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Treatment with a dedicated bifurcation sirolimus-eluting cobalt-chromium stent for distal left main coronary artery disease: rationale and design of the POLBOS LM study

Taku Asano[1,2], MD; Norihiro Kogame[1,3], MD; Yoshinobu Onuma[4,5], MD, PhD; Rodrigo Modolo[1,6], MD; Ply Chichareon[1,7], MD; Thierry Lefèvre[8], MD; Jacek Legutko[9], MD, PhD; Franck Digne[10], MD; Marie-Angèle Morel[5], BSc; Patrick W. Serruys[4]*, MD, PhD; Robert J. Gil[11,12], MD, PhD

The authors' affiliations can be found in the Appendix paragraph.

T. Asano and N. Kogame contributed equally to this article.

GUEST EDITOR: Antonio Colombo, MD; *Interventional Cardiology, Centro Cuore Columbus, Milan, Italy*

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KEYWORDS

- bifurcation
- drug-eluting stent
- left main

Abstract

Aims: The aim of this study is to demonstrate the non-inferiority of the BiOSS LIM C sirolimus-eluting cobalt-chromium bifurcation dedicated stent against the XIENCE stent regarding the patient-oriented composite endpoint (POCE) at 12 months among patients with left main coronary artery disease (LMCA).

Methods and results: The POLBOS LM study is a single-arm, prospective, multicentre study enrolling 260 patients (SYNTAX score ≤32) with a pre-specified performance goal based on the results of the EXCEL trial with contemporary percutaneous coronary intervention (PCI) for LMCA disease. Patient enrolment will comply with objective inclusion criteria of diameter stenosis ≥50% in the LMCA based on off-line quantitative coronary angiography (QCA) analysed by an independent core laboratory using dedicated bifurcation QCA software. The BiOSS LIM C is used for the treatment of LMCA disease with the same specific technical classification as for the BiOSS LIM (modified MADS classification) and the stent implantation is optimised by using pre-specified intravascular ultrasound criteria. The primary endpoint is POCE (a composite of all-cause death, stroke, any myocardial infarction, and any revascularisation) at 12 months.

Conclusions: The POLBOS LM study will indicate the efficacy of the BiOSS LIM C stent with contemporary PCI for distal left main bifurcation lesions in comparison with the XIENCE stent from the recent EXCEL trial, as a performance index.

**Corresponding author: Department of Cardiology, National University of Ireland, University Road, Galway, H91 TK33, Ireland. E-mail: patrick.w.j.c.serruys@gmail.com*

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Abbreviations

CABG	coronary artery bypass grafting
FFR	fractional flow reserve
iFR	instantaneous wave-free ratio
IVUS	intravascular ultrasound
KBI	kissing balloon inflation
LMCA	left main coronary artery
PCI	percutaneous coronary intervention
POT	proximal optimisation technique
QCA	quantitative coronary angiography

Introduction

BACKGROUND

Left main coronary artery (LMCA) disease is associated with a relatively large amount of myocardium at risk; therefore, percutaneous coronary intervention (PCI) for LMCA disease has been considered one of the challenging subsets. Coronary artery bypass grafting (CABG) has shown good long-term clinical outcome for LMCA disease, whereas, in historical studies of PCI for LMCA, a higher incidence of repeat revascularisation has been reported[1]. The lesion frequently involves bifurcation segments, especially when a lesion is located in the distal part of the LMCA[2]. In that case, stenting techniques tend to be complex, being associated with a high incidence of adverse events[1]. However, stent technology and implantation techniques have evolved with concomitant medical therapy such as $P2Y_{12}$ inhibitors, statins and PCSK9 inhibitors.

As a consequence, the clinical outcomes after LMCA stenting have become comparable to CABG for low- and intermediate-risk patients[3-5]. In the SYNTAX trial, which was the comparison trial of major adverse cardiac and cerebrovascular events (MACCE) between PCI using a first-generation paclitaxel-eluting stent and CABG, 705 patients had LMCA disease (LMCA subgroup). The five-year MACCE rate of the patients with low and intermediate SYNTAX scores (0-22 and 23-32) treated with PCI was comparable to that of the patients in the CABG group (low: 30.4% for PCI versus 31.5% for CABG, p=0.74; intermediate: 32.7% versus 32.3%, p=0.88)[3,6]. In the PRECOMBAT trial, comparing clinical outcomes after PCI using a first-generation sirolimus-eluting stent versus CABG in patients with LMCA disease (average SYNTAX score: 25), the five-year MACCE rate was comparable (17.5% for PCI versus 14.3% for CABG, p=0.26)[5]. The recent EXCEL trial was a prospective, international, open-label, multicentre trial that randomised 2,900 patients to compare PCI using a best-in-class stent (XIENCE; Abbott Vascular, Santa Clara, CA, USA) versus CABG in patients with LMCA disease with a SYNTAX score ≤32. In that trial, the three-year MACCE (all-cause mortality, stroke, or MI) rate in the PCI arm was non-inferior to the one in the CABG arm (15.4% versus 14.7%, p for non-inferiority=0.02)[4]. However, simultaneously with the publication of the EXCEL trial, the NOBLE trial (1,201 patients) reported that PCI treatment for LMCA disease failed to achieve non-inferiority against CABG in terms of the MACCE (all-cause mortality, non-procedural MI, any repeat coronary revascularisation and stroke) rate at five years[7]. In a recent meta-analysis including four studies as described previously, PCI and CABG showed comparable safety in patients with LMCA disease and low to intermediate SYNTAX scores, whereas repeat revascularisation was more common after PCI[8]. This suggests that the indication of PCI for LMCA disease should be discussed on a case-by-case basis by a local Heart Team.

THE BiOSS LIM C BIFURCATION-DEDICATED STENT AND THE RATIONALE OF THE STUDY

The difficulty of PCI treatment for LMCA lesions is presumably ascribed to the morphological complexity of the bifurcation such as vessel-size mismatch between the proximal main trunk and the distal branch, which can cause malapposition of the struts in the main trunk. Additionally, a complex multiple stent strategy is often required, which may result in considerable overlap and malapposition of the struts. It was reported that a two-stent strategy was associated with a stiffening process of the systolic and diastolic change in bifurcation angle and that this issue was an independent predictor of adverse events[9].

Dedicated bifurcation stents have been developed to reduce these potential issues. The BiOSS LIM C sirolimus-eluting cobalt-chromium stent (Balton, Warsaw, Poland) is a dedicated coronary bifurcation stent for provisional side branch stenting with a strut thickness of 70 µm. The device is designed for implantation from the proximal main vessel to the distal main vessel **(Figure 1)**, consisting of two main parts with different diameters with a 2.0-2.4 mm middle zone with two connecting struts. The ratio of the proximal part diameter to the distal part diameter varies between 1.15 and 1.3 mm, ensuring physiological compatibility and optimal flow conditions[10]. The bottle-shaped device balloon ensures the proximal optimisation technique (POT)-like effect after BiOSS LIM C implantation[11]. The maximum expansion capacity of the BiOSS LIM C is 6.15 mm, which is comparable to that of the XIENCE (5.6 mm).

In the POLBOS II trial, the previous iteration of the BiOSS LIM sirolimus-eluting stent with 316L stainless steel demonstrated comparable one-year clinical outcomes to conventional drug-eluting stents in patients with bifurcation lesions[12]. The BiOSS stent was further upgraded using a cobalt-chromium platform (BiOSS LIM C stent). In a porcine model, the BiOSS LIM C stent showed comparable histological vascular healing to the Orsiro stent (Biotronik, Bülach, Switzerland) 28 days after implantation[11]. The first-in-man trial of the BiOSS LIM C stent, which investigated the clinical outcomes of 48 patients with bifurcation lesions 12 months after the implantation, demonstrated a high device success rate (100%) and low three-month events (one target lesion revascularisation [2.1%] and no spontaneous MI or stent thrombosis)[13]. In addition, a recent study of the BiOSS LIM in LM treatment suggested that this device may reduce resource utilisation (guidewire, balloon, contrast media) versus conventional DES[14].

