Optical coherence tomography-guided coronary stent implantation compared to angiography: a multicentre randomised trial in PCI – design and rationale of ILUMIEN IV: OPTIMAL PCI

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KEYWORDS

- intravascular ultrasound
- optical coherence tomography
- stent optimisation
- percutaneous coronary intervention

Abstract

Aims: Randomised trials have demonstrated improvement in clinical outcomes with intravascular ultrasound (IVUS)-guided percutaneous coronary intervention (PCI) compared with angiography-guided PCI. The ILUMIEN III trial demonstrated non-inferiority of an optical coherence tomography (OCT)- versus IVUS-guided PCI strategy in achieving similar post-PCI lumen dimensions. ILUMIEN IV is a large-scale, multicentre, randomised trial designed to demonstrate the superiority of OCT- versus angiography-guided stent implantation in patients with high-risk clinical characteristics (diabetes) and/or complex angiographic lesions in achieving larger post-PCI lumen dimensions and improving clinical outcomes.

Methods and results: ILUMIEN IV is a prospective, single-blind clinical investigation that will randomise between 2,490 and 3,656 patients using an adaptive design to OCT-guided versus angiography-guided coronary stent implantation in a 1:1 ratio. The primary endpoints are: (1) post-PCI minimal stent area assessed by OCT in each randomised arm, and (2) target vessel failure, the composite of cardiac death, target vessel myocardial infarction, or ischaemia-driven target vessel revascularisation. Clinical follow-up will continue for up to two years. The trial is currently enrolling, and the principal results are expected in 2022.

Conclusions: The large-scale ILUMIEN IV randomised controlled trial will evaluate the effectiveness of OCT-guided versus angiography-guided PCI in improving post-PCI lumen dimensions and clinical outcomes in patients with diabetes and/or with complex coronary lesions. Trial registration: NCT03507777

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Abbreviations

DES drug-eluting stent
EEL external elastic lamina
IVUS intravascular ultrasound
MSA minimal stent area
OCT optical coherence tomography
PCI percutaneous coronary intervention
TVF target vessel failure

Introduction

Angiography, the most commonly used imaging modality to guide percutaneous coronary intervention (PCI), has several known limitations, including imprecision in determining plaque morphology, vascular remodelling, and atherosclerosis burden[1,2]. It is suboptimal in identifying stent underexpansion, malapposition, thrombus, residual dissection, and plaque protrusion[3]. These limitations can partly be overcome by intravascular ultrasound (IVUS)[1,2], which allows cross-sectional tomographic imaging of the vessel wall. Findings from large observational cohort studies, randomised trials, and meta-analyses have shown that, by achieving larger luminal dimensions compared with angiography guidance, IVUS-guided drug-eluting stent (DES) implantation reduces major adverse cardiovascular events, including target lesion revascularisation, stent thrombosis and cardiac mortality[4-8]. Despite these results and guideline recommendations[9], IVUS-guided PCI remains infrequently used. Difficulty in image interpretation due to relatively low axial resolution (50-200 μm), poor discrimination of plaque subtypes, additional procedural time and incremental cost are often cited as principal reasons for low IVUS adoption rates.

Optical coherence tomography (OCT) is a newer intravascular imaging modality that provides rapid acquisition of higher resolution images (10-20 μm) compared with IVUS, thus allowing more accurate identification of thrombus, lipid, calcium, fibrous cap thickness, dissections, plaque prolapse, stent malapposition, and strut coverage (although tissue penetration depth is lower with OCT than with IVUS)[10]. OCT also measures luminal and stent dimensions more accurately than IVUS[11]. Nonetheless, few studies of OCT-guided stenting have been performed[10,12]. In the ILUMIEN III randomised controlled trial, in patients with non-complex lesions, an OCT-specific stent sizing and optimisation strategy was safe and non-inferior to IVUS and angiography guidance with respect to post-PCI luminal dimension, the primary endpoint of the trial. Moreover, OCT was superior in achieving larger stent expansion compared with angiography[3]. The ILUMIEN IV trial was thus designed to assess whether this OCT-guided PCI strategy would result in improved clinical outcomes compared with angiographic guidance, driven by an increased minimal stent area (MSA).

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Methods

OBJECTIVE AND STUDY DESIGN

ILUMIEN IV is a prospective, single-blind randomised controlled trial assigning subjects to OCT- versus angiography-guided coronary stent implantation in a 1:1 ratio **(Figure 1)**. The objective of the trial is to demonstrate the superiority of OCT-guided PCI in (a) achieving larger acute post-PCI lumen dimensions, and (b) improving cardiovascular outcomes in patients with diabetes and/or complex lesions. The clinical investigation is being conducted at approximately 100 centres in North America (USA and Canada), Europe, Middle East, and Asia-Pacific. Up to 3,656 randomised patients and approximately 375 roll-in patients will be enrolled. The expected duration of patient recruitment is approximately two years and all enrolled patients will be followed for two years. The total duration of the study is expected to be five years. The trial was designed by the principal investigators, steering committee, and sponsor (Abbott, Santa Clara, CA, USA) and is registered at ClinicalTrials.gov (unique identifier: NCT03507777). The trial is funded by Abbott. Since the initiation of the study in March 2018, one formal protocol amendment has been submitted and approved by the US FDA.

STUDY POPULATION, INCLUSION AND EXCLUSION CRITERIA

The key general and angiographic inclusion/exclusion criteria for enrolment in the ILUMIEN IV trial are shown in **Supplementary Table 1**. Briefly, using an adaptive design, between 2,490 and 3,656 patients undergoing clinically indicated PCI with XIENCE everolimus-eluting stents (Abbott Vascular, Santa Clara, CA, USA) will be enrolled if they have either (a) high-risk clinical features, defined as medication-treated diabetes mellitus, and/or (b) one or more complex lesions, defined as:

i. A target lesion responsible for either
   - Non–ST-segment myocardial infarction, defined as a clinical syndrome consistent with an acute coronary syndrome and a minimum troponin of 1 ng/dL (may or may not have returned to normal), or
   - ST-segment myocardial infarction >24 hours from the onset of ischaemic symptoms

ii. Long or multiple lesions, defined as intended total stent length (continuous or separated) in any single target vessel ≥28 mm.

iii. A bifurcation lesion intended for treatment with a stent in both the main branch and side branch wherein the side branch stent is ≥2.5 mm in diameter by angiographic visual estimation.

iv. Angiographic severe calcification, defined as visible calcification on both sides of the vessel wall in the absence of cardiac motion.

v. A chronic total occlusion; randomisation is permitted only after successful crossing with antegrade wire escalation and predilatation.

vi. Diffuse or multifocal pattern in-stent restenosis with lesion at or within the existing stent margin(s).

The principal rationale for inclusion of complex target lesions and/or diabetic patients in the ILUMIEN IV trial was to include a study population in whom the event rate after contemporary DES implantation is still suboptimal despite angiographic guidance. Identification of the candidate target lesions and clinical risk characteristics was based on an analysis of pooled individual patient

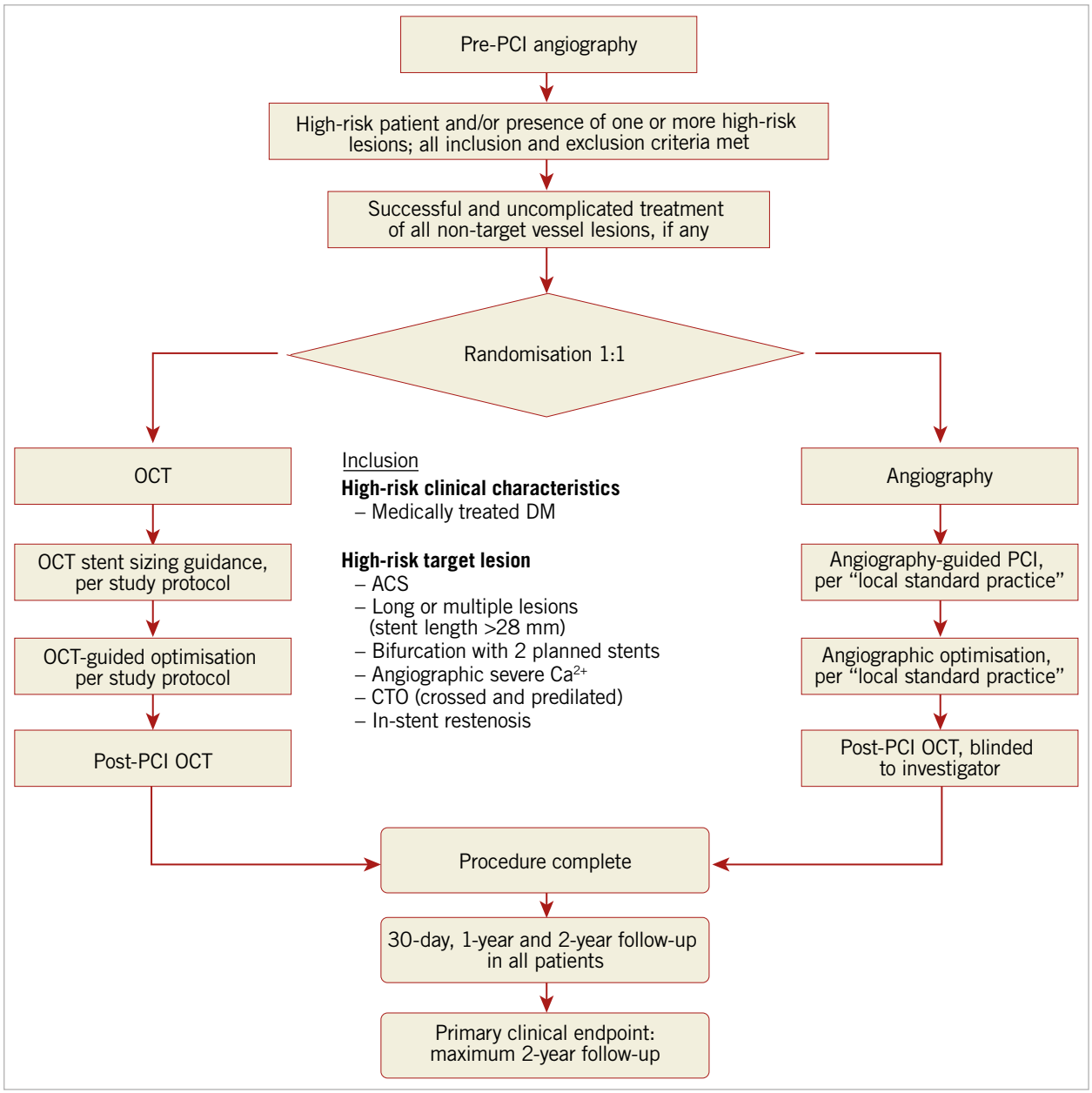

Figure 1. *Patient flow for screening, randomisation, and follow-up in the ILUMIEN IV trial. OCT: optical coherence tomography; PCI: percutaneous coronary intervention*

randomised controlled trial and registry data[13,14] **(Supplementary Table 2)**, as described in **Supplementary Appendix 1**. Patients with advanced chronic kidney disease (creatinine clearance ≤30 ml/min/1.73 m^2) and not on dialysis are excluded due to the risk of contrast-induced nephropathy; however, patients with end-stage renal disease on dialysis are eligible for enrolment. Patients with ST-segment myocardial infarction within 24 hours of symptom onset are excluded because of the relatively high rates of non-analysable pre-PCI OCT acquisitions due to high thrombus burden, inefficacy of thrombectomy to reduce the thrombus burden, and poor blood clearance[15]. Of note, very long lesions, multiple complex coronary lesions, including in-stent restenosis, bifurcation lesions, and chronic total occlusions were excluded from the ILUMIEN III trial. The superior resolution of OCT would be expected to be of greater clinical impact in this complex subset of lesions in which the risk of stent failure is higher than in non-complex lesions, especially in high-risk patient cohorts such as diabetics[16]. Thus, the principal hypothesis of the ILUMIEN IV trial is that, in patients with diabetes and/or complex coronary lesions, the better morphologic lesion characterisation, superior procedural planning, and enhanced DES optimisation (correcting suboptimal results and major procedural complications) afforded by OCT compared with angiography will result in improved acute procedural results and superior long-term clinical outcomes.

In addition to the inclusion criteria of diabetic patients and/or complex lesion characteristics, target lesions must have a visually

estimated or quantitatively assessed diameter stenosis of ≥70% or diameter stenosis ≥50% plus non-invasive or invasive evidence of ischaemia or haemodynamic significance, or be deemed to be the culprit lesion responsible for a biomarker-positive acute coronary syndrome (e.g., presence of plaque disruption or thrombus). Based on visual estimation on pre-PCI angiography, the estimated stent diameters must be ≥2.5 mm and ≤3.5 mm. This criterion is mandated in order to comply with the US FDA instructions for the use of coronary OCT systems, and to exclude stent implantation in very small target vessels that are frequently located at the distal ends of the arteries where the rapid-exchange length of the OCT catheter may preclude imaging of diseased segments. In addition, these criteria exclude stent implantation in very large target vessels for which stent failure rates are recognised to be relatively low with angiographic guidance alone[13]. Nonetheless, if the measurements on OCT are outside the visually estimated angiographic diameter range, stent sizing and post-dilatation will be based on the OCT measurements, following the detailed study protocol. Up to two target lesions requiring PCI may be present in any single target vessel, with a maximum of two target vessels in one subject allowed for randomisation. Thus, up to four randomised target lesions per patient in a maximum of two target vessels, including major side branches, may be included. The intended target lesions will be declared prior to randomisation. Complex multivessel coronary disease with a SYNTAX score ≥33 is excluded unless the Heart Team, including a cardiac surgeon, concludes that PCI is appropriate (e.g., the surgical risk is too high). Left main coronary target lesions are excluded.

PRIMARY ENDPOINTS AND SAMPLE SIZE CALCULATION

There are two separately powered co-primary endpoints, both of which must be met to declare trial success **(Supplementary Table 3)**. (1) The imaging endpoint is the final post-PCI MSA per target lesion assessed by OCT (a blinded OCT run will be performed in the angiography-guided arm after all interventions) by an independent imaging core laboratory masked to treatment allocations. (2) The clinical co-primary endpoint is target vessel failure (TVF), defined as the composite of cardiac death, target vessel myocardial infarction, or ischaemia-driven target vessel revascularisation, assessed at up to two years **(Supplementary Table 3)**. Clinical events will be monitored on-site, and an independent clinical events committee will adjudicate all events after review of original source documents, blinded to treatment assignment.

