Reduced duration of dual antiplatelet therapy using an improved drug-eluting stent for percutaneous coronary intervention of the left main artery in a real-world, all-comer population: Rationale and study design of the prospective randomized multicenter IDEAL-LM trial

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Background Continuous improvements in stent technology make percutaneous coronary intervention (PCI) a potential alternative to surgery in selected patients with unprotected left main coronary artery (uLMCA) disease. The optimal duration of dual antiplatelet therapy (DAPT) in these patients remains undetermined, and in addition, new stent designs using a bioabsorbable polymer might allow shorter duration of DAPT.

Study design IDEAL-LM is a prospective, randomized, multicenter study that will enroll 818 patients undergoing uLMCA PCI. Patients will be randomized in a 1:1 fashion to intravascular ultrasound-guided PCI with the novel everolimus-eluting platinum-chromium Synergy stent with a biodegradable polymer (Boston Scientific, Natick, MA) followed by 4 months of DAPT or the everolimus-eluting cobalt-chromium Xience stent (Abbott Vascular, Santa Clara, CA) followed by 12 months of DAPT. The total follow-up period will be 5 years. A subset of 100 patients will undergo optical coherence tomography at 3 months.

End points The primary end point will be major adverse cardiovascular events (composite of all-cause mortality, myocardial infarction, and ischemia-driven target vessel revascularization) at 2 years. Secondary end points will consist of the individual components of the primary end point, procedural success, a device-oriented composite end point, stent thrombosis as per Academic Research Consortium criteria, and bleeding as per Bleeding Academic Research Consortium criteria.

Summary IDEAL-LM is designed to assess the safety and efficacy of the novel Synergy stent followed by 4 months of DAPT vs the Xience stent followed by 12 months of DAPT in patients undergoing uLMCA PCI. The study will provide novel insights regarding optimal treatment strategy for patients undergoing PCI of uLMCA disease (www.clinicaltrials.gov, NCT 02303717). (Am Heart J 2017;187:104-111.)

Patients with a significant lesion in an unprotected left main coronary artery (uLMCA) benefit from revascularization and coronary artery bypass graft (CABG) surgery has traditionally been the preferred treatment.[1] However, in recent years, percutaneous coronary intervention (PCI) has emerged as a potential alternative to CABG. Recent trials showed comparable rates of major adverse cardiac and cerebrovascular events after 1 to 2 years between patients with uLMCA lesions, treated with either PCI or CABG.[2-4] This also holds true for overall event rates after 5 years of follow-up, albeit with a higher need for repeat revascularization after PCI.[5,6] Consequently, current international guidelines recommend PCI as an acceptable treatment option for selected patients with uLMCA disease.[7-9]

Recently, the NOBLE trial evaluated CABG vs PCI as treatment of uLMCA lesions and suggested a superior 5-year outcome for CABG, owing to higher rates of nonprocedural myocardial infarction (MI), repeat revascularizations, and, although unexplained, ischemic

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strokes beyond 1 year in the PCI group.[10] However, the coronary stents used in the NOBLE trial were first-generation drug-eluting stents (DES) and biolimus-eluting stents. Second-generation drug-eluting stents, in particular everolimus-eluting stents, have been shown to reduce rates of repeat revascularization.[11] Indeed, another recent trial, the EXCEL trial, almost exclusively used everolimus-eluting stents in uLMCA lesions and showed noninferiority of PCI to CABG after 3 years in patients deemed eligible for both PCI and CABG.[12]

Stent technology

Since the introduction of bare-metal stents, stent platform technology has continued to evolve with progressive improvements in deliverability, conformability, and both radial and longitudinal strength.[13,14] With the advent of DES, potent antiproliferative agents were added to reduce neointimal proliferation. These were usually embedded in polymers to control drug release, and over time, these polymers have become increasingly biocompatible with the aim of reducing inflammation and accelerating healing.[14] The metallic materials used for the stent platform have also undergone changes going from stainless steel and cobalt-chromium in the earlier-generation stents to platinum-chromium in the later-generation DES, with advantages including increased radial strength, fracture resistance, and radio-opacity.[15,16] Stent struts have become thinner, which reduces flow disturbances and improves endothelial coverage.[17]

