ECRI-010

POLish Bifurcation Optimal treatment Strategy study for Left Main bifurcation PCI (POLBOS LM)

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Sponsor:
European Cardiovascular Research Institute (ECRI)
Westblaak 98
3012 KM Rotterdam
The Netherlands

CRO:
Cardialysis
Westblaak 98
3012 KM Rotterdam
The Netherlands

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1 PROTOCOL SYNOPSIS

Protocol Number	ECRI-010
POLBOS LM	POLish Bifurcation Optimal treatment Strategy study for Left Main bifurcation PCI. *A prospective, multicenter single arm study in patients with an indication for unprotected left main bifurcation revascularization*.
Study phase	Post-marketing
Investigational (Study) Device	The BiOSS LIM C (Bifurcation Optimization Stent System, Balton, Warsaw, Poland). The BiOSS LIM C is a dedicated bifurcation stent covered with a mixture of a biodegradable polymer and the antiproliferative substance sirolimus. BiOSS LIM C will be used for treatment of the Left-Main bifurcation, according to its instructions for use. The Alex-Plus cobalt-chromium sirolimus eluting stent (Balton, Warsaw, Poland) will be used for treatment of distal left-main side branches according to its instructions for use (i.e. proximal segments of the left anterior descending and left circumflex arteries as well as the ramus intermedius if the latter vessel is part of a trifurcation). All other lesions (other than left-main bifurcations) will be treated with XIENCE family everolimus-eluting coronary stent systems. e.g. XIENCE V, XIENCE PRIME, XIENCE Xpedition, Xience PRO (PRO, PRO 48, PRO LL en PROx), Xience ALPINE, Xience Sierra or any next generation of the XIENCE family everolimus-eluting coronary stent system.
Objective	To establish the safety and efficacy of the BiOSS LIM C with respect to Patient oriented Composite Endpoint (PoCE) at 12 months in a “real world” left-main bifurcation population and as compared with a pre-specified performance goal (OPC).
Design	A prospective, multicenter, single arm study in patients with an indication for distal unprotected left main revascularization (either isolated distal left main disease or associated with disease in other

	coronary arteries). The treatment strategy consists of contemporary PCI of the left-main bifurcation following diagnostic angiography demonstrating significant distal unprotected left main disease and local Heart Team discussion applying the anatomic SYNTAX Score. The presence of a significant lesion (%DS≥50) in any of the left main bifurcation segments (i.e., distal left main, ostial LAD or ostial LCX) must be confirmed by the academic team core lab (Rotterdam, NL) using dedicated bifurcation QCA. Pre-procedure iFR is mandatory to explore the physiological importance of the left main bifurcation. IVUS pre-procedure may be performed up to discretion of the investigator. IVUS assessment post-stent implantation for optimization of BiOSS LIM C deployment is highly recommended according to ESC guidelines (Class IIa (Level of Evidence: B)[1, 2] The patients will be followed through 12 months to assess the clinical status and major clinical events with a potential for additional follow-up to 3 years.
Number of Patients	A total of 260 patients will be enrolled to receive treatment with the BiOSS LIM C study device.
Investigational Sites	Approximately 15 sites in Europe will participate.
Primary Endpoint	<u>Primary endpoint:</u> The primary endpoint for this trial is defined as the patient-oriented composite endpoint (PoCE) at 12 months post-procedure. PoCE is a composite measure of: - All-cause mortality - Stroke (modified Rankin Scale (mRS≥1)) - Any Myocardial Infarction (MI)* (includes nontarget vessel territory) - Any unplanned revascularization for ischemia (includes all target and nontarget vessels)

	**Definition EXCEL study (APPENDIX I: Definitions)*
Secondary Endpoints	Secondary Endpoints (evaluated at each follow-up visit/contact) 1. Composite Endpoints • Patient Oriented Composite Endpoint (PoCE) defined as the composite of all-cause death, stroke, any MI*, and any revascularization (for all follow-up contacts other than 12 months) • Target Vessel Failure (TVF) defined as cardiac death, TV MI*, and clinically indicated target vessel revascularization • Device Oriented Composite Endpoint (DoCE)/TLF defined as cardiac death, TV MI* and clinically-indicated target lesion revascularization (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 • Ischemic • Hemorrhagic 4. Myocardial Infarction* • All MI (periprocedural, spontaneous, Q-wave and non Q-wave), • Target Vessel/ Non-Target Vessel MI 5. Revascularization • Any revascularization • Target Lesion revascularization (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 revascularization (TVR) (any, clinically-indicated TVR, non-clinically indicated TVR) • Non-Target Vessel revascularization 6. Stent thrombosis according to ARC classification

	Definition EXCEL study (APPENDIX I: Definitions)
Inclusion and Exclusion 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 (following ESC guidelines, IA recommendation, for revascularization in patients with stable angina or silent ischemia[2]) requiring revascularization . In case pre-procedural IVUS is available a left main MLA ≤6.0mm^2 is considered equivalent to the core lab DS ≥50%). 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. Left main vessel diameter ≥3.0 mm and ≤4.5 mm, and main branch vessel diameter ≤3.75mm, measured by visual assessment. 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 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 >2.5mg/dL, or creatinine clearance ≤30mL/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 7 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. 18. The patient is not allowed to participate in another investigational device or drug study for at least 12 months after enrollment.

Antiplatelet Medication	All patients must receive dual anti-platelet therapy, being aspirin (ASA) and platelet aggregation inhibition therapy for at least 12 months after PCI (with the choice of agent left to the discretion of the investigator) followed by ASA monotherapy indefinitely.
Statistical Analysis Plan	**Primary Analysis:** The primary efficacy endpoint is based on comparison to pre-specified performance goal based on the PCI arm of the EXCEL study[3]. The study is powered at 80% to show non-inferiority of the BiOSS LIM C compared with XIENCE EES. The primary analysis will be based on an intent-to-treat (ITT) patient population. **Assumptions:** Power = 80% One-sided alpha = 5% Non-inferiority margin of 6.3% PCI (XIENCE) PoCE – 16.7% at 12 months (365 days)[3] *(EXCEL study, PCI cohort, data on file).* The BiOSS LIM C expected PoCE assumption is based on an assumed no difference in event rate as compared to the objective performance goal (OPC – EXCEL study). **Study Sample Size Calculation: 260 Patients** A sample size calculation of 256 analyzable patients is required using the assumptions above, PASS software, and a non-inferiority Fisher Exact test for one proportion. This number is increased to 260 patients accounting for some attrition.

1.1 Schedule of Assessments:

Schedule of Events	Baseline (prePCI)	Procedure	Post-procedure\ Discharge	30 days (±7 days)	6 months (±14 days)	1 year (±30 days)
				Visit	TC Contact	Visit
Inclusion/Exclusion Criteria	•					
Pregnancy test*	•					
Left Main Medina class**	•					
SYNTAX Score	•		•[9]			
Informed Consent	•					
Demographics, Medical History, vital signs	•					
Anginal status	•		•	•	•	•
12-Lead ECG	•[1]		•[2]	•		•
LVEF	•[3]					
Blood Laboratory (WBC, platelets, Hemoglobin, Hematocrit, serum Creatinine, HbA1c)	•[4]					
Cardiac enzymes (CKMB, Troponin)	•[5]		•[6]			
Cardiac Medications	•		•	•	•	•
Angiography[7]	•	•				
iFR[7]		•[i]				
IVUS[7]		•[ii]				
Serious Adverse Events[8]		•	•	•	•	•

Notes:

*For females of childbearing-potential only

**Diameter Stenosis (DS%) and Medina class of the distal left main must be confirmed by the academic core lab in Rotterdam using dedicated QCA bifurcation software prior to enrollment.

[1] ECG at time of screening must be performed within 72 hours prior to PCI procedure.

[2] ECG within 24 hours post-procedure or at discharge, whichever comes first.

[3] Left ventricular ejection fraction (LVEF) must be assessed within 14 days prior to enrollment, either by echocardiography, MRI, or contrast left ventriculography.

[4] Blood chemistry: WBC, Platelets, Hb, Ht, serum Creatinine, HbA1c) at time of screening must be performed within 28 days prior to PCI procedure

[5] CK-MB (preferred), or Troponin (cTn) if CK-MB is not available, are drawn within 24 hours prior to the start of the PCI procedure. Blood can be withdrawn from the arterial sheath prior to the index procedure.

For patients showing elevated Troponin (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] CK-MB (preferred), or Troponin (cTn) if CK-MB is not available, are determined within 10-14 hours and 22-26 hours post-procedure or at discharge if sooner. If cardiac enzymes are elevated (CK >2ULN with iso-enzyme CKMB, CKMB >3 ULN, or cTn/hs-cTn >35 ULN), serial measurements of cardiac enzymes must be taken until a decline is noted.

[i] iFR pre-procedure is mandatory to explore the physiological importance of the left main bifurcation disease.

[ii] IVUS assessment post-stent implantation for optimization of BiOSS LIM C deployment is highly recommended according to ESC guidelines (Class IIa, level of evidence: B)

[7] Collect and forward to central Core Lab (material collection only).

[8] For all intercurrent angiographies and revascularizations (incl. stent thrombosis, etc.), the angiogram must be sent to the Monitor organization and/or CRO (Cardialysis).

[9] It is recommended to attempt achieving a residual SYNTAX Score ≤8 post PCI. A SYNTAX Score assessment post-PCI is optional for the investigators.

Note: In the event of intercurrent illnesses, interventions, adverse events, or treatment failure, effort should be made to complete the required observations as much as possible.

2 INTRODUCTION

2.1 Background

Percutaneous revascularization for unprotected left main coronary artery disease (ULMCA) was short of a taboo subject in the field of interventional cardiology, until the early 2000s.

The first, historical, randomized control trial (RCT) comparing coronary artery by-pass graft surgery (CABG) and percutaneous coronary intervention (PCI) was conducted in Poland, in 105 patients, and reported in 2008 by Buszman et al. (LEMANS trial) in the Journal of American College of Cardiology[4]. This trial used a surrogate mechanistic endpoint (left ventricular ejection fraction, LVEF) at 12 months and showed that the patients with (ULMCA) treated with PCI had favorable early outcomes in comparison with the CABG group at 12 months. LVEF was significantly improved only in the PCI cohort and after > 2 years, major adverse cardiac events (MACE) free survival was similar in both groups, with a trend towards improved survival after (PCI). In a critical editorial, Taggart et al. reminded at that time the medical community that CABG is traditionally regarded as the standard of care because it is well documented and demonstrates durable survival advantage[5]. He concluded that CABG should indeed remain the preferred revascularization method in good surgical candidates with ULMCA. In the meantime, a number of registries comparing PCI vs. CABG in patients with ULMCA who were poor or non-candidates for CABG were also published[6-12].

Nevertheless, it was only in 2003 that a larger trial of all-comer patients with three vessels disease (3VD) and ULMCA was designed[13]. The 1- and 5 years follow-up results of this trial were published in 2009 and 2013 respectively [14, 15] and supported the conclusion that PCI for ULMCA, with or without 3VD, and with an intermediate SYNTAX Score (<32) was an acceptable alternative treatment to surgery. However, the entire trial including 3VD and ULMCA did not achieve globally non-inferiority. In the meantime, Park et al. conducted the PRECOMBAT trial, in which they randomly assigned 600 patients with ULMCA between CABG and PCI[16]. The primary endpoint was a major adverse cardiac and cardiovascular events (MACCE) composite, including all-cause death, any myocardial infarction (MI), stroke or ischemia-driven target vessel revascularization (TVR) and the study was designed to demonstrate non-inferiority of PCI vs. CABG. They showed that PCI with sirolimus eluting stents (SES) was non-inferior to CABG with respect to MACCE, however the non-inferiority margin was wide and the result could not be considered clinically directive. A comparison of PCI vs. CABG according to the completeness of revascularization in severe CAD showed, in a patient-level pooled analysis of the SYNTAX, PRECOMBAT, and BEST trials, a complete revascularization (CR)

of 61.7% (57.2% with PCI and 66.8% with CABG). Patients undergoing PCI with incomplete revascularization had a higher risk for death from any cause (adjusted hazard ratio [aHR]: 1.43; 95% confidence interval [CI]: 1.03 to 2.00; p = 0.036) and the composite of death, myocardial infarction, and stroke (aHR: 1.48; 95% CI: 1.14 to 1.92; p = 0.003). The authors concluded that the ability to achieve CR should enter into the decision algorithm for choice of revascularization strategy [17]. In 2010, the EXCEL trial (1905 patients) was designed, aiming to demonstrate a non-inferiority outcome in a primary endpoint consisting of death, stroke, and MI at 3 years in patients with ULMCA and a SYNTAX Score <32[18]. This study achieved its primary endpoint of non-inferiority[3], whereas the Noble trial (1201 patients), which was published in 2016 and included a composite of death, non-procedural MI, stroke and repeat PCI as a primary end-point failed to achieve non-inferiority[19].

