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THE PRESENT AND FUTURE

REVIEW TOPIC OF THE WEEK

Revascularization in Severe Left Ventricular Dysfunction

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JACC JOURNAL CME

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CME Objective for This Article: After reading this article, the reader should be able to: 1) understand the evidence and uncertainties regarding the role of myocardial revascularization by either CABG or PCI added to guidelines-directed medical therapy in improving survival and quality of life in patients with coronary artery disease and left ventricular systolic dysfunction; 2) compare and contrast the relative value of clinical demographics, imaging, and functional testing in identifying patients with heart failure and reduced ejection fraction who will derive the greatest benefit from surgical revascularization; 3) explain the limitations of assessing myocardial viability and myocardial ischemia for selecting candidates for revascularization in the setting of severe left ventricular dysfunction; and 4) discuss the role of adjunctive procedures such as mitral valve surgery and surgical ventricular reconstruction when added to coronary artery bypass graft surgery in the setting of severe left ventricular dysfunction.

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Revascularization in Severe Left Ventricular Dysfunction

ABSTRACT

The highest-risk patients with heart failure with reduced ejection fraction are those with ischemic cardiomyopathy and severe left ventricular systolic dysfunction (ejection fraction ≤35%). The cornerstone of treatment is guideline-driven medical therapy for all patients and implantable device therapy for appropriately selected patients. Surgical revascularization offers the potential for improved survival and quality of life, particularly in patients with more extensive multivessel disease and the greatest degree of left ventricular systolic dysfunction and remodeling. These are also the patients at greatest short-term risk of mortality with coronary artery bypass graft surgery. The short-term risks of surgery need to be balanced against the potential for long-term benefit. This review discusses the evolving data on the role of surgical revascularization, surgical ventricular reconstruction, and mitral valve surgery in this high-risk patient population. (J Am Coll Cardiol 2015;65:615–24) © 2015 by the American College of Cardiology Foundation.

The estimated population prevalence of heart failure in the developed world is 1% to 2% (1). In the United States, an estimated 5.1 million adults are living with heart failure (2) and at least one-half have heart failure with reduced ejection fraction (HF-REF) (3). The most common etiology of HF-REF in the developed world is ischemic heart disease, which is associated with >60% of diagnoses (4). Patients with ischemic causes of left ventricular (LV) systolic dysfunction have significantly higher mortality rates than those with nonischemic etiologies (5). This more aggressive course represents the convergence of ischemia, myocardial fibrosis, and endothelial dysfunction, which are superimposed on the inherent progressive nature of LV dysfunction, often with associated comorbidities, such as diabetes, which accelerate the adverse clinical trajectory.

The cornerstone of treatment for patients with HF-REF remains guideline-directed medical therapy (GDMT) (3,6), which is associated with significant improvement in survival and quality of life. The most commonly considered surgical interventions for patients with HF-REF are coronary artery bypass graft surgery (CABG), at times paired with surgical ventricular reconstruction (SVR), and surgery for mitral valve regurgitation. Percutaneous coronary intervention (PCI) has been less well studied. Other procedures with the potential to prolong life in patients with HF-REF include insertion of implantable cardioverter-defibrillators, cardiac resynchronization therapy (CRT) among those with left bundle branch block, and orthotopic heart transplantation and LV assist devices in highly selected patients with advanced disease (3). In patients with HF-REF who have coronary artery disease (CAD), an essential question is whether flow-limiting coronary stenosis should be treated with CABG. We summarize observational studies, clinical trial data, and current thinking on patient selection for revascularization in severe LV systolic dysfunction.

SURGICAL REVASCULARIZATION: OBSERVATIONAL REPORTS

Until the STICH (Surgical Treatment for Ischemic Heart Failure) trial, data supporting the role of surgical revascularization for patients with HF-REF were primarily observational and often drawn from only a single institution. These studies comparing survival in patients treated surgically versus medically suggested uniformly that CABG enhances survival in patients with HF-REF and CAD (7–14). Reductions in mortality with surgery compared with medical therapy ranged from 10% to >50%. However, most of these studies either date from the 1960s and 1970s, before the advent of beta-blockers and inhibitors of the renin-angiotensin-aldosterone system, or fail to provide sufficient detail to determine if medical management would be optimal by current standards.

