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XLIMus drug eluting stent: A randomIzed controlled Trial to assess endothelialization. The XLIMIT trial

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ABSTRACT

Background: Thin strut 3rd generation drug eluting stents offer the potential advantage over the previous generation of better technical performance and reduced neointimal proliferation parameters, which are linked to mid and late term device failure.
Aim: To evaluate the performance of the Xlimus sirolimus-eluting stent (SES) against the Synergy everolimus-eluting stent (EES) in terms of device reendothelialization in patients undergoing PCI for coronary artery disease (CAD).
Methods: XLIMIT is a multicenter randomized controlled trial targeting 180 patients requiring percutaneous coronary interventions (PCI). Patients will be treated with Xlimus SES or Synergy EES implantation and randomization will be performed in a 2:1 ratio. The primary endpoint will be the reendothelialization grade of the Xlimus stent in terms of strut coverage and neointimal hyperplasia volume as compared to Synergy. Secondary endpoints will be represented by clinical and procedural outcomes. The first patient was enrolled on February 2019.
Conclusions: A clearer understanding of the endothelialization process of new generation DES could significantly impact the treatment with dual antiplatelet therapy in the future. Moreover, although not powered for clinical end-points, the XLIMIT trial will provide randomized data in a population with minimal exclusion criteria.
Trial registration: ClinicalTrials.gov Identifier: NCT03745053. Registered on November 19, 2018.
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1. Introduction

Over the last four decades, PCI has become one the most frequently performed medical procedures worldwide. Most of its success is related to its long-term efficacy and safety, which have progressively increased from balloon angioplasty to bare metal stents and, finally, to drug-eluting stents.

Of note, the introduction of drug-eluting stents (DES) is probably responsible of the most significant improvement in the efficacy of PCI due to the reduction in restenosis rates following the release of anti-proliferative drugs, which suppress neointimal hyperplasia [1,2].

Since their release, DES technology has undergone a continuous development in many of its characteristics such as stent design, strut thickness, optimal loading, improved kinetics of drugs, and new polymer technology. All these improvements led to the current generation of DES [3,4].

Specifically, thin strut thickness provides greater conformability and deliverability with lower risk of arterial injury. Moreover, it is responsible of less shear disturbances, reducing peri-strut inflammation and fibrin deposition which finally contribute to improved reendothelialization [5].

The Synergy everolimus-eluting stent (EES) (Boston Scientific, Marlborough, MA, USA) and the recently introduced Xlimus sirolimus-eluting stent (SES) (Cardionovum GmbH, Bonn, Germany) are both ultra-thin devices (strut thickness of 74 μm for Synergy, 73 μm for Xlimus) with an abluminal biodegradable polymer coating that should reduce acute and long-term thrombogenicity due to rapid reendothelialization. In addition, Xlimus is characterized by better mechanical properties than traditional DESs improving its navigability in tortuous lesions.

Whilst the efficacy of the Synergy stent system has been widely tested [6–13], there is still no randomized data studying the performance of the Xlimus, but only a limited size registry [14].

The aim of the XLIMIT randomized controlled trial is to compare the Xlimus SES to the Synergy EES in terms of device reendothelialization and cardiovascular outcomes in patients undergoing percutaneous coronary intervention.

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2. Methods

2.1. Study population and eligibility criteria

The XLIMIT study is a multicenter randomized controlled trial designed to assess the efficacy of the Xlimus SES and to compare it with Synergy EES.

The study will enroll 180 patients aged >18 years old with documented coronary artery disease (CAD) and indication to PCI for stable/unstable angina or non-ST elevated myocardial infarction (NSTEMI). Stents will be implanted to treat de novo lesions in vessels with a reference diameter (RVD) of 2.5 to 4 mm. Subjects will be required to have either target lesion (TL) ≥70% or a stenosis ≥50% to <70% with abnormal fractional flow reserve (iFR/FFR), elevated cardiac biomarkers, or objective evidence of myocardial ischemia (abnormal stress or imaging stress test). Patients with ST–elevated myocardial infarction, left main disease, chronic total occlusions (CTO), venous graft disease or in-stent restenosis (ISR) will be excluded per-protocol.

