Clinical update

Management of left main disease: an update

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A severe narrowing of the left main coronary artery (LMCA), usually due to atherosclerosis, jeopardizes a large area of myocardium and increases the risk of major adverse cardiac events. Management strategies for LMCA disease include coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI). In general, PCI offers more rapid recovery and a lower early adverse event rate, whereas CABG offers a more durable procedure. The largest of six LMCA trials comparing PCI with CABG recently reported that in patients with site-reported low or intermediate anatomical complexity PCI was non-inferior to CABG with respect to the composite of death, stroke, or myocardial infarction at 3 years. This result was obtained on a background of contemporary PCI standards, including safer and more effective stents, intravascular imaging and physiology assessment. This review updates on the current management of LMCA disease, with an emphasis on clinical data and procedural knowledge supporting the use of PCI in a growing proportion of patients.

Keywords

Left main • Left main coronary artery • Percutaneous coronary intervention • Coronary artery bypass grafting

Preamble

In usual anatomies, the left main coronary artery (LMCA) arises from the aorta within the left sinus of Valsalva, runs between the pulmonary trunk and the left atrial appendage and then bifurcates into the left anterior descending (LAD) and the left circumflex (LCx) arteries.1 A significant narrowing of the LMCA jeopardizes a large area of myocardium (more than two-thirds of the left ventricle in a right-dominant circulatory system) and increases the risk of major adverse cardiac events.2,3 The most common cause of LMCA disease is atherosclerosis, which is rarely focal (Figure 1) and involves the bifurcation in ~80% of the cases, usually extending from the LMCA to the LAD and sparing the flow-divider (the carina).4–7

Management strategies for LMCA disease include coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI), and rarely medical therapy alone. Coronary artery bypass grafting has been the standard of care for many years, due to its established mortality benefit over medical therapy.8 The first case of LMCA PCI was performed by Andreas Gruentzig on 21 November 1977, prior to the stent era.9 Approximately 40 years later, advocates of CABG and PCI still debate on which strategy should be ‘first-line’ for LMCA, and the comparative efficacy and safety of the two therapies has been the purpose of several randomized controlled trials over the years.4,5,10–13 The largest and most contemporary of these comparisons recently reported that in patients with LMCA disease and low or intermediate anatomical complexity as measured by the anatomic SYNTAX score, PCI was non-inferior to CABG with respect to the composite of death, stroke, or myocardial infarction (MI) at 3 years.10 In the largest pooled analysis of trials comparing PCI and CABG, no difference in mortality at 5 years was noted in the subgroup of patients with LMCA disease.14 These results will likely inform upcoming clinical guidelines for myocardial revascularisation and eventually lead to an increase in the volume of LMCA PCIs performed worldwide. Importantly, when PCI of the LMCA is undertaken, there is increasing awareness of the need for achieving optimal procedural outcomes through the use of the available technologies, including safer and more effective stents, intravascular imaging, and physiology assessment. On this background, this review describes the current management of LMCA disease, with an emphasis on clinical data and procedural knowledge supporting the use of PCI in a growing proportion of patients.

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Clinical outcomes of left main coronary artery revascularization

Trials of percutaneous coronary intervention vs. coronary artery bypass grafting

Six randomized clinical trials have compared PCI with CABG in the setting of LMCA disease (Table 1), but only two of them—EXCEL and NOBLE—were conducted in the era of second-generation drug-eluting stents (DES). In the EXCEL trial—the largest LMCA trial conducted so far (1905 randomized patients at 126 sites in 17 countries)—the composite of death, stroke, or MI occurred at 3 years in 15.4% of patients treated with PCI with a cobalt chromium fluoropolymer-based everolimus-eluting stent and 14.7% of patients treated with CABG (P for non-inferiority = 0.02, P for superiority = 0.98). Percutaneous coronary intervention resulted in a lower rate of death, stroke, or MI compared with CABG within the first 30 days (4.9% vs. 7.9%, P = 0.008), the major powered secondary endpoint of the trial, driven by fewer cases of large MI. Percutaneous coronary intervention also reduced major periprocedural adverse events by 65% (8.1% vs. 23.0%, P < 0.001), driven by fewer major arrhythmias, infections, reoperations, bleeding, and transfusions than after CABG. There were no significant differences in the 3-year rates of death, stroke, and MI as individual endpoints between the two strategies, although MI occurred more frequently in patients assigned to PCI after 30 days. Percutaneous coronary intervention also was associated with a higher 3-year risk of ischaemia-driven revascularization. When ischaemia-driven revascularization was included in the 3-year primary endpoint, the criterion for non-inferiority was still met (23.1% vs. 19.1%, P for non-inferiority = 0.01). Finally, PCI resulted in more rapid recovery and greater improvement in quality of life at 30 days compared with CABG, although both procedures resulted in similar quality of life and angina relief at 3 years. Of note, EXCEL excluded from enrolment patients without equipoise for both surgical and percutaneous revascularization after heart team review and those with site-assessed high SYNTAX scores, although 24% of patients actually presented with high SYNTAX score based on angiographic core-laboratory analysis.

