STARRING OPTICAL COHERENCE TOMOGRAPHY DURING PERCUTANEOUS CORONARY INTERVENTIONS GUIDANCE: THE OCTAGEM REGISTRY

I. NCT study number:

II. Center: Fondazione Policlinico Universitario Agostino Gemelli, IRCCS

III. PROTOCOL SYNOPSIS

Title	Definition of intra-procedural optical coherence tomography (OCT) clinical impact both in terms of revascularization indication and procedural result.
Design	Observational ambispective cohort study. Single-centre, retrospective, observational registry (I phase) Single-centre prospective, observational registry (II phase)
Objective	To explore the role of intra-procedural OCT in order to optimize coronary revascularization in terms of procedural results and long-term clinical outcome.
Device/drug planned	None
Registration	The study will be register on www.clinicaltrial.gov site after local Ethic Committee approval
Study Population	All subjects over 18 years who are undergoing an OCT coronary assessment during clinically indicated coronary angiogram regardless of the clinical syndrome (silent ischemia, effort angina or acute coronary syndrome).
Estimated population size	2200 (based on annual OCT-guided procedure rate of ~150) for the retrospective phase. 1000 (based on annual OCT-guided procedure rate of ~150) for the prospective phase
Statistical hypothesis	On the basis of previous clinical studies testing clinical impact of OCT use during percutaneous coronary revascularization and preliminary experience of the steering committee, we estimated: **Non-interventional arm**: a cumulative incidence of 5% for the

	composite clinical end-point and of 20% for the OCT-defined vulnerable plaque are assumed. For the study purpose a sample size of 986 patients was computed assuming a HR of 0.80 favoring patients without OCT-defined plaque vulnerability, and aiming to a 2-sided alpha level of 0.05 and a power of 80%. To accommodate for possible missing investigations or withdrawals, sample size was increased to 1100 patients. **Interventional arm**: a cumulative incidence of 25% for the OCT-defined suboptimal stent implantation and of 12% for the composite clinical end-point are assumed. For the primary study purpose a sample size of 1858 patients is computed assuming a HR of 0.85 favoring patients without suboptimal stent implantation OCT criteria, and aiming to a 2-sided alpha level of 0.05 and a power of 80%. To accommodate for possible missing investigations, sample size will be increased to 2100 patients. The study enrolment will be considered complete when the required target population has been enrolled. A patient is considered enrolled in the study when he/she has signed the informed consent form (point of enrolment).
Study Centre	Fondazione Policlinico Universitario Agostino Gemelli, IRCCS
Coordinating Clinical Investigator	Dr. Enrico Romagnoli Fondazione Policlinico Universitario Agostino Gemelli, IRCCS, Rome, Italy

Primary Endpoints	Predictive clinical value of vulnerable plaque OCT criteria at mid and long term outcome in patients with non-obstructive coronary artery disease (MINOCA/INOCA). Predictive clinical value of plaque/stent OCT parameters at mid and long term outcome in patients undergoing percutaneous coronary revascularization Clinical composite endpoint: cardiac death, target-vessel myocardial infarction, target lesion revascularization, and stent thrombosis
Secondary Endpoints	**Non-interventional**: clinical impact of the single pre-specified OCT features of plaque vulnerability: - Minimum lumen area <3.5 mm2; - Fibrous cap minimum thickness <65 μm; - Lipid arc extension >180°; - Presence of macrophages; - Superficial and deep calcified nodules - Ulceration/Erosion/Dissection - Layered tissue - Plaque burden (%) - Optical flow ratio (OFR) **Interventional**: clinical impact of the single pre-specified OCT features of the stented lesions: - Edge dissection with a width ≥200μm. - Reference narrowing: lumen area <4.5mm^2 in presence of significant residual plaque adjacent to stent endings; - Malapposition >200μm; - In-stent minimum lumen area (MLA) <4.5mm^2; - In-stent MLA <80% of the average reference lumen area; - Intrastent plaque/thrombus protrusion ≥500μm in thickness. - Stent deformation/geometry - Neo-carina shaping at bifurcation - Post-procedural optical flow ratio (OFR)

