In patients with significant obstructive left main coronary artery disease, initial studies showed that coronary artery bypass graft surgery (CABG) improved long-term survival compared with medical therapy.1-3 Since publication of these studies, CABG has been considered the standard of care for revascularization of left main coronary artery disease in the absence of previous bypass grafts to branches of the left coronary artery—so-called unprotected left main (ULM) revascularization. Subsequently, clinical studies have evaluated various methods for percutaneous revascularization of ULM coronary disease. The current American College of Cardiology/American Heart Association/Society for Cardiovascular Angiography and Interventions (ACC/AHA/SCAI) guidelines for percutaneous coronary intervention (PCI) and the Appropriateness Use Criteria (AUC) for coronary revascularization both provide guidance regarding left main coronary revascularization.4-6 This article provides an overview of the current recommendations and the ongoing clinical studies evaluating left main revascularization.

CLINICAL PRACTICE GUIDELINE RECOMMENDATIONS

Clinical practice guidelines present a comprehensive literature review with recommendations for practice that represent a mix of the best available data and existing expert opinion. As such, the clinical practice guidelines aim to provide recommendations for the best possible care. The current PCI guideline documents provide recommendations for several clinical presentations in patients with left main coronary artery disease.5 The guidelines state that it is a class III recommendation, meaning PCI is not recommended in patients with asymptomatic ischemia or class I, II, or III angina and left main disease who are eligible for CABG. This is based on expert opinion, a review of registry data using bare metal stents (BMS), and some of the initial registry data with drug-eluting stents (DES) in patients with left main disease. In patients with unstable angina or non-ST-segment elevation myocardial infarction (NSTEMI) who are not candidates for CABG, the guidelines assign a class IIa recommendation, meaning PCI is reasonable in such patients with ULM disease. For patients with unstable angina or NSTEMI who are candidates for CABG, PCI for ULM disease is considered a class III indication and thus, should not be performed. Both of these recommendations are based on cohort studies and subgroup analysis derived from larger studies in NSTEMI patients.

AUC FOR CORONARY REvascularization

In an effort to respond to the need for the rational use of health care services and the delivery of high-quality care, the American College of Cardiology Foundation (ACCF) adopted a process to determine the appropriateness of cardiovascular tests and procedures for selected patient indications.7,8 The ultimate objective of AUC is to improve patient care and health outcomes. The criteria are developed around clinical indications meant to identify common clinical scenarios seen in contemporary practice and provide what is considered reasonable care. Not all patients seen in clinical practice are represented in the AUC because there are often additional clinical features that make the management of an individual patient unique. Therefore, the
AUC are not intended to completely replace the judgment of the physician. In 2009, the ACCF in partnership with several other professional organizations developed AUC for coronary revascularization. These AUC are intended to provide a framework for discussions regarding revascularization between patients and physicians. An appropriate revascularization procedure was defined as:

Coronary revascularization is appropriate when the expected benefits, in terms of survival or health outcomes (symptoms, functional status, and/or quality of life) exceed the expected negative consequences of the procedure.

In total, the writing committee developed 180 clinical scenarios for coronary revascularization devised around five core characteristics of patients: (1) the stability of the symptoms (acute coronary syndrome, stable angina, etc.); (2) severity of angina (asymptomatic, Canadian Cardiovascular Society Class I, II, III, or IV); (3) extent of ischemia present on testing (high-risk findings vs non–high-risk findings) and, in certain scenarios, the presence or absence of other prognostic factors, such as depressed left ventricular function or diabetes; (4) extent of medical therapy; and (5) extent of coronary disease (1-, 2-, or 3-vessel disease, with or without proximal LAD or left main coronary disease).

