EuroIntervention

Optical coherence tomography in patients with acute coronary syndrome

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KEYWORDS
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Abstract

Optical coherence tomography (OCT) is a novel invasive imaging technology that allows *in vivo* assessment of the coronary wall with high resolution (approximately 15 micron). OCT offers a number of specific diagnostic features to study culprit lesions in patients suffering from acute coronary syndrome (ACS). Clinical OCT studies in patients presenting with ACS were able to confirm post mortem histopathology findings and shed light on the dynamic nature of atherosclerotic plaque formation, modification and rupture. OCT confirmed *in vivo* that the incidence of target lesion and remote TCFA varies with the clinical syndrome of the patients, being most pronounced in patients with acute myocardial infarction as compared to patients with stable angina. In culprit lesions where rupture of a fibrous cap has been documented, the fibrous cap thickness was in the range of 50 micron and macrophage density was elevated. Encouraging small scale clinical studies evaluated treatment effects in this population. OCT was used to demonstrate statin effects on fibrous cap thickness or the effects of different stent designs. The markedly improved image quality and user-friendliness of the second generation, Fourier-domain OCT, will allow large scale clinical application and thus, will increase our understanding of the pathophysiology and the prevention of ACS.

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Introduction

Pathophysiology and coronary morphology in patients with acute coronary symptoms (ACS) are gaining more attention. Acute coronary syndromes caused by the rupture of a coronary plaque are common initial and often fatal manifestations of coronary atherosclerosis in otherwise healthy subjects. The detection of the lesions with high risk of rupture (the so called "vulnerable plaques") would be of main importance for the prevention of future ACS. Optical coherence tomography (OCT) has emerged as one of the most promising tools to assess patients with ACS and to detect key features of plaques at high risk for rupture, due to its ability to provide unique information on plaque composition, the thickness of the fibrous cap, the presence of macrophages and thrombi, and tissue collagen composition or indentify rare causes of ACS, such as spontaneous coronary dissection[1,2].

OCT features of plaque characterisation

OCT evaluates the optical properties of biological tissue. For clinical application, OCT signals are usually displayed as greyscale or false colour intensity maps, whereas OCT offers a variety of ways for signal analysis and display, which are currently mainly used in preclinical research. For research on ACS, a number of OCT features are of particular interest, as they allow the assessment of structures *in vivo*, that have been described in great detail by histopathology studies in patients dying from ACS, namely lipid/necrotic core rich, thin cap fibroatheroma (TCFA) and plaque rupture (Figure 1).

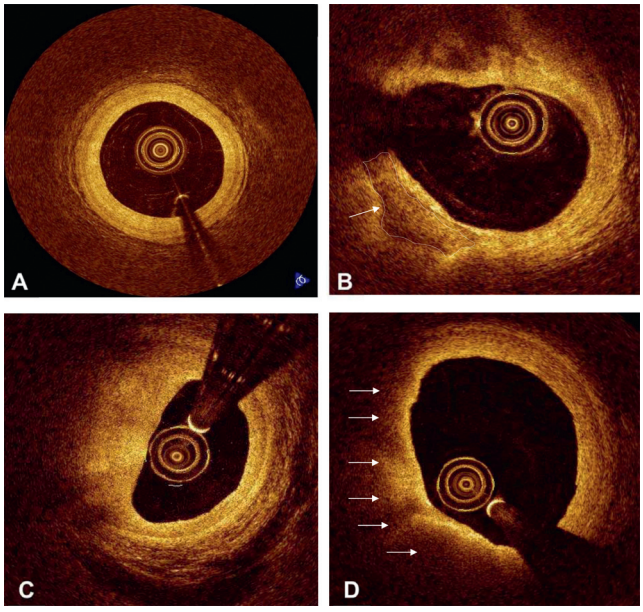

Figure 1. OCT plaque characterisation, clinical examples. A. Mild intimal thickening, the media corresponds to the signal poor, "dark" band, the adventitia is delineated B. Calcified plaque. Calcifications appear as sharply delineated, signal poor regions (dotted line). C. Eccentric fibrofatty plaque. Note the three-layer appearance from 12 to 6 o'clock position, while the remaining plaque shows a gradual attenuation of the OCT signal. D. Eccentric lipid-rich plaque. The OCT signal is intense but drops rapidly (arrows).

