As physicians, there are few decisions that we are asked to make that are more important than how to best manage patients with critical disease of the left main coronary artery. For such patients, effective revascularization is essential to prolong life and preserve health. Soon after its introduction, coronary artery bypass graft surgery (CABG) became established as standard of care for left main disease (LMD). Over the last 3 decades, this gold standard has been challenged by the steady advance of the percutaneous coronary intervention (PCI) technique and technology, with recent clinical studies suggesting that this lesser invasive approach may offer real benefits to a selected cohort of LMD patients. Pending the results from ongoing randomized trials, what proportion of patients with LMD are currently appropriately managed with PCI, and how should they be selected? Assessing the current evidence base to answer these questions requires understanding of both the surgical and interventional perspective. The present editorial presents both viewpoints to inform the referring physician and heart team treating today’s patient with LMD.

**THE CASE FOR SURGICAL REVASCULARIZATION OF LMD**

Ever since the randomized trials comparing CABG with medical therapy were performed more than 4 decades ago, CABG has been the standard of care for LMD. Although only 150 patients with LMD were randomized, the 3-year mortality in patients undergoing CABG was less than one-third (9% vs. 31%) that of medically treated patients, and there was a 2-fold increase (13.3 vs. 6.6 years) in median survival (1-4). Observational studies found similar benefits of CABG in patients with LMD (5).

In this issue of the Journal, the 5-year results from the PRECOMBAT (Premier of Randomized Comparison of Bypass Surgery Versus Angioplasty Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease) trial (6) suggest that PCI may be as effective as CABG for the treatment of selected patients with LMD. Similarly, the SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) trial also found that patients with LMD treated with PCI survived as well as those treated with CABG (nonsignificantly different 5-year rates of major adverse cardiovascular and cerebral events [MACCE]) (7). However, comparable outcomes were confined to those with low or intermediate coronary artery disease (CAD) complexity (SYNTAX scores ≤32). Patients with complex CAD (SYNTAX scores ≥33) performed better (lower mortality and MACCE rates) with CABG. Others have reported similar findings (8). It should thus not be surprising that the mean SYNTAX score of the patients in the PRECOMBAT trial was only 24.4 in the PCI group and 25.8 in the CABG group.

Although these observations suggest that some patients with LMD may have acceptable outcomes with PCI, the majority of patients with LMD have complex CAD that is best treated with surgery. In a registry study of patients with LMD undergoing CABG (predating PCI as therapy for LMD), the majority of patients had concomitant triple-vessel disease (9). Only 4% had isolated LMD, 13% had LMD and single-vessel disease, and 27% had LMD with double-vessel
disease. Low and intermediate SYNTAX scores occur in patients with isolated LMD and LMD associated with single-vessel and sometimes double-vessel disease. High SYNTAX scores in patients with LMD are found in advanced double-vessel disease and in most cases of triple-vessel disease (8). In the SYNTAX surgical registry, the extent of CAD was too complex for PCI (mean SYNTAX score 37.8) (10). Combining together the surgical registry with the randomized LMD with complex CAD cohorts, nearly 60% of patients enrolled in the SYNTAX trial with LMD were best treated surgically.

In addition, patients with triple-vessel CAD (without LMD) in the SYNTAX trial had better outcomes with CABG than PCI (7), with lower 5-year rates of mortality, myocardial infarction (MI), and repeat revascularization. The finding that patients with 3-vessel CAD have better outcomes with CABG was recently confirmed in the BEST (Randomized Comparison of Coronary Artery Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients With Multivessel Coronary Artery Disease) trial, which used contemporary everolimus-eluting stents in the PCI group (11). Because the majority of patients with LMD also have 3-vessel CAD, most patients with LMD will have superior outcomes with CABG.

Why is CABG a better option for most patients with LMD? By achieving more complete revascularization than PCI, CABG is more effective at relieving ischemia; by bypassing longer segments of atherosclerosis, it may also pre-emptively exclude vulnerable plaques, thereby avoiding future clinical events. Incomplete revascularization after PCI compared with CABG is especially common in patients with complex CAD (12). In the large-scale ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial, only 40% of patients with acute coronary syndromes treated with PCI had a residual SYNTAX score (RSS) of zero (complete revascularization), and the majority of those had low baseline CAD complexity (SYNTAX scores <22) (13). Only 12% of patients with baseline SYNTAX scores ≥22 had a zero RSS after PCI. Higher RSS was associated with greater composite rates of death, MI, or need for repeat reintervention. The direct relationship between the extent of ischemia and adverse outcomes has been well documented (14).

