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This paper also includes supplementary data published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-20-00772

KEYWORDS

- drug-eluting stent
- multiple vessel disease
- stable angina

Abstract

Aims: The purpose of the Multivessel TALENT trial is to compare clinical outcomes of the novel Supraflex Cruz stent with those of the SYNERGY stent in patients with three-vessel disease (3VD) undergoing state-of-the-art percutaneous coronary intervention (PCI).

Methods and results: In this prospective, randomised, 1:1 balanced, multicentre, open-label trial, 1,550 patients with *de novo* 3VD without left main disease will be assigned to the Supraflex Cruz or SYNERGY arm. The following treatment principles of "best practice" PCI will be applied: Heart Team consensus based on SYNTAX score II treatment recommendation, functional lesion evaluation by quantitative flow ratio (QFR), stent optimisation by intravascular imaging, optimal pharmacological treatment and prasugrel monotherapy. The primary endpoint is a non-inferiority comparison of the patient-oriented composite endpoint (POCE) of all-cause death, any stroke, any myocardial infarction, or any revascularisation, at 12 months post procedure. The powered secondary endpoint is a superiority comparison of the vessel-oriented composite endpoint (VOCE), defined as vessel-related cardiovascular death, vessel-related myocardial infarction, or clinically and physiologically indicated target vessel revascularisation, at 24 months.

Conclusions: The Multivessel TALENT trial will be evaluating a novel treatment strategy for complex coronary artery disease with state-of-the-art PCI based on angiography-derived QFR with novel ultra-thin Supraflex Cruz stents, compared with SYNERGY stents. Clinical Trial Registration URL: https://www.clinicaltrials.gov/ct2/show/NCT04390672. Unique Identifier: NCT04390672

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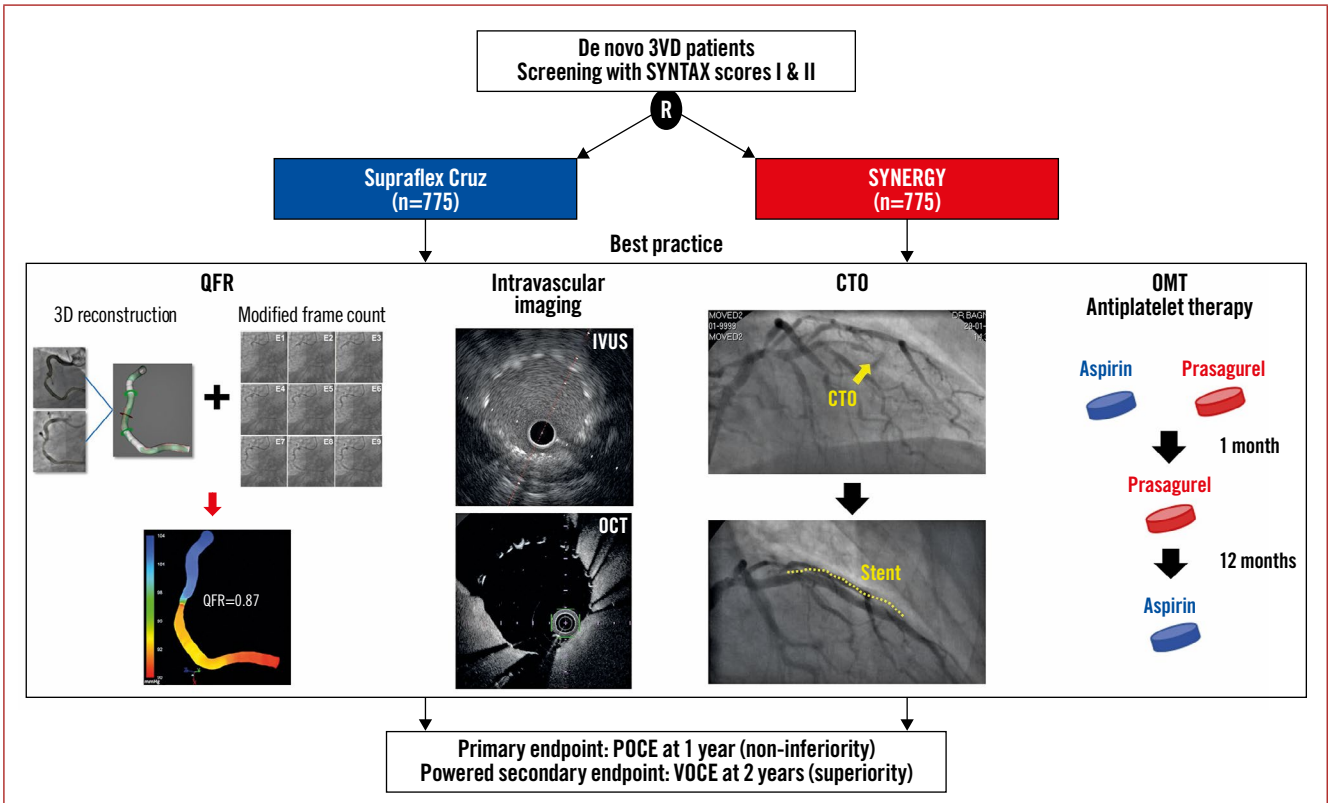
SUBMITTED ON 16/06/2020 - REVISION RECEIVED ON 1st 13/08/2020 / 2nd 08/09/2020 - ACCEPTED ON 09/09/2020



Visual summary. *Flow chart of the Multivessel TALENT trial. 3VD: three-vessel disease; QFR: quantitative flow ratio; IVUS: intravascular ultrasound; OCT: optical coherence tomography; CTO: chronic total occlusion; OMT: optimal medical therapy; POCE: patient-oriented composite endpoint; VOCE: vessel-oriented composite endpoint*

Abbreviations

3VD	three-vessel disease
DOCE	device-oriented composite endpoint
FFR	fractional flow reserve
iFR	instantaneous wave-free ratio
IVUS	intravascular ultrasound
MI	myocardial infarction
OCT	optical coherence tomography
PCI	percutaneous coronary intervention
POCE	patient-oriented composite endpoint
QFR	quantitative flow ratio
TLR	target lesion revascularisation
VOCE	vessel-oriented composite endpoint

Introduction

The all-comers TALENT trial[1] demonstrated non-inferiority of the biodegradable polymer-coated and ultra-thin strut sirolimus-eluting Supraflex™ stent (Sahajanand Medical Technologies, Mumbai, India) compared to the durable polymer-coated everolimus-eluting XIENCE stent (Abbott Vascular, Santa Clara, CA, USA) in terms of occurrence of the device-oriented composite endpoint (DOCE) at one year (cardiac death, target vessel myocardial infarction [MI], or clinically indicated target lesion revascularisation [TLR]) (4.9% in the Supraflex arm vs 5.3% in the XIENCE arm, $p_{non\text{-}inferiority}<0.0001$). In the per-protocol analysis, a 61% relative reduction of clinically indicated TLR was found in the Supraflex arm compared to the XIENCE arm (1.2% in the Supraflex arm vs 3.1% in the XIENCE arm, p=0.021). This result was corroborated by the fact that thin-strut drug-eluting stents (DES) decrease acute thrombogenicity and promote faster endothelialisation, compared with thick-strut DES[2,3]. The Supraflex Cruz stent is basically similar in many respects to the Supraflex stent (a biodegradable polymer-coated, ultra-thin strut sirolimus-eluting stent, with the same density of cytostatic drug), but has long dual Z connectors from "valley to valley" between the strut rings, instead of short S-links connecting "peak to peak" of the strut rings. The new mechanical platform increases the flexibility, trackability and pushability of the stent[4]. In addition, the Supraflex Cruz uses a softer balloon for stent retention and retrieval post deployment. Furthermore, the proximal shaft of the balloon was redesigned to improve the crossability of the device. These are essential assets in the treatment of complex coronary artery disease. Therefore, we designed a new randomised controlled trial with the novel Supraflex Cruz stent in patients with *de novo* three-vessel disease (3VD) without left main disease.

The recent SYNTAX II trial in patients with 3VD[5] applied five treatment principles described as "best practice" in the field of percutaneous coronary intervention (PCI)[6] **(Supplementary Table 1)**:

(i) patient selection based on SYNTAX score II[7] recommendation and assessment of equipoise mortality with surgical treatment by Heart Team consensus[5]; (ii) physiological assessment of stenotic lesions by pressure-derived instantaneous wave-free ratio (iFR) or fractional flow reserve (FFR) and treatment targeting only the functionally significant lesions[8]; (iii) post-stent optimisation by intravascular imaging[9]; (iv) PCI of chronic total occlusion (CTO) performed by locally accredited experts in CTO[10]; and (v) optimal medical treatment before, during and after PCI[11].

Physiological assessment, iFR/FFR for all vessels can be time-consuming, expensive and cumbersome. Therefore, the designers of the trial replaced the pressure wire-derived physiological assessment with an angiography-derived physiological assessment, quantitative flow ratio (QFR)[12]. In addition, novel antiplatelet therapy strategies, such as short-duration dual antiplatelet therapy (DAPT) and $P2Y_{12}$ inhibitor monotherapy, have recently shown safety and superior efficacy in patients with multivessel disease[13] when compared to conventional DAPT. Therefore, DAPT with aspirin and prasugrel for one month, followed by 11 months of prasugrel monotherapy, will be implemented and followed by aspirin monotherapy at one year.