Patients with known hypersensitivity to Heparin, Aspirin, Clopidogrel, Ticlopidine, Sirolimus, Everolimus or contrast media, pregnancy, history of bleeding or known coagulation disorders, life expectancy of <1 year or unable to undergo all follow-up examinations and procedures will be also excluded (Table 1 – inclusion and exclusion criteria).

2.2. Enrollment and procedure

After the identification of the TL, and the collection of patient's written consent to participate, randomization to Xlimus SES or Synergy EES will be performed using a web-based case report form (CRF) in a 2:1 ratio. The same CRF will be used to collect all the demographic and procedural data.

Prior to the procedure, patients will be adequately pre-medicated according to local standard practices. It is recommended that all patients receive aspirin and a loading dose of Clopidogrel 600 mg, or prasugrel 60 mg or ticagrelor 180 mg, unless patients were already taking an antiplatelet for at least 5 days prior to procedure.

PCIs will be performed according to general practice and current international guidelines [15]. Any lesion characteristic or localization will be allowed for enrollment. The use of iFR/FFR for the assessment of angiographically intermediate lesions is recommended. If clinically indicated, intravascular ultrasound (IVUS) or optical coherence tomography (OCT) may be used at operator's discretion. Treatment of all TL within a single PCI procedure is encouraged; however, staged interventions can be performed to patients with multivessel disease but only using the allocated stent platform. Medical therapy during the PCI procedure and in the follow-up will follow current practice guidelines [15].

Table 1
Inclusion and exclusion criteria. CAD: coronary artery disease; PCI: percutaneous coronary intervention; LVEF: left ventricular ejection fraction; CTO: chronic total occlusion.

Inclusion criteria	– Age ≥ 18 years old – Documented CAD: stable or unstable angina; NSTEMI – Target de novo lesion in a vessel with a significant stenosis suitable for PCI – Target lesion is in a vessel with reference diameter between 2.5 mm and 4 mm – Patient able to sign written informed consent and willing to participate to follow-up visits and procedures
Exclusion criteria	– ST-elevated myocardial infarction – Known hypersensitivity to: heparin, aspirin, clopidogrel, ticlopidine, sirolimus, everolimus, zotarolimus, inox steel and/or contrast media – Pregnancy – History of bleeding or known coagulation disorders – Target vessel PCI in the previous 3 months – Life expectancy of <1 year – Patients participating to other studies – LVEF <30% – Cardiogenic shock at the time of randomization – Left main or venous graft lesion – In-stent restenosis or CTO

2.3. Devices description

Synergy EES has a thin-strut (74–81 μm) platinum chromium (PtCr) metal alloy platform with a 4 μm bioabsorbable polylactic (PLGA) abluminal polymer which elutes the drug. Elution is complete by 90 days, and polymer absorption is essentially complete by 120 days [7–10].

The stent platform of the XLIMUS is made of cobalt chromium L 605 and the stent is available in a 6-, 8-, or 10-cell structure design (closed cell architecture). It consists of a RX (Rapid Exchange) Delivery System with 140 cm working length. The struts thickness is 73 μm and the 6-cell design is for stenting of coronary artery diameter of 2.25–2.50 mm, 8-cell structure is used for stenting of 2.75–3.50 mm artery diameters, and the 10-cell is for larger artery diameter lesions (up to 5 mm). The XLIMUS has an innovative hydrophilic coated shaft and an extra-low tip profile (crossing profile = 0.90 mm) to access the most tortuous lesions. The highly biocompatible polylactic acid (PLLA) drug containing release matrix degrades smoothly and provides an optimal release kinetic profile. Within 30 days, about 70% of the antiproliferative drug is distributed into the surrounding arterial tissue of the stent struts, ensuring a highly effective inhibition of smooth muscle cell migration and proliferation. Elution is complete by 90 days, and polymer absorption is essentially complete by 120 days. Pharmacokinetic study results confirm sustained antiproliferative drug efficacy up to 120 days.