An expert technical panel consisting of 17 members was asked to review the available evidence and determine if the clinical scenarios were appropriate for revascularization. To prevent bias in the rating process, the technical panel was deliberately composed of physicians with varying perspectives on coronary revascularization and was not composed solely of experts (interventional cardiologists and cardiovascular surgeons) in the procedure under evaluation. The majority of panel members represented general and noninvasive cardiology, general medicine, outcomes researchers, and payer representatives. The goal of the technical panel was to rate the specific clinical scenarios for the appropriateness of coronary revascularization in the described setting. By intent, the majority of the AUC do not address the mode of revascularization (PCI or CABG). Patients with a significant ULM stenosis (defined as ≥50% luminal diameter narrowing) were believed to be at significant risk for future cardiovascular events such that revascularization was considered appropriate for patients ranging from asymptomatic status to class III angina. To provide further guidance for patients with significant symptoms and advanced coronary artery disease, the technical panel was asked to provide ratings on the method of coronary revascularization specifically in patients with advanced coronary artery disease. Recognizing that there can be mitigating clinical circumstances that might favor one form of revascularization over another, the panel was asked to rate these clinical scenarios with the assumption that the patient was an acceptable candidate for either PCI or CABG. The panel rated CABG as appropriate for patients with isolated ULM disease or ULM disease associated with additional coronary disease (Table 1). In contrast, PCI was rated as inappropriate in the same clinical scenarios.

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<th>CABG</th>
<th>PCI</th>
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<tr>
<td>No diabetes and normal LVEF</td>
<td>Diabetes</td>
</tr>
<tr>
<td>Two-vessel CAD with proximal LAD artery stenosis</td>
<td>A</td>
</tr>
<tr>
<td>Three-vessel CAD</td>
<td>A</td>
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<tr>
<td>Isolated left main stenosis</td>
<td>A</td>
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<td>Left main stenosis and additional CAD</td>
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Abbreviations: CAD, coronary artery disease; LAD, left anterior descending; LVEF, left ventricular ejection fraction; A, appropriate; U, uncertain; I, Inappropriate.

BALLOON ANGIOPLASTY AND BARE-METAL STENTS FOR ULM DISEASE

Since the early 1980s, clinicians have attempted PCI in patients with ULM disease with the hope of providing durable clinical outcomes, thus avoiding CABG. Initial attempts using percutaneous balloon angioplasty were associated with an unacceptable incidence of abrupt closure, dissection, and restenosis. These periprocedural complications led to poor clinical outcomes with 1-year mortality rates of nearly 30%,9,10 Given these unfavorable outcomes, CABG surgery remained the preferred therapy for ULM revascularization, as reflected in several subsequent guideline documents.4,11,12

With the introduction of BMS and concomitant thienopyridine use in the 1990s, the complications of residual dissections and abrupt closure associated with PCI procedures were markedly reduced,13-15 which quickly led to the widespread use of BMS during PCI and new attempts at treating ULM disease by stenting. Initial small registries showed that the periprocedural complication rate in this setting was substantially reduced compared with balloon angioplasty.16-18 However, the rates of restenosis and repeat revascularization remained between 20% and 30%.17,19 Due to these high rates of repeat revascularization, the strategy of BMS treatment for ULM was not formally studied compared with CABG in large randomized trials.

ULM INTERVENTION: DES ERA

Since the introduction DES in 2003, several small registry reports regarding the use of DES in ULM intervention have been published.20-22 A meta-analysis of 17 of these observational cohorts in ULM disease found that there was wide variation in patient presentation and clinical syndromes, from chronic angina to acute coronary syndromes, and a wide variation in anatomic subtypes treated from ostial and midshaft to bifurcation disease.23 This analysis showed a periprocedural mortality of 5.5%, with significant variation in the need for repeat revascularization (0%–44%). Another meta-analysis of 10 observational studies of 3,773 patients found no difference in the rates of death, myocardial infarction, or stroke between PCI and CABG at 3 years.24 However, in this meta-analysis, PCI was associated with a significantly higher rate of target vessel revascularization (odd ratio 4.36, confidence interval 2.6–7.32). Recently, the first small, randomized trial (Le Mans, n = 105) reported the results of DES versus CABG in left main disease.25 The study found that the primary endpoint, which was defined as a change in left ventricular ejection fraction was greater at 1 year in the PCI group compared with the CABG group (3.3% ± 6.7% vs 0.5% ± 0.8%; P = .047). Patients performed equally well on stress tests and angina status improved similarly in the two groups. PCI was associated with a lower 30-day risk of major adverse events, major adverse cardiac and cerebrovascular events, and shorter hospitalizations. Total and event-free 1-year survival and left main target vessel failure were similar in the two groups. After more than 2 years, major cardiac and cerebrovascular event-free survival was similar in both groups, with a trend toward improved survival after PCI.