The imaging hypothesis of the study is that OCT guidance is superior to angiography guidance in achieving a larger final MSA. The post-PCI MSA has repeatedly been shown to be the strongest and most consistent stent-related parameter to predict DES clinical outcomes[17-25]. To detect a minimum difference in MSA of 0.4 mm^2 with a standard deviation of 2.2 mm^2, 1,600 subjects randomised 1:1 to OCT versus angiography will provide 95% power to detect superiority with a one-sided α of 0.025. After 1,600 subjects are enrolled, the primary endpoint of MSA will be internally assessed between the groups by a blinded committee. If a larger MSA in the OCT-guided arm is demonstrated, the trial will continue enrolling subjects to assess the clinical co-primary endpoint. Otherwise, the trial may be terminated for futility. The final MSA endpoint will be tested and reported in all subjects in whom a stent was implanted.

The clinical hypothesis is that OCT guidance is superior to angiography guidance with respect to TVF rates at two years. The sample size is based on an assumption of cumulative TVF rates in the angiography-guided arm at one and two years of 8.0% and 12.0%, respectively. The basis for these rates is provided in **Supplementary Appendix 2**, **Supplementary Table 4** and **Supplementary Table 5**. To detect a 35% reduction in hazard with OCT guidance, assuming a 5% rate of loss to follow-up each year, 2,490 subjects randomised 1:1 to OCT guidance versus angiography guidance would provide 85% power to demonstrate superiority with a one-sided α of 0.025. When 50% of the anticipated TVF events have occurred (n=194), the data safety monitoring board will decide whether sample size adjustment is needed. If the interim analysis indicates the need for a sample size increase, enrolment will be adjusted up to a total of 3,656 subjects in an adaptive design[26].

PRE-SPECIFIED SECONDARY ENDPOINTS

If both primary imaging and clinical endpoints are met, numerous secondary endpoints will be examined, categorised as: i) procedural measures; ii) angiographic measures (based on core laboratory quantitative coronary angiography); iii) OCT-defined measures (based on core laboratory quantitative OCT assessments); iv) clinical outcomes (assessed at 30 days, one year, and two years); v) patient-reported outcomes; and vi) costs and cost-effectiveness analyses. A detailed description of the secondary endpoints is provided in **Supplementary Table 3**.

OCT IMAGE ACQUISITION AND STENT OPTIMISATION PROTOCOL

Intravascular OCT is performed using a commercially available system (the ILUMIEN™ OPTIS™, OPTIS Integrated, and OPTIS Mobile systems; Abbott Vascular) that incorporates a rapid exchange catheter (Dragonfly™ DUO, Dragonfly™ OPTIS™, Dragonfly™ OpStar™ Imaging Catheter; Abbott Vascular) and an integrated pullback system (18-36 mm/s), acquiring images at high (~15 μm) axial resolution with blood displacement. Images are acquired after predilation, if necessary, and after administration of intracoronary nitroglycerine. The automated OCT-angiography co-registration (where available) will be used to guide PCI in the OCT arm of the study according to the stent sizing and optimisation algorithm, slightly modified from the methodology described in the ILUMIEN III trial[3]. The algorithm includes measurement of the external elastic lamina (EEL)-based vessel diameter in the proximal and distal reference segments, and has been designed to achieve larger stent dimensions and more complete lesion coverage than would occur with sizing to the proximal and distal reference lumens[3]. An overview of the OCT-guided stent optimisation algorithm and details for post-implant stent

optimisation are summarised in **Figure 2**. A step-by-step description of OCT image acquisition to guide procedure planning and decision making together with several representative examples are provided in **Supplementary Appendix 3** and **Supplementary Figure 1-Supplementary Figure 6**.

In brief, the proximal and distal reference mean EEL-based diameters will be measured, and the distal reference EEL diameter will be rounded down to the nearest available stent size (usually in 0.25 mm increments) to determine stent diameter. If the EEL cannot be adequately visualised, the stent diameter is chosen using the

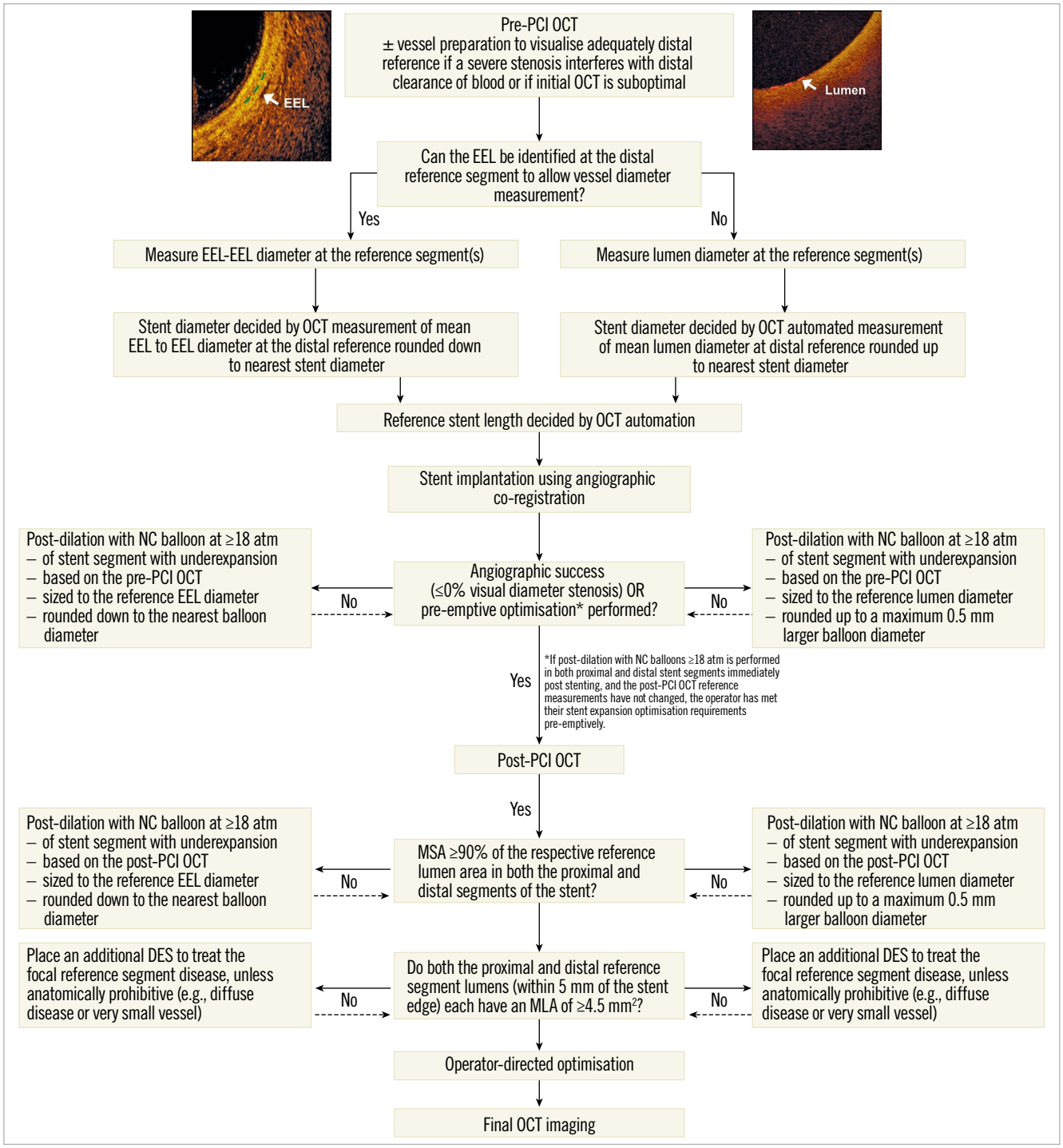

Figure 2. *The algorithm for OCT-guided PCI optimisation in ILUMIEN IV. OCT-guided assessment pre-PCI through stent implantation. Vessel diameter must be assessed as the EEL-EEL diameter at the reference segments, unless the EEL cannot be identified, in which case luminal measures are used. OCT-guided optimisation post stent implantation is described per EEL-based diameter measurement and per lumen-based diameter measurement. EEL: external elastic lamina; MLA: minimal lumen area; MSA: minimal stent area; NC: non-compliant; OCT: optical coherence tomography*

mean lumen diameter at the distal reference rounded up to the next stent size. Stent length will be determined by the distance from distal to proximal reference site using the OCT automated lumen detection feature. After stent deployment, optimisation will be performed with non-compliant balloons in the proximal and distal segments of the stent based on the respective EEL or lumen diameter measurements by rounding down (EEL) or up (lumen) to the nearest non-compliant balloon size. Following optimisation, OCT imaging will be repeated and, if necessary, iterative high-pressure or larger non-compliant balloon inflations performed, based on new reference segment measurements, in an attempt to achieve acceptable stent expansion (an MSA of at least 90% in both the proximal and distal segments of the stent relative to the closest reference segment). Following OCT-guided stent expansion optimisation, the proximal and distal reference segments, defined as 5 mm from the edges of the stent, are examined for inflow/outflow disease. If both the proximal and distal reference segments have a minimal lumen area ≥4.5 mm^2, no further treatment is necessary. If there is untreated reference segment disease defined as a focal minimal lumen area <4.5 mm^2 in either proximal or distal reference segments following the additional OCT run, an additional DES must be implanted unless anatomically prohibitive (e.g., biological vessel tapering, distal diffuse disease, absence of landing zone). If there is a major edge dissection, defined as ≥60° of the circumference of the vessel at the site of dissection and ≥3 mm in length, it is recommended that additional DES be placed to correct the abnormality unless anatomically prohibitive.

To ensure that the participating sites follow the detailed study protocol, rigorous training was provided during the preparatory and roll-in phases of the trial. The investigators performed online training in which they were required to interpret images and perform measurements based on the study protocol. Investigators also attended in-person training conducted by the principal investigators or a sponsor representative trained directly by the principal investigators and were required to pass an in-person examination using the commercial OCT software prior to enrolment. Additionally, an online system for monitoring protocol compliance with the OCT-guidance procedures is utilised whereby the OCT core laboratory rapidly assesses the images received and sends a report back to the study sites within 72 hours to provide feedback. The report includes the core laboratory OCT measurements and determination of any minor or major protocol violations. If major protocol violations were present, the operator will be asked to stop enrolling participants until they receive further training. If an operator accrues three major protocol violations, they may be asked to withdraw from the study although their previously enrolled randomised patients will remain in the study for intention-to-treat analysis.

DATA COLLECTION AND ANALYSIS

Quantitative analyses of the data will be performed at OCT and angiography core laboratories (Cardiovascular Research Foundation, New York, NY, USA). All primary and secondary endpoints and their relationship to OCT use or the PCI procedure are adjudicated to pre-specified definitions by an independent clinical events committee (Cardiovascular Research Foundation) after review of original source documents, except for site-reported secondary endpoints specified in **Supplementary Table 3**. Data management and study analyses are performed by the sponsor. Details of the planned statistical analyses appear in **Supplementary Appendix 4**. The primary analysis will be intention-to-treat, but a separate per protocol analysis will be performed as a sensitivity analysis. Missing data will be left missing. Imputation for the co-primary endpoints of MSA or TVF will not be performed. The principal investigators and chairman have complete access to the database and accept responsibility for the design and conduct of the study, all study analyses, and the drafting and editing of the principal and subsequent reports.

Discussion

By providing detailed visualisation of vessel architecture and accurate measurement of vessel dimensions, OCT offers the potential to improve acute PCI results and subsequent clinical outcomes compared to the standard angiography guidance. The ILUMIEN IV trial is designed to establish superiority of OCT-guided PCI in achieving larger luminal dimensions post PCI and clinical superiority of the OCT guidance strategy in lowering TVF in patients with diabetes and/or complex lesions treated with contemporary DES.

Limitations

Since this is a trial design manuscript, there are no limitations to specify at this time.

Conclusions

The trial is currently recruiting, with 1,650 patients enrolled at the time of manuscript submission. The principal results of ILUMIEN IV are expected in 2022.

Impact on daily practice

ILUMIEN IV is a large randomised trial that will determine whether OCT guidance will improve post-PCI luminal dimensions and clinical outcomes compared with the standard angiography guidance in patients with diabetes and/or complex coronary lesions.

Funding

ILUMIEN IV is funded by Abbott (Santa Clara, CA, USA).

Conflict of interest statement

Z.A. Ali reports institutional research grants to Columbia University and Cardiovascular Research Foundation from Abbott and Cardiovascular Systems Inc., being a consultant for Abbott, Amgen, AstraZeneca, Abiomed, Boston Scientific, Cardinal Health, Opsens Medical, and ACIST Medical, holding equity in Shockwave Medical, and receiving grants from the National Heart,

Lung and Blood Institute. U. Landmesser reports being a consultant for Abbott, Boston Scientific, and Biotronik. A. Maehara reports grant support from Abbott Vascular and Boston Scientific, and being a consultant for Conavi Medical Inc. M. Matsumura reports being a consultant for Terumo Corporation. G. Guagliumi reports institutional grant support from Abbott Vascular, Boston Scientific, Infraredx, and St. Jude Medical, and being a consultant for Abbott Vascular, Boston Scientific, and St. Jude Medical. M.J. Price reports consulting fees and speaker's honoraria from Abbott Vascular, AstraZeneca, Boston Scientific, Chiesi USA, and Medtronic, consulting fees from W.L. Gore & Associates, and ACIST Medical, and grants (to the institution) from Daiichi Sankyo. J.M. Hill reports personal fees, grants and equity in Shockwave Medical, and personal fees and grants from Abbott Vascular, Boston Scientific and Abiomed. T. Akasaka reports honoraria and grants from Abbott Vascular Japan, and Daiichi-Sankyo Pharmaceutical Inc., and institutional grants from Boston Scientific, Nipro and Terumo. F. Prati reports consultant honoraria from Abbott Vascular and Amgen. H.G. Bezerra reports institutional grant support from Abbott Vascular, and consulting fees and honoraria from Abbott Vascular, Medtronic, and Abiomed. W. Wijns reports institutional grant support from Endotronix and HealthWatch, personal fees from MicroPort, and being a co-founder of Argonauts, an innovation facilitator and medical advisor of Rede Optimus Research. Gary S. Mintz reports honoraria from Boston Scientific, Philips, Terumo, and Medtronic. R.J. McGreevy, Z. Zhang, R.J. Rapoza and N.E.J. West are employees of Abbott Vascular. N.E.J. West is a stockholder in Abbott. G.W. Stone reports speaker or other honoraria from Cook, Terumo, Qool Therapeutics and Orchestra Biomed, being a consultant to Valfix, TherOx, Vascular Dynamics, Robocath, HeartFlow, Gore, Ablative Solutions, Miracor, Neovasc, V-Wave, Abiomed, Ancora, MAIA Pharmaceuticals, Vectorious, Reva, and Matrizyme, and holding equity/options from Ancora, Qool Therapeutics, Cagent, Applied Therapeutics, Biostar family of funds, SpectraWave, Orchestra Biomed, Aria, Cardiac Success, MedFocus family of funds, and Valfix. O. Ben-Yehuda reports being an employee of the Cardiovascular Research Foundation, which has received research grants from Abbott Vascular. The other authors have no conflicts of interest to declare.