Xlimus SES will be compared with Synergy EES, a thin-strut (74–81 μm) platinum chromium (PtCr) metal alloy platform with a 4 μm bioabsorbable polylactic (PLGA) abluminal polymer which elutes the drug.

2.4. Follow-up and data collection

Follow-up is scheduled at 6 and 12 months after the index procedure. Visits will include clinical examination, EKG and blood tests. At 6 months, patients will also undergo a control coronary angiography with OCT of the target vessel.

All the follow-up data as well as any serious adverse events including death, MI, revascularization, stent thrombosis and bleeding will be entered into the CRF. The study will be subject to on-site monitoring to secure the integrity of the data (Fig. 1 – study flow chart).

2.5. Coronary angiography assessment and OCT analysis

Coronary angiograms will be obtained at baseline, immediately after stenting, and at 6-months follow-up.

The images will be analyzed using a validated edge detection system by a core laboratory. Minimal lumen diameter (MLD), reference vessel diameter (RVD), and percent diameter stenosis at baseline, post-procedure and at follow-up will be measured, respectively. Acute gain is defined as the difference between the MLD immediately after the procedure and the baseline. Late lumen loss is defined as the difference between the MLD immediately after the procedure and at follow-up. Loss index is defined as the ratio between late lumen loss and acute lumen gain. Angiographic restenosis is defined as diameter stenosis ≥50% by quantitative coronary angiography (QCA) within a previously stented segment (stent and 5 mm proximal and distal) at the follow-up angiogram. Restenosis patterns will be assessed using the Mehran classification system.

OCT examinations of target vessel will be performed after intracoronary administration of 200 μg of nitroglycerin.

Analyses will be performed every 2 cross-sections (mean distance of 0,4 mm) according to conventional definitions derived from expert consensus documents [16–19] using an off-line software (LightLab Consolle, Westford, Massachusetts, USA). Neointimal volume will be