Based on these results, we generated the hypothesis that one-year clinical outcomes after BiOSS LIM C implantation in

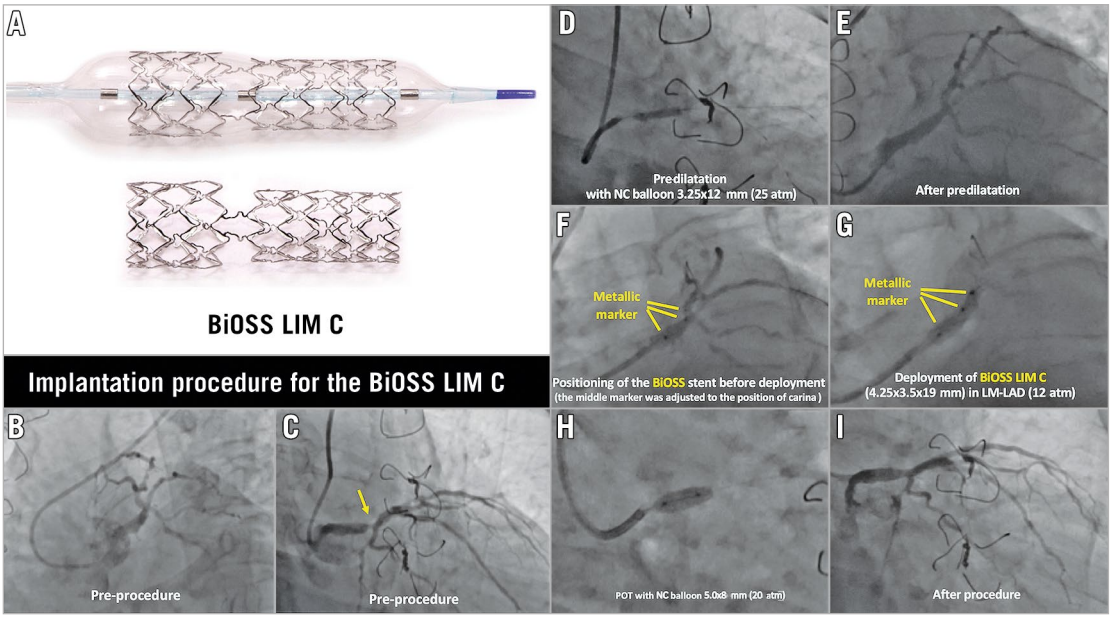

Figure 1. *BiOSS® Stent/Bottle® Balloon structures and a case example of BiOSS® implantation in the LMCA. A) The macroscopic appearance of the BiOSS LIM C stent and its delivery balloon. The diameter of the balloon in the proximal and distal parts is different, reflecting the natural tapering of bifurcation anatomy. The transitional zone (corresponding to the bifurcation) is free from ring, but connects the proximal and distal parts with the two links. This enables easy access to the side branch after stenting in the main branch. The balloon has three metallic markers which are placed at the distal edge, transitional zone, and proximal edge. During implantation, the mid marker should be located at the point of the bifurcation carina, so that the transitional zone is precisely located in the polygon of confluence. B) – I) Example of an implantation procedure of the BiOSS LIM C stent. The patient had a Medina 1,0,0 left main bifurcation lesion (B & C). After predilatation with a non-compliant balloon 3.25×12 mm at 25 atm (D & E), the BiOSS stent was advanced in the LM towards the LAD. The BiOSS stent 4.25×3.5 ×19 mm was positioned precisely at the position of the carina using a metallic marker (F). After the deployment of the BiOSS stent 4.25×3.5 ×19 mm (G), the proximal optimisation technique was performed with a non-compliant balloon 5.0x8 mm at 20 atm (H). Final angiography demonstrated an excellent result (I). LAD: left anterior descending; LM: left main; POT: proximal optimisation technique*

patients with distal unprotected LMCA disease are non-inferior to the best-in-class stent (XIENCE). Therefore, we designed a single-arm prospective study – the POLish Bifurcation Optimal treatment Strategy study for Left Main bifurcation PCI (POLBOS LM study) with a pre-specified performance goal based on the results of the EXCEL trial as recommended by the ESC/EAPCI task force on devices[15].

Methods

STUDY DESIGN

The POLBOS LM study is a prospective, multicentre, single-arm study in patients with an indication for distal unprotected left main revascularisation. The treatment strategy consists of contemporary PCI of the left main bifurcation following diagnostic angiography, on which a significant distal left main disease (diameter stenosis [%DS] ≥50%) is confirmed by using dedicated bifurcation quantitative coronary angiography (QCA) software, and a local Heart Team discussion applying the anatomical SYNTAX score (<33) **(Supplementary Figure 1)**[16]. This single-arm study is designed with a pre-specified performance goal based on the EXCEL trial; therefore, the patient selection and event definitions of the current trial are formulated to be comparable to those of the EXCEL trial (NCT01205776). The POLBOS LM study has been registered at www.clinicaltrials.gov (NCT03508219).

The BiOSS LIM C will be used for the treatment of the left main bifurcations. For the potential additional treatment of proximal and distal left main lesions, the ALEX® PLUS cobalt-chromium sirolimus-eluting single stent (Balton) will be used in order to avoid the unexpected interaction of the XIENCE stent in the LMCA lesion. Other non-LMCA lesions will be treated with XIENCE stents for the sake of comparability with an objective performance index trial such as the EXCEL trial, in the present case **(Supplementary Appendix 1)**.

The primary hypothesis of the current trial is that the BiOSS LIM C is non-inferior to the pre-specified performance goal in terms of the 12-month patient-oriented composite endpoint (POCE) consisting of all-cause mortality, stroke (modified Rankin Scale [mRS] ≥1), any MI and any unplanned revascularisation for ischaemia.

PATIENT POPULATION AND INDICATION FOR LMCA STENTING

Patients with silent ischaemia or chronic stable angina who have a *de novo* lesion in the distal unprotected LMCA and whose anatomical SYNTAX score is less than 33 are eligible if they fulfil

the following objective criteria: 1) %DS of the target lesion in the LMCA is ≥50% confirmed by off-line QCA analysed by the independent core laboratory (CORRIB Core Lab, Galway, Ireland) using dedicated bifurcation software (CAAS; Pie Medical Imaging, Maastricht, the Netherlands) prior to the treatment[17] with documented ischaemia (e.g., fractional flow reserve [FFR] ≤0.80)[18] (in case preprocedural IVUS is available, a left main minimum lumen area [MLA] ≤6.0 mm² is considered equivalent to the DS ≥50% by the core lab) **(Figure 2)**[19], 2) Medina classification for the target lesion in the LMCA is confirmed by off-line QCA, 3) the reference vessel diameter of the distal LMCA is ≥3.0 mm and ≤4.5 mm, and the distal main branch vessel diameter is ≤3.75 mm by visual estimation, 4) clinical and anatomical eligibility for PCI as agreed by the local Heart Team. Patients with stabilised acute coronary syndromes with elevated troponin (high-sensitivity troponin, troponin I or troponin T) at baseline (within 24 hrs pre-PCI) may also be included in the current study, if all of the following conditions are fulfilled: 1) the values of creatine kinase (CK) and creatine kinase myocardial band (CK-MB) are within the normal range; 2) the value of troponin at follow-up should be within a 20% range of the value of the first sample or have dropped; 3) ECG is normal.

Patients who have a lesion in the LMCA with Medina classification (0,0,1) or with chronic total occlusion/visible thrombus in any bifurcation segments are not eligible for the current trial. Detailed inclusion and exclusion criteria are presented in **Supplementary Table 1**. Patients will be included at approximately 15 international sites located in Poland, France, and Italy.

iFR MEASUREMENT PRIOR TO PCI

The importance of physiology-guided PCI has become increasingly evident recently. However, few data are available on the use of coronary physiology to guide management in unprotected left main coronary artery disease[1]. It was reported that, in the assessment of LMCA disease, there were discrepancies in pressure indices between FFR and resting indices such as iFR and Pd/Pa, because the change in coronary flow from rest to maximal hyperaemia is greater in vessels supplying greater amounts of myocardium, such as the LMCA[20].

