Cardiac Transplantation and Surgery for Heart Failure

Survival in Patients With Severe Ischemic Cardiomyopathy Undergoing Revascularization Versus Medical Therapy Association With End-Systolic Volume and Viability

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Background—The value of assessment of viability as a predictor of surgical revascularization benefit in ischemic cardiomyopathy has recently been questioned in a large trial. We sought to determine whether the contribution of viability as myocardial scar burden (SB) to predict revascularization outcomes could be modulated by end-systolic volume index (ESVi).

Methods and Results—Delayed hyperenhancement–MRI was obtained in 450 patients with ≥70% stenosis in ≥1 epicardial coronary artery (75% men; median age, 62.8 ± 10.7 years; mean left ventricular ejection fraction, 23 ± 9%; mean ESVi, 115 ± 50 mL) from 2002 to 2006. SB was quantified as scar percentage (infarcted mass/total left ventricular mass). Subsequent surgical revascularization was performed in 245 (54%) patients and subsequent percutaneous coronary interventions were performed in 28 (6%) patients. A propensity score was developed for revascularization. Cox proportional hazards models of all-cause mortality were used for risk adjustment. Over a mean follow-up of 5.8 ± 2.7 years, 186 (41%) deaths occurred. After adjusting for prior revascularization, sex, diabetes, age, use of cardiac resynchronization therapy, implantable cardioverter defibrillator, mitral regurgitation, and mitral valve procedures; an interaction between scar percentage and ESVi ($P = 0.016$) and an interaction between post-MRI revascularization and ESVi ($P = 0.0017$) were independently associated with mortality. ESVi demonstrated a significant interaction with revascularization and female sex, such that enhanced survival was associated with ESVi. ESVi also showed an interaction with SB; better survival was associated with lower volumes and less scar.

Conclusions—ESVi and SB provide independent, incremental prognostic value in patients with severe ischemic cardiomyopathy. The risk associated with SB should not be assessed in isolation.

Key Words: survival ■ viability imaging ■ revascularization ■ ischemic cardiomyopathy ■ cardiac MRI

Testing for myocardial viability is often used to inform the revascularization decisions in patients with ischemic cardiomyopathy (ICM) and severe systolic left ventricular dysfunction (LVD). Contrary to numerous previous observational studies, the STICH viability substudy suggested that viability testing did not predict differential outcomes based on treatment type. Because this study has limitations (viability testing was not randomized, and more sensitive, higher-resolution imaging techniques, such as PET and MRI, were not utilized), the utility of viability assessment in guiding revascularization is now controversial.

Delayed hyperenhancement–cardiac magnetic resonance (DHE-CMR) identifies areas of myocardial infarction (MI) with a high degree of accuracy and reproducibility. Myocardial scar burden (SB) is an independent predictor of mortality in ICM. Furthermore, cardiac magnetic resonance (CMR) is also considered the gold standard for the assessment of LV volumes and ejection fraction (EF). This technique therefore provides an ideal model to understand the interaction between infarct size (SB) and end systolic volume index (ESVi) in the prediction of survival in patients with ICM and severe LVD treated with medical therapy (medRx) or revascularization.

Methods

Study Design
We examined 450 patients with ICM (LVEF ≤40% with ≥70% stenosis in ≥1 epicardial coronary vessel on angiography and/or history of MI or coronary revascularization), who were referred for myocardial viability assessment with CMR between January 2002 and December 2006. Patients with standard CMR contraindications were not imaged. Patients were retrospectively categorized to 1 of 2 comparison groups, based on whether they underwent a coronary artery bypass graft (CABG) procedure at any time after the index...
CMR; patients not treated with CABG were considered to have been treated medically.

Clinical and demographic variables were collected. Baseline risk factors and clinical variables were obtained from electronic medical records. MedRx, including β-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACE-I/ARB), spironolactone, and statin therapy was recorded. Post-CMR coronary revascularization (either percutaneous or surgical) and implantable cardioverter-defibrillators (ICD)/cardiac resynchronization therapy (CRT) implantation was also recorded. Echocardiographic data obtained within 1 month of the CMR study were used.