SURGICAL REVASCULARIZATION: CLINICAL TRIALS IN CHRONIC STABLE ANGINA

Findings from early trials comparing medical therapy with CABG for the treatment of stable angina can only be loosely applied to the care of patients with HF-REF

in the current era, because both surgical techniques and medical therapy have significantly improved. Arterial grafts were rarely used, and medical therapy largely consisted of only nitrates (typically isosorbide dinitrate) and inconsistent use of beta-blockers like propranolol; the medical therapy arms were neither uniform nor standardized (15-20). In addition, patients with severe LV dysfunction were largely excluded. The European Surgery Study (16,19) enrolled only patients with left ventricular ejection fraction (LVEF) ≥50%. In the Veterans Administration Cooperative Study (15,18), 26% of patients had ejection fraction (EF) <45%, but none were considered to have severe LV dysfunction. CASS, the National Heart, Lung, and Blood Institute (NHLBI) Coronary Artery Surgery Study (17), excluded patients with LVEF <35% and/or in New York Heart Association functional classes III to IV. Only 160 patients enrolled in CASS had mild to moderate LV dysfunction (EF of 35% to 49%), of whom only 78 had 3-vessel CAD, the single subgroup with improved survival with surgical compared with medical therapy (20). Patients with LVEF <35% were not randomized in CASS but were reported in the CASS registry (10). In a meta-analysis of 7 clinical trials of medical therapy versus CABG from the 1970s and 1980s (21), only 7% of patients (n = 178) had LVEF <40%.

Unfortunately, more contemporary trials studying treatments for CAD that included an intensive medical regimen, such as the MASS-II (Medicine, Angioplasty, or Surgery Study) trial and the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial, excluded patients with severe LV dysfunction (22,23). The BARI 2D (Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes) trial included patients with LV dysfunction but only enrolled 17.5% with LVEF <50% (24). The ISCHEMIA (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches) trial is currently enrolling patients but excluding those with LVEF <35% (25).

TRIALS OF SURGICAL VERSUS PERCUTANEOUS REVASCULARIZATION

Several trials have compared PCI (balloon angioplasty, bare-metal stents, and drug-eluting stents) and CABG in patients with multivessel CAD. Among 27 randomized controlled trials comparing these 2 revascularization strategies (26), the overwhelming majority of patients had preserved LV systolic function (EF >50%). None specifically focused on patients with heart failure and/or LV systolic dysfunction. Two relatively large trials that included patients with LV dysfunction were BARI (Bypass Angioplasty Revascularization Investigation) (27), in which 22% of patients had LVEF <50%, and AWESOME (Angina With Extremely Serious Operative Mortality Evaluation) (28), in which 21% had LVEF <35%. Subgroup analyses in patients with LV dysfunction from these trials suggest no difference in outcome between PCI and CABG (29,30), but combined these analyses involve <500 patients and include PCI with both balloon angioplasty and bare-metal stents.

The most recent trials comparing PCI with CABG failed to provide more clarity. Only approximately 2% of patients enrolled in the SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) trial had LVEF <30% (31). More recently, the NHLBI-sponsored FREEDOM (Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease) trial (32) reported similar outcomes with PCI with drug-eluting stents and CABG in patients with LVEF <40%, but only 32 patients (2.5%) were in this pre-specified subgroup. Thus, the available data are insufficient to adequately compare PCI and CABG in patients with severe LV dysfunction.

