Abstract
Left main stem (LMS) disease is identified in up to 5% of diagnostic angiography cases, and is associated with significant morbidity and mortality due to the proportion of myocardium it subtends. In the past 10 years, there has been a significant change in the way we contemplate treating lesions in the LMS due to evolving experience and evidence in percutaneous coronary intervention (PCI) strategies and technologies. This has been reflected in recent changes in European and International guidance on managing patients with this lesion subset. Here, the authors provide an overview of the current literature regarding the management of LMS disease using PCI in light of new developments and emerging concepts in this field, specifically looking at the recent EXCEL trial.

Keywords
Left main stem, percutaneous coronary intervention, coronary artery bypass grafting, EXCEL, major adverse cardiovascular events, target lesion revascularisation, MI

Evidence from Randomised Controlled Trials
The first large RCT comparing PCI to CABG in LMS disease was the SYNTAX trial, in which 1,800 patients were randomised to receive either the first-generation TAXUS (Boston Scientific) DES or CABG. Prior to randomisation, diagnostic angiograms were scored based on the SYNTAX score, which was originally developed to objectively quantify anatomical and lesion complexity. Cases were then divided into tertiles (SYNTAX score of 0–22, 23–32 and >32) based on lesion complexity. It became apparent that CABG was superior when treating complex disease (i.e. SYNTAX score of >32), with equivalent MACCE in the lower two tertiles. The 5-year follow-up data demonstrated MACCE rates of 36.9% in the PCI group versus 31% in the CABG group (p=0.12), with higher rates of stroke with CABG (1.5% versus 4.3%, p=0.03) and higher rates of repeat revascularisation with PCI (26.7% versus 15.5%, p<0.01). CABG had better outcomes in both high and intermediate tertiles at 5 years. The 10-year follow-up results in the LMS subgroup have since been published and demonstrate a similar trend in MACCE to the 1-year follow-up data (n=1689, 26% mortality with PCI versus 28% with CABG, p=0.019), with similar outcomes across the whole cohort, but a statistically greater benefit of CABG in the highest risk group based on lesion complexity (28% mortality in three-vessel disease with PCI versus 21% with CABG).
Other smaller RCTs that have assessed the non-inferiority of LMS PCI to CABG include the LE MANS and PRECOMBAT trials, as well as a trial by Boudriot et al.12-14 These studies had different endpoints and were also limited by sample size, older-generation stents and the lack of recommended intracoronary imaging.

More recently, the 5-year follow-up data from the Evaluation of XIENCE versus Coronary Artery Bypass Graft Surgery for Effectiveness of Left Main Revascularization (EXCEL) and the NOBLE trials have been published.15,16 NOBLE was a non-inferiority trial that randomised 1,201 patients with LMS disease to either PCI using DESs (BioMatrix Flex stent) or CABG.17 Interestingly, this trial demonstrated inferiority in the PCI-treated group at 5-year follow-up (p=0.0002). This was driven by higher MACCE (all-cause mortality, non-procedural MI, repeat revascularisation or stroke) rates in the PCI group (28.4% versus 19%, 95% CI [1.24–2.01]), caused by higher rates of non-procedural MI (7.6% versus 2.7%, 95% CI 1.66-5.39) and repeat revascularisation (17% versus 10.2%, 95% CI [1.25–2.40]). There were no significant differences in all-cause mortality (9.4% versus 8.7%, 95% CI [0.74–1.59]) or stroke (4% versus 2%, 95% CI [0.86–3.55]).17

The EXCEL trial was also a non-inferiority trial, in which 1,905 patients with LMS disease of low or intermediate complexity (as assessed by the SYNTAX score, i.e. <32) to either PCI using a second-generation Xience fluoropolymer-based cobalt-chromium everolimus DES (948 patients) or CABG (957 patients).18 The primary endpoint was a composite of death from any cause, stroke or MI at 3 years. The secondary endpoints were a composite of death from any cause, stroke or MI at 30 days, and a composite of death, stroke, MI or ischaemia-driven revascularisation at 3 years.