The SYNTAX (Synergy Between Percutaneous Coronary Interventions With Taxus [Boston Scientific Corporation, Natick, MA] and Cardiac Surgery) trial, with a prespecified left main subgroup (n = 705), represents the largest comparison between DES and CABG for left main revascularization.26 The SYNTAX trial found a similar rate of the combined endpoint of death, myocardial infarction, and stroke at 1 year between PCI (7%) and CABG (9.2%) (P = .29). Compared with CABG, there was a higher rate of repeat revascularization with the PCI strategy at 1 year (12% vs 6.7%; P = .002). Several subanalyses from the left main cohort are being performed. These include analysis of all patients with left main disease, and analysis of patients with isolated left main disease and/or a low SYNTAX score. It should be noted that of the 705 patients with left main disease in the SYNTAX trial, only 91 had isolated left main disease compromising just 5% of the total patients in SYNTAX. Taken in total, all of the small trials, meta-analyses and data from SYNTAX are encouraging but they should be viewed mainly as hypothesis generating. Such subgroup analyses will likely identify areas for future prospective clinical trials aimed at changing clinical practice guidelines and AUC.

The most challenging subgroup of patients with ULM disease consists of those who present with an acute coronary syndrome. This subgroup was examined in a report from the Global Registry of Acute Coronary Events (GRACE) investigators.27 Of 43,018 patients enrolled in GRACE between 2000 and 2007, 1,799 had significant ULM disease and underwent PCI alone (n = 514), CABG alone (n = 612), or no revascularization (n = 673). In-hospital mortality was 11%, 5.4% and 7.6% for those treated by PCI, CABG or no revascularization,
respectively (P < .001) At 6 months, mortality was 5.4% in the PCI group, 1.6% in the CABG group, and 10% in those not undergoing revascularization (P < .005). Although both PCI and CABG were significantly associated with improved survival compared with an initial strategy of no revascularization, CABG was associated with a five-fold increase in stroke compared with either PCI or no revascularization. Patients undergoing PCI more frequently presented with ST-segment elevation myocardial infarction, after a cardiac arrest, or in cardiogenic shock. The authors concluded that PCI is now the most common and preferred revascularization strategy in patients with acute coronary syndromes, with CABG often delayed and performed in lower-risk patients, leading to good 6-month survival. However, they also concluded that both revascularization strategies can be used in a complementary fashion.

SUMMARY OF CURRENT EVIDENCE AND PATIENT DISCUSSIONS

The available evidence for PCI with DES of ULM stenosis consists of several observational studies that have been compiled into meta-analyses. Although some of the initial results are encouraging, these studies suffer from potential selection bias and variation in the patient populations evaluated. Nevertheless, the profile of these two modes of revascularization is becoming clearer. It appears that death and myocardial infarction occur with equal frequency, but repeat revascularizations remain higher with PCI compared with CABG. Some analyses show no difference in the rate of stroke, yet other data suggest a higher rate of stroke with CABG.

For patients with ULM stenosis without mitigating circumstances, the totality of current evidence and guideline recommendations would favor CABG as preferred mode of revascularization. Patients with isolated left main lesions and/or low SYNTAX scores should understand that the current recommendations and available evidence favor revascularization by CABG but that emerging data may well change PCI with DES from inappropriate to uncertain in the AUC. However, as is frequently the case in daily practice, there are mitigating circumstances that increase the risk of CABG surgery. In these circumstances, the evolving data continue to support the option of PCI performed under careful circumstances and by experienced operators as an alternative to CABG.

CONCLUSION

Patients with ULM disease represent a population at high risk for future cardiovascular events. Current clinical practice guidelines and AUC strongly recommend coronary revascularization in these patients if technically feasible. The majority of data leading to recommendations regarding the method of revascularization still favor CABG in patients who are acceptable candidates for either procedure. More data continue to emerge regarding the use of DES for the treatment of ULM stenosis. As these data accumulate and are carefully evaluated for their quality and relevance, the clinical practice guidelines and AUC will likely require re-evaluation and updating. Ultimately, a well-designed, long-term, randomized trial of ULM stenting versus CABG will be needed to determine which mode of revascularization is most favorable and identify subgroups most likely to benefit from these two modes of revascularization.

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