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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

Running title: Rationale and design of the POLBOS LM study

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ABSTRACT

Aims
To demonstrate the noninferiority of the BiOSS LIM C sirolimus-eluting cobalt-chromium bifurcation dedicated stent against the Xience stent regarding patients 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 multi-centre study enrolling 260 patients (SYNTAX score ≤32) with pre-specified performance goal based on the results of the EXCEL trial with contemporary percutaneous coronary intervention (PCI) for LMCA disease. Patient enrollment will comply with objective inclusion criteria of
diameter stenosis ≥50% in LMCA based on off-line quantitative coronary angiography (QCA) analyzed by an independent core laboratory using dedicated-bifurcation QCA software. The BiOSS LIM C is used for the treatment of LMCA disease with the specific technical classification for the BiOSS LIM (modified MADS classification) and the stent implantation is optimized by using pre-specified intravascular ultrasound criteria. Primary endpoint is POCE (a composite of all-cause death, stroke, any myocardial infarction, and any revascularization) at 12 months.

**Conclusion**

The POLBOS LM study will indicate the efficacy of 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.

**Condensed abstract**

The POLBOS LM study is a single-arm prospective multi-center study enrolling 260 patients with pre-specified performance goal based on the results of the EXCEL trial with contemporary PCI for LMCA disease. Patient enrollment will comply with objective inclusion criteria of diameter stenosis ≥50% in LMCA based on off-line QCA using dedicated-bifurcation QCA software. The BiOSS LIM C is used for the treatment of LMCA disease with the specific technical classification for the BiOSS LIM (modified MADS classification) and the stent implantation is optimized by using pre-specified IVUS criteria. Primary endpoint is patient oriented composite endpoint at 12 months.
Abbreviations

CABG - Coronary artery bypass graft

FFR - Fractional flow reserve

iFR - instantaneous wave-free ratio

IVUS - Intravascular ultrasound

KBI - Kissing balloon inflation

LMCA - Left main coronary artery LMCA

PCI - Percutaneous coronary intervention

POT - Proximal optimization 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 graft (CABG) has shown good long-term clinical outcome for the LMCA disease whereas in the historical studies of PCI for LMCA, a higher incidence of repeat revascularization has been reported.\(^1\) Especially when a lesion is located in the distal part of the LMCA, the lesion frequently involves bifurcation segments.\(^2\) In that case, stenting techniques tend to be complex, being associated with high incidence of adverse events.\(^1\) However, the stent technology and the implantation techniques have evolved with concomitant medical therapy such as P2Y\(_{12}\) inhibitor, statin and PCSK9 inhibitor.

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 first-generation paclitaxel-eluting stent and CABG, 705 patients had LMCA disease (LMCA subgroup). The 5-year MACCE rate of the patients with low and intermediate SYNTAX Score (0-22 and 23-32) treated with PCI was comparable to 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 first-generation sirolimus-eluting stent versus CABG in patients with LMCA disease (average SYNTAX Score: 25), 5-
year MACCE rate was comparable (17.5% for PCI versus 14.3% for CABG, P= 0.26). The recent EXCEL trial was a prospective, international, open-label, multicenter trial that has randomized 2,900 patients to compare PCI using best-in-class stent (XIENCE: Abbott vascular, Santa Clara, CA, USA) versus CABG in the patients with LMCA disease with SYNTAX score ≤32. In that trial, 3-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). 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 MACCE (all-cause mortality, non-procedural MI, any repeated coronary revascularization and stroke) rate at 5 years. In the 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 Score, whereas repeat revascularization is more common after PCI. This suggests that indication of PCI for LMCA disease should be discussed on a case-by-case basis in 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 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 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 strut thickness of 70 \(\mu\)m. The device is designed for the implantation from proximal main vessel to distal main vessel (Figure 1) and consists 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, ensuring physiological compatibility and optimal flow conditions.\(^\text{10}\) The bottle-shape device balloon ensures the proximal optimization technique (POT)-like effect after BiOSS LIM C implantation.\(^\text{11}\) The maximum expansion capacity of the BIOSS LIM C is 6.15 mm, which is comparable to the one 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 1-year clinical outcomes to conventional drug-eluting stents in patients with bifurcation lesion.\(^\text{12}\) The BiOSS stent was further upgraded using cobalt-chromium platform (BiOSS LIM C stent). In a porcine model, the BiOSS LIM C stent showed comparable histological vascular healing to the Orsiro stents (Biotronik, Bülach, Switzerland) 28 days after implantation.\(^\text{11}\) The first-in-man trial of BiOSS LIM C stent, which investigated clinical outcomes of 48 patients with bifurcation lesion 12 months after the implantation,
demonstrated high device success rate (100%) and low 3-month events (one target lesion revascularization [2.1%] and no spontaneous MI or stent thrombosis).\textsuperscript{13} In addition, a recent study in BIOSS LIM in LM treatment suggests that this device may reduce the resources utilization (guidewire, balloon, contrast media) versus conventional DES.\textsuperscript{14}

