Left Main Revascularization
Reality Versus the Real World

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In the 1970s and 1980s, the mortality in medically treated patients with unprotected left main (ULM) coronary artery disease was ≈30% at 1 year and ≈50% at 5 years. That era also witnessed the completion of 2 randomized controlled trials (RCTs) of coronary artery bypass graft surgery (CABG) versus medical therapy, still the only such studies performed to date, which demonstrated (in a grand total of 150 randomized patients) that CABG reduced 5-year mortality from 36.5% to 16.0% (P=0.004), with mean survival increased by ≈1.7 years per patient. These results were subsequently confirmed in the nonrandomized Coronary Artery Surgery Study (CASS) registry in 1484 patients, as well as in other observational studies. CABG, thereafter, rightly became established as the unquestioned standard of care for treatment of ULM disease, a recommendation that persists in today’s societal guidelines from both the United States and Europe, and in the US Appropriate Use Criteria.

See Article by Park et al

ULM stenoses are located proximally in the coronary tree and are typically short in length, and have therefore, represented an attractive target for percutaneous coronary intervention (PCI) ever because the development of balloon angioplasty by Andreas Gruntzig, whose third patient had a severe ULM lesion. The procedural unpredictability of balloon angioplasty, however, coupled with frequent restenosis resulted in an unacceptably high rate of early and late mortality after ULM treatment, including Gruntzig’s patient, who died suddenly 4 months after the procedure. Bare metal stents (BMS) largely solved the acute procedural issues of recoil and dissection, and dual antiplatelet therapy reduced acute and late thrombotic complications, although restenosis rates remained excessive. Drug-eluting stents (DES) further reduced angiographic and clinical restenosis by 50% to 70% compared with BMS (depending on lesion complexity), prompting the performance of 4 trials in which 1611 patients with ULM disease were randomized to first generation DES versus CABG. At 1 year, DES resulted in similar rates of death and myocardial infarction (MI) as CABG, with lower rates of stroke (odds ratio [95% confidence interval [CI]], 0.15 [0.03–0.67]; P=0.01), but higher rates of unplanned repeat revascularization (odds ratio [95% CI], 2.25 [1.54–3.28]; P<0.001). A Bayesian meta-analysis confirmed similar 1-year mortality rates with PCI and CABG in ULM disease, with survival after both revascularization techniques being better than with medical therapy alone. However, the relative benefits of CABG may increase over time, and in this regard only 1 trial has followed patients out to 5 years, the Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX) trial, in which 705 of a total of 1800 randomized patients had ULM disease. The 5-year rates of major adverse cardiac and cerebrovascular events (death, MI, stroke, or unplanned revascularization) were not significantly different in the ULM cohort after treatment with Taxus paclitaxel-eluting stents (PES) compared with CABG (36.9% versus 31.0% respectively; hazard ratio [95% CI], 1.23 [0.95–1.59]; P=0.12), although stroke was more common with CABG and repeat revascularization was more common with PCI. Major adverse cardiac and cerebrovascular event rates at 5 years were significantly increased in PES–treated patients with anatomic Syntax scores ≥33 (46.5% versus 29.7%; P=0.003), versus being nearly identical in those with lower Syntax scores (31.3% versus 32.1%; P=0.74). It should be emphasized that because the primary end point of the overall SYNTAX trial was not met, these ULM subgroup results must be considered hypothesis generating. Moreover, 45% of screened patients with ULM disease in the SYNTAX trial were excluded from randomization because of excessively complex coronary artery disease, 89% of whom underwent CABG. The randomized SYNTAX results, therefore, apply to a carefully selected cohort. Nonetheless, on the basis of these and other nonrandomized studies, the most recent guidelines provide a class II indication for PCI in patients with ULM disease with either simple (class IIa) or moderately complex (class IIb) anatomy, with the details varying slightly between the United States and Europe. Moreover, in both the sets of guidelines, PCI remains class III for highly complex disease (eg, Syntax score ≥33), whereas CABG is class I for all anatomic classes, assuming surgical eligibility. These guidelines are mirrored in the more patient oriented Appropriate Use Criteria recommendations.

These endorsements have resulted in an increase in the number of patients with ULM disease treated with PCI, especially in Europe, although not a single adequately powered RCT of DES versus CABG in ULM coronary artery disease has been completed. Moreover, none of the completed randomized trials included contemporary DES. This latter consideration is of particular importance because meta-analyses of large-scale RCTs strongly suggest that current generation DES reduce the rates of death, MI, stent thrombosis, and revascularization compared not...
only with first generation DES but also to BMS. Few patients in these trials, however, had ULM disease, and no randomized trial has specifically compared the outcomes of first and second generation DES in this cohort. In a nonrandomized, propensity-matched comparison of 344 ULM patients treated with Xience everolimus-eluting stents (EES) versus PES, treatment with EES was associated with reduced 2-year rates of target lesion failure (7.6% versus 16.3%; P=0.01) and stent thrombosis (1.7% versus 7.0%; P=0.02). Similarly, among 186 ULM patients undergoing PCI at 2 centers between 2006 and 2010, use of second generation compared with first generation DES was associated with lower 2-year rates of MI, stent thrombosis, and target vessel revascularization. Conversely, in a multicenter retrospective registry of 770 patients undergoing PCI with ULM disease, no significant differences in propensity score adjusted 3-year outcomes were noted between EES and PES.