All-cause mortality was ascertained by social security death index and was used as the primary end point. This study was approved by the institutional review board with a waiver of individual consent.

CMR Protocol

CMR examinations were performed on 1.5-T MR scanners (Sonata and Avanto, Siemens Medical Solutions, Erlangen, Germany), using 40 to 45 mT/m maximum gradient strength, 200 T/m/s maximum slew rate) with ECG gating. For assessment of global cardiac function, steady-state free precession (SSFP) sequences were acquired (slice thickness, 8–10 mm in contiguous short-axis images). LV volumes and LVEF were calculated on short-axis SSFP images. DHE-CMR images were obtained in long- and short-axis orientations, approximately 15 to 20 minutes after injection of 0.2 mmol/kg of gadolinium dimenglumine, with segmented inversion-recovery (IR) gradient echo sequences (GRE) for studies performed in 2002 to 2003 and phase-sensitive IR spoiled GRE sequence for studies performed after 2003 (spatial resolution of 1.5–2.1×1.1–1.4 mm).

DHE-CMR Analysis

DHE-CMR images were analyzed using a custom analysis multivendor package (Qi Imaging, Redwood City, CA). Endocardial and epicardial myocardial edges were manually delineated on DHE-CMR images. Scar was defined by intensity ≥2 standard deviations above user-defined viable myocardium (Figure 1). Areas that were identified as scar by the software but not deemed to be scar by the user were excluded manually by the user. SB was automatically determined as percentage of total myocardium (infarct volume/mass divided by total LV volume/mass). Each study was also semiquantitatively graded, with a standard American Heart Association 17-segment model, on a 5-point scale (0, no DHE; 1, DHE of 1% to 25% of LV segment; 2, DHE extending to 26% to 50%; 3, DHE extending to 51% to 75%; and 4, DHE extending to 76% to 100%). To further semiquantitatively define the extent/transmurality of scar tissue, a transmurality score and the total scar score was calculated, as previously defined.3 CMR analysis was completely blinded from the clinical analysis.

Statistical Analysis

Baseline demographic data, risk factors, and clinical variables were descriptively summarized with continuous variables expressed as mean±SD and categorical data presented as percentage frequency. Differences between the groups were compared with the Student t test and analysis of variance for continuous variables and the χ2 test for categorical variables. All-cause mortality was the primary end point. Linear regression analysis was performed to test for associations with ESVi.

Propensity analysis was performed to correct for clinically significant associations with post-CMR treatment. Propensity scoring was based on age, sex, clinical risk factors, LVEF, LV volumes, SB, and ICD/CRT. Multivariable Cox proportional hazards modeling (CPH) was used to assess the association of CMR variables and survival after adjusting for baseline differences. Covariate selection for model entry was based on clinical experience and identification of known correlates of mortality. Survival functions stratified by key CMR parameters were plotted using the Kaplan-Meier method and were compared using log-rank tests. Based on the final CPH model, predicted survival was graphically depicting for predefined values of covariates of interest while holding the remaining covariates constant at typical values. Three predefined interactions (LVESVI×sex, LVESVI×CABG, CABGXsex) were examined and individually added to the CPH model and evaluated, using a partial likelihood ratio test. The use of ICD and CABG after the index test was treated as a time-dependent covariate in the CPH.

Statistical comparisons were performed with SPSS version 10.0 (SPSS Inc, Chicago, IL). The S-PLUS 2000 (Release 2) software package (Insightful Corp, Seattle, WA) with supplemental libraries (Hmisc, Design) was used for multivariable analyses. A value of P<0.05 was considered significant. The models were carefully examined, when applicable, for proportional hazards assumption, multicollinearity, and the additive value of the terms. The proportional hazards assumption was examined using a 2 test of Schoenfeld residuals after initial graphical inspection of Schoenfeld residuals for each covariate versus log(Time). To assess multicollinearity, we examined variance inflation factors (VIF; values >4 considered concerning for multicollinearity) as well as inspecting correlation coefficients between the covariates of the final CPH model.

