EuroIntervention
2025;21:571-580
DOI: 10.4244/EIJ-D-24-00829

Prasugrel monotherapy versus standard DAPT in STEMI patients with OCT-guided or angio-guided complete revascularisation: design and rationale of the randomised, multifactorial COMPARE STEMI ONE trial

Valeria Paradies[1,2]*, MD; Nicolas M. Van Mieghem[2], MD, PhD; Rohit M. Oemrawsingh[3], MD, PhD; Gert Richardt[4], MD, PhD; Giovanni Esposito[5], MD, PhD; Gianluca Campo[6], MD, PhD; Francesco Burzotta[7], MD, PhD; Paolo Canova[8], MD, PhD; Axel Linke[9], MD; Italo Porto[10], MD, PhD; Daniela Trabattoni[11], MD; Koen Teeuwen[12], MD, PhD; Tom Adriaenssens[13], MD, PhD; Petr Kala[14], MD, PhD; Goran Stankovic[15], MD, PhD; Ria van Vliet[1], BSc; Daniele Giacoppo[16,17,18], MD, PhD; Joost Daemen[2], MD, PhD; Pieter C. Smits[1], MD, PhD

Corresponding author: Department of Cardiology, Maasstad Hospital, Maasstadweg 21, 3079 DZ, Rotterdam, the Netherlands. E-mail: paradiesvaleria@gmail.com

This paper also includes supplementary data published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-24-00829

ABSTRACT

Monotherapy with a potent $P2Y_{12}$ receptor antagonist after 1 month of dual antiplatelet therapy (DAPT) may reduce bleeding in the absence of increased ischaemic events compared to 12-month DAPT in patients with acute coronary syndrome undergoing percutaneous coronary intervention (PCI). PCI guidance with optical coherence tomography (OCT) may enhance stent expansion. COMPARE STEMI ONE is an international, multicentre, open-label, randomised controlled trial. In 1,656 ST-segment elevation myocardial infarction (STEMI) patients, prasugrel monotherapy after 1 month of DAPT, as compared to standard 12-month prasugrel-based DAPT, will be tested for non-inferiority for the primary composite endpoint of net adverse clinical events – defined as all-cause death, myocardial infarction, stroke, or Bleeding Academic Research Consortium Type 3 or 5 bleeding events – at 11 months after randomisation. Furthermore, an ancillary substudy will test the superiority of OCT-guided versus angiography-guided staged complete revascularisation in achieving a larger minimal stent area (MSA) in non-culprit lesions during staged procedures. COMPARE STEMI ONE is the first randomised controlled trial assessing an abbreviated 1-month DAPT regimen followed by prasugrel monotherapy in the context of STEMI. The trial will also study the value of OCT-guided PCI in terms of the MSA of non-culprit lesions and may elucidate potential synergies between intravascular imaging-guided PCI and abbreviated DAPT regimens. (ClinicalTrials.gov: NCT05491200)

KEYWORDS: antiplatelet therapy; optical coherence tomography; STEMI

SUBMITTED ON 09/09/2024 - REVISION RECEIVED ON 1st 11/11/2024 / 2nd 03/01/2025 - ACCEPTED ON 04/02/2025

Antiplatelet therapy plays a pivotal role in reducing thrombotic complications and systemic ischaemic events among acute coronary syndrome (ACS) patients undergoing percutaneous coronary intervention (PCI), albeit with an increased risk of bleeding[1]. In the early phase following PCI for ACS, an aggressive antithrombotic therapy outweighs the risk of bleeding complications. In the maintenance phase (after 30 days), this benefit is counteracted by subsequent higher rates of major bleeding complications, particularly in real-life clinical settings, where patient complexity impacts both haemorrhagic and thrombotic risks[2]. New-generation drug-eluting stents (DES) and the adoption of intravascular imaging to optimise PCI have reduced the incidence of stent thrombosis and may justify a less intensive antithrombotic therapy[3,4].

Recent randomised controlled trials (RCTs) have explored the hypothesis that abbreviated dual antiplatelet therapy (DAPT) with potent $P2Y_{12}$ antiplatelet drugs may mitigate bleeding risk without increasing ischaemic events[5-7]. In the absence of compelling data supporting the superiority of one agent over the other, the choice between prasugrel and ticagrelor is primarily driven by physician preference, relative contraindications, market availability, and patient characteristics. This has resulted in an increased use of ticagrelor at discharge[8]. Although the ISAR-REACT 5 Trial demonstrated a lower incidence of the composite endpoint of death, myocardial infarction (MI) or stroke with prasugrel than ticagrelor in 4,018 ACS patients, limited data are available for abbreviated prasugrel-based DAPT in ACS[9-11].

Up to 50% of patients with ACS present with multivessel disease (MVD)[12]. Multiple studies have validated the importance of complete revascularisation, demonstrating fewer unplanned revascularisations and reductions in cardiovascular mortality and spontaneous MI[13-16]. The European Society of Cardiology (ESC) guidelines endorse a Class I recommendation for complete revascularisation in ST-segment elevation MI (STEMI) patients with MVD, either during the index procedure or within 45 days[17]. Intravascular imaging optical coherence tomography (OCT) may provide valuable insights into plaque characteristics, including fatty content, fibrous cap thickness, lesion severity, lesion length, and stent landing zones before treatment. It may also help assess stent expansion, apposition, lesion coverage and possible complications after PCI[17,18]. However, no data exist on the use of intravascular imaging in the context of complete revascularisation or an abbreviated DAPT regimen in the context of STEMI.

Methods

OBJECTIVES AND STUDY DESIGN

COMPARE STEMI ONE is an international, multicentre, open-label, randomised controlled trial with a 1:1 randomisation comparing prasugrel-based short DAPT (30-45 days) followed by prasugrel monotherapy versus a standard DAPT regimen in STEMI patients in terms of net adverse clinical events (NACE). In the subgroup of STEMI patients with MVD, a subrandomisation compares OCT-guided complete revascularisation versus angiography-guided complete revascularisation in terms of efficacy and safety endpoints.

The primary objective of this study is to demonstrate the non-inferiority of 30-45 days of DAPT followed by prasugrel monotherapy versus standard 12-month DAPT (acetylsalicylic acid [ASA]+prasugrel) in patients admitted for STEMI treated with primary PCI regarding the net composite endpoint of ischaemic and bleeding events.

The ancillary objective of the study is to demonstrate the superiority of OCT-guided revascularisation of non-culprit lesion(s) compared to an angiography-guided approach in terms of minimal stent area (MSA) in patients with MVD who undergo staged complete revascularisation after primary PCI.

The clinical investigation is being conducted in up to 20 centres across Europe. A total of 1,656 STEMI patients, 50% with MVD, will be enrolled and followed up for 3 years.

Patients with MVD who have been randomised to either angio- or OCT-guided PCI and who do not fulfil the eligibility criteria for DAPT randomisation at 30-45 days will be included in the analysis of the co-primary endpoint (post-PCI MSA) and will remain in a parallel registry, receiving clinical follow-up at 1 year.

The study design appears in **Figure 1**.

RANDOMISATION AND TREATMENT ALLOCATION

Patients are screened for inclusion immediately after STEMI diagnosis. Patients will be screened and enrolled to achieve a 1:1 trial population of single-vessel disease (SVD) and MVD patients. During the index procedure, only the culprit lesion will be treated as per standard of care. Patients with MVD will undergo staged complete revascularisation within 15 days. During the staged procedure, patients will be randomised 1:1 to OCT-guided or angio-guided PCI. All patients will undergo an OCT study at the end of PCI.

At 30-45 days, patients with SVD and MVD will be randomised to prasugrel monotherapy (ASA discontinuation) or standard prasugrel-based DAPT if no ischaemic or major bleeding event and no protocol violation have occurred **(Figure 2)**. Among patients with MVD, randomisation to prasugrel monotherapy or DAPT at 30-45 days will be stratified based on the staged revascularisation strategy (OCT- or angio-guided) to ensure balance in the study treatment algorithms. Prasugrel monotherapy or prasugrel-based standard DAPT will be given in an open-label manner.

Abbreviations

ACS	acute coronary syndrome	**DES**	drug-eluting stent	**NACE**	net adverse clinical events
ASA	acetylsalicylic acid	**DSMB**	data and safety monitoring board	**OCT**	optical coherence tomography
BARC	Bleeding Academic Research Consortium	**MSA**	minimal stent area	**PCI**	percutaneous coronary intervention
DAPT	dual antiplatelet therapy	**MVD**	multivessel disease		

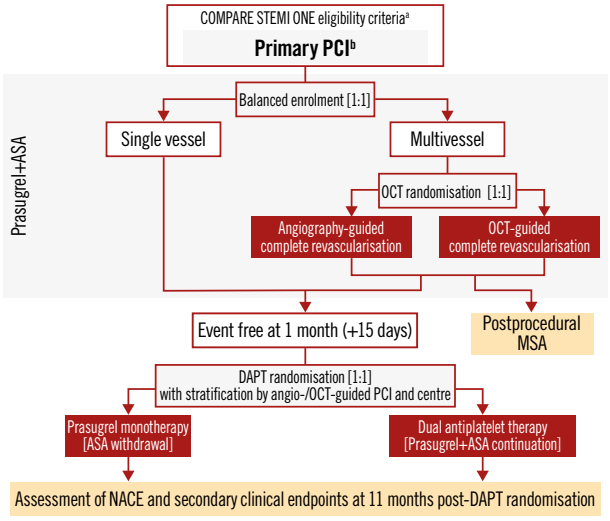

Figure 1. *Study design flowchart. [a]Loading with prasugrel is among the inclusion criteria. [b]Revascularisation of only the culprit lesion is recommended. ASA: acetylsalicylic acid; DAPT: dual antiplatelet therapy; MSA: minimal stent area; NACE: net adverse clinical events; OCT: optical coherence tomography; PCI: percutaneous coronary intervention*

BALANCED SCREENING AND ENROLMENT

Patients will be screened and enrolled to achieve a 1:1 trial population of SVD and MVD patients. Out of every group of 30 patients screened and enrolled per site, 15 patients should present with MVD. After the enrolment of 15 patients with SVD, screening and enrolment of those patients will be temporarily halted until the target number of MVD patients in each group has been reached and vice versa.

STUDY POPULATION, INCLUSION AND EXCLUSION CRITERIA

Consecutive patients admitted for STEMI undergoing primary PCI will be screened and considered for inclusion in the study. Eligible patients will receive ASA as per standard of care and a prasugrel loading dose of 60 mg, followed by 30-45 days of DAPT (ASA+prasugrel 10 mg). In patients with multivessel disease, only primary PCI of the culprit lesion will be allowed during the index procedure. Staged PCI of the non-culprit lesion(s) will be planned within 15 days. During the staged PCI procedure, OCT will be performed at the end of PCI of each vessel, but patients will be randomly assigned 1:1 to OCT- or angio-guided stent optimisation.

The XIENCE everolimus-eluting platform (Abbott) will be the preferred stent for the study. Other DES platforms will be used as bailout options. Details on study devices and study procedures are shown in **Supplementary Appendix 1** and **Supplementary Appendix 2**.

All patients with no ischaemic or major bleeding event at the 1-month office visit following primary PCI will be randomised 1:1 to receive prasugrel monotherapy (ASA discontinuation) for 11 months or DAPT continuation for 11 months (standard 12-month DAPT duration). The randomisation will occur at 1 month, within a 15-day window, to take into account those patients with MVD undergoing staged complete revascularisation.

Figure 1 displays the trial randomisation schemes for STEMI patients with SVD and MVD.

