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Tissue characterisation and primary percutaneous coronary intervention guidance using intravascular ultrasound: rationale and design of the SPECTRUM study

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ABSTRACT

Introduction Intravascular ultrasound (IVUS) improves clinical outcome in patients undergoing percutaneous coronary intervention (PCI) but dedicated prospective studies assessing the safety and efficacy of IVUS guidance during primary PCI are lacking.

Methods and analysis The SPECTRUM study is a prospective investigator-initiated single-centre single-arm observational cohort study aiming to enrol 200 patients presenting with ST-segment elevation myocardial infarct undergoing IVUS-guided primary PCI. IVUS will be performed at baseline, postintervention and postoptimisation (if applicable), using a 40–60 MHz high-definition (HD) system. Baseline tissue characterisation includes the morphological description of culprit lesion plaque characteristics and thrombus as assessed with HD-IVUS. The primary endpoint is target vessel failure at 12 months (defined as a composite of cardiac death, target vessel myocardial infarction and clinically driven target vessel revascularisation). The secondary outcome of interest is IVUS-guided optimisation, defined as IVUS-guided additional balloon dilatation or stent placement. Other endpoints include clinical and procedural outcomes along with post-PCI IVUS findings.

Ethics and dissemination The protocol of this study was approved by the Ethics Committee of the Erasmus University Medical Center, Rotterdam, the Netherlands. Written informed consent is obtained from all patients. Study findings will be submitted to international peer-reviewed journals in the field of cardiovascular imaging and interventions and will be presented at international scientific meetings.

Trial registration number NCT05007535.

Key questions

What is already known about this subject?
► Intravascular ultrasound (IVUS)-guided percutaneous coronary intervention (PCI) improves clinical outcomes in a broad spectrum of patients.
► Patients with ST-segment elevation myocardial infarction (STEMI) were vastly underrepresented in clinical trials and dedicated studies are lacking.

What does this study add?
► This prospective observational study will be the first to present dedicated procedural, imaging, safety, and outcome data on the use of IVUS in patients with STEMI.

How might this impact on clinical practice?
► The results of this study will provide important insights on the impact of IVUS-guided primary PCI in patients with STEMI.

INTRODUCTION

Intravascular ultrasound (IVUS) allows accurate characterisation of arterial morphology and vessel size in patients with coronary artery disease undergoing percutaneous coronary intervention (PCI).[1]

Recent trials and meta-analyses have shown that IVUS-guided PCI reduces target vessel failure and mortality as compared with angiography-guided PCI.[2–6] The overall body of evidence on the superiority of IVUS- as compared with angiography-guided stenting is built on studies focusing on patients with complex coronary artery disease, or study populations with mainly chronic coronary syndromes or non-ST-segment elevation acute coronary syndromes.[2 3 7 8] Whereas dedicated prospective data in patients presenting with ST-segment elevation myocardial infarction (STEMI) undergoing contemporary PCI are lacking, several retrospective studies and subgroup analyses of prospective registries suggested a beneficial effect of IVUS-guided PCI in STEMI.[9–13]

As primary PCI is challenged by a more complex lesion morphology and the presence of thrombus, the use of IVUS during primary PCI has the potential to optimise PCI outcome by several means. First, IVUS allows a better understanding of the underlying plaque morphology. It can visualise specific culprit lesion plaque characteristics, such as plaque ruptures and attenuation, which might be associated with no-reflow and subsequent higher mortality.[14–17] Moreover, IVUS can be used for the identification of disease extent and for the differentiation between thrombus and calcium, which often remains elusive based on angiography alone.[1 15 18 19] The presence of thrombus, calcium or a mixture of both has significant impact on lesion preparation strategies and concomitant pharmacotherapy. Furthermore, IVUS allows accurate assessment of post-PCI findings like underexpansion, malapposition, edge dissections and geographic miss, which are linked to future adverse events and may trigger additional optimisation strategies.[2 3 20 21] Finally, improved imaging quality (using a 40–60 MHz high-definition IVUS (HD-IVUS) catheter) facilitates better image interpretation, which could be of particular interest to patients with complex plaque morphology as seen in patients presenting with STEMI.