We used the Society of Cardiovascular Angiography and Interventions (SCAI) definition of MI after PCI or CABG, which included three main criteria.19 First, in patients with normal baseline creatinine kinase-MB (CK-MB), the definition of MI is based on when the peak CK-MB (measured within 48 hours) of the procedure rises to ≥10 times the local laboratory upper limit of normal (ULN) or to ≥5 times the local laboratory ULN with new pathological Q-waves in ≥2 contiguous leads or new persistent left bundle branch block (LBBB), or in the absence of CK-MB measurements, and a normal baseline cardiac troponin (cTn), a cTn I (or T) level (measured within 48 hours of the PCI) rises to ≥70 times the local laboratory ULN, or ≥35 times the local laboratory ULN with new pathological Q-waves in ≥2 contiguous leads, or new persistent LBBB. Second, in patients with already elevated baseline CK-MB (or cTn) in whom the biomarkers are stable or falling, the definition of MI is based on the rise of CK-MB (or cTn) by an absolute increment equal to those levels recommended above from the most recent pre-procedure level. Third, in patients with elevated baseline CK-MB (or cTn) in whom the biomarker levels have not been shown to be stable or falling, the definition of MI is based on the rise in CK-MB (or cTn) by an absolute increment equal to those levels recommended above plus new ST-segment elevation or depression plus signs consistent with a clinically relevant MI, such as new-onset or worsening heart failure or sustained hypotension.19 This is in contrast with the use of the third and fourth universal definition of MI specifically for type 4a for PCI-related MI and type 5 for CABG-related MI.20,21

The reasons for utilising the SCAI definition (for MI) that have been cited are based on the best available evidence linking biomarker abnormalities to subsequent mortality in large clinical trials, it avoids ascertainment bias and uses the same criteria for PCI and CABG. It is also said to avoid the pitfall of tabulating MI events that are small enough not to have clinical impact and instead permits assessment of MI events that are likely to be clinically relevant.22 At 3 years, the primary endpoint occurred in 15.4% of patients in the PCI group and in 14.7% of patients in the CABG group (difference: 0.7% points, upper 97.5% confidence limit: 4% points, p=0.02 for non-inferiority; HR: 1.00, 95% CI [0.79–1.26], p=0.98 for superiority). The secondary endpoint at 30 days occurred in 4.9% of patients in the PCI group and 7.9% in the CABG group (p=0.001 for non-inferiority, p=0.008 for superiority). The secondary endpoint at 3 years occurred in 23.1% of patients in the PCI group and 19.1% in the CABG group (p=0.01 for non-inferiority, p=0.10 for superiority).

The 5-year outcomes of the EXCEL trial were presented at the Transcatheter Cardiovascular Therapeutics (TCT) conference in 2019.16 At 5 years, the primary outcome occurred in 22% of patients in the PCI group and in 19.2% of patients in the CABG group (difference 2.8% points, 95% CI [−0.9, 6.5], p=0.13).15 The incidence of cardiovascular death (5% and 4.5%, respectively; difference 0.5%, 95% CI [-1.4, 2.5]) and MI (10.6% and 9.1%, respectively; difference 1.4% points, 95% CI [−1.3, 4.2]) was similar in the PCI and CABG arms. Ischaemia-driven revascularisation was also more frequent in the PCI arm compared with the CABG arm (16.9% versus 10%; difference, 6.9% points; 95% CI [3.7–10.0]). Death due to any cause occurred more frequently in the PCI arm compared with the CABG arm (13% versus 9.9%, difference: 3.1% points, 95% CI [0.2–6.1]). Eighteen of 30 deaths due to any cause in the PCI arm were adjudicated as non-cardiovascular deaths; five were definite cardiovascular deaths and seven had an undetermined cause. There was a non-significant increase in stroke rate in the CABG treatment group.

