Navigating Optimal Revascularization for Unprotected Left Main Disease in Changing Interventional Seas*

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Unprotected left main coronary artery (ULMCA) disease is observed in 4% of coronary angiograms and is often associated with disease in other coronary arteries. Without the foresight of an oracle, the selection of the most appropriate coronary revascularization strategy for a patient with ULMCA disease associated with complex multivessel coronary disease (MVD) can be difficult. It is guided, in part, by accurately predicting a patient's clinical outcome using risk prediction tools and determining the impact on this outcome of competing revascularization strategies: percutaneous coronary intervention (PCI) or cardiac surgery. Although surgical revascularization has traditionally been the cornerstone of therapy for ULMCA disease with MVD, there is an increasing role for PCI, especially in patients who present with increased surgical risk.

The SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) study (1) defined patients with MVD by anatomy alone: the SYNTAX score (SS). The investigators confirmed that SS tertiles of ≤22, 23 to 32, and ≥33 predicted the interventional but not surgical outcomes of revascularized patients (2) and that surgical revascularization was superior to PCI in the whole cohort, out to 5 years, except in those with the lowest SS (3). The majority of the early difference was driven by myocardial infarction and the need for repeat revascularization in the PCI group. However, in those with ULMCA disease and low to intermediate SS (<33), there was no significant difference in major adverse cardiac and cerebrovascular events (MACCEs) between surgery and PCI. Ostial and midshaft ULMCA lesions have traditionally been the realm of the interventionist, but distal ULMCA disease is more common and more difficult to treat by PCI. Importantly, SYNTAX included distal disease, and the findings hold true for PCI in any ULMCA location. However, the SYNTAX-LE MANS (Left Main Coronary Artery Stenting) study (4) demonstrated an in-stent restenosis rate of 7.6% at 15 months that was associated with MACCEs (predominantly repeat revascularization), and this occurred more frequently in distal-stented ULMCA lesions. Similar results to those of SYNTAX were seen in PRECOMBAT (Premier of Randomized Comparison of Bypass Surgery Versus Angioplasty Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease) with no reported difference in MACCEs at 2 years but increased ischemia-driven revascularization in the PCI group (5).

Complex ULMCA and MVD PCI, without intravascular ultrasound guidance and using a possibly inferior paclitaxel-eluting stent, could be further improved upon by using second-generation everolimus-eluting stents (EES) and contemporary PCI techniques, particularly when treating distal ULMCA bifurcation lesions. Two randomized controlled trials, EXCEL (Evaluation of Xience Prime versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization; NCT01205776) and Left-Main/NOBLE (Coronary Artery Bypass Grafting Vs Drug Eluting Stent Percutaneous Coronary Angioplasty in the Treatment of Unprotected Left Main Stenosis; NCT01496651), will compare revascularization strategies in a low- to intermediate-SS (<33) ULMCA disease cohort. There remain concerns

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regarding the durability of the PCI result, particularly in distal ULMCA stented lesions. Propensity-matched registry data followed to 8 years demonstrated a higher MACCE rate (repeat revascularization and myocardial infarction but not death or stroke) in ULMCA treated with PCI compared with off-pump surgery (6). At present, guidelines recommend a heart team approach (Class I, Level of Evidence: C) informed by the SS (Class Ila, Level of Evidence: B) with surgery given a Class I, Level of evidence: B indication and PCI at best given a Class Ila, Level of Evidence: B indication, although for those with complex disease who could be managed surgically, there is a Class III, Level of Evidence: B indication for PCI (7).

The SS is far from perfect, though. It is a surrogate for clinical variables and fails to capture all important clinical information that has prognostic importance. It is subjective and therefore has interobserver and intraobserver variability problems (8), particularly in the adjudication of bifurcations, and it relies too heavily on angiographic rather than physiological lesion assessment to determine the need for lesion treatment. Furthermore, it exaggerates the weighting given to chronic total occlusions (CTOs), and, particularly pertinent for ULMCA intervention, it overstates the risk attributable to the bifurcation angle.