The 'Tissue characterisation and primary percutaneous coronary intervention guidance using intravascular ultrasound' (SPECTRUM) study is the first dedicated prospective study designed to assess the safety and efficacy of IVUS-guided primary PCI in an all-comers STEMI population.

METHODS AND ANALYSIS
Study design
The SPECTRUM study is a prospective investigator-initiated single-centre single-arm observational cohort study performed in the Erasmus University Medical Center, Rotterdam, the Netherlands. The study aims to enrol a total of 200 consecutive patients undergoing IVUS-guided primary PCI. All patients will be followed up to 12 months.

Study population
All adult patients presenting with STEMI undergoing primary PCI for a native coronary artery culprit lesion with an angiographic vessel reference diameter ≥2.25 mm are eligible. STEMI is defined according to the fourth universal definition of myocardial infarction.[22] Cardiogenic shock and presentation ≥12 hours after symptom onset are exclusion criteria.

Study endpoints
The primary endpoint is target vessel failure (TVF) at 12 months, which is defined as a composite of cardiovascular death, target vessel myocardial infarction and clinically driven target vessel revascularisation.[23] The secondary outcome of interest is IVUS-guided optimisation, defined as IVUS-guided additional balloon dilatation or stent placement. Three types of IVUS-guided optimisation are distinguished: (1) IVUS-guided additional balloon dilatation or stent placement after angiographically successful PCI; (2) IVUS-guided additional balloon dilatation or stent placement after angiographically unsuccessful PCI; (3) IVUS-guided additional balloon dilatation or stent placement without knowledge of the angiographic success (ie, the operator performs IVUS-guided optimisation after initial treatment without first making a coronary angiogram, for example to reduce contrast use). Angiographically successful PCI is defined as (Thrombolysis in Myocardial Infarction 3 flow with <30% residual stenosis). Other endpoints include clinical and procedural outcomes along with post-PCI IVUS findings (table 1). Moreover, tissue characterisation includes the morphological description of culprit lesion plaque characteristics and thrombus as assessed with HD-IVUS at baseline. All IVUS definitions are further explained below in a separate section.

Table 1	Overview of study endpoints
Primary endpoint	► Target vessel failure (12 months) Composite of cardiac death, target vessel myocardial infarction, clinically driven target vessel revascularisation
Secondary endpoint	► IVUS-guided optimisation IVUS-guided additional balloon dilatation or stent placement
Other endpoints	
Clinical	► TVF (30 days) ► Maces (30 days, 12 months) Composite of all-cause mortality, any myocardial infarction and repeat revascularisation ► Individual components of TVF and MACE (30 days, 12 months)
IVUS	► Post-PCI findings Including underexpansion, malapposition, edge dissections, high plaque burden at stent edges, residual focal lesions
Procedural	► Major intraprocedural complications Including type C–F dissections, perforations, slow flow or no-reflow, major side branch occlusion (>2 mm)
Angiographic	► Final TIMI flow ► Final myocardial blush grade