Methods

STUDY DESIGN

The Multivessel TALENT study (ClinicalTrials.gov, NCT04390672) is a prospective, randomised, 1:1 balanced, controlled, multicentre, open-label study comparing clinical outcomes between the Supraflex Cruz and SYNERGY™ (Boston Scientific, Marlborough, MA, USA) stents. Approximately 60 sites in Europe will participate **(Supplementary Table 2)**. Randomisation will be performed via web-based software, and will be stratified by centre and blocked, with randomly permuted block sizes of two and four, after written consent is obtained and QFR is analysed by a blinded core lab **(Supplementary Figure 1)**.

Patients with *de novo* 3VD without left main disease will be treated according to state-of-the-art PCI after selection based on SYNTAX score II treatment recommendations (i.e., PCI only or equipoise coronary artery bypass grafting [CABG]/PCI) and Heart Team discussion[5]; functional evaluation for stenotic lesion (ESC guidelines [GL], I,A)[8] by QFR; intravascular ultrasound (IVUS)/optical coherence tomography (OCT) optimisation (ESC GL, IIa,B)[9]; contemporary CTO techniques[10] (if applicable); and optimal medical therapy[11].

Patients will be followed up for two years after the index procedure and contacted at 30 days, 6 months, 12 months and 24 months. The informed consent form (ICF) will also contain a provisional agreement for a five-year follow-up. This five-year follow-up will be performed at the sole discretion of the chief investigator, sponsor and grant giver, if funding is available. All clinical events will be adjudicated by an independent clinical events committee (CEC). Serious adverse events will be periodically reviewed by an independent data safety and monitoring board (DSMB). Details on the composition, roles, and responsibilities of the Coordinating Centre/Academic Research Organisation, Steering Committee, CEC, and DSMB are described in **Supplementary Appendix 1**. The data management plan and quality control are presented in **Supplementary Appendix 2** and **Supplementary Appendix 3**.

PATIENT POPULATION

A total of 1,550 patients with *de novo* 3VD without left main disease, for whom PCI only or equipoise CABG/PCI has been recommended according to the SYNTAX score II and local Heart Team consensus, will be randomised in a 1:1 fashion to Supraflex Cruz versus SYNERGY stents. Inclusion and exclusion criteria are listed in **Supplementary Table 3**.

STUDY ENDPOINTS

The primary endpoint for this trial is a non-inferiority comparison of the patient-oriented composite endpoint (POCE) of the Supraflex Cruz cohort to the SYNERGY cohort at 12 months post procedure. POCE[14] is a composite clinical endpoint of all-cause death, any stroke, any MI, or any repeat revascularisation. The definition of MI will follow the Society for Cardiovascular Angiography and Interventions (SCAI) consensus for periprocedural MI ≤48 hours[15], and Fourth Universal Definition (FUD) for MI >48 hours after the index procedure[16]. The powered secondary endpoint is a superiority comparison in the per-protocol analysis - at the vessel level - of the vessel-oriented composite endpoint (VOCE)[17], a composite of vessel-related cardiovascular death, vessel-related MI, or clinically and physiologically indicated target vessel revascularisation (CPI-TVR), at 24 months post procedure. Other secondary endpoints are described in **Supplementary Table 4**[14,18].

QFR AND FUNCTIONAL SYNTAX SCORE ANALYSIS IN CORE LAB

QFR will be analysed off-line by QAngio XA 3D/QFR imaging software (Medis Medical Imaging Systems, Leiden, the Netherlands) before randomisation, and identification of functionally significant lesions will be provided to sites as an indication for treatment **(Supplementary Figure 2)**. Details of the QFR analysis are described in **Supplementary Appendix 4**. At that time, the anatomical SYNTAX score I and functional SYNTAX score will be calculated by an independent core lab (CORRIB Core Lab, Galway, Ireland). The functional SYNTAX score will be used to generate the SYNTAX score III that predicts the major adverse cardiac and cerebrovascular events (MACCE) rate as well as the all-cause mortality in patients undergoing PCI[5,7,19].

DEVICES

The Supraflex Cruz is the next-generation Supraflex stent. It is designed with open cells and dual valley-to-valley links between strut rings **(Supplementary Figure 3A)**. The strut thickness is 60 µm across all diameters (2.00-4.5 mm). The conformal coating layer comprises the drug blended with a biodegradable polymeric matrix. The average thickness of the coating ranges from 4 to 6 µm. The Supraflex Cruz is coated with sirolimus at a concentration

of 140 μg/cm^2. The drug is 80% released within four weeks; the remainder is released over a period of three months. The polymers gradually degrade in 10 to 12 months. **Supplementary Figure 3B** displays the mechanical characteristics of the Supraflex Cruz, as documented according to the International Organization for Standardization (ISO), compared to other commercially available drug-eluting stents[4].

The SYNERGY stent is used as the control device **(Supplementary Figure 3A, Supplementary Figure 3B)**.

INDEX AND STAGED PROCEDURES

With respect to CTO revascularisation, a locally accredited expert will be selected in all centres to be part of the Multivessel TALENT team, and contemporary CTO techniques[10] will be applied. In case of stent delivery failure, it is recommended first to try the comparator stent (crossover)[18].

The use of IVUS/OCT pre PCI will be left to the discretion of the investigator; however, IVUS/OCT for optimising stent implantation after stent deployment is mandated[9]. **Supplementary Figure 4** shows the criteria for stent optimisation.

Staged procedures are permitted and will be encouraged for more complex cases (e.g., revascularisation of total occlusions) to increase the likelihood of complete revascularisation and to decrease the risk of contrast-induced nephropathy[20]. The recommended timing of all planned elective staged PCI procedures is within two weeks post index procedure (with an upper limit of eight weeks). When the staged procedure is performed beyond eight weeks, such a procedure is considered as a clinical event. Staged procedures are only allowed in non-target vessels. The patient should receive the stents assigned during the original index procedure.

DEVICE AND PROCEDURE SUCCESS

Device success (lesion basis) is defined as successful delivery and implantation of the assigned device in the intended location with the final residual stenosis being less than 20% (preferably by quantitative coronary angiography [QCA]). Procedure success is defined as device success without POCE or stent thrombosis during the index procedure hospital stay (maximum of seven days)[18].

ADJUNCTIVE PHARMACOLOGICAL THERAPY

Preloading with aspirin 300 to 325 mg at least two hours before the PCI is mandatory unless the patient already receives chronic aspirin therapy. Prasugrel preloading therapy is also mandatory. For patients already receiving chronic prasugrel therapy, preloading with a dose of 60 mg of prasugrel is mandatory at least two hours before the PCI procedure. Switching from clopidogrel or ticagrelor to prasugrel should be conducted according to the consensus document[21] **(Supplementary Figure 5)**. In addition, atorvastatin 80 mg, rosuvastatin 40 mg, or a PCSK-9 inhibitor must be administered at least 24 hours before the PCI, regardless of low-density lipoprotein (LDL) level, if not taking any statin at a maximum dose in the 24 hours prior to the loading dose[22].

ANTIPLATELET THERAPY AFTER PCI

After PCI, all patients must receive DAPT with aspirin and prasugrel for one month, followed by 11 months of prasugrel monotherapy. At one year, prasugrel monotherapy should be replaced by aspirin monotherapy **(Supplementary Figure 1)**. The dose of aspirin and prasugrel will be 75-100 mg and 10 mg per day, respectively. The dose of prasugrel should be decreased to 5 mg in patients with a weight <60 kg or age >75 years[23].

STATISTICAL ANALYSIS

For the primary analysis of the primary endpoint, the intention-to-treat population will be used: all patients will be analysed according to their assigned treatment group, regardless of the treatment actually received. The proportion of patients reaching a POCE at 12 months in each study arm will be estimated using a Kaplan-Meier estimator. A one-sided 95% confidence interval of the difference in weighted proportions will be compared to the non-inferiority limit (absolute risk increase of 4.28%), with a corresponding one-sided p-value for non-inferiority to be reported.

The primary analysis of the powered secondary endpoint will be a per-protocol analysis at vessel level. The definition of the per-protocol population is shown in **Supplementary Appendix 5**. The proportion of vessels reaching a VOCE by 24 months in each study arm will be estimated using a Kaplan-Meier estimator. Cluster-robust standard errors will be used to account for the correlation of VOCE measurements within a patient. A two-sided, cluster-robust 95% confidence interval of the difference in proportions will be compared to zero difference, with a corresponding two-sided p-value for superiority to be reported.

Other secondary endpoints will be analysed in the intention-to-treat principle as appropriate (according to the assumed distribution of each outcome). For these analyses, the focus will be on the point estimates and confidence intervals for hypothesis generation.

A secondary analysis of the primary endpoint and all its secondary clinical endpoints will also be conducted in the as-treated and per-protocol population. The definition of the as-treated population is shown in **Supplementary Appendix 5**.

