The debate about the role of coronary revascularization on top of optimal medical therapy for patients with obstructive coronary artery disease (CAD) and stable symptoms remains vibrant. Despite significant progress in understanding risk factors for atherosclerosis and altering those risk factors at the level of populations, the “double whammy” of the aging of the population as a whole, coupled with enormous increases in diabetes mellitus and obesity, consign us to decades of continued concern about how to treat documented obstructive CAD.

Based on the commonsense notion that “relieving” an obstruction should improve the outcomes of patients with obstructive CAD by opening the artery more freely to flow, a large industry has been built to provide revascularization with coronary bypass surgery and percutaneous coronary intervention (PCI). Countless patients have been led to believe that “fixing” the artery with a stent would prevent heart attack and death. This benefit appears to be a critical part of medical care for patients with ST-segment elevation myocardial infarction and non–ST-segment elevation acute coronary syndromes and in the setting of severe 3-vessel or left main CAD (especially with left ventricular dysfunction).1,2 However, the appropriate course of action for patients with stable symptoms and less severe CAD continues to be debated.

A series of trials, including the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial in particular, have solidified the evidence that emerged from previous smaller trials: for patients with mild or no symptoms, modest CAD, and good left ventricular function, revascularization does not significantly improve survival; furthermore, it has no impact on the risk of death or myocardial infarction (MI)! These empirical findings are so counterintuitive to the commonsense notion of “relieving coronary obstruction” that COURAGE has been subjected to major and persistent attacks on its validity and generalizability.3 The report in this issue of Circulation: Cardiovascular Quality and Outcomes by Mancini and colleagues4 adds significant clarity to some points that have been debated, while leaving other questions for future articles to address.

First, the results lay to rest the critique that the revascularization procedure itself was suboptimal in COURAGE, especially with regard to the Veterans Health Administration (VHA) system, which enrolled many of the trial’s subjects. Although VHA subjects were clearly sicker, with more severe CAD, more prior bypass surgery, and a preponderance of other risk factors, outcomes in the VHA system were comparable with non-VHA outcomes in every measurement. Furthermore, a comparison of COURAGE results with data from the National Cardiovascular Data Registry revealed no major differences in key measures of angiographic success, although a rigorous comparison is not possible because the respective databases were not assembled under directly comparable circumstances.

Second, the angiographic analysis adds interesting information about sex differences in coronary anatomy and outcomes. Women enrolled in COURAGE had less severe obstructive disease, as manifested by more single-vessel disease; however, among subjects with single-vessel disease, women were more likely to have obstruction of the proximal left anterior descending coronary artery. As expected, women had smaller-diameter arteries. Procedural success rates, however, did not differ as a function of sex, despite apparent differences prior to adjustment.

Third, the importance of the fundamental distribution of proximal coronary artery stenoses is confirmed by the analysis of jeopardy score,5 and there is a hint that complete revascularization may be a desirable goal. Figure 1 in the article by Mancini and colleagues shows a direct relationship between severity of CAD, by either jeopardy score or number of diseased vessels, and the likelihood of dying or having an MI. Unfortunately, the plots demonstrate that revascularization did not add significant benefit as a function of the very significant increase in risk. Even after excluding periprocedural MI, patients with a jeopardy score $>3$ or 3-vessel CAD had a $>20\%$ chance of death or MI in a follow-up period of only 4.7 years. These findings should serve as a warning that we have not yet reached a point of adequate technological development regarding therapies for CAD, especially given the report that these patients were receiving effective doses of proven medical therapies for secondary prevention.

COURAGE has accumulated a treasure trove of information about angiographic findings and outcomes in patients with CAD and symptoms of chronic stable angina. The trial was completed in May 2007, yet this is the first major publication to come from a deep and rich angiographic substudy. The investigators should be encouraged to complete more detailed analyses expeditiously to address some instructive issues for the clinical and clinical research community.
First, what is the interobserver variability of visual reporting of coronary artery stenosis among clinicians versus quantitative or core laboratory measurement? Assuming that a rational decision has been made about whether to obtain a coronary angiogram, the decision about revascularization depends on the interpretation of the angiogram. Previous reports indicate significant variability concerning the presence, severity, and characteristics of coronary lesions. If such variability is again documented, even with the markedly improved resolution of current technology, it could provide a sufficient rationale for rethinking our current approach to individualization of therapy. Especially with “same-sitting” PCI as the standard, decisions regarding most PCI procedures are based on the judgment of a single angiographer, without oversight at the point of care and with little opportunity for retrospective review. This practice pattern continues despite the advent of digital angiography (enabling rapid sharing of images across broad geographic distances) and standards that now make it entirely feasible to have every angiogram reviewed by more than one person, with the clinical history and examination also accessible.

What are the contributions of clinical, laboratory, angiographic, and health services delivery characteristics to patient outcomes? Rather than using more valuable journal space to defend the trial against critics, the investigators are urged to provide insight into the key outcomes of interest to patients and their doctors. Given the richness of the data and the relatively high event rates, using the outcomes of death; death or MI; and death, MI, or repeat revascularization as the end points, how much do detailed angiographic factors add to clinically apparent knowledge? For the clinical factors, how much of the observed outcome differences in subgroups is explained by angiographic differences, as in the case of women? On the surface, women had worse outcomes, but it appears that this was mostly explained by smaller-diameter arteries. COURAGE gives us a chance to learn about other key subgroups in a similar manner.

The COURAGE investigators went against the tide to create a valuable dataset. The main lesson from the trial is secure; it is now time to seek greater insight into the determinants of outcomes in this population, which has been so meticulously characterized.

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References


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Angiographic Profiles in Courage
Robert M. Califf

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