Based on these results, we generated the hypothesis that 1-year clinical outcomes after BiOSS LIM C implantation in patients with distal unprotected LMCA disease is non-inferior to the best-in-class stent (XIENCE) and therefore designed a single arm prospective study - the POLish Bifurcation Optimal treatment Strategy study for Left Main bifurcation PCI (POLBOS LM study) with pre-specified performance goal based on the results of the EXCEL trial as recommended by the ESC/EAPCI task force on device.\textsuperscript{15}

METHODS

Study design

The POLBOS LM study is a prospective, multicenter single arm study in patients with an indication for distal unprotected left main revascularization. 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] \textgreater=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).\textsuperscript{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 bifurcation. For the potential additional treatment of proximal and distal left-main lesion, the Alex-Plus cobalt-chromium sirolimus-eluting single stents (Balton, Warsaw, Poland) 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 the objective performance index trial such as the EXCEL trial, in the present case (Supplementary methods).

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 12-month patient-oriented composite endpoint (POCE) consisting of all-cause mortality, stroke (modified Rankin Scale [mRS≥1]), any MI and any unplanned revascularization for ischemia.

**Patient population and indication of LMCA stenting**

Patients with silent ischemia 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 in case of fulfilling the following objective criteria: 1) %DS of the target lesion in LMCA is ≥50% confirmed by off-line QCA analyzed by the independent core laboratory (Cardialysis BV, Rotterdam, the Netherlands) using a dedicated-bifurcation
software (CAAS bifurcation software, Pie Medical Imaging, Maastricht, the Netherlands) prior to the treatment\textsuperscript{17} with documented ischemia (e.g. fractional flow reserve (FFR) ≤0.80)\textsuperscript{18}, in case pre-procedural IVUS is available a left main minimum lumen area (MLA) ≤6.0 mm\textsuperscript{2} is considered equivalent as the DS ≥50% by core lab (Figure 2)\textsuperscript{19}, 2) Medina classification for the target lesion in LMCA is confirmed by offline QCA, 3) reference vessel diameter of the distal LMCA is ≥3.0 mm and ≤4.5 mm, and distal main branch vessel diameter ≤3.75 mm measured by visual estimation, 4) clinical and anatomical eligibility for PCI as agreed by the local heart team. Patients with stabilized acute coronary syndromes with elevated Troponin (high sensitivity troponin, Troponin I or Troponin T) at baseline (within 24h pre-PCI) may be also included in the current study, if all of the followings are fulfilled: 1) the value of creatine kinase (CK) and creatine kinase myocardial band (CK-MB) are within normal range; 2) the value of troponin at follow-up should be within 20% range of the value of the first sample or have dropped; 3) ECG is normal.

The 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. The detailed inclusion and exclusion criteria are presented in the 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 been 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 hyperemia is greater in vessels supplying greater amounts of myocardium, such as 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, California) prior to PCI for exploratory purposes. iFR is measured distal to the target lesion in both proximal LAD and LCX (two measurements). For the sake of 3-dimensional angiography reconstruction, which will be used for the sub-study, wire positions are recorded in two angiographic views at least separated by 30 degrees apart preceding iFR measurement and followed by iFR pullback.