THE STICH TRIAL

The STICH trial is the only prospective, randomized, controlled trial to specifically investigate the role of CABG in patients with LVEF ≤35% who are also receiving GDMT. This NHLBI-sponsored trial tested 2 hypotheses among patients with LVEF ≤35% and CAD amenable to CABG (33): the surgical revascularization hypothesis evaluated CABG compared with GDMT alone (n = 1,212), and the surgical ventricular reconstruction hypothesis compared CABG with and without SVR (n = 1,000). Patients with Canadian Heart Association functional class III or IV angina and those with left main coronary artery stenosis ≥50% were excluded from the surgical revascularization arm but were eligible for the surgical ventricular reconstruction arm. GDMT included renin-angiotensin-aldosterone system inhibitors, beta-blockers, statins, and antiplatelet agents titrated to optimal doses; diuretic agents and digitalis were also used. If possible, surgical therapy included at least 1 internal thoracic conduit, which was accomplished in 91% (34).

ABBREVIATIONS AND ACRONYMS

CABG = coronary artery bypass graft

CAD = coronary artery disease

CRT = cardiac resynchronization therapy

EF = ejection fraction

GDMT = guideline-directed medical therapy

HF-REF = heart failure with reduced ejection fraction

LV = left ventricular

LVEF = left ventricular ejection fraction

MR = mitral regurgitation

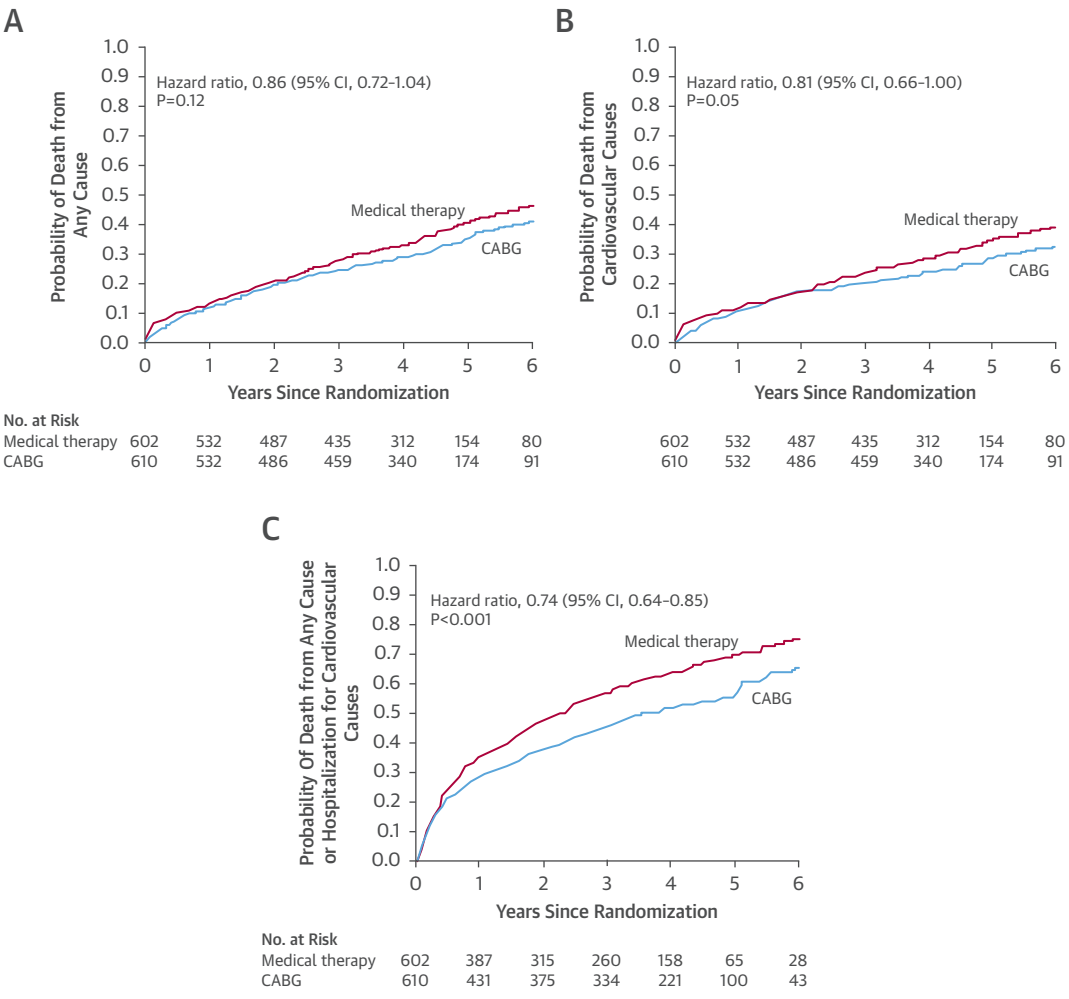
NHLBI = National Heart, Lung, and Blood Institute

