



# Percutaneous Coronary Intervention Versus Coronary Artery Bypass Grafting in Treatment of Unprotected Left Main Stenosis

Yasir Taha<sup>1</sup> · Rajan A. G. Patel<sup>2</sup> · Jayant Bagai<sup>3</sup> · Rajesh Sachdeva<sup>1</sup> · Gautam Kumar<sup>4</sup> · Anand Prasad<sup>5</sup> · Sandeep Nathan<sup>6</sup> · Timir K. Paul<sup>7</sup>

Published online: 18 March 2019

© Springer Science+Business Media, LLC, part of Springer Nature 2019

## Abstract

**Purpose of Review** This article reviews the latest data on unprotected left main (ULM) percutaneous coronary intervention (PCI) versus coronary artery bypass graft (CABG) surgery, with a focus on the NOBLE and EXCEL trials.

**Recent Findings** In EXCEL trial, the primary endpoint at 3 years was 15.4% in the PCI group and 14.7% in the CABG group ( $p = 0.02$  for non-inferiority of PCI versus CABG). In NOBLE, the primary endpoint at 5 years was 28% and 18% for PCI and CABG, respectively (HR 1.51, CI 1.13–2.0, which did not meet the criteria for non-inferiority of PCI to CABG;  $p$  for superiority of CABG was 0.0044). Higher repeat revascularization and non-procedural myocardial infarction were noted in PCI group but there was no difference in all-cause or cardiac mortality between the two groups.

**Summary** A heart team approach with appropriate patient selection, careful assessment of LM lesions, and meticulous procedural technique makes PCI a valid alternative to CABG for ULM stenosis.

**Keywords** Left main · Percutaneous coronary intervention · Coronary artery bypass graft

## Introduction

The left main (LM) coronary artery supplies up to 84% of the left ventricular myocardium [1]. Therefore, high-grade unprotected (i.e., not protected by a patent bypass graft) left main (ULM) stenosis places a large myocardial territory at risk for ischemia [2]. Significant ULM stenosis, defined as > 50%

diameter stenosis, is noted in approximately 5% of patients undergoing coronary angiography for any reason, and up to 25% of those with acute coronary syndrome (ACS) [2]. Medical therapy alone is inferior to CABG in patients with significant ULM stenosis [3]. A meta-analysis of 8 trials including 4850 patients demonstrated that coronary revascularization in addition to medical therapy resulted in a 79% and

---

This article is part of the Topical Collection on *Ischemic Heart Disease*

---

✉ Timir K. Paul  
pault@etsu.edu

Yasir Taha  
ytaha@msm.edu

Rajan A. G. Patel  
rajpatel@gmail.com

Jayant Bagai  
jayant.bagai@vanderbilt.edu

Rajesh Sachdeva  
rsachdeva@msm.edu

Gautam Kumar  
gautam.kumar@emory.edu

Anand Prasad  
PrasadA@uthscsa.edu

Sandeep Nathan  
snathan@medicine.bsd.uchicago.edu

<sup>1</sup> Morehouse School of Medicine, Atlanta, GA, USA

<sup>2</sup> Ochsner Medical Center, New Orleans, LA, USA

<sup>3</sup> Vanderbilt University Medical Center, Nashville, TN, USA

<sup>4</sup> Emory University School of Medicine, Atlanta, GA, USA

<sup>5</sup> University of Texas at San Antonio, San Antonio, TX, USA

<sup>6</sup> University of Chicago, Chicago, IL, USA

<sup>7</sup> Division of Cardiology, Department of Internal Medicine, East Tennessee State University, 329 N State of Franklin Rd, Johnson City, TN 37604, USA

80% relative risk reduction in 5-year mortality with CABG and PCI, respectively, compared to medical therapy alone [4]. Stent restenosis was a significant drawback to the use of balloon angioplasty or bare metal stents. This issue has been largely overcome with drug-eluting stents (DES) [5]. Further advancements in stent technology led to the development of second-generation drug-eluting stents (DES2). These stents have thinner struts (80–90  $\mu\text{m}$ ) composed of cobalt or platinum alloy in comparison to the first generation (DES1) (sirolimus- and paclitaxel-eluting stents) that had much thicker, 130–140  $\mu\text{m}$ , stainless steel struts [6]. Basic laboratory and histopathological data reveals thinner struts exhibit more complete endothelialization compared with thicker struts with lower likelihood of intimal hyperplasia [6]. Vessels treated with DES2 experienced lower target lesion revascularization compared to DES1. Therefore, outcomes with DES2 are hypothesized to be improved as compared with CABG. This paper summarizes the current body of RCT data comparing PCI with CABG for ULM stenosis, with a focus on the two recent RCTs which exclusively utilized DES2.

## Discussion of Available Trial Data

Currently published randomized controlled trials (RCT) on PCI versus CABG are summarized in Table 1. Approaches in choosing PCI versus CABG for ULM stenosis in different clinical scenarios are outlined in Table 2.