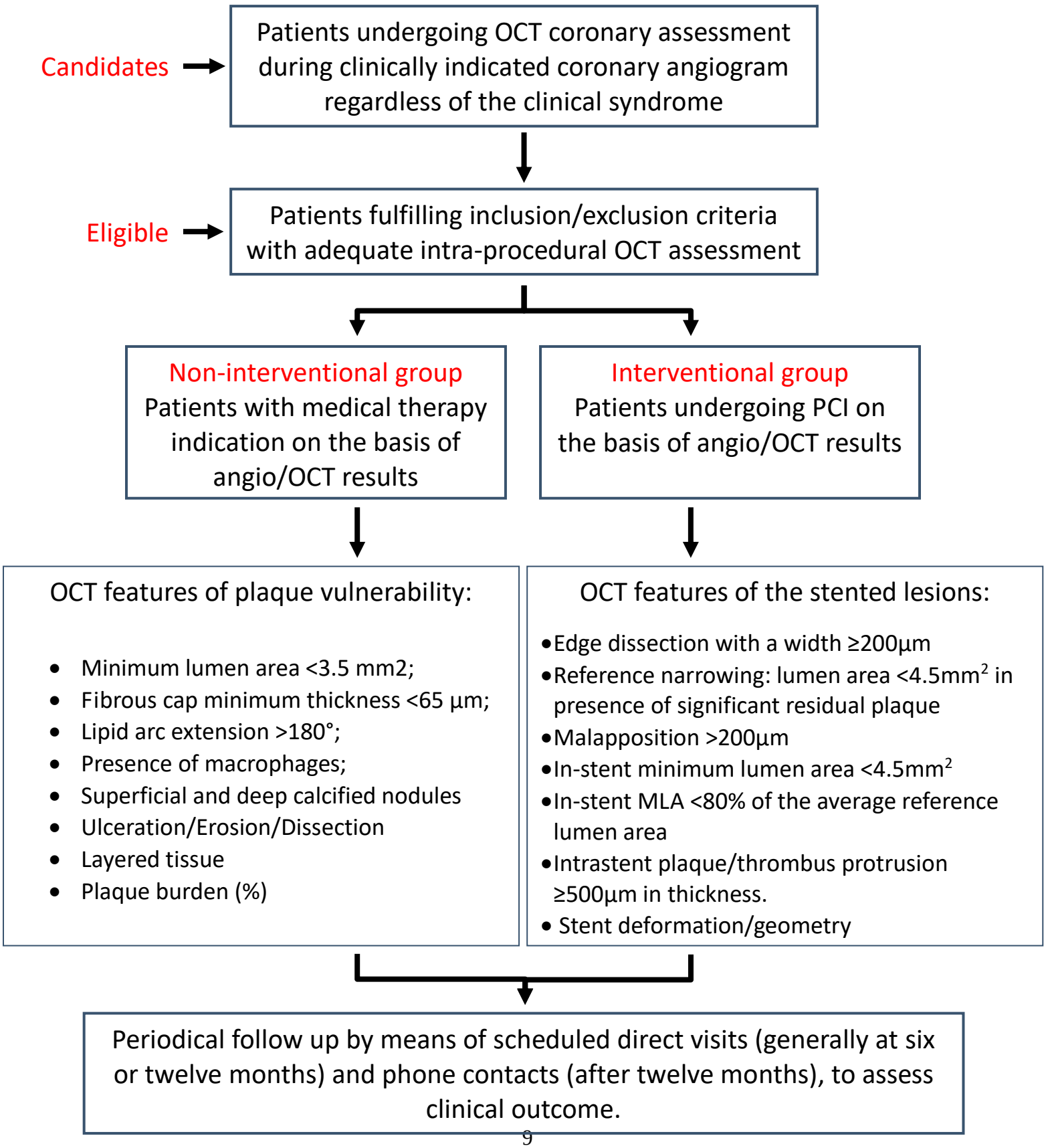
Selection Criteria	*Inclusion criteria* • Age ≥18 years; • Patients with clinical indication to coronary angiography undergoing intra-procedural OCT regardless of the clinical syndrome; • Patients with at least one end-procedural OCT assessment with a sufficient acquisition length to address the whole length of plaque or stented segments plus the proximal and distal reference segments • Patient has been informed of the nature of the study, agrees to its provisions, and has provided written informed consent as approved by the Ethical Committee of the respective clinical site. *Exclusion criteria* • Female with childbearing potential or lactating; • Acute or chronic renal dysfunction (defined as creatinine greater than 2.0 mg/dl and/or GFR <30 ml/min); • Advanced heart failure (NYHA III-IV) • Previous heart transplantation • Co-morbidities that could interfere with completion of study procedures, or life expectancy less than 1 year; • Participating in another investigational drug or device trial that has not completed the primary endpoint or would interfere with the endpoints of this study; • Heavily calcified lesion or tortuous vessel which cannot be successfully imaged by OCT • Lesion located at the ostium or in angulated (>70°), sharp take-off vessel;
Data source	Data regarding procedures will be exported from the currently used cath-lab database (Suite ESTENSA), while data regarding clinical outcome (e.g. in-hospital course) will be exported from the general hospital database (Trackcare).

Safety/Adverse Event management	All adverse events observed during the study will be collected and recorded. Adverse events involving medical devices can be classified as incidents and deficiency, the aforementioned, as identified by the following definitions, will be reported to the National Competent Authority and to the Manufacturer according to the provisions of current legislation for medical devices (EU Regulation 745/ 2017 and Legislative Decree 5 August 2022, n.137 and subsequent communications from the Ministry of Health). In the case of a medical device, it means for • any untoward medical occurrence, unintended disease or injury or any untoward clinical signs, including an abnormal laboratory finding, in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the investigational device.; • any inadequacy in the identity, quality, durability, reliability, safety or performance of an investigational device, including malfunction, use errors or inadequacy in information supplied by the manufacturer; • any incident, malfunction or alteration of the characteristics or performance of a device made available on the market, including the error of use caused by the ergonomic characteristics, as well as any inadequacy in the information provided by the manufacturer and any unwanted side effects. A serious incident is defined as any incident which, directly or indirectly, has caused, may have caused or may cause one of the following consequences:

	a) death of the patient, user or other person b) serious deterioration, temporary or permanent impairment of the state of health of the patient, the user or another person; c) a serious threat to public health
Data error control	To limit the error in the assessment of OCT parameters and clinical outcome, only patients with adequate images quality (i.e. good OCT pullback quality), and complete clinical data collection (e.g. all clinical and procedural variables potentially affecting clinical course) will be enrolled in this study. These data will be recorded and used to perform a multivariable analysis for the study endpoints.
Statistical analysis	Continuous variables will be reported as mean (standard deviation) or median (interquartile range) and compared by means of paired t or Mann-Whitney tests, when appropriate. Categorical variables will be reported as raw numbers (%) and compared by means of Pearson chi-square, Fisher exact or log-rank tests, when appropriate. Survival analysis will be conducted for the secondary clinical end-point by means of both Kaplan-Meier method and/or Cox proportional hazard analysis. Multivariable logistic regression model will be used to identify independent outcome predictors and to calculate their adjusted hazard ratios (HRs) with associated 95% confidence intervals (CI). The Hosmer and Lemeshow goodness-of-fit test will be

	used to assess model calibration. A two tailed, p value <0.05 has been established as the level of statistical significance for all tests.
Study Timelines	Enrolment start: September 2025 Estimated last patient out: September 2031. Retrospective phase I: patients screening and data collection: 24 months Prospective phase II: Patients screening and data collection: 6 years (+5 follow up) Data analysis: 3 month Manuscript draft: 2 month