IVUS, intravascular ultrasound; MACE, major adverse cardiovascular event; PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction; TVF, target vessel failure.
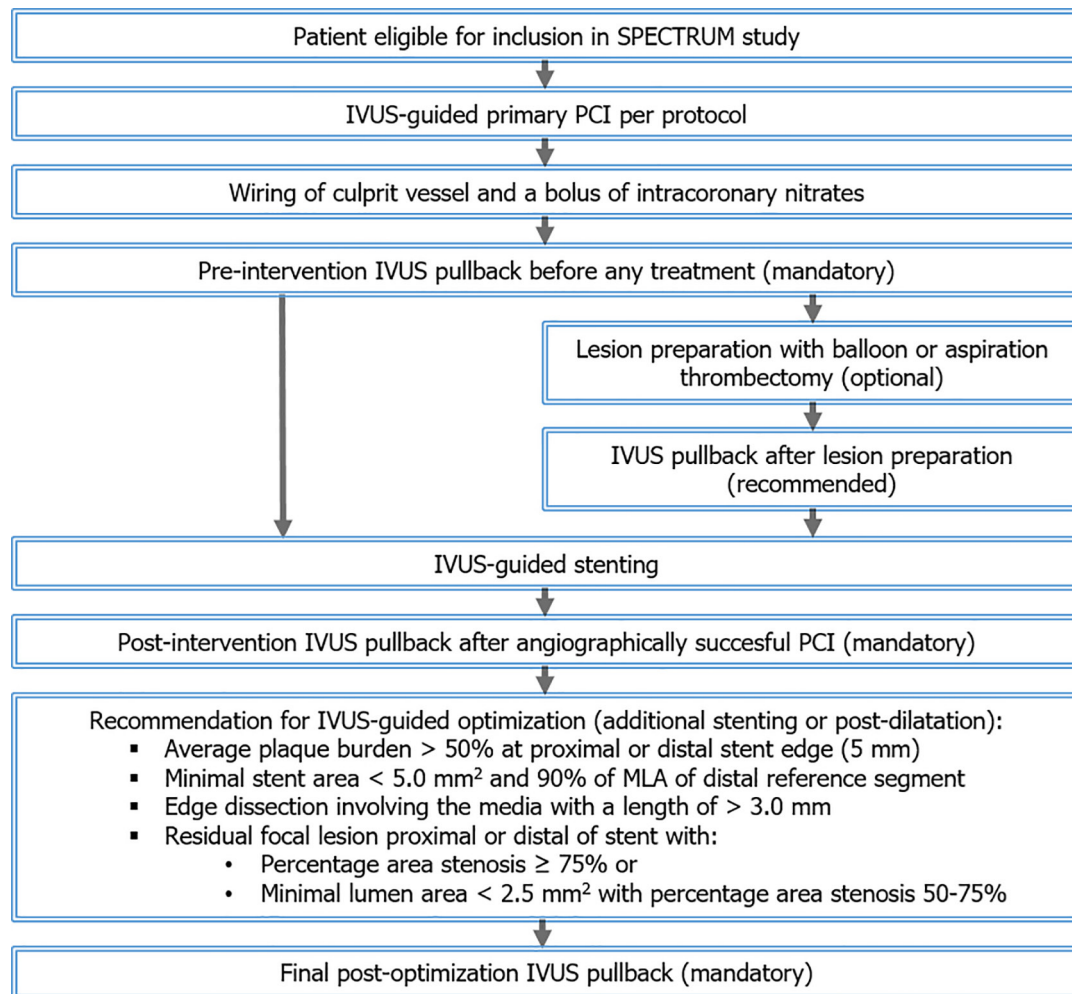
Figure 1 Protocol for IVUS-guided primary PCI, including the recommended optimisation criteria for IVUS-guided optimisation. IVUS, intravascular ultrasound; MLA, minimal lumen area; PCI, percutaneous coronary intervention.

Study materials

Intravascular imaging will be preferably performed with the multifrequency high-definition (40–60 MHz) IVUS system (Kodama, ACIST Medical Systems, Eden Prairie, Minnesota, USA). Stenting will be preferably performed with the Firehawk Sirolimus Target Eluting Coronary Stent System (Microport, Shanghai, China). Both devices are Conformité Européenne approved and routinely used in clinical practice.

Study procedure

Besides the protocolised use of IVUS, procedures will be performed according to routine practice and current guidelines, including the use of aspirin and P2Y12 inhibitors, transradial access as first option and peri-procedural use of heparin (activated clotting time >250 s).

Figure 1 shows the protocol for IVUS-guided primary PCI. Directly after vessel wiring (so before any lesion preparation, ie, balloon dilatation, aspiration thrombectomy or stent placement) and a bolus of intracoronary nitrates, the IVUS catheter is advanced and pulled back automatically after disengagement of the guiding catheter. This is considered the 'preintervention IVUS pullback'. Lesion preparation (eg, predilatation, aspiration thrombectomy) is performed at the operators discretion; a subsequent IVUS pullback is recommended. Consequently, IVUS-guided stenting is performed followed by postdilatation (if necessary). After angiographically successful PCI, a post-PCI IVUS pullback will be performed starting at least 2 centimeters distal to the most distal stent edge (or treated segment in case of balloon dilatation only). This is considered the 'postintervention IVUS pullback'. Subsequent IVUS-guided optimisation (additional stenting or postdilatation) is recommended based on predefined optimisation criteria (figure 1).[2] If IVUS-guided optimisation is performed, a final 'postoptimisation IVUS pullback' is required. All pullbacks with the Kodama IVUS system are performed with an automated pullback speed of 2.5 mm/s, acquiring 60 frames per second (24 frames per mm). All patients will be discharged on high-intensity statins and antithrombotic therapy as per current guideline recommendations.[24]