The American College of Cardiology Foundation/Society for Cardiovascular Angiography and Interventions/Society of Thoracic Surgeons/American Association for Thoracic Surgery/American Heart Association/American Society of Nuclear Cardiology/Heart Failure Society of America/Society of Cardiovascular Computed Tomography 2012 Appropriate Use Criteria for Coronary Revascularization Focused Update rated CABG for LMD as appropriate and PCI for LMD as uncertain or inappropriate, depending on CAD complexity (15). They are correct; more evidence is needed before recommending PCI for the treatment of LMD.

THE (EVOLVING) CASE FOR INTERVENTIONAL REVASCULARIZATION OF LMD

Although CABG is the historical gold standard for treatment of LMD, the outcomes of PCI have been steadily improving and now rival or may have surpassed CABG in several scenarios. Even with the first-generation paclitaxel-eluting stents used in the PCI arm of the SYNTAX trial, the 5-year outcomes of PCI were equivalent (or even superior, with lower mortality) in the approximate two-thirds of randomized patients with LMD with low and intermediate CAD complexity (SYNTAX scores ≤32) (16). These results have now been replicated in the present report from the PRECOMBAT trial, in which the 5-year composite rate of major adverse cardiac events (death, MI, or stroke) were not significantly different between first-generation sirolimus-eluting stents and CABG in LMD (6). Clinical characteristics may also differentiate patients likely to benefit from PCI rather than CABG, even in those with extensive CAD (17). And PCI results in lower rates of total and disabling stroke than CABG, an important consideration in patients with LMD in whom the perioperative stroke risk is increased (18). After mortality, stroke is the most feared complication of major surgery. This fact, coupled with the lesser invasive nature of PCI with improved early quality of life and faster return to normal activities than with CABG (19), makes PCI an attractive alternative to major surgery for most patients as long as the long-term outcomes are not prohibitively worse. Such patient-centered decision-making must be strongly considered when discussing revascularization options.

Importantly, the results of PCI in LMD are steadily improving over time. Several nonrandomized studies have suggested that current-generation everolimus-eluting stents result in improved outcomes in LMD compared with first-generation drug-eluting stents (DES) (20,21). At the Asan Medical Center in Seoul, Korea, the transition to contemporary DES, coupled with improvements in interventional technique, imaging, physiological lesion assessment, and pharmacotherapy, has resulted in steady improvements in PCI outcomes for multivessel disease over a 15-year period (despite increasingly complex patient and lesion characteristics), whereas the results of CABG
have been static (22). Consequently, the outcomes following PCI have now matched or exceeded those following CAGB at this high-volume institution, which accordingly has been associated with a greater proportion of patients referred to PCI over time. Although PCI with even the best DES is likely to result in somewhat higher rates of repeat revascularization procedures than CAGB in patients with complex CAD, this contingency represents an acceptable trade-off for many patients, given the other attributes of the lesser invasive approach.

In this regard, achieving reasonably complete revascularization is important in patients with CAD, and CAGB should be favored in patients in whom PCI is likely to result in a high RSS (e.g., >8). CAGB is thus likely to remain the preferred approach in patients with extremely advanced CAD, although this gap is narrowing, given advances with PCI techniques in chronic total occlusions and other complex anatomies. Moreover, achieving functional revascularization of all ischemic territories may be superior to complete anatomic revascularization (23), the topic of the ongoing FAME 3 (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation 3) randomized trial (NCT02100722). Success rates of PCI for complex CAD are also operator and site dependent (as is true for CAGB), a sometimes uncomfortable fact that must be acknowledged when revascularization referral decisions are made.

Ultimately, whether PCI with contemporary devices and techniques is equal or superior to CAGB for selected patients with LMD rests on the results from adequately powered randomized trials. In this regard, 2 ongoing studies, the EXCEL (Evaluation of XIENCE PRIME Everolimus-Eluting Stent System [EECSS] or XIENCE V EECSS Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization; NCT01205776) and NOBLE (Nordic-Baltic-British Left Main Revascularization; NCT01496651) trials have completed randomizing more than 3,100 patients with LMD and simple to moderately complex concomitant CAD to contemporary DES versus CAGB. The outcomes from these trials, expected in the fall of 2016, will importantly shape the perspectives expressed in this present editorial—at least until the next major advances in interventional and surgical revascularization are realized!

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