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EDITORIAL COMMENT

CABG for Complex CAD: When Will Evidence-Based Practice Align With Evidence-Based Medicine?*

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Myocardial revascularization is an important treatment modality for patients with coronary artery disease (CAD), especially for patients who have complex angiographic disease that is not fully ameliorated by optimal medical therapy (OMT) and lifestyle intervention. When faced with such treatment decisions, clinicians inevitably have to weigh the relative risks, benefits, and treatment preferences of the patient when it is mutually agreed that revascularization is the most prudent and appropriate clinical course. Clinical practice guidelines from multiple professional societies inform practitioners that the dual goals of myocardial revascularization are to, first and foremost, reduce the incidence of death or myocardial infarction (MI), if such prognostically important clinical event reduction can be realistically achieved, and second, to reduce angina and ischemia while improving the functional status of the patient with CAD (1–3). However, in patients with stable CAD and chronic angina, the role of myocardial revascularization in improving survival and reducing MI is much less clear.

Several recent randomized controlled trials have addressed the comparative benefits of percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG) surgery in patients with chronic angina and stable CAD (4–7). In the aggregate, the preponderance of scientific evidence supports the benefit of CABG surgery compared with PCI, particularly for the important subsets of patients with multivessel CAD and/or concomitant diabetes mellitus, in whom there has been a consistently observed rate of cardiac event reduction with CABG surgery. Yet, despite these data, when confronted with the choice of "which revascularization option is most appropriate?" many cardiologists and internists continue to recommend PCI for their patients, even among those with extensive, multivessel CAD. Although obviously many factors play into such clinical decisions, including patient preference, as cited previously, and the fact that PCI is inherently less invasive than CABG surgery, it is nonetheless important for clinicians to be apprised of the totality of outcomes data that are relevant to evidence-based clinical decision-making when both the physician and patient are faced with therapeutic revascularization choices. This raises 2 important questions. 1) Are there reliable outcomes data that physicians can access to better inform their patients with regard to the potentially important differences that may exist in terms of overall survival and MI-related death between PCI and CABG surgery? 2) As a corollary, if such scientific evidence were to show a convincing survival benefit in favor of CABG surgery versus PCI, is it possible (or likely) that such clinically relevant prognostic information might alter both physician thinking and perceived patient preference, if it is discussed openly and transparently in the overall context of detailing the respective benefits of the 2 revascularization treatment options in high-risk CAD patients?

In this issue of the *Journal*, Milojevic et al. (8) provide important detailed information on the

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causes of death associated with PCI versus CABG surgery during a 5-year follow-up of the prospective, randomized SYNTAX (TAXUS Drug-Eluting Stent Versus Coronary Artery Bypass Surgery for the Treatment of Narrowed Arteries) trial in which 1,800 patients with extensive angiographic CAD (left main [LM] and 3-vessel disease) underwent revascularization that was undertaken through the "Heart Team" approach for consensus decision-making. The international SYNTAX trial was conducted by well-respected clinical researchers and subject matter experts who employed an "all-comers" design, including only CAD patients who were eligible for both revascularization approaches (6). The publication of the main study findings in 2009 have significantly affected clinical practice in patients with complex CAD.

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Although the overall SYNTAX trial showed a lower incidence of major adverse cardiac and cerebrovascular events (MACCEs) in CABG-treated patients compared with PCI over time, the differences between groups for the pre-specified secondary endpoint of death, MI, or stroke were essentially not different between the groups (6). However, by 5 years, these results showed a more significant separation between the CABG- and PCI-treated patients for cardiac death, MI, repeat revascularization, and MACCEs, which were all significantly in favor of CABG (9). Of note, a detailed breakdown of the exact causes of death in SYNTAX did not exist, nor for that matter, has there been such a detailed comparison in previous randomized trials in which deaths were adjudicated by an independent clinical event committee when comparing long-term outcomes between CABG and PCI.