In the current study, irrespective of QCA results, all patients will be interrogated with iFR (Verrata® and PrimeWire Prestige®; Volcano Corp., San Diego, CA, USA) prior to PCI for exploratory purposes. iFR is measured distal to the target lesion in both the proximal LAD and the LCX (two measurements). For the sake of three-dimensional angiography reconstruction, which will be used for the substudy, wire positions will be recorded in two angiographic views at least 30 degrees apart preceding iFR measurement and followed by iFR pullback.

IMPLANTATION OF THE BiOSS LIM C IN THE LMCA

As mentioned above, the protocol mandates that the distal LM bifurcation is treated with the BiOSS LIM C stent. Whenever

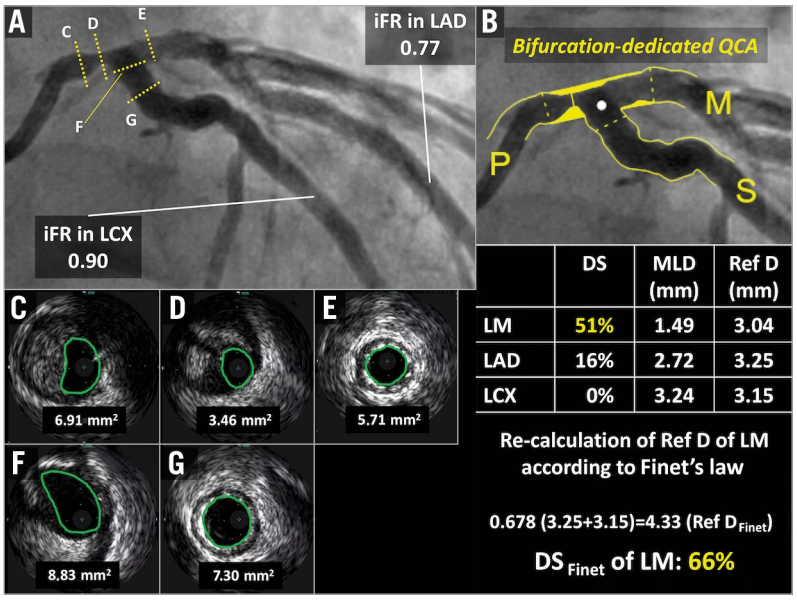

Figure 2. *Quantitative coronary angiography of a left main bifurcation using dedicated bifurcation software. A) The first patient of the POLBOS LM study had a Medina 1,0,0 left main bifurcation lesion. B) QCA analysis using dedicated bifurcation software showed significant stenosis (DS of left main: 51%). However, the reference diameter (Ref D) of the left main was underestimated due to diffuse left main disease. Therefore, the Ref D of the left main was recalculated using Finet's law, resulting in a DS of the left main of 66%. After enrolment, preprocedural MLA measured by IVUS was 3.46 mm² in the distal left main (C-G). The preprocedural iFR value in the LAD and LCX was measured (A). DS: diameter stenosis; IVUS: intravascular ultrasound; LAD: left anterior descending; LCX; left circumflex; LM: left main; MLA: minimal lumen area; QCA: quantitative coronary angiography; RD: reference diameter*

additional stenting for the proximal or distal left main lesion is needed, the ALEX PLUS stent will be used.

The recommended BiOSS stent implantation strategies as described in the protocol are derived from the MADS classification **(Figure 3)**[21]. However, considering the anatomical variability of the left main bifurcation, the selection of the stenting technique strategy is left to the operator's discretion.

Whenever there is a low possibility of side branch occlusion after BiOSS stent implantation, "main branch stenting across side branch" is recommended. If the ostium of the side branch has a significant residual stenosis after BiOSS implantation (DS >50% by visual estimation, or FFR ≤0.80/iFR ≤0.89 or obvious flow deterioration [TIMI flow <3]), additional side branch dilatation by kissing balloon inflation (KBI) is recommended[4,22]. In case of residual issues in the ostium of the side branch after KBI, a second BiOSS or ALEX PLUS stent implantation in the side branch is recommended ("provisional T stenting and protrusion [TAP]" and "culotte stenting"). A case example with culotte stenting using two BiOSS stents is presented in **Supplementary Figure 2**.

The decision to use an upfront two-stent technique rather than a single crossover stent technique should be considered when the side branch is large (>3 mm), with significant disease (DS >50% by dedicated bifurcation QCA/DS >70% by visual angiography with a length >5 mm, or confirmation of a large plaque burden [>60%] on IVUS), or when there are other special anatomic considerations (e.g., heavy calcification)[23]. In that case, "DK crush stenting" is recommended in combination with BiOSS for the main branch and the ALEX PLUS stent for the side branch[24].

Apart from the stenting procedure described above, the interventional procedure, intraprocedural anticoagulation, and dual antiplatelet therapy (DAPT) are according to the current clinical guidelines[18].

POST-PROCEDURAL IVUS

In the current study, usage of IVUS for optimisation of the stent implantation is highly recommended, according to the ESC guideline (IIA)[18]. Performing post-dilation according to the criteria of minimum stent areas (MSA) is recommended based on the criteria adopted in the EXCEL trial[4]. In the IVUS criteria of the current study, MSA or MLA in the LMCA, LAD and LCX are preferably dilated with MSA/MLA >8.5, 6.0, and 5.5 mm^2, respectively **(Supplementary Figure 3)**. POT and balloon dilatation in the distal branch (the so-called distal optimisation technique) are systematically recommended.

STAGED PROCEDURE

A staged procedure is defined as a planned elective second PCI procedure at a separate setting for optimal completion of the PCI. The criteria for staging are left to the operator's best judgement. Given the complexity of unprotected LMCA patients, it is