IVUS imaging analysis

Based on a feasible target to dedicately analyse a maximum of 300 IVUS pullbacks, only the first 100
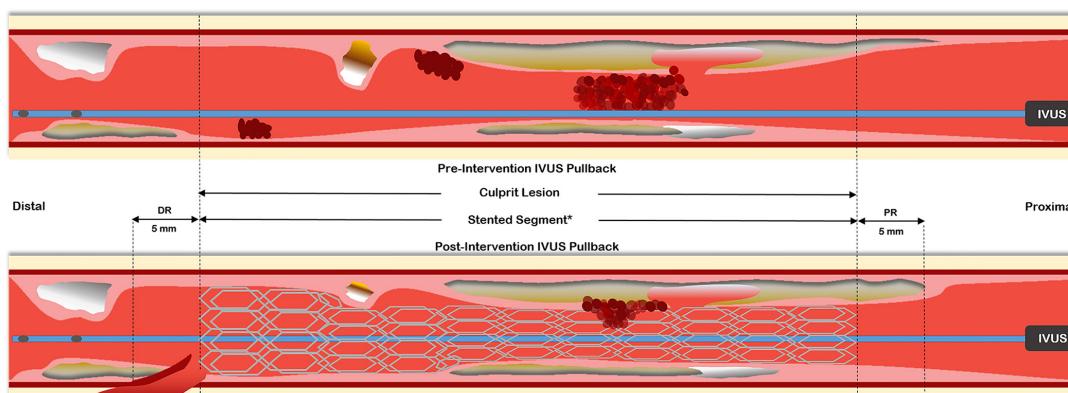
Figure 2 Culprit lesion, stented segment and reference segments based on preintervention and postintervention IVUS pullback. The culprit lesion segment on the preintervention pullback is matched based on the stented (or treated) segment on the postintervention IVUS pullback. * Or treated segment if only balloon dilatation is performed. DR, distal reference; IVUS, intravascular ultrasound; PR, proximal reference.

patients with (1) full availability of Kodama HD-IVUS pullbacks (including a postoptimisation IVUS pullback in case of IVUS-guided optimisation) and (2) regions of interest that can be matched appropriately on the preintervention and postintervention IVUS pullback, will be subject to the extensive imaging analysis. For these patients, the following regions of interest will be analysed: (1) culprit lesion on the preintervention IVUS pullback; (2) the stented segment ±5 mm of the proximal and distal stent edge on the postintervention IVUS pullback; (3) the stented segment ±5 mm of the proximal and distal stent edge on the postoptimisation IVUS pullback (if applicable). The culprit lesion segment on the preintervention pullback will be matched (based on side branches) to the stented segment on the postintervention IVUS pullback (figure 2). If stenting is not performed (eg, only balloon dilatation), the region of interest on the postintervention IVUS pullback is the treated segment ±5 mm proximal and distal.

Systematic quantitative and qualitative IVUS analyses, including baseline tissue characterisation of culprit lesion characteristics and thrombus, as well as the assessment of post-PCI findings, will be performed per 0.5 millimeter by the Erasmus University Medical Center academic corelab, using dedicated software (QCU-CMS, Leiden University Medical Center, LKEB, Division of Imaging Processing, V.4.69).

For the remaining 100 patients only a simplified IVUS analysis of the postintervention and postoptimisation (if applicable) IVUS pullbacks will be performed. This simplified IVUS analysis is further explained below.

