EDITORIALS

Refining the Art and Science of Coronary Stenting

Stephen G. Ellis, M.D.

The broad goals of treatment for patients with coronary artery disease are improvement in survival and a reduction in the risk of myocardial infarction and symptoms of coronary disease. The circumstances under which revascularization with the use of percutaneous coronary intervention (PCI) or bypass surgery is needed, and the optimal means of providing revascularization for patients with multivessel coronary disease, remain enigmatic. Much of our evidence base is badly outdated.[1,2] Fortunately, several large clinical trials are under way, and early results of some of these trials are available. For example, the 1-year results of the SYNTAX (Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) trial (ClinicalTrials.gov number, NCT00114972), which compares bypass surgery with PCI and the placement of drug-eluting stents, have recently been reported. Longer-term results and those from other trials are eagerly awaited.

What seems to be clear, however, is that except in the case of patients with acute coronary syndromes[3] and perhaps those with extensive ischemia,[4] the usual practice of revascularization with PCI does not reduce the risk of myocardial infarction or improve survival, for three reasons. First, it is now well recognized that the severity of the stenosis is only weakly associated with the risk of plaque rupture; second, PCI treats only short segments of the coronary-artery tree; and third, PCI has occasional complications. A reduction in the frequency of these hard end points can be achieved with medical therapies such as treatment with antiplatelet agents, statins, and in some contexts, beta-blockers and angiotensin-converting–enzyme inhibitors. PCI does, of course, reduce angina. The COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial (NCT00007657),[5] confirming the results of smaller studies[6] but with more contemporary therapy, underscores these facts. Even the studies that have suggested a survival benefit of bypass surgery, as compared with medical therapy, for patients with unprotected left main or triple-vessel disease and diminished left ventricular function can be criticized because the medical therapies used in these studies, which were performed decades ago, barely resemble the optimal medical therapy that is available today.[1,2]

This concept is critically important because it suggests that with contemporary PCI, optimal revascularization under most circumstances may well be the minimal treatment required to improve symptoms. Therefore, nothing further should be done, so as not to risk unnecessary complications.

On the other hand, nonrandomized surgical studies involving patients with multivessel disease have consistently shown improved survival with complete, as compared with incomplete, revascularization — findings that have led to the widespread belief that complete revascularization is necessary for optimal results.[7] This conclusion may be challenged, however, since the subgroup of patients in whom complete revascularization can be achieved is quite different from the subgroup of patients in whom it cannot. In addition, extrapolating from the results of surgical studies to PCI may not be relevant, because PCI treats shorter segments of the coronary-artery tree than does bypass surgery.

Remarkably, only one randomized trial of PCI has attempted to address the issue of whether complete revascularization is required for the best results in patients with multivessel disease,[8]

and this study was not definitive owing to its small size. The study showed no significant differences in outcomes through 4 years of follow-up between total revascularization and revascularization of only "culprit vessels."

This is the context for the FAME (Fractional Flow Reserve versus Angiography for Multivessel Evaluation) trial. The FAME investigators, who report their results in this issue of the *Journal*,[9] sought to clarify whether PCI performed on the basis of fractional flow reserve (FFR) as compared with PCI as it is commonly performed — guided by angiography — might improve the outcomes in patients with multivessel disease.

FFR assessment of the severity of coronary lesions was developed more than a decade ago by Pijls and colleagues, and it has been well validated.[10] The weak correlation between stenosis of 40 to 70% of the diameter, as determined angiographically, and flow limitation during hyperemic stress is well recognized. With FFR, maximal hyperemia is attained by dilation of the distal microvasculature through administration of intravenous or intracoronary adenosine. Once hyperemia is achieved, the percent distal pressure retained across the stenosis in question is measured with the use of a guidewire. FFR values of less than 75% have been correlated with ischemia as assessed by more traditional nuclear imaging. Values in the 75 to 80% range have been considered to be intermediate indicators of ischemia. The safety of deferring PCI in patients with relatively simple disease and an FFR of 75% or more was previously demonstrated in the DEFER study.[11]

