Is Viability Imaging Still Relevant in 2012?

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Is Viability Imaging Still Relevant in 2012?

**WITH THE PUBLICATION OF THE STICH (Surgical Treatment for Ischemic Heart Failure) trial (1) and the viability substudy (2), questions have arisen regarding the utility of viability testing in patients with left ventricular systolic dysfunction and coronary artery disease (CAD) prior to revascularization decisions. Prior observational studies and meta-analyses (3) had suggested that those with viability demonstrated on noninvasive testing fared better with revascularization, whereas those without might fare worse.**

In this issue of *iJACC*, we present 2 opposing takes on the literature in a timely and topical *iForum*. The first from Drs. Chareonthaitawee and Gersh presents the pro side, that viability testing remains relevant in 2012. The second from Dr. Panza concludes the contrary. It is intriguing that both sets of authors reflect on the same literature and come to different conclusions. Both sides discuss the PARR-2 (PET and Recovery Following Revascularization Phase 2) study (4), the first truly randomized controlled trial of viability testing in this patient population. Unfortunately, the clinicians who enrolled patients in this particular trial did not always follow the recommendations of the positron emission tomography (PET) findings, leaving the interpretation of the study fairly flexible and pointing out the difficulty of pulling off a study with such a complex design. Drs. Chareonthaitawee and Gersh argue that PARR-2 supports the utility of viability testing in this patient population. Unfortunately, the clinicians who enrolled patients in this particular trial did not always follow the recommendations of the positron emission tomography (PET) findings, leaving the interpretation of the study fairly flexible and pointing out the difficulty of pulling off a study with such a complex design. Drs. Chareonthaitawee and Gersh argue that PARR-2 supports the utility of viability testing in this patient population. Unfortunately, the clinicians who enrolled patients in this particular trial did not always follow the recommendations of the positron emission tomography (PET) findings, leaving the interpretation of the study fairly flexible and pointing out the difficulty of pulling off a study with such a complex design. Drs. Chareonthaitawee and Gersh argue that PARR-2 supports the utility of viability testing in this patient population. Unfortunately, the clinicians who enrolled patients in this particular trial did not always follow the recommendations of the positron emission tomography (PET) findings, leaving the interpretation of the study fairly flexible and pointing out the difficulty of pulling off a study with such a complex design. Drs. Chareonthaitawee and Gersh argue that PARR-2 supports the utility of viability testing in this patient population. Unfortunately, the clinicians who enrolled patients in this particular trial did not always follow the recommendations of the positron emission tomography (PET) findings, leaving the interpretation of the study fairly flexible and pointing out the difficulty of pulling off a study with such a complex design. Drs. Chareonthaitawee and Gersh argue that PARR-2 supports the utility of viability testing in this patient population. Unfortunately, the clinicians who enrolled patients in this particular trial did not always follow the recommendations of the positron emission tomography (PET) findings, leaving the interpretation of the study fairly flexible and pointing out the difficulty of pulling off a study with such a complex design.

The concepts of myocardial viability and viability testing are logical and mechanistically sound (6). Reasonable, though nondefinitive, evidence from over 100 nonrandomized studies of more than 3,000 patients with viability has been a source of controversy. Nonrandomized studies performed over 2 decades ago suggested that using coronary artery bypass graft (CABG) in moderate-to-severe ischemic LV systolic dysfunction may lead to prognostic benefit, but the results were offset by limitations in study design and the high perioperative risks prevalent at that time (6). Uncertainty regarding the optimal treatment strategy in these patients has, therefore, provided the rationale for viability testing.

The bottom line is that controversy lingers and this underlies our interest at *iJACC* to present this to our readers. Clearly, there is room for further investigation in this arena to definitively answer this important question in clinical cardiovascular medicine.

**Viability Testing Remains Relevant in Ischemic Left Ventricular Dysfunction**

Panithaya Chareonthaitawee, MD
Bernard J. Gersh, MB, ChB, DPhil

**RATIONALE FOR VIABILITY TESTING BASED ON OBSERVATIONAL STUDIES.**

Despite advances in therapy, the morbidity and mortality of moderate-to-severe ischemic left ventricular (LV) systolic dysfunction remain high (5). In the absence of angina, the relative value of revascularization over medical therapy has been a source of controversy. Nonrandomized studies performed over 2 decades ago suggested that using coronary artery bypass graft (CABG) in moderate-to-severe ischemic LV systolic dysfunction may lead to prognostic benefit, but the results were offset by limitations in study design and the high perioperative risks prevalent at that time (6). Uncertainty regarding the optimal treatment strategy in these patients has, therefore, provided the rationale for viability testing.