Assessment of plaque composition and the presence of lipid/necrotic core

The propensity of atherosclerotic lesions to destabilise and rupture is highly dependent on their composition. In comparison with histology OCT, has demonstrated to be highly sensitive and specific for characterising different types of atherosclerotic plaques ranging from 71-98% for fibrous plaques, 95-97% for fibro-calcific plaques, and 90-94% for lipid-rich plaques in comparison to histology[3]. *Ex vivo* validations have also shown that OCT is superior to conventional and integrated backscatter IVUS for the characterisation of coronary atherosclerotic plaque composition. *In vivo*, OCT is able to identify most of the architectural features identified by IVUS and may be superior for the identification of lipid pools[4] (Figure 2).

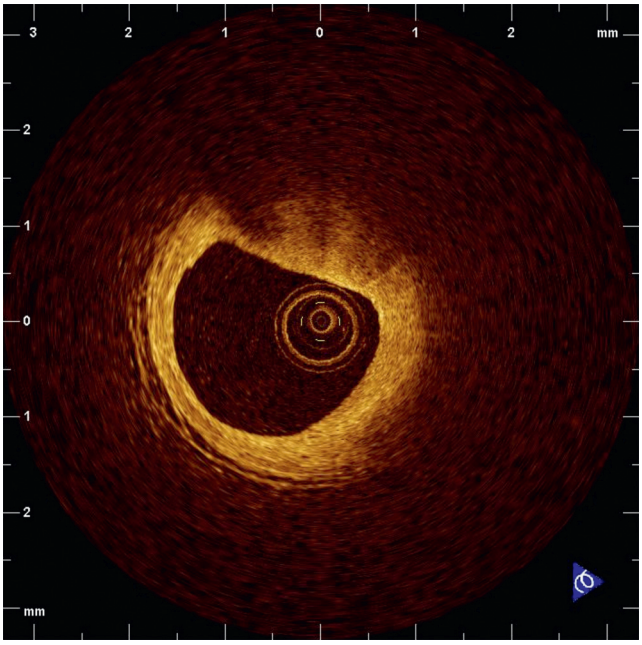

Figure 2. Eccentric lipid-rich plaque with thin fibrous cap in 11 to 2 o'clock position.

However, interpretation of OCT images is observer dependent and can be hampered by the limited penetration depth of OCT. A study comparing OCT to histopathology reported a lower sensitivity for plaque components. Misclassification occurred in 41% of lesions predominantly due to the inability to distinguish calcium deposits from lipid pool caused by incomplete penetration depth into the vessel wall[5]. In the future, quantitative tissue characterisation, e.g., by attenuation imaging, might overcome this limitation[6].

Identification of thin cap fibroatheroma (TCFA)

Autopsy studies of sudden cardiac death victims have shown that the most frequent cause of the coronary occlusion is rupture of a thin-cap fibroatheroma (TCFA) plaque. Such lesions are characterised by a large necrotic core with a thin fibrous cap usually <65 microns in thickness. OCT allows the diagnosis of thin fibrous cap atheroma with a sensitivity of 90% and a specificity of 79% when compared to histopathology[7].

Assessment of fibrous cap thickness

While conventional intracoronary imaging techniques such as IVUS or IVUS-VH do not have enough resolution (currently in the range of 150 micron) to directly visualise and evaluate in detail the fibrous cap, OCT has demonstrated in correlation with histological examinations that it is able to provide accurate measurements of the thickness of the fibrous cap[8].

Assessment of tissue collagen composition

A fibrous cap is predominantly composed of collagen, synthesised by intimal smooth muscle cells, which together impart mechanical integrity. Mechanisms that weaken the cap and potentially lead to plaque instability include collagen proteolysis and impeded collagen synthesis, resulting in a net reduction in collagen content, thinning and disorganisation of collagen fibre orientation. Polarisation-sensitive (PS) imaging enhances OCT by measuring tissue birefringence, a property that is elevated in biological tissues containing proteins with an ordered structure, such as organised collagen. PS-OCT imaging can provide both, conventional greyscale OCT as well as PS-OCT images, in one single pullback through the coronary. PS-OFDI birefringence has been demonstrated to be highly related to total collagen content in atherosclerotic plaques as well as in fibrous plaques *in vitro*[9].

Visualisation of macrophage accumulation within plaque

Intense infiltration by macrophages of the fibrous cap is another of the features of the vulnerable plaques. An *ex vivo* study by Tearney et al, demonstrated OCT could be able to quantify macrophage within the fibrous cap[10].

