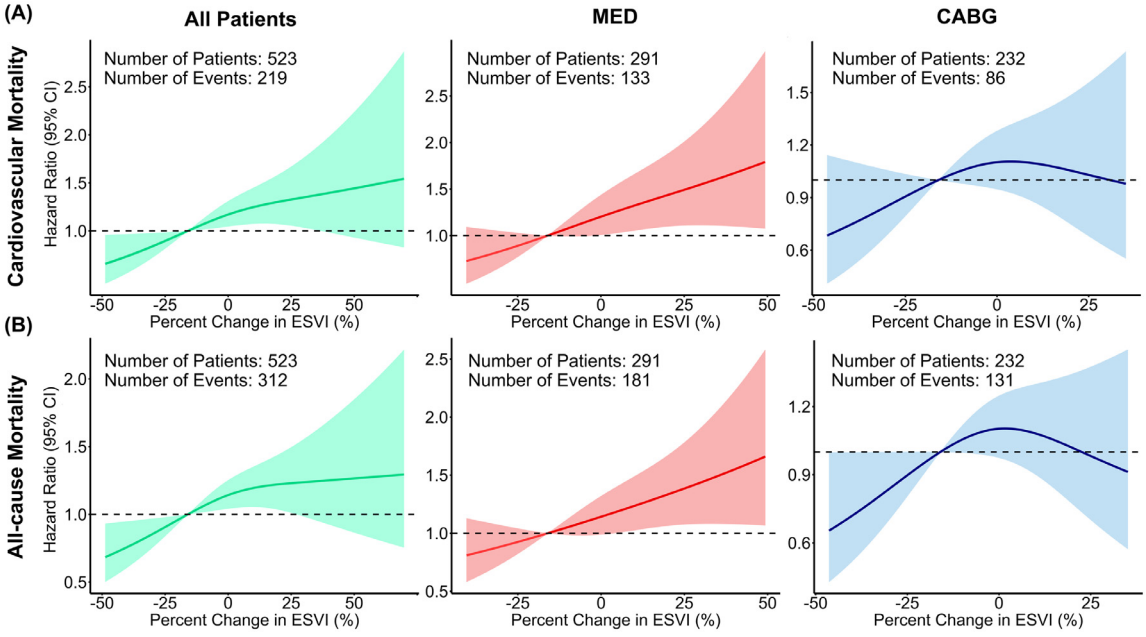

Figure 2. Association between change in ESVI and long-term outcomes, delineated by restricted cubic splines. The association between change in ESVI with **(A)** cardiovascular mortality, and **(B)** all-cause mortality, in overall patients, MED arm and CABG arm. The reference point is set to a 16% reduction in ESVI. Adjusted for age, sex, baseline ESVI, baseline LVEF, diabetes mellitus, atrial fibrillation, renal insufficiency and stroke.

CABG, coronary artery bypass grafting; ESVI, end-systolic volume index; LVEF, left ventricular ejection fraction; MED, optimal medical therapy.

0.86; 95% CI, 0.77-0.96), and a 19% lower risk in MED arm (HR 0.81; 95% CI, 0.69-0.95), but this association was not observed in CABG arm (HR 0.93; 95% CI, 0.79-1.09) (Table 2). In the sensitivity analyses based on 478 patients with paired echocardiographic measurements, the results remained robust. (Supplementary Table S2). When we excluded patients who crossover between the MED and the CABG arm, and analysed the remaining 486 patients based on the per-protocol principle, the results remained consistent (Supplementary Table S3). The composite outcome of death from any cause or cardiovascular hospitalisation was analysed as an additional outcome, and the results were summarised in Supplementary Table S4.

ESVI reduction ≥ 16% and outcomes

As calculated by the X-tile software, the most appropriate clinical cut-off value of change in ESVI was determined to be a 16% reduction. Of the 523 included patients, 132 (25.2%) had a more than 16% reduction in ESVI, of whom 65 (22.3%) in the MED arm and 67 (28.9%) in the CABG arm. The baseline characteristics of patients with or without a more than 16% reduction in ESVI are summarised in Supplementary Table S5. Patients with a more than 16% reduction in ESVI were more likely to have a history of stroke.