The bottom line is that controversy lingers and this underlies our interest at *iJACC* to present this to our readers. Clearly, there is room for further investigation in this arena to definitively answer this important question in clinical cardiovascular medicine.
Recent trials of viability testing—steps in LV systolic dysfunction. Testing in moderate-to-severe ischemic (5,9) and support the use of viability testing in the American College of Cardiology/American Heart Association practice guidelines (10) can culminated in a class IIa recommendation for viability testing in moderate-to-severe ischemic LV systolic dysfunction.

**Revascularization or Medical Therapy**

In the presence of viability, a 79.6% reduction in mortality was noted with revascularization versus medical therapy. Without myocardial viability, there was no significant difference in mortality between the 2 treatment groups. Adapted, with permission, from Allman et al. (3).

These key observational findings have culminated in a class IIa recommendation for viability testing in the American College of Cardiology/American Heart Association practice guidelines (5,9) and support the use of viability testing in moderate-to-severe ischemic LV systolic dysfunction.

**Recent trials of viability testing—steps in the right direction. PARR-2.** Thus far, the major limitation of the viability literature is the lack of randomized controlled trials (RCT) of viability testing. This was addressed partly by the PARR-2 trial, a noteworthy, and the largest to date, RCT of PET viability testing (4). PARR-2 stratified patients with severe LV systolic dysfunction (presumed ischemic) to recent angiography or not, then randomized to PET-guided management (n = 218) versus standard care without PET (where an alternative test could be considered [n = 212]). At 1 year, PARR-2 demonstrated no significant difference in the composite primary outcome of cardiac death, myocardial infarction (MI), or recurrent hospitalization between the 2 arms.

Although well-conducted, PARR-2 had lower adherence to PET-guided recommendations, which may have reduced the ability to detect a difference in the primary outcome. When only patients adhering to PET-guided recommendations were included, the PET adherence group had significantly better outcome than the standard care group did (adjusted hazard ratio: 0.62). Furthermore, 39% of patients in the PET arm and about two-thirds of patients in the standard arm had at least 1 other form of functional testing within 3 months before or after randomization, which may have introduced a significant crossover effect and bias against PET. Third, patients in the PET arm with prior testing had significantly better outcomes than those in: 1) the standard arm with other testing; 2) the standard arm without other testing; and 3) the PET arm without prior testing. All of which suggests that an algorithm with PET after initial testing might provide clinical benefits. Thus, whereas randomization in PARR-2 demonstrated no significant difference in the composite primary outcome of cardiac death, myocardial infarction (MI), or recurrent hospitalization between the 2 arms.

PARR-2 were: 1) revascularization and revascularization work-up rates differed significantly relative to viability extent, suggesting that PET had an important impact on management decisions; and 2) PET-assisted management yielded a significant mortality benefit in patients without recent angiography, perhaps by optimizing patient selection for revascularization work-up and subsequent decision making.

**STICH—OVERALL TRIAL.** The clinical equipoise between surgical and nonsurgical management of ischemic LV systolic dysfunction has led to the STICH trial, to date, the largest RCT of CABG versus medical therapy in moderate-to-severe ischemic LV systolic dysfunction (1). This rigorously conducted trial randomized 1,212 patients to medical therapy versus medical therapy plus CABG. By intention-to-treat analysis, no significant difference in the primary endpoint of all-cause death was observed between the 2 randomized arms at a median follow-up of 56 months. However, whereas adherence to randomization strategies was reasonably high, crossover occurred in 17% of patients assigned to medical therapy and 9% of patients assigned to CABG, potentially reducing the treatment effect. When as-treated and per-protocol analyses were performed, highly significant differences in the primary outcome favoring CABG were observed (Fig. 2). Furthermore, compared with those assigned to medical therapy, patients assigned to CABG had significantly lower rates of secondary endpoints, including cardiovascular and combined all-cause death or hospitalization for heart failure (HF).