Visualisation of plaque rupture and intracoronary thrombosis

Plaque rupture with subsequent thrombosis is the most frequent cause of ACS. OCT can identify intracoronary thrombus and plaque rupture with high accuracy[11]. Furthermore, Kume et al, demonstrated that OCT might be able to distinguish between white and red thrombus. Red thrombi, predominantly consisting of red blood cells, appear in OCT as high-backscattering structures with dorsal, signal-free, shadowing while white thrombi, predominantly consisting of platelets and white blood cells, appear as a low-backscattering structures[12]. OCT could be helpful to identify the culprit lesion in ACS and might provide additional information about the underlying cause that lead to the plaque rupture (Figure 3).

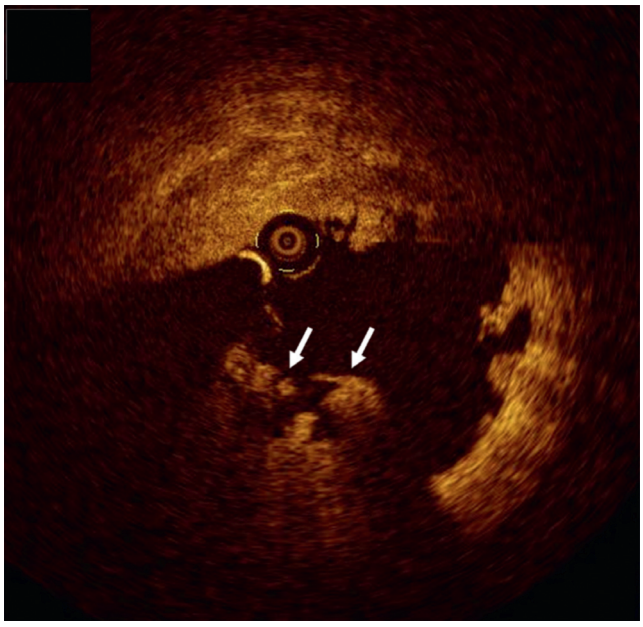

Figure 3. Intracoronary thrombus formation. Red thrombus is protruding into the lumen (arrows), dorsal shadowing obscures the artery wall.

Clinical observations in patients presenting with ACS

In patients presenting with ACS and STEMI, several authors have evaluated the OCT appearance of culprit coronary lesions and confirmed *in vivo* a link between lipid-rich plaque, TCFA, macrophage infiltration and clinical syndrome (Figures 4, 5).

In patients with ACS, a series of studies showed, that the incidence of lipid-rich plaque is related to the clinical presentation but not to diabetes[13] or gender[14]. In a study comparing patients with different clinical presentation, TCFA culprit lesions showed an increasing incidence from 20 to 70% in three patient groups, stable angina, ACS and STEMI[15]. In STEMI patients, the incidence of plaque rupture was 73% by when assessed by OCT, significantly higher than that detected by both angioscopy (47%, p=0.035) and IVUS (40%, p=0.009)[16]. The incidence of multiple TCFA within the epicardial coronary tree is higher in patients presenting with acute myocardial infarction (38%) as compared to patients presenting with stable angina (0%)[17]. Similarly, in a study with patients with acute coronary syndrome, 64% of patients had more than one TCFA by 3-vessel OCT analysis[7]. TCFA tend to cluster in predictable spots within the proximal segment of the LAD, namely near side branches, opposite the side branch bifurcation. Inter-observer variability in the *in vivo* diagnosis of TCFA is low (kappa 0.88)[18]. However, the prognostic value of the presence of non-culprit TCFA as observed by OCT still needs to be established[19].

In a Japanese series of STEMI patients, the incidence of plaque rupture was 73% with a fibrous cap thickness (mean 49±21 µm)[16]. A significantly thinner cap has been observed ruptured plaques with symptom onset at rest as compared to symptom onset at exercise[20]. Another study demonstrated at plaque rupture sites a greater macrophage density than at non-ruptured sites[21]. Macrophage density in the fibrous cap correlated with the white blood cell count[22]. Plaque rupture sites in patients with ACS are associated with up regulation of fractalkine and CX3CR1-expressing mononuclear cells[23].

These clinical observations are important, as they do not only confirm histopathology observations, but also offer the potential to assess atherosclerotic plaque and its dynamic changes in a longitudinal way.

