

The influence of Ezetimibe on Coronary Plaque Composition in Patients with ST Segment Elevation Myocardial Infarction

An invasive study based on Optical Coherence
Tomography and Intravascular Ultrasound with iMap™

The OCTIVUS Trial

PhD Thesis

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1. Acknowledgments

2 Abbreviations

ACS	Acute coronary syndrome	NC	Necrotic core
BMS	Bare-metal stent	NIH	Neointimal hyperplasia
FT	Fibrotic tissue	OCT	Optical coherence tomography
CAG	Coronary angiography	PAV	Percentage atheroma volume
CSA	Cross sectional area	PCI	Percutaneous coronary intervention
CT	Calcified tissue	PES	Paclitaxel-eluting stent
DES	Drug-eluting stent	STEMI	ST elevation myocardial infarction
EEM	External elastic membrane	TAV	Total atheroma volume
FT	Fibrotic tissue	TCFA	Thin-cap fibroatheroma
IH	Intimal hyperplasia	ThCFA	Thick-cap fibroatheroma
IRA	Infarct related artery	VH	Virtual histology
ISA	Incomplete stent apposition	ZES	Zotarolimus eluting stent
IVUS	Intravascular ultrasound		
LT	Lipidic tissue		
MLA	Minimum lumen area		

3 List of Papers

- I. Influence of Ezetimibe in addition to high dose Atorvastatin Therapy on Plaque Composition in Patients with ST Elevation Myocardial Infarction assessed by Intravascular Ultrasound with iMap: The OCTIVUS trial (Submitted)
- II. Influence of Ezetimibe on Plaque Morphology in Patients with ST Elevation Myocardial Infarction assessed by Optical Coherence Tomography: The OCTIVUS trial
- III. The Impact of Guidewire Artifact in assessment of Tissue Composition with iMap™ using Intravascular Ultrasound (Submitted)
- IV. Apposition, Coverage, Expansion and Peri-Stent Remodeling of the Resolute Integrity Drug eluting Stent in patients with ST Segment Elevation Myocardial Infarction assessed with Optical Coherence Tomography and Intravascular Ultrasound

4 Background

Cardiovascular diseases (CVDs) remain the leading cause of death globally and more people die annually from CVDs than from any other cause. In 2012, an estimated 17.5 million people died from CVDs and of these 7.4 millions died due to coronary heart disease.¹

The mortality and morbidity in the developed world following acute myocardial infarctions have improved over the last decades, and especially in the setting of ST segment elevation myocardial infarction (STEMI), the improvement in logistic handling, reduced delay during transportation, optimized pre-hospital treatments, and in-hospital interventional treatment have radically improved patient outcome^{2,3}.

The pharmacological treatment following acute coronary syndromes aims at reducing the atherosclerotic disease progression within the vessel wall through a stabilization of the atherosclerotic plaque thereby reducing the risk of future plaque ruptures⁴. At present, the statins are the drugs of choice. At the same time, thrombocytic inhibitors such as aspirin and clopidogrel are cornerstones in the reduction of the thrombocytic aggregation in relation to the diseased vessel wall⁵.

Our understanding of the underlying disease process is greatly enhanced by his-

topathological research⁶, and in recent years, new in-vivo intravascular imaging modalities such as intravascular ultrasound (IVUS) and most recently optical coherence tomography (OCT) have entered the arena and provided new insights into the pathology of the atherosclerotic vessel wall, but also to a better understanding of the histological healing following intimal damage and coronary stent implantation⁷.

4.1 Coronary atherosclerosis

The coronary artery vessel wall consists of three distinct layers with an intimal layer facing the lumen, followed by a medial layer consisting of smooth muscle cells, and finally the adventitia consisting of connective tissue. The vessel wall itself is partly supplied with oxygen and nutrients from the vessel lumen supplemented by dedicated small artery branches, the *vasa vasorum*⁸. Among other things, cholesterol carrying proteins like *low-density lipoprotein* (LDL) are transiting the intimal layer by continuous removal by *high-density lipoprotein* (HDL)⁹. Over time, if this build-up exceeds the removal, accumulation occurs resulting in formation of a coronary plaque. In the initial stage, fat is deposited in “fatty streaks”¹⁰, but over a course of decades, oxidation of cholesterol initiates an inflammatory response

mediated by the endothelial cells. Macrophages are recruited for LDL removal and thereby forming “foam cells”. If successful removal fails, macrophages will eventually rupture leaving behind cellular remnants resulting in a further immune response and thus the initiation of a “snow-ball effect” resulting in a fibroatheroma. The plaque formation results in gradual intimal thickening and a compensatory stretching of the media and adventitia referred to as positive remodeling¹¹. However, when compensatory mechanisms fail, the intimal expansion results in lumen reduction and eventually obstruction. Due to the nature of positive remodeling, the atherosclerotic progression remains asymptomatic for many years, and is not detectable in coronary artery angiography that only assesses the lumen and not the vessel wall.

4.2 Plaque composition and vulnerability

The inflammatory nature of plaque formation and progression results in deposits of extra-cellular material as calcium and free cholesterol and other lipids¹². Abundance of accumulated cholesterol tends to form cholesterol crystals, which mechanically can disrupt the plaque even further¹³. Histologically, the center of this decay is characterized as a necrotic core (NC). The surrounding plaque tissue consists of fibrotic tissue (FT) and smooth muscle cells

together with lipidic tissue (LT) and calcium deposits forming calcific tissue (CT). A NC is separated from the vessel lumen by a fibrous cap. The thickness of this cap (FCT) together with the extent of the NC are important factors for the vulnerability of the plaque¹⁴. Histopathological studies have demonstrated, that coronary thrombus formation is closely related to plaque ruptures, and that thin cap fibroatheromas (TCFA) are independent risk factors for future coronary events¹⁵.

Increasing amounts of plaque in the vessel wall correlates directly with the risk of clinical events¹⁵. The total atheroma volume (TAV) can be measured with IVUS, and is together with the plaque burden, which is the percentage of TAV of the volume of the entire vessel (percentage atheroma volume, PAV), often used as surrogate markers of atherosclerotic disease in longitudinal studies with IVUS¹⁶. Since the beginning of the millennium, numerous longitudinal IVUS studies have shown, that lipid lowering with statins results in a slow-down of plaque progression or even plaque regression, and that this effect correlates positively with LDL reduction¹⁷.

IVUS has in the past decade been expanded with spectral analysis of radio frequency data resulting in the ability to differentiate the atheroma tissue into FT, LT, CT and NC and are commercially

available as Virtual Histology (VH) or iMap™ Tissue Characterization.¹⁸

In the *Providing Regional Observations to Study Predictors of Events in the Coronary Tree* study (PROSPECT)¹⁵, a PAV $\geq 70\%$, presence of TCFA and a minimal lumen area (MLA) $\leq 4.0 \text{ mm}^2$ were found to be independent predictors of future coronary events.

Several VH-based studies have been conducted in order to assess the effect of lipid lowering treatment on plaque composition but so far with mixed results¹⁹⁻²⁷.

4.3 Lipid lowering treatment

Statins (or HMG-CoA reductase inhibitors) has been shown to reduce mortality and morbidity following coronary infarction^{28,29}. Statins inhibits the 3-hydroxy-3-methyl-glutaryl-CoA reductase that is the rate controlling enzyme in the pathway leading to cholesterol synthesis in the liver³⁰. The inhibition leads to an up-regulation of LDL receptors resulting in increased LDL clearance from the bloodstream. The clinical preventive mechanisms of statins are multifactorial and may be related to improved endothelial function, modulated inflammatory response, coronary plaque stabilization, and inhibition of thrombus formation³¹. The clinical effects are correlated to LDL reduction²⁹, and other ways to obtain LDL reduction

has been investigated. Ezetimibe binds to the Niemann-Pick C1-like 1 protein (NPC1L1) in the small intestine thereby inhibiting cholesterol reabsorption³².

Ezetimibe has a supplementary effect when used together with statins³³. Its clinical effect has recently been assessed in the *IMProved Reduction of Outcomes: The Vytorin Efficacy International Trial* (IMPROVE-IT)^{34,35} finding a reduction in its primary endpoint (a composite of cardiovascular death, myocardial infarction, unstable angina pectoris, coronary revascularization beyond 30 days and stroke).

4.4 Intravascular imaging modalities for assessment of coronary atherosclerosis

Intravascular imaging is obtained via imaging catheters advanced over a guide-wire inserted into the coronary artery through a guiding catheter. By use of either ultrasonic sound waves or infrared light, a two-dimensional cross-sectional image of the surrounding vessel wall can be obtained by a rotating imaging probe. By simultaneous pullback of the catheter, a longitudinal image can be constructed.

4.4.1 Intravascular ultrasound

IVUS is based on ultrasonic waves emitted by a piezoelectric transducer with a typical frequency range of 20-45 MHz corresponding to wavelengths from 35 to 80

μm . This enables for a maximal axial resolution of 15-20 μm ³⁶. The maximal scanning depth is approximately 15 mm and is dependent on the ultrasound frequency (Higher frequency, lower scanning depth). Longitudinal image rendering is obtained by transducer pullback with speeds ranging from 0.5 to 1 mm/s. Frame rate relies directly on rotational speed and is 30 frames/s.

IVUS image acquisition allows for clear visualization of lumen contour and of the external elastic membrane (EEM) and is still the golden standard in volumetric plaque measurement and assessment of vessel remodeling. IVUS was the former golden standard in stent assessments, but is now largely succeeded by OCT that permits greatly improved axial resolution³⁷.

4.4.2 The iMap™ tissue characterization

Spectral analysis of radio frequency data allows for differentiation of tissue subtypes depending on specific backscatter patterns reflected by the tissue. Different implementations of this technique are commercially available¹⁸. The iMap™ tissue characterization is developed and marketed by Boston Scientific (MA, USA) and is based on image acquisition using a mechanical IVUS catheter system. The technique has been validated ex-vivo in a

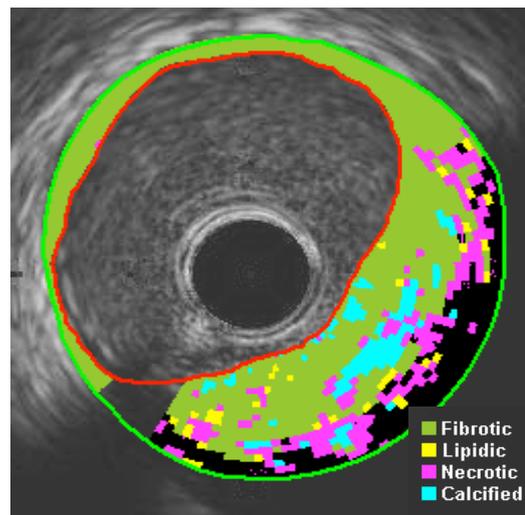


Figure 4-1 Example of the iMap™ color-coding.

histological study³⁸. The patterns are analyzed by computer software algorithms that compares the patterns with a database obtained from histologically validated samples of human coronary arteries. The examined tissue is thereby categorized into the four plaque components: FT, LT, CT, and NC³⁹. An example of the color-coding for iMap™ is shown in **Figure 4-1**.

4.4.3 Optical coherence tomography

OCT can be considered as an optical analogue to IVUS utilizing a high power, broadband light source emitted on the target tissue through an advanced optic fiber. Due to the very high travel speed of light, picture rendering cannot be based on measurements of time delay as in IVUS, and instead a principle of interferometry is applied. By this technique, the emitted light is divided by a semi-transparent mirror (**Figure 4-3**) into a sample arm and a reference arm. Light from the sample arm hits the sample and is reflected to a

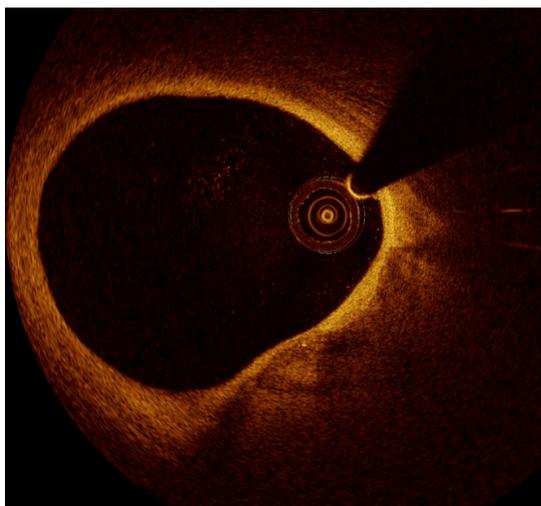


Figure 4-2 Example of OCT plaque presentation. A lipo-calcific plaque is located from 3 o'clock to 7 o'clock.

degree depending on the physical properties of the sample tissue. The reference arm leads to a mirror that reflects the light back towards a collector in which the reference is remerged with the sample arm resulting in an interference pattern that is registered by a photoreceptor. Only light returning from the mirror and sample with an identical travel distance (the co-

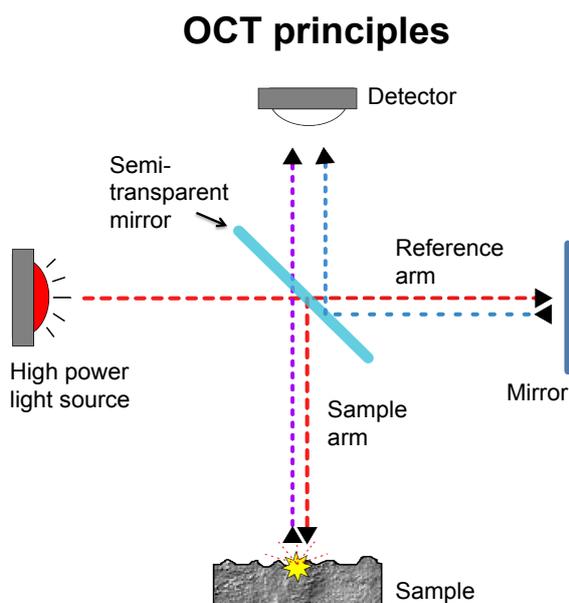


Figure 4-3 Schematic illustration of OCT image acquisition.

herence length) gives rise to an interference pattern. In time domain OCT (TD-OCT), the scanning depth can be altered through physical displacement of the reference mirror. In a fourier-domain OCT (FD-OCT) system, the mirror distance is fixed, and instead difference in scanning depths are obtained by analyzing patterns of various frequencies simultaneously or sequentially by use of a “wavelength-swept laser source”. FD-OCT has a better signal to noise ratio, and an image acquisition speed more than ten times faster than TD-OCT. For these reasons, FD-OCT is predominant in the OCT-systems currently available.

4.5 The Resolute™ Integrity drug eluting stent

The Resolute™ Integrity is a second-generation drug eluting stent (DES) developed and marketed by Medtronic Inc. (Santa Rosa, CA, USA). It is based on the Integrity™ platform, which consists of a single Cobalt-Chromium wire with sinusoidal bends altogether wrapped around a mandrel and fused at its communication points with the wire in the previous loop⁴⁰. The platform was designed for high flexibility and deliverability. Despite its strut thickness of 90 μm, the design maintains a high radial strength⁴¹. The stent is covered by the durable BioLinx™ polymer

comprising 3 subcomponent together forming a hydrophilic coating containing its antiproliferative drug, the zotarolimus - a lipophilic derivate of sirolimus⁴². Eighty-five percent of the drug is released within 60 days, and the remaining within a total of 180 days⁴³.

The physical performance of the design, and the clinical safety and performance of the Resolute™ Integrity has been reported in several trials⁴⁰.

4.5.1 Percutaneous coronary intervention in a STEMI setting

Stent deployment can be challenging in a STEMI setting. The culprit lesion is not always that well defined due to presence of thrombus and diffuse vessel spasm. Furthermore, the patient can be in a state of acute heart failure or arrhythmia, and percutaneous coronary intervention (PCI) must be planned accordingly within a limited time frame. This leads to an increased risk of underestimation of the correct stent diameter and suboptimal placement in the vessel with the respect to the culprit lesion⁴⁴.

Stent underexpansion is known to be an important risk factor for later stent thrombosis. Studies have shown, that a minimum stent area (MSA) of less than 5 mm² is an independent risk factor for stent restenosis and thrombosis^{45,46}. The pre-

valence of this problem in STEMI patients is sparsely reported in literature⁴⁴, and especially studies implementing IVUS or OCT acquisitions within few days after primary PCI, are rare⁴⁷. It is well known, that the high thrombus burden in a STEMI setting comprises an increased risk of distal thrombus embolization⁴⁸. This risk is probably further increased by high-pressure stent deployment forcing operators to accept less expansion in order of achieving maximum vessel perfusion. Overall, PCI in STEMI patients is associated with a good clinical outcome, however, the incidence of target lesion failure is higher in patients with more complex lesions than in patients with simpler lesions^{49,50}. Furthermore, an annual risk of late and very late stent thrombosis in the order of 0.5% is known to exist⁵¹⁻⁵⁴, and the risk of thrombosis within 3 years has been shown to be increased in first generation DES compared to bare metal stents⁵⁵.

Strut coverage is considered a major risk factor for later stent thrombosis⁵⁶. The amount of coverage is both related to stent strut apposition and the composition of the underlying vessel wall. In STEMI patients, malapposition can be the result of insufficient expansion, but also resolved thrombus jailed between the strut and the vessel can be a contributing factor⁵⁷.

5 Hypothesis

Intensive lipid lowering with ezetimibe 10 mg/day in addition to high dose statin treatment with atorvastatin 80 mg/day in statin naïve patients treated with primary percutaneous intervention (PCI) due to STEMI results in:

- Coronary plaque regression assessed by greyscale IVUS.
- Improved coronary plaque composition with reduction in NC assessed with iMap™.
- Increased thickness of the fibrous cap assessed by OCT.

6 Aims

The primary objective of this thesis was to assess the coronary plaque progression and composition at baseline and after 12 months in statin naïve patients presenting with first time STEMI randomized to 1) treatment with atorvastatin 80 mg/day + ezetimibe 10 mg/day, or 2) treatment with atorvastatin 80 mg/day + placebo.

Secondarily, the expansion, malapposition, healing, and vessel response following implantation of the Resolute™ Integrity DES were assessed.

This led to the following aims:

- I. To assess change in coronary plaque volume and composition together with vessel remodeling after 12 months using IVUS with iMap™ in a non-infarct related artery (Paper 1).
 - II. To assess changes in coronary plaque morphology and fibrous cap thickness in a non-infarct related artery after 12 months using OCT (Paper 2).
 - III. To describe the impact of the guidewire artifact on iMap™ assessments of a coronary plaque (Paper 3).
- To describe post percutaneous intervention and 12 months OCT and IVUS findings following deployment of the Resolute™ Integrity drug eluting stent in STEMI patients (Paper 4).

7 Patients

In the period from June 2011 to June 2013, 87 statin naïve patients admitted for primary PCI were enrolled in the study. In- and exclusion criteria's are listed on page **Fejl! Bogmærke er ikke defineret.** A flowchart showing the screening process and the study course for enrolled patients is provided in **Figure 7-1**.

At baseline, eligible patients were put on high dose statin treatment with atorvastatin 80 mg/day and randomized to receive additional placebo or ezetimibe 10 mg for 12 months in a blinded design with the study drug provided by the hospital pharmacy.

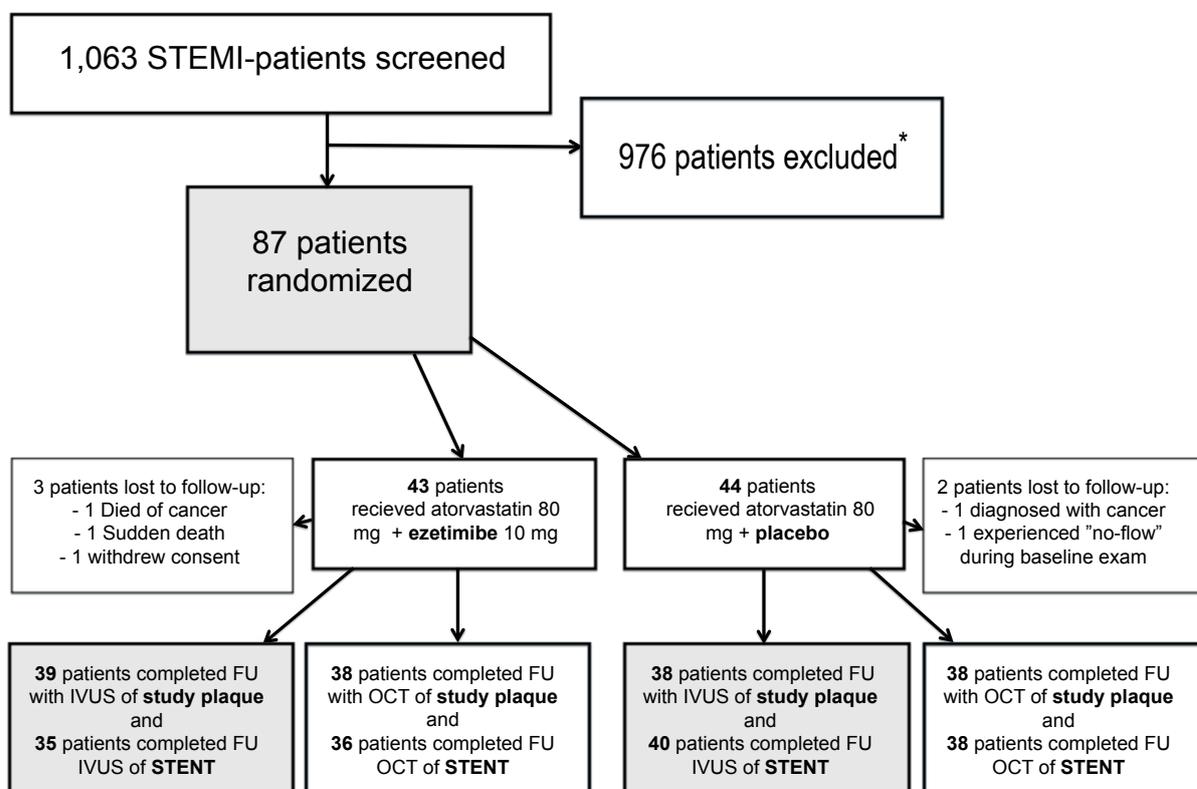
Patients were followed for 12 months with clinical controls and safety blood

samples after 1, 3, and 6 months. A independent clinician monitored the laboratory results in order to maintain the blinding of the investigator. In case of signs of adverse events, the supervisor took steps accordingly to normal clinical practice.

All adverse events and serious adverse events were registered in the case report file, and the project was continuously monitored by the GCP-unit (Good Clinical Practice) of Odense University Hospital.

The study was approved by the Danish Ethical Committee (project ID: S-201 001 00) and the Danish Medical Agency (EudraCT 2010-022604-45).

7.1 Flowchart of patients screened



*) Patients excluded:

Ongoing or previous lipid lowering treatment	280	Cancer <5 years or suspicion of cancer	17
Discharged before randomization	103	BMS	16
Age	103	Poor compliance expected	15
Other DES than Resolute Integrity	84	No capacity for study examinations	10
Cardiac arrest / hypothermia	52	Only POBA	9
Belonging to other hospital district	50	Alcohol abuse	9
No consent	40	Participation in conflicting study	5
Home address in foreign region	32	No angiographic study plaque	5
Critically unstable (ICU-patient)	26	Other language than English or Danish	5
Other critical illness	26	Creatinine >176 mmol/l	4
OCT or IVUS not feasible	21	Other	4
Included in commercial study	19	Participation in commercial study	4
Investigator unavailable for inclusion	18	Drug abuse	2
No coronary intervention performed	17		

Figure 7-1

7.2 Inclusion Criteria

1. First time STEMI.
2. Statin naïve.
3. Age >18 and <81 years.
4. 20%< angiographic diameter stenosis <50% on a not previously revascularized native coronary artery.
5. In fertile women: Ongoing contraception with intra uterine device or hormonal contraception.

7.3 Exclusion Criteria

1. Pharmacologic lipid lowering treatment before index hospitalization.
2. Atrial fibrillation, not well rate-controlled.
3. Ventricle frequency variation with more than a factor 2 over 1 minute.
4. Unconscious patients.
5. History of statin induced myopathy, or serious hypersensitivity reaction to other HMG-CoA reductase inhibitors (statins) including Atorvastatin.
6. Pregnant women, women who are breast feeding, and women of childbearing potential who are not using chemical or mechanical contraception or have a positive serum pregnancy test (a serum-human chorionic gonadotrophin [Beta-HCG] analysis).
7. History of malignancy (unless a documented disease free period

exceeding 5-years is present) with the exception of basal cell or squamous cell carcinoma of the skin. Women with a history of cervical dysplasia would be permitted to enter the study provided they had three consecutive clear Papanicolaou (Pap) smears.

8. Uncontrolled hypothyroidism (TSH > 1.5 x upper limit normal).
9. Abnormal lung function tests.
10. History of alcohol or drug abuse within the last 5 years (this may affect compliance).
11. Current active liver disease (ALT/SGPT >2 x upper limit normal or severe hepatic impairment (to protect patient safety as directed on the labels of currently approved statins).
12. Unexplained creatine kinase (CK > 3 x upper limit normal) (To protect patient safety) (will be increased at baseline because of acute ST segment elevation myocardial infarction a few days before enrolment).
13. Serum creatinine >176mmol/L.
14. Participation in another investigational drug study less than 4 weeks before enrolment in the study, or according to subjects local ethics committee requirements where a larger period is stipulated (to avoid potential misinterpretation of overlapping adverse events).
15. Treatments with cyclosporine.
16. Treatment with gemfibrozil.

8 Methods

8.1 Patient enrollment

Patients were screened for inclusion on a daily basis during the inclusion period. Patients eligible for inclusion were informed about the OCTIVUS trial and offered inclusion by the investigator. After obtaining written consent, patients were scheduled for repeated coronary angiography (CAG) the following workday after the primary PCI. Treatment with atorvastatin and study drug was postponed until baseline IVUS and OCT examinations were performed. Patients were designated a study-ID-number in chronologic order of enrollment (1-87).

8.2 Randomization procedure and study drug preparation

The randomization was done as block randomization and as a part of the study drug preparation by the hospital pharmacy. The study drug was prepared in accordance with “Good Manufacturing Practice for medicinal products” and consisted of a non-transparent gelatin capsule containing one capsule of MSD ezetimibe 10 mg embedded in lactose (active drug) OR lactose only (placebo). Portions of 365 capsules were delivered for every patient labeled with the patient randomization

number. The randomization list was kept by the pharmacy until unblinding of the study.

8.3 Image acquisitions

8.3.1 Coronary angiography

Prior to repeated CAG, peri- and post-PCI recordings were reviewed. Patients were all in dual antiplatelet therapy due to their recent infarction. A bolus of 200 µg of nitroglycerin was administered intracoronary prior to angiographic recordings. Two angiographic projections of the chosen non-infarct related artery (IRA) with a study plaque (The study vessel) was obtained in order of optimal visualization of side branches used as point de repère in future baseline-follow segment matching. The IRA was projected accordingly. All images were stored on a network based DICOM system.

The follow-up examinations were performed in the same manner using the same angiographic projections.

8.3.2 OCT

The OCT acquisition was performed following patient heparinization with unfrac-tionated heparin (5,000 IU). A 2.7 French C7 Dragonfly™ Imaging Catheter (Light-Lab Imaging, Inc., St. Jude Medical, St.

Paul, MN, USA) was introduced to the study vessel and advanced to a point distal to the study plaque including eventual side branches. The OCT-system was the C7-XR™ or Ilumien™ system (LightLab Imaging, Inc., St. Jude Medical, St. Paul, MN, USA). An automated pullback with a pullback speed of 20 mm/s was initiated by a manually flush with 20 ml of undiluted Visipaque® contrast. The total pullback length was 54 mm (system maximum). Every pullback was manually inspected for sufficient quality and repeated if necessary. OCT catheter placement was recorded angiographically for reference. The IRA was examined from at point minimum 5 mm distal to the distal stent edge and the pullback should also include a proximal 5 mm reference segment.

At follow-up, baseline angiographic recording were assessed in order of correct OCT catheter placement. Image acquisition was performed as described for baseline. In IRA, stent edges were used for correct catheter placement.

All examinations were assigned a randomly generated examination-ID-number linked to the study-ID by a coding list maintained by a study nurse in order of patient ID blinding to the investigator during offline analysis. Examinations were achieved to DVD's in RAW format.

8.3.3 Reproducibility in OCT plaque assessment

An interobserver reliability analysis was performed in 10 randomly selected baseline-follow cases (20 pullbacks in total) all analyzed by two independently dedicated observers with respect to lipid arc, macrophage arc, mean FCT, calcium arc and lipo-calcific arc. Numbers of identified frames with ThCFA were compared, and FCT analysis was done in 70 matched frames containing a fibrous cap at baseline.

8.3.4 IVUS with iMap™

IVUS was performed following OCT in both the study vessel and the IRA. An IVUS catheter (Atlantis™ SR Pro) initially flushed with heparinized saline water and connected to an iLab™ system (both Boston Scientific, USA) was introduced to the study vessel observing the same criteria's with respect to vessel characteristics as OCT. Due to the longer pullback capacity of the IVUS system, a more distal location was preferred. Catheter placement was recorded angio-graphically. Automatic pullback was initiated after ensuring acceptable picture quality with a pullback rate of 0.5 mm/s. The pullback was terminated when reaching the guiding catheter or the aorta.

The IRA was recorded after IVUS guided advancement of the catheter to a

point at least 5 mm distal to the distal stent edge. Pullback speed and procedure was as described for the study vessel but was terminated, when a minimum of 5 mm proximal to the proximal stent edge was recorded.

The iMap™ data was automatically generated by the iLab™-system until a software upgrade, after which the generation should be manually initiated.

Follow-up examinations were performed in the same order and manner.

All examinations were designated the same examination-ID as described in the OCT section and were achieved to DVD's in DICOM format.

8.3.5 The iMap™ reproducibility and impact of guidewire artifact

An issue specifically associated with mechanical IVUS systems is the presence of a guidewire artifact, that gives rise to a misinterpretation by the iMap™ algorithm categorizing it as NC⁵⁸. As the location of the artifact might differ between different pullbacks, an assessment of the impact on quantitative and qualitative measurements was needed, and the ability to exclude the artifact for off-line analysis evaluated (paper 3).

In 10 baseline examinations, we did a reproducibility study in order of determining the intra-catheter variation, and the

impact of the guidewire artifact on iMap™ assessment in scenarios with and without the use of a guidewire.

The IVUS acquisition in the study vessel was performed in two consecutive pullbacks using the same IVUS catheter, and with the guidewire in place. This was followed by another two pullbacks performed after the retraction of the guidewire. In all pullbacks, the position of the IVUS catheter was unaltered, and only the imaging probe was moving within its sheath.

All data was achieved to DVD's. Details regarding offline analysis are described in a later section.

8.4 Offline image analysis

8.4.1 IVUS with iMap™ analysis

The Echoplaque 4.0 Analysis Software (INDEC Medical Systems, CA, USA) was used for IVUS and iMap™ analysis. Examinations blinded for patients ID were imported from DVD's. The study plaque was matched with an exact corresponding length between baseline and follow-up examinations using side branches as anatomic landmarks. For every iMap™-containing frame (i.e. every 0.5 mm), EEM and lumen contours were traced manually. This approach was chosen, as every second iMap™-containing frame otherwise would be assessed more or less

randomly (mainly due to systolic-diastolic motion) as a result of Echoplaque’s automatic interpolation of EEM and lumen contours between analyzed frames. The guidewire artifacts – where present – was masked in every analyzed frame using Echoplaque’s “no-fly-zone” option. The preset angle of this “no-fly-zone” was used consequently. For iMap™ analysis, “Confidence Level Lower Bound” was set at 0 percent and “Necrotic Confidence Upper Bound” was set at 100 percent.

Vessel and lumen volume was calculated within Echoplaque as respectively $\sum EEM_{CSA}$ and $\sum LUMEN_{CSA}$, where EEM_{CSA} =external elastic membrane cross-sectional area, and $LUMEN_{CSA}$ =luminal cross-sectional area. TAV was defined as vessel volume minus lumen volume, and PAV was defined as (TAV/vessel volume) x 100%. Echoplaque calculated volumetric iMap™ data after definition of lumen, EEM contours, and “no-fly zones”.

A sub segment containing the frame with maximal PAV was identified, and the proximal and distal 5 mm reference segments were included for separate volumetric analysis with respect to greyscale and iMap™ data. In case of a very proximal or distal location of the maximal PAV frame, the surrounding 5 mm borders were adjusted accordingly, so that a total of 10 mm was obtained.

For the pullbacks obtained for the purpose of guidewire artifact assessment (8.3.5), the analysis of the entire pullbacks, was performed as described above, however, for the pullbacks containing a guidewire artifact, additional data was extracted without prior artifact exclusion.

8.4.2 OCT analysis

OCT analysis was performed using the Ilumien™ Optis™ Offline Review Workstation (Sct Jude Medical, Minnesota, USA) by an experienced analyst. Stent analysis was performed in collaboration with a team of co-workers under surveillance of the experienced analyst. The analyst was blinded for patient data and baseline-follow-up sequence. A person unrelated to the analysis procedure performed the examination-ID matching. Corresponding baseline-follow-up segments were matched based on anatomic landmarks or stent edges. Every pullback was reviewed for suitability for analysis with respect to image quality, sufficient flushing of the lumen, and sufficient image depth. Inadequate pullbacks were excluded. Catheter calibration was confirmed or adjusted when needed. The first and last frames together with all frames for every 1 mm in between were analyzed.

Lumen cross sectional area (CSA) was measured and a lumen volume was calculated as $0.2 \text{ mm} \times \sum LUMEN_{CSA}$.

All data was processed into the final data variables using a data extraction sheet (**Appendix A+B**).

8.4.2.1 OCT plaque assessment

Plaque assessment was performed in accordance with published recommendations⁵⁹⁻⁶¹. A matching segment was identified and processed with the automatic lumen contour with manual correction when needed.

Examples of plaque presentation are illustrated in **Figure 8-1**. Arcs for lipid, calcium and combined lipid and calcium (lipocalcific arc) were measured together with macrophage arc.

Occurrence of cholesterol crystals, microvessels and intimal ruptures were registered. For lipid arc, the numbers of individual arcs measuring at least 90 degrees were registered separately.

A fibroatheroma was defined as a segment of the vessel wall with high attenuation underneath a fibrous cap in combination with loss of an identifiable medial layer.

The FCT was defined as the distance from the intimal-lumen border to the lumen edge of the lipid pool characterized by a rapid rise in attenuation. For every lipid segment identified, a FCT was measured and characterized as TCFA if less than 65 μm . Otherwise the cap was characterized as a thick cap fibroatheroma

(ThCFA). TCFA length was measured in a frame-by-frame manner, and two or more segments were regarded as one TCFA unless distance in between was more than 5 mm (25 frames).

The frame with the minimum FCT at baseline was matched with the corresponding frame at follow-up, and the same FCT was re-measured for comparison.

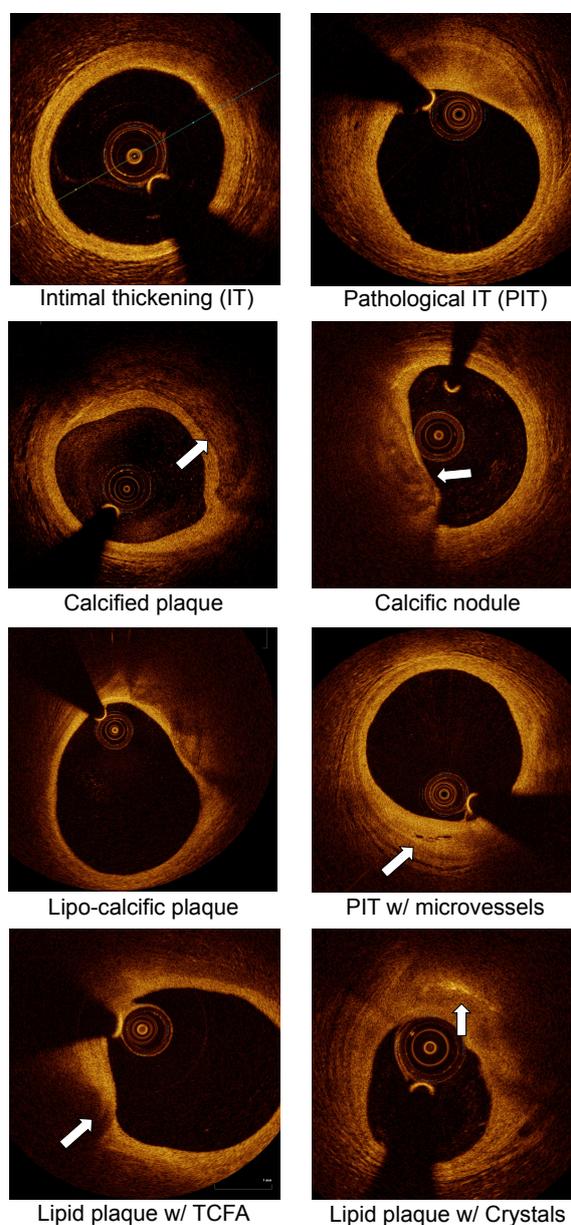


Figure 8-1: Examples of plaque presentation by OCT.