IVUS definitions

Quantitative and qualitative IVUS parameters are defined as follows. The vessel (based on external elastic membrane (EEM)) cross-sectional area (CSA), lumen CSA and plaque CSA are calculated for cross-sectional frames of the culprit lesion, stented segment and reference segments. Vessel CSA is only determined if at least 180° of the EEM is visible. Lumen CSA is the area central to the intimal edge or thrombus border. Plaque CSA is vessel CSA—lumen CSA and plaque burden (PB) is plaque CSA/vessel CSA × 100%.[25] The minimal lumen area (MLA) is the smallest lumen CSA and the minimal stent area (MSA) is the smallest stent CSA in the stented segment (360° of stent struts visible with no longitudinal discontinuation). Moreover, the smallest lumen CSA in the stent is considered the in-stent MLA. The remodelling index is calculated as the vessel CSA at the MLA divided by the average of the proximal and distal vessel CSA of the culprit lesion segment.[25]

Different plaque types in the culprit lesion are determined as follows: Calcified plaque (high echogenicity with signal attenuation), fibrofatty plaque (a mix of soft and fibrous plaque with low to intermediate echogenicity and no signal attenuation) and soft-attenuated plaque (low echogenicity and backward signal attenuation without presence of calcium).[25 26] Furthermore, a distinction is made between concentric and eccentric plaque and in case of calcium also between superficial or deep calcium.

For the assessment of culprit lesion plaque characteristics and thrombus morphology, the following definitions are used. Thrombus can be recognised as intraluminal mass with a layered, lobulated or pedunculated appearance.[25] In general, three types of thrombus can be recognised on IVUS.[18 19] Acute thrombus (platelet aggregation) is defined as an acoustic in-homogenous bright 'spontaneous contrast' appearance with sharp delineation and no clear signal attenuation. Subacute thrombus has a more homogeneous acoustic appearance and thus appears darker. It has a light to dark grey appearance with white speckles and less clear delineation. Also moderate to severe signal attenuation might be observed. The most acoustic homogeneous type of thrombus is organised thrombus (granulation), which we define as a homogeneous dark appearance, clearly starting from the lumen wall with sharp delineation and in some cases mild signal attenuation. The maximum thrombus angle and the
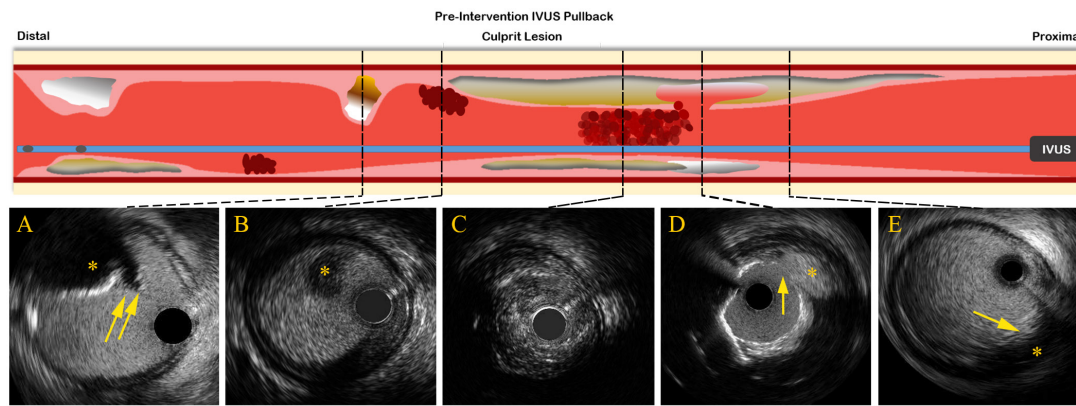
Figure 3 Preintervention IVUS findings related to STEMI. Culprit lesion plaque characteristics and thrombus morphology that will be studied with IVUS. (A) Convex calcium (asterisk) that protrudes into the lumen. The arrows indicate the irregular surface. (B) Organised thrombus (asterisk), visualised as an acoustic homogeneous dark appearance with sharp delineation. (C) Minimal lumen area with 360° of subacute thrombus. Subacute thrombus boundaries are less strict and signal attenuation can be appreciated. (D) Plaque rupture (arrow) with blood speckling inside the plaque cavity (asterisk). (E): Soft plaque (arrow) with attenuation (asterisk) in the absence of calcium. IVUS, intravascular ultrasound; STEMI, ST-segment elevation myocardial infarction.

amount of thrombus containing frames are determined as well (for culprit segment and full preinterventional pullback).