SAMPLE SIZE CALCULATION

Assuming a 1:1 treatment allocation ratio, a one-sided significance level (alpha) of 0.05, a POCE event rate for SYNERGY of 10.7% at 12 months in 3VD[5], a non-inferiority margin of 4.28% (risk ratio: 1.4), and no difference in event rate between the two groups, 751 patients per arm are required to achieve 85% power to show non-inferiority of the Supraflex Cruz to the SYNERGY. Taking into account an attrition rate of approximately 3%, these numbers increase to 775 in each group, giving a total randomised sample of 1,550 patients.

The powered secondary analysis will be conducted to test superiority in VOCE for the Supraflex Cruz, compared to SYNERGY, at the vessel level on a per-protocol principle[17]. Based on analysis from the SYNTAX II trial[5], the proportion of per-protocol vessels with a VOCE at two years was assumed to be 6.51% in the

SYNERGY arm, and the correlation of multiple VOCE measurements within patients was 0.45. A minimally important effect of a relative reduction by 37.5% in the Supraflex Cruz arm (VOCE: 4.07%) was chosen. Given that the sample size is fixed for the primary outcome at 1,550 participants and assuming an attrition rate of 5% before two years, this gives 1,472 participants with VOCE measurements for analysis. Within-patient correlation of VOCE results in a design effect of 1.54 (assuming a mean of 2.2 vessels per patient which are treated with PCI)[24]. Thus, the effective sample size of all vessels in analysis is 1,472*2.2/1.54=2,103. A test of statistical superiority for a difference in proportions uses cluster-robust standard errors with a type-1 error of 0.05 and these parameters will thus have a power of 80%.

PRE-SPECIFIED SUBGROUP ANALYSES

Pre-specified subgroup analyses are listed in **Supplementary Appendix 6**. For these analyses, the study does not have significant power to demonstrate non-inferiority/superiority for the Supraflex Cruz arm over the SYNERGY arm, meaning that the results are considered exploratory (hypothesis-generating) only.

Discussion

The Multivessel TALENT trial compares clinical outcomes between novel ultra-thin Supraflex Cruz and SYNERGY stents in patients with *de novo* 3VD without left main disease, applying the five treatment principles of "best practice" PCI[6]. Our hypothesis is based on the results of the per-protocol analysis of the TALENT trial that indicates a 61% reduction in clinically indicated TLR[1]. In addition, a meta-analysis also demonstrated that newer-generation ultra-thin strut DES significantly reduced target lesion failure driven by fewer procedural and spontaneous myocardial infarctions, compared with thicker-strut second-generation DES[25].

Treatment strategies for complex coronary artery disease have been improved since the enrolment period of the SYNTAX II study[13,26]. First, patient selection is based on SYNTAX score II recommendations[7] and Heart Team consensus[5,27]. Second, novel physiological methods to assess ischaemia have been developed[12]. The diagnostic accuracy of QFR, that does not require pharmacologic hyperaemia induction, for identifying an FFR of ≤0.80 has been demonstrated in the FAVOR Pilot study. Thereafter, the FAVOR II China and FAVOR II Europe-Japan studies also demonstrated the diagnostic accuracy of QFR for detecting functionally significant lesions in comparison with 2D-QCA, using FFR as reference standard[28]. In a systematic review and Bayesian meta-analysis, Collet et al confirmed the high sensitivity and specificity of QFR against pressure wire-derived physiological assessment[12]. Therefore, the systematic physiological assessment for all vessels by QFR becomes reasonable in terms of cost, time, and safety. Third, the benefit of IVUS-guided PCI has been demonstrated in the ULTIMATE and IVUS-XPL trials[29], and intravascular imaging for post-stent optimisation is recommended in an expert consensus document[9]. Fourth, the presence of a CTO was the strongest independent predictor of incomplete revascularisation in the PCI arm of the SYNTAX trial[30]. Operator skill and use of specific techniques and devices are key determinants of PCI success[5]; therefore, a locally accredited expert in CTO is recommended to be selected in all participating centres, and an algorithm of treatment is advised[31]. Regarding antiplatelet therapy after PCI as a part of optimal medical treatment, the sub-analysis of the GLOBAL LEADERS trial and the TWILIGHT study demonstrated the clinical benefit of ticagrelor monotherapy after short DAPT in patients with 3VD[13,26]. The ISAR-REACT 5 trial demonstrated that, in patients who presented with acute coronary syndromes, the incidence of death, MI, or stroke was significantly lower among those who received prasugrel than among those who received ticagrelor[23]. Since the landmark analysis at one year did not demonstrate any difference between ticagrelor monotherapy and aspirin monotherapy in clinical outcomes during the second year of the GLOBAL LEADERS trial, the monotherapy with prasugrel will be interrupted after one year and switched back to aspirin monotherapy. Therefore, in this 3VD trial, the antiplatelet therapy will be as follows: DAPT with aspirin and prasugrel for one month, followed by 11 months of prasugrel monotherapy, replaced by aspirin monotherapy at one year.

Limitations

Patients with *de novo* 3VD will be treated according to state-of-the-art PCI. As previously stated for the SYNTAX II trial, it will not be possible to identify the most influential factor of clinical benefit among the five treatment principles of best practice. On the other hand, this is a prospective, randomised trial comparing clinical outcomes between Supraflex Cruz and SYNERGY stents and the non-inferiority or even the superiority of one device versus the other will be the most tangible result of this trial.

There is no consensus on the width of a non-inferiority margin in non-inferiority trials[32]. In the TALENT and DESSOLVE III trials, both non-inferiority margins were 4.0% (risk ratio: 1.5) in the DOCE (cardiac death, target vessel MI, and clinically indicated TLR)[1,33]. A non-inferiority margin of 4.28% (relative risk ratio: 1.4) for POCE at 12 months is more stringent than in the above-mentioned trials.

Conclusions

The Multivessel TALENT trial will assess state-of-the-art PCI for complex coronary artery disease. It will develop "best practice" PCI in terms of physiological assessment using QFR, apply a novel antiplatelet therapy strategy, and subsequently assess the non-inferiority and possibly the superiority of the novel ultra-thin Supraflex Cruz stent compared to the SYNERGY stent.

Impact on daily practice

This study could establish PCI with the novel ultra-thin Supraflex Cruz stent as an attractive option for revascularisation in patients with *de novo* 3VD without left main disease.

Funding

The Multivessel TALENT trial is an investigator-initiated trial sponsored by The National University of Ireland Galway which received funding from SMT (Sahajanand Medical Technologies, Mumbai, India). The role of the funding source and the responsibilities of the sponsor are outlined in **Supplementary Appendix 7**.

Conflict of interest statement

H. Hara reports a grant for studying overseas from the Japanese Circulation Society, a grant-in-aid for JSPS Fellows and a grant from the Fukuda Foundation for Medical Technology. J.H.C. Reiber is Chief Scientific Officer of Medis Medical Imaging Systems bv, the company that developed the QFR. A. Zaman reports consultancy and/or lecture fees from SMT, Boston Scientific, Abbott Vascular, and HeartFlow. W. Wijns reports institutional grants from SMT and MicroPort, and personal fees from MicroPort, being a co-founder of Argonauts, an innovation facilitator, and being a medical advisor to Rede Optimus Research. P.W. Serruys reports personal fees from Biosensors, Micel Technologies, Sino Medical Sciences Technology, Philips/Volcano, Xeltis, and HeartFlow, outside the submitted work. M. Sabaté has received consultancy fees from Abbott Vascular and iVascular outside the submitted work. The other authors have no conflicts of interest to declare.

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Supplementary data

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The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-20-00772

Supplementary data

Supplementary Appendix 1. The composition, roles, and responsibilities of the Coordinating Centre/Academic Research Organisation, Steering Committee, Clinical Events Committee (CEC), and Data Safety Monitoring Board (DSMB)

Coordinating Centre/Academic Research Organisation

The sponsor has delegated specific tasks to the Health Research Board - Clinical Research Facility, Galway (HRB-CRFG), as the coordinating centre. Whenever "sponsor" is mentioned, this includes its delegate(s) as applicable. Responsibilities and roles are described in "Responsibilities of the sponsor".

Steering Committee

The Steering Committee which includes the chief investigator is responsible for the overall design, conduct, and supervision of the study. The Steering Committee also reviews the progress of the study at regular intervals to ensure participant safety and study integrity.

Clinical Events Committee (CEC)

The Clinical Events Committee (CEC) is an independent committee comprised of interventional cardiologists who are not participants as site investigators in the study. The CEC is responsible for the categorisation of death, MI, revascularisation, stent thrombosis, stroke and bleeding, based on the definitions in the protocol. Prior to any CEC activity, a study-specific CEC charter will be developed, which will describe the events to be adjudicated, the minimum amount of data required, and the algorithm to be followed in order to classify the events.

Data Safety Monitoring Board (DSMB)

Serious adverse events (events leading to serious disability or admission to hospital, life-threatening events or death) will be periodically reviewed and analysed by an independent DSMB. Members of this board are not affiliated with any (interventional) cardiology site enrolling patients into the trial, are not participating in the trial, and will declare any conflicts of interest should they arise. Based on safety data, the DSMB may recommend that the Steering Committee modify or stop the clinical trial. All final decisions regarding clinical trial/investigation modifications, however, rest with the Chief Investigator, Steering Committee and Sponsor.