8.4.2.2 OCT stent assessment

Stent borders were defined as the first and the last cross sections of the stented segment where struts were visible (assessed in a frame by frame manner). The 5 mm reference segments adjacent to the distal and the proximal stent borders were assessed for every 1 mm beginning at the first frame immediately following the stent border (0.2 mm apart).

By definition, all struts were uncovered at baseline. At follow-up, all stent struts were marked and assessed for level of tissue coverage in the following categories (**Figure 8-2**): 1. Definitely uncovered, 2. Uncovered fibrin, 3. Partially uncovered, 4. Covered protruding, 5. Covered embedded, and 6. Covered proliferative (neointimal thickness >250 μm). For covered struts, the thickness of the neointimal layer was measured from the center of the strut reflection to the lumen border following a line towards the center of the stent.

covered, 4. Covered protruding, 5. Covered embedded, and 6. Covered proliferative (neointimal thickness >250 μm). For covered struts, the thickness of the neointimal layer was measured from the center of the strut reflection to the lumen border following a line towards the center of the stent.

Based on the metallic strut plus abluminal polymer thickness of the Resolute™ Integrity stent of 97 μm (91+6 μm), malapposition was defined as a strut-to-vessel-wall distance >97 μm measured from the center of the luminal stent reflection to the transition zone from lumen to the intimal layer. For every malapposed strut, a malapposition distance was measured.

The stent expansion compared to nominal stent size and reference segments was assessed by dividing the minimum stent area (MSA) derived by OCT with the nominal stent size area ($\text{STENT}_{\text{NOM,CSA}}$) calculated from the nominal stent diameter (nSD) as $\pi \times \left(\frac{\text{nSD}}{2}\right)^2$, and with the mean CSA of the proximal and distal reference site (REF_{CSA}) calculated as (Mean proximal reference CSA + mean distal reference CSA)/2. Stent size selection accuracy was defined as $\text{STENT}_{\text{NOM,CSA}} / \text{REF}_{\text{CSA}}$.

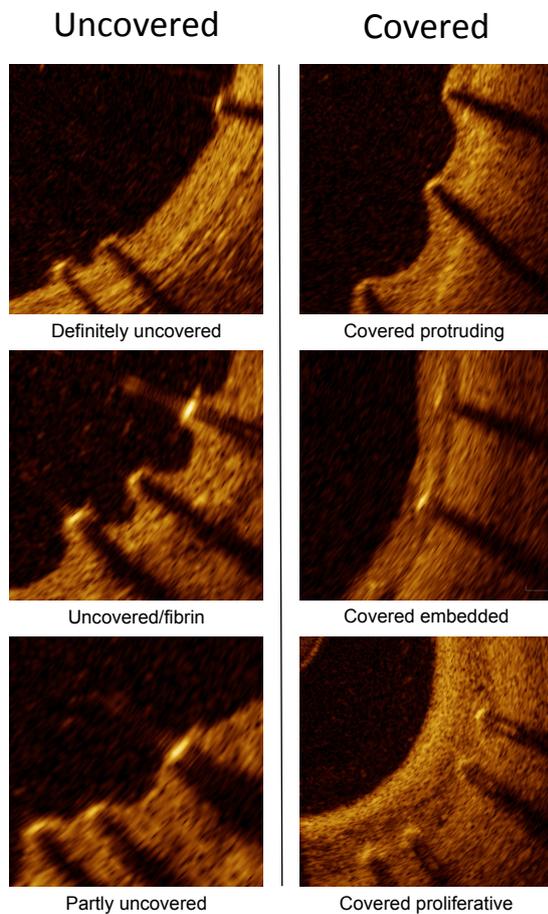


Figure 8-2 Classification of strut coverage.

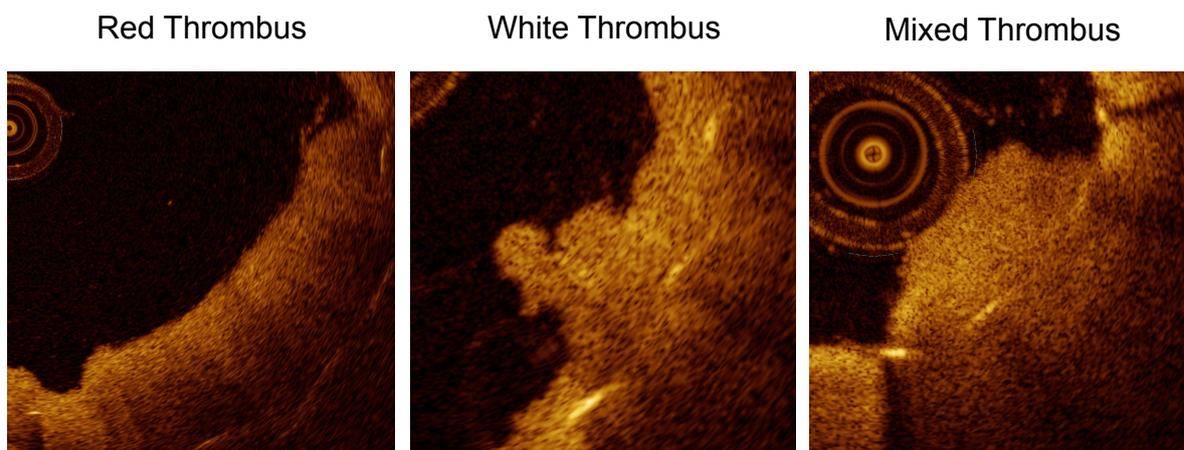


Figure 8-3 OCT thrombus presentation.

A coronary evagination was defined as an outward expansion of the luminal border between two apposed struts with a depth exceeding that of the strut thickness. A major evagination was defined as evaginations occurring in three adjacent frames with a depth >10% of the stent diameter.

Presence of thrombus was registered and a differentiation into white, red, and mixed thrombus was done as illustrated in **Figure 8-3**.

Malapposed struts were identified, and the malapposition distance for each was defined as the distance from the center of the strut reflection to the intimal border following a line crossing the center of the stent lumen. At follow-up, patients with complete resolved malapposition, persistent malapposition, and late acquired malapposition were identified. Strut mapping was not implemented and malapposition

on a strut level from baseline to follow-up was not be tracked.

8.5 Statistics

All statistical analysis was performed with SPSS 22.0 (IBM Corporation, New York, USA). Categorical data was presented as frequencies and percentages and compared using chi-square test. Normal distributed continuous data was presented as mean±SD and compared using a Student's t-test or presented as median with inter quartile range (IQR) and compared using the Mann-Whitney U test when normality testing failed. A Shapiro-Wilks test and Q-Q plots were used for normality testing. A paired samples t-test or Wilcoxon Matched-Pair Signed-Rank test was used in comparison of changes from baseline to follow-up. A two-sided p-value of <0.05 was considered statistical significant.

9 Results

9.1 Study population

For reference, see flowchart on page 16. Eighty-seven patients were enrolled in the study and assigned to the placebo or ezetimibe treatment arms (ezetimibe, n=43; placebo, n=44). Baseline examinations failed for one person due to vasospasm resulting in temporarily no-flow in the study vessel. During the follow-up period, one patient died from pulmonary cancer, and one patient withdrew consent. One patient died from sudden cardiac arrest within one week after the PCI, but the exact cause of death was not elucidated, as autopsy was omitted. In five patients, either baseline or follow-up IVUS of study vessel could not be achieved or was unsuitable for analysis. A total of 77 patients completed IVUS follow-up of the study vessel, but iMap™ data was only available in 66 patients: In three patients, iMap™ was lost during export to DVD, in other three patients adjustment to the scanning depth was done (iMap™ is only generated at 5 mm scanning depth), and in the remaining five patients, iMap™ data was not processed prior to export as a result of a system upgrade that changed the iLab system to discard iMap™ data by default unless

active steps were taken to avoid it. Mean time to follow-up was 353±14 days in the ezetimibe group and 356±13 days in the placebo group (p=ns).

Complete and analyzable baseline and follow-up examinations of the Resolute™ Integrity stent with OCT were available in 74 patients and in 76 patients for IVUS.

Three cases of target lesion revascularizations in the study period were performed, in two excluding IRA for follow-up assessment: One patient developed angina within 2 months after PCI and was treated for at stenosis proximal to the stent. One patient had complete target vessel closure (a dominant right coronary artery) first detected at follow-up, where repeated PCI restored flow, and the third patient had extreme but asymptomatic intimal hyperplasia in the stent with severe stenosis. This patient was successfully treated with new PCI at follow-up. In one case, the stent was inaccessible at baseline due to early vessel closure within 24 hours of PCI, and in another patient, the IRA could not be wired at follow-up, and consequently IVUS and OCT of the stent was not possible.

Baseline characteristics are listed in **Table 9-1**. The groups were well balanced. Two patients in the ezetimibe group had suspected adverse events to atorvastatin:

One patient was changed from atorvastatin to low dose rosuvastatin after 3 months due to elevated liver enzymes, and the other patient had to discontinue atorvastatin for the last 2 months of follow-up due to worsening of a preexisting rheu-

matic condition. One patient in the placebo group was unintentionally changed to simvastatin 40 mg by the local hospital prior to initial discharge and remained on that treatment undetected for the remaining 51 weeks.

9.2 Baseline and procedure characteristics

	Ezetimibe (n=43)	Placebo (n=44)	P
Age, years	55.3±11.0	57.2±9.1	0.38
Male gender, n (%)	39 (90.7)	36 (81.8)	0.23
Hypertension, n (%)	7 (16.3)	8 (18.2)	0.81
Current smoking, n (%)	25 (58.1)	23 (52.3)	0.74
Family disposition, n (%)	19 (44.2)	22 (50.0)	0.59
Diabetes, n (%)	1 (2.3)	1 (2.3)	0.99
Total Cholesterol >5 mmol/l, n (%)	32 (74.4)	30 (68.2)	0.64
HbA1c (mmol/mol)	39.0 (36.0, 41.0)	37.0 (36.0, 41.0)	0.98
Systolic blood pressure, mmHg	129.7±21.4	125.0±19.8	0.29
Diastolic blood pressure, mmHg	78.1±18.2	75.1±10.2	0.34
Heart rate, beats/min	71.0 (60.0, 83.0)	68.0 (60.0, 81.5)	0.62
Weight	86.0 (78.0, 95.0)	85.0 (76.8, 94.0)	0.81
BMI (kg/m ²)	27.3 (25.1, 29.2)	27.4 (24.6, 29.4)	0.99
LVEF	50.0 (40.0, 55.0)	50.0 (45.0, 60.0)	0.20
Single vessel disease, n (%)	33 (76.7)	29 (65.9)	0.43
Infarct related artery, n (%)			0.11
RCA	11 (25.6)	20 (45.4)	
LAD	27 (48.3)	15 (34.1)	
LCx	5 (14.9)	9 (15.9)	
Study vessel, n (%)			0.07
RCA	16 (37.2)	11 (25.0)	
LAD	12 (27.9)	23 (52.3)	
LCx	15 (34.9)	10 (22.7)	
Prior cardiovascular medications, n (%)			
β-blockers	0 (0.0)	2 (4.5)	0.16
Calcium antagonists	4 (9.3)	3 (6.8)	0.67
ACE inhibitors	4 (9.3)	3 (6.8)	0.67
ATII inhibitors	0 (0.0)	1 (2.3)	0.32
Diuretics	1 (2.3)	3 (6.8)	0.32
Guidewire used during pullbacks, n (%)			0.81
Present	27 (69.2)	26 (66.7)	
Not present	12 (30.8)	13 (33.3)	

Table 9-1

9.3 Lipids

Lipid values are presented in **Table 9-2**.

The baseline LDL values were significantly lower in the ezetimibe group.

Total cholesterol decreased with 47% in

the ezetimibe group and 39% in the placebo group, and correspondingly LDL decreased with 62% vs. 52%. More patients in the ezetimibe group reached of <1.8 mmol/l (86.0% vs. 50.0%, p<0.001).

	Ezetimibe n=39 Mean±SD	Placebo n=41 Mean±SD	p-value
Total cholesterol			
Baseline (mmol/l)	5.3±0.9	5.7±1.0	0.09
Follow-up (mmol/l)	2.9±1.0	3.5±0.7	0.001
Change (mmol/l)	-2.5±1.0	-2.3±0.7	0.039
Percent change %	-46.8±16.4	-38.9±9.7	<0.001
p-value baseline vs follow-up	<0.001*	<0.001	<0.001
HDL			
Baseline (mmol/l)	1.1±0.3	1.1±0.3	0.59
Follow-up (mmol/l)	1.1±0.3	1.1±0.3	0.48
Change (mmol/l)	0.06±0.3	-0.03±0.2	0.50
Percent change %	-3.6±25.8	-1.1±18.1	0.27
p-value baseline vs follow-up	0.36*	0.14	0.36
LDL			
Baseline (mmol/l)	3.7±0.7	4.1±0.9	0.010
Follow-up (mmol/l)	1.4±0.8	2.0±0.5	<0.001
Change (mmol/l)	-2.3±0.9	-2.2±0.7	0.29
Percent change %	-62.0±19.2	-52.4±10.9	<0.001
p-value baseline vs follow-up	<0.001	<0.001	<0.001
Triglycerides			
Baseline (mmol/l)	1.3±0.8	1.2±0.8	0.55
Follow-up (mmol/l)	0.9±0.8	1.0±0.6	0.07
Change (mmol/l)	-0.3±0.9	-0.1±0.7	0.08
Percent change %	-18.5±50.1	4.0±54.0	0.03
p-value baseline vs follow-up	0.025	0.24	0.24

Table 9-2 Lipid values at baseline and follow-up

9.3.1 Cholesterol and LDL change from baseline

In Figure 9-, bar charts depicting baseline, follow-up, and absolute changes from baseline values are shown. In **Figure 9-2**, scatterplots depicting relative and absolute LDL changes from baseline vs. baseline

values for the ezetimibe and placebo groups are shown. LDL differed between groups at baseline, and the absolute LDL reduction was similar in both groups. However, there was a larger relative reduction in the ezetimibe group. The absolute LDL reduction correlated with baseline values.

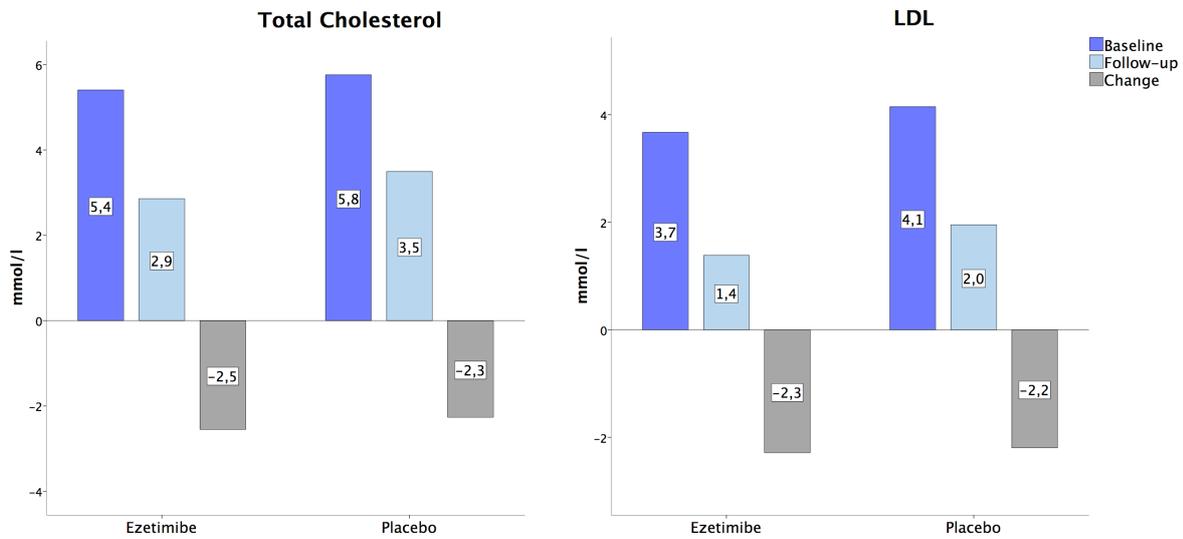


Figure 9-1 Total cholesterol and LDL median values at baseline and follow-up.

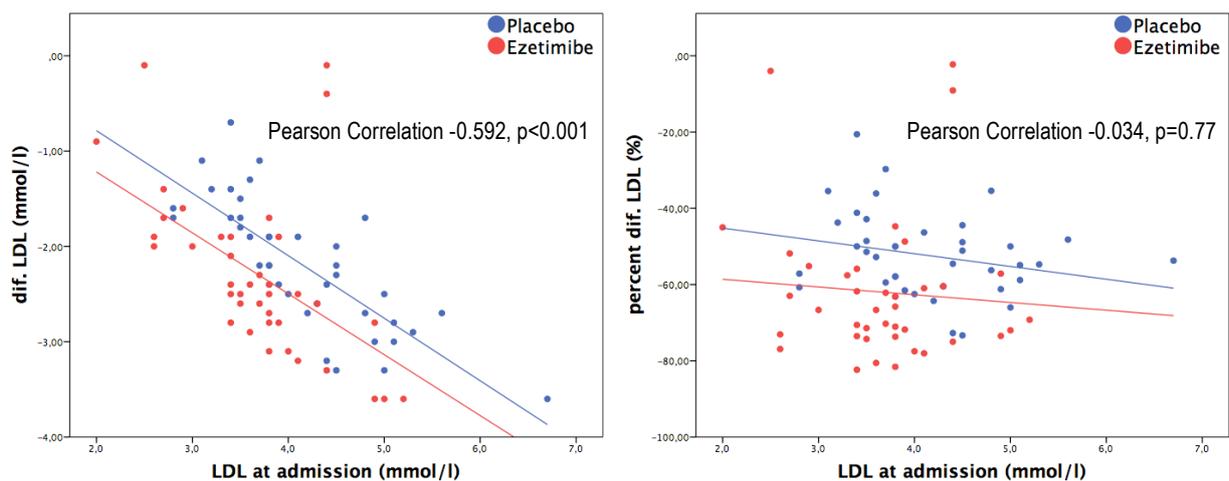


Figure 9-2 Scatterplots depicting absolute (to the left) and relative (to the right) LDL changes from baseline vs. baseline values for the placebo and ezetimibe groups. Absolute change in LDL correlates positively with baseline values.

9.4 Influence of ezetimibe on the coronary plaque

9.4.1 Greyscale IVUS findings

Greyscale findings for the entire pullback are presented in **Table 9-3** and findings for the 10 mm most diseased segment in **Table 9-4**.

There were no significant differences in any of the greyscale variables at base-

line. At follow-up, TAV in the entire region changed significantly in the ezetimibe group but not in the placebo group. Likewise, PAV changed significantly from baseline to follow-up in the ezetimibe group but not in the placebo group. In the ezetimibe group, a significant vessel and lumen volume reduction in the entire region was found.

	Entire pullback		p
	Ezetimibe	Placebo	
Lesion length, mm	34.4±9.0	35.4±10.9	0.84
Vessel Volume, mm³			
Baseline	513.7 (392.7, 716.5)	533.8 (359.3, 711.8)	0.93
Follow-up	491.4 (364.8, 573.0)	529.5 (335.3, 676.6)	0.57
Change	-29.4 (-44.3, -4.6)*	-11.9 (-39.6, 19.7)	0.12
Lumen Volume mm³			
Baseline	311.5 (236.9, 391.7)	324.6 (187.5, 422.0)	0.85
Follow-up	293.2 (213.7, 372.1)	326.0 (194.7, 394.8)	0.80
Change	-12.0 (-29.2, 4.3)*	-6.9 (-22.8, 16.9)	0.21
TAV mm³			
Baseline	200.0 (135.6, 311.9)	218.4 (163.5, 307.9)	0.63
Follow-up	189.3 (126.4, 269.1)	212.2 (149.9, 394.8)	0.39
Change	-11.3 (-25.5, -2.4)*	-10.3 (-28.6, 9.8)	0.56
PAV %			
Baseline	40.1±8.6	43.3±9.4	0.12
Follow-up	39.2±9.0	42.2±10.7	0.18
Change	-0.9±2.6*	-1.1±3.7	0.91
Max PAV %			
Baseline	70.6±28.4	79.9±38.8	0.23
Follow-up	65.3±28.2	73.3±36.8	0.28
Change	-0.8±6.7*	-2.7±8.2*	0.53

Table 9-3 Greyscale IVUS findings in the entire pullback. Data presented as Mean±SD / median (IQR). Significant changes from baseline: *p<0.05.

In the 10 mm most diseased segment, vessel volume, TAV, and PAV changed significantly from baseline in both groups. Change in LDL from baseline was found

to correlate weakly with change in PAV in the entire pullback (Spearman correlation - 0.249, p=0.031).

	Most diseased 10 mm		
	Ezetimibe	Placebo	p
Lesion length, mm	-	-	-
Vessel Volume, mm³			
Baseline	164.9 (123.0, 186.4)	146.8 (126.9, 188.6)	0.64
Follow-up	151.1 (115.9, 192.4)	145.4 (113.6, 173.5)	0.65
Change	-5.9 (-16.2, 2.6)*	-7.0 (-17.3, 6.1)*	0.83
Lumen Volume mm³			
Baseline	81.5 (61.2, 105.5)	69.4 (58.8, 92.9)	0.09
Follow-up	83.1 (65.3, 108.6)	71.7 (55.7, 91.6)	0.07
Change	-0.9(-7.7, 5.6)	-1.9 (-7.6, 6.5)	0.84
TAV mm³			
Baseline	67.4 (48.3, 95.2)	74.5 (54.9, 99.6)	0.42
Follow-up	60.0 (42.2, 82.0)	68.0 (44.9, 93.6)	0.32
Change	-4.0 (-11.6, 2.4)*	-5.3 (-14.6, 4.2)*	0.57
PAV %			
Baseline	43.8 (34.5, 51.8)	50.2 (40.9, 56.3)	0.034
Follow-up	41.7 (34.0, 49.0)	46.5 (36.6, 60.2)	0.07
Change	-2.2 (-5.4, 0.7)*	-1.0 (-5.3, 1.0)*	0.67
Max PAV %			
Baseline	54.1 (43.6, 61.7)	61.3 (47.1, 70.9)	0.041
Follow-up	40.6 (32.8, 52.4)	48.1 (39.2, 62.9)	0.52
Change	-10.0 (16.6, -3.3)*	-6.8 (-13.7, -1.4)*	0.13

Table 9-4 Greyscale IVUS findings in the 10 mm most diseased segment. Data presented as Mean±SD / median (IQR). Significant changes from baseline: *p<0.05.

9.4.2 Change in iMap™ assessed composition

The iMap™ findings are presented in **Table 9-5 and Figure 9-3**. In the entire region, the distribution of tissue components was balanced between the two groups. For both groups there was a signi-

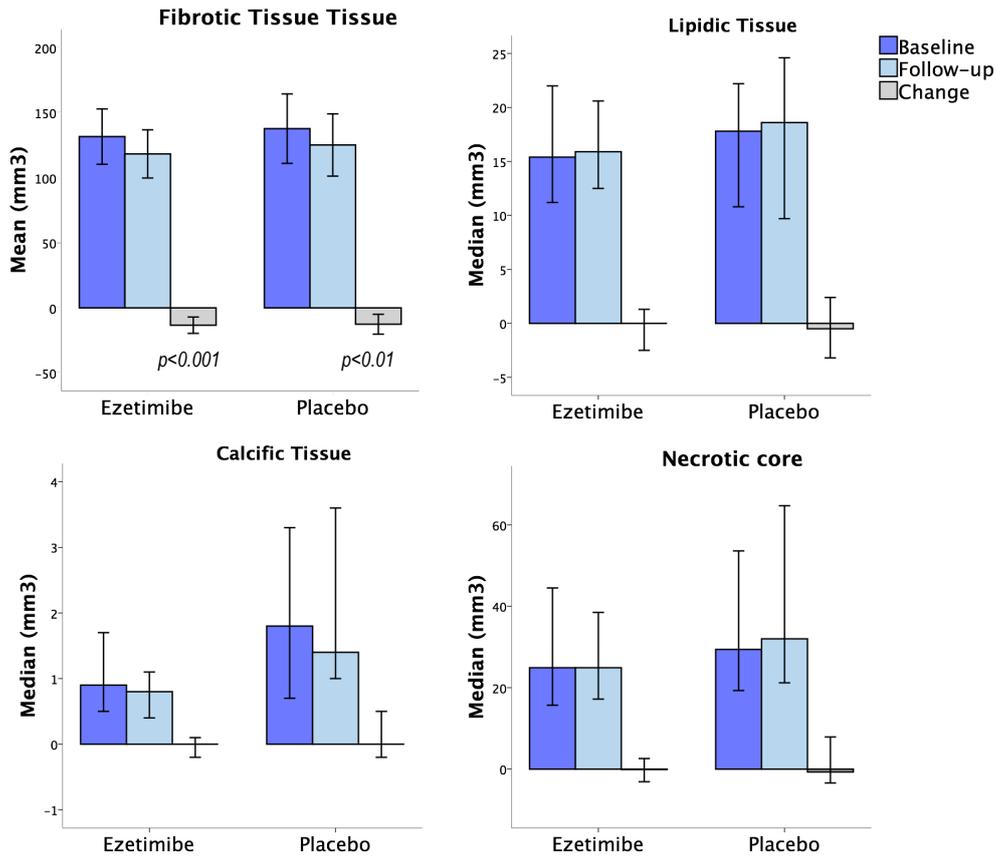
ficant decrease in FT. In the placebo group, we found a modest increase in the relative distribution of NC.

In the most diseased 10 mm segment, we found a similar relative distribution of tissue components as in the entire region, and there was a similar absolute decrease in fibrotic tissue.

	Entire pullback			Most diseased 10 mm		
	Ezetimibe	Placebo	p	Ezetimibe	Placebo	p
Lesion length	33.7±8.8	36.7±10.9	0.23	-	-	-
Fibrotic tissue, mm³						
Baseline	131.6±61.9	137.7±72.7	0.87	42.9 (28.1, 50.5)	37.5 (27.9, 47.7)	0.59
Follow-up	118.3±53.9	125.2±65.2	0.64	32.3 (25.2, 44.9)	31.0 (23.3, 47.4)	0.72
Change	-13.3±18.3*	-12.6±20.8*	0.72	-4.0 (-10.3, -1.9)*	-5.4 (-10.6, -0.6)*	0.69
Fibrotic tissue, %						
Baseline	65.1±12.1	63.8±12.7	0.76	70.0±14.1	65.9±15.1	0.31
Follow-up	63.7±10.3	60.5±12.5	0.25	67.9±13.7	63.7±15.1	0.28
Change	-1.3±6.7	-3.4±5.4*	0.18	-2.1±7.5	-2.2±7.2	0.95
Lipidic tissue, mm³						
Baseline	15.4 (9.5, 25.3)	17.8 (9.3, 27.1)	0.80	5.7±3.1	5.6±2.8	0.92
Follow-up	15.9 (10.3, 21.4)	18.6 (8.4, 26.5)	0.51	5.5±2.8	5.4±2.8	0.92
Change	0.0 (-3.3, 1.8)	-0.5 (-3.7, 4.3)	0.59	-0.2±1.9	-0.2±1.6	0.92
Lipidic tissue, %						
Baseline	9.0 (6.0, 10.0)	8.0 (7.0, 9.0)	0.71	9.1±3.3	8.8±3.3	0.68
Follow-up	9.0 (8.0, 10.0)	8.0 (7.0, 10.0)	0.37	9.9±3.8	9.4±3.2	0.45
Change	1.0 (-1.0, 2.0)	0.0 (-1.0, 2.0)	0.66	0.8±2.5	0.5±2.5	0.69
Calcified tissue, mm³						
Baseline	0.9 (0.3, 1.8)	1.8 (0.5, 3.8)	0.06	0.2 (0.1, 0.9)	0.5 (0.2, 1.7)	0.17
Follow-up	0.8 (0.3, 1.3)	1.4 (0.7, 4.5)	0.038	0.2 (0.1, 0.6)	0.5 (0.1, 1.3)	0.12
Change	0.0 (-0.4, 0.4)	0.0 (-0.4, 0.6)	0.58	-0.1 (-0.2, 0.1)	-0.0 (-0.2, 0.3)	0.69
Calcified tissue, %						
Baseline	0.0 (0.0, 1.0)	1.0 (0.0, 2.0)	0.019	0.6 (0.2, 1.4)	0.9 (0.4, 2.8)	0.15
Follow-up	0.0 (0.0, 1.0)	1.0 (0.0, 2.0)	0.006	0.6 (0.2, 1.3)	0.9 (0.5, 2.1)	0.08
Change	0.0 (0.0, 0.0)	0.0 (0.0, 1.0)	0.46	-0.0 (-0.3, 0.2)	0.0 (-0.5, 0.5)	0.83
Necrotic core, mm³						
Baseline	24.9 (11.9, 51.3)	29.4 (16.3, 78.5)	0.31	8.5 (4.6, 18.0)	10.2 (7.3, 21.9)	0.35
Follow-up	24.9 (15.3, 54.5)	32.0 (16.0, 88.7)	0.21	9.2 (4.2, 18.2)	11.0 (4.7, 22.9)	0.39
Change	-0.1 (-5.2, 4.3)	-0.7 (-6.0, 15.8)	0.35	-0.2 (-2.2, 2.3)	-0.3 (-2.7, 2.6)	0.78
Necrotic core, %						
Baseline	14.0 (7.0, 21.0)	17.0 (11.0, 24.0)	0.25	15.7 (10.8, 26.1)	19.0 (12.4, 35.1)	0.31
Follow-up	14.0 (10.0, 20.0)	20.0 (12.0, 29.0)	0.07	17.3 (12.5, 28.6)	20.2 (15.7, 36.5)	0.25
Change	1.0 (-1.0, 3.0)	1.0 (-1.0, 6.0)*	0.33	1.6 (-2.2, 4.7)	1.7 (-2.3, 6.9)	0.71

Table 9-5 IVUS iMap™ results for the entire pullback and the most diseased 10 mm segment. Data presented as Mean±SD / median (IQR). Significant changes from baseline: *p<0.05

Entire region



Most diseased segment

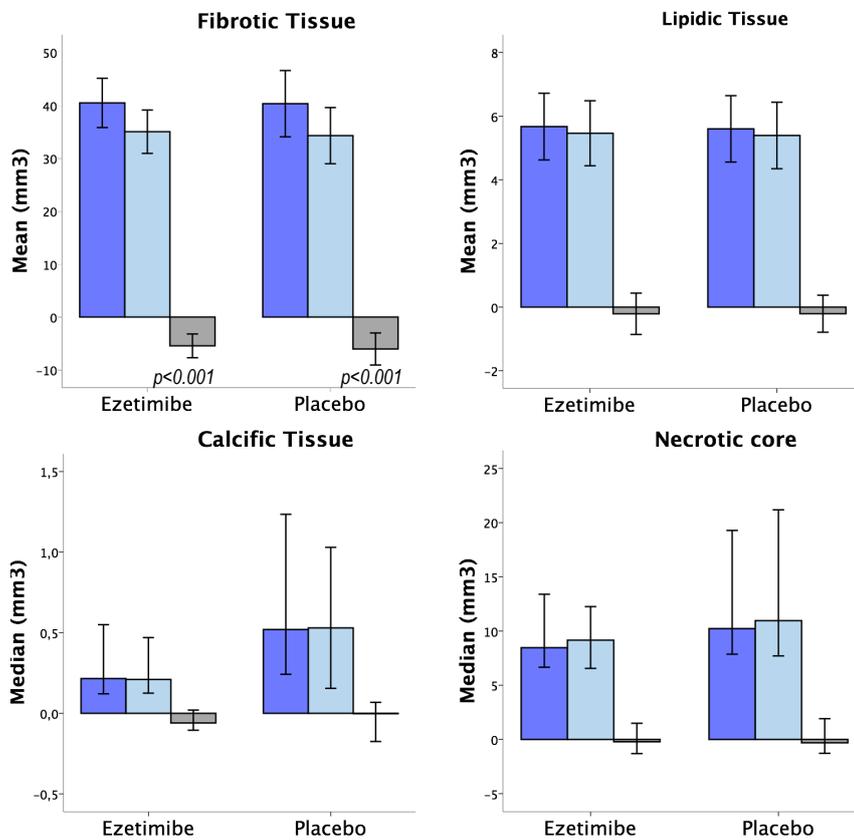


Figure 9-3 Graphical presentation of absolute iMap™ volumes at baseline and follow-up.

9.4.2.1 Topographic localization of MLA and maximum NC and PAV sites

The amount of plaque burden is generally higher in more proximal parts of the coronary tree. In angiographic assessments, the MLA site tends to be the target of intervention. However, the bulge of coronary plaque is not necessarily located in the same area⁶². **Figure 9-4** shows the relative localization of the frames containing the MLA site, the max NC site, and the max

PAV site. The green vertical lines marks the proximal and the distal limits of the maximum IVUS plaque segment length for the study population, and the vertical blue line marks the mean plaque segment length in the population. The MLA site stands out by its more distal location in the segment, while the NC and the PAV sites more often resides clearly proximal in the segment. There was no significant difference between the location of the NC and PAV site in this study.

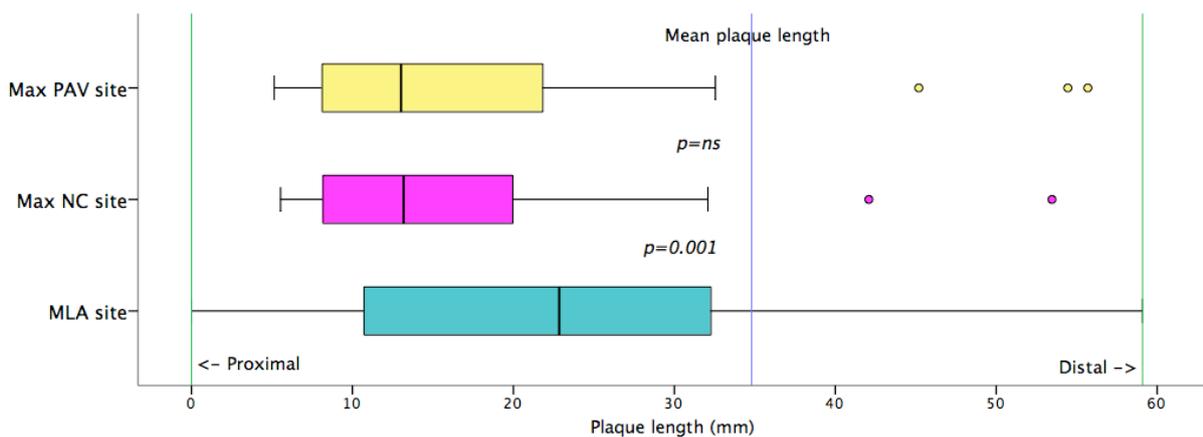


Figure 9-4 Topographic localization of MLA, max NC, and max PAV sites in plaque segment. Green lines show outer limits for the maximum region length, and the blue line shows the mean plaque segment length.

9.4.3 iMap™ intracatheter variation

In **Table 9-6**, the absolute iMap™ volumetric results of two consecutive pullbacks without (Pb1 and Pb2) and with guidewire

(Pb1+gw and Pb2+gw) in 10 patients are shown.

In pullbacks without guidewire, the intracatheter variation was non-significant, but in pullbacks with guidewire, a single significant variation in LT was found.