Furthermore, the presence of plaque rupture and convex calcium will be assessed. Plaque rupture is defined as plaque ulceration with an intimal tear detected in a fibrous cap with or without blood speckling in a cavity behind the ruptured intima.[25 27] Convex calcium is defined as a bulgy calcified plaque (bright appearance with signal attenuation) that protrudes into the lumen on both cross-sectional and longitudinal views and can have an irregular surface.[27 28] It can be compared with a calcified nodule on optical coherence tomography. Figure 3 shows an overview of culprit lesion plaque characteristics and thrombus morphology that will be studied with IVUS.

Postintervention IVUS characteristics of interest include stent expansion, PB at stent edges, edge dissections and residual focal lesions. Stent expansion is considered sufficient if the MSA is >5.0 mm^2 or if the stent is expanded >90%, calculated as MSA / MLA of distal reference segment × 100%.[2] The PB at the proximal and distal stent edge is considered high in case average PB in the reference segments exceeds >50%.[2] Edge dissections are divided into intimal and medial dissections. An edge dissection involving the media with a length of >3.0 mm is considered to be clinically relevant.[2] A residual focal lesion is defined as a remaining lesion outside the stented segment with (1) a percentage area stenosis ≥75% or 2) an MLA <2.5 mm^2 with a percentage area stenosis of 50%–75% distal or proximal of the stented segment, not including coronary spasm.[29] Percentage area stenosis is calculated as (lumen CSA reference – lumen CSA lesion)/lumen CSA reference × 100%. The procedure is considered 'optimal based on IVUS' if the stent is well expanded with low PB at the stent edges and if no clinically relevant edge dissections or residual focal lesions are present. If this does not apply, the procedure is considered 'suboptimal based on IVUS'.[2]

Furthermore, the presence of haematomas, malapposition and thrombus protrusion is assessed. A subintimal haematoma is defined as accumulation of blood between intima and media, whereas a submedial haematoma is defined as accumulation of blood behind the media. Malapposition is defined as the presence of multiple malapposed stent struts in at least three consecutive frames (side branches excepted). Thrombus protrusion is defined as thrombus protruding in the lumen covering multiple stent struts.[18 19] Figure 4 shows an overview of stenting-related complications and other relevant postintervention findings that will be studied with IVUS.

For the remaining 100 patients, the simplified IVUS analysis of the postintervention and postoptimisation IVUS pullbacks is performed to decide whether treatment was 'optimal' or 'suboptimal' based on IVUS. This simplified analysis includes the following: (1) MSA; (2) MLA at distal reference segment (to determine underexpansion); (3) PB at the proximal and distal reference segments; (4) clinically relevant edge dissections and (5) residual focal lesions. The simplified method starts with the identification of four landmark frames: the first and last frame of the proximal and distal reference segment. Additionally, the cross-sections in the reference segments with the visually determined MLA are identified. If this frame coincides with a landmark frame, an adjacent distal or proximal frame is selected. Subsequently, the cross-section with the visually determined MSA is identified. The MSA is calculated based on the contouring of the visually determined MSA frame, whereas the MLA and PB are calculated based on the contouring of the three described frames in each reference segment. Finally, assessment of clinically relevant edge dissections and
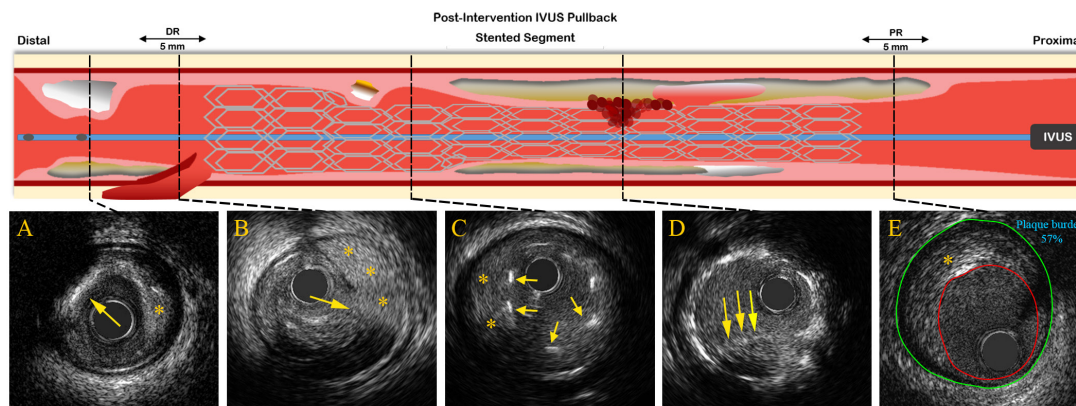
Figure 4 Post-PCI findings that will be studied with IVUS. (A) Residual focal lesion distal from the stented and distal reference segment. The calcified (arrow) and fibrous plaque (asterisk) cause luminal narrowing. (B) A submedial edge dissection (arrow) with blood speckling and accumulation of blood (asterisks) behind the media, defined as a submedial haematoma that compromises the lumen. (C) Malapposition, shown as lumen (asterisks) between malapposed stent struts (small arrows) and the intimal edge. (D) Small stent area due to underexpansion with thrombus protruding into the lumen (arrows) covering multiple stent struts. (E) Large fibrofatty plaque (asterisk) causing a high plaque burden in the proximal reference segment. DR, distal reference; PCI, percutaneous coronary intervention; PR, proximal reference; IVUS, intravascular ultrasound.