Reflecting on the collective body of evidence accumulated from the EXCEL, SYNTAX and PRECOMBAT trials, the current US recommendations for left main revascularization were set as IIa(B) (weight of evidence/ opinion in favor of usefulness/ efficacy) and IIb(B) for SYNTAX scores of ≤22 and <33 respectively[20]. In analogy, the European revascularization guidelines recommendations are I(B) for SYNTAX scores <23) and IIa(B) for SYNTAX scores 23-32[2]. In the future, the recommendation for PCI could become class I, with PCI being no longer simply an acceptable alternative for CABG but even the preferred choice in selected patients. In addition, with 2 more RCT, the current B-level of evidence for LM revascularization by PCI or CABG should be upgraded to A. It is unlikely that in the near future another major trial, sponsored by a device corporation, will take place, considering the huge costs of the SYNTAX and EXCEL studies.

On the other hand, left main treatment in latter two trials means, in 80% of cases, treatment of the left main bifurcation, and in the current interventional armamentarium there is no dedicated device (bifurcated stent) to address this condition. To date, only two dedicated devices exist for treating bifurcations, the TRYTON and the BiOSS LIM. The BiOSS device is characterized by its provisional approach of the side branch and by the special configuration of the balloon that has two different diameters in its profile. Because of these characteristics, the BiOSS device is respecting the fractal division of the flow and the diameter of the vessel and represents a very attractive and promising option for the treatment of LM bifurcation disease.

As mentioned above, the likelihood of another RCT of PCI vs CABG is very low and only two trial scenarios are plausible: 1) A RCT of BiOSS LIM versus a conventional DES, designed for non-inferiority and using the same criteria as the EXCEL trial or 2) The assessment of BiOSS LIM versus Objective Performance Index (OPI), based on the most recent results of the XIENCE stent in distal - bifurcated left main disease.

2.2 **BiOSS clinical program**

The BiOSS® (Bifurcation Optimization Stent System) Clinical Programme has started in 2008. The first BiOSS® stent was a bare metal one, but shortly after a paclitaxel-eluting version has been introduced to the market – the BiOSS Expert® stent. After acceptable results of the BiOSS Expert® stent in the all-comer population [21] as well as in distal LM stenosis [22] a way for improvement was to change the paclitaxel into the –olimus drug. The sirolimus has been chosen and the BiOSS LIM® stent was developed. Recently new version of BiOSS stent was developed, the cobalt-chromium sirolimus-eluting BiOSS LIM C.

The BiOSS LIM C® is a dedicated bifurcation balloon expandable stent made of cobalt-chromium alloy (strut thickness 70 µm) releasing sirolimus (1.4 µg/mm2) from the surface of a biodegradable coating comprised of a copolymer of lactic and glycolic acids (PGLA). The degradation of the polymer lasts approximately 8 weeks. The BiOSS LIM C® stent consists of two main separate parts with different diameters: wider proximally, and distally smaller. The proximal part is always a bit shorter than the distal one (avg. 1 mm). The ratio of the proximal part to the distal one varies between 1.15 to 1.3, ensuring physiological compatibility and optimal flow conditions. There is a 2.0 – 2.4 mm middle zone with two connecting struts after the BiOSS® stent implantation. This zone ensures “self–positioning” of a stent after balloon deflation, as well as the opening to side branch. There are three lengths (16, 19 and 24 mm) of BiOSS® stents available on the market. The nominal foreshortening of the stent is less than 0.5% and the stent strut/vessel area ratio varies between 15 – 18% [23].

The stent is crimped on a bottle-shaped balloon (Bottle®, Balton, Warsaw, PL). Bottle® balloons are available in a wide range of sizes and lengths allowing the left main (LM) treatment as well. The balloon nominal pressure is 10 atm, whereas the rated burst pressure is 18 atm. The balloon is semi-compliant with an increase in a diameter size of 0.25 mm at 12 atm, both proximally and distally.

Delivery system for BiOSS LIM C® stent is a rapid exchange one compatible with 0.014” guide wires and with 5Fr (1.63mm internal diameter) guiding catheters. The BiOSS LIM C® stent is introduced over a single guide wire, which (in the opposite to other dedicated systems guided on two guide wires) eliminates the risk of wire wrap (twisting) or other complications with double guide wire driven systems.

After wiring the main branch and the side branch, predilations could be performed according to the operator’s preferences, however is only recommended in case of any signs of calcium and fibrosis. The BiOSS LIM C® stent’s delivery balloon has three markers: distal and

proximal indicating stent edges and one mid marker showing the mid zone. The mid-marker should be placed exactly at the tip of the carina. Therefore, it is very important to find the best projection where the distal left-main carina is visible, e.g. spider view (LAO45°/caudal35°), caudal30°, RAO30°/caudal30°). This ensures that after deployment the contralateral to SB wall is covered with struts to the same extent as the proximal main vessel part of the bifurcation. This is achieved by self-centering properties of the device (due to special shape of connecting struts) and the "closure" configuration between proximal and distal parts of the stent. The BiOSS LIM C® design reduces the risk of carina shift as well as the SB ostium compromise [24]. Additionally, the Bottle® balloon shape ensures the proximal optimization technique (POT)-like effect at once after BiOSS® implantation, however post-dilation of its proximal part (real POT) seems to improve clinical results [25].

Since the beginning the BiOSS® stent construction raised the question, whether a 2.0 - 2.4 mm long middle zone of that stent was the weakest part predisposing to restenosis and intrastent thrombosis. An IVUS study on the device in non-LM bifurcations disclosed a different mechanism of lumen enlargement in coronary bifurcation lesions treated with provisional approach between classical DES and the BiOSS® stent. Despite, comparable luminal gain the BiOSS® stent was associated with less luminal compromise and plaque redistribution at the level of the SB in-flow in the bifurcation segment [24]. Moreover, the analysis of restenosis patterns in POLBOS I, in the FIM BiOSS LIM® Registry as well as in the BiOSS LIM® in LM registry denies those assumptions [22, 25, 26]. In the following paragraph, earlier studies with BiOSS® stent are summarized.

2.2.1 BIOSS® Registries

In the first-in-man trial 60 patients form three countries were enrolled (mean age 66.4 ± 11 years, 28.3% of female). There were 21.7% of patients with NSTE-ACS, 78.3% with hypertension, 38.3% with diabetes, 28.3% had previous MI, and 46.7% and 10% underwent prior revascularization, respectively, PCI and coronary artery bypass graft. At 12 months, the cumulative major adverse cardiovascular events rate was 11.7%. During follow-up (11 ± 1 months) there was 1 non-cardiac death (1.7%), 1 non-ST-elevated myocardial infarction (1.7%) due to restenosis and no case of stroke or in-stent thrombosis. Overall TLR was 8.3% (clinically driven TLR - 1.7%, angiographically driven - 6.6%). The side branch was treated with an additional classical DES implantation in 23.3% of cases[27].

In the second registry 74 cases with distal LM were analyzed. Seventy-three of 74 patients (aged 67±9 years, 23% women, 20.3% NSTE-ACS, SYNTAX score 22.4±4.4) were successfully treated with the BiOSS LIM® stent, with additional side branch classical DES

placement in 11 patients (14.9%). Periprocedural MI occurred in one (1.4%) patient. The 12-month MACE rate was 9.5% without cardiac death or definite stent thrombosis. TLR and MI rates were 6.8% (n=5) and 2.7% (n=2), respectively. This report showed that implantation of the dedicated bifurcation BiOSS LIM® stent in distal LM stenosis in patients with moderate SYNTAX score was safe and effective. Also, these results suggested that the sirolimus-eluting BiOSS LIM® stent have better results than the paclitaxel-eluting BiOSS Expert® stent. Moreover, this stent might offer an interesting option in coronary bifurcation treatment, especially when there is a large difference in the diameter between the main vessel and the main branch[26]. The vast majority of implantations were possible using radial access (more than 90%) and 6F compatible equipment (including also LM cases). Rewiring of the SB after BiOSS® Expert stent implantation was relatively easy (lower device profile, and no guide wires criss-crossing or improper device orientation was observed. The device success rate was 100%.

2.2.2 Randomized clinical trials

The POLBOS I study was the first randomized clinical trial[25]. The aim of POLBOS I trial was to compare bifurcation treatment with any classical DES to the dedicated bifurcation paclitaxel-eluting stent BiOSS Expert®. The second aim was to study the effect of final kissing balloon inflation (FKB) on clinical outcomes. Between October 2010 and January 2013, 243 patients with stable coronary artery disease or non-ST-elevation acute coronary syndrome were assigned 1:1 to one of two treatment strategies: BiOSS Expert® stent versus classical DES implantation. Coronary angiography was performed at 12 months. The primary end-point was composite of cardiac death, MI, and target lesion revascularization (TLR) at 12 months. BiOSS Expert® was implanted in 120 patients (49.4%) and DES in 123. The target vessel was LAD (52% vs 70%) followed by LM (22% vs 15%). In DES Group 38.2% were paclitaxel-eluting stents. There were 3 stent implantation failures (2 in DES and 1 in BiOSS group). Side-branch treatment with DES was required in 10% of cases in both groups. At 12 months, cumulative MACE incidence was similar in both groups: 13.3% vs 12.2% (P=0.7). TLR rate was significantly higher in BiOSS Group comparing to DES, 11.5% vs 7.3% (P=0.02). In further analysis, when comparing BiOSS Group to only PES subgroup from DES, the rate of TLR in both groups was comparable (11.5% vs 10.6%, NS). Moreover, when comparing LM bifurcation vs non-LM bifurcation lesions BiOSS Expert® was significantly superior to DES in treatment of distal LM stenosis (TLR: 7.4% vs 11.1%, P=0.04). The rates of clinically-driven TLR in our study were markedly lower in BiOSS as well as in DES Groups, 5.8% and 3.2% (NS), respectively. This is comparable to the best results of DES in coronary bifurcation treatment.

Subgroup analysis regarding FKB versus no FKB revealed that in both groups (BiOSS Group and DES Group) FKB was related with higher rate of SB stenting, longer time of

fluoroscopy and treated lesions were more frequently localized in LM. However, in FKB subgroups there was significantly lower rate of restenosis in BiOSS Group (8.1% vs 13.2%, P<0.05) as well as in DES Group (4.9% vs 9.5%, P<0.05). Interestingly, in DES Group the rate of restenosis in FKB+POT subgroup was even lower (1/42, 2.4%). It strongly suggests to optimize the process of the BiOSS® stent implantation despite its design.

The POLBOS I trial established an important benchmark for future studies with new generations of BiOSS® stents eluting -olimus drugs and utilizing newer stent materials. Therefore the POLBOS II was the continuation of the concept of POLBOS I, where BiOSS LIM® was compared with regular DES. Worth stressing is the fact that interim analysis of POLBOS II also suggests, similarly to POLBOS I study, that a more aggressive protocol (FKB and POT) during BiOSS® stent implantation yielded better angiographic and clinical outcomes.

2.2.3 Study Aims

This protocol will establish clinical outcomes of the BiOSS LIM C in a left-main bifurcation population and compared with a pre-specified performance goal.

3 OBJECTIVE

To establish the safety and efficacy of the BiOSS LIM C with respect to Patient oriented Composite Endpoint (PoCE) at 12 months in a "real world" left-main bifurcation population and compared with a pre-specified performance goal.

**Since the sample size and power calculation of the POLBOS LM study is based on the outcome of the EXCEL trial as an objective performance goal, the in- and exclusion criteria, general recommendations for practice, treatment and (endpoint) definitions are similar to the EXCEL protocol as published in NEJM and referred as such.*[3]

4 DESIGN OF THE TRIAL

A prospective, multicenter single arm study in patients with an indication for distal unprotected left main revascularization (either isolated distal left main disease or associated with disease in other coronary arteries). The treatment strategy consists of contemporary PCI of the left-main bifurcation following diagnostic angiography demonstrating significant distal left main disease and Medina classification (using dedicated bifurcation QCA software to confirm Medina classification) and local Heart Team discussion applying the anatomic SYNTAX Score.

The BiOSS LIM C (Balton, Warsaw, Poland) will be used for treatment of the Left-Main bifurcation, according it's instructions for use. The Alex-Plus cobalt-chromium sirolimus eluting stent (Balton, Warsaw, Poland) will be used for treatment of distal left-main side branches according it's instructions for use (i.e. proximal segments of the left anterior descending and left circumflex arteries as well as the ramus intermedius if the latter vessel is part of a trifurcation).

The presence of a significant lesion (%DS≥50) in any of the left main bifurcation segments (i.e., distal left main, ostial LAD or ostial LCX) must be confirmed by the academic team core lab (Rotterdam, NL) using dedicated bifurcation QCA.. Pre-procedure iFR is mandatory to explore the physiological importance of the left main bifurcation. IVUS may be performed up to discretion of the investigator.

IVUS assessment post-stent implantation for optimization of BiOSS LIM C deployment in the left-main bifurcation is highly recommended (according to ESC guidelines, class IIA)[2]. OCT assessment may be performed up to discretion of the investigator.

