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VASCULAR HEALING AFTER CORONARY STENTING EVALUATED BY OPTICAL COHERENCE TOMOGRAPHY

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To my family

ABSTRACT

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Optical coherence tomography (OCT) is a novel intracoronary imaging application for the assessment of native lesions and coronary stents. The purpose of this thesis was to evaluate the safety and feasibility of frequency-domain OCT (FD-OCT) based on experiences of the Satakunta Central Hospital (I). Early vascular healing was evaluated after implantation of endothelial progenitor cell capturing (II) and bio-active titanium-nitride-oxide coated stents (III) in two studies, each with 20 patients. Vascular healing was also compared after implantation of bio-active and everolimus-eluting stents on 28 patients after 9-month follow-up (IV). Long-term vascular healing of bio-active and paclitaxel-eluting stents was assessed in the last study with 18 patients (V).

The results indicate that FD-OCT is safe and feasible (I). Both bio-active and endothelial progenitor cell capturing stents showed near-complete endothelialisation after one-month follow-up, which is desirable when prolonged dual anti-platelet therapy needs to be avoided after stenting (II and III). Endothelialisation of bio-active stents showed a predictable pattern at mid-term and long-term follow up (IV and V). Endothelialisation of everolimus-eluting stents was not complete at 9 months follow-up, which may suggest that interruption of dual antiplatelet therapy at this time point may not be safe (IV). Finally, delayed vascular healing may be present in patients treated with paclitaxel-eluting stents as long as 4 years from implantation, which reinforces the previously raised concerns on the long-term safety of this device (V).

Keywords: optical coherence tomography, stent, percutaneous coronary intervention, vascular healing, endothelialisation

TIIVISTELMÄ

Tuomas Lehtinen-Svahn

SEPELVALTIMON PARANEMISEN ARVIOIMINEN
VALOKERROSKUVAUKSELLA STENTTAUKSEN JÄLKEEN

Turun yliopisto, Lääketieteellinen tiedekunta
Kardiologia ja kardiovaskulaarilääketiede
Kliininen tohtoriohjelma
Sydänkeskus, Satakunnan keskussairaala
Sydänkeskus, Turun yliopistollinen keskussairaala

Turun yliopiston julkaisuja
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Valokerroskuvaus on uusi suonensisäinen kuvantamismenetelmä sepelvaltimoiden ja sepelvaltimostenttien tutkimiseen. Väitöskirjatyön tarkoituksena oli arvioida menetelmän turvallisuutta ja käyttökelpoisuutta Satakunnan keskussairaalan kokemusten perusteella (I). Suonen varhaista paranemista arvioitiin endoteelisolujen esiasteita houkuttelevan stentin (II) sekä bioaktiivisen, titaanityppioksidilla päällystetyn stentin (III) asennuksen jälkeen kahdessa osatyössä, joissa kummassakin oli 20 potilasta. Verisuonen paranemista verrattiin myös bioaktiivisen stentin sekä everolimuusia vapauttavan lääkestentin välillä 9 kuukauden seurannan jälkeen 28 potilaalla (IV). Suonen pitkäaikaisparanemista verrattiin bioaktiivisen stentin ja paklitakselia vapauttavan lääkestentin välillä 18 potilaalla (V).

Tulokset osoittavat, että sepelvaltimon valokerroskuvaus on turvallinen ja käyttökelpoinen (I). Sekä bioaktiivinen että endoteelisolujen esiasteita houkutteleva stentti endotelisoituivat lähes täydellisesti kuukaudessa, mikä on edullista, jos pitkäkestoista verihiutaleiden kaksoisestolääkitystä halutaan välttää (II ja III). Bioaktiivinen stentti endotelisoitui ennustettavalla tavalla keskipitkän ja pitkän seuranta-ajan jälkeen (IV ja V). Everolimuusia vapauttavan stentin endotelisaatio ei ollut täydellistä 9 kuukauden seurannassa, mikä voi viitata siihen, ettei verihiutaleiden kaksoisestolääkityksen keskeyttäminen tässä vaiheessa ole turvallista (IV). Lopuksi, verisuonen viivästynyttä paranemista todettiin jopa neljän vuoden kuluttua paklitakselia vapauttavan stentin asennuksesta, mikä vahvistaa aiemmin heränneitä epäilyjä tämän stentin turvallisuudesta (V).

