Does Imaging-Guided Selection of Patients with Ischemic Heart Failure for High Risk Revascularization Improve Identification of Those with the Highest Clinical Benefit?

Myocardial Imaging Should Not Exclude Patients With Ischemic Heart Failure From Coronary Revascularization

Eric J. Velazquez, MD

Ischemic heart failure (HF) is an emerging health crisis. Coronary artery disease (CAD) affects 16.8 million Americans. Decades of advances in the management of risk factors of acute coronary syndromes and chronic coronary atherosclerosis have increased survival and extended the treatment time horizon for affected patients, thus transforming CAD into a chronic condition. In an aging population, these advances have led to the paradox of an increasing population with attributable risk for CAD and a population projected to grow in size, with 5.7 million affected Americans in 2005 and 10 million projected by 2037. Enhanced survival from myocardial infarction accompanied by some degree of myocardial injury is now considered the basis for HF development in industrialized nations. Evaluation of temporal trends at the community level suggests that HF incidence in contrast to other cardiovascular diseases has not declined and increasingly affects older adults. The cost of HF care is already enormous and continues to grow, with hospital discharges for HF up 171% in 2006 from the previous decade, and direct costs estimates for HF in 2009 >$37 billion, with readmission rates for HF showing no signs of abatement. Therefore, ischemic HF likely represents the most dangerous intersection of common cardiac-related pathologies with substantial future societal impact in terms of patient suffering and healthcare consumption.

Response by Mielniczuk and Beanlands on p 279

Cardiovascular Imaging in Ischemic HF: Current Indications and Limitations

The angiographic presence and severity of intraluminal epicardial coronary artery lesions are associated with incremental mortality in patients with suspected CAD and HF. Among patients with CAD, left ventricular morphological, hemodynamic, and functional abnormalities are well-established and powerful independent predictors of clinical outcomes. Coupled with congestive symptoms, end-organ dysfunction, and functional impairment, the concomitant presence of CAD and left ventricular abnormalities defined by cardiovascular imaging are the sine qua non of ischemic HF. Bioengineering innovations over several decades have led to noninvasive imaging modalities (eg, echocardiography, cardiac radionuclide, PET, cardiac magnetic resonance, and cardiac CT) that complement and may obviate invasive angiography to provide detailed information on the essential elements needed to make an ischemic HF diagnosis.

Several recent comprehensive publications have reviewed the available imaging technologies currently used by clinicians in managing HF. Although current HF guidelines recommend a comprehensive echocardiogram as the single most useful diagnostic test in patients with HF, many cardiac
imaging techniques provide additional and potentially valuable diagnostic and prognostic information.13 Thereby, multimodality cardiac imaging is now routine, and most physicians caring for patients with HF gather information not only on traditional parameters, such as left ventricular systolic function, but also on chamber size and morphology, diastolic and filling parameters, valve function, myocardial tissue characterization, myocardial mechanics, ventricular synchrony, epicardial coronary artery flow, myocardial perfusion for viability and ischemia, and myocardial metabolism. Although physiologically informative, few standards exist, and precious little outcome data are available on whether and how different imaging parameters should be integrated into the care of a patient with ischemic HF and what individual or set of parameters beyond knowledge of CAD and left ventricular function are required to guide treatment decisions.

Currently, the medical management of chronic HF is predicated on the assessment of left ventricular systolic dysfunction. Randomized trials of agents tested on patients with HF and moderate to severe left ventricular systolic dysfunction have led to a standard drug cocktail that reduces morbidity and mortality.13 Unfortunately, similar agents tested in the sizeable population of patients with HF with preserved left ventricular systolic function have led to minimal, if any, effects on clinical outcomes.13 Likewise, implantable cardioverter-defibrillators and cardiac resynchronization devices are now standard options for patients with depressed left ventricular function, with limited evidence to support implantation in patients with HF with preserved function.13 Whether imaging-derived indices of myocardial mechanical asynchrony should guide implantation of cardiac resynchronization devices is an active and unresolved controversy fueled by concerns raised regarding the reproducibility and validity of the results of a large prospective observational study and the lack of randomized trials.14,15 At this juncture, HF guidelines do not identify cardiac imaging beyond a measure of left ventricular systolic function to select medical or device therapy, although myocardial perfusion imaging to define ischemia and viability is denoted as a class II (acceptable) guideline in patients who are potential candidates for revascularization.13

Revascularization in Ischemic Heart Failure: Yes, No, orMaybe?