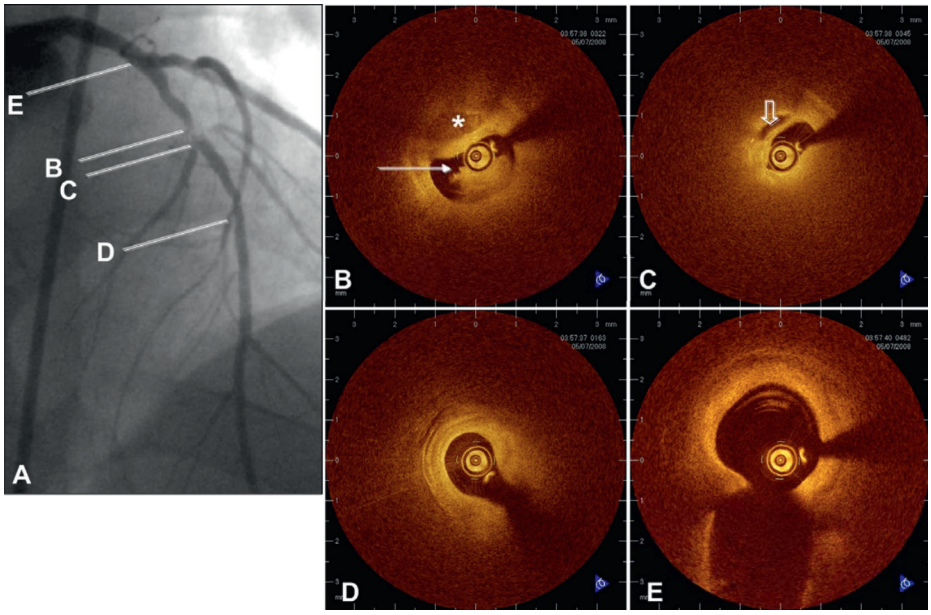

Figure 4. OCT findings in a patient presenting with STEMI, caused by a lesion in the mid LAD. A. Coronary angiogram, showing a subtotal lesion in the LAD B. Lesion site: a calcified plaque is visible in 12 o'clock position (signal poor with sharply delineated borders, asterix) while in 6 o'clock position, there is thrombus (arrow) protruding into the lumen C. Lesion site: A dissection flap is visible in 12 o'clock position (arrow), while extensive red thrombus is obscuring the vessel circumference. C. Distal reference D. Proximal vessel segment, bifurcation of LAD/LCx.

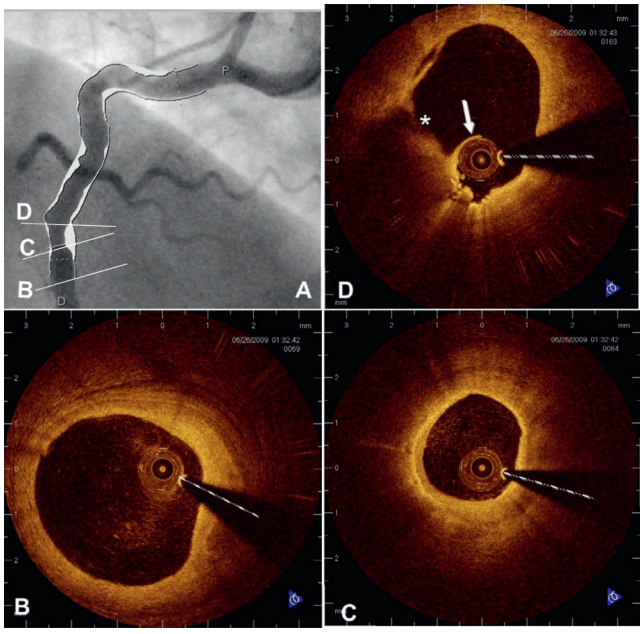

Figure 5. Plaque rupture in a patient presenting with NSTEMI. A. Coronary angiogram of the right coronary artery (online QCA: RD=3.47 mm, MLD=2.01 mm, 42% diameter stenosis). B. Distal reference C. Minimal lumen area showing 360 degrees of lipid-rich plaque D. Lesion site showing plaque rupture with a dissection flap (arrow) protruding into the lumen, while the necrotic core (asterix) is directly exposed the blood flow.

