

Severe ischemic cardiomyopathy—a new answer in management?

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An estimated 5.7 million adults in the United States have congestive heart failure (1,2). Furthermore, given our aging population and advancement in treatment, it is estimated that the prevalence of congestive heart failure will increase 0.7% by 2030 leading to a 215% increase in cost for treatment (1). Significant coronary artery disease (CAD) is still the most common cause of congestive heart failure in developed countries, commonly referred to as ischemic cardiomyopathy (3). The population-attributable risk in the United States has been estimated to be 68% in men and 56% in women (4). This patient population was found to have a shorter survival as compared to those with nonischemic cardiomyopathy (3). However, the role of revascularization of patients with CAD and left ventricular (LV) systolic dysfunction is not well established, particularly for patients with severe LV dysfunction [ejection fraction (EF) $\leq 35\%$].

Over the last 40 years, based on three landmark trials (5-7), coronary artery bypass surgery (CABG) has been recommended as management to help relieve disabling symptomatic angina in patients with extensive CAD. Patients with CAD and reduced LV systolic function were often underrepresented in these trials, particularly those with severe LV systolic dysfunction (EF $\leq 35\%$) who were frequently excluded. These patients who present primarily with heart failure symptoms, as opposed to angina, represent a challenge for appropriate management. Revascularization is commonly offered to these patients based on evidence from retrospective observational trials demonstrating improvement in contractile function of viable but dysfunctional myocardium (8-11) and improved long term survival (12,13) after revascularization. Contemporary goal directed medical therapy has been shown to improve LV function (14,15) and improve survival in heart failure

patients (16,17). In addition, patients with heart failure and LV dysfunction have known higher mortality risk with CABG compared to those without heart failure symptoms and normal LV function (18). Thus, there is clinical uncertainty of the incremental benefits of CABG relative to its risks in patients with ischemic cardiomyopathy in the current clinical era.

The European Society of Cardiology Guidelines currently recommends revascularization for patients with ischemic cardiomyopathy only for relief of angina (19). ACCF/AHA guidelines state that revascularization with CABG is reasonable to improve mortality for patients with mild to moderate LV dysfunction and significant CAD when viable myocardium is present, or for patients with severe LV dysfunction, heart failure symptoms and significant CAD. The guidelines also go further and state that CABG may be considered with the intent of improving survival in patients with ischemic heart disease and severe LV dysfunction (EF $< 35\%$) and operable coronary anatomy whether or not viable myocardium is present (20). The Surgical Treatment for Ischemic Heart Failure Extension Study (STICHES), which was recently published in *The New England Journal of Medicine*, provides compelling outcomes that will impact the clinical management of these patients (21).

The STICHES trial (21) is the ten year follow up to the Surgical Treatment for Ischemic Heart Failure (STICH) trial (22). In that original study, which was published in 2011, the investigators compared patients with CAD and symptomatic severe cardiomyopathy treated with CABG versus medical therapy (22). The study enrolled a total of 1,212 patients between 2002 and 2007 who had an ejection fraction of 35% or less and coronary artery disease that was amenable to CABG. Of note, patients with $\geq 50\%$ left-

main coronary-artery stenosis or Canadian Cardiovascular Society class III and Class IV angina were not included in the study. The two groups were randomized to either CABG or optimal medical therapy alone. After 5 years follow up, there was no statistical difference in the primary endpoint of all-cause mortality between CABG versus medical therapy, although there was a trend in favor of CABG. Secondary endpoint analyses did show lower rates of death from cardiovascular causes with CABG. These results lead to an update in the ACCF/AHA guidelines with the recommendation that CABG may be considered for improving survival in patients with SIHD with severe LV dysfunction (Class IIb, Level of Evidence: B). Based on the findings of the STICH trial, the primary investigators felt that the lack of an unequivocally significant difference between the groups was likely related to limited power and limited duration of the follow-up than true lack of benefit with CABG, and thus follow-up was continued for an additional five years.

At 10 year follow up, the STICHES trial showed 58.9% of patients in the CABG group and 66.1% of patients in the medical therapy group had died ($P=0.02$). The median survival was 7.73 years for the coronary artery bypass surgery group and 6.29 years for the medical-therapy group. The number needed to treat to prevent one death was 14 patients. A total of 40.5% patients in the CABG group and 49.3% in the medical therapy group had died of cardiovascular disease ($P=0.006$). Looking at the secondary endpoint of all-cause death or hospitalization for cardiovascular causes, results again favored the CABG treated patients versus the medical-therapy group (76.6% vs. 87.0%, $P<0.001$).

As has been noted with other studies, there was an increased risk of early death with CABG. The investigators noted that CABG was associated with a three-time higher risk of death within the first 30 days after randomization than with medical therapy alone, with similar differences in risk up to the second year of follow-up. Significant benefit with CABG only began to accrue after the first two years. Thus, the upfront risks of performing CABG are offset by a durable effect that translates into an increasing clinical benefit for at least 10 years. Improvements in myocardial protection techniques, surgical skills, use of the left internal mammary artery conduit and perioperative care have all contributed to increase overall survival as compared to the initial landmark trials 40 years ago (5).

The STICHES trial supports revascularization with CABG in patients with significant CAD and severe LV

dysfunction. Whether a similar benefit can be obtained for revascularization with percutaneous coronary intervention in this cohort is not known. There is very limited data on PCI compared to medical therapy for patients with LV dysfunction and significant CAD with mixed results (23-25). Although the data supporting revascularization with CABG for patients with severe LV dysfunction is more robust, particularly with the addition of data from the STICHES trial, there have not been any contemporary randomized controlled trials with PCI in this patient population.

The STICHES trial provides compelling evidence that many physicians already believe to be true. Namely, that for patients with significant CAD and severely reduced ejection fraction, revascularization with CABG provides significant benefit over optimal medical therapy in this high risk population. Going forward, patients presenting with heart failure and LV systolic dysfunction who are noted with significant CAD, need to be identified for a discussion on the possible benefits of CABG in addition to optimized medical therapy. Of note, patients still need to be aware of the immediate risks of coronary artery bypass surgery versus medical therapy as outlined earlier. Future investigations need to be conducted on whether a similar benefit is obtainable for revascularization with PCI.

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Footnote

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