The SYNERGY everolimus-eluting stent (Boston Scientific, Natick, MA) is an example of a latest-generation DES and is based on a platinum-chromium platform with a strut thickness of 74 μm. In contrast to the commonly used durable polymers, it has a biodegradable polymer applied only on the abluminal side of the stent and which is fully absorbed within 3 to 4 months. These changes were introduced to improve early endothelialization of the stent struts, accelerate vessel healing, and reduce the risk of both stent thrombosis and restenosis. In previous studies, this device has been shown to have a very low incidence of reintervention with excellent clinical outcomes.[18-20]

In uLMCA PCI, there are potentially large differences between proximal and distal vessel diameters, and so the overexpansion capability of the stent is another important factor influencing outcomes. Unfortunately, manufacturers often do not specify maximal overexpansion capabilities. In vitro testing of the overexpansion capabilities of commonly used stent platforms has shown that the 4.0-mm Xience Prime stent (Abbott Vascular, Santa Clara, CA) can be maximally expanded to 5.6 mm using a 6.0-mm balloon.[21] However, this is at the expense of stent structure deformation with potentially adverse clinical effects. In contrast to this, the manufacturer of the Synergy stent specifies an overexpansion capability to 5.75 mm for a 4.0-mm stent without stent deformation, which could be a beneficial feature for uLMCA PCI.

Duration of dual antiplatelet therapy

Another important factor influencing long-term outcome after PCI is the duration of dual antiplatelet therapy (DAPT). In previous studies using first-generation DES, a significant association was observed between discontinuation of DAPT and the occurrence of thrombotic events in the first 6 to 12 months after the procedure. Based on these findings, current European Society of Cardiology (ESC) guidelines recommend 6 to 12 months of DAPT after DES implantation.[7] However, recent randomized trials using second-generation everolimus- or zotarolimus-eluting DES demonstrated no reduction in stent-related ischemic events with prolonged DAPT but an excess of bleeding complications.[22,23] In the Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intima Hyperplasia (PRODIGY) study, the primary outcome (all-cause mortality, MI, or stroke) was similar for patients randomized to 6 or 24 months of DAPT therapy.[23] The Optimized Duration of Clopidogrel Therapy Following Treatment With the Zotarolimus-Eluting Stent in Real-World Clinical Practice (OPTIMIZE) trial showed that in patients with stable coronary artery disease or low-risk acute coronary syndrome (ACS) treated with zotarolimus-eluting stents, 3 months of DAPT was noninferior to 12 months with regard to net clinical adverse events and cerebral events, that is, without significantly increasing the risk of stent thrombosis.[24] These findings were confirmed by meta-analyses, which included the PRODIGY and OPTIMIZE trials.[25,26] This suggests that DAPT for 3 to 6 months could be safe after implantation of second-generation DES, even in some patients with recent ACS.

Study aims

Stent failure in the uLMCA is potentially catastrophic emphasizing the necessity of identifying the best available stent and the optimal duration of DAPT after PCI in this location. Complete apposition and early endothelial coverage of the stent struts should allow for a shorter duration of DAPT. Accordingly, the IDEAL-LM study will evaluate the SYNERGY stent (Boston Scientific) followed by 4 months of DAPT to the current standard of care XIENCE stent (Abbott Vascular) followed by 12 months of DAPT with regard to noninferiority for safety and efficacy end points in patients undergoing uLMCA PCI.

Study design

IDEAL-LM is a prospective, randomized, multicenter (34 sites in France, the Netherlands, Poland, Russia, Germany, and United Kingdom) study in patients with uLMCA disease and an indication for coronary artery revascularization who have been discussed in the local Heart Team and accepted for PCI. Patients are

randomized in a 1:1 fashion to the SYNERGY stent arm (study cohort) or to the XIENCE stent arm (control cohort). Randomization is performed using Web-based software (e-DREAM system) with random blocks according to center. Randomization occurs at the time of the index procedure before PCI. Dual antiplatelet therapy will be stopped after 4 months in the study cohort, whereas in the control cohort, it will be continued for 12 months. The use of intravascular ultrasound (IVUS) to optimize stent deployment is strongly encouraged in both groups in accordance with the most recent ESC guidelines.[8] A subgroup of 100 patients will have angiographic follow-up with optical coherence tomography (OCT) 3 months after treatment. The study flowchart is depicted in Figure.