No significant difference was found between PCI and CABG in the composite outcome of death, stroke or MI at 5 years for patients with LMS disease with low or intermediate anatomical complexity, as assessed by the SYNTAX score.

There were three distinct intervals of relative efficacy between PCI and CABG. From 0 to 30 days, there were a greater number of events (death, stroke or MI) in the CABG group (8%) than in the PCI group (4.9%). From 30 days to 1 year, event rates were similar for PCI (4.1%) and CABG (3.8%), but between 1 and 5 years, PCI patients experienced a higher rate of events than their CABG counterparts (15.1% and 9.7%, 95% CI [1.23–2.12], with curves continuing to diverge over time. This is similar to the 10-year follow-up in the SYNTAX trial, which demonstrated a clear benefit for CABG in the higher SYNTAX tertiles, based on complexity, even at 10 years.20

Following the EXCEL and NOBLE trials, in 2018 the European Society of Cardiology–European Association for Cardio-Thoracic Surgery (ESC/EACTS) jointly published the guidelines on myocardial revascularisation, in which LMS revascularisation with low SYNTAX LMS CAD was considered a class I level of evidence A for both PCI and CABG, and intermediate SYNTAX LMS CAD as a class Ia level of evidence A for PCI (IA for CABG).21

Controversies

Following the TCT presentation of the 5-year EXCEL data, there has been significant controversy regarding the use of the SCAI definition of MI, rather than the universal definition, being implemented. The SCAI definition of MI includes clinically relevant Ms, rather than basing the diagnosis mainly on biomarker elevation, which is the case in the universal definition.24 In December 2019, the EACTS withdrew its support from the chapter of the joint ESC/EACTS practice guidelines for myocardial revascularisation in LMS disease due to concerns regarding misleading results from the EXCEL trial because of the use of the SCAI definition for
MI. There was also concern regarding the underrepresentation of the higher rate of all-cause mortality detected within the PCI arm of the trial. The authors of the EXCEL trial responded and stated that this was an underpowered secondary endpoint, and therefore, was statistically uncertain; the clinical events committee adjudicated the excess to be due to non-cardiovascular causes. The EXCEL trial data are currently undergoing independent review by the New England Journal of Medicine and the Cardiovascular Research Foundation, which should clarify the published findings.

**Stent Technologies**

As with any PCI therapy, especially LMS PCI, it is important to minimise the need for further revascularisation. It is therefore vital to reduce the incidence of in-stent restenosis (ISR) and stent thrombosis (ST). Newer stent technology has led to improvements in restenosis, with data demonstrating that DESs are associated with a better outcome than bare metal stents, and same-generation DESs have shown similar clinical and angiographic outcomes.

**Evidence Assessing the Impact of Lesion Location**

Previous registry data have shown that approximately two-thirds of significant unprotected LMS disease involves the distal bifurcation. MACCE and target-vessel revascularisation are more prevalent in distal LMS disease compared with ostial or shaft disease, as shown by Naganuma et al. in the DELTA registry. An analysis of the cohort from the ISAR-LEFT-MAIN study has also shown the need for multiple stents as an independent predictor of adverse MACCE. Similar outcomes were seen in a subset of the SYNTAX and EXCEL trials. The DELTA registry demonstrated worse outcomes for PCI of distal LMS versus ostial/midshaft LMS. Overall, CABG was better for repeat revascularisation compared with PCI.

**Evidence for the Use of Intravascular Imaging**

Intravascular ultrasound (IVUS) has been given a level IIa (B) indication by the ESC for use in LMS PCI to assess stenosis severity. IVUS guidance for LMS PCI has never been formally investigated in an RCT, but registry data suggest improved outcomes.