Similar to other large RCT in the contemporary era, STICH randomized a very small proportion of eligible patients at 127 sites in 26 countries over 5 years, averaging only 2 patients per site per year. The outcome of the large number of screened patients who did not undergo randomization was not reported. Suitable surgical candidates may not have been randomized and...
A noteworthy substudy—viability.

From revascularization.

Systolic dysfunction may derive benefit with moderate-to-severe ischemic LV dysfunction and does not dispel the long-standing notion that some patients among those who underwent testing were present, including differences in race, prior MI, percutaneous coronary intervention, proximal left anterior descending coronary artery stenosis, symptom status, medication use, LV ejection fraction, and volumes. In addition to overall trial limitations (Table 1), the STICH viability substudy, like its observational predecessors, did not mandate viability testing or randomize according to viability testing results. Rather, viability testing was performed at the clinician’s discretion in about one-half of eligible patients. Moreover, significant differences in baseline characteristics between patients with and without viability testing were present, including differences in race, prior MI, percutaneous coronary intervention, proximal left anterior descending coronary artery stenosis, symptom status, medication use, LV ejection fraction, and volumes. The STICH investigators state that they cannot exclude the possibility that viability testing results could have influenced clinical decision making, because there was a nonsignificant trend toward higher rates of CABG among patients who underwent viability testing on the day of randomization or on the following day than there was among those who underwent testing before randomization. Thus, whereas the substudy has the major strength of being part of a rigorously conducted RCT, the results should be interpreted

may have undergone operations, whereas patients included in the RCT may have been those in whom the efficacy of revascularization was already in doubt because they were less suitable, or perhaps even unsuitable, potentially biasing against surgery. Thus, STICH, though rigorous, still leaves uncertainty regarding optimal management and does not dispel the long-standing notion that some patients with moderate-to-severe ischemic LV systolic dysfunction may derive benefit from revascularization.

STICH—viability. A noteworthy substudy of STICH addressed the efficacy of viability testing (2). This nonrandomized viability substudy included 601 patients who underwent optional viability testing by single-photon emission computed tomography (SPECT), dobutamine echocardiography, or both, and who were randomly assigned to CABG (n = 298) versus medical therapy (n = 303). In the 487 patients with evidence of viability, 244 patients were assigned to CABG and 243 to medical therapy. In the 114 patients without viability, 54 were assigned to CABG and 60 to medical therapy. At a median follow-up of 5.1 years, several key findings were noted. First, patients with viable myocardium had lower overall rates of the primary outcome of death (hazard ratio: 0.64; p = 0.003) than patients without viable myocardium did. However, after adjustment for other significant baseline prognostic variables in the multivariate model, viability status was no longer significantly associated with death. Second, lower rates of the secondary endpoints of cardiovascular death (hazard ratio: 0.61; p = 0.003), and a composite of death or hospitalization for cardiovascular causes (hazard ratio: 0.59; p < 0.001) were noted in patients with myocardial viability than for patients without viability. On multivariate analysis, the relationship between myocardial viability and death from cardiovascular causes was not significant, whereas the relationship between viability and the composite of death or hospitalization for cardiovascular causes remained significant. Third, there was no significant interaction between myocardial viability and study group assignment to CABG or medical therapy with respect to death, cardiovascular death, or the composite endpoint. However, there was a nonsignificant trend suggesting greater benefit of CABG in patients without viability (Fig. 3). Fourth, analysis according to treatment actually received showed no interaction between viability status and treatment with respect to primary and secondary outcomes.

The STICH viability substudy raises valid questions regarding the efficacy of viability testing, but its strengths and weaknesses should be examined before generalizing results beyond the study population. In addition to overall trial limitations (Table 1), the STICH viability substudy, like its observational predecessors, did not mandate viability testing or randomize according to viability testing results. Rather, viability testing was performed at the clinician’s discretion in about one-half of eligible patients. Moreover, significant differences in baseline characteristics between patients with and without viability testing were present, including differences in race, prior MI, percutaneous coronary intervention, proximal left anterior descending coronary artery stenosis, symptom status, medication use, LV ejection fraction, and volumes. The STICH investigators state that they cannot exclude the possibility that viability testing results could have influenced clinical decision making, because there was a nonsignificant trend toward higher rates of CABG among patients who underwent viability testing on the day of randomization or on the following day than there was among those who underwent testing before randomization. Thus, whereas the substudy has the major strength of being part of a rigorously conducted RCT, the results should be interpreted
VIABILITY IMAGING IN 2012

The presence of viable myocardium. Lastly, the sample size of the group with nonviable myocardium was relatively small and might be underpowered to detect significant differences in the endpoints between the treatment groups.