All analyses are carried out aiming to protect the safety of the trial participants.

Supplementary Appendix 2. Data management plan

1. Direct access to source data/documents

Direct access will be granted to authorised representatives from the sponsor, and the regulatory authorities to permit trial-related monitoring, audits and inspections. Consent from

patients/legal representatives for direct access to data will also be obtained. The patients' confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

2. Data handling and record keeping

Data will be entered by all the sites in the study and will be handled and stored at the Health Research Board - Clinical Research Facility Galway (HRB-CRFG). It will be pseudo-anonymised and then processed by members of the research team at the HRB-CRFG. Data will also be submitted to SMT and will be stored pseudo-anonymised indefinitely.

3. Data collection, source documents and case report forms

Source documents are original documents, data, and records from which the participant's data are obtained. These include but are not limited to: original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, or evaluation checklists, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, X-rays, participant files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial). Identification of any data to be recorded directly in the Electronic Data Capture (EDC) system (that has no prior written or electronic record or data, like a questionnaire) is considered to be source data. Source data could be either paper-based or electronic.

The investigator and study staff are responsible for maintaining a comprehensive and centralised filing system (Investigator Site File) of all study-related essential documentation, suitable for inspection at any time by representatives from the sponsor and/or applicable regulatory authorities. Essential documents include:

- Participant files containing informed consent form (ICF) and supporting copies of source documentation as used for EDC completion. In addition, all original source documents supporting entries in the EDC must be maintained and be readily available.
- Study files containing the protocol with all amendments, Investigator's Brochure (IB), copies of relevant essential documents required prior to commencing a clinical study, and all correspondence to and from the independent Ethics Committee (IEC) and Sponsor.

Investigator and study staff should ensure that only authorised personnel, monitors or auditors have access to the study data.

These documents will be used to enter data on the case report forms. Once registered to a trial the patient will be provided with a unique, study-specific participant identifier and this will be the only way the patient will be identified in the database. Data will be directly entered into the Clinical Data Management System (CDMS) by the site staff.

The CDMS or EDC system is validated for use in clinical studies and allows the application of software logic to set-up data entry screens and data checks to ensure the completeness and accuracy of the data entered by the site personnel. Logic checks are applied to ensure data are complete and reflect the clinical data requirements of the study.

To protect data in the EDC system, all access to the EDC system is password-protected. All relevant study personnel (sponsor, site, Academic Research Organisation [ARO] or other) seeking access to the EDC system will follow a training before access is granted. The Investigator maintains an authorised signature log of appropriately qualified and trained site personnel to whom study duties have been delegated. All site personnel authorised to make entries and/or corrections on the EDC system are included on the authorised signature log. The EDC contains a system-generated audit trail that captures any changes made to a data field, including who made the change, why the change was made and the date and time it was made.

Data entry is by single data entry. Data queries will be generated within the CDMS for the investigational site as required to clarify data discrepancies or request missing information. The designated site staff will be required to respond to these queries and these responses will be reviewed by the Data Management Team. Any amendments to the data will be tracked within the audit trail of the CDMS.

Data reported on the case report forms that are derived from source documents must be consistent with the source documents or the discrepancies must be explained. All documents will be stored safely in confidential conditions. On all study-specific documents other than the signed consent, the participant will be referred to by the study participant identification number/code.

Patient identification on the case report form (CRF) will be through their unique trial identifier allocated at the time of enrolment. No names or other identifying details will be recorded on the CRF or in any other format.

4. Data reporting

Central data management will be performed by the Data Management Centre at the HRB-CRFG. This is applicable for data recorded in the EDC system as well as for data from other (external) sources, e.g., laboratory results, ECG, adjudication committees. Data received from external sources such as central labs will be reconciled to the EDC system. (S)AEs in the EDC will be reconciled with the safety database.

The Lead Data Manager will develop a Data Management Plan (DMP) which will detail all activities relating to the management of the clinical data. All project-specific data management documentation will be filed in a Data Management File (DMF). The Data Management Team will also develop a CDMS to store the clinical data. This will be developed following the relevant Data Management standard operating procedures (SOPs) and adhering to regulatory and appropriate legislative requirements.

Local user access to the electronic CRF will be controlled via assigned usernames and passwords, approved by the study Data Manager based at NUIG. Access to the central study database will be governed by HRB-CRFG SOPs and signed off by the Lead Site Investigator. Audit trails will log all transactions of data into and out of the system including time, date, user ID and the records involved. All external electronic communication with the central database will be protected by using Secure Socket Layer technology. The main database will be hosted in a secure enterprise scale data centre.

The research team will take every precaution to respect privacy in accordance with relevant legislation and EU directives on protection of individuals with regard to the processing of personal data.

The data in the study database will be pseudo-anonymised, so that a number will be assigned to each patient which will be mapped to identifiable patient details at each hospital site only. This means that the data in the database are non-identifiable but will permit re-identification by the local site investigator in case of emergencies and requirement to follow up the patient.

The data for this study may be transferred within and/or outside the EU in line with reporting requirements. For data transferred outside the EU, the data controller must be assured of the legality and privacy safeguards of the transfer and ensure adherence to all other applicable legislative and regulatory requirements including General Data Protection Regulation (GDPR) and Clinical Trial legislation pertaining to such data transfer.

Supplementary Appendix 3. Quality control and quality assurance

1. Compliance to the standards and regulations

The protocol, informed consent form (ICF) and other study-related documents will be submitted to the Ethics Committee (EC) and any other regulatory body as required per local regulations. The trial will be performed in accordance with the current approved protocol, Good Clinical Practice, ISO 14155, relevant regulations and SOPs as appropriate.

2. Protocol compliance

The investigators will conduct the study in compliance with the protocol and give approval/favourable opinion by the EC and the appropriate regulatory authority as required. All protocol modifications will be submitted to the ethics committees for review in accordance with the governing regulations. The site investigator should report any trial-related deviations, violations or serious breaches of Good Clinical Practice (GCP) and/or the trial protocol to the sponsor/delegate. The Principal Investigators (Pis) will report any serious breaches of GCP to the sponsor immediately after becoming aware of them.

3. Monitoring arrangements

In accordance with guidelines and regulations, monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and sponsor requirements.

The sponsor or the sponsor's representatives will perform on-site monitoring visits throughout the study, according to the monitoring manual, to verify adherence to the protocol/amendment(s); verify authenticity, completeness, accuracy, and consistency of the data; verify that the rights and well-being of human participants are protected; and verify adherence to guidelines and regulations.

The monitor should have access to participant medical records and other study-related records needed to verify the entries on the EDC. In case an electronic Patient Dossier (ePD) is used, controlled read-only access for the monitor should be arranged. If the ePD has not been validated, or the Monitor cannot be given access, a procedure must be available for generating certified copies of the source.

The monitor communicates and documents deviations from the protocol, SOPs, guidelines and regulations to the Investigator and verifies that appropriate action designed to prevent recurrence of the detected deviations is taken.

4. Quality control

Quality control procedures will be implemented beginning with the EDC and data quality control checks that are run on the database. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution. In addition, monitoring visits and possibly audits and inspections will ensure oversight of the full quality control process.

5. Audit and inspection

To ensure compliance with guidelines and regulations, a member of the sponsor's quality assurance unit may arrange to conduct audits to assess the performance of the study at the study sites and of the study documents originating there. The investigator will be informed of the audit as required.

In addition, inspections by regulatory health authority representatives and EC(s) are possible. The investigator should notify the sponsor immediately of any such inspection.
Audits and inspections may occur at any time during or after completion of the study.

Supplementary Appendix 4. Methods

QFR acquisition protocol

In QFR computation, two projections at least 25 degrees apart are obtained for each lesion of interest after intracoronary injection of nitroglycerine **(Supplementary Table 5)**. An end-diastolic frame is selected in each angiographic view and is used for the three-dimensional reconstruction of the segmented vessel. The reference vessel is selected in healthy segments preferably proximal and distal to the lesion of interest. The contrast frame count is performed in an angiographic run with contrast movement clearly visualised and preferably with frames from the same cardiac cycle. Frame count-based contrast-QFR is used for all analysis in order to determine the flow velocity [28].

Supplementary Appendix 5. Definition of the as-treated (AT) and per-protocol (PP) populations

As-treated (AT)

In as-treated analysis, patients or vessels are categorised according to the actual device implanted during the procedure. For example, a patient is randomised to the SYNERGY arm but actually treated with the Supraflex Cruz. This patient is categorised as being in the Supraflex Cruz group. The same principle applies to the vessel-level analysis. The deferred vessels are treated as the allocated arm. Whenever stent types other than the originally allocated stent are used in combination with the allocated stent in the same vessel (for VOCE)/patient (for POCE), such a vessel/patient is categorised according to the original allocation (randomisation).

PP - device - for patient level

The PP population (patient level) set will consist of all patients who have received only the assigned study stent at the index procedure(s). Patients who do not receive a study stent, or who receive any stent other than the study stent, will be excluded from the PP population (patient level).

PP - device - for vessel level

The PP vessel data set will consist of all vessels that have received only the assigned study stent at the index procedure(s). Vessels that do not receive a study stent, or that receive any stent other than the study stent to which they were randomised, will be excluded from the PP vessel data set.