PCI = percutaneous coronary intervention

SVR = surgical ventricular reconstruction

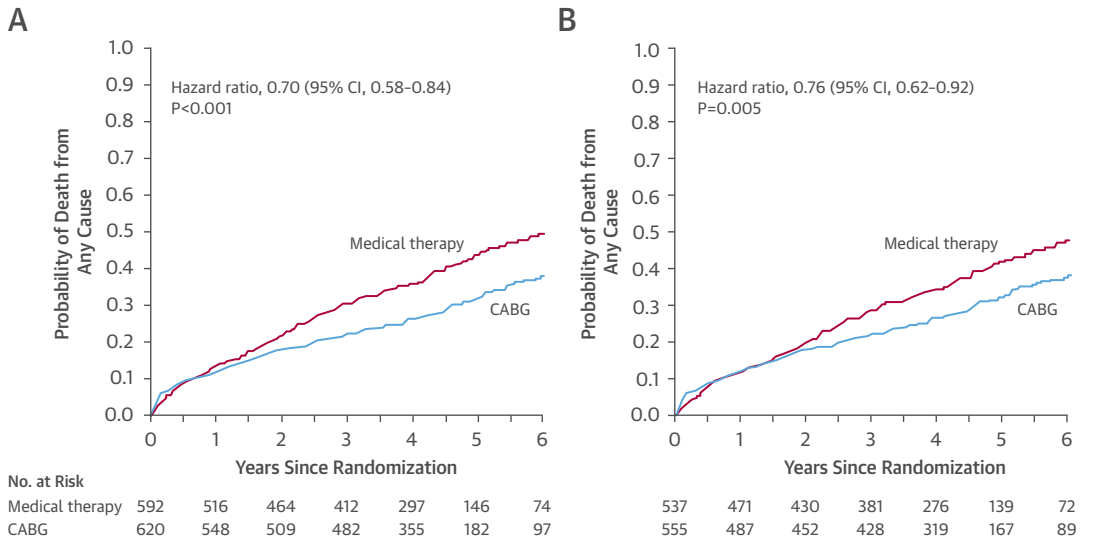
THE STICH REVASCULARIZATION HYPOTHESIS. The 1,212 patients in this arm of the trial were enrolled in 99 sites in 22 countries (34). Using a pre-specified intention-to-treat analysis, no significant difference was observed in the primary outcome of all-cause mortality between patients randomized to CABG versus GDMT over a median follow-up period of 56 months (**Figure 1A**). Notably, the CABG group had improved rates of death from cardiovascular causes and improved rates of a combined endpoint of death from any cause and hospitalization for heart failure, which were pre-specified secondary endpoints (**Figures 1B and C**) (34). In addition, as-treated, per-protocol, and adjusted analyses to account for patient crossovers all suggested an overall favorable effect of CABG on primary and secondary outcomes (**Figure 2**) (34,35). Moreover, using the Kansas City Cardiomyopathy Questionnaire (36), CABG resulted in greater improvement in measures of symptoms and quality of life. Blinded endpoint adjudication and mode of death analyses revealed that CABG exerted a benefit across all common causes of death among patients with HF-REF: sudden death, pump failure death, and death from myocardial infarction (37). We believe these findings show an overall benefit of CABG against the background of GDMT in patients with severe ischemic LV dysfunction. As part of STICHES (STICH Extended Study), patients

FIGURE 1 Survival Analyses in the STICH Trial Using an Intention-to-Treat Analysis



(A) The primary endpoint was all-cause mortality. Secondary endpoints were **(B)** cardiovascular mortality and **(C)** all-cause mortality plus hospitalization for heart failure. Reproduced with permission from Velazquez et al. (34). CABG = coronary artery bypass graft surgery; CI = confidence interval; STICH = Surgical Treatment for Ischemic Heart Failure.