IV. STUDY FLOW CHART



V. CLINICAL STUDY SCHEDULE

Baseline				**Follow-up**
Event	**Screen**	**Enrolment**	**Discharge**	**Any contact**
Informed consent signed	X			
Inclusion/exclusion criteria	X			
Physical examination	X			X*
Medical and cardiac history	X			
Diagnosis			X	X*
Clinical status			X	X
Clinical indication to coronary angiography	X			
ECG	X		X	X*
Medical regimen	X	X	X	X
Adverse event monitoring			X	X
Angiography (QCA)*		X		
OCT		X		
Phone call or e-mail				X

*To be performed in case of adverse event

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VII. BACKGROUND AND STUDY RATIONALE

The potential efficacy of intravascular imaging techniques in reducing adverse clinical outcomes after percutaneous coronary intervention (PCI) has been evidenced in several observational studies and large meta-analyses (1-4). Similarly, intravascular imaging could represent a valid help in proper assessment and management of intermediate/ambiguous lesions (5,7).

In this context, frequency domain optical coherence tomography (FD-OCT) is the newest intracoronary imaging technique designed for a better definition of coronary atherosclerosis and its functional consequences (8-11). Indeed, OCT with its innovative high-resolution imaging (in the range of 10-15 microns) system allows in vivo characterization of intraluminal and endothelial structures (8,9); in particular, it permits semi-automated accurate insights regarding plaque vulnerability, thrombus burden, stent apposition, struts coverage and neo-intimal growth.

In terms of plaque assessment, the OCT allows not only the evaluation of pathogenetic mechanism underlying the clinical syndrome (i.e. plaque ulceration or erosion) (12,13) but consents an accurate individuation of vulnerable plaques, typically characterized by large superficial lipid pool, thin fibrous cap and variable local signs of inflammation (14-16). Identification of these plaque features with imaging modalities is potentially a valid approach to classify patients at increased risk of myocardial infarction (MI) (17).

Moreover, OCT represents a new angle of view to address the adequacy of stent deployment. Besides enabling assessment of intravascular ultrasound (IVUS)-validated predictors of major adverse cardiac events (MACE), including minimum lumen area (MLA) and inflow/outflow disease, the high resolution of OCT technique permits detection of features that may be missed by IVUS, such as malapposition, intra-stent plaque/thrombus protrusion, or edge dissection.

The CLIMA and CLI-OPCI registries clearly disclosed that potential OCT clinical impact in a real-world population: the CLIMA showed the predictive value of vulnerable plaque identification in non-obstructive coronary artery disease; CLI-OPCI I demonstrated a lower rate of composite of cardiac death or non-fatal MI at 1-year in OCT-guided PCIs; while CLI-OPCI II showed that some end-procedural OCT parameters were significantly associated with an increased MACE risk during follow up. Finally, OCT is capable to depict vessel/stent interaction in terms of malapposition, struts coverage (e.g. uneven healing) and neo-intima formation; this important information could allow the identification of stents at increased risk of thrombosis (e.g. vascular healing delay and incomplete endothelialisation) and the need for a prolonged dual antiplatelet therapy (DAPT) (9, 18-21).

Thus, the purpose of the OCTAGEM registry is to confirm the utility of plaque/stent OCT assessment (i.e. OCT guidance) over the standard coronary angiography evaluation. In particular, this ambispective cohort study aims to validate the use of the predictive quantitative OCT criteria identified in the retrospective CLIMA/CLI-OPCI registries in order to optimize procedural and long-term clinical outcomes.

VIII. STUDY PLAN

9.1. Objective of the study

The aim of the study is to relate presence of OCT-defined criteria of plaque vulnerability and suboptimal stent implantation with following clinical events.

9.2. Study design

This is an observational ambispective cohort study collecting all consecutive patients undergoing OCT

evaluation during a clinically indicated coronary angiography. Patients will be enrolled at the time of OCT assessment and prospectively investigated to evaluate clinical outcome.

Clinical status leading to the index coronary angiography, exams and any specific documentation (e.g. previous cardiac history, 12-led electrocardiogram and medical therapy) at the time of OCT evaluation will be collected using a pre-specified dedicated database. In order to ensure a maximal quality of the records, data entry, variable definitions, end-points, and post–procedural follow up are standardized and agreed on by all operators. Moreover, research technicians periodically will verify completeness and accuracy of the database in order to assure <5% of missing data for each variable. Due to the exploratory nature of this project, no preliminary indication for OCT assessment will be recommended and intra-procedural techniques (e.g. PCI) will be left to each operator's discretion.

All patients fulfilling inclusion/exclusion criteria will be followed by means of scheduled direct visits (generally at six and twelve months) and phone contacts (after twelve months). in order to verify the clinical status of the patient. In case of any adverse event or new hospitalization, additional visits will be planned; source documents will be obtained and examined in detail by a specific clinical-event committee that adjudicated each event to a specific culprit lesion. Written informed consent will be obtained from all patients for data management and for phone/direct visit during follow-up.

9.3. *Study endpoints*

Primary endpoint

Predictive value of OCT-defined plaque vulnerability (non-interventional arm) and suboptimal stent deployment (interventional arm) in terms of clinical composite endpoint: cardiac death, target-vessel myocardial infarction, target lesion revascularization, and stent thrombosis.