After full adjustment, patients with a more than 16% reduction in ESVI were significantly associated with a lower risk of cardiovascular mortality in the overall cohort (HR 0.55; 95% CI, 0.39-0.78), and MED arm (HR 0.45; 95% CI, 0.27-0.74), but this association did not reach statistical significance in CABG arm (HR 0.71; 95% CI, 0.43-1.18). Similarly, patients with a more than 16% reduction in ESVI were significantly associated with a lower risk of all-cause mortality in the overall cohort (HR 0.62; 95% CI, 0.47-0.81), and MED arm (HR 0.56; 95% CI, 0.38-0.82), but the results was not statistically significant in CABG arm (HR 0.73; 95% CI, 0.49-1.09) (Table 3). Cumulative incidence curves showed that patients with a more than 16% reduction in ESVI had a lower incidence of cardiovascular mortality and all-cause mortality in the overall cohort and MED arm, but no statistical significance was observed in the CABG arm (Figure 3).

Baseline ESVI, left ventricular volume change and post-therapeutic ESVI

In both treatment arms, change in ESVI was negatively correlated with baseline ESVI (MED: r = -0.21, P < 0.001; CABG: r = -0.16, P = 0.017) (Supplementary Figure S4). Change in LVEF was negatively correlated with change in ESVI (MED: r = -0.57, P < 0.001; CABG: r = -0.64, P < 0.001) (Supplementary Figure S5), but was not correlated with baseline ESVI (MED: r = 0.06, P = 0.315; CABG: r = 0.06, P = 0.342) (Supplementary Figure S6). The association between a more than 16% reduction in ESVI and clinical outcomes remained generally consistent in the subgroup analyses based on baseline ESVI (≤ 60 mL/m²; 60-90 mL/m²; and > 90 mL/m²) (Supplementary Table S6). Kaplan-Meier curves showed that patients with post-therapeutic ESVI < 60 mL/m² had a significantly lower incidence of all-cause mortality, both in the MED arm and the CABG arm (Supplementary Figure S7).

Discussion

The key findings of the current post-hoc analysis of the STICH trial can be summarised as follows: (i) left ventricular volume reduction was more likely to occur among patients undergoing CABG; (ii) the decreased change in ESVI was associated with a lower risk of cardiovascular and all-cause mortality in patients undergoing medical therapy alone, but this association was not observed in CABG treated patients; (iii) the most

Outcome	Group	No. of Events/ Patients (%)	Change in ESVI from baseline to 4-month, per 1-SD decrement[a] Hazard Ratio (95% Confidence Interval)			
			Unadjusted	Model 1	Model 2	Model 3
Cardiovascular Mortality	All patients	219/523 (41.9)	0.93 (0.82-1.05)	0.94 (0.83-1.06)	0.85 (0.74-0.97)	0.83 (0.72-0.95)
	MED	133/291 (45.7)	0.89 (0.77-1.04)	0.90 (0.77-1.05)	0.80 (0.67-0.95)	0.78 (0.65-0.94)
	CABG	86/232 (37.1)	1.01 (0.83-1.23)	1.01 (0.84-1.22)	0.93 (0.76-1.13)	0.90 (0.74-1.10)
All-cause Mortality	All patients	312/523 (59.7)	0.96 (0.86-1.06)	0.96 (0.86-1.07)	0.89 (0.79-0.99)	0.86 (0.77-0.96)
	MED	181/291 (62.2)	0.94 (0.81-1.08)	0.94 (0.81-1.09)	0.83 (0.71-0.97)	0.81 (0.69-0.95)
	CABG	131/232 (56.5)	1.00 (0.85-1.17)	1.00 (0.86-1.17)	0.96 (0.82-1.13)	0.93 (0.79-1.09)

***Table 2*: Association between change in ESVI from baseline to 4-month and long-term outcomes.**
CABG, coronary artery bypass grafting; ESVI, end-systolic volume index; LVEF, left ventricular ejection fraction; MED, optimal medical therapy; SD, standard deviation.
Model 1 adjusted for age and sex;
Model 2 adjusted for age, sex, baseline ESVI and baseline LVEF;
Model 3 adjusted for age, sex, baseline ESVI, baseline LVEF, diabetes mellitus, atrial fibrillation, renal insufficiency and stroke.
[a] Per 1-SD indicates a 26% change in ESVI.