Variable	No guidewire			With guidewire		
	Pb1	Pb2	p-val.	Pb1+gw	Pb2+gw	p-val.
Vessel Vol. (mm ³)	576.2±213.5	574.6±212.6	0.46	578.8±218.3	575.1±215.6	0.21
Lumen Vol. (mm ³)	361.0±148.9	358.5±149.7	0.49	361.5±150.3	358.9±153.2	0.48
Plaque Vol. (mm ³)	215.2±74.6	216.1±77.7	0.81	217.3±77.7	216.1±76.5	0.78
NC (mm ³)	42.0±37.0	43.7±40.8	0.29	53.5±40.8	51.0±39.3	0.15
FT (mm ³)	150.3±58.4	149.8±56.6	0.81	139.5±60.9	141.3±58.8	0.59
LT (mm ³)	19.0±9.2	18.8±9.1	0.54	20.2±8.8	19.6±8.6	0.03
CT (mm ³)	2.4±3.3	2.4±3.3	0.54	2.7±3.3	2.6±3.5	0.45

Table 9-6

9.4.4 Guidewire artifact influence on iMap™ reproducibility

The mean ($\frac{pb1+pb2}{2}$) iMap™ results obtained in three different scenarios, with guidewire (I), without guidewire (II), and with guidewire and offline guidewire artifact exclusion (III), are shown in **Table 9-7**. Scenario (II) was considered to be the reference, as disturbance by an artifact was absent.

When comparing scenario (I) with (II), the guidewire artifact resulted in a signi-

ficant relative and absolute overestimation of NC. Correspondingly, the artifact reduced the amount of FT detected in both absolute and relative terms. A minor difference in relative LT was seen as well.

On the other hand, the exclusion of the artifact in scenario (III) resulted in relative distributions not different from the reference scenario (II). The absolute results were, however, significantly different except for CT.

Variable	With guidewire (I)	Without guidewire (II)	With guidewire artifact excluded (III)	p-value I vs. II	p-value II vs. III
NC (%)	22.7±14.5	18.2±13.8	18.8±14.1	<0.001	0.32
LT (%)	9.2±3.3	8.7±3.5	8.8±3.6	0.04	0.64
CT (%)	1.3±1.2	1.0±0.9	1.4±1.3	0.18	0.11
FT (%)	66.8±17.3	72.0±17.1	70.9±17.3	<0.001	0.15
NC (mm ³)	52.3±40.0	42.8± 8.8	37.15±32.6	0.002	0.04
FT (mm ³)	140.4±59.7	150.1±57.4	127.3±52.9	0.01	<0.001
LT (mm ³)	19.9±8.7	18.9±9.1	16.3±7.5	0.15	0.01
CT (mm ³)	2.7±3.4	2.4±3.3	2.5±3.2	0.11	0.49

Table 9-7 Relative and absolute iMap™ assessments for NC, LT, CT, and FT are shown in three different acquisition scenarios (I-III). Relative values differ between (I) and (II) for NC, LT and FT, but do not differ between (II) and (III).

9.4.5 OCT assessed change in plaque morphology

Results are presented in **Figure 9-6** (following page). Mean FCT for all fibroatheromas and FCT of the corresponding minimal cap thickness at follow-up was increased in both groups.

With respect to plaque features, lipid arc and macrophage arc was significantly reduced in both groups, while lipo-calcific arc did not change statistical significant from baseline. An increase of calcium arc only statistical significant in the placebo group was found.

Examples of OCT findings in corresponding frames from baseline to follow-up are illustrated in **Figure 9-5**.

Examination for correlation between percentage changes in mean and minimum FCT, lipid arc, calcium arc, lipo-calcific arc, and macrophage arc with the percentage changes in LDL/HDL ratio and baseline LDL was performed but none was found to be significant. In the present study, no data on changes in inflammatory markers such as CRP were available, but assuming that percentage change in lipid arc could reflect change in TAV, a test for correlation with LDL/HDL ratio was performed but no correlation was found.

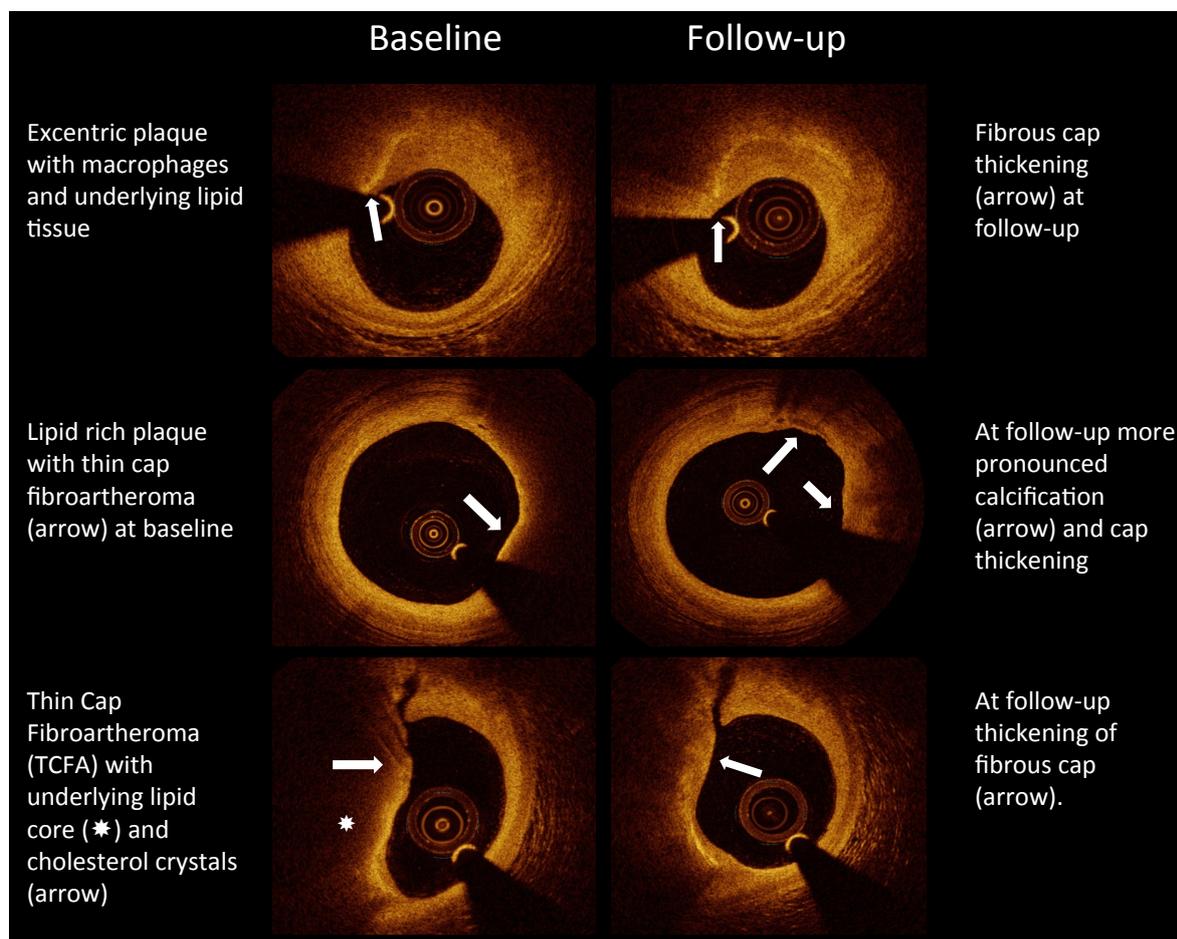


Figure 9-5 Changes in plaque appearance from baseline.

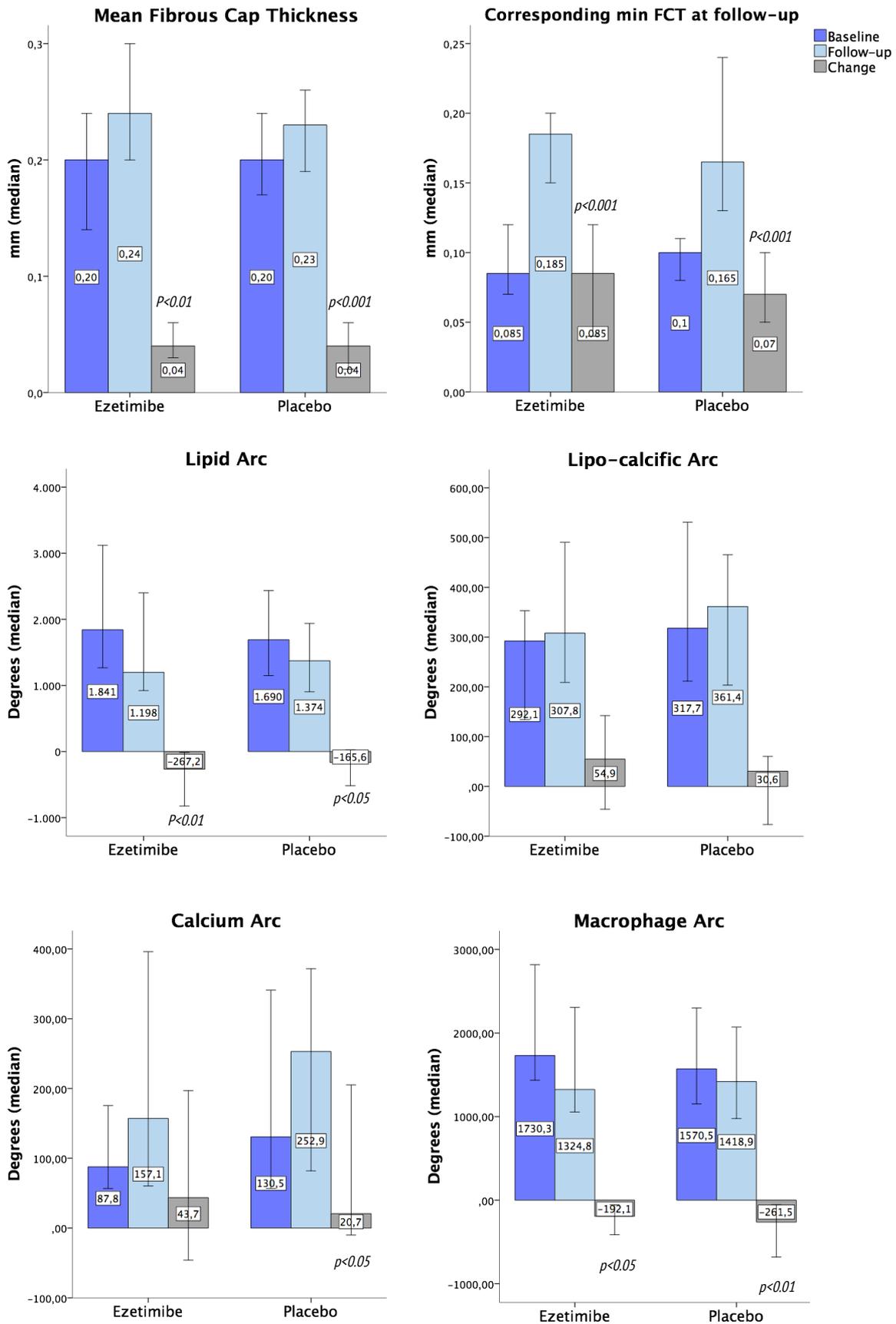


Figure 9-6 OCT findings for plaque constituents

9.4.5.1 OCT plaque assessment reproducibility

By Intra Class Coefficient (ICC) analysis there was found to be excellent correlation for lipid arc, and lipocalc arc (0.87, 0.99, and 0.98 respectively), and good correlation for FCT, macrophage arc, and calcium arc (0.77, 0.74, and 0.75). For num-

bers of identified ThCFA's, there was also found to be excellent correlation (0.92).

The level of agreement was graphically assessed with respect to mean values for the 20 pullbacks in Bland-Altman plots shown in **Figure 9-7**. In general, acceptable agreements were found.

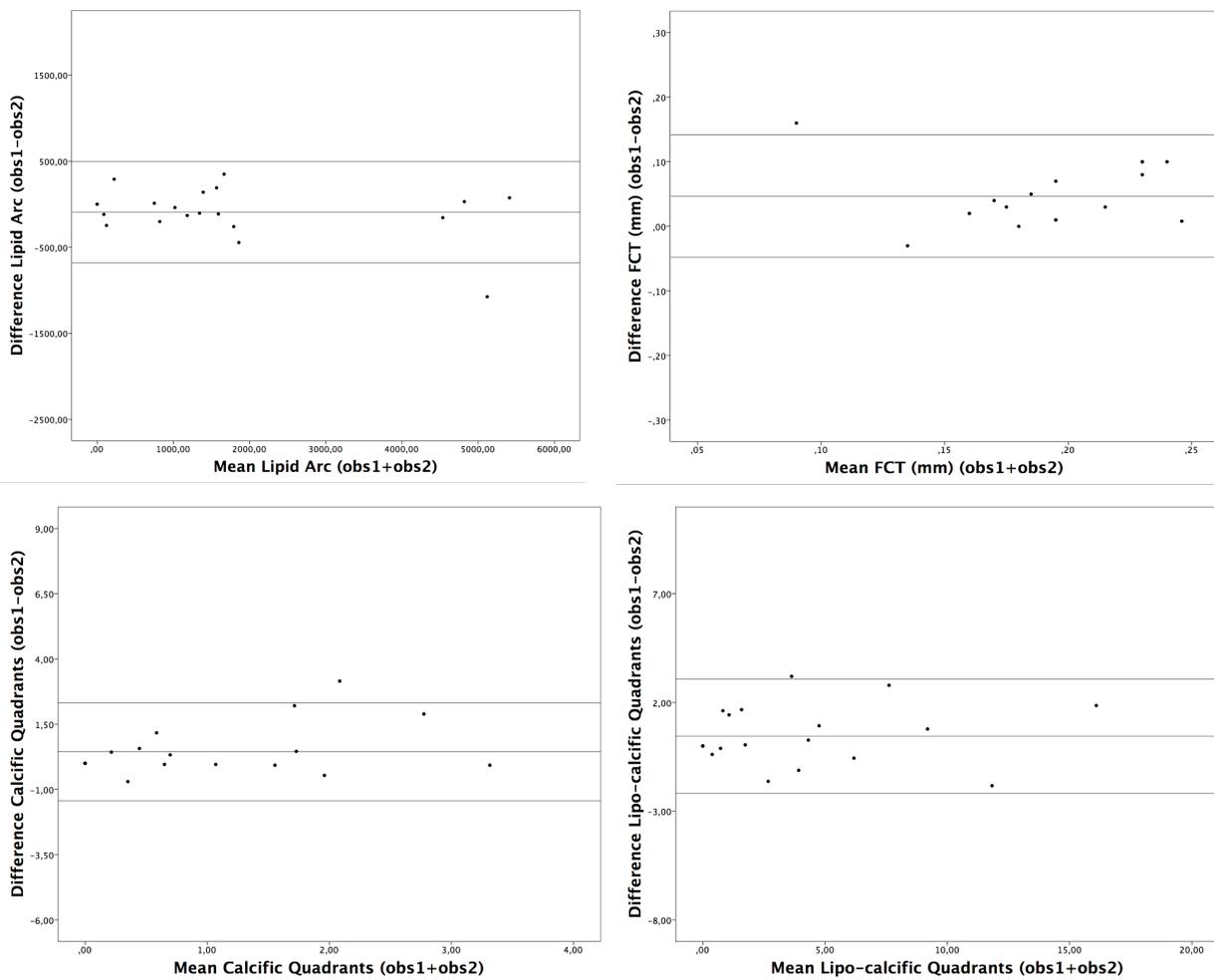


Figure 9-7

9.5 The Resolute™ Integrity in STEMI patients

9.5.1 Stent expansion

Results are presented in **Table 9-8**. The nominal stent CSA / mean reference CSA ratio was 1.1 ± 0.30 . The MSA at baseline compared to the corresponding reference segments revealed, that a relatively high

degree of underexpansion was present. In 37.8% of patients, we found an MSA of less than 5 mm^2 . Stent expansion compared to the nominal stent size CSA of the stent initially chosen by the operator was ranging from 0.28 to 0.99 and was <0.90 in 64 (86.5%) patients. At follow-up, no signs of stent recoiling were found and both the MSA and the stent volume were unchanged after 12 months.

Stent expansion	Baseline	Follow-up	p-value
MSA	6.1 (3.9, 7.4)	6.0 (4.2, 7.6)	0.98
Intra-stent lumen volume, mm^3	140.3 (96.2, 184.7)	117.7 (83.5, 168.8)	<0.001
Overall Minimal luminal area, mm^2	4.5 (3.4, 6.4)	3.8 (2.7, 6.1)	<0.001
Mean CSA, distal ref. segment, mm^2	6.5 (4.7, 8.5)	6.3 (4.0, 7.9)	0.004
Mean CSA, prox. ref. segment, mm^2	7.8 (5.6, 10.8)	7.3 (4.8, 9.9)	0.005
MSA / REF_{CSA}	0.80 ± 0.2	-	-
MSA / $\text{STENT}_{\text{NOM,CSA}}$	0.75 ± 0.2	-	-
Patients with MSA $<5 \text{ mm}^2$, n (%)	28 (37.8)	-	-
Stent size selection			
Accuracy ($\text{STENT}_{\text{NOM,CSA}} / \text{REF}_{\text{CSA}}$)	1.1 ± 0.30	-	-

Table 9-8

9.5.2 Stent strut apposition

Results are presented in **Table 9-9**. Malapposition at baseline was found in 79.7% of patients corresponding to 5.8% of all struts. These numbers were reduced to

28.4% and 0.6% respectively at follow-up. Complete resolved malapposition was seen in 69.5% of patients with baseline malapposition, and late acquired malapposition was seen in 4.0% of the study population.

Malapposition	Baseline	Follow-up	p-value
Analyzable struts, n	18,875	19,208	0.14
Number of struts per cross section, n	13.0±1.8	13.2±1.6	0.29
Patients with malapposition (% of patients)	59 (79.7)	21 (28.4)	<0.001
Total number of malapposed struts, n	1097	113	<0.001
Percentage malapposed struts, %	5.8	0.6	<0.001
Resolved, n ptt. (% of baseline)	-	41 (69.5)	-
Persistent, n ptt. (% of baseline)	-	18 (30.5)	-
Late acquired, n ptt. (% of follow-up)	-	3 (14.3)	-
Maximal malapposition distance, µm	360 (200, 550)	305 (243, 618)	0.039
OCT Extra stent volume, mm ³	0.6 (-3.3, 6.7)	-12.9 (-26.0, -7.0)	<0.001
Patients with pos. value, n (%)	40 (54.8)	8 (10.8)	<0.001
- Thereof late acquired, n (%)	-	1 (1.4)	-

Table 9-9

In order to determine a cut-off value for maximum malapposition distance predictive for malapposition resolvement after twelve months, a receiver operating characteristics (ROC) curve was constructed defining the optimum cut-off value to 430 µm (**Figure 9-8**).

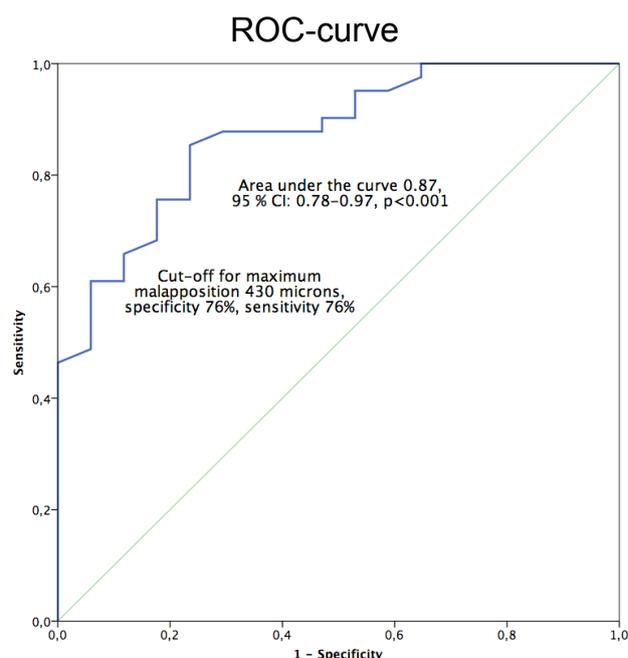


Figure 9-8

9.5.3 Stent strut coverage

The results for stent strut coverage are presented in **Table 9-10**. By definition, all struts were uncovered at baseline. At

follow-up, 11.3% of all struts were uncovered, and 7% of patients had complete coverage. Significantly more uncovered struts were found in patients with malapposed struts at baseline (p=0.004).

Coverage	Baseline	Follow-up	p-value
Number of uncovered struts, n (%)	18,875 (100)	2,177 (11.3)	<0.001
In ptt.s with baseline malapp., n (%)	-	2017 (92.7)*	-
In ptt.s. without baseline malapp., n (%)	-	160 (7.3)*	-
Number of uncov. malapposed struts, n (‰)	-	78 (4.1)	-
Completely covered, n patients (%)	-	7 (9.5)	-
Total number of struts at side-branches, (‰)	269 (14.3)	151 (7.9)	<0.01
Percent of side-branch struts uncovered, %	-	47.0	-
Median intimal thickness, μm	-	120.0 (60)	-

Table 9-10 *) Difference between those with and without baseline malapposition, p=0.004.

One patient was found to have an extreme but asymptomatic IH at follow-up with an MLA reduction to 0.73 mm², and target vessel revascularization was performed at follow-up. This patient had a 2.75/18 mm stent expanded to a baseline MSA of 4.0 mm² compared to a mean reference seg-

ment CSA of 5.99 mm². By OCT, there was mid-stent underexpansion and moderate residual proximal thrombus material. The tissue behind the stent was lipid rich with cholesterol crystals and obscured media. OCT baseline and follow-up findings are shown in **Figure 9-9**.

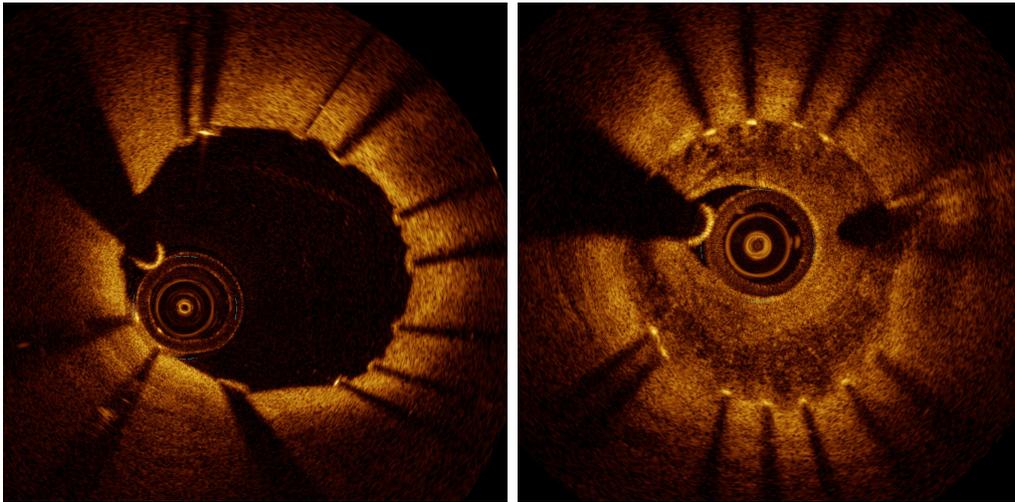


Figure 9-9 Case with extreme intimal hyperplasia. Left: baseline, right: follow-up.

9.5.4 Thrombus

Thrombus was a frequent finding in the study cohort and was seen in 90.5% of patients at baseline (mean number of quadrants 3.9 ± 5.5). Summarized thrombus prevalence of one or more quadrants was seen in 73.0% of patients. At follow-up, signs of thrombus were present in 18.9%

of patients (mean number of quadrants 0.5 ± 0.3). Summarized thrombus prevalence of one or more quadrants per patient was not present. **Figure 9-10** shows the relative distribution of numbers of quadrants on red, white, and mixed thrombus at baseline and follow-up.

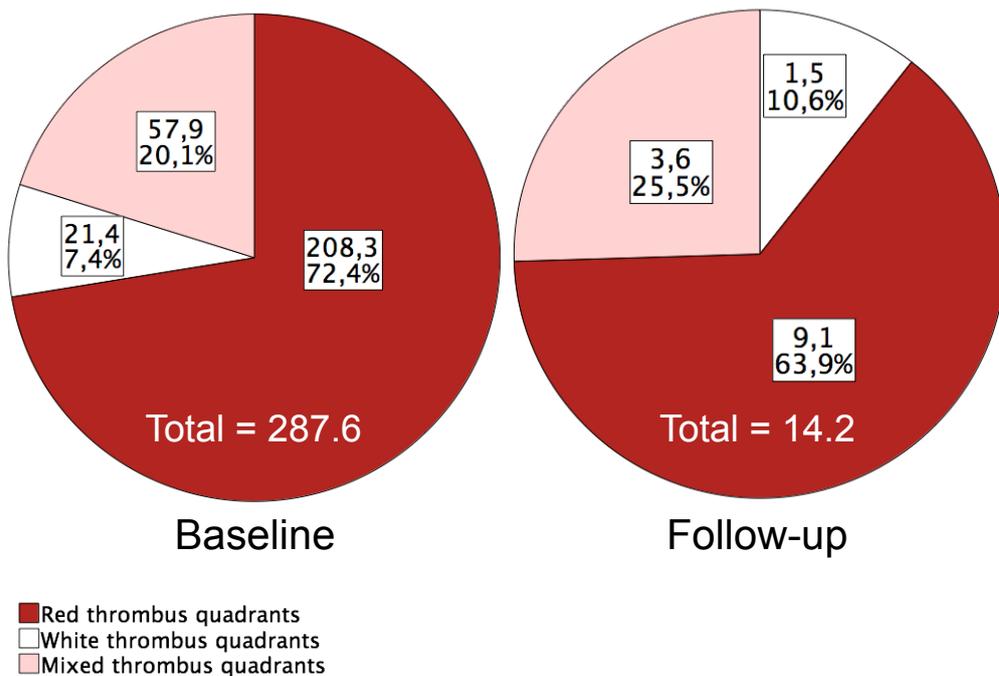


Figure 9-10 Thrombus distribution at baseline and follow-up

9.5.5 Stented vessel remodeling

IVUS was used in the assessment of vessel remodeling from baseline. Vessel, lumen, and plaque volume were calculated for the stent segment and the distal and proximal

reference segments and shown in the table below. Overall there was plaque regression and vessel volume reduction in all segments. Significant lumen reduction was found in the reference segments, but interestingly not in the stent segment.

IVUS measurements	Baseline	Follow-up	p-value
Stent segment	<i>n</i> =76	<i>n</i> =76	
Lumen volume, mm ³	140.6 (108.9, 183.4)	139.1 (104.7, 176.7)	0.090
Vessel volume, mm ³	314.7 (244.3, 417.0)	310.1 (244.1, 379.6)	<0.001
Peri-stent plaque volume, mm ³	170.8 (129.7, 235.5)	156.0 (120.2, 208.3)	<0.001
Proximal reference segment	<i>n</i> =72	<i>n</i> =72	
Lumen volume, mm ³	40.7 (30.7, 54.6)	37.2 (29.2, 49.5)	0.005
Vessel volume, mm ³	84.4 (68.6, 103.7)	78.4 (59.0, 99.2)	<0.001
Plaque volume, mm ³	41.0 (30.5, 53.0)	36.1 (25.3, 47.7)	<0.001
Distal reference segment	<i>n</i> =75	<i>n</i> =75	
Lumen volume, mm ³	37.1 (25.8, 50.6)	36.6 (24.7, 45.4)	0.032
Vessel volume, mm ³	68.0 (44.6, 87.1)	61.6 (41.0, 78.8)	<0.001
Plaque volume, mm ³	28.7 (17.7, 39.2)	23.4 (16.2, 38.4)	<0.001

Table 9-11

The distribution of cases with respect to changes in vessel volume and peri-stent plaque volume is shown in the scatter plot on **Figure 9-11**.

A positive linear correlation between percentage change in plaque and vessel volume was found (Pearsons Correlation 0.66, $p < 0.001$), and positive remodeling of more than 5% was identified in 23 patients and correspondingly, negative remodeling in was found in 51 patients.

In one patient, positive remodeling of more than 5% together with plaque regression was found. This was mainly driven by an intra-stent lumen gain of 30.7% and by OCT and IVUS, the patient had large amount of intra-stent thrombus at baseline, suggesting that most of the plaque regression in fact was thrombolysis, but signs of minor (<10% of stent diameter) evaginations were seen in the mid-stent section (**Figure 9-12**).

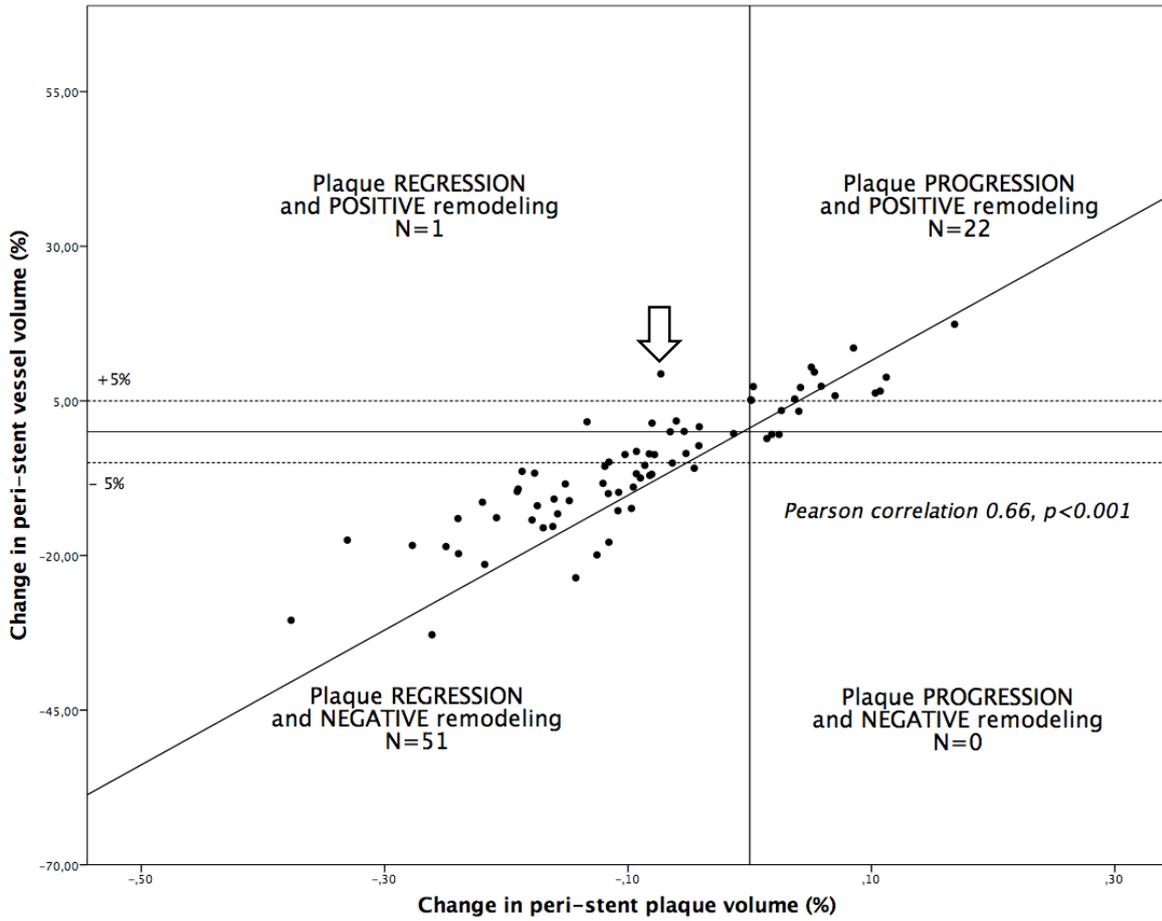


Figure 9-11 Relation between relative changes in peri-stent plaque volume (x-axis) and the relative changes in peri-stent vessel volume (y-axis). Patient with positive remodeling and plaque regression marked with arrow.

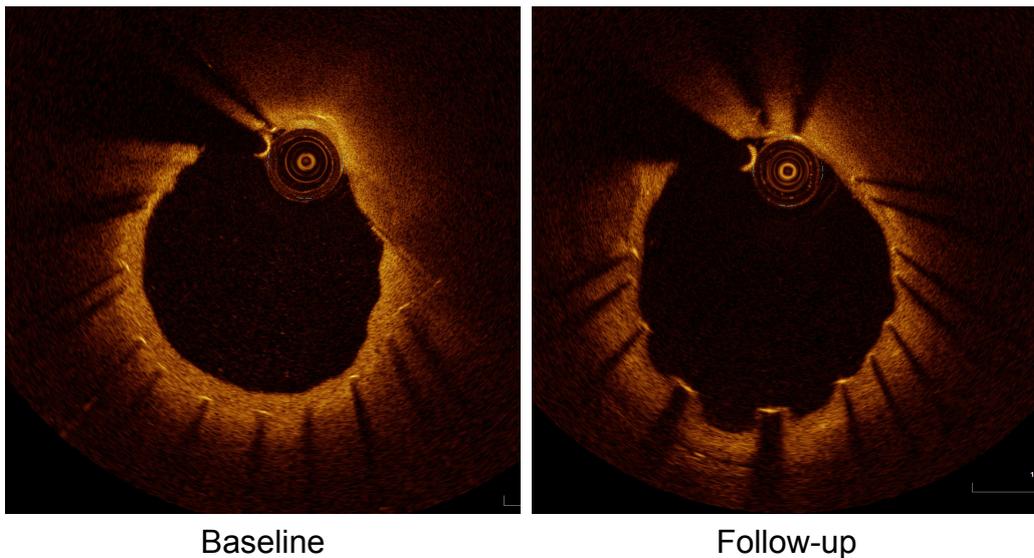


Figure 9-12 Case marked with arrow in Figure 9-9. Thrombotic material was lining the stent at baseline and a lipid rich plaque was seen behind the stent. Minor evaginations and thrombus resolution was found at follow-up.

10 Discussion

The benefits of statin treatment with respect to patient outcome are well established^{28,63,64} and more potent statins like atorvastatin and rosuvastatin results in further improvement in clinical outcome compared to less potent statins^{63,65,66}. This correlates with the findings in several randomized trials using serial IVUS based quantitative volumetric plaque measurements, where statins have been shown to result in slowdown in plaque progression or even plaque regression, when high potent statins are used⁶⁷⁻⁷¹. A linear correlation between plaque regression and clinical outcome has been established⁷², and IVUS has become the golden standard in longitudinal studies of plaque progression/regression and makes it achievable to “screen” novel drugs for potential effects prior to their entrance in larger and more expensive clinical outcome trials¹⁷.

In high-risk patients, the benefits of LDL lowering are not limited to those with higher baseline LDL levels but is also seen in subgroups with low baseline levels^{73,74}, and much attention is directed at finding ways to obtain further reduction of LDL

levels in these patients. Ezetimibe has been widely used to obtain target LDL-values in patients not tolerating high dose or high potent statins.

Recently, the results of the *IMProved Reduction of Outcomes: The Vytorin Efficacy International Trial* (IMPROVE-IT) has been presented^{34,35}. In this large multicenter trial based on 18,144 randomized patients, the effect of ezetimibe compared to placebo as addition to simvastatin 40 mg in high-risk acute coronary syndrome (ACS) patients was evaluated. A significant reduction in the primary endpoint (a composite of cardiovascular death, myocardial infarction, unstable angina pectoris, coronary revascularization beyond 30 days and stroke) was found, and IMPROVE-IT was the first trial showing a beneficial clinical effect of LDL-reduction in high-risk ACS patients not mediated by statin. This result corresponds well with the conception of “lower is better” with respect to LDL-reduction, and additional clinical benefits might be obtainable by lowering LDL even further.

10.1 Lipids

Addition of ezetimibe 10 mg/day to atorvastatin 80 mg/day for twelve months resulted in a significantly larger relative reduction in total cholesterol and LDL compared to atorvastatin monotherapy. The cholesterol and LDL reduction in the placebo-group was comparable with similar study cohorts in previous trials^{70,75}, and the addition of ezetimibe resulted in a further relative reduction of LDL of 25.5% which is in line with a trial evaluating additional effect of ezetimibe to high dose statins⁷⁶. Few trials assessing ezetimibe in combination with statins have been published, and these are based on non statin naïve patient populations selecting patients with higher baseline LDL levels and/or ongoing statin treatment^{20,77}. This might explain, that a larger relative LDL reduction was found in the present trial.

10.2 Greyscale IVUS findings

In the ezetimibe group, IVUS showed a significant reduction in TAV and PAV together with a reduction in total luminal and vessel volume.

