EDITORIAL COMMENT

Should Ischemia Guide Revascularization?*

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Although both coronary artery bypass graft surgery (CABG) and percutaneous coronary intervention (PCI) are well established and frequently performed, decisions concerning revascularization in stable ischemic heart disease (SIHD) remain difficult. Both forms of therapy should reduce ischemia, decreasing angina (1–4). In some patients reduction in ischemia might prevent future cardiovascular events. Nonetheless, the main diagnostic test that evaluates the choice of whether to revascularize, the choice between CABG and PCI, and the extent of revascularization remains coronary arteriography, which evaluates the anatomic distribution and severity of coronary artery disease, not ischemia per se. Thus, 3 questions concerning ischemia in relation to revascularization are raised. Should ischemia guide the decision of whether to revascularize patients with SIHD? Should ischemia guide the decision between CABG and PCI? Should ischemia guide which vessels to revascularize?

The paper by Kim et al. (5) in this issue of the Journal directly addresses the third question, although the inherent decisions guiding therapy of the patients studied concerns all 3 questions. This is an observational study of 5,340 patients, of whom 2,587 underwent PCI and 2,753 underwent CABG. Myocardial perfusion imaging (MPI) was performed in 42.3%, leading to 12.4% of PCI and 21.8% of CABG patients undergoing ischemia-guided revascularization. The non-ischemia-guided revascularization might be divided into: 1) those who had MPI ischemia but whose revascularization did not match the areas of ischemia; 2) those who had MPI but did not have ischemia; and 3) those who did not have MPI. Because this was an observational study, statistical methods were appropriately used to reduce confounding. At 5 years, ischemia-guided therapy was associated with reduced incidence of the composite of death, myocardial infarction (MI), stroke, and repeat revascularization in the PCI group but not the CABG group. This association was entirely due to reduced repeat revascularization in ischemia-guided patients.

Can this study be used to try to establish whether ischemia-guided PCI but not CABG causes a reduction in repeat revascularization compared with non-ischemia-guided PCI? Furthermore, can this study be used to establish that ischemia-guided revascularization does not reduce death, MI, or stroke compared with non-ischemia-guided revascularization? The answers to both questions are uncertain. Because this is an observational study, and because all statistical methods can only correct for observed variables, there might remain unmeasured or inadequately measured variables that could confound this set of observations.

The implications of the nature of the mismatch are also not clear. There might be revascularization of patients in whom ischemic areas were not revascularized as well as no-ischemic areas that were revascularized. The latter would include the small number of patients with normal MPIs that underwent revascularization. There might also be patients in the group without MPI in whom revascularization was to areas that were ischemic, just not demonstrated by testing. The cleanest comparison might be those with MPI ischemia, with and without mismatched revascularization. This yielded a hazard ratio for ischemia-guided of 0.75 (p = 0.13) for revascularization and, interestingly, a hazard ratio of 0.75 (p = 0.046) for death, MI, or stroke. However, the decision to not revascularize ischemic areas might represent sound decision making, considering the angiographically defined anatomy. Similarly the decision to revascularize apparently non-ischemic areas might be due to overly enthusiastic revascularization but also concern, given the angiographic anatomy, that the MPI represented a false negative.

The MPI scans were not interpreted for reversibility, meaning that ischemia could not be differentiated from scar. This is potentially critical, because revascularization of areas with transmural scar is unlikely to offer clinical benefit. Thus, such areas in this study—although labeled ischemic—would appropriately not have been revascularized, biasing the analysis to the null.

This study is part of a large although certainly not definitive published data. A critical study concerning how to guide revascularization was the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) trial (6). In the FAME trial, 1,005 patients with multivessel coronary artery disease were randomized to undergo PCI with and without fractional flow reserve (FFR). The number of stents placed was 1.9 ± 1.3 and 2.7 ± 1.2 in the FFR and non-FFR arms, respectively (p < 0.001). At 1 year, the relative risk of death or MI was 0.66 (95% confidence interval: 0.44 to 0.98) in the FFR compared with non-FFR arm. Because all patients underwent revascularization, this benefit would seem to be related to avoiding unnecessary

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revascularization of non ischemic areas. As a randomized trial, the FAME trial is free of treatment selection bias and would seem to be more supportive than an observational study of an ischemia-guided approach.

Should ischemia be used to decide which patients should undergo revascularization? Observational studies have suggested that patients with ischemia benefit from revascularization (7). However, the benefits of revascularization in patients with ischemia was perhaps best shown in the ACIP (Asymptomatic Cardiac Ischemia Pilot) study (8). In the ACIP study 558 patients with SIHD and ischemia were randomized to angina-guided (n = 183), angina plus ischemia-guided (n = 183), or revascularization by PCI or CABG (n = 192). At 2 years, mortality was 6.6% in the angina-guided, 4.4% in the ischemia-guided, and 1.1% in the revascularization strategies (p < 0.02). The incidence of death or MI was 12.1% in the angina-guided, 8.8% in the ischemia-guided, and 4.7% in the revascularization strategies (p < 0.04). In the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial, however, PCI was shown to decrease ischemia and reduce angina but not decrease death or MI (9). Most patients in the COURAGE trial had demonstrable ischemia, although generally not severe. This will be further assessed in the ongoing ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) trial, which will be targeted to patients with more severe ischemia than those in the COURAGE trial. Older studies comparing CABG with medical therapy show a benefit of surgery in patients with left main disease, 3-vessel disease, abnormal left ventricular function, and extensive disease on coronary angiography (10–12). Most recently the MAAS II trial (Second Medical, Angioplasty, or Surgery Study) showed a lower incidence of MI in patients randomized to CABG compared with medical therapy or PCI (13). Trials and observational studies comparing PCI with CABG have not included evaluation of ischemia (14–17).

Because revascularization in SIHD can reduce inducible ischemia and relieve angina, selecting patients for revascularization on the basis of the presence of ischemia would seem to be appropriate. However, it is not well-established which patients benefit by relieving ischemia with revascularization leading to decreased mortality or nonfatal events. Further data concerning whether ischemia-guided revascularization decreases events will have to wait for the outcome of the ISCHEMIA trial.

**REFERENCES**


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