JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
© 2015 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER INC.

VOL. 66, NO. 19, 2015
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2015.08.880

EDITORIAL COMMENT

Angina in Revascularization of Ischemic Cardiomyopathy

The Whole Quilt, or Just a STICH?*

Jeffrey B. Geske, MD, Bernard J. Gersh, MB, ChB, DPhil

In this issue of the *Journal*, Jolicœur et al. (1) assessed the role of angina in regard to the outcomes of revascularization of ischemic cardiomyopathy by performing a subgroup analysis of the STICH (Surgical Treatment for Ischemic Heart Failure) trial (2). Angina has long played a central role in the management of patients with coronary artery disease (CAD) and ischemic cardiomyopathy, with some current guidelines citing the presence of angina as a major influence upon the decision to perform coronary revascularization (3). The authors pose 3 questions:

1. Does angina confer an adverse prognosis in patients with left ventricular (LV) systolic dysfunction?
2. Does angina predict a survival benefit in patients undergoing coronary artery bypass grafting (CABG)?
3. Does CABG relieve angina better than medical therapy alone in patients with LV dysfunction?

SEE PAGE 2092

Of 1,212 patients with LV ejection fraction ≤35% randomized to CABG versus medical therapy, 770 reported the presence of angina. When stratifying solely on the basis of the presence or absence of angina, there was no difference in all-cause mortality in patients randomized to medical therapy alone. However, in the relatively few (7.5%) patients with Canadian Cardiovascular Society class III or IV angina, worse all-cause mortality was noted. Data from the entire STICH population demonstrated a modest reduction in all-cause death and cardiovascular hospitalization in patients undergoing CABG compared with medical therapy alone (hazard ratio [HR]: 0.74; 95% confidence interval [CI]: 0.64 to 0.85; $p < 0.001$) (2); yet, somewhat counterintuitively, in this subset analysis of patients with and without angina analyzed by intention to treat, CABG did not reduce all-cause death in patients with angina. However, when crossovers were considered, CABG did reduce all-cause mortality in patients with and without angina. CABG was more likely to improve symptoms of angina compared with medical therapy alone, a finding that was consistent throughout follow-up.

With these data, the authors conclude that "the presence or absence of angina should not be used as a discriminating factor to decide for or against revascularization as an initial treatment strategy, so far as subsequent prognosis is concerned" (1). This sweeping statement must be put into the context of the trial population. Beyond potential enrollment biases, trial subjects were largely male (87.8%), young (~60 years of age), and recruited outside of North America. Angina classification was not standardized across sites, and relatively few of the patients studied had Canadian Cardiovascular Society class III/IV angina. Furthermore, there are several confounding factors: patients without angina were more likely to have diabetes and had more viable myocardium, whereas long-acting nitrates were utilized more frequently in patients with angina. Although the authors' conclusion is appropriate to the trial population, it may not apply to patients with more severe angina or even to patients with LV dysfunction as a whole.

Analyses of STICH data have demonstrated that the severity of CAD burden directly influences the benefits of CABG (4). Similarly, in the CASS (Coronary

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

From the Department of Medicine, Division of Cardiovascular Diseases, Mayo Clinic, Rochester, Minnesota. Both authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Artery Surgery Study), a survival benefit was associated with CABG in patients with LV dysfunction and 3-vessel disease CAD (5). However, the extent of CAD does not necessarily translate to the severity (or even presence) of angina. The degree of luminal stenosis, magnitude of ischemic myocardium, and resultant angina may be discordant, particularly in patients known to exhibit atypical angina, such as women and those with diabetes. However, an analysis of patients in the CASS registry on the basis of the predominance of angina versus heart failure symptoms revealed that those with angina as the predominant symptom and an ejection fraction ≤35% had better survival following CABG than patients with mostly heart failure symptoms (6). Does the difference from the present study relate to interval evolution of medical therapy, or are we seeing a selection effect?

The concepts of reversible LV dysfunction following revascularization and hibernating myocardium are decades old (7,8). It is worthwhile, however, to clarify terminology that is often interchanged. Viable myocardium refers to nonscarred tissue with potential for recovery and may be normally functioning at rest (with inducible ischemia) or stunned at rest (in the presence of resting ischemia). In contrast, hibernating myocardium is a term applied retrospectively to denote myocardium that improves following revascularization (9). In considering the complex interplay of angina and viability, it is worth revisiting the STICH viability substudy data (10). Whereas patients with presence of viable myocardium had better outcomes than those without (HR: 0.64; 95% CI: 0.48 to 0.86; $p = 0.003$), CABG did not result in an incremental survival benefit in patients with viability when compared with medical therapy alone (HR: 0.86; 95% CI: 0.64 to 1.16; p = NS). There have been many proposed explanations for this result, including the unblinded and nonrandomized nature of viability testing, the combination of viability techniques (single-photon emission computed tomography and dobutamine echocardiography), dichotomous classification of viability (as opposed to continuous assessment), and a relatively small subset with 3-vessel CAD (36%). Regardless, the results raised many questions regarding the utility of viability testing within this patient population.