The numerical reduction of PAV in the entire region was very similar to *The Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin versus Atorvastatin* (SATURN)⁷⁵ (-0.99 (-1.19 to -0.63)% in the atorvastatin

arm after 2 years follow-up), and *Effect of very high-intensity statin therapy on regression of coronary atherosclerosis* study (ASTEROID)⁶⁹ (-0.98±3.15%) although this study used high dose rosuvastatin for 2 years. Our findings for change in TAV in the most diseased 10 mm segment are slightly more pronounced compared to the findings in the atorvastatin arm of *Reversal of Atherosclerosis with Aggressive Lipid Lowering* study (REVERSAL)⁷⁰ (-4.2±12.8 mm³) and similar to the findings in ASTEROID (-6.1±10.1 mm³). The relatively high degree of absolute regression despite shorter time of follow-up in our study probably reflect, that it is based on a high-risk STEMI population, and correspondingly our baseline levels for both PAV and TAV tends to be higher than in available studies on low risk populations. More recently the *Integrated biomarker imaging study* (IBIS-4) on STEMI patients was published¹⁹. In this trial, 103 STEMI patients underwent IVUS in a non-infarct related artery and were treated with rosuvastatin 40 mg/day and followed for 13 months. Compared to the current trial, there was a higher prevalence of diabetes, hypertension, family history of cardiovascular disease and smoking. In contrast to the present trial, 9.8% of the patients were treated with statin prior to enrollment. A significant decrease in PAV of -0.9 (-1.56 to -0.25)%

in the entire region together with a decrease in TAV of 5.5 (-8.99 to -2) mm³ and PAV -2.94 (-3.89 to -1.98)% in the 10 mm most diseased segment was found, which are of similar magnitude as the changes found in the present trial.

10.3 Changes in coronary plaque composition

The iMap™ study showed no significant change in NC and no difference between groups, but a significant decrease in FT was found in both groups.

The vulnerable plaque is preceded by an increase in lipid content in the arterial wall (notably the intimal layer) together with infiltration with inflammatory cells resulting in formation of a fibroatheroma containing a necrotic core. These developments in combination with progressive thinning of the fibrous cap are both features that invoke much interest, as necrotic core can be determined in vivo by IVUS with spectral frequencies analysis⁷⁸ and measurements of the fibrous cap thickness can be obtained by OCT⁷⁹.

10.3.1 Influence on iMap™ tissue characterization

The IBIS-4 study found no change in NC, but similar to our findings, there was a decrease in fibrous tissue. Other studies have investigated changes in plaque composition caused by statins using VH-

IVUS^{25,21} with mixed results. In a study comparing high dose vs. low dose rosuvastatin on STEMI patients, a reduction in NC was found in the high dose group together with a reduction of fibrous tissue²². In another study evaluating fluvastatin in patients with stable angina, an increase of fibrous tissue, a decrease in fibro-fatty tissue but no change in NC was found²³. No studies have so far utilized iMap™ for this purpose. The effect of ezetimibe in combination with atorvastatin 80 mg/day compared to standard statin treatment has previously been studied in only one VH-IVUS based trial in patients with stable angina²⁰. No difference between treatment arms with respect to plaque composition was found although a relative small increase in NC in the placebo group was observed.

The current study demonstrates an additional ezetimibe-effect not previously described in coronary arteries resulting in significant plaque regression. Like in other trials published, we did, however, not find any evidence supporting, that the clinical gains from LDL lowering could be related to change in plaque composition assessed by iMap™.

10.3.2 Influence on OCT morphology

No previous studies have assessed the influence of ezetimibe on coronary plaque morphology in STEMI patients.

Jang et al. reported in 2005, that TCFA was more present in patients with myocardial infarction (MI) compared to stable angina, and accordingly FCT in lipid rich plaques was generally found to be thicker in patients with stable angina⁸⁰.

It has been suggested, that some of the beneficial effects of statin treatment might rely on plaque stabilization by increasing the thickness of the fibrous cap. In a non-randomized prospective study in patients with MI, Takarada et al. have shown, that lipid lowering with statin following MI resulted in a greater increase of FCT compared to similar patients not treated with statin⁸¹. The same group published a study in 2010 in 82 patients with non-ST-segment elevation MI describing the correlation in greyscale IVUS assessed TAV and OCT measured FCT with LDL/HDL ratio and C-reactive protein (CRP) levels over a 9 month period⁸². It was found, that TAV and FCT did not intercorrelate, however, a correlation between percentage changes in TAV and LDL/HDL ratio and percentage change in FCT and C-reactive protein was found.

In a recent trial by Habara et al., the effects of ezetimibe as addition to fluvastatin was examined using OCT⁷⁷. Ninety patients with stable angina and documented hypercholesterolemia had a target vessel examined with OCT. Patients without an identifiable fibrous cap were

excluded leaving 63 patients to randomization to fluvastatin plus ezetimibe or fluvastatin alone. OCT was performed in 57 patients after approximately 9 months. No significant change in MLA or lumen area at the minimum FCT site was found, but in both groups there was a significant reduction in lipid arc at the minimum FCT site, and an increase in minimum FCT in both groups with a significant difference between groups.

The current trial confirms the findings from earlier trials, that LDL-lowering treatment with statin causes an increase in FCT and a reduction of lipid arc, but it does not confirm a correlation between lipid arc reduction and the degree of change in LDL-values. The additional LDL reduction by ezetimibe in this trial does not give rise to a further increase in FCT, but with respect to lipid content only the ezetimibe group was found to have a significant reduction in numbers of lipid quadrants, and the reduction of lipid arc was also numerically larger in the ezetimibe group although not statistically different.

10.4 Impact of the guidewire artifact

The impact of the guidewire artifact was found to be negligible with respect to classical grey scale IVUS assessments with no statistical difference between the

two approaches. Furthermore, the difference between two sequential and correlating pullbacks (with and without guidewire) was not significant consistent with good intra-catheter and intra-observer reliability. However, the study confirms earlier findings, that the guidewire artifact is interpreted by the iMap™ algorithm as NC making direct comparison of iMap™ data between two subsequent pullbacks difficult mainly because the artifact in different pullbacks may reside in different parts of the plaque. The NC compartment is otherwise small in its overall representation in plaque tissue, but it might be overestimated, when the artifact involves an area with a high plaque burden. This problem is inherent to iMap™'s dependence on a mechanical rotating catheter system and is not an issue for Virtual Histology systems utilizing fixed crystals and no sheath technique. This makes direct comparison of iMap™ results between pullbacks without and with guidewire difficult, but our study showed, that offline artifact exclusion resulted in a similar relative distribution, and the intra-catheter reliability remained intact allowing for comparison in longitudinal studies. There was an agreement between results of pullbacks without guidewire and with guidewire and artifact exclusion, but our findings points towards the presence of a proportional bias meaning that the level of

agreement seems to vary through the range of measurements. The two methods are thus not suited for interchangeable use through a longitudinal study.

In an earlier study by Heo et al., the reproducibility of iMap™ with respect to both inter- and intra-observer and inter- and intra-catheter variability was examined in a similar number of patients (20 and 5 patients respectively)⁵⁸. It was found, that iMap™ measurements were more sensitive to inter-observer variations and especially NC, because its quantification is sensitive to the tracing of EEM and thus determination of plaque burden. It was also noted; that the guidewire artifact constituted a problem, but the impact hereof was not specifically evaluated. It was concluded, that the classical grey-scale assessments together with iMap™ assessment was reproducible on a level that compares to VH.

Longitudinal IVUS plaque progression studies using iMap™ acquisitions have not yet been published, and because such studies typically aim at describing minor shifts in plaque composition a way to circumvent this problem are warranted. A simple solution is to simply omit the use of the guidewire during pullbacks, but this increases the risk of procedural complications and should be avoided. In the light of our finding, it seems, however, feasible to overcome this issue – especially

by excluding the artifact prior to analysis - making iMap™ a useful addition to other plaque assessment modalities.

10.5 The Resolute Integrity in STEMI patients

Stent strut malapposition at baseline was seen in the majority of patients but was mainly resolved at follow-up and was related to the maximum malapposition distance at baseline. After 12 months, nearly all struts were covered, although strut coverage was seldom complete. Uncovered struts were more common in areas with malapposition at baseline. Extreme IH was rare, and the median percentage of IH was low. A high prevalence of stent underexpansion with MSA less than 5 mm² was found. Thrombus were frequent at baseline but were largely resolved at follow-up. Peri-stent negative vessel remodeling occurred in the majority of patients and was related to plaque regression, while positive remodeling predominately was associated with plaque progression. Major evaginations were not encountered.

10.5.1 Stent expansion, apposition and coverage

PCI in STEMI patients is challenged by multiple factors. The presence of thrombus and vasoconstriction, can result in underestimation of the vessel size and conse-

quently to implantation of an undersized stent and later stent malapposition. Forceful overexpansion is associated with increased risk of vessel injury and distal embolization. The finding of stent underexpansion in the present trial underscores the significance of this challenge. In the IVUS substudy of the *Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction* study (HORIZONS-AMI), a low post PCI MSA was found to be an independent risk factor for restenosis⁴⁵. No studies have reported the incidence of stent underexpansion in STEMI populations, and only 1 study was found to provide IVUS assessment in the days after primary PCI⁴⁷. In this study assessing safety and feasibility of a self-expanding STENTYS DES in STEMI patients, IVUS was performed post PCI and after 3 days, and interestingly demonstrates an increase in distal reference segment of 19%, which translates to a baseline stent size estimation of 0.84 (100/119) very similar to the findings in the present trial.

The Resolute Integrity™ has previously been studied with OCT in three trials – in all of these in comparison to other second generation DES. In a substudy of the *RESOLUTE All Comers trial*⁸³ comparing Resolute Integrity™ with Xience V™ (Abbott Vascular, Santa Clara, CA, USA), 30 “all comer” patients (6 of

which presented with STEMI) with a total of 50 stents in the Resolute subgroup were analyzed after 13 months reporting 1.8% malapposed struts, 7.4% uncovered struts, and a neointimal thickness of 116 ± 99 μm . In a later *Comparison of neointimal coverage between zotarolimus-eluting stent and everolimus-eluting stent using Optical Coherence Tomography* study (COVER OCT)⁸⁴, 51 patients with de novo lesions were randomized to Xience V™ (26 patients) or Endeavor Resolute™ (25 patients) with post PCI OCT and follow-up after 9 months. Twenty-two patients in the Endeavor subgroup (including 10 patients presenting with acute coronary syndrome (ACS)) had OCT performed at follow-up finding 0.7% malapposed struts, 3.3% uncovered struts, and a neointimal thickness of 124 ± 42 μm . Recently, the *Activity of Platelets after Inhibition and Cardiovascular Events: Optical Coherence Tomography* study (APICE OCT)⁸⁵ was conducted on ACS patients evaluating completeness of neointimal coverage at 6 months in the everolimus eluting PROMUS element™ DES (Boston Scientific) vs. Resolute Integrity™. A total of 31 patients were examined with OCT in the Resolute group (hereof 12 patients with STEMI). The findings were: 1.1% malapposed struts, 7.9% uncovered struts, and 0.3% malapposed and uncovered struts.

Due to differences in study design, patient populations, and length in time of follow-up, a direct comparison with these trials are difficult, however, the present trial had a higher proportion of uncovered struts, closest to, but higher than, the RESOLUTE All Comers trial, that had a longer time to follow-up, but few STEMI patients. In the setting of ACS a higher incidence of malapposition has been shown^{86,87} - a predisposing factor for impaired strut coverage. In this context, it is surprising, that compared to the findings in the present and other trials, malapposition was found to occur more often in the RESOLUTE All Comers trial despite longer follow-up, but this may reside in differences in baseline and procedure characteristics. The gain in neointimal thickness was comparable to the other studies, and the percentage neointimal volume of 10.1% in APICE OCT is similar to our findings.

10.5.2 Thrombus

It has previously been shown by IVUS, that the thrombus burden is higher in patients with STEMI compared to in patients with non-STEMI⁸⁸. An OCT study on forty STEMI patients has shown, that thrombus material are present in all patients with STEMI despite good angiographic result⁸⁹. This is similar to the findings in the present trial. The fact that

some patients in the present study did not present with thrombus at baseline might be explained by the postponed OCT acquisition compared to the mentioned trial in which acquisition was post PCI.

10.5.3 Infarct related vessel remodeling

Zotarolimus eluting stents (ZES) have previously been compared to first gene-

ration paclitaxel eluting stents (PES) in serial IVUS studies finding positive vessel remodeling in PES, but not or to a lesser extent in ZES⁹⁰⁻⁹². These studies were based on the older Resolute Endeavor, which used a different stent polymer with different properties. Major coronary evaginations, were not observed by OCT among the cases with positive remodeling in the present trial.

11 Conclusions

Twelve months treatment with ezetimibe resulted in:

- a) Ezetimibe resulted in a further reduction in total cholesterol and LDL compared to placebo.
- b) In the IVUS study of the entire segment, ezetimibe resulted in plaque regression together with lumen volume reduction not found in the placebo group. There was however no effect in the iMap™ assessed plaque composition compared to placebo.
- c) Ezetimibe resulted in a reduction in numbers of lipid quadrants of at least 90 degrees not found in the placebo group. In both groups, an increase in FCT and a reduction of lipid arc was found, but no differences between groups were observed.
- d) The macrophage arc was reduced in both groups suggesting reduced inflammatory response not further enhanced by ezetimibe.
- e) The guidewire artifact had impact on the iMap™ assessment, but offline exclusion of the guidewire artifact prior to iMap™ analysis

was possible and yielded similar relative distribution of plaque components as without guidewire and acceptable intra-catheter reproducibility allowing for valid assessment without compromising patient safety.

In patients treated for STEMI with primary PCI using the Resolute™ Integrity DES, the following were observed:

- a) Stent underexpansion was a frequent finding and might be related to vessel spasm and thrombus mass.
- b) The Resolute™ Integrity DES was found to be associated with low incidences of late acquired malapposition.
- c) The percentage of uncovered struts at follow-up was low.
- d) Thrombus was present in most patients at baseline but was largely resolved at follow-up.
- e) There was an overall plaque regression and a limited positive remodeling associated with plaque progression.

12 Limitations

- The study is based on a relatively small number of patients not allowing detection of minor impacts of ezetimibe treatment.
- The time of follow-up was limited compared to other longitudinal studies, where follow-up were often 2 years.
- Only one vessel was chosen for analysis, and the used OCT system provides limited pullback capabilities further reducing the size of baseline-follow-up matched plaque for comparison.
- The non-infarct related artery might not reflect the infarct related artery with respect to plaque burden and composition.
- Strut malapposition at baseline might be underestimated due to high prevalence of thrombus.

13 Future perspectives

The findings of the present trial show, that aggressive lipid lowering with ezetimibe has the potential to enhance plaque regression even further and could represent a useful addition in patients not reaching target LDL values on high dose statins or in patients not tolerating statins.

The implementation of OCT in plaque assessment makes way for a better qualitative assessment of morphologic plaque features, but can also provide semi-quantitative assessments of value in future prospective study designs. Together with IVUS, OCT provides more complete plaque characterization of coronary vessel

disease including visualization of signs of ongoing inflammation and the option to directly measure the fibrous cap thickness.

The study is among very few others describing the intracoronary events in the days after STEMI and provides additional knowledge to our understanding of the underlying pathogenesis, but also to insights to the special challenges related to stent deployment in STEMI patients. In future studies, alternative approaches in STEMI patients – like deferred stenting – could benefit from intravascular imaging assessments like the ones utilized in the present trial.

14 Summary

The main purpose of the OCTIVUS trial was to assess the influence of the cholesterol absorption inhibitor ezetimibe on plaque composition in patients with ST segment elevation myocardial infarction (STEMI). This was accomplished by use of intravascular ultrasound (IVUS) for volumetric plaque assessment and iMap™ for tissue characterization. Furthermore, plaque morphology including measurement of the fibrous cap thickness (FCT) was assessed by optical coherence tomography (OCT).

Secondarily, OCT and IVUS assessment with respect to stent size, expansion, apposition, and thrombus burden after the initial implantation of the Resolute™ Integrity drug eluting stent in a STEMI cohort was performed. After 12 months, neo-intimal coverage, remodeling, and reference segment response was investigated.

Ezetimibe was found to further reduce the total cholesterol and low-density lipoprotein (LDL) levels when added to atorvastatin 80 mg. The absolute reduction in LDL was correlating with baseline LDL values.

The guidewire artifact resulting from iMap™'s dependence on a mechanical IVUS catheter system was shown to have

impact on iMap™ assessment, but could be adjusted for by offline exclusion of the artifact resulting in good reproducibility and reliable measurements compared to assessments performed without a guidewire thus allowing a guidewire to be used in iMap™ acquisition.

In a non-infarct related artery, it was found, that the most diseased segment of the vessel wall resided more proximal than the site with the minimum luminal area – which in case of stenosis would be the “natural” target for intervention.

Assessed by IVUS, ezetimibe resulted in a significant plaque regression together with negative vessel remodeling, and in both treatment arms, the iMap™ assessment showed a reduction in fibrotic tissue, but ezetimibe did not result in additional changes compared to placebo.

The OCT plaque study showed, that lipid lowering resulted in an increased FCT, a reduction of lipid content, and in a reduction of macrophage plaque infiltration. However, ezetimibe did not further influence plaque morphology compared to placebo.

In a STEMI setting, stent size assessment is challenged by high frequency of thrombotic material and target vessel spasm, and stent deployment can be difficult due to risk of distal embolization of

thrombotic material – especially when high balloon pressures are applied. Correspondingly, stent underexpansion was a frequent finding. Presence of thrombus was frequent and consisted predominantly of red thrombus material. Some degree of baseline malapposition assessed by OCT was present in most patients but in most patients it had subsided at follow-up.

The Resolute™ Integrity was well endothelialized after 12 months. One patient had severe but asymptomatic initial hyperplasia treated with repeated percutaneous intervention at follow-up.

Stent underexpansion was frequently seen with a minimal stent area less than 5 mm² seen in 38% of patients. Minimum lumen area was reduced to less than 4 mm² at baseline in some patients due to stent underexpansion, and in two cases target lesion revascularization was needed during the study period. There were no signs of stent recoil, and no stent fractures were identified.

Overall, IVUS demonstrated plaque regression and negative vessel remodeling, and in patients with positive remodeling, the development was driven by plaque progression and no major evaginations were encountered.

15 Dansk resumé (Danish summary)

Hovedformålet med OCTIVUS studiet var at vurdere påvirkningen af kolesterolabsorptions hæmmeren ezetimibe på plaquekompositionen hos patienter med ST elevations myokardieinfarkt (STEMI).

Klassisk gråskalerings intravaskulær ultralyd (IVUS) blev anvendt til volumetrisk plaque udmåling, og iMap™ blev benyttet til vævskarakterisation.

Plaquemorfologi – herunder udmåling af den fibrøse kappetykkelse (FCT) - blev yderligere vurderet ved hjælp af optisk kohærens tomografi (OCT).

Sekundært blev stentstørrelse, ekspansion, apposition og trombebyrde efter implantation af den medicin afgivende Resolute™ Integrity stent hos STEMI patienter vurderet med OCT og IVUS. Karrets respons på implantation blev vurderet med hensyn til neointimal væv dækning, remodellering omkring stenten og i de tilstødende referencesegmenter.

Ezetimibe 10 mg som tillæg til atorvastatin 80 mg medførte en yderligere reduktion af total kolesterol og low-density lipoprotein (LDL) i forhold til monoterapi med atorvastatin. Den absolutte reduktion i LDL korrelerede med udgangs LDL-værdierne, hvilket ikke var tilfældet med den relative reduktion.

Guidewireartifaktet, som skyldes at iMap™ baserer sig på et mekanisk IVUS-kateter, påvirkede iMap™ kvantificeringen, men kunne korrigeres ved offline eksklusjon af artifaktet hvorved der blev opnået god reproducerbarhed og pålidelighed af målingerne sammenholdt med udmålinger foretaget uden guidewire.

I et ikke-infarktamt studiekar, blev det fundet, at det mest syge område var lokaliseret proksimalt i karret i forhold til det sted, hvor lumenforsnævringen var størst, og som i tilfælde af stenose ville være det logiske angrebepunktet for en intervention.

IVUS viste, at ezetimibe medførte signifikant plaque regression og negativ remodellering, og i begge interventionsarme blev der med iMap™ fundet reduktion af fibrotisk væv, men ezetimibe medførte ikke yderligere ændringer i forhold til placebo.

OCT-studiet viste, at lipidsænkende behandling øger FCT, nedsætter lipidindholdet i karvæggen samt reducerer forekomsten af makrofager, men ezetimibe medførte ikke yderligere ændringer sammenlignet med placebo.

Hos STEMI patienter er valg af stentstørrelse vanskeliggjort af en høj forekomst af trombotisk materiale og spasmer i det kar, som er ramt af blodproppen.

Stentimplantationen vanskeliggøres herudover af risikoen for distal trombe embolisering - særligt ved anvendelse af høje ballontryk. I overensstemmelse hermed viste studiet, at stenten ofte var underekspanderet i forhold til de tilhørende reference-segmenter. Forekomst af blodpropmateriale var hyppig og bestod ved baseline overvejende af rød trombe. De fleste patienter havde nogen grad af malapposition ved baseline, men denne var betydelig reduceret ved follow-up.

Resolute™ Integrity stenten var godt vævsdækket efter 12 måneder. En patient udviklede svær asymptomatisk hyperplasi inde i stenten og blev ballonudvidet ved follow-up.

Stent underekspansion var hyppigt forekommende, og et minimalt stent areal

under 5 mm^2 blev fundet hos 38% af patienterne. Området med det mindste lumen areal var under 4 mm^2 ved baseline hos nogle patienter grundet underekspansion af stenten, og hos to af disse blev der behov for ny ballonudvidelse i løbet af projektperioden. Der blev ikke fundet tegn til, at stenten blev deformeret, og ingen stentbrud blev påvist.

IVUS viste, at der overvejende indtrådte plaqueregression omkring stenten, hvilket resulterede i negativ remodellering af det stentede kar, og hos de patienter, hvor der blev fundet positiv remodellering, var dette ledsaget af samtidig plaque progression, og der blev ikke påvist større evaginationer.

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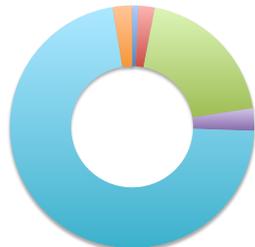
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17 Appendices

17.1 Appendix A: Example of the OCT PLAQUE Data extraction sheet.

27/01/15		OCTIVUS		93.xlsx	
OCT Plaque Data Extraction					
Lesion Characteristics		Frame:	Lumen:	TCFA	Frame: Lumen:
Lesion length (mm)	19			n TCFA	1
Lesion start	87		13,60	Min TCFA thickness	0,03 141 12,03
Lesion end	182		12,10	Max TCFA thickness	0,06 180 12,47
Mean luminal area	11,53			Mean TCFA thickness	0,05
Min. Luminal Area	6,07	117		Total TCFA Arc	54,50
Lumen Volumen	219,07			Min TCFA Arc	54,50 167 13,10
Distance to guiding (mm)	N/A	0		Max TCFA Arc	54,50 167 13,10
				Mean TCFA Arc	54,50
PIT				n TCFA quadrants	0,61
n frames PIT	18			TCFA1 length	9,70
Min PIT thickness	0,61	101	13,09	TCFA2 length	0,00
Max PIT thickness	1,04	181	12,20	Mean TCFA length	9,70
Mean PIT thickness	0,81			TCFA1 frame start	131 7,79
				TCFA1 frame end	180 12,47
Calcified Plaque				TCFA2 frame start	0 0,00
n calcified lesions	0			TCFA2 frame end	0 0,00
Total calcified arc	0,00				
Min calcified arc	0,00	0	0,00	ThCFA	
Max calcified arc	0,00	0	0,00	n ThCFAs	10
Mean calcified arc	N/A			Min ThCFA thickness	0,07 166 13,28
Min calcified depth	0,00	0	0,00	Max ThCFA thickness	0,37 121 6,69
Max calcified depth	0,00	0	0,00	Mean ThCFA thickness	0,18
Mean calcified depth	N/A				
Min calc thickness	0,00	0	0,00	Overall cap thickness	
Max calc thickness	0,00	0	0,00	Min cap thickness	0,03 141 12,03
Mean calc thickness	N/A			Max cap thickness	0,37 121 6,69
n calcified quadrants	0,00			Mean cap thickness	0,12
Fatty Calcific Plaque				Macrophages	
n fatty-calcified lesions	6			n macrophages	27
Total fatty-calcified angle	274,60			Total macrophage angle	3366,90
Min fatty-calcific arc	12,50	131	7,79	Min macrophage arc	21,60 141 12,03
Max fatty-calcific arc	68,60	176	13,55	Max macrophage arc	359,70 121 6,69
Mean fatty-calcific arc	45,77			Mean macrophage arc	124,70
Min fatty-calc. thickness	0,23	131	7,79	Min macrophage depth	0,03 131 7,79
Max fatty-calc. thickness	0,40	146	15,05	Max macrophage depth	0,48 87 13,60
Mean Fatty-calc. thickness	0,34			Mean macrophage depth	0,15
Min fatty-calcific depth	0,06	146	15,05	n macrophage quadrants	37,41
Max fatty-calcific depth	0,73	176	13,55		
Mean fatty-calcified depth	0,25			Other findings	
n fatty-calcified quadrants	3,05			n crystals	1
Lipid Plaque				Min crystal depth	0,00 0 0,00
n lipid lesions	15			Max crystal depth	0,59 136 8,92
Total lipid angle	2435,72			Mean crystal depth	0,59
Min lipid arc	85,10	146	15,05	n microvessels	8
Max lipid arc	288,20	116	6,18	Min MVE depth	0,14 166 13,28
Mean lipid arc	143,91			Max MVE depth	0,39 171 13,25
n lipid quadrants	27,06			Mean MVE depth	0,28
"True" quadrants:	13			n calcific nodule	0
				Mean calc nodule depth	N/A

17.2 Appendix B: Example of the OCT STENT Data extraction sheet.

Date: 27/01/15		The OCTIVUS Trial		78oct2.xlsx	
OCT Stent Data Sheet					
Lesion Characteristics					
Stent length (mm)	18,4	Frame:		Lumen:	
Stent Start	37			7,8	
Stent End	130			6,36	
Mean luminal area stent	8,15				
Mean in-stent luminal diameter	3,20				
Mean Stent area	8,65				
Max Stent area	10,89	106			
MSA	6,01	51			
Stent Volume	159,10				
Lumen Volume	150,02				
IH volume	9,09				
IH %	5,71				
MLA in STENT	5,67	51		5,67	
Stent coverage					
n Struts	235	Malapposed:		SB:	
n "Definitely uncovered"	2	2	0	0	0
n "Uncovered Fibril"	5	0	0	0	0
n "Partially Uncovered"	46	2	0	0	0
n "Covered Protruding"	7	0	0	0	0
n "Covered Embedded"	169	0	0	0	0
n "Covered Proliferated"	6	0	0	0	0
Dissections					
n dissections	0				
Min flap thickness	0,00	0			
Max flap thickness	0,00	0			
Mean flap thickness	N/A				
Min flap length	0,00	0			
Max flap length	0,00	0			
Mean flap length	N/A				
Min dissection arc	0,00	0			
Max dissection arc	0,00	0			
Mean dissection arc	N/A				
Total Dissection arc	0,00				
n dissection quadrants	0,00				
Min diss cavity area	0,00	0			
Max diss cavity area	0,00	0			
Mean diss cavity area	N/A				
Min Act lumen	0,00	0			
Max Act lumen	0,00	0			
Mean Act lumen	N/A				
Min effective lumen	0,00	0			
Max effective lumen	0,00	0			
Mean effective lumen	N/A				
Prox dissection length	0,0				
Distal dissection length	0,0				
Flap area 1	0,00	0			
Flap area 2	0,00	0			
n Intra-stent dissections	0				
Total intra-stent dissections length	0,0				
n intra-plaque	0				
Total intra-plaque length	0,0				
Calcific Nodule					
n Intra-stent Nodules	0				
n extra-stent Nodules	0				
Thrombus					
Total thrombus angle	0,00	White:	Red:	Mixed:	Total:
n thrombus entries	0	180,60	0,00	0,00	180,60
n thrombus quadrants	0,00	9	0	0	9
		2,01	0,00	2,01	
n Covered Struts with Thrombi at FU	0				
n Uncovered Struts with Thrombi at FU	0				
Overall MLA	5,67				
Prox ref seg start					
Prox ref seg start	131			6,18	
Prox ref seg end	156			11,98	
Dist ref seg start	36			8,38	
Dist ref seg end	16			6,53	
Prox ref MLA	131			6,18	
Dist ref MLA	16			6,53	
Prox ref seg mean area				8,80	
Dist ref seg mean area				7,18	
Prox ref seg max area				11,98	
Dist ref seg max area				8,38	
Stent coverage					
					
Apposition					
n malapposed	4			Frame:	
% uncovered malapposed	1,70				
Min malapposed area	0,00	0			
Max malapposed area	0,00	0			
Mean malapposed area	N/A				
Total malapposed area	0,00				
Min malapposed depth	0,25	96			
Max malapposed depth	0,27	96			
Mean malapposed depth	0,26				
Intimal thickness					
Min intimal thickness	0,00			Frame:	
Max intimal thickness	0,44			81	
Mean IH (covered struts)	0,12				
% uncovered	22,55				
% malapposed	1,70				
Max covered embedded	0,24			76	
Overall IH mean	0,09				
Evaginations					
n evaginations	0				
Min evagination depth	0	0			
Max evagination depth	0,00	0			
Mean evagination depth	N/A				
Total evagination area	0,00				
Min evagination area	0	0			
Max evagination area	0,00	0			
Mean evagination area	N/A				
Prolapse					
n region tissue prolaps	0,00				
Min tissue prolaps length	0,00	0			
Max tissue prolaps length	0,00	0			
Mean tissue prolaps length	N/A				
Total tissue prolaps area	0,00				
Min tissue prolaps area	0,00				
Max tissue prolaps area	0,00				
Mean tissue prolaps area	N/A				

Paper 1

Influence of Ezetimibe in addition to high dose Atorvastatin Therapy on
Plaque Composition in Patients with ST Elevation Myocardial Infarction
assessed by Intravascular Ultrasound with iMap: The OCTIVUS trial

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Abstract

Background: Statins ability to induce plaque regression assessed by intravascular ultrasound (IVUS) is well established. The aim of the trial was to examine the influence of ezetimibe in addition to high dose statin on plaque composition and volume using IVUS with spectral analysis of radiofrequency data (iMap) in statin-naïve patients with first-time ST-segment Elevation Myocardial Infarction treated with primary percutaneous intervention.

Methods: Eighty-seven patients were treated with atorvastatin 80 mg and further randomized (1:1) to ezetimibe 10 mg or placebo. IVUS with iMap was performed at baseline and after 12 months in a non-infarct related artery. The primary endpoint was change in necrotic core (NC) after 12 months. Secondary endpoints were changes in fibrotic tissue (FT), lipid tissue (LT), calcific tissue (CT), total atheroma volume (TAV), and percentage atheroma volume (PAV).

Results: Complete iMap data was available in 66 patients. There was no change in NC in either group (ezetimibe group 24.9 (11.9, 51.3) mm³ to 24.9 (15.3, 54.5) mm³, p=ns, placebo group (29.4 (16.3, 78.5) mm³ to 32.0 (16.0, 88.7) mm³, p=ns). FT in the ezetimibe group was reduced from 137.7±72.7 mm³ to 118.3±53.9 mm³, p<0.001, and in the placebo group from 131.6±61.9 mm³ to 125.2±65.2 mm³, p<0.01 (p=ns between groups). LT, and CT did not change significantly. TAV was reduced in the ezetimibe group from 200.0 (135.6, 311.9) mm³ to 189.3 (126.4, 269.1) mm³, p=0.001 and in the placebo group from 218.4 (163.5, 307.9) mm³ to 212.2 (149.9, 394.8) mm³, p=ns (p=ns between groups). PAV was reduced in the ezetimibe group from 40.1±8.6% to 39.2±9.0%, p<0.05 and in the placebo group from 43.3±9.4% to 42.2±10.7%, p=ns (p=ns between groups).

Conclusion: Ezetimibe in addition to high dose atorvastatin therapy for twelve months was associated with a reduction in TAV and PAV but did not influence on NC content.

Key-words

Atorvastatin; plaque regression; IVUS; statin naïve

Abbreviations

CT	=	Calcified Tissue
FT	=	Fibrotic tissue
IVUS	=	Intravascular ultrasound
LT	=	Lipidic tissue
NC	=	Necrotic core
PAV	=	Percentage atheroma volume
PCI	=	Percutaneous coronary intervention
STEMI	=	ST Elevation Myocardial Infarction
TAV	=	Total atheroma volume

Introduction

Plaque instability and rupture are preceded by accumulation of lipids within the intimal layer of the coronary vessel wall. Some plaques are prone to become unstable, and the tissue composition of the plaque is of importance since development of inflammatory processes, infiltration with macrophages and formation of a necrotic core are related to plaque progression towards greater instability. Pathological studies have demonstrated, that plaque ruptures are more likely to develop in plaques with a necrotic core covered by a thin fibrous cap (Thin-Cap Fibroatheroma, TCFA)(1). The *Providing Regional Observations to Study Predictors of Events in the Coronary Tree* (PROSPECT) study showed, that future coronary events more often arises in areas characterized by high plaque burden, luminal stenosis, and presence of TCFA(2).

In large clinical outcome trials, high dose statins significantly reduced cardiovascular events(3, 4), and plaque regression assessed by intravascular ultrasound (IVUS) has been shown to correlate with clinical outcome(5). In the search for better ways to assess temporal changes in plaque composition, classical greyscale IVUS has been expanded with spectral analysis of radio-frequency data referred to as Virtual Histology (VH-IVUS, Volcano Therapeutics), Integrated Backscatter IVUS (IB-IVUS) and Tissue Characterization with iMap (Boston Scientific). With these technologies it is possible to assess the plaque composition in vivo and stratify tissue types into fibrotic (FT), lipidic (LT), calcific (CT), or necrotic subtypes (NC)(6). Ex vivo validation studies have shown high sensitivity and specificity compared to histological findings(7–12). Studies evaluating the effect of potent statins have demonstrated a modest reduction in necrotic core in a non treated coronary artery in unselected patients referred for percutaneous coronary intervention (PCI)(13) and in statin naïve patients admitted with STEMI(14). Other studies have shown varying results(13–19).

Serial IVUS studies have proven, that diminished plaque progression correlates with achieved low density lipoprotein (LDL) reduction, and that plaque regression was induced when LDL was reduced to below 2.0 mmol/l (77.2 mg/dL)(20).

The cholesterol inhibitor ezetimibe has been shown to induce additional LDL-reduction when added to statin treatment(21). This might potentially lead to an improved plaque regression and composition compared to high dose statin therapy alone. The aim of the present trial was to evaluate the influence of ezetimibe in addition to high dose atorvastatin on plaque composition after 12 months in statin naïve patients with ST segment elevation myocardial infarction (STEMI) using the IVUS iMap technique.

Patients and methods

Setting and design

The *Plaque Composition in Patients with acute ST Segment Elevation Myocardial Infarction assessed by Optical Coherence Tomography and IntraVascular UltraSound with iMap* (OCTIVUS) trial (NCT01385631) was a single center double-blinded randomized trial including statin naïve patients with first time STEMI. During their admission for primary PCI, a plaque in a non-infarct related coronary artery (IRA) was examined. The study was approved by the Danish Ethical Committee (project ID: S-201 001 00) and the Danish Medical Agency (EudraCT 2010-022604-45).

In the period June 2011 to June 2013 a total of 1,062 patients were admitted with STEMI, and of these 87 patients were included.

The inclusion criteria were: 1) first time STEMI; 2) no prior treatment with statins or other lipid lowering drugs; and 3) a non-significant lesion in one of the two non-culprit coronary arteries (angiographic diameter stenosis >20% and <50%).

The exclusion criteria were: 1) age below 18 or above 81 years; 2) unconscious patients; 3) serum creatinine >176 µmol/l; 4) hypothyroidism (TSH >1.5 x ULN [upper limit of normal]); 5) current liver disease (Alkaline phosphatase >2 x ULN); 6) unexplained creatine kinase >3 x ULN; 7) alcohol or drug abuse within the last five years; 8) prior myopathy or serious hypersensitivity reaction caused by statins; 9) women with child-bearing potential who were not using chemical or mechanical contraception; 10) pregnant or breastfeeding women; 11) history of malignancy unless a disease-free period of more than five years was present; 12) participation in another randomized trial; 13) treatment with cyclosporine or fibrates.