This study is investigator initiated and has been designed by the Glasgow Jubilee National Hospital (Glasgow, Scotland) and the Thoraxcenter Rotterdam (Erasmus Medical Center, Rotterdam, the Netherlands). The study was approved by local institutional review boards and adheres to the principles of the Declaration of Helsinki and Good Clinical Practice. The study is registered on www.clinicaltrials.gov NCT02303717.

Study objectives and end points

The primary objective is to establish the noninferiority of the SYNERGY stent relative to the XIENCE stent for prevention of the composite primary end point of major adverse cardiac events (MACE). A major secondary objective is to compare the outcomes of both patient groups with the uLMCA cohort from the SYNTAX trial, thereby allowing a comparison of outcomes with contemporary stent technology to those with first-generation permanent paclitaxel-eluting polymer DES.[2,27]

Primary end points. Both the primary and secondary end points will be adjudicated by an independent and blinded clinical end point committee (CEC). The primary end point is the rate of MACE, which is a composite end point of death from any cause, MI, or ischemia-driven target vessel revascularization (TVR), at 2 years after the PCI procedure.

Secondary end points. The secondary end points consist of the individual components of the primary end point; procedural success (attainment of <30% residual stenosis of the target lesion and no in-hospital device-oriented composite end points defined as cardiac death, MI not clearly attributable to a nontreated vessel, and clinically indicated target lesion revascularization); device-oriented composite end point and its individual components at 1 month, 6 months, and annually up to 3 years; stent thrombosis according to the Academic Research Consortium definition at all time points[28]; the composite of Bleeding Academic Research Consortium (BARC) 3 or 5 at 24 months according to the BARC definition[29]; and the individual bleeding events (BARC 1, 2, 3, 4, and 5) according to the BARC definition[29];

Secondary invasive end points consist of OCT end points. The primary OCT end point will be the Healing Score. This is a weighted index assigning points to 4 parameters: presence of filling defect (4 points), presence of both malapposed and uncovered struts (3 points), presence of uncovered struts alone (2 points), and presence of malapposition alone (1 point). Secondary OCT end points will be percentage of uncovered struts, percentage of malapposed struts, lumen area, lumen diameter, minimal lumen diameter, scaffold area, incomplete stent apposition area, mean prolapse area, number of frames with dissection, calculated stent length, malapposition distance, and mean thrombus area.