**Implantation of BiOSS LIM C in LMCA**

As mentioned above the protocol mandated that the distal LM bifurcation is treated with BiOSS LIM C stent. Whenever 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 for side branch occlusion after the BiOSS stent implantation, “main branch stenting across side branch” is recommended. If the ostium of side branch has a residual significant stenosis after the 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 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 a culotte stenting by using two BiOSS stents is presented in Supplementary figure 2.

The decision to use a up-front 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 >5mm, 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 main branch and Alex-puls stent for side branch. 24

Apart from stenting procedure as described above, interventional procedure, intraprocedural anticoagulation, and dual anti-platelet therapy are performed according to the current clinical guidelines. 18
Post-procedural IVUS

In the current study, usage of IVUS for the optimization of the stent implantation is highly recommended, according to the ESC guideline (IIA). 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 LMCA, LAD and LCX are preferably dilated with MSA/MLA >8.5, 6.0, and 5.5 mm², respectively. (Supplementary figure 3). POT and balloon dilatation in distal branch so called distal optimization technique are systematically recommended.

Staged procedure

Staged procedure is defined as a planned elective second PCI procedure at a separate setting to optimally complete the PCI. The criteria for staging are left to the operator’s best judgement. Given the complexity of the unprotected LMCA patients, it is 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 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 “retouching” again during the staged procedure.

The recommended timing of a planned staged procedure is optimally within 4 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.\textsuperscript{25} In the POLBOS study it is recommended to attempt achieving a residual SYNTAX Score ≤8 post PCI.

**Concomitant medications**

Preloading with aspirin 300 to 325 mg is required at least 2 hours before PCI. Pre-PCI loading of the P2Y\textsubscript{12} inhibitors is mandatory, where the selection of either clopidogrel, prasugrel or ticagrelor is left to the discretion of the investigator. After PCI, dual antiplatelet therapy (DAPT) consisting of aspirin and one of the P2Y\textsubscript{12} inhibitors is mandated at least one year after PCI and 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 statin or PCSK9 inhibitor is strongly recommended along with optimization of all medical therapies.\textsuperscript{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.\textsuperscript{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.\textsuperscript{18}

**Clinical follow-up**

Hospital visits are planned at 1 month (±7 days) and 1 year (±30 days). A phone contact is scheduled at 6 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 3 years after index procedure. Laboratory testing and other tests are described in Supplementary methods. Data will be entered into a web-based eCRF. Data entry will be monitored according to a pre-specified monitoring plan (Cardialysis).

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 revascularization including all target and non-target vessels (Table 1). To keep consistency with the EXCEL trial, the primary endpoint in the current study applies the same definition for MI as the EXCEL trial. In particular, peri-procedural 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 2 contiguous leads or new persistent non-rate related 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), CK-MB $\geq 5x$ and $\geq 10x$ are considered equivalent to cTn $\geq 35x$ and $\geq 70x$, respectively in the current study.\textsuperscript{29} Stent thrombosis is defined according to the ARC definition.\textsuperscript{28} All definitions of study endpoint are described in Supplementary methods. Clinical events will be adjudicated by an independent clinical event committee.

**Statistical considerations and sample size calculation**

The primary efficacy endpoint is based on the comparison to the prespecified 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 1-year POCE. The primary analysis will be based on an intent-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 its standard deviation. In the sample size calculation with PASS software, 256 analyzable 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 enrollment status is shown in Supplementary table 2.
Discussion

Pre-specified subgroup analyses will be performed for 1-stent versus 2-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 the results are considered exploratory (hypothesis generating) only.

Several other sub-studies are planned, taking advantages of the current study using multi-modality assessments (angiography, iFR and IVUS). The impact of anatomical (QCA) and physiological information (iFR) in LMCA on 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 pull-back 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 stenting strategy on the shear stress.

Limitation

The present study has several limitations. First, this is a non-randomized study comparing dedicated bifurcation stent with best-in-class DES (Xience). Second, the maximum nominal length of 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.
CONCLUSION

The POLBOS LM study will indicate the efficacy of 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 POLBOS LM study is to demonstrate the noninferiority of BiossLIM C bifurcation dedicated stent to the best in class Xience stent in the EXCEL trial in patients with unprotected left main bifurcation lesion. Favourable result might provide us with alternative option for a challenging left main bifurcation treatment in clinical practice.

