**EDITORIAL COMMENT**

**Coronary Revascularization for Patients With Diabetes**

**Updated Data Favor Coronary Artery Bypass Grafting***

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Diabetes mellitus, by virtue of myriad processes, including its effects reducing vascular nitric oxide and prostacyclin production and increasing endothelin, angiotensin II, tissue factor activity, and platelet activity (1,2), wreaks havoc on coronary and other arteries, leading to diffuse and often unstable coronary atherosclerosis. It is also a risk factor for poor outcomes after both percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) (3).

Numerous randomized controlled trials have compared outcomes after PCI and CABG in patients with diabetes. Many observational studies on the same topic have also been published, but they are difficult to interpret because of inherent biases (patients were referred to one or another treatment for a reason, and outcomes were better when physicians chose revascularization strategies than when patients were randomized in the Bypass Angioplasty Revascularization Investigation trial) (4). In 2009, Hlatky et al. (5) summarized the results of randomized controlled trials in a meta-analysis of 10 randomized trials from the balloon angioplasty and bare-metal stent era. In 1,233 patients with diabetes, 8-year mortality rates were significantly lower with CABG, 22% versus 34%, and there was a significant statistical interaction in the entire 7,812-patient analysis for diabetes and form of revascularization (p = 0.014) (5).

Since then, drug-eluting stents and newer forms of antiplatelet therapy have been introduced, and surgical techniques have been refined. In addition, long-term follow-up of 2 major relevant comparative trials, SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) and CARDIA (Coronary Artery Revascularization in Diabetes) (6,7), has been completed. The findings of a further trial, VA CARDS (Veterans Affairs Coronary Artery Revascularization in Diabetes Study), are reported in this issue of the *Journal* (8), and the results of the larger FREEDOM (Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease) trial were just presented at the 2012 meeting of the American Heart Association.

SYNTAX was designed as a noninferiority study with major adverse cardiac or cerebrovascular events as the primary study endpoint, enrolling patients with 3-vessel or left main coronary artery disease. PCI patients received the paclitaxel-eluting Taxus stent (Boston Scientific Corporation, Natick, Massachusetts). In the entire study after 4 years, both overall and cardiac death were lower in the CABG than the PCI group (8.8% vs. 11.7%, p = 0.048, and 4.3% vs. 7.6%, p = 0.004, respectively). Differences were driven primarily by results from patients with SYNTAX scores > 22.

Patients with diabetes (n = 452) were a predefined subset of interest. Some of the findings are not as well recognized as they ought to be, as they are available only in supplemental online material. At 3 years, major adverse cardiac or cerebrovascular events occurred in 37.0% and 22.9% of the PCI and CABG patients with diabetes, respectively (p = 0.002). The composite of death, stroke, or myocardial infarction (MI), considered by some more relevant because it excludes the less impactful target vessel revascularization, occurred in 16.3% and 14.0% of the PCI and CABG patients, respectively (p = 0.53). Death occurred in 13.6% and 8.7% of the PCI and CABG patients, respectively (p = 0.11). From the vantage point of PCI, patients with diabetes requiring insulin fared particularly poorly, with cardiac death occurring in 12.6% compared with 4.5% with CABG (p = 0.06) and the composite of death, stroke, and MI occurring in 22.7% compared with 13.6% with CABG (p = 0.11). Differences for patients requiring only oral hypoglycemic agents were much more modest, 11.5% versus 8.4% and 12.2% versus 14.2%, respectively. One year, but not 3-year, results by SYNTAX score have also been reported (9). In that analysis, rates of major adverse cardiac and cerebrovascular events were higher with PCI than CABG for scores > 22, but this was driven primarily by differences in rates of target vessel revascularization, and there was no apparent relationship between SYNTAX scores and the outcomes of PCI versus CABG for the end point of stroke or MI. There was, however, a significant apparent difference in mortality rates for patients with SYNTAX scores > 32, favoring CABG, 4.1% versus 13.5% (p = 0.04). Given the large number of subset comparisons in SYNTAX, one must be cautious, however, not to overinterpret the meaning of a low p value, as the opportunity for spurious findings is high.