Avainsanat: sepelvaltimon valokerroskuvaus, stentti, sepelvaltimon pallolaajennus, verisuonen paraneminen, endotelisaatio

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ABBREVIATIONS

ACCF	American College of Cardiology Foundation
ACS	acute coronary syndrome
ADE	automated differential echogenicity
ADP	adenosine diphosphate
AHA	American Heart Association
AMI	acute myocardial infarction
AS	area stenosis
BES	biolimus-eluting stent
BMS	bare metal stent
BVS	bioresorbable vascular scaffold
BP	blood pressure
CABG	coronary artery by-pass grafting
CAD	coronary artery disease
CFR	coronary flow reserve
CSA	cross-sectional area
DAPT	dual anti-platelet therapy
DES	drug-eluting stent
DS	diameter stenosis
EES	everolimus-eluting stent
ESC	European Society of Cardiology
EPC	endothelial progenitor cell
FD-OCT	frequency-domain (or Fourier-domain) optical coherence tomography
FFR	fractional flow reserve
HR	hazard ratio
iFR	instantaneous wave-free ratio
IMR	index of microvascular resistance
ISA	incomplete stent apposition
ISR	in-stent restenosis
IB-IVUS	integrated backscatter intravascular ultrasound
IVUS	intravascular ultrasound
LLL	late lumen loss
LST	late stent thrombosis
MACE	major adverse cardiac event
MI	myocardial infarction
MLA	minimum lumen area
MLD	minimum lumen diameter
NIH	neointimal hyperplasia
NIRS	near-infrared spectroscopy
NSTE-ACS	non-ST-elevation acute coronary syndrome

NSTEMI	non-ST-elevation myocardial infarction
OCT	optical coherence tomography
PCI	percutaneous coronary intervention
PES	paclitaxel-eluting stent
PET	positron emission tomography
POBA	plain old balloon angioplasty
QCA	quantitative coronary angiography
SCAI	Society for Cardiac Angiography and Interventions
SES	sirolimus-eluting stent
SPECT	single-photon emission computed tomography
ST	stent thrombosis
STEMI	ST-elevation myocardial infarction
TD-OCT	time-domain optical coherence tomography
TCFA	thin-cap fibroatheroma
TIMI	thrombolysis in myocardial infarction
TITANOX	titanium-nitride-oxide
TLR	target-lesion revascularization
TTE	transthoracic echocardiography
TVR	target-vessel revascularization
VH-IVUS	virtual histology intravascular ultrasound
VLST	very late stent thrombosis
ZES	zotarolimus-eluting stent

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which are referred to in the text by their respective Roman numerals:

I. Lehtinen T, Nammas W, Airaksinen JK, Karjalainen PP. Feasibility and safety of frequency-domain optical coherence tomography for coronary artery evaluation: a single-center study. Int J Cardiovasc Imaging. 2013;29:997-1005.

II. Lehtinen T, Kiviniemi TO, Ylitalo A, Mikkelsson J, Airaksinen JK, Karjalainen PP. Early vascular healing after endothelial progenitor cell capturing stent implantation. J Invasive Cardiol. 2012;24:631-5.

III. Annala AP, Lehtinen T, Kiviniemi TO, Ylitalo A, Nammas W, Karjalainen PP. Vascular healing early after titanium-nitride-oxide-coated stent implantation assessed by optical coherence tomography. J Invasive Cardiol. 2013;25:186-9.

IV. Karjalainen PP, Kiviniemi TO, Lehtinen T, Nammas W, Ylitalo A, Saraste A, Mikkelsson J, Pietilä M, Biancari F, Airaksinen JKE. Neointimal coverage and vasodilator response to titanium-nitride-oxide-coated bioactive stents and everolimus-eluting stents in patients with acute coronary syndrome: Insights from the BASE-ACS trial. Int J Cardiovasc Imaging. 2013;29:1693-703.