PP - device and strategy - for patient level

The PP population (patient level) set will consist of all patients who have received only the assigned study stent in all the intended target lesions defined by QFR or all invasive physiological assessment at the index procedure(s). Patients who do not receive a study stent, or who receive any stent other than the study stent, or patients who have a deferred lesion

treated or a to be treated lesion deferred, will be excluded from the PP population (patient level).

PP - device and strategy - for vessel level

The PP vessel data set will consist of all vessels that have received only the assigned study stent in all the intended target lesions defined by QFR or all invasive physiological assessment at the index procedure(s). Vessels that do not receive a study stent, or that receive any stent other than the study stent to which they were randomised, will be excluded from the PP vessel data set.

All possible options are shown in **Supplementary Table 6**.

Supplementary Appendix 6. Pre-specified subgroup analyses

Concomitant disease and baseline risk factors

1. Treatment in relation to age at the time of randomisation.
2. Treatment in relation to sex.
3. Treatment in relation to BMI at the time of randomisation.
4. Treatment in relation to hypertension status at the time of randomisation.
5. Treatment in relation to hyperlipidaemia status at the time of randomisation.
6. Treatment in relation to diabetes status at the time of randomisation.
7. Treatment in relation to renal function at the time of randomisation.
8. Treatment in relation to smoking status.
9. Treatment in relation to COPD at the time of randomisation.
10. Treatment in relation to PVD at the time of randomisation.
11. Treatment in relation to history of cardiovascular disease.
12. Treatment in relation to history of stroke or TIA.
13. Treatment in relation to EF at the time of randomisation.
14. Treatment in relation to WBC at the time of randomisation.
15. Treatment in relation to platelets at the time of randomisation.
16. Treatment in relation to high bleeding risk according to ARC definition at the time of randomisation.
17. Treatment in relation to TWILIGHT inclusion criteria at the time of randomisation.
18. Impact of bleeding scores (PRECISE-DAPT, DAPT, CRUSADE, ACUITY, PARIS score) in risk stratifying bleeding and ischaemic events and their interaction with treatment.
19. Impact of SYNTAX score and its derived scores (functional SYNTAX score, SYNTAX score II, logistic clinical SYNTAX score) in risk stratifying bleeding and ischaemic events and their interaction with treatment.

Clinical presentation

20. Treatment in relation to clinical presentation (CCS or non-STEMI) at the time of randomisation.

21. Treatment in relation to the status of CHF at the time of randomisation.
22. Treatment in relation to atrial fibrillation at the time of randomisation.
23. Treatment in relation to blood pressure at the time of randomisation.
24. Treatment in relation to heart rate at the time of randomisation.
25. Treatment in relation to CRP at the time of randomisation.
26. Treatment in relation to cardiac biomarker at the time of randomisation.

PCI procedure

27. Impact of QFR/FFR/iFR pre and post PCI on ischaemic events.
28. Impact of IVUS/OCT pre and post PCI on ischaemic events.
29. Treatment regimen in relation to procedure time.
30. Treatment regimen in relation to specific lesion subsets including:
    a. Bifurcation
    b. CTO (stratified by J-CTO, EuroCTO score)
    c. Small vessels (≤2.75 mm)
31. Treatment regimen in relation to staged procedures.
32. Treatment regimen in relation to access site (radial, femoral).
33. Treatment regimen in relation to complex procedure according to ESC definition.
34. Treatment regimen in relation to stenting:
    a. Single stent length >30 mm
    b. Total stent length >60 mm
    c. Overlapping stents
35. Impact of residual SYNTAX score and residual functional SYNTAX score.

Medication

36. Treatment regimen in relation to medical therapy including:
    a. Anticoagulant
    b. ACE-I
    c. Beta-blocker
    d. Statin
    e. PCSK-9 inhibitor
    f. Insulin
    g. SGLT-2
    h. DPP-4
    i. Proton pump inhibitor
    j. NSAID
37. Impact of adherence to antiplatelet therapy.

Supplementary Appendix 7. The role of the funding source and responsibilities of the sponsor

The role of the funding source (SMT)

The funder will have no role in the study design, data collection, management, analysis or interpretation.

Responsibilities of the sponsor (The National University of Ireland Galway)

1. Sponsor role

The sponsor has overall responsibility for the conduct of the study, including assurance that the study satisfies international standards and the regulatory requirements of the relevant (competent) authorities.

2. General duties

Prior to allowing the sites to start enrolling participants into the study, the sponsor is responsible for selecting investigators, ensuring that Ethics Committee (EC) approvals are obtained where applicable, and signing the investigator site agreement with the investigators and/or hospitals. It is the sponsor's responsibility to ensure that the study is conducted according to guidelines and regulations, the study protocol, and any conditions of approval imposed by the EC or regulatory authorities. Additionally, the sponsor will ensure proper clinical site monitoring.

3. Selection of clinical investigators and sites

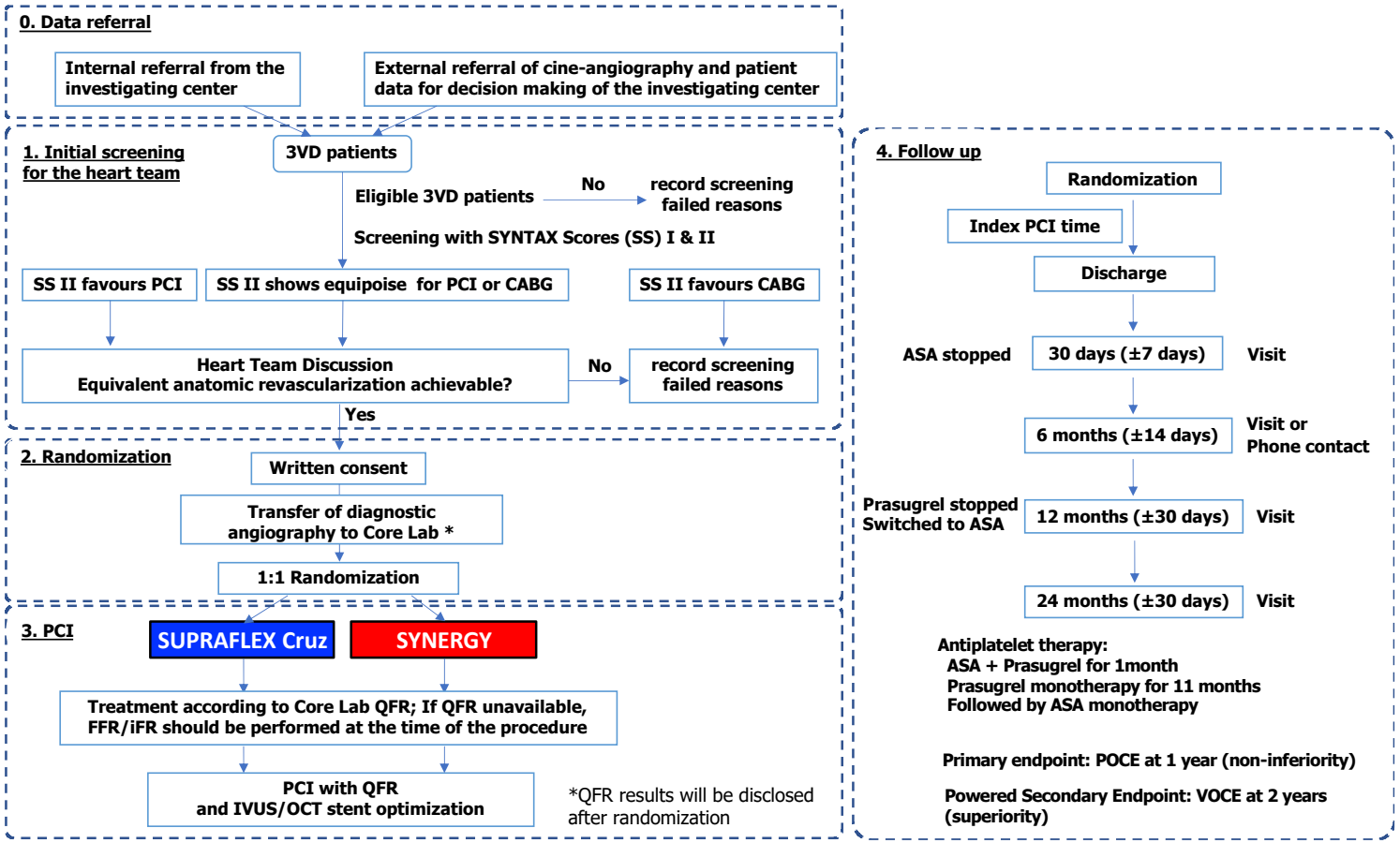
The sponsor will select qualified investigators and facilities which have an adequate study patient population to meet the requirements of the investigation.