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Supplementary data

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Supplementary Table 2. Relative risks of one-year target vessel failure in patients with high-risk clinical and lesion characteristics.

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Supplementary Table 4. Summary of one-year target vessel failure rates reported for high-risk subgroups.

Supplementary Table 5. Summary of two-year target vessel failure reported for high-risk subgroups.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-20-00501

Supplementary data

Supplementary Appendix 1. Study population, inclusion and exclusion criteria

The general and angiographic inclusion/exclusion criteria for enrolment in the ILUMIEN IV trial are summarised in **Supplementary Table 1**.

Rationale for inclusion criteria in ILUMIEN IV

Trials included in the analysis

To perform a comprehensive, patient-level pooled analysis, we combined data from seven prospective, randomised, controlled trials and one registry maintained at the Cardiovascular Research Foundation (New York, NY, USA) in which follow-up of patients treated with contemporary DES was available for at least one year. As the purpose of the analysis was to assess the rates of target lesion/vessel failure with contemporary DES, only patients treated with second- or third-generation DES in those studies were included in the analysis. Target vessel failure (TVF) was defined as cardiac death, target vessel MI, or target vessel revascularisation. Endpoints were evaluated at one year.

The following seven trials and single registry were included in the analysis: A Trial of Everolimus-Eluting Stents and Paclitaxel-Eluting Stents for Coronary Revascularization in Daily Practice (COMPARE); A Prospective, Randomized, Multicenter Trial to Assess an Everolimus-Eluting Coronary Stent System (PROMUS Element) for the Treatment of up to Two De Novo Coronary Artery Lesions (PLATINUM); A Clinical Evaluation of the Investigational Device XIENCE V Everolimus Eluting Coronary Stent System (EECSS) in the Treatment of Subjects With de Novo Native Coronary Artery Lesions (SPIRIT III); DUrable Polymer-based STent CHallenge of Promus Element Versus ReSolute Integrity (DUTCH PEERS); Randomized Multicenter Trial in All Comers Population Treated Within Eastern NeThErlands-2 (TWENTE II); Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System in the Treatment of Subjects With de Novo Native Coronary Artery Lesions (SPIRIT IV); Comparison of the Everolimus Eluting (XIENCE-V, XIENCE-Prime or PROMUS Stent) With the Biolimus A9 Eluting NOBORI Stent in All-comers (COMPARE II); and the Assessment of Dual Antiplatelet Therapy With Drug-Eluting Stents (ADAPT-DES). All patients had reached the one-year follow-up period.

Statistical analysis

The independent predictors of events were determined by multivariable Cox regression, adjusted by study, with the number of variables for each model sparingly chosen according to their historical relationship to each outcome measure in prior studies to avoid overfitting (at least 10 events per variable). Variables entered into the model are as follows: age, sex, diabetes, hypertension, hyperlipidaemia, prior coronary artery bypass grafting (CABG), prior MI, prior PCI, body mass index, clinical presentation-ACS (STEMI, NSTEMI), moderate/severe calcification, bifurcation lesions, chronic total occlusion, long lesions, in-stent restenosis, chronic kidney disease, American College of Cardiology (ACC) class C lesion, reference vessel diameter, percent diameter stenosis, and total stent length. The results of the analysis are summarised in **Supplementary Table 2**.

Supplementary Appendix 2. Primary and secondary endpoints and definitions

The list of primary and secondary endpoints and their definitions are summarised in **Supplementary Table 3**.

Estimation of effects on minimal stent area (MSA) in sample size calculations

We used a threshold of 0.4 mm^2 for the difference in MSA between OCT- and angiography-guidance arms in our study size calculations based on superiority of OCT versus angiography guidance. This threshold was determined from the mean difference between the OCT and angiography arms in the ILUMIEN III trial: OCT 6.18±2.17 mm^2 and angiography 5.77±1.92 mm^2, p=0.12. This threshold for OCT guidance to achieve larger MSAs is thus appropriate to determine "futility" of continuing the recruitment in the pre-determined interim analysis.

Estimation of target vessel failure (TVF) rates in sample size calculations

Assumptions made in estimation of overall TVF rates included the following. Prevalence of the high-risk subgroups in the ILUMIEN IV population was assumed as 30% for acute coronary syndromes (ACS), 5% for severe calcification, 15% for long/multiple lesions, 10% for bifurcations, 30% for diabetes mellitus, 5% for chronic total occlusion (CTO) and 5% for in-stent restenosis (ISR). The subgroup percentages sum to 100%, and no adjustments were made for subject occurrence in multiple subgroups. In publications where TVF was not reported, the reported rate of target lesion failure (TLF) was multiplied by 1.2 to calculate an adjusted TVF value. Reported nine-month data in some publications were multiplied by 5/4 to calculate an adjusted one-year rate.

The supporting data for one-year TVF, summarised in **Supplementary Table 4**, are from 16 published studies. The one-year subgroup TVF rates determined from the literature were 9.0% for ACS, 16.4% for severe calcification, 8.8% for long/multiple lesions, 11.0% for bifurcations, 5.8% for diabetes mellitus, 8.3% for CTO and 11.0% for ISR. The weighted overall one-year TVF rate was calculated as 8.7%. The supporting data for two-year TVF, summarised in **Supplementary Table 5**, are from seven published studies and unpublished results from the ADAPT-DES trial (N=8,582). The two-year literature search did not include any bifurcation articles, therefore the assumptions for subgroup prevalence in ILUMIEN IV were adjusted to 30% for ACS, 10% for severe calcification, 20% for long/multiple lesions, 30% for diabetes mellitus, 5% for CTO and 5% for ISR. The two-year subgroup TVF rates determined from the literature were 10.3% for ACS, 16.4% for severe calcification, 10.6% for long/multiple lesions, 16.2% for diabetes mellitus, 13.0% for CTO and 26.2% for ISR. The weighted overall two-year TVF rate was calculated as 13.7%.

A clinical judgement was made to lower slightly the assumed event rates compared to the historical data summarised above in order to account for improvement in clinical outcomes over time. Thus, the TVF rates for the angiographic arm in ILUMIEN IV were assumed to be 8% at one year and 12% at two years. Since this is a randomised trial, deviation from the assumed rates should not impact on the clinical meaningfulness of the conclusion as long as superiority can be established. The OCT-guided arm is expected to have a reduction of 35% in hazard ratio compared to the angiography-guided arm. This was a conservative estimate based on the risk reduction from two large randomised controlled trials comparing IVUS- to angiography-guided PCI of approximately 50% [6,7].

Supplementary Appendix 3. OCT- and angiography-guided procedures

The following is a description of the image acquisition and treatment steps to be used during the index percutaneous coronary intervention (PCI) procedure.

Pre-PCI angiography and angiographic criteria for target lesions

Intracoronary (IC) nitrates should be administered prior to diagnostic angiography for both arms of the study, unless precluded by low blood pressure. Anticoagulation for imaging and PCI must be achieved with either unfractionated heparin, bivalirudin or enoxaparin, with or without glycoprotein IIb/IIIa inhibitors, according to local standard of care, prior to insertion of any guidewire for imaging or PCI in a coronary artery.

For inclusion in the trial, a planned use of stents and post-dilatation balloons with visually estimated diameters of ≥2.5 mm and ≤3.5 mm based on the pre-PCI angiographic images is required. After assessment of predilatation and/or stent implantation result, usage of post-dilatation balloons outside of this diameter range is allowed per investigator judgement. This instruction applies to both the OCT-guided and angiography-guided arms. The purpose of this restriction is to limit enrolment to lesions where OCT guidance is most likely to provide benefit, eliminating very large and small vessels which have inherently low and high target failure rates, respectively, and stay within the OCT instructions for use.

Randomisation to angiography-guided stenting

If the patient is randomised to angiography-guided stent implantation, PCI will be performed and optimised with angiography guidance according to local standard practice. At the end of the stenting procedure, a blinded OCT must be performed. This blinded OCT run is for study purposes only – the operator may not view the OCT results and may not make additional treatment decisions on the basis of this OCT image acquisition. To do so will be considered a major protocol violation.

Randomisation to OCT-guided stenting

If the patient is randomised to OCT-guided stent implantation, stenting will be performed with OCT guidance according to a slightly modified version of the ILUMIEN III: OPTIMIZE PCI algorithm [3]. The overall procedural approach for OCT-guided stent implantation and post-implant optimisation can be found in the flow charts in **Figure 2** in the main article, respectively. A detailed, case-based guidance for performance of the PCI procedures is described below together with several representative examples **(Supplementary Figure 1–Supplementary Figure 6)**.

OCT image acquisition

OCT acquisition is required pre- and post-stent implantation for patients randomised to OCT-guided stent implantation. IC nitrate must be administered for each target vessel treated prior to each OCT image acquisition, unless precluded by low blood pressure.

If the imaging catheter will not cross the lesion prior to stenting, vessel preparation (balloon predilatation – standard, cutting or scoring balloon, or atherectomy), with or without a guide extension catheter, may be used to facilitate OCT imaging catheter passage prior to stenting. In the event the OCT catheter cannot pass despite adequate lesion preparation facilitated with a guide catheter extension, the investigator should perform the intervention as per local standard of care and follow the OCT-guided algorithm following stent placement. In the event that the OCT catheter cannot pass even after stent placement,

treatment should be per local standard of care. Intravascular ultrasound must not be used in the target vessel in either the OCT-guided or angiography-guided arm except as a bail-out strategy for emergent, life-threatening conditions such as acute closure without obvious cause.

For subjects in the OCT arm, it is recommended that imaging is performed using the motorised pullback device at 75 mm pullback, five frames per mm over 2.1 secs for OCT. If possible, the imaging run should start at least 1 cm distal to the angiographic extent of the lesion and continue until the end of image acquisition for OCT. For standard pullback using power injectors (recommended), the recommended contrast injection volume is 14 ml at an injection rate of 4 ml/s in the left coronary artery and 12 ml at an injection rate of 3 ml/s in the right coronary artery. For large vessels, injecting contrast at 4 ml/sec for four seconds and thus a total of 16 mL of contrast is recommended. For operators using manual injection, the recommended contrast injection volume is 14 ml in the left coronary artery and 12 ml in the right coronary artery.

If available, the OPTIS Integrated System angiographic co-registration function should be utilised. If OCT angiography co-registration is not available, during the OCT pullback, a cine angiogram in the desired angiographic view(s) must be acquired so that the utility of delivered contrast is maximised and that the OCT pullback can be co-registered with the angiogram by visual estimation.

Following completion of stenting in the target vessel (of one or two target lesions), when the angiographic appearance is considered optimal and all interventional equipment would be otherwise removed, a post-PCI OCT run is performed. If additional PCI is required and performed based on the findings of the post-PCI OCT acquisition (to optimise the result based on the OCT findings per the modified OPTIMAL PCI algorithm [3]), an additional OCT run must be performed to record the impact of the OCT-guided optimisation.

For any bifurcation within a lesion, where the side branch is visually estimated to be ≥2.5 mm, the branch must be protected with a guidewire during PCI to prevent abrupt closure, irrespective of whether it is planned for provisional or two-stent strategy. In the case of a two-stent bifurcation lesion, pre-stent OCT imaging is required in both the main and side branches, but post-stent OCT imaging is required in the main branch only. Post-stent OCT imaging in the side branch is recommended but not mandated. For evaluation of stent expansion in the side branch of two-stent bifurcation lesions, minimal stent area (MSA) in the side branch will be compared to the distal reference in the side branch (i.e., dividing the stented segment in the side branch into segments is not required).

Selection of the stent diameter by OCT

Stent diameter will be determined by measuring the distal reference external elastic lamina (EEL) to EEL diameter, if visible by OCT (which was the case in 77% of distal reference segments in the ILUMIEN III: OPTIMIZE PCI [3]). Examples of EEL and lumen-based measurements are shown in **Supplementary Figure 1-Supplementary Figure 3**.

The EEL need not be contiguous for the purpose of choosing stent diameter. If there is sufficient EEL present on either side of the vessel to allow measurement through the middle of the vessel (**Supplementary Figure 1C, Supplementary Figure 1C'**), the EEL can and should be preferentially used to choose the stent diameter.

The stent diameter must be chosen using the EEL to EEL diameter(s) at the distal reference, rounded down to the next stent size. For example, if the distal reference EEL measures 3.2 mm x 3.1 mm, the mean EEL is 3.15 mm, and thus a 3.0 mm stent diameter should be chosen**.** If the EEL is equal to an

existing stent size, the stent chosen should be equal to the EEL measurement and no rounding down is required.

If the distal reference EEL cannot be identified, the stent diameter should be chosen using the mean lumen diameter at the distal reference, rounded up to the next stent size. For example, if the distal reference lumen measures 2.5 mm×2.6 mm, the mean lumen diameter is 2.55 mm, and thus a 2.75 mm stent diameter should be chosen**.** If the lumen diameter is equal to an existing stent size, the stent chosen should still be the next larger stent size - i.e., rounding up is always required if lumen-based measurements are used.

If a XIENCE stent of the appropriate diameter is commercially available but not in stock at the study site, a XIENCE stent diameter must be used that will adequately expand with post-dilatation to the intended dimensions; usually this will be the next smaller stent diameter. If that XIENCE diameter size is also not available, another drug-eluting stent of the appropriate diameter may be used.

In cases where the luminal border cannot be adequately visualised by OCT, the reference sites and stent size (length and diameter) will be determined by angiography.

For inclusion in the trial, a planned use of ≥2.5 mm and ≤3.5 mm stents and post-dilatation balloons based on pre-PCI angiographic visual estimation is required. If after pre-PCI OCT assessment it is determined from the measurement protocol described above that stents and/or balloons larger (or smaller) than this diameter range should be used, this adjustment is allowed and appropriate diameter stents and/or post-dilatation balloons must be used per the OCT protocol guidance. In the long tapering lesions, the use of large balloons should be limited to the segment of the stent where the EEL diameter measurements are at least as large as the stent or balloon diameter.