FIGURE 2 Survival Analyses in the STICH Trial According to Actual Treatment Received



(A) As-treated and **(B)** per-protocol analyses to adjust for early crossovers indicate significant reduction in mortality rates with surgical (CABG) compared with medical therapy. Reproduced with permission from Velazquez et al. (34). Abbreviations as in Figure 1.

in the STICH trial are continuing to be followed up to 10 years after initial randomization (38).

THE STICH REVASCULARIZATION HYPOTHESIS: SUBSET ANALYSES. Additional analyses of the STICH trial have been performed to identify subsets of patients with CAD and severe LV dysfunction most likely to benefit from revascularization. The initial target of these analyses was myocardial viability assessment, which was prospectively programmed into the design of the STICH trial. Multiple observational analyses and meta-analyses suggest that viability testing may be a powerful tool that will not only predict improvement in LV function after CABG but will also identify patients with CAD and HF-REF with the greatest survival benefit from CABG compared with GDMT (39,40). These analyses are limited by their retrospective design, heterogeneous methodology to define viability, lack of adjustment for key baseline variables such as age and comorbidities, and the potential that selection of patients for CABG might have been influenced in some studies by the results of viability testing. Most importantly, these cohort studies were performed before the advent of modern GDMT, with very few patients receiving beta-blockers. Although the STICH trial provides important insights, it does not definitively address the role of viability testing in all HF-REF patients. In the original trial design, viability testing with single-photon emission computed tomography was required for study entry. However, due to low enrollment, the protocol was revised to make single-photon emission computed tomography or viability testing with low-dose dobutamine echocardiography optional but strongly encouraged (33). As a result, 601 of the 1,212 patients enrolled in the revascularization hypothesis arm underwent assessment of myocardial viability. On the basis of prespecified definitions of the magnitude of viable LV myocardium with imaging, patients were subdivided into those with predominantly viable versus predominantly nonviable myocardium (41). The viability analysis did not identify patients who would preferentially benefit from CABG. Not surprisingly, over a median 5.1-year follow-up period, patients with viable tissue represented a cohort with a lower mortality of 37% versus 51% in patients without myocardial viability. However, after adjustment for other prognostic variables, myocardial viability was not associated with improved survival, suggesting that patient comorbidities and severity of LV remodeling were more important determinants of survival. Moreover, there was no significant interaction with respect to mortality between viability status and assignment to CABG or GDMT ($p = 0.53$). 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 current recommendations for revascularization in the 2013 American College of Cardiology/American Heart Association guideline for the management of heart failure (3), which indicates that, in the absence of angina, CABG may be considered for 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). Although the primary viability analysis in the STICH trial was on the basis of a pre-determined dichotomous separation of patients with viable versus nonviable myocardium, a separate analysis in which the viability data were analyzed as continuous variables also failed to show an association between myocardial viability and improved survival with CABG (41).

Further analysis of imaging data in the STICH trial was performed to assess inducible myocardial ischemia in 399 of 1,212 patients in whom stress imaging was performed using single-photon emission computed tomography or dobutamine echocardiography. This analysis failed to show enhanced survival with CABG in any subgroups (42). This was unanticipated and ran counter to the prevailing wisdom from observational studies and previous trials in patients with normal LV systolic function or less severe LV dysfunction. Similarly, circulating levels of brain natriuretic peptide and soluble tumor necrosis factor α receptor 1 were strongly related to survival in both the surgical and medical cohorts but did not identify those with a survival advantage with CABG (43).

