

EDITORIAL COMMENT

Is it Form or Function?

The “COURAGE” to Ask*

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Treatment selection for stable ischemic heart disease patients remains a work in progress. The stable ischemic heart disease guidelines published in 2012 (1) address 2 pathways to progress from medical therapy only toward revascularization: unsatisfactorily controlled symptoms or high-risk features on the basis of noninvasive testing. For patients without compelling symptoms, the risk stratification by noninvasive ischemia testing provides the gateway to move beyond medical therapy only. The ongoing ISCHEMIA (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches) trial (2) is using this measure in an attempt to identify a relatively high-risk

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group in whom revascularization may be beneficial. Much of the rationale for the trial springs from the failure of the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial (3) or the BARI 2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes) trial (4) to show a survival benefit for revascularization, and therefore a group with increased cardiovascular risk using improved revascularization technology will be tested in the ISCHEMIA trial.

A most interesting substudy of the COURAGE trial by Mancini et al. (5), which set out to explore the impact of the anatomic and ischemic burden of disease as well as any synergistic effect on clinical outcomes, is reported in this issue of *JACC: Cardiovascular Interventions*. The investigators studied 621 patients who had both baseline angiograms and single-photon emission computed tomography imaging studies. An anatomic burden score was created to reflect the degree of myocardial jeopardy produced by stenotic lesions. To determine independent predictors of death, myocardial infarction, or non-ST-segment

elevation acute coronary syndromes, a logistic survival analysis was used. The overall outcomes of the COURAGE trial are well known, so it was no surprise that the 313 patients with optimal medical therapy plus percutaneous coronary intervention did not differ from the 308 patients assigned to optimal medical therapy alone. Although the number of patients in this substudy is modest, the baseline characteristics were quite similar to the overall COURAGE trial. Whereas the treatment assignment did not predict outcomes, the impact of the quantitative anatomic burden “form” and the ischemic burden “function” were quite interesting. The degree of ischemia did not predict the clinical outcome, whereas the extent of anatomic obstruction of the coronary arteries did. Left ventricular dysfunction was, as expected, also a predictor of adverse events. So, 2 points were established. First, neither the coronary anatomy nor myocardial ischemia nor the combination of the 2 interacted with the therapeutic assignment to predict outcome. Second, which is perhaps more interesting, was that left ventricular ejection fraction and the anatomic burden of disease at baseline were predictors of the combined endpoints of death, myocardial infarction, or non-ST-segment elevation acute coronary syndromes, but the ischemic burden was not.

These findings may have implications for the ongoing ISCHEMIA trial and for the selection of revascularization for patients outside that trial. Clearly, this trial is limited by the fact that it is a post hoc substudy with a modest sample size, but the hypothesis that it generates should not be discounted. To become eligible for the ISCHEMIA trial, patients must have perfusion imaging that indicates >10% stress-induced ischemia. Randomization occurs prior to any angiographic assessment of the anatomic burden of disease. Patients assigned to medical therapy proceed without angiograms, and patients assigned to invasive measures undergo coronary angiography. One might ask, on the basis of this COURAGE substudy, why the anatomic burden of disease is a more potent predictor of outcome than the degree of ischemia. The investigators touch on this point, but perhaps some additional speculation is in order. For patients with stable ischemic heart disease, ischemia reflects the degree of obstruction to blood flow that is hemodynamically determined. This may result from high-grade stenoses or total occlusions. One can imagine that a patient with a total occlusion of an anterior descending coronary artery and collateral supply from other vessels would have a large ischemic burden, but if there is not extensive atherosclerosis in the other vessels, the potential for an acute coronary event may be limited. Conversely, a patient with an extensive anatomic burden of disease may have many plaques that are potentially vulnerable to producing an acute event. In other words, the presence of ischemia is not what produces most clinical events but rather the vulnerable plaque that leads to a sudden occlusion or embolization of a previously functioning conduit. One might ask in retort why ischemia has always

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been viewed as a risk factor for clinical events. Patients with increasing degrees of ischemia are likely to also have increasing burden of anatomic disease, but in this current observation on patients having both parameters measured, the anatomic disease trumps the measure of chronic ischemia.

What are the implications of this observation for the ISCHEMIA trial and for selection of therapy outside that trial? If the anatomic burden of disease is a potent predictor of outcomes, should the use of angiography in chronic stable ischemic disease patients be liberalized? That is not an option in the ISCHEMIA trial where the decision has been made to use ischemia as the gatekeeper for entry into the trial. I believe the findings here provide good news and bad news for the ISCHEMIA trial. First, the good news. Because the COURAGE trial consisted mostly of patients with <10% ischemia, the ISCHEMIA trial will undoubtedly include patients with a greater anatomic burden of disease and who will therefore more likely benefit from revascularization. On the other hand, the bad news. Because there is no anatomic burden of disease used in the eligibility for the trial, some patients with the greatest predictive risk of events may be excluded. Others with extensive ischemia but less compelling anatomic burden may be included. There remains, however, an opportunity to evaluate "form" versus "function" in this trial. The ISCHEMIA trial has built into its protocol a baseline computed tomographic angiogram, the results of which are blinded to the investigators. The purpose of this study is to eliminate patients with left main disease who would have not been suitable for medical therapy alone and to eliminate patients without significant stenoses. Although this computed tomographic angiogram does not play a role in the selection of patients for the trial, it will provide a post hoc opportunity to evaluate the prognostic importance of the anatomic burden of disease, and we may learn whether anatomy, once again, trumps ischemia in this higher-risk study group. For patients outside the ISCHEMIA trial, the value of the anatomic burden of disease raises important questions

concerning algorithms for investigation of patients with stable ischemic heart disease. Should angiograms be restricted to patients with higher risk scores from noninvasive evaluations of ischemia, or should some be considered for angiography? What will be the future role of computed tomographic angiography be in these patients? Although this substudy of the COURAGE trial does not answer all of these questions, it certainly raises the possibility that form may sometimes trump function in predicting cardiovascular events.

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