There must be an intent to implant a stent in all target lesions (i.e., planned stent implantation). However, if OCT assessment of a target lesion with in-stent restenosis (ISR) shows that the predominant mechanism of the ISR is underexpansion (not neointimal hyperplasia), then balloon only treatment without additional stent is allowed. Additionally, in the infrequent instances where implantation of a stent is deemed unnecessary based on the OCT imaging after enrolment of the patient (e.g., certain culprit lesions of ACS such as spontaneous dissection, embolism or plaque erosion), the patient will remain in the study and the data will be used in the intention-to-treat analysis.

Assessment of the target lesion length by OCT

The proximal and distal reference segments are initially identified by angiography and then confirmed by performing preprocedural OCT pullback across the target segment (**Figure 2** in the main article). In cases in which a severe stenosis would interfere with distal clearance of blood, or if the lumen border at both (proximal and distal) reference segments cannot be detected by OCT, vessel preparation is strongly recommended with balloon dilatation or other modalities (e.g., cutting balloon, atherectomy, thrombectomy, etc.) as deemed necessary by the operator, followed by OCT imaging.

When the lumen borders at both reference segments can be measured, the reference cross-section will be selected at the sites with the largest lumen using the OCT Lumen Profile software where sufficient external elastic lamina is visible to allow measurement of stent diameter. This is typically situated several mm away from the angiographic lesion shoulders. If sufficient EEL cannot be visualised at the initially chosen reference cross-section, the reference cross-section is adjusted ±5 mm to identify a cross-section where the EEL is visible sufficiently to allow stent diameter measurement per protocol. The stent length will be determined by automatic measurement from the distal to the proximal reference site using the OCT Lumen Profile software. The automated length should be adjusted on the side of the artery which is

more normal to a XIENCE stent length **(Supplementary Figure 3)**. If a XIENCE stent of appropriate length is commercially available but not in stock at the study site, an alternative drug-eluting stent of the appropriate length may be used. Overlapping XIENCE stents must only be used for planned treatment of long lesions where a XIENCE stent of appropriate length is not available.

Stent implantation and initial optimisation

Stent implantation should be guided by angiographic co-registration, if available. Positioning stents at the intended segments can be confirmed with angiographic co-registration to improve the accuracy of stent placement and reduce geographic miss **(Supplementary Figure 4)**.

After initial stent deployment and angiographic optimisation procedures (including post-dilatation and/or additional stents as necessary), if the visually assessed residual angiographic diameter stenosis is >0%, OCT-guided PCI optimisation based on the pre-PCI OCT run should be performed to achieve this angiographic target. Post-dilatation should be performed in the angiographic segment with visually assessed diameter stenosis >0% using non-compliant balloons at ≥18 atmospheres with diameters no larger than the closest pre-PCI OCT mean reference vessel EEL (if the EEL is visible) **(Figure 2, Supplementary Figure 2)**, or, if the EEL was not measurable, up to 0.5 mm larger than the closest pre-PCI OCT mean reference lumen diameter **(Figure 2, Supplementary Figure 2)**. If post-dilation is performed pre-emptively, prior to the post-PCI OCT using the above algorithm, the post-dilation requirements have been met pre-emptively. If there is underexpansion in one or more locations within the stented segment, post-dilatation should be limited to the underexpanded location(s) using short focal balloon(s) (6–8 mm in length) with a diameter that is appropriately matched to the vessel size at that location.

OCT after stent implantation

The overall flow chart for post-implant stent optimisation per EEL diameter and per lumen diameter is shown in **Figure 2** in the main article.

If, after initial stent deployment (including post-dilatation and/or additional stents as necessary), the visually assessed residual angiographic diameter stenosis is ≤0%, or pre-PCI OCT-guided optimisation has already been performed, OCT images are acquired to determine whether acceptable stent expansion is achieved (defined as MSA of the proximal segment ≥90% of the proximal reference lumen area and MSA of the distal segment ≥90% of the distal reference lumen area) **(Figure 2, Supplementary Figure 5, Supplementary Figure 6)**. If, based on the post-PCI OCT run, acceptable stent expansion is not achieved, regardless of whether or not this is associated with major malapposition, post-dilatation must be performed in the segment(s) with underexpansion using non-compliant balloons at ≥18 atmospheres with the balloon diameter no larger than the closest post-PCI OCT reference vessel EEL to EEL diameter (if the EEL is visible), or up to 0.5 mm larger than the closest post-PCI OCT mean reference lumen diameter (if the EEL is not measurable) **(Figure 2)**. In situations where the reference EEL is very large (≥4.5 mm), the operator is asked to consider using the OCT automated mean reference segment lumen rounded up no more than 0.5 mm to select the post-dilation balloon. While it is recommended that further attempts be made until the protocol-defined optimal stent expansion is achieved, it is at the discretion of the operator to decide the number and extent of further interventions, at all times taking patient safety into consideration.

For PCI optimisation, whenever EEL-EEL measurement is possible, this measurement should be used rather than luminal measurements to optimise stent underexpansion. For example, if two opposing segments of EEL can be measured to choose the stent diameter at the distal reference but not the proximal reference, and both are underexpanded post PCI, the distal segment of the stent should be treated using

EEL-guided optimisation **(Figure 2)**, and the proximal segment of the stent should be treated using lumen-guided optimisation **(Figure 2)**.

Following OCT-guided optimisation of stent expansion, the proximal and distal reference segments, defined as 5 mm from the edges of the stent, are examined for inflow/outflow disease **(Supplementary Figure 6)**. If both the proximal and distal reference segments have an MLA ≥4.5 mm^2, no further treatment is necessary. If there is untreated reference segment disease defined as focal MLA<4.5 mm^2 in either proximal or distal reference segments following the additional OCT run, an additional drug-eluting stent must be placed unless anatomically prohibitive (e.g., vessel tapering, distal diffuse disease, absence of landing zone, etc.). If there is a major edge dissection, defined as ≥60 degrees of the circumference of the vessel at site of dissection and ≥3 mm in length, it is recommended that an additional drug-eluting stent be placed to correct the abnormality unless anatomically prohibitive, particularly at the distal stent edge (e.g., vessel tapering, distal diffuse disease, absence of landing zone, etc.).

If a long stent (≥28 mm) was required to cover the lesion such that the proximal and distal reference lumen dimensions were different by ≥0.5 mm, then multiple non-compliant balloons of different diameters should be chosen for proximal and distal inflation to achieve optimal stent expansion in each stent segment with underexpansion. If the underexpansion is located in the mid segment of a long stent (≥28 mm), post-dilatation within the middle segment should be performed with a balloon sized to the average of the proximal and distal reference measurements. Caution should be exercised in post-dilatation of long stented segments (≥28 mm) where the stent is located in a tapering vessel and/or where the stent covers multiple side branches. Caution should also be exercised in post-dilatation of lesions with severe calcification (especially calcific protruding nodule) or vessel angulation.

In the event of balloon-only treatment of ISR lesions (where stent underexpansion is the primary mechanism for ISR), acceptable stent expansion may be defined as minimal lumen area (MLA) of the proximal segment ≥90% of the proximal reference lumen area and MLA of the distal segment ≥90% of the distal reference lumen area.

If any additional PCI is performed (i.e., operator directed) on the study lesion, an additional OCT pullback with associated algorithmic assessment must be performed. A further final OCT is required if the algorithmic assessment required further PCI. The operator may not perform further PCI after the final OCT; however, prior to the final OCT, the operator may perform any PCI necessary. The operator may obtain feedback from a member of the team, such as a technician, nurse, study coordinator, etc., as to whether the final blinded OCT run was technically adequate, with good lumen clearance, capturing at least 10 mm distal and 10 mm proximal to the stented segment. Following the blinded OCT run, a final test coronary contrast injection or recorded cine angiogram may be taken to insure vessel patency without complications.

Multivessel PCI

Patients requiring multivessel PCI may be enrolled. Up to two target vessels may be randomised. Up to two non-target vessels may also be treated, but only one non-target vessel may be treated during the index procedure. In the case of triple vessel disease, at least one non-target vessel must be treated outside the index procedure.

The possible combinations of treated vessels during the index procedure are as follows:

1. One vessel PCI:

One target vessel randomised with one or two target lesions, all of which must be amenable to OCT-guided stenting.

2. Two vessel PCI:
i) two target vessels randomised each with one or two target lesions, all of which must be amenable to OCT-guided stenting.
ii) one non-randomised non-target vessel treated with no restriction on the number or types of lesion, but all must be treated successfully and without complication, followed by one target vessel randomised with one or two target lesions, all of which must be amenable to OCT-guided stenting.

Non-randomised lesions:

Non-randomised lesions requiring PCI in up to two non-target vessels may be treated either:

a) >30 days prior to the study procedure (in one or two non-target vessels) if the procedure was unsuccessful or complicated; or
b) >24 hours prior to the study procedure (in one or two non-target vessels) if the procedure was *successful and uncomplicated* defined as a final lesion angiographic diameter stenosis <30% for all treated non-target lesions, with TIMI 3 flow in these vessels, without perforation, cardiac arrest or need for defibrillation or cardioversion or hypotension/heart failure requiring mechanical or intravenous haemodynamic support or intubation, and with no post-procedure biomarker elevation >normal; or
c) during the study procedure (only one non-target vessel allowed), in which case all non-target vessel lesions must be treated prior to randomisation and such treatment must have been *successful and uncomplicated* (defined more stringently as angiographic diameter stenosis <10% for all treated non-target lesions, with TIMI 3 flow in the vessel, without final dissection ≥NHLBI type B, perforation anytime during the procedure, prolonged chest pain (>5 minutes) or prolonged ST-segment elevation or depression (>5 minutes), or cardiac arrest or need for defibrillation or cardioversion or hypotension/heart failure requiring mechanical or intravenous haemodynamic support or intubation); or
d) >48 hours after the index study procedure (in one or two non-target vessels).

There is no restriction on the number and type of non-target lesions that can be treated in a non-target vessel.

A second randomised target vessel:

Lesions requiring PCI in a 2nd target vessel (randomised lesions) may be treated during the index procedure (as long as no non-target vessels were treated during the same procedure) or staged >24 hours after the index procedure. However, all staged randomised procedures must be completed within two months (preferably one month) after the study procedure. The original treatment assignment must be used to guide all staged procedures.

In two-vessel disease where all vessels require treatment during the index procedure and both meet eligibility criteria and qualify as target vessels, it is permitted to designate one vessel as non-target and the other vessel as target at the investigator's discretion.

In three-vessel disease where all vessels meet the eligibility criteria and would qualify as target vessels, it is permitted to designate one of the three eligible vessels as non-target since no more than two target vessels may be randomised. However, it is encouraged to randomise two qualifying target vessels, unless the investigator's judgement dictates otherwise.

Supplementary Appendix 4. Interim analysis

After 1,600 subjects are randomised, the primary endpoint of MSA will be tested to compare OCT-guided and angiography-guided arms. If the superiority in the OCT-guided arm is demonstrated, the trial will keep enrolling subjects until the target number of TVF events has been adjudicated. Otherwise the Steering Committee will determine whether to terminate the trial for futility. If an interim analysis indicates that a sample size increase is required to maintain conditional power, the enrolment can be adjusted up to a total of 3,656 subjects.

Final statistical analysis

The primary analysis will include all randomised subjects. Subjects will be analysed on an intention-to-treat basis. A sensitivity analysis will be performed for per protocol analysis. There will be no imputations for missing values of the co-primary endpoints of MSA or TVF.

The primary imaging outcome: minimal stent area (MSA)

The mean of the MSA will be compared in the OCT- and angiography-guided arms. The two-sample t-test assuming equal variance at one-sided 2.5% significance level will be used to test the differences of the MSA between two arms. The equal variance assumption will be validated using the Folded F-test. If the Folded F-test is significant at a level of 0.05, an unequal variance t-test based on the Satterthwaite method will be used. The two-sample t-test requires the assumption of normality for each of the two arms. If the data fail to meet this assumption per the Shapiro-Wilk test, the superiority test will be carried out using a Wilcoxon rank-sum test. A linear mixed model will also be used to test the differences between two arms as additional analysis. The model will include treatment arm as fixed effect and random intercept in the subject level accounting for the correlation among the lesions within one subject. Significance must be demonstrated with both methods to claim superiority of OCT guidance compared with angiography guidance.

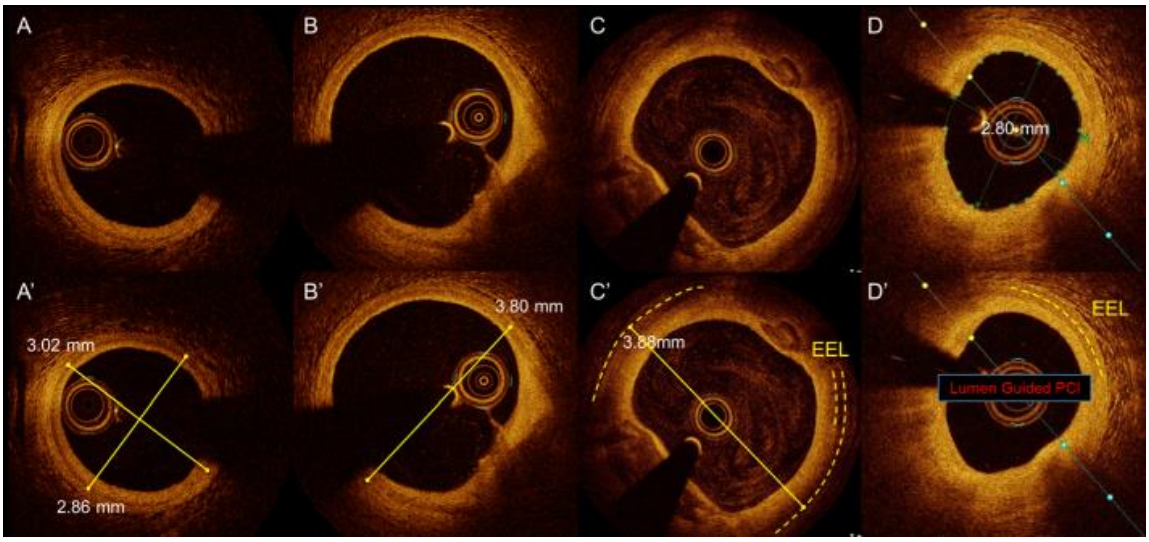
The primary clinical outcome: target vessel failure (TVF)

The rate of the co-primary endpoint of TVF is estimated as the time to the first TVF. Log-rank test will be performed for hypothesis testing. The analysis will be constructed from the day of randomisation (day 0) through the end of follow-up. For patients with events, the last follow-up date will be the day of the first documented TVF. For the patients without events, the last follow-up date will be the last study contact date recorded, which includes the last study visit, the last date of contact and the death date.