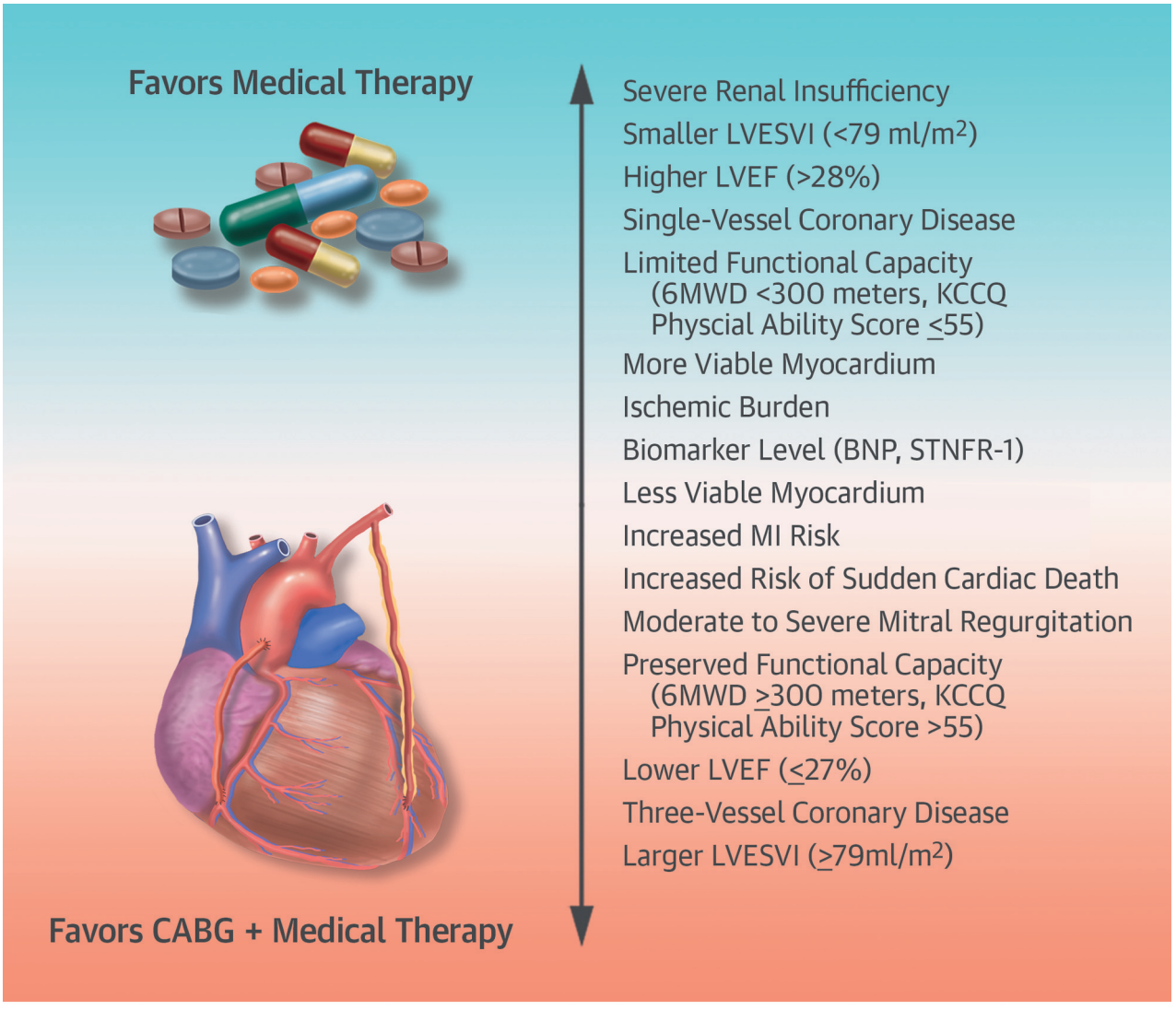
These data suggest that the observed survival benefits of CABG in patients with severe LV dysfunction are driven primarily by factors other than biomarkers or objective measures of myocardial viability and ischemia. Factors associated with higher survival rates with CABG include functional status as assessed by a 6-min walk and/or the Kansas City Cardiomyopathy Questionnaire (44) and the interaction of angiographic severity of CAD, severity of LV systolic dysfunction, and severity of LV remodeling (as assessed by end-systolic volume index) (45). Patients with preserved effort tolerance but with multivessel CAD, lower EF, and higher end-systolic volume index were most likely to benefit from CABG with respect to long-term survival (**Central Illustration**).

