Pitfalls Assessing the Role of Drug-Eluting Stents in Multivessel Coronary Disease

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The role of percutaneous coronary intervention (PCI) in the treatment of multivessel coronary artery disease remains intensely debated and highly editorialized. Although an increasing number of patients with multivessel disease have been treated with PCI, controversy remains regarding the evidence to support such a strategy. With the innovation of drug-eluting stents (DES), a vast expansion in the proportion of patients with multivessel disease undergoing PCI occurred with a subsequent decline in coronary artery bypass surgery procedures. Recent concerns over the safety and clinical efficacy of DES have prompted significant re-evaluation of revascularization strategies.

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The scientific rationale for coronary artery bypass grafting (CABG) in patients with multivessel disease regarding medical therapy is based on several important randomized clinical trials summarized in a meta-analysis article by Yusuf and colleagues [1] in 1994. More recently, the Bypass Angioplasty Randomized Investigation (BARI) trial demonstrated a survival benefit among diabetics with multiple-vessel disease treated with bypass surgery in comparison with balloon angioplasty [2]. From these studies, we have derived the majority of indications for contemporary CABG—double or triple vessel disease including high grade proximal left anterior descending coronary artery stenosis, triple vessel disease in diabetic patients, triple vessel disease in the setting of left ventricular dysfunction, left main disease and intractable angina after failure of other therapies.

The scientific rationale for increasing the use of PCI with DES in patients with multivessel coronary disease has been extrapolated from clinical trials including the BARI trial assessing balloon angioplasty and the Arterial Revascularization Therapies Study (ARTS) assessing bare metal stents [2, 3]. The key finding in both of these studies was that PCI accomplished less complete revascularization but did not diminish early to mid-term survival [4, 5]. These findings, coupled with the diminishment of in-stent re-stenosis achieved with DES, have encouraged the current practice of ischemia-directed revascularization in patients with multivessel coronary disease. A third major clinical trial, the Surgery or Stent trial on bare metal stents trial, showed a 1-year and 5-year survival benefit for CABG versus PCI, although this result has largely been overlooked [6, 7].

As elaborated by Taggart [8] in the 2006 Thomas B. Ferguson lecture to The Society of Thoracic Surgeons, these trials systematically enrolled patients with limited disease burden who had little plausible survival benefit from surgery versus medical therapy. In these trials, more than 90% of screened patients were excluded from randomization, frequently due to anatomic complexity of the coronary lesions deeming ineligibility for entry into the PCI arm [8]. In addition, many patients randomized in these studies did not have left anterior descending coronary artery disease. In other words, these investigations only represented a small portion of the spectrum of multivessel disease, but their results were used to justify PCI in much more anatomically complex patients without corroborating evidence. Evidence from total population-based studies such as the New York State registry indicate that when all patients are considered, CABG provides superior survival in the setting of all patients with left anterior descending coronary artery disease and at least one other diseased vessel [9]. Importantly, this survival benefit is evident in a 2-year to 3-year time span.

In this issue of The Annals, Yang and colleagues [10] present one of the few studies comparing contemporary coronary bypass to PCI in the DES era. As the study was not randomized, there were clear differences in the anatomic complexity and medical comorbidities between the patients. Patients who underwent CABG were more likely to have unstable angina, poorer ejection fraction, more left anterior descending coronary artery and triple-vessel disease, and a higher incidence of diabetes, which is generally associated with more diffuse and distal coronary disease. Patients who underwent CABG achieved more complete revascularization, and remarkably more than 95% of patients received multiple arterial grafting. The almost exclusive use of multiple arterial grafting in the surgical group and DES in the PCI group enable evaluation of state-of-the-art techniques with both modalities. The authors found that PCI patients had increased repeat revascularization and more importantly, increased myocardial infarction within the first year after revascularization compared with CABG patients, although the sample sizes were small. As seen in the ARTS and BARI trials, the diabetic patients particularly benefited from surgical revascularization.
The results of this study provide further evidence that “ischemia-directed” or “functional” revascularization, more appropriately termed “incomplete revascularization,” is an inferior strategy in patients with true multiple vessel coronary disease. In the current discussion of surgery versus stents, one critical question has largely been ignored: Does re-stenosis cause recurrent cardiac events in PCI patients? This question was investigated in the BARI trial in which two-thirds of mid-term increases in myocardial jeopardy after PCI occurred in nonangioplasted arteries [11]. Future adverse cardiac events were also more common in the incompletely revascularized BARI patients [12]. In the ARTS trial, 1-year mortality was twofold higher among PCI patients with incomplete revascularization versus PCI patients with complete revascularization, although this was not significant due to a lack of statistical power [13]. Population-based PCI data from the New York State registry have convincingly shown that incomplete revascularization was highly associated with early and late cardiac mortality [14]. Few comparative studies between CABG and PCI, including the current study by Yang and colleagues [10], adequately account for location and complexity of lesions, size of target vessels, and quality of distal outflow, all strong determinants of late clinical outcome. Randomized trials can eliminate this confounding effect, but as mentioned previously, these have hedged the issue by randomizing select anatomic subgroups and have often excluded more complex cases. Patients with blockages in small coronary arteries (<2.75 mm) were excluded from the ARTS trial. The authors of the ARTS trial stated that their study also avoided patients with lesions nonamenable to PCI, such as chronic total occlusions in an attempt to show complete revascularization in all randomized patients [13]. As a result, the anatomic disease complexity of the ARTS patients was actually lower than even the BARI trial patients, which was performed 5 years earlier in the pre-stent era [13]. Although currently enrolling trials of DES versus CABG including SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) and FREEDOM (Future Revascularization Evaluation in Patients With Diabetes Mellitus—Optimal Management of Multivessel Disease) have encouraged inclusion of a wider variety of lesions sets into the randomization, data from the SYNTAX run-in phase suggests that significant variation in anatomic complexity between PCI and CABG patients still exists [15]. Indeed the registries of the nonrandomized patients screened for these trials may provide as much robust data regarding revascularization outcomes as the randomized analysis.

There is also a growing concern about stent thrombosis (ST) in these more complex lesion sets. Early ST was reported to occur in 1% to 1.5% of patients enrolled in the early DES trials in which patients typically received only a single stent and had less complex lesions [16, 17]. In the ARTS trial, ST occurred in 1.1% of stented lesions, but 2.8% of patients at 1 year with single antiplatelet therapy [3]. The potential additive effects of ST in multivessel stenting procedures is yet to be determined. Increased rates of ST with DES versus BMS have recently been reported with more complex lesion types (including long lesions and calcified lesions) and in diabetics [18, 19]. It is not possible to clarify the relative roles of stent thrombosis, re-stenosis, disease progression, and incomplete revascularization from the current analysis by Yang and colleagues [10], but a combination of these factors lead to their finding of increased myocardial infarction after PCI with DES in this small group of patients.

Although larger observational studies and clinical trials will continue to attempt to clarify the role of PCI, CABG and medical therapy in multivessel coronary disease, careful, stratified recruitment of specific anatomic subsets, and pre-specified subgroup comparisons will be required to provide definitive guidance. In the meantime, cardiovascular practitioners must distill, out of the data currently available, an optimal revascularization strategy individualized for each patient.

References

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