residual focal lesions is based on the previously described definitions.

Data management and follow-up

Patient, procedural and imaging data will be stored prospectively in a dedicated local research database.

Follow-up will be obtained using an in-house developed dedicated platform (CathSuite). CathSuite facilitates online patient-reported outcome measurements (PROMs) by email or text message, renouncing the need for sending questionnaires or standardised telephone calls to obtain follow-up data. Every study patient that is alive (checked through civil municipal registry) will automatically receive a unique link by email or text message at 30 days and 12 months after the study procedure. This link refers to the online PROMs form, where patients are asked to indicate the occurrence of events, such as myocardial infarction or PCI and if so, when and in which hospital the patient was admitted. All reported events cause a trigger notifying our CathSuite staff to collect and upload additional information. All collected triggers will be adjudicated by an independent clinical event committee. For patients with no email or without response, the online PROMs form is completed during a telephone call. A patient is considered lost to follow-up if he/she does not complete the PROMs form and cannot be reached by telephone. For this study no additional tests, outpatient clinic visits or procedures are necessary according to the study protocol.

Sample size

With 400–500 patients undergoing primary PCI in our hospital every year and the assumption that~40% of patients will be included, the sample size of 200 patients is a pragmatic target that on the one hand enables calculation of the proportion of events with sufficiently narrow CIs, and on the other hand completion of the study

inclusion within 12–18 months. If the percentage of patients with TVF at 12 months is 10%, the sample size of 200 allows us to provide a 95% CI of (6% to 14%).[30]

Statistical analysis

The percentage of patients with the primary composite endpoint will be presented with 95% CI and the Kaplan-Meier method will be used to display cumulative incidence over time. The percentage of patients with IVUS-guided optimisation will also be presented with 95% CI. Moreover, the different types of IVUS-guided optimisation will be plotted against the predefined IVUS optimisation criteria.

The Shapiro-Wilk test will be used to investigate whether continuous variables are normally distributed. Normally distributed continuous variables will be presented as mean±SD, whereas non-normally distributed variables will be displayed as median±IQR. Categorical variables will be presented as counts and percentages.

Univariable and multivariable (in case of sufficient number of events) Cox proportional hazards regression analysis will be performed to evaluate relationships between IVUS derived parameters and TVF. Moreover, association between pre-interventional IVUS derived characteristics and procedural outcome variables, including IVUS-guided optimisation, will be investigated by means of univariable and multivariable linear and logistic regression analysis as appropriate (for continuous and binary outcomes variables, respectively).

Changes in continuous and categorical IVUS measurements between postintervention and postoptimisation IVUS pullbacks will be investigated using paired t-tests (normally distributed variables), Wilcoxon signed-rank tests (non-normally distributed variables) and the McNemar test (binary variables) as appropriate.

All tests will be two-tailed and a p<0.05 will be considered statistically significant. Latest version of SPSS (V.28) and R (if necessary) will be used for statistical analysis.

Study status and timeline

The first patient was included in the study on 10 November 2020. We expect to finish enrolment in H1 of 2022 and complete follow-up 1 year later in H1 of 2023.

DISSEMINATION

The findings of this study will be submitted to international peer-reviewed journals in the field of cardiovascular imaging and interventions. The study results will be presented at international scientific cardiovascular meetings.

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