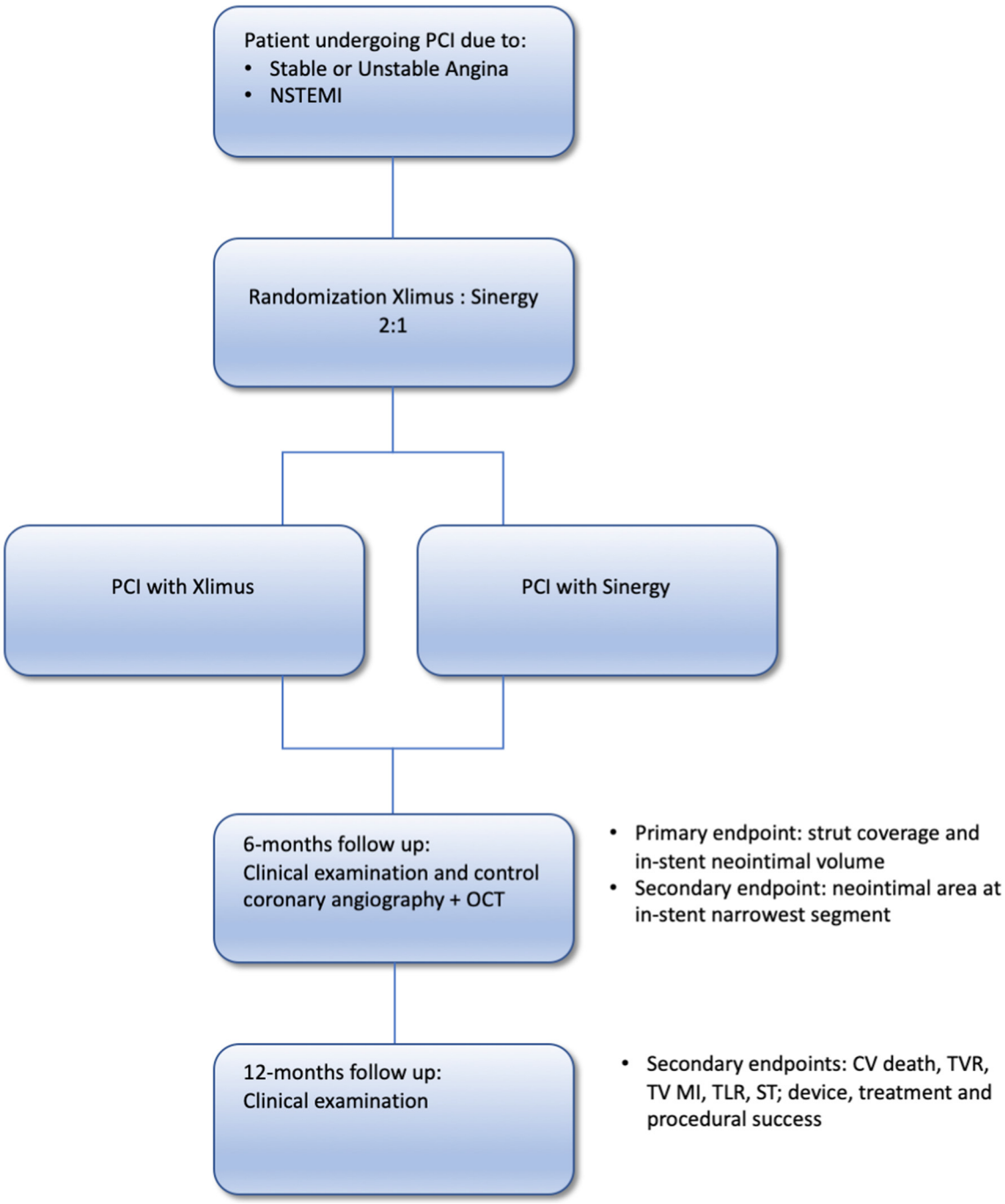

Fig. 1. TVR: target vessel revascularization; TV MI: target vessel myocardial infarction; TLR: target lesion revascularization; ST: stent thrombosis; OCT: optical coherence tomography; NSTEMI: non-ST-elevated myocardial infarction; PCI: percutaneous coronary intervention.

calculated in all analyzed cross-sections and volumetric measurements will be compared in the two groups.

All OCT sequences will be analyzed by an independent and validated Core laboratory with specific expertise in intravascular imaging. Personnel blinded to procedural data and clinical outcome will perform all assessments off-line.

In all the analyzed cross-sections, the assessment of neointimal thickness will be calculated as the difference between the stent contour and the luminal contour. Volumetric measurements will be obtained applying the Simpson rule [20].

Stent with suboptimal strut visualization (i.e. inability of OCT to address all stent struts in a specific cross-section) in >10% of total stent struts will be excluded from final analysis.

2.6. Study outcomes

The primary endpoint of the trial is the reendothelialization grade of the Xlimus stent in terms of struts coverage and neointimal hyperplasia volume as compared to the Synergy stent at 6 months.

Neointimal area calculated at the narrowest luminal area segment of target vessel will represent the secondary endpoint as well as cardiovascular death, target vessel MI or target vessel failure (TVF), target lesion revascularization (TLR), stent thrombosis (ST), device success at 24 h, target lesion success at 24 h and procedural success at 24 h.

All clinical end points will be adjudicated by an independent event adjudication committee (EAC) made up of interventional and non-interventional cardiologists who are not participants in the study. The

EAC will be in charge of the categorization of clinical events and clinical endpoints in the study which are based on protocol.