4. Training of investigators and site personnel and site monitoring

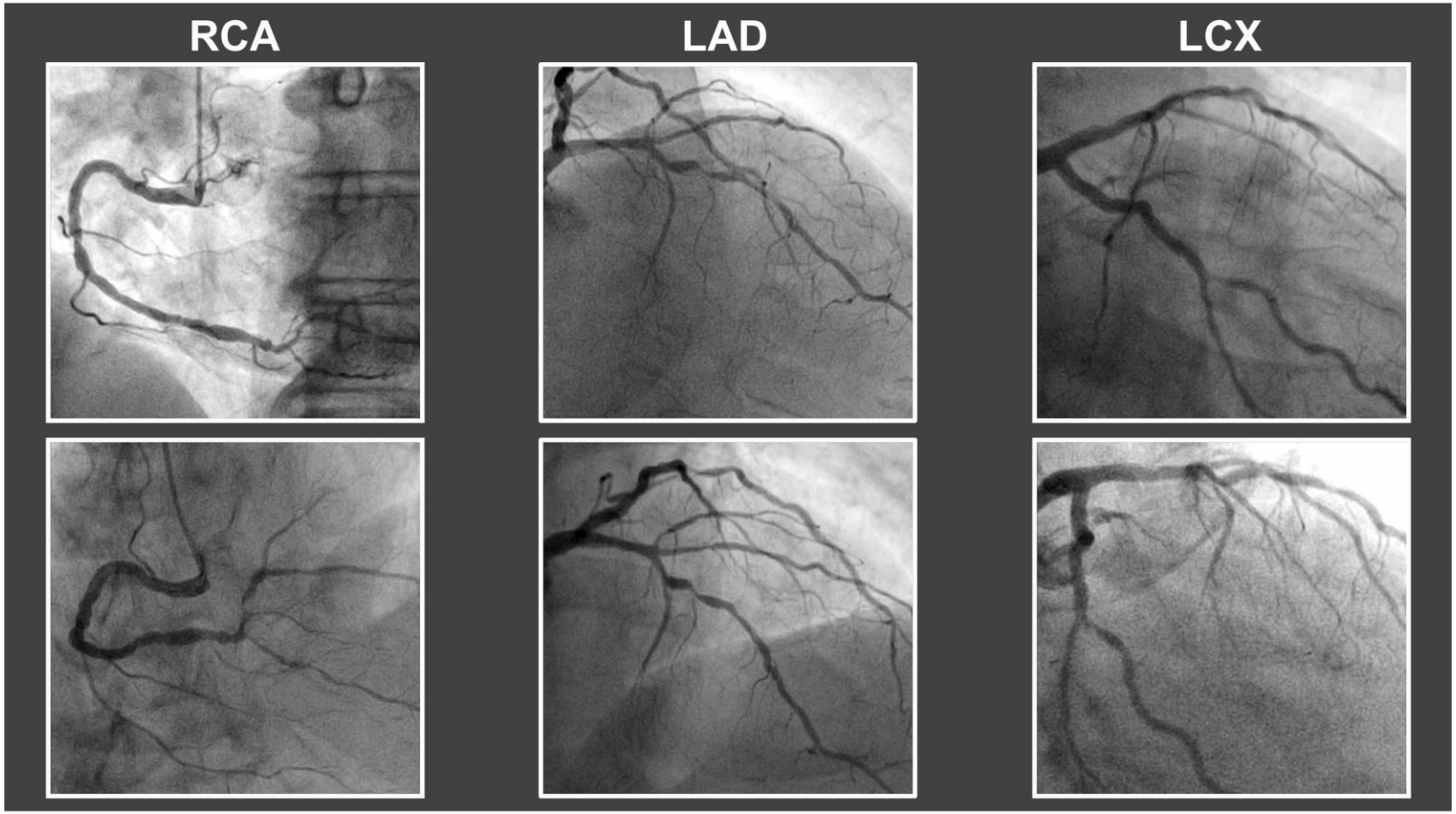
The training of the investigator and appropriate clinical site personnel will be the responsibility of the sponsor, and may be conducted during an investigator meeting, a site initiation visit and/or other appropriate training sessions. Training of site staff not present during the initiation visit will be the responsibility of the investigator.

5. Continuous risk benefit analysis

The sponsor is responsible for the continuous assessment of the risk-benefit analysis throughout the study.

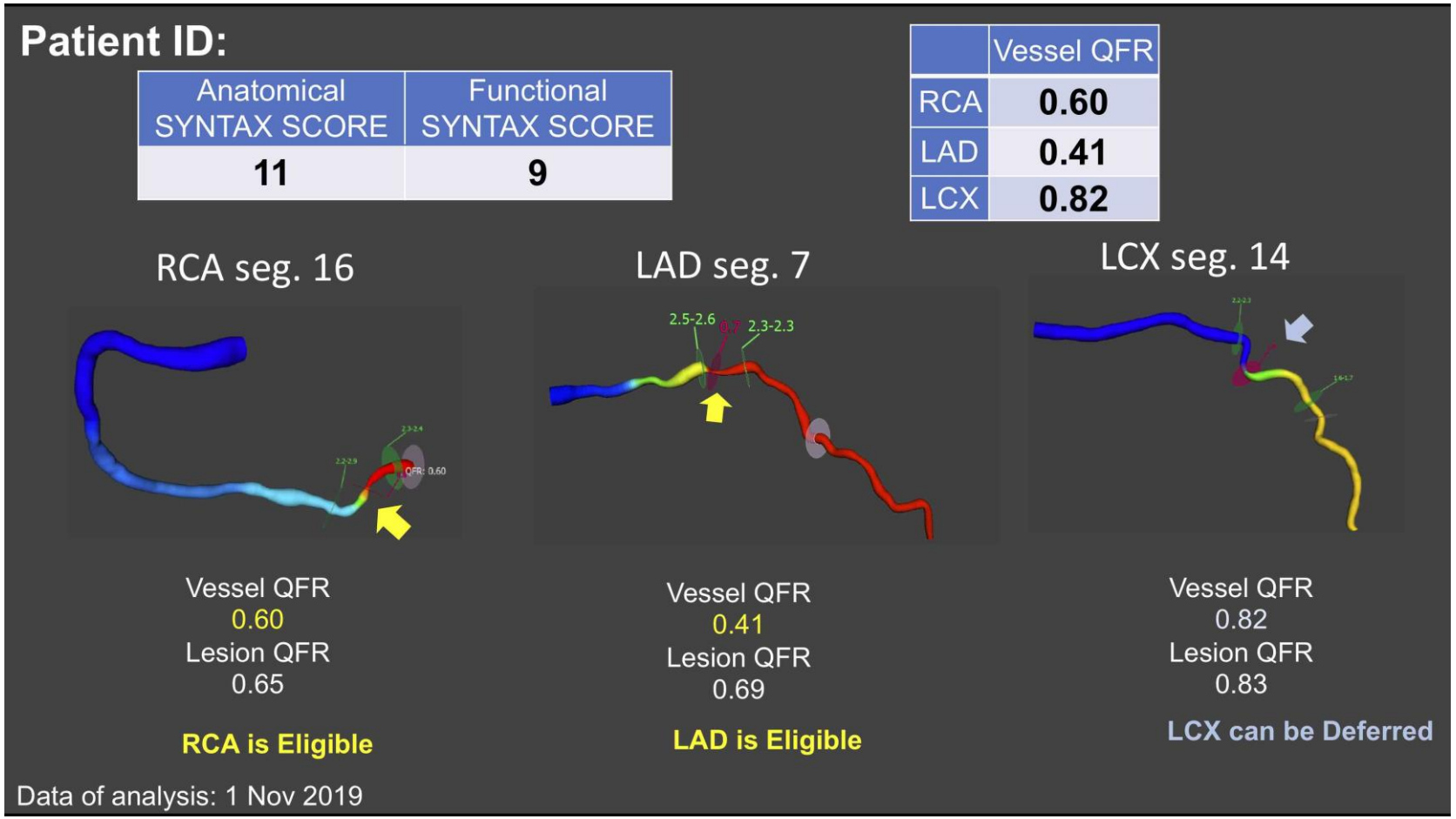


Supplementary Figure 1. Study flow chart.
ASA: acetylsalicylic acid (aspirin); CABG: coronary artery bypass graft; FFR: fractional flow reserve; iFR: instantaneous wave-free ratio; IVUS: intravascular ultrasound; OCT: optical coherence tomography; PCI: percutaneous coronary intervention; POCE: patient-oriented composite endpoint; QFR: quantitative flow ratio; SS: SYNTAX score; 3VD: three-vessel disease without left main disease; VOCE: vessel-oriented composite endpoint



Supplementary Figure 2A. QFR assessment.

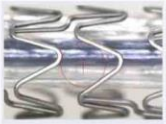
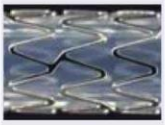
Two projections of angiography for QFR assessment in each vessel.