Secondary endpoints

Individual incidence and clinical impact of the single pre-specified OCT features of plaque vulnerability including:

- Minimum lumen area <3.5 mm2;
- Fibrous cap minimum thickness <65 μm;
- Lipid arc extension >180°;
- Presence of macrophages;
- Superficial and deep calcified nodules
- Ulceration/Erosion/Dissection
- Layered tissue
- Plaque burden (%)

Individual incidence and clinical impact of the single pre-specified OCT features of the stented lesions:

- Edge dissection ≥200μm in width.
- Reference narrowing (lumen area <4.5mm^2 in presence of significant residual plaque adjacent to stent endings);
- Malapposition >200μm in thickness;
- In-stent minimum lumen area (MLA) <4.5mm^2;
- In-stent MLA <80% of the average reference lumen area;
- Intra-stent plaque/thrombus protrusion ≥500μm in thickness.
- Stent deformation/geometry
- Neo-carina shaping at bifurcation

9.4. Number or patients

This study is a spontaneous, not randomized, observational registry evaluating the role of intra-procedural OCT. All consecutive subjects undergoing OCT assessment during coronary angiography will be screened for eligibility.

On the basis of previous clinical studies testing clinical impact of OCT use during PCI and preliminary experience of the steering committee (3-5), we estimated:

- **Non-interventional arm**: a cumulative incidence of 5% for the composite clinical end-point and of 20% for the OCT-defined vulnerable plaque are assumed. For the study purpose a sample size of 986 patients was computed assuming a HR of 0.80 favoring patients without OCT-defined plaque vulnerability, and aiming to a 2-sided alpha level of 0.05 and a power of 80%. To accommodate for possible missing investigations or withdrawals, sample size was increased to 1100 patients.
- **Interventional arm**: a cumulative incidence of 25% for the OCT-defined suboptimal stent implantation and of 12% for the composite clinical end-point are assumed. For the primary study purpose a sample size of 1858 patients is computed assuming a HR of 0.85 favoring patients without suboptimal stent implantation OCT criteria, and aiming to a 2-sided alpha level of 0.05 and a power of 80%. To accommodate for possible missing investigations, sample size will be increased to 2100 patients.

A patient is considered enrolled in the study when he/she has signed the informed consent form (point of enrolment).

9.5. Patients selection criteria

The patient enrolment will be carried out in an ambispective sequential way, so that all patients undergoing coronary artery assessment by OCT could participate in the study and therefore, be evaluated according to the selection criteria defined in the protocol.

The patients enrolled in this clinical evaluation should have a clinical profile that fully meets the inclusion criteria listed below. Moreover, if even one of the exclusion criteria is present the Investigator must exclude the patient from the clinical evaluation.

Inclusion criteria

- Age ≥18 years;
- Patients with clinical indication to coronary angiography undergoing intra-procedural OCT regardless of the clinical syndrome;
- Patients with at least one end-procedural OCT assessment with a sufficient acquisition length to address the whole length of plaque or stented segments plus the proximal and distal reference segments
- Patient has been informed of the nature of the study, agrees to its provisions, and has provided written informed consent as approved by the Ethical Committee of the respective clinical site.

Exclusion criteria

- Female with childbearing potential or lactating;
- Acute or chronic renal dysfunction (defined as creatinine greater than 2.0 mg/dl);
- Advanced heart failure (NYHA III-IV)
- Previous heart transplantation

- Co-morbidities that could interfere with completion of study procedures, or life expectancy less than 1 year;
- Participating in another investigational drug or device trial that has not completed the primary endpoint or would interfere with the endpoints of this study;
- Heavily calcified lesion and/or tortuous vessel which cannot be successfully imaged by OCT
- Lesion located at the ostium or in angulated (>70°), sharp take-off vessel;

9.6. Clinical s*tudy schedule*

The study will be performed in accordance with the European Regulation ISO 14155 part 1 and 2 (2009) and Good Clinical Practice (GCP). Respect of patient's rights will be granted during the study phase according to the most recent version of the Helsinki Declaration.

This clinical protocol requires that the Investigator perform an accurate evaluation of the patient prior to the enrolment phase. The Investigator also has the responsibility of assessing the patient's clinical status at the scheduled follow up. Subjects not completing at least 1 year follow up will not be considered enrolled in this study: a phone call should be scheduled in order to verify the clinical status of the patient and the occurrence of any adverse event.

Data to be collected at the enrollment and during the clinical follow-up visits are:

- Demographic data documentation;
- Clinical examination: the patient must undergo a clinical examination during all follow-up visits required by this protocol, or when adverse events occur;
- Blood analysis: The evaluation of CK, CK-MB and Troponin must be performed in all the cases in which an adverse event occurs, or when required by the Investigators;

• Electrocardiography (ECG): Twelve-lead electrocardiograms will be collected at the time of the procedure and will be repeated at the clinical visits and in case of any adverse event.

• Angiography: the diagnostic coronarography performed at the time of OCT evaluation, must be collected to evaluate the location, to classify the coronary vessel stenosis and to assess the lesion. Any additional angiography should be also collected, for the proper end-point adjudication. It is important that all the coronary angiographies are performed in standard conditions and with a reproducible method, as they must provide images suitable for a quantitative analysis (QCA). The angiographic examination must be performed according to the guidelines provided by the Core-Lab to perform an accurate evaluation of QCA.

• OCT: the OCT examination must be performed according to the guidelines provided by expert's consensus documents

9.7. ***Follow up procedures***

Patients will undergo a clinical visit, where an ECG will be performed to evaluate the patient status and the medication regimen and any adverse event occurred since the previous contact will be recorded. In case of additional coronary angiography, the exams will be used to assess target vessel patency. All patients will be required to adhere to the following schedule outlined below unless they have withdrawn their consent or died. The reason(s) the patient is not followed must be documented on the Case Report Form (CRF). The date of the study index procedure is considered day zero. All patients will undergo telephone/e-mail-based interviews and/or office-based direct visits for end-point adjudication according to standard institutional guidelines. During follow-up assessment, the following information are to be recorded:

• Clinical status assessment;

• Adverse Event assessment, including all cardiac events;

• Record cardiac medications (with specific focus on antiplatelet and antithrombotic therapy);

If patient reports any adverse events, that in the opinion of the investigator, are considered serious, the patient should return to the investigator's facility for a medical history and physical exam in order to further assess the event.

Long-term follow up data will be obtained by means of phone-based interview in the following years.