V. Lehtinen T, Airaksinen KE, Ylitalo A, Karjalainen PP. Stent strut coverage of titanium-nitride-oxide coated stent compared to paclitaxel-eluting stent in acute myocardial infarction: TITAX-OCT study. Int J Cardiovasc Imaging. 2012;28:1859-66.

1. INTRODUCTION

The first coronary balloon angioplasty was performed in 1977 (1). At first, it was often complicated by restenosis of the target vessel or abrupt vessel occlusion due to dissection. As a solution to this problem, a metallic expandable intracoronary stent was developed in 1987 (2). This innovation lowered the risk of restenosis and the need for repeated procedures and improved the safety of the procedure by reducing the risk of abrupt vessel occlusion. However, the use of metallic stents in percutaneous coronary intervention (PCI) gave rise to a new phenomenon, in-stent restenosis (ISR) (3). This phenomenon led to the development of drug-eluting stent (DES) (4, 5). These metallic stents were covered with cytostatic drugs bound to a polymer in order to reduce restenosis by inhibiting the proliferation of smooth muscle cells. DES proved to be superior when compared to bare-metal stents (BMS) in reducing the ISR, without difference in mortality (6).

Stent thrombosis (ST) is a serious but rare complication of PCI, often leading to myocardial infarction (MI) or death. According to the widely accepted classification by the Academic Research Consortium, ST can be stratified based on timing of its occurrence after stenting as either acute (0 to 24 hours), subacute (>24 hours to 30 days), late (>30 days to 1 year) and very late (>1 year) (7). Depending on the certainty of the event, ST can also be classified as definite, probable and possible. In the era of BMS, most cases of ST occurred within one month from implantation. Brachytherapy, that was once used to treat ISR, was associated with increased risk of late stent thrombosis (LST) and since then, increased concern has arisen over the increased risk of LST or very late stent thrombosis (VLST) with first-generation DES (6, 8, 9). Pathological studies have revealed the association of incomplete vascular healing and LST (10).

Optical coherence tomography (OCT) is a novel invasive imaging modality which has been applied earlier in ophthalmology (11-13). When compared to other imaging modalities, it has superior axial resolution of up to 10 μm, which allows reliable visualization of intracoronary structures and stent endothelialisation. The recent advances in coronary OCT technology with the development of frequency-domain OCT (or Fourier-domain OCT, FD-OCT) have made this technique more feasible with the avoidance of proximal balloon occlusion that was required with the older time-domain (TD-OCT) technique. Incomplete stent endothelialisation has been proposed as a surrogate for the risk of stent thrombosis (ST) (10). The reports of very late stent thrombosis (VLST) of the first-generation DES and delayed endothelialisation associated with it have made this an important aspect in the development of new stents. OCT is currently the only clinically available intravascular imaging application to reliably evaluate stent endothelialisation. Intravascular ultrasound (IVUS), the most widely applied invasive intracoronary imaging modality, lacks the resolution to assess this feature. In PCI for patients with elevated risk of bleeding or in situations where elective surgery is needed shortly after PCI, unnecessary prolongation of dual antiplatelet therapy (DAPT) after stent implantation needs to be

avoided without predisposing the patient to the risk of ST. OCT has been used to assess stent healing in the latter clinical setting, but prospective studies are currently lacking to support the clinical use of OCT in determining the length of DAPT (14). Due to its high resolution, OCT is a useful tool in the evaluation for the mechanisms behind ST (15, 16).

Alternative solutions to DES have been developed in order to reduce risk of ST without compromising the inhibition of restenosis. Titanium is widely applied in prostheses and implants due to its good biocompatibility. The concept of bio-active stent (BAS) was created by coating a metallic stent with titanium-nitride-oxide (TITANOX) (17). It has proved to be safe and feasible in several studies on patients with stable angina pectoris as well as acute coronary syndromes (ACSs) (18, 19). It has shown to reduce the frequency of MI and LST in long-term follow-up when compared to paclitaxel-eluting stents (PESs) (20).