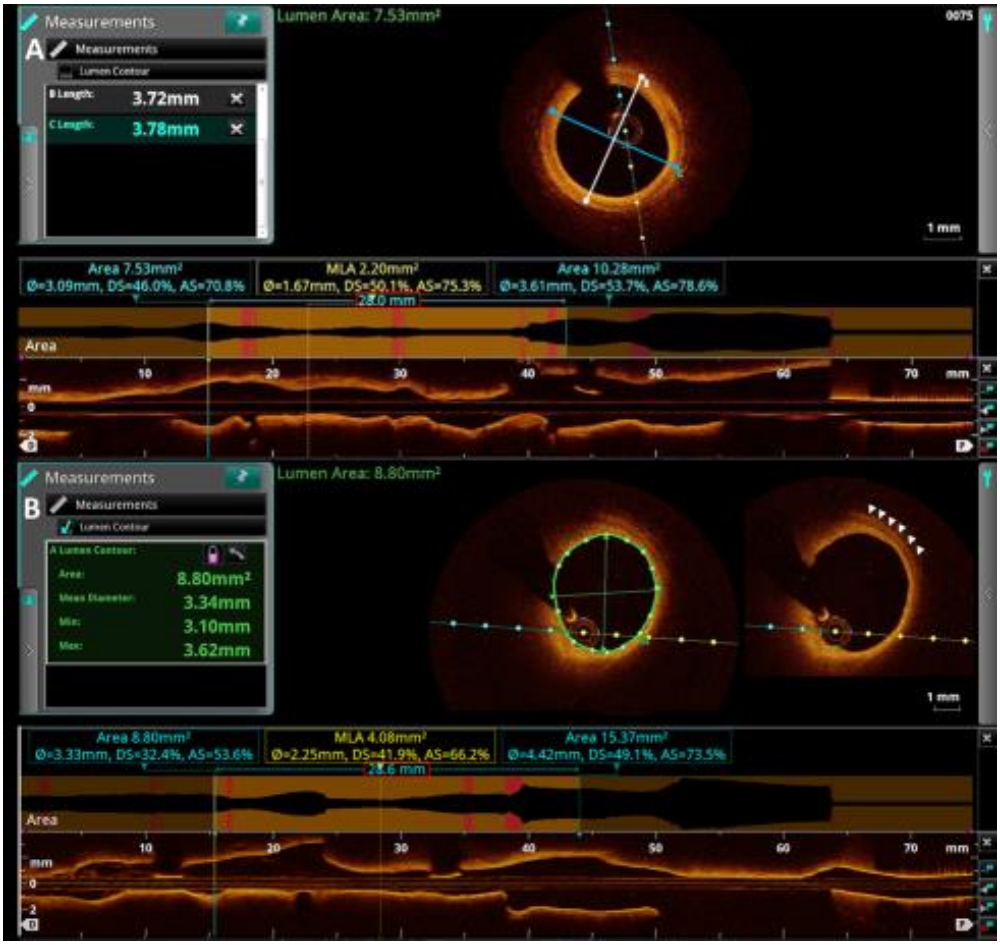
The probability of being free from the first documented TVF will be estimated using survival analysis (Kaplan-Meier method with Greenwood's standard error) by randomised arms.

A Cox regression model with one covariate of treatment arm will be used to test the proportional hazard assumption. The assumption will be assessed by SAS PROC PHREG using ASSESS statement. The baseline characteristics will be summarised and compared between the patients who complete the study and who are censored. The censoring distribution will also be checked between treatment groups.

If the assumption of proportional hazard is not satisfied, analysis for TVF will be based on the Com-Nougue approach which utilises the difference in Kaplan-Meier failure rate estimates. The power simulated for the primary endpoint based on the Com-Nougue approach was very similar to that calculated using the asymptotic approach (difference <0.5%). Therefore, for the powered calculation, an asymptotic test was used to approximate the power for the Com-Nougue approach using NCSS PASS 13.



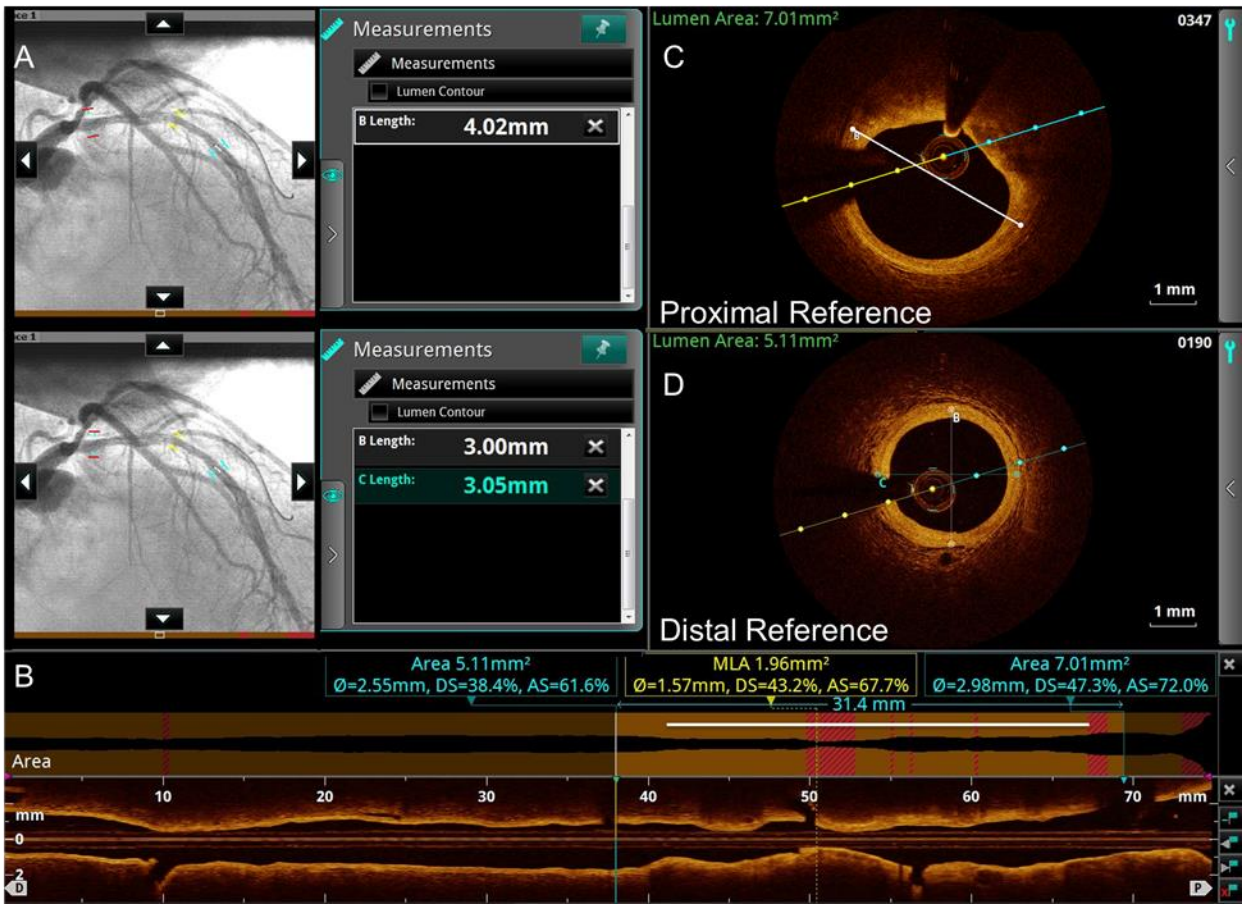
Supplementary Figure 1. EEL measurement for determination of stent diameter.
Stent diameter should be determined by measuring the distal reference mean EEL diameter, if visible by OCT, rounded down to the nearest available XIENCE stent diameter.
A-A'. The distal reference EEL measures 3.02 mm x 2.86 mm; the mean EEL is 2.94 mm, and thus a 2.75 mm diameter XIENCE stent should be chosen.
B-B'. If only a single EEL measurement is possible, this measurement should be used for determination of stent diameter. In this case the distal reference EEL measures 3.80 mm. Thus a 3.50 mm diameter XIENCE stent should be chosen.
C-C'. The distal reference EEL measures 3.88 mm. Note, a single EEL measurement is possible despite non-contiguous EEL measures. This measurement should be used for determination of stent diameter. Thus a 3.50 mm diameter XIENCE stent should be chosen.
D-D'. The distal reference EEL can only be measured on a single side of the vessel, precluding the use of the EEL for measurement of stent diameter. The mean lumen diameter, upsized to the closest stent size, should be used to determine stent diameter. In this case the lumen diameter was 2.98 mm x 2.61 mm; the mean lumen reference diameter was 2.80 mm, and thus a 3.00 mm XIENCE stent should be chosen.



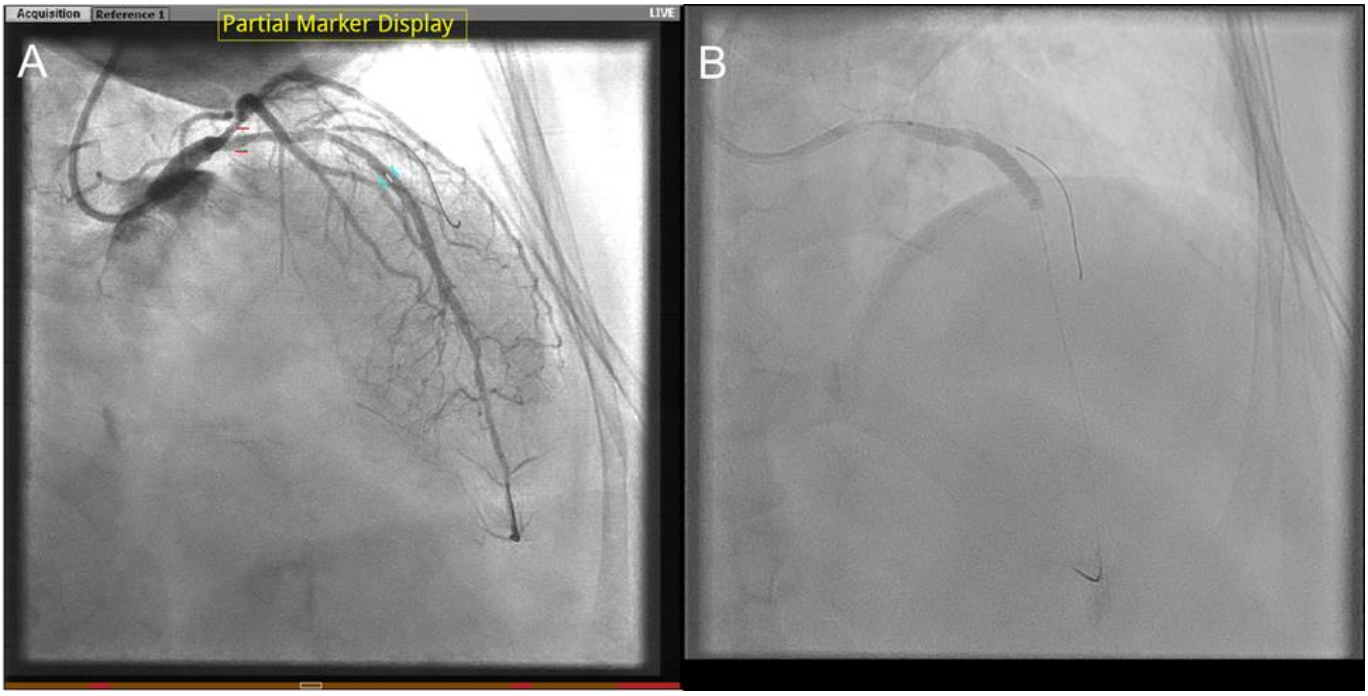
Supplementary Figure 2. OCT-guided stent sizing.
When the vessel diameter can be determined by EEL reference segment measurements, the mean EEL to EEL diameter should be used to determine stent diameter.

Example A. Two measurements of vessel diameter from EEL to EEL are shown using the measurement function: 3.72 mm (white text) and 3.78 mm (blue text) corresponding to the white and blue measurement lines on the OCT cross-section. Per protocol the mean of these two measurements ([3.72+3.78]/2=3.75 mm) is rounded down to the nearest stent size, and therefore a 3.5 mm diameter stent is chosen. The distance from distal to proximal reference (red box) is 28 mm, and thus a 3.5 x 28 mm XIENCE stent is chosen.
When the vessel diameter cannot be determined by measurement to the EEL, the mean lumen diameter should be used to determine stent diameter.

Example B. The EEL is only visible in a single quadrant of the OCT cross-section (white arrows). Automated measures identify the mean reference lumen diameter as 3.34 mm. Per protocol the mean lumen diameter is rounded up to the nearest stent size, and therefore a 3.5 mm diameter stent is chosen. The distance from distal to proximal reference (red box) is 28.6 mm, and thus a 3.5 x 28 mm XIENCE stent is chosen.