THE ROLE FOR ADJUNCTIVE SURGICAL VENTRICULAR RECONSTRUCTION. Pathophysiological changes in LV structure and function in patients with HF-REF include remodeling of the left ventricle from its normal elliptical to a more spherical shape, resulting in a dysfunctional, less efficient ventricle and portending a worse prognosis. SVR may potentially reverse-remodel the left ventricle and restore some of its original functional capacity (46–48). The procedure involves removing or excluding akinetic or dyskinetic segments of the anterior wall and reshaping the left ventricle to restore its original elliptical form.

Observational data in unblinded series suggested that SVR was relatively safe, and was associated with reduced LV volume, improved LV systolic function, improved symptoms, and high survival rates at 5 years (46–48). However, it was uncertain whether SVR combined with CABG would result in improved outcomes of patients with ischemic cardiomyopathy compared with CABG alone, especially when combined with GDMT. This equipoise led to the surgical ventricular reconstruction arm of the STICH trial, the only randomized clinical trial to address the role of SVR in patients with HF-REF (49). Patients were eligible if they had coronary obstructions amenable to surgical revascularization, severe systolic dysfunction with LVEF ≤35%, and dominant LV anterior akinesia or dyskinesia that was amenable to SVR. A total of 1,000 patients were randomized to CABG alone versus CABG plus SVR against the background of GDMT. The primary outcome was a composite of all-cause mortality and cardiac hospitalization. Patients who underwent SVR had significantly lower LV volumes on short-term follow-up, with a reduction in end-systolic volume index of 19% versus 6% in those receiving CABG alone. However, there was no significant difference between the 2 therapies for the primary outcome with a median follow-up of 4 years. There also were no differences between the 2 groups in terms of secondary endpoints, including repeat hospitalizations, symptoms, or quality of life (49). SVR added to CABG does not appear to improve quality of life compared with CABG alone but does increase health care costs (50).

Reconciling the difference between the observational data supporting SVR and the findings from the STICH trial has led to intriguing discussions (51,52) and observations. A secondary analysis examined the influence of baseline LV volumes and LVEF on outcomes. Counter to the original premise and existing clinical thinking that patients with larger, already-remodeled ventricles would benefit from CABG plus SVR instead of CABG alone, patients with smaller baseline LV end-systolic and end-diastolic diameters were more likely to benefit, suggesting a possible benefit of SVR before extensive remodeling

CENTRAL ILLUSTRATION **Revascularization in Heart Failure: Proposed Contributing Factors Influencing the Decision for Revascularization in Patients With Severe Left Ventricular Dysfunction**



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Genetics, biomarkers, ischemia, viability assessment, and presence of mitral regurgitation do not have as significant an impact on this decision as risk of sudden death and recurrent infarction, functional capacity, multivessel coronary artery disease, and severity of left ventricular remodeling. BNP = B-type natriuretic peptide; CABG = coronary artery bypass graft surgery; KCCQ = Kansas City Cardiomyopathy Questionnaire; LVEF = left ventricular ejection fraction; LVESVI = left ventricular end systolic volume index; MI = myocardial infarction; 6MWD = 6-min walk distance; STNFR-1 = soluble tumor necrosis factor receptor 1.

(53,54). The extent of myocardial viability in the dysfunctional anterior wall does not appear to be an important determinant of survival in patients undergoing SVR (55).