Results

Patient Characteristics

Our study sample (n=450) was predominantly male (75%), with a mean age of 62.8±10.7 years. Patients were divided into groups undergoing medRx and CABG (Table 1). Patients in both groups had similar prevalence of risk factors (Table 1); however, CABG patients had larger body surface areas (BSA) and were less likely to have had previous revascularizations. There was no significant difference in regard to medRx or ICD/CRT implantation between the 2 groups. Sixty-seven patients undergoing CABG had concomitant DOR procedure. Propensity analysis was performed to assess the presence of significant associations with post-CMR treatment (CABG versus medRx). With respect to the distribution of these CABG procedures, of 244 CABGs performed, 239 (98.0%) occurred within 6 months of the index test, 1 CABG (0.4%) between 6 months to 1 year, 2 CABGs (0.8%) between 1 and 2 years, and 2 CABGs (0.8%) beyond 2 years after the index test.

CMR Findings

Patients had severe LVD, mild right ventricular (RV) systolic dysfunction, and severely dilated ventricles (Table 2). The total scar score was 1.33±0.76, the mean scar percentage on DHE-MR was 29.6±17.1%, and the number of segments with transmural or near transmural scar was 3.6±3.4 (approximately 20% of segments).

Patients undergoing post-CMR revascularization versus medRx had a similar degree of LV and RV dysfunction. Similarly, there was no significant difference in ESVi between the 2
groups. The mean SB was significantly greater in medRx versus CABG patients.

Outcome Events

Over a mean follow-up of 5.8±2.7 years, there were 186 deaths (90 in CABG patients and 96 medRx patients). Unadjusted variables associated with death are listed in Table 3. Age, BSA, sex, subsequent revascularization, hypertension, diabetes, and hyperlipidemia were unadjusted associations of mortality. SB, mitral regurgitation (MR) assessed by vena contracta, and deceleration time were imaging unadjusted variables associated with death are listed in Table 3. Age, BSA, sex, subsequent revascularization, hypertension, diabetes, and hyperlipidemia were unadjusted associations of mortality. SB, mitral regurgitation (MR) assessed by vena contracta, and deceleration time were imaging unadjusted variables associated with mortality. Patients with high SB had worse outcomes compared with those with smaller SB (Figure 2).

Table 1. Baseline Demographics

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total Study (n=450)</th>
<th>CABG (n=245)</th>
<th>Medical Rx (n=205)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>62.8±10.7</td>
<td>63.0±9.9</td>
<td>62.6±11.6</td>
<td>0.75</td>
</tr>
<tr>
<td>BSA, m²</td>
<td>1.92±0.24</td>
<td>1.95±0.23</td>
<td>1.89±0.25</td>
<td>0.01</td>
</tr>
<tr>
<td>Male</td>
<td>339 (75.3%)</td>
<td>190 (77.6%)</td>
<td>142 (70.7%)</td>
<td>0.23</td>
</tr>
<tr>
<td>HTN</td>
<td>232 (51.6%)</td>
<td>127 (51.8%)</td>
<td>105 (51%)</td>
<td>0.90</td>
</tr>
<tr>
<td>DM</td>
<td>168 (37.3%)</td>
<td>94 (38.4%)</td>
<td>74 (36.1%)</td>
<td>0.62</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>223 (49.6%)</td>
<td>113 (46.1%)</td>
<td>110 (53.7%)</td>
<td>0.11</td>
</tr>
<tr>
<td>Prior CABG/PCI</td>
<td>200 (44.4%)</td>
<td>34 (13.9%)</td>
<td>75 (36.6%)</td>
<td>0.001</td>
</tr>
<tr>
<td>β-blocker</td>
<td>361 (80.2%)</td>
<td>206 (84.1%)</td>
<td>155 (75.6%)</td>
<td>0.19</td>
</tr>
<tr>
<td>ACE-i/ARB</td>
<td>355 (78.5%)</td>
<td>203 (82.9%)</td>
<td>152 (74.1%)</td>
<td>0.24</td>
</tr>
<tr>
<td>Statin</td>
<td>342 (76%)</td>
<td>185 (75.5%)</td>
<td>157 (76.6%)</td>
<td>0.85</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>79 (17.6%)</td>
<td>45 (18.4%)</td>
<td>34 (16.7%)</td>
<td>0.14</td>
</tr>
<tr>
<td>ICD</td>
<td>163 (36.2%)</td>
<td>94 (38.4%)</td>
<td>69 (33.7%)</td>
<td>0.30</td>
</tr>
<tr>
<td>CRT</td>
<td>55 (12.2%)</td>
<td>30 (12.2%)</td>
<td>25 (12.2%)</td>
<td>0.99</td>
</tr>
<tr>
<td>QRS</td>
<td>116±28</td>
<td>121.19±29</td>
<td>112.28±27</td>
<td>0.001</td>
</tr>
</tbody>
</table>