Until now, the concepts of myocardial viability, the rationale for viability testing, and the outcomes based on the presence or absence of viability appear logical and rational and are supported by robust pathophysiological mechanisms. It is, therefore, difficult to understand the seemingly counterintuitive STICH findings of the slightly but nonsignificantly better outcome of CABG in patients without versus with viability and the lack of significant interaction between viability and study group assignment with respect to outcomes. A potential explanation is that patients without viability in STICH were a sicker group, as noted by significant differences in baseline characteristics and, as described in prior trials, the greatest benefit of revascularization over medical therapy on survival is in “sicker” patients.

Viability testing—conclusions. These well-conducted contemporary studies highlight the complexities of decision making in this population but have their limitations and do not provide sufficient grounds for abandoning the logical concept of viability. In this context, it is also difficult to discount the reasonable evidence from the last 2 decades and the rational pathophysiological mechanisms. Limitations notwithstanding, PARR-2 and STICH have been excellent steps in the right direction, and like many good trials, have generated new questions regarding patient selection for revascularization, including the extent of viability, the role of stress-induced ischemia, the impact of LV remodeling, the interaction of viability and scar, and the duration of myocardial dysfunction, along with procedural issues of incomplete revascularization and ischemic damage, and considerations of comorbidities.

Figure 3. Interaction Between Viability Status and Treatment Assignment With Respect to Mortality

In the STICH (Surgical Treatment for Ischemic Heart Failure) viability substudy, there was no significant interaction between viability status and treatment assignment with respect to 5-year mortality by intention-to-treat analysis. However, there was a nonsignificant trend, suggesting the benefit of CABG was greater in patients without viability. Adapted, with permission, from Bonow et al. (2). Abbreviations as in Figure 2.

Table 1. Limitations of the STICH Viability Substudy

<table>
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<tr>
<th>Limitations of overall trial</th>
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<tr>
<td>Crossover in 17% of patients assigned to medical therapy and 9% of patients assigned to CABG</td>
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<td>Randomization of a very small proportion of eligible patients</td>
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<td>Average of only 2 patients per site per year at 127 sites in 26 countries over 5 years</td>
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<td>Outcome of the large number of patients screened but not randomized not reported</td>
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<table>
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<th>Limitation</th>
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<tr>
<td>Lack of randomization in viability substudy</td>
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<td>Optional viability testing performed at clinician’s discretion</td>
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<td>Only about one-half of eligible patients from the main trial</td>
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<tr>
<td>Significant differences in baseline characteristics between those with versus those without viability testing</td>
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<td>Nonsignificant trend toward higher rates of CABG among patients with viability testing on the day of randomization or on the following day than among those who had testing before randomization</td>
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<td>Acceptable viability tests do not have highest sensitivity or negative predictive value for identifying viable myocardium</td>
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<tr>
<td>Binary classification of viability with controversial thresholds for extent and uptake</td>
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<td>Stress-induced ischemia not consistently addressed by viability testing</td>
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<td>Revascularization not guided by the presence of viable myocardium</td>
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<td>Small sample size of the group with nonviable myocardium</td>
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CABG = coronary artery bypass graft; STICH = Surgical Treatment for Ischemic Heart Failure.
I N PATIENTS WITH CAD, HF is the result of LV systolic dysfunction and accounts for about 60% to 70% of the HF cases that develop in the United States (10). The concept that chronic LV dysfunction in the setting of CAD is due to irreversibly damaged myocardium was long ago outdated by the realization that viable myocardium may be present in areas with impaired contraction and that systolic function may recover after revascularization.

Several uncontrolled studies have shown, individually and in pooled analyses, that patients with ischemic cardiomyopathy and myocardial viability show recovery of systolic function and greater survival if revascularized, compared with patients treated only with medical therapy (3,7,8). Hence, the concept has emerged that detection of viable myocardium is a prerequisite for the surgical treatment of ischemic cardiomyopathy and, by extension, that revascularization should be withheld in the absence of viability.

