Viability, Remodeling, and CABG
Another STICH in the Shroud of Observation-Based Paradigm?*

Marvin A. Konstam, MD

Following myocardial infarction, left ventricular (LV) remodeling is characterized by increased LV end-diastolic and end-systolic volumes (ESV) and decreased LV ejection fraction (EF) (1). This process is driven by elongation of infarcted zones and changes within the unaffected myocardium, including myocyte hypertrophy and interstitial collagen deposition. With medical therapy, revascularization, or cardiac resynchronization, the probability of reversing this process is greater where there is a greater proportion of viable myocardium, as assessed by noninvasive imaging (2-4).

Based on a series of observational analyses (2,5,6), the extent of viability has been used to predict a greater LV functional benefit and improved survival from coronary artery bypass graft (CABG) versus medical therapy. This practice is not supported by results of a prior analysis of data from the randomized, controlled STICH (Surgical Treatment for Systolic Heart Failure) trial (7). However, additional studies have suggested that LV functional improvement following CABG is diminished in patients with greater LV volumes (8,9). These findings suggest that CABG may confer survival benefit only among patients with substantial viability, in the absence of severe remodeling. A report by Bonow et al. (10) in this issue of JACC does not support this hypothesis, examining survival among patients randomized to CABG versus medical therapy alone in patients with myocardial viability without severe LV ESV enlargement. In this analysis, patients in the STICH trial who had viability assessed and had substantial myocardial viability with LV ESV ≥84 ml/m² showed no survival benefit with CABG, compared with medical therapy alone, similar to patients with larger LV ESV and similar to the overall STICH population.

The extent of LV remodeling is a strong independent predictor of survival, and LV volumes represent the biomarker that comes closest to representing a surrogate for mortality in patients with heart failure and reduced LVEF, given the strong correlation between intervention’s effects on LV volumes and on mortality (11,12). It is reasonable to hypothesize that in patients with more remodeling, there is less opportunity for reversal and therefore less opportunity for improved survival with any intervention. Likewise, it is reasonable to hypothesize that an LV with lesser degrees of viability represents a poorer substrate for reversing remodeling and improving LV function. Importantly, viability and remodeling are not fully independent. Less viability is likely to be associated with larger LV volumes.

In the STICH trial, there was no benefit of randomization to CABG, compared with medical therapy alone, in patients with coronary artery disease amenable to CABG and LVEF ≤35%, in the absence of either left main coronary artery stenosis or Canadian Cardiovascular Society class III or IV angina, despite medical therapy (13). We have now learned that these findings were consistent in a subgroup of patients with myocardial viability and a limited degree of LV remodeling. There are 2 broad possibilities to explain why findings from the STICH trial did not substantiate those of the nonrandomized observational analyses.

The first is that the absence of substantiation within the STICH study results from discordance between the STICH population and those of the observational analyses. It may be difficult to demonstrate benefit within a subgroup when the overall population showed no benefit. This combination would imply an adverse effect of CABG in the remaining population. The STICH population had characteristics that may have limited the overall ability to demonstrate

*Editorials published in JACC: Cardiovascular Imaging reflect the views of the authors and do not necessarily represent the views of JACC: Cardiovascular Imaging or the American College of Cardiology.

From the CardioVascular Center, Tufts Medical Center, Tufts University School of Medicine, Boston, Massachusetts. Dr. Konstam has reported that he has no relationships relevant to the contents of this paper to disclose.
CABG benefit, compared with the earlier analyses. One difference is the greater background use of contemporary treatments, including beta-blockers, renin-angiotensin-aldosterone system inhibitors, and implantable cardioverter-defibrillators. These treatments have many of the same benefits expected from CABG, including reversal of remodeling, prevention of recurrent ischemic events, and prevention of lethal arrhythmias. The mortality rate in the medical arm of the STICH trial (13) was lower than that among patients showing myocardial viability and treated medically across a meta-analysis of older observational cohorts (2).

A second differential characteristic of the STICH population is that patients believed to be most likely to benefit from CABG may have been selected out, either by design or by clinician preference. Patients with the highest grades of angina were excluded by protocol, both for ethical reasons and because the STICH hypothesis was that CABG would increase survival even among patients in whom there was not a clinical imperative toward surgery. Additionally, investigators likely had pre-conceived opinions about CABG benefit, leading to exclusion of patients with substantial ischemia on noninvasive imaging and with more severe multivessel disease. Such patients probably heavily populated the observational cohorts, helping to drive CABG benefit.

A second possible explanation for the absence of corroboration by the STICH trial of earlier observations is that the latter were influenced by either: 1) bias, as occurs from nonrandomized treatment selection; and/or 2) absence of an adequate control group. In patients with greater viability and less remodeling, non-randomized assignment to medical therapy may have been on the basis of greater comorbidity, thus biasing the result in favor of CABG. It is possible that in patients with less viability or greater remodeling, patients were less readily stratified according to other comorbidities, so that CABG assignment was not as biased in that respect. Without controls, it is possible that the findings of dependence of LV functional improvement with CABG on the absence of severe remodeling might have been present without CABG.

The findings of Bonow et al. (10) may represent another cautionary tale regarding conclusions of non-randomized observational analyses. Adjustment for covariate imbalance resulting through nonrandomized treatment assignment is never complete. In the STICH trial, randomization removes any possible selection bias. However, as opposed to other circumstances in which a primary endpoint finding of a large randomized trial refuted a prior paradigm (14), the present analysis was in post-hoc subsets, drawn only from the cohort that underwent 1 of several methods of viability assessment. Therefore, the analysis by Bonow et al. (10) cannot definitively refute prior conclusions. The hypotheses generated by observational analyses are best tested primarily and prospectively within randomized controlled trials.

We are now less certain of the value of global viability assessment, with or without LV volume measurement, in predicting clinical benefit from CABG. There remains adequate rationale for matching regional viability with coronary revascularization targets as a means to guide decision making. Also, given the nature of the present analysis, we cannot rule out a value of deploying global viability assessments for predicting CABG benefit, particularly within populations underrepresented in the STICH trial. Nevertheless, these findings call for caution in interpreting prior observational analyses used to justify such practice.

**REPRINT REQUESTS AND CORRESPONDENCE:** Dr. Marvin A. Konstam, Tufts Medical Center, Box 108, 800 Washington Street, Boston, Massachusetts 02111. E-mail: mkonstam@tuftsmedicalcenter.org.

**REFERENCES**


KEY WORDS coronary artery bypass surgery, coronary artery disease, heart failure, myocardial viability