Four RCTs comparing PCI with DES1 and CABG for ULM stenosis were published between 2008 and 2011. These included LEMANS (2008), SYNTAX-LM (2010), a study by Boudriot et al. (2011) and PRECOMBAT (2011) [10, 12, 13, 14].

### Four Previously Published Randomized Trials

In the LEMANS trial, patients were randomized to PCI received either DES1 (35%) or bare metal stents (65%) versus CABG. The initial study was reported in 2008 with the 10-year follow-up of this trial published recently [9, 13]. There were no differences in mortality, myocardial infarction (MI), stroke, and repeat revascularization (RR) between PCI and CABG at 10 years in patients with low to moderate complexity disease. The probability of very long-term survival up to 14 years was comparable in the two groups, although there was a trend for higher major adverse cardiovascular and cerebrovascular event (MACCE)-free survival with PCI [9]. Boudriot et al. randomized patients to PCI with sirolimus-eluting stents (DES1) or CABG. PCI was non-inferior to CABG for 12-month MACCE-free survival but was associated with a higher RR rate [10]. The PRECOMBAT study recently reported 5-year outcomes and showed no difference in MACCE between PCI with sirolimus-eluting stents (DES1)

and CABG, with higher ischemia-driven target vessel revascularization with PCI [11]. The LM cohort of the 1800 patients included in the SYNTAX trial consisted of a pre-defined and adequately powered group of 705 patients [12]. There was no difference in MACCE between PCI with paclitaxel-eluting stents (DES1) and CABG at 5 years in the entire LM cohort [15]. However, RR was more common, and stroke was less common with PCI. MACCE and cardiac death were significantly higher in patients with SYNTAX score > 33, who underwent PCI compared with CABG.

### Recently Published EXCEL and NOBLE Trial

The EXCEL and NOBLE trials were reported in 2016 and are the only RCTs in which CABG was compared with DES2 for the treatment of ULM stenosis [7, 8].

With 1905 patients in 17 countries at 126 centers, EXCEL is the largest ULM PCI trial published to date [7]. In contrast to the SYNTAX trial which used DES1, DES2 were used in EXCEL. Patients with ULM with stable angina (60%) or ACS (40%) were randomized to PCI or CABG. SYNTAX score was  $\leq 22$  in 32%, 23–32 in 43%, and  $\geq 33$  in 25% of patients in the PCI group. The DES2 used in this trial was fluoropolymer-based everolimus-eluting stent (XIENCE, Abbott Vascular). In the PCI group, 82% of cases involved the LM bifurcation. Intravascular ultrasound (IVUS) was used in 77% of cases. The primary composite endpoint of death, stroke, or MI at 3 years was 15.4% in the PCI group and 14.7% in the CABG group ( $p = 0.02$  for non-inferiority of PCI versus CABG; hazard ratio 1.00, 0.79, to 1.26;  $p = 0.98$  for superiority). Outcomes at 30 days were superior with PCI due to fewer MI (3.9% vs. 6.2%, HR 0.63, 0.42–0.95,  $p = 0.02$ ) [8]. Of note, PCI offers the advantage of avoiding surgically related complications of CABG (the secondary endpoints of major bleeding, infections, arrhythmias, and reoperations 8.1% in the PCI group vs. 23.0% in CABG group,  $p < 0.001$ ) [8].

NOBLE was a European trial conducted at 36 sites including 1201 patients [7]. Patients with ULM and up to three additional noncomplex lesions, with stable angina (82%) or ACS (18%), were randomized to PCI or CABG. Patients with complex multivessel coronary artery disease (CAD), chronic total occlusions, and bifurcation lesions requiring two stents were excluded. The DES2 used in this trial was the biolimus-eluting stent (Biomatrix Flex, Biosensors, Morges, Switzerland). In the PCI group, 88% of cases involved the LM bifurcation, and a two-stent approach was used in 35% cases. The majority (55%) underwent treatment of just the LM, whereas 33% had one additional lesion and 9% had two additional lesions treated. Post-PCI IVUS was used in 74% of cases [7]. The primary endpoint was MACCE at 5 years, defined as the composite of all-cause mortality, stroke, RR, or non-procedural MI. MACCE were 28% and 18% for

**Table 1** Summary of currently published randomized controlled trials on PCI vs CABG for left main coronary artery disease