Another example of novel alternative stent technology is the endothelial-progenitor-cell (EPC) capturing stent (21). This is a stent which is designed to attract circulating EPC's to enhance stent endothelialisation. In experimental models, the EPC-capturing stent has been shown to endothelialize very rapidly, even as fast as 24 hours (22). The hypothesis was that rapid endothelialisation also reduces proliferation of myocytes and thus restenosis. Despite initial promising results, the reduction of ISR with rapid endothelialisation in larger randomized trials has not appeared to be a successful strategy (23). However, as rapid endothelialisation is generally considered a surrogate for reduced risk of ST, a stent with these qualities is favourable in special situations where bleeding risk is elevated.

The aims of this thesis are to assess the safety and feasibility of the use of FD-OCT based on the experiences of a single centre; and to evaluate the vascular healing and stent endothelialisation of different stents at different time points after PCI.

2. REVIEW OF THE LITERATURE

2.1 Invasive imaging of the coronary anatomy

2.1.1 Coronary angiography

Coronary angiography is considered to be the golden standard for the assessment of coronary anatomy and pathology. The principles of the procedure and image acquisition are well documented (24). Although other non-invasive imaging modalities are increasingly used for diagnostic purposes, coronary angiography is mandatory when revascularization with either coronary artery by-pass grafting (CABG) or PCI is considered for coronary artery disease (CAD). Rapid invasive evaluation of coronary arteries and identification of the culprit lesion is essential for the modern management of patients with ACSs, and is a prerequisite for PCI often performed consecutively.

However, coronary angiography has several limitations in the assessment of coronary pathology. Coronary angiogram is a two-dimensional representation of a three-dimensional structure. It only allows visualization of the contours of the vessel lumen while giving limited information on the structures of the vessel wall or eccentric coronary lesions. Angulation, lesion foreshortening, overlapping of coronary branches, heavily calcified lesions and diffuse reference vessel disease can complicate the interpretation of coronary angiogram. Post-mortem studies have shown the limitations of coronary angiography to detect significant coronary lesions (25-29). While technological advances have led to improved image quality, the basic principles of image acquisition have remained the same, with inherent limitations, many of which cannot be circumvented. With the increasing knowledge of the pathology and pathophysiology of CAD, the shortcomings of coronary angiography in the assessment of coronary lesion severity and morphology, in the guidance of complex PCI and in post-PCI evaluation have become evident (30-35). There is significant inter-observer variability in the visual assessment of the coronary angiogram (26, 36, 37). The introduction of quantitative coronary angiography (QCA) has decreased this inter-observer variability when compared to visual estimation (37) and the use of three-dimensional reconstructions may further improve the assessment of intermediate lesions (38). In daily clinical practice however, the evaluation of stenosis severity is usually based on visual assessment and the use of QCA is generally limited to research purposes. Additional information on coronary anatomy and physiology is required for the assessment of ambiguous lesions and to optimize results in complex or high-risk PCI.

2.1.2 Intravascular ultrasound

2.1.2.1 Introduction

IVUS was the first widely adopted invasive imaging modality to provide complementary information to coronary angiography (39). IVUS is able to provide detailed information on vascular dimensions, lesion morphology, plaque composition and plaque burden. It has shown to be superior to coronary angiography in the assessment of lesion severity (31, 32, 34). Imaging is performed by introducing a catheter with a small ultrasound transducer at the distal end into the coronary artery. The transducer may be either a single-element rotating transducer or a solid-state electronic phased-array transducer (40-42). The latter technology has the benefit of better trackability and the lack of non-uniform rotational distorsion artefacts. With motorized pull-back of the catheter, a series of cross-sectional images are generated. Typical IVUS catheter has an ultrasound transducer with a frequency of 20 – 45 MHz, giving an axial resolution of 100 – 200 μm, lateral resolution of 200 – 300 μm and tissue penetration of 10 mm (43). Frame rate is typically 30 frames/second and the maximal scan diameter 15 mm. Technical specifications for IVUS are summarised in Table 1.