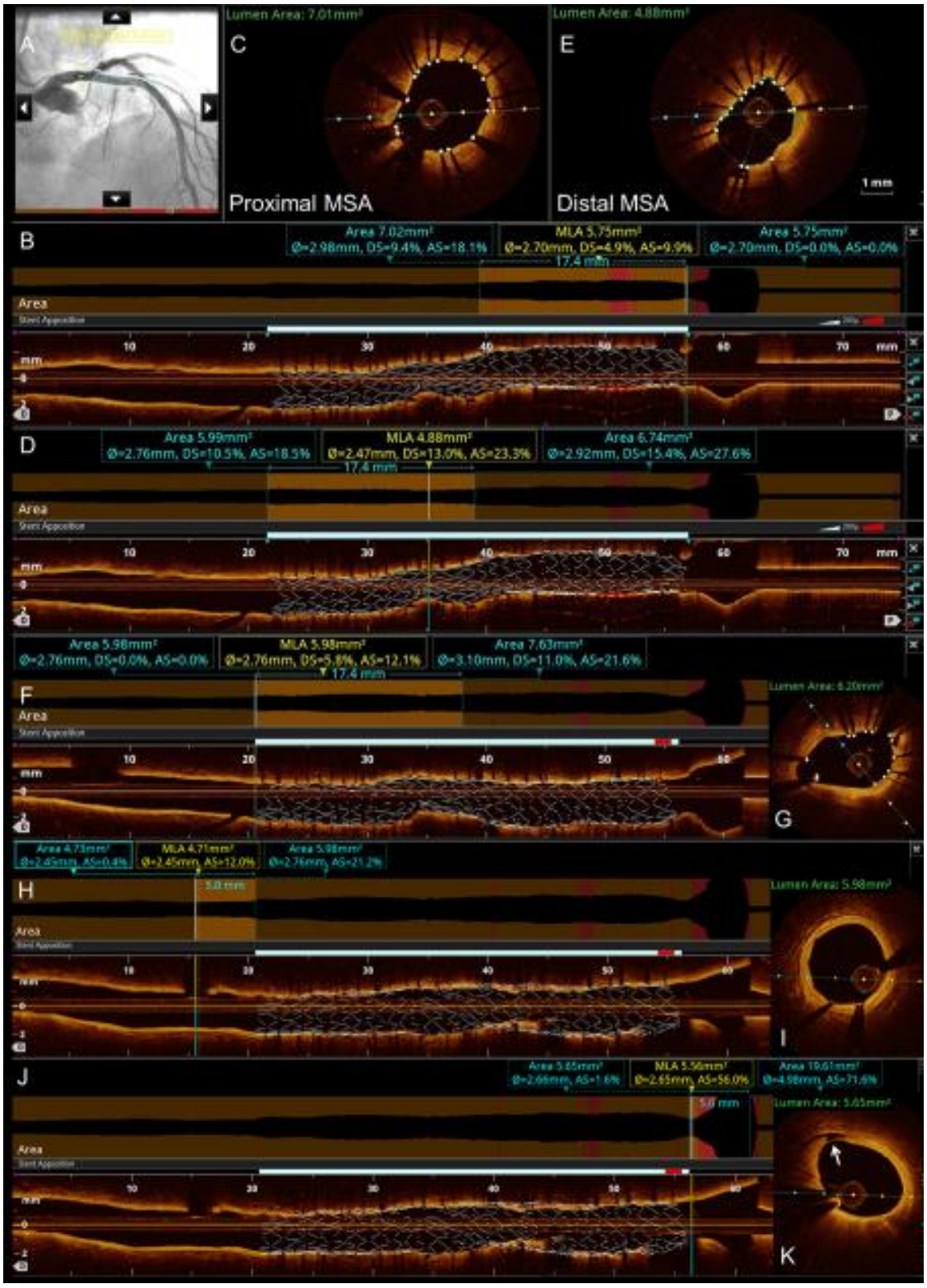


Supplementary Figure 3. Pre-PCI OCT with proximal and distal reference images.
A) OCT at baseline confirmed that the locations of the distal (blue) and proximal (red) reference segments as suggested by angiography were appropriate, being minimally diseased.
B) The lesion length was determined by OCT to be 28 mm (white bar). OCT cross-sectional images were scrolled from the edges of the lesion on either side to identify vessel segments with minimal disease and clearly identifiable EEL, resulting in the choice of a 33 mm long stent.
C) At the proximal reference segment approximately 180 degrees of EEL is visualised, allowing a single measurement of EEL for stent sizing through the middle of the vessel. The measured EEL diameter of the proximal segment (B, white line) was 4.02 mm. A mean EEL diameter could not be calculated as only one EEL measurement could be made.
D) At the distal reference segment 360 degrees of EEL are visualised, allowing multiple measurements of EEL for stent sizing. The measured EEL diameters of the distal reference segment were (B, white line) 3.00 mm and (C, blue line) 3.05 mm resulting in a mean EEL diameter of 3.03 mm. The smallest mean EEL diameter from both distal and proximal reference segments was 3.03 mm (distal reference) and per protocol this was rounded down to the nearest 0.25 mm and thus a 3.0 mm diameter by 33 mm long stent was chosen.

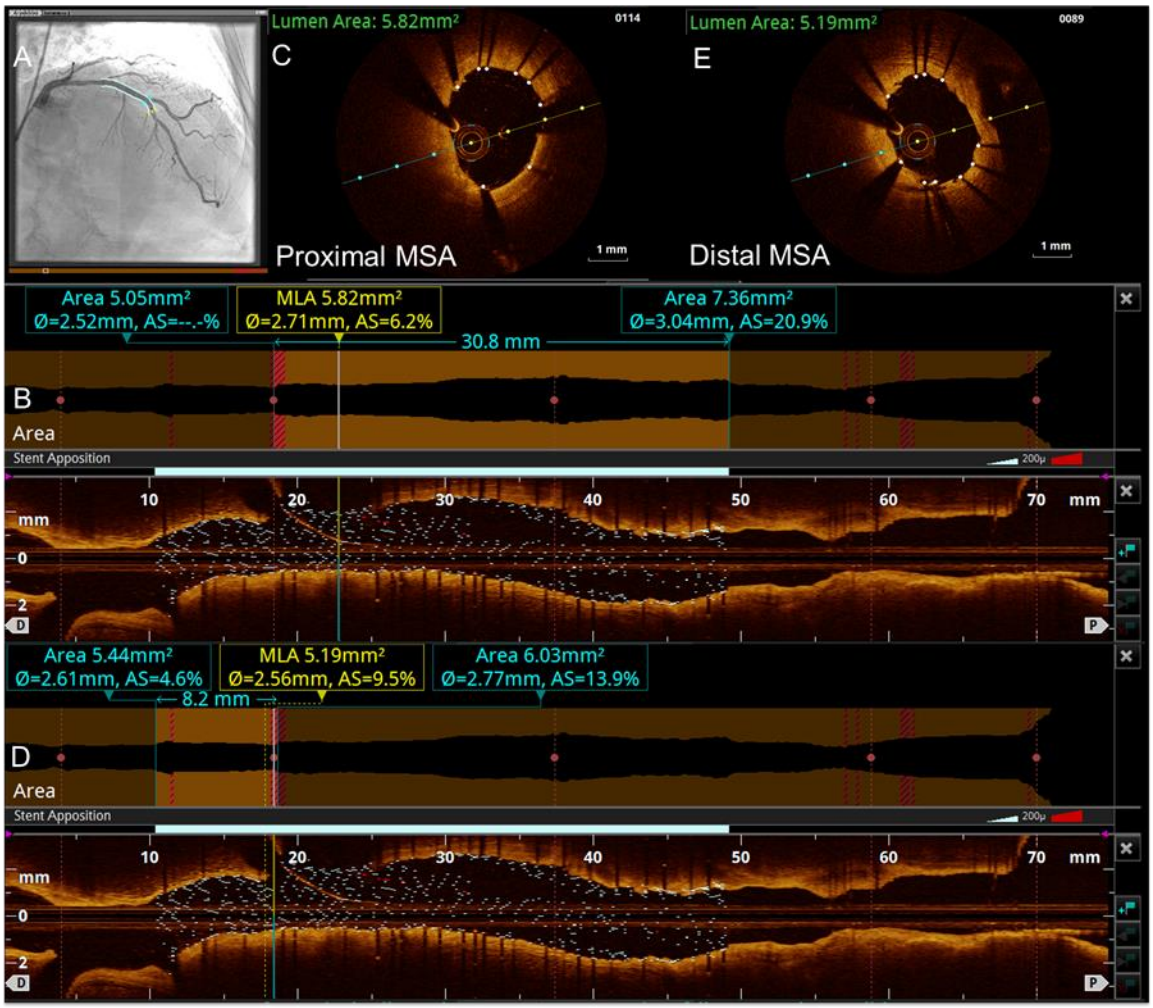


Supplementary Figure 4. Angiographic co-registration guided stent implantation.
A) OPTIS OCT angiographic co-registration is activated, allowing visualisation of the proximal reference (red marker in **Supplementary Figure 4A, Supplementary Figure 3C)** and distal reference (blue marker in **Supplementary Figure 4A, Supplementary Figure 3D)**, and used as a reference screen to guide stent placement.

B) Stent implantation location on real-time fluoroscopy is based upon the OPTIS OCT angiographic co-registration reference screen.


A
C
Lumen Area: 7.01mm²
Proximal MSA
E
Lumen Area: 4.88mm²
Distal MSA
1 mm
B
Area 7.02mm²
Ø=2.98mm, DS=9.4%, AS=18.1%
MLA 5.75mm²
Ø=2.70mm, DS=4.9%, AS=9.9%
Area 5.75mm²
Ø=2.70mm, DS=0.0%, AS=0.0%
17.4 mm
Area
Stent Apposition
10
20
30
40
50
60
70
mm
D
Area 5.99mm²
Ø=2.76mm, DS=10.5%, AS=18.5%
MLA 4.88mm²
Ø=2.47mm, DS=13.0%, AS=23.3%
Area 6.74mm²
Ø=2.92mm, DS=15.4%, AS=27.6%
17.4 mm
Area
Stent Apposition
10
20
30
40
50
60
70
mm
Area 5.98mm²
Ø=2.76mm, DS=0.0%, AS=0.0%
MLA 5.98mm²
Ø=2.76mm, DS=5.8%, AS=12.1%
Area 7.63mm²
Ø=3.10mm, DS=11.0%, AS=21.6%
17.4 mm
F
Area
Stent Apposition
10
20
30
40
50
60
mm
Lumen Area: 6.20mm²
G
Area 4.73mm²
Ø=2.45mm, AS=0.4%
MLA 4.71mm²
Ø=2.45mm, AS=12.0%
Area 5.98mm²
Ø=2.76mm, AS=21.2%
H
5.0 mm
Area
Stent Apposition
10
20
30
40
50
60
mm
Lumen Area: 5.98mm²
I
J
Area 5.65mm²
Ø=2.66mm, AS=1.6%
MLA 5.56mm²
Ø=2.65mm, AS=56.0%
Area 19.61mm²
Ø=4.98mm, AS=71.6%
5.0 mm
Area
Stent Apposition
10
20
30
40
50
60
mm
Lumen Area: 5.65mm²
K

Supplementary Figure 5. Post-PCI OCT with assessment of stent expansion.
Following baseline OCT for stent selection, predilatation with a 2.5 mm diameter x 15 mm compliant balloon at 12-14 atm was performed. Following this a 3.0 mm diameter x 34 mm drug-eluting stent was implanted at 12 atm.
A) Angiography revealed 0% residual diameter stenosis and per protocol OCT was repeated. Per protocol the stent length was divided in half and criteria for MSA assessed in each half.
B) In the proximal half of the stented segment,
C) automated measures measured an MSA of 7.01 mm^2 and a proximal reference lumen area of 5.75 mm^2 (blue and yellow box) equating to a residual AS of 0.0% ([[1-(7.01/5.75)] x100]=-21.9% area stenosis) confirming criteria for optimal MSA were met.
D) In the distal half of the stented segment,
E) automated measures measured an MSA of 4.88 mm^2 (yellow box) and a distal reference lumen area of 5.99 mm^2 (blue box) and thus stent expansion was unacceptable ([[1-(4.88/5.99)] x100]=18.5% area stenosis). Post-dilation was performed with a 3.0 mm diameter x 15 mm long non-compliant balloon focused to the area of underexpansion at >20 atmospheres.
F) Following post-dilation in the distal half of the stented segment,
G) automated measures measured an MSA of 6.20 mm^2 and a distal reference lumen area of 5.98 mm^2 (blue and yellow box) and thus stent expansion was optimal ([[1-(6.20/5.98)] x100]=-3.6% area stenosis).
H-K) OCT imaging post-stent demonstrated no major dissection, malapposition or tissue/thrombus prolapse. Arrow in panel K points to a minor dissection that does not need treatment with a DES.



Supplementary Figure 6. Post-PCI OCT in a long lesion with a non-target lesion bifurcation (provisional).

A) Angiography revealed 0% residual diameter stenosis, and thus per protocol OCT was repeated.

B) & C) Per protocol the stented segment was divided at the bifurcation, facilitated by 3D bifurcation mode highlighting bifurcations ≥1.5 mm (red dot in automated measures), and criteria for MSA assessed in each segment. In the proximal segment, automated measures found an MSA of 5.82 mm² (green text) and a proximal reference lumen area of 7.36 mm² (blue text) equating to a residual area stenosis (AS) of 20.9% ([[1-(5.82/7.36)] x100]=20.9%), confirming criteria for MSA were not met and that post-dilation and proximal optimisation technique need to be performed.

D) & E) In the distal stented segment, automated measures found an MSA of 5.19 mm² (yellow text) and a distal reference lumen area of 5.44 mm² (blue text), and thus stent expansion was acceptable ([[1-(5.19/5.44)] x100]=4.6% area stenosis, or 95.4% stent expansion).

Supplementary Table 1. Inclusion and exclusion criteria.

General inclusion criteria (all must be present)

1. Subject must be at least 18 years of age.
2. Subject must have evidence of myocardial ischaemia (e.g., stable angina, silent ischaemia [ischaemia in the absence of chest pain or other anginal equivalents], unstable angina, or acute myocardial infarction) suitable for elective PCI.
3. Subject must undergo planned XIENCE stent implantation during a clinically indicated PCI procedure.
4. Subject must provide written informed consent prior to any study-related procedure.

Angiographic inclusion criteria

Either criterion 1 and/or 2 must be present:

1. Target lesions in subjects who are clinically deemed to be high-risk from medically treated diabetes, OR
2. Complex lesion(s) with at least one target lesion in each target vessel planned for randomisation meeting at least one of the following criteria:
   i. Target lesion is the culprit lesion responsible for either:
      - NSTEMI, defined as a clinical syndrome consistent with an acute coronary syndrome and a minimum troponin of 1 ng/dL (may or may not have returned to normal), OR
      - STEMI >24 hours from the onset of ischaemic symptoms
   ii. Long or multiple lesions (defined as intended total stent length [continuous or separated] in any single target vessel ≥28 mm),
   iii. Bifurcation intended to be treated with two planned stents, where the planned side branch stent is ≥2.5 mm in diameter by angiographic visual estimation.
   iv. Angiographic severe calcification (defined as angiographically visible calcification on both sides of the vessel wall in the absence of cardiac motion),
   v. Chronic total occlusion (randomisation performed only after successful antegrade wire escalation crossing and predilatation),
   vi. Diffuse or multi-focal pattern in-stent restenosis at or within the existing stent margin(s).

Criteria 3-6 must all be present:

3. Target lesion(s) must be located in a native coronary artery with a visually estimated or quantitatively assessed %DS of ≥70% or ≥50%, respectively, plus one or more of the following:
   i. An abnormal functional test (e.g., invasive physiological lesion assessment, stress test) signifying ischaemia in the distribution of the target lesion(s) or
   ii. Biomarker positive acute coronary syndromes suggestive of plaque disruption or thrombus.
4. Target lesion(s) must be located in a native coronary artery with reference vessel diameter by visual estimation of ≥2.50 and ≤3.5 mm.
5. Maximum two target lesions in any single vessel and in maximum two separate target vessels (including branches) can be included. Thus, up to four randomised target lesions per patient in maximum two target vessels are allowed.
6. Target lesions are amenable to OCT-guided PCI (i.e., no lesion-specific angiographic exclusion criteria are present, see below)

General exclusion criteria (all must be absent)

1. STEMI ≤24 hours from the onset of ischaemic symptoms.
2. Creatinine clearance ≤30 ml/min/1.73 m² (as calculated by MDRD formula for estimated GFR) and not on dialysis. Note: chronic dialysis dependent patients are eligible for enrolment regardless of creatinine clearance.
3. Hypotension, shock or need for mechanical support or intravenous vasopressors at the time the patient would be undergoing the index procedure.