In the NOBLE trial (1201 patients enrolled from 36 centres in northern Europe), the primary endpoint was a composite of all-cause mortality, non-procedural MI, stroke, or repeat revascularization. The Kaplan–Meier 5-year estimates of this combined outcome were 29% for PCI and 19% for CABG, exceeding the limit for non-inferiority. The difference in favour of CABG was statistically significant (P for superiority = 0.0066), and was driven by significantly higher rates of non-procedural MI and repeat revascularization in the PCI arm.

Although the conclusions of the EXCEL and NOBLE trials on the surface appear discordant, a number of contributing factors should be acknowledged. Firstly, the primary endpoint included repeat revascularization (a typical driver of the difference between the two procedures in previous trials and registries) only in the NOBLE trial. The EXCEL trial used a 4.2% absolute margin for non-inferiority, as agreed by a group of more than 100 physicians not related to the study sponsor (including similar proportions of interventional cardiologists and cardiac surgeons), while the NOBLE trial used a 35% relative non-inferiority margin derived from the SYNTAX trial (where the prespecified margin of non-inferiority was 6.6%).

Secondly, the definition of MI was different between the two studies, in that periprocedural MI was included in the EXCEL trial and excluded in the NOBLE trial. However, the definition of periprocedural MI used in the EXCEL trial signified extensive myonecrosis (peak CK-MB >10 normal in most cases) that has been linked to prognostic consequences. Thirdly, the type of DES used in the PCI arms of the studies was different (e.g. the thin-strut everolimus-eluting stent in the EXCEL trial vs. a thicker-strut stainless steel biolimus-eluting stents in about 90% of patients in the NOBLE trial). This difference may have an impact on clinical outcomes as also reflected by the different rates of definite stent thrombosis reported in the two studies (0.7% in the EXCEL and 3% in the NOBLE trial).

Fourthly, although the median duration of follow-up was similar in both trials, the study outcomes of the EXCEL trial were reported in the form of Kaplan–Meier estimates at 3 years, while those of the NOBLE trial were reported at 5 years. Although longer follow-up is

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Figure 1 Spectrum of left main coronary artery disease presentations. White arrows highlight case examples of focal severe angiographic stenoses of the left main coronary artery located at the level of the ostium (left panel), the shaft (mid panel), or the distal bifurcation involving the ostia of the left anterior descending and left circumflex arteries (right panel). Diffuse left main coronary artery disease extending in multiple locations (e.g. ostium to shaft, shaft to distal, or ostium to distal) is a frequent presentation.
<table>
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<tr>
<th>Trial</th>
<th>Year</th>
<th>Sites</th>
<th>N</th>
<th>SS (mean)</th>
<th>DM (%)</th>
<th>ACS (%)</th>
<th>Distal (%)</th>
<th>MVD (%)</th>
<th>Stent</th>
<th>Primary endpoint (PCI vs. CABG)</th>
<th>Key secondary endpoints at the longest FU (PCI vs. CABG)</th>
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| LE MANS¹⁰,¹⁵      | 2008 | NR    | 105 | NR        | 18     | NR      | 58         | 91      | BMS, DES    | Change in LVEF at 1 year: **3.3 ± 6.7%** vs. **0.5 ± 0.8%**, *P* = 0.047 | • Death, CVA, MI, or repeat revascularization at 10 years: **52.2%** vs. **62.5%**, *P* = 0.42  
|                   |      |       |     |           |        |         |            |         |             | • Death at 10 years: **21.6%** vs. **30.2%**, *P* = 0.41                                | • CVA at 10 years: **4.3%** vs. **6.3%**, *P* = 0.58  
|                   |      |       |     |           |        |         |            |         |             | • MI at 10 years: **8.7%** vs. **10.4%**, *P* = 0.68                                   | • Repeat revascularization at 10 years: **26.1%** vs. **31.3%**, *P* = 0.39                    |
| SYNTAX LM¹²,¹⁶    | 2010 | 85    | 705 | 30        | 25     | 30      | 61         | 68      | DP-PES      | Death, CVA, MI, or repeat revascularization at 1 year: **15.8%** vs. **13.6%**, *P* = 0.44 | • Death, CVA, MI, or repeat revascularization at 5 years: **36.9%** vs. **31%**, *P* = 0.12  
|                   |      |       |     |           |        |         |            |         |             | • Death/CVA/MI at 5 years: **19%** vs. **20.8%**, *P* = 0.57                          | • Death at 5 years: **12.8%** vs. **14.6%**, *P* = 0.53  
|                   |      |       |     |           |        |         |            |         |             | • CVA at 5 years: **1.5%** vs. **4.3%**, *P* = 0.03                                  | • MI at 5 years: **8.2%** vs. **4.8%**, *P* = 0.10  
|                   |      |       |     |           |        |         |            |         |             | • Repeat revascularization at 5 years: **26.7%** vs. **15.5%**, *P* < 0.001           | • Repeat revascularization at 1 year: **2%** vs. **5%**, *P* for non-inferiority <0.001   |
|                   |      |       |     |           |        |         |            |         |             | • Death or MI at 1 year: **5%** vs. **7.9%**, *P* for non-inferiority <0.001          | • MI at 1 year: **3%** vs. **3%**, *P* for non-inferiority = 0.002                          |
|                   |      |       |     |           |        |         |            |         |             | • Repeat revascularization at 1 year: **14%** vs. **5.9%**, *P* for non-inferiority = 0.35 |                                                                                                |

