

Supplementary Material

Supplementary Material 1

Inclusion criteria

The following inclusion criteria must be met to enrol a patient in the clinical investigation:

- Age ≥ 18 years
- Patients with evidence of myocardial ischaemia (e.g. stable angina, silent ischaemia, unstable angina, or acute myocardial infarction) undergoing at least OCT-guided lesion evaluation (OCT-scan using the devices must be performed either to guide PCI (following the MLD-MAX-algorithm or to investigate a coronary lesion for further clinical treatment)
- Written informed consent to participate in this clinical investigation (defined as legally effective, documented confirmation of a subject's (or their legally authorised representative or guardian) voluntary agreement to participate in a particular clinical study). The possibility is given that the patient can still sign the consent form within 48h after the intervention to participate in this study. This is possible because no additional examinations and interventions are performed and the patient would still receive his stent therapy even if he did not sign the informed consent. Stent implantation is not part of the study and is performed on a routine basis in participating hospitals.

Exclusion criteria

Since ILUMIEN-V-AERO is an all-comer registry, there are no dedicated exclusion criteria.

Supplementary Material 1A

Subgroup ILUMIEN-IV comparison group (PCI):

Since ILUMIEN-V-AERO is an all-comers registry, there are no specific inclusion criteria beyond those previously mentioned. To enable comparison with the ILUMIEN-IV study, propensity score matching will be performed between our real-world OCT-guided PCI cohort and the ILUMIEN-IV¹ population. The inclusion criteria for ILUMIEN-IV are as follows:

High angiographic-risk lesion(s), with at least one target lesion in each target vessel planned for treatment meeting at least one of the following criteria:

- i. Target lesion is the culprit lesion responsible for either:
 - - NSTEMI, defined as a clinical syndrome consistent with an acute coronary syndrome and a minimum troponin of 1 ng/dL (may or may not have returned to normal), OR
 - - STEMI >24 hours from the onset of ischaemic symptoms
- ii. Long or multiple lesions (defined as intended total stent length in any single target vessel ≥ 28 mm),
- iii. Bifurcation intended to be treated with 2 planned stents (i.e. in both the main branch and side branch), and where the planned side branch stent is ≥ 2.5 mm in diameter by angiographic visual estimation,
- iv. Angiographic severe calcification (defined as angiographically visible calcification on both sides of the vessel wall in the absence of cardiac motion),
- v. Chronic total occlusion (CTO) (enrolment and randomisation in this case performed only after successful antegrade wire escalation crossing and pre-dilatation),
- vi. In-stent restenosis of diffuse or multi-focal pattern. Lesion must be at or within the existing stent margin(s) and have angiographically visually-assessed DS $\geq 70\%$ or DS $\geq 50\%$ with non-invasive or invasive evidence of ischaemia

All target lesions must have a visually estimated or quantitatively assessed %DS of either $\geq 70\%$, or $\geq 50\%$ plus one or more of the following: an abnormal functional test (e.g. fractional flow reserve, stress test) signifying ischaemia in the distribution of the target lesion(s) or biomarker positive ACS with plaque disruption or thrombus.

Supplementary Material 2A

Primary outcome:

The primary outcome for the ILUMIEN-IV² comparison group (PCI) are related to stent expansion:

Stent expansion is defined by the Minimal-Stent-Area (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 occurs at the proximal most side branch.

- Optimal stent expansion (categorical variable): The MSA of the proximal segment is $\geq 90\%$ of the proximal reference lumen area and the MSA of the distal segment is $\geq 90\%$ of the distal reference lumen area.
- Acceptable stent expansion (categorical variable): The MSA of the proximal segment is $\geq 80\%$ of the proximal reference lumen area and the MSA of the distal segment is $\geq 80\%$ of the distal reference lumen area.
- Unacceptable stent expansion (categorical variable): The MSA of the proximal segment is $< 80\%$ of the proximal reference lumen area, and/or the MSA of the distal segment is $< 80\%$ of the distal reference lumen area.
- Post-PCI stent expansion (%) (continuous variable): The MSA divided by the average of proximal and distal reference lumen areas x 100.

In case either segment (proximal or distal) of the stent meets criteria for unacceptable stent expansion, the stent is considered to have unacceptable stent expansion. Both segments of the stent must meet 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.

Supplementary Material 2B

Secondary outcome (including OCT definitions):

For the ILUMIEN-IV¹ comparison group (PCI):

1) Minimal-Stent-Area

Final Post-PCI MSA (per target lesion basis) assessed by final-OCT after PCI

2) Mean stent expansion

The mean stent area (stent volume/analysed stent length) divided by the average of proximal and distal reference lumen areas x 100.