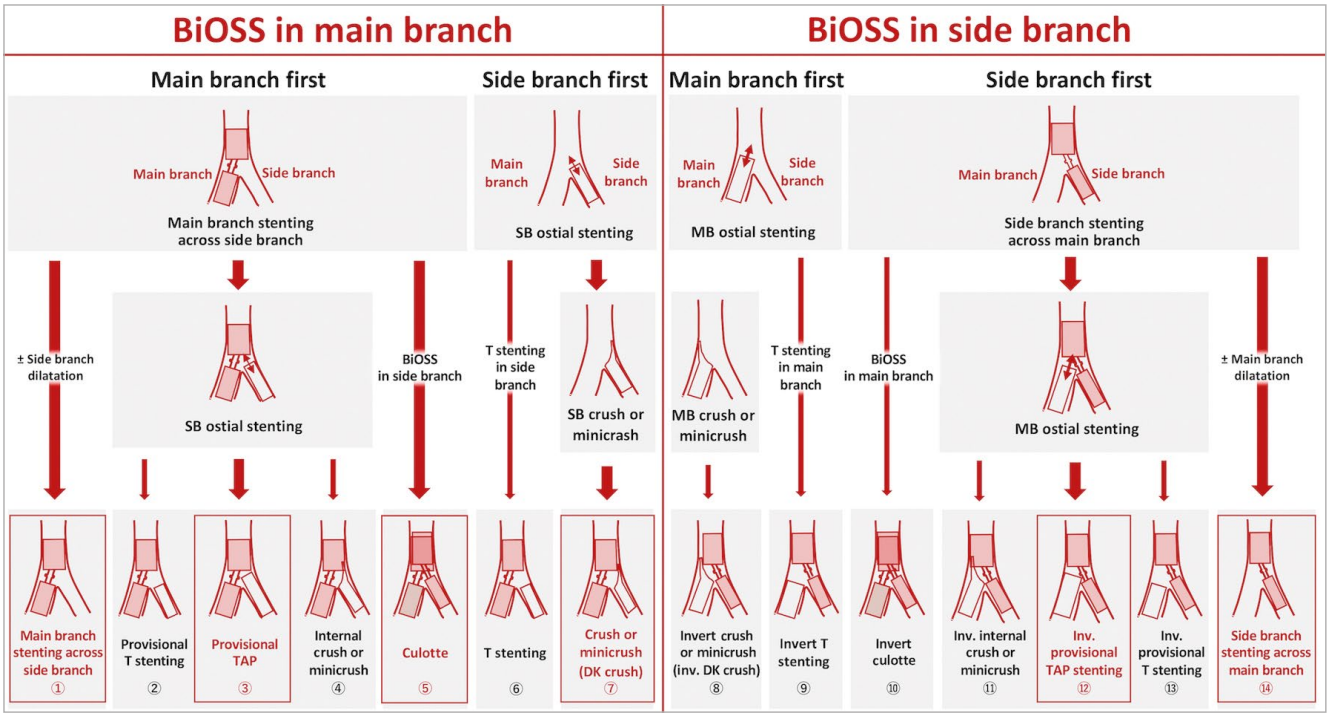

Figure 3. *BiOSS stent implantation strategies. The techniques with a red framed box are recommended in the protocol. In case of usage of two BiOSS stents (culotte technique: ⑤, ⑩), the sizes of the MB and SB should be comparable. TAP techniques ③⑫ are not recommended in cases with a bifurcation angle >70° where T stenting ②⑬ is recommended. DK: double kissing; MB: main branch; SB: side branch; TAP: T-stenting and small protrusion*

anticipated that a substantial number of patients may fall into the category of staged procedures. If the patient requires a staged procedure, this is documented at the time of the index procedure. The reasons for staging and the specific lesions planned to be treated in the staged procedure are documented in the electronic case report form (eCRF). Stented segment(s) treated during the index procedure should not be treated by "retouching" again during the staged procedure.

The recommended timing of a planned staged procedure is optimally within four weeks (28 days), and it is strongly recommended that it is completed within 45 days. A staged procedure will not affect the original follow-up schedule.

The residual SYNTAX score is an objective measure of the degree and complexity of residual stenosis after PCI[25]. In the POLBOS study attempting to achieve a residual SYNTAX score ≤8 post PCI is recommended.

CONCOMITANT MEDICATIONS

Preloading with aspirin 300 to 325 mg is required at least two hours before PCI. Pre-PCI loading of the $P2Y_{12}$ inhibitors is mandatory, where the selection of either clopidogrel, prasugrel or ticagrelor is left to the discretion of the investigator. After PCI, DAPT consisting of aspirin and one of the $P2Y_{12}$ inhibitors is mandated for at least one year after PCI; the status of DAPT will be carefully documented in the eCRF. Optimal medical therapy with strict control of LDL cholesterol (target of ≤1.8 mmol/l) by using a statin or a PCSK9 inhibitor is strongly recommended along with optimisation of all medical therapies[26]. At least one daily dose of atorvastatin 80 mg or rosuvastatin 40 mg should be administered, as performed in the EXCEL trial, before the PCI (within 12 hours), regardless of LDL level and history of prior statin use[27]. The use of other medications prior to PCI (e.g., beta-blockers, angiotensin-converting enzyme inhibitors) is left to the discretion of the treating physicians, but should be applied as recommended by the ESC guideline[18].

CLINICAL FOLLOW-UP

Hospital visits are planned at one month (±7 days) and one year (±30 days). A phone contact is scheduled at six months (±14 days). An assessment of the angina status (Canadian Cardiovascular Society [CCS] grading or Braunwald classification), compliance to protocol-required medications, other cardiovascular drug use and any serious adverse events will be recorded during clinical follow-up visits. The enrolled patients will be followed up until a maximum of three years after the index procedure. Laboratory testing and other tests are described in **Supplementary Appendix 2**. Data will be entered into a web-based eCRF. Data entry will be monitored according to a pre-specified monitoring plan (CORRIB Core Lab).

ENDPOINTS

The primary endpoint of the current study is defined as POCE at 12 months post procedure. POCE is a composite of all-cause mortality, stroke (modified Rankin scale [mRS ≥1]), any MI and any unplanned clinically indicated revascularisation including all target and non-target vessels **(Table 1)**[28]. To keep consistency with the EXCEL trial, the primary endpoint in the current study applies the same definition of MI as the EXCEL trial. In particular, periprocedural MI is defined as the occurrence within 72 hours after PCI of either CK-MB ≥10x ULN or CK-MB ≥5x ULN in combination with any of the following: 1) new pathological Q-waves in at least two contiguous leads or new persistent non-rate-related left bundle branch block (LBBB), 2) angiographically documented native coronary artery occlusion or new severe stenosis with thrombosis and/or diminished epicardial flow, or 3) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. Although the definition of the EXCEL trial did not comprise cardiac troponin (cTn),

Table 1. Endpoints.

Primary endpoint	
Patient-oriented composite endpoint (POCE) at 12 months post procedure. POCE is a composite measure of: – All-cause mortality – Stroke (modified Rankin Scale ≥1) – Any myocardial infarction (MI)* – Any unplanned revascularisation for ischaemia	
Secondary endpoints	
Secondary endpoints (evaluated at each follow-up visit/contact)	
1. Composite endpoints	– POCE for all follow-up contacts other than 12 months – Target vessel failure (TVF) defined as cardiac death, target vessel MI*, and clinically indicated target vessel revascularisation – Device-oriented composite endpoint (DOCE)/TLF defined as cardiac death, target vessel MI* and clinically indicated target lesion revascularisation (DOCE will be reported both including the left main target lesion only and all target lesions)
2. Mortality	– All death – Cardiac death – Non-cardiac death (vascular and non-cardiovascular)
3. Stroke	– All – Ischaemic – Haemorrhagic
4. Myocardial infarction*	– All MI (periprocedural, spontaneous, Q-wave and non-Q-wave) – Target vessel/non-target vessel MI
5. Revascularisation	– Any revascularisation – Target lesion revascularisation (TLR) (any, clinically indicated TLR, non-clinically indicated TLR). (TLR will be reported both including the left main target lesion only and all target lesions) – Target vessel revascularisation (TVR) (any, clinically indicated TVR, non-clinically indicated TVR) – Non-target vessel revascularisation
6. Stent thrombosis according to ARC classification[28]	
*Definition is based on the EXCEL study[4].	

CK-MB ≥5x and ≥10x are considered equivalent to cTn ≥35x and ≥70x, respectively, in the current study[29]. Stent thrombosis is defined according to the ARC definition[28]. All definitions of the study endpoint are described in **Supplementary Appendix 3**. Clinical events will be adjudicated by an independent clinical events committee.

STATISTICAL CONSIDERATIONS AND SAMPLE SIZE CALCULATION

The primary efficacy endpoint is based on comparison to the pre-specified performance goal based on the EXCEL trial. The study is powered at 80% to show non-inferiority of the BiOSS LIM C compared with the XIENCE stent in terms of one-year POCE. The primary analysis will be based on an intention-to-treat patient population. By using the POCE rate of the XIENCE arm with distal LMCA disease in the EXCEL trial (16.7%, as referring to data on file only available to the primary investigators of the EXCEL trial, not available in the public domain), the non-inferiority margin was calculated as 6.3%. A one-sided 95% upper confidence bound will be calculated for the POCE rate at 12 months, using Kaplan-Meier estimates and their standard deviation. In the sample size calculation with PASS software, 256 analysable patients are required based on the assumptions described above. In total, 260 patients will be included from 17 European centres in the current study, accounting for some attrition. Current enrolment status is shown in **Supplementary Table 2**.

Discussion

Pre-specified subgroup analyses will be performed for the one-stent versus the two-stent technique for unprotected LMCA disease. For these subgroups, the primary endpoint and secondary endpoints will be evaluated. The subgroups will not have significant power, meaning that the results are considered exploratory (hypothesis-generating) only.