THE ROLE FOR MITRAL VALVE SURGERY. Secondary mitral regurgitation (MR) stemming from LV remodeling and dysfunction is a common complicating feature in patients with CAD and HF-REF, often creating difficult management decisions. Ischemic MR arises from mitral annular dilation, restricted systolic closure of the mitral valve leaflets, or both. Restricted motion in ischemic MR is primarily attributed to LV remodeling with tethering of normal-appearing mitral leaflets from apical and lateral

papillary muscle displacement after an infarction and secondarily attributed to inadequate mitral leaflet closure due to LV dysfunction and/or dyssynchrony (56).

Ischemic MR contributes to heart failure morbidity and is a powerful marker of poor prognosis in patients with CAD and LV dysfunction (57–60). The presence of even mild degrees of secondary MR (with small regurgitant volumes that would be well tolerated in a patient with mitral valve prolapse) identifies patients with LV dysfunction who have a higher risk of mortality than those without MR (58,60,61). However, in an individual patient, it is often difficult to ascertain whether ischemic MR is merely a marker of the severity of LV dysfunction or is contributing to progressive LV dysfunction. Hence, whether secondary MR should be targeted for therapy remains uncertain (62). The results of surgery for secondary ischemic MR are unproven and unpredictable in improving patient outcomes and have never been tested against medical therapy for LV dysfunction in a prospective randomized trial.

Because ischemic MR is primarily a manifestation of LV remodeling and systolic dysfunction, the initial focus of therapy should be GDMT (63). The survival and symptomatic benefit of beta-blockers is associated with reverse LV remodeling, which also results in reduced MR (64). The same effects are achieved with appropriately selected patients with CRT (65). Surgical intervention should be considered only after GDMT and CRT are unsuccessful in improving symptoms, with the understanding that current data from nonrandomized studies indicate no beneficial effect on mortality (66,67). In addition, surgical mitral valve repair is often not durable in ischemic MR (68,69) due to progression of the underlying LV dysfunction. Data from the NHLBI Cardiothoracic Surgery Network randomized trial of surgery for severe ischemic MR (69) reported greater durability with mitral valve replacement compared with repair, even among highly experienced surgeons. In patients undergoing CABG, mitral valve repair or replacement should be strongly considered in those with severe MR (63). Regarding management of moderate MR in patients undergoing CABG, the second randomized trial from the Cardiothoracic Surgery Network reported no differences in LV end-systolic volume index at 12 months in patients receiving CABG plus mitral valve repair compared to CABG alone (70). That trial was not powered to address clinical outcomes. Two previous small randomized trials of CABG versus CABG plus mitral annuloplasty demonstrated longer procedure times but greater symptomatic improvement and reverse remodeling with concomitant mitral repair (71,72). These 3 trials were not designed to assess mortality, and the majority of patients had LVEF >35%.

Percutaneous mitral valve therapies are of particular interest in patients at high risk for surgical intervention, including those with secondary MR related to CAD and HF-REF. Promising results have been reported from Europe in such patients who remain symptomatic despite GDMT and CRT (73–75). Two ongoing randomized trials of transcatheter valve repair versus medical management (76,77) may clarify whether targeting the mitral valve in addition to GDMT improves outcomes of patients with ischemic MR.

CONCLUSIONS

The highest-risk patients with HF-REF are those with ischemic cardiomyopathy. The cornerstone of treatment is GDMT for all patients and CRT for appropriately selected patients. In accordance with the results of the STICH trial, we believe that surgical revascularization offers improved survival and quality of life, particularly in patients with more extensive multivessel disease and the greatest degree of LV systolic dysfunction and remodeling, who are also at the greatest short-term risk of mortality with CABG. SVR does not appear to add to the clinical benefits of CABG in patients with more severely remodeled ventricles. Concomitant mitral valve surgery is warranted in patients undergoing CABG with severe ischemic MR; clinical trial data have questioned the indications for concomitant mitral valve surgery in those with moderate MR. Frank discussions with patients regarding the balance of the short-term risks of surgery against the potential for long-term benefit are essential.

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