Outcome	Group	No. of Events/ Patients (%)	ESVI reduction from baseline to 4-month ≥ 16% Hazard Ratio (95% Confidence Interval)			
			Unadjusted	Model 1	Model 2	Model 3
Cardiovascular Mortality	All patients	219/523 (41.9)	0.65 (0.47-0.91)	0.65 (0.46-0.90)	0.59 (0.42-0.83)	0.55 (0.39-0.78)
	MED	133/292 (45.7)	0.53 (0.33-0.85)	0.54 (0.34-0.87)	0.49 (0.30-0.79)	0.45 (0.27-0.74)
	CABG	86/231 (37.1)	0.88 (0.54-1.41)	0.82 (0.50-1.33)	0.74 (0.45-1.24)	0.71 (0.43-1.18)
All-cause Mortality	All patients	312/523 (59.7)	0.71 (0.54-0.93)	0.70 (0.53-0.91)	0.66 (0.50-0.86)	0.62 (0.47-0.81)
	MED	181/292 (62.2)	0.63 (0.43-0.91)	0.66 (0.45-0.97)	0.59 (0.40-0.86)	0.56 (0.38-0.82)
	CABG	131/231 (56.5)	0.85 (0.58-1.25)	0.78 (0.53-1.15)	0.79 (0.53-1.16)	0.73 (0.49-1.09)

***Table 3*: Association between a more than 16% reduction in ESVI and long-term outcomes.**
CABG, coronary artery bypass grafting; ESVI, end-systolic volume index; LVEF, left ventricular ejection fraction; MED, optimal medical therapy; SD, standard deviation.
Model 1 adjusted for age and sex;
Model 2 adjusted for age, sex, baseline ESVI and baseline LVEF;
Model 3 adjusted for age, sex, baseline ESVI, baseline LVEF, diabetes mellitus, atrial fibrillation, renal insufficiency and stroke.

appropriate threshold of change in ESVI on clinical outcomes was determined to be a 16% reduction in ESVI.

In 2019, Panza and his colleagues analysed 318 patients who underwent myocardial viability assessment and had paired imaging in the STICH trial, and found that no association was observed between improvement in LVEF at 4-month follow-up and the subsequent death.[17] Although both LVEF and ESVI were derived from end-systolic volume, these two parameters had different clinical implications: LVEF represents the left ventricular segmental systolic function while ESVI represents the degree of left ventricular size remodeling, and ESVI was generally considered a prognostic indicator independent of LVEF. In the present study, the change in ESVI was analysed as a continuous variable and as a dichotomous variable based on the statistically most appropriate cut-off value, which might provide underlying information associated with left ventricular volume change from different perspectives.

Previous studies have found an association between larger baseline left ventricular volume and poorer clinical outcomes in patients with ischaemic cardiomyopathy.[3,4,18] Besides, the therapeutic effects on