All other lesions (other than left-main bifurcations) will be treated with XIENCE family everolimus-eluting coronary stent systems.
e.g. XIENCE V, XIENCE PRIME, XIENCE Xpedition, Xience PRO (PRO, PRO 48, PRO LL en PROx), Xience ALPINE, XIENCE Sierra or any next generation of the XIENCE family everolimus-eluting coronary stent system.

Clinical data will be adjudicated by an independent Clinical Event Committee.

The patients will be followed through 12 months to assess the clinical status and major clinical events (with a potential for possible follow-up for a total of 3 years).

5 ENDPOINTS

5.1 Primary Endpoint

The primary endpoint for this trial is defined as the patient-oriented composite endpoint (PoCE) at 12 months post-procedure. PoCE is a composite measure of

- All-cause mortality
- Stroke (modified Rankin Scale (mRS≥1)
- Any Myocardial Infarction* (includes nontarget vessel territory)
- Any unplanned revascularization for ischemia (includes all target and nontarget vessels)

5.2 Secondary Endpoints at all follow-up visits/contacts

1. Composite Endpoints
   - Patient Oriented Composite Endpoint (PoCE) defined as the composite of all-cause death, stroke, any MI*, and any revascularization (for all follow-up contacts other than 12 months)
   - Target Vessel Failure (TVF) defined as cardiac death, TV MI*, and clinically indicated target vessel revascularization
   - TLF (DoCE) defined as cardiac death, TV MI* and clinically-indicated target lesion revascularization (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
   - Ischemic
   - Hemorrhagic
4. Myocardial Infarction*
   - All MI (periprocedural, spontaneous, Q-wave and non Q-wave),
   - Target Vessel/ Non-Target Vessel MI
5. Revascularization
   - Any revascularization
   - Target Lesion revascularization (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 revascularization (TVR) (any, clinically-indicated TVR, non-clinically indicated TVR)
   - Non-Target Vessel revascularization
6. Stent thrombosis according to ARC classification

* *Definition EXCEL study (APPENDIX I: Definitions)*

6 PATIENT SELECTION

A total of 260 patients will be enrolled to receive treatment with the BiOSS LIM C study device.

Patients participating in the study must meet all of the following criteria.

6.1 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 (following ESC guidelines, IA recommendation, for revascularization in patients with stable angina or silent ischemia) requiring revascularization. In case pre-procedural IVUS is available a left main MLA ≤6.0mm^2 is considered equivalent to the core lab DS ≥50%).
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. Left main vessel diameter ≥3.0 mm and ≤4.5 mm, and main branch vessel diameter ≤3.75mm, measured by visual assessment. 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 (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

6.2 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
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 >2.5mg/dL, or creatinine clearance ≤30mL/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 7 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.
18. The patient is not allowed to participate in another investigational device or drug study for at least 12 months after enrollment.

7 STUDY PROCEDURES

7.1 Patient Information and Informed Consent

All relevant information on the study will be summarized in the Informed Consent Form (ICF) which consists of the patient information and consent form. A sample ICF is provided as a document separate to this protocol. The ICF must have the approval of the IRB/EC.

The background of the proposed trial and the benefits and risks of the procedures and trial should be explained to the patient. The patient must sign the consent form prior to any study-specific assessment being performed. Failure to obtain signed, informed consent renders the patient ineligible for the trial. The patient will receive a copy of the signed informed consent for his/her records. The originally signed ICF is stored in the Investigators Site File and ICF copies in the patient's medical records.

In the event that the patient cannot read or write, an impartial witness formatted ICF (as determined by local law) will be allowed provided detailed documentation of the process is recorded in the patient's case history and the witness signs and dates the appropriate ICF. The witness shall be present throughout the process; all information shall be read aloud and explained. Whenever possible, the patient shall personally sign and date the consent form. The witness shall always sign and date the consent form to attest that the information was accurately explained and that the informed consent was freely given.

The investigator and/or designee must clearly document the process of obtaining informed consent in the patient's source documents. The voluntary process of obtaining informed consent confirms the patient's willingness to participate in the study. It is the investigator's responsibility to ensure that the informed consent process is performed in accordance with EC requirements and country specific regulations. Study patients will be assured that they may withdraw from the study at any time and for any reason.

The date and time of signing the ICF must be reported in the electronic case report form.

The patient Informed Consent will also contain the potential for possible follow-up for a total of 3 years, with data collected via telephone contacts. Follow-up after 1 year and for up to 3 years will be performed at the sole discretion of the Sponsor and Grant giver, if funding is available.

7.2 Baseline evaluation

All patients will have the following activities conducted prior to the PCI procedure:

- Anatomical SYNTAX Score.
- Medina classification and iFR assessment of the left main bifurcation.
- Baseline demographics, angina status, vital signs and pregnancy test (as required)
- Relevant medical and cardiac history
- Required anti-platelet medications
- 12-lead electrocardiogram (within 72 hours to PCI procedure)
- Left ventricular ejection fraction (LVEF) within 14 days prior to PCI (either by echocardiography, MRI, or contrast left ventriculography).
- Laboratory tests

  - WBC, platelets, hemoglobin, hematocrit, serum creatinine and HbA1c (within 28 days prior to PCI)

  - Cardiac Biomarkers (CK-MB, or Troponin (cTn) if CK-MB is not available) is draw prior to the index PCI procedure (within 24 hours prior to PCI).

  For patients showing elevated Troponin (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.

7.3 Enrollment

Enrollment will occur after all inclusion criteria are met and no exclusion criteria are present. All patients participating in this clinical trial will have informed consent obtained after diagnostic angiography. “Ad hoc” left-main bifurcation PCI is not permitted.
Enrollment will only occur if the patient meets the *angiographic* inclusion criteria*: 1) distal left-main lesion must have ≥50% diameter stenosis confirmed by the academic core lab using dedicated QCA bifurcation software with documented ischemia or FFR ≤0.80 (following ESC guidelines, IA recommendation, for revascularization in patients with stable angina or silent ischemia) requiring revascularization; 2) Medina class has been confirmed and 3) target distal left-main lesion must have a reference vessel diameter ranging from ≥3.0 mm to ≤4.5 mm, and main branch vessel diameter ≤3.75mm.
*Each case must be forwarded to the academic core lab (Rotterdam, NL) to be reviewed/confirmed prior to enrollment.

A patient is considered enrolled in the study when he/she has signed and dated the informed consent form and DS% and Medina class has been confirmed by the academic core lab. In case pre-procedural IVUS is available a left main MLA <6.0mm2 is considered equivalent to the core lab DS ≥50%).All patients having distal left main disease but are not enrolled in this study will be documented on a screening log.

7.4 Left-Main Stent implantation Procedure

The BiOSS LIM C stent will be used for treatment of the Left-Main bifurcation, according to its instructions for use. The Alex Plus stent will be used for treatment of distal left-main side branches according to its instructions for use (i.e. proximal segments of the left anterior descending and left circumflex arteries as well as the ramus intermedius if the latter vessel is part of a trifurcation). All other lesions (other than left-main bifurcation) will be treated with XIENCE family everolimus-eluting coronary stent system.

7.4.1 Pre-procedural QCA, physiological assessment (FFR/iFR) and IVUS

Before stent implantation, QCA of the distal left main bifurcation should be performed using (dedicated) bifurcation software to confirm the significant stenosis and the Medina classification (DS% ≥50% in at least one of the branches, with the exception of Medina 0,0,1). It is important to find the best projection where the distal left-main carina is clearly visible. The recommended projection is the spider view in LAO45°/caudal35° (and caudal30° and/or RAO30°/caudal30°). There is no restriction regarding lesion length.

Pre-procedure iFR is mandatory to explore the physiological importance of the left main bifurcation (refer to Appendix III). Pre-procedural IVUS and FFR is up to operators' discretion (refer to Appendix II)

According to QCA/IVUS assessment of the proximal main branch (left-main) and distal main branch (e.g. LAD/LCX) the appropriate BiOSS LIM C stent size is selected.

Before predilatation, the guide-wire should be advanced into both branches (LAD and LCX). Predilations could be performed according to the operator's preferences and according to the morphology of the bifurcation. Lesion preparation (including cutting balloon, scoring balloon, rotablator, etc.) is strongly recommended in case of any signs of calcification and fibrosis. IVUS investigation pre-procedure will provide additional information e.g. on the need of pre-dilatation, etc.

The choice of vascular access for PCI (e.g. femoral or radial) and the choice and use of vascular closure devices are left to the operator's discretion.

7.4.2 Optimal distal Left-main PCI - recommendations

7.4.2.1 Provisional single stent technique strategy

A provisional single stent technique is strongly recommended whenever possible with the stent size selected to match the distal branch reference vessel. In the majority of cases, the BiOSS LIM C stent may be placed towards the LAD across the LCX. In case of a large LCX with a significant stenosis, an alternative approach to implant the BiOSS LIM C towards the LCX could be performed – if the angle between LAD and LCX is <90°.

- **BiOSS LIM C stent implantation**

The BiOSS LIM C stent is introduced over a single guide wire, which (in contrast to other dedicated systems guided on two guide wires) eliminates the risk of wire wrap (twisting) or other complications with double guide wire driven systems. The BiOSS LIM C stent delivery balloon has three markers: distal and proximal indicating stent edges and one mid marker showing the mid zone. The mid-marker should be placed exactly at the tip of the carina, therefore it is very important to find the optimal projection where the carina is best visualized (e.g. LAO45°/caudal35°). This ensures that after deployment the contralateral to the side branch wall is covered with struts to the same extent as the proximal main vessel part of the bifurcation. This is achieved by self-centering properties of the device (due to special shape of connecting struts) and the “closure” configuration between proximal and distal parts of the stent. The bottle balloon shape ensures the proximal optimization technique (POT)-like effect at once after BiOSS LIM C implantation.

At implantation, it is recommended to inflate the delivery balloon for at least 20 seconds. A second inflation with the delivery balloon is highly recommended if well tolerated by the patient.

In case of a true trifurcation (i.e. a direct take-off of the intermediate branch from the left-main) positioning of the BiOSS LIM C across LAD and LCX should be considered and then additional action for those vessels must be taken. In case of a relatively small size intermediate branch (<3.0 mm) a so called false trifurcation (1st marginal branch high take off) the BiOSS LIM C stent may be placed across the LCX or rarely across the LAD in relation to vessel size and stenosis involvement. For main branch (MB) the larger vessel with longer lesion should be taken into account.

- **Side branch dilatation**

If the side branch origin (usually the ostial LCX) has a residual stenosis <50% with TIMI 3 flow, and without a significant dissection, the decision to dilate the side branch is left to the discretion of the operator. If the decision is made not to dilate the side branch, a short (usually 8 mm) non-compliant balloon within the left main segment should be used (proximal optimisation technique (POT)) to fully expand the stent in the left main. If there is uncertainty concerning the adequacy of side branch patency, an FFR/iFR determination is recommended, with a value of FFR ≤0.80/iFR≤0.89 indicating that side branch dilatation should be performed[32 33]. If there is significant (>50%) stenosis or other signs of sub-optimal side branch appearance (e.g. dissection or FFR ≤0.80/iFR≤0.89), it is strongly recommended to utilize kissing balloons after a single stent crossover technique, with long inflations of 60 seconds or more if tolerated by the patient to attempt to manage the ostial sidebranch lesion without additional stent implantation. POT before re-wiring is left to the discretion of the operator. The technique of post-stent kissing balloons in this circumstance includes the use of non-compliant short balloons in both branches with balloon sizing according to the distal reference vessel diameters, initial dilation of the side branch balloon at moderate pressures (8 to 12 atm), followed by simultaneous inflation/deflation of both balloons (8 to 12 atm).