Inclusion and exclusion criteria that are relevant during the index procedure and the 1-month clinical follow-up visit are tabulated in **Table 1**. Further details on investigational

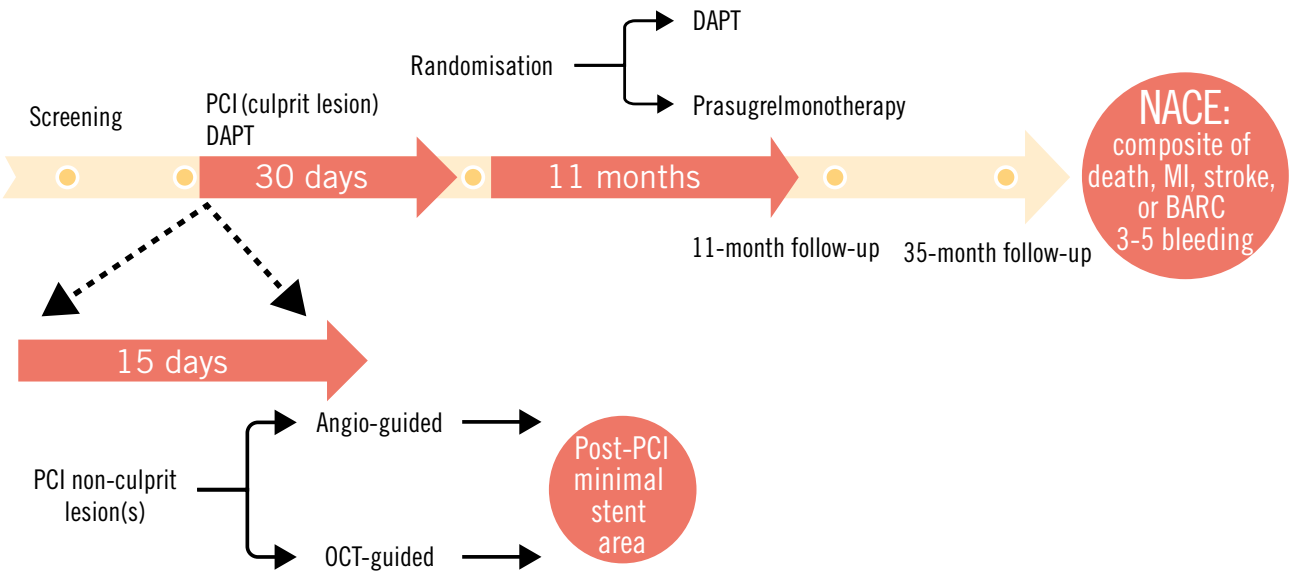

Figure 2. *Timeline of COMPARE STEMI ONE. BARC: Bleeding Academic Research Consortium; DAPT: dual antiplatelet therapy; NACE: net adverse clinical events; OCT: optical coherence tomography; PCI: percutaneous coronary intervention*

Table 1. Inclusion and exclusion criteria.

Inclusion criteria
Eligibility at index procedure:
Patients of 18 years and above
Written or witnessed oral consent
All STEMI patients who are scheduled to be treated with PCI:
Chest discomfort suggestive of cardiac ischaemia ≥20 min at rest with 1 of the following ECG features:
ST-segment elevation ≥2 contiguous ECG leads
New or presumably new left bundle branch block
Eligibility at DAPT randomisation visit (30-45 days):
All patients who have provided informed consent
Compliance to DAPT with no regimen modifications (non-adherence Academic Research Consortium)
No occurrence of significant event (such as MI, unplanned revascularisation, stent thrombosis, stroke, major vascular complication/bleeding BARC Type 3 or greater)
Successful revascularisation: successful delivery and deployment of the study device(s), with final residual stenosis of <30% (visually) for all target lesions
Complete revascularisation performed when more than 1 significant lesion, in staged procedure(s) occurring within 15 days from the index procedure. Physiological assessment highly recommended for lesions with stenosis between 50% and 90%
Exclusion criteria
Patients on oral anticoagulation
Contraindication to $P2Y_{12}$ inhibitors and/or to CardioAspirin or to any of the excipients (hypersensitivity, history of any stroke or transient ischaemic attack within the last 12 months, active bleeding or haemorrhagic diathesis, fibrin-specific fibrinolytic therapy less than 24 h before randomisation, severe hepatic dysfunction (Child-Pugh C), history of asthma induced by the administration of salicylates or substances with a similar action, notably non-steroidal anti-inflammatory medicines, history of gastrointestinal perforation or acute gastrointestinal ulcers, severe cardiac failure (NYHA Class III or IV), combination with methotrexate at doses of 15 mg/week or more)
Patients who have received $P2Y_{12}$ inhibitors other than prasugrel in the ambulance (ticagrelor or clopidogrel loading dose) or are already on $P2Y_{12}$ inhibitors may be enrolled in the protocol, provided that the prasugrel loading dose is administered at admission, according to current guideline recommendations
Concomitant oral or intravenous therapy with strong CYP3A inhibitors (e.g., ketoconazole, itraconazole, voriconazole, telithromycin, clarithromycin, nefazodone, ritonavir, saquinavir, nelfinavir, indinavir, atazanavir, grapefruit juice >1 L/day), CYP3A substrates with narrow therapeutic indices (e.g., cyclosporine, quinidine), or strong CYP3A inducers (e.g., rifampin)
Patient use of rifampicin, phenytoin, carbamazepine, dexamethason, phenobarbital
Platelet count <100,000/μL at the time of screening
Anaemia (haemoglobin <10 g/dL) at the time of screening
Comorbidities associated with life expectancy <1 year
Pregnancy, giving birth within the last 90 days, or lactation (see **Supplementary Appendix 3** for females of childbearing potential)
PCI indication for stent thrombosis or previous history of definite stent thrombosis
Non-deferrable major surgery on DAPT after PCI
Cardiogenic shock
Out-of-hospital cardiac arrest unless survivors of ventricular arrythmia with prompt return of spontaneous circulation

BARC: Bleeding Academic Research Consortium; DAPT: dual antiplatelet therapy; ECG: electrocardiogram; MI: myocardial infarction; NYHA: New York Heart Association; PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction

and concomitant treatments are shown in **Supplementary Appendix 3** and **Supplementary Appendix 4**.

ENDPOINTS

PRIMARY ENDPOINTS

The study will primarily assess the following endpoints:

- NACE: composite endpoint of all-cause death, myocardial infarction, stroke or Bleeding Academic Research Consortium (BARC) Type 3 or 5 bleeding at 11 months post-DAPT randomisation;
- postprocedural MSA: final post-PCI MSA assessed by OCT in each randomised arm, measured at an independent OCT core laboratory blinded to imaging modality assignment.

SECONDARY ENDPOINTS

The following secondary endpoints will be assessed at 2, 11 and 35 months:

- major adverse cardiac and cerebrovascular events (MACCE): composite endpoint of cardiovascular death, myocardial infarction or stroke;
- BARC Type 3 or 5 bleeding;
- incidence of target vessel failure: composite of cardiac death, target vessel myocardial infarction (per-protocol [PP] MI definition), or ischaemia-driven target vessel revascularisation;
- incidence of stent thrombosis (definite or probable as defined by the Academic Research Consortium [ARC]).

Procedural outcomes and additional clinical endpoints are listed in **Table 2**. Definitions are provided in **Supplementary Appendix 5**.

SAMPLE SIZE CALCULATION

With respect to the antiplatelet therapy study component, a sample size of 1,500 subjects was deemed necessary to assess the non-inferiority of short DAPT followed by prasugrel monotherapy compared with standard prasugrel-based DAPT, with 80% power at a 1-sided α of 0.025. This calculation was based on the assumptions of an anticipated event rate of 3.5% in both groups at 11 months following randomisation (i.e., 12 months post-PCI), consistent with previous studies on DAPT duration after contemporary DES implantation; a non-inferiority margin of 2.0%, corresponding to a hazard ratio of 1.59; an accrual period of 42 months; and a 1:1 treatment allocation ratio. The analysis will be primarily conducted in the per-protocol population. Considering an expected rate of dropout and protocol violations of 10%, the final sample size was increased to 1,650[5,6,10,19].

With respect to the intravascular imaging guidance study component, in patients with multivessel disease undergoing early staged complete revascularisation, OCT-guided stent optimisation was assumed to produce a 0.4 mm² mean reduction in MSA after PCI compared with angiography-guided stent optimisation, assuming a common standard deviation of 2.0 mm² [20]. The analysis will be primarily conducted in the intention-to-treat (ITT) population. Patients will undergo 1:1 stratification in terms of antithrombotic treatment. A sample size of 788 subjects was deemed necessary to test superiority with 80% power at a 2-sided α of 0.05. Considering an expected rate of dropout and protocol violations of 5%, the final sample size was increased to 828.

Considering that the reported prevalence of MVD in STEMI patients is 50%, doubling the intravascular imaging guidance study sample size of 828 subjects led to a total of 1,656. In conclusion, a sample size of 1,656 subjects was determined to comprehensively encompass both components of COMPARE STEMI ONE.

PRESPECIFIED SUBGROUP ANALYSIS

Analysis of the primary endpoints will be performed in prespecified subgroups defined by the following:

- Age (<75, ≥75 years old)
- Sex (male/female)
- Diabetes mellitus (yes/no)
- High bleeding risk according to the ARC High Bleeding Risk (ARC-HBR) definition (yes/no)
- Bifurcation lesion treated with 2 stents
- Complex high-risk indicated procedures defined as at least one of the following:
  a. Angiographic heavy calcification
  b. Ostial lesion
  c. True bifurcation lesion involving side branch ≥2.5 mm
  d. Left main lesion
  e. Chronic total occlusion
  f. In-stent restenosis
  g. Long lesion (estimated stent length >28 mm)
  h. Patient with an indication for PCI for any lesion and in need of elective mechanical circulatory support-assisted PCI (staged procedure)

Subgroup analyses will be performed with the Cox proportional hazards model after testing for interaction between the variable defining the subgroup and treatment effect.

STATISTICAL ANALYSIS

The following analysis population sets will be defined for the assessment of study endpoints.

The ITT population consists of enrolled subjects who have been randomised. Subjects will be analysed according to the treatment group they were assigned. The co-primary endpoint of MSA will be analysed from the ITT population.

The primary endpoint of NACE will be assessed in the PP population. This population will include all randomised participants who completed the 11-month follow-up without prasugrel or DAPT disruption and remained free of ischaemic and major bleeding. Based on the MASTER DAPT trial results, the anticipated rate of discontinuation of prasugrel will be less than 10%. Here below is the preliminary list of major protocol deviations that will lead to exclusion from the PP population:

- inclusion/exclusion criteria not fulfilled or randomisation criteria not fulfilled;
- non-compliance to the treatment assigned by the randomisation.

Like sensitivity, non-inferiority will be tested in the ITT population.

Details on statistical analysis are displayed in **Supplementary Appendix 6**.

DATA COLLECTION AND ANALYSIS

The co-primary endpoint of post-PCI MSA assessed by OCT in each randomised arm will be measured at an independent OCT core laboratory (CERC, Massy, France) blinded to imaging modality assignment.

An independent clinical events committee (CEC) will adjudicate all primary and secondary endpoints. Definitions of all primary and secondary endpoints are summarised in **Table 2**. An independent data safety monitoring board (DSMB) will oversee the safety and wellbeing of the participating subjects, ensure the study's scientific integrity, and recommend actions based on potential safety issues, including study suspension or termination based on prespecified suspension criteria. The organisation and composition of the DSMB and CEC are described in **Supplementary Table 1** and **Supplementary Table 2**. Details on follow-up appear in **Supplementary Appendix 7**.

Discussion

The conventional approach to STEMI patients undergoing PCI involves aggressive antithrombotic therapy with DAPT, despite the known increased risk of bleeding, especially in the maintenance phase post-PCI[2]. The COMPARE STEMI ONE trial investigates the non-inferiority of an abbreviated DAPT regimen of 1 month followed by prasugrel monotherapy. The rationale is grounded in the hypothesis that a reduced DAPT duration curtails bleeding risks without compromising its antithrombotic efficacy in reducing ischaemic events[7]. A few randomised trials

Table 2. Procedural outcomes.