CABG indicates coronary artery bypass graft; BSA, body surface area; HTN, hypertension; DM, diabetes mellitus; PCI, percutaneous coronary intervention; ACE-i, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ICD, implantable cardioverter-defibrillator; and CRT, cardiac resynchronization therapy.

Table 2. Imaging Characteristics

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total Study (n=450)</th>
<th>CABG (n=245)</th>
<th>Medical Rx (n=205)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scar, %</td>
<td>29.56±17.15</td>
<td>26.8±17.0</td>
<td>33.1±16.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Deceleration time, ms</td>
<td>186±60</td>
<td>191±63</td>
<td>179±54</td>
<td>0.03</td>
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<tr>
<td>LV mass index</td>
<td>82.2±21.7</td>
<td>82.6±23.2</td>
<td>81.8±20.5</td>
<td>0.60</td>
</tr>
<tr>
<td>EDVI</td>
<td>146.8±50.0</td>
<td>146.2±46.0</td>
<td>147.6±54.4</td>
<td>0.40</td>
</tr>
<tr>
<td>ESVI</td>
<td>115.3±49.5</td>
<td>114.1±44.2</td>
<td>116.8±54.1</td>
<td>0.55</td>
</tr>
<tr>
<td>LV EF by CMR</td>
<td>23.1±9.0</td>
<td>23.3±8.4</td>
<td>22.9±9.7</td>
<td>0.53</td>
</tr>
<tr>
<td>RV EF by CMR</td>
<td>42.6±13.9</td>
<td>43.5±14.0</td>
<td>41.5±13.6</td>
<td>0.13</td>
</tr>
<tr>
<td>RV ESVI</td>
<td>46.2±28.1</td>
<td>44.2±27.4</td>
<td>48.56±28.8</td>
<td>0.10</td>
</tr>
<tr>
<td>Mitral regurgitation</td>
<td>0.33±0.27</td>
<td>0.31±0.27</td>
<td>0.35±0.26</td>
<td>0.12</td>
</tr>
</tbody>
</table>

CABG indicates coronary artery bypass graft; LV, left ventricular; EDVI, end-diastolic volume index; ESVI, end-systolic volume index; LV EF, LV ejection fraction; CMR, cardiac magnetic resonance; RV EF, right ventricular ejection fraction; and RV ESVI, right ventricular end-systolic volume index.