Trial and term	Number of patients	Mean SYNTAX score	Secondary endpoint			Primary endpoint				
			Outcome	CABG	PCI	p	Outcome	CABG	PCI	p
NOBLE 2017 5 years [7••]	N 1201 DM 15% ACS 17%	22	Repeat revascularization	10%	16%	0.032	Composite: Repeat revascularization	19%	29%	0.007
			Stroke	2%	5%	0.073	Death			
EXCEL 2017 3 years [8••]	N 1905 DM 29% ACS 24%	21	Death	9%	12%	0.77	Stroke, non-procedural MI			
			MI (non-procedural)	2%	7%	0.004	Composite: death, stroke, or MI.	14.7%	15.4%	Non-inferiority = 0.02 Superiority = 0.98
LEMANS 2008–2016 1 and 10 years [9]	N 105 DM 18% ACS not reported	Not reported	Ischemia-driven revascularization	7.5%	12.6%	0.001				
			Stroke	2.9%	2.3%	0.37				
Boudriot et al 2011 1 year [10]	N 201 DM 36% ACS not reported	23	Death	5.9%	8.2%	0.11				
			MI	8.3%	8%	0.64				
PRECOMBAT 2011 1 and 5 years [11]	N 600 DM 32% ACS 45%	25	Composite	19.1%	23.1%	Non-inf 0.01				
			Repeat revascularization (10 years)	31.3%	26.1%	0.39	Left ventricular ejection fraction LVEF change at 1 year	0.5±0.8%	3.3±6.7%	0.047
SYNTAX-LM 2010	N 705 DM 25%	30	Stroke (10 years)	6.3%	4.3%	0.58				
			Death (10 years)	30.2%	21.6%	0.41				
Boudriot et al 2011 1 year [10]	N 201 DM 36% ACS not reported	23	MI (10 years)	10.4%	8.7%	0.68				
			Composite	62.5%	52.2%	0.42				
PRECOMBAT 2011 1 and 5 years [11]	N 600 DM 32% ACS 45%	25	Repeat revascularization	5.9%	14%	Non-inf 0.19	Death, MI, or repeat revascularization at 1 year.	13.9%	19%	Non-inferiority = 0.19
			Death or MI	7.9%	5%	Non-inf <0.001				
SYNTAX-LM 2010	N 705 DM 25%	30	Death	5%	2%	Non-inf <0.001				
			MI	3%	3%	Non-inf 0.002				
Boudriot et al 2011 1 year [10]	N 201 DM 36% ACS not reported	23	Repeat revascularization (5 years)	7.3%	13%	0.02	Death, stroke, MI or Ischemia-driven target lesion revascularization (1 year)	6.7%	8.7%	Non-inferiority = 0.01
			Stroke (5 years)	0.7%	0.7%	0.99				
PRECOMBAT 2011 1 and 5 years [11]	N 600 DM 32% ACS 45%	25	Death (5 years)	7.9%	5.7%	0.32				
			MI (5 years)	1.7%	2%	0.76				
SYNTAX-LM 2010	N 705 DM 25%	30	Death, stroke, or MI (5 years)	9.6%	8.4%	0.66				
			Death, stroke, MI, or ischemia-driven target lesion revascularization (5 years)	14.3%	17.5%	0.26				
SYNTAX-LM 2010	N 705 DM 25%	30	Repeat revascularization (5 years)	15.5%	26.7%	<0.001	Death, stroke, mi, or repeat	13.6%	15.8%	Non-inferiority = 0.19
			Repeat revascularization (5 years)	15.5%	26.7%	<0.001				

**Table 1** (continued)

Trial and term	Number of patients	Mean SYNTAX score	Secondary endpoint		Primary endpoint			
			Outcome	p	Outcome	PCI	p	
1 and 5 years [12] ACS 30%			Stroke (5 years)	4.3%	1.5%	0.03	revascularization (1 year)	
			Death (5 years)	14.6%	12.8%	0.53		
			MI (5 years)	4.8%	8.2%	0.10		
			Death, stroke, or MI (5 years)	20.8%	19%	0.57		
			Death, stroke, mi, or repeat revascularization (5 years)	31%	36.9%	0.12		

ACS acute coronary syndrome, DM diabetes mellitus, LVEF left ventricular ejection fraction, MI myocardial infarction, PCI percutaneous coronary intervention, CABG coronary artery bypass graft

PCI and CABG, respectively (HR 1.51, 1.13–2.0, which did not meet the criteria for non-inferiority of PCI to CABG); *p* for superiority of CABG over PCI was 0.0044. Interestingly, 1-year MACCE rates were similar in PCI and CABG. Higher RR (15% for PCI vs. 10% for CABG (HR 1.50, 1.04–2.17, *p* = 0.0304) and non-procedural MI (6% for PCI vs. 2% for CABG (HR 2.87, 1.40–5.89, *p* = 0.0040) were responsible for the higher MACCE rates with PCI. RR was due to new lesions in non-stented segments rather than for the treated LM lesion [7••]. There was no difference in all-cause or cardiac mortality between the two groups. SYNTAX score was not associated with MACCE in the PCI group. While early stroke was more common in the CABG group, an unexpected, numerically higher rate of late stroke was noted in the PCI group, with no overall difference in the two groups at 5 years [7••].