All patients provided written, informed consent, and the study was performed in accordance with the rules for good clinical practice (GCP) and monitored by the GCP-department at Odense University Hospital.

All study patients were angiographic re-examined with a supplementary IVUS of a study plaque in a non-IRA. It was intended to investigate the patient the next day after the primary PCI procedure, but during either weekends or holydays, the examination was done at the first coming workday.

The patients were then treated with atorvastatin 80 mg/day and block randomized (1:1) by envelope method to additional ezetimibe 10 mg/day or placebo. The randomization procedure was administered by the hospital pharmacy who also supplied the blinded study medicine.

IVUS including iMap was performed after 1 year.

Endpoints

The primary endpoint was change in NC after 12 months in a non-infarct related coronary artery not previously revascularized in statin naïve patients admitted with STEMI. Other iMap endpoints were change in FT, LT, and CT together with changes in total atheroma volume (TAV) and percentage atheroma volume (PAV).

IVUS-procedure

The IVUS pullback was performed using the iLab System with a mechanical 40 MHz Atlantis SR Pro IVUS catheter (Both Boston Scientific, USA). Unfractionated heparin (5,000 IE) was administered prior to the procedure. The catheter position was determined and matched angiographically by visualization of side-branches (point de repere). Nitroglycerin 200 µg was administered intracoronary prior to the pullback. An automatic pullback was performed with a standard pullback speed of 0.5 mm/s and was terminated when reaching the guiding catheter or the aorta. iMap data was obtained in every 30th frame (0.5 mm) but was unobtainable in very large vessels giving need for deviation from the standard scanning depth of 5 mm.

All examination cases were assigned to randomly generated examination ID numbers corresponding to a list managed by a person not involved in the study and archived to DVD's.

IVUS off-line analysis

IVUS pullbacks were analyzed by a single dedicated operator (MH), who was blinded both to treatment assignment and temporal sequence of paired examinations. All analysis was carried out using Echoplaque 4.0 (Indec Medical Systems, Santa Clara, CA, USA). Baseline and the corresponding follow-up pullbacks were carefully matched to include as much overlapping segment as possible respecting the need for sufficient picture quality. Cross sectional area (CSA) for Lumen and the external elastic membrane (EEM) were traced manually in every frame containing iMap data, i.e. for every 30th frame (0.5 mm). In 25 patients, IVUS pullbacks were performed without a guidewire, and in other 10 patients, double pullbacks with and without guidewire were done in order of determine the impact of the guidewire artifact on the iMap assessment. In patients, where only pullbacks without guidewire were done at baseline, the same approach was used at follow-up. In pullbacks performed with guidewire, the resulting artifact was omitted from the iMap analysis by applying special masks called "No-fly zones" within EchoPlaque. The preset angle of the "no-fly zone" was left unchanged. The frame with maximum PAV in every pullback was determined. A volumetric assertion of the 10 mm most diseased segment was performed with respect to gray scale

IVUS measurements and iMap data. Vessel and lumen volume was calculated within Echoplaque as respectively $\sum EEM_{CSA}$ and $\sum LUMEN_{CSA}$, where EEM_{CSA} =external elastic membrane cross-sectional area, and $LUMEN_{CSA}$ =luminal cross-sectional area. TAV was defined as vessel volume minus lumen volume, and PAV was defined as $(TAV/vessel\ volume) \times 100\%$. Echoplaque calculated volumetric iMap data after definition of lumen, EEM contours, and “no-fly zones”. For iMap analysis, “Confidence Level Lower Bound” was set at 0 percent and “Necrotic Confidence Upper Bound” was set at 100 percent.

Statistical analysis

All statistical analysis was performed with SPSS 21.0 (IBM Corporation, New York, USA). Categorical data are presented as frequencies and percentages and compared using chi-square test. Normal distributed continuous data are presented as mean \pm SD and compared using a Student’s t-test or presented as median with inter quartile range (IQR) and compared using the Mann-Whitney U test when normality testing failed. A Shapiro-Wilk test was used together with Q-Q-plots for this assessment. A paired samples t-test or Wilcoxon Matched-Pair Signed-Rank test was used in comparison of changes from baseline to follow-up. A two-sided p-value of <0.05 was considered statistical significant. Linear correlations were tested with Pearsons correlation and in case of non-linearity, a Spearman correlation was used.

The sample size calculation was based upon an estimation approach, because the effect of atorvastatin in combination with ezetimibe on plaque components was unknown. We estimated a change in NC of 25% in the ezetimibe group and 15% in the placebo group with a SD of 16.5%, alpha error of 0.05, and a power of 80%. Thus, a minimum of 44 patients in each treatment group (a total of 88 patients) was pre-specified for enrolment.

Results

Patient population

A total of 87 patients were enrolled in the study and assigned to the ezetimibe or placebo treatment arms (ezetimibe, n=43; placebo, n=44) on top of treatment with atorvastatin 80 mg. Mean time from primary PCI to IVUS of a study lesion in a non-infarct related artery was 29.3 ± 16.5 hours. Baseline examinations failed for 1 person. Four patients were lost to invasive follow-up (1 patient died of sudden cardiac arrest, 1 patient died of pulmonary cancer found after baseline examination, 1 patient got a disseminated cancer, and 1 patient withdrew consent). In 5 patients, either baseline or follow-up IVUS of the target vessel could not be achieved or was unsuitable for analysis. The mean

follow-up time was 353 ± 14 days in the ezetimibe group and 356 ± 13 days in the placebo group ($p=ns$). Seventy-seven patients completed IVUS follow-up, but iMap data was only available in 66 patients (iMap data in 3 patients was lost during export to DVD, in 3 patients adjustment to the scanning depth was done, and in the remaining 6 patients, iMap data was not processed prior to export as a result of a system upgrade).

Baseline characteristics are listed in **table 1**. The two groups were well balanced. Two patients in the ezetimibe group had suspected adverse events to atorvastatin: One patient had the statin therapy changed from atorvastatin to low dose rosuvastatin after 3 months due to elevated liver enzymes, and the other patient had to discontinue atorvastatin due to worsening of a preexisting rheumatic condition. In one patient in the placebo group the statin treatment was unintentionally changed to simvastatin 40 mg by the local hospital prior to initial discharge and the patient continued on that treatment. All patients were maintained in their designated treatment arm for the analysis in concordance with intention to treat.

Lipids

Cholesterol and LDL values at baseline and follow-up are presented in **table 2**. The baseline LDL values were significantly lower in the ezetimibe group compared to the placebo group (3.7 ± 0.7 mmol/l vs. 4.1 ± 0.9 mmol/l, $p=0.010$). Total cholesterol and LDL decreased respectively 50.7% and 66.7% in the ezetimibe group and 40.4% and 53.7% in the placebo group (all $p<0.001$). The ezetimibe group had significantly ($p<0.001$) greater reductions for both total cholesterol and LDL compared to the control group and more patients in the ezetimibe group reached recommended values of <1.8 mmol/l (86.0% vs. 50.0%, $p<0.001$). **Fig. 1** illustrates the correlation between baseline LDL values (x-axis) and respectively the absolute and relative changes in LDL after 12 months (y-axis). The absolute change correlated with baseline values, but the relative change did not.

Greyscale IVUS findings

Greyscale findings are presented in **table 3**. There was no significant difference between groups in PAV, TAV, vessel, or lumen volume at baseline between the two groups. At follow-up, TAV, PAV, vessel, and lumen volume in the entire region changed significantly in the ezetimibe group, but not in the placebo group.

For the 10 mm most diseased segment, vessel volume, TAV, and PAV changed significantly from baseline to follow up in both groups, but none of the changes differed significantly between the groups.

iMap findings

The iMap findings are presented in **table 4** and depicted in **fig. 2**. In the entire region, the distribution of tissue components was balanced between the two groups. For both groups there was a significant decrease in FT after 12 months. There was no change in NC in the ezetimibe group, but in the placebo group, we found a modest increase in the relative distribution of NC. In none of the groups, there was any change from baseline in LT or CT.

In the most diseased 10 mm segment, we found a similar relative distribution of tissue components as in the entire region, and there was a similar absolute decrease in fibrotic tissue, but no changes in LT, CT, or NC.

Discussion

Addition of ezetimibe to atorvastatin 80 mg/day for twelve months resulted in a significantly 25% greater relative reduction in LDL compared to atorvastatin as monotherapy. In the ezetimibe group only, IVUS of the entire segment showed a significant reduction in TAV and PAV together with a reduction in total luminal and vessel volume. In the 10 mm most diseased segment, vessel volume, TAV, and PAV were reduced in both groups, and no change in vessel volume or lumen volume was found. The iMap data showed no significant change in necrotic core, whereas a significant decrease in FT was found in both groups.

The numerical reduction of PAV in the entire region was comparable to the results for the atorvastatin arm of *The Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin versus Atorvastatin* (SATURN)(22) after 2 years of follow-up and to the *Effect of very high-intensity statin therapy on regression of coronary atherosclerosis* study (ASTEROID)(23) although the latter used high dose rosuvastatin for 2 years.

The relatively high degree of absolute regression despite shorter time of follow-up in our study probably reflects, that it was based statin-naïve patients selected from a high-risk STEMI population, and correspondingly, our baseline levels for both PAV and TAV tended to be higher than in studies on populations with lower risk. In both groups, the reduction in TAV in the most diseased 10 mm segment was similar to the findings in the atorvastatin arm of *Reversal of*

Atherosclerosis with Aggressive Lipid Lowering study (REVERSAL)(24) ($-4.2 \pm 12.8 \text{ mm}^3$), and to the findings in the ASTEROID study ($-6.1 \pm 10.1 \text{ mm}^3$).

In the *Integrated biomarker imaging study* (IBIS-4) trial, 103 STEMI patients underwent IVUS in a non-infarct related artery and were treated with rosuvastatin 40 mg/day and followed for 13 months. Like in the present study, the IBIS-4 study showed no change in the NC, but there was a decrease in fibrous tissue. Furthermore, they found a significant decrease in PAV for the entire region together with a decrease in TAV and PAV in the 10 mm most diseased segment. Although 9.8% of the patients were treated with statin prior to enrollment, the findings were similar to the findings in the present trial.

Several other studies have investigated changes in plaque composition associated with statins using VH-IVUS(19, 13) with varying results. In a previous study in our institution comparing high dose vs. low dose rosuvastatin in STEMI patients, a reduction in NC was found in the high dose group together with a reduction of fibrous tissue(14). In another study evaluating fluvastatin in patients with stable angina, an increase of fibrous tissue, a decrease in fibro-fatty tissue but no change in NC was found(17). Both of these studies used VH-IVUS(14, 17). No studies have so far used the tissue characterization with iMap for this purpose. The effect of ezetimibe in combination with atorvastatin 80 mg/day compared to standard statin treatment has previously only been studied in a single VH-IVUS based trial in patients with stable angina(25). No significant difference in plaque composition between treatment arms was found although a relative but small significant increase in NC in the placebo group was observed.

The benefits of statin treatment with respect to patient outcome are well established(26, 3, 27). Furthermore, use of more potent statins like atorvastatin and rosuvastatin results in further improvement in clinical outcome compared to less potent statins(3, 4, 28). This is in agreement with the findings in several randomized trials using serial IVUS based on quantitative volumetric plaque measurements, where statins have been shown to result in slowdown of plaque progression or even plaque regression, when high potent statins are used(29, 30, 23, 24, 31). In the present trial, an aggressive lipid treatment was applied in both intervention arms, and accordingly, plaque regression in the most diseased segment was induced in both groups. A positive linear relationship between reduced plaque progression assessed by IVUS and clinical outcome has been reported(32). Thus, IVUS has become the gold standard in longitudinal studies of plaque progression/regression and makes it achievable to “screen” novel drugs for potential effects prior to their evaluation in larger expensive clinical outcome trials(20).

Recently, the results of the *IMProved Reduction of Outcomes: The Vytorin Efficacy International Trial* (IMPROVE-IT) has been presented(33, 34). In this large multicenter trial based on 18,144 randomized patients, the effect of ezetimibe compared to placebo as addition to simvastatin 40 mg in high-risk acute coronary syndrome (ACS) patients was evaluated. A significant reduction in the primary endpoint (a composite of cardiovascular death, myocardial infarction, unstable angina pectoris, coronary revascularization beyond 30 days and stroke) was found. IMPROVE-IT was the first trial showing a beneficial clinical effect of LDL-reduction in high-risk ACS patients not mediated by statin therapy only. This result corresponds well with the conception of “lower is better” with respect to LDL-reduction, and together the findings in the present trial, there is reason to assume, that additional clinical benefits might be obtainable by lowering LDL even further.

Study limitations

The limited number of patients is a major limitation as change in iMap subtypes have been shown to be minor within the given timeframe. The numbers included in the iMap-analysis were further reduced of technical reasons. Furthermore the impact of the guidewire artifact – although adjusted for – may have led to over- or underestimation of changes in necrotic core. Compared to Virtual Histology, only one ex vivo validation study has been published for iMap, and its implementation on an in vivo STEMI population might yield different results.

Conclusion

Ezetimibe in combination with high dose atorvastatin treatment for twelve months was associated with a reduction in TAV, while FT was reduced in both the ezetimibe and placebo groups.

Funding

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Conflicts of interests

LOJ has received research grants from Terumo, Biotronik, St Jude Medical, and Biosensors to her institution and honoraria from Abbott Vascular, AstraZeneca, St Jude Medical and Biotronik. The other authors had nothing to disclose.

Perspectives

Competency in Medical Knowledge

IVUS determined plaque regression mediated by statins correlates with clinical patient outcome.

Ezetimibe enhances plaque reduction, but do not alter iMap assessed plaque composition.

Competency in Patient Care:

Ezetimibe could contribute to optimize compliance with target lipid values as setup by clinical guidelines.

Translational Outlook

Plaque characterization with iMap may predict vulnerability in non-infarcted coronary arteries, but in the present study, intensive lipid lowering therapy did not induce changes in composition detectable by iMap after 12 months, and is thus not suitable for short-term detection of minor influence of lipid lowering agents.

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Figure Legends

Figure 1: Scatterplots depicting absolute (to the left) and relative (to the right) LDL changes from baseline vs. baseline values for the placebo and ezetimibe groups. Absolute change in LDL correlates positively with baseline values.

Figure 2: Graphical presentation of absolute changes in iMap composition in entire region and the 10 mm most diseased segment. The p-values are supplied when <0.05 .

Table 1: Baseline and procedure characteristics

	Ezetimibe (n=43)	Placebo (n=44)	p
Age, years	55.3±11.0	57.2±9.1	0.38
Male gender, n (%)	39 (90.7)	36 (81.8)	0.23
Hypertension, n (%)	7 (16.3)	8 (18.2)	0.81
Current smoking, n (%)	25 (58.1)	23 (52.3)	0.74
Family disposition, n (%)	19 (44.2)	22 (50.0)	0.59
Diabetes, n (%)	1 (2.3)	1 (2.3)	0.99
Total Cholesterol >5 mmol/l, n (%)	32 (74.4)	30 (68.2)	0.64
HbA1c (mmol/mol)	39.0 (36.0, 41.0)	37.0 (36.0, 41.0)	0.98
Systolic blood pressure, mmHg	129.7±21.4	125.0±19.8	0.29
Diastolic blood pressure, mmHg	78.1±18.2	75.1±10.2	0.34
Heart rate, beats/min	71.0 (60.0, 83.0)	68.0 (60.0, 81.5)	0.62
Weight	86.0 (78.0, 95.0)	85.0 (76.8, 94.0)	0.81
BMI (kg/m ²)	27.3 (25.1, 29.2)	27.4 (24.6, 29.4)	0.99
LVEF	50.0 (40.0, 55.0)	50.0 (45.0, 60.0)	0.20
Single vessel disease, n (%)	33 (76.7)	29 (65.9)	0.43
Infarct related artery, n (%)			0.11
RCA	11 (25.6)	20 (45.4)	
LAD	27 (48.3)	15 (34.1)	
LCx	5 (14.9)	9 (15.9)	
Study vessel, n (%)			0.07
RCA	16 (37.2)	11 (25.0)	
LAD	12 (27.9)	23 (52.3)	
LCx	15 (34.9)	10 (22.7)	
Prior cardiovascular medications, n (%)			
β-blockers	0 (0.0)	2 (4.5)	0.16
Calcium antagonists	4 (9.3)	3 (6.8)	0.67
ACE inhibitors	4 (9.3)	3 (6.8)	0.67
ATII inhibitors	0 (0.0)	1 (2.3)	0.32
Diuretics	1 (2.3)	3 (6.8)	0.32
Guidewire used during pullbacks, n (%)			0.81
Present	27 (69.2)	26 (66.7)	
Not present	12 (30.8)	13 (33.3)	

Table 2: Lipid values

	Ezetimibe n=39 Mean±SD	Placebo n=41 Mean±SD	p
Total cholesterol			
Baseline (mmol/l)	5.3±0.9	5.7±1.0	0.09
Follow-up (mmol/l)	2.9±1.0	3.5±0.7	0.001
Change (mmol/l)	-2.5±1.0	-2.3±0.7	0.039
Percent change median % (IQR)	-46.8±16.4	-38.9±9.7	<0.001
p-value baseline vs follow-up	<0.001	<0.001	<0.001
HDL			
Baseline (mmol/l)	1.1±0.3	1.1±0.3	0.59
Follow-up (mmol/l)	1.1±0.3	1.1±0.3	0.48
Change (mmol/l)	0.06±0.3	-0.03±0.2	0.50
Percent change median % (IQR)	-3.6±25.8	-1.1±18.1	0.27
p-value baseline vs follow-up	0.14	0.36	
LDL			
Baseline (mmol/l)	3.7±0.7	4.1±0.9	0.010
Follow-up (mmol/l)	1.4±0.8	2.0±0.5	<0.001
Change (mmol/l)	-2.3±0.9	-2.2±0.7	0.29
Percent change median % (IQR)	-62.0±19.2	-52.4±10.9	<0.001
p-value baseline vs follow-up	<0.001	<0.001	
Triglycerides			
Baseline (mmol/l)	1.3±0.8	1.2±0.8	0.55
Follow-up (mmol/l)	0.9±0.8	1.0±0.6	0.07
Change (mmol/l)	-0.3±0.9	-0.1±0.7	0.08
Percent change median % (IQR)	-18.5±50.1	4.0±54.0	0.03
p-value baseline vs follow-up	0.025	0.24	

Table 3: Greyscale IVUS results

	Entire pullback			Most diseased 10 mm		
	Ezetimibe	Placebo	p	Ezetimibe	Placebo	p
Lesion length, mm	34.4±9.0	35.4±10.9	0.84	-	-	-
Vessel Volume, mm³						
Baseline	513.7 (392.7, 716.5)	533.8 (359.3, 711.8)	0.93	164.9 (123.0, 186.4)	146.8 (126.9, 188.6)	0.64
Follow-up	491.4 (364.8, 573.0)	529.5 (335.3, 676.6)	0.57	151.1 (115.9, 192.4)	145.4 (113.6, 173.5)	0.65
Change	-29.4 (-44.3, -4.6)*	-11.9 (-39.6, 19.7)	0.12	-5.9 (-16.2, 2.6)*	-7.0 (-17.3, 6.1)*	0.83
Lumen Volume mm³						
Baseline	311.5 (236.9, 391.7)	324.6 (187.5, 422.0)	0.85	81.5 (61.2, 105.5)	69.4 (58.8, 92.9)	0.09
Follow-up	293.2 (213.7, 372.1)	326.0 (194.7, 394.8)	0.80	83.1 (65.3, 108.6)	71.7 (55.7, 91.6)	0.07
Change	-12.0 (-29.2, 4.3)*	-6.9 (-22.8, 16.9)	0.21	-0.9(-7.7, 5.6)	-1.9 (-7.6, 6.5)	0.84
TAV mm³						
Baseline	200.0 (135.6, 311.9)	218.4 (163.5, 307.9)	0.63	67.4 (48.3, 95.2)	74.5 (54.9, 99.6)	0.42
Follow-up	189.3 (126.4, 269.1)	212.2 (149.9, 394.8)	0.39	60.0 (42.2, 82.0)	68.0 (44.9, 93.6)	0.32
Change	-11.3 (-25.5, -2.4)*	-10.3 (-28.6, 9.8)	0.56	-4.0 (-11.6, 2.4)*	-5.3 (-14.6, 4.2)*	0.57
PAV %						
Baseline	40.1±8.6	43.3±9.4	0.12	43.8 (34.5, 51.8)	50.2 (40.9, 56.3)	0.034
Follow-up	39.2±9.0	42.2±10.7	0.18	41.7 (34.0, 49.0)	46.5 (36.6, 60.2)	0.07
Change	-0.9±2.6*	-1.1±3.7	0.91	-2.2 (-5.4, 0.7)*	-1.0 (-5.3, 1.0)*	0.67
Max PAV %						
Baseline	70.6±28.4	79.9±38.8	0.23	54.1 (43.6, 61.7)	61.3 (47.1, 70.9)	0.041
Follow-up	65.3±28.2	73.3±36.8	0.28	40.6 (32.8, 52.4)	48.1 (39.2, 62.9)	0.52
Change	-0.8±6.7*	-2.7±8.2*	0.53	-10.0 (16.6, -3.3)*	-6.8 (-13.7, -1.4)*	0.13

Greyscale IVUS findings in the entire pullback and the most diseased 10 mm segment. Data presented as Mean±SD / median (IQR). Significant changes from baseline: * p<0.05

Table 4: iMap results

	Entire pullback			Most diseased 10 mm		
	Ezetimibe	Placebo	p	Ezetimibe	Placebo	p
Lesion length	33.7±8.8	36.7±10.9	0.23	-	-	-
FT, mm³						
Baseline	131.6±61.9	137.7±72.7	0.87	42.9 (28.1, 50.5)	37.5 (27.9, 47.7)	0.59
Follow-up	118.3±53.9	125.2±65.2	0.64	32.3 (25.2, 44.9)	31.0 (23.3, 47.4)	0.72
Change	-13.3±18.3*	-12.6±20.8*	0.72	-4.0 (-10.3, -1.9)*	-5.4 (-10.6, -0.6)*	0.69
FT, %						
Baseline	65.1±12.1	63.8±12.7	0.76	70.0±14.1	65.9±15.1	0.31
Follow-up	63.7±10.3	60.5±12.5	0.25	67.9±13.7	63.7±15.1	0.28
Change	-1.3±6.7	-3.4±5.4*	0.18	-2.1±7.5	-2.2±7.2	0.95
LT, mm³						
Baseline	15.4 (9.5, 25.3)	17.8 (9.3, 27.1)	0.80	5.7±3.1	5.6±2.8	0.92
Follow-up	15.9 (10.3, 21.4)	18.6 (8.4, 26.5)	0.51	5.5±2.8	5.4±2.8	0.92
Change	0.0 (-3.3, 1.8)	-0.5 (-3.7, 4.3)	0.59	-0.2±1.9	-0.2±1.6	0.92
LT, %						
Baseline	9.0 (6.0, 10.0)	8.0 (7.0, 9.0)	0.71	9.1±3.3	8.8±3.3	0.68
Follow-up	9.0 (8.0, 10.0)	8.0 (7.0, 10.0)	0.37	9.9±3.8	9.4±3.2	0.45
Change	1.0 (-1.0, 2.0)	0.0 (-1.0, 2.0)	0.66	0.8±2.5	0.5±2.5	0.69
CT, mm³						
Baseline	0.9 (0.3, 1.8)	1.8 (0.5, 3.8)	0.06	0.2 (0.1, 0.9)	0.5 (0.2, 1.7)	0.17
Follow-up	0.8 (0.3, 1.3)	1.4 (0.7, 4.5)	0.038	0.2 (0.1, 0.6)	0.5 (0.1, 1.3)	0.12
Change	0.0 (-0.4, 0.4)	0.0 (-0.4, 0.6)	0.58	-0.1 (-0.2, 0.1)	-0.0 (-0.2, 0.3)	0.69
CT, %						
Baseline	0.0 (0.0, 1.0)	1.0 (0.0, 2.0)	0.019	0.6 (0.2, 1.4)	0.9 (0.4, 2.8)	0.15
Follow-up	0.0 (0.0, 1.0)	1.0 (0.0, 2.0)	0.006	0.6 (0.2, 1.3)	0.9 (0.5, 2.1)	0.08
Change	0.0 (0.0, 0.0)	0.0 (0.0, 1.0)	0.46	-0.0 (-0.3, 0.2)	0.0 (-0.5, 0.5)	0.83
NC, mm³						
Baseline	24.9 (11.9, 51.3)	29.4 (16.3, 78.5)	0.31	8.5 (4.6, 18.0)	10.2 (7.3, 21.9)	0.35
Follow-up	24.9 (15.3, 54.5)	32.0 (16.0, 88.7)	0.21	9.2 (4.2, 18.2)	11.0 (4.7, 22.9)	0.39
Change	-0.1 (-5.2, 4.3)	-0.7 (-6.0, 15.8)	0.35	-0.2 (-2.2, 2.3)	-0.3 (-2.7, 2.6)	0.78
NC, %						
Baseline	14.0 (7.0, 21.0)	17.0 (11.0, 24.0)	0.25	15.7 (10.8, 26.1)	19.0 (12.4, 35.1)	0.31
Follow-up	14.0 (10.0, 20.0)	20.0 (12.0, 29.0)	0.07	17.3 (12.5, 28.6)	20.2 (15.7, 36.5)	0.25
Change	1.0 (-1.0, 3.0)	1.0 (-1.0, 6.0)*	0.33	1.6 (-2.2, 4.7)	1.7 (-2.3, 6.9)	0.71

IVUS iMap results for the entire pullback and the most diseased 10 mm segment. Data presented as Mean±SD / median (IQR). Significant changes from baseline: * p<0.05

Figures

Change in LDL

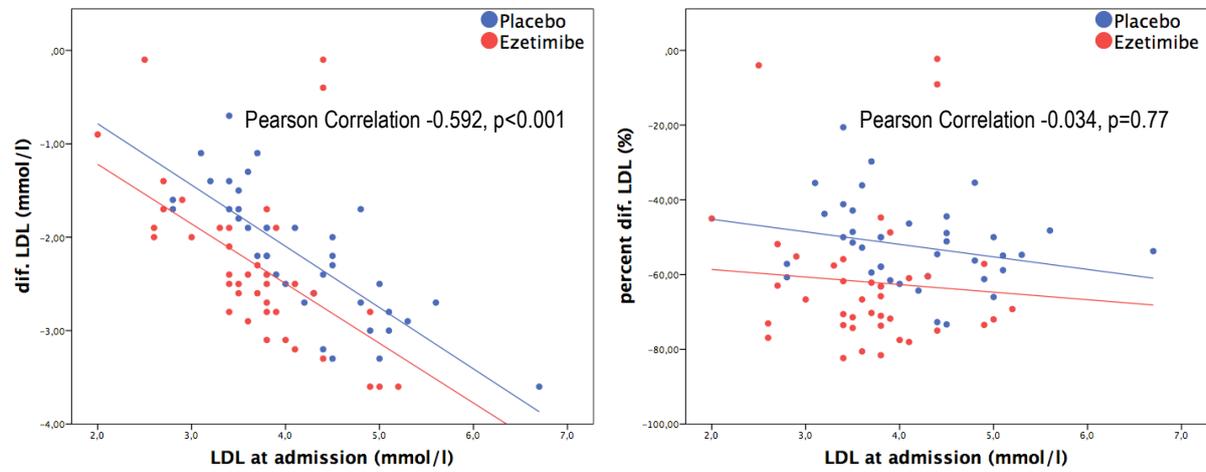
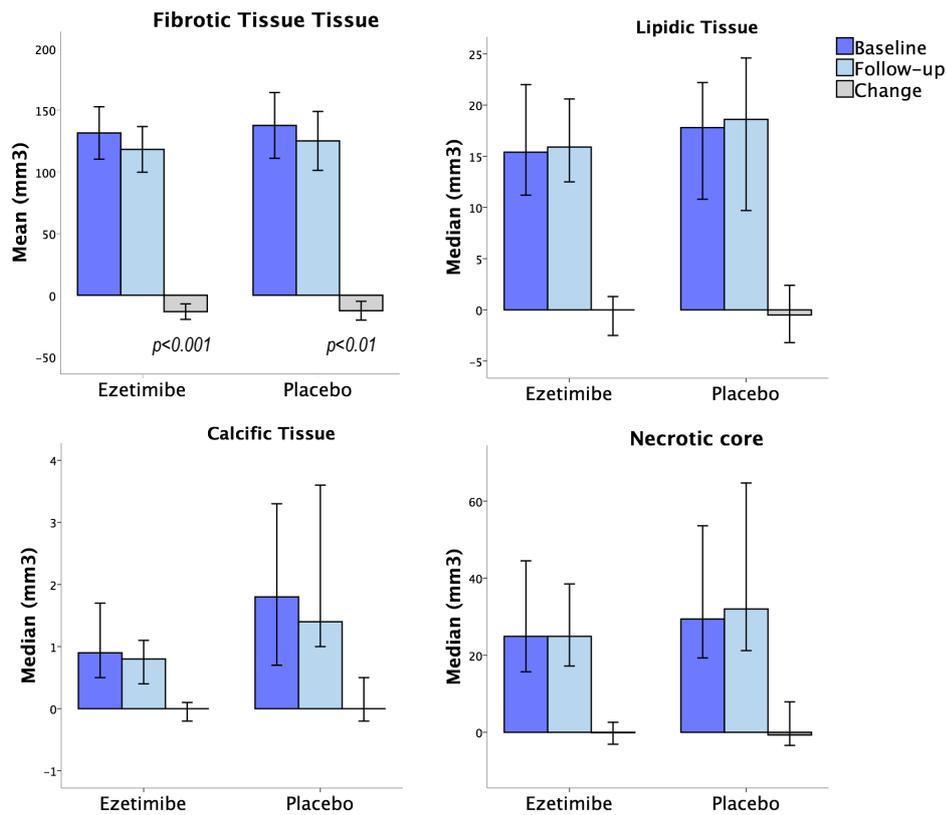


Figure 1

Entire region



Most diseased segment

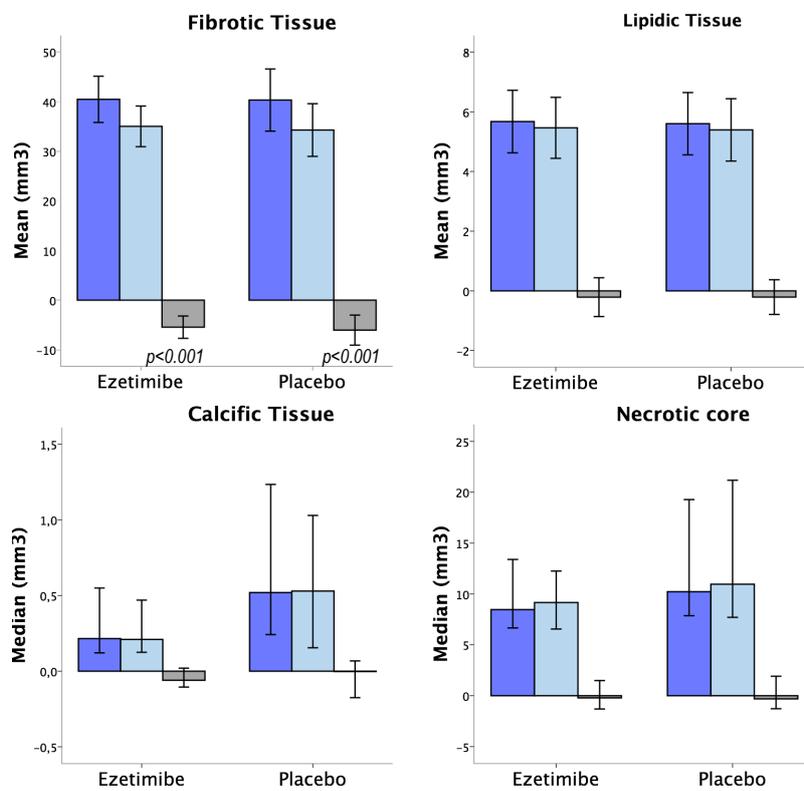


Figure 2

Paper 2

Influence of Ezetimibe on Plaque Morphology in Patients with ST
Elevation Myocardial Infarction assessed by Optical Coherence
Tomography: The OCTIVUS trial

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Abstract

Background:

The benefits of statin treatment are well established. Further reduction in levels of Low Density Lipoprotein (LDL) can be obtained by additional treatment with the cholesterol absorption inhibitor ezetimibe. The aim of the trial was to examine the influence of ezetimibe on plaque morphology in patients with ST-segment Elevation Myocardial Infarction (STEMI) with respect to fibrous cap thickness (FCT) and arcs for lipid plaque, calcific plaque, and macrophages using Optical Coherence Tomography (OCT).

Methods and results:

In 87 statin naïve patients with STEMI treated with primary percutaneous intervention, a study plaque was assessed with OCT in a non-infarct related coronary artery at baseline and after 12 months. All patients were treated with atorvastatin 80 mg and randomized (1:1) to ezetimibe 10 mg (n=43) or placebo (n=44). An increase in median FCT (ezetimibe 200 (140, 260) μm to 240 (190, 305) μm (p=0.002) vs. placebo 205 (135, 260) μm to 230 (180, 270) μm (p<0.001), between groups p=ns), a reduction in lipid arc (ezetimibe 1728.5 (1022.5, 3904.7) $^{\circ}$ to 1164.5 (736.6, 2580.1) $^{\circ}$ (p=0.001) vs. placebo 1671.6 (978.3, 2868.7) $^{\circ}$ to 1373.7 (791.2, 2267.3) $^{\circ}$ (p=0.019), between groups p=ns), and macrophage arc (ezetimibe 1730.3 (965.7, 2984.4) $^{\circ}$ to 1324.8 (819.0, 2819.7) $^{\circ}$ (p<0.05) vs. placebo 1570.5 (794.7, 3016.8) $^{\circ}$ to 1418.9 (584.1, 2501.1) $^{\circ}$ (p<0.01), between groups p=ns) were observed.

Conclusion:

LDL lowering with atorvastatin 80 mg for 12 months increased FCT and decreased lipid and macrophage content. Supplementary therapy with ezetimibe had no further effect.

Clinical Trial Registration:

Clinicaltrials.org, NCT01385631

Key Words:

STEMI, OCT, ezetimibe, atorvastatin

Introduction

Plaque instability and rupture is preceded by accumulation of lipids within the intimal layer of the coronary vessel wall. Some plaques are prone to become unstable, and the tissue composition of the plaque is of importance, since development of inflammatory processes, infiltration with macrophages, and accumulation of necrotic tissue are related to plaque progression towards greater instability¹.

Pathological studies have demonstrated, that plaque ruptures are more likely to develop in plaques with a lumen-near necrotic core covered by a thin fibrous cap (Thin Cap Fibroatheroma, TCFA)². The benefits of statin treatment are well established in clinical trials³, and it has been shown, that more aggressive low-density lipoprotein (LDL) lowering with statins reduce mortality even further⁴. The mechanism is thought to rely on plaque stabilization through a combination of plaque regression and increased fibroatheroma cap thickness (FCT), and studies have demonstrated, that intensive statin therapy can halt or reverse the plaque progression⁵⁻⁷ and reduce plaque vulnerability by increasing FCT⁸.

Optical Coherence Tomography (OCT) – a near infrared light-based imaging modality – is due to its very high spatial resolution (~10 µm) the leading imaging modality in the assessment of FCT and other lumen near structures like thrombi, dissections, intimal erosions, and plaque ruptures. OCT is limited by its relatively poor tissue penetration and can often not assess structures like the external elastical membrane (EEM) or structures beneath lipid tissue and is thus not suitable for volumetric plaque assessment.

Additional optimization of patient treatment by use of other lipid lowering agents than statins have the potential to improve patient outcome even further as recently shown in the *IMProved Reduction of Outcomes: The Vytarin Efficacy International Trial (IMPROVE-IT)*⁹.

The aim of the *Plaque Composition in Patients with acute ST Segment Elevation Myocardial Infarction assessed by Optical Coherence Tomography and IntraVascular*

UltraSound with iMap (OCTIVUS) trial was to evaluate the influence of the cholesterol absorption inhibitor ezetimibe (Merck Sharp & Dohme, MSD, Kenilworth, New Jersey, USA) in addition to high dose atorvastatin on coronary plaque morphology in a cohort of statin naïve patients treated with primary percutaneous intervention (PPCI) due to ST elevation Myocardial Infarction (STEMI). This was accomplished by use of OCT with focus on FCT, lipid and calcium content, macrophage infiltration, and cholesterol crystals in a plaque of a non-infarct related coronary artery.