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| PRECOMBAT13,17 | 2011 | 13    | 600  | 25        | 32     | 45      | 64         | 73      | DP-SES           | 94      | Death, stroke, MI, ID-TLR at 1 year: 8.7% vs. 6.7%, P for non-inferiority = 0.01 | *Death, stroke, MI, or ID-TLR at 5 years: 17.5% vs. 14.3%, P = 0.26*  
|            |      |       |      |           |        |         |            |         |                  |         | *Death, stroke, or MI at 5 years: 8.4% vs. 9.6%, P = 0.66*  
|            |      |       |      |           |        |         |            |         |                  |         | *Death at 5 years: 5.7% vs. 7.9%, P = 0.32*  
|            |      |       |      |           |        |         |            |         |                  |         | *Stroke at 5 years: 0.7% vs. 0.7%, P = 0.99*  
|            |      |       |      |           |        |         |            |         |                  |         | *MI at 5 years: 2% vs. 1.7%, P = 0.76*  
|            |      |       |      |           |        |         |            |         |                  |         | *Repeat revascularization at 5 years: 13% vs. 7.3%, P = 0.02*  |
| EXCEL4     | 2017 | 126   | 1905 | 21        | 29     | 24      | 81         | 51      | DP-EES           | 99      | Death, stroke, or MI at 3 years: 15.4% vs. 14.7%, P for non-inferiority = 0.02, P = 0.98 for superiority | *Death, stroke, MI, or IDR at 3 years: 23.1% vs. 19.1%, P for non-inferiority = 0.01*  
|            |      |       |      |           |        |         |            |         |                  |         | *Death at 3 years: 8.2% vs. 5.9%, P = 0.11*  
|            |      |       |      |           |        |         |            |         |                  |         | *Stroke at 3 years: 2.3% vs. 2.9%, P = 0.37*  
|            |      |       |      |           |        |         |            |         |                  |         | *MI at 3 years: 8.0% vs. 8.3%, P = 0.64*  
|            |      |       |      |           |        |         |            |         |                  |         | *IDR at 3 years: 12.6% vs. 7.5%, P < 0.001*  
|            |      |       |      |           |        |         |            |         |                  |         | *Death at 5 years: 12% vs. 9%, P = 0.77*  
|            |      |       |      |           |        |         |            |         |                  |         | *Stroke at 5 years: 5% vs. 2%, P = 0.073*  
|            |      |       |      |           |        |         |            |         |                  |         | *Non-procedural MI at 5 years: 7% vs. 2%, P = 0.004*  
|            |      |       |      |           |        |         |            |         |                  |         | *Repeat revascularization at 5 years: 16% vs. 10%, P = 0.032*  |
| NOBLE5     | 2017 | 36    | 1201 | 22        | 15     | 17      | 81         | NR      | BP-BES, DP-SES   | 93      | Death, stroke, non-procedural MI, repeat revascularization at 5 years: 29% vs. 19%, P = 0.0066 | |

ACS, acute coronary syndrome; BMS, bare metal stent; BP-BES, biodegradable-polymer biolimus–eluting stent; CVA, cerebrovascular accident; DES, drug-eluting stent; DM, diabetes mellitus; DP-EES, durable-polymer everolimus–eluting stent; DP-SES, durable-polymer sirolimus–eluting stent; DP-PES, durable-polymer paclitaxel–eluting stent; FU, follow-up; IDR, ischaemia–driven revascularization; ID-TLR, ischaemia–driven target lesion revascularization; IMA, internal mammary artery; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MVD, multivessel disease; NR, not reported; SYNTAX, SYNTAX score.
generally expected to favour CABG over PCI, a sizeable proportion of saphenous vein grafts is known to degenerate between 3 and 5 years, and bilateral arterial grafting was quite low in both the EXCEL (28%) and NOBLE (8%) trials. As such, long-term follow-up from the available trials is of utmost interest and the local heart teams should be aware of the limitations of the existing literature with respect to the maximum follow-up available in contemporary randomized comparisons of PCI and CABG. Finally, a higher rate of stroke was observed in the PCI arm of the NOBLE trial at 5 years (5% vs. 2% in the CABG group, P = 0.07). These events mostly occurred between 30 days and 5 years (e.g. beyond the periprocedural period), an inexplicable finding not seen in any other randomized trial of PCI vs. CABG which likely was due to chance. In the EXCEL trial, the rates of stroke at 3 years were 0.6% and 1.3% in the PCI and CABG arm, respectively (P = 0.15).