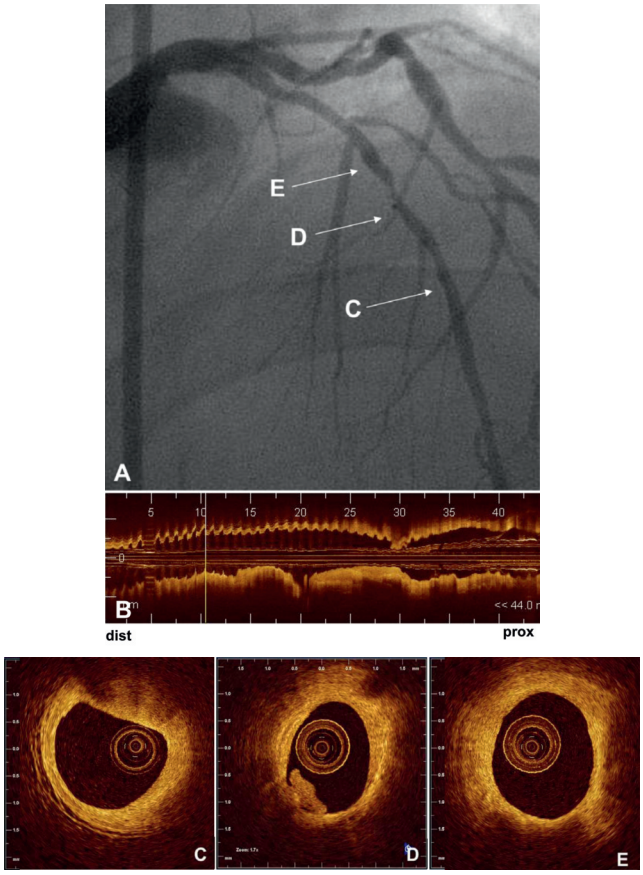

Figure 6. Multiple target vessel TCFA in a patient presenting with ACS. A. Coronary angiogram demonstrating a short, subtotal lesion of the LAD B. Longitudinal view of the OCT pullback C. distal non-flow limiting TCFA D. Target lesion showing lumen narrowing and mural thrombus in 7 o'clock position E. proximal non-flow limiting TCFA.

OCT assessment of treatment effects in ACS patients

OCT is increasingly used to assess treatment effects in patients presenting with ACS. It can be applied to study the acute effects of manual of rheolytic thrombus aspiration[24]. Likewise, OCT is used to

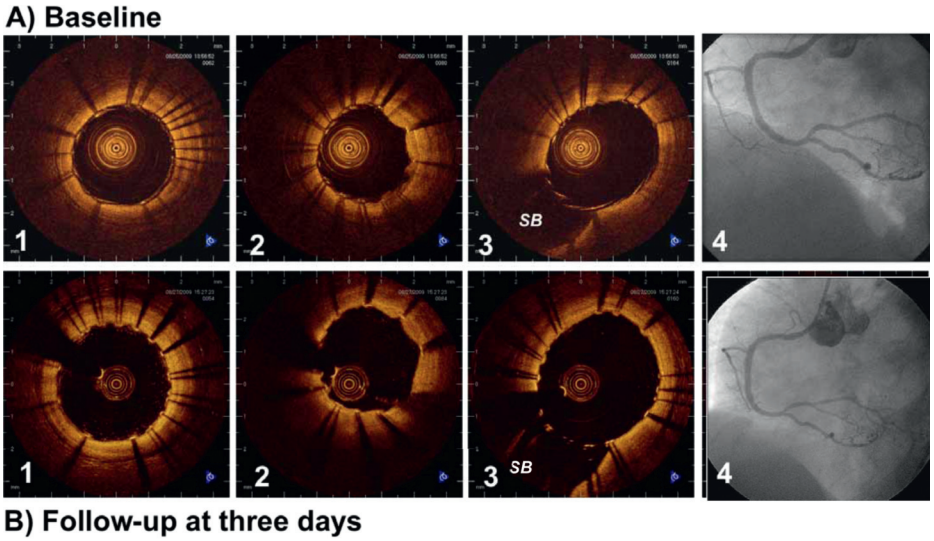

Figure 7. OCT assessment of acute treatment effects in a patient undergoing primary PCI with implantation of a self-expanding stent (Stentys). A. Baseline, immediately after stent implantation B. Three days follow-up (apposition protocol); 1-3 are corresponding OCT images at both study time points. 1) Good stent expansion 2) Minimal lumen area with thrombus protruding between the stent struts at baseline that resolved ad follow up 3) Proximal stent portion with side branch ostium in 7 o'clock position. At three days follow-up early strut coverage is visible.