Any adverse event will be evaluated and adjudicated by a specific committee unware of the primary end-point results.

9.8. Study duration

The enrolment phase will terminate on September 2031or when 3200 patients will be enrolled.

Retrospective phase. Patients screening and data collection will be completed in 24 months using available data sources.

Prospective phase. Patients screening and data collection will be completed in 6 years. Data analysis and manuscript draft will require 3 months each. The estimated total duration study is 11 years (6 enrolment + 5 follow up).

A minimum follow-up period of 1 year will be mandatory for all enrolled patients. Every effort must be made to ensure that all subjects will be contacted for their follow-up evaluations. These evaluations will be scheduled as close as possible to pre-specified intervals. If a subject will not be reachable and the follow-up could not be scheduled, the subject will be considered lost to follow-up and not included in the final analysis.

9.9. Patient withdrawal

Patients may withdraw from the study at any time and for any reason, without affecting their right to be followed by the Investigator. Every patient should be encouraged to remain in the study until they have

completed at least the1 year follow-up. If the patient prematurely discontinues from the study, for any reason, a final evaluation will be completed for that patient and the reason for withdrawal will be documented. All documentation concerning the patient must be as complete as possible and the patient will not be replaced in the study. A patient will be considered as completed his/her participation in the study if concluding at least 1-year follow-up period.

IX. DEFINITIONS

All outcomes were defined according to the Academic Research Consortium recommendations (22). ***Angiographic failure*** will be defined as revascularization with final TIMI <3 flow and/or residual stenosis >30%.

Cardiac death was defined as any death due to cardiac cause, procedure-related deaths, and death of unknown cause.

Target vessel new Myocardial infarction (MI) will be defined as an increase in the cardiac biomarker troponin at least 10 times above the normal value (according to the local lab range) along with at least one of the followings: 1) symptoms of ischemia; 2) new or presumed new significant ST-segment or T-wave changes or new left bundle branch block; 3) development of new pathologic Q waves on an electrocardiogram; 4) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality; or 5) identification of an intracoronary thrombus by angiography or autopsy (23).

Target lesion revascularization (TLR) will be defined as any revascularization procedure performed because of angiographic restenosis/thrombosis >70% at the site of the culprit lesion or restenosis >50% (core lab QCA assessment) associated with clinical or objective evidence of inducible myocardial ischemia. Any revascularization procedure performed on the stented vessel was defined as Target vessel revascularization (TVR).

OCT assessment of plaque/stent will be based on conventional definitions reported in expert consensus OCT documents (9,11,24-27) and utilizing the cut-off points identified in the previous CLI-OPCI registries (3,4,26-28). In particular, the following were considered significant findings:

Minimum lumen area <3.5 mm2: measured along the entire length of the assessed coronary segment (29);

***Fibrous cap minimum thickness <65 µm*:** fibrous cap will be defined as a signal-rich homogeneous band overlying a lipid core. Fibrous cap thickness will be measured at the thinnest portion and TCFA will be diagnosed in presence of a lipid-rich plaque and a fibrous cap thickness of ≤65m (15,30)

***Lipid plaque with lipid arc extension >180°*:** a lipid plaque will be defined as a signal-poor region diffusely bordered by overlying signal-rich bands corresponding to a fibrous cap; a plaque will be defined as lipid-rich if containing 2 or more lipid quadrants (31);

Presence of macrophages: inflammatory cells macrophages accumulations, will be characterized at visual estimation as signal-rich, distinct, or confluent punctate regions that exceed the intensity of background speckle noise (15,32). To identify more accurately local inflammation a two-step algorithm will be applied onto OCT ROIs in order to distinguish between inflamed and non-inflamed regions (12).

Edge dissection: the presence of a linear rim of tissue with a width ≥200µm and a clear separation from the vessel wall or underlying plaque, that was adjacent (<5 mm) to a stent edge (4).

Reference lumen narrowing: lumen area <4.5mm^2 in presence of significant residual plaque adjacent to stent endings (4);

Malapposition: stent-adjacent vessel lumen distance >200µm (4,24,25);

In-stent minimum lumen area (MLA) <4.5mm^2 (4,5);

In-stent MLA <80% of the average reference lumen area (4,5);

Intra-stent plaque/thrombus protrusion: tissue prolapsing between stent struts extending inside a circular arc connecting adjacent struts or intraluminal mass ≥500μm in thickness with no direct continuity with the surface of the vessel wall or highly backscattered luminal protrusion in continuity with the vessel wall and resulting in signal-free shadowing (24,26,28).

Stent thrombosis will be assessed utilizing the Academic Research Consortium (ARC) definition (22) as definite or probable, and as acute (<24 hours), subacute (>24 hours to 30 days), late (31 to 360 days), or very late (>360 days). The definition of definite stent thrombosis required the presence of an acute coronary syndrome with angiographic or autopsy evidence of in-stent thrombus or occlusion. Probable stent thrombosis included unexplained deaths within 30 days after the procedure or acute MI involving the target-vessel territory without angiographic confirmation.

X. MATERIALS AND METHODS

Frequency-domain Optical Coherence tomography (FD-OCT)

Imaging acquisition. FD-OCT will be performed with a validated non-occlusive technique (9). After intracoronary injection of nitroglycerin 200 μg, OCT images will be acquired with a commercially available system (Ilumien Optis or Ultreon™ from St Jude Medical, Westford, MA, USA) after positioning of the Dragonfly OCT catheter (LightLab Imaging Inc/St Jude Medical, Westford, MA, USA) distal to the target segment. During OCT image acquisition, the blood will be displaced by means of angiographic contrast media injection through the guiding catheter with an automated power injector (Acist, Bracco, Milan, Italy). OCT pull-back speed will be set at 20 mm/sec and OCT images will be calibrated adjusting the Z-offset.