4. CHF (Killip class ≥2 or NYHA class ≥3)
5. LVEF ≤30% by the most recent imaging test within three months prior to procedure. If no LVEF test result within three months is available, it must be assessed by echocardiography, multiple gated acquisition (MUGA), magnetic resonance imaging (MRI), ventriculography (LV gram) or other method.
6. Unstable ventricular arrhythmias.
7. Inability to take DAPT (both aspirin and a $P2Y_{12}$ inhibitor) for at least 12 months in the patient presenting with an ACS, or at least six months in the patient presenting with chronic coronary syndrome (previously termed stable CAD), unless the patient is also taking chronic oral anticoagulation in which case a shorter duration of DAPT may be prescribed per local standard of care.
8. Planned major cardiac or non-cardiac surgery within 24 months after the index procedure.

   Note: Major surgery is any invasive operative procedure in which an extensive resection is performed, e.g., a body cavity is entered, organs are removed, or normal anatomy is altered.

   Note: Minor surgery is an operation on the superficial structures of the body or a manipulative procedure that does not involve a serious risk. Planned minor surgery is not excluded.
9. Prior PCI within the target vessel within 12 months.

   Note: Prior PCI within the target vessel within 12 months is allowed for in-stent restenosis (target lesion is the prior PCI site) if no more than one layer of previously implanted stent is present.

   Note: In-stent restenosis involving two or more layers of stent implanted at any time prior to index procedure (i.e., an earlier episode of in-stent restenosis previously treated with a second stent) is excluded.
10. Any planned PCI within the target vessel(s) within 24 months after the study procedure, other than a planned staged intervention in a second randomised target vessel.

    Note: Planned staged interventions must be noted at the time of randomisation, and the decision to stage may be modified within 24 hours of completion of the index PCI. See Section 6.5.3.8 for more details of multi lesion and vessel treatment.

    Note: PCI in non-target vessels is permitted >48 hours after the index procedure.
11. Any prior PCI in a non-target vessel within 24 hours before the study procedure, or within previous 30 days if unsuccessful or complicated.

    Note: Patients requiring non-target vessel PCI may be enrolled and the non-target vessel(s) may be treated in the same index procedure as the randomised lesions (in all cases prior to randomisation), as long as treatment of the lesion(s) in the non-target vessel is successful and uncomplicated.

    Successful and uncomplicated definition for non-target vessel treatment during the index procedure: Angiographic diameter stenosis <10% for all treated non-target lesions, with TIMI 3 flow in this vessel, without final dissection ≥NHLBI type B, perforation anytime during the procedure, prolonged chest pain (>5 minutes) or prolonged ST-segment elevation or depression (>5 minutes), or cardiac arrest or need for defibrillation or cardioversion or hypotension/heart failure requiring mechanical or intravenous haemodynamic support or intubation).
12. Subject has known hypersensitivity or contraindication to any of the study drugs (including all $P2Y_{12}$ inhibitors, one or more components of the study devices, including everolimus, cobalt, chromium, nickel, platinum, tungsten, acrylic and fluoropolymers, or radiocontrast dye that cannot be adequately pre-medicated.
13. Subject has received a solid organ transplant which is functioning or is active on a waiting list for any solid organ transplants with expected transplantation within 24 months.
14. Subject is receiving immunosuppressant therapy or has known immunosuppressive or severe autoimmune disease that requires chronic immunosuppressive therapy (e.g., human immunodeficiency virus, systemic lupus erythematosus, etc.). Note: corticosteroids are not included as immunosuppressant therapy.
15. Subject has previously received or is scheduled to receive radiotherapy to a coronary artery (vascular brachytherapy), or the chest/mediastinum.
16. Subject has a platelet count <100,000 cells/mm^3 or >700,000 cells/mm^3.
17. Subject has a documented or suspected hepatic disorder as defined as cirrhosis or Child-Pugh ≥ Class B.

18. Subject has a history of bleeding diathesis or coagulopathy or has had a significant gastro-intestinal or significant urinary bleed within the past six months.
19. Subject has had a cerebrovascular accident or transient ischaemic neurological attack (TIA) within the past six months, or any prior intracranial bleed, or any permanent neurologic defect, or any known intracranial pathology (e.g., aneurysm, arteriovenous malformation, etc.).
20. Subject has extensive peripheral vascular disease that precludes safe 6 Fr sheath insertion. Note: femoral arterial disease does not exclude the patient if radial access may be used.
21. Subject has life expectancy <2 years for any non-cardiac cause.
22. Subject is currently participating in another investigational drug or device clinical study that has not yet completed its primary endpoint.
23. Pregnant or nursing subjects and those who plan pregnancy in the period up to two years following index procedure. Female subjects of child-bearing potential must have a negative pregnancy test done within seven days prior to the index procedure per site standard test.
24. Presence of other anatomic or comorbid conditions, or other medical, social, or psychological conditions that, in the investigator's opinion, could limit the subject's ability to participate in the clinical investigation or to comply with follow-up requirements, or impact on the scientific soundness of the clinical investigation results.

Angiographic exclusion criteria (all must be absent)

1. SYNTAX score ≥33, unless a formal meeting of the Heart Team, including a cardiac surgeon, concludes that PCI is appropriate.
2. Planned use of any stent <2.5 mm in a target vessel based on visual estimation (note: a smaller stent may be used in a bail-out scenario, e.g., to treat a distal dissection, but its use cannot be planned prior to enrolment).
3. Planned use of a stent or post-dilatation balloon ≥3.75 mm for the target lesion (see the angiographic inclusion criteria for the one exception to this exclusion criterion).
4. Severe vessel tortuosity or calcification in a target vessel such that it is unlikely that the OCT catheter can be delivered (note: severe vessel calcification is allowed if it is expected that the OCT catheter can be delivered at baseline or after vessel preparation with balloon predilatation or atherectomy).
5. The target vessel has a lesion with DS ≥50% that is not planned for treatment at the time of index procedure.
6. The target lesion is in the left main coronary artery.
7. The target lesion is in a bypass graft conduit; a native coronary artery may be randomised if a prior bypass graft conduit to the vessel is totally occluded, but not if it is patent.
8. The target lesion is an ostial right coronary artery stenosis.
9. The target lesion is a stent thrombosis.
10. Planned use of any stent other than XIENCE in a target lesion.

CAD: coronary artery disease; DAPT: dual antiplatelet therapy; DS: diameter stenosis; NSTEMI: non-ST-segment elevation myocardial infarction; OCT: optical coherence tomography; PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction

Supplementary Table 2. Relative risks of one-year target vessel failure in patients with high-risk clinical and lesion characteristics.

	RR (95% CI)	*p*-value
Diabetes	1.50 (1.28-1.76)	<0.0001
NSTEMI	1.42 (1.31-1.54)	<0.0001
Stent length >28 mm	1.14 (1.06-1.23)	<0.001
Bifurcation	1.31 (1.11-1.56)	0.0019
Moderate to severe calcium	1.62 (1.37-1.91)	0.06
Chronic total occlusion	1.31 (0.99-1.75)	<0.0001
In-stent restenosis	1.88 (1.57-2.26)	<0.0001
CKD/ESRD	1.82 (1.55-2.13)	<0.0001

Data derived from a pooled analysis of studies from references 12 and 13.
CI: confidence interval; CKD: chronic kidney disease; ESRD: end-stage renal disease; NSTEMI: non-ST-elevation myocardial infarction; RR: relative risk

Supplementary Table 3. ILUMIEN IV primary and secondary endpoints and definitions.

Primary endpoints

1. Final post-PCI MSA (per target lesion basis) assessed by OCT in each randomised arm.
2. Target vessel failure: composite of cardiac death, TV-MI, or ID-TVR assessed at up to two years.

Secondary endpoints

OCT-defined secondary endpoints

1. Stent expansion: defined by the MSA achieved in the proximal and distal stented segments relative to their respective reference lumen areas. The stent length is divided into two equal segments (proximal and distal) except for lesions containing a bifurcation (visually estimated side branch ≥2.5 mm). When there is a bifurcation present, rather than splitting the stent into two halves, the division occurs at the proximal most side branch.

- Acceptable stent expansion (categorical variable): the MSA of the proximal segment is ≥90% of the proximal reference lumen area and the MSA of the distal segment is ≥90% of the distal reference lumen area.
- Unacceptable stent expansion (categorical variable): the MSA of the proximal segment is <90% of the proximal reference lumen area, and/or the MSA of the distal segment is <90% of the distal reference lumen area.

Both segments of the stent must meet acceptable stent expansion criteria to be considered acceptable. If acceptable stent expansion (by operator assessment) is not achieved in either the distal or proximal segments of the stent in the OCT-guided arm according to the post-PCI OCT, further post-stent expansion with higher pressures and/or larger balloons must be performed per protocol if the post-PCI OCT EEL measurements now suggest a larger balloon be used.

- Post-PCI stent expansion (%) (continuous variable): the MSA divided by the average of proximal and distal reference lumen areas × 100.

2. Mean stent expansion: the mean stent area (stent volume/analysed stent length) divided by the average of proximal and distal reference lumen areas × 100.

3. Intra-stent plaque protrusion and thrombus: defined as any intraluminal mass protruding at least 0.2 mm within the luminal edge of a stent strut, further classified as:

- Major: protrusion area/stent area at site of tissue protrusion ≥10% and the minimal intrastent flow area (MSA–protrusion area) is unacceptable (<90% of respective proximal or distal reference area).
- Minor: protrusion area/stent area at site of tissue protrusion is <10%, or is ≥10% but the minimal intraluminal flow area (MSA–protrusion area) is acceptable (≥90% of respective proximal or distal reference area).

If thrombus or major protrusion is detected by operator in the OCT-guided arm, thrombus aspiration, further high-pressure balloon inflation and/or an additional stent implantation may be considered.

4. Untreated reference segment disease: focal disease with untreated MLA <4.5 mm^2 within 5 mm from the proximal and/or distal stent edges. Subclassified as:

i. Low (≤90° of lipid arc)
ii. Medium (>90° to <180° of lipid arc)
iii. High (≥180° of lipid arc)

If untreated reference segment disease with an MLA <4.5 mm^2 is detected by operator in either the proximal reference (inflow disease) or distal reference (outflow disease), an additional stent must be placed, unless there are anatomic reasons not to treat the residual disease (e.g., diffuse distal disease or significant vessel tapering).

5. Edge dissection: classified as:
   i. Major (%): ≥60° of the circumference of the vessel at site of dissection and ≥3 mm in length.
   ii. Minor (%): any visible edge dissection <60° of the circumference of the vessel or <3 mm in length.

   Edge dissections are further classified as:
   i. Intimal (limited to the intima layer, i.e., not extending beyond the internal elastic lamina).
   ii. Medial (extending into the media layer).
   iii. Adventitial (extending through the external elastic lamina).

If a major edge dissection is detected in the OCT-guided arm, an additional stent should be placed to cover the dissected segment, particularly if the site of dissection is at the distal stent edge.

6. Stent malapposition: frequency (%) of incompletely apposed stent struts, defined as stent struts clearly separated from the vessel wall without any tissue behind the struts with a distance from the adjacent intima of ≥0.2 mm and not associated with any side branch.

Malapposition is classified as:
- Major: if associated with unacceptable stent expansion (as defined above).
- Minor: if associated with acceptable stent expansion (as defined above).

If major malapposition is detected during the procedure in the OCT arm, further stent expansion must be performed.

7. Border detection (in the angiography arm, post-PCI OCT imaging): the visibility of the external elastic lamina (EEL) border on OCT will be evaluated at both reference sites (proximal and distal) and the MSA, and classified into 3 grades:
   i. Good: ≥75% (270°) of visible circumference.
   ii. Moderate: ≥50% (180°) - <75% (270°) of visible circumference.
   iii. Poor: <50% (180°) of visible circumference.

8. Intra-stent lumen area (intra-stent flow area): stent area minus any protrusion (plaque protrusion or thrombus).

9. Effective lumen area (total flow area): intra-stent lumen area plus any area of malapposition between the stent and the vessel wall (lumen border/plaque border).

Angiography-defined secondary endpoints

Measured by quantitative coronary angiography:
1. Final (post-PCI) minimal lumen diameter.
2. Final (post-PCI) percent diameter stenosis.
3. Acute lumen gain.
4. Maximum device size (stent or post-dilatation balloon): reference vessel diameter ratio.
5. Post-PCI target vessel TIMI flow rate.
6. Angiographic complications: worst complication (anytime during the procedure) and final (post PCI and all imaging): dissection on angiography ≥NHLBI type B, perforations (Ellis classification), intraprocedural thrombotic events (including slow-flow, no-reflow, side branch closure, distal embolisation, and intraprocedural stent thrombosis).

Device usage and procedural endpoints

1. Device usage, site-reported, assessed per subject:
   i. Total stent length.
   ii. Total number of stents.

iii. Maximum stent size.
iv. Post-dilatation (yes/no).
v. Total number of post-dilatation balloons.
vi. Maximum post-dilatation balloon size.
vii. Maximum device size (stent or post-dilatation balloon).
viii. Maximum inflation pressure (atm; stent or post-dilatation balloon).

2. Procedure time: first wire insertion to guide catheter removal, fluoroscopy time, radiation exposure.
3. Contrast use: contrast volume (mL).
4. Contrast-induced nephropathy: serum creatinine rise >25% or absolute increase >0.5 mg/dL (44.2 µmol/L).
5. Procedural success: defined as A) angiographic core laboratory-assessed final (post-PCI) lesion angiographic diameter stenosis <30% and target vessel TIMI 3 flow without any of the angiographic complications listed above; plus B) the absence of site-assessed prolonged ST-segment elevation or depression (>30 minutes), cardiac arrest or need for defibrillation or cardioversion or hypotension/heart failure requiring mechanical or intravenous haemodynamic support or intubation, or procedural death.
6. Procedural complications: defined as (A) angiographic core laboratory-assessed complications listed above occurring anytime during the procedure; or (B) site-assessed prolonged ST-segment elevation or depression (>30 minutes), cardiac arrest or need for defibrillation or cardioversion or hypotension/heart failure requiring mechanical or intravenous haemodynamic support or intubation, or procedural death.
7. OCT performance success (site reported, OCT arm only): OCT imaging performed both pre- and post-PCI.
8. OCT imaging-related procedural complications: any procedural complications (e.g., angiographic dissection, perforation, thrombus, acute closure) requiring any active intervention (e.g., prolonged balloon inflations, additional stent implantation, pericardiocentesis, intubation, haemodynamic support or pressors, defibrillation or cardioversion) or death adjudicated by the clinical events committee as definitely or likely attributable to the physical performance of OCT imaging (e.g., passing the catheter through the vasculature or stent, or injecting contrast to clear the blood for imaging). For this definition, adverse events that arise due to changes in PCI strategy as the result of OCT findings are not considered OCT imaging-related procedural complications.
9. Additional interventions based on pre-PCI or post-stenting OCT (site reported, assessed per subject, OCT arm only): interventions that are solely based on OCT imaging that would not have been performed based on angiographic guidance alone.

i. Use of larger balloon.
ii. Use of higher inflation pressures.
iii. Use of additional inflations.
iv. Use of additional stent(s).
v. Thrombus aspiration.
vi. Performance of atherectomy.
vii. Other interventions.

