Coronary artery disease (CAD) affecting the left main (LM) stem was first described in 1912 by Herrick, who reported the case of a 55-year-old man who developed cardiogenic shock and subsequently died 2 days after his initial presentation with chest pain. Autopsy revealed LM thrombus with underlying atherosclerotic stenosis. LM CAD has since been observed in approximately 3% to 4% of patients undergoing diagnostic coronary angiography and carries with it a poor prognosis, partly due to the significant area of myocardium at risk.

The rationale for revascularization in the setting of unprotected LM (ULM) CAD has been established on the basis of multiple studies demonstrating a mortality benefit with coronary artery bypass grafting (CABG) compared to medical therapy. In a comparison of long-term follow-up for patients with significant (> 50%) LM CAD from the CASS registry, the cumulative 15-year survival rate of those who initially underwent CABG surgery (1,153 patients) was 37% versus 27% in the medically treated group (331 patients).

CURRENT GUIDELINE RECOMMENDATIONS

Accordingly, CABG has traditionally been considered the standard treatment for patients with ULM CAD, and the most recent American College of Cardiology Foundation/American Heart Association guidelines for CABG surgery suggest surgical revascularization for patients with significant (≥ 50% diameter stenosis) LM CAD to improve survival as a class I recommendation (level of evidence B).

However, there is a growing body of evidence suggesting that, in appropriately selected patients, percutaneous coronary intervention (PCI) for ULM CAD may also be a reasonable strategy. The most recent guidelines for PCI propose a class Ila recommendation for PCI in ULM CAD as a reasonable alternative to CABG in selected patients, specifically those who have favorable anatomic features with low risk of PCI complications and high likelihood of procedural success and good long-term outcome (low SYNTAX score ≤ 22, ostial or trunk LM CAD), when clinical features may otherwise predict a significantly higher risk of adverse surgical outcomes (Society of Thoracic Surgeons predicted operative mortality risk ≥ 5%). A similar recommendation (class IIa) has also been made for patients presenting with acute coronary syndromes and found to have a ULM culprit lesion but are not suitable surgical candidates. Patients who have acute ST-elevation myocardial infarction with a ULM culprit lesion are also considered in this group when there is TIMI grade < 3 flow distally and PCI can be performed more rapidly and safely than CABG.

Furthermore, in patients who have ULM CAD and anatomic features associated with a low to intermediate risk of PCI complications, such as those with a SYNTAX score < 33 or bifurcation LM CAD, PCI is considered a reasonable alternative to CABG when those patients are at high surgical risk (eg, moderate-to-severe chronic obstructive pulmonary disease, disability from previous stroke, or previous cardiac surgery) and has been given a class IIa recommendation. Patients who have unfavorable anatomy for PCI and who are good candidates for CABG surgery should not undergo PCI (class III recommendation).

PCI COMPARED TO CABG FOR LM DISEASE

There are four published randomized controlled trials (RCTs) (Table 1) comparing PCI to CABG in the setting of LM CAD, as well as numerous meta-analyses comparing the aggregate data. Overall, major clinical outcomes 1 year after revascularization have been found to be similar with PCI and CABG. Mortality and myocardial infarction rates have been equivalent at 1-, 2-, and 5-year follow-up. PCI is associated with a lower risk of stroke but a higher rate of repeat revascularization.

The first RCT comparing PCI to CABG, the LE MANS study, randomly assigned 105 patients with ULM CAD to either PCI (52 patients) or CABG (53 patients). Although only 35% of patients in the PCI group received a drug-eluting stent (DES) and 72% of patients in the CABG group had a left internal mammary graft placed, PCI was associ-
ated with a significantly lower 30-day risk of major adverse cardiac and cerebrovascular events (MACCE) compared to CABG (1% vs 7%; \( P = .006 \)). After more than 2 years, MACCE-free survival was similar in both groups, with a trend toward improved survival after PCI. However, the study was limited by the relatively small number of patients randomized.