2.7. Statistical analysis

2.7.1. Sample size determination

Sample size determination has been based on data obtained from historical cases in a published database including >1500 lesions [16].

We assumed a mean value of in-stent neointimal volume formation of 15 ± 7.5% in the Synergy EES group after 6-months, and a clinically relevant volume reduction of 4% with the Xlimus SES, leading to a mean of 11%. Thus, aiming for a two-tailed α of 0.05 and 80% power at a Student's *t*-test, the required total sample would be of 129 patients (43 in Synergy EES group and 86 in Xlimus SES group). This sample size has to be increased to 135 patients (45 in Synergy EES group and 90 in Xlimus SES group) to consider potential suboptimal image acquisition in 3% of cases. Finally, foreseeing a 25–30% cumulative rate of drop-outs and patients not performing the 6 months angiographic follow-up, it is reasonable to enroll 60 pts. in the Synergy EES group and 120 in the novel Xlimus SES group to test the superiority hypothesis. Moreover, if the superiority hypothesis will not be demonstrated, with 180 patients (60 pts. in the Synergy EES group and 120 Xlimus SES group) it will be possible to test the non-inferiority hypothesis with a one-tailed significance level α of 0.05 (equivalent to a 90% confidence interval), a power of about 0.80 and a non-inferiority threshold of 3%, thus assuming that the two treatments are actually equivalent. The non-inferiority of Xlimus SES will be claimed if the upper 90% confidence limit of the difference between Xlimus SES and Synergy EES will be <3%.

2.7.2. Statistical methods

Descriptive statistics (arithmetic mean, median, minimum and maximum and standard deviation) will be calculated for quantitative variables. Absolute frequencies and percentages will be obtained for qualitative variables. Summary statistics will be presented according to treatment allocation. 95% confidence intervals will be also provided, unless otherwise specified.

All statistical tests will be performed at two-sided $\alpha = 0.05$.

Student's *t*-test or Mann-Whitney *U* test will be used to compare quantitative variables depending if they are normally distributed or not; $\chi 2$ or Fisher's exact tests will be used to compare qualitative variables.

The primary endpoint and the neointimal area calculated at the site of minimal lumen area at 6-month FU, measured with OCT will be analyzed by means of the Student's *t*-test for the superiority hypothesis. The confidence interval approach will be used for the non-inferiority hypothesis on the primary endpoint.

The probability of not occurrence of clinical secondary endpoints at 12 months (cardiac death, target-vessel MI and clinically indicated TLR, cardiac death, target-vessel MI, TLR, and ST) will be estimated using the Kaplan-Meier method and compared between the two treatment groups by means of the Log-rank test, followed by the Proportional Hazard Cox's model to assess predictive models in consideration of the baseline characteristics statistically associated with the events and the following variables: treatment group, age, gender, number of vessel treated, stent length, number of stents, insulin therapy requirement. Clinically appropriate thresholds will be considered to group the quantitative variables in classes.

With the considered sample size, a satisfactory power value of at least 0.80 is obtained at a Log-rank test carried out at 0.05 (two tailed) significance level if the difference in survival probability is at least 0.20 from a baseline ranging from 0.45 to 0.85.

The clinical secondary endpoints at 24 h (device success, lesion success, and procedural success) will be compared by means of the Fisher's exact test. With the considered sample size, a satisfactory power value of at least 0.80 is obtained for a difference of at least >0.15, considering a baseline proportion of about 0.80.

2.7.3. Ethical considerations

This study is conducted in accordance with the ethical principles of the Declaration of Helsinki (2013). The protocol of this study has been read and approved by the Ethics Committee of participating hospitals. Printed informed consent and detailed information about the study will be offered to patients before randomization.

All information and data of this trial are encrypted and stored in an online database accessible only to main researchers and administrators.