Before the development of current guideline-based medical therapy for CAD, coronary artery bypass graft (CABG) surgery as a means of myocardial revascularization was the most effective approach for anginal relief for patients with disabling symptoms. The safety and efficacy of CABG for the treatment of chronic stable angina was established through randomized clinical trials that enrolled patients in the 1970s and a meta-analysis incorporating individual patient data from these trials and reporting that an initial strategy of CABG over medical therapy conferred an overall survival advantage of 39% at 5 years, which decreased to 32% at 7 years and 19% at 10 years.16 The CABG Trialists reported that the benefit of CABG was greater among those with more extensive CAD, such as patients with 3-vessel disease and involvement of the proximal left anterior descending coronary artery and left main coronary artery, but was limited or nonexistent among other patient subsets. Overall, these studies enrolled only a minimal number of patients with HF symptoms (>7%) and excluded patients with low left ventricular ejection fractions from randomization. Subset analyses, however, led to recommendations that patients with ischemic HF but without substantial angina were considered poor candidates for revascularization,17,18 which influenced care for decades.

Outcomes of CABG and medical therapy during the 1970s are unlikely to represent those available today. Substantial declines in risk-adjusted mortality rates for CABG have occurred because of the near-universal use of the left internal mammary artery conduit, modifications to cardiopulmonary bypass, and myocardial protection techniques along with enhanced surgical skill and cardiac anesthesia care, among other reasons.19,20 Enhanced medical therapy has also likely led to improved long-term graft patency and improvements in clinical outcomes. For example, although the CABG Trialists reported that 9.9% of patients randomized to CABG received a left internal mammary artery and 25.5% were on antiplatelet agents at 1 year, left internal mammary artery use was >94% and 97% and aspirin use >93% and 88% among patients randomized to CABG in the more-recent BARI 2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes) and SYNTAX (Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) trials, respectively.21,22 Furthermore, although the guidelines for chronic stable angina and HF now list multiple class I, level A evidence approaches and medications for chronic CAD and HF, most were unavailable or underused during the 1970s.13,23 This proliferation of contemporary medical alternatives to myocardial revascularization to treat angina led to uncertainty with regard to the incremental benefits relative to risks of procedural approaches such as CABG or percutaneous coronary intervention (PCI) to treat CAD and HF.

The commonly held belief that prompt coronary revascularization by PCI or CABG is necessary to manage chronic CAD has been challenged by the results of several important randomized clinical trials. The OAT (Occluded Artery Trial) investigators randomized 2166 patients to test the hypothesis that routine PCI of an occluded artery 3 to 28 days after myocardial infarction would improve the time to composite outcome of death, reinfarction, or HF compared with medical therapy, but found otherwise.24 Similarly, the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial investigators found that PCI did not decrease death or nonfatal myocardial infarction compared with optimal medical therapy among 2287 randomized patients.25 In COURAGE, PCI provided a significant early advantage in quality of life that disappeared at 36 months,
with no overall cost savings. More recently, BARI 2D investigators reported results on 2368 patients with diabetes and CAD randomized to medical therapy or revascularization by either PCI or CABG and showed no significant differences in death or major cardiovascular events after an average of 5.3 years. The OAT, COURAGE, and BARI 2D trial results highlight the effectiveness of contemporary CAD medical management. Not surprisingly, these trials enrolled few patients with HF or even modest left ventricular systolic dysfunction, which further underscores the limited contemporary randomized data for revascularization in ischemic HF.

The Surgical Treatment for Ischemic Heart Failure (STICH) trial was undertaken to directly address this evidence gap. In the STICH revascularization hypothesis, 1212 patients with CAD amenable to CABG and a left ventricular ejection fraction ≤35% without medically refractory disabling angina or a significant left main coronary artery stenosis were randomized to CABG with intensive medical therapy or intensive medical therapy alone. After a median follow-up of 56 months, the primary end point of all-cause mortality occurred in 41% of those randomized to medical therapy alone compared with 36% randomized to CABG, which did not reach statistical significance (hazard ratio [HR] with CABG, 0.86; 95% CI, 0.72–1.04; \( P = 0.12 \)). The overall rates of cardiovascular mortality and death or cardiovascular hospitalization were statistically lower among patients randomized to CABG. Furthermore, analyses of the primary and secondary end points based on the treatments received and after adjustment for baseline variables also favored CABG. As expected, the procedural risk among those randomized to CABG led to a higher early observed mortality risk that persisted for ≈2 years. Although the STICH trial found a more modest effect for surgical revascularization than was hypothesized, the totality of results support a favoring CABG. As expected, the procedural risk among those randomized to CABG led to a higher early observed mortality risk that persisted for ≈2 years. Although the STICH trial found a more modest effect for surgical revascularization than was hypothesized, the totality of results support the findings that can occur in uncontrolled, nonrandomized, and mostly retrospective case series in which treatments were not systematically applied and selection bias likely occurred. Two meta-analyses summarized the findings of prior studies to evaluate the association among viability results, revascularization, and short-term clinical outcomes and reported that revascularization of viable myocardium led to improved clinical outcomes compared with medical therapy; importantly, no differences in clinical outcomes were observed by treatment for nonviable patients.