The recently published 5-year follow-up data from the SYNTAX trial demonstrated no significant difference in MACCE between PCI and CABG (36.9% vs 31%; \( P = .12 \)) in the LM CAD subgroup.\(^{19} \) However, those in the LM subgroup with higher SYNTAX scores (≥33) who underwent PCI had a significantly higher MACCE rate compared to those in the CABG group (46.5% vs 29.7%; \( P < .01 \)). These results suggest that in LM CAD, with low to intermediate SYNTAX scores (≤32), PCI is a reasonable alternative to CABG.

Boudriot et al randomly assigned 201 patients with ULM CAD to undergo sirolimus-eluting stenting (100 patients) or CABG (101 patients) and found that the combined rates for death and myocardial infarction were comparable (5% for PCI vs 7.9% for CABG; noninferiority \( P < .001 \)).\(^{13} \) However, PCI was found to be inferior to CABG at 1-year follow-up with respect to freedom from major adverse cardiac events. This was mainly driven by higher repeat revascularization rates, although death and myocardial infarction rates were noninferior in PCI patients with lower perioperative morbidity.

The PRECOMBAT trial was a prospective, open-label study and is the largest published RCT comparing DES to CABG for ULM CAD.\(^{14} \) Patients with ULM CAD were randomly assigned to PCI with sirolimus-eluting stents (300 patients) or CABG (300 patients). At 2-year follow-up, there was no statistical difference between the two groups in the primary endpoint of MACCE (12.2% for PCI vs 8.1% for CABG; \( P = .12 \)) or in all-cause mortality (2.4% for PCI vs 3.4% for CABG; \( P = .45 \)). Ischemia-driven target vessel revascularization was higher in the PCI group compared to those undergoing CABG (9% vs 4.2%; \( P = .02 \)). However, due to an initial overestimation of event rates in the CABG group, the study was underpowered, and although PCI was shown to be noninferior to CABG, there was a wide noninferiority margin that may have confounded the results. Nevertheless, the overall results are consistent with the other three RCTs.

Data from the 1,611 randomized patients in all four RCTs published thus far suggest that patients with ULM CAD have similar major clinical outcomes with PCI and CABG when they are appropriately selected and are lower risk; however, there is a higher rate of target vessel revascularization with PCI. These findings have also been supported by a number of meta-analyses. One of the largest of these examined aggregate data from 11,148 patients from the four published RCTs and 23 other observational studies.\(^{18} \) The meta-analysis again demonstrated that in appropriately selected patients with ULM CAD, PCI was associated with no excess in all-cause mortality, a lower risk of stroke, and a similar composite safety outcome (all-cause mortality, non-fatal myocardial infarction, and stroke) compared to CABG. However, PCI was associated with a higher rate of repeat revascularization.

It is possible that the routine performance of follow-up repeat angiography in the PCI group in these trials may have increased the rate of target vessel revascularization; there are data suggesting that planned follow-up angiography leads to a 1.7-times higher rate of reintervention.\(^{20} \) Clinically, surveillance coronary angiography after ULM PCI is also no longer recommended, because this strategy is not able to predict late or very late in-stent thrombosis and was therefore removed from the 2009 STEMI/PCI focused update.\(^{21} \)