Outcomes
Stent expansion
Stent expansion is 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 2 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 is based upon the midpoint of the most proximal 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.
In case either segment (proximal or distal) of the stent meets the criteria for unacceptable stent expansion, the stent is considered to have unacceptable stent expansion. Both segments of the stent must meet the acceptable stent expansion criteria to be considered acceptable. In case a respective reference segment cannot be measured, the determination will be made with only one of the two reference (proximal or distal) segments.
Post-PCI stent expansion (%) (continuous variable): the MSA divided by the average of proximal and distal reference lumen areas x 100.
Mean stent expansion (%) (continuous variable)
The mean stent area (stent volume/analysed stent length) divided by the average of proximal and distal reference lumen areas x 100.
Edge dissections
Edge dissections will be tabulated as follows:
Major (%): ≥60° of the circumference of the vessel at the site of dissection and ≥3 mm in length
Minor (%): any visible edge dissection <60° of the circumference of the vessel or <3 mm in length
Edge dissections will be further classified as:
Intimal: limited to the intima layer, i.e., not extending beyond the internal elastic lamina
Medial: extending into the media layer
Adventitial: extending through the external elastic membrane/lamina
Stent malapposition
Defined as the frequency (%) of incompletely apposed stent struts (defined as stent struts clearly separated from the vessel wall [lumen border/plaque surface] 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 will be further classified as follows:
Major: if associated with unacceptable stent expansion (as defined above)
Minor: if associated with acceptable stent expansion (as defined above)
Border detection
The visibility of the vessel EEL border by OCT will be evaluated at both reference sites (proximal and distal), after intervention, and then classified into 3 grades:
Good: ≥75% (270°) of the visible circumference
Moderate: ≥50% (180°) to <75% (270°) of the visible circumference
Poor: <50% (180°) of the visible circumference
Untreated reference segment disease
Defined as focal disease with untreated MLA <4.5 mm^2 within 5 mm from the proximal and/or distal stent edges.
Subclassified by the amount of untreated lipid plaque, divided into 3 grades:
Low: ≤90° of lipid arc
Medium: >90° to <180° of lipid arc
High: ≥180° of lipid arc
Additional procedural and clinical endpoints
Device usage endpoints (site reported; assessed per subject)
Total stent length
Total number of stents
Maximal stent size
Post-dilatation (yes/no)
Total number of post-dilatation balloons
Maximal post-dilatation balloon size
Maximal device size (stent or post-dilatation balloon)
Maximum inflation pressure (atm; stent or post-dilatation balloon)

Table 2. Procedural outcomes (cont'd).

Outcomes
Additional procedural and clinical endpoints
Procedure time (first wire insertion to guide catheter removal)
Fluoroscopy time
Radiation exposure
Contrast use
Contrast-induced nephropathy (serum creatinine rise >25% or absolute increase >0.5 mg/dL)
Need for renal replacement therapy
OCT performance success (site reported) (OCT arm only)
OCT imaging performed both pre- and post-PCI
Additional interventions on the basis of the pre-PCI or post-stent OCT-imaging run that would not have been performed based on angiographic guidance alone (site reported; assessed per subject; OCT arm only)
Use of larger balloon
Use of higher inflation pressures
Use of additional inflation(s)
Use of additional stent(s)
Thrombus aspiration
Performance of atherectomy
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)

All procedural outcomes are OCT defined (OCT core laboratory assessed). Subjects in the angiography-guided arm will undergo a post-PCI OCT run. Assessed per target lesion. EEL: external elastic lamina; MLA: minimal lumen area; MSA: minimal stent area; OCT: optical coherence tomography; PCI: percutaneous coronary intervention

focusing on DAPT regimen in ACS (6 vs 12 months in SMART-DATE and DAPT-STEMI and 3 vs 12 months in REDUCE) have attempted to shed light on the optimal timing for DAPT discontinuation, aiming to shorten the duration of $P2Y_{12}$ inhibitor administration. Results were concordant in reporting the non-inferiority of an abbreviated (3-6 months) DAPT regimen as compared to the standard 12-month DAPT regimen[21-23]. There is a paucity of head-to-head comparison data for ASA versus $P2Y_{12}$ inhibitor monotherapy following a short period of DAPT[24]. A recent meta-analysis involving 73,126 patients showed a significantly higher risk of myocardial infarction and a similar risk of bleeding with ASA monotherapy as compared to $P2Y_{12}$ inhibitor monotherapy following short-term DAPT after PCI[25].

Recent trials exploring abbreviated DAPT have yielded favourable results for a single $P2Y_{12}$ inhibitor strategy. A non-prespecified *post hoc* analysis of the GLOBAL LEADERS trial in ACS patients investigated the efficacy of ticagrelor monotherapy compared to ASA plus ticagrelor after 1 month of DAPT. Between 1 and 12 months post-PCI, ASA was associated with an increased bleeding risk (1.5% vs 0.8%; p for superiority=0.004) and did not appear to enhance the benefit of ticagrelor on ischaemic events (2.0% vs 1.5%; p for superiority=0.07)[26]. The findings from the TWILIGHT trial revealed that administering ticagrelor monotherapy following an uneventful 3-month DAPT post-PCI in high-risk patients led to less bleeding without increased ischaemic events[5]. In the TICO Study (3,056 ACS patients), 3 months of DAPT followed by ticagrelor monotherapy resulted in a significant reduction of major bleeding and cardiovascular events at 1 year compared to 12-month ticagrelor-based DAPT[27]. In line with previous studies, the ULTIMATE-DAPT RCT showed that ACS patients can benefit from discontinuing ASA and maintaining ticagrelor monotherapy after 1 month of DAPT, resulting in less bleeding and similar major adverse cardiac event rates[28]. Consistently, in 2,850 ACS patients undergoing PCI, 1-month DAPT followed by ticagrelor monotherapy was non-inferior and superior to 12-month DAPT for the 1-year composite outcome of death, myocardial infarction, stent thrombosis, stroke, or major bleeding[29].

However, these results have not been consistent across trials investigating different $P2Y_{12}$ inhibitors. In patients with ACS and successful PCI, clopidogrel monotherapy after 1 to 2 months of DAPT failed to demonstrate non-inferiority compared to standard 12-month DAPT for the net clinical benefit[10]. The STOPDAPT-3 trial failed to achieve the primary endpoint of superiority in reducing bleeding events (BARC 3 or 5) and showed a potential increase in the risk of subacute stent thrombosis in patients allocated to prasugrel monotherapy at a dosage of 3.75 mg/day immediately following PCI[10,11].

Several RCTs are currently investigating either a prasugrel-based or ticagrelor-based single antiplatelet regimen after 0-3 months of DAPT in ACS patients **(Figure 3)**. The design of the COMPARE STEMI ONE trial is unique in focusing exclusively on a full-dose prasugrel-based regimen in the context of STEMI[30,31]. The potentially better ischaemic profile

Trial	Population	Intervention	Control	Outcomes
COMPARE STEMI ONE NCT05491200	1,656 STEMI	30-45 d DAPT-> P monotherapy	P+ASA 12 m	12-month NACE
TARGET-FIRST NCT04753749	2,246 ACS	1 m DAPT-> T/P monotherapy	T/P+ASA 12 m	12-month NACE and BARC 2 bleeding
LEGACY NCT05125276	3,090 NSTEMI	PCI-> T/P monotherapy	T/P+ASA 12 m	12-month MACE and BARC ≥ 2 bleeding
MATE NCT04937699	2,856 ACS	1 m DAPT-> 5 m T monotherapy->C	T+ASA 12 m	12-month NACE
NEOMINDSET NCT04360720	3,400 ACS	PCI->T/P monotherapy	T/P+ASA 12 m	12-month MACE and BARC ≥ 2 bleeding

Figure 3. *Overview of current RCTs investigating $P2Y_{12}$ inhibitor monotherapy in ACS patients. ACS: acute coronary syndrome; ASA: acetylsalicylic acid; BARC: Bleeding Academic Research Consortium; C: clopidogrel; DAPT: dual antiplatelet therapy; MACE: major adverse cardiac events; NACE: net adverse clinical events; NSTEMI: non-STEMI; P: prasugrel; PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction; T: ticagrelor*

of prasugrel over ticagrelor, which was demonstrated in the ISAR-REACT 5 Trial, adds to the rationale of our trial[9].

In addressing the multifaceted nature of STEMI patients, the COMPARE STEMI ONE trial takes a step further by examining the benefit of OCT-guided complete revascularisation in patients with MVD and addressing the growing interest in leveraging intravascular imaging to optimise procedural outcomes[4,20,32,33]. Recently, the Impact of IntraVascular UltraSound Guidance on Outcomes of Xience Prime Stents in Long Lesions trial (IVUS-XPL Study), conducted at 20 centres in the Republic of Korea, revealed a significant interaction between intravascular ultrasound (IVUS) use and DAPT duration, suggesting that IVUS-guided stent optimisation may yield more favourable results with shorter DAPT[34].

The COMPARE STEMI ONE RCT will explore synergies between a shortened DAPT duration and OCT-guided revascularisation for STEMI patients with MVD. The potential implications of this dual approach for optimising patient outcomes remain a particular point of interest.

We recognise that the choice of an absolute non-inferiority margin of 2.0 results in a relative non-inferiority margin that is higher than those used in previous trials. This decision, however, was driven by the low, but realistic, expected event rates in our study population. In this context, our approach reflects a pragmatic balance between feasibility and statistical rigour.

Conclusions

In summary, the multicentre, randomised, open-label COMPARE STEMI ONE trial addresses critical clinical questions regarding the optimal strategy and choice of antiplatelet therapy in STEMI patients undergoing PCI. By integrating intravascular imaging into the paradigm of complete revascularisation, the trial may also provide meaningful insights into the optimal antithrombotic treatment of STEMI patients with MVD.

Authors' affiliations

1. Department of Cardiology, Maasstad Hospital, Rotterdam, the Netherlands; 2. Department of Cardiology, Cardiovascular Institute, Thoraxcenter, Erasmus University Medical Center, Rotterdam, the Netherlands; 3. Department of Cardiology, Amphia Hospital, Breda, the Netherlands; 4. Department of Cardiology, Asklepios Klinik Bad Oldesloe, Bad Oldesloe, Germany; 5. Department of Advanced Biomedical Sciences, University of Naples "Federico II, Naples, Italy; 6. Cardiology Unit, Azienda Ospedaliero Univesitaria di Ferrara, Cona (FE), Italy; 7. Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy; 8. Ospedale Papa Giovanni XXIII, Bergamo, Italy; 9. Cardiology Department, Heart Center Dresden University, Dresden, Germany; 10. Cardiovascular Disease Unit, IRCCS Ospedale Policlinico San Martino, Genoa, Italy; 11. Department of Interventional Cardiology, Centro Cardiologico Monzino, IRCCS, Milan, Italy; 12. Cardiology Department, Catharina Hospital, Eindhoven, the Netherlands; 13. Department of Cardiovascular Medicine, University Hospitals Leuven, Leuven, Belgium and Department of Cardiovascular Sciences, Katholieke Universiteit Leuven, Leuven, Belgium; 14. The University Hospital Brno, Medical Faculty of Masaryk University, Brno, Czech Republic; 15. Department of Cardiology, University Clinical Center of Serbia, Belgrade, Serbia and Faculty of Medicine, University of Belgrade, Belgrade, Serbia; 16. Department of General Surgery and Surgical-Medical Specialties, University of Catania, Catania, Italy; 17. Cardiovascular Research Institute, Mater Private Hospital, Royal College of Surgeons in Ireland, Dublin, Ireland; 18. ISAResearch Zentrum, German Heart Center, Munich, Germany

Funding

The trial is investigator initiated with an unrestricted grant provided by Abbott, Santa Clara, CA, USA. The authors are solely responsible for the design, conduct and analyses of this

study, as well as the drafting and editing of the paper and its final content.

Conflict of interest statement

V. Paradies declares a research grant from Abbott Vascular via the institution; speaker fees from Abbott Vascular, Boston Scientific, and Elixir; and an educational grant from Terumo via the institution. P.C. Smits has received consultancy fees and institutional research grants from Abbott Vascular. R. M. Oemrawsingh declares speaker fees from Abbott Vascular and an educational grant from Terumo. F. Burzotta declares speakers' fees from Abbott, Abiomed, Medtronic, Edwards Lifesciences, and Terumo. The other authors have no conflicts of interest relevant to the contents of this paper to declare.