2.1.2.2 Assessment of stenosis severity

The ability of IVUS to discriminate haemodynamically significant, ischemia-producing lesions among angiographically moderate stenoses has been studied extensively. A good correlation was found between minimum lumen area (MLA) ≥ 4.0 mm^2 with invasively measured Doppler-wire coronary flow reserve CFR ≥ 2.0 (44). MLA ≤ 4.0 mm^2 could accurately predict a haemodynamically significant stenosis associated with a reversible perfusion defect in myocardial stress perfusion imaging with SPECT (45). Deferral of PCI for intermediate lesions with MLA ≥ 4.0 mm^2 appeared safe based on the follow-up study of 300 patients (46) . Most of the studies have used fractional flow reserve (FFR) as a reference, with a threshold for FFR for haemodynamically significant stenosis < 0.75 or < 0.80. Predictors of haemodynamically significant FFR < 0.75 were MLA ≤ 4.0 mm^2, IVUS area stenosis (AS) $> 70\%$, minimum lumen diameter (MLD) ≤ 1.8 mm and lesion length > 10 mm (47). The sensitivity and specificity of MLA < 4.0 mm^2 to discriminate a stenosis with FFR < 0.75 were 92 % and 56 % respectively (46, 47). Based on these findings, MLA ≥ 4.0 mm^2 by IVUS has been accepted as a threshold for non-ischemia-producing lesion which justifies deferral of PCI in vessels other than the left main coronary artery.

Despite many efforts, no IVUS-derived parameter has been shown to consistently predict an ischemia-producing lesion with sufficient accuracy. In several studies using FFR as a reference, various cut-off values for different IVUS parameters have been proposed, but their diagnostic accuracy remains insufficient. MLA < 3.0 mm^2 combined with AS > 60 % predicted FFR < 0.75 with 92.0% sensitivity and 88.5% specificity (48). In another study, MLA ≥ 2.4 mm^2 discriminated lesions with FFR < 0.80 with 90 % sensitivity but

only 60 % specificity (49). Yet another study showed that MLA < 2.8 mm^2 best predicted FFR < 0.75 (sensitivity 79.7 %, specificity 80.3 %) and MLA < 3.2 mm^2 for FFR < 0.8 (sensitivity 69.2%, specificity 68.3%) (50). Since the hemodynamic significance of a stenosis is dependent on various other anatomical, physiological and clinical factors such as the calibre of the vessel, the length and eccentricity of the stenosis, collateral circulation and the amount of viable myocardium supplied by the vessel, it appears unlikely that a uniform anatomical threshold value for haemodynamically significant stenosis could exist. In a study with smaller-sized vessels, MLA ≤ 2.0 mm^2, plaque burden of ≥ 80 %, and lesion length of ≥ 20 mm predicted an FFR of < 0.75 with good sensitivity and specificity (51).

The revascularization for significant left main lesions improves survival when compared to medical therapy (52). Thus the accurate evaluation of ambiguous left main stenoses is crucial. The ability of coronary angiography to detect a haemodynamically significant left main stenosis is limited, even when QCA is used (53). IVUS has been used to assess ambiguous left main stenoses. A threshold of 5.9 mm^2 for MLA was associated with an FFR < 0.75 based on a study of 55 patients with angiographically moderate (40 – 70 %) stenosis in the left main (54). In a prospective multicentre trial with 354 patients with ambiguous left main stenosis, deferral of PCI when MLA > 6.0 mm^2 was shown to be safe (55). A higher cut-off value of MLA ≥ 7.5 mm^2 for deferring PCI has been proposed earlier based on an observational study (56). For left main lesions, a cut-off for MLA ≥ 6.0 mm^2 has been traditionally used to defer revascularisation, but again, as the same limitations apply as in non-left main lesions, a uniform cut-off for ischemia-producing lesions in the left main cannot be given.