### Table 1. Published RCTs Comparing PCI to CABG for ULM CAD

<table>
<thead>
<tr>
<th>RCT</th>
<th>n</th>
<th>Mean SYNTAX Score</th>
<th>DES Use</th>
<th>LIMA Use</th>
<th>Major Endpoints</th>
<th>Follow-Up (y)</th>
<th>Event Rate</th>
<th>PCI</th>
<th>CABG</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LE MANS(^{10} ) (2008)</td>
<td>105</td>
<td>25</td>
<td>35%</td>
<td>81%</td>
<td>Death, MI, TVR, CVA, ST</td>
<td>1</td>
<td>30.7%</td>
<td>24.5%</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>SYNTAX(^{12,19} ) (2010)</td>
<td>705</td>
<td>30</td>
<td>100%</td>
<td>97%</td>
<td>Death, MI, TVR, CVA</td>
<td>5</td>
<td>36.9%</td>
<td>31%</td>
<td>.12</td>
<td></td>
</tr>
<tr>
<td>Boudriot et al(^{13} ) (2011)</td>
<td>201</td>
<td>24</td>
<td>100%</td>
<td>99%</td>
<td>Death, MI, TVR</td>
<td>1</td>
<td>19%</td>
<td>13.9%</td>
<td>.19(^b)</td>
<td></td>
</tr>
<tr>
<td>PRECOMBAT(^{14} ) (2011)</td>
<td>600</td>
<td>25</td>
<td>100%</td>
<td>94%</td>
<td>Death, MI, TVR, CVA</td>
<td>1</td>
<td>8.7%</td>
<td>6.7%</td>
<td>.01(^b)</td>
<td></td>
</tr>
</tbody>
</table>


\(^{b}\)Noninferiority comparison.

Abbreviations: CVA, cerebrovascular accident; LIMA, left internal mammary artery; MI, myocardial infarction; ST, stent thrombosis; TVR, target vessel revascularization.
THE EXCEL TRIAL

The ongoing EXCEL trial (NCT01205776) is a prospective, unblinded, randomized, multicenter trial aiming to enroll 2,600 patients from 165 United States and overseas sites in a 1:1 fashion to either PCI using a Xience everolimus-eluting stent (Abbott Vascular, Santa Rosa, CA) (n = 1,300) or CABG (n = 1,300) in patients found to have significant LM CAD and a SYNTAX score of ≤ 32. The primary endpoint will be all-cause mortality, myocardial infarction, or stroke at 3 years after the index procedure. All randomized subjects will be followed for at least a 5-year period after the procedure. EXCEL will be the largest RCT comparing PCI to CABG for LM CAD and the first to use a second-generation DES with improved safety and clinical outcomes. The trial is well designed, and a propensity score–matched 3-year comparison of PCI versus CABG in patients with LM CAD and a SYNTAX score ≤ 32 in an Italian registry suggested that the EXCEL trial has the potential to change the current class of recommendation for PCI in the LM but is unlikely to show superiority over CABG.\(^{22}\)

CONTEMPORARY STRATEGIES FOR LM PCI

Case Selection

Anatomic considerations play an important role in case selection. Of the 705 patients in the SYNTAX trial with LM CAD, the distribution of disease was distal only (54%), ostial only (23%), mid-shaft only (15%), and ostial and distal disease together in 7% of cases.\(^{12}\) Furthermore, LM CAD was seen most often in combination with three-vessel disease (37%) and with two-vessel disease in 31% of cases. LM CAD was seen with single-vessel CAD in 20%, and isolated LM CAD was seen in 13% of patients. Patients with isolated LM CAD and LM CAD with single-vessel CAD had fewer target vessel revascularization events compared to those with LM CAD combined with two- or three-vessel CAD.

Accordingly, it is reasonable to consider PCI for ULM CAD in patients, especially nondiabetics, with low to intermediate SYNTAX scores (≤ 32) and, in particular, patients who have isolated LM CAD or LM with single-vessel CAD. Furthermore, ostial or mid-shaft LM lesions are technically easier compared to distal LM lesions involving the bifurcation or trifurcation, which require a higher level of operator expertise and experience. Patients at high operative risk for CABG may also be considered for percutaneous revascularization.