The findings of NOBLE are similar to those of the SYNTAX trial but differ from the findings of EXCEL. The disparity in the conclusions between NOBLE and EXCEL may be partly due to differences in study design, endpoints, and the type of stent. The absolute margin for non-inferiority in EXCEL was 4.2%, compared with a 35% relative non-inferiority margin in NOBLE [16]. The primary endpoint assessment was changed from 5 years to 3 years in the NOBLE trial due to low event rates, and Kaplan Meier estimates were used to report 5-year outcomes [7••, 8••]. These estimates could have been affected by a change in risk for patients entering the study at different time points. Importantly, RR (which is uniformly lower in patients treated with CABG compared with PCI) was included in the primary composite endpoint in NOBLE, but not in EXCEL [7••]. Periprocedural MI, defined as creatine phosphokinase elevation > 10 × upper limit of normal, was included in the composite endpoint in EXCEL, whereas it was not included in NOBLE. A thin-strut everolimus-eluting stent was used in EXCEL compared with a thicker-strut biolimus-eluting stent was used in most patients in NOBLE. The higher incidence of stroke, between 1

**Table 2** Approaches in choosing PCI versus CABG in different clinical scenarios

Clinical situation	PCI	CABG	Evidence
Limited life expectancy	Favors PCI		Similar 1-year MACCE between PCI and CABG in NOBLE trial
Complex LM bifurcation stenosis		Favors CABG	Despite a low SYNTAX score, CABG may offer an advantage over PCI for this lesion subset
Isolated ostial or shaft LM stenosis with low SYNTAX score	Favors PCI		

LM left main, PCI percutaneous coronary intervention, CABG coronary artery bypass graft, MACCE major adverse cardiac and cerebrovascular events, NOBLE Nordic-Baltic-British Left Main Revascularization trial

and 5 years, among PCI treated patients in NOBLE contributed to the better composite outcome with CABG in NOBLE. This finding is difficult to explain but may have been related to discontinuation of dual antiplatelet therapy at 1 year. In EXCEL, the rates of stroke at 3 years were comparable between PCI and CABG [8••].

The divergence of outcome curves between PCI and CABG often becomes evident in later years, when the incidence of de novo lesions increases. This results in higher MI and RR in patients treated with PCI. On the other hand, saphenous vein graft degeneration is a continuous process and this may influence even longer term (10 years) follow-up. Longer term follow-up of the NOBLE and EXCEL might be important in understanding the relative strengths and weaknesses of PCI and CABG for LM disease.

### Post NOBLE and EXCEL Meta-analyses

Giacoppo et al. conducted a meta-analysis of 4 RCTs: SYNTAX-LM cohort, PRECOMBAT, NOBLE, and EXCEL [17]. Comparable rates of the composite outcome of all-cause death, MI and stroke at the longest available follow-up were noted in the PCI and CABG groups (HR 1.06, 0.90–1.24,  $p = 0.48$ ). The highest relative weight in this meta-analysis was from the EXCEL trial. A moderate degree of heterogeneity was noted, due to NOBLE, which was the only trial favoring CABG. PCI was associated with a significantly higher risk of RR compared with CABG (HR 1.70, 1.42–2.05,  $p < 0.001$ ), with no difference in RR risk between DES1 and DES2. Palmerini et al. performed a meta-analysis of six RCTs comparing outcomes between PCI with DES2 and CABG with a total of 4686 patients [18]. Similar to the findings of EXCEL, PCI was associated with significantly better 30-day outcomes compared with CABG: all-cause death or MI (OR 0.69, 0.49–0.98,  $p = 0.04$ ), and stroke (OR 0.36, 0.16–0.82,  $p = 0.007$ ). A significant interaction was noted between time and treatment effect, and PCI associated with lower MI and stroke in the first 30 days and CABG associated with lower MI and RR thereafter [18]. At a median follow-up of 39 months, there was no difference in individual outcomes of all-cause death, cardiac death, or stroke. A significant interaction was also noted between cardiac death and RR with the SYNTAX score, such that the upper SYNTAX score tertile ( $> 33$ ) was associated with increased cardiac mortality and RR with PCI. One strength of this meta-analysis was that there was no significant heterogeneity noted between trials for the long-term outcomes of all-cause or cardiac mortality [18]. Sardar et al. performed another comprehensive meta-analysis of data from five RCTs (one additional study was included to the previous meta-analysis) comparing PCI with DES versus CABG for ULMCA stenosis and demonstrated a similar risk of all-cause mortality, cardiovascular death, MI, stroke, and the combined risk of death, MI, or stroke (MACE) in the 2

treatment groups [19]. However, the risk of any revascularization or TVR was significantly higher in the PCI with DES group [19]. Another recently published meta-analysis using individual patient level data on 11,518 patients from 11 trials, of which 4478 patients had ULM disease, demonstrated no benefit of CABG over PCI in a 5-year mortality (HR 1.07, 0.93–1.91;  $p = 0.65$ ) [20]. Interestingly, the presence of diabetes and the SYNTAX score did not influence 5-year outcomes in the ULM group [20].

### Impact of DES Generation

PCI outcomes have improved significantly from the DES1 era to the current era of DES2. In the EXCEL trial, stent thrombosis was noted in only 0.7% of cases and was lower than the rate of symptomatic saphenous vein graft occlusion [7••, 8••]. In contrast, stent thrombosis with DES1 use was high and similar to rates of saphenous vein graft occlusion in the SYNTAX trial [12•]. Stent thrombosis rate associated with the biolimus-eluting stent in NOBLE was also significantly higher at 3% compared with EXCEL in which a thinner-strut stent was used [7••, 8••]. However, DES2 have not had a significant impact on the rate of RR following ULM PCI. In the meta-analysis by Giacoppo, the risk of RR was not influenced by DES generation [17, 18]. This can be hypothesized that RR may be due to progression of de novo disease outside the stented segment. This offers a clear advantage for CABG which bypasses long segments of diseased coronary artery, whereas stents have no effect on de novo lesions.