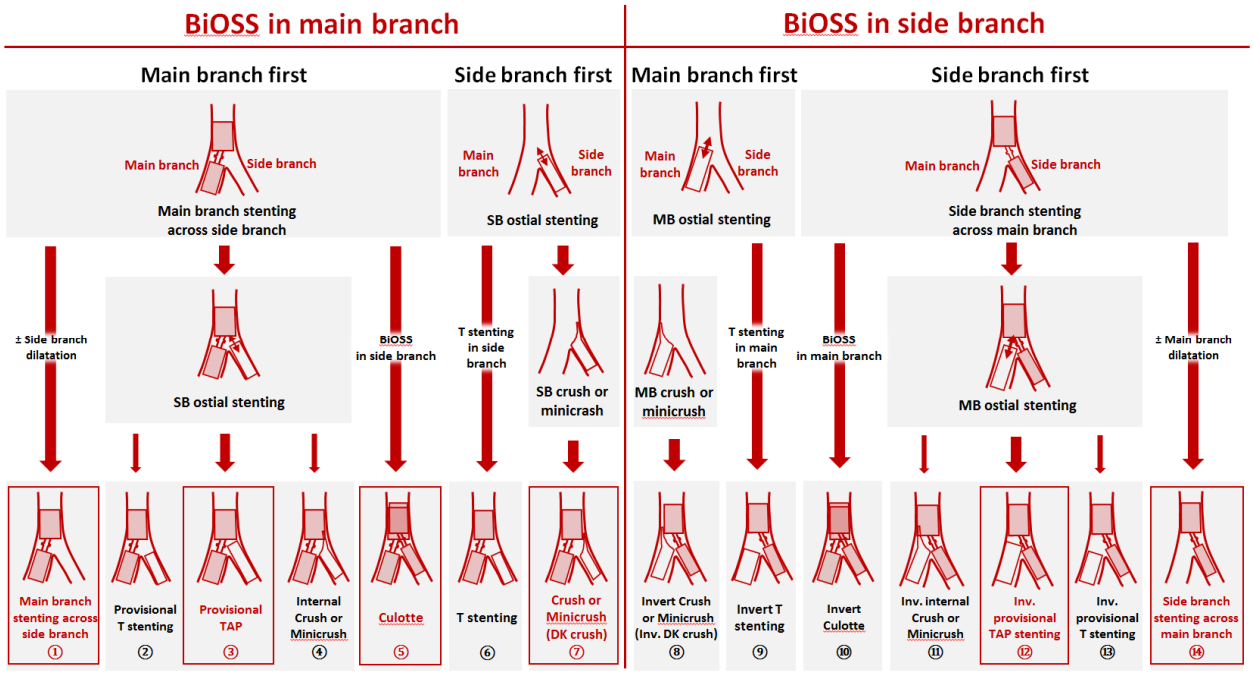
◦ Guidelines for ***a provisional second stent***:
If the side branch is still suboptimal in appearance despite multiple balloon inflations, based upon the following criteria: severe dissection (≥grade B), TIMI flow <3, or "severe stenosis" >70% DS (visual estimate) or ≥50% (dedicated bifurcation QCA software) or IVUS MLA ≤6.0 mm^2 with plaque burden >60%, or FFR ≤0.80/iFR≤0.89 – a provisional second stent should be strongly considered.

◦ The ***technique for a (provisional) second stent*** is left to the operator's best judgment and may include any the following: T-and-protrusion (TAP) stentingTAP, mini-crush (reverse crush), or culotte bifurcation stent techniques (e.g. two BiOSS LIM C stents, however the second BiOSS LIM C stent might be shorter). The use of ***kissing balloons after (provisional) second stents*** is strongly recommended. The technique of post-stent kissing balloons in this circumstance includes the use of non-compliant short balloons in both branches with balloon sizing according to the distal reference vessel diameters, initial dilation with the side branch balloon at high pressures (≥18 atm), followed by simultaneous inflation and deflation of both balloons (8-12 atm). Re-POT is highly recommended at the end of the procedure.

7.4.2.2 Primary two stent technique strategy

The decision to use a ***primary two stent technique strategy*** rather than a single crossover stent technique should be considered when the side branch (usually the LCX) 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). [34]
Considering the anatomic variability of the distal LM bifurcation, the final decision to select a primary two stent technique strategy is left to the operator's best judgment. The choice of a particular distal bifurcation stent strategy is also left to the operator's best judgment and may include TAP, DK-crush, or culotte stent techniques. In this study, based on recent studies which suggest superiority of DK-crush technique over other implant techniques, the preferred two-stent technique is DK-crush in combination with BiOSS LIM C and Alex-plus stents. [35] The DK-crush technique should be particularly used in difficult side-branch anatomies and large angles between MB and SB. The Cullote stent technique perfectly covers the carina region (e.g. two BiOSS LIM C stents, -however second BiOSS LIM C might be shorter) especially in cases with bifurcation angle <90°. The TAP technique (with BiOSS LIM C and Alex-plus stents) is also convenient allowing main vessel treatment as first step.

◦ The use of ***kissing balloons after primary two stent technique*** is mandatory. The technique of post-stent kissing balloons in this circumstance includes the use of noncompliant short balloons within the margins of the stents in both branches with balloon sizing according to the distal reference vessel diameters, initial dilation of the side branch balloon at high pressures (≥18 atm), followed by simultaneous inflation/deflation of both balloons (8-12 atm). Re-POT is highly recommended at the end of the procedure.



The implantation techniques with a red framed box are recommended in the protocol.
It is recommended that the techniques requiring BiOSS stent in the side branch ⑤⑧-⑭ are applied to bifurcations with comparable sized branches (MB and SB). TAP technique ③⑫ are not recommended in case the bifurcation angle >70°; in that case, T-stenting ②⑬ are recommenced.

7.4.3 Post-procedural IVUS

According to the ESC guidelines (IIA), IVUS guidance to optimize the results of intervention in the left main is strongly recommended. The details of guidance are described in appendix II. [2] In the study reported by Kang et al, minimum stent areas were measured in ostial left anterior descending artery (5 mm from carina) and ostial left circumflex (5 mm from carina), polygon of confluence (POC: confluent zone of the LAD and LCX) and proximal left main (5 mm from POC). The cut-offs that best predicted in-stent restenosis (ISR) on a segmental basis were 5.0 mm^2 (ostial LCX), 6.3 mm^2 (ostial LAD), 7.2 mm^2 (POC), and 8.2 mm^2 (proximal LM). Iterative IVUS and post-dilation should be performed according to the so-called 5-6-7-8 rule of criteria, until the minimum stent areas of the proximal LM, the POC, the ostial LAD and the ostial LCX are at least 8, 7, 6 and 5 mm^2 respectively. Severe dissections present by IVUS (residual true lumen within the dissection flap below the above-mentioned cut-offs) should in general receive an additional stent. Malapposition with stent area below the cut-offs should in general be treated by additional post-dilatation with larger balloons. If IVUS is used to guide treatment of ULMCA lesions, it is recommended that IVUS also be used to guide treatment of important non-LMCA lesions in the LAD, LCX, and RCA.

To summarize, the implantation protocol for left main stenting is as follows:

- Pre-procedure iFR is mandatory to explore the physiological importance of the disease;
- Pre-procedural IVUS might be very valuable but is up to operator's discretion;
- wiring of both branches;
- main vessel predilatation and/or side branch predilatation according to the operator's decision. However, in case of any calcification and fibrosis proper lesion preparation (including e.g. rotablator, cutting balloon) is strongly advised;
- stent implantation - inflation for at least 20 seconds. A second inflation with the delivery balloon is highly recommended if well tolerated by the patient;
- proximal optimalization technique (POT) with a short non-compliant properly sized balloon;
- side branch postdilatation with properly sized balloon is left to the operators' discretion. Side branch stent implantation if necessary;
- final kissing balloon inflation at operator's discretion;
- Re-proximal optimization technique (re-POT) with short non-compliant properly sized balloon;
- IVUS assessment for post-stent optimization is highly recommended according to ESC guidelines (for criteria see Kang et al. [1]).

7.5 Hemodynamic support

Hemodynamic support for PCI patients with ULMCA lesions is usually not required but there is significant variability in the perceived need for hemodynamic support among experienced operators and sites. Criteria for required hemodynamic support may include systemic hypotension, severe pulmonary hypertension, severely reduced ejection fraction, extreme anatomic complexity (e.g. severely calcified left main lesion with intended use of rotational atherectomy), and/or patient instability before or during the procedure. The decision regarding the use hemodynamic support, either elective and planned or urgently required due to patient instability, and the type of support device is left to the operator's best judgment.

7.6 Staged procedures

Procedural "staging" in PCI subjects 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 judgment. Given the complexity of the ULMCA patients it is anticipated that a substantial number of patients may fall into the category of staged procedures.

In general, the decision to stage is based on the overall extent and complexity of coronary disease, the case complexity (intra-procedure difficulty encountered by the operator), the duration of the procedure, assessment of radiation exposure, the total volume of contrast utilized, the clinical stability of the subject, and other subject-related factors (diabetes, renal function, etc.).
If the patient requires a staged procedure, this should be documented at the time of the index procedure and the reason(s) for staging must be documented in the eCRF and source documents. Furthermore, the need for staging, and all specific lesions planned to be treated during the staged procedure should be declared beforehand in the eCRF at the time of initial baseline procedure. Stented segment(s) treated during the initial baseline procedure should not be treated again during the staged procedure.

The recommended timing of a planned staged procedure is optimally within 4 weeks, but 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. A correlation has been found between residual SYNTAX Score post PCI and mortality [36]. In the POLBOS study it is recommended to attempt achieving a residual SYNTAX Score ≤8 post PCI.

7.7 Concomitant Medical Therapy

7.7.1 Pre PCI medication

Aspirin. Preloading with aspirin 300 to 325 mg at least 2 hrs before the PCI is mandatory. For patients already receiving chronic aspirin therapy, the loading dose of 300 to 325 mg of aspirin should still be given. Either regular or chewable tablets or intravenous aspirin is mandatory for the loading dose in patients not on chronic aspirin before the ULMCA PCI.

ADP antagonists. ADP antagonist pre-loading therapy is mandatory. The choice of one of the followings agent is left to the discretion of the investigator. For patients already receiving chronic ADP antagonist therapy, pre-loading is still mandatory.

- clopidogrel 300-600 mg before PCI (even if patient is on chronic clopidogrel therapy); or
- at sites in countries where it is approved and is commercially available prasugrel 60 mg >1 hr before PCI; or ticagrelor 180 mg >1 hr before PCI.

Pre-PCI statin therapy. Optimal medical therapy with strict control of LDL (target of≤1.8 mmol/l) is strongly recommended, along with optimization of all medical therapy – rosuvastatin/atorvastatin (according to the guidelines). Several randomized trials have demonstrated that high dose statin therapy decreases PCI-related myonecrosis in patients undergoing stent implantation, whether or not the patient is already taking chronic statin therapy [37, 38 39 40]. Therefore, in the absence of absolute contraindications to statin use (e.g. severe allergy with prior use), at least one dose of the following statin regimens should be administered before the PCI (within 12 hours), regardless of LDL level and history of prior statin use.

- atorvastatin 80 mg daily
- rosuvastatin 40 mg daily

Other medications. The use of other medications prior to PCI (e.g. beta-blockers, ACE inhibitors) is left to the discretion of the treating physicians.

7.7.2 Intra-procedure adjunctive pharmacology

During the procedure, patients should receive bolus and maintenance doses of unfractionated heparin to avoid excess coagulation. The currently recommended target activated clotting time (ACT) is at least > 250 sec during coronary angioplasty. If Angiomax® (bivalirudin) is used instead of heparin an ACT does not need to be measured or recorded. Refer to the package insert for bivalirudin for indications, contraindications, warnings and precautions.
In patients who do not receive Glycoprotein (GP) IIb/IIIa inhibitors, a weight-adjusted unfractionated heparin bolus (70 to 100 IU per kg) will be administered to achieve a target ACT of >250 sec. In patients who receive GP IIb/IIIa inhibitors, a weight-adjusted unfractionated heparin bolus (50 to 70 IU per kg) will be administered to achieve a target ACT of >200 sec. Post-procedural heparin infusions are not recommended during GP IIb/IIIa therapy. The currently recommended target ACT for eptifibatide and tirofiban is less than 300 sec during coronary angioplasty.
GP IIb/IIIa inhibitors are strongly discouraged in patients adequately pre-loaded with an ADP antagonist (clopidogrel, prasugrel, or ticagrelor), especially if bivalirudin is used.

7.7.3 Post-procedural Medication Regimen

Antiplatelet therapy

Please refer to the specific package insert for clopidogrel, prasugrel or ticagrelor for indications, contraindications, warnings and precautions. Chronic daily ADP antagonist therapy is mandated for at least one year after PCI. The choice of agent is left to the discretion of the investigator, local standard of care and drug availability.

All patients must receive a maintenance dose of clopidogrel 75 mg/day. In case of prasugrel the maintenance dose is 10 mg/day (the dose of prasugrel may be decreased to 5mg/day in patients with a weight <60 kg or age >75 years) or in case of ticagrelor the maintenance dose is 90 mg bid.

Note1: prasugrel and ticagrelor have no label for elective PCI.

A daily ADP antagonist must be given for at least one year in the absence of major complications, and is recommended for the duration of the trial in the absence of major bleeding or other complications. ADP antagonists should not be discontinued within the first year after DES implantation unless absolutely necessary for major bleeding, major trauma, or major surgery necessitating discontinuation of antiplatelet therapy (e.g. intracranial surgery). Many surgeries can safely be performed while the patient is on dual antiplatelet therapy. If a patient on dual antiplatelet therapy requires surgery, strong consideration should be given to performing the surgery without antiplatelet agent discontinuation. If a particular dual antiplatelet therapy must be discontinued, a GP IIb/IIIa bridging strategy up until the time of surgery may be considered, followed by reloading of the ADP antagonist as soon as possible post surgery.

Aspirin

Following the PCI procedure, all patients should continue on aspirin (minimum of 75 mg/day up to 162 mg/day or dose per standard hospital practice) indefinitely.
Aspirin should not be discontinued for CABG or other reasons unless absolutely necessary.

Note2: avoid maintenance doses of aspirin above 100 mg daily for patients prescribed to ticagrelor.

All DAPT (including start and stop times of interrupted DAPT) and other cardiac medications will be recorded for data collection at each visit. Extended DAPT will be at the discretion of the

investigator.