References

1. Capodanno D, Angiolillo DJ. Timing, Selection, Modulation, and Duration of $P2Y_{12}$ Inhibitors for Patients With Acute Coronary Syndromes Undergoing PCI. *JACC Cardiovasc Interv.* 2023;16:1-18.
2. Angiolillo DJ, Galli M, Collet JP, Kastrati A, O'Donoghue ML. Antiplatelet therapy after percutaneous coronary intervention. *EuroIntervention.* 2022;17:e1371-96.
3. Giustino G, Baber U, Sartori S, Mehran R, Mastoris I, Kini AS, Sharma SK, Pocock SJ, Dangas GD. Duration of dual antiplatelet therapy after drug-eluting stent implantation: a systematic review and meta-analysis of randomized controlled trials. *J Am Coll Cardiol.* 2015;65:1298-310.
4. Stone GW. Intravascular Imaging Guidance for PCI: A "Real-Time" Updated Network Meta-analysis. ESC 2023. 28 August 2023. Amsterdam, the Netherlands.
5. Baber U, Dangas G, Angiolillo DJ, Cohen DJ, Sharma SK, Nicolas J, Briguori C, Cha JY, Collier T, Dudek D, Džavik V, Escaned J, Gil R, Gurbel P, Hamm CW, Henry T, Huber K, Kastrati A, Kaul U, Kornowski R, Krucoff M, Kunadian V, Marx SO, Mehta S, Moliterno D, Ohman EM, Oldroyd K, Sardella G, Sartori S, Shlofmitz R, Steg PG, Weisz G, Witzenbichler B, Han YL, Pocock S, Gibson CM, Mehran R. Ticagrelor alone vs. ticagrelor plus aspirin following percutaneous coronary intervention in patients with non-ST-segment elevation acute coronary syndromes: TWILIGHT-ACS. *Eur Heart J.* 2020;41:3533-45.
6. Tomaniak M, Chichareon P, Modolo R, Takahashi K, Chang CC, Kogame N, Spitzer E, Buszman PE, van Geuns RM, Valkov V, Steinwender C, Geisler T, Prokopczuk J, Sabaté M, Zmudka K, Rademaker-Havinga T, Tijssen JGP, Jüni P, Hamm C, Steg PG, Onuma Y, Vranckx P, Valgimigli M, Windecker S, Baber U, Anderson R, Dominici M, Serruys PW. Ticagrelor monotherapy beyond one month after PCI in ACS or stable CAD in elderly patients: a pre-specified analysis of the GLOBAL LEADERS trial. *EuroIntervention.* 2020;15:e1605-14.
7. Giacoppo D, Matsuda Y, Fovino LN, D'Amico G, Gargiulo G, Byrne RA, Capodanno D, Valgimigli M, Mehran R, Tarantini G. Short dual antiplatelet therapy followed by $P2Y_{12}$ inhibitor monotherapy vs. prolonged dual antiplatelet therapy after percutaneous coronary intervention with second-generation drug-eluting stents: a systematic review and meta-analysis of randomized clinical trials. *Eur Heart J.* 2021;42:308-19.
8. Basra SS, Wang TY, Simon DN, Chiswell K, Virani SS, Alam M, Nambi V, Denktas AE, Deswal A, Bozkurt B, Ballantyne CM, Peterson ED, Jneid H. Ticagrelor Use in Acute Myocardial Infarction: Insights From the National Cardiovascular Data Registry. *J Am Heart Assoc.* 2018;7:e008125.
9. Schüpke S, Neumann FJ, Menichelli M, Mayer K, Bernlochner I, Wöhrle J, Richardt G, Liebetrau C, Witzenbichler B, Antoniucci D, Akin I, Bott-Flügel L, Fischer M, Landmesser U, Katus HA, Sibbing D, Seyfarth M, Janisch M, Boncompagni D, Hilz R, Rottbauer W, Okrojek R, Möllmann H, Hochholzer W, Migliorini A, Cassese S, Mollo P, Xhepa E, Kufner S, Strehle A, Leggewie S, Allali A, Ndrepepa G, Schühlen H, Angiolillo DJ, Hamm CW, Hapfelmeier A, Tölg R, Trenk D, Schunkert H, Laugwitz KL, Kastrati A; ISAR-REACT 5 Trial Investigators. Ticagrelor or Prasugrel in Patients with Acute Coronary Syndromes. *N Engl J Med.* 2019;381:1524-34.
10. Watanabe H, Morimoto T, Natsuaki M, Yamamoto K, Obayashi Y, Ogita M, Suwa S, Isawa T, Domei T, Yamaji K, Tatsushima S, Watanabe H, Ohya M, Tokuyama H, Tada T, Sakamoto H, Mori H, Suzuki H, Nishikura T, Wakabayashi K, Hibi K, Abe M, Kawai K, Nakao K, Ando K, Tanabe K, Ikari Y, Morino Y, Kadota K, Furukawa Y, Nakagawa Y, Kimura T; STOPDAPT-2 ACS Investigators. Comparison of Clopidogrel Monotherapy After 1 to 2 Months of Dual Antiplatelet Therapy With 12 Months of Dual Antiplatelet Therapy in Patients With Acute Coronary Syndrome: The STOPDAPT-2 ACS Randomized Clinical Trial. *JAMA Cardiol.* 2022;7:407-17.
11. Natsuaki M, Watanabe H, Morimoto T, Yamamoto K, Obayashi Y, Nishikawa R, Ando K, Domei T, Suwa S, Ogita M, Isawa T, Takenaka H, Yamamoto T, Ishikawa T, Hisauchi I, Wakabayashi K, Onishi Y, Hibi K, Kawai K, Yoshida R, Suzuki H, Nakazawa G, Kusuyama T, Morishima I, Ono K, Kimura T. An Aspirin-Free Versus Dual Antiplatelet Strategy for Coronary Stenting: STOPDAPT-3 Randomized Trial. *Circulation.* 2024;149:585-600.
12. Paradies V, Waldeyer C, Laforgia PL, Clemmensen P, Smits PC. Completeness of revascularisation in acute coronary syndrome patients with multivessel disease. *EuroIntervention.* 2021;17:193-201.
13. Gershlick AH, Khan JN, Kelly DJ, Greenwood JP, Sasikaran T, Curzen N, Blackman DJ, Dalby M, Fairbrother KL, Banya W, Wang D, Flather M, Hetherington SL, Kelion AD, Talwar S, Gunning M, Hall R, Swanton H, McCann GP. Reply: Complete Revascularization in Patients Undergoing Primary Percutaneous Coronary Intervention for STEMI: Is It Really What We Should Be Doing? *J Am Coll Cardiol.* 2015;66:332-3.
14. Smits PC, Abdel-Wahab M, Neumann FJ, Boxma-de Klerk BM, Lunde K, Schotborgh CE, Piroth Z, Horak D, Wlodarczak A, Ong PJ, Hambrecht R, Angerås O, Richardt G, Omerovic E; Compare-Acute Investigators. Fractional Flow Reserve-Guided Multivessel Angioplasty in Myocardial Infarction. *N Engl J Med.* 2017;376:1234-44.
15. Engstrøm T, Kelbæk H, Helqvist S, Høfsten DE, Kløvgaard L, Holmvang L, Jørgensen E, Pedersen F, Saunamäki K, Clemmensen P, De Backer O, Ravkilde J, Tilsted HH, Villadsen AB, Aarøe J, Jensen SE, Raungaard B, Køber L; DANAMI-3—PRIMULTI Investigators. Complete revascularisation versus treatment of the culprit lesion only in patients with ST-segment elevation myocardial infarction and multivessel disease (DANAMI-3—PRIMULTI): an open-label, randomised controlled trial. *Lancet.* 2015;386:665-71.
16. Mehta SR, Wood DA, Storey RF, Mehran R, Bainey KR, Nguyen H, Meeks B, Di Pasquale G, López-Sendón J, Faxon DP, Mauri L, Rao SV, Feldman L, Steg PG, Avezum Á, Sheth T, Pinilla-Echeverri N, Moreno R, Campo G, Wrigley B, Kedev S, Sutton A, Oliver R, Rodés-Cabau J, Stanković G, Welsh R, Lavi S, Cantor WJ, Wang J, Nakamya J, Bangdiwala SI, Cairns JA; COMPLETE Trial Steering Committee and Investigators. Complete Revascularization with Multivessel PCI for Myocardial Infarction. *N Engl J Med.* 2019;381:1411-21.
17. Byrne RA, Rossello X, Coughlan JJ, Barbato E, Berry C, Chieffo A, Claeys MJ, Dan GA, Dweck MR, Galbraith M, Gilard M, Hinterbuchner L, Jankowska EA, Jüni P, Kimura T, Kunadian V, Leosdottir M, Lorusso R, Pedretti RFE, Rigopoulos AG, Rubini Gimenez M, Thiele H, Vranckx P, Wassmann S, Wenger NK, Ibanez B; ESC Scientific Document Group. 2023 ESC Guidelines for the management of acute coronary syndromes. *Eur Heart J.* 2023;44:3720-826.
18. Prati F, Romagnoli E, La Manna A, Burzotta F, Gatto L, Marco V, Fineschi M, Fabbiocchi F, Versaci F, Trani C, Tamburino C, Alfonso F, Mintz GS. Long-term consequences of optical coherence tomography findings during percutaneous coronary intervention: the Centro Per La Lotta Contro L'infarto - Optimization Of Percutaneous Coronary Intervention (CLI-OPCI) LATE study. *EuroIntervention.* 2018;14:e443-51.
19. Hahn JY, Song YB, Oh JH, Chun WJ, Park YH, Jang WJ, Im ES, Jeong JO, Cho BR, Oh SK, Yun KH, Cho DK, Lee JY, Koh YY, Bae JW, Choi JW, Lee WS, Yoon HJ, Lee SU, Cho JH, Choi WG, Rha SW, Lee JM, Park TK, Yang JH, Choi JH, Choi SH, Lee SH, Gwon HC; SMART-CHOICE Investigators. Effect of $P2Y_{12}$ Inhibitor Monotherapy vs Dual Antiplatelet Therapy on Cardiovascular Events in Patients Undergoing Percutaneous Coronary Intervention: The SMART-CHOICE Randomized Clinical Trial. *JAMA.* 2019;321:2428-37.
20. Ali ZA, Landmesser U, Maehara A, Matsumura M, Shlofmitz RA, Guagliumi G, Price MJ, Hill JM, Akasaka T, Prati F, Bezerra HG, Wijns W, Leistner D, Canova P, Alfonso F, Fabbiocchi F, Dogan O, McGreevy RJ, McNutt RW, Nie H, Buccola J, West NEJ, Stone GW; ILUMIEN IV

Investigators. Optical Coherence Tomography-Guided versus Angiography-Guided PCI. *N Engl J Med.* 2023;389:1466-76.

21. Hahn JY, Song YB, Oh JH, Cho DK, Lee JB, Doh JH, Kim SH, Jeong JO, Bae JH, Kim BO, Cho JH, Suh IW, Kim DI, Park HK, Park JS, Choi WG, Lee WS, Kim J, Choi KH, Park TK, Lee JM, Yang JH, Choi JH, Choi SH, Gwon HC; SMART-DATE investigators. 6-month versus 12-month or longer dual antiplatelet therapy after percutaneous coronary intervention in patients with acute coronary syndrome (SMART-DATE): a randomised, open-label, non-inferiority trial. *Lancet.* 2018;391:1274-84.

22. Kedhi E, Fabris E, van der Ent M, Buszman P, von Birgelen C, Roolvink V, Zurakowski A, Schotborgh CE, Hoorntje JCA, Eek CH, Cook S, Togni M, Meuwissen M, van Royen N, van Vliet R, Wedel H, Delewi R, Zijlstra F. Six months versus 12 months dual antiplatelet therapy after drug-eluting stent implantation in ST-elevation myocardial infarction (DAPT-STEMI): randomised, multicentre, non-inferiority trial. *BMJ.* 2018;363:k3793.

23. De Luca G, Damen SA, Camaro C, Benit E, Verdoia M, Rasoul S, Liew HB, Polad J, Ahmad WA, Zambahari R, Postma S, Kedhi E, Suryapranata H; Collaborators. Final results of the randomised evaluation of short-term dual antiplatelet therapy in patients with acute coronary syndrome treated with a new-generation stent (REDUCE trial). *EuroIntervention.* 2019;15:e990-8.