Several other substudies are planned, taking advantage of the current study using multimodality assessments (angiography, iFR and IVUS). The impact of anatomical (QCA) and physiological information (iFR) in the LMCA on the stenting procedure and procedure outcome will be assessed. The correlation between quantitative flow ratio (QFR), which is angiography-derived FFR, and iFR in LMCA disease including their pullback index curves will be investigated. Additionally, we will assess QFR for LMCA disease and computed flow dynamics simulation with 3D reconstruction by using angiography and IVUS to investigate the impact of the stenting strategy on the shear stress.

Limitations

The present study has several limitations. First, this is a non-randomised study comparing a dedicated bifurcation stent with a best-in-class DES (XIENCE). Second, the maximum nominal length of the BiOSS LIM C is 24 mm. If the lesion is longer than 24 mm, additional stent (ALEX PLUS) implantation will be required proximally or distally.

Conclusions

The POLBOS LM study will indicate the efficacy of the BiOSS LIM C stent with contemporary PCI for distal left main bifurcation lesions in comparison with the XIENCE stent from the recent EXCEL trial, as a performance index.

Impact on daily practice

The aim of the POLBOS LM study is to demonstrate the non-inferiority of the BiOSS LIM C bifurcation-dedicated stent to the best-in-class XIENCE stent in the EXCEL trial in patients with unprotected left main bifurcation lesions. A favourable result might provide us with an alternative option for a challenging left main bifurcation treatment in clinical practice.

Appendix. Authors' affiliations

1. Department of Cardiology, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands; 2. Department of Cardiology, St. Luke's International Hospital, Tokyo, Japan; 3. Department of Cardiology, Toho University Medical Center Ohashi Hospital, Tokyo, Japan; 4. Department of Cardiology, National University of Ireland, Galway, Ireland; 5. CORRIB Core Lab, Galway, Ireland; 6. Department of Internal Medicine, Cardiology Division, University of Campinas (UNICAMP), Campinas, Brazil; 7. Division of Cardiology, Department of Internal Medicine, Faculty of Medicine, Prince of Songkla University, Songkhla, Thailand; 8. Ramsay Générale de Santé - Institut Cardiovasculaire Paris Sud, Hopital Privé Jacques Cartier, Massy, France; 9. Institute of Cardiology, Jagiellonian University Medical College, John Paul II Hospital, Krakow, Poland; 10. Cardiology Department, Centre Cardiologique du Nord, Saint Denis, France; 11. Department of Invasive Cardiology, Central Clinical Hospital of the Ministry of Interior, Warsaw, Poland; 12. Mossakowski Medical Research Centre of Polish Academy of Science, Warsaw, Poland.

Guest Editor

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Conflict of interest statement

Y. Onuma is a member of the advisory board of Abbott Vascular. J. Legutko is a member of the advisory board of and has received lecture fees from Philips/Volcano and Abbott Vascular and received a lecture fee from Balton. P.W. Serruys is a consultant for Volcano and a member of the advisory board of Abbott Vascular. R. Gil has received a lecture fee from Balton. The other authors

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Supplementary data

Supplementary Appendix 1. Treatment of non-LMCA lesions.

Supplementary Appendix 2. Laboratory testing and other tests pre and post PCI.

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Supplementary Table 2. Number of patients enrolled per site on 1st July 2019.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-19-00361

Supplementary data

Supplementary Appendix 1. Treatment of non-LMCA lesions

To maintain comparability with the EXCEL trial, all other non-left main lesions will be treated with the XIENCE family of everolimus-eluting coronary stent systems. According to the strategy of the EXCEL trial, pre-treatment confirmation of significant FFR (≤0.8) or iFR (≤0.89) is recommended for the indication of PCI for non-LMCA lesions, which is different from the treatment of the LMCA, unless there is evident territorial information on ischaemia as assessed by a non-invasive imaging modality (e.g., stress cardiac echo or single-photon emission computed tomography). For the treatment of non-LMCA lesions, post-dilatation with a non-compliant balloon is highly recommended according to the post-procedural IVUS image. MSA should be more than 5.5 mm^2 as assessed on IVUS if applicable.

Supplementary Appendix 2. Laboratory testing and other tests pre and post PCI

A complete blood count with differential, creatinine and HbA1c is measured within 28 days prior to PCI. Cardiac biomarkers (CK-MB, troponin or high-sensitivity troponin if CK-MB is not available) are taken within 24 hours prior to PCI, 12±2 and 24±2 hours after PCI or at discharge if sooner. Twelve-lead electrocardiography (ECG) is performed pre procedure, within 24 hours post procedure, and at discharge. Ejection fraction at baseline, derived from echocardiography, magnetic resonance imaging, computed tomography or ventriculogram, has to be documented in the eCRF.

Supplementary Appendix 3. Study definitions

MYOCARDIAL INFARCTION (MI)

EXCEL study definition

Periprocedural/post-procedural MI:

Defined as the occurrence within 72 hours after PCI of either:

- CK-MB ≥10x ULN or cTn* (I or T) ≥70x ULN, OR
- CK-MB ≥5x ULN or cTn* (I or T) ≥35x ULN in combination with any of the following:

- new pathological Q-waves in at least two contiguous leads or new persistent non-rate-related LBBB, or

- angiographically documented native coronary artery occlusion or new severe stenosis with thrombosis and/or diminished epicardial flow, or

- imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

*while the EXCEL definition did not comprise cTn, we consider equivalence CK-MB ≥10x versus cTn ≥70x and CK-MB ≥5x versus cTn ≥35x[29]

Spontaneous MI◊

Defined as the occurrence >72 hours after any PCI of:

- a rise and/or fall of cardiac biomarkers (CK-MB or troponin) >1x ULN combined with:

- ECG changes indicative of new ischaemia (ST-segment elevation or depression, in the absence of other causes of ST-segment changes such as left ventricular hypertrophy [LVH] or bundle branch block [BBB]), or

- Development of pathological Q-waves (≥0.04 seconds in duration and ≥1 mm in depth) in ≥2 contiguous precordial leads or ≥2 adjacent limb leads) of the ECG, or

- Angiographically documented graft or native coronary artery occlusion or new severe stenosis with thrombosis and/or diminished epicardial flow, or

- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

Each MI will also be adjudicated as:

- ST-segment elevation MI (STEMI)
- Non-ST-segment elevation MI (NSTEMI)
- Each STEMI and NSTEMI will be subcategorised as
  - Q-wave
  - Non-Q-wave
  - Unknown (no ECG or ECG not interpretable)

Target vessel myocardial infarction

Myocardial infarction not clearly attributable to a non-target vessel.

Non-target vessel myocardial infarction

Myocardial infarction clearly attributable to a non-target vessel.

◊ for poolability and/or comparison with other studies we may also adjudicate spontaneous MI according to the third universal definition.

Myocardial infarction according to the third universal definition (2012)[30]
MI type 1: Spontaneous MI
Spontaneous myocardial infarction related to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus in one or more of the coronary arteries leading to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis. The patient may have underlying severe CAD but on occasion non-obstructive or no CAD. Needed criteria: o Detection of rise and/or fall of cardiac biomarkers (**preferably troponin**) with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischaemia with **at least one of the following**: o Symptoms of ischaemia o New or presumed new significant ST-segment-T-wave (ST-T) changes o New LBBB o Development of pathological Q-waves in the ECG o Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

○ Identification of an intracoronary thrombus by angiography or autopsy
MI type 2: MI secondary to an ischaemic imbalance
In instances of myocardial injury with necrosis where a condition other than CAD contributes to an imbalance between myocardial oxygen supply and/or demand, e.g., coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachyarrhythmias/bradyarrhythmias, anaemia, respiratory failure, hypotension, and hypertension with or without LVH.
MI type 3: MI resulting in death when biomarker values are unavailable
Cardiac death with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes or new LBBB, but death occurring before blood samples could be obtained, before cardiac biomarker could rise, or in rare cases cardiac biomarkers were not collected.
MI type 4a: MI related to PCI (<48 hours post PCI)
Adjudicated per EXCEL/SCAI definition only, see above.
MI type 4b: MI related to stent thrombosis
Myocardial infarction associated with stent thrombosis is detected by coronary angiography or autopsy in the setting of myocardial ischaemia and with a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile URL.
MI type 4c: MI related to restenosis
Myocardial infarction in the presence of restenosis defined as ≥50% stenosis at coronary angiography or a complex lesion associated with a rise and/or fall of cTn values >99th percentile URL and no other significant obstructive CAD of greater severity following: ○ Initially successful stent deployment (<30% stenosis), OR ○ Initially successful dilatation of a coronary stenosis with balloon angioplasty (<50%)
MI type 5: MI related to CABG (<48 hours post CABG)
Adjudicated per EXCEL definition only, see below.