Further complicating the matter, STICH data suggests that in patients with severe LV dysfunction, inducible myocardial ischemia does not identify patients with worse prognosis or greater benefit from CABG (11). How do we synthesize these data and apply them to clinical practice? In managing patients with ischemic cardiomyopathy, can we blind ourselves to the presence of angina, ischemia, and viability? One possible explanation for the discrepancy between ischemia and observed outcomes is the extent of underlying scar burden, which was not considered in this analysis. Hachamovitch et al. (12) studied a large cohort of patients undergoing adenosine or exercise-stress single-photon emission computed tomography myocardial perfusion scintigraphy and found that in patients without an extensive scar burden (defined as scar encompassing >10% of myocardium), significant ischemia was predictive of survival benefits associated with early revascularization, whereas patients with extensive scar did not achieve such benefits. These data imply that ischemia is a predictor of outcomes; however, its influence may be superseded by the presence of a significantly scarred underlying substrate. Scar burden and extensive remodeling may similarly lead to the observed disconnect between measures of viability and outcomes.

The STICH trial has provided substantial information on the influence (or lack thereof) of viability, ischemia, and now the presence or absence of angina. Although the main finding, that CABG provides a modest benefit in a sick group of patients with LV dysfunction, is intuitive, other STICH trial results have been unexpected and raised many further questions. Established concepts of viability, ischemia, and angina have been placed into question. Do the results mean that these factors should be discounted as influences on decision making for revascularization? Certainly not. Rather, these data suggest that as ischemic heart disease progresses, there comes a point in the natural history when the severity of LV dysfunction, extent of scarring, and adverse ventricular remodeling may overwhelm viability and ischemia as the major determinants of prognosis. In such patients, the incremental benefits of revascularization over optimal medical therapy alone may be minimal.

We agree that viability testing should not be a routine part of the evaluation in patients with LV dysfunction, but there are subsets in whom it may be helpful. As with many trials, providing an answer to one question generates a host of others. How applicable are the STICH results outside of the population studied? How much scar negates the influence of viability? In the presence of severe LV dysfunction, at what point are the benefits of revascularization over medical therapy lost? Because STICH trial data have shown a trend toward survival benefit of revascularization, irrespective of the presence or absence of viability (9) (more so in patients with 3-vessel CAD [3]), we must consider the pluripotent effects of revascularization beyond improvement in regional

contractile function of hibernating myocardium. The effect of revascularization on prevention of ventricular arrhythmias, improved diastolic hemodynamics, attenuation of maladaptive remodeling, or a host of other factors may prove paramount in certain patient populations.

In conclusion, integration of these results into clinical practice necessitates careful attention to the patient population that was studied. When treating patients with lesser degrees of LV dysfunction, CAD that is not completely revascularizable, or patients at high surgical risk, additional information, such as the extent of viability, extent of ischemia, scar burden, and the effect of angina symptoms on quality of life, may still be helpful in the therapeutic decision-making process.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Bernard J. Gersh, Department of Cardiovascular Diseases, Mayo Clinic, 200 First Street, SW, Gonda 5-368, Rochester, Minnesota 55905-0001. E-mail: gersh.bernard@mayo.edu.

REFERENCES

1. Jolicœur EM, Dunning A, Castelvecchio S, et al. Importance of angina in patients with coronary disease, heart failure, and left ventricular systolic dysfunction: insights from STICH. J Am Coll Cardiol 2015;66:2092–100.

2. Velazquez EJ, Lee KL, Deja MA, et al., for the STICH Investigators. Coronary-artery bypass surgery in patients with left ventricular dysfunction. N Engl J Med 2011;364:1607–16.

3. McMurray JJ, Adamopoulos S, Anker SD, et al., for the ESC Committee for Practice Guidelines. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. Eur Heart J 2012;33:1787–847.

4. Panza JA, Velazquez EJ, She L, et al. Extent of coronary and myocardial disease and benefit from surgical revascularization in ischemic LV dysfunction [corrected]. J Am Coll Cardiol 2014;64:553–61.

5. Passamani E, Davis KB, Gillespie MJ, et al. A randomized trial of coronary artery bypass surgery. Survival of patients with a low ejection fraction. N Engl J Med 1985;312:1665–71.

6. Alderman EL, Fisher LD, Litwin P, et al. Results of coronary artery surgery in patients with poor left ventricular function (CASS). Circulation 1983;68:785–95.

7. Rahimtoola SH. The hibernating myocardium. Am Heart J 1989;117:211–21.

8. Chatterjee K, Swan HJ, Parmley WW, et al. Depression of left ventricular function due to acute myocardial ischemia and its reversal after aortocoronary saphenous-vein bypass. N Engl J Med 1972;286:1117–22.

9. Shah BN, Khattar RS, Senior R. The hibernating myocardium: current concepts, diagnostic dilemmas, and clinical challenges in the post-STICH era. Eur Heart J 2013;34:1323–36.

10. Bonow RO, Maurer G, Lee KL, et al., for the STICH Trial Investigators. Myocardial viability and survival in ischemic left ventricular dysfunction. N Engl J Med 2011;364:1617–25.

11. Panza JA, Holly TA, Asch FM, et al. Inducible myocardial ischemia and outcomes in patients with coronary artery disease and left ventricular dysfunction. J Am Coll Cardiol 2013;61:1860–70.

12. Hachamovitch R, Rozanski A, Shaw LJ, et al. Impact of ischaemia and scar on the therapeutic benefit derived from myocardial revascularization vs. medical therapy among patients undergoing stress-rest myocardial perfusion scintigraphy. Eur Heart J 2011;32:1012–24.

KEY WORDS coronary artery bypass, coronary artery disease, myocardial ischemia, viability