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EDITORIAL COMMENT

Revascularization Decisions in Coronary Artery Disease

Hitting a Moving Target*

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The subspecialty of percutaneous coronary intervention (PCI) can be considered in 3 eras of technological evolution, from balloon angioplasty (BA) to bare-metal stents (BMS) to drug-eluting stents (DES), with patient outcomes improving with each advance. At the same time, surgical outcomes have been refined, with pan-arterial revascularization, lesser invasive approaches minimizing aortic manipulation, and pharmacological optimization. Given this rapid evolution in devices, drugs, and technique, can evidence-based medicine be used to guide revascularization decisions in patients with complex coronary artery disease *today*?

Numerous randomized trials have been performed comparing PCI to coronary artery bypass grafting (CABG) over the last 30 years to inform clinical practice. Early studies (with BA only, in which internal mammary artery grafts were not required, and pharmacology [even aspirin!] was not standardized) have little relevance to current practice. Greater weight must be afforded to contemporary trials. The main outcome measures must be ranked in terms of their relative importance: death > stroke > myocardial infarction (MI), followed by repeat revascularization, quality of life, and cost. Results may vary in patients with multivessel disease (MVD) and left main disease (LMD), and according to left ventricular ejection fraction and diabetes; as such, thoughtful analysis of all these data is no small undertaking.

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Patients with MVD. Hlatky et al. (1) performed a patient-level pooled meta-analysis of 10 randomized PCI versus CABG trials (n = 7,812) in the BA era. PCI and CABG had nonsignificantly different 5-year rates of death and death/MI, with consistency in most subgroups (including depressed left ventricular ejection fraction, 3-vessel disease, and proximal left anterior descending coronary artery [LAD] involvement), except for elderly and diabetic patients, in whom survival was greater with CABG. In the next era, Daemon et al. (2) performed a patient-level pooled meta-analysis from 4 randomized trials (n = 3,051) of BMS only versus CABG. The 5-year rates of mortality and composite death/MI/stroke were nearly identical, including in patients with diabetes and advanced age.

A meta-analysis of 4 studies (n = 3,895) of first-generation DES versus CABG also found similar 1-year rates of death and composite death/MI/stroke (3). Five-year follow-up from the SYNTAX trial, however, showed increasing benefits with CABG over time, principally in patients with intermediate and high-risk SYNTAX scores (reflecting greater anatomic complexity for PCI) (4). Improved event-free survival (and reduced mortality) was also noted in the FREEDOM (Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease) trial among diabetic patients (most of whom had 3-vessel disease) randomized to first-generation DES versus CABG (5). Analysis from the SYNTAX (SYNergy Between PCI With TAXUS and Cardiac Surgery) trial, however, suggests that the presence of diabetes per se does not affect long-term survival after PCI versus CABG, independent of anatomic disease complexity and other clinical variables (6).

Patients with unprotected LMD. Results of BA and BMS in LMD were disappointing, but have substantially improved with DES. A meta-analysis of 4 randomized trials (n = 1,611) demonstrated similar 1-year rates of death and composite death/MI/stroke with first-generation DES and CABG (7). In the SYNTAX trial, 5-year outcomes were at least as favorable with paclitaxel-eluting stents (PES) in patients with low and intermediate SYNTAX scores, but clearly superior with CABG in high SYNTAX score patients (4). Clinical variables may also affect the relative outcomes after PCI and CABG in complex coronary artery disease (6).

The present study. Ali and colleagues (8) present an updated random-effects meta-analysis of randomized trials with first-generation DES versus CABG in patients with 1-vessel proximal LAD disease (2 trials, n = 319), MVD (4 trials, 4,210 patients, 77% diabetic, most with 3-vessel disease), and LMD (3 trials, n = 801). During follow-up ranging from 6 to 60 months, CABG-treated MVD patients had lower rates of mortality, MI, and repeat revascularization, but higher rates of stroke. CABG-treated LMD patients had similar rates of mortality and MI, less frequent revascularization, but higher rates of stroke. PCI and CABG outcomes were similar in patients with 1-vessel proximal LAD disease, but limited power resulted in wide confidence intervals of the point estimates. Limitations of this meta-analysis include lack of patient-level data, precluding

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time-to-event and subgroup analyses. The possibility of publication bias favoring CABG was also evident. Most importantly, as noted by the authors, only first-generation DES were utilized in these studies.