The SS has been refined by several groups to incorporate clinical data. The Global Risk Classification combines the SS with the European System for Cardiac Operative Risk Evaluation score (ES), thereby improving the accuracy of mortality prediction from a C statistic of 0.68 to 0.73 (9). The SYNTAX score II, in which the anatomic SS has been augmented with clinical variables, is undergoing prospective validation in the SYNTAX II (NCT02015832) and EXCEL trials. In addition, recategorization of angiographically determined lesions included in the SS by fractional flow reserve (FFR)—the so-called functional SS (10)—has confirmed that the burden of functional disease is often lower than that defined anatomically with improved outcome prediction. Taken together, more accurate risk prediction tools may further open the door for ULMCA PCI.

Intervention has also moved on. Not only have stents gotten better, but the liberal use of intravascular imaging to guide ULMCA intervention achieves better short-term results, which translate into improved outcomes. Multivessel disease is being assessed by FFR to eradicate all ischemia-producing lesions and improving outcomes, and the percutaneous treatment of CTOs has been revolutionized. The application of retrograde and subintimal techniques used in a hybrid strategy has enabled CTO success in upward of 85% to 90% of patients. Together, both FFR guidance and CTO PCI have increased the complete revascularization (CR) rate, improving prognosis. This evolution perhaps makes the once contemporary SYNTAX trial data obsolete; the CR rate was only 52% in the PCI arm of the SYNTAX trial.

The paper by Migliorini et al. (11) in this issue of JACC: Cardiovascular Interventions is a retrospective registry that assesses the utility of anatomic (SS) and clinical (ES) tools to risk-stratify patients undergoing ULMCA and MVD intervention with EES. The investigators performed mandatory angiographic and 3-year clinical follow-up for comparison with the ULMCA PCI cohort in SYNTAX. It is important to consider these data in context; the study was conducted at an accomplished interventional center, with respectable CTO success rates (87%), a high CR rate (70%), and frequent use of intravascular ultrasound to guide ULMCA PCI (68%). Bifurcation lesions were treated with evidence-based techniques.

Overall 1-year mortality for the SS ≥33 PCI-treated cohort was 13.3%, rising to 18.8% at 3 years. This is higher than the mortality rate of SYNTAX PCI-randomized patients, although the ES was 4-fold higher, indicating that theirs was a higher risk cohort. The investigators conclude that ULMCA disease with a high SS (≥33) should not be a barrier to PCI with EES, as a high SS was not an independent predictor of mortality. However, ES was independently predictive of mortality. The 1-year mortality rate was 1.6% in those with ES <6 and SS ≥33 and highest in those with ES >6 and SS ≥33 at 19.5%. Those with SS <33 and ES <6 had the lowest mortality at 1 year (0.8%). The ULMCA in-stent restenosis rate was 4.9% (compared with 7.6% in SYNTAX) and was not influenced by the SS.

This study furthers our knowledge of patient selection for ULMCA PCI with complex MVD, but we are still some way off from fully understanding the optimal revascularization strategy for patients with high SS and ULMCA disease. Migliorini et al. (11) provide reassurance that at centers with experienced CTO operators, at which CR is likely, anatomy alone should not dictate the revascularization strategy. PCI with EES produces excellent outcomes in all anatomies, but in particular when the ES is low. However, the surgical results are equally good in this group and perhaps more durable. The surgeons have set the bar at a high level. A pragmatic interventionist may recommend tackling the CTO first and, if successful, continue to treat the ULMCA by PCI. If not,
refer for surgery. This approach minimizes the risk for incomplete revascularization and possibly improves the PCI outcome.

What we can at least agree on is that more trials are needed before ULMCA PCI in the setting of complex MVD becomes mainstream. If anatomic complexity is no barrier to ULMCA PCI, a randomized controlled trial confirming noninferiority of PCI in a high-SS cohort is necessary as the next step, if EXCEL demonstrates noninferiority of ULMCA PCI in low-to intermediate-SS anatomies. Contemporary PCI techniques should be compared with contemporary surgery, with mandatory use of second- or even third-generation EES, FFR, and/or intravascular ultrasound guidance, performed at experienced CTO centers to ensure a fair comparison. That being said, it will be challenging to go head to head with surgery in this patient group—intervention has, after all, been burned before.

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