Funding

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Conflict of interest

advisory board Abbott Vascular. R.G.: Receipt of lecture fee: Balton. The other authors have no conflicts of interest to declare.
REFERENCE


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FIGURE LEGENDS

Figure 1. BiOSS® Stent / Bottle® Balloon Structures and a case example of the BiOSS® implantation in LMCA

The macroscopic appearance of the BiOSS LIM C stent and its delivery balloon is shown in panel A. Diameter of the balloon in the proximal and distal part is the different reflecting natural tapering of bifurcation anatomy. Transitional zone (corresponding to bifurcation) is free from ring, but connecting proximal and distal part with the two links. This enables easy access to the side branch after the stenting in the main branch. The balloon has three metallic markers which are placed in the distal edge, transitional zone, and proximal edge. During implantation mid marker should be located the point of the bifurcation carina, so that transitional zone is precisely located in polygon of confluence. Panel B to I show an example of an implantation procedure of the BiOSS LIM C stent. The patient had Medina 1, 0, 0 left main bifurcation lesion (panel B and C). After the pre-dilatation with non-compliant balloon 3.25 x 12 mm at 25 atm (panel D and E), the BiOSS stent was advanced in the LM toward LAD. The BiOSS stent 4.25 x 3.5 x 19 mm was positioned precisely at the position of the carina using metallic marker (panel F). After the deployment of the BiOSS stent 4.25 x 3.5 x 19 mm (panel G), proximal optimization technique was performed with non-compliant balloon 5.0 x 8 mm at 20 atm (panel H). The final angiography demonstrated excellent result (panel I).

LAD: left anterior descending, LM: left main, POT: proximal optimization technique.

Figure 2. Quantitative coronary angiography of a left main bifurcation using a dedicated-bifurcation software

The first patient of the POLBOS LM study had Medina 1, 0, 0 left main bifurcation lesion (panel A). In panel B, QCA analysis using a dedicated-bifurcation software showed
significant stenosis (DS of left main: 51%). However, reference diameter (Ref D) of left main was underestimated due to diffuse left main disease. Therefore, Ref D of left main was recalculated using Finet law, resulted in DS of left main of 66%. After enrollment, preprocedural MLA measured by IVUS was 3.46mm² in the distal left main (panel C-G). Preprocedural iFR value in the LAD and LCX was measured (panel A).


**Figure 3. BiOSS stent implantation strategies**

The techniques with a red framed box are recommended in the protocol. In case of two-BiOSS-stent usage (Culotte technique: 5, 10) size of MB and SB should be comparable. TAP technique 3, 12 are not recommended in case with the bifurcation angle >70° where T stenting 2, 13 are recommended.

MB: main branch, SB: side branch, TAP: T-stenting and small protrusion and DK: double kissing
## Table 1. Endpoints