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Heretofore, the only diabetes-specific trial of PCI versus CABG in the current era was the CARDIA trial, enrolling 510 patients with proximal complex left anterior descending coronary artery or multivessel disease between 2002 and 2007. One-year results have been published (7), and the 5-year data were recently presented at the European Society of Cardiology (Kevin J. Beatt, MD, slides and personal communication, 2012). Seventy-one percent of PCI-treated patients received sirolimus-eluting stents, and 29% received bare-metal stents. This was designed as a noninferiority trial with the primary outcome of the composite of death, MI, and stroke. Criteria for PCI noninferiority were not met. Long-term rates for the PCI and CABG cohorts for the primary end point were 26.6% and 20.5%, respectively (p = 0.11). Rates for death were 14.0% and 12.6%, respectively (p = 0.53). Significant differences were seen for the end points of nonfatal MI (14.0% vs. 6.3%, p = 0.007) and repeat revascularization (21.9% vs. 8.3%, p < 0.001) for the PCI and CABG groups, respectively. Only 1-year outcomes for the insulin-dependent and non-insulin-dependent subgroups have been reported, and there are no data available by SYNTAX score as of yet. At 1 year, the primary outcome in the insulin-dependent cohorts tended to be worse for PCI compared with CABG (17.4% vs. 10.3%), but the interaction p value did not approach statistical significance.

The results of the 1,900-patient FREEDOM trial have yet to be fully digested but seem to show a clear benefit from CABG in patients with diabetes with predominantly 3-vessel disease, regardless of SYNTAX score. It is important to assess the consistency of results across trials and venues. The findings of the VA CARDS study, comparing PCI and CABG results in patients with diabetes, with either single-vessel proximal left anterior descending coronary artery or multivessel left anterior descending coronary artery disease, published herein (8) are consistent with the results of these other trials but raise a number of questions. First, in an incomplete and underpowered study in which death was not the primary end point and in which there was a nearly statistically significant imbalance in initial left ventricular function favoring CABG, how should one interpret the “statistically significant” difference in mortality at 2 years in this study favoring CABG, 5.0% versus 21.0% (p = 0.02)? Acknowledging the small number of events, one must recognize that this apparent difference may be due to the play of chance. It would have been useful if the investigators had provided the causes of death for these patients. That said, and considering at last count from these 4 relatively contemporary trials that there were 159 deaths in the CAGB groups and 244 deaths in the PCI groups, one cannot ignore these findings.

Second, how should one interpret the higher rate of nonfatal MI in the CABG group, particularly considering the novel definition used in the study? Most trials in this field define periprocedural PCI infarction as creatine kinase-MB elevation ≥ 3 times the upper limit of normal and require enzyme elevation or Q waves on electrocardiography to define late MI. In this study, periprocedural MI required creatine kinase-MB elevation ≥ 5 times the upper limit of normal, and the finding of a fixed ≥ 20% myocardial perfusion defect detected during annual nuclear studies was also considered an MI. Thus, in this study, some events that might be considered periprocedural PCI MIs were missed. The appropriate definition of periprocedural PCI infarction is highly debated at present, however. Late fixed perfusion defects predominated in the CABG group. The meaning of this finding, which may have been due to severe bypass graft narrowing or MI, is not clear. Use of more traditional definitions in this study would have led to the conclusion that CABG was superior to PCI.

Third, why, particularly when the Veterans Affairs (VA) system has contributed many important randomized trials in the field of coronary artery disease, dating from the original VA Cooperative Bypass Surgery trial and extending more recently to studies such as the Veterans Affairs Non-Q-Wave Infarction Strategies In-Hospital and Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation trials, could the VA system not complete such an important study? Many have recognized the increasing difficulty of performing randomized controlled trials in United States, often due to stifling regulations and cost, but one would have thought that perhaps the VA system would be less subject to these issues. The report provides inadequate information to answer this question, but VA leadership should carefully consider why this important study could not be completed.

Fourth, and possibly related to the third question, how can one explain the diminutive percent of angiographically eligible patients screened in this study? Only 9% of patients with diabetes undergoing clinically indicated catheterization were angiographically eligible in the study. Using the Cleveland Clinic database (2010 to present) as a comparator and using a more stringent definition (excluding stenoses < 70%), we would have estimated that 31% of patients with diabetes would have been eligible.

Amalgamating these data, a logical conclusion appears to be that because CABG excludes longer segments of coronary arteries than PCI treats, hence potentially exposing patients with diabetes to lesser risk for clinically important plaque progression, it produces superior outcomes. Perhaps someday, more powerful lipid-lowering agents (e.g., PCSK9 inhibitors) may minimize this risk to the extent that only severe lesions rather than severely atherosclerotic segments will need to be revascularized in patients with diabetes with angina. Until then, it seems, on the basis of the current body of evidence, that CABG should be preferred over PCI in patients with diabetes and multivessel disease with complex anatomy exemplified by SYNTAX scores > 22, and perhaps even all patients with diabetes with multivessel disease. That said, we still need further data regarding the important interaction between lesion number and complexity and clinical outcomes with the 2 approaches.
Furthermore, patients will continue to have unique risk patterns and values. The best recommendations will contextualize an individual's needs relative to the body of data generally favoring surgery.

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REFERENCES


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