24. Koo BK, Kang J, Park KW, Rhee TM, Yang HM, Won KB, Rha SW, Bae JW, Lee NH, Hur SH, Yoon J, Park TH, Kim BS, Lim SW, Cho YH, Jeon DW, Kim SH, Han JK, Shin ES, Kim HS; HOST-EXAM investigators. Aspirin versus clopidogrel for chronic maintenance monotherapy after percutaneous coronary intervention (HOST-EXAM): an investigator-initiated, prospective, randomised, open-label, multicentre trial. *Lancet.* 2021;397:2487-96.

25. Andò G, De Santis GA, Greco A, Pistelli L, Francaviglia B, Capodanno D, De Caterina R, Capranzano P. $P2Y_{12}$ Inhibitor or Aspirin Following Dual Antiplatelet Therapy After Percutaneous Coronary Intervention: A Network Meta-Analysis. *JACC Cardiovasc Interv.* 2022;15:2239-49.

26. Tomaniak M, Chichareon P, Onuma Y, Deliargyris EN, Takahashi K, Kogame N, Modolo R, Chang CC, Rademaker-Havinga T, Storey RF, Dangas GD, Bhatt DL, Angiolillo DJ, Hamm C, Valgimigli M, Windecker S, Steg PG, Vranckx P, Serruys PW; GLOBAL LEADERS Trial Investigators. Benefit and Risks of Aspirin in Addition to Ticagrelor in Acute Coronary Syndromes: A Post Hoc Analysis of the Randomized GLOBAL LEADERS Trial. *JAMA Cardiol.* 2019;4:1092-101.

27. Kim BK, Hong SJ, Cho YH, Yun KH, Kim YH, Suh Y, Cho JY, Her AY, Cho S, Jeon DW, Yoo SY, Cho DK, Hong BK, Kwon H, Ahn CM, Shin DH, Nam CM, Kim JS, Ko YG, Choi D, Hong MK, Jang Y; TICO Investigators. Effect of Ticagrelor Monotherapy vs Ticagrelor With Aspirin on Major Bleeding and Cardiovascular Events in Patients With Acute Coronary Syndrome: The TICO Randomized Clinical Trial. *JAMA.* 2020;323:2407-16.

28. Ge Z, Kan J, Gao X, Raza A, Zhang JJ, Mohydin BS, Gao F, Shao Y, Wang Y, Zeng H, Li F, Khan HS, Mengal N, Cong H, Wang M, Chen L, Wei Y, Chen F, Stone GW, Chen SL; ULTIMATE-DAPT investigators. Ticagrelor alone versus ticagrelor plus aspirin from month 1 to month 12 after percutaneous coronary intervention in patients with acute coronary syndromes (ULTIMATE-DAPT): a randomised, placebo-controlled, double-blind clinical trial. *Lancet.* 2024;403:1866-78.

29. Hong SJ, Lee SJ, Suh Y, Yun KH, Kang TS, Shin S, Kwon SW, Lee JW, Cho DK, Park JK, Bae JW, Kang WC, Kim S, Lee YJ, Ahn CM, Kim JS, Kim BK, Ko YG, Choi D, Jang Y, Hong MK; T-PASS (Ticagrelor Monotherapy in Patients Treated With New-Generation Drug-Eluting Stents for Acute Coronary Syndrome) Investigators. Stopping Aspirin Within 1 Month After Stenting for Ticagrelor Monotherapy in Acute Coronary Syndrome: The T-PASS Randomized Noninferiority Trial. *Circulation.* 2024;149:562-73.

30. Tarantini G, Smits PC, Lhermusier T, Honton B, Rangé G, Piot C, Lemesle G, Ruiz Nodar JM, Godin M, Madera Cambero M, Motreff P, Cuisset T, Bouchez D, Poezevara Y, Cayla G. A prospective study comparing short versus standard dual antiplatelet therapy in patients with acute myocardial infarction: design and rationale of the TARGET-FIRST trial. *EuroIntervention.* 2023;19:240-7.

31. van der Sangen NMR, Küçük IT, Sivanesan S, Appelman Y, Ten Berg JM, Verburg A, Azzahhafi J, Arkenbout EK, Kikkert WJ, Pisters R, Jukema JW, Arslan F, van 't Hof A, Ilhan M, Hoebers LP, van der Schaaf RJ, Damman P, Woudstra P, van de Hoef TP, Bax M, Anthonio RL, Polad J, Adriaenssens T, Dewilde W, Zivelonghi C, Laanmets P, Majas R, Dijkgraaf MGW, Claessen BEPM, Henriques JPS. Less bleeding by omitting aspirin in non-ST-segment elevation acute coronary syndrome patients: Rationale and design of the LEGACY study. *Am Heart J.* 2023;265:114-20.

32. Kang DY, Ahn JM, Yun SC, Hur SH, Cho YK, Lee CH, Hong SJ, Lim S, Kim SW, Won H, Oh JH, Choe JC, Hong YJ, Yoon YH, Kim H, Choi Y, Lee J, Yoon YW, Kim SJ, Bae JH, Park DW, Park SJ; OCTIVUS Investigators. Optical Coherence Tomography-Guided or Intravascular Ultrasound-Guided Percutaneous Coronary Intervention: The OCTIVUS Randomized Clinical Trial. *Circulation.* 2023;148:1195-206.

33. Holm NR, Andreasen LN, Neghabat O, Laanmets P, Kumsars I, Bennett J, Olsen NT, Odenstedt J, Hoffmann P, Dens J, Chowdhary S, O'Kane P, Bülow Rasmussen SH, Heigert M, Havndrup O, Van Kuijk JP, Biscaglia S, Mogensen LJH, Henareh L, Burzotta F, H Eek C, Mylotte D, Llinas MS, Koltowski L, Knaapen P, Calic S, Witt N, Santos-Pardo I, Watkins S, Lønborg J, Kristensen AT, Jensen LO, Calais F, Cockburn J, McNeice A, Kajander OA, Heestermans T, Kische S, Eftekhari A, Spratt JC, Christiansen EH; OCTOBER Trial Group. OCT or Angiography Guidance for PCI in Complex Bifurcation Lesions. *N Engl J Med.* 2023;389:1477-87.

34. Hong SJ, Shin DH, Kim JS, Kim BK, Ko YG, Choi D, Her AY, Kim YH, Jang Y, Hong MK; IVUS-XPL Investigators. 6-Month Versus 12-Month Dual-Antiplatelet Therapy Following Long Everolimus-Eluting Stent Implantation: The IVUS-XPL Randomized Clinical Trial. *JACC Cardiovasc Interv.* 2016;9:1438-46.

Supplementary data

Supplementary Appendix 1. Study device.
Supplementary Appendix 2. Study procedures.
Supplementary Appendix 3. Investigational treatments.
Supplementary Appendix 4. Concomitant treatments.
Supplementary Appendix 5. Definitions.
Supplementary Appendix 6. Statistical analysis.
Supplementary Appendix 7. Detailed follow-up and study management.
Supplementary Table 1. DSMB members.
Supplementary Table 2. CEC members.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-24-00829

Supplementary data
Supplementary Appendix 1. Study device.

1. Optical coherence tomography
Optical coherence tomography will be performed using either Dragonfly OPSTAR or Dragonfly OPTIS Catheter, both manufactured by St. Jude Medical, now part of Abbott Laboratories, Abbott Park, Illinois (US)

The OCT guiding catheter will serve as investigational device. OCT is an established intravascular imaging modality that provides high-resolution images of plaque microarchitecture, stent placement and size and strut coverage and has obtained a class II indications for stent optimization in the context of clinical setting. The ILUMIEN IV trial found that an EEL-based stent optimization strategy for OCT was safe and resulted in similar MSA to that of IVUS-guided PCI with a trend toward larger MSA compared to angiography guidance in patients with diabetes and/or with complex coronary lesions.

A recent meta-analysis including 20 randomised trials of intravascular imaging-guided PCI compared with angiography-guided PCI in 12,428 patients with chronic and acute coronary syndromes resulted in reductions in the primary composite outcome of target lesion failure by 31% compared with angiography guidance.
OCT has a class IIa recommendation for stent optimization in the current European Guidelines on myocardial revascularization.

2. Drug eluting stents
The Xience Stent Family devices will serve as the preferred stent for the study.
Notably, the XIENCE everolimus-eluting stent (EES) has been associated with the lowest rates of early, late and very late stent thrombosis (ST).
STOPDAPT was the first prospective multi-center single-arm study assessing DAPT cessation at 3 months after EES implantation. Using the CoCr-EES group in the RESET trial as a historical comparison group, cumulative incidence of the primary endpoint was found to be lower in the STOPDAPT than in the RESET (2.8 versus 4.0 %, P = 0.06) and adjusted hazard ratio was 0.64 (95 % CI 0.42-0.95, P = 0.03). The cumulative incidence of definite/probable ST was lower in the STOPDAPT than in the RESET [0 patient (0 %) versus 5 patients (0.3 %), P = 0.03].
Among 3047 patients (37% ACS) undergoing PCI with everolimus eluting stent (EES) enrolled in the STOPDAPT-2 trial, 1 month of DAPT followed by clopidogrel monotherapy, compared with 12 months of DAPT with aspirin and clopidogrel, resulted in a significantly lower rate of a composite of cardiovascular and bleeding events. The primary endpoint occurred in 2.36% with 1-month DAPT and 3.70%with 12-month DAPT (absolute difference, −1.34%[95%CI, −2.57%to −0.11%]; hazard ratio [HR], 0.64 [95%CI, 0.42-0.98]), meeting criteria for noninferiority (P < .001) and for superiority (P = 0.04).
The findings from the STOP DAPT 3 trial suggest that, among Korean patients undergoing percutaneous coronary intervention (PCI) with Xience drug-eluting stents (DES) for acute coronary syndrome (ACS) or those deemed to be at high bleeding risk, prasugrel monotherapy at a dosage of 3.75 mg/day did not demonstrate superiority over dual antiplatelet therapy (DAPT) comprising aspirin (81-100 mg/day) and prasugrel (3.75 mg/day) in terms of bleeding events. Yet, information regarding the safety characteristics of the most recent iteration of everolimus-eluting stents (EES) when used in conjunction with long-term prasugrel monotherapy at guideline-based dosages in STEMI patients is currently lacking.

Supplementary Appendix 2. Study procedures.

1. Recommended criteria for optimal stent implantation

The investigator should perform the procedure aiming to achieve optimal stent implantation according to local standard of care by angiography and findings from OCT in the OCT-guided arms. If the patient randomizes to OCT-guided stent implantation, stenting will be performed with OCT-guidance according to a MLD-MAX algorithm as described below. OCT is required pre- and post-stent implantation for patients randomized to OCT-guided stent implantation.

Angiographic criteria

Residual diameter stenosis <20% without edge dissection, thrombus, major side branch occlusion, no-reflow.

2. Pre PCI OCT criteria

MORPHOLOGY

Severe calcification

Presence of ≥180° of calcium in at least one cross section with minimal thickness >0.5mm.

LENGTH

Select Landing Zones

Visually scan for largest luminal area in lumen profile proximally and distally. The stent length will be determined by measuring from the distal to the proximal reference site using the OCT longitudinal automation. If sufficient EEL cannot be visualized 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 sufficient to allow stent diameter measurement.

Place landing zones in healthy tissue (as determined by greatest EEL visualization).

Adjust to arrive at an available stent length.

Note: In the absence of EEL to represent healthy tissue find the largest lumen to avoid areas of TCFA or lipid pools so as to not land your stent edge in these high risk areas.

DIAMETER

Choose Stent Diameter

Stent diameter will be determined by measuring the distal reference mean-EEL diameter, if visible by OCT. The stent diameter should be chosen using the mean EEL diameter at the distal reference, rounded down to the nearest 0.25 mm. 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 nearest 0.25 mm.