Patients and methods

Setting and design

The OCTIVUS trial (NCT01385631) was a single center double blinded randomized trial including patients with first time STEMI during their admission for PPCI. The study was approved by the Danish Ethical Committee (project ID: S-201 001 00) and the Danish Medical Agency (EudraCTnummer 2010-022604-45).

The inclusion criteria were: 1) first time STEMI; 2) no prior treatment with statins or other lipid lowering drugs; and 3) a non-significant lesion in one of the two non-infarct related arteries (IRA) (angiographic diameter stenosis >20% and <50%).

The exclusion criteria were: 1) age below 18 or above 81 years; 2) unconscious patients; 3) serum creatinine >176 $\mu\text{mol/l}$; 4) hypothyroidism (TSH >1.5 x ULN [upper limit of normal]); 5) current liver disease (Alkaline phosphatase >2 x ULN); 6) unexplained creatine kinase >3 x ULN; 7) alcohol or drug abuse within the last five years; 8) prior myopathy or serious hypersensitivity reaction caused by statins; 9) women with child-bearing potential who were not using chemical or mechanical contraception; 10) pregnant or breastfeeding women; 11) history of malignancy unless a disease-free period of more than five years was

present; 12) participation in another randomized trial; 13) treatment with cyclosporine or fibrates.

All patients provided written, informed consent, and the study was performed in accordance with the rules for good clinical practice (GCP) and monitored by the GCP-department of Odense University Hospital.

All study patients underwent repeated angiographic examination with OCT of a study plaque in a non-IRA. It was intended to investigate the patient the next day after the primary PCI procedure, but during either weekends or holydays, the examination was done at the first coming workday.

The patients were hereafter designated to atorvastatin 80 mg/day and randomized (1:1) to additional ezetimibe 10 mg/day or placebo. The Odense University Hospital Pharmacy supplied the blinded study medication and administered the envelope randomization procedure.

Patients were followed with clinical controls after 1, 3, and 6 months, and the follow up OCT was performed after 1 year.

Endpoints

The primary endpoint was the change in FCT after 12 months compared to baseline in a non-infarct related coronary artery not previously revascularized in statin naïve STEMI patients. Secondary endpoints were changes in minimum, maximum and matched minimum baseline FCT, lipid arc, lipocalcific arc, calcific arc, macrophage arc, numbers of TCFA's and thick cap fibroatheromas (ThCFA's) and cholesterol crystals.

OCT-procedure

OCT was performed with the Lightlab Cx7 or the Ilumien System with a Dragonfly OCT catheter (Sct Jude Medical, Minnesota, USA). The catheters were initially flushed with contrast (Visipaque[®]) and wiped with heparinized saline water activating the hydrophilic coating. Catheter placement was guided angiographically by visualization of side-branches (point de repere). The pullback was initiated automatically by manual flushing of the vessel with 20 ml of contrast (Visipaque[®]). Pullback speed was 20 mm/s, and the total pullback distance of the system was 55 mm. Repeated pullback was performed in case of insufficient image quality or incomplete acquisition of the segment of interest.

All examinations were assigned to randomly generated examination ID numbers corresponding to a list managed by a person not involved in the study and archived to DVD's.

OCT off-line analysis

OCT pullbacks were analyzed using proprietary software developed by Sct Jude Medical (Sct Jude Medical, Minnesota, USA). Plaque evaluation was performed in accordance with previously published reviews and recommendations¹⁰⁻¹². A matching segment was identified and processed with the automatic lumen contour with manual correction when needed. A frame for every 1 mm was analyzed in addition to the first and last frame in the segment. Arcs for lipid, calcium and combined lipid and calcium (lipocalc arc) were measured together with macrophage arc, and the occurrence of cholesterol crystals was registered. For every pullback, the minimum, maximum and cumulative total for every arc was registered. Examples are depicted in **fig. 1**. For lipid arc, the numbers of individual arcs measuring at least 90 degrees were registered separately. A fibroatheroma was defined as a segment of the vessel wall with high attenuation underneath a fibrous cap and combined with loss of an

identifiable EEM. FCT was defined as the distance from the intimal-lumen border to the lumen edge of the lipid pool characterized by a rapid rise in attenuation. For every lipid segment identified, a FCT was measured and characterized as TCFA if less than 65 μm . Otherwise the cap was characterized as ThCFA. TCFA length was measured in a frame-by-frame manner, and two or more segments were regarded as one TCFA unless distance in between was more than 5 mm (25 frames). The frame with the minimum FCT at baseline was matched with the corresponding frame at follow-up, and the same FCT was re-measured for comparison.

Statistical analysis

All statistical analysis was performed with SPSS 22.0 (IBM Corporation, New York, USA). Categorical data are presented as frequencies and percentages and compared using chi-square test. Normal distributed continuous data are presented as mean \pm SD and compared using a Student's t-test or presented as median with inter quartile range (IQR) and compared using the Mann-Whitney U test when normality testing failed. A Shapiro-Wilks test and Q-Q plots were used for normality testing. A paired samples t-test or Wilcoxon Matched-Pair Signed-Rank test was used in comparison of changes from baseline to follow-up. A two-sided p-value of <0.05 was considered statistical significant. Intraclass Correlation statistics (ICC) using "Two-way mixed, absolute agreement" was used for interobserver variation analysis.

Results

Patient population

Flow-chart regarding screening, enrollment and follow-up is depicted in **fig. 2**. In the period June 2011 to June 2013 a total of 1062 patients were admitted with STEMI, and of these 87

patients were enrolled in the study and assigned to the ezetimibe (n=43) or placebo (n=44) treatment arms. Baseline examinations failed for 1 person. Four patients were lost to invasive follow-up (2 patients died, 1 patient got cancer, and 1 patient withdrew consent). OCT at baseline or follow-up could not be achieved or was unsuitable for analysis in 6 patients. Thus 76 patients had complete OCT baseline and follow-up data. Mean time to follow-up was 354.2 ± 13.3 days and did not differ significantly between the two groups.

Baseline characteristics are listed in **table 1**, and the two groups were well balanced. Two patients in the ezetimibe group had suspected adverse events to atorvastatin: One patient was switched from atorvastatin to low dose rosuvastatin after 3 months due to elevated liver enzymes, and the other patient had to discontinue atorvastatin due to worsening of a preexisting rheumatic condition. One patient in the placebo group was unintentionally switched to simvastatin 40 mg by the local hospital prior to initial discharge within the first week of follow-up and continued on this treatment unnoticed until final follow-up examination. All analysis was performed on an intention-to-treat basis.

Lipids

Lipid values at baseline and follow-up are presented in **table 2**. The baseline mean LDL value was significantly lower in the ezetimibe group. Total cholesterol decreased with 50.7% in the ezetimibe group and 40.4% in the placebo group ($p < 0.01$ between groups), and correspondingly LDL decreased with 66.7% vs. 53.7% ($p < 0.001$ between groups). More patients in the ezetimibe group LDL values of < 1.8 mmol/l (86.0% vs. 50.0%, $p < 0.001$). HDL was unchanged from baseline in both groups, while triglycerides were reduced in the ezetimibe group. The LDL/HDL ratio was significantly reduced in both groups, with a greater reduction in the ezetimibe group.

In **fig. 3**, a scatter plot illustrates the correlation between baseline LDL values (x-axis) and respectively the absolute and relative changes in LDL after 12 months (y-axis). The absolute change is correlated with baseline values, while this was not the case with the relative change.

OCT findings

Results are presented in **table 3**. Mean and minimum FCT for all fibroatheromas and FCT of the matched minimum FCT at follow-up were increased in both groups. No change in the maximum FCT was found. At baseline, 13 TCFAs's were identified in 10 patients in the ezetimibe group and 12 TCFA's in 9 patients in the placebo group (between groups, $p=0.84$). At follow-up, TCFAs were reduced to 4 ($p<0.05$) in the ezetimibe group and 5 in the placebo group ($p<0.01$), between groups $p=ns$. Similar, we found at baseline 474 frames with ThCFA's in the ezetimibe group and 447 frames in the placebo group ($p=ns$). At follow-up, this was reduced to 418 frames in the ezetimibe group and 410 frames in the placebo group ($p=ns$ between groups and baseline vs. follow-up). With respect to plaque features, macrophage arc and lipid arc was significantly reduced in both groups, while lipocalcific arc did not change statistical significant from baseline. The number of lipid quadrants ≥ 90 degrees was reduced but only significantly in the ezetimibe group (8.5 (12.0) to 5 (13.0) ($p<0.05$) vs. 7.5 (9.0) to 6 (12.0) ($p=ns$)). A statistical significant increase of calcium arc was found in the placebo group. At baseline, cholesterol crystals were identified in 34 patients (placebo 21, ezetimibe 13, $p<0.05$). There was no change in numbers of cholesterol crystals in either group, but the degree of change differed between groups ((placebo 64 to 46, $p=ns$ vs. 41 to 50, $p=ns$), between groups $p<0.05$). Examples of OCT findings in corresponding frames from baseline to follow-up are illustrated in **fig. 4**.

We examined for correlation between percentage changes in mean and minimum FCT, lipid arc, calcium arc, lipocalcific arc, and macrophage arc with the percentage changes in LDL/HDL ratio (Pearson Correlation -0.16, -0.08, 0.08, -0.19, 0.14 and 0.06 respectively) and baseline LDL (Pearson Correlation -0.18, -0.07, -0.04, -0.00, 0.11 and 0.02 respectively) but found none to be significant.

Reproducibility

An interobserver reliability analysis was performed in 10 randomly selected cases with the corresponding baseline and follow-up examinations (20 pullbacks in total) all analyzed by two independently dedicated observers (LA and MH) with respect to FCT, lipid arc, macrophage arc, calcium arc, and lipocalcific arc. Numbers of identified frames with ThCFA was compared, and FCT analysis was done in 70 matched frames containing a fibrous cap at baseline. By ICC analysis there was found to be excellent correlation for lipid arc, and lipocalc arc (0.87, 0.99, and 0.98 respectively), and good correlation for FCT, macrophage arc, and calcium arc (0.77, 0.74, and 0.75). The ICC for numbers of identified ThCFA's was excellent (0.92).

Discussion

The present study evaluated the influence on coronary plaque morphology of ezetimibe in addition to high dose statin in STEMI patients. The addition of ezetimibe to high dose statin resulted in a significantly larger relative reduction in total cholesterol, LDL, and triglycerides compared to atorvastatin alone. In both groups we found an increase in overall and matched FCT, a significant decrease in arcs of lipid and macrophages, and increase in calcific plaque although only statistical significant in the placebo group. In the ezetimibe group, there was a

significant decrease in numbers of lipid quadrants. Besides a minor difference in change of numbers of cholesterol crystal, there was no statistical difference in changes between groups for any endpoints.

It is assumed, that the vulnerable plaque is preceded by an increase in lipid content in the arterial wall (notably the intimal layer) together with infiltration by inflammatory cells resulting in formation of a fibroatheroma containing a necrotic core. These developments in combination with progressive thinning of the fibrous cap are both features that invoke interest, as necrotic core can be determined in vivo by IVUS with spectral frequencies analysis^{13,14} and measurements of the fibrous cap thickness can be obtained by OCT¹⁵. It has been reported, that TCFA is more often present in coronary infarction patients compared to stable angina, and accordingly, FCT in lipid rich plaques has generally been found to be thicker in the latter group of patients¹⁶.

It has been suggested, that some of the beneficial effects of statin treatment might rely on plaque stabilization by increase of the thickness of the fibrous cap. In a non-randomized prospective study in STEMI patients, Takarada et al.⁸ showed, that lipid lowering with statin following myocardial infarction resulted in a higher increase of FCT compared to patients not treated with statin. This is in accordance with our results, however, the study by Takarada et al.⁸ had limitations due to its non-randomized design, where patients with high baseline lipid values were retrospectively selected, and the groups compared were not assigned in advance. Furthermore, the target vessel was the IRA with a plaque located <10 mm from the “culprit site”, and the stent type might have differed between groups, with a theoretical variation in impact on the stent near vessel wall plaque segment. The minimum FCT in the statin group was increased from $151 \pm 110 \mu\text{m}$ at baseline to $280 \pm 120 \mu\text{m}$ at follow-up. Compared to our findings, we did find a somewhat similar increase in the matched FCT, but it is noteworthy, that this increase was relatively high compared to our findings of the corresponding increase

in mean, maximum, and minimum FCT for the entire segment. This might to some extent rely on the frame selection method used in both studies, that was strongly based on anatomical landmarks, which might increase the likelihood of exaggerated differences from baseline when compared to mean values.

In another study, Takarada et al. described the correlation between percentage changes after 9 months in IVUS assessed total atheroma volume (TAV) and OCT measured FCT in patients with non-STEMI. Furthermore, correlations between percentage changes in TAV and FCT with percentage changes in LDL/HDL ratio and C-reactive protein (CRP) levels were explored¹⁷. No correlation between change in TAV and FCT was found, however, a correlation between percentage change in TAV and LDL/HDL ratio and percentage change in FCT and CRP was reported. Assuming that a change in TAV could be reflected in a change in lipid arc, we examined for correlation between change in lipid arc and LDL/HDL ratio, but found none.

The influence of ezetimibe in patients with acute coronary syndrome (ACS) has been addressed in a recent randomized but open-label trial published by Habara et al¹⁸, ezetimibe as addition to fluvastatin was examined using OCT. Ninety patients with stable angina and documented hypercholesterolemia had a target vessel examined with OCT. Patients without an identifiable fibrous cap were excluded leaving 63 patients to randomization to fluvastatin plus ezetimibe or fluvastatin alone. OCT was performed in 57 patients after approximately 9 months. The authors found a significant reduction in lipid arc at the minimum FCT site, and an increase in minimum FCT in both groups with a significant difference between groups in favor of ezetimibe. In concordance with the findings of Takarada et al¹⁷, a relation between increased FCT and decreased inflammatory response assessed by CRP was found. Compared to the present trial, the findings of lipid arc reduction of approximately 18% and FCT increase of approximately 89% in the ezetimibe group is somewhat more pronounced

compared to our findings, where lipid arc was reduced by approximately 16% and matched FCT increased approximately 71%. We did, however, not find any significant difference between groups, which might be explained by the differences in study design and patient population. In the trial by Habara et al¹⁸, patients were required to have a lipid rich plaque to be identified by OCT for participation, and hypercholesterolemia or ongoing statin treatment were additional inclusion criterias. Finally, fluvastatin is a weaker statin than atorvastatin, and it was administered in only moderate dose (30 mg/day). All patients in the present trial were treated with a high dose atorvastatin, and the LDL reduction in the placebo group superseded the changes found in the ezetimibe arm by Habara et al. In the present trial, we did not evaluate inflammatory markers, but we did find decreased macrophage infiltration suggesting a reduced inflammatory response.

The current trial confirms the findings in earlier trials, that LDL-lowering treatment with statin causes an increase in FCT and a reduction of lipid arc, but it does not confirm a correlation with lipid arc reduction and the degree of change in LDL-values. The additional LDL reduction by ezetimibe in our study did not give rise to a further increase in FCT, but with respect to lipid content only, the ezetimibe group was found to have a significant reduction of numbers of lipid quadrants, and the reduction of lipid arc was also numerically larger in the ezetimibe group although not statistical different.

Study limitations

The study is based on a relatively small number of patients. Furthermore, only one vessel was chosen for analysis, and the used OCT system provides limited pullback capabilities further reducing the size of baseline-follow-up matched plaque for comparison.

Conclusion

Ezetimibe in addition to high dose statin resulted in an increase in FCT, and a reduction in lipid arc and macrophage arc. The change was, however, not statistical different from that of placebo. A reduction in distinct lipid quadrants was only significant in the ezetimibe group.

Funding

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Conflicts of interests

LOJ has received research grants from Terumo, Biotronik, St Jude Medical, and Biosensors to her institution and honoraria from Abbott Vascular, AstraZeneca, St Jude Medical and Biotronik. Mintz and Akiko (?). The other authors have nothing to disclose.

Figure legends

Figure 1: Examples and definitions of OCT measurements. Top: 1) **Macrophages**. Signal rich with backscatter. 2) **Intimal thickness** measurement. $<600 \mu\text{m}$ defined as "intimal thickening" and $>600 \mu\text{m}$ as Pathological Intimal Thickening (PIT). 3) **Crystals**. Signal rich, well defined, stent-strut-like appearance. No of clusters counted. 4) **FCT**-measurement: ThCFA $>65 \mu\text{m}$, TCFA $<65 \mu\text{m}$. Signal rich cap with sudden raise in attenuation and loss of signal corresponding to underlying lipid content. 5) **Macrophage arc** measurement. 6) **Lipid arc** measurement. Defined as vessel wall with "loss of media" caused by attenuation of light in lipid tissue. Bottom section: (to the left) **Calcium arc**: Well defined low signal plaque. (to the right) **Lipocalcific arc**: More heterogenous less defined borders

Figure 2: OCTIVUS Flow chart.

Figure 3: Scatterplots depicting absolute (to the left) and relative (to the right) LDL changes from baseline vs. baseline values for the placebo and ezetimibe groups. Absolute change in LDL correlates positively with baseline values.

Figure 4: Examples of plaque presentation at baseline and follow-up. a) Excentric plaque with macrophages and underlying lipid tissue. b) Lipid rich plaque with thin cap fibroatheroma (arrow) at baseline. c) Thin Cap Fibroatheroma (TCFA) with underlying lipid core (★) and cholesterol crystals (arrow). d) Fibrous cap thickening (arrow) at follow-up. e) At follow-up more pronounced calcification (arrow) and cap thickening. f) At follow-up thickening of fibrous cap (arrow).

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Figures

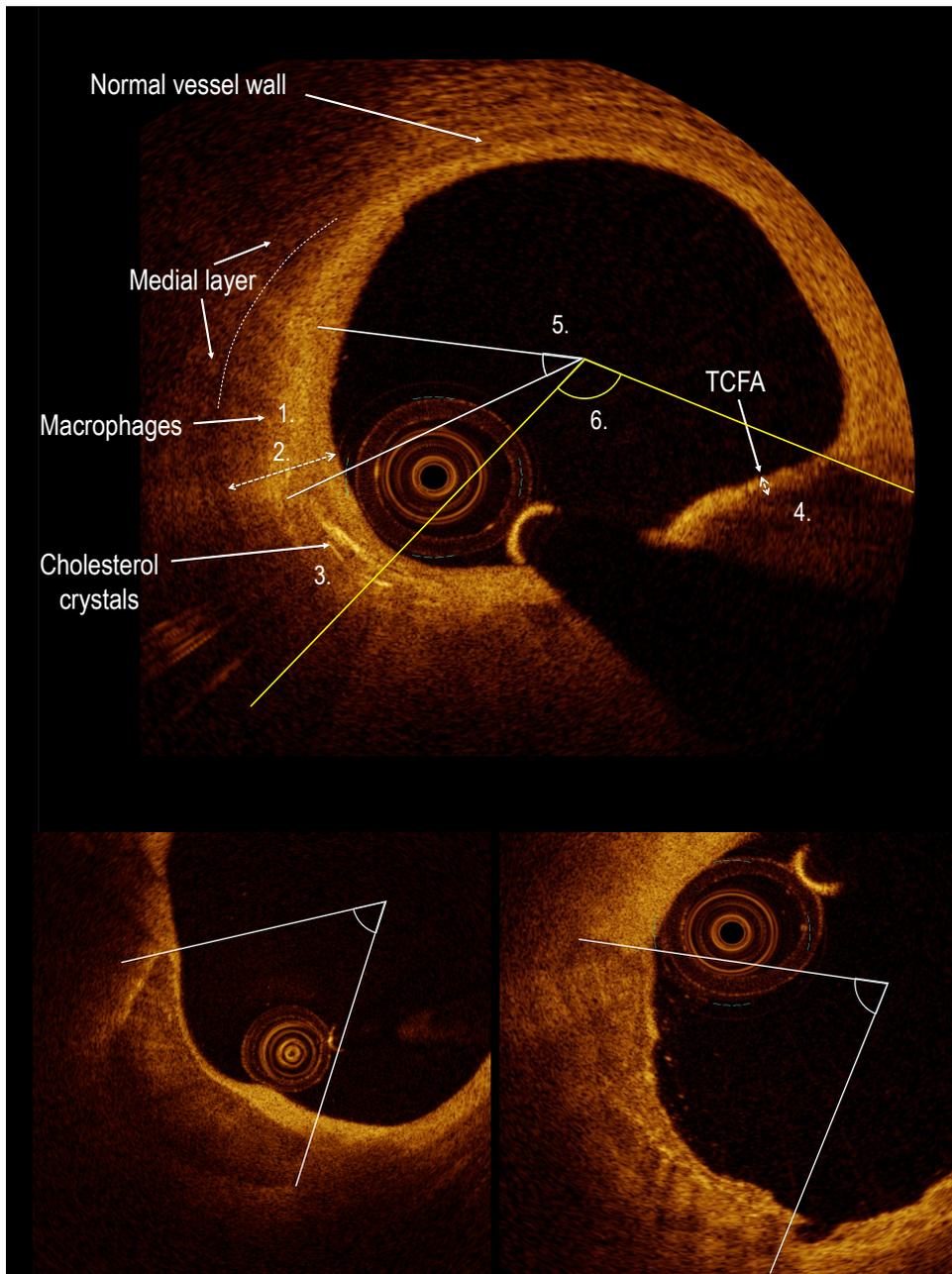
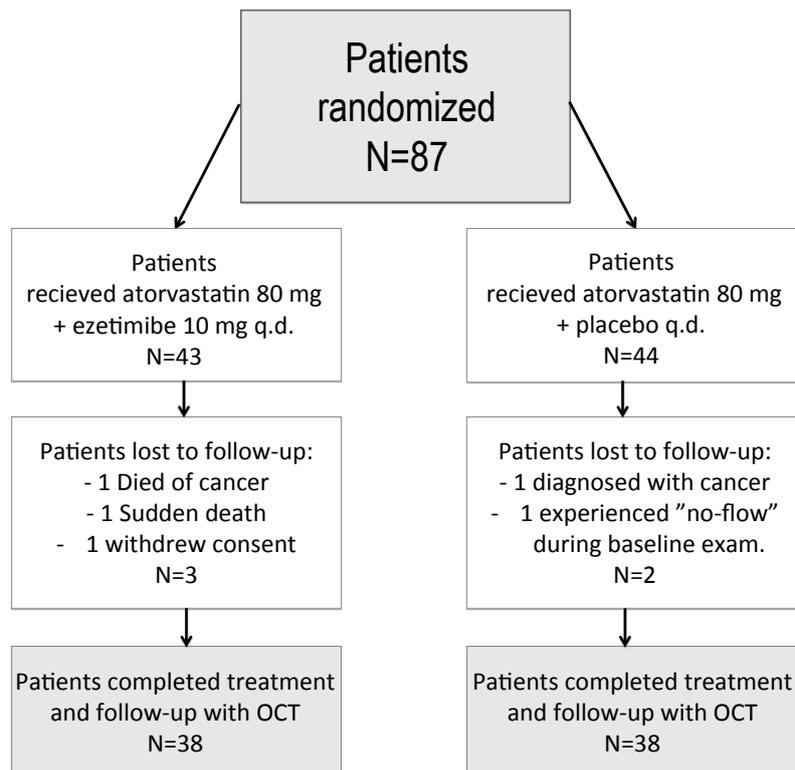


Figure 1

**Figure 2**

Change in LDL

Correlation of LDL reduction from baseline

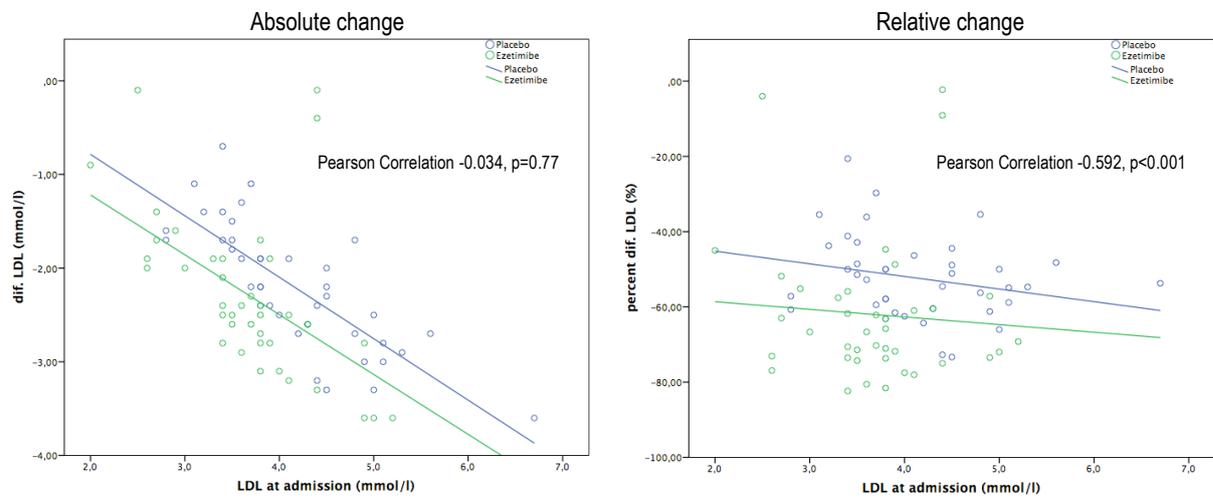


Figure 3

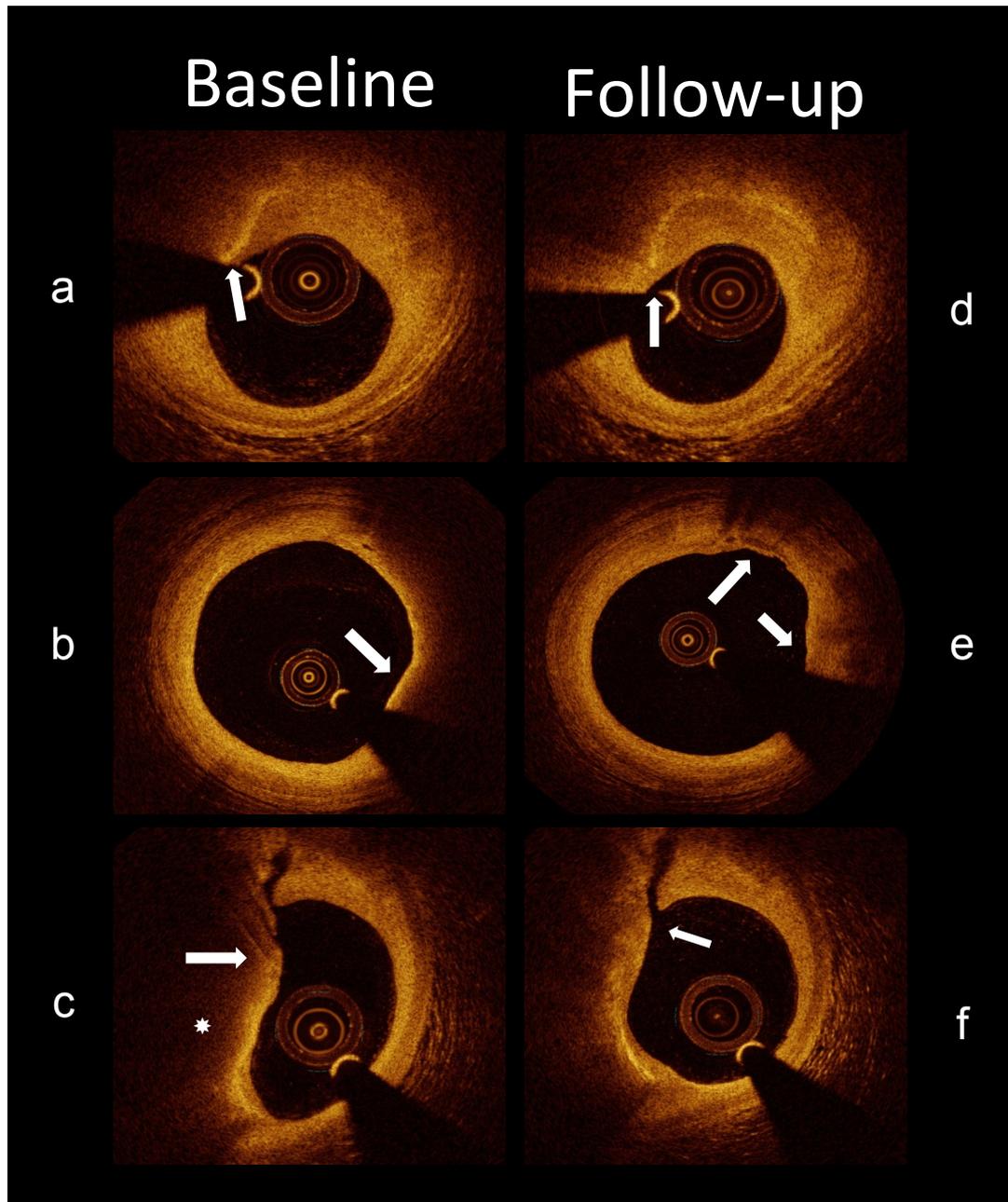


Figure 4

TABLE 1 BASELINE AND PROCEDURE CHARACTERISTICS

	Ezetimibe (n=43)	Placebo (n=44)	p
Age, years	55.3±11.0	57.2±9.1	0.38
Male gender, n (%)	39 (90.7)	36 (81.8)	0.23
Hypertension, n (%)	7 (16.3)	8 (18.2)	0.81
Current smoking, n (%)	25 (58.1)	23 (52.3)	0.74
Family disposition, n (%)	19 (44.2)	22 (50.0)	0.59
Diabetes, n (%)	1 (2.3)	1 (2.3)	0.99
HbA1c (mmol/mol)	39.0 (36.0, 41.0)	37.0 (36.0, 41.0)	0.98
Systolic blood pressure, mmHg	129.7±21.4	125.0±19.8	0.29
Total Cholesterol >5 mmol/l, n (%)	32 (74.4)	30 (68.2)	0.64
Diastolic blood pressure, mmHg	78.1±18.2	75.1±10.2	0.34
Heart rate, beats/min	71.0 (60.0, 83.0)	68.0 (60.0, 81.5)	0.62
Weight	86.0 (78.0, 95.0)	85.0 (76.8, 94.0)	0.81
BMI (kg/m ²)	27.3 (25.1, 29.2)	27.4 (24.6, 29.4)	0.99
LVEF	50.0 (40.0, 55.0)	50.0 (45.0, 60.0)	0.20
Single vessel disease, n (%)	33 (76.7)	29 (65.9)	0.43
Infarct related artery, n (%)			0.11
RCA	11 (25.6)	20 (45.4)	
LAD	27 (48.3)	15 (34.1)	
LCx	5 (14.9)	9 (15.9)	
Study vessel, n (%)			0.07
RCA	16 (37.2)	11 (25.0)	

LAD	12 (27.9)	23 (52.3)	
LCx	15 (34.9)	10 (22.7)	
Prior cardiovascular medications, n (%)			
β -blockers	0 (0.0)	2 (4.5)	0.16
Calcium antagonists	4 (9.3)	3 (6.8)	0.67
ACE inhibitors	4 (9.3)	3 (6.8)	0.67
ATII inhibitors	0 (0.0)	1 (2.3)	0.32
Diuretics	1 (2.3)	3 (6.8)	0.32

TABLE 2 LIPID VALUES

	Ezetimibe	Placebo	
	n=39	n=41	p
	Mean±SD / median	Mean±SD / median	
	(IQR)	(IQR)	
Total cholesterol			
Baseline (mmol/l)	5.3±0.9	5.7±1.0	0.09
Follow-up (mmol/l)	2.9±1.0	3.5±0.7	0.001
Change (mmol/l)	-2.5±1.0	-2.3±0.7	0.039
Percent change %	-46.8±16.4	-38.9±9.7	<0.001
p-value baseline vs follow-up	<0.001	<0.001	<0.001
HDL			
Baseline (mmol/l)	1.1±0.3	1.1±0.3	0.59
Follow-up (mmol/l)	1.1±0.3	1.1±0.3	0.48
Change (mmol/l)	0.06±0.3	-0.03±0.2	0.50
Percent change %	-3.6±25.8	-1.1±18.1	0.27
p-value baseline vs follow-up	0.14	0.36	
LDL			
Baseline (mmol/l)	3.7±0.7	4.1±0.9	0.010
Follow-up (mmol/l)	1.4±0.8	2.0±0.5	<0.001
Change (mmol/l)	-2.3±0.9	-2.2±0.7	0.29
Percent change %	-62.0±19.2	-52.4±10.9	<0.001
p-value baseline vs follow-up	<0.001	<0.001	
LDL/HDL ratio			
Baseline	3.4±1.0	3.8±1.1	0.13

Follow-up	1.4±0.8	1.8±0.5	0.002
Percentage change	-59.6±17.8	-50.3±15.1	0.001
p-value baseline vs follow-up	<0.001	<0.001	
Triglycerides			
Baseline (mmol/l)	1.3±0.8	1.2±0.8	0.55
Follow-up (mmol/l)	0.9±0.8	1.0±0.6	0.07
Change (mmol/l)	-0.3±0.9	-0.1±0.7	0.08
Percent change %	-18.5±50.1	4.0±54.0	0.03
p-value baseline vs follow-up	0.025	0.24	

TABLE 3 OCT RESULTS

	Ezetimibe	Placebo	p
	Median (IQR) / Mean±SD	Median (IQR) / Mean±SD	
Baseline			
Overall minimum FCT μm	85 (50, 130)	100 (60, 120)	0.96
Overall maximum FCT μm	375 (310, 530)	395 (305, 445)	0.66
Overall mean FCT μm	200 (140, 260)	205 (135, 260)	0.96
Lipid arc $^{\circ}$	1728.5 (1022.5, 3904.7)	1671.6 (978.3, 2868.7)	0.73
Lipid quadrant ($\geq 90^{\circ}$), n	8.5 (5.0, 16.0)	7.5 (5.0, 14.0)	0.76
Calcium arc $^{\circ}$	81.0 (56.7, 155.7)	130.5 (51.8, 335.3)	0.43
Lipo-calcific arc $^{\circ}$	274.1 (90.0, 499.5)	285.3 (86.4, 624.6)	0.68
Macrophage arc $^{\circ}$	1730.3 (965.7, 2984.4)	1570.5 (794.7, 3016.8)	0.56
Cholesterol crystals, n	1.1±2.6	1.7±2.3	0.041
Follow-up			
Matched minimum FCT μm	185.0 (140, 230)	165.0 (120, 255)	0.70
Overall minimum FCT μm	100 (75, 170)	115 (90, 160)	0.62
Overall maximum FCT μm	410 (365, 475)	380 (300, 460)	0.11
Overall mean FCT μm	240 (190, 305)	230 (180, 270)	0.32
Lipid arc $^{\circ}$	1164.5 (736.6, 2580.1)	1373.7 (791.2, 2267.3)	0.83
Lipid quadrant ($\geq 90^{\circ}$), n	5.0 (3.0, 15.0)	6.0 (3.5, 13.0)	0.88
Calcium arc $^{\circ}$	96.3 (50.4, 253.8)	191.7 (58.5, 371.7)	0.45
Lipo-calcific arc $^{\circ}$	306.9 (185.9, 491.4)	344.7 (90.9, 469.8)	0.96
Macrophage arc $^{\circ}$	1324.8 (819.0, 2819.7)	1418.9 (584.1, 2501.1)	0.61
Cholesterol crystals, n	1.3±2.1	1.2±2.2	0.56

Change from baseline

Matched min FCT μm	79.4 \pm 102.3*	89.2 \pm 72.3*	0.89
Overall minimum FCT μm	20.0 \pm 73.0*	40.9 \pm 85.7*	0.88
Overall maximum FCT μm	77.0 \pm 130.2	13.8 \pm 115.4	0.84
Overall mean FCT μm	40.0 \pm 60.7*	41.2 \pm 70.8*	0.71
Lipid arc $^{\circ}$	-267.2 (-866.3, 3.8)*	-165.6 (-651.4, 34.6)*	0.37
Lipid quadrants ($\geq 90^{\circ}$), n	-2.5 (-4.0, 0.5)*	-1.0 (-4.5, 1.5)	0.57
Calcium arc $^{\circ}$	43.7 (-32.9, 172.8)	20.7 (-9.9, 205.2)*	0.77
Lipo-calcific arc $^{\circ}$	54.9 (-94.1, 181.4)	30.6 (-100.8, 90.9)	0.53
Macrophage arc $^{\circ}$	-192.2 (-558.0, 59.4)*	-261.5 (-903.6, 13.5)*	0.57
Cholesterol crystals, n	0.2 \pm 2.2	-0.5 \pm 1.7	0.029

Change from baseline * p<0.05

Paper 3

The Impact of Guidewire Artifact in assessment of Tissue Composition with iMap™ using Intravascular Ultrasound

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ABSTRACT

Purpose: Tissue Characterization using iMap™ in conjunction to Intravascular Ultrasound (IVUS) is a method to assess plaque composition with respect to Necrotic Core (NC), Lipidic Tissue (LT), Calcified Tissue (CT) and Fibrotic Tissue (FT). The guidewire artifact may potentially hamper the iMap™-assessment, but the use of a guidewire is necessary due to safety concerns. The aim of this study was to evaluate the difference in measurements between serial pullbacks with and without guidewire thereby assessing the impact of the guidewire artifact on the quantitative measurements.