Study population

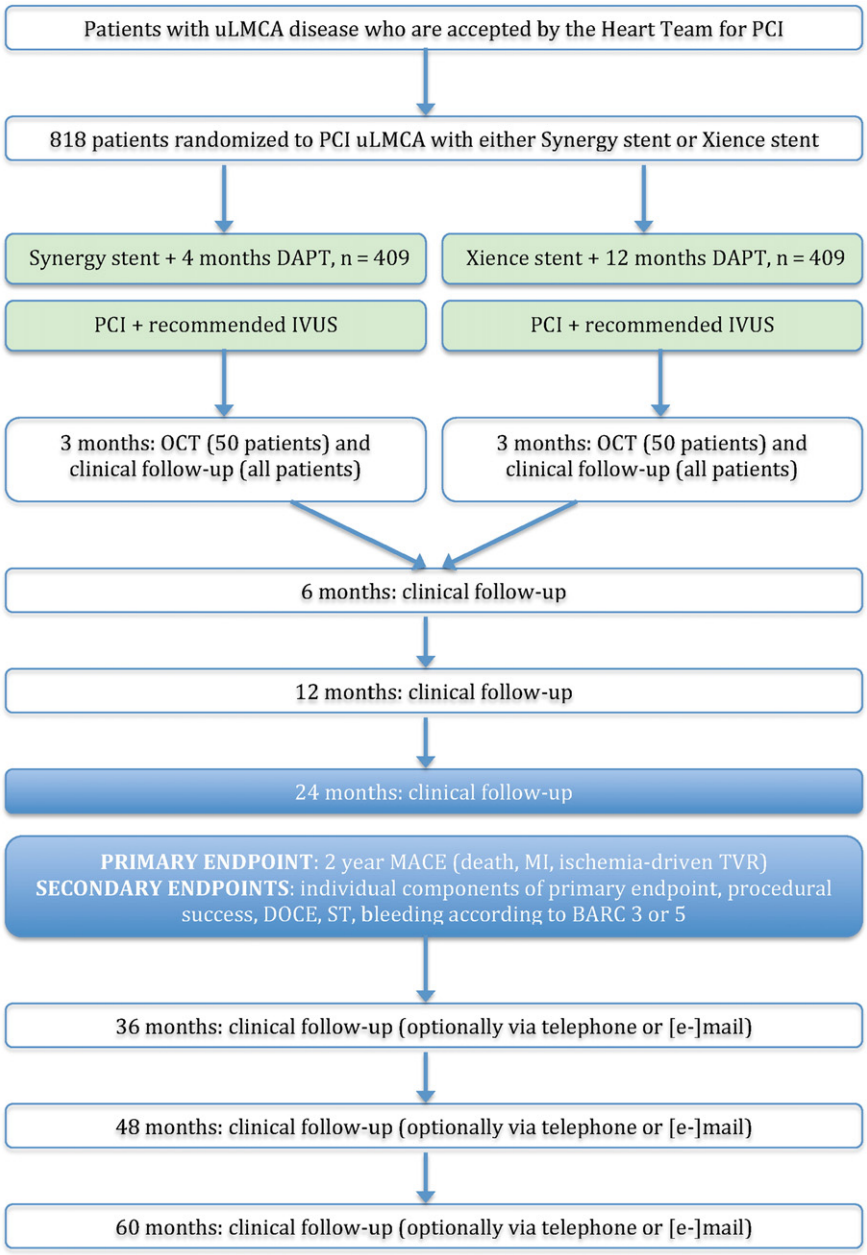
The local Heart Team consisting of an interventional cardiologist and a cardiac surgeon assesses patients for indication of revascularization in accordance with ESC guidelines.[8] Patients with a visual uLMCA stenosis of 50% to 90% and (non)invasive evidence of hemodynamic significance or >90% or a stenosis were eligible. The revascularization strategy in patients should be determined early by the Heart Team based on the patient's clinical status, as well as the severity and distribution of the coronary artery disease (Syntax Score) and the characteristics of the lesion.[8] The complete inclusion and exclusion criteria are shown in Table 1. There are no exclusions based on either the number of non–left main lesions or the Syntax Score.

Study stents

Synergy everolimus-eluting platinum-chromium stent. The Synergy stent has a platinum-chromium platform with a strut thickness of 74 μm and a radial strength higher than cobalt-chromium and stainless steel platforms.[15,16] This stent is coated on the abluminal side with a biodegradable poly(DL-lactide-coglycolide) layer which is hydrolyzed to carbon dioxide and water over a period of 120 days. This polymer is mixed with an everolimus dose that is similar to that of Xience stents (1 μg/mm^2) and that is released over a period of 90 days. The stent received Conformité Européenne mark on October 31, 2012. The Synergy stent is manufactured by Boston Scientific and is available in sizes of 2.25, 2.5, 2.75, 3.0, 3.5, 3.5, and 4.0 mm and in lengths of 8, 12, 16, 20, 24, 28, 32, and 38 mm. Compared with the Xience stents, there are no specific deployment requirements for the Synergy stent. The Synergy stent itself is also the subject of registered currently recruiting trials such as EVOLVE short DAPT (NCT02605447) and SENIOR (NCT02099617), which will provide further data on clinical outcomes.

