To STICH or not to STICH: We know the answer, but do we understand the question?

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How Would You Treat This Patient?

A 75-year-old 70-kg male patient reports having worsening shortness of breath over the past 2 years and now must stop to catch his breath after climbing 1 or 2 flights of stairs. He has no angina pectoris. He has electrocardiographic evidence of an old transmural anterior myocardial infarction. His comorbidities include hypertension and hyperlipidemia. Examination reveals some leg edema and an S3 gallop, but findings are otherwise unremarkable. The hemoglobin level is 150 g/L, and the creatinine value is 120 mg/L. An echocardiogram shows a moderately dilated left ventricle with anterior akinesia, mild mitral regurgitation, and an ejection fraction of 29%. Medications include angiotensin-converting enzyme inhibition, β -blockade, a diuretic, and a statin. The coronary angiogram shows triple-vessel disease with an occluded left anterior descending artery and an occluded right coronary artery. Both vessels fill retrogradely from a large circumflex artery that has one high-grade stenosis in the obtuse marginal branch. All vessels are good targets for coronary artery bypass grafting (CABG). A fluorodeoxyglucose positron emission tomographic scan viability study reveals a scar in parts of the anterior wall and the apex and viability in the posterior wall and the septum.

This patient has ischemic heart failure with evidence of ventricular remodeling after anterior infarction. Should he be treated medically, or should he be referred for revascularization? If revascularization is chosen, should the ventricular shape be corrected? Whatever your decision is, it may be the exact opposite from that of the next physician.

The STICH (Surgical Treatment for Ischemic Heart failure) trial is the first prospective randomized study in the history of coronary artery surgery to specifically assess the potential benefit of CABG in patients with heart failure and coronary artery disease. The trial tests two hypotheses: (1) CABG combined with intensive medical therapy improves long-term survival compared with medical therapy alone and (2) surgical ventricular restoration (SVR) combined with CABG and medical therapy improves survival free of hospitalization compared with CABG and medical therapy without SVR. Contrary to expectations, there is an astonishing lack of convincing evidence for either of these treatment modalities in this patient population. Thus, a trial aimed at detecting the best treatment strategies in this continuously growing patient population should be welcomed with high interest and support among physicians in the field. The question "to STICH or not to STICH" should be unanimously answered with "to STICH." Yet the trial, professionally organized and adequately funded, is experiencing difficulties in recruiting patients into strata in which randomization into the medical treatment arm is possible. One may assume that the reason for these recruitment difficulties is a treatment bias in the medical

community toward one treatment option. It is therefore striking to realize that such a bias does not exist. As stated previously, the chosen treatment arm for eligible patients not randomized may differ completely from one center to the next. We believe that the differences in clinical management decisions regarding the treatment of patients with heart failure and coronary artery disease are based on personal physician perspectives and experiences and not on firm clinical trial evidence. Thus, treatment decisions seem to result from alternate interpretations of the question, “to STICH or not to STICH?”

To treat patients such as the one we presented with a greater degree of confidence, we must focus on addressing 3 basic questions.

1. Does CABG provide a survival benefit in patients with coronary artery disease and heart failure?
2. What is the role of viability testing?
3. Which patients should be considered for SVR?

Coronary Revascularization in Heart Failure: Where Is the evidence?

Our patient has graftable 3-vessel disease and good targets for bypass grafting. Why should CABG not be performed on him?

Nine trials have compared a strategy of initial CABG with one of initial medical therapy, and 3 were of considerable size in terms of patient enrollment, ie, the Coronary Artery Surgery Study (CASS), the Veterans Affairs study, and the European study. In all studies, the inclusion criteria included the presence of stable angina and, therefore, are unlikely to represent many patients with ischemic heart failure. Yusuf and colleagues¹ suggested in an overview of these trials that CABG provides a survival benefit specifically in high-risk patients (ie, patients with triple-vessel disease, left ventricular dysfunction, or both). However, these conclusions have been seriously challenged.² Specifically, the analysis was questioned because the described survival benefit was mainly due to the results of the European study.^{2,3} This study was the only trial that demonstrated a sustained difference in cumulative mortality at 12 years, but its conclusions were critiqued because of excess mortality in the medical treatment arm.³