3. POST PCI OCT criteria

MEDIAL DISSECTION

Following OCT-guided stent expansion optimization, the proximal and distal reference segments, defined as 5mm from the edge of the stent, are examined for major dissection and/or inflow/outflow disease. If both the proximal and distal reference segments have an MLA ≥4.50 mm2 and there is no major edge dissection, no further treatment is necessary.

However, in the presence of a major edge dissection, defined as dissection that penetrates medial layer and that are greater than one quadrant arc, or significant residual reference segment disease, defined as MLA in either of the reference segments <4.50 mm2, additional DES should be placed to correct the abnormality unless anatomically prohibitive (eg. biological vessel tapering, distal diffuse disease, absence of landing zone).

Following OCT-guided stent edge and reference segment optimization, the procedure should be complete and a final OCT run must be performed. If any other additional PCI is performed on the study lesion after OCT-guided stent edge and reference segment optimization, a final OCT run must be performed.

APPOSITION

Address Gross Malapposition

Criteria: Malapposition indicator shows longer than 3 mm of significant (≥0.3 mm from wall) malapposition (43)

Common Practice: Dilate with semi-compliant balloon at low pressure.

If malapposition is detected by operator assessment during the procedure in the OCT-guided arm and meets the criteria for major malapposition (i.e. malapposition associated with unacceptable stent expansion), further stent expansion must be performed. The degree of stent underexpansion (acceptable or unacceptable) should guide the intervention rather than amount of malapposition.

XPANSION

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 optimization has already been performed, OCT should be performed to determine whether acceptable stent expansion is present (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).

If not achieved, post dilatation should 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 mean reference vessel EEL (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). After post-dilatation, OCT should be repeated to determine whether acceptable stent expansion has been achieved, and if not, the process repeated iteratively with higher pressures. However, the diameter of the non-compliant post dilatation balloon chosen should not be larger than the post-PCI OCT determined mean reference vessel diameter (EEL), or no more than 0.5 mm larger than the mean reference segment lumen nearest to the dilatation site (if the EEL cannot be measured). While it is recommended that further PCI attempts be made until the protocol-defined optimal stent deployment is achieved, it is up to the operator to decide the number and degree of further interventions, at all times considering patient safety.

Supplementary Appendix 3. Investigational treatment.

1. Investigational treatment

Patients with STEMI planned for primary PCI will be treated by the ambulance as per local standard of care with Prasugrel 60 mg loading dose and Aspirin 150–300 mg per os or 250–500 mg i.v. bolus. During the index procedure the culprit lesion will be treated as per standard of care. Patients presenting with MVD will be allocated to receive a complete revascularization OCT-guided or a complete revascularization angio-guided during the first instalment of non-culprit lesions PCI (OCT randomization).

Enrolment into the study will require providing written informed consent after the index procedure, in any case prior to receiving any study related treatment. A subject will be considered enrolled in the study when the Informed Consent has been completed and the subject satisfies all the inclusion and exclusion criteria. Subject will be enrolled at pre-hospital discharge visit.

At 30-45 days after index procedure, patients will return for an in-person visit to assess for ischemic or bleeding events, medication status and randomization eligibility. If 30-45 days inclusion criteria are met, patients will be randomized in a 1:1 fashion via a web based, digital, Electronic Data Capture system (Castor) to receive 11 months Prasugrel monotherapy or Prasugrel-based standard DAPT for the next 11 months (DAPT randomization).

2. Multivessel treatment

Patients with MVD will be randomized to receive a complete OCT-guided versus complete angio-guided revascularization. OCT randomization will occur at the time of non-culprit lesions treatment, therefore during the first instalment of staged procedure(s), via a web based Electronic Data Capture system. There are no restrictions in number of lesions to be treated during the index procedure, however the last instalment of complete revascularization must be performed within 15 days after the index procedure.

The assessment of the non-culprit lesions between 50% to 90% at angiography, will be left to operator's discretion.

Moreover, in the OCT-guided arm all non-culprit lesions must be treated using OCT-guidance, regardless of the timing of revascularization.

3. OCT-guided PCI

Careful patient, vessel and lesion selection will be performed by physicians with extensive experience in the use of OCT imaging. OCT pre stenting is required per protocol.

The MLD-MAX OCT algorithm is strongly recommended.

Following the intracoronary injection of nitrates, the target segment will be assessed with two orthogonal angiographic projections and by OCT imaging for an accurate evaluation of the vessel, lesion severity, and intraluminal characteristics. Among the OCT-guided group, coronary stenting will be performed in order to achieve recommended OCT criteria for optimal stent implantation (supplementary appendix 2), while in the angiography-guided PCI group, coronary stenting will be performed as per local standard of care.

OCT is required post-stent implantation for patients randomized to OCT-guided stent implantation. After post-dilatation, OCT should be repeated to determine whether acceptable stent expansion has been achieved. In case of not acceptable stent expansion (supplementary appendix 2), post dilatation should be performed in the segment(s) with underexpansion, and postdilatation repeated iteratively with higher pressures. It is up to the operator to decide the number and degree of further interventions, at all times taking into account patient safety.

The proximal and distal reference segments, defined as 5mm from the edge of the stent, are examined for major dissection and/or inflow/outflow disease. If both the proximal and distal reference segments have an MLA ≥4.50 mm2 and there is no major edge dissection, no further treatment is necessary.

However, in the presence of a major edge dissection, additional DES should be placed to correct the abnormality unless anatomically prohibitive (eg. biological vessel tapering, distal diffuse disease, absence of landing zone).

Following OCT-guided stent edge and reference segment optimization, the procedure should be complete and a final OCT run must be performed. If any other additional PCI is performed on the study lesion after OCT-guided stent edge and reference segment optimization, a final OCT run must be performed.

No further intervention should be performed following the final OCT, although coronary contrast injection or recorded cine angiogram may be taken to insure vessel patency without complication after wire and catheter removal.

4. Angio-guided PCI

The operator will perform the procedure as per local standard of care. At the end of the procedure an OCT pullback will be performed. No further intervention may be performed following the OCT run. In case of major complications defined as medial dissection further interventions will be left to operators' discretion.

5. DAPT regimen

30-45 days DAPT (Prasugrel + ASA) followed by Prasugrel monotherapy maintenance dose of 10 mg once per day for 11 months. (A reduced maintenance dose of 5 mg daily is recommended in patients at the age of 75 years or older or with a body weight of less than 60 kg)

Or

12 months standard DAPT therapy (Prasugrel + ASA) maintenance dose of 10 mg once per day. (A reduced maintenance dose of 5 mg daily is recommended in patients at the age of 75 years or older or with a body weight of less than 60 kg) + Aspirin 75–100 mg p.o. daily
After 1 year, Prasugrel will be stopped in both arms and replaced by aspirin monotherapy in the short DAPT therapy arm.

Supplementary Appendix 4. Concomitant treatments.

1.Oral antiplatelet therapy
At enrolment patients may receive a 150–300 mg per os or 250–500 mg i.v. bolus loading dose of aspirin as per standard of care in the ambulance or at the spoke/hub centre

2. Other oral antiplatelet therapy

Concomitant treatment with any other oral anti-platelet drug (Clopidogrel, ticlopidine) is not allowed in the study. Of note, patients who were at the time-point of study enrolment already on Clopidogrel maintenance dose will stop Clopidogrel therapy. Patients who have received Ticagrelor loading dose in the ambulance or are already on Ticagrelor, will receive 60 mg Prasugrel loading dose, 24 hours after the last Ticagrelor dose. Patients who have received Clopidogrel loading dose in the ambulance or are already on Clopidogrel, will receive 60 mg Prasugrel loading dose at admission, irrespective of prior Clopidogrel timing and dosing. Patients who are already on Prasugrel will not receive any loading dose and continue with Prasugrel administration as per standard of care.

3. GPIIb/IIIa receptor antagonists
Upstream (in ambulance) use of GPIIb/IIIa receptor antagonists is not recommended as a concomitant treatment but will be left to physician's discretion. In lab use of GPIIb/IIIa receptors antagonists after the angiogram is possible and not discouraged. This use will have to be identified as being a strategy of choice or a bail out use during PCI.
Bail-out use of GPIIb/IIIa receptors antagonists is allowed for thrombotic complications.

4. Parenteral anticoagulants
Short-term treatment with approved parenteral anticoagulants (eg. unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), bivalirudin, fondaparinux) is allowed. However, long-term treatment with LMWH in outpatients (at venous thrombosis treatment doses) in combination with study medication is not allowed. Concomitant treatment with venous thrombosis prophylaxis doses is allowed.

5. Oral anticoagulants
Concomitant treatment with oral anticoagulant drugs is not permitted during the study. However, some patients will require oral anticoagulation during the follow-up of the study, e.g., because they develop atrial fibrillation (CHA2DS2-VASc Sore ≥2), incur deep vein thrombosis, pulmonary embolism, or cardiac thrombus formation. If triple or dual therapy is considered to be required, it is recommended in the protocol to switch from Prasugrel to Clopidogrel.

6. Other cardiac medications
Other cardiac medications (e.g., β-blockers, ACE inhibitors, statins etc.) will be given according to the judgment of patient's physician and current guidelines.

7. Fibrinolytics
A patient is not eligible for inclusion into the study if fibrinolytic therapy has been given in the 24 hours prior to randomisation or is planned to be administered for STEMI or any other condition. Fibrinolytic treatment is not permitted during the study.

8. **Intravenous P2Y12 receptor inhibitors**

The administration of i.v. P2Y12 receptor inhibitors will at operator's discretion according to guidelines recommendations.

Supplementary Appendix 5. Definitions.

BLEEDING

All potential bleeding events will be primarily adjudicated according to Bleeding Academic Research Consortium (BARC) classification

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

Obs: Platelet transfusions should be recorded and reported, but are not included in these definitions until further information is obtained about the relationship to outcomes. * Corrected for transfusion (1 U packed red blood cells or 1 U whole blood=1g/dL hemoglobin). † Cell saver products will not be counted.

DEATH

All deaths will be categorized as cardiac, cardiovascular, non-cardiovascular or undetermined

based on the definitions below.

Cardiac death:

Cardiac death is defined as death resulting from an acute myocardial infarction, sudden cardiac death and death due to heart failure and death due to other cardiac causes

Cardiovascular death:

Cardiovascular Death is defined as death resulting from an acute myocardial infarction, sudden cardiac death, death due to heart failure, death due to stroke, death due to cardiovascular (CV) procedures, death due to CV haemorrhage, and death due to other cardiovascular causes.

Death due to Acute Myocardial Infarction:

Death by any mechanism (arrhythmia, heart failure, low output) within 30 days after a myocardial infarction (MI) related to the immediate consequences of the myocardial infarction, such as progressive congestive heart failure (CHF), inadequate cardiac output, or refractory arrhythmia. If these events occur after a "break" (e.g., a CHF and arrhythmia free period of at least a week), they should be designated by the immediate cause, even though the MI may have increased the risk of that event (e.g., late arrhythmic death becomes more likely after an acute myocardial infarction (AMI)). The acute myocardial infarction should be verified to the extent possible by the diagnostic criteria outlined for acute myocardial infarction or by autopsy findings showing recent myocardial infarction or recent coronary thrombus. Sudden cardiac death, if accompanied by symptoms suggestive of myocardial ischemia, new ST elevation, new LBBB, or evidence of fresh thrombus by coronary angiography and/or at autopsy should be considered death resulting from an acute myocardial infarction, even if death occurs before blood samples or 12-lead electrocardiogram (ECG) could be obtained, or at a time before the appearance of cardiac biomarkers in the blood. Death resulting from a procedure to treat a myocardial infarction percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG), or to treat a complication resulting from myocardial infarction, should also be considered death due to acute MI. Death resulting from an elective coronary procedure to treat myocardial ischemia (i.e., chronic stable angina) or death due to a MI that occurs as a direct consequence of a CV investigation/procedure/operation should be considered as a death due to a CV procedure.