7.8 **Hospital Discharge (post-PCI to hospital discharge)**

At discharge, from the hospital where the index procedure took place, an assessment of angina status and cardiovascular drug use will be performed. Any Serious Adverse Events will be recorded and an ECG will be performed. The patient must be informed of the required DAPT medication and follow-up visits per protocol should be scheduled prior to discharge.

In addition, CK-MB (preferred) or Troponin (cTn) if CK-MB is not available, in the post-procedure hospitalization period should be taken at 12 hrs (±2 hrs; i.e. 10-14 hrs) and 24h (±2 hrs; i.e. 22-26 hrs) post procedure or at discharge if sooner.
If cardiac enzymes are elevated (CKMB >3 ULN, or cTn/hs-cTn >35 ULN), serial measurements of cardiac enzymes must be taken until a decline is noted. In any case of cardiac enzyme elevation (CK >2ULN with iso-enzyme CKMB, CKMB >3 ULN, or cTn/hs-cTn >35 ULN) at least two samples (with an preferred interval of 6 hours) should be obtained prior to discharge.
Additional serial troponins or CK-MBs should be drawn at any time in case of any adverse cardiac event.

7.9 **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 anginal status, compliance to protocol-required medications, other cardiovascular drug use and any Serious Adverse Events will be recorded during clinical follow-up visits. An ECG will be performed.
Patients with typical cardiac symptoms or evidence of progressive heart disease should in most cases undergo repeat cardiac catheterization; stress testing should not be performed, especially in the patient with possible recurrent disease in the left main stem.
Because of the risk of exercise-induced stent thrombosis, in no case should routine follow-up exercise stress testing be performed within 8 weeks after stent implantation.

7.10 **Unscheduled Angiography/Intervention**

For all unscheduled angiographies and revascularizations, the angiogram must be sent to the CRO, regardless of whether target or non-target vessel revascularization was performed. The Clinical Event Committee (CEC) will adjudicate the type of revascularization indicating if the revascularization is clinically indicated or not clinically indicated, etc. (See Appendix I:

Definitions). Routine follow-up angiography (in the asymptomatic patient) is not permitted in this study and the reasons for follow-up angiography will be closely tracked in the case report form.

In patients who do undergo follow-up angiography, repeat PCI or CABG may only be performed with evidence of ischemia, requiring one of the following to be present:

- ≥70% diameter stenosis of the treated or new lesions by visual angiographic assessment
- In the case of a visually estimated diameter stenosis of ≥50% to <70%, either
  - evidence of definite ischemia in the territory of the diseased vessel by prior non-invasive stress* testing with imaging evaluation showing ischemia in the questioned myocardial territory, and/or
  - IVUS minimal stent area ≤6.0 mm^2 for left main lesions or ≤4.0 mm_2 for non left main lesions, and/or
  - intra-procedure FFR≤0.80/iFR≤0.89.

*stress test is not advised within 8 weeks after stent implantation.

IVUS is preferred for assessment of left main lesions, and iFR is preferred for assessment of non-left main lesions. In particular, after left main stent implantation, the ostial LCX may often appear significantly or even severely stenosed in the absence of symptoms or ischemia ("pseudostenosis"). All patients with a suspected ostial LCX stenosis, regardless of the degree of angiographic severity (unless occluded), are highly recommended to have demonstrated an iFR≤0.89 (or FFR≤0.80 when available) in the LCX prior to repeat revascularization, unless there is unequivocal evidence of lateral wall ischemia on non-invasive stress testing.

7.11 **Discontinuation of Follow-Up**

At any time during the study, the patient may withdraw their participation from the study. Follow-up is only discontinued at the explicit request of the patient. This decision should be an independent decision that is documented in the patient study files. Survival status should be collected within legal and ethical boundaries for all patients enrolled who withdrew participation from the study. Data generated of any patient withdrawn from the trial will be included in the analysis unless the patient explicitly forbids the use of any data which should be documented by the site.

All patients are encouraged to return for all scheduled follow-up visits, and to provide appropriate contact information to accommodate completion of required telephone follow-ups. The investigator will attempt to contact the patient at each follow-up visit, independent of any

missed follow-ups. The investigator should make 3 documented attempts per required follow-up visit.

Patients who have discontinued the trial prematurely will not be replaced.

7.12 **Patients Lost to Follow-Up**

A patient would be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Only after failing to contact the patient at the final follow-up visit, the patient is considered lost to follow-up after last contact. Site personnel are expected to make diligent and documented attempts to contact patients who fail to return for a scheduled visit. It must be a high priority to obtain at least survival data on all patients lost to follow-up. Survival status will be collected within legal and ethical boundaries for all patients enrolled. Vital status will be searched in public sources at the end of the 1 year follow-up period. If vital status is known at the last study visit, the patient will not be considered lost to follow-up, notification of death by civil registry will be accepted.

8 STATISTICAL DESIGN AND ANALYSIS

The primary efficacy endpoint is based on comparison to pre-specified performance goal based of the EXCEL study[3]. The study is powered at 80% to show non-inferiority of the BiOSS LIM C compared with XIENCE EES. The primary analysis will be based on an intent-to-treat (ITT) patient population.

The ITT population set consists of all patients who have provided informed consent and have been enrolled. All patients will be analyzed according to assigned treatment group, regardless of the treatment actually received.

8.1 Primary Analysis

The primary analysis is an analysis of the primary endpoint, being PoCE at 12-months. The study is powered at 80% to show non-inferiority for the BiOSS LIM C when compared to XIENCE. The BiOSS LIM C suspected PoCE assumption is based on the assumption of no difference in event rates between BiOSS LIM C and XIENCE.

The 95% one-sided confidence interval will be calculated for the PoCE rate at 12 months, using Kaplan-Meier estimates at 12 months and its standard deviation; the KM-estimate is assumed to be normally distributed.

The upper limit of the interval will be compared with a performance target, being the reported PoCE in the EXCEL trial plus a non-inferiority margin. If the 95% interval excludes the performance target, BiOSS LIM C will be considered to be non-inferior to XIENCE (this accounts to an one-sided non-inferiority testing with a significance level (alpha of 5%).

Statistical analyses will be performed with either SAS software system (SAS Institute Inc., Cary, North Carolina) version 9.3 or higher.

8.2 Sample Size Calculations

Assumptions:
Power = 80%
One-sided alpha = 5%
Non-inferiority margin of 6.3%
XIENCE PoCE – 16.7% at 12M *(Reference: EXCEL study, PCI cohort, data on file).*

The BiOSS LIM C expected PoCE assumption is based on an assumed no difference in event rate as compared to the objective performance goal (OPC – EXCEL study).

A sample size calculation of 256 analyzable patients is required using the assumptions above, PASS software, and a non-inferiority Fisher Exact test for one proportion. This number is increased to 260 patients accounting for some attrition.

8.3 Subgroup Analysis

A pre-specified subgroup analyses will be performed for 1 stent versus 2 stent approach distal left-main PCI. 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.

8.4 Description of Data

Patient demographics, medical history, risk factors, pre- and post-procedure lesion characteristics, procedure characteristics, and outcome variables will be summarized using descriptive statistics.

8.5 Calculating days to event

When calculating the days-to-event, the date the event took place will be compared to the date of informed consent, also in case a staged procedure took place. For stent thrombosis however, the date the event took place will be compared to the date of the index procedure, also in case a staged procedure took place.

In the EXCEL trial, where the OPC is derived from, the date of randomization was used as ‘day 0’. By using the date of informed consent as ‘day 0’ for all components of the primary endpoint the POLBOS LM PoCE rate is comparable with the OPC.

8.5.1 Continuous variables

For all continuous variables the number of observations, mean, standard deviation and the 95% two-sided confidence interval for the mean is calculated. When required also median, Q1 and Q3 will be presented.

8.5.2 Categorical variables

Categorical variables are summarized by treatment in frequencies, percentages, a 95% two-sided confidence interval for the percentage is calculated.

8.5.3 Time dependent variables

Time dependent variables will be summarized by frequency and by Kaplan-Meier estimates and its 95% confidence intervals.

8.6 Missing data

Every effort will be undertaken to minimize missing data. Kaplan-Meier estimates will censor incomplete data at the date of last available follow-up information, assuming complete reporting of all events up to that date and event status unknown after that date.

Other missing information will be assumed Missing Completely at Random (MCAR). No imputation will take place for these data, nor is any sensitivity analysis planned.

9 SAFETY REPORTING

9.1 Serious Adverse Events (SAEs) Definitions

An AE is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in patients, users or other persons, whether or not related to the investigational medical device.

An AE is classified as "serious" if the event:

- Led to death;

  Note: death is an outcome, and the term 'death' should not ordinarily be reported as the SAE. The immediate cause of death should be specified (eg,'cardiorespiratory arrest'), unless the cause of death is not known or cannot reasonably be discerned.
- Led to serious deterioration in the health of a patient that:
  - Resulted in a life threatening illness or injury;

    Note: life-threatening means that in the opinion of the investigator, the subject was at immediate risk of death from the event as it occurred. This does not include an event that, had it occurred in a more severe form, might have caused death.
  - Resulted in a permanent impairment of a body structure or a body function;
  - Required in patients hospitalization or prolongation of existing hospitalization;

    Note: hospitalization is defined as inpatient admission, overnight. Hospitalization does not include presentation and care within an emergency department.
  - Resulted in medical or surgical intervention to prevent permanent impairment to a body structure or a body function.
- Led to fetal distress, fetal death or a congenital abnormality or birth defect.

NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without unusual deterioration in health, is not considered an adverse event.

9.2 Anticipated Adverse Device Effects

Anticipated adverse device effects for the BiOSS LIM C (and ALEX Plus) stent are described in the protocol (section 9.5). For safety reporting purposes, the list of known risks in section 9.5 will serve as Reference Safety Information. If the applicable device Instructions For Use's (IFUs) are updated during the study with a significant impact, section 9.5 may be amended.

9.3 **Device Malfunctions**

If the investigator observes device malfunctions that led or might have led to a death or serious deterioration in health of a patient, user or other person, or has complaints with regard to defects in the medical devices, the investigator shall, within 24 hours of such observation, report such device malfunction or complaint to the device manufacturer, with a copy of the report to the sponsor. Sponsor shall be responsible to take necessary actions in response to a device malfunction to protect the safety of the trial patients, e.g. temporary suspension of the trial. The device manufacturer shall be responsible for handling all complaints and reported device malfunctions in respect of the quality of medical devices, for determining the measures to be taken due to such observations or complaints and for ensuring that all necessary actions are taken including, but not limited to, any necessary action in connection with the recall of the medical devices or the reporting of incidents to competent authorities if deemed appropriate by the device manufacturer. Discussions regarding such device malfunction or complaints will be held between the device manufacturer and the participating site.

9.4 **SAE Reporting**

The investigator will monitor the occurrence of Serious Adverse Events (SAEs) for each patient during the course of the study. For the purpose of this protocol, the reporting of SAEs begins directly after patient has signed informed consent through the last follow-up visit. If an event fulfills the criteria for SAE, then this shall be reported in the eCRF immediately, but at the latest within 24 hours of the clinic study staff having become aware of this, including their judgment regarding causal relationship of the event to the trial. At the time the event is reported in the eCRF, no event-supporting source documentation needs to be sent. Event supporting source documents will be requested by the sponsor (via monitoring organization and/or CRO) for the purpose of potential clinical event adjudication and reporting purposes. All SAEs will be followed until the event has been resolved (with or without sequelae).

Sponsor is responsible for the classification of serious adverse events and ongoing safety evaluation of the clinical investigation and shall review the investigator's assessment of all serious adverse events and determine and document in writing the sponsor’s determination of seriousness and relationship to the investigational device; in case of disagreement between the sponsor and the principal investigator(s), both opinions shall be reflected.

Safety reporting will be in accordance with “Clinical investigation of medical devices for human patients (ISO 14155:2011,IDT) and the “guidelines on medical devices vigilance system” by the

European Commission (MEDDEV2.12 rev 08, Jan 2013) and in compliance with local country law. Primary endpoints will be collected as SAEs and presented in periodic reports, however will be excluded from expedited reporting. These include the following events:

- all-cause mortality
- Stroke (modified Rankin Scale (mRS≥1)
- Any Myocardial Infarction (includes non-target vessel territory)
- Any unplanned revascularization for ischemia (includes all target and non-target vessels

9.5 **Risk Analysis**

Percutaneous coronary interventions (PCI) and intravascular stenting may offer certain advantages as compared to conventional surgical techniques. In addition, coronary stenting with DES have been performed successfully for several decades and is considered a standard treatment for coronary revascularizations. Thus, there is extensive clinical and commercial experience worldwide with cardiac catheterization and interventional procedures and it is expected that the procedural risks in this study and existing stenting procedure will not be significantly different. Aside from the potential direct benefits of a *dedicated* bifurcation stent to the patient included in this study, there may be benefits to future patients based upon the results of the study.