<table>
<thead>
<tr>
<th>Primary Endpoint</th>
<th>Secondary Endpoints (evaluated at each follow-up visit/contact)</th>
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<tbody>
<tr>
<td><strong>Primary Endpoint</strong></td>
<td>Patient-oriented composite endpoint (POCE) at 12 months post-procedure.</td>
</tr>
<tr>
<td>POCE is a composite measure of:</td>
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<tr>
<td>- All-cause mortality</td>
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<tr>
<td>- Stroke (modified Rankin Scale ≥1)</td>
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<tr>
<td>- Any Myocardial Infarction (MI)*</td>
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<tr>
<td>- Any unplanned revascularization for ischemia</td>
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<tr>
<td><strong>Secondary Endpoints</strong></td>
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<tr>
<td>1. Composite Endpoints</td>
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<tr>
<td>• POCE for all follow-up contacts other than 12 months</td>
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<tr>
<td>• Target Vessel Failure (TVF) defined as cardiac death, target-vessel MI*, and clinically indicated target vessel revascularization</td>
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<tr>
<td>• Device Oriented Composite Endpoint (DOCE)/TLF defined as cardiac death, target-vessel MI* and clinically-indicated target lesion revascularization (DOCE will be reported both including the left-main target lesion only and all target lesions)</td>
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<tr>
<td>2. Mortality</td>
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<tr>
<td>• All death</td>
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<td>• Cardiac death</td>
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<tr>
<td>• Non-cardiac death (vascular and non-cardiovascular)</td>
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<tr>
<td>3. Stroke</td>
<td></td>
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<td>• All</td>
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<td>• Ischemic</td>
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<tr>
<td>• Hemorrhagic</td>
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<tr>
<td>4. Myocardial Infarction*</td>
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<tr>
<td>• All MI (periprocedural, spontaneous, Q-wave and non-Q-wave),</td>
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<tr>
<td>• Target Vessel/ Non-Target Vessel MI</td>
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<td>5. Revascularization</td>
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<td>• Any revascularization</td>
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<tr>
<td>• Target Lesion revascularization (TLR) (any, clinically-induced TLR, non-clinically indicated TLR). (TLR will be reported both including the left-main target lesion only and all target lesions)</td>
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</tbody>
</table>
- Target Vessel revascularization (TVR) (any, clinically-indicated TVR, non-clinically indicated TVR)
- Non-Target Vessel revascularization

6. Stent thrombosis according to ARC classification 28

*Definition is based on the EXCEL study*4
Implantation procedure of BiOSS LIM C

Pre-procedure

Pre-dilatation with NC balloon 3.25x12 mm (25atm)

After pre-dilatation

Positioning of the BiOSS stent before deployment (the middle marker was adjusted to the position of carina)

Deployment of BiOSS LIM C (4.25x3.5x10mm) in LM-LAD (12atm)

After procedure
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<table>
<thead>
<tr>
<th></th>
<th>DS</th>
<th>MLD (mm)</th>
<th>Ref D (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LM</td>
<td>51%</td>
<td>1.49</td>
<td>3.04</td>
</tr>
<tr>
<td>LAD</td>
<td>16%</td>
<td>2.72</td>
<td>3.25</td>
</tr>
<tr>
<td>LCX</td>
<td>0%</td>
<td>3.24</td>
<td>3.15</td>
</tr>
</tbody>
</table>

Re-calculation of Ref D of LM according to Finet law

0.678 (3.25+3.15)=4.33 (Ref D_{Finet})

DS_{Finet} of LM: 66%
Supplementary methods

Treatment of non-LMCA lesions

To maintain the comparability with the EXCEL trial, all other non-left main lesions will be treated with the XIENCE family 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 the PCI for non-LMCA lesions, which is different from the treatment of treatment of LMCA, unless there is evident territorial information of ischemia as assessed by 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 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.

Laboratory testing and other tests pre- and post-PCI

Complete blood count with differential, creatinine and HbA1c are 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) are performed pre-procedure, within 24 hours post-procedure, at discharge. Ejection fraction at baseline, derived from echo cardiograph, magnetic resonance imaging, computed tomography or ventriculogram has to be documented in the eCRF.
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 academic core lab) with documented ischemia or FFR ≤0.80 requiring revascularization.
   - 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 <6mm2), the investigator is allowed to include the patient in the trial.
2. Left-Main Medina classification 100, 110, 101, 011, 010, 111 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 ischemia, chronic stable angina or stabilized acute coronary syndromes with normal cardiac biomarker values