Importantly, most of the findings regarding myocardial viability have been based on the results of small and retrospective trials. Patients enrolled in these studies were selected for viability testing or revascularization in an unblinded fashion and, therefore, these reports suffer from selection and treatment biases. In addition, important questions can be raised regarding crucial methodological issues that affect the practical application of information regarding myocardial viability for decision making. The available studies show no consistency with regard to the definition of viability. Moreover, there is no consensus regarding whether viability is a dichotomous or a continuous variable and there is no definition of uniform qualitative or quantitative thresholds.

Prospective efforts to address the viability question. Given the limitations of published studies addressing this issue, uncertainty remains as to how to apply this information to clinical practice. To date, 3 studies have prospectively addressed the viability question.

The PARR-2 trial was the first to prospectively attempt to answer the question of whether viability assessment has a positive impact on the outcome of patients with ischemic LV dysfunction considered for revascularization (4). In this clinical strategy study, 430 patients were randomized to undergo either imaging-assisted (using PET assessment of viability) or standard management regarding the decision about revascularization. Imaging investigators analyzed the likelihood of recovery of LV function using a pre-defined algorithm based on a quantitative assessment of scar and viable myocardium. The interpretation and recommendations were sent to the treating physicians who then decided whether or not to perform revascularization. The primary endpoint was the composite of death, MI, and cardiac hospitalization within 12 months. The primary analysis failed to show a significant difference in favor of patients randomized to the PET-guided arm (p = 0.16). Unfortunately, in about 25% of patients, the imaging-based recommendations were not followed by the treating physicians. When only patients who adhered to the recommendations were considered in a post hoc analysis, there was a statistically significant benefit for the PET-guided strategy versus standard care (p = 0.019). A number of major limitations in the design and conduct of the study have been pointed out by others (11). Most notably, the PARR-2 study was based on the presumption that PET assessment of viability correctly identifies those patients who derive benefit from revascularization (imaging-based recommendation bias) and included in its design different treating physicians’ perceptions regarding the potential benefit of this intervention (clinical decision bias). Hence, neither the interaction between imaging results and treatment nor the interaction between treatment and outcome was free of preconceived notions of benefit.

The HEART (Heart Failure Revascularisation Trial) was an unblinded clinical study that aimed to randomize 800 patients with symptomatic HF, LV ejection fraction ≤35%, and evidence of substantial myocardial viability to either conservative management or coronary angiography with the intention of revascularization (12). Unfortunately, the study was stopped early due to problems with recruiting and funding. Of the 138 patients enrolled, 69 were randomized to a strategy of revascularization, but only 45 ultimately underwent a procedure. There were no differences in mortality by intention-to-treat, suggesting a lack of benefit of revascularization therapy in patients with viability. However, the trial was clearly underpowered to address this endpoint.

The STICH trial. The STICH trial is an investigator-initiated, National Heart, Lung, and Blood Institute–funded ran-
domized trial designed to test the hypothesis that, in patients with HF, LV ejection fraction ≤35%, and CAD amenable to revascularization, CABG combined with intensive medical therapy, when compared with medical therapy alone, improves long-term survival.

STICH enrolled 1,212 patients who were randomized to medical therapy alone or to medical therapy plus CABG and who were followed until at least 400 deaths occurred. Briefly, after a median follow-up of 56 months, there was no statistically significant difference between the 2 treatment arms in the primary outcome of overall mortality (p = 0.12). Patients assigned to revascularization with CABG had lower rates of cardiovascular mortality (p = 0.05) and the composite endpoint of overall mortality plus cardiovascular hospitalization (p < 0.001) (1).

A total of 601 of the 1,212 (49.6%) patients enrolled in STICH underwent assessment of myocardial viability with either SPECT or dobutamine echocardiography. These patients, who were randomly assigned to receive medical therapy alone (303 patients) or medical therapy plus CABG (298 patients), formed the basis of the STICH myocardial viability substudy (Fig. 4). Of the 601 patients, 487 were found to have substantial viability using pre-specified criteria for each imaging method based on the number of viable myocardial segments. The remaining 114 patients were considered as without viability. The number of deaths among patients with viability (178 or 37%) was significantly lower than among patients without viability (58 or 51%) (p = 0.003).