Methods: In 10 patients an angiographic non-significant study plaque was assessed with IVUS and iMap™. Four subsequent pullbacks of the same segment - 2 with and 2 without guidewire - were performed. In the off-line analysis of pullbacks over a guidewire, the artifact was both included and manually excluded from the offline iMap™ quantification.

Results: Vessel, lumen and plaque volume did not differ significantly between the two pullback techniques (576 ± 216 , 360 ± 151 and 216 ± 76 (mm³) with guidewire vs. 575 ± 213 , 359 ± 149 and 215 ± 75 (mm³) without guidewire, $p=ns$). There was no difference in relative plaque composition with respect to NC, LT, CT, or FT after offline exclusion of the guidewire artifact compared to pullbacks without guidewire (18.8 ± 14.1 , 8.8 ± 3.6 , 1.4 ± 1.3 and 70.9 ± 17.3 (%) vs. 18.2 ± 13.8 , 8.7 ± 3.5 , 1.0 ± 0.9 and 72.0 ± 17.1 (%), all $p=ns$). Intra-catheter variability in subsequent pullbacks when artifact was excluded was comparable to subsequent pullbacks without guidewire (Divergence between NC samples 18.9% and 16.6% respectively).

Conclusions:

A guidewire can be used in iMap plaque assessment.

Key words:

IVUS; tissue characterization; iMap; guidewire artifact; plaque

Introduction

In the field of atherosclerotic plaque assessment with respect to tissue composition, classical grey scale intravascular ultrasound (IVUS) has been expanded with spectral analysis of radio-frequency data referred to as (among others) Virtual Histology (VH-IVUS, 20 MHz phased-array transducer, 2.9 F Eagle Eye™ Gold, Volcano Therapeutics), Integrated Backscatter IVUS (IB-IVUS based on RF-data from IVUS systems), and iMap™ (40 MHz revolving transducer, 3.2 F Atlantis, Boston Scientific Corporation, Natick, MA USA). For iMap™, this technique results in tissue differentiation into four subtypes: Necrotic Core (NC), Lipidic Tissue (LT), Calcified Tissue (CT) and Fibrotic Tissue (FT). A review describing these techniques has previously been published[1]. Ex vivo validation studies have shown high sensitivity and specificity compared to histological findings[2–7]. Animal models yields less correlating results in validation studies[8].

Both techniques have their limitations especially due to technical difficulties in the way the systems correct for various artifacts, i.e. far-field plaque signal drop, calcification, stent, and guidewire artifacts.[9] The major benefit of the iMap™ system is the higher spatial resolution of the system improving the ability to differentiate plaques with respect to details like the presence of fibrous cap and intimal damage. However, the image clarity in the far field can be reduced in 40 MHz compared to 20 MHz systems[9]. The sheath based catheter type used in the iMap™ system allows a smooth and uniform pullback enhancing the assessment of plaque volume.[10]

IVUS pullbacks are normally performed using a guidewire, which for iMap™ gives rise to a guidewire artifact due to its dependence on a mechanical revolving catheter type. The iMap™ system categorizes the majority of this artifact as NC in a way similar to the interpretation of far field plaque and in the acoustic shadow of calcium. This artifact potentially hampers the iMap™-assessment, but can be overcome by doing pullbacks with the guidewire retracted.

In scientific studies, every artifact constitutes a problem and makes data assessment difficult. Especially in plaque regression studies, where a change over time needs to be evaluated, a way to adjust for artifacts is imperative. It is of special concern, that the location of the guidewire artifact is unpredictable and probably alters between different pullbacks and thereby challenges the ability to compare two corresponding pullbacks.

Of safety concerns, the manufacturer recommends the use of a guidewire, and this study aims at determining the impact of the artifact and the possibility to adjust for it in an offline analysis. Furthermore, we wish to examine the intra-catheter variability by comparing sequential pullbacks with the same catheter.

Methods

The present study was a substudy of the *Plaque Composition in Patients with acute ST Segment Elevation Myocardial Infarction assessed by Optical Coherence Tomography and IntraVascular UltraSound with iMap* (OCTIVUS) trial (NCT01385631) which was a single center double blinded randomized trial comparing the effect of ezetemibe to placebo in patients with first time STEMI and 12 months follow-up evaluating a none significant plaque in a none-stented coronary artery. The study was approved by the Danish Ethical Committee (project ID: S-201 001 00) and the Danish Medical Agency (EudraCT 2010-022604-45).

The present substudy population consisted of 10 consecutive patients enrolled in the main trial. A clinically non-significant study plaque (angiographic diameter stenosis <50% and >20%) in a non-infarct related artery was assessed with IVUS with iMap™ using an iLab™ System with the Atlantis™ SR Pro 40 MHz IVUS catheter. We set out to compare 3 different approaches with respect to tissue characterization of the plaque: I) Ordinary pullback over a guidewire with offline iMap quantification of the plaque defined by lumen and vessel contours, II) avoidance of the guidewire artifact by performing pullbacks without a guidewire in place, and III) Same physical pullback as I) but implementing offline exclusion of the guidewire artifact by masking the artifacts using EchoPlaques built-in ability to implement “no-fly-zones”, which is an option to exclude a specific slice of the vessel wall from the iMap™ analysis. The preset angle of the no-fly-zone was used without further adjustment as depicted in **fig. 1**.

In all cases, analyses were done in 2 consecutive pullbacks in order of determining and adjust for the intra-catheter variation. To obtain this, 4 pullbacks were performed: Two with a guidewire in place followed by 2 without a guidewire. The same catheter was used for all pullbacks during the procedure, and the catheter was not moved from the coronary artery between pullbacks. The pullbacks without guidewire (3) served as a reference assuming that this method yields results closest to the actual plaque composition. 200 µg of nitroglycerin was administered once prior to the first pullback. A side-branch was used as point of reference in order of matching the segments angiographically and during offline IVUS analysis. On patient level, the corresponding 4 pullbacks were matched including as long an overlapping segment as possible (34.5±6.0 mm). The pullbacks were analyzed offline (using EchoPlaque 4.0 Software, INDEC Systems, CA, USA) determining luminal contour, plaque + media and external elastic membrane (EEM) volume. The iMap™ data was stored for every 0.5 mm, and values for NC, FT, CT, and LT were automatically delivered after tracing of the lumen and EEM contours in every

frame containing iMap™ data. Echoplaques standard settings for “Confidence Lower Bound” and “Necrotic Confidence Upper Bound” were used (0% and 100% respectively).

Statistical analysis

Continuous data was expressed as mean±SD, and statistical analysis was done using SPSS version 21.0 (IBM Corporation, New York, USA). Corresponding pullbacks were compared using a paired sample T-test. Bland-Altman plots were constructed showing the relation between mean and difference in volumes of plaque plus media, FT, CT, NC, and LT in the three different types of pullback assessment: (1) with guidewire and no exclusion, (2) with guidewire and artifact excluded using "no-fly-zones", and (3) without guidewire.

Results

Intra-catheter variability

Comparisons of classical grey-scale measurements in two subsequent pullbacks without (Pb1 and Pb2), and with guidewire (Pb1+gw and Pb2+gw) are summarized in **table 1**. There were no significant differences in the vessel, lumen, or plaque volumes. In the iMap results comparing 2 subsequent pullbacks without guidewire and 2 pullbacks with guidewire and inclusion of the guidewire artifact, only the volume of LT in pullbacks with guidewire differed between the first and second pullback ($20.2\pm 8.8 \text{ mm}^3$ vs. $19.6\pm 8.6 \text{ mm}^3$, $p=0.03$).

Comparison between omission of guidewire and handling of artifact

The mean values obtained by the 3 different assessment techniques are summarized in **table 2**. No difference in lumen, plaque, and vessel volumes was found, but as expected, the absolute values of the iMap™-subtypes were affected by the guidewire mainly caused by the systems misinterpretation of the artifact as NC. The relative distribution was, however, not different between pullbacks without guidewire and pullbacks with guidewire, when the artifact was excluded prior to analysis using "no-fly-zones". In contrast the inclusion of the artifact resulted in a significant difference in measured volumes of NC, FT, and LT compared to pullbacks without guidewire ($22.7\pm 14.5\%$ vs. $18.2\pm 13.8\%$ ($p<0.001$), $9.2\pm 3.3\%$ vs. $8.7\pm 3.5\%$ ($p=0.04$) and $66.8\pm 17.3\%$ vs. $72.0\pm 17.1\%$ ($p<0.001$)). We constructed Bland-Altman plots (**Fig. 2**) showing mean volumes (x-axis) against difference in relative volumes (y-axis) for the total plaque volume and for the 4 different iMap™-subtypes in all of the three test settings (without guidewire, with guidewire and artifact included in analysis, and with guidewire but artifact excluded from

analysis). Limits of agreement are defined as the mean difference \pm 1.96 SD. The relative difference is most pronounced in cases, where only a small amount of the plaque type of interest was present - predominated by calcium (**Fig. 2, fourth row**). For the grey-scale volumetric assessments, the mean of percentage difference was close to 0 (-0.77 – 0.12), and the limits of agreement showed only a modest deviation indicating, that the difference between 2 measurements was expected to diverge <3.2% for vessel volume, <3.7% for lumen volume, and 16.9% for plaque volume. In the iMap measurements, the mean percentage difference was low in pullbacks without guidewire (-5.21 – 0.86) but more deviating in pullbacks with guidewire (artifact included: -6.82 – 1.85, artifact excluded: -9.61 – 1.46), and correspondingly the limits of agreement were wider indicating, that for pullbacks with guidewire and the artifact excluded, the difference between 2 pullbacks was expected to diverge 18.9% for NC, 27.7% for CT, 14.0% for LT, and 19.2% for FT. For pullbacks without guidewire, the corresponding divergence was respectively 16.6%, 55.6%, 17.1%, and 8.0%.

To test the agreement between the reference (pullbacks without guidewire) and the pullbacks with guidewire and artifact exclusion, we constructed Bland-Altman plots for all 4 subtypes (**fig. 3**) showing the mean relative distribution (x-axis) and the difference in relative distribution (y-axis). These show acceptable agreements, modest for LT and worst for CT. For necrotic core in particular the limits of agreement was 23.7 to -37.6, indicating that the difference between 2 measurements was expected to diverge <30.7 percent points. The mean in relative difference was -7.0% reflecting the reduced plaque available for assessment caused by the artifact exclusion.

Discussion

In this study we found, that the impact of the guidewire artifact is negligible with respect to classical grey scale IVUS assessments with no statistical difference between the two approaches. Furthermore, the difference between two sequential and correlating pullbacks (with and without guidewire) was not significant consistent with good intra-catheter and intra-observer reliability. However, the study confirmed earlier findings, that the guidewire artifact was interpreted by the iMap™ algorithm as NC making direct comparison of iMap data between two subsequent pullbacks difficult. The location of the artifact in relation to the vessel wall and the intimal plaque may vary in its location between different pullbacks. The NC compartment has a small overall representation in plaque tissue, but an artifact involving an area with high plaque burden can potentially exaggerate its presence. This problem is inherent to iMap™'s dependence on a

mechanical rotating catheter system and is not an issue for Virtual Histology systems utilizing fixed crystals and no sheath technique. This makes direct comparison of iMap™ results between pullbacks without and with guidewire difficult, but our study showed, that offline artifact exclusion resulted in a similar relative distribution, and the intra-catheter reliability remained intact allowing for comparison in longitudinal studies. There is an agreement between results of pullbacks without guidewire and with guidewire and artifact exclusion, but our findings point towards the presence of a proportional bias meaning that the level of agreement seems to vary through the range of measurements (**fig. 3**), and the 2 methods are not suited for interchangeable use through a longitudinal study.

In an earlier study by Heo et al., the reproducibility of iMap™ with respect to both inter- and intra-observer and inter- and intra-catheter variability was examined in a similar number of patients (20 and 5 patients respectively)[10]. It was found, that iMap measurements were more sensitive to inter-observer variations and especially NC, because its quantification is sensitive to the tracing of EEM and thus determination of plaque burden. It was also noted; that the guidewire artifact constituted a problem, but the impact hereof was not specifically evaluated. It was concluded, that the classical grey-scale assessments together with iMap assessment was reproducible on a level that compares to VH.

Longitudinal IVUS plaque progression studies using iMap™ acquisitions have not yet been published, and because such studies typically aim at describing minor shifts in plaque composition a way to circumvent this problem are warranted. A simple solution is to simply omit the use of the guidewire during pullbacks, but this increases the risk of procedural complications and should be avoided. In the light of our finding, it seems, however, feasible to overcome this issue – especially by excluding the artifact prior to analysis - making iMap™ a useful addition to other plaque assessment modalities.

Conclusion

With respect to classical lumen, plaque and vessel volume assessment, pullbacks without and with guidewire both allowed for assessment with good agreement between two subsequent pullbacks and no significant difference in the results could be obtained. The guidewire artifact had impact on the iMap™ assessment, but offline exclusion of the guidewire artifact prior to iMap™ analysis was possible and yielded similar relative distribution of plaque components as without guidewire and acceptable intra-catheter reproducibility allowing for valid assessment without compromising patient safety.

Conflicts of interest

LOJ has received research grants from Terumo, Biotronik, St Jude Medical, and Biosensors to her institution and honoraria from Abbott Vascular, AstraZeneca, St Jude Medical and Biotronik. The other authors had nothing to disclose.

Table and figure legends

Figure 1: The Guidewire Artifact before (A) and after (B) exclusion. Preset angle used in the study.

Figure 2: Bland-Altman plots. Pullbacks without guidewire, pullbacks with guidewire inclusion of the artifact in analysis and third pullbacks with guidewire and artifact excluded.

Figure 3: Bland-Altman plots showing agreement in iMap assessments for pullbacks without guidewire (reference) to pullbacks with guidewire and artifact excluded with “no-fly-zones”.

Table 1:

Intra-catheter variability. Comparison of two subsequent pullbacks: Without (Pb1 + Pb2) and with guidewire (Pb1+gw and Pb2+gw).

Variable	Pb1	Pb2	p-value	Pb1+gw	Pb2+gw	p-value
Vessel Vol. (mm ³)	576.2±213.5	574.6±212.6	0.46	578.8±218.3	575.1±215.6	0.21
Lumen Vol. (mm ³)	361.0±148.9	358.5±149.7	0.49	361.5±150.3	358.9±153.2	0.48
Plaque Vol. (mm ³)	215.2±74.6	216.1±77.7	0.81	217.3±77.7	216.1±76.5	0.78
NC (mm ³)	42.0±37.0	43.7±40.8	0.29	53.5±40.8	51.0±39.3	0.15
FT (mm ³)	150.3±58.4	149.8±56.6	0.81	139.5±60.9	141.3±58.8	0.59
LT (mm ³)	19.0±9.2	18.8±9.1	0.54	20.2±8.8	19.6±8.6	0.03
CT (mm ³)	2.4±3.3	2.4±3.3	0.54	2.7±3.3	2.6±3.5	0.45

Data is expressed as mean±SD.

Table 2:

Difference between corresponding pullbacks with (I) and without (II) guidewire and with guidewire excluded (III).

Variable	With guidewire (I)	Without guidewire (II)	With guidewire artifact excluded (III)	p-value I vs. II	p-value II vs. III
NC (%)	22.7±14.5	18.2±13.8	18.8±14.1	<0.001	0.32
LT (%)	9.2±3.3	8.7±3.5	8.8±3.6	0.04	0.64
CT (%)	1.3±1.2	1.0±0.9	1.4±1.3	0.18	0.11
FT (%)	66.8±17.3	72.0±17.1	70.9±17.3	<0.001	0.15
Vessel Volume (mm ³)	576.9±216.9	575.4±213.0	576.9±216.9	0.74	1.00
Lumen Volume (mm ³)	360.2±151.7	359.8±149.2	360.2±151.7	0.90	1.00
Plaque Volume (mm ³)	216.7±76.8	215.7±75.9	216.7±76.8	0.81	1.00
NC (mm ³)	52.3±40.0	42.8±38.8	37.15±32.6	0.002	0.04
FT (mm ³)	140.4±59.7	150.1±57.4	127.3±52.9	0.01	<0.001
LT (mm ³)	19.9±8.7	18.9±9.1	16.3±7.5	0.15	0.01
CT (mm ³)	2.7±3.4	2.4±3.3	2.5±3.2	0.11	0.49

Data is expressed as mean±SD. "Without guidewire" used as reference.

Figure 1

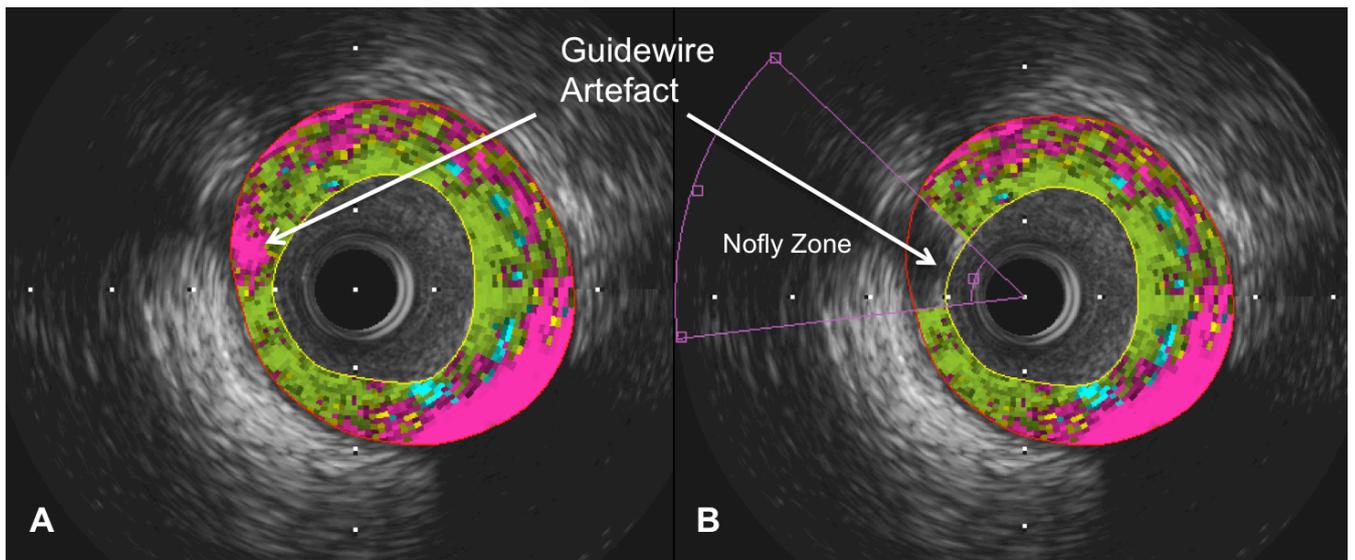


Figure 2

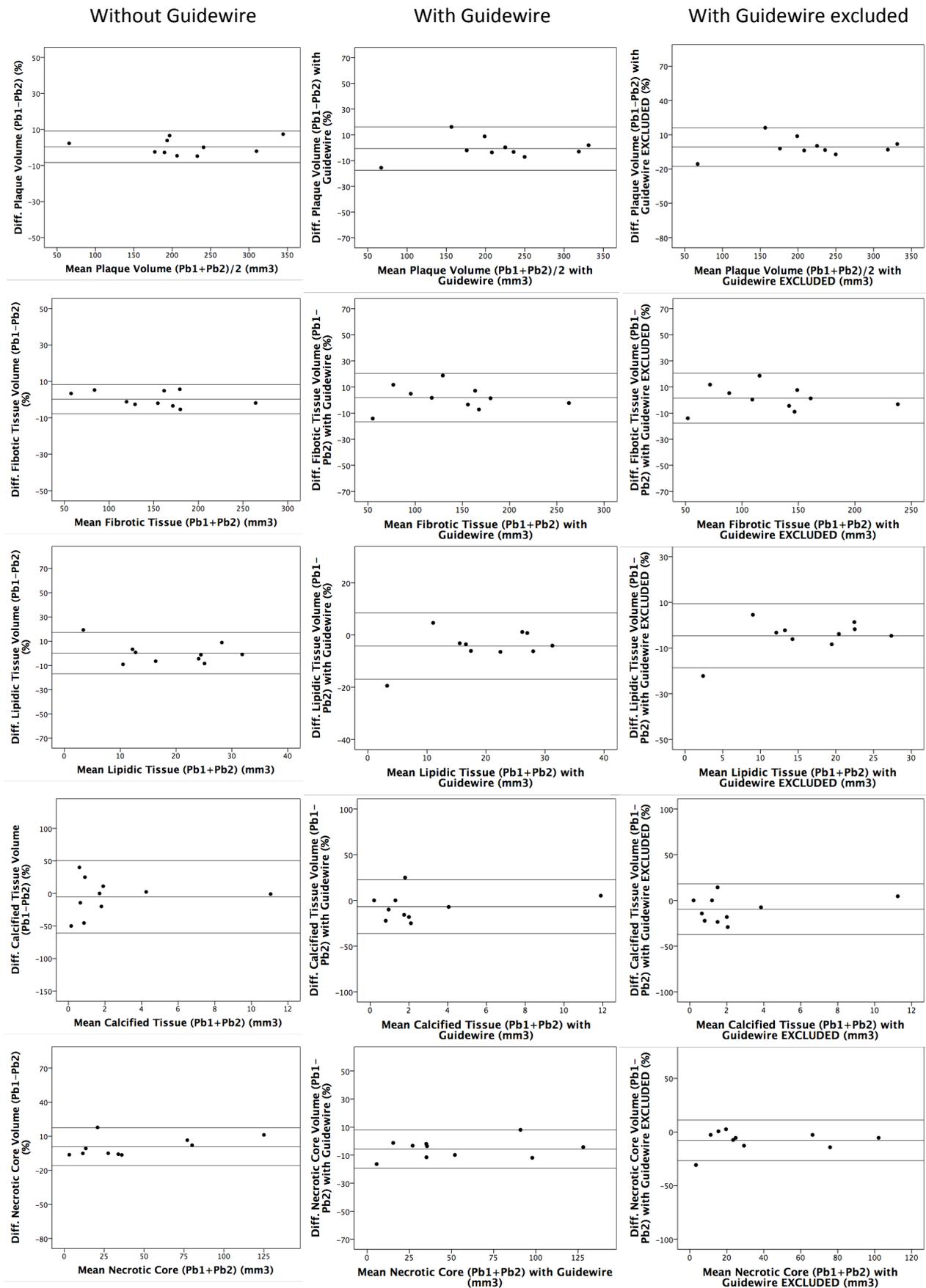
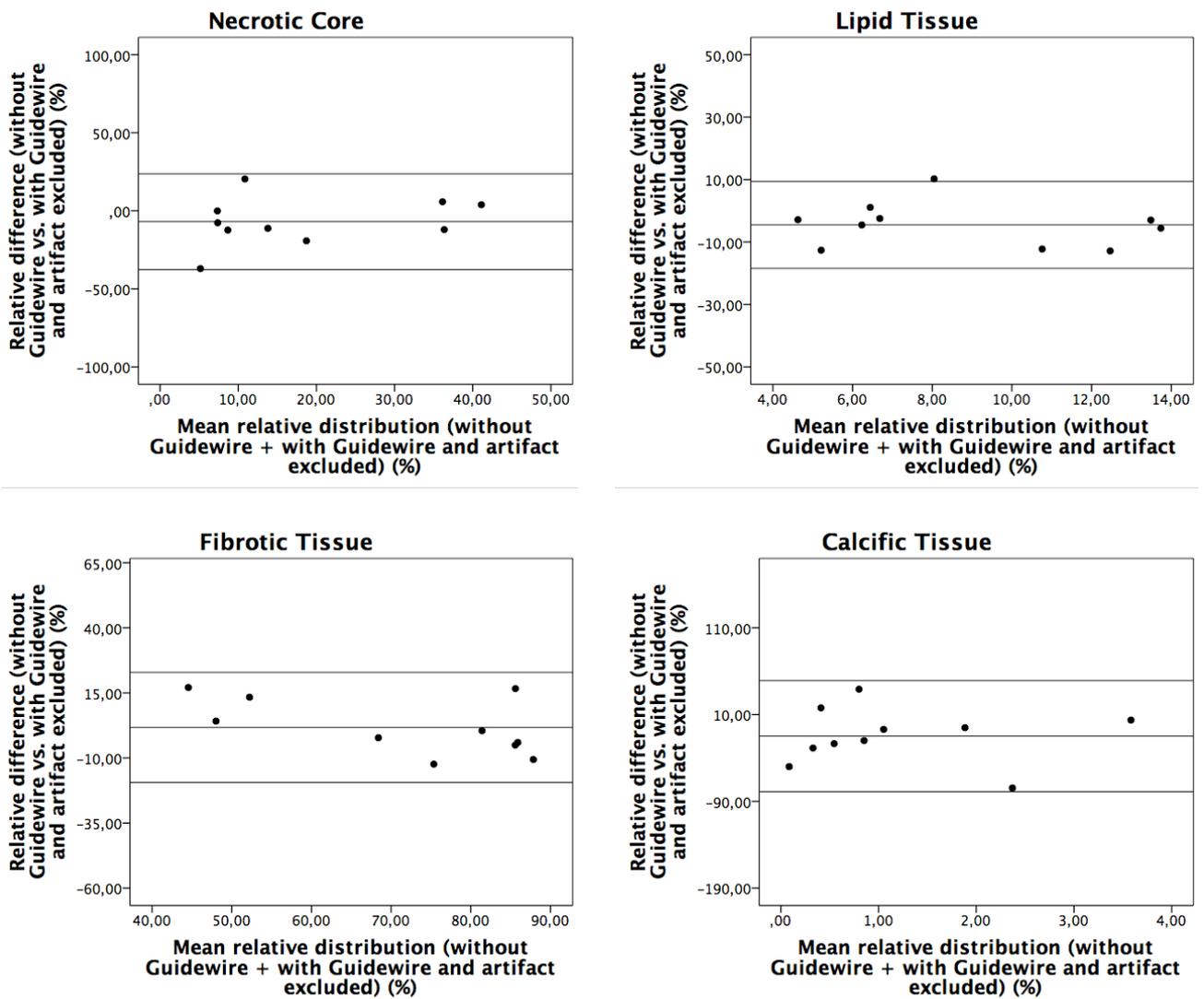


Figure 3



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Paper 4

Apposition, Coverage, Expansion and Peri-Stent Remodeling of the Resolute Integrity Drug eluting Stent in patients with ST Segment Elevation Myocardial Infarction assessed with Optical Coherence Tomography and Intravascular Ultrasound

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Abstract

Background:

Primary percutaneous coronary intervention (PCI) in ST Elevation Myocardial Infarction (STEMI) is associated with greater risk of late stent malapposition and stent thrombosis despite improvements following the advent of second-generation drug eluting stents (DES). The aim of this trial was to assess expansion, apposition, coverage, and peri-stent remodeling after 12 months following implantation of the Resolute Integrity™ DES in a STEMI cohort.

Methods and results:

Eighty-seven patients with STEMI admitted for primary PCI were enrolled and examined with intravascular ultrasound (IVUS) and optical coherence tomography (OCT) of the stented vessel within 72 hours after primary PCI and after 1 year. Endpoints were malapposition, coverage, stent expansion, and peri-stent remodeling. Complete baseline-follow-up data was acquired in 76 patients with IVUS and 74 patients with OCT. Malapposed struts was found in 5.8% post-PCI and 0.6% after 12 months identified by OCT. Percentage uncovered struts after 12 months was 11.3% and the overall median neointimal thickness was 120.0 (100, 160) μm . At baseline, a minimal stent area (MSA) $<5 \text{ mm}^2$ was found in 37.8% of patients. Peri-stent plaque regression and negative remodeling of the stented segment was found by IVUS (median 170.8 (129.7, 235.5) mm^3 to 156.0 (120.2, 208.3) mm^3 and 314.7 (244.3, 417.0) mm^3 to 310.1 (244.1, 379.6) mm^3 respectively, both $p < 0.001$).

Conclusion:

Malapposition was mainly resolved and coverage nearly complete 12 months after stent implantation in STEMI patients treated with the Resolute integrity stent. MSA $<5 \text{ mm}^2$ was a frequent finding. At follow up, there was plaque regression and negative remodeling.

Clinical Trial Registration:

Clinicaltrials.org, NCT01385631

Key Words:

STEMI, OCT, IVUS, DES

Introduction

Primary percutaneous coronary intervention (PCI) with coronary stent implantation is the treatment of choice in the setting of ST segment elevation myocardial infarction (STEMI)^{1,2}. Earlier problems with intimal hyperplasia (IH) resulting in gradual restenosis and a need for repeated target lesion revascularization (TLR)³ was a frequent finding after bare metal stents implantation, but this problem has largely been overcome by the advent of drug eluting stent (DES)⁴. A small and persistent cumulative risk of late and very late stent thrombosis (ST) later emerged as an issue, especially in the first generation of DES^{5,6}. The risk of very late ST has been found to be related to insufficient stent strut coverage, presence of strut malapposition and stent underexpansion^{6-8,7}.

Compromised healing may be related to a host reaction against the durable polymer and stent platform and the second generation of DES has addressed this issue by refining the polymer design and composition together with further development of the stent drug itself and the factors determining its temporal release from the polymer⁹. It has been shown, that delayed healing are more common in association with DES-implantation due to myocardial infarction compared to stable coronary disease, possibly explained by more pronounced pathology in the vessel wall¹⁰.

Second generation DES has largely superseded BMS and first generation DES and has been shown to be superior with respect to safety and efficacy in clinical trials¹¹. Very late ST and IH remain, however, still a concern and the object for intensive research within the field of intravascular coronary imaging, in which intravascular ultrasound (IVUS) and later optical coherence tomography (OCT) has contributed with great insight into the pathological mechanisms and morphological details related to stent deployment and vessel response.

In the setting of STEMI, vasoconstriction and intraluminal thrombus may increase the risk of stent size underestimation, stent underexpansion and strut malapposition caused by later resolution of thrombus jailed between the stent and the underlying vessel wall¹² together with a reduced vascular tonus.

The second generation Resolute Integrity™ stent™ (Medtronic, Minneapolis, Minnesota, USA) is based on a cobalt chromium single wire platform coated with a hydrophilic biocompatible polymer (BioLinx™) containing the Zotarolimus drug¹³, which is a highly lipophilic derivative of sirolimus¹⁴. The aim of the present study was to assess malapposition, strut coverage, stent expansion and peri-stent remodeling evaluated by OCT and IVUS after 12 months in STEMI population.

Patients and methods

Setting and design

The present study is a sub-study of the *Plaque Composition in Patients with acute ST Segment Elevation Myocardial Infarction assessed by Optical Coherence Tomography and IntraVascular UltraSound with iMap* (OCTIVUS) trial (NCT01385631) which was a single center double blinded randomized trial comparing the effect of ezetimibe to placebo in patients with first time STEMI and 12 months follow-up evaluating a none significant plaque in a none-stented coronary artery.

In the period June 2011 to June 2013, a total of 1062 patients were admitted for primary PCI due to STEMI, and of these, 87 patients were included.

Being a substudy to the OCTIVUS trial the inclusion criteria's were the same as in the main trial:

1) first time STEMI; 2) no prior treatment with statins or other lipid lowering drugs; 3) a non-significant lesion in one of the two non-culprit coronary arteries (angiographic diameter stenosis >20% and <50%), and 4) PPCI of the culprit lesion with the Resolute Integrity™ DES.

The exclusion criteria were: 1) age below 18 or above 81 years; 2) unconscious patients; 3) serum creatinine >176 µmol/l; 4) hypothyroidism (TSH >1.5 x ULN [upper limit of normal]); 5) current liver disease (Alkaline phosphatase >2 x ULN); 6) unexplained creatine kinase >3 x ULN; 7) alcohol or drug abuse within the last five years; 8) prior myopathy or serious hypersensitivity

reaction caused by statins; 9) women with child-bearing potential who were not using chemical or mechanical contraception; 10) pregnant or breastfeeding women; 11) history of malignancy unless a disease-free period of more than five years was present; 12) participation in another randomized trial; 13) treatment with cyclosporine or fibrates.

The study was approved by the Danish Ethical Committee (project ID: S-201 001 00) and the Danish Medical Agency (EudraCT 2010-022604-45). All patients provided written, informed consent, and the study was performed in accordance with the rules for good clinical practice (GCP) and monitored by the GCP-department of Odense University Hospital.

All study patients were angiographic re-examined with a supplementary OCT and IVUS of the Resolute Integrity™ stent implanted segment in the infarct related artery after the primary PCI. It was intended to investigate the patient the next day after the primary PCI procedure, but during weekends or holydays, the examination was done at the first coming workday. The OCT and IVUS recordings were completely documentary without any influence on the performed index PCI. Invasive follow-up with repeated OCT and IVUS were performed after 1 year.

Endpoints

Study endpoints were: (1) strut level stent malapposition at baseline and after 12 month; (2) coverage assessed with OCT after 12 months; (3) Stent expansion compared to nominal stent size and the reference segment determined by OCT at baseline; (4) vessel remodeling in the stented segment and in the distal and proximal 5 mm reference segments adjacent to stent edges.

OCT-procedure

OCT was performed with the Lightlab Cx7 and later the Ilumien System both utilizing a Dragonfly™ OCT catheter (Sct Jude Medical, Minnesota, USA). Unfractionated heparin dose (5000 IU) and 0.2 mg of nitroglycerine was administered intracoronary just prior to the procedure. The catheters were initially flushed with contrast (Visipaque™) and wiped with heparinized saline water activating the hydrophilic coating. Catheter placement was guided angiographically by visualization of the implanted stent ensuring an adjacent reference segment of at least 5 mm. The pullback was initiated automatically by manual flushing of the vessel with 20 ml of contrast. Pullback speed was 20 mm/s, and the total pullback distance of the system was 55 mm. Repeated pullback was performed in case of insufficient image quality or incomplete acquisition of the segment of interest.

All examinations were assigned to randomly generated examination ID numbers corresponding to a list managed by a person not involved in the study and archived to DVD's.

OCT off-line analysis

OCT pullbacks were analyzed using the Ilumien™ Optis™ Offline Review Workstation (Sct Jude Medical, Minnesota, USA) by a team consisting of one dedicated OCT-analyst assisted by two supervised technicians. Prior to analysis, all pullbacks were carefully calibrated. Stent borders were defined as the first and the last cross sections of the stented segment where struts were visible (assessed in a frame by frame manner). A frame for every 1 mm was analyzed together with the frames defining the distal and proximal stent borders. The 5 mm reference segments adjacent to the distal and the proximal stent borders were assessed for every 1 mm beginning the first frame immediately following the stent border (0.2 mm apart). For all segments, the lumen cross sectional area (CSA) was measured and a lumen volume was calculated as $0.2 \text{ mm} \times \sum \text{LUMEN}_{\text{CSA}}$.

All struts were per definition uncovered at baseline, and definition for coverage after 12 months are illustrated in **fig. 1**. Struts were marked and assessed for level of tissue coverage (Categories: 1.

definitely uncovered, 2. uncovered fibrin, 3. partially uncovered, 4. covered protruding, 5. covered embedded, and 6. covered proliferative). In this study, we only differentiated between "covered" (category 4-6) and "uncovered" (category 1-3). For covered struts, the thickness of the neointimal layer was measured from the center of the strut reflection to lumen border following a line towards the center of the stent.