### Left Main Revascularization Guidelines Overview

The 2017 ACC/AHA/SCAI appropriate use criteria for coronary revascularization in patients with stable ischemic heart disease give a class I recommendation for a heart team approach prior to both CABG and PCI in patients with ULM stenosis [21]. Calculation of the SYNTAX score is a class IIa recommendation. PCI for ULM stenosis is a class IIa recommendation if anatomic complexity associated with a low risk of PCI procedural complications and a high likelihood of good long-term outcome (e.g., a low SYNTAX score  $< 22$ , ostial or trunk left main stenosis, and clinical characteristics that predict a significantly increased risk of adverse surgical outcomes) (such as STS-predicted risk of operative mortality  $\geq 5\%$ ) are present. A class IIb recommendation is given for PCI if there is bifurcation disease, or a SYNTAX score of 23–32 and CABG morbidity is high or if STS score  $> 2\%$ . PCI is rated class III or harmful if unfavorable anatomy for PCI is present in patients who are good candidates for CABG. The 2018 ESC guidelines on myocardial revascularization give a class I recommendation for ULM PCI if SYNTAX score  $< 22$ , class IIa for SYNTAX score between 23 and 32, and class III for SYNTAX score  $\geq 33$  [22].

## Left Main PCI: “The Pearls Are in the Details”

### Role of the Heart Team

A heart team approach is recommended by the 2011 ACC/AHA PCI guidelines [23]. In addition to technical feasibility, the likelihood of achieving “complete revascularization” with either approach should be assessed. The 2018 ESC guidelines recommend completeness of revascularization should be prioritized, when considering the decision between CABG and PCI (class I recommendation) [22].

### Risk Scores for Decision Making Between PCI and CABG

Both anatomic and clinical scores have been developed and validated to predict outcomes with PCI and CABG, and hence guide decision making. While the SYNTAX score has been extensively validated as a tool of anatomic complexity and predictor of short- and long-term outcomes in patients with ULM stenosis, it does not take into account any clinical variables [24]. The SYNTAX score was not predictive of MACCE in the NOBLE trial. Rather, CABG was associated with better outcomes, compared with PCI, in the sub-group of patients with low SYNTAX score (< 22) and equivalent outcomes in patients with higher scores. This may be because most patients in the NOBLE trial had bifurcation LM stenosis. In such a patient group, the SYNTAX score can be low even in the presence of an isolated complex bifurcation LM stenosis as defined previously. Such patients may have improved outcomes with CABG. This represents a limitation of the SYNTAX score in guiding treatment selection in patients with LM CAD, compared with its utility in patients with non-left main multivessel CAD. This is highlighted by the fact that a variable interaction between SYNTAX score and PCI outcomes was noted in different RCTs. In the SYNTAX trial and the meta-analysis by Palmerini et al., significant differences were noted in PCI outcomes based on the SYNTAX score tertiles, whereas no interaction was noted in PRECOMBAT, EXCEL, and NOBLE. Other risk scores which take clinical variables into account in addition to anatomic variables in the SYNTAX score have been developed and validated. These include the SYNTAX II, Clinical SYNTAX Score (CSS), and the Global Risk Score [25–27]. The SYNTAX score II adds clinical factors, namely gender, age, chronic obstructive pulmonary disease, peripheral vascular disease, left ventricular ejection fraction (LVEF), and creatinine clearance to the SYNTAX score [25]. Diabetes is an important comorbidity which favors CABG over PCI in multivessel CAD but is not associated with a significant effect on 5-year mortality for LM disease in the absence of significant multivessel CAD [28].

## Role of Intravascular Ultrasound and Fractional Flow Reserve

In a study comparing IVUS and fractional flow reserve (FFR), an IVUS-derived minimum cross-sectional area (MLA) < 5.9 mm<sup>2</sup> correlated with an ischemic FFR [27, 29]. Therefore, in most cases, a MLA  $\geq$  6 mm<sup>2</sup> indicates that LM revascularization can be safely deferred. An MLA < 4.5 mm<sup>2</sup> has been proposed to indicate a significant stenosis in the case of an isolated ostial or shaft stenosis [30]. FFR can also be used in place of IVUS to determine if significant flow limitation is present, and a value of 0.80 or lower is abnormal. The details on technical issues and interpretation are beyond the scope of this review. Briefly, in the presence of the downstream branch stenosis in addition to LM stenosis, placing the FFR wire into a non-stenotic branch vessel will allow measurement of the true FFR as long as the stenosis in the other branch vessel is not severe. [31]. However, in case of ambiguity, the LM MLA can be assessed with IVUS to guide decision making.