Meta-analyses of percutaneous coronary intervention vs. coronary artery bypass grafting

In a meta-analysis of the 4 largest studies of LMCA revascularization with follow-up available at 3 to 5 years, incorporating data from the EXCEL and NOBLE trials, the hazard ratio (HR) for death, stroke, or MI with PCI compared with CABG was neutral (1.06) in a random-effects model (P = 0.60).22 Based on individual patient data reconstruction, the Kaplan–Meier estimates of death, stroke, or MI at 5 years were 18.3% for PCI and 16.8% for CABG (P = 0.52). No statistically significant subgroup interaction for this combined outcome was noted across studies based on the generation of DES used for PCI (P for interaction = 0.25). There were no significant differences in the pooled effects for death (HR 1.04, P = 0.77) and cardiac death (HR 1.00, P = 0.99). The endpoints of MI and stroke were also not significantly different between PCI and CABG (HRs of 1.48, P = 0.17 and 0.87, P = 0.72, respectively) but these outcomes were confounded by high heterogeneity across the trials. Repeat revascularization was consistently higher with PCI in all trials, outcomes were confounded by high heterogeneity across the trials. In another meta-analysis, including all the six trials available so far, missing data were collected by the principal investigators, enabling further subgroup analyses.23 PCI was found to significantly reduce death, MI, or stroke by 36%, and stroke by 64% within 30 days. Percutaneous coronary intervention reduced periprocedural MI by 33%, largely driven by the results of the EXCEL trial, but this effect was offset by 93% more spontaneous MIs beyond 30 days after PCI. Cardiac death differed in relation to angiographic complexity, such that it tended to be lower with PCI among patients with low SYNTAX scores and higher in patients with high SYNTAX scores.23 Head et al.14 recently published a large (n = 11 518) collaborative, pooled analysis of individual patient data from 11 trials comparing PCI and CABG for LMCA or multivessel coronary artery disease (CAD). Among 4478 patients with LMCA disease, the 5-year rate of death was similar between PCI and CABG (10.7% vs. 10.5%, HR 1.07, 95% confidence interval 0.87–1.33; P = 0.52), regardless of diabetes status and SYNTAX score.

Guidelines for left main revascularization

Recommendations for LMCA revascularization have slowly evolved over time in both Europe and the USA as new evidence became available (Figure 2). Released after the publication of the SYNTAX trial, the 2010 guidelines for myocardial revascularization and the 2013 guidelines for stable CAD from the European Society of Cardiology recommended CABG regardless of anatomic complexity (Class I, level of evidence A), and PCI with IIa or IIb classes of recommendations and levels of evidence B for selected LMCA patients depending on lesion location, vessel involvement and/or SYNTAX score.27,28 Based on current 2014 guidelines from the European Society of Cardiology, LMCA patients with stable angina or silent ischaemia should undergo revascularization in case of a >90% stenosis or in case of a ≥50% to 90% stenosis with documented ischaemia or fractional flow reserve (FFR) ≤ 0.80 (Class I, level of evidence A).29 Coronary artery bypass grafting is recommended in all patients with stable CAD with suitable coronary anatomy and low predicted surgical mortality (Class I, level of evidence B). The recommendations for PCI vary depending on whether the SYNTAX score is low (Class I, level of evidence B), intermediate (Class IIa, level of evidence B), or high (Class III, level of evidence B). Corresponding classes for PCI of the LMCA across SYNTAX score tertiles from the USA guidelines (also from 2014) are currently IIa, IIb, and III.30 Both guidelines emphasize the need for a Heart Team approach when revascularization strategies for LMCA disease are appraised. However, neither the 2014 European Society of Cardiology or USA guidelines incorporated data from the EXCEL and NOBLE trials, as well as the results of the pooled analysis from Head et al. Updated societal guidelines from

Registries of left main coronary artery percutaneous coronary intervention

Large registries of revascularization for LMCA disease representing different geographies are useful resources to generalize the findings from randomized trials in the daily scenario. The Fu-Wai, IRIS-MAIN and DELTA-2 registries cover a treatment period that goes from 2004 to 2015.6,23,26 Compared with PCI patients enrolled in the EXCEL trial, the mean SYNTAX score in these registries tended to be higher but still fell in the low to intermediate risk category (Table 2). In the DELTA-2 study, the largest registry of LMCA PCI with second-generation DES (n = 3986), Kaplan–Meier estimates of events at 2 years were 9.5% and 16.7% for death or target vessel revascularization, respectively.6 Hazard ratios for PCI vs. CABG with respect to the composite of death, stroke, or MI were 1.06 and 0.91 in the two registries with 3-year follow-up available,23,26 the comparable rates with the two revascularization options thus being consistent with the conclusions from the EXCEL trial.
both continents reflecting these contemporary results are expected this year and may expand the recommendations for PCI in LMCA disease, e.g. to selected patients with high SYNTAX scores.14,31