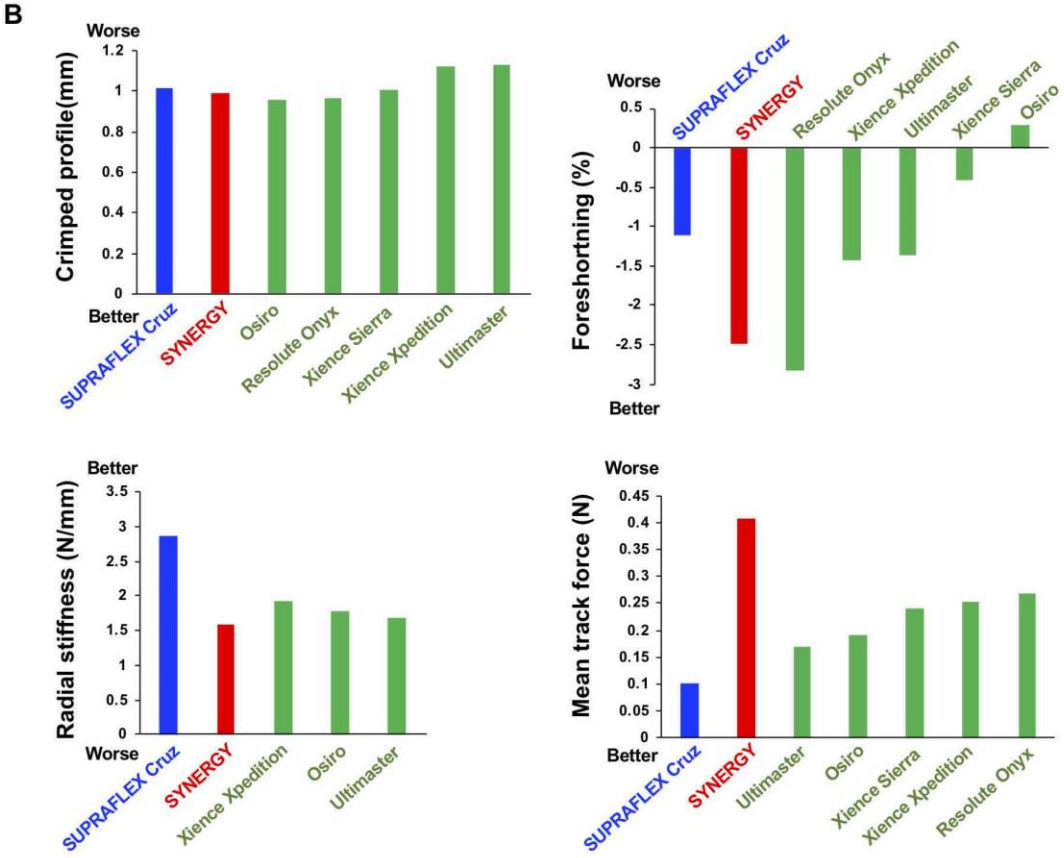
Supplementary Figure 2B. QFR assessment.

Results of QFR, anatomical SYNTAX score I, and functional SYNTAX score by core lab.

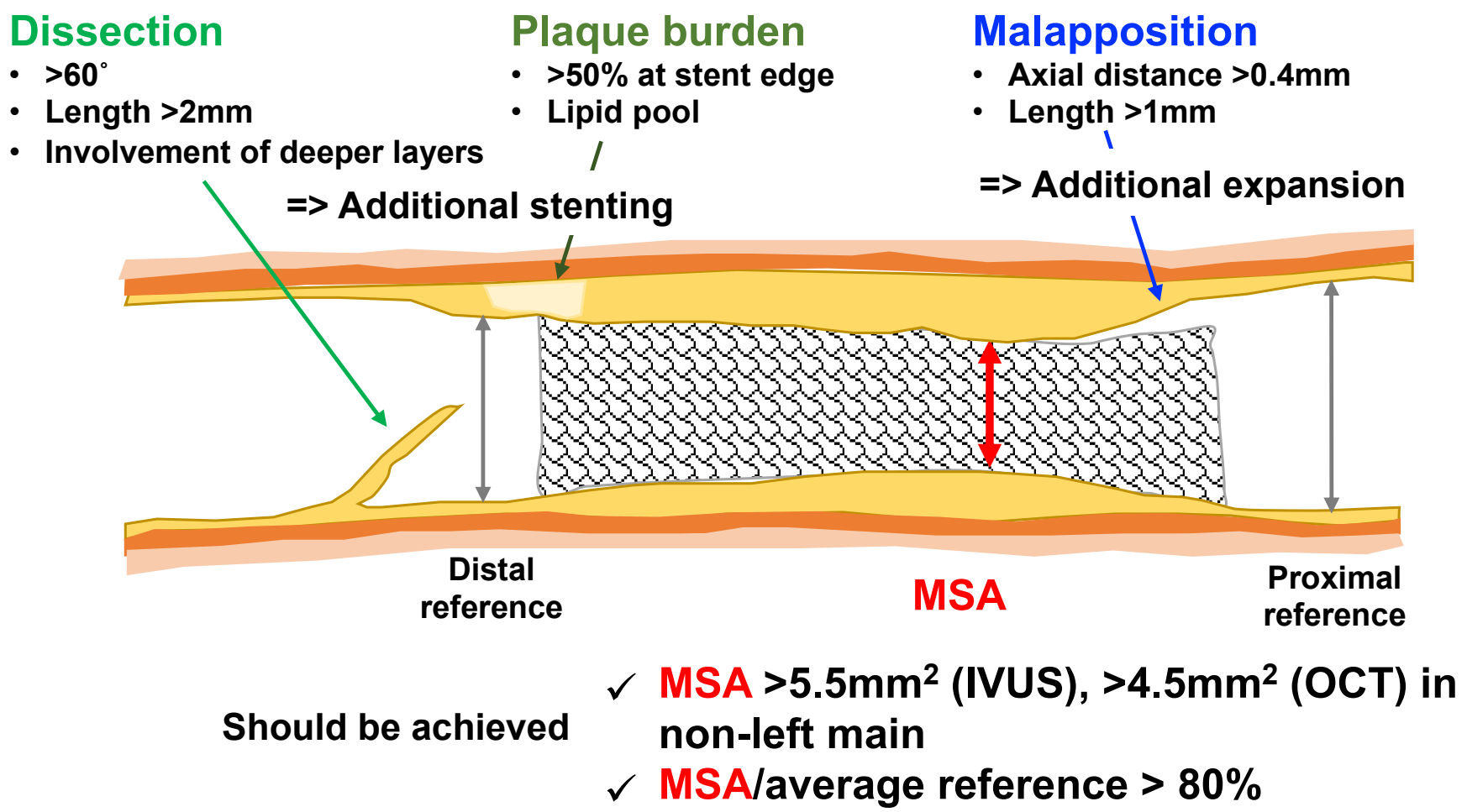
A

Stent	Stent design	Stent platform	Strut thickness	Drug	Coating	Polymer
SUPRAFLEX Cruz		Cobalt chromium	60 μm (2.00-4.5mm)	Sirolimus	Biodegradable	PLLA+PLCL +PVP
SYNERGY		Platinum chromium	74 μm (2.25-2.75mm) 79 μm (3.00-3.5mm) 81 μm (>3.5mm)	Everolimus	Biodegradable	PLGA