### ULM PCI—Technical Issues

The details of how to perform ULM PCI are key to optimal outcomes [16, 32]. However, a complete discussion of this topic is beyond the scope of this review. The 2018 ESC guidelines provide a class IIa recommendation for an annual operator volume for left main PCI of at least 25 cases per year [22]. The DK-CRUSH V study showed lower rates of target vessel failure, target vessel MI, and stent thrombosis in 482 patients, with true bifurcation lesions of the distal LM, randomized to DK-CRUSH versus provisional stenting (PS) [33]. Absolute benefit of the two-stent approach was greater in patients with complex LM bifurcation stenosis compared with simpler lesions. The most recent consensus statement from the European Bifurcation Club recommends a provisional approach for the side branch in most cases of distal LM bifurcation lesions [34]. The DK-CRUSH technique has shown superior outcomes compared with culotte or provisional stenting in patients with true LM bifurcation lesions [33, 35]. DK-CRUSH technique is preferred over provisional T-stenting in true LM bifurcation with a class IIb recommendation in the 2018 ESC guidelines [22]. The EBC MAIN trial is highly anticipated among ULM PCI operators. The hypothesis is that the single stent provisional approach is better than planned two-stent approach [36]. Regardless of the technique, stent optimization by using pre- and post-PCI IVUS, and ensuring adequate minimum stent cross-sectional area using a proximal optimization technique and final kissing balloon inflation (FKBI) in cases of a two-stent strategy, is mandatory for improved outcomes. Selection of an appropriately sized stent with high-pressure post-dilatation is key in LM ostium stenosis. IVUS guidance was associated with a significant improvement in a 3-year mortality compared with angiographic

guidance in propensity-matched patients [37, 38]. Finally, risk assessment to determine the safety of PCI is crucial. Adequate hemodynamic support should be considered prior to complex distal left main PCI, especially in the presence of an occluded or non-dominant right coronary artery, left ventricular ejection fraction  $\leq 35\%$ , multivessel CAD, need for atherectomy, or significant comorbidities that may lead to hemodynamic instability during procedure.

## Conclusions

Favorable outcomes of ULM PCI with newer generation DES may affect treatment decisions of CABG versus PCI. CABG offers the advantage of bypassing long segments of disease. In patients treated with PCI, de novo lesions outside the stented segments can lead to recurrent MI and the need for RR. Higher rates of residual angina in patients treated with PCI can also contribute to higher rates of repeat revascularization. Despite these limitations, excellent outcomes can be achieved with PCI, in properly selected patients with ULM stenosis. Advances in stent design and technology (such as newer generation DES) and PCI technique (high-pressure stent deployment and IVUS guidance) have contributed to the improved efficacy of PCI. Improved safety, with low 30-day mortality ( $< 0.5\%$ ) and procedural MI (5%), have been reported with PCI in RCTs. The availability of mechanical circulatory support devices, although less extensively studied in these trials (only 5.2% of patients in Excel trial received mechanical circulatory support), may also improve the safety of PCI in this setting. At the same time, surgical techniques have also improved as reflected by lower rates of stroke and death in a more contemporary trial like EXCEL. A heart team approach with appropriate patient selection, careful assessment of LM lesions, and meticulous procedural technique makes PCI a viable option for ULM stenosis. With advances in stent technology and deployment techniques in complex and high-risk ULM disease, further studies are needed to validate the current optimism for PCI as a valid alternative to CABG or perhaps as part of a hybrid revascularization strategy with CABG.

## Compliance with Ethical Standards

**Conflict of Interest** Yasir Taha, Rajan A.G. Patel, Jayant Bagai, Rajesh Sachdeva, Gautam Kumar, and Timir K. Paul declare that they have no conflict of interest.

Anand Prasad reports the following: Speaker: AstraZeneca, Abiomed, Gilead; Consultant: Osprey Medical, GE; Research: ACIST Medical, Medtronic.

Sandeep Nathan has served as a consultant for Medtronic, Inc.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