Table 3. Unadjusted Analysis

<table>
<thead>
<tr>
<th>Variables</th>
<th>Hazard Ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>1.04 (1.03, 1.06)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BSA, m²</td>
<td>0.36 (0.16, 0.66)</td>
<td>0.001</td>
</tr>
<tr>
<td>Female</td>
<td>1.47 (1.08, 2.00)</td>
<td>0.018</td>
</tr>
<tr>
<td>Prior CABG/PCI</td>
<td>1.05 (0.79, 1.39)</td>
<td>0.744</td>
</tr>
<tr>
<td>Subsequent CABG</td>
<td>0.64 (0.48, 0.85)</td>
<td>0.002</td>
</tr>
<tr>
<td>HTN</td>
<td>1.51 (1.13, 2.02)</td>
<td>0.005</td>
</tr>
<tr>
<td>DM</td>
<td>1.35 (1.02, 1.79)</td>
<td>0.039</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>1.67 (1.03, 1.82)</td>
<td>0.03</td>
</tr>
<tr>
<td>β-blocker</td>
<td>0.75 (0.54, 1.04)</td>
<td>0.93</td>
</tr>
<tr>
<td>ACE-i/ARB</td>
<td>0.84 (0.60, 1.17)</td>
<td>0.31</td>
</tr>
<tr>
<td>Statin</td>
<td>0.88 (0.63, 1.25)</td>
<td>0.49</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>0.83 (0.56, 1.23)</td>
<td>0.34</td>
</tr>
<tr>
<td>ICD</td>
<td>0.75 (0.55, 1.02)</td>
<td>0.06</td>
</tr>
<tr>
<td>CRT</td>
<td>0.93 (0.61, 1.42)</td>
<td>0.73</td>
</tr>
<tr>
<td>EDVI, per mL</td>
<td>1.001 (0.999, 1.004)</td>
<td>0.35</td>
</tr>
<tr>
<td>ESVI, per mL</td>
<td>1.001 (0.999, 1.004)</td>
<td>0.31</td>
</tr>
<tr>
<td>LV EF by CMR, per %</td>
<td>0.994 (0.978, 1.010)</td>
<td>0.43</td>
</tr>
<tr>
<td>RV EF by CMR, per %</td>
<td>0.99 (0.98, 1.00)</td>
<td>0.59</td>
</tr>
<tr>
<td>RV ESVI, per mL</td>
<td>1.004 (0.999, 1.009)</td>
<td>0.12</td>
</tr>
<tr>
<td>Scar percentage, per %</td>
<td>1.012 (1.004, 1.021)</td>
<td>0.003</td>
</tr>
<tr>
<td>Mitral regurgitation</td>
<td>3.112 (1.896, 5.109)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Deceleration time, ms</td>
<td>0.997 (0.994, 1.000)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Cl indicates confidence interval; BSA, body surface area; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; HTN, hypertension; DM, diabetes mellitus; ACE-i, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ICD, implantable cardioverter-defibrillator; CRT, cardiac resynchronization therapy; EDVI, end-diastolic volume index; ESVI, end-systolic volume index; LV EF, LV ejection fraction; CMR, cardiac magnetic resonance; RV EF, right ventricular ejection fraction; and RV ESVI, right ventricular end-systolic volume index.

Survival Modeling

CPH modeling revealed that after adjustment for potential confounders and propensity score for revascularization, age (P =< 0.001), interaction between ESVI and scar burden
Of 186 deaths on follow-up, 24 occurred within 90 days and 50% likelihood of CABG referral graff; MV, mitral valve; RVESVi, right ventricular end-systolic volume index; ICD, implantable cardioverter-defibrillator; and ESVI, end-systolic volume index.

(\(P=0.016\)), interaction between ESVI and CABG \((P=0.0017)\), post-MRI revascularization \((P=0.046)\), sex \((0.043)\), mitral regurgitation \((P=0.004)\), and RV ESVI \((P=0.03)\) were found to be independently associated with mortality (Table 4). A significant 3-way interaction between SB, revascularization, and sex was present.

To address the potential impact of waiting-time bias, we examined several approaches for assigning follow-up time: (1) follow-up time beginning at the index CMR study (the primary analysis, waiting time bias unaddressed); (2) exclusion of all events occurring in the first 6 months after the index study from the analysis (patients censored at the time of event); (3) exclusion of all events occurring in the first 6 months after the index study not considered in the analysis unless the patient had undergone CABG (ie, definitive treatment assignment made); and (4) in patients undergoing CABG, follow-up time counted as medical therapy until revascularization occurred, after which they were considered CABG patients. Compared with the primary analysis, no material differences were present between these models with respect to probability values or magnitude and direction of beta coefficients. The primary difference occurred with the second and third models compared with the first model due to the loss of events with the elimination of certain early deaths (model 1: 166 events; model 2: 134 events; model 3: 152 events).