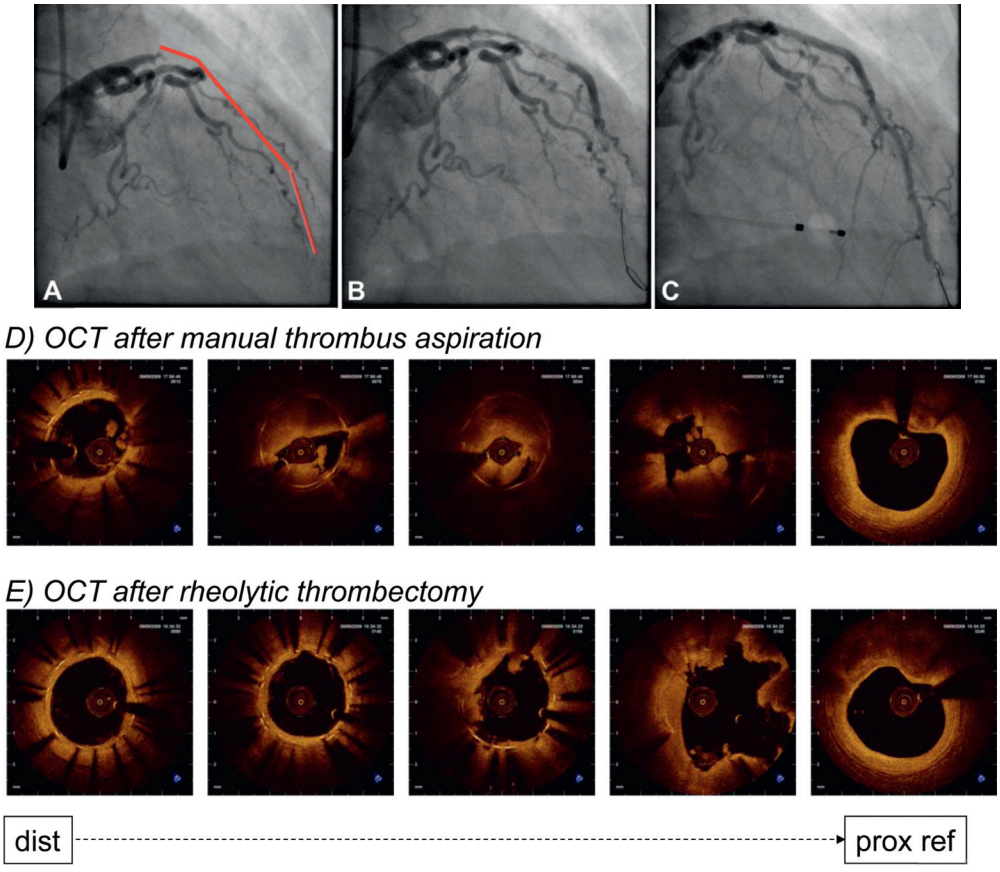

Figure 8. OCT assessment of acute treatment effects in a patient presenting with STEMI caused by late DES thrombosis. A. Coronary angiogram preprocedure showing occlusion of the LAD stents B. Coronary angiogram after predilatation with a 1.5 mm balloon and manual thrombus aspiration. C. Coronary angiogram after rheolytic thrombectomy. D. OCT pullback after manual thrombus aspiration demonstrating high residual thrombus burden E. OCT pullback after rheolytic thrombectomy demonstrating substantial reduction in thrombus load.

assess the long-term effects of drug eluting stents in acute myocardial infarction[25]. The latter study illustrated, that drug eluting stents in a STEMI population showed a higher rate of incomplete strut apposition and incomplete tissue coverage at long term follow-up than in patients treated for stable angina. This observation has driven the evaluation of self-expanding stent concepts for treatment

of STEMI patients, e.g. being currently evaluated in the "apposition" study family. Likewise, OCT is being used to assess treatment effects aimed at stabilising thin fibrous caps, such as change in fibrous cap thickness during statin therapy[26] or dedicated scaffolds[27].

Conclusion

In patients with ACS, intracoronary OCT has a unique capability to visualise features of TCFA *in vivo*. Small scale clinical studies confirmed that OCT is suitable to assess treatment effects and allows for longitudinal trials to study the dynamic nature of coronary artery disease and plaque vulnerability. The markedly improved image quality and user-friendliness of the second generation, Fourier-domain OCT[28], will allow large scale clinical application and thus, will help to increase our understanding of the pathophysiology and the prevention of ACS and myocardial infarction.

Appendix for figures

All OCT examples were acquired with Lightlab Imaging, Boston, MA, USA, OCT systems.

ACS: acute coronary syndrome
DES: drug eluting stent
LAD: left anterior descending artery
LCx: left circumflex artery
NSTEMI: non ST-elevation myocardial infarction
QCA: quantitative coronary angiography
RCA: right coronary artery
STEMI: ST-elevation myocardial infarction
TCFA: thin cap fibroatheroma

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