Sudden Cardiac Death:

Death that occurs unexpectedly, not following an acute AMI, and includes the following

deaths:

- Death witnessed and occurring without new or worsening symptoms.
- Death witnessed within 60 minutes of the onset of new or worsening cardiac symptoms, unless documented (i.e. by ECG or other objective) to be due to acute myocardial infarction.
- Death witnessed and attributed to an identified arrhythmia (e.g., captured on an electrocardiographic (ECG) recording, witnessed on a monitor, or unwitnessed but found on implantable cardioverter-defibrillator review).
- Death after unsuccessful resuscitation from cardiac arrest. Death after successful resuscitation from cardiac arrest and without identification of a noncardiac etiology.
- Unwitnessed death without other cause of death (information regarding the patient's clinical status preceding death should be provided, if available).

General Considerations

A subject seen alive and clinically stable 24 hours prior to being found dead without any evidence or information of a specific cause of death should be classified as "sudden cardiac death."

Typical scenarios include:

- Subject well the previous day but found dead in bed the next day
- Subject found dead at home on the couch with the television on
- Deaths for which there is no information beyond "Patient found dead at home" may also be classified as "death due to other cardiovascular causes".

Death due to Heart Failure or Cardiogenic Shock:

Death due to Congestive Heart Failure refers to a death in association with clinically worsening symptoms and/or signs of heart failure not following an acute MI.

Deaths due to heart failure can have various etiologies, including single or recurrent myocardial infarctions, ischemic or non-ischemic cardiomyopathy, hypertension, or valvular disease. Cardiogenic shock not occurring in the context of an acute myocardial infarction or as the consequence of an arrhythmia occurring in the absence of worsening heart failure is defined as systolic blood pressure (SBP) < 90 mm Hg for greater than 1 hour, not responsive to fluid resuscitation and/or heart rate correction, and felt to be secondary to cardiac dysfunction and associated with at least one of the following signs of hypoperfusion:

- Cool, clammy skin or
- Oliguria (urine output < 30 mL/hour) or
- Altered sensorium or
- Cardiac index < 2.2 L/min/m^2

Cardiogenic shock can also be defined if SBP < 90 mm Hg and increases to ≥ 90 mm Hg in less than 1 hour with positive inotropic or vasopressor agents alone and/or with mechanical support.

Death due to Stroke refers to death after a stroke that is either a direct consequence of the stroke or a complication of the stroke. Acute stroke should be verified to the extent possible by the diagnostic criteria outlined for stroke.

Death due to Cardiovascular procedures refers to death caused by the immediate complications of a cardiac procedure and excludes death resulting from procedures to treat an acute MI or the complications resulting from an acute MI.

Death due to Cardiovascular Hemorrhage refers to death related to hemorrhage such as a non-stroke intracranial hemorrhage, non-procedural or non-traumatic vascular rupture (e.g., aortic aneurysm), or hemorrhage causing cardiac tamponade.

Death due to Other Cardiovascular Causes: Death due to Other Cardiovascular Causes refers to a cardiovascular death not included in the above categories (e.g., pulmonary embolism or peripheral arterial disease).

Non-cardiovascular death:

Non-cardiovascular death is defined as any death that is not thought to be due to a cardiovascular cause. The following categories may be collected:

- Non-Malignant Causes
- Pulmonary
- Renal
- Gastrointestinal
- Hepatobiliary
- Pancreatic
- Infection (includes sepsis)
- Non-infectious (e.g., systemic inflammatory response syndrome (SIRS))
- Haemorrhage*, excluding haemorrhagic strokes and bleeding in the setting of coronary revascularization
- Non-cardiovascular procedure or surgery
- Accidental (e.g., physical accidents or drug overdose) or trauma
- Suicide
- Prescription Drug Error (e.g., prescribed drug overdose, use of inappropriate drug, or drug-drug interaction)
- Neurological process that is not a stroke or haemorrhage
- Other non-cardiovascular, specify: _____

*Examples: Death due to GI bleeding is not considered a CV death. Death due to retroperitoneal hematoma following PCI is considered CV death. Death due to intracerebral haemorrhage is considered CV death.

Malignant Causes

Death results directly from the cancer;

OR

Death results from a complication of the cancer (e.g. infection, complication of surgery / chemotherapy / radiotherapy);

OR

Death results from withdrawal of other therapies because of concerns relating to the poor prognosis associated with the cancer. Cancer deaths may arise from cancers that were present

prior to randomization or which developed subsequently should be further classified (worsening prior malignancy; new malignancy).

Undetermined cause of death:

Undetermined cause of death refers to a death not attributable to one of the above categories of cardiovascular death or to a non-cardiovascular cause, due to absence of any information (e.g., the only available information is "patient died"). The use of this category of death is discouraged and should apply to a minimal number of cases when no information at all on the circumstances of death are available (i.e. found on obituary of local newspaper). In all circumstances the reviewer will use all available information to attribute to one of the categories based on best clinical judgment.

For each death event an assessment will be made as to whether the event was caused, on the basis of the totality of the evidence, by a bleeding (ie a fatal bleeding occurred) or not.

MYOCARDIAL INFARCTION

For the primary analysis, MI endpoint will be defined based on the fourth universal definition of myocardial infarction with the exception of periprocedural MI after PCI, which will be defined according to the SCAI definition.

For secondary analyses, PCI-related MI according to the Fourth Universal MI definition (type 4a) will be also adjudicated.

1. Spontaneous MI (>48 hours after intervention, MI type 1)

Symptoms suggestive of ischemia/infarction in association with ECG, cardiac biomarker or pathologic evidence of infarction as follows:

- Detection of a rise and/or fall of cardiac biomarker values (preferably cardiac troponin T or I) with at least one value above the 99th percentile upper reference limit and with at least one of the following:
- Symptoms of ischemia
- New or presumed new significant ST segment-T wave (ST-T) changes or new LBBB
- Development of new Q waves in the ECG
- Evidence of new loss of viable myocardium or new regional wall motion abnormality
- Identification of an intracoronary thrombus by angiography or autopsy

Spontaneous MI typically occurs after the periprocedural period and may be secondary to late stent complications or progression of native disease (e.g., non-culprit lesion plaque rupture). Performance of ECG and angiography supports adjudication to either a *target* or *non-target vessel or lesion* in most cases.

Type 2 MI

In instances of myocardial injury with necrosis where a condition other than CAD contributes to an imbalance between myocardial oxygen supply and/or demand, e.g. coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachy/bradyarrhythmias, anemia, respiratory failure, hypotension, and hypertension with or without LVH.

Type 3 MI

Cardiac death with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased.

Type 4a MI (not used for primary analysis)

Type 4 MI is defined by elevation of cTn values (>5 x URL) occurring within 48h of the procedure in patients with normal baseline values (≤URL) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling.

In addition, at least one of the following is required:

- New ischaemic ECG changes (this criterion is related to type 4a MI only);
- Development of new pathological Q waves;
- Imaging evidence of loss of viable myocardium that is presumed to be new and in a pattern consistent with an ischaemic aetiology;
- Angiographic findings consistent with a procedural flow-limiting complication such as coronary dissection, occlusion of a major epicardial artery or graft, side-branch occlusion-thrombus, disruption of collateral flow or distal embolization.

Type 4b MI

Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of evidence of myocardial ischaemia and with a rise and/or fall of cardiac biomarker values with at least one value above the URL.

Type 4c MI

A spontaneous MI where a restenosis is the only angiographic explanation

Type 5 MI

Coronary artery bypass grafting (CABG) related MI is defined by elevation of troponin values (>10 x URL) occurring within 48h of the procedure in patients with normal baseline cTn values (≤URL).

In addition, at least one of the following is required:

- New ischaemic ECG changes (this criterion is related to type 4a MI only);
- Development of new pathological Q waves;
- Imaging evidence of loss of viable myocardium that is presumed to be new and in a pattern consistent with an ischaemic aetiology;
- Angiographic findings consistent with a procedural flow-limiting complication such as coronary dissection, occlusion of a major epicardial artery or graft, side-branch occlusion-thrombus, disruption of collateral flow or distal embolization.

2. Periprocedural MI after PCI (within 48 hours after PCI)

Periprocedural MI is defined based on the SCAI definitions as follows:

1) In patients with normal baseline CK-MB: The peak CK-MB measured within 48 hours of the procedure rises to ≥10x the local laboratory ULN, or to ≥5x ULN with new pathologic Q-waves in ≥2 contiguous leads or new persistent LBBB, OR in the absence of CK-MB measurements and a normal baseline cTn, a cTn (I or T) level measured within 48 hours of the PCI rises to ≥70x the local laboratory ULN, or ≥35x ULN with new pathologic Q-waves in ≥2 contiguous leads or new persistent LBBB.

2) In patients with elevated baseline CK-MB (or cTn) in whom the biomarker levels are stable or falling: The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above from the most recent pre-procedure level.

3) In patients with elevated CK-MB (or cTn) in whom the biomarker levels have not been shown to be stable or falling: The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above plus new ST-segment elevation or depression plus signs consistent with a clinically relevant MI, such as new onset or worsening heart failure or sustained hypotension.

REPEAT REVASCULARIZATION

According to ARC on clinical end points in coronary stent trials.

Target Lesion Revascularization (TLR)

TLR is defined as any repeat percutaneous intervention of the target lesion or bypass surgery of the target vessel performed for restenosis or other complication of the target lesion. All TLR should be classified prospectively as clinically indicated or not clinically indicated by the investigator prior to repeat angiography. The target lesion is defined as the treated segment from 5 mm proximal to the scaffold and to 5 mm distal to the scaffold.

Target Vessel Revascularization (TVR)

TVR is defined as any repeat percutaneous intervention or surgical bypass of any segment of the target vessel. The target vessel is defined as the entire major coronary vessel proximal and distal to the target lesion which includes upstream and downstream branches and the target lesion itself.

Non Target Lesion Revascularization (Non-TLR)

Any revascularization in the target vessel for a lesion other than the target lesion is considered a non-TLR.

Non Target Vessel Revascularization (Non-TVR)

Revascularization of the vessel identified and treated as the non-target vessel at the time of the index procedure.

Clinically-driven Revascularization (CD-TLR/CD-TVR)

A revascularization is considered clinically driven if associated with any of the following:

- Positive functional ischemia study including positive FFR/iFR.
- Ischemic symptoms and angiographic diameter stenosis ≥ 50% by QCA.
- Angiographic diameter stenosis ≥ 70% QCA without angina or positive functional study.

A revascularization of the target lesion/target vessel resulted of scaffold disruption or complications during instrumentation of the vessel for protocol-mandated invasive imaging, will be considered NO clinically-driven TLR/TVR.

STENT THROMBOSIS

Stent Thrombosis is defined by the Academic Research Consortium as follows:

Definite stent thrombosis is considered to have occurred by *either* angiographic or pathological confirmation:

a. Angiographic confirmation of stent thrombosis†

The presence of a thrombus‡ that originates in the stent or in the segment 5 mm proximal or distal to the stent and presence of at least 1 of the following criteria within a 48-hour time window:

- Acute onset of ischemic symptoms at rest
- New ischemic ECG changes that suggest acute ischemia
- Typical rise and fall in cardiac biomarkers (refer to definition of spontaneous MI: Troponin or CK-MB > 99th percentile of URL)
- Nonocclusive thrombus. Intracoronary thrombus is defined as a (spheric, ovoid, or irregular) noncalcified filling defect or lucency surrounded by contrast material (on 3 sides or within a coronary stenosis) seen in multiple projections, or persistence of contrast material within the lumen, or a visible embolisation of intraluminal material downstream
- Occlusive thrombus TIMI 0 or TIMI 1 intrastent or proximal to a stent up to the most adjacent proximal side branch or main branch (if originates from the side branch)

b. Pathological confirmation of stent thrombosis

Evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy

†The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is not considered a confirmed stent thrombosis (silent occlusion)

‡Intracoronary thrombus

Probable stent thrombosis:

Clinical definition of probable stent thrombosis is considered to have occurred after intracoronary stenting in the following cases:

- Any unexplained death within the first 30 days.
- Irrespective of the time after the index procedure, any myocardial infarction (MI), which is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause.

Possible stent thrombosis:

Clinical definition of possible stent thrombosis is considered to have occurred with any unexplained death from 30 days following intracoronary stenting until end of trial follow up.