With any procedure there are risks and complications. The following is a list of known adverse events (alphabetical order) that may result from stent intervention. This list serves as Safety Reference Information for this study and presents all adverse events that will be considered anticipated.

- Allergic reactions
- Aneurysm
- Arrhythmias
- Arterial wall dissection
- Bypass rupture
- Cardiac tamponade
- Death
- Fever
- Fistula formation
- Haemorrhage
- Hypotension/Hypertension
- Infection and pain in vascular access site
- Myocardial infarction

- Prolonged angina pectoris
- Pseudoaneurysm
- Reactions for antiplatelet (antithrombotic) and contrast preparations
- Renal failure
- Repeated vessel narrowing
- Stroke
- The need for urgent CABG (Coronary Artery Bypass Graft) procedure
- Thrombosis (acute, subacute and chronic), embolism
- Unsuccessful placing of the stent in the planned area
- Vascular spasm
- Vessel closure
- Vessel perforation

10 QUALITY CONTROL AND QUALITY ASSURANCE

10.1 Compliance to Standards and Regulations

The protocol, informed consent form and other study-related documents will be submitted to the Ethics Committee (EC) / Institutional Review Board (IRB). The study will be performed in accordance with the Declaration of Helsinki.

The trial will only start at a clinical site after written approval of the study has been obtained from the appropriate national EC/IRB.

10.2 Data Recording

It is the requirement of ISO and the expectation of the Sponsor that for all data entered into the eCRF source documentation is available at the clinical site. In case of an electronic Patient Dossier (ePD) controlled access for the Monitor should be arranged. If the ePD has not been validated, or the Monitor cannot be given access, a procedure must be available for generating certified copies of the source. Which copies are necessary and the origin of the sources must be described in the Source Data Identification checklist (to be signed by the PI).

10.3 Quality Assurance and Monitoring

Monitoring the clinical investigation at the study site is the responsibility of the monitoring organization through trained and qualified Clinical Research Associates (CRAs).

The monitoring organization will discuss the investigator's patient enrollment prediction as well as other feasibility criteria at the time of contracting.

Monitoring visits will be performed according to the monitoring plan. During on-site monitoring, the Informed Consent Forms will be checked and a sample of clinical data will be verified against eCRF data. Patient confidentiality will be maintained at all time. Emphasis will be on the complete reporting by the study staff of SAEs.

Each clinical site will be visited during the study to ensure a high degree of data quality. These site monitoring visits will be conducted to verify that the data are authentic, accurate and complete, that the safety and rights of patients are protected, that the study is conducted

according to the protocol, and compliant with all applicable regulatory requirements. The investigator and the head of the medical institution (where applicable) agree to allow the CRA direct access to all relevant documents. It is important that the investigator and the study staff are available during the monitoring visit and possible audits and that sufficient time is devoted. Findings from the review and source documents will be discussed with the investigator. Remote site monitoring will also be performed to ensure complete quality study data and adherence to the protocol. On a regular basis, the monitoring organization will contact each site to discuss the progress of the study with respect to patient enrollment, timely attendance of patients to their follow-up visits, data query resolution and other relevant study aspects according to the monitoring plan.

At the end of the trial, a close out visit may be performed at each participating clinic to resolve any outstanding issues and to perform final source data verification.

There will be regular teleconferences between the Sponsor and the monitoring organization to discuss site management issues.

10.4 **Data management**

The data collection will be performed through an electronic CRF (eCRF). The investigator or an authorized member of the investigational team must sign all completed eCRFs that require a signature by using an electronic signature (a password will be provided by the data management center at the start of the study). Clinical data management will be performed in accordance with data cleaning procedures. Appropriate computer edit programs will be run to verify the accuracy of the database. The investigator will be queried on incomplete, inconsistent or missing data.

10.5 **On-site Audits**

To ensure compliance with regulatory requirements, a member of the Sponsor's (or a designated CRO's) quality assurance unit, may arrange to conduct an audit to assess the performance of the study at the study site and of the study documents originating there. The investigator agrees to cooperate with the Sponsor and/or its designee in the conduct of these audits and provide access to medical records and other relevant documentation, as required. The investigator/institution will be informed of the audit outcome.

Regulatory authorities worldwide may inspect the investigator during and after the study. The investigator should contact the sponsor immediately if this occurs, and must cooperate with the regulatory authority inspections as required.

11 ORGANISATION

11.1 Sponsor

In this investigator-initiated trial, the European Cardiovascular Research Institute (ECRI) will act as Sponsor (ECRI-Trials B.V., PO Box 2125, 3000 CC Rotterdam, The Netherlands). The Sponsor's responsibilities are described in chapter 15.

11.2 Steering Committee

The Steering Committee is responsible of the overall management of the study at the highest level. Their names, roles and responsibilities are described in a separate Charter. The Steering Committee is responsible for global oversight of the trial progress (review and approval of the protocol and study design; review day-to-day trial progression (such as executional coordination, finances, safety, communication, delegation to committees); regular teleconference; and final approval of the investigational sites. The Steering Committee interacts with the Sponsor on study progress and related issues.

11.3 Clinical Event Committee (CEC)

The Clinical Events Committee (CEC) is an independent committee comprised of interventional cardiologists who are not participants in the study. The CEC is responsible for the categorization of Death, MI, stroke, revascularization and stent thrombosis, based on the definitions in the protocol. Prior to any CEC activity, a CEC Charter will be developed, which will describe the events to be adjudicated, the minimum amount of data required, and the algorithm followed in order to classify the events.

11.4 Data Management

Data management will be conducted by the Clinical Research Organization (CRO) Cardialysis (Cardialysis B.V., PO Box 2125, 3000 CC Rotterdam, The Netherlands).

11.5 Site Management and Monitoring

The CRO Cardialysis will be responsible for initial submissions to Ethics Committees/IRB's, site management and monitoring.

11.6 **Safety Reporting**

Sites are responsible for reporting of incidents, including device malfunctions, to the device manufactures. Manufacturers are responsible for vigilance reporting of device malfunctions to the authorities. Therefore, no expedited safety reporting is foreseen.
The CRO Cardialysis is responsible for event reporting to the EC/IRB according to local and national requirements.

11.7 **Statistical Analysis**

The CRO Cardialysis is responsible for the statistical analysis.

12 DATA HANDLING AND RECORD KEEPING

12.1 Source Documentation (SD)

Regulations require that investigators maintain information in the patient's medical records that corroborate data collected in the electronic Case Report Form (eCRF). In order to comply with these regulatory requirements, at minimum, the following is a list of information that should be maintained and made available as required by monitors and/or regulatory inspectors:

- Medical history/physical condition of the study patient before involvement in the study sufficient to verify investigational plan entry criteria;
- Dated and signed notes on the day of entry into the study, protocol number, clinical site, patient number assigned and a statement that informed consent was obtained and is on file in the patient medical chart;
- Notations on abnormal lab results;
- (Serious) Adverse Events reported and their resolution, including supporting documents such as discharge summaries, cath lab reports, ECGs, lab results;
- Notes regarding investigational plan-required and prescription medications taken during the study (including start and stop dates);
- Study patient's condition upon completion of or withdrawal from the study.

12.2 Record Retention

All eCRF information, study records, reports and source documents that support the eCRF must be retained in the files of the responsible investigator according to national requirements following notification by the Sponsor or designee that all investigations have been completed, and will further be retained in accordance with local and international guidelines as identified in the Investigator Site Agreement. This documentation must be accessible upon request by international regulatory authorities or the Sponsor (or designee). The Sponsor or designee must approve archiving or transfer of the documentation for relocation purpose of premises, in writing, prior to the actual file transfer. The investigator must notify the Sponsor, in writing, of transfer location, duration, and the procedure for accessing study documentation. The investigator must contact the Sponsor, or designee, before the destruction of any records and reports pertaining to the study to ensure they no longer need to be retained.

If the investigator retires, relocates, or for other reasons withdraws from assuming primary responsibility for keeping the study records, custody per written notice must be submitted to the Sponsor, or designee, indicating the name and address of the person accepting primary responsibility. The EC/IRB must be notified in writing of the name and address of the new custodian.

13 PUBLICATION POLICY

The Steering Committee and investigators are committed to the publication and widespread dissemination of the results of the study. Data from this study will not be withheld regardless of the findings.

The POLBOS LM trial is an investigator-initiated and scientifically driven study nested within the European Cardiovascular Research Institute (ECRI) and set up in collaboration with Balton corporation (Balton, Warsaw, Poland). All public presentations and manuscript generation and submissions will be led under the auspices of the Principal Investigators who will organize and lead a Publications Committee. However, this study represents a joint effort between investigators, ECRI and collaborators, and as such, the parties agree that the recommendation of any party concerning manuscripts or text shall be taken into consideration in the preparation of final scientific documents for publication or presentation.

The final locked database will be housed at the data management center, Cardialysis. Cardialysis will not publicly release data or study-related material, presentations, or manuscripts without the express permission of the Principal Investigators. All Principal Investigators will be listed as authors on all abstracts and publications, and as such must agree to their submission. The publication and/or presentation of results from a single trial site are not allowed until publication and/or presentation of the multi-center results. All single site data for public dissemination must be generated from the central database – local database projects are not permitted. All proposed publications and presentations resulting from or relating to the study (whether from multicenter data or single site analysis) must be submitted to the Publications Committee for review and approval prior to submission for publication or presentation.

The Steering Committee will receive any proposed publication and/or presentation materials prior to submission of the presentation or the initial submission of the proposed publication in order for the materials to be timely reviewed by all parties.

14 INVESTIGATOR RESPONSIBILITIES

14.1 Investigator Responsibility/Performance

Prior to starting enrolment of patients, the investigator must read and understand this study protocol, and must sign and date the Protocol Signature page. The Investigator Site Agreement documents agreement to all conditions of the study protocol and agreement to conduct the study accordingly. This study will be conducted in accordance with the Declaration of Helsinki and other applicable regulatory requirements or any conditions of approval imposed by the EC/IRB or regulatory authorities.

14.2 Required Documents

The following documents must be submitted to Sponsor, or designee prior to patient enrolment:

- Signed Protocol Signature Page
- Recent (≤ 2 years old) signed and dated English Curriculum Vitae (CVs) of the Principal Investigator and co-investigators of the clinical site. These CVs should clearly show the investigator's and co-investigators' qualifications and experience.
- Copy of the written confirmation of the EC/IRB regarding approval of the protocol including version number and date, patient information sheet and informed consent form, including version and date and other adjunctive patient material.
- List of EC/IRB members, including name, title, occupation and any institutional affiliation of each member. If the EC/IRB member list is not available, the General Assurance or EC/IRB Recognition Number should be provided.
- Signed Investigator Site Agreement.

14.3 Ethics Committee (EC) / Institutional Review Board (IRB) Approval

According to the local regulations, the investigator must have all necessary approvals, including written approval from the EC/IRB of the clinical site or other accepted EC/IRB prior to enrolling patients in the study. A copy of the written approval must be provided to Sponsor and should include the following:

- Statement of EC/IRB approval for the proposed study at the clinical site
- Date the study was approved and the duration of the approval
- Listing of any conditions attached to the approval

- Identification of the approved Primary Investigator
- Signature of the EC/IRB chairperson
- Acknowledgement of the Co-Investigators
- EC/IRB approval of the informed consent form (if applicable)
- EC/IRB approval of the final protocol (if applicable).

Any substantial amendments to the protocol, as well as associated consent form changes, will be submitted to the EC/IRB and written approval obtained prior to implementation. Minor changes which do not affect the patient's safety will be patient to notification.

Serious Adverse Event (SAE) reports will be submitted to the EC/IRB as requested by the Sponsor, EC/IRB and/or local regulations. Annual and final reports will be provided to the EC/IRB as required.

14.4 **Informed Consent**

Prior to study start, the investigator must obtain written EC/IRB approval for the informed consent form. A copy of the Patient Information and the signed and dated informed consent will be provided to the study patient. The original must be retained in the patient medical records at the study site. The study must be explained to the study patients in lay language. Study patients will be assured that they may withdraw from the study at any time and for any reason and receive alternative conventional therapy as indicated.

14.5 **Reporting Requirements**

The investigator should notify the EC/IRB in writing within three months after completion, termination, or discontinuation of the study at the site. The same procedure will be applied to Competent Authority where required.

Site responsibilities for submitting data and reports:

Type of data/report	**Completed by Site within**	**Process**
Adverse Events	Ongoing Basis	Collected in patient hospital file

Serious Adverse Event Notification eCRF	24 hours	Enter eCRF pages within 24 hours of awareness of event
Enrollment	Immediate	Enter eCRF pages immediate
eCRF (baseline, follow-up visits, etc.)	Ongoing basis	Collected in the eCRF
Angiographic films (diagnostic angiography*, indexPCI, staged procedures), physiological recordings, IVUS recordings (if available) and angiographic films of revascularizations and stent thrombosis (if applicable) *The diagnostic angiogram of all cases must be forwarded to the academic core lab (Rotterdam, NL) to be reviewed/confirmed prior to enrollment.	Ongoing basis	Collected by site and forwarded to CRO/Core lab within 7 days
Device malfunctions	Ongoing basis	Collected by site and provided to device manufacturer
Annual Reports	Forward as requested by EC/IRB	Copy to be provided to Sponsor and EC/IRB
Final Report	Forward within 3 months of study completion or termination	Copy to be provided to Sponsor and EC/IRB

15 SPONSOR RESPONSIBILITIES

15.1 Role of ECRI

As Sponsor, ECRI has the overall responsibility for the conduct of the study, including assurance that the study satisfies international standards and the regulatory requirements of the relevant competent authorities.