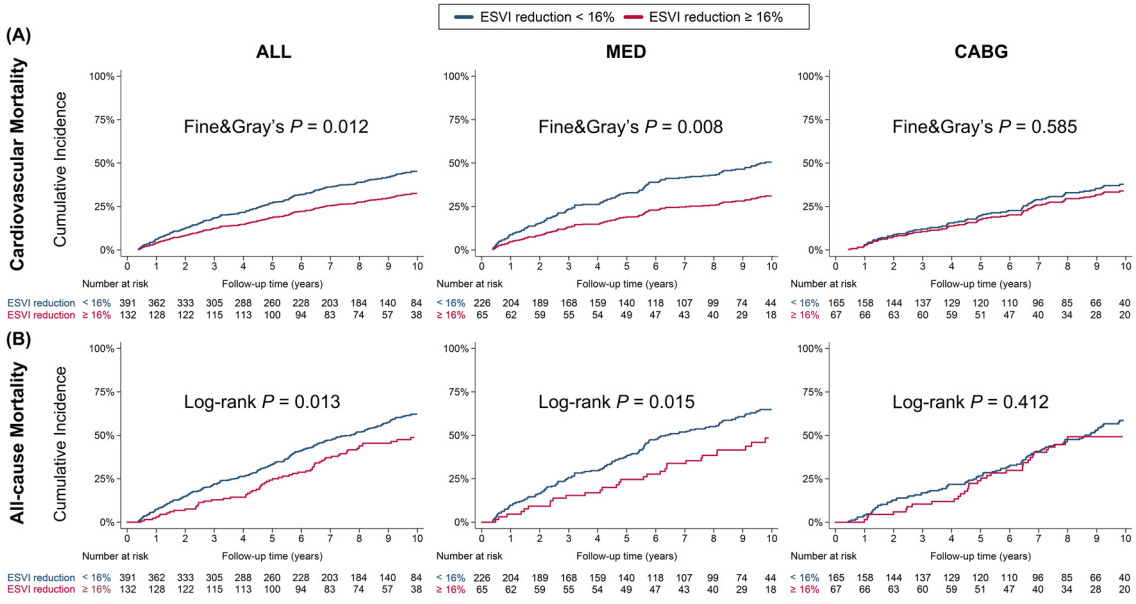

Figure 3. Cumulative incidence of patients with or without ESVI reduction ≥16%. (A) Cumulative incidence function for cardiovascular mortality with death from other causes as a competing risk, and **(B)** Kaplan-Meier estimated cumulative incidence of all-cause mortality in patients with or without a more than 16% reduction in ESVI.
ESVI, end-systolic volume index.

left ventricular volume were reported to play beneficial effects on heart failure prognosis after angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs)[19,20] or beta-blockers therapy.[21,22] Therefore, in drug development for heart failure, the recovery of left ventricular volume was expected a putative mechanism that mediates the favorable therapeutic effects of medical therapy,[8] and was considered a potential surrogate endpoint on heart failure outcomes.[23] In line with these pioneering investigations, our study supports the relevance of left ventricular volume change as a prognostic factor in pharmacologically treated ischaemic cardiomyopathy patients.

However, the prognostic value of left ventricular volume change was not evident in patients undergoing CABG. Our findings were in accordance with Samady and his colleagues, who reported that failure to improve left ventricular function after surgical revascularisation for ischaemic cardiomyopathy was not associated with worse outcome.[24] Moreover, Michler et al. performed a post-hoc analysis of hypothesis 2 of the STICH trial and reported that postoperative reduction of ESVI $\geq$ 30% was not associated with better prognosis in patients undergoing CABG alone.[25] Taken together with these messages, the left ventricular volume change was likely not associated with the survival benefits of CABG in patients with ischaemic cardiomyopathy.

Our findings showed that change in ESVI from baseline to 4 months was significant in CABG but not MED arm, yet the association between change in ESVI and mortality was significant only in the MED arm. This potential contradiction could be explained from several perspectives. First, the positive therapeutic efficacy of medical therapy on left ventricular remodeling was a long-lasting process and might not completely reveal at an early time point. In some patients with poor medical responsiveness, the recovery of ventricular volume might not occur as early as the 4-month follow-up. Second, patients in the CABG arm also received medical therapy, thus the reduction in ESVI was a concomitant effect of both medical therapy and surgical procedure. Moreover, CABG was more likely to have an immediate or short-term therapeutic efficacy attributed to myocardial revascularisation. For these reasons, it is reasonable that the ESVI reduction in the CABG arm was more significant than the MED arm at 4-month follow-up. Third, the average reduction in ESVI could only represent the overall ESVI change in the entire MED or CABG arm, whereas our findings on the association between change in ESVI and long-term prognosis were derived based on the individual outcome of every independent patient. Our study could provide value in individualised prognostic evaluation, regardless of the average ESVI change in the overall population.