STROKE

Stroke is defined as an acute episode of focal or global neurological dysfunction caused by central nervous system (CNS) vascular injury as a result of hemorrhage or infarction.

CNS includes brain, spinal cord and retina.

Classification:

Ischemic Stroke

Ischemic stroke is defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by CNS infarction. Evidence of infarction is defined as"Pathological, imaging, or other objective evidence of acute cerebral, spinal cord, or retinal focal ischemic injury in a defined vascular distribution; or

In absence of the above (i.e. imaging or autopsy unavailable), clinical evidence of cerebral, spinal cord, or retinal focal ischemic injury is based on symptoms persisting ≥24 hours or until death, and other etiologies excluded.

Note, Hemorrhagic infarction, defined as a parenchymal hemorrhage after CNS infarction, is considered an ischemic stroke

Cerebral Hemorrhage

Hemorrhages in the CNS are classified as stroke if they are nontraumatic, caused by a vascular event, and result in injury to the CNS. The diagnoses included in this section are intracerebral hemorrhage (intraparenchymal and intraventricular) and subarachnoid hemorrhage (both aneurysmal and nonaneurysmal). In contrast, traumatic hemorrhages will not be characterized as stroke. Subdural hematoma will not be classified as a stroke.

Stroke caused by intracerebral hemorrhage

Rapidly developing clinical signs of neurological dysfunction (focal or global) attributable to a focal collection of blood within the brain parenchyma or ventricular system that is not caused by trauma.

Stroke caused by subarachnoid hemorrhage

Rapidly developing signs of neurological dysfunction (focal or global) and/or headache because of bleeding into the subarachnoid space (the space between the arachnoid membrane and the pia mater of the brain or spinal cord), which is not caused by trauma.

Contrast-induced nephropathy (CIN)

Contrast use; contrast induced nephropathy (defined as serum creatinine rise >25% or absolute increase >0.5 mg/dL); need for renal replacement therapy.

Non-adherence Academic Research Consortium Consensus Classification

Captures the type of non-adherence

Type 1: Deviations from the prescribed regimen.

Intermittent variability in medication dose/exposure that does not fulfil criteria for non-adherence Types 0, 2, or 3 definitions.

a. Change in dose not pre-specified by protocol

b. Under-exposure: intake of <95% of the prescribed doses

c. Over-exposure: intake of >105% of the prescribed doses

Type 2: Temporary discontinuation

Omission of >_1 dose of prescribed medication resulting in loss of pharmacological effect, within the protocol-defined time frame, followed by resumption

of the prescribed regimen

Type 3: Permanent discontinuation

Permanent discontinuation of prescribed medication (resulting in loss of pharmacological effect based on a drug-specific pharmacological life within the protocol-defined time frame).

Supplementary Appendix 6. Statistical analysis.

The following analysis population sets will be defined for the assessment of study endpoints.

1. Intention-to-treat population (ITT)

ITT population is made out of enrolled subjects who have been randomized. Subjects will be analysed according to the treatment group they were assigned.

The coprimary endpoint of MSA will be analysed from the ITT population.

2. Per protocol population (PP)

Subjects of ITT who completed the treatment originally allocated without any major protocol deviations affecting the assessment or interpretation of the study endpoints. Here below, the preliminary list of major protocol deviations that will lead to exclusion from PP population:

- Inclusion/exclusion criteria not fulfilled or randomization criteria not fulfilled
- Non-compliance to the treatment assigned by the randomization

The primary endpoint of NACE will be performed from the PP population in all those randomized participants who completed the 11 months follow-up without Prasugrel or DAPT disruption. PP analyses are indeed recommended for investigating noninferiority since crossover/non-adherence in the ITT population may bias the results toward noninferiority. With respect to the analysis on antithrombotic therapy strategies, patients who will experience an ischemic or major bleeding event from primary PCI to the mandatory office visit at 30-45 days (randomization) will be excluded.

Based on MASTER DAPT trial results the anticipated rate of discontinuation of Prasugrel will be less than 10%.

As sensitivity, noninferiority will be tested in the ITT population.

3.Statistical Analysis Plan

Categorical variables will be reported as counts and proportions and assessed by $\chi 2$ or Fisher exact test , as appropriate. Continuous variable will be reported as mean ± standard deviation or median [interquartile range] and assessed by Student t or Mann-Whitney test, as appropriate.

All time-to-event endpoints will consist of right-censored variables describing the status until the occurrence of the event (first event for endpoint that may recur) or drop out (lost to follow-up and withdrawal from the study or death before the occurrence of the endpoint). Incidences between traeatment groups will be computed by Kaplan-Meier method and differences will be assessed by test log-rank test. Hazard ratios and 95% confidence intervals will be computed by Cox proportional hazards regression. The proportionality assumption will be formally assessed by Grambsch-Therneau test and Schoenfeld residuals. Alternative models with time-varying coefficient will be used in case of violation of the proportionality assumption.

With respecto to the clinical analysis on antithrombotic therapy strategies, the hypothesis is that prasugrel monotherapy is noninferior to standard DAPT (control) in terms of NACCE, as assessed 11 months after randomization (12 months after PCI). Noninferiority will be demonstrated with 80% of power if in the per-protocol cohort the upper limit of the one-sided 97.5% confidence intervalwill be below the absolute noninferiority rate difference of 2.0%. If the requirement for non-inferiority will be met, testing for superiority of prasugrel monotherapy to standard DAPT will performed at a one-sided alpha level of 0.025 as an exploratory analysis.

Prespecified subgroup analyses with the for interaction will be performed. An adjustment for multiplicity is planned in case of detection of significant treatment-by-subgroup interaction. Consistentency between intention-to-treat, per-protocol, and as-treated analyses will be assessed. Sensitivity analyses by 6-month landmark time point will be conducted. Finally, mixed-effects models with stratification by participating centre in the random component will be performed.

In the subgroup of patients with multivessel disease, the interaction between antithrombotic therapy regimens (i.e. short DAPT followed by prasugrel monotherapy versus standard prasugrel-based DAPT) and the type of guidance to achieve revascularization completeness (i.e., OCT- versus angiography-guided) for the primary and key secondary endpoints will be formally explored by Cox proportional hazards regression models including the two factors as covariates alongside their interaction term.

With respecto to the imaging analysis on revascularization completion guidance, the hypothesis is that OCT guidance is superior to angiography guidance in achieving a larger final MSA. The superiority of OCT-guided PCI to angiography-guided PCI will be demostrated with 80% of power for a minimum mean increase in MSA of 0.4 mm2 at a one-sided alpha level of 0.025. Time-to-event analysis will be performed according to the methodology illustrated for the antithrombotic therapy analysis

Supplementary Appendix 7. Detailed follow-up and study management.

1. Follow up

Follow-up is scheduled at 2,11 and 35 months post DAPT randomization. All follow-up visits are preferably scheduled as a visit to outpatient clinic. If patients are unable or unwilling to visit the outpatient clinic, the scheduled visit can be replaced by a telephone call except for the follow-up occurring at 11 months.

2. Data collection at follow-up

Patients are informed that data are collected at scheduled follow-ups as well as at unscheduled visits.

The pre-procedural data to be collected include medical history and cardiac medications pre-PCI.

The procedural details of the index PCI include location of treated lesions, number of stents, stent length, stent diameter, type of stents and complications etc.

The post-procedural medication is recorded as well as clinical events (MACCE and bleeding) that may occur after the study medication has been administered.

At each visit, the following information is collected:

- Major adverse cardiac and cerebral events
- Vital status
- Potential acute coronary syndrome
- Potential stroke of any aetiology (ischemic, haemorrhagic and indeterminate)
- Stent thrombosis
- ANY clinically overt bleeding events
- Coronary revascularization (PCI or coronary artery bypass grafting [CABG])
- Prescription and compliance of antiplatelet medication

3. Withdrawal of individual subjects

At any time during the study, the subject may withdraw their participation from the study. Every patient is encouraged to remain in the study until they have completed the protocol-required follow-up period. Patients who deviate from the randomization order continue to be followed up as per standard of care.

Clinical follow-up is only discontinued if the patient explicitly forbids the continuation of follow-up. This decision should be an independent decision that is documented in the patient study files. Survival status should be collected within legal and ethical boundaries for all subjects randomized who withdrew participation from the study. If follow-up is discontinued prematurely, the reason for discontinuation is documented. In case of discontinuation, the already collected data remain in the database unless the patient explicitly requests complete deletion of the records, which should be documented by the site. The study subjects may also be withdrawn at any time at the discretion of the investigator and/or the patient’s treating physician, if it is deemed to be in the patient's best interest (e.i clinical worsening for which IMPs are contraindicated, see definition of Non-adherence Academic Research Consortium Consensus Classification, appendix 6).

Moreover, the clinical trial may be discontinued prematurely for new information leading to unfavourable risk-benefit judgment of the Investigational Medicinal Products (IMPs), e.g. due to evidence of inefficacy of the IMPs, or occurrence of significant previously unknown adverse reactions or unexpectedly high intensity or incidence of known adverse reactions or other unfavourable safety findings. An independent data safety monitoring board will provide external oversight to detect evidence of adverse effects (safety) and will provide recommendation to Advisory panel and PIs with respect to trial conduct.

4. Lost to follow-up

A subject would be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. If a subject is unable to return for a clinic visit or unable to be contacted by telephone, diligent attempts to contact the subject are made to obtain subject required information. All attempts are documented in the source documents. Only after failing to contact the subject at the final follow-up visit, the subject is considered lost to follow-up after last contact. It must be a high priority to obtain at least survival data on all subjects lost to follow-up. Survival status will be collected within legal and ethical boundaries for all subjects randomized. Vital status will be searched in public sources at the end of the follow-up period. If vital status is known at the last study visit, the subject will not be considered lost to follow-up.

5. Non-adherence to the study protocol DAPT regimen

At 30-45 days after index procedure patients will be screened for eligibility criteria including adherence to the prescribed DAPT regimen.

The non-adherence will be classified according to the Non-adherence Academic Research Consortium (NARC)[1]. The gradient of adherence ranges from optimal adherence to the study protocol (Type 0), through suboptimal treatment implementation (Type 1) to treatment discontinuation classified as temporary (Type 2), where the period exceeds the pharmacological effect of the study drug but treatment is recommenced, or permanent (Type 3). Optimal adherence, classified as Type 0, allows for 5% tolerance, during the study timeframe, from that defined per protocol.

Only patients who at 30-45 days post index procedure are on NARC type 0 will be randomized. At 11 month of follow up patients who are on NARC type 1 will be considered for analysis while patients on NARC type 2 or 3 will be excluded.

6. Termination of patient participation

The patient participation in the study ends if any of the following occurs:

- Patient has completed the study
- Patient is lost to follow-up
- Patient premature termination
- Study premature termination

After study termination, subjects who took part in the study will be followed as per sites standard practices. Medical therapy (including antiplatelet therapy) will be as prescribed by the subject's physician.

Supplementary Table 1. DSMB members.

Name	Specialty	Affiliation
Prof. Jan Tijssen (Chair)	Statisticus	The Academic Medical Center - University Of Amsterdam
Prof. Davide Capodanno (Member)	Interventional Cardiologist	Cardio-Thoracic-Vascular and Transplant Department, Azienda Ospedaliero-Universitaria Policlinico "Gaspare Rodolico – San Marco", University of Catania, Catania, Italy
Prof. Roxana Mehran (Member)	Interventional Cardiologist	Icahn School of Medicine at Mount Sinai, New York, New York, USA

Supplementary Table 2. CEC members.

Name	Specialty	Affiliation
Prof. Emanuele Barbato (Chair)	Interventional Cardiologist	Department of Clinical and Molecular Medicine, Sapienza University of Rome, Italy
Prof. Lorenz Raber (Member)	Interventional Cardiologist	Department of Cardiology, Bern University Hospital, University of Bern, Bern, Switzerland
Prof. George Vlachojannis (Member)	Interventional Cardiologist	
Prof. Giulio Giuseppe Stefanini (Member)	Interventional Cardiologist	Cardio Center, Humanitas Research Hospital IRCCS, Milan, Italy