Patients primarily enrolled have rights to withdraw at any time point and the reasons will be documented.

3. Discussion

The XLIMIT multicenter trial will test the efficacy and safety of the Xlimus stent compared to the Synergy stent.

The aims of the study can be summarized in the following points:

1. To assess the Xlimus SES reendothelialization and in-stent neointimal hyperplasia volume at 6 months (primary outcome) as compared to Synergy EES
2. Support the efficacy of the stent in terms of device, procedural and target lesion success at 24 h (secondary outcomes)
3. Demonstrate the safety and efficacy of the implant in terms of cardiovascular death, target vessel MI, TVF, TLR and ST at 12 months (secondary outcomes)

Durable polymers of first-generation DES were considered one of the main causes of stent thrombosis and in-stent restenosis due to persistent arterial wall inflammation and delayed vascular healing. Although the current durable polymer DES shows less long-term complications in comparison with precedent technologies, a huge effort has been put in the development of bioabsorbable polymer stents with the aim of improving late procedural outcomes [21,22].

Synergy EES is one of the new generation thin strut stents with abluminal bioabsorbable polymer and has shown good clinical and procedural results in several studies [7–13].

In the EVOLVE II trial, target lesion failure (TLF) and TLR rates were 6.7 and 2.6% at 1 year, respectively [8].

In the all-comers BIO-RESORT study, the 1-year TLF and TLR rates in the Synergy arm were 4.0% and 2.0% respectively [11].

In a large registry conducted in Asia, despite the vast majority of patients having complex lesions (type B2 or C), 1-year TLF rate was 5.8% and TLR rate 1.3% [23].

In another registry of 185 high bleeding risk patients who underwent short dual-antiplatelet therapy (DAPT) (78.4% with discontinuation by 3 months), no stent thrombosis was reported and only three patients required target-vessel revascularization at 1 year [24].

A sub-study from the Swedish SCAAR registry made a comparison between Synergy EES and other new generation DES showing that the cumulative rate of restenosis (1.1% vs. 1.0%, adjusted HR: 1.24; 95% CI: 0.88–1.75; $P = 0.21$) and stent thrombosis (0.4% vs. 0.5%, adjusted HR: 0.97; 95% CI: 0.63–1.50; $P = 0.17$) up to 1 year were low in both the Synergy and other new generation DES group [12].

For what concerns the acute setting, in a recent multicenter registry enrolling 1008 patients with ACS treated with PCI and Synergy EES, the primary endpoint (composite of cardiac death, myocardial infarction and target lesion revascularization) occurred in 3% of the population at 12 months, confirming the good performance of the device [25].

The Xlimus SES has similar characteristics and structure as the Synergy EES, with additional features designed to improve its trackability across complex anatomy, such as an innovative hydrophilic-coated shaft and an extra-low tip profile (crossing profile 0.90 mm).

The biggest study available on the Xlimus is a prospective registry on 200 consecutive patients with 255 complex de novo lesions. The stent showed good technical performance with a delivery success rate of 98% in patients and in 98.4% of lesions. Xlimus SES was successfully

implanted on the first attempt with a single guidewire in 88% of patients and in 81.6% of lesions. Additional techniques to facilitate stent delivery (i.e., buddy wire, anchoring-balloon or child-in-mother catheter) were necessary in 18.4% of lesions. Implantation failure was seen in 4 lesions (1.6%). Moreover, although the sample size was relatively small, the 9% rate of MACE at 12 months was comparable to what has been reported in other studies on 2nd- and 3rd-generation DES [26,12].

4. Trial status

Recruitment started in February 2019 and is estimated to be completed in December 2020.

5. Conclusions

The XLIMIT trial will provide insights into the endothelialization process of the Xlimus sirolimus eluting stent compared to the Synergy everolimus eluting stent. Although not powered for clinical endpoints, a “minimally” selected population is of particular significance as it will test the real-world performance of the new device.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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