General duties

Prior to allowing the sites to start enrolling patients into the study, the Sponsor is responsible for selecting investigators, ensuring EC/IRB approvals are obtained where applicable, and signing the Investigator Site Agreement with the investigators and/or hospitals. It is the Sponsor's responsibility to ensure that the study is conducted according to ISO 14155, the Declaration of Helsinki, and other applicable regulatory requirements, the study protocol, and any conditions of approval imposed by the EC/IRB or regulatory authorities. Additionally, the Sponsor will ensure proper clinical site monitoring.

Selection of clinical investigators and sites

The Sponsor will select qualified investigators and facilities which have adequate study patient population to meet the requirements of the investigation.

Training of investigator and site personnel and site monitoring

The training of the investigator and appropriate clinical site personnel will be the responsibility of the Sponsor, or designee, and may be conducted during an investigator meeting, a site initiation visit and/or other appropriate training sessions. Periodic monitoring visits will be conducted to ensure that all clinical patient data are properly documented and that the study is properly conducted.

Documentation

The Sponsor, or designee will collect, store, guard and ensure completion by the relevant parties of the following documents;

- All study relevant documents (protocol, Investigator's Brochure, EC/IRB approval and comments, competent authority notification and comments, patient information and informed consent template, relevant correspondence, etc.)
- Signed and dated electronic Case Report Form (eCRFs)

- Records of any Serious Adverse Events (SAEs) reported to the Sponsor during the clinical investigation
- Any statistical analyses and underlying supporting data
- Final report of the clinical investigation

15.2 **Insurance**

The sponsor maintains clinical trial insurance coverage for this study in accordance with the laws and regulations of the country in which the study is performed.
Reimbursement, indemnity and insurance shall be addressed in a separate agreement on terms agreed upon by the parties.

15.3 **Supplemental Applications**

As appropriate, the Sponsor will submit changes to the study protocol to the investigators to obtain EC/IRB re-approval.

15.4 **Submitting Reports**

The Sponsor will submit the appropriate reports identified by the regulations. This includes withdrawal of any EC/IRB approval, interim (if any) and final reports.

15.5 **Maintaining Records**

The Sponsor will maintain copies of correspondence, data, SAEs and other records related to the clinical study. The Sponsor will maintain records related to the signed Investigator Site Agreements according to requirements set forth by ISO14155.

CRO, Core Laboratories and clinical sites will maintain study records according to local requirements for this type of study.

15.6 **Audit**

The Sponsor is responsible for auditing the study to ensure compliance with GCP and regulatory requirements, a member of the Sponsor's (or a designated CRO's) quality assurance unit and may arrange to conduct an on-site audit to assess the performance of the study at the study

site and of the study documents originating there.

15.7 **Confidentiality**

All data and information collected during this study related to the participating patient will comply with the standards for protection of privacy based on applicable local/ national requirements for patient's confidentiality. All data used in the analysis and summary of this study will be anonymous, and without reference to specific study patients' names. Access to study subject files will be limited to authorized personnel of the Sponsor, the investigator, and research staff. Authorized regulatory personnel have the right to inspect and copy all records pertinent to this study, but all efforts must be made to remove the subject's personal data. Anonymized (imaging) data may be provided to Balton corporation (Balton, Warsaw, Poland) the Grant giver of the study and/or to Philips-Volcano (Volcano Europe BVBA/SPRL) being a supporting industry with regard to the iFR.

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17 APPENDIX I: DEFINITIONS

ACUTE SUCCESS DEFINITIONS

Per-protocol definitions:

[Device Success (Lesion Basis)]

Successful delivery and deployment of the BiOSS LIM C device at the intended target lesion (i.e. left-main bifurcation) and successful withdrawal of the delivery system with attainment of final in-stent residual stenosis of <30% (preferably by on-line QCA).

[Procedure Success (Patient Basis)]

Successful delivery and deployment of the BiOSS LIM C device at the intended target lesion (i.e. left-main bifurcation) and successful withdrawal of the delivery system with attainment of final in-stent residual stenosis of <30% (preferably by on-line QCA) for all intended target lesions without the occurrence of TLF during the index procedure hospital stay (maximum of 7 days).

Historical definition (EXCEL study):

[Device Success]

Successful balloon inflation with or without stenting and the achievement of a residual stenosis <50% of the main stem side branch (left anterior descending coronary artery and/or the left circumflex artery). The balloon inflation and/or stenting could have been preceded by adjunctive device use (e.g., Angiojet, rotational atherectomy etc.)

ADVERSE EVENT

Adverse Event (AE)	Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including abnormal laboratory finding) in patients, users or other persons, whether or not related to the investigational medical device NOTE 1 This includes events related to the investigational medical device or the comparator. NOTE 2 This includes events related to the procedures involved (any procedure in the clinical investigation plan). NOTE 3 For users or other persons, this definition is restricted to events related to the investigational medical device.
Adverse Device Effect (ADE)	Adverse event related to the use of an investigational medical device

	NOTE 1 This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, or the operation, or any malfunction of the investigational medical device. NOTE 2 This includes any event that is the result of a use error or intentional misuse.
Serious Adverse Event (SAE)	Adverse event that a) led to death, b) led to serious deterioration in the health of the subject, that either resulted in 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, or 3) in-patient hospitalization or prolongation of existing hospitalization, or 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, c) led to fetal distress, fetal death or a congenital abnormality or birth defect NOTE 1: This includes device deficiencies that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate. These are handled under the SAE reporting system. NOTE 2: A planned hospitalization for pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health, is not considered to be a serious adverse event.
Serious Adverse Device Effect (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Unanticipated Serious Adverse Device Effect (USADE)	Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report. NOTE Anticipated: is an effect which by its nature, incidence, severity or outcome has been previously identified in the risk

	analysis report.
Device deficiency	Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error and inadequate labeling.
Device malfunction	Failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or study protocol.
Incident	Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a patient, or user or of other persons or to a serious deterioration in their state of health.
Relationship of Adverse Event to the investigational treatment, device and/or procedure	• Certain: Event or laboratory test abnormality, with plausible time relationship to device use and/or procedure. It cannot be explained by disease or other drugs. • Probable: Event or laboratory test abnormality, with plausible time relationship to device and/or procedure. Unlikely to be attributed to disease or other drugs. • Possible: Event or laboratory test abnormality, with plausible time relationship to device and/or procedure. Could also be explained by disease or other drugs. • Unlikely: Event or laboratory test abnormality, with a time to device use and/or procedure that makes a relationship improbable (but not impossible). • Unassessable: Event or laboratory test abnormality, more data is needed for proper assessment.

ANGINA PECTORIS

Braunwald Classification of Unstable Angina:

Severity		Clinical Circumstances		
		A	**B**	**C**
		Develops in presence of extracardiac condition that intensifies myocardial ischemia (secondary UA)	Develops in the absence of extracardiac condition (primary UA)	Develops within 2 weeks after acute myocardial infarction (postinfarction UA)
I	New onset of severe angina or accelerated angina; no rest pain	IA	IB	IC
II	Angina at rest within past month but not within preceding 48 hr (angina at rest, subacute)	IIA	IIB	IIC
III	Angina at rest within 48 hr (angina at rest, acute)	IIIA	IIIB Troponin negative IIIB Troponin positive	IIIC

Canadian Cardiovascular Society (CCS) Classification of Stable Angina:

CLASS	
0	Asymptomatic
I	Angina with strenuous exercise
II	Angina with moderate exertion
III	Angina with mild exertion • Walking 1-2 level blocks at a normal pace • Climbing 1 flight of stairs at a normal pace
IV	Angina at any level of physical exertion

I. Ordinary physical activity does not cause angina; for example walking or climbing stairs, angina occurs with strenuous or rapid or prolonged exertion at work or recreation.

II. Slight limitation of ordinary activity; for example, angina occurs walking or stair climbing after meals, in cold, in wind, under emotional stress or only during the few hours after awakening, walking more than two blocks on the level or climbing more than one flight of ordinary stairs at a normal pace and in normal conditions.

III. Marked limitation of ordinary activity; for example, angina occurs walking one or two blocks on the level or climbing one flight of stairs in normal conditions and at a normal pace.

IV. Inability to carry on any physical activity without discomfort - angina syndrome may be present at rest.

Bleeding

BARC Bleeding Classification ***(Circulation. 2011 Jun 14;123(23):2736-47)***
Type 0 No Bleeding
Type 1 Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a health care professional may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare prefessional..
Type 2 Any overt, actionable sign of hemorrhage (e.g. more bleeding than would be expected for a clinical circumstance; including bleeding found by imaging alone) that **does not** fit the criteria for Types 3, 4, or 5, but **does** meet at least one of the following criteria: 1) Requiring non-surgical, medical intervention by a health care professional 2) Leading to hospitalization or increased level of care 3) Prompting evaluation
Type 3 Type 3a ▪ Overt bleeding plus hemoglobin drop of 3 to < 5 g/dL* (provided hemoglobin drop is related to bleed) Any transfusion with overt bleeding Type 3b ▪ Overt bleeding plus hemoglobin drop ≥ 5 g/dL* (provided hemoglobin drop is related to bleed) ▪ Cardiac tamponade ▪ Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid) ▪ Bleeding requiring vasoactive agents Type 3c ▪ Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation; does include intraspinal). • Subcategories; Confirmed by autopsy or imaging or lumbar puncture ▪ Intra-ocular bleed compromising vision
Type 4 - CABG–related bleeding ▪ Perioperative intracranial bleeding within 48 hrs ▪ Reoperation following closure of sternotomy for the purpose of controlling bleeding ▪ Transfusion of ≥ 5 units of whole blood or packed red blood cells within a 48 period†. ▪ Chest tube output ≥ 2L within a 24 hour period If a CABG - related bleed is not adjudicated as at least a Type 3 severity event, it will be classified as 'not a bleeding event'
Type 5 - Fatal Bleeding Type 5a ▪ Probable fatal bleeding: no autopsy or imaging confirmation, but clinically suspicious Type 5b ▪ Definite fatal bleeding: overt bleeding or autopsy or imaging confirmation

Platelet transfusions should be recorded and reported but are not included in these definitions until further information is obtained about the relationship to outcomes.

If a CABG-related bleed is not adjudicated as at least a type 3 severity event, it will be classified as not a bleeding event. If a bleeding event occurs with a clear temporal relationship to CABG (i.e., within a 48-h time frame) but does not meet type 4 severity criteria, it will be classified as not a bleeding event.
*Corrected for transfusion (1 U packed red blood cells or 1 U whole blood = 1 g/dL hemoglobin).
†Cell saver products are not counted.
CABG indicates coronary artery bypass graft

DEATH

(ARC)[42]

The deaths will be adjudicated per the ARC definition. All deaths are considered cardiac unless an unequivocal non-cardiac cause can be established. Specifically, any unexpected death even in patients with coexisting potentially fatal non-cardiac disease (e.g. cancer, infection) should be classified as cardiac.

- **Cardiac death:**
  Any death due to proximate cardiac cause (e.g. MI, low-output failure, fatal arrhythmia), unwitnessed death and death of unknown cause, all study procedure related deaths including those related to concomitant treatment.
- **Vascular death:**
  Death due to non-coronary vascular causes such as cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular cause.
- **Non-cardiovascular death:**
  Any death not covered by the above definitions such as death caused by infection, malignancy, sepsis, pulmonary causes, accident, suicide or trauma.

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[43]

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.

Myocardial infarction according to Third Universal definition (2012)[44]
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**:

○ 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) [43]

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 ≤4mm^2 for non left main lesions or ≤6mm^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 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) [42]

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 thrombosis

- 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:
  - Any unexplained death within the first 30 days‡
  - 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:

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 assist (of a person). Can be left alone for a few days.
4	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.
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. **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

18 APPENDIX II: IVUS AND IFR (FFR) RECOMMENDATIONS[3]

Pre-revascularization assessment of intermediate distal ULMCA Lesions

1. Prior to Randomization

The presence of significant lesion(s) in any of the left main bifurcation segments (i.e., distal left main, ostial LAD or ostial LCX) must be confirmed by the academic core lab (Cardialysis B.V., Rotterdam, NL) using dedicated bifurcation QCA software.

If the distal ULMCA lesion is deemed insignificant, the lesion should in most cases not be treated unless, for example, treatment of an ostial LAD or ostial LCX lesion necessitates left main treatment (left main equivalence), or the lesion is irregular or otherwise disrupted (i.e., Medina 011 or 010). PCI of other lesions should be performed as clinically indicated.