The FAME investigators randomly assigned 1005 patients who had multivessel coronary artery disease and who had not had a myocardial infarction with ST-segment elevation in the 5 days before PCI to either FFR-based treatment, in which stents would be placed only in lesions with an FFR of less than 80%, or conventional PCI, guided by angiography alone. Since a reduction in the risk of death or myocardial infarction with any form of PCI would not be anticipated in these patients, a more selective targeting of lesions that are objectively associated with ischemia might be expected to reduce costs and decrease the rate of complications without diminishing the expected beneficial effect. Perhaps not surprisingly, major adverse cardiac events at 1 year were seen less frequently in patients who had undergone the FFR-based intervention than in those who had undergone the standard intervention (13.2% vs. 18.3%, P=0.02). Inspection of the Kaplan–Meier curves suggests that this benefit has two components: an early reduction in the rate of myocardial infarction and a later reduction in the need for revascularization.

Although this study was carefully performed, several aspects deserve clarification so that the reader can better put the results in perspective. First, how did the investigators decide which lesions to treat in the patients assigned to the standard intervention? On what basis did the investigators decide whether to treat lesions with 50 to 70% stenosis in small- and medium-size vessels? In the article devoted to a description of their study design, the authors said, "The investigator must state which lesions will be stented based on visual assessment of the angiogram."[12] The current article describes this somewhat differently: "The investigator indicated which lesions had stenosis of at least 50% of their diameter and were thought to require PCI on the basis of angiographic appearance and clinical data."[9] Interventional cardiology is not usually practiced in a vacuum. In how many patients was regional perfusion assessed by means of stress testing, which is commonly performed to determine which lesions to stent?

Second, were contemporary adjunctive pharmacologic agents used? How many patients were pretreated with thienopyridines? What antithrombin agents were used? How often and under what circumstances were glycoprotein IIb/IIIa antagonists used?

Third, what was the rate of periprocedural myocardial infarction in the group of patients who underwent the standard intervention? The rate is not explicitly stated but appears to be approximately 7.5% on the basis of the data presented (Fig. 3C in the article). Is this too high for a patient population such as the one in the FAME study? In that study, patients had what I consider a modest SYNTAX score of 14 (on the scale used in the SYNTAX study to assess the extent and severity of coronary artery disease, a study in which the average SYNTAX score was 29±11) and only a third of the patients had acute coronary syndrome. By contrast, infarction rates in the COURAGE trial, the REPLACE-2 (Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events 2) trial (NCT00395447), and the

ISAR-REACT (Intracoronary Stenting and Antithrombotic Regimen–Rapid Early Action for Coronary Treatment) trial (NCT00373451), all of which had patient populations that were similar to the FAME study population, were 3.0%, 6.6%, and 3.7%, respectively. Might the standard-intervention group in the FAME study have been unlucky?

Fourth, the centers that were chosen to participate in this study had a long-standing interest in FFR. Can the study results be generalized to other centers?

Finally, perhaps the research question addressed in the trial was itself something of a "straw man," since FFR does not have to be used on all or none of the stenoses that might be treated but rather can be used selectively.

History has shown us that not all statistically significant results from studies of this size are repeatable. It is likely, however, on the basis of results from other relevant trials noted above, that the investigators are on to something. A validation study addressing the issues raised here would be very helpful for the interventional cardiology community. In the meantime, interventional cardiologists should recognize the limitations of coronary angiography and PCI, while of course not forgetting their benefits.

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Antipsychotic Agents and Sudden Cardiac Death — How Should We Manage the Risk?

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Antipsychotic medications are commonly used across the entire age spectrum, both within and outside their labeled (and evidence-based) indications.[1,2] Three atypical antipsychotic medications, olanzapine (Zyprexa, Eli Lilly), risperidone (Risperdal, Janssen), and quetiapine (Seroquel, AstraZeneca) are among the 10 top-selling drugs worldwide, with a combined sales volume of $14.5 billion in 2007.[3]

A thorough evaluation of risks is particularly important in the case of medications that are used so frequently and in such diverse patients, many of whom (e.g., children and the elderly) are particularly vulnerable. The effect of most antipsychotic medications on the electrophysiology of the heart has long been known, and several studies have shown an association between older, conventional (typical) antipsychotic medications (e.g., haloperidol and thioridazine) and death,[4] including sudden cardiac death.[5] In this issue of the *Journal*, Ray et al.[6] have now extended our knowledge of this problem to atypical antipsy-