It is noteworthy that the therapeutic mechanism differs between the pharmacological and surgical approaches. The major mechanism of ACEIs/ARBs and beta-blockers in medical therapy is to reduce the left ventricular preload and afterload, decrease oxygen consumption and protect the heart from overwhelming pressure, which plays a crucial role in the attenuation or reversal of left ventricular remodeling.[8] Therefore, change in ESVI could mirror the pharmacological therapeutic efficacy on clinical outcomes. Nevertheless, the main purpose of CABG is to enable complete revascularisation, which increases coronary blood flow to the ischaemic myocardial territories, improves the contractile reserve of the hibernating, and resurrects stunned myocardium, while ventricular volume appears not to directly measure the intrinsic myocardial recovery.[26-28] For these reasons, CABG might have the potential to overcome the detrimental effect of left ventricular enlargement and alleviate the mortality in this population, which might not be accomplished by medical therapy alone. Although our results show that post-operative ESVI < 60 mL/m^2 was associated with a lower risk of mortality in CABG patients, the change in ESVI reflects the dynamic process of ventricular size remodeling after CABG, which provides additional information compared with post-operative ESVI at a single time point.

How we should incorporate these findings into the clinical decision needs further elucidation. According to our findings, approximately 25% of ischaemic cardiomyopathy patients had a more than 16% reduction in ESVI at 4-month follow-up, which could be considered as a pragmatic prognostic indicator to evaluate the pharmacological treatment efficacy in patients undergoing medical therapy alone. However, the clinical relevance of the reduction in ESVI was somewhat influenced by the baseline ESVI, as the association between change in ESVI and clinical outcomes became statistically significant only after adjusted for baseline ESVI. For patients undergoing CABG, patients with or without postoperative left ventricular volume recovery nevertheless have similar long-term outcomes. However, we could not rule out the possibility that the lack of statistical significance might be due to the relatively small sample size, whereas the potential association between ESVI reduction and outcomes in the CABG arm could not be completely dismissed. In routine clinical practice, surgeons should not only rely on postoperative left ventricular functional recovery for long-term outcomes evaluation, in order not to underestimate the potential survival benefits achieved by CABG.

Our study should be interpreted within the context of its limitations. First, patients with an increase in ESVI after CABG might potentially have a higher risk of short-term mortality thus were systematically excluded from the study, and the paired ESVI at baseline and 4-month was only available in 523 of the remaining 1134 patients (46.1%). Despite sensitivity analysis proving the robustness of our results, the non-randomised sample might lead to selection bias, and the relatively

limited sample size prevented us from adjusting all potential confounders and might be underpowered for definite conclusions. Second, the therapeutic effect on left ventricular volume change is a time-dependent process thus our interpretation is affected by short-term follow-up ventricular assessment. In addition, the determination of a 16% reduction in ESVI as the clinical threshold was only based on the 4-month endpoint in the current dataset, which should not be considered dogmatic postulates in clinical decisions, and needs external validation before further generalisation. Finally, our findings stemming from 10-year follow-up were based on relatively outdated surgical techniques and medical therapy. However, evidence from contemporary treatments could only be obtained from studies with short-term follow-up. Our findings should be conservatively interpreted and considered only as explorative and hypothesis-generating, but the present study provides a comprehensive depiction into the association between left ventricular volume change, surgical revascularisation and long-term outcomes in patients with ischaemic cardiomyopathy. Besides, these findings have the potential to provide mechanistic insights into how medical therapy or surgical revascularisation might affect prognosis, which helps in clinical therapeutic-decision making and could be factored into the design of future investigations.

In conclusion, among patients with ischaemic cardiomyopathy, left ventricular volume change was associated with long-term prognosis after medical therapy alone, whereas was likely not an optimal benchmark for evaluating the survival benefits associated with CABG. A more than 16% reduction in ESVI might assist in therapeutic efficacy evaluation, and could be considered a pragmatic prognostic indicator in medically treated patients.

Contributors

All co-authors have made substantial and intellectual contributions to the work and approved the submitted article. ML and ZW conceived and designed the research, which was then revised and refined by XZ and XL. Data analyses, interpretation and visualisation were performed by ZZ, XZ, ML, BJ and GF. ZZ, ZW and ML have verified the underlying data. The manuscript was written by ZZ and revised by all co-authors. All authors confirm that they had full access to all the data in the study and accept the responsibility to submit for publication.

Data sharing statement

The data are available from the National Heart, Lung, and Blood Institute's Biologic Specimen and Data Repository Information Coordinating Centre (BioLINCC) via an approved proposal by the institutional review board.

Declaration of interests

The authors declare that there are no conflicts of interest.

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Supplementary materials

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