Of 186 deaths on follow-up, 24 occurred within 90 days and 35 within 180 days. Of these, 12 (5.8%) of the former and 12 (9.2%) of the latter in medically treated patients, approximately half of these patients had >50% likelihood of CABG referral (based on propensity score), suggesting that the net impact of misclassification bias was unlikely to be significant.

In a subgroup comparison of Dor+CABG versus CABG alone, there was no difference in survival between groups after risk adjustment with a propensity score.

### Outcomes and Revascularization

The risk increased in association with increasing SB and ESVI in both the revascularized patients and those who were medically treated. However, when patients were stratified into those with smaller and larger ESVI, the risk was more strongly associated with survival in those with larger ESVI. Interestingly, there was no unadjusted correlation with SB and ESVI (Figure 3), with relatively equal frequency of patients with large SB and large ESVI compared with patients with large SB and smaller ESVI. The association of increasing ESVI with the relative hazard of CABG relative to medRX is summarized in Figure 4. The adjusted interactions are summarized in Table 5, which emphasizes the interaction of ESVI and SB, as well as CABG with ESVI, CABG with sex, and CABG with sex and ESVI. There was no significant difference in outcomes in patients undergoing CABG with smaller ESVI compared with medRX. However, beginning at an ESVI of 100 ml/m², the confidence intervals remain <1, with an increasing benefit with CABG with increasing ESVI.

In linear regression analysis, ESVI was associated with LVMi \((P<0.001; \beta=-0.9140)\), RV-EF \((P=0.001; \beta=-0.9737)\), left bundle-branch block \((P<0.001; \beta=21.4777)\), prior CABG \((P=0.006; \beta=-5.8764)\), diabetes \((P=0.013; \beta=-9.0473)\), subsequent Dor \((P=0.017; \beta=1.3992)\), MR \((P=0.02; \beta=14.0733)\), and SB \((P=0.023; \beta=0.2521)\) after risk adjustment.

### Discussion

Our results show that both SB and ESVI, quantified by CMR, were independent and incremental variables associated with mortality. Although SB was associated with overall risk, SB alone was not associated with differential outcomes based on post-CMR treatment. After adjustment for potential confounders, survival analyses identified significant interactions between SB, ESVI, and outcomes after treatment. Increasing risk reduction with CABG versus medically treated patients was seen in patients with the largest ventricles and greatest amount of SB (Table 4).

### Scar Assessment and Outcome

The approach to identifying which patients with severe LVD may benefit from revascularization has mainly focused on

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**Table 4. Multivariable Cox Proportional Hazard Analysis Model**

<table>
<thead>
<tr>
<th>Variables</th>
<th>(\beta)</th>
<th>Standard Error</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.0502</td>
<td>0.0081</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Scar, %</td>
<td>-0.0060</td>
<td>0.0116</td>
<td>0.6080</td>
</tr>
<tr>
<td>ESVI, mL/m²</td>
<td>-0.0005</td>
<td>0.0041</td>
<td>0.8980</td>
</tr>
<tr>
<td>CABG</td>
<td>1.1166</td>
<td>0.5588</td>
<td>0.0457</td>
</tr>
<tr>
<td>CABG, time-dependent covariate</td>
<td>0.0002</td>
<td>0.0007</td>
<td>0.7700</td>
</tr>
<tr>
<td>MV repair/replacement</td>
<td>0.4348</td>
<td>0.2263</td>
<td>0.0547</td>
</tr>
<tr>
<td>Female</td>
<td>1.0929</td>
<td>0.5400</td>
<td>0.0430</td>
</tr>
<tr>
<td>Mitral regurgitation</td>
<td>0.4995</td>
<td>0.2398</td>
<td>0.0037</td>
</tr>
<tr>
<td>RVESVi, mL</td>
<td>0.0072</td>
<td>0.0034</td>
<td>0.0349</td>
</tr>
<tr>
<td>ICD</td>
<td>-0.3138</td>
<td>0.2054</td>
<td>0.1270</td>
</tr>
<tr>
<td>ICD, time-dependent covariate</td>
<td>-0.0009</td>
<td>0.0004</td>
<td>0.0245</td>
</tr>
<tr>
<td>ESVI×scar, %</td>
<td>0.0002</td>
<td>0.0001</td>
<td>0.0161</td>
</tr>
<tr>
<td>CABG×female sex</td>
<td>-1.5973</td>
<td>0.8103</td>
<td>0.0487</td>
</tr>
<tr>
<td>CABG×ESVI</td>
<td>-0.0147</td>
<td>0.0047</td>
<td>0.0017</td>
</tr>
<tr>
<td>Female×ESVI</td>
<td>-0.0074</td>
<td>0.0039</td>
<td>0.0579</td>
</tr>
<tr>
<td>Female×CABG×ESVI</td>
<td>0.0178</td>
<td>0.0063</td>
<td>0.0049</td>
</tr>
<tr>
<td>Propensity score</td>
<td>0.8321</td>
<td>0.5561</td>
<td>0.1350</td>
</tr>
</tbody>
</table>