2.1.2.3 Characterization of plaque composition

Tissue characterization of the standard IVUS is based on visual estimation of a grey-scale signal intensity map. Atherosclerotic coronary lesions have been classified into four categories: 1) Soft plaque has lower echogenicity than the adventitia, 2) calcified plaque has higher echogenicity than the adventitia and shows acoustic shadowing, 3) fibrous plaque has intermediate echogenicity, and 4) mixed plaque has less than 80 % of the features of any other single subtype (57). To improve tissue characterization, several computer-assisted techniques have been developed. These are based on either radiofrequency (RF) analysis or image based analysis (58).

The first application of radiofrequency backscatter signal analysis was called virtual histology IVUS (VH-IVUS, Volcano Therapeutics) (59-61). It combines the envelope amplitude of the reflected RF-signals and the underlying frequency content to distinguish tissue components and after computerized processing, different tissue components are represented as distinct colours (60). VH-IVUS has been shown to correlate with histology specimens from directional coronary atherectomy, ex-vivo coronary arteries and with carotid endarterectomy (61-63). However, in a pig model for atherosclerosis with histologic validation, the accuracy of VH-IVUS to detect the extent of necrotic

lipid core was poor (64). Another application based on similar RF-signal processing technology is called iMAP-IVUS (Boston Scientific), in which the different tissue components are represented as different colours analogous to VH-IVUS (65). Third application for tissue characterization, integrated backscatter IVUS (IB-IVUS) applies a fast Fourier transformation of the backscattered RF signals calculating the intensity of signals measured in dB (66). Different tissue components reflect RF-signals at different power levels and are again colour-coded for visualization. The method has been validated with ex-vivo histology and in-vivo coronary angioscopy (67). In a study with histological ex-vivo validation, IB-IVUS appeared to have good correlation with histological and TD-OCT findings and was better than TD-OCT in quantifying lipid pools (68). Fourth application to improve IVUS tissue characterization, three-dimensional automated differential echogenicity (ADE), differs from the previously mentioned in that it is a software for computerized post-processing image analysis of grey-scale IVUS to detect differences in plaque composition in longitudinal studies (69).

IVUS has potential for discrimination of coronary lesions into stable and unstable plaques. Unstable or vulnerable plaques are characterised by a large lipid core, thin fibrous cap and mobile echoes indicating thrombus or necrotic material, whereas stable plaques have more fibrous tissue or calcification (70). Plaques with a fibrous cap less than 65 μm thick are called thin-cap fibroatheromas (TFCAs) (71). IVUS is able to image the full thickness of the vessel wall but is unable to penetrate through calcified lesions, which cause shadowing. The resolution of IVUS is insufficient for the measurement of the fibrous cap of TCFAs. With the computerized analysis of RF-signals or grey-scale images discussed above, identification of vulnerable plaques appears possible, but this methodology is not well validated (72). In a prospective study of 697 patients with ACS who underwent three-vessel IVUS after PCI, the lesions associated with recurrent events during the follow-up were more likely to be characterized by a plaque burden of $\geq$ 70 % or MLA $\leq$ 4.0 mm^2 or to be classified as TCFAs by radiofrequency IVUS (73). PCI for haemodynamically non-significant lesions is not recommended irrespective of their features of vulnerability in stable CAD and the clinical significance of plaque characterization in this setting is uncertain (72).

2.1.2.4 Interavascular ultrasound guided percutaneous coronary intervention

IVUS-guided PCI with BMS has shown to be associated with lower rates of target-vessel revascularisation (TVR) and larger postprocedural MLD without any benefit in death or MI (74). This may be due to more frequent use of postdilatation, larger-diameter balloons and higher pressures in IVUS-guided PCI (75-77). While IVUS-guidance appears to reduce restenosis with BMS, there does not appear to be similar benefit regarding restenosis when DESs are used. In a study with 210 patients, IVUS-guided PCI with DES did not reduce MACE or ST after 18 months follow-up (78). In another study with 284 patients comparing angiographically-guided versus IVUS-guided PCI in complex lesions, there was no difference in MACE after 24-month follow-up while

the postprocedural MLD was significantly larger in the IVUS-guided PCI group (79). In a retrospective propensity-score matched analysis of 884 comparing IVUS-guided vs. angiographically-guided PCI with DES, there were reduced rates of ST at 30 days and 12 months in the IVUS-guided group (0.5 % vs. 1.4 %, p = 0.046 and 0.7 % vs. 2.0 %, p = 0.014 respectively) (80).