Careful consideration of bleeding risk and compliance with dual-antiplatelet therapy prior to LM PCI is important given the potentially catastrophic significance of stent thrombosis of the LM stem. Additionally, genotyping for a CYP2C19 loss of function variant or platelet function testing may be considered to guide the choice of P2Y\(_12\) inhibitor in this subgroup of patients, notwithstanding the lack of definitive prospective data supporting the clinical use of these assays.\(^{23}\)

Although the larger caliber of the LM stem may be perceived to offset the benefit of a DES over a bare-metal stent (BMS), there are no large RCTs comparing DES to BMS for the treatment of ULM CAD. However, in a large meta-analysis of 44 studies involving PCI for ULM CAD, statistically significant improved outcomes with DES compared to BMS were seen in terms of mortality, myocardial infarction, target vessel revascularization, and major adverse cardiac events.\(^{24}\) Therefore, appropriately sized DES should be preferred over BMS for ULM CAD.

Procedural Considerations

Hemodynamic support devices (intra-aortic balloon counterpulsation, Impella [Abiomed, Danvers, MA]) may be considered in cases of left ventricular dysfunction or advanced CAD, especially if the right coronary artery is diseased or nondominant. Intravascular imaging to assess LM size and lesion characteristics and to confirm stent apposition and expansion should be performed routinely with LM PCI.\(^ {25}\) Typically, given the proximal location of the LM, guide support is usually not an issue. Shorter guiding catheters, such as the Judkins left curve, that will not seat deeply in the LM are preferred, and a 7-F system will facilitate equipment delivery if a two-stent approach is required. Wiring both the left anterior descending and circumflex arteries is prudent prior to dilation, and using diluted contrast for the inflation balloons allows for faster deflation times.

A provisional stenting strategy of the distal LM bifurcation has been favored based on data from the Nordic Bifurcation Study, which demonstrated longer procedure times, increased contrast use, and a higher incidence of peri-procedural myocardial infarction with an intended two-stent strategy.\(^ {26}\) However, a planned two-stent strategy may be chosen in certain situations, especially if there is a high risk of compromising the left circumflex artery, if there is significant ostial disease extending > 5 mm beyond the carina, or if subsequent access may be challenging.

There are a number of techniques to choose from when considering planned two-stent bifurcation stenting—simultaneous kissing stents, Culotte, crush and its modifications, T-stenting, and T-and-protrusion. There are no data supporting any particular bifurcation strategy, and the choice of technique should be made based on anatomical and lesion characteristics. As the angle formed between the LM and left circumflex approaches 90°, a T-stent or a T-and-protrusion technique are feasible. More obtuse angles forming a Y-shaped carina may be addressed using a crush, one of its modifications, or a Culotte technique. Regardless of the choice of technique, however, final kiss-
ing-balloon inflation using noncompliant balloons should always be performed.\textsuperscript{27,28}

Finally, ad hoc PCI should never be performed, and after diagnostic angiography confirming LAD CAD, there should be an opportunity for the patient to have a discussion of risks and benefits with a multidisciplinary heart team, which should include an interventional cardiologist, a cardiothoracic surgeon, and a noninvasive cardiologist.

Exceptional circumstances in which immediate PCI for ULM CAD may be performed include a flow-limiting dissection, hemodynamic or electrical instability, or a similar emergent clinical scenario such as ST-elevation myocardial infarction, with the LM being the site of the culprit lesion. Typically in these situations, PCI can be performed more expeditiously than CABG, and the potential increased risk of target vessel revascularization is offset by the need to achieve rapid reperfusion and avoid an imminent fatal catastrophe.\textsuperscript{29}

CONCLUSION

Recent advances in interventional technologies and techniques, together with a growing body of RCT data in patients with ULM CAD, have allowed PCI to become a viable and safe alternative to CABG in appropriately selected patients with favorable anatomy and/or high surgical risk. Based on the available evidence, the current guideline recommendations are reasonable and correctly underline the importance of appropriate patient selection. The ongoing EXCEL trial will clarify the role of PCI with the current-generation DES in ULM CAD and has the potential to bring further change to the current treatment paradigm; it will add to the evidence that now allows us to have more informed discussions with patients considering their options for revascularization in the setting of LM disease.

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