Based on a physical strut plus abluminal polymer thickness of the Resolute Integrity™ stent of 97 μm (91+6 μm), malapposition was defined as a strut-to-vessel-wall distance >97 μm measured from the center of the luminal stent reflection to the transition zone from lumen to the intimal layer. For every malapposed strut, a malapposition distance was measured. For every stent, the presence of malapposition at baseline was regarded as *acute*. Malapposition present at baseline could be *resolved* or *persistent* after 12 months. Presence of malapposition after 12 month not present at baseline was classified as *late acquired*. Extra-stent volume was defined as peri-stent lumen volume minus stent volume.

Focal stent expansion was assessed by dividing the minimum stent area (MSA) derived by OCT with the nominal stent CSA ($STENT_{NOM,CSA}$) calculated from the nominal stent diameter (nSD) as $\pi \times (nSD/2)^2$ and with the OCT assessed mean reference area (REF_{CSA}) at baseline ((Mean proximal reference CSA + mean distal reference CSA)/2). Stent size selection accuracy was defined as $STENT_{NOM,CSA} / REF_{CSA}$.

A coronary evagination was defined as an outward expansion of the luminal border between two apposed struts with a depth exceeding that of the strut thickness. A major evagination was defined as evaginations occurring in three adjacent frames with a depth >10% of the stent diameter.

Intravascular ultrasound imaging and analysis

IVUS acquisitions were performed with an Atlantis™ SR Pro 40 MHz catheter and the iLab system (Boston Scientific, Natick, MA, USA). Immediately after the OCT recordings, the IVUS catheter

was flushed with heparinized saline water and advanced to approximately 10 mm distal to the stented segment. An automatic pullback was used and a segment of at least 10 mm proximal and distal for the stented segment was acquired. A frame rate of 30 frames/s and a pullback speed of 0.5 mm/s were used. IVUS pullbacks were analyzed off-line using the EchoPlaque 4.0 software (INDEC Medical Systems, CA, USA) by one dedicated IVUS-analyst at intervals of 1 mm.

The $LUMEN_{CSA}$ was measured as the area defined by the luminal vessel contour, and the external elastic membrane EEM_{CSA} was measured at the leading edge of the adventitia. The $PLAQUE_{CSA}$ in reference segments was calculated as the EEM_{CSA} minus the $LUMEN_{CSA}$. Volumetric calculation of total vessel-, lumen-, and plaque volume together with malapposition volume was performed in EchoPlaque, and peri-stent plaque volume was calculated as vessel volume minus stent volume. Extra-stent volume was calculated as peri-stent lumen volume minus stent volume. Positive and negative remodeling was defined as, respectively, an increase or a decrease in peri-stent vessel volume of more than 5% compared to baseline.

Statistical analysis

All statistical analysis was performed with SPSS 22.0 (IBM Corporation, New York, USA). Categorical data are presented as frequencies and percentages and normal distributed continuous data are presented as mean \pm SD or presented as median with inter quartile range (IQR) when normality testing failed. A Shapiro-Wilks test and Q-Q plots was used for normality testing. A paired samples t-test or Wilcoxon Matched-Pair Signed-Rank test was used in comparison of changes from baseline to follow-up. A two-sided p-value of <0.05 was considered statistical significant.

Results

Patient population and procedure characteristics

A total of 87 patients were enrolled in the main study (**fig. 2**). Baseline examinations failed for one person. Four patients were lost to invasive follow-up (One patients died of sudden cardiac arrest, one patient died from pulmonary cancer, one patient got disseminated cancer, and one patient withdrew consent). Complete, matched, and analyzable baseline and follow-up examinations with OCT were available in 74 patients and in 76 patients for IVUS. Median time to follow-up was 357 (346, 365) days. Baseline characteristics are listed in **table 1**.

Stent apposition

Stent strut apposition is shown in **table 2**. Approximately 80% of patients had malapposition at baseline assessed with OCT, and in those malapposition was resolved in 69% at follow-up. Late acquired malapposition was found in three patients. A receiver operating characteristics curve (**fig. 3**) showed a cut-off for the acute maximal malapposition distance predictive for resolved malapposition at follow-up to be 430 μm .

Strut coverage

Strut coverage was fully complete at follow-up in seven patients (9.2%), and numbers of uncovered struts represented 11.3% of the total number of struts analyzed (**table 2**). There was an overweight of uncovered struts at follow-up in patients with baseline malapposition. Neointimal hyperplasia (**table 3**) was 10.8% with considerable variation between patients. **Fig. 4** shows the baseline and follow-up minimal luminal area (MLA) in the study population. Twenty-nine patients (39.2%) had a MLA of less than 4 mm^2 at baseline increasing to 39 (52.0%) at follow-up. Thirty-four of the

remaining patients retained a MLA of more than 4 mm². Overall, a significant reduction in MLA was found after 12 months compared to baseline.

Stent expansion

Quantitative OCT and IVUS data are listed in **table 2**, and calculated assessments of relative stent expansion at baseline and follow-up are provided in **table 3**. In 37.8 % of patients, we found an MSA of less than 5 mm². The $STENT_{NOM,CSA} / REF_{CSA}$ ratio was 1.10. The MSA / $STENT_{NOM,CSA}$ ratio of the stent initially chosen by the operator was ranging from 0.28 to 1.24 and was <0.90 in 65 (85.5%) patients.. The focal stent expansion compared to reference segment (MSA / REF_{CSA}) was 0.80 at baseline. Both the MSA and the stent volume were unchanged after 12 months.

Vessel remodeling

Vessel remodeling was assessed by IVUS (**table 2**). Overall a significant regression of plaque and vessel volume was found in both reference segments and the stented area. IVUS assessed intra-stent lumen did not change. There was no change in IVUS assessed malapposition area. Case variations in plaque and volume changes in the stented area are illustrated in **fig. 5**. A linear correlation between percentage change in peri-stent plaque and vessel volume was found, and positive remodeling >5% was identified in 23 patients and correspondingly, negative remodeling in 51 patients. Positive remodeling together with plaque regression was only observed in one patient (marked with arrow in **fig. 5**) in which thrombus resolution and minor evaginations were identified. By OCT, malapposition detected by positive extra-stent volume was identified at follow-up in eight patients (10.8%), and of those, IVUS demonstrated positive remodeling in two, both in combination with plaque progression. No signs of major evaginations were identified in the patients with positive remodeling.

Discussion

The main findings of the present study were: (1) stent strut malapposition occurred in the majority of patients but was mainly resolved at follow-up and was related to the maximum malapposition distance at baseline. (2) Nearly all struts were covered after 12 months, although strut coverage was seldom complete. Uncovered struts were more frequently found in areas with malapposition at baseline. Extreme IH was rare, and the median percentage of IH was low. (3) Stent under-expansion was a frequent finding and the selected stents tended to be undersized compared to OCT-derived reference segments. (4) Peri-stent negative vessel remodeling occurred in the majority of patients and was related to plaque regression, while positive remodeling predominately was associated with plaque progression. No major evaginations were encountered.

The study population differs in some aspects from the overall STEMI population as a consequence of the inclusion criteria of the main trial. Patients are younger than the general STEMI population, and have no history of ischemic heart disease. Mainly patients with unknown diabetes were included, as patients with manifest diabetes normally would be on statin treatment and thus excluded during the screening process.

The Resolute Integrity™ stent has previously been studied with OCT in three trials – in all of these in comparison to other second generation DES: (I) In a sub-study of the *RESOLUTE All Comers trial*¹⁵ comparing Resolute Integrity™ with Xience V™ (Abbott Vascular, Santa Clara, CA, USA), 30 “all comer” patients (6 of which presented with STEMI) with a total of 50 stents in the Resolute subgroup were analyzed after 13 months. (II) In the later *ComparisOn of neointimal coverage between zotaRolimus-eluting stent and everolimus-eluting stent using Optical Coherence Tomography* study (COVER OCT)¹⁶, 51 patients with de novo lesions were randomized to Xience V™ (26 patients) or Endeavor Resolute™ (25 patients) with post PCI OCT and follow-up after 9

months. Twenty-two patients in the Endeavor subgroup (including 10 patients presenting with acute coronary syndrome (ACS)) had OCT performed at follow-up. (III) Latest, the *Activity of Platelets after Inhibition and Cardiovascular Events: Optical Coherence Tomography study (APICE OCT)*¹⁷ was conducted on ACS patients evaluating neointimal coverage at 6 months in the everolimus eluting PROMUS element™ DES (Boston Scientific) vs. Resolute Integrity™. A total of 31 patients were examined with OCT in the Resolute group (hereof 12 patients with STEMI).

In the setting of ACS a higher incidence of malapposition - a predisposing factor for impaired strut coverage - has been shown^{18,12}. Compared to the findings in the present and other trials, malapposition at follow-up was found to occur more often in the RESOLUTE All Comers trial¹⁵ which may reside in differences in baseline and procedure characteristics together with a longer time to follow-up. Only COVER OCT¹⁶ provided data on baseline malapposition where a lower percentage of malapposed struts was found compared to the present trial. This could be explained by a lower prevalence of ACS in the COVER OCT trial, where only 11.4% of patients presented with STEMI. The stent diameter and maximum balloon pressure were similar to in the present trial.

Compared to the other trials, the percentage of uncovered struts was higher in the present trial. In the COVER OCT¹⁶ 16.7% of stents were completely covered after 9 months compared to 9.5% in the present trial. This finding might rely on the study population as previous studies^{19,20} have shown delayed coverage in ACS patients compared to patients with stable coronary disease. However, the available studies did not provide specified data regarding coverage on their ACS subgroups. The neointimal thickness in the present trial was similar compared to the trials mentioned above.

In STEMI patients, the presence of thrombus and vasoconstriction may result in underestimation of the vessel size and consequently an undersized stent may be implanted and increased risk of stent malapposition may occur. Furthermore, forceful expansion might be associated with increased risk of vessel injury and distal embolization²¹. The finding of stent

underexpansion in the present trial underscores the significance of this challenge. In the IVUS substudy of the *Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction* study (HORIZONS-AMI), a low post PCI MSA was found to be an independent risk factor for restenosis²². No studies have previously reported the incidence of stent underexpansion in STEMI populations, and only one study was found to provide delayed IVUS assessment within the following days after primary PCI²³. In that study assessing safety and feasibility of a self-expanding STENTYS DES in STEMI patients, IVUS was performed post PCI and after 3 days, and demonstrated an increase in the distal reference segment of 19%.

Zotarolimus eluting stents (ZES) have previously been compared to first generation paclitaxel eluting stents (PES) in serial IVUS studies where positive vessel remodeling was documented in PES treated lesions, but not - or to a lesser extent - in ZES²⁴⁻²⁶ treated lesions. These studies were based on the older Endeavor™ DES, which used a different stent polymer (based on phosphoryl choline), which had a less prolonged drug release compared to the Biolinx™ polymer.

Study limitations

The study population in this trial was selected according to the criteria's in the main trial. Although treatment arm assignment in the main trial was randomized, differences in measured values could be affected by ezetimibe. Baseline malapposition might be underestimated by thrombus material.

Conclusion

PCCI with The Resolute Integrity™ DES was found to be associated with nearly complete coverage after 12 months and low incidens of late acquired malapposition. Stent underexpansion was a frequent finding probably related to vasoconstriction and/or thrombus mass. There was an overall plaque regression and a limited positive remodeling associated with plaque progression.

Funding

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Conflicts of interests

LOJ has received research grants from Terumo, Biotronik, St Jude Medical, and Biosensors to her institution and honoraria from Abbott Vascular, AstraZeneca, St Jude Medical and Biotronik. The other authors had nothing to disclose.

Figure legends

Figure 1: Illustration of definitions for strut coverage. All identified struts were categorized according to coverage as illustrated above. The 3 subcategories to the left are all regarded as "uncovered", and the 3 subcategories to the right as "covered".

Figure 2: Flow chart depicting screening and enrollment of the trial.

Figure 3: Receiver operating characteristics (ROC) curve: The best cut-off for resolved incomplete stent apposition at follow-up was an acute maximal malapposition distance of 430 μm .

Figure 4: Scatterplot of MLA at baseline (x-axis) vs. MLA at follow-up (y-axis) with reference lines showing relations to $\text{MLA} = 4.0 \text{ mm}^2$ dividing patients in 4 subgroups: (1) Patients with MLA loss at follow-up, (2) Patients with preservation of $\text{MLA} > 4 \text{ mm}^2$, (3) Patients with preserved $\text{MLA} < 4 \text{ mm}^2$, and (4) Patients with MLA gain at follow-up. One patient (marked with arrow) was found to have an extreme but asymptomatic IH with an MLA reduction to 0.73 mm^2 , and target vessel revascularization was performed at follow-up. This patient had a 2.75/18 mm stent expanded to a baseline MSA of 4.0 mm^2 compared to a mean reference segment CSA of 5.99 mm^2 . By OCT, there was mid-stent underexpansion and moderate residual proximal thrombus material. The tissue behind the stent was lipid rich with cholesterol crystals and obscured media.

Figure 5: Scatterplot depicting the relation between relative changes in peri-stent plaque volume (x-axis) and the relative changes in peri-stent vessel volume (y-axis). Reference lines marks the $\pm 5\%$ borders for vessel remodeling and divide patients in 4 subgroups: (1) Patients with positive remodeling and plaque regression, (2) patients with positive remodeling and

plaque progression, (3) patients with negative remodeling and plaque regression, and (4) patients with negative remodeling and plaque progression. A linear positive correlation was found. Arrow marks patient with both plaque regression and positive remodeling. Review of OCT from this patient revealed, that the plaque regression was mainly driven by thrombus resolution, but signs of minor (<10% of stent diameter) evaginations were seen in the mid-stent section.

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Figures

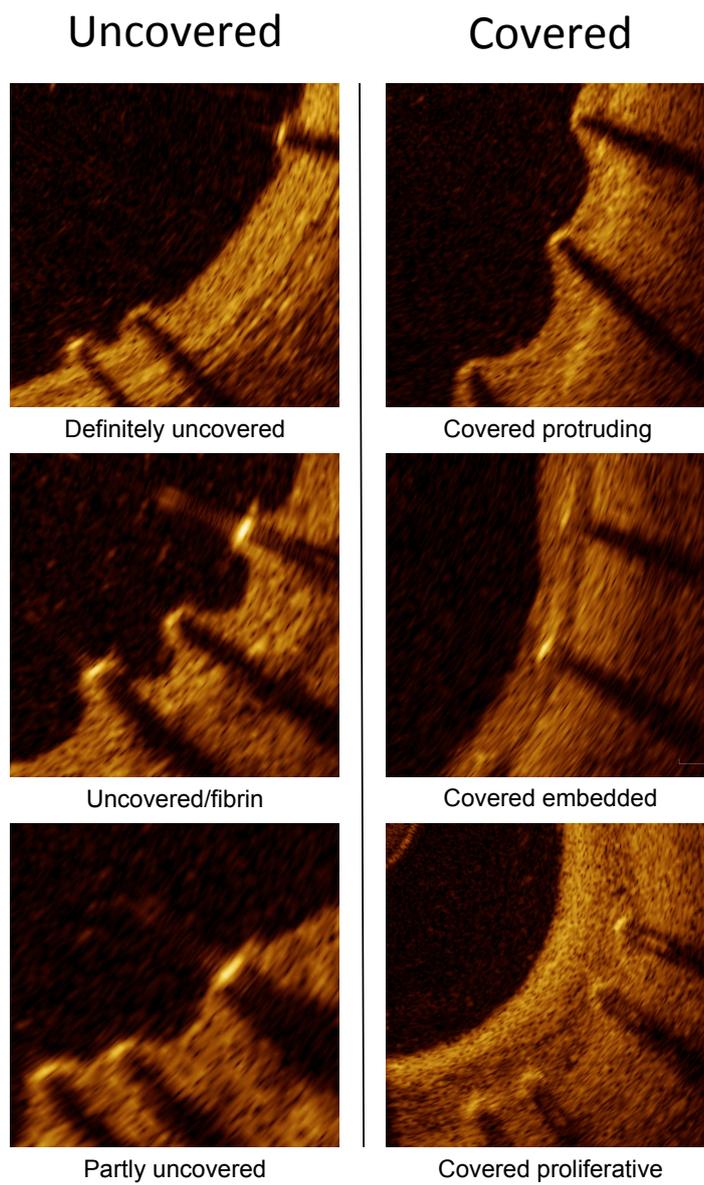


Figure 1

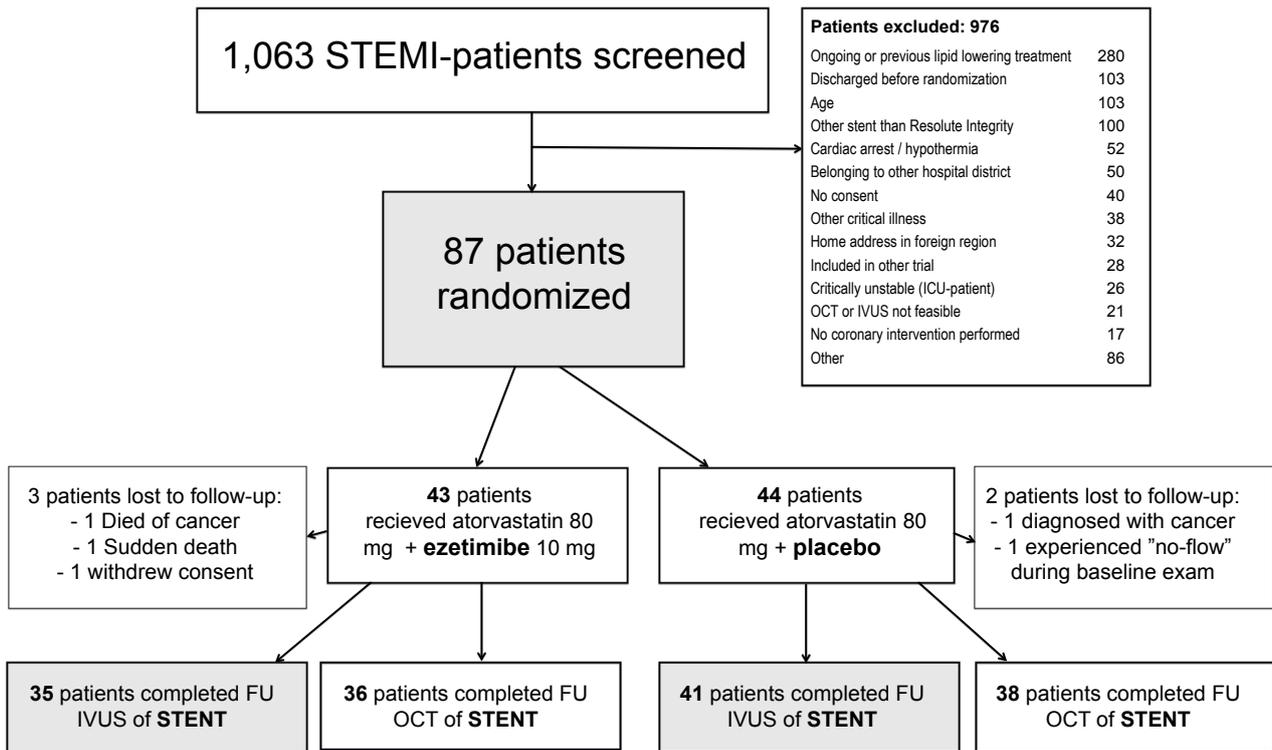


Figure 2

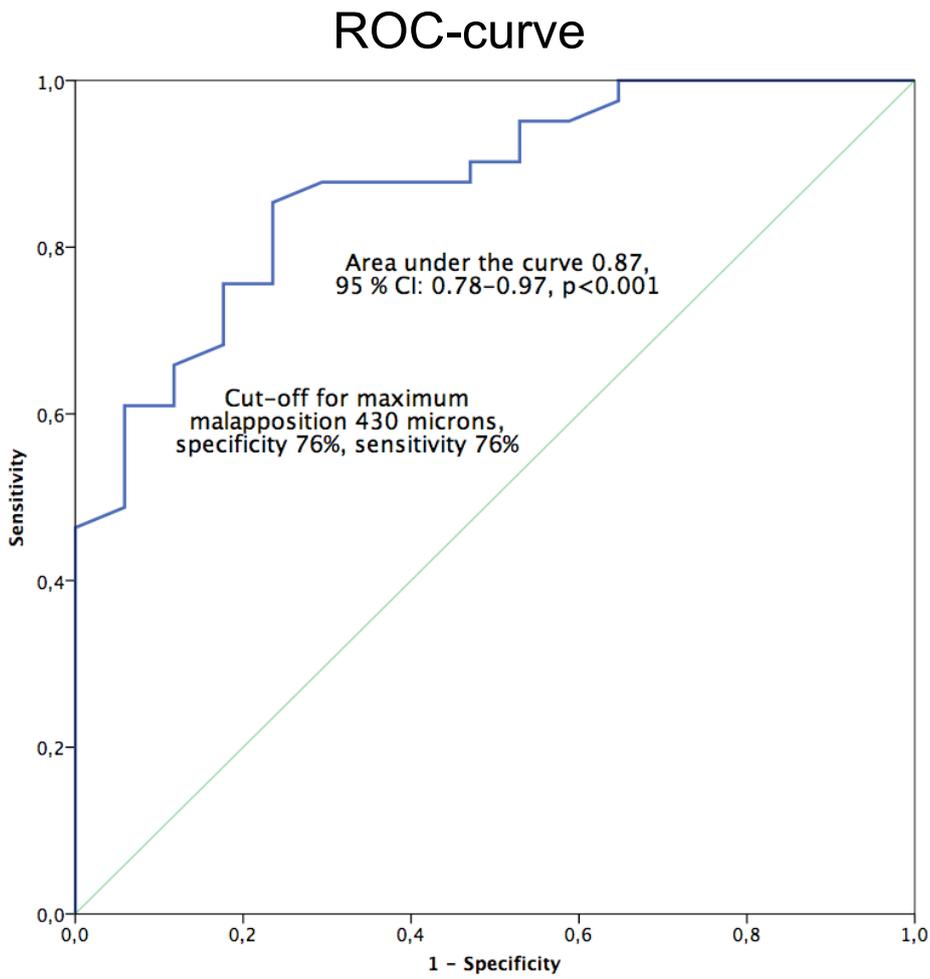


Figure 3

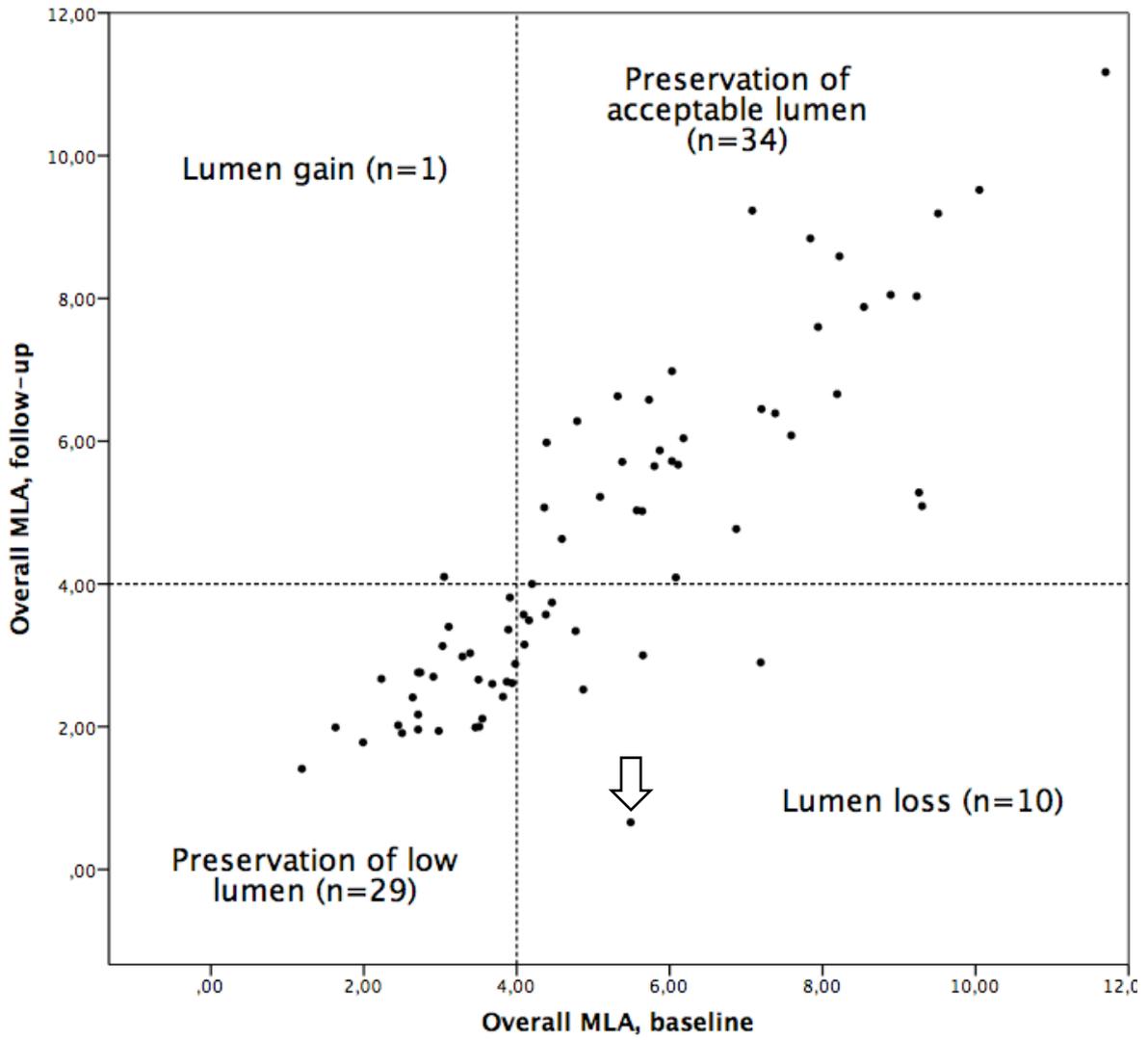


Figure 4

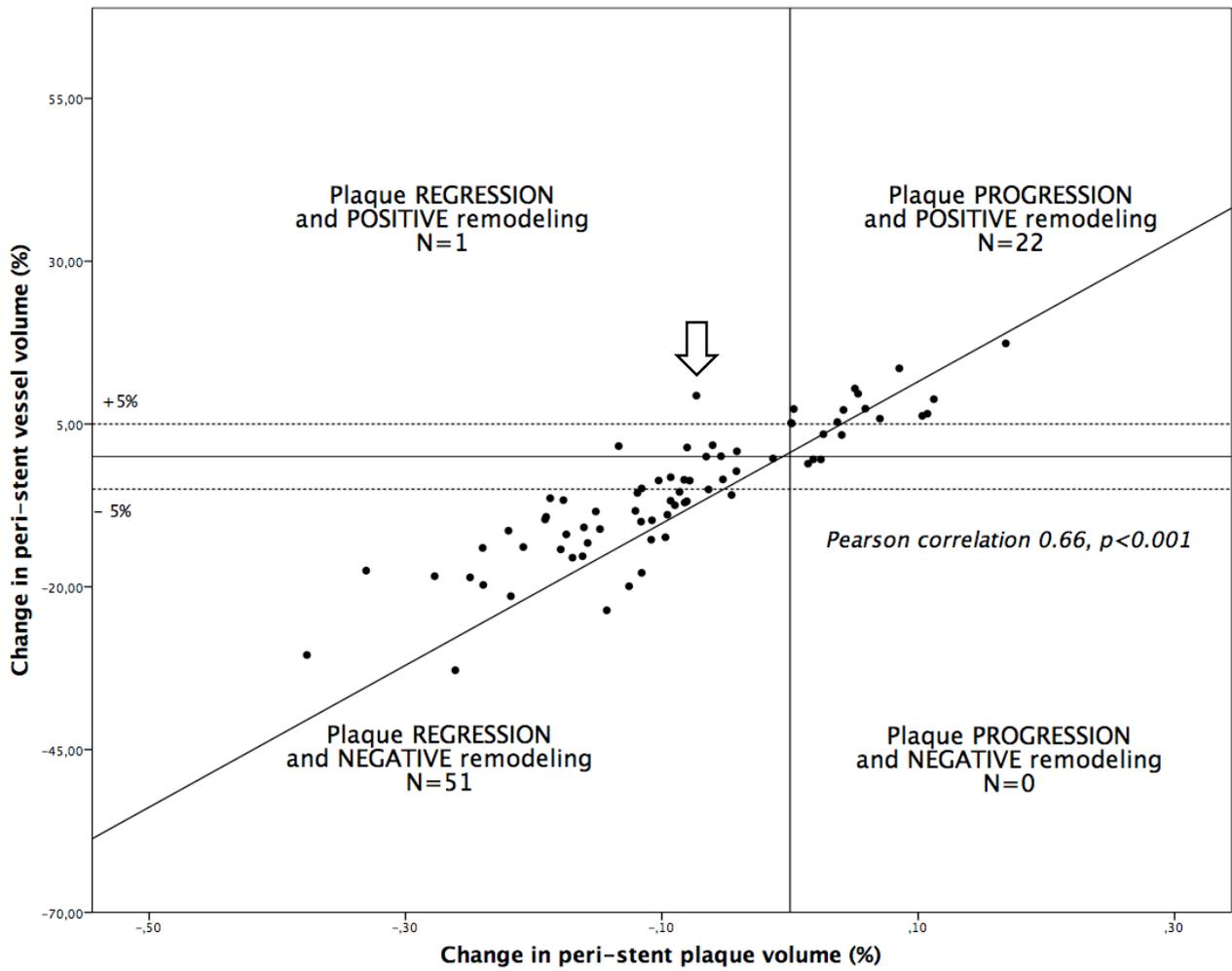


Figure 5

	Mean±SD / median (IQR) (n=74)
Age, years	55.8±10.2
Male gender, n (%)	63 (85.1)
Hypertension, n (%)	15 (20.3)
Current smoking, n (%)	41 (55.4)
Family disposition, n (%)	37 (50.0)
Diabetes, n (%)	2 (2.7)
Total Cholesterol >5 mmol/l, n (%)	57 (77.0)
HbA1c (mmol/mol)	38.0 (36.0, 41.0)
Systolic blood pressure, mmHg	126.3±20.2
Diastolic blood pressure, mmHg	75.4±11.6
Cardiovascular medications prior to admission, n (%)	
β-blockers	2 (4.5)
Calcium antagonists	3 (6.8)
ACE / ATII inhibitors	4 (9.1)
Diuretics	3 (6.8)
BMI (kg/m ²)	27.3 (24.9, 29.2)
Single vessel disease, n (%)	53 (71.6)
Infarct related artery, n (%)	
RCA	25 (33.8)
LAD	37 (50.0)
LCx	12 (16.3)
Lesion type, n (%)	

A	8 (10.8)
B1/B2	21 (28.4)
C	45 (60.8)
GP IIa/IIIb inhibitor, n (%)	28 (37.8)
Pre-PCI TIMI 0, n (%)	39 (52.7)
Angiographic reference vessel diameter, mm	3.1±0.5
Lesion length, mm	15.7±7.3
Stent length, mm	19.7±7.7
Nominal stent CSA, mm ²	7.1 (5.9, 9.6)
Max balloon pressure, atm	14.8±2.8
Thrombectomy, n (%)	15 (20.3)
ADP blockers	64 (86.5%)
ASA	74 (100%)

RCA = Right coronary artery, LAD = Left anterior descending artery, LCx = Left circumflex artery. Lesion type A: simple lesion, Lesion type B1/B2: more complex lesion, Lesion type C:

Complex lesion. TIMI = Thrombolysis in Myocardial Infarction, 0=no flow, 1=penetration without perfusion, 2=partial reperfusion, and 3=normal flow.

	Baseline	Follow-up	p-
	n=74	n=74	value
Table 2: OCT Stent assessment	Mean±SD / median	Mean±SD / median	
	(IQR)	(IQR)	
Malapposition			
Analyzable struts, n	18,875	19,208	0.14
Number of struts per cross section, n	13.0±1.8	13.2±1.6	0.29
Patients with malapposition (% of patients)	59 (79.7)	21 (28.4)	<0.001
Total number of malapposed struts, n	1097	113	<0.001
Percentage malapposed struts, %	5.8	0.6	<0.001
Resolved, n ptt. (% of baseline)	-	41 (69.5)	-
Persistent, n ptt. (% of baseline)	-	18 (30.5)	-
Late acquired, n ptt. (% of follow-up)	-	3 (14.3)	-
Maximal malapposition distance, µm	360 (200, 550)	305 (243, 618)	0.039
OCT Extra stent volume, mm ³	0.6 (-3.3, 6.7)	-12.9 (-26.0, -7.0)	<0.001
Patients with pos. value, n (%)	40 (54.8)	8 (10.8)	<0.001
- Thereof late acquired, n (%)	-	1 (1.4)	-
Coverage			
Number of uncovered struts, n (%)	18,875 (100.0)	2,177 (11.3)	<0.001
In ptt.s with baseline malapp., n (%)	-	2017 (92.7)*	-
In ptt.s. without baseline malapp., n (%)	-	160 (7.3)*	-
Number of uncov. malapposed struts, n	-	78 (4.1)	-
(‰)			
Completely covered, n patients (%)	-	7 (9.5)	-
Total no.s of struts at side-branch., (‰)	269 (14.3)	151 (7.9)	<0.01

Percent of side-branch struts uncovered, %	-	47.0	-
Intimal thickness, μm	-	120.0 (100, 160)	-
Expansion			
MSA / REF_{CSA}	0.80 \pm 0.2	-	-
MSA / $\text{STENT}_{\text{NOM,CSA}}$	0.75 \pm 0.2	-	-
Patients with MSA $<5 \text{ mm}^2$, n (%)	28 (37.8)	-	-
Stent size selection			
Accuracy ($\text{STENT}_{\text{NOM,CSA}} / \text{REF}_{\text{CSA}}$)	1.1 \pm 0.30	-	-

***⁾ Difference between those with and without baseline malapposition, p=0.004.**

Table 3: Quantitative data	Baseline	Follow-up	p-value
	Mean±SD / median (IQR)	Mean±SD / median (IQR)	
OCT	<i>n=74</i>	<i>n=74</i>	
Stent length, mm	19.6±6.1	19.8±6.3	0.13
Stent volume, mm ³	134.6 (96.4, 190.5)	133.1 (94.1, 189.3)	0.96
Minimal stent area, mm ²	6.1 (3.9, 7.4)	6.0 (4.2, 7.6)	0.98
Intra-stent lumen volume, mm ³	140.3 (96.2, 184.7)	117.7 (83.5, 168.8)	<0.001
Overall Minimal luminal area, mm ²	4.5 (3.4, 6.4)	3.8 (2.7, 6.1)	<0.001
Mean CSA, distal ref. segment, mm ²	6.5 (4.7, 8.5)	6.3 (4.0, 7.9)	0.004
Mean CSA, proximal ref. segment, mm ²	7.8 (5.6, 10.8)	7.3 (4.8, 9.9)	0.005
Neointimal volume, mm ³	-	12.9 (7.0, 26.0)	-
Neointimal volume, %	-	10.8±10.4	-
IVUS			
Stent segment	<i>n=76</i>	<i>n=76</i>	
Lumen volume, mm ³	140.6 (108.9, 183.4)	139.1 (104.7, 176.7)	0.090
Vessel volume, mm ³	314.7 (244.3, 417.0)	310.1 (244.1, 379.6)	<0.001
Peri-stent plaque volume, mm ³	170.8 (129.7, 235.5)	156.0 (120.2, 208.3)	<0.001
Proximal reference segment	<i>n=72</i>	<i>n=72</i>	
Lumen volume, mm ³	40.7 (30.7, 54.6)	37.2 (29.2, 49.5)	0.005
Vessel volume, mm ³	84.4 (68.6, 103.7)	78.4 (59.0, 99.2)	<0.001
Plaque volume, mm ³	41.0 (30.5, 53.0)	36.1 (25.3, 47.7)	<0.001
Distal reference segment	<i>n=75</i>	<i>n=75</i>	
Lumen volume, mm ³	37.1 (25.8, 50.6)	36.6 (24.7, 45.4)	0.032

Vessel volume, mm ³	68.0 (44.6, 87.1)	61.6 (41.0, 78.8)	<0.001
Plaque volume, mm ³	28.7 (17.7, 39.2)	23.4 (16.2, 38.4)	<0.001
Malapposition volume, mm ³	0.40 (0.1, 1.0)	0.33 (0.1, 1.6)	0.99
IVUS Extra stent volume, mm ³	-2.8 (-7.0, -0.2)	-7.5 (-14.9, -2.0)	<0.001