PERIPROCEDURAL MYOCARDIAL INFARCTION (SCAI 2013) [29]

Periprocedural MI according to SCAI 2013 definition
Periprocedural MI after PCI or CABG (<48 hours post PCI or CABG)

Periprocedural MI according to SCAI 2013 definition
For patients with normal baseline cardiac biomarkers: any of the following criteria: • CK-MB ≥10×ULN or cTn (I or T) ≥70×ULN, OR • CK-MB ≥ 5×ULN or cTn (I or T) ≥35×ULN in combination with any of the following: - New pathologic Q-waves in ≥2 contiguous leads, OR - New persistent LBBB For patients with elevated baseline cardiac biomarkers: any of the following criteria: • When biomarker levels are stable or falling, there should be new CK-MB elevation by an absolute increment of ≥10×ULN (or ≥70×ULN for cTnI or T) from the previous nadir level. • When biomarker levels have not been shown to be stable or falling, there should be a further rise in CK-MB or troponin beyond the most recently measured value by an absolute increment of ≥10×ULN in CK-MB or ≥70×ULN in cTn 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. While not currently recommended as part of this definition, use of post-CABG ECGs, indices of haemodynamic instability, and imaging studies demonstrating new wall motion abnormalities are suggested to complement biomarker elevations post CABG to improve specificity.

REVASCULARISATION

Target lesion

A lesion revascularised in the index procedure (or staged procedure). The left main target lesion extends from the distal left main stem to the end of the 5 mm proximal segments of the left anterior descending and left circumflex arteries as well as the ramus intermedius if the latter vessel has a vessel diameter of ≥2 mm.

Target vessel

The target vessel is defined as the entire major coronary vessel proximal and distal to the target lesion including upstream and downstream branches and the target lesion itself. The left main and any vessel originating from the left main coronary artery or its major branches is, by definition, considered a target vessel for the purposes of this trial (unless either the LAD or LCX is occluded at baseline and no attempt was made to revascularise these territories by PCI).

Target vessel non-target lesion

The target vessel but non-target lesion consists of a lesion in the epicardial vessel/branch that contains the target lesion; however, this lesion is outside of the target lesion by at least 5 mm distal or proximal to the target lesion determined by coronary angiography.

Non-target vessel

For the purposes of this trial, the only possible non-target vessel would be the right coronary artery and its major branches that were not treated by PCI at the index procedure (unless either the LAD or LCX is occluded at baseline and no attempt was made to revascularise these territories by either PCI or CABG).

Target vessel revascularisation (TVR)

Target vessel revascularisation is any repeat percutaneous intervention of the target vessel or bypass surgery of the target vessel.

Target lesion revascularisation (TLR)

Target lesion revascularisation is defined as any repeat percutaneous intervention of the target lesion or bypass surgery of the target vessel.

Clinically indicated revascularisation (CI-TLR/TVR)

Revascularisation will be considered ischaemia-driven if the target lesion diameter stenosis is ≥50% by QCA and any of the following criteria for ischaemia are met:

- Positive functional ischaemia study including positive FFR/iFR corresponding to the area served by the target lesion; or
- Ischaemic ECG changes at rest in a distribution consistent with the target vessel; or
- Typical ischaemic symptoms referable to the target lesion; or

- IVUS of the target lesion with a minimal lumen area (MLA) of ≤4 mm^2 for non-left main lesions or ≤6 mm^2 for left main lesions. If the lesions are de novo (i.e., not restenotic), the plaque burden must also be ≥60%; or
- FFR of the target lesion ≤0.80 or iFR of the target lesion ≤0.89.

A target lesion revascularisation for a diameter stenosis less than 50% might also be considered ischaemia-driven by the clinical events committee if there was a markedly positive functional study or ECG changes corresponding to the area served by the target lesion.

STENT THROMBOSIS

(ARC definition) [28]

Stent thrombosis should be reported as a cumulative value at the different time points and with the different separate time points. Time 0 is defined as the time point after the guiding catheter has been removed and the patient has left the catheterisation lab.

Timing:

- Acute stent thrombosis*: 0-24 hours post stent implantation
- Subacute stent thrombosis*: >24 hours-30 days post stent implantation
- Late stent thrombosis†: 30 days-one year post stent implantation
- Very late stent/ thrombosis†: >1 year post stent implantation

* Acute/subacute can also be replaced by early stent thrombosis. Early stent thrombosis (0-30 days) - this definition is currently used in the community.

† Including "primary" as well as "secondary" late stent thrombosis; "secondary" late stent thrombosis is a stent thrombosis after a target segment revascularisation.

Categories:

- Definite
- Probable
- Possible

Definitions of each category are as follows.

- **Definite stent thrombosis**

Definite stent thrombosis is considered to have occurred by either angiographic or pathologic confirmation.

Angiographic confirmation of stent thrombosis*

The presence of a thrombus† that originates in the stent or in the segment 5 mm proximal or distal to the stent and presence of at least one of the following criteria within a 48-hour time window:

- Acute onset of ischaemic symptoms at rest
- New ischaemic ECG changes that suggest acute ischaemia
- Typical elevation or depression in cardiac biomarkers (refer to definition of spontaneous MI)
- Non-occlusive thrombosis
    - Intracoronary thrombus is defined as a (spherical, ovoid, or irregular) non-calcified filling defect or lucency surrounded by contrast material (on three sides or within a coronary stenosis) seen in multiple projections, or persistence of contrast material within the lumen, or a visible embolisation of intraluminal material downstream.
- Occlusive thrombus
    - TIMI 0 or TIMI 1 in-stent or proximal to a stent up to the most adjacent proximal side branch or main branch (if it originates from the side branch).

* The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is not considered a confirmed stent thrombosis.

† Intracoronary thrombus.

Pathological confirmation of stent thrombosis

Evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy.

- **Probable stent thrombosis**

  Either of the following occurring after stent implantation will be considered a probable stent thrombosis:

    - Any unexplained death within the first 30 days‡

- Irrespective of the time after the index procedure, any MI that is related to documented acute ischaemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause.

‡ For studies with an ST-elevation MI population, one may consider the exclusion of unexplained death within 30 days as evidence of probable stent thrombosis.

- **Possible stent thrombosis**

  Clinical definition of possible stent thrombosis is thrombosis considered to have occurred with any unexplained death from 30 days following intracoronary stenting until the end of trial follow-up.