The major premise underlying imaging-guided revascularization is that improved perfusion to at-risk dysfunctional, but viable myocardium will lead to functional recovery and ameliorate the ischemic HF disease process, with symptomatic and survival benefits for patients beyond medical therapy alone (which patients should receive regardless of revascularization). For this premise to be valid, viability must be a highly discriminative and an essential surrogate marker of the critical biological pathway by which revascularization solely acts to modify outcomes. Revascularization of patients with viable myocardium should lead to better clinical outcomes than medical therapy alone. Conversely, revascularization of nonviable myocardium should lead to worse clinical outcomes than medical therapy alone. Although a relatively small and retrospective study, Samady et al reported that post-CABG survival did not depend on functional recovery. Recently, several important prospective studies in patients with ischemic HF have been reported that further challenge the conventional wisdom that myocardial viability is an effective surrogate of clinical outcomes with revascularization.

The PARR-2 (PET and Recovery Following Revascularization 2) study randomized 418 patients with suspected ischemic HF who were candidates for revascularization to a PET-viability strategy or to standard of care to determine whether a PET-viability strategy led to improved clinical outcomes at 1 year. For patients randomized to PET, recommendations regarding the likelihood of functional recovery were provided to treating clinicians on nonblinded interpretation of the imaging and based on the extent of scarred versus viable myocardium. Adherence to the
imaging-guided protocol based on the rates of revascularization or work-up for revascularization was imperfect (66.0%–86.2%). After 1 year of follow-up, the composite primary end point of cardiac death, myocardial infarction, or recurrent cardiac hospitalization occurred in 30% of those randomized to PET-assisted care versus 36% randomized to standard care (HR, 0.78; 95% CI, 0.58–1.1; P=0.15). Although the study design did not mandate a specific treatment and the care received deviated from the expected PET-assisted clinical algorithm, the PARR-2 study was a pragmatic and generalizable evaluation of imaging because it was used by many clinicians and did not support the use of viability as a surrogate marker for the effect of revascularization on outcomes in ischemic HF.

The HEART (Heart Failure Revascularization) study used a positive viability test as a gateway to select patients with ischemic HF for randomization to an invasive strategy of coronary angiography and subsequent revascularization by PCI or CABG or medical therapy alone.41 In the HEART study, patients were excluded if they did not have substantial viable myocardium. Because of slow enrollment, this study randomized 138 of the planned 800 before early termination (69 to the invasive strategy and 69 to standard of care medical therapy). Forty-five patients in the invasive arm and 5 in the medical therapy arm underwent revascularization. After 59 months median follow-up, the rates of mortality were 38% for those randomized to an invasive strategy and 37% for those randomized to medical therapy. Although the HEART trial only enrolled patients with viable myocardium and was substantially underpowered, the results cast further doubt on the utility of viability testing to select patients for revascularization.

In the STICH trial, postrandomization myocardial viability testing by either dobutamine stress echocardiography, radionuclide imaging, or both was strongly recommended, with costs subsumed by the study if not done before randomization.42 Viability testing was performed according to a standardized protocol and evaluated by core laboratories blinded to randomized assignment and subsequent clinical outcomes. Among the 601 patients with interpretable viability studies, 298 were randomized to CABG, and 303 were randomized to intensive medical therapy independent of viability testing results. The presence of viable myocardium, defined a priori, selected for a lower-risk cohort: 37% of those with viability compared with 51% without viability died during the median follow-up of 5.1 years. When added to prognostic baseline clinical variables in a multivariable model of mortality, the presence of viability was not significantly associated with mortality. Furthermore, no significant interaction was found between myocardial viability measured by blinded core laboratories, treatment allocated by randomization, and any of the primary or secondary outcomes.

The STICH viability testing cohort is unique because it represents the first information available to evaluate whether myocardial viability testing predicts a treatment interaction with long-term mortality in a randomized trial where the decision regarding revascularization could not be influenced by the viability test results. These results represent the best available evidence on imaging-guided selection for revascularization. Based on the results of the STICH trial, if viability-guided selection were to be applied to 100 STICH-like patients to exclude them from subsequent CABG, 5 patients would experience a preventable cardiovascular death, and 10 patients would experience a preventable death or cardiovascular hospitalization over ≈5 years.