Irrespective of this difference of opinion, it is important to realize that none of these studies included the patient population represented by our patient, ie, those with coronary artery disease, severely compromised contractile function (ie, ejection fraction <35%), and symptoms of heart failure rather than angina. In addition, only the CASS study enrolled patients ($n = 780$) with impaired left ventricular function (ejection fraction 35%-50%)⁴ and assessed patients with ejection fractions less than 35% ($n = 631$).⁵ In both reports, the outcomes were similar. CABG provided a survival benefit over initial medical therapy only if angina was the leading symptom. The 10-year survival in the random-

ized group was 80% for CABG, compared with 59% for medical therapy ($P = .01$),⁴ and the 3-year survival in the registry patients was 84% for CABG and 68% for medical therapy ($P < .05$).⁵ However, when the leading symptom was heart failure, the 10-year survival in the randomized patients (72% and 76%)⁴ and the 3-year survival in the registry patients (55% for both groups)⁵ was the same in the 2 treatment arms. On the basis of these results, both decisions made for our patient may be considered correct. It is therefore not surprising that 2 respected bodies of experts have published opposing statements regarding the treatment of this patient population. The CASS investigators write that “patients with overt heart failure and the absence of ischemic symptoms should not receive surgery,”⁵ whereas the Heart Failure Guidelines of the Agency for Health Care Policy and Research read, “It is not clear whether patients whose predominant symptom is heart failure rather than angina benefit from bypass surgery.”⁶ The latter opinion more accurately reflects current opinion, because evidence from CASS is now more than 20 years old, and optimum medical and surgical therapies have changed considerably over this time.

In addition to the scarcity of the available data, decision making at present is further complicated because the randomized and the retrospective cohort and observational studies were performed before major advances had been made in medical therapy for heart failure and before substantial improvements had been made in the safety of surgical procedures performed in these high-risk patients. It is interesting to note in this context that no randomized trial comparing CABG versus medical therapy for with heart failure has been performed in the last 10 years. Thus, a prospective, randomized, multicenter trial (such as the STICH trial) seems in order. However, this trial may no longer be necessary because technological advances have improved the capacity to image and diagnose the viability of underperfused myocardial territories.

The Effect of Viability Testing on Decision Making in Surgical Revascularization

Viability testing may be used to guide decision making in patients with dysfunctional areas of their myocardium.⁷ Our patient has proof of viability in most regions of the heart (except in the anterior wall) in addition to his graftable 3-vessel disease. Thus, any type of revascularization should allow the myocardium to recover its function. Is it therefore acceptable to consider the patient for medical therapy or for enrollment into the STICH trial? How can the potential decision to treat the patient medically be defended?

Many studies have suggested that viability testing is useful for decision making.⁷ However, one must be aware that there are no prospective randomized trials assessing the value of viability testing in patients with coronary artery disease and contractile dysfunction. In addition, the studies

that evaluated the effect of nuclear or positron emission tomography viability imaging on intermediate or long-term survival did not meet all or even most of the criteria put forth by the Evidence-Based Medicine Working Group criteria for the assessment of articles on therapeutic interventions and prognosis.

Most of these studies show major methodologic deficiencies, including a broad mix of patients (ejection fraction, 24% to >50%; fraction of patients in New York Heart Association class III-IV, 19% to 100%), small sample sizes (from 35 to 137 per group), and no consideration of baseline characteristics (more patients with angina were sent for viability testing). These and more aspects have been reviewed and illustrated in detail elsewhere.⁸ Thus, many patients included in the STICH population are not considered in these studies. The most important and limiting methodologic weakness of previous studies is perhaps the inherent selection bias. Treatment allocation to CABG or medical therapy was made in most studies by physicians who requested and, in some cases, interpreted the viability tests. In addition, recent data with β -blockers suggest that functional improvement in viable myocardium is not dependent necessarily on revascularization,⁹ thus adding further evidence to the debate.

The current level of evidence regarding the use of viability imaging is flawed and considered inadequate. Therefore, a randomized clinical trial is mandated and necessary to evaluate the usefulness of viability imaging in decision making for or against revascularization. Another role of viability testing may be to risk-stratify patients for CABG. Although the simple demonstration of viable myocardium may not predict a long-term survival benefit of CABG over medical management, it may prove to be a predictor of operative risk.