STROKE

All strokes with stroke severity of modified Rankin Scale (mRS) ≥1 will be included in the primary endpoint. Stroke severity will be classified using an adaptation of the modified Rankin Scale (www.strokecenter.org/trials/scales/rankin.html) as follows:

Scale	Disability
0	No stroke symptoms at all. (May have other complaints).
1	No significant disability despite persistent stroke symptoms. Able to carry out all usual duties and activities.
2	Slight disability. Unable to carry out usual activities, but able to look after affairs without assistance. Could live alone.
3	Moderate disability. Requiring some help, but able to walk without assistance (of a person). Can be left alone for a few days.
4	Moderate to severe disability. Unable to walk without assistance (of a person). Unable to attend to own bodily needs without assistance. Could be left alone for a few hours of a day.
5	Severe disability. Bedridden, incontinent, and requiring constant nursing care and attention and 24-hour supervision.
6	Dead.
	Stroke: modified Rankin score ≥1

Strokes may be further sub-classified as follows:

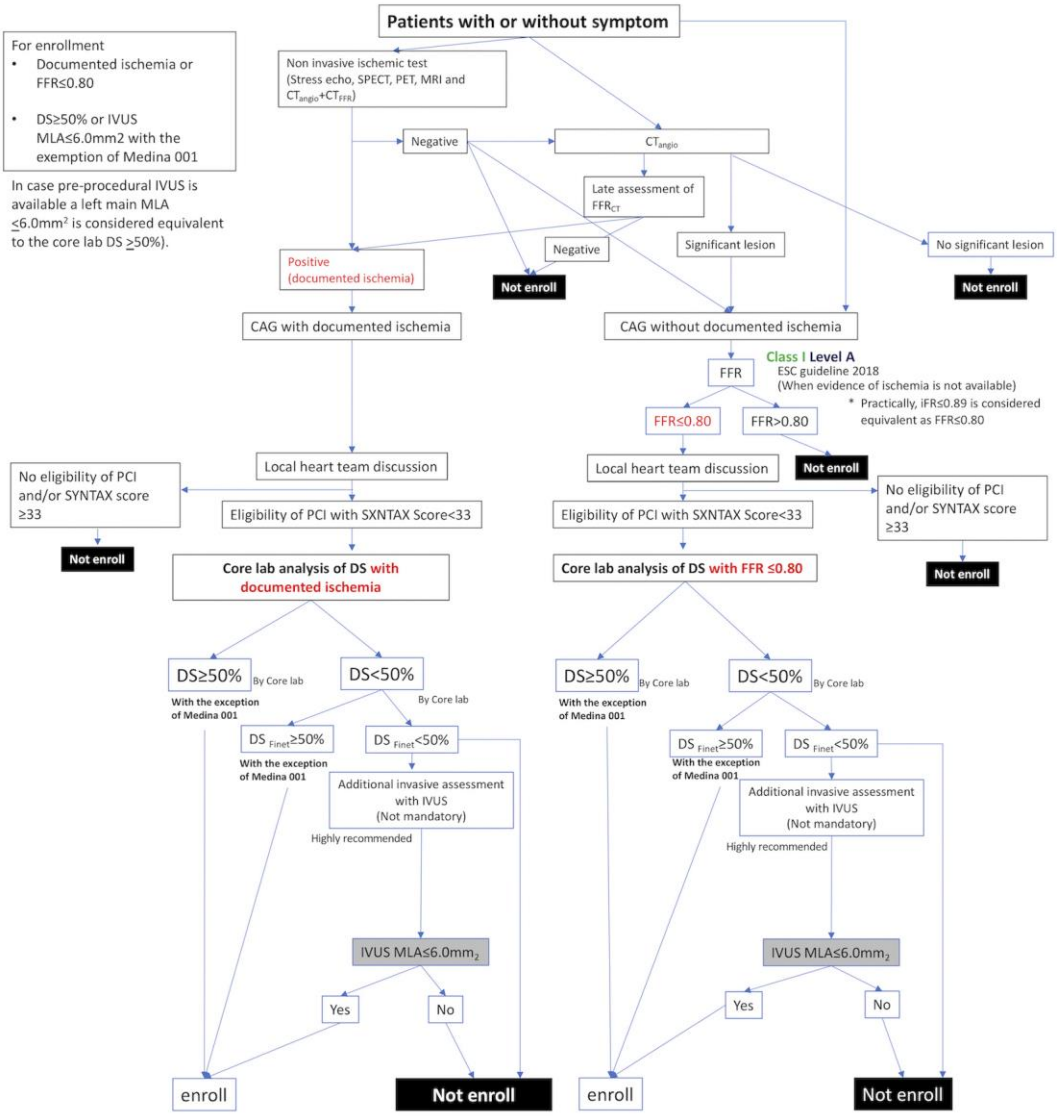
1. **Ischaemic** (non-haemorrhagic): a stroke caused by an arterial obstruction due to either a thrombotic (e.g., large vessel disease/atherosclerotic or small vessel disease/lacunar) or embolic aetiology.
2. **Haemorrhagic**: a stroke due to a haemorrhage in the brain as documented by neuroimaging or autopsy. This category will include strokes due to primary intracerebral haemorrhage (intraparenchymal or intraventricular), ischaemic strokes with haemorrhagic transformation (i.e., no evidence of haemorrhage on an initial imaging study but appearance on a subsequent scan), subdural haematoma*, and primary subarachnoid haemorrhage.

*All subdural haematomas that develop during the clinical trial should be recorded and classified as either traumatic or non-traumatic.

3. **Unknown**: the stroke type could not be determined by imaging or other means (e.g., lumbar puncture, neurosurgery, or autopsy) or no imaging was performed.

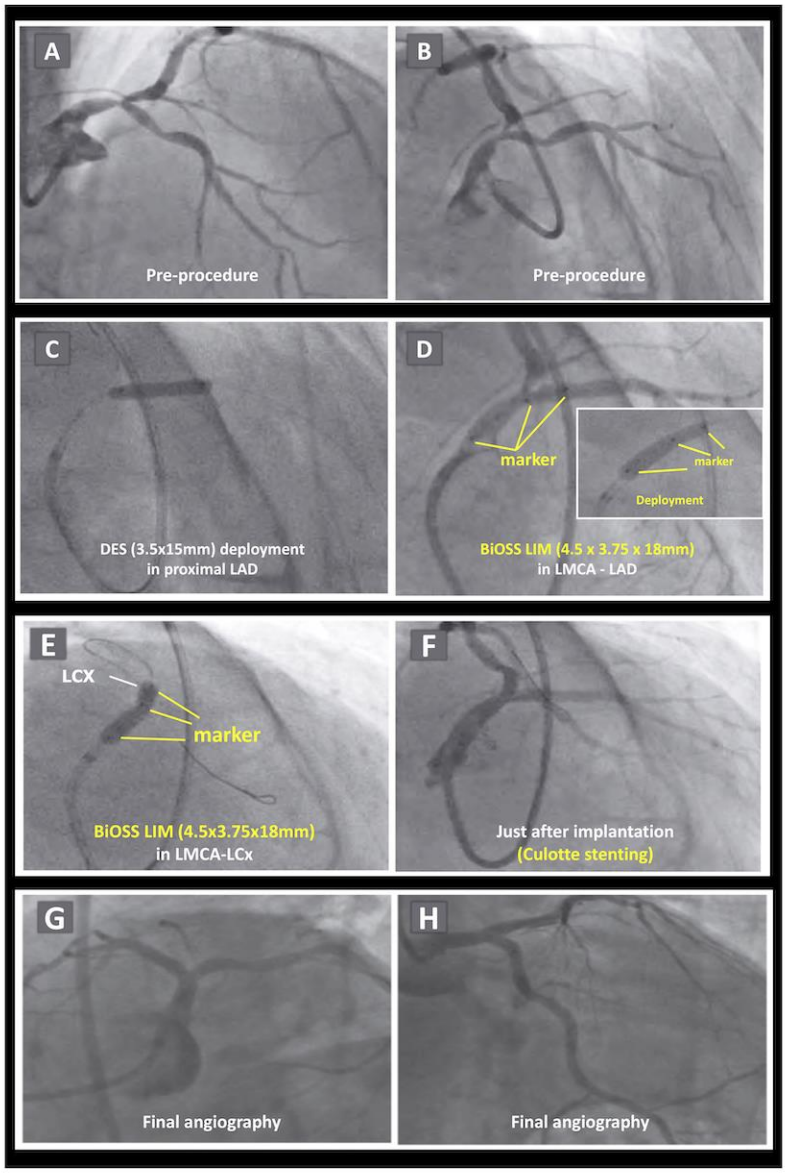
Transient ischaemic attack (as compared to stroke) is defined as:

• New focal neurologic deficit with rapid symptom resolution, usually one to two hours, always within 24 hours
• Neuroimaging without tissue injury