**Publisher's Note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

## References

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

1. Kalbfleisch H, Hort W. Quantitative study on the size of coronary artery supplying areas postmortem. *Am Heart J.* 1977;94:183–8.
2. Ragosta M, Dee S, Sarembock IJ, Lipson LC, Gimble LW, Powers ER. Prevalence of unfavorable angiographic characteristics for percutaneous intervention in patients with unprotected left main coronary artery disease. *Catheter Cardiovasc Interv.* 2006;68:357–62.
3. Yusuf S, Zucker D, Peduzzi P, Fisher LD, Takaro T, Kennedy JW, et al. Effect of coronary artery bypass graft surgery on survival: overview of 10-year results from randomised trials by the Coronary Artery Bypass Graft Surgery Trialists Collaboration. *Lancet.* 1994;344:563–70.
4. Shah R, Morsy MS, Weiman DS, Vetrovec GW. Meta-analysis comparing coronary artery bypass grafting to drug-eluting stents and to medical therapy alone for left main coronary artery disease. *Am J Cardiol.* 2017;120:63–8.
5. Al Ali J, Franck C, Filion KB, Eisenberg MJ. Coronary artery bypass graft surgery versus percutaneous coronary intervention with first-generation drug-eluting stents: a meta-analysis of randomized controlled trials. *JACC Cardiovasc Interv.* 2014;7:497–506.
6. Joner M, Nakazawa G, Finn AV, Quee SC, Coleman L, Acampado E, et al. Endothelial cell recovery between comparator polymer-based drug-eluting stents. *J Am Coll Cardiol.* 2008;52:333–42.
7. Mäkikallio T, Holm NR, Lindsay M, Spence MS, Erglis A, Menown IBA, et al. Percutaneous coronary angioplasty versus coronary artery bypass grafting in treatment of unprotected left main stenosis (NOBLE): a prospective, randomised, open-label, non-inferiority trial. *Lancet.* 2016;388:2743–52 This is a well-designed European multicenter randomized trial with a > 1200 sample size with 5 years follow-up data.
8. Stone GW, Sabik JF, Serruys PW, Simonton CA, Généreux P, Puskas J, et al. Everolimus-Eluting Stents or Bypass Surgery for Left Main Coronary Artery Disease. *N Engl J Med.* 2016;375: 2223–35. This prospective randomized trial addressing the question with 3 years follow-up has the largest sample size ( $N=1905$ ). The results of this trial are likely more generalizable as it had 126 sites in 17 countries including USA.
9. Buszman PE, Buszman PP, Banasiewicz-Szkróbka I, Milewski KP, Żurkowski A, Orlik B, et al. Left main stenting in comparison with surgical revascularization: 10-year outcomes of the (Left Main Coronary Artery Stenting) LE MANS Trial. *JACC Cardiovasc Interv.* 2016;9:318–27.
10. Boudriot E, Thiele H, Walther T, Liebetrau C, Boeckstegers P, Pohl T, et al. Randomized comparison of percutaneous coronary intervention with sirolimus-eluting stents versus coronary artery bypass grafting in unprotected left main stem stenosis. *J Am Coll Cardiol.* 2011;57:538–45.
11. Ahn J-M, Roh J-H, Kim Y-H, Park D-W, Yun S-C, Lee PH, et al. Randomized Trial of stents versus bypass surgery for left main coronary artery disease: 5-year outcomes of the PRECOMBAT Study. *J Am Coll Cardiol.* 2015;65:2198–206 This landmark trial has a good sample size with 5-year follow-up outcome results. This