Quantitative analyses and definitions. The acquired OCT coronary images will be analyzed off-line using a proprietary OCT console (St Jude Medical, Inc., USA) by expert readers blinded to patient

outcome. Readers will evaluate the image quality of each OCT pull-back, and only acquisitions that meet the pre-specified image-quality requirements will be eligible for analyses. OCT images will be deemed of good quality if they allow both an accurate measurement of lumen and a qualitative definition of the superficial plaque components. Images will be excluded if the boundary between the lumen and the vessel wall is not discernible along a continuous arc of at least 270˚ around the center of the lumen.

Conventional definitions derived from expert consensus OCT documents (9) will be applied. In presence of atherosclerotic lesions, FD-OCT analysis will be performed at minimum lumen are (MLA) site (MLA site analysis) and along the entire plaque (plaque analysis) in every cross-section. At the MLA site the following measurements will be obtained: lumen area, minimal and maximal diameters, mean diameter, and asymmetric index calculated as (maximal diameter-minimal diameter)/maximal diameter.

Plaque composition analyses. Atherosclerotic cross-sections will be distinguished into fibrous, lipid, and calcified by OCT according standardized definitions (9,33). Briefly, fibrous plaque exhibits homogeneous highly backscattering (i.e. signal-rich) regions; calcified plaque is identified by the presence of signal-poor regions with sharply delineated upper and/or lower borders; lipid-rich plaque shows diffusely bordered, signal-poor regions with overlying signal-rich bands, corresponding to fibrous cap. A non-diseased vessel cross-section is imaged as a three-layered structure by OCT (33). The analysis will include other anatomical features: presence of TCFA, lipid pool circumferential extension, local inflammation, and thrombus. The mechanism of local thrombosis will be categorized into ulceration vs erosion.

Inflammatory cells quantification. Inflammatory cells will be evaluated applying tissue property indexes including signal attenuation (34), normalized standard deviation (35), and granulometry index (32,36). These indexes will be assessed using a custom developed software written using the Matlab

(MathWorks, Inc.) according to a validated methodology (32). Signal attenuation refers to the signal loss with depth in the OCT image and will be calculated by fitting exponential curves of OCT signal to the signal profile of the pixels.

Coronary angiography and quantitative coronary analysis (QCA)

Angiographic images will be acquired according to validated standards: the diagnostic angiographic examination should be performed in order to identify the presence of atherosclerotic lesions, in at least two views. QCA analysis will be performed with a validated edge detection system (CAAS Version 5.9, Pie Medical Imaging, Maastricht, the Netherlands). The guiding catheter tip (6 F or greater) filled with contrast medium must be clearly visible in each recorded angiogram. Angiographic projections, which may lead to a foreshortening of the target vessel, should be avoided in order to obtain a more accurate evaluation of the QCA parameters. Reference vessel diameter, minimal lumen diameter, percentage of diameter stenosis (DS), and stenosis length will be measured in diastolic frames from orthogonal projections according to validated protocols for all identified lesions (37).

XI. STUDY ORGANIZATION

12.1. Clinical Events Committee

The Clinical Events Committee (CEC) is an independent adjudication body comprised of interventional and/or non-interventional cardiologists who are not participants in the clinical investigation. The CEC will review and adjudicate all cases of endpoint events (Composite endpoint). The Clinical Events Committee will meet regularly to review and adjudicate all clinical events in which the required minimum data is not available according to pre-specified CEC guidelines. The Committee will also review and rule on all deaths that occur throughout the trial.

12.2. Statistical analysis

Continuous variables will be reported as mean (standard deviation) or median (interquartile range) and compared by means of unpaired t or Mann-Whitney tests, when appropriate. Categorical variables will be reported as raw numbers (%) and compared by means of Pearson chi-square, Fisher exact or log-rank tests, when appropriate. Survival analysis will be conducted for clinical end-points by means of both Kaplan-Meier method and/or Cox proportional hazard analysis.

Combined adverse events will be evaluated on a per-patient hierarchical basis, thus each patient could provide only one hard event per event type. Intention to treat analysis will be used throughout, with end-points analysed at the patient level.

Multivariable logistic regression model will be used to identify independent outcome predictors and to calculate their adjusted hazard ratios (HRs) with associated 95% confidence intervals (CI). The Hosmer and Lemeshow goodness-of-fit test will be used to assess model calibration.

A two tailed, p value <0.05 has been established as the level of statistical significance for all tests. All statistical analyses will be carried out using SPSS software (SPSS inc., Chicago, Illinois).

12.3. Ethics committee review and approval

Local Ethical Committee (EC) approval for the protocol has been obtained by investigators (ID 7262) and the study has been registered in the ClinicalTrial.gov registry (https://clinicaltrials.gov)

12.4. Patients information and informed consent

Informed consent for the procedure is mandatory for the participation in the study and must be obtained from all subjects and/or their legal representative(s) as per local regulations. The investigator must inform every subject in details about the nature of the study, its purpose, the treatments, the reasonably expected benefits, the expected duration and the approximate number of subjects involved and the subject's responsibilities. Study subjects must additionally be informed that:

1. Participation in this study is voluntary and that he/she may withdraw from this study at any time for any reason and that that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physicians.
2. Any foreseeable circumstances and/or reasons under which the subject's participation in the study may be determined.

12.5. Confidentiality and patient data protection

All information and data concerning subjects or their participation in this study will be considered confidential. Only those working on protocol, the independent Ethics Committee and regulatory authorities will have access to subject medical records and other study documents for verification of study procedures and data without violating the confidentiality of the subject. All data used in the analysis and reporting of this evaluation will not bear identifiable reference to the subjects.