Xience everolimus-eluting cobalt-chromium stent. The Xience everolimus-eluting cobalt-chromium stent platform has a strut thickness of 81 μm and consists of 3 types: Xience V, Xience Prime, and Xience Xpedition.

Figure



Study flow diagram. DOCE indicates device-oriented composite end point; ST, stent thrombosis.

The stent is coated with a formulation containing everolimus embedded in a nonerodible polymer. The polymer is loaded with 1 μg/mm^2 of everolimus with a maximum nominal drug content of 232 μg. All Xience stent systems use an identical stent and stent-contacting balloon materials and identical drug-coating formulations and drug-dosing densities. The Xience stent is manufactured by Abbott Vascular and is available in sizes of 2.25, 2.5, 2.75, 3.0, 3.25, 3.5, and 4.0 mm and in lengths of 8, 12, 15, 18, 23, 28, 33, and 38 mm.

Study drugs

Preprocedural and periprocedural medication. Patients will be treated with anticoagulation therapy according to local hospital practice. In case of patients presenting with ACS, the following periprocedural

Table 1. Inclusion and exclusion criteria

Inclusion criteria

1. Patient has an indication for revascularization of the LMCA in accordance with ESC guidelines.
2. Patient has been discussed in the Heart Team with the cardiac surgeon before PCI, after which patient is accepted for PCI.
3. Patient's age is at least 18 y.
4. Patient understands and accepts the meaning and aims of the study and is willing to provide written informed consent.
5. Patient is willing to comply with specified follow-up evaluation and can be contacted by telephone.

Exclusion criteria

1. Patient is not able to receive antiplatelet treatment due to contraindications.
2. Patient has a known allergy to acetylsalicylic acid, clopidogrel, prasugrel, or ticagrelor.
3. Patient is in cardiogenic shock at the time of treatment.
4. Patient had an ST-elevation MI within the 5 d before treatment.
5. Patient has planned surgery within 12 mo after treatment.
6. Patient has a history of bleeding diathesis or active major bleedings.
7. Patient had surgery within 15 d before treatment.
8. Patient participates in other trial, which did not yet reach its primary end point.
9. Patient has a life expectancy of <12 mo.
10. Patient has a hypersensitivity or contraindication to everolimus or structurally related compounds, cobalt, chromium, nickel, tungsten, acrylic, and fluoropolymers.
11. Patient is female with childbearing potential not taking adequate contraceptives or is currently breastfeeding.

loading doses are required: aspirin 200-500 mg (if not previously on aspirin treatment) and either clopidogrel 300-600 mg or ticagrelor 180 mg or prasugrel 60 mg.

Postprocedural medication. For the Synergy stent group, the duration of DAPT will be 4 months, which is the time required for the polymer to be resorbed, and for the Xience stent group, the duration of DAPT will be 12 months. In patients on long-term oral anticoagulation due to a preexisting condition (eg, atrial fibrillation), the duration of triple therapy will be 4 months for the Synergy stent group and 6 months for the Xience stent group,[30] but the treating physician is allowed to reduce this time if the patient is at high risk for bleeding.

Study procedures

Pre-PCI and PCI procedure. Eligible patients will receive oral and written information concerning the study. Written and signed informed consent is required before any study-specific procedure. Patients will undergo standard coronary angiography to identify the target lesion. Treatment of other lesions is allowed and the treatment order is at the operator's discretion, but it is advised to use the same stent type as the study stent. Usual standards of care will be followed when performing the procedure. If a staged procedure is planned, treatment of the non–target vessel should be performed within 30 days, again preferably using the same stent type as the study stent.

Predilatation of the target lesion is recommended but left to the discretion of the operator. Standard stenting procedures will be performed according to the local routine practice. For LMCA bifurcation lesions, treatment strategy is per operator discretion. Provisional stenting with side branch opening is the preferred option, but 2-stent approaches (T-stenting, TAP, Culotte, and Crush) are all acceptable. All procedural complications and adverse events will be recorded throughout the implant procedure.