*Note: For patients showing elevated Troponin (cTn) (e.g. non-STEMI patients) at baseline (within 24h 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 enrollment
2. Prior PCI of any other (non-left main bifurcation) coronary artery lesion within 6 months (<6 months) prior to enrollment.
3. Left-Main Medina classification 001.
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 proximal LAD and proximal LCX)
7. Direct stenting of the left main bifurcation
8. Prior CABG at any time prior to enrollment
<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>9.</td>
<td>Patient requiring or may require additional surgery (cardiac or non-cardiac) within one year</td>
</tr>
<tr>
<td>10.</td>
<td>Ongoing myocardial infarction or recent myocardial infarction with cardiac biomarker levels still elevated.</td>
</tr>
<tr>
<td>11.</td>
<td>Known renal insufficiency (e.g. serum creatinine &gt;2.5mg/dL, or creatinine clearance ≤30mL/min, or patient on dialysis).</td>
</tr>
<tr>
<td>12.</td>
<td>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.</td>
</tr>
<tr>
<td>13.</td>
<td>Patients unable to tolerate, obtain or comply with dual antiplatelet therapy for at least 12 months.</td>
</tr>
<tr>
<td>14.</td>
<td>Patient is a woman who is pregnant or nursing (a pregnancy test must be performed within 7 days prior to the index procedure in women of child-bearing potential).</td>
</tr>
<tr>
<td>15.</td>
<td>Concurrent medical condition with a life expectancy of less than 12 months.</td>
</tr>
<tr>
<td>16.</td>
<td>The patient is unwilling/not able to return for outpatient clinic at 12-month follow-up.</td>
</tr>
<tr>
<td>17.</td>
<td>Currently participating in another trial and not yet at its primary endpoint.</td>
</tr>
</tbody>
</table>
### Supplementary table 2. Number of patients enrolled per site on 1st July 2019

<table>
<thead>
<tr>
<th>Principal Investigator</th>
<th>Site name</th>
<th>City</th>
<th>Country</th>
<th>Number of enrollments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Robert Gil</td>
<td>Central Clinical Hospital of the Ministry of Interior</td>
<td>Warsaw</td>
<td>Poland</td>
<td>19</td>
</tr>
<tr>
<td>Carlo Briguori</td>
<td>Clinica Mediterranea</td>
<td>Naples</td>
<td>Italia</td>
<td>13</td>
</tr>
<tr>
<td>Jacek Legutko</td>
<td>John Paul II Specialist Hospital</td>
<td>Krakow</td>
<td>Poland</td>
<td>5</td>
</tr>
<tr>
<td>Franck Digne</td>
<td>Centre Cardiologique du Nord</td>
<td>Saint Denis</td>
<td>France</td>
<td>4</td>
</tr>
<tr>
<td>Adam Witkowski</td>
<td>The Cardinal Stefan Wyszynski</td>
<td>Warsaw</td>
<td>Poland</td>
<td>3</td>
</tr>
<tr>
<td>Mohammed Abdellaoui</td>
<td>Mutual Hospital Group</td>
<td>Grenoble</td>
<td>France</td>
<td>3</td>
</tr>
<tr>
<td>Luc Maillard</td>
<td>Clinique Axium</td>
<td>Aix en Provence</td>
<td>France</td>
<td>2</td>
</tr>
<tr>
<td>Maciej Lesiak</td>
<td>Poznan University of Medical Sciences</td>
<td>Poznan</td>
<td>Poland</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>51</strong></td>
</tr>
</tbody>
</table>
Supplementary figure legends

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 with a culotte stenting by using two BiOSS stents

The patient had Medina 1, 1, 1, left main bifurcation lesion (panel A and B). One drug eluting stent 3.5 x 15 mm was deployed in the proximal LAD (panel C). The BiOSS LIM C stent 4.5 x 3.75 x 18 mm was deployed precisely in the left main toward LAD under metallic marker guidance (panel D). Wire re-crossing toward LCX was easily performed due to precisely placed transitional zone. The second BiOSS stent 4.5 x 3.75 x 18 mm was deployed in the left main toward LCX (panel E). Coronary flow toward both branches was well preserved even just after culotte stenting (panel F). The final angiography demonstrated excellent result (panel G and H).

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

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 LMCA, LAD and LCX are preferably dilated with MSA/MLA >8.5, 6.0, and 5.5 mm², respectively.
IVUS: intravascular ultrasound, LMCA: left main coronary artery, LAD: left anterior descending, LCX: left circumflex, MSA: minimum stent area and MLA: minimum lumen area
Study definitions

MYOCARDIAL INFARCTION (MI)

EXCEL study definition

Peri/Post procedure 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 2 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 EXCEL definition did not comprise cTn, we consider equivalence CK-MB ≥10x versus cTn ≥70x and CK-MB ≥5x versus cTn ≥35x

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 ischemia [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 subcategorized 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 Third Universal definition.