Impact of contemporary DES and pharmacotherapy. Compared with first-generation DES, contemporary devices with thinner struts and more biocompatible polymers have substantially enhanced safety and efficacy (9). Notably, fluoropolymer-coated everolimus-eluting stents have reduced stent thrombosis rates by as much as 72% compared with first-generation DES (10). Because stent thrombosis occurred in 10.6% (!) of PES-treated patients in the SYNTAX trial, being solely responsible for major adverse cardiac events in 5.1% of patients (11), substitution of PES with everolimus-eluting stents may narrow or eliminate treatment gaps with CABG. New antithrombin agents (bivalirudin) and antiplatelet agents (ticagrelor and prasugrel) have further reduced MI, stent thrombosis, and death in PCI patients (12,13), and statins may prevent periprocedural infarction and contrast nephropathy (14,15). CABG outcomes have also continued to improve, however (16), mandating contemporary trials of state-of-the-art approaches to guide truly informed treatment decisions.

Reflections on component endpoints. Caution must be applied when examining low-frequency component endpoints from underpowered trials. Nevertheless, repeat revascularization procedures have consistently been required less frequently after CABG than PCI, although the differences have narrowed with the transition from BA to BMS to DES. It is doubtful, however, that further DES improvements will completely eliminate this advantage of CABG in the most complex patients. Conversely, stroke rates have consistently been higher with CABG than PCI (17), and quality of life is superior for several months after PCI (18); it is unlikely that CABG advances will eliminate these advantages of PCI. Valid assessment of MI rates between PCI and CABG is hindered by ascertainment bias and variations in definitions (including what constitutes a clinically relevant MI [19]). Most importantly, large-scale contemporary trials are required to determine whether there are differences in survival between the 2 approaches, and if so, in which patient subgroups.

Conclusions. As a practical matter, ongoing advances in technology, medications, technique, and experience are not reflected in societal guidelines and appropriate use criteria until well after publication of large-scale trials—and progress keeps marching on. It is an uncomfortable fact that some studies are nearly outdated by the time of their completion, and thus may be less than definitive. Current studies comparing first-generation DES to CABG fall into this category. Ongoing trials with contemporary DES versus CABG (NCT01205776, NCT01496651, NCT00997828) may narrow this evidence gap. Pending these data, the informed clinician must consider the clinical and anatomic factors in each individual that may affect PCI versus CABG outcomes (one size does not fit all!), present the pros and cons of each therapy (acknowledging equipoise where it exists), and allow patient preference to play an important role in clinical decision making (20). Within this framework, however, patients do benefit from physician expertise and judgment, and general principles based on current evidence and experience may be considered to guide treatment recommendations (Table 1).

Table 1. Considerations for Selecting PCI Versus CABG in Patients With Complex Stable Ischemic Heart Disease

	Factors Favoring PCI	Factors Favoring CABG
Anatomic complexity for PCI (e.g., chronic total occlusions, heavy calcification, difficult bifurcations)	Absent	Present
Anatomic complexity for CABG (e.g., poor distal runoff)	Present	Absent
SYNTAX score	Low to mid	Mid to high
CABG risks (e.g., altered mental status, chronic lung disease, porcelain aorta, prior mediastinal radiation)	Present	Absent
Likely complete ischemic revascularization with PCI	Yes	No
Diabetes, left ventricular function, age, sex, renal insufficiency (independent of anatomic disease complexity and extent)	More data needed	
High compliance likely with dual antiplatelet agents and follow-up	Good	Poor
Patient preference	More rapid recovery, lower stroke rate	Single procedure, greater durability
Operator expertise	Expert interventionalists	Expert surgeons

CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention.

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