Intravascular ultrasound. Intravascular ultrasound will be performed after stent implantation and possible postdilatation, as recommended.[31,32] Postdilatation will aim to achieve a minimum stent area of >8.5 mm^2 in the carina and >5.5 mm^2 in the ostium of the left anterior descending and circumflex arteries. The IVUS analyses will be explorative and performed at the study sites because these are not mandatory and not randomized.

Optical coherence tomography. Optical coherence tomography is a catheter-based technology producing ultra-high-resolution, cross-sectional, intravascular images from backscattered infrared signals. It has a resolution of 5 to 20 μm, which is higher than IVUS and enables optimal plaque identification, detection of thin tissue structures (eg, reendothelialization, neointimal proliferation, and dissections), and visualization of stent struts.[33] Baseline OCT will not be performed. Based on test runs subject to quality control by the core laboratory and the feasibility of performing the OCT protocol procedure in the specified time frame, 5 sites have been selected to perform post-PCI OCT at 3 months. Optical coherence tomography of the stented region of the target vessel including 5 mm proximal and distal will be performed in 100 patients. It will be performed with the St Jude Lightlab C7 Dragonfly Imaging Catheter (St Paul, MN). Optical coherence tomography analyses will be performed by an independent core laboratory.

Follow-up period. Evaluation before discharge will be performed and will include the assessment of adverse events and medication as well as an electrocardiogram. Patients will be followed up for a total of 60 months after PCI with assessments at 3, 6, 12, 24, 36, 48, and 60 months (see Figure). The assessments at 36, 48, and 60 months may be conducted via telephone or (e-)mail. A 3-month follow-up, coronary angiography and OCT will be performed following local protocols in a subset of 100 patients.

Study definitions

Baseline variables will include gender, age, height, weight, complete medical history, all medication used up to 3 months before enrollment, and laboratory assessments.

Death will be considered cardiac unless an unequivocal noncardiac cause can be established. Unwitnessed death and death of unknown cause will be considered cardiac. Death will be considered vascular when due to cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, aortic dissection, or any other vascular cause. Death will be classified as noncardiovascular when the cause is not covered by the above definitions (including

death due to infection, sepsis, pulmonary causes, accident, or suicide). Myocardial infarction will be defined according to the third universal definition, and periprocedural myocardial infarction according to the Society for Cardiovascular Angiography and Interventions criteria.[34,35] Definite, probable, and possible stent thrombosis and the location of revascularizations will be adjudicated per the Academic Research Consortium definitions.[28] Bleeding will be assessed in accordance with the BARC definitions.[29]

Statistical considerations

Statistical analyses. The trial will be powered for noninferiority testing of the primary end point between patients enrolled in the Synergy stent group with short-duration DAPT vs the Xience stent group with longer-duration DAPT. The primary analysis will be performed at 24 months after the index procedure and will be based on the principle of intention to treat. Baseline characteristics will be compared between both treatment groups using the Wilcoxon rank sum test or analysis of variance test based on their distributions. Categorical variables will be compared between groups using the likelihood-ratio χ^2 test or Fisher exact test. Estimation of the cumulative MACE rate will be performed using the Kaplan-Meier method and events between treatment groups will be compared by the log-rank test. Using a proportional hazards model, hazard ratios with 95% CIs will be calculated as Synergy arm vs Xience arm, with values >1 indicating increased hazard in the Synergy arm. The proportionality assumptions will be checked by visual estimation after plotting the log cumulative hazard vs (log) time at follow-up after index procedure and by applying a test for nonproportional hazards using the Schoenfeld residuals.[36] For secondary end points, differences in absolute outcome values (incidences) will be statistically tested between groups by using Fisher exact test or Pearson χ^2 test. Two-sided 95% CIs of the difference in percentages between treatments will be calculated using exact methods. Kaplan-Meier estimates and survival curves will be displayed along with log-rank test results.