12.6. Source documents

All data will be exported from the currently used cath-lab database (ESTENSA Suite), while clinical data and in-hospital course will be obtained from the general hospital database (Trackcare). Source documents are original hospital records, clinical charts, screening log, patient identification list/enrolment log, original laboratory report, memoranda, pharmacy dispensing records, recorded data from automated instruments, transcriptions certified after verification as being accurate, magnetic or electronic media, xrays, subject's files, and records kept at the laboratories and medico-technical departments involved in the study. The investigator must maintain source documents for each patient in the study. To limit the impact of confounding factors or selection bias, all clinical and procedural variables potentially affecting clinical outcome will be recorded and used to perform a multivariable analysis for the study endpoints.

12.7. Case report form (CRF)

Electronic Case Report Forms (CRFs) will be used to collect all patient data during the course of the study. Good Clinical Practice Guidelines require that Investigators maintain information in the study patient's medical records that corroborate data collected on the CRFs. The Investigator must complete and he appropriate CRFs; completed CRFs will be reviewed for accuracy verified with the source documentation and collected by the study monitor. The CRFs with incomplete or inaccurate data will require correction by the Investigator.

The OCT core laboratory will provide the electronic CRFs for the study:

1. Enrolment phase: form collecting demographic data including clinical status, clinical history and pharmacological treatment, risk factors, diagnostic angiography and OCT assessment.
2. Follow-up visit scheduled or unscheduled: form collecting data related to the clinical status and pharmacological treatment of the patient collected during the scheduled follow-up visits or any visits that occurred outside of the required schedule (unscheduled follow-up).
3. Adverse event: section that must always be completed by reporting the occurred adverse events, as well as the treatment performed and the clinical outcomes (e.g. death of patient, surgical or percutaneous revascularization), during the entire period in which the patient participated in the study.

12.8 Final study report

Upon completion or termination of the study, the principal investigator will submit a final written report to the Ethics Committee. The report must be submitted within 12 months of completion or termination of the trial.

12.9. Clinical data collection and management

12.9.1. Monitoring

An initiation visit will be conducted to ensure that the investigator clearly understands and accepts the obligations incurred in undertaking the clinical investigation set forth in ICH-GCP, ISO 14155-1 (2009), and that the facilities are suitable for the conduction of the clinical study.

The coordinating centre will ensure proper clinical site monitoring, which includes but is not limited to review of CRFs, 100% of source data verification, parity checks with the source documentation (including operator work sheets retained with CRF documentation and hospital charts) and verification of the obtained patient informed consent.

Periodic monitoring visits will be conducted frequently enough to ensure throughout the clinical investigation that the investigator's obligations as set forth in ICH-GCP and ISO 14155-1 (2009) are being fulfilled and that the facilities continue to be acceptable. Personal contact between the monitor and the investigators will be maintained throughout the investigation, and the monitor will visit the investigators at the site of the investigation.

A close-out visit will be conducted at the completion of the study to ensure that all patient data are properly documented.

12.9.2. *Clinical Data Management*

The clinical data obtained during this clinical study must be completed on the appropriate CRFs (or attached to these forms) provided by the coordinating centre. In order to collect mandatory missing data and to clarify unreadable or inconsistent data, clarifications will be requested to the Investigator through Data Clarification Forms (DCFs) and the database will be updated accordingly. The entire

process of the clinical data treatment (from the collection to the final statistical analysis) will be conducted following the internal standard operative procedures in accordance with the European regulations ISO 14155 (2009).

12.10. Publication policy

The coordinating clinical investigator and the principal investigators are committed to the publication and widespread dissemination of the results of the study. This study represents a joint effort all investigators, and as such, the parties agree that the recommendation of any party concerning manuscript or text shall be taken into consideration in the preparation of final scientific documents for publication or presentation. Authorship will include the investigators in order of patient recruitment. The number of authors will be determined according to the rules of the addressed scientific journal.