In the current study, Milojevic et al. (8) undertook a detailed review of the subclassified causes of death, including cardiovascular (cardiac and vascular), noncardiovascular, or undetermined causes. The overall randomized study population (n = 1,800) underwent this careful adjudicated review of deaths, as did the 2 nested registries in which patients qualified for only 1 of the 2 randomized treatments (PCI registry, n = 198; CABG registry, n = 1,077). Thus, the current analysis comprised an extensive, detailed, blinded analysis of the causes of death in 3,075 SYNTAX patients. There were substantial, and in many instances, significant differences in cause of death outcomes between CABG- and PCI-treated patients, especially for cardiovascular and cardiac deaths, which were significantly higher in patients randomized to PCI compared with CABG (9.6% vs. 5.8%; p = 0.008, and 9.0% vs. 5.0%; p = 0.003), respectively. In addition, there was an overall 23% increase in all-cause mortality among PCI-treated patients (n = 123) versus the CABG-treated patients (n = 97), although this numerical excess was not significant (hazard ratio: 1.23; 95% confidence interval: 0.94 to 1.60). Nevertheless, across all categories, the death endpoints were concordant and in favor of reduced mortality in the CABG-treated patients.

Although almost one-half of all deaths after CABG (49.4%) were cardiovascular in origin, and largely were a consequence of heart failure, arrhythmia, or other causes, more than two-thirds of the deaths after PCI (68%) were also cardiovascular in origin, but these deaths were driven by fatal MI. The rates of MI-related deaths were striking; there was a 10-fold higher rate in PCI-treated patients (4.1%) compared with CABG-treated patients (0.4%). Although these differences were not as apparent in the respective PCI and CABG registry cohorts, it is important to recognize that the nested registries were directionally concordant with the randomized trial findings because it related to the causes of death, whereas the overall small sample sizes (only 57 of 198 patients in the PCI registry and 79 of 1,077 patients in the CABG registry) make it difficult to interpret the significance of these findings. In the aggregate, the cause of death analysis from SYNTAX shows a rather remarkably consistent long-term prognostic benefit of CABG surgery for both cardiovascular and all-cause mortality versus PCI in patients with extensive CAD during the 5-year follow-up.

In addition to these important prognostic findings, there are additional notable observations from this study. Significant independent predictors of both increased all-cause and cardiac mortality included medically treated patients with diabetes, those with peripheral arterial disease, patients with previous MI, patients with low ejection fractions, and those with incomplete revascularization, whereas patients treated with OMT (aspirin, inhibitors of the renin-angiotensin system, beta-blockers, and particularly statins) had significantly lower rates of death among patients who underwent revascularization. These findings formed the basis for a recent paper from the SYNTAX group that secondary prevention medications elicited a proportionately greater impact on mortality reduction than did PCI or CABG in patients with complex CAD (10). This is certainly plausible because most late MIs and cardiac events may actually emanate from new plaque ruptures in nonflow-limiting (or initially noninstrumented) coronary arteries. Clearly, these data argue persuasively for more broad-based adoption of guideline-directed OMT as the principal treatment strategy

accompanying myocardial revascularization to reduce subsequent cardiovascular events.

Lastly, the investigators highlight what should be the most important clinical takeaway of this important analysis for practicing cardiologists—namely, that treatment with PCI instead of CABG was an independent predictor of increased cardiac death (hazard ratio: 1.56; 95% confidence interval: 1.09 to 2.44; p = 0.045), and this was especially notable among subsets of patients with extensive 3-vessel CAD and/or a SYNTAX score ≥33, as well as in diabetic patients. Among this latter group, similar findings have been observed in both the BARI-2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes) (5) and FREEDOM (Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease) trials (7), and in meta-analyses that diabetic patients have improved survival when revascularization with CABG is performed (11–13). As such, the scientific evidence to date convincingly supports the clinical benefits of CABG surgery versus PCI for cardiovascular event reduction, including a very strong trend for reducing all-cause mortality. Nevertheless, if the most important and direct goal in managing patients with complex CAD is reducing cardiac death or MI-related death, CABG surgery appears to be the preferred revascularization approach to achieve these objectives.

In summary, the compelling results of this unique SYNTAX cause of death analysis provides clear and unambiguous direction of the superiority of CABG surgery over PCI in the higher risk subsets of patients with extensive CAD who might be expected to derive proportionately greater clinical benefit with surgical revascularization and particularly with respect to prevention of MI. Both physician and patient preferences will necessarily determine the final decision in these clinical settings. However, as a profession, it is important to ensure that these important scientific findings are framed appropriately in evidence-based discussions with patients. Whether such enlightened dialogue will appropriately shift the current treatment paradigm from PCI to CABG remains unclear.

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