The effect measure is the risk difference expressed as the difference in the MACE rate among patients randomized to treatment with the Synergy stent to that among patients treated with the Xience stent at 24 months. Noninferiority will be achieved if the upper limit of the 1-sided 95% CI of the absolute risk difference is less than the noninferiority margin of 7.5%. If noninferiority has been established, superiority testing will be performed, as well as calculation of 2-sided 95% CIs, both applied to the intention-to-treat population. Statistical analysis will be performed by Diagram B.V. (Zwolle, the Netherlands) using SPSS 20.0 (SPSS, Chicago, IL) or SAS 9.2 (SAS, Cary, NC). All statistical tests will be interpreted at a 2-sided significance level of .05 and all CIs at a 2-sided level of 95%.

Sample size justification. The primary end point for the study is the 24-month MACE rate, expressed as the proportion of patients who experience MACE within 730 days after randomization. We anticipate a 20% incidence of the primary end point in both groups. This assumption is based on the 1- and 5-year major adverse cardiac and cardiovascular event rates (15.8% and 36.9%) of the SYNTAX left main substudy,[2,5] the 18-month major adverse cardiac and cardiovascular event rate (8.9% for an everolimus-eluting stent and 10.8% for a sirolimus-eluting stent) of the PRECOMBAT-2 study,[4] the 1-year TVR rate (19.6%) of "the Milan experience,"[37] and the 2-year combined end point of death and TVR (17.2%) of the MAIN-COMPARE study.[38] These studies compared PCI to CABG for uLMCA treatment. Studies evaluating 2 different stents for uLMCA treatment showed similar event rates. The 2-year combined end point of death, MI, and TVR of the ISAR-LEFT MAIN study was 21.3% for a paclitaxel-eluting stent and 20.6% for a sirolimus-eluting stent.[39] In the ISAR-LEFT MAIN 2 study, the same end point was 17.5% for a zotarolimus-eluting stent and 14.3% for an everolimus-eluting stent after 1 year of follow-up.[40] As such, for the IDEAL-LM trial, a 20% MACE rate at 2 years was considered realistic.

The primary objective of the trial is to establish the noninferiority of the Synergy stent relative to the Xience stent for prevention of MACE. The effect measure is the risk difference expressed as the difference in the MACE rate among patients randomized to treatment with the Synergy stent (index, r_1) to that among patients randomized to treatment with the Xience stent (control, r_0). The null hypothesis is that the risk difference ($r_1 - r_0$) is larger than or equal to the specified noninferiority margin of 7.5%. The alternative hypothesis is that the difference in the MACE rate is less than 7.5%. The null hypothesis of inferiority of the Synergy stent to the Xience stent will be rejected if the upper bound of 95% CI of risk difference ($r_1 - r_0$) falls below 7.5%. With 409 patients per arm (a total study population of 818 patients), the study has 85% power to reject the null hypothesis of inferiority of the Synergy stent to the Xience stent. The inclusion of 818 patients was completed on September 30 2016.

Study organization and data management

Data collection/data management/record keeping. The imaging analyses will be performed by an independent core laboratory (Cardialysis, Rotterdam, the Netherlands). A data safety monitoring board will be appointed to assess the safety of the patients participating in the study. Because blinding is not possible because of differences in stent appearance and duration of DAPT, a CEC will be appointed to adjudicate all clinical study end point events. The clinical source documents will be redacted in such a way that members of the CEC will be unaware of the treatment arm the patient has been

assigned to. This process is overseen by a contract research organization that is responsible to provide blinded data to the CEC. The sponsor reserves the right to stop the study if this is the recommendation of the data safety monitoring board and/or CEC.

Summary

IDEAL-LM is a prospective, randomized, multicenter study that will compare the 2-year efficacy and safety of the novel Synergy stent followed by 4 months of DAPT to the commonly used Xience stent followed by 12 months of DAPT in patients with an indication for PCI of an uLMCA. The study will provide novel insights into the optimal treatment strategy for uLMCA disease (www.clinicaltrials.gov NCT02303717).

Disclosures

The authors have no personal conflicts of interest to declare related to this study. Boston Scientific provided institutional research support for monitoring, core laboratory analysis, and independent clinical event adjudication. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the manuscript, and its final contents.

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