The Role of Surgical Ventricular Reconstruction for Patients With Ischemic Heart Failure

Our patient has a further aspect of disease that may influence decision making: he shows evidence of a dilating (ie, remodeling) ventricle and has an akinetic scar in the anterior wall. Thus, he could be considered for revascularization combined with surgical ventricular reconstruction.

Surgery on the left ventricle has been performed for decades. Cooley and Hallman¹⁰ were the first to describe the exclusion of a large left ventricular aneurysm by using a patch. Although aneurysmectomy for large anterior or posterior aneurysms with thinning of the wall has gained its place in most cardiac surgical centers, controversy still exists regarding whether similar techniques may also be useful in treating patients with dilated ventricles and scarred regions of the heart when the shape is not seriously distorted by an aneurysm. Dor¹¹ described an endoventricular patch plasty for the reconstruction of a ventricle after myocardial infarction in the early 1990s and went on in 1998 to dem-

onstrate that the results of this technique were just as good in patients with akinetic regions in their ventricles as in patients with dyskinetic—ie, aneurysmatic—regions. Although the Dor procedure has been adopted by several centers, it has not found general acceptance. Possible reasons include a lack of evidence that demonstrates improvements in morbidity or mortality with this technique in patients with ischemic heart failure. A recent retrospective database analysis assessed morbidity and mortality in patients with ischemic cardiomyopathy and dilated ventricles who were referred for CABG. The outcome was significantly better in the groups that received CABG plus ventricular reconstruction (ie, a Dor procedure) compared with patients who received CABG alone.¹² Many other studies have been published presenting mortality rates and long-term survival after surgery on the left ventricle. None has been conducted in a prospective, randomized manner with an acceptable number of patients. The operative mortality in these studies ranges between 0% and 20%, and the reported 5-year survival hovers around 70% for most studies, regardless of the study year and the reconstruction technique used. Although this observation may suggest that the ventricular repair technique has less of an effect on outcome, this is confounded by the fact that patients with increasingly complicated and high-risk disease have been undergoing operations in recent years.

The pathophysiologic processes that lead to the development of ischemic heart failure have also changed over the years, mainly because of major improvements in the treatment of patients with acute myocardial infarctions and in medical therapy. The implications of these changes for surgery on the ventricle were the basis for an entire issue of *Seminars in Thoracic and Cardiovascular Surgery* in 2001. They have resulted in modifications to the Dor procedure with respect to the size and shape of the reconstructed left ventricle. The modified Dor procedure is also known as SVR.

Initial results with the SVR technique have recently been published in a 3-year observational study by the RESTORE group.¹³ The surgeons in this international group performed this procedure on 662 patients who mainly had akinetic defects in the anterior wall. The results have been promising, although any conclusions on the incremental efficacy of SVR relative to CABG must be made with caution because of the absence of a control group in the RESTORE registry. The ejection fraction improved on average by 10% ($29.7\% \pm 11.3\%$ to $40.0\% \pm 12.3\%$), and the patients had a subjective benefit, as indicated by a significant improvement in their New York Heart Association classification (from III-IV to I-III). Hospital mortality was 7.7%, and 3-year survival was 89%. Despite these promising data, the results were challenged by a report from Elefteriades and colleagues,¹⁴ who demonstrated a similar improvement in contractile function in a small and selected group of patients

in whom isolated CABG surgery was performed. In addition to this controversy, several questions remain and will not be answered unless they are investigated in a prospective randomized fashion. First, it is not clear whether SVR provides a survival benefit over CABG alone (an answer may arise from the second hypothesis of the STICH trial). Second, it is unknown whether a reduction in the volume of a dilated ventricle improves survival; and, finally, it is not clear whether the reconstruction is actually able to revert or stop the remodeling processes after the infarct. Thus, current evidence does not allow us to satisfactorily answer the question as to whether our patient should undergo SVR.

In summary, the appropriate treatment of patients with ischemic heart failure is currently unknown, yet there is no shortage of opinion regarding "optimum treatment." This balance of opinion highlights the need for sound clinical evidence and underscores the very nature of clinical equipoise. The STICH trial is designed and powered to answer fundamental clinical questions regarding the ischemic heart failure population. Will coronary revascularization prolong survival in patients with heart failure who have no symptoms of angina? How valuable are current imaging modalities for predicting candidates for medical or surgical management? Is there a clinical benefit to SVR? In many respects, the STICH trial will revisit a subset of patients examined by CASS, but in the current era of optimum medical and surgical therapy.

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