Because the STICH viability results were not as expected, concerns have been raised that the thresholds set by the STICH trial before analyses of the viability studies collected and the specificity of the imaging modalities used (ie, radionuclide and dobutamine stress echocardiography versus cardiac magnetic resonance or PET) confounded the evaluation of viability testing and led to a report at odds with the true biological relationship among viability testing results, treatment allocation to CABG, and clinical outcomes. To address these concerns, a series of simulations (reassignments) using the STICH viability data were performed to address whether hypothetical 10% or 25% improvements in the actual observed performance characteristics for STICH viability tests would have led to a different clinical interpretation. The STICH viability investigators observed and reported the following outcomes across 4 groups over the mean follow-up of 5.1 years: (1) 309 patients with viability survived, (2) 178 patients with viability died, (3) 56 patients without viability survived, and (4) 58 patients without viability died. If the viability test results perfectly predicted survival, groups 1 and 4 identified STICH patients in whom viability testing performed as expected, and groups 2 and 3 identified STICH patients in whom viability testing did not perform as expected. Without altering any baseline, clinical, or outcome data on the 601 patients for whom previous viability assessment analyses have been reported, a random 10% (and subsequently 25%) of the patients in group 2 were reassigned to group 4; similarly, patients in group 3 were reassigned to group 1. Manipulating the observed data to simulate a 10% and 25% reassignment of patients defined as viable and died to nonviable and, conversely, patients defined as nonviable and survived to viable led to reductions in the HR and narrower CIs all in favor of viability (observed HR, 0.64; 95% CI, 0.48–0.86; P=0.003; 10% reassignment HR, 0.48; 95% CI, 0.36–0.63; P<0.001; 25% reassignment HR, 0.29; 95% CI, 0.22–0.37; P<0.001). The effect of this simulation on the interaction of viability testing outcomes, treatment allocation, and mortality is shown in Figure 1. These data support that neither substantial modification of the viability thresholds set in STICH for the radionuclide and dobutamine stress echocardiography tests analyzed nor more specificity of the testing itself hypothesized to result from the use of perhaps more-discriminative imaging modalities would have altered the relationship observed or
the conclusions reported previously, namely, that myocardial viability testing does not identify patients with ischemic HF who should or should not undergo revascularization.

The major advantage of a randomized clinical trial over a well-conducted observational study is the minimization of treatment (not necessarily selection) bias. PARR-2, HEART, and the STICH viability subgroup analysis are not immune from selection bias, and the results must be interpreted cautiously. Nonetheless, these prospective studies are the best evidence about the interaction of treatment and myocardial imaging in the ischemic HF population. Furthermore, the populations enrolled (at least for STICH) represent patients for whom CABG is considered in the United States.43

Ischemia testing for prognosis is valuable, although its role is likely limited among patients with greater reductions in left ventricular function.44–46 Myocardial perfusion imaging for ischemia in an HF population is not well studied. STICH trial analyses on the results of ischemia testing that are currently under way are expected to be informative, although limited by cohort size. Whether ischemia testing can serve as a gateway test for revascularization in patients with relatively preserved left ventricular function has recently been proposed.47–49 Previous head-to-head comparisons between medical therapy and revascularization to reduce ischemia have been disappointing,50,51 but they may not represent what is possible when ischemia is present above a certain threshold, when HF is present, or what can be expected with current therapeutic approaches. An important clinical trial is under way that will address this important knowledge gap.52 Until then, whether and how ischemia testing should be used in decision-making regarding revascularization will remain unclear.

Deductive pathophysiological reasoning suggests that the presence of viability would select the perfect candidate for revascularization, but the findings of PARR-2, HEART, and the STICH viability subgroup analysis are at odds with this reasoning. Should we be surprised? How can we explain these results? DeMets and Califf53 provided a framework that can be adapted to better understand these results (Figure 2). If a proposed marker (ie, myocardial viability) is a true surrogate for the effect of an intervention (revascularization) on an outcome (survival) for the clinical syndrome of interest (ischemic HF), 2 criteria must be fulfilled: Changes in the surrogate marker must differentially predict the relevant clinical outcome; the surrogate marker must fully, or nearly fully, capture the biological effect of the intervention on the outcome of interest. A true surrogate marker lies directly on a causal biological pathway between the clinical syndrome and the clinical outcome and leads to a specific treatment that also lies on the causal pathway between the syndrome and...
outcome. If the surrogate and the intervention do not lie within a causal pathway or if there are multiple pathways between the clinical syndrome and the outcome, then the marker will not perform adequately as a surrogate, and its use may lead to avoidable medical errors. Unfortunately, there are now many examples in cardiology and HF of biologically attractive surrogate markers developed on the grounds of biologically plausible pathophysiology and promising obser-