B

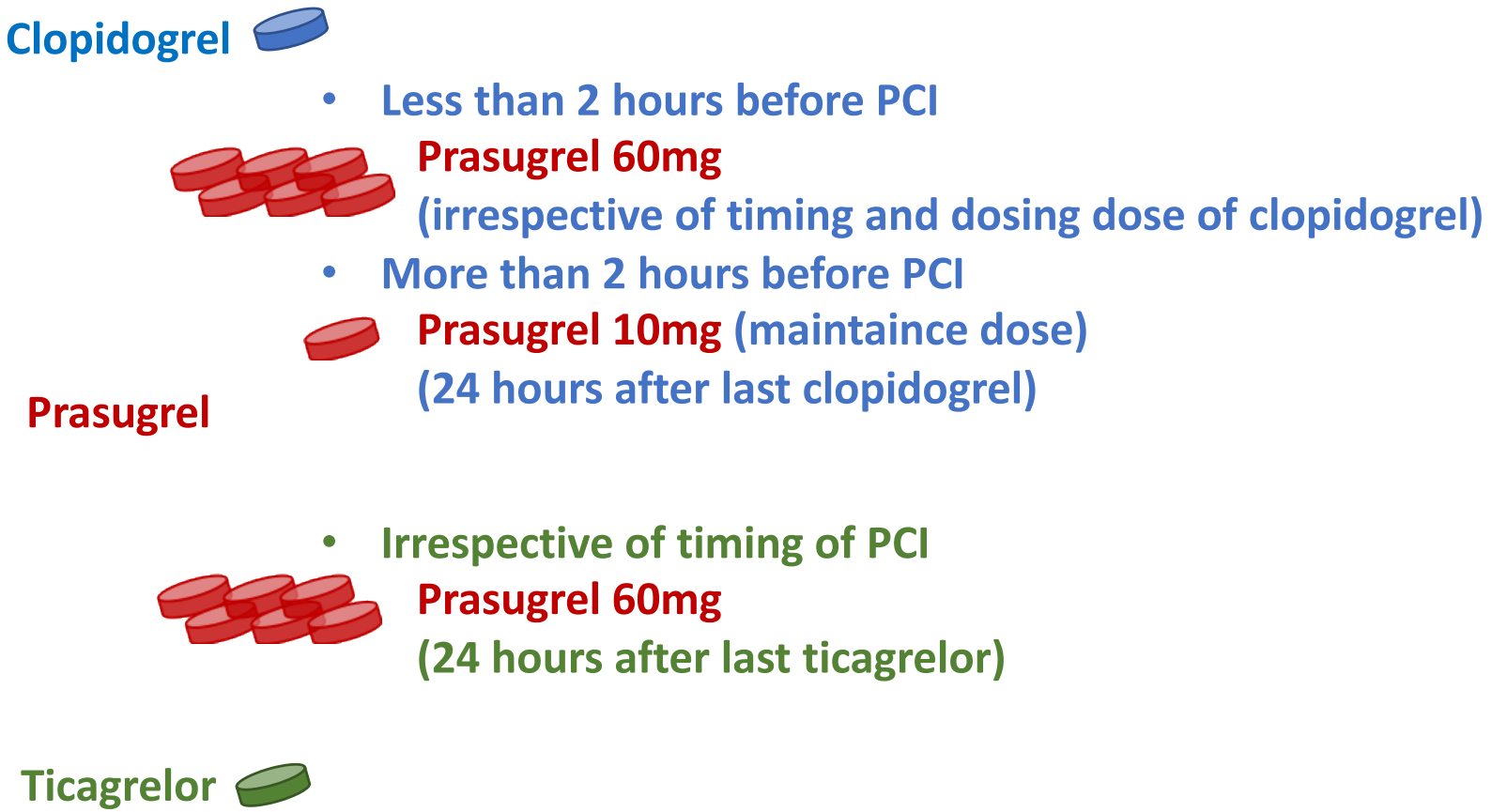


Supplementary Figure 3. Characteristics of Supraflex Cruz and SYNERGY stents.
A) Comparison between Supraflex Cruz and SYNERGY stents.
PLCL: poly-L-lactide-co-caprolactone; PLGA: poly lactic-co-glycolic acid; PLLA: poly-L-lactide; PVP: polyvinylpyrrolidone
B) Mechanical properties (crimped profile, foreshortening, radial stiffness, and mean track force for pushability) of Supraflex Cruz, SYNERGY and widely used stents. Tests were performed on Supraflex Cruz (2.50x40 mm), SYNERGY (2.5x38 mm), Orsiro (2.50x40 mm), Resolute Onyx (2.5x38 mm), XIENCE Sierra (2.5x38 mm), XIENCE Xpedition (2.5x38 mm), and Ultimaster (2.5x38 mm).



Supplementary Figure 4. Stent optimisation by intravascular imaging.

IVUS: intravascular ultrasound; MSA: minimal stent area; OCT: optical coherence tomography



Supplementary Figure 5. Switching from clopidogrel or ticagrelor to prasugrel**.**

Supplementary Table 1. Five treatment principles for "best practice" in the field of percutaneous coronary intervention (PCI).

Five treatment principles	
i.	Patient selection based on SYNTAX score II recommendation and Heart Team consensus
ii.	Targeted PCI based on physiological assessment using resting and hyperaemic indices
iii.	Use of intracoronary imaging for post-stent optimisation
iv.	PCI of chronic total coronary occlusion for complete revascularisation
v.	Optimal medical treatment before, during and after PCI

Supplementary Table 2. A preliminary list of countries and the number of centres.

List of countries	Number of centres
Ireland	5
The Netherlands	4
Germany	8
Poland	11
United Kingdom	10
France	6
Spain	11
Italy	5

Supplementary Table 3. Inclusion and exclusion criteria.

(A) Inclusion criteria

1. Male or female patients ≥18 years.
2. At least 1 stenosis (angiographic, visually determined *de novo* lesions with ≥50% DS) in all 3 major epicardial territories (LAD and/or side branch, LCX and/or side branch, RCA and/or side branch) supplying viable myocardium without left main involvement*.
3. The vessel should have a reference vessel diameter ranging from ≥2.25 mm to ≤4.5 mm (no limitation on the number of treated lesions, vessels, or lesion length).
4. Patients with chronic coronary syndrome or stabilised acute coronary syndromes**.
5. All anatomical SYNTAX scores are eligible for initial screening with the SYNTAX score II, provided that the SYNTAX score II recommends equipoise risk (PCI or CABG) or PCI only.
6. Patient has been informed of the nature of the study and agrees to its provisions and has provided written informed consent as approved by the Ethics Committee and is willing to comply with all protocol-required evaluations.
7. Agree with conditional longer follow-up from 2 to 5 years, yearly.

* Patients with ostial LAD or ostial LCX - Medina 0,0,1 or Medina 0,1,0 - may be enrolled. Patients with hypoplastic RCA (or LCX) with absence of descending posterior and presence of a lesion in the LAD and LCX (or RCA) territories may be included as a 3VD equivalent.

** In subjects showing elevated troponin (e.g., non-STEMI patients) at baseline (within 72 hrs pre-PCI), an additional blood sample must be collected prior to randomisation to confirm that the elevated troponin levels are stable or have dropped, or CK-MB and CK levels are within normal range, and the ECG does not show ST-elevation.

(B) Exclusion criteria

1. Under the age of 18.
2. Unable to give informed consent.
3. Patient is a woman who is pregnant or nursing (a pregnancy test must be performed within 7 days prior to the index procedure in women of child-bearing potential according to local practice).
4. Known contraindication to medications such as aspirin, heparin, bivalirudin, prasugrel and ticagrelor.
5. Prior PCI or prior CABG.
6. Ongoing ST-elevation myocardial infarction (STEMI).
7. Cardiogenic shock.
8. Concurrent medical condition with a life expectancy of less than 2 years.
9. Currently participating in another trial and not yet at its primary endpoint.
10. Patient with both ostial LAD and ostial LCX stenosis, or left main stenosis.
11. Previous intracranial haemorrhage.

Supplementary Table 4. Endpoints.

Primary endpoint

- Non-inferiority comparison of POCE at 12 months.

Powered secondary endpoint

- Superiority comparison in the per protocol analysis (per vessel level) of VOCE [17] at 24 months.

Other secondary endpoints

1. Composite of POCE at 24 months.
2. All individual components of POCE and VOCE at 12 and 24 months.
3. TLF/DOCE defined as cardiac death, TV MI* and clinically indicated target lesion revascularisation at 12 and 24 months.
4. TVF defined as cardiovascular death, TV MI* and clinically indicated target vessel revascularisation at 12 and 24 months.
5. Rates of individual components of TLF at 12 and 24 months.
6. Definite/probable stent thrombosis rates according to ARC-2 [14] classification at 12 and 24 months.
7. Device success [18].
8. Procedure success defined as device success and free from POCE at discharge.

POCE [14] is a composite clinical endpoint of (i) all-cause death, (ii) any stroke (modified Rankin scale ≥1), (iii) any MI, or (iv) any repeat revascularisation.

VOCE [17] is a composite of (i) vessel-related cardiovascular death, (ii) vessel-related periprocedural and spontaneous MI, or (iii) CPI-TVR (clinically and physiologically indicated target vessel revascularisation).

* Definition of MI will follow the SCAI consensus for periprocedural MI ≤48 hours [15], and the Fourth Universal Definition (FUD) for MI >48 hours after the index procedure [16].

Supplementary Table 5. Recommended projections for specific lesion segments.

Vessel/bifurcation	1st view	2nd view
LM+LAD/LCX	RAO 20, caudal 25	AP, caudal 10
LAD/diagonal	AP, cranial 45	RAO 35, cranial 20
LCX/OM	LAO 10, caudal 25	RAO 25, caudal 25
Proximal+mid RCA	LAO 45, caudal 0	AP, caudal 0
PLA/PDA	LAO 45, caudal 0	LAO 30, caudal 30

Two good projections at least 25 degrees apart are required.
AP: anterior posterior; LAD: left anterior descending; LAO: left anterior oblique; LCX: left circumflex artery; LM: left main; OM: obtuse marginal; PDA: posterior descending artery; PLA: posterolateral artery; RAO: right anterior oblique; RCA: right coronary artery

Supplementary Table 6. All possible options for study population.

QFR/FFR/iFR	Allocated stent	Comparator stent	Other stent	As-treated	Per-protocol device	Per-protocol device and strategy
Compliant	+	-	-	Allocated	Included	Included
Compliant	+	-	+	Included according to original allocation	Excluded	Excluded
Compliant	+	+	-	Included according to original allocation	Excluded	Excluded
Compliant	+	+	+	Included according to original allocation	Excluded	Excluded
Compliant	-	-	-	Included according to original allocation	Included	Included
Compliant	-	-	+	Excluded	Excluded	Excluded
Compliant	-	+	-	Included as comparator arm	Excluded	Excluded
Compliant	-	+	+	Included as comparator arm	Excluded	Excluded
Non-compliant	+	-	-	Included according to original allocation	Included	Excluded
Non-compliant	+	-	+	Included according to original allocation	Excluded	Excluded
Non-compliant	+	+	-	Included according to original allocation	Excluded	Excluded
Non-compliant	+	+	+	Included according to original allocation	Excluded	Excluded
Non-compliant	-	-	-	Excluded	Excluded	Excluded
Non-compliant	-	-	+	Excluded	Excluded	Excluded
Non-compliant	-	+	-	Included as comparator arm	Excluded	Excluded
Non-compliant	-	+	+	Included as comparator arm	Excluded	Excluded

“Compliant” means compliant in all vessels, and “non-compliant” means non-compliant in one or more vessels to the results of QFR/FFR/iFR.