ESVI indicates end-systolic volume index; CABG, coronary artery bypass graft; MV, mitral valve; RVESVi, right ventricular end-systolic volume index; ICD, implantable cardioverter-defibrillator; and ESVI, end-systolic volume index.
viability assessment. DHE-CMR is an accurate technique in the assessment of myocardial viability,9 which is able not only to detect the presence but also to delineate transmurality of myocardial scar. Transmural extent of scar has been correlated with functional recovery after revascularization.10 However, the prognostic implications of viability assessment and the benefit of revascularization in patients with severe ICM continues to be unclear.1–3,11,12

To the best of our knowledge, this study represents the largest study of patients with ICM and severe LVD undergoing viability assessment with CMR. Our study population had severe LVD, EF 23±9% and enlargement, ESVI 115.3±49.5 mL (normal LV ESVI, 15–38 cc/m²)13 in the setting of a significant extent of SB, and mild-moderate MR. In this regard, our study cohort was similar to the STICH viability substudy cohort (mean LVESVi of 91.7 cc/m² assessed by echocardiography), as several studies have demonstrated that echo underestimates ESV by up to 35 mL. The mortality rate was 41% over a mean follow-up of 5.8 years, reflecting the high-risk nature of our patient population. Furthermore, the rate of surgical revascularization was high (54%) despite the high-risk nature of our patient population. Because the CMR results were used clinically to guide the decision to revascularize, propensity analysis was conducted to determine the presence of significant associations with post-CMR treatment.

Interaction of Scar and ESV
The finding that there is increasing benefit of CABG with increasing scar and ESVi is probably a reflection of the high risk associated with scarred, severely dilated ventricles as well as the effectiveness of medical therapy for patients with less dilated ventricles. The mechanisms by which revascularization improves risk in patients with increasing ESVi and SB are not clear and require further study. The presence of significant SB probably augments LV load and wall stress, which probably further triggers adverse remodeling.14,15 Because the assessment of ischemia was not available in these CMR studies, it is unclear how ischemic burden affects these findings. However, a previous study demonstrated that there was increasing benefit with early revascularization despite the presence of ischemic/viable myocardium.16 It may be that higher SB is an indicator of more severe coronary artery disease and may also be a marker of concomitant ischemia, arrhythmic substrate, and/or adverse remodeling in the surrounding viable region. Mechanisms by which revascularization may improve outcomes in the setting of increasing ESVi include: decreasing the increased ischemic burden due to increased ESVi; providing greater potential for improved myocardial function in the viable segments; regression of hypertrophy and ESVi, and stabilization of increased arrhythmic substrate.

Limitations
Although our patient cohort represents the patient population seen at a tertiary referral center, the impact of selection biases and missing/unmeasured variables may affect the findings in this study. Patients with prior CRT±ICD were excluded from this study because of contraindications for MRI, potentially further affecting selection bias. In the absence of randomized, controlled trials using DHE-MRI to assess myocardial viability and ventricular volumes, multivariable modeling of our observational data were conducted. Data regarding functional status (New York Heart Association classification) and the quantification of ischemia were not available in this study.