Pre-procedure iFR is mandatory to explore the physiological importance of the left main bifurcation.

1a. IVUS Criteria

IVUS criteria to defer revascularization is a distal ULMCA minimum lumen area (MLA) >6.0 mm^2 [45]. Conversely, if the left main MLA is ≤6.0 mm^2, the distal ULMCA lesion may be considered to be hemodynamically significant and considered equivalent to the core lab DS ≥50%.. In order to determine the true MLA, it may be necessary to image back to the aorto-ostial junction from both the LAD and LCX; the smaller of the two MLAs is the more accurate and should be used for decision-making. Practically, however, this is only necessary if the first pullback shows an MLA >6.0 mm^2.

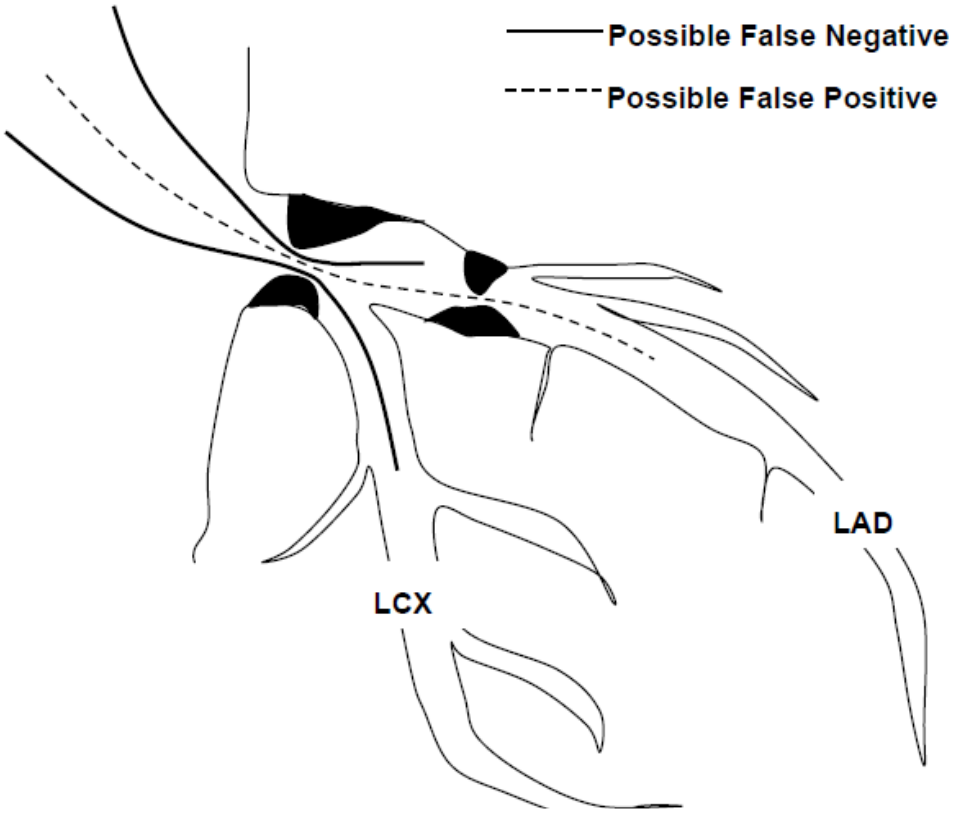
1b. FFR /iFR Criteria

Deferral of borderline distal left main lesions with a negative FFR has been demonstrated to be safe.[46] In the present study, the FFR criteria used to defer revascularization of the distal ULMCA is an FFR >0.80.[47, 48] This is most useful if there are no other lesions in both the LAD and LCX (otherwise there may be false positive and false negative FFR measurements in the ULMCA). The pressure wire transducer should be positioned just distal to distal ULMCA lesion and proximal to any secondary lesions, as long as there is a major branch after the left main which appears angiographically nearly normal for adequate runoff (e.g. the LAD or a large diagonal).

Although scarce data of iFR usage in left main are available, the same considerations may be applied for iFR with a cut-off of 0.89.

For a detailed iFR acquisition protocol please refer to Appendix III.

Note: See figure below. If there is also a tight stenosis in the proximal LAD distal to the ULMCA bifurcation lesion, and the FFR transducer is placed between these lesions, FFR may be false negative (>0.80); if the transducer is placed distal to a second hemodynamically significant lesion, the FFR may be false positive (≤0.80); therefore, IVUS evaluation is strongly preferred.



IVUS for PCI Guidance of distal ULMCA PCI

The use of IVUS to guide distal ULMCA intervention is strongly recommended as a publication describing the results of a large non randomized but adjusted registry suggests that 3-year mortality may be improved with IVUS-guided DES implantation of the (distal) ULMCA. [49]
In patients in whom IVUS is used to guide PCI, it is strongly recommended that both the LAD

and LCX be imaged *prior to* intervention back to the aorto-ostial junction to assist with stent size and length selection. If the distal ULMCA disease extends into the ostial/proximal LAD (as it does in the majority of subjects), it is recommended that stent length be selected so as to end the stent in a segment of LAD with a plaque burden <50%. With cross-over technique, a preprocedural minimal lumen area (MLA) of <3.7 mm2 within the LCX ostium as well as pre-procedural plaque burden of >56% at the LCX ostium were predictive of a poststenting FFR <0.80. [50] While there are no IVUS criteria for selecting a one-stent (cross-over) vs. a two-stent strategy, in general a LCX ostium lumen area >4.0 mm2 or a plaque burden ≤60% in a short segment of disease may indicate that a one-stent (cross-over) strategy will be adequate.

Iterative IVUS and post-dilation should be performed until the distal ULMCA minimum stent area is >8.5mm2 and the ostial/proximal LAD minimum stent area is at least >6.0mm2 and preferably matched to the distal reference vessel diameter if larger. Observational data in non-LMCA lesions has shown that in general the larger the minimal stent area the lower the likelihood of restenosis and stent thrombosis [18, 51-53] and thus post-dilation with non compliant balloons sized up to 0.25-0.50 mm less than the IVUS determined true vessel diameter (average media-media dimension) to safely achieve the largest maximal luminal dimension is recommended. It is strongly recommended that IVUS is also performed post-stenting from at least one epicardial coronary artery, usually the LAD, with pullback into the aorta (disengaging the guide to ensure the ostium is not missed). If a 1-stent technique is used (most commonly from the ULMCA into the LAD, “crossing over” the LCX), it is desirable but not mandatory that the ostial LCX also be imaged post-intervention if possible. If a 2-stent technique is used, IVUS pullback across the LAD and LCX is strongly recommended if the IVUS catheter passes easily into the LCX. *LCX or side branch imaging should not be pursued aggressively to avoid IVUS related (or pressure wire-related) complications.* If the IVUS catheter or pressure wire can be safely positioned into the LCX, then, in general, an LCX ostium lumen area >4.0mm2 (single stent strategy) or >5.5mm2 (two stent strategy) or an FFR >0.80 (single stent strategy) indicates that no further intervention is necessary. [18, 51-53]

Severe dissections present by IVUS (residual true lumen within the dissection flap below the above-mentioned criteria in each segment [LM: 8.5 mm2, LAD: 6.0 mm2, LCX: 5.5 mm2]) should in general receive an additional stent. Malapposition with stent area below the above-mentioned cut-off criteria in respective segment should in general be treated by additional post-dilatation with larger balloons.

IVUS and iFR for Guidance of other lesion (non-distal ULMCA PCI)

Pre-intervention non-distal ULMCA lesion assessment

To avoid unnecessary interventions with subsequent peri-procedural and late myocardial infarctions and repeat revascularization procedures[54] PCI of non ischemia producing lesions should in general not be performed. Whereas IVUS is strongly recommended (preferable to FFR) to assess intermediate ULMCA stenoses, it is just as strongly recommended that iFR be performed (preferable to IVUS) in all intermediate non-LMCA lesions (those with an angiographic diameter stenosis <70% by visual estimate), unless there is a positive nuclear or echocardiographic noninvasive study with ischemia clearly present in the distribution of that lesion. In the setting of serial stenoses, stenting should only be performed if the iFR beyond all narrowings is ≤0.89 (or FFR≤0.80 if available).[55] . After stenting the first lesion, iFR is measured again and any residual narrowing causing an iFR ≤0.89 (or FFR≤0.80 if available) is stented. (.) For sites that do not use FFR/iFR, it is strongly recommended that pre-interventional IVUS is used in all intermediate lesions (those with a visually estimated angiographic stenosis of <70% (unless there is a positive nuclear or echocardiographic noninvasive study with ischemia clearly present in the distribution of that lesion). A significant lesion by IVUS criteria that should be stented has both a minimal luminal area (MLA) of ≤4 mm2 *and* a plaque burden of >60%. In the absence of extenuating circumstances (e.g. plaque rupture, etc.), lesions that do not have both of these criteria should not undergo PCI.

Although scarce data of iFR usage in left main are available, the same considerations may be applied for iFR with a cut-off of 0.89.

IVUS guidance of non-ULMCA stenting

If IVUS is used to guide treatment of ULMCA lesions, it is recommended that IVUS also be used to guide treatment of important non-LMCA lesions in the LAD, LCX, and RCA circulations. XIENCE stent size and length should be selected and optimized to achieve a minimum stent area >5.5mm2 in non ULMCA lesions (with post-dilation with non compliant balloons sized up to 0.25-0.5mm less than the IVUS determined true vessel diameter (average media-to-media dimension), and to end the stents in arterial segments with a plaque burden <50%. Severe dissections present by IVUS (residual true lumen within the dissection flap ≤5.5mm2 either proximal or distal to the stent) should in general receive an additional stent. Malapposition with stent area ≤5.5mm2 should in general be treated by additional post-dilatation with larger balloons.

Follow-up

Since the site of restenosis after distal ULMCA bifurcation intervention is typically the ostium of the LCX, and since many presumed ostial LCX restenoses are angiographic artifacts (i.e. appear angiographically severe, but in fact are not hemodynamically significant), [56] it is strongly recommended that FFR/iFR be performed before treating any presumed restenotic lesions in the ostial LCX location (regardless of angiographic severity, unless totally occluded) unless there is unequivocal lateral wall ischemia by nuclear or echocardiographic noninvasive testing. If the FFR is >0.80 or iFR > 0.89, the ostial LCX lesion should not be treated and, thus, TLR (and possible procedural complications) avoided. For sites that do not use FFR/iFR, it is strongly recommended that pre-interventional IVUS of the ostial LCX be performed instead with an MLA >4.0mm2 used as the criteria to defer intervention and avoid TLR [57]. Similarly, prior to performing a repeat intervention elsewhere in the coronary tree, if the visually assessed angiographic diameter stenosis is <70%, ischemia should be documented according to either a positive nuclear or echocardiographic noninvasive test in the distribution of the recurrent lesion, or an FFR ≤0.80/iFR ≤0.89 , or IVUS with a MLA ≤4.0 mm2.

19 APPENDIX III: IFR ACQUISION PROTOCOL

0. give NTG, at least 60 seconds before performing measurements.

1. connect wire
2. wait for wire to stabilize
3. insert wire in guiding catheter
4. advance pressure sensor of pressure wire to end of guide catheter
5. zero aortic pressure to atmospheric pressure [PA ZERO]
6. normalize aortic pressure to distal pressure measurement [NORMALIZE]
7. screenshot or short recording, do recording in FFR mode

[LAD]
8. advance pressure wire distal to the bifurcation stenosis in main branch (e.g. LAD)
9. wait for 10 sec for any reactive hyperemia (e.g. due to contrast injection)
10. measure iFR twice (to uncover any upward drift of the value due to remaining reactive hyperemia)
11. measure Pd/Pa in 'FFR mode' for 20 seconds without inducing hyperemia
12. keep wire in position, record angiogram with sufficient contrast filling
13. go in orthogonal view, keep wire in original position, acquire angiogram
14. wait for 10 sec for any reactive hyperemia (e.g. due to contrast injection)
15. measure iFR pullback and record angiogram during the pullback. Retract the wire into guiding catheter
16. screenshot or short recording to confirm absence of drift, perform recording in 'FFR mode' (if drift is more than +/- 0.02, redo normalization and measurement)

[LCX]
17. advance pressure wire distal to bifurcation stenosis in side branch (e.g. LCX)
18. wait for 10 sec for any reactive hyperemia (e.g. due to contrast injection)
19. measure iFR twice (to uncover any upward drift of the value due to remaining reactive hyperemia)
20. measure Pd/Pa in 'FFR mode' for 20 seconds without inducing hyperemia
21. keep wire in position, record angiogram with sufficient contrast filling
22. go in orthogonal view, keep wire in original position, acquire angiogram
23. wait for 10 sec for any reactive hyperemia (e.g. due to contrast injection)
24. measure iFR pullback. Retract the wire into guiding cathether
25. screenshot or short recording to confirm absence of drift, do recording in 'FFR mode' (if drift is more than +/- 0.02, redo normalization and measurement