In this issue of Circulation: Cardiovascular Interventions, Park et al from the Asan Medical Center in Seoul, South Korea provide a retrospective nonrandomized examination of their prodigious experience with ULM coronary artery revascularization in 2618 patients during 3 historical time periods based on the type of stent used in patients undergoing PCI: only BMS (1995–1998), early DES (2003–2006), with the vast majority treated with the Cypher sirolimus-eluting stent, and late DES (2007–2010), during which most PCI patients were treated with sirolimus-eluting stent or EES. Over time, the proportion of patients receiving PCI rather than CABG increased at their center from 35% to 52%. More notably, risk adjusted survival and composite outcomes improved over time for PCI, but were stable for CABG. As such, whereas in the BMS period the results of ULM PCI were substantially inferior to CABG, in the most contemporary experience nearly identical per patient-year rates of composite major adverse cardiac and cerebrovascular events were achieved with DES and CABG. Specifically, in 2007 to 2010, DES was associated with lower mortality (hazard ratio [95% CI] for CABG versus PCI, 2.28 [1.20–4.33]) and composite death/MI/stroke (hazard ratio [95% CI], 2.09 [1.27–3.44]), although long-term revascularization rates remained superior for CABG (hazard ratio [95% CI], 0.19 [0.08–0.45]).

The improved outcomes with PCI relative to CABG observed over time in this study cannot simply be ascribed to differences in stent type. Concomitant with evolution in stent selection, numerous other procedural changes occurred in PCI strategy, including treatment of more lesions (and with more stents), treatment of a greater proportion of patients with ULM distal bifurcation involvement (but more often with the simpler 1-stent cross-over technique), more frequent use of intravascular ultrasound imaging (which has been associated with reduced stent thrombosis and improved event-free survival after ULM stenting), and improved chronic medical treatments, including dual antiplatelet therapy and statins. Moreover, the practice of CABG evolved over time as well, with greater use of off-pump surgery, more frequent grafting with the left internal mammary artery, and also improved chronic pharmacotherapy. Finally, the profile of patient comorbidities evolved as well over time, with higher risk and more complex patients being treated with both PCI and CABG, although with differences in risk profiles clearly evident.

These results are provocative, and prompt discussion as to whether PCI with contemporary DES and the adjunctive drugs, devices, and techniques used in the recent period should now be considered standard of care (class I) for many patients with ULM disease. This study also challenges the relevance of randomized trials, such as SYNTAX to today’s practice. Unfortunately, despite the careful nature of this study, the present analysis must be considered hypothesis generating only. First, these results reflect the outcomes achieved at a single center, and must be proven to be generalizable before their implications should be widely considered. More importantly, treatment strategy in nonrandomized observational real world studies is often dictated by unmeasured variables, which cannot be accounted for by even the most sophisticated multivariable propensity-adjusted analyses. For example, surgical ineligibility is rarely documented per se, but is strongly associated with increased mortality after PCI of ULM disease, even after adjusting for evident high-risk features which may have precluded CABG. Thus, adequately powered, meticulously conducted RCTs are typically required to change practice, and if inclusive enough so as to obviate generalizability concerns, more accurately represent reality (the truth). However, in addition to generating hypotheses, comparative effectiveness studies, such as the present one provide complementary use to RCTs by documenting changes in practice patterns and overall outcomes, as well as identifying low frequency safety issues.

Fortunately, 2 contemporary randomized trials of PCI versus CABG in ULM disease are well underway. In the Evaluation of Xience Prime or Xience V Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL) trial, 1905 patients at 126 centers in 17 countries with ULM disease and a Syntax score ≤32 have been randomized to Xience EES versus CABG, with a primary composite end point of death/MI/stroke measured at median follow-up of 3 years, powered for sequential noninferiority and superiority testing. In the Nordic-Baltic-British Left Main Revascularization Study (NOBLE) trial, 1200 patients at 36 European centers with ULM disease and ≤3 additional noncomplex lesions have been randomized to PCI with DES (biolimus-eluting stents recommended) versus CABG, with a primary composite end point of major adverse cardiac and cerebrovascular events (excluding index procedural MI) measured at median follow-up of ≥3 years, powered for noninferiority testing. The results of both the trials are expected in the fall of 2016, and if positive, only then might PCI achieve class I status for treatment of ULM disease. Moreover, with the EXCEL and NOBLE results in hand, it will be fascinating to revisit the Asan Medical Center-Left Main Revascularization (ASAN-MAIN) registry to reexamine the similarities and differences between reality and the real world.

Disclosures
Dr Stone is a past consultant for Boston Scientific.

References


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