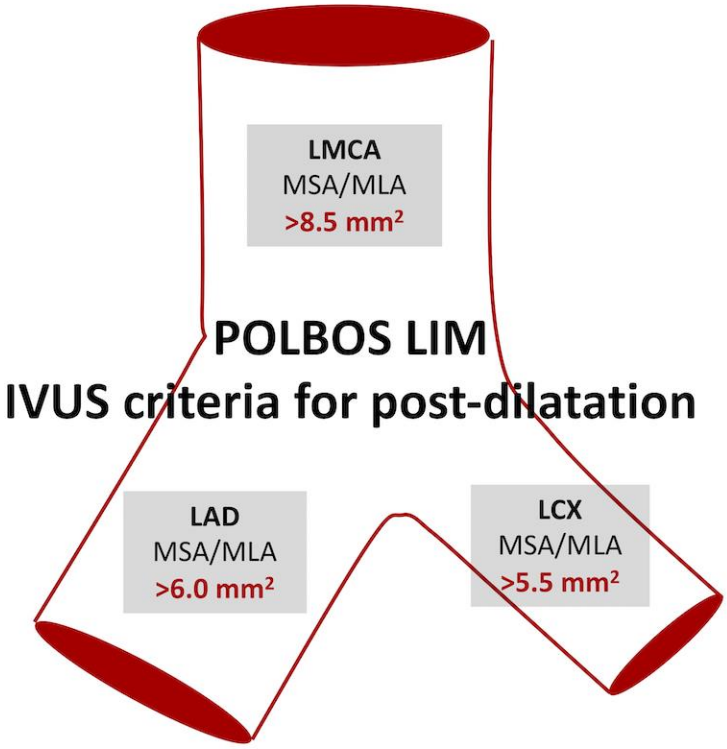
Supplementary Figure 1. Patient flow before and after core lab analysis.

CAG: coronary angiography; CT: computed tomography; DS: diameter stenosis; ESC: European Society of Cardiology; FFR: fractional flow reserve; iFR: instantaneous wave-free ratio; IVUS: intravascular ultrasound; LMCA: left main coronary artery; MLA: minimum lumen area; MRI: magnetic resonance imaging; PET: positron emission tomography; SPECT: single-photon emission computed tomography



Supplementary Figure 2. A case example using culotte stenting with two BiOSS stents. The patient had a Medina 1,1,1, left main bifurcation lesion (A & B). One drug-eluting stent 3.5x15 mm was deployed in the proximal LAD (C). The BiOSS LIM C stent 4.5x3.75x18 mm was deployed precisely in the left main towards the LAD under metallic marker guidance (D). Wire re-crossing towards the LCX was easily performed due to a precisely placed transitional zone. The second BiOSS stent 4.5x3.75x18 mm was deployed in the left main towards the LCX (E). Coronary flow towards both branches was well preserved even just after culotte stenting (F). The final angiography demonstrated an excellent result (G & H).

DES: drug-eluting stent; LAD: left anterior descending; LCx: left circumflex; LM: left main



Supplementary Figure 3. The IVUS criteria of the POLBOS LM study.

It is recommended to perform post-dilation according to the criteria of minimum stent areas (MSA) based on the criteria adopted in the EXCEL trial. In the IVUS criteria of the current study, MSA or MLA in the LMCA, LAD and LCX are preferably dilated with MSA/MLA >8.5, 6.0, and 5.5 mm², respectively.

IVUS: intravascular ultrasound; LAD: left anterior descending; LCX: left circumflex; LMCA: left main coronary artery; MLA: minimum lumen area; MSA: minimum stent area

Supplementary Table 1. Eligibility criteria.

Inclusion criteria:

Patients to be included in the study must meet the following inclusion criteria:

1. Patient has distal unprotected left main coronary artery (ULMCA) disease with angiographic diameter stenosis (DS) ≥50% (confirmed by off-line QCA, using dedicated QCA bifurcation software by an academic core lab) with documented ischaemia or FFR ≤0.80 requiring revascularisation.
   - In case of mismatch between diameter stenosis and FFR/iFR (i.e., DS <50% and FFR <0.80/iFR <0.89) the investigator is allowed to include the patient in the trial.
   - In case of mismatch between diameter stenosis and IVUS (i.e., DS <50% and IVUS MLA <6 mm^2), the investigator is allowed to include the patient in the trial.
2. Left main Medina classification 1,0,0; 1,1,0; 1,0,1; 0,1,1; 0,1,0; 1,1,1 confirmed by on-line or off-line QCA, using dedicated QCA bifurcation software.
3. Clinical and anatomic eligibility for PCI as agreed by the local Heart Team including anatomic SYNTAX score (<33).
4. Distal left main reference vessel diameter ≥3.0 mm and ≤4.5 mm, and main branch vessel diameter ≤3.75 mm. All target lesions must be located in a native coronary artery.
5. Patient with silent ischaemia, chronic stable angina or stabilised acute coronary syndromes with normal cardiac biomarker values.
   Note: For patients showing elevated troponin (cTn) (e.g., non-STEMI patients) at baseline (within 24 hrs pre-PCI) an additional blood sample must be collected prior to the PCI procedure to confirm that:
   • hs-cTn or troponin I or T levels are stable, i.e., the value should be within 20% range of the value found in the first sample at baseline, or have dropped
   • CK-MB and CK levels are within normal range
   If hs-cTn or troponin I or T levels are stable or have dropped, the CK-MB and CK levels are within normal ranges, and the ECG is normal, the patient may be included in the study.
6. Male or female patients ≥18 years.
7. Able to understand and provide informed consent and comply with all study procedures including follow-up.

Exclusion criteria:

1. Prior PCI of the left main bifurcation at any time prior to enrolment.
2. Prior PCI of any other (non-left main bifurcation) coronary artery lesion within six months (<6 months) prior to enrolment.
3. Left main Medina classification 0,0,1.
4. Any segment of the left main bifurcation (distal left main, ostial LAD or ostial LCX) presenting with a chronic total occlusion.
5. Any segment of the left main bifurcation (distal left main, ostial LAD or ostial LCX) containing a visible thrombus.
6. Excessive angulation of the left main bifurcation (i.e., an angulation >90° between the proximal LAD and the proximal LCX).

7. Direct stenting of the left main bifurcation.
8. Prior CABG at any time prior to enrolment.
9. Patient requiring or may require additional surgery (cardiac or non-cardiac) within one year.
10. Ongoing myocardial infarction or recent myocardial infarction with cardiac biomarker levels still elevated.
11. Known renal insufficiency (e.g., serum creatinine >2.5 mg/dL, or creatinine clearance ≤30 mL/min, or patient on dialysis).
12. Known contraindication or hypersensitivity to sirolimus, everolimus, cobalt-chromium, or to medications such as aspirin, heparin, bivalirudin, and all of the following four medications: clopidogrel bisulfate, ticlopidine, prasugrel, ticagrelor.
13. Patients unable to tolerate, obtain or comply with dual antiplatelet therapy for at least 12 months.
14. Patient is a woman who is pregnant or nursing (a pregnancy test must be performed within seven days prior to the index procedure in women of child-bearing potential).
15. Concurrent medical condition with a life expectancy of less than 12 months.
16. The patient is unwilling/not able to return for outpatient clinic at 12-month follow-up.
17. Currently participating in another trial and not yet at its primary endpoint.

Supplementary Table 2. Number of patients enrolled per site on 1st July 2019.

Principal investigator	Site name	City	Country	Number of enrolments
Robert Gil	Central Clinical Hospital of the Ministry of Interior	Warsaw	Poland	19
Carlo Briguori	Clinica Mediterranea	Naples	Italy	13
Jacek Legutko	John Paul II Specialist Hospital	Krakow	Poland	5
Franck Digne	Centre Cardiologique du Nord	Saint Denis	France	4
Adam Witkowski	The Cardinal Stefan Wyszynski Institute of Cardiology	Warsaw	Poland	3
Mohammed Abdellaoui	Mutual Hospital Group	Grenoble	France	3
Luc Maillard	Clinique Axium	Aix en Provence	France	2
Maciej Lesiak	Poznan University of Medical Sciences	Poznan	Poland	2
Total				51