Reason(s) for additional interventions will be documented by the site (e.g., more calcium than anticipated, greater stent underexpansion than appreciated angiographically, greater malapposition than appreciated angiographically, greater tissue protrusion or thrombus burden than appreciated angiographically, more severe edge dissection than appreciated angiographically, residual reference segment disease not appreciated angiographically, other).

Clinical endpoints

Assessed at 30 days, 1 year and 2 years:
1. TLF: cardiac death, TV-MI, or ID-TLR.
2. All-cause mortality.
3. Cardiac and non-cardiac mortality.
4. All MI.
5. TV-MI and non-TV-MI.
6. Periprocedural MI and non-periprocedural MI.
7. All revascularisation.
8. ID revascularisation and non-ID revascularisation.
9. ID-TVR, ID-TLR, and ID non-TLR TVR.

10. Definite, probable and definite/probable stent thrombosis (Academic Research Consortium definition).
11. Relationship between immediate post-procedure OCT parameters (e.g., MSA, procedural success, malapposition, dissection, protrusion) and two-year endpoint rates (e.g., TVF, TLF, all-cause mortality, cardiac death, TV-MI, all MI, ID-TLR, ID-TVR, and stent thrombosis).

Patient-reported outcomes

EuroQoL 5D (EQ-5D-5L) survey to assess overall health status will be administered during this study in-hospital (required at baseline, optional post-procedure), and at 30-day, 1-year and 2-year follow-up.

Cost-effectiveness

Cost per quality-adjusted life year and TVF event prevented by OCT guidance.

ID-TLR: ischaemia-driven target lesion revascularisation; ID-TVR: ischaemia-driven target vessel revascularisation; MI: myocardial infarction; MLA: minimal lumen area; MSA: minimal stent area; NHLBI: National Heart, Lung, and Blood Institute; OCT: optical coherence tomography; PCI: percutaneous coronary intervention; TIMI: Thrombolysis In Myocardial Infarction; TLF: target lesion failure; TVF: target vessel failure; TV-MI: target vessel myocardial infarction

Supplementary Table 4. Summary of one-year target vessel failure rates reported for high-risk subgroups.

Subgroup	Study	N	Stent	TVF rate (%)	Notes	Adjusted TVF rate (%)	Adjusted TVF rate (%) weighted by (N/N_{total})	Subgroup estimated prevalence in ILUMIEN IV	Subgroup weighted TVF rate (%)
ACS	Kalkman et al *Catheter Cardiovasc Interv*. 2017;90:E31-E37	498	Combo (DES)	7.1	• Reported rate was TLF, multiplied by adjustment factor of 1.2 to calculate adjusted TVF • Example calculation of "Adjusted TVF rate (%) weighted by (N/N_{total})" provided here: o 8.52 x (498/623) = 6.81	8.52	6.81		
	Sudhir et al *Catheter Cardiovasc Interv*. 2013;82:E385-E394	125	XIENCE/TAXUS	9.1/8.5	• AMI only (STEMI / NSTEMI), does not include unstable angina • Values shown are identified in literature review as XIENCE/TAXUS arms, however that is incorrect – they are AMI/non-AMI subgroups of the single-arm XIENCE V USA trial • The AMI value only was correctly used as basis for calculation • Reported rate was TLF, used adjustment factor of 1.2 to calculate adjusted TVF • Example calculation of "Adjusted TVF rate (%) weighted by (N/N_{total})" provided here: o 10.92 x (125/623) = 2.19	10.92	2.19		
	ACS studies N_{total}	**623**					**9.00**	**0.3**	**2.70**
Severe calcification	Généreux et al *Am J Cardiol*. 2015;115:1685-1690	443	2nd gen DES	16.4	• Reported rate is for MACE – cardiac death, MI, TVR	16.4	16.4		
	Severe calcification studies N_{total}	**443**					**16.4**	**0.05**	**0.82**
Long/multiple lesions	Bouras et al *Catheter Cardiovasc Interv*. 2017;89:984-991	323	XIENCE	8.9	• Reported rate is for very long lesion (VLL) subgroup • Reported rate was TLF, multiplied by adjustment factor of 1.2 to calculate adjusted TVF	10.68	4.36		

Subgroup	Study	N	Stent	TVF rate (%)	Notes	Adjusted TVF rate (%)	Adjusted TVF rate (%) weighted by (N/N_{total})	Subgroup estimated prevalence in ILUMIEN IV	Subgroup weighted TVF rate (%)
					• Pooled population from SPIRIT/ XIENCE V USA				
	Patra et al *Cardiovasc Revasc Med*. 2016;2017:160-164	185	XIENCE/Resolute	4.0/5.0	• Reported rate was TLF, multiplied by adjustment factor of 1.2 to calculate adjusted TVF • Used average of Resolute/XIENCE rates for calculation	5.40	1.26		
	Lesiak et al *J Interv Cardiol*. 2016;29:47-56	182	Bioabsorbable polymer SES/durable polymer EES	6.9/8.6	• Reported rate was TLF, multiplied by adjustment factor of 1.2 to calculate adjusted TVF • Used average of BP-SES and DP-EES arms • Reported rate was for 9 months, multiplied by adjustment factor of (5/4) to get adjusted 12-month TVF	11.63	2.67		
	Teirstein et al *Catheter Cardiovasc Interv*. 2015;85:207-215	102	EES	3.2	• Reported rate was TLF, multiplied by adjustment factor of 1.2 to calculate adjusted TVF	3.84	0.49		
	Long/multiple lesions studies N_{total}	**792**					**8.78**	**0.15**	**1.32**
Bifurcations	Chen et al *J Am Coll Cardiol*. 2013;61:1482-1488	419	2nd gen DES	6.2/16.3	• Reported rate is for MACE – cardiac death, MI, TVR • Used average of crush/culotte arms	11.25	3.57		
	Généreux et al *J Am Coll Cardiol*. 2015;65:533-543	349	Provisional 2nd gen DES arm	12.8	• Used results from provisional stent arm • Sample size for provisional stent arm should be N=349 for provisional group only • Reported rate was for 9 months, the adjustment factor of (5/4) was used to get adjusted 12-month rate	16.00	4.23		
	Song et al *JACC Cardiovasc Interv*. 2012;5:1133-1140	258	2nd gen DES 2-stent/provisional strategy	9.2/9.4	• Used average of 2-stent and provisional strategy arms	9.3	1.82		

Subgroup	Study	N	Stent	TVF rate (%)	Notes	Adjusted TVF rate (%)	Adjusted TVF rate (%) weighted by (N/N_{total})	Subgroup estimated prevalence in ILUMIEN IV	Subgroup weighted TVF rate (%)
	Pan et al *Catheter Cardiovasc Interv*. 2012;80:1165-1170	293	SES/EES provisional strategy	6.2/6.1	• Used average of SES and EES arms	6.15	1.37		
	Bifurcations studies N_{total}	**1,319**					**10.99**	**0.1**	**1.10**
Diabetes mellitus	Kalkman et al *Int J Cardiol*. 2017;226:60-64	181	Combo DES	4.4/6.8/20.3	• Reported rates are TLF • Reported TLF rates are for subgroups: non-DM/non-ITDM/ITDM • Sample size for combined non-ITDM/ITDM subgroups should be N=181 • A weighted average of the reported non-ITDM and IDTM rates multiplied by the TLF adjustment factor of 1.2 was used to calculate adjusted TVF rate	12.21	0.64		
	Kang et al *EuroIntervention*. 2014;10:74-82	2,404	EES/SES	3.1/4.7	• Used all EES and SES results • Reported TVF rates are for non-DM and DM subgroups, used DM subgroup rate for adjusted TVF	4.7	3.26		
	Muramatsu et al *JACC Cardiovasc Interv*. 2014;7:482-493	882	EES	6.3	• XIENCE (EES) arm results • Reported outcome is TLF (DoCE), the adjustment factor of 1.2 was used to calculate adjusted TVF rate • Reported value should be 6.3% for entire EES population of N=882	7.56	1.92		
	Diabetes mellitus studies N_{total}	**3,467**					**5.82**	**0.3**	**1.75**
CTO	Teeuwen et al *JACC Cardiovasc Interv*. 2017;10:133-143	330	Bioabsorbable polymer SES/durable polymer EES	9.9/6.6	• Used average of BP-SES and DP-EES arms	8.25	8.25		
	CTO studies N_{total}	**330**					**8.25**	**0.05**	**0.41**
ISR	Lee et al	409	DES / DEB	9.2/17.9	• Reported TLF rates are for DES and DEB study arms, used	11.04	11.04		

Subgroup	Study	N	Stent	TVF rate (%)	Notes	Adjusted TVF rate (%)	Adjusted TVF rate (%) weighted by (N/N_{total})	Subgroup estimated prevalence in ILUMIEN IV	Subgroup weighted TVF rate (%)
	Int J Cardiol. 2017;230:181-190				DES arm rate for adjusted TVF • Sample size for DES arm should be N=409 • Reported rate was TLF, multiplied by adjustment factor of 1.2 to calculate adjusted TVF				
	ISR studies N_{total}	**409**					**11.04**	**0.05**	**0.55**
Grand total across subgroups	**All studies N_{total}**	**7,383**							**8.65**

Supplementary Table 5. Summary of two-year target vessel failure reported for high-risk subgroups.

Subgroup	Study	N	Stent	Reported TVF rate (%)	Notes	Adjusted TVF rate (%)	Adjusted TVF rate (%) weighted by (N/N_{total})	Subgroup estimated prevalence in ILUMIEN IV	Subgroup weighted TVF rate (%)
ACS	van Houwelingen et al *Rev Esp Cardiol (Engl Ed)*. 2016;69:1152-1159	817	Resolute / Promus Element	7.4/6.1	• AMI only (STEMI / NSTEMI), does not include unstable angina • Used average of Resolute and Promus Element arms for adjusted TVF	6.75	1.36		
	Jimenez et al *Cardiovasc Revasc Med*. 2016;17:355-361	264	Ultimaster/XIENCE	6.3/9.4	• AMI only (STEMI / NSTEMI), does not include unstable angina • Used average of Ultimaster and XIENCE arms for adjusted TVF	7.85	0.51		
	Zbinden et al *J Am Heart Assoc*. 2016;5:e003255	407	BP-SES/DP-EES	5.2/10.7	• STEMI subgroup results only, does not include NSTEMI or unstable angina • Reported rate was TLF • Used the average of the reported BP-SES and DP-EES rates multiplied by the TLF adjustment factor of 1.2 to get adjusted TVF rate	9.54	0.96		
	ADAPT-DES trial	2,575	2nd gen DES	11.8	• Unpublished data provided by CRF • N=2,575 is an estimate: multiplied full ADAPT DES population N=8,582 by estimated ACS	11.8	7.47		

Subgroup	Study	N	Stent	Reported TVF rate (%)	Notes	Adjusted TVF rate (%)	Adjusted TVF rate (%) weighted by (N/N_{total})	Subgroup estimated prevalence in ILUMIEN IV	Subgroup weighted TVF rate (%)
					prevalence of 0.3				
	ACS studies N_{total}	**4,063**					**10.30**	**0.3**	**3.09**
Severe calcification	Huisman et al *Am Heart J*. 2016;175:121-129	342	Resolute/EES	16.4	• Severe calcification subgroup result reported • Sample size for severe calcification subgroup should be N=342	16.4	16.4		
	Severe calcification studies N_{total}	**342**					**16.4**	**0.1**	**1.64**
Long or multiple lesions	Teirstein et al *Catheter Cardiovasc Interv*. 2015;85:207-215	102	EES	8.8	• Reported rate was TLF, multiplied by adjustment factor of 1.2 to get adjusted TVF	10.56	10.56		
	Long or multiple lesions studies N_{total}	**102**					**10.56**	**0.2**	**2.11**
Diabetes mellitus	ADAPT-DES trial	2,783	2nd gen DES	18.1/17.5	• Unpublished data provided by CRF • Used average of two unidentified groups to determine adjusted TVF	17.80	13.53		
	Silber et al *JACC Cardiovasc Interv*. 2013;6:357-368	878	Resolute	7.1/8.0/13.7	• Reported rate was TLF • Reported rates are for subgroups: non-DM/non-ITDM/ITDM • Sample size for combined non-ITDM/ITDM subgroups should be N=878 • A weighted average of the reported non-ITDM and IDTM rates multiplied by the TLF adjustment	11.31	2.71		

Subgroup	Study	N	Stent	Reported TVF rate (%)	Notes	Adjusted TVF rate (%)	Adjusted TVF rate (%) weighted by (N/N_{total})	Subgroup estimated prevalence in ILUMIEN IV	Subgroup weighted TVF rate (%)
					factor of 1.2 was used to calculate adjusted TVF rate				
	Diabetes mellitus studies N_{total}	**3,661**					**16.24**	**0.3**	**4.87**
CTO	Azzalini et al *Catheter Cardiovasc Interv*. 2017;89:820-828	910	Mainly DES	15.0/13.0	• Rates are with and without rotational atherectomy • Used reported event rate of 13% for overall population and reported N=910	13.0	13.0		
	CTO studies N_{total}	**910**					**13.0**	**0.05**	**0.65**
ISR	ADAPT DES trial	429	2nd gen DES	26.6/25.8	• Unpublished data provided by CRF • Used average of two unidentified groups to determine adjusted TVF • N=429 is an estimate: multiplied full ADAPT DES population N=8,582 by estimated ISR prevalence of 0.05	26.2	26.2		
	ISR studies N_{total}	**429**					**26.2**	**0.05**	**1.31**
Grand total across subgroups	**All studies N_{total}**	**9,507**							**13.67**