EDITORIALS

Coronary Revascularization in Context

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Coronary-artery bypass grafting (CABG), introduced in 1968, was the only method of coronary revascularization until 1977, when percutaneous balloon angioplasty was first performed. The complications of balloon angioplasty (acute vessel closure in 3 to 5% of patients and restenosis in almost half) prevented its use in patients with severe coronary artery disease. In the 1990s, the introduction of bare-metal stents led to reduced rates of these complications. The improved short-term and long-term procedural success with percutaneous coronary intervention (PCI) allowed for its safe and effective performance in patients with severe coronary artery disease. By the year 2000, more PCI procedures than CABG procedures were being performed in the United States. In early 2000, drug-eluting stents were approved for use in Europe and North America, after studies showed a markedly reduced incidence of restenosis with drug-eluting stents as compared with bare-metal stents. Subsequently, the use of drug-eluting stents was rapidly adopted; in 2006, a total of 253,000 CABG procedures and 1,131,000 PCI procedures were performed in the United States,[1] with drug-eluting stents used in 90% of the PCIs.[2]

Do CABG and PCI result in similar outcomes? A recent review[3] of 23 randomized, controlled comparisons of CABG and PCI (by means of balloon angioplasty or bare-metal stenting) in approximately 10,000 patients showed that CABG was superior to PCI in relieving angina and averting repeat revascularization procedures. The rates of survival at 1, 5, and 10 years were similar for the two procedures, even though CABG carried a higher risk of stroke (1.2%, vs. 0.6% with PCI). However, most of the 23 studies did not involve patients with severe coronary artery disease (i.e., left main or three-vessel coronary artery disease) and did not use the latest revascularization techniques.

In this issue of the *Journal*, Serruys et al. describe the Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) trial[4] (ClinicalTrials.gov number, NCT00114972), in which 1800 patients with left main or three-vessel coronary artery disease were randomly assigned to undergo CABG or PCI (with drug-eluting stents) to determine which was the better revascularization strategy. Previously published studies comparing the two procedures in such patients were single-center, nonrandomized trials with relatively small numbers of patients, and the results were inconsistent: some[5] showed that CABG was associated with fewer major adverse events, whereas others[6-8] showed that the outcomes with CABG and with PCI were similar.

In the SYNTAX trial, patients treated with PCI involving drug-eluting stents were more likely than those undergoing CABG to reach the primary end point of the study — death from any cause, stroke, myocardial infarction, or repeat revascularization — within 12 months after randomization (17.8% of patients vs. 12.4%). In an analysis of secondary end points, the two treatment groups had similar rates of death from any cause, stroke, or myocardial infarction (7.6% for PCI and 7.7% for CABG). Patients undergoing PCI were more likely than those undergoing CABG to require repeat revascularization (13.5% vs. 5.9%) but were less likely to have a stroke (0.6% vs. 2.2%). The investigators do not discuss whether the strokes were related to the procedure or whether the risk of having a stroke was influenced by differences between the two groups in the occurrence of atrial fibrillation, use of aspirin or other antiplatelet agents, or presence of risk factors for atherosclerosis.

The study has several notable strengths. First, it was a prospective, multicenter trial in which a large number of patients were enrolled at 85 centers in Europe and the United States. Second, it attempted to include "all comers" with left main or three-vessel coronary artery disease. In contrast to previously published comparisons of PCI and CABG, in which only about 10% of screened patients were included, the enrollment rate in the SYNTAX trial was impressively high, with 71% of screened patients enrolled in the randomized or registry cohorts. Third, the study used state-of-the-art CABG and PCI (with arterial grafts and drug-eluting stents, respectively), both with excellent results. Fourth, a "heart team" consisting of an interventional cardiologist and cardiac surgeon reviewed each subject's data (including findings on coronary angiography), after which they reached agreement on which procedure or procedures should be offered to that subject.

The study also has limitations. First and most important, the follow-up period was only 12 months; the outcomes of PCI and CABG over a longer period of follow-up in patients with severe coronary artery disease are unknown. Second, since most of the patients (78%) were men, it is unknown whether these findings are applicable to women. Third, the patients who underwent CABG were less likely to receive optimal medical therapy (i.e., statins, aspirin or other antiplatelet agents, and angiotensin-converting–enzyme [ACE] inhibitors or angiotensin II–receptor antagonists), which may have contributed to their increased risk of stroke.

How should revascularization be accomplished in a patient with left main or three-vessel coronary artery disease? All pertinent data, including that from diagnostic angiography, should be reviewed by a cardiac surgeon and interventional cardiologist to determine the likelihood of safe and effective revascularization with PCI and with CABG. To ensure this kind of thorough review, coronary revascularization should not be performed at the time of diagnostic angiography, thereby allowing the heart team sufficient time to review all the data, reach a consensus, and discuss the findings with the patient. In the SYNTAX trial, the time from diagnostic angiography to revascularization averaged 6.9 days in the PCI group and 17.4 days in the CABG group.

An occasional patient is unable or unwilling to take dual antiplatelet agents (aspirin and clopidogrel), which are necessary after placement of a drug-eluting stent. In others, complete revascularization can be accomplished much more effectively with CABG than with PCI. Approximately one third of the patients in the SYNTAX study had one of these two issues. Such patients should be encouraged to undergo CABG. Conversely, patients with serious coexisting conditions or vessels unsuitable for grafting (about 5% of patients in the SYNTAX study) are poor candidates for CABG; they should be encouraged to undergo PCI.