Standards of left main percutaneous coronary intervention

Risk stratification

The long-term prognosis of LMCA patients undergoing revascularization can be meaningfully stratified by means of anatomical and clinical variables collectively integrated into risk scores.22 This information is useful to inform patients and their families, as well as to guide decision-making for PCI or CABG within the Heart Team. The SYNTAX score is a purely anatomical scoring system that grades the coronary vasculature based on the extent of CAD and lesion complexity.33 LMCA disease frequently presents with downstream multivessel involvement, which requires a careful appraisal when it comes to decide the best option for revascularization.14 In general, patients with high SYNTAX scores undergoing PCI are less likely to achieve complete revascularization, 16 although increasing use of physiology guidance to identify those territories requiring revascularization and modern techniques for recanalization of chronic total occlusions may improve outcomes in patients with extensive disease.34

Notably, in the pooled analysis of Head et al.,14 mortality from PCI and CABG did not differ at 5 years in patients with LMCA disease according to the SYNTAX score tertile. Indeed, modifications of the SYNTAX score have been introduced over time to refine its prognostic ability.25 For example, the SYNTAX score 2 attains moderate discrimination for 4-year mortality after PCI or CABG by integration of seven clinical (age, sex, chronic obstructive pulmonary disease, peripheral vessel disease), imaging (left ventricular ejection fraction), laboratory (creatinine clearance), and angiographic (presence of LMCA disease) domains.36–38 However, the value of the SYNTAX score 2 for decision-making in LMCA revascularization has not been investigated as extensively as for the SYNTAX score.

In the derivation cohort of the SYNTAX score 2, comprised of patients with LMCA disease and/or three-vessel disease from the SYNTAX trial, diabetes mellitus was not a modulator of the relative rates of 4-year survival after PCI or CABG by integration of seven clinical (age, sex, chronic obstructive pulmonary disease, peripheral vessel disease), imaging (left ventricular ejection fraction), laboratory (creatinine clearance), and angiographic (presence of LMCA disease) domains.36–38 However, the value of the SYNTAX score 2 for decision-making in LMCA revascularization has not been investigated as extensively as for the SYNTAX score.

In the derivation cohort of the SYNTAX score 2, comprised of patients with LMCA disease and/or three-vessel disease from the SYNTAX trial, diabetes mellitus was not a modulator of the relative rates of 4-year survival after PCI or CABG.36 In the large individual patient data pooled meta-analysis of Head et al.,14 diabetes mellitus modified the treatment effect of PCI vs. CABG on 5-year mortality in patients with multivessel disease, but not in those with LMCA disease.

Strategy and technique

Left main coronary artery patients treated by experienced operators (e.g. operators who performed at least 15 LMCA PCIs per year for at least 3 consecutive years) have better short- and long-term outcomes compared with LMCA patients treated by operators who are less experienced.39 PCI of the LMCA ostium or shaft is a straightforward procedure that is associated with a lower need for late repeat revascularization than PCI of the distal bifurcation.40 The ostium of the LMCA lacks the tunica adventitia and is richer in smooth muscle
cells and elastic tissue than any other portion of the LMCA and its branches, which requires attention to ensure that stent expansion is adequate.41 From a technical standpoint, the distal LMCA differs from the other bifurcations in several characteristics (Figure 3). The European Bifurcation Club recommends a provisional side branch approach in most cases of distal bifurcation LMCA disease (Figure 4).43 This includes adjunctive plaque modification as necessary (e.g. in case of severe calcification) and a single stent approach with proximal optimization. While the provisional approach is sufficient in a vast proportion of patients, the threshold for placing a second stent in the side branch may be lower in LMCA compared with non-LMCA bifurcations. Bailout side branch stenting may be carried out after main branch stenting with the T and small protrusion (TAP) or culotte techniques. When there is a high chance of bailout stenting, then it is preferable to undertake a planned two-stent strategy, particularly in cases with long LCx lesions, high risk of LCx compromise or difficult access. Elective two-stent strategies include T- or TAP-stenting, culotte and mini-crush or double-kissing crush techniques. All two-stent strategies should be finalized with a kissing balloon inflation and proximal optimization.43 Simultaneous kissing stents may also be considered for the haemodynamically unstable patient, although this approach has fallen out of favour because of the creation of a new carina and side branch access issues. Two moderate-sized randomized trials have compared the double-kissing crush technique with the culotte and provisional stenting strategies, respectively, for the treatment of true LMCA bifurcations lesions involving the ostium of the side branch.45,46 In both studies, the double-kissing crush technique significantly reduced the primary composite ischaemic endpoint (Table 3). As such, double-kissing crush has emerged as a preferred approach for true distal LMCA bifurcation lesions, although this technique is technically challenging and should be performed by expert operators. The European Bifurcation Club Left Main Study (EBC MAIN), another randomized trial comparing single vs. dual stenting strategies for the treatment of true bifurcation LMCA lesions, is ongoing (Table 4).47