However, this association was rendered not significant in a multivariable model (p = 0.21). There was no significant interaction between viability status and treatment for the primary endpoint of overall mortality in the intention-to-treat analysis (p = 0.53) or in the treatment-received analysis (p = 0.96). Similar results were observed for the secondary endpoints of cardiovascular mortality and the composite of overall mortality plus cardiovascular hospitalization. The lack of interaction between viability status and treatment was also found in a number of pre-specified analyses that included assessment based on median viability scores (to separate the study population in 2 groups with approximately equal numbers of patients) and assessment of viability as a continuous variable. In addition, the findings were similar when patients who underwent SPECT or dobutamine echocardiography were considered separately (2). These findings contrast sharply with those of retrospective studies and meta-analyses that also divided patients into 2 treatment modalities (medical therapy or revascularization) and 2 viability subgroups (with and without myocardial viability).

The STICH substudy is the first to address this interaction in the context of a clinical trial with random treatment assignment and imaging analysis by core laboratory investigators blinded to all clinical information using pre-specified criteria for assessment of viability status. However, a number of important limitations must be consid-

![Figure 4. Flowchart of the STICH Myocardial Viability Substudy](image-url)
erred, primarily the fact that the substudy only included one-half of the patients enrolled in the STICH revascularization hypothesis trial, and that the performance of a viability test was decided by the recruiting investigators using 1 (or both) of 2 different imaging methodologies. This latter limitation could have resulted in imaging-selection bias, such that the proportion of patients with a substantial amount of myocardial viability was greater among those included in the substudy than in those who did not undergo viability testing. This may explain the low proportion (19%) of patients without viability included in the substudy. Although this could have negatively influenced the ability to detect a differential effect of CABG according to viability status, there are no firm grounds to speculate that a diametrically opposed finding could have resulted from inclusion of all STICH patients into the substudy, given the striking lack of interaction observed between viability and treatment in all the analyses performed.

Implications. None of the prospective efforts to address the viability question supports the use of viability testing as the arbitrator in the decision-making process regarding revascularization in patients with ischemic cardiomyopathy. This appears to contradict the notion that revascularization of non-viable segments lacks a reasonable mechanistic underpinning. Further, it is opposed to the postulate that improvement in systolic function with revascularization (only possible in viable segments) is associated with better prognosis. Hence, clinicians are now presented with the dilemma of reconciling plausible biological concepts already incorporated into practice with the opposing findings of recent clinical trials.

Different possibilities may help explain these discrepancies. First, limitations in study design and completion may have prevented the detection of a true interaction between viability status and the benefit of revascularization. The ideal clinical trial—one in which the results of viability testing do not influence inclusion into the study or treatment allocation—has yet to be conducted, and likely never will be given the findings of the STICH trial. However, despite its limitations, one must not overlook the fact that the STICH substudy randomized 487 patients with substantial amounts of viable myocardium to medical therapy with or without revascularization, and yet its results were far from even suggesting a preferential benefit of CABG in these patients compared with those without viability. Second, it is possible that the advances in medical and device therapy have markedly reduced the added benefit of revascularization, such that it is difficult to demonstrate further improvement in clinical outcomes. Third, the benefit of CABG may not be related to revascularization of viable segments but rather to revascularization of potentially ischemic segments. Further exploration of this hypothesis using the STICH trial database is currently underway. Similarly, the critical information may lie not in the presence but rather in the absence of viability using methods such as cardiac magnetic resonance that focus on the detection of myocardial scarring. Finally, one must consider that the greatest benefit of CABG may be limited to those patients with more advanced forms of the disease, including those with a relatively small amount of viable myocardium.

Do the results of the STICH trial suggest that testing for myocardial viability testing is fruitless and should be abandoned? Perhaps not entirely, but they certainly do not lend evidence to the widespread use of viability results as a prerequisite for CABG in patients with ischemic LV dysfunction. Patients with ischemic cardiomyopathy constitute a heterogeneous population with an extremely complex condition in which multiple factors play an important prognostic role. In this context, it would be simplistic to expect that a single feature (i.e., the presence of viable myocardium) would provide an unequivocal answer to a critical question for all patients.

Contrary to the hopes of investigators and physicians involved in the care of these patients, the findings of prospective studies have not simplified the decision-making process regarding CABG in ischemic cardiomyopathy. Instead, they are valuable in that they demystify the emphasis previously placed—without appropriate evidence—in the significance of myocardial viability. These results once again underscore the importance of testing a hypothesis in a prospective trial before adopting it as dogma. In the clinical arena, these observations remind physicians to consider the multiplicity of factors involved in the decision-making process for patients with complex medical conditions.

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REFERENCES

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