If safe and complete revascularization is feasible with either PCI or CABG — as was true in roughly 60% of the patients in the SYNTAX study — an assessment of coronary anatomical characteristics should be performed, and a SYNTAX score assigned.[9,10] The presence of complex coronary anatomical features (assigned a high SYNTAX score) identifies patients with an increased risk of a suboptimal outcome with PCI; they should be encouraged to undergo CABG. Conversely, patients with less complex coronary anatomical features (i.e., a low SYNTAX score) should be presented with the advantages and disadvantages of each procedure and allowed to choose between them. Irrespective of which procedure is performed, the patient should receive optimal medical therapy involving an antiplatelet agent (or agents), a statin, and an ACE inhibitor, if appropriate.

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1. Lloyd-Jones D, Adams R, Carnethon M, et al. Heart disease and stroke statistics — 2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2009;119(3):e21-e181.
2. Spaulding C. The question of drug-eluting stent safety: then and now. Am J Cardiol 2008;102:Suppl:12J-17J.
3. Bravata DM, Gienger AL, McDonald KM, et al. Systematic review: the comparative effectiveness of percutaneous coronary interventions and coronary artery bypass graft surgery. Ann Intern Med 2007;147:703-16.
4. Serruys PW, Morice M-C, Kappetein AP, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med 2009;360:961-72.
5. Hannan EL, Wu C, Walford G, et al. Drug-eluting stents vs. coronary-artery bypass grafting in multivessel coronary disease. N Engl J Med 2008;358:331-41.
6. Daemen J, Boersma E, Flather M, et al. Long-term safety and efficacy of percutaneous coronary intervention with stenting and coronary artery bypass surgery for multivessel coronary artery disease: a meta-analysis with 5-year patient-level data from the ARTS, ERACI-II, MASS-II, and SoS trials. Circulation 2008;118:1146-54.

7. Seung KB, Park D-W, Kim Y-H, et al. Stents versus coronary-artery bypass grafting for left main coronary artery disease. N Engl J Med 2008;358:1781-92.
8. Buszman PE, Kiesz SR, Bochenek A, et al. Acute and late outcomes of unprotected left main stenting in comparison with surgical revascularization. J Am Coll Cardiol 2008;51:538-45.
9. Sianos G, Morel M-A, Kappetein AP, et al. The SYNTAX score: an angiographic tool grading the complexity of coronary artery disease. EuroIntervention 2005;1:219-27.
10. Valgimigli M, Serruys PW, Tsuchida K, et al. Cyphering the complexity of coronary artery disease using the Syntax score to predict clinical outcome in patients with three-vessel lumen obstruction undergoing percutaneous coronary intervention. Am J Cardiol 2007;99:1072-81.

Eosinophils in Asthma — Closing the Loop or Opening the Door?

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Although the origin of the concept that eosinophils are critical to asthma pathobiology remains controversial, there is consensus that Paul Ehrlich first identified a bilobed nucleated cell as an "eosin"-ophil in 1879 on the basis of the cell's granular uptake of his newly discovered dye. These cells were soon found in airway tissues and "catarrh" (sputum) of patients with asthma. Over the years, eosinophils were identified as a prominent cell type in asthma, yet their role as either an "effector" or "innocent bystander" was not confirmed until the publication of articles by Nair et al.[1] and Haldar et al.[2] in this issue of the *Journal*.

In each of these studies, treatment with mepolizumab, a monoclonal antibody against interleukin-5 (a proeosinophilic cytokine), significantly reduced the number of lung and blood eosinophils in a small group of patients with severe corticosteroid-resistant asthma. Since both studies showed a significant reduction in asthma exacerbations in patients receiving mepolizumab, it would seem that the eosinophil does, in fact, play a central role in asthma and its outcomes. Or does it?

To address this question, it may be helpful to review the role of eosinophils in asthma. Soon after Ehrlich's studies, asthma was considered to be an eosinophilic disease, with a general consensus that eosinophils were the sentinel inflammatory cell. This view prevailed until two clinical studies[3,4] of a mononclonal antibody against interleukin-5 were completed about a decade ago. One of these studies used a laboratory model of human asthma on the basis of an inhaled-allergen challenge, and the other study analyzed traditional safety and efficacy measures in patients with mild-to-moderate asthma. The results of both these studies were completely negative with respect to the role of eosinophils in the asthma outcomes that were measured. The combination of these studies hit the "eosinophil as center of the asthma universe" community by storm; soon many researchers were questioning the wisdom of focusing on eosinophils as the key effector cell in asthma.

With these findings in mind, an emerging appreciation of the heterogeneity of asthma led to the description of two asthma phenotypes on the basis of the presence or absence of tissue eosinophils.[5] Patients with asthma who had eosinophilia had greater airway remodeling and more exacerbations, whereas those without eosinophilia had more airway obstruction. Subsequently, numerous studies supported the concept that although many patients with asthma do not have any eosinophilic inflammation, the presence of such inflammation identifies a more exacerbation-prone phenotype.[6-9]

The identification of this "eosinophilic" phenotype led to two clinical trials[8,10] in which investigators modified the amount of corticosteroid (which has antieosinophilic effects) that the patients were receiving on the basis of the number of eosinophils in the sputum. The investigators, who were from the same groups as the authors of the two studies in this issue of the *Journal*, reported that the use of eosinophil numbers in sputum to determine the corticosteroid dose lowered the rate of asthma exacerbations. Furthermore, in the absence of eosinophils, a safe reduction in the corticosteroid dose was possible without triggering exacerbations. However, since corticosteroids have many effects on inflammatory processes beyond that on eosinophils, the causative role of eo-