**Stent selection**

The design of a stent may impact its expansion capability, an important attribute in the setting of LMCA PCI where proximal optimization is used to correct for the mismatch in vessel size between the LMCA, LAD, and LCx. Large diameter mismatches increase the risk of overstretching or under-expansion with malapposition; the stent model design should be always considered for optimal sizing.48 Most DES are now available in sizes of 4.5 and/or 5.0 mm and have sufficient cell opening capacity, facilitated by proximal optimization. In the EXCEL trial, the risk of definite thrombosis at 3 years with the durable-polymer everolimus-eluting stent was only 0.7%.4 In a randomized comparison, the use of zotarolimus-eluting and everolimus-eluting stents provided comparable clinical and angiographic outcomes at 1-year follow-up.49 In a pooled analysis of three prospective registries involving unrestricted use of various second-generation DES for LMCA disease, no significant between-group differences were found in several ischaemic endpoints, and the incidence of stent thrombosis was <1% for all type of stents.50 Trials comparing biodegradable- vs.
durable-polymer DES and dedicated vs. standard DES in patients with LMCA disease are ongoing (Table 4).

Intravascular imaging guidance

Intravascular ultrasound (IVUS) characterizes the vessel size and the distribution of the plaque within the LMCA and its daughter branches, enabling accurate minimal lumen area (MLA) measurements at the cross-sectional level. In a prospective study, an IVUS-derived MLA of \( > 6 \) mm\(^2\) identified candidates for safe deferral of LMCA revascularization.\(^{51}\) In patients with isolated ostial and shaft intermediate LMCA stenosis, a smaller MLA of \( < 4.5 \) mm\(^2\) has been proposed as a useful surrogate of functional significance.\(^{52}\) Ideally, a dual pullback from the LAD and LCx should be used to fully characterize the LMCA bifurcation and avoid overestimation, for example, of the MLA at the LCx ostium from a LAD pullback. After stent implantation, IVUS guidance (with post-dilation as necessary) ensures adequate expansion at the level of the ostial LAD, the ostial LCx, the polygon of confluence (e.g. the convergence zone of the LMCA, LAD, and LCx) and the LMCA above the polygon of confluence, achievement of which has been associated with improved survival.\(^{53}\)

IVUS is also helpful in detecting post-stenting complications (e.g. dissection, stent deformation) and guide their appropriate management. In observational studies, elective stenting with IVUS guidance has been shown to reduce long-term mortality and improve clinical outcomes compared with angiographic guidance alone.\(^{54-56}\) Optical coherence tomography is a feasible alternative to IVUS for the assessment of non-ostial LMCA disease prior and after stenting.\(^{57,58}\)

Physiology guidance

Physiology guidance by means of FFR or instantaneous wave-free ratio (iFR) may be helpful in the evaluation of intermediate or ambiguous LMCA lesions.\(^{59}\) In this setting, the visual-functional mismatch between coronary angiography and FFR can be as high as 30–40%,\(^{60,61}\) and deferring LMCA PCI based on FFR values \( > 0.75 \) or \( 0.80 \) has been shown to be safe.\(^{61-63}\) The LMCA location poses some challenges in FFR evaluation due to the frequent distal location with involvement of the LAD and LCx ostia requiring a dual pullback, and because the value may be influenced (either raised or lowered) by the presence and the amount of myocardium supplied by severe tandem lesions downstream in the coronary vasculature, depending on the position of the pressure sensor.\(^{62}\) This effect may be avoided by positioning the pressure wire in a non-diseased vessel,\(^{64,65}\) although this theoretically may also lead to an artificially higher FFR value. Using iFR ‘scout’ pullbacks might also be useful in such situations by facilitating a physiological mapping of individual serial stenoses.\(^{66}\) Other potential applications of FFR/iFR for LMCA PCI guidance include the post-stenting evaluation of jailed LAD and LCx ostial lesions and the

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**Figure 3** Characteristics of the left main coronary artery bifurcation which makes it a more challenging lesion than other non-left main coronary artery bifurcations. (A) A case example of notable mismatch between the left main coronary artery and the left anterior descending artery, hampering the selection of an adequately sized stent (e.g. a large diameter stent sized to the left main coronary artery implanted across the left circumflex may result in dissection or perforation of the left anterior descending artery; a smaller diameter stent sized to the left anterior descending artery may result in malapposition in the left main coronary artery). (B) A case example of left main coronary artery disease in a left-dominant coronary system, jeopardizing a large territory of myocardium.
assessment of non-LMCA stenoses (followed by treatment as necessary).