In the EXCEL trial, 290 of the 948 patients randomised to PCI had both pre- and post-PCI IVUS. However, IVUS guidance was used in 722 of the 948 patients at some stage of the procedure, and it was strongly recommended to optimise stenting. In a subset of these 722 patients, it was found that a small initial minimal stent area (MSA), measured by IVUS after LMS PCI, was associated with adverse events (including death, MI and stent thrombosis) during long-term follow-up. Three MSA tertiles were assessed as small (4.4–8.7 mm²), intermediate (8.8–10.9 mm²) and large (11–17.8 mm²), with a primary endpoint of all-cause mortality, MI or stroke. A graded relationship was found between MSA tertiles with an improved primary endpoint and increasing MSA size (19.4%, n=32/172 in the smallest tertile; 16.1%, n=26/169 in the intermediate tertile; and 9.6%, n=15/163 in the largest tertile; p=0.01 for smallest versus largest tertile). A substudy in the NOBLE trial also demonstrated a significant reduction in TLR (5.1% versus 11.6%, p=0.01) with IVUS-guided stent optimisation for LMS PCI, but no difference in MACCE was found.

**Guidelines on LMS Revascularisation**

European and US societies have issued guidelines on revascularisation of patients with LMS disease. CABG maintains a class 1 indication across all anatomical subgroups. It is interesting to note that PCI assumes a stronger position in the ESC guidelines, with a class 1 recommendation in patients with a low SYNTAX score and 2A for an intermediate score. In contrast, the American College of Cardiology (ACC) guidelines give only a 2A recommendation for PCI for low scores and a 2B for intermediate scores.

Both societies are in agreement about the superiority of CABG for patients with a high SYNTAX score.

**Published European and US Guidelines for the Follow-up of Patients after Myocardial Revascularisation, Including LMS Intervention**

In all studies to date on the optimal follow-up after PCI, the gain from discovering patients with restenosis is obscured by the high rate of false-positive exercise ECG tests indicating ischaemia. Therefore, simple exercise ECG testing is not recommended for follow-up, and a non-invasive imaging approach is preferred. Specific studies clarifying which subset of patients benefits more from a specific follow-up approach are missing. The ESC guidelines for the follow-up for patients receiving revascularisation give a class 1C level of guidance to following patients up for symptomatic review after 3 months. If patients remain symptomatic, then a class 1C level of guidance is given to suggest further coronary angiography for these patients. If patients remain asymptomatic following high-risk PCI (including LMS PCI), then a level of evidence of Ib C is given for routine coronary angiography, or non-invasive stress testing at 6 months, 1 year and 5 years following PCI.

In the past, follow-up angiography was recommended (class IIa) between 2 and 6 months after PCI in patients who underwent unprotected left main revascularisation based on the 2005 ACC/American Heart Association PCI guidelines. This recommendation was removed in the 2009 focused update.

**Conclusion**

Following the recent publication of outcome data from large RCTs, there is now evidence to demonstrate equipoise between PCI and CABG management in patients with LMS disease with a low-to-intermediate SYNTAX score. As well as new-generation DES technologies and more advanced intravascular imaging modalities, this may lead to a change in practice with regard to treating these patients with PCI. This is especially important for the discussion of treatment options with the patient. It is important to consider that we do not have any longer follow-up data from these trials, and this these will be anticipated in the coming years. There is, however, an increase in spontaneous MI seen in PCI patients (both in the NOBLE and EXCEL trials), which at 5 years was balanced by an increase in procedural MIs in CABG patients (in the EXCEL trial), as well as consistent observations of increased repeat revascularisation in PCI patients (in all three trials: SYNTAX, NOBLE and EXCEL).

The EXCEL trial is undergoing independent review following the controversy discussed earlier. This controversy has led to loss of patient and public trust, and wide publication and escalation of the concerns in the media. It has also led to a deterioration in the relationship between the PCI community and the cardiothoracic surgical community. With the findings of the independent reviews, it is hoped that these relationships can be restored and strengthened.

From the viewpoint of the PCI community, the EXCEL trial has demonstrated significant advances in the outcomes of patients undergoing revascularisation for LMS disease with PCI, and this should still be considered within the forum of the multidisciplinary heart team when discussing optimal revascularisation within this patient group on an individualised basis and with patient involvement.
EXCEL Trial: The Interventionalists’ Perspective

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