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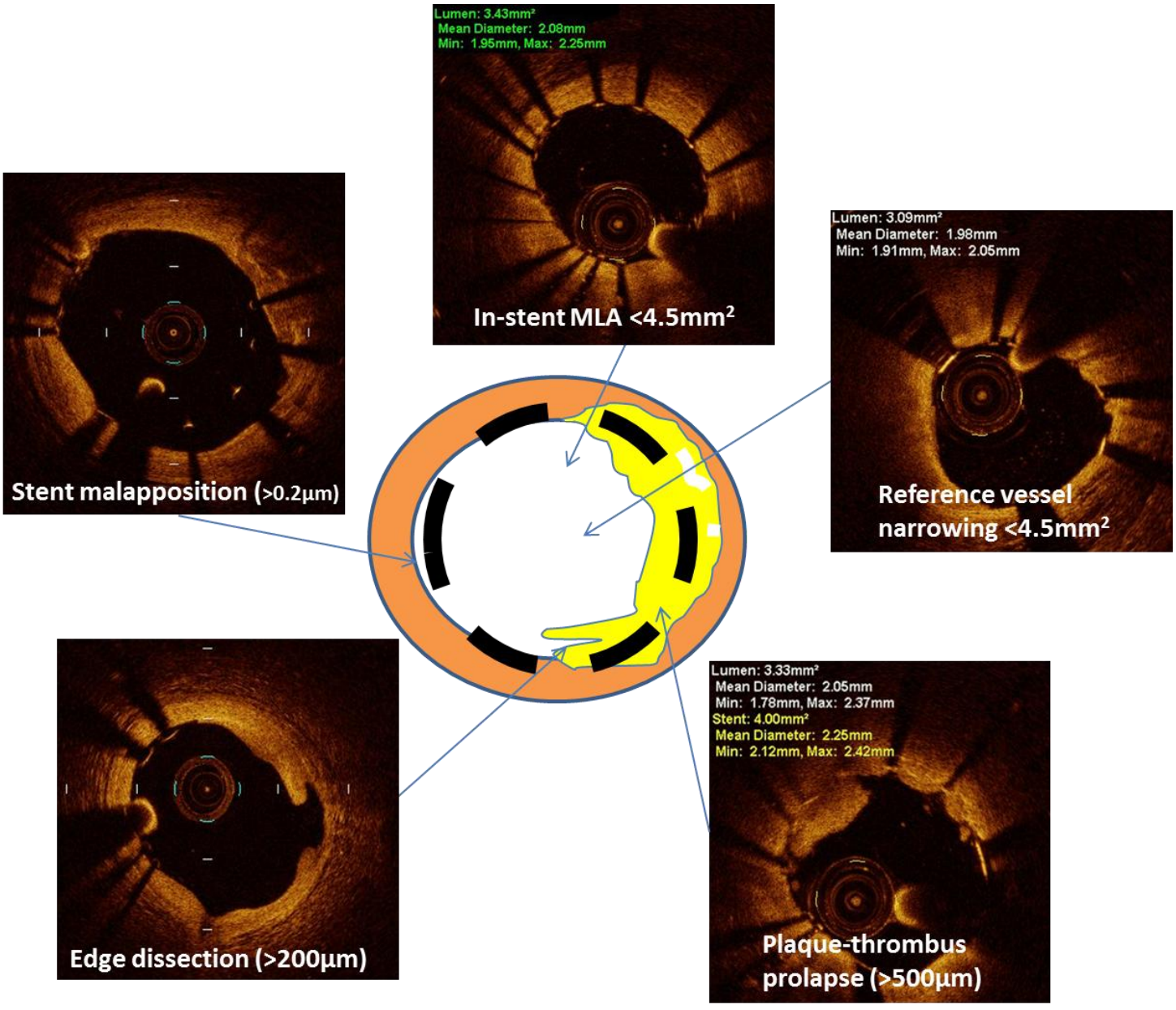
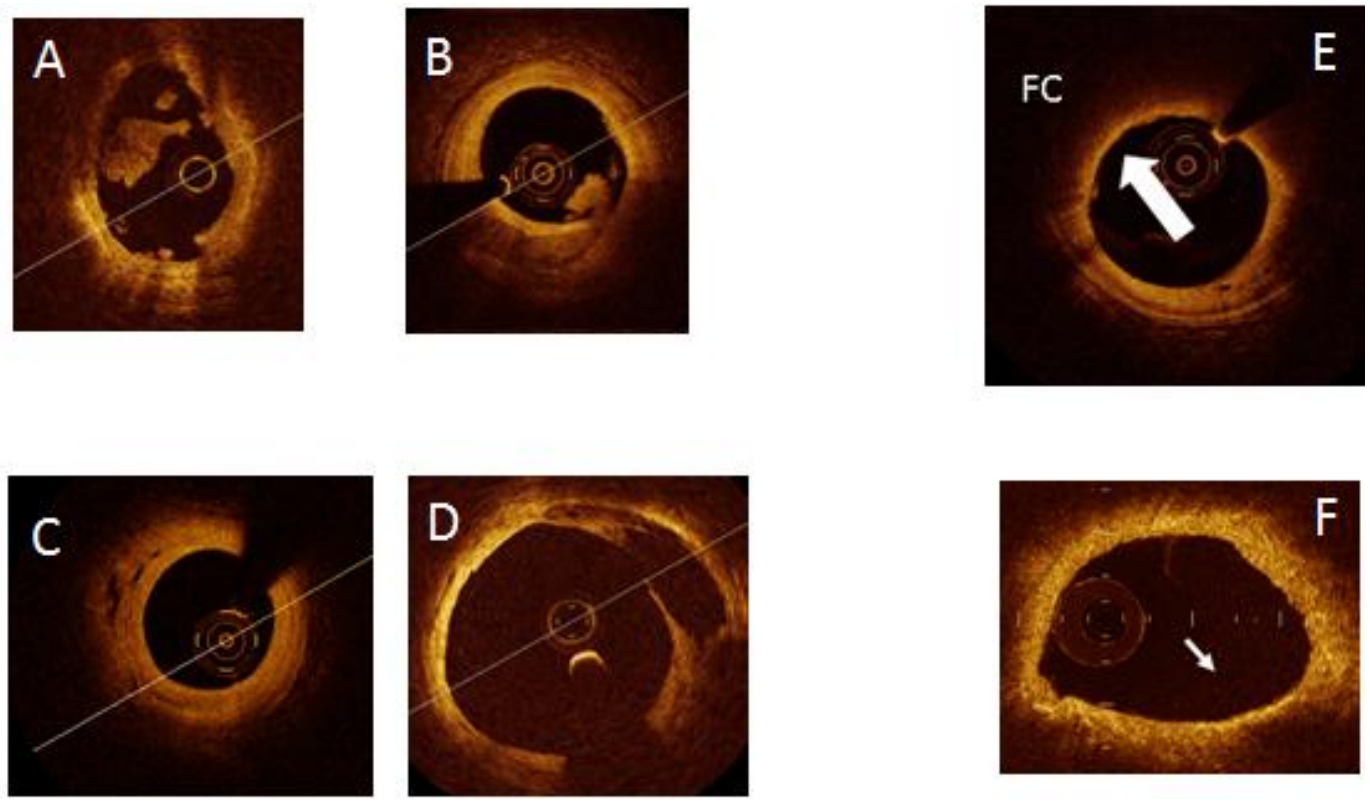
XIII. FIGURES

1. Interventional group



2. Non-interventional group



Panel A: acute thrombosis due erosions. OCT shows an acute thrombus on a regular surface without atherosclerotic plaque beneath the lumen.

Panel B: acute thrombosis caused by ulceration. A superficial thrombus located at the shoulder of the plaque is shown. Plaque rupture connecting the lumen with lipid pool is appreciated at the shoulder site.

Panel C: old thrombosis, likely due to erosion with a layered aspect at OCT.

Panel D: old ulcerations with the plaque cavity in contact with lumen without superficial thrombosis.

Panel E: Vulnerable plaque with thin fibrous cap and large lipid component.

Panel F: Atherosclerotic plaque with lipid necrotic core and high inflammatory content.