**Medical therapy**

Despite the undisputed benefits of guideline-directed medical therapy for secondary prevention after PCI, compliance has been shown to be low even in the controlled environment of randomized clinical trials. In a review of five trials which included SYNTAX and EXCEL, compliance with the combination of any antiplatelet agent, beta-blocker, and statin was only 63% at 1 year and 53% at 5 years, with higher proportions noted in PCI-treated compared with CABG-treated patients. There is a lack of information regarding the benefit and risk of different durations of dual antiplatelet therapy after LMCA PCI.

**Percutaneous coronary intervention in the emergency setting**

In a Swiss registry, about 5% of patients undergoing primary PCI for ST-segment elevation MI received a stent in the LMCA. In-hospital mortality for these patients was about 4-fold higher than in non-LMCA lesions, and the mortality of patients presenting with cardiogenic shock at admission was 55%. Patients with acute MI due to LMCA disease should be stabilized with appropriate haemodynamic support and undergo immediate PCI. Salvage PCI of the LMCA may be also required due to iatrogenic complications such as dissection (e.g. guiding catheter manipulation), perforation (e.g. retrograde chronic total occlusion recanalization), or occlusion (e.g. transcatheter aortic valve implantation), all of which are associated with high mortality and are best avoided.

**Conclusions**

Against a background of accruing supporting evidence, LMCA PCI has become a viable option in daily practice not only for patients whose characteristics resemble those of patients randomized in the EXCEL trial, but also for patients who do not fulfil the trial criteria (e.g. those with acute MI or unsuitability for CABG). In general, PCI offers more rapid recovery and a lower early adverse event rate, whereas CABG offers a more durable procedure (Figure 5). However, the relative outcomes of PCI vs. CABG are determined by a complex interplay of patient comorbidities, coronary anatomic complexity and ventricular function, and other less tangible factors such as operator expertise and likely medication compliance. Whether the individual patient with LMCA disease is best served by PCI vs. CABG is a decision that should be made by the local heart team consisting of a general cardiologist, interventional cardiologist, and cardiac surgeon, considering the clinical circumstances, the
<table>
<thead>
<tr>
<th>Trial</th>
<th>Year</th>
<th>Sites</th>
<th>N</th>
<th>SS (mean)</th>
<th>DM (%)</th>
<th>ACS (%)</th>
<th>True bifurcation (1,1,1 or 0,1,1) (%)</th>
<th>Comparison</th>
<th>SB pre-D</th>
<th>Bailout SB stenting (Provisional group)</th>
<th>FKI (%)</th>
<th>Primary endpoint (Group 1 vs. 2)</th>
<th>Key secondary endpoints at the longest FU (Group 1 vs. 2)</th>
</tr>
</thead>
</table>
| DKCRUSH-III  | 2013 | 18    | 419 | 31        | 31     | 72      | 100                                 | DK-Crush vs. culotte stenting | NR       | NA                                    | 100 vs. 100 | Cardiac death, MI, or TVR 1 year: 6.2% vs. 16.3%, P = 0.001 | • Cardiac death at 3 years: 1.4% vs. 2.9%, P = 0.34  
• MI at 3 years: 3.4% vs. 8.2%, P = 0.037  
• TLR at 3 years: 3.8% vs. 14%, P < 0.001  
• ST at 3 years: 0% vs. 3.9%, P = 0.004  
• Restenosis at 8 months: 6.8% vs. 12.6%, P = 0.037  
• Cardiac death at 1 year: 1.2% vs. 2.1%, P = 0.48  
• Target- vessel MI at 1 year: 0.4% vs. 2.9%, P = 0.03  
• Clinically-driven TLR at 1 year: 3.8% vs. 7.9%, P = 0.06  
• ST at 1 year: 0.4% vs. 3.3%, P = 0.02  
• Restenosis at 13 months: 7.1% vs. 14.6%, P = 0.10 |
| DKCRUSH-V    | 2017 | 26    | 482 | 31        | 27     | 72      | 100                                 | DK-Crush vs. provisional stenting | 40%      | 47%                                    | 100 vs. 79 | Cardiac death, target-vessel MI, or clinically-driven TLR at 1 year: 5% vs. 10.7%, P = 0.02 |