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**Myocardial infarction according to Third Universal definition (2012)**

### 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:

- 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:
  - Symptoms of ischaemia
  - New or presumed new significant ST-segment-T wave (ST-T) changes
  - New LBBB
  - Development of pathological Q waves in the ECG
  - 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, tachy-/brady-arrhythmias, anemia, 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 ischemia and presumed new ischemic 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 ischemia and with a rise and/or fall of cardiac biomarkers 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.

PERI-PROCEDURAL MYOCARDIAL INFARCTION (SCAI 2013)

Peri-procedural MI according to SCAI 2013 definition

Peri-procedural MI after PCI or CABG (<48 hours post-PCI or CABG)

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 hemodynamic 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 revascularized 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 are occluded at baseline and no attempt was made to revascularize 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 are occluded at baseline and no attempt was made to revascularize these territories by either PCI or CABG).

[Target Vessel Revascularization (TVR)]
Target vessel revascularization is any repeat percutaneous intervention of the target vessel or bypass surgery of the target vessel.

[Target Lesion Revascularization (TLR)]
Target lesion revascularization is defined as any repeat percutaneous intervention of the target lesion or bypass surgery of the target vessel.

[Clinically-Indicated Revascularization (CI-TLR/TVR)]
Revascularization will be considered ischemia-driven if the target lesion diameter stenosis is ≥50% by QCA and any of the following criteria for ischemia are met:
- Positive functional ischemia study including positive FFR/iFR corresponding to the area served by the target lesion; or
- Ischemic ECG changes at rest in a distribution consistent with the target vessel; or
- Typical ischemic symptoms referable to the target lesion; or
- IVUS of the target lesion with a minimal lumen area (MLA) of ≤4mm² for non left main lesions or ≤6mm² 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 revascularization for a diameter stenosis less than 50% might also be considered ischemia-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) 32
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 left the catheterization 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 - 1 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 revascularization.

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 ischemic symptoms at rest
  - New ischemic ECG changes that suggest acute ischemia
  - Typical elevation or depression in cardiac biomarkers (refer to definition of spontaneous MI)
  - Nonocclusive thrombus
    - Thrombus Intracoronary thrombus is defined as a (spheric, ovoid, or irregular) noncalcified filling defect or lucency surrounded by contrast material (on 3 sides or within a coronary stenosis) seen in multiple projections, or persistence of contrast material within the lumen, or a visible embolization 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 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 occurred after stent implantation will be considered a probable stent thrombosis:
  o Any unexplained death within the first 30 days‡
  o Irrespective of the time after the index procedure, any MI* that is related to documented acute ischemia 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 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 considered to have occurred with any unexplained death from 30 days following intracoronary stenting until 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:

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

Stroke: Modified Rankin score ≥1
Strokes may be further sub-classified as follows:

1. **Ischemic** (Non-hemorrhagic): 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 etiology.

2. **Hemorrhagic**: a stroke due to a hemorrhage in the brain as documented by neuroimaging or autopsy. This category will include strokes due to primary intracerebral hemorrhage (intraparenchymal or intraventricular), ischemic strokes with hemorrhagic transformation (i.e., no evidence of hemorrhage on an initial imaging study but appearance on a subsequent scan), subdural hematoma, * and primary subarachnoid hemorrhage.

*All subdural hematomas that develop during the clinical trial should be recorded and classified as either traumatic versus nontraumatic.

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 Ischemic Attack (as compared to stroke) is defined as:

- New focal neurologic deficit with rapid symptom resolution, usually 1-2 hours, always within 24 hours
- Neuroimaging without tissue injury
For enrollment:
- Documented ischemia or FFR<0.80
- DS≥50% or IVUS MLA≤6.0mm² with the exemption of Medina O01

In case pre-procedural IVUS is available a left main MLA ≤6.0mm² is considered equivalent to the core lab DS ≥50%.

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POLBOS LIM

IVUS criteria for post-dilatation

LMCA
MSA/MLA
>8.5 mm²

LAD
MSA/MLA
>6.0 mm²

LCX
MSA/MLA
>5.5 mm²

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