3) Intra-stent plaque protrusion and thrombus

Defined as a mass attached to the luminal surface or floating within the lumen, meeting the following criteria: Protrusion/thrombus is defined as any intraluminal mass protruding at least 0.2 mm within the luminal edge of a stent strut, and will be further classified as follows:

Major: Protrusion area/Stent area at site of tissue protrusion $\geq 10\%$ and the minimal intrastent flow area (MSA – protrusion area) is unacceptable ($< 90\%$ of respective proximal or distal reference area)

Minor: Protrusion area/Stent area at site of tissue protrusion is $< 10\%$, or is $\geq 10\%$ but the minimal intraluminal flow area (MSA – protrusion area) is acceptable ($\geq 90\%$ of respective proximal or distal reference area)

4) Untreated reference segment disease

Defined as focal disease with untreated MLA $< 4.5 \text{ mm}^2$ within 5 mm from the proximal and/or distal stent-edges. Sub-classified by the amount of untreated lipid plaque, divided into 3 grades: Low ($\leq 90^\circ$ of lipid arc), Medium ($> 90^\circ - < 180^\circ$ of lipid arc) and High ($\geq 180^\circ$ of lipid arc).

5) Edge dissection

Edge dissections will be tabulated as:

Major: ≥ 60 degrees of the circumference of the vessel at site of dissection and ≥ 3 mm in length

Minor: any visible edge dissection < 60 degrees of the circumference of the vessel or < 3 mm in length

6) Stent malapposition

Defined as 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:

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

Stent malapposition will be tabulated as: Major (%); Minor (%); All (Major and Minor) (%)

7) Procedural details

Procedural details of the OCT-guided PCI-procedure following the MLD-MAX-algorithm including procedure time (first wire insertion to guide catheter removal), fluoroscopy time, radiation exposure, contrast use; contrast induced nephropathy (defined as serum creatinine rise >25% or absolute increase >0.5 mg/dL (44.2µmol/L)); need for renal replacement therapy. Further: Adjunctive tools for plaque modification, 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).

8) Procedural complications

Defined as prolonged ST-segment elevation or depression (>30 minutes), cardiac arrest or need for defibrillation or cardioversion or hypotension/heart failure requiring mechanical or intravenous hemodynamic support or intubation or procedural death.

9) Clinical outcome at 30 days (+7 days) and 6 months (+14 days)

Target lesion failure (TLF - cardiac death, Target vessel myocardial infarction (TV-MI) or ischaemia-driven target lesion revascularisation (ID-TLR); unplanned hospitalisation for unstable angina.

10) Clinical outcome endpoint definitions

Cardiac Death:

Deaths attributed to immediate cardiac causes (e.g., myocardial infarction, low-output heart failure, or fatal arrhythmias), unwitnessed deaths, deaths of undetermined aetiology, and all procedure-related fatalities, including those associated with concomitant therapeutic interventions

TV-MI:

Spontaneous MI is defined according to the 4th Universal Definition of Myocardial infarction². TV-MI is characterised as a myocardial infarction occurring in the vascular region of the previously treated target vessel. This includes MI linked to stent thrombosis or restenosis at the target lesion. However, MI within 48 hours post-procedure or death with signs of myocardial ischaemia, but without clear evidence of target vessel involvement, will not be categorised as TV-MI.

ID-TLR:

The target lesion is the treated segment, including a 5-mm margin both proximal and distal to the stent or intervened segment. Target lesion revascularisation (TLR) refers to the re-opening of a restenosed or occluded target lesion through stenting, balloon angioplasty, or surgical bypass grafting. TLR is considered ischaemia-driven if it is associated with any of the following: a positive ischaemia test (such as exercise test, stress echocardiography, magnetic resonance imaging, or fractional/coronary flow reserve); ischaemic symptoms with a ≥50% diameter stenosis on angiography; or a ≥70% diameter stenosis without ischaemic symptoms or a positive functional test.

Unplanned Hospitalisation for Unstable Angina:

Unplanned hospitalisation for unstable angina is defined as an emergency admission with typical anginal symptoms occurring after discharge from the initial OCT-guided procedure.

References:

1. 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, Fabbiochi 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(16):1466-1476. doi: 10.1056/NEJMoa2305861
2. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD; Executive Group on behalf of the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the Universal Definition of Myocardial Infarction. Fourth Universal Definition of Myocardial Infarction (2018). *J Am Coll Cardiol.* 2018;72(18):2231-2264. doi: 10.1016/j.jacc.2018.08.1038