ACS, acute coronary syndrome; DM, diabetes mellitus; FKI, final kissing balloon inflation; FU, follow-up; MI, myocardial infarction; NA, not applicable; NR, not reported; pre-D, pre-dilatation; SB, side branch; SS, SYNTAX score; ST, stent thrombosis; TLR, ischaemia-drive target lesion revascularization; TVR, target vessel revascularization.
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Country</th>
<th>N</th>
<th>Population</th>
<th>Intervention</th>
<th>Control</th>
<th>Follow-up</th>
<th>Primary outcome measure(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDEAL-LM (NCT02303717)</td>
<td>Randomized</td>
<td>UK</td>
<td>818</td>
<td>Left main disease PCI</td>
<td>BP-EES Provisional stenting</td>
<td>DP-EES Planned 2-stent strategy</td>
<td>24 months</td>
<td>Death, MI, ischaemia-driven TVR</td>
</tr>
<tr>
<td>EBC-MAIN (NCT02497014)</td>
<td>Randomized</td>
<td>Denmark, France, Germany, Italy, Latvia, Serbia, Spain, UK</td>
<td>450</td>
<td>Left main bifurcation disease PCI</td>
<td>Provisional stenting</td>
<td></td>
<td>12 months</td>
<td>Death, MI, or TLR</td>
</tr>
<tr>
<td>ATP Study (NCT02127138)</td>
<td>Randomized</td>
<td>China</td>
<td>316</td>
<td>Left main bifurcation disease PCI</td>
<td>Active transfer of plaque technique</td>
<td>Provisional stenting</td>
<td>12 months</td>
<td>TLR</td>
</tr>
<tr>
<td>OPTIMAL (NCT03282773)</td>
<td>Randomized</td>
<td>China</td>
<td>480</td>
<td>Left main disease and acute myocardial infarction</td>
<td>Deferred DES implantation</td>
<td>Immediate DES implantation</td>
<td>30 days</td>
<td>Death or MI</td>
</tr>
<tr>
<td>POLBOS II (NCT02198300)</td>
<td>Randomized</td>
<td>Poland</td>
<td>202</td>
<td>Left main bifurcation PCI</td>
<td>Biolimus-eluting dedicated bifurcation DES</td>
<td>DES</td>
<td>12 months</td>
<td>Death, MI, or TLR</td>
</tr>
<tr>
<td>TRUNC (NCT02800837)</td>
<td>Observational</td>
<td>Italy, Switzerland, UK</td>
<td>200</td>
<td>Left main disease PCI</td>
<td>Self-expanding DES</td>
<td>NA</td>
<td>1 year</td>
<td>Cardiac death, target vessel MI, clinically-driven TLR, Death, MI or TLR</td>
</tr>
<tr>
<td>OPTIMUM (NCT02996877)</td>
<td>Observational</td>
<td>USA</td>
<td>800</td>
<td>High-risk left main or multivessel disease PCI</td>
<td>PCI plus GDMT</td>
<td>NA</td>
<td>30 days</td>
<td>Death, MI, or TLR</td>
</tr>
<tr>
<td>MAIN COMPARE (NCT02791412)</td>
<td>Observational</td>
<td>South Korea</td>
<td>2000</td>
<td>Left main disease PCI</td>
<td>PCI</td>
<td>CABG</td>
<td>10 years</td>
<td>Death, MI, revascularization</td>
</tr>
<tr>
<td>IRIS-MAIN (NCT01341327)</td>
<td>Observational</td>
<td>China, South Korea, Malaysia, Taiwan, Thailand</td>
<td>10000</td>
<td>Left main disease PCI</td>
<td>PCI</td>
<td>CABG, GDMT</td>
<td>10 years</td>
<td>NR</td>
</tr>
<tr>
<td>ROLEX (NCT03316833)</td>
<td>Observational</td>
<td>Italy</td>
<td>450</td>
<td>Left main disease PCI</td>
<td>DP-ZES</td>
<td>NA</td>
<td>12 months</td>
<td>Cardiac death, target vessel MI, ischaemia-driven TLR, Cardiac death, non-periprocedural MI, TLR, ST</td>
</tr>
<tr>
<td>eTRYTON-LM (NCT02765646)</td>
<td>Observational</td>
<td>Germany</td>
<td>100</td>
<td>Left main bifurcation disease PCI</td>
<td>Dedicated bifurcation stent</td>
<td>NA</td>
<td>9 months</td>
<td>Cardiac death, non-periprocedural MI, TLR, ST</td>
</tr>
</tbody>
</table>

BP-EES, biodegradable-polymer everolimus-eluting stent; CABG, coronary artery bypass grafting; GDMT, guideline-directed medical therapy; DES, drug-eluting stent; DP-EES, durable-polymer everolimus-eluting stent; DP-ZES, durable-polymer zotarolimus-eluting stent; MI, myocardial infarction; NA, not applicable; NR, not reported; PCI, percutaneous coronary intervention; TLR, target lesion revascularization; TVR, target vessel revascularization; ST, stent thrombosis.
Figure 5 Determinants of decision-making and patient consent in revascularization choices for left main coronary artery disease in patients amenable to both percutaneous coronary intervention and coronary artery bypass grafting. Advantages of each procedure are reported in bold. CABG, coronary artery bypass grafting; LMCA, left main coronary artery; PCI, percutaneous coronary intervention; PROMs, patient-reported outcomes.
References


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;9:1564–1572.