- in turn gives more applicable real life mid- to long-term follow-up perspectives.
12. Morice M-C, Serruys PW, Kappetein AP, Feldman TE, Stähle E, Colombo A, et al. Outcomes in patients with de novo left main disease treated with either percutaneous coronary intervention using paclitaxel-eluting stents or coronary artery bypass graft treatment in the Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery (SYNTAX) trial. *Circulation*. 2010;121:2645–53. The acronym SYNTAX is well known to cardiologists as the foundation of coronary artery disease and PCI complexity assessment. This is the trial that initiated SYNTAX score.
  13. Buszman PE, Kiesz SR, Bochenek A, Peszek-Przybyla E, Szkrobka I, Debinski M, et al. Acute and late outcomes of unprotected left main stenting in comparison with surgical revascularization. *J Am Coll Cardiol*. 2008;51:538–45.
  14. Park S-J, Kim Y-H, Park D-W, Yun S-C, Ahn J-M, Song HG, et al. Randomized trial of stents versus bypass surgery for left main coronary artery disease. *N Engl J Med*. 2011;364:1718–27.
  15. Morice M-C, Serruys PW, Kappetein AP, Feldman TE, Stähle E, Colombo A, et al. Five-year outcomes in patients with left main disease treated with either percutaneous coronary intervention or coronary artery bypass grafting in the synergy between percutaneous coronary intervention with taxus and cardiac surgery trial. *Circulation*. 2014;129:2388–94.
  16. Fajadet J, Capodanno D, Stone GW. Management of left main disease: an update. *Eur Heart J* [Internet] 2018; Available from: <https://doi.org/10.1093/eurheartj/ehy238>
  17. Giacoppo D, Colleran R, Cassese S, Frangieh AH, Wiebe J, Joner M, et al. Percutaneous Coronary Intervention vs Coronary Artery Bypass Grafting in Patients With Left Main Coronary Artery Stenosis: A Systematic Review and Meta-analysis. *JAMA Cardiol*. 2017;2:1079–88.
  18. Palmerini T, Serruys P, Kappetein AP, Genereux P, Riva DD, Reggiani LB, et al. Clinical outcomes with percutaneous coronary revascularization vs coronary artery bypass grafting surgery in patients with unprotected left main coronary artery disease: A meta-analysis of 6 randomized trials and 4,686 patients. *Am Heart J*. 2017;190:54–63.
  19. Sardar P, Giri J, Elmariah S, Chatterjee S, Kolte D, Kundu A, et al. Meta-Analysis of Drug-Eluting Stents Versus Coronary Artery Bypass Grafting in Unprotected Left Main Coronary Narrowing. *Am J Cardiol*. 2017;119:1746–52.
  20. Head SJ, Milojevic M, Daemen J, Ahn J-M, Boersma E, Christiansen EH, et al. Mortality after coronary artery bypass grafting versus percutaneous coronary intervention with stenting for coronary artery disease: a pooled analysis of individual patient data. *Lancet*. 2018;391:939–48.
  21. Patel MR, Calhoun JH, Dehmer GJ, Grantham JA, Maddox TM, Maron DJ, et al. Correction to: ACC/AATS/AHA/ASE/ASNC/SCAI/SCCT/STS 2017 Appropriate Use Criteria for Coronary Revascularization in Patients With Stable Ischemic Heart Disease. *J Nucl Cardiol* [Internet] 2018; Available from: <https://doi.org/10.1007/s12350-018-1292-x>
  22. Neumann F-J, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J* [Internet] 2018; Available from: <https://doi.org/10.1093/eurheartj/ehy394>
  23. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *Circulation*. 2011;124:e574–651.
  24. Serruys PW, Morice M-C, Kappetein AP, Colombo A, Holmes DR, Mack MJ, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med*. 2009;360:961–72.
  25. Sotomi Y, Cavalcante R, van Klaveren D, Ahn J-M, Lee CW, de Winter RJ, et al. Individual long-term mortality prediction following either coronary stenting or bypass surgery in patients with multivessel and/or unprotected left main disease: An external validation of the SYNTAX Score II Model in the 1,480 Patients of the BEST and PRECOMBAT Randomized Controlled Trials. *JACC Cardiovasc Interv*. 2016;9:1564–72.
  26. Capodanno D, Miano M, Cincotta G, Caggegi A, Ruperto C, Bucalo R, et al. EuroSCORE refines the predictive ability of SYNTAX score in patients undergoing left main percutaneous coronary intervention. *Am Heart J*. 2010;159:103–9.
  27. Capodanno D, Caggegi A, Miano M, Cincotta G, Dipasqua F, Giacchi G, et al. Global risk classification and clinical SYNTAX (synergy between percutaneous coronary intervention with TAXUS and cardiac surgery) score in patients undergoing percutaneous or surgical left main revascularization. *JACC Cardiovasc Interv*. 2011;4:287–97.
  28. Bhatt DL. CABG the clear choice for patients with diabetes and multivessel disease. *Lancet*. 2018;391:913–4.
  29. Jasti V, Ivan E, Yalamanchili V, Wongpraparut N, Leesar MA. Correlations between fractional flow reserve and intravascular ultrasound in patients with an ambiguous left main coronary artery stenosis. *Circulation*. 2004;110:2831–6.
  30. Park S-J, Ahn J-M, Kang S-J, Yoon S-H, Koo B-K, Lee J-Y, et al. Intravascular ultrasound-derived minimal lumen area criteria for functionally significant left main coronary artery stenosis. *JACC Cardiovasc Interv*. 2014;7:868–74.
  31. Daniels DV, van't Veer M, Pijls NHJ, van der Horst A, Yong AS, De Bruyne B, et al. The impact of downstream coronary stenoses on fractional flow reserve assessment of intermediate left main disease. *JACC Cardiovasc Interv*. 2012;5:1021–5.
  32. Rab T, Sheiban I, Louvard Y, Sawaya FJ, Zhang JJ, Chen SL. Current interventions for the left main bifurcation. *JACC Cardiovasc Interv*. 2017;10:849–65.
  33. Chen S-L, Zhang J-J, Han Y, Kan J, Chen L, Qiu C, et al. Double kissing crush versus provisional stenting for left main distal bifurcation lesions: DKCRUSH-V randomized trial. *J Am Coll Cardiol*. 2017;70:2605–17.
  34. Lassen JF, Burzotta F, Banning AP, Lefèvre T, Darremont O, Hildick-Smith D, et al. Percutaneous coronary intervention for the left main stem and other bifurcation lesions: 12th consensus document from the European Bifurcation Club. *EuroIntervention*. 2018;13:1540–53.
  35. Chen S-L, Xu B, Han Y-L, Sheiban I, Zhang J-J, Ye F, et al. Comparison of double kissing crush versus Culotte stenting for unprotected distal left main bifurcation lesions: results from a multicenter, randomized, prospective DKCRUSH-III study. *J Am Coll Cardiol*. 2013;61:1482–8.
  36. Chieffo A, Hildick-Smith D. The European Bifurcation Club Left Main Study (EBC MAIN): rationale and design of an international, multicentre, randomised comparison of two stent strategies for the treatment of left main coronary bifurcation disease. *EuroIntervention*. 2016;12:47–52.
  37. Puri R, Kapadia SR, Nicholls SJ, Harvey JE, Kataoka Y, Tuzcu EM. Optimizing outcomes during left main percutaneous coronary intervention with intravascular ultrasound and fractional flow reserve: the current state of evidence. *JACC Cardiovasc Interv*. 2012;5:697–707.
  38. Park S-J, Kim Y-H, Park D-W, Lee S-W, Kim W-J, Suh J, et al. Impact of intravascular ultrasound guidance on long-term mortality in stenting for unprotected left main coronary artery stenosis. *Circ Cardiovasc Interv*. 2009;2:167–77.