Figure 2. A, Setting in which myocardial viability is an ideal surrogate for the effect of revascularization on clinical outcomes. B, Myocardial viability is not in the causal pathway between the syndrome of ischemic heart failure and survival. Revascularization has no effect on survival. C, Multiple causal pathways are active that determine survival in ischemic heart failure, and revascularization only affects the pathway mediated through myocardial viability. D, Multiple causal pathways are active that determine survival in ischemic heart failure, and revascularization affects survival through nonviability-mediated pathways. E, Myocardial viability is not in the pathway or is insensitive to the effect of revascularization on improving survival.
vational, uncontrolled studies that performed suboptimally when put to the test of a randomized trial\textsuperscript{54–57}; the use of viability testing to guide revascularization in ischemic HF must now be added to this list.

Conclusions

Despite major advances in medical therapy, revascularization procedures, and electromechanical devices, patients with ischemic HF continue to experience unacceptably high rates of morbidity and mortality. Multimodality cardiac imaging plays a critical and incontrovertible role in diagnosis and defining prognosis. To date, appropriately constructed studies are limited, but those available do not support excluding patients from the potential benefits of revascularization based solely on the results of imaging tests. The integration of information must be further refined across modalities to optimize fidelity in diagnosis and prognosis while attention is directed to the construction of randomized controlled trials in well-defined cohorts of imaging-based treatment allocation using morbidity and mortality outcomes. Noninvasive cardiac imaging represents one of medicine’s grand achievements, but it has led to an even greater challenge for the future. As the cost of cardiac imaging escalates for an increasingly aged population in need of more cardiovascular care, clinicians should demand evidence from pragmatic, real-world, comparative effectiveness studies of cardiovascular imaging to guide optimal use and limit misuse.\textsuperscript{58}

Acknowledgments

I thank Doreen Bain, Lilin She, and Hussein Al-Khaldi of the Duke Clinical Research Institute for their help in manuscript preparation and statistical review.

Sources of Funding

This article was funded by the Duke Clinical Research Institute.

Disclosures

Dr Velazquez serves as the principal investigator for the STICH Extension Study (HL105853-01).

References


15. Abraham J, Abraham TP. Is echocardiographic assessment of dysynchrony useful to select candidates for cardiac resynchronization therapy? Echocardiography is useful before cardiac resynchronization therapy if QRS duration is available. Circ Cardiovasc Imaging, 2008;1:79–84.


The premise behind trial designs evaluating a therapeutic intervention is the observation that a treatment is causally linked to outcomes. However, when evaluating diagnostic tools, demonstrating benefit depends on (1) accuracy, (2) interpretation, (3) management decision, and (4) treatment efficacy. Improving performance characteristics of a test alone, as in Dr Velazquez’s example, may not alter test-outcome relationships if it does not address these points. The primary outcomes of STICH (Surgical Treatment for Ischemic Heart Failure) and COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) were that revascularization does not provide benefit over medical therapy. So how do we identify patients who may benefit? The COURAGE Nuclear Substudy indicates that ischemia reduction is key to improved outcome. This is also the primary mechanism for revascularization benefit. Hachamovitch et al45 and PARR-2 (PET and Recovery Following Revascularization 2) demonstrated that increasing ischemia or hibernation (eg, mismatch) increases the likelihood of revascularization benefit. Mechanisms other than viability alone contribute to the response to revascularization (Figure 2D). Two of these alternate mechanisms are ischemia and hibernation (ie, subtypes of viability). These were either not—or not adequately—addressed in STICH. Lower-risk, STICH-like patients (>80% of patients with viability) should not need viability imaging but may have already had ischemia testing. For a sicker cohort (more disease, poor targets, comorbidities), the importance of ischemia and hibernation becomes even more relevant in decision-making. The totality of the evidence today supports a role for ischemia and hibernation testing in appropriate patients. The ongoing randomized controlled trial AIMI-HF (Advanced Imaging Modalities in Heart Failure) will address the role of ischemia and viability testing in heart failure and help to provide needed comparative effectiveness insights.
Myocardial Imaging Should Not Exclude Patients With Ischemic Heart Failure From Coronary Revascularization
Eric J. Velazquez

doi: 10.1161/CIRCIMAGING.111.964650

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circimaging.ahajournals.org/content/5/2/271