Furthermore, the CMR findings were used to guide therapy. Although we used propensity scoring to assess for significant associations with post-CMR treatment, propensity methods can only account for variables that are measured. It is possible that patients who were not referred for revascularization were at higher risk in ways that were not measured. Importantly, these comparisons of post-CMR survival by treatment are based on retrospective categorization of patients, an approach with its own limitations. Since we are retrospectively aware of the actual treatment received by the patient but not any possible planned treatments not carried out due to intercedent adverse events, misclassification bias of events may have occurred.

Table 5. Definition of Significant Interactions

<table>
<thead>
<tr>
<th>Model Degrees of Freedom</th>
<th>Interaction Added</th>
<th>LL</th>
<th>−2 LL</th>
<th>Change in Model Degrees of Freedom</th>
<th>χ²</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>Baseline model</td>
<td>−812.7</td>
<td>1625.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>ESVi×CABG</td>
<td>−811.0</td>
<td>1622.0</td>
<td>1</td>
<td>−3.4</td>
</tr>
<tr>
<td>14</td>
<td>Female×CABG</td>
<td>−809.9</td>
<td>1619.8</td>
<td>1</td>
<td>−2.2</td>
</tr>
<tr>
<td>16</td>
<td>ESVi×CABG×female</td>
<td>−805.4</td>
<td>1610.8</td>
<td>2</td>
<td>−9.0</td>
</tr>
<tr>
<td>17</td>
<td>ESVi×scar, %</td>
<td>−802.8</td>
<td>1605.6</td>
<td>1</td>
<td>−5.2</td>
</tr>
</tbody>
</table>

LL indicates log likelihood; ESVi, end-systolic volume index; and CABG, coronary artery bypass graft.

The addition of each of the interactions included in the model is significant, based on partial likelihood tests of nested models.

Figure 4. Risk-adjusted hazard ratio of coronary artery bypass graft versus medical treatment with varying end-systolic volume index (ESVi), based on Cox proportional hazards results.
Follow-up MRI was not performed systematically in our patient cohort to assess the presence of reverse remodeling in response to treatment. This is important in relation to conclusions about the effectiveness of the Dor procedure, as the degree of volume reduction is undefined.

Clinical Relevance
Patients with ICM and severe LVD benefit from various therapies (medications, revascularization, or device therapy) as the result of restoration of LV size, shape, and EF.17–20 However, the mortality in such patients remains high, and the benefits of revascularization might be outweighed by the predicted periprocedural risks. Viability assessment is often performed in the hope of identifying which patients will derive the greatest benefit from revascularization. However, the recent publication of the STICH viability study has brought this into question because it failed to demonstrate an impact of viability on predicting differential outcomes.

The current study found that ESVi was the strongest variable that was associated with differential outcomes, and SB offered further risk stratification through its interaction with ESVi. The fact that substantial improvement in survival was seen in patients with increasing ESVi and SB suggests that aggressive revascularization may offer the greatest risk reduction in this extremely high-risk patient group. This finding implies that revascularization in the setting of LVD results in improved survival by a mechanism other than relieving ischemia caused by obstructive coronary artery disease. Future randomized, prospective controlled trials will need to be conducted to determine if ESVi, ischemic burden, and SB assessed by CMR reliably predict differential outcomes in patients with severe ICM.

Conclusions
ESVi and SB provide independent, incremental prognostic value in patients with ICM and severe LVD. SB provides independent prognostication regardless of treatment type and offers further differential prognostic value based on treatment type, mainly through its interaction with ESVi. ESVi identifies differential benefit with revascularization compared with medRx in this high risk population.

Acknowledgments
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Survival in Patients With Severe Ischemic Cardiomyopathy Undergoing Revascularization Versus Medical Therapy: Association With End-Systolic Volume and Viability
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