In the MAIN-COMPARE study, the outcomes of 756 patients undergoing IVUS-guided PCI for left main were compared to a propensity-matched cohort with angiographic guidance. In the 201 matched pairs there was a trend towards lower mortality in the IVUS-guided versus angiography-guided group after 3-year follow-up (6.0% versus 13.6%, p = 0.063) (81). In 145 pairs receiving DES, the 3-year mortality was significantly lower in the IVUS-guided group (4.7% versus 16.0%, p = 0.048) while there was no difference in the outcomes when BMS was implanted (81). IVUS can be used to decide on treatment strategy of bifurcation lesions and to optimize stent deployment. In a propensity-matched analysis 487 pairs of a registry of 1668 patients receiving DES for non-left main bifurcation stenoses, the incidence of death or MI was significantly lower in the IVUS-guided group compared to the angiography-guided group (3.8 % vs. 7.8%, p = 0.03) (82). In a study of 90 bifurcation lesions using a single-stent approach, pre-procedural IVUS evaluation of the side-branch showed that MLA $\geq$ 2.4 mm^2 in the ostium was associated with post-intervention FFR $\geq$ 0.80 after the main stent deployment with a predictive value of 98 % (83).

The current ESC guidelines on the management of stable CAD state that IVUS may be considered (IIb) to characterize lesions and improve stent deployment, but uniform cut-off values are not given and FFR measurement is preferred in the assessment of hemodynamic severity (72). The ACCF/AHA/SCAI guidelines for PCI state that it is reasonable (IIa) to use IVUS to assess angiographically indeterminant left main stenoses and to determine the reason of restenosis; and that IVUS may be considered (IIb) to assess intermediate non-left main stenoses, to guide coronary stent implantation and to determine mechanism of ST (84). In the ACCF/AHA/SCAI guidelines it is stated that for left main coronary stenoses, MLD < 2.8 mm or MLA < 6mm^2 suggests a physiologically significant lesion and the patient may benefit from revascularization; that revascularization may be safely deferred when MLA > 7.5 mm^2; and when MLA is between 6 – 7.5 mm^2 further assessment such as FFR is recommended (84). It is recognized that for non-left main stenoses, MLD > 2.0 mm and MLA > 4.0 mm^2 correlate with low event rates and that for smaller-diameter arteries with MLA < 3.0 mm^2, FFR may be preferred in the assessment of the significance of stenosis (84).

2.1.2.5 Evaluation of stent thrombosis

The mechanisms of ST with DES have been studied extensively by IVUS. Mechanisms of early, late and very late stent thrombosis appear to be different. ST may be due to early discontinuation of DAPT, inadequate response to DAPT or stent or lesion related factors. Early ST is usually considered to be caused by a technical problem during PCI or early discontinuation of DAPT. In an IVUS substudy of the HORIZONS-AMI trial,

patients with early ST had smaller lumen measurements, larger plaque burden and more frequent stent edge dissections than controls (85). Patients with early ST also had higher amount of TIMI 0/1 flow before and after PCI. Only one patient out of 12 patients with ST had discontinued DAPT, for two patients the DAPT status was uncertain. In a registry of 2,575 patients treated with SES, ST occurred in 21 patients (0.8 %) after a median of 14 days from PCI (86). When IVUS data from those 15 patients in whom PCI was performed using IVUS-guidance were analysed, stent underexpansion and significant residual reference segment stenoses were associated with ST. Late and very late ST has been recognized after the introduction of first-generation DES (8, 9). Reported IVUS findings associated with ST include late acquired incomplete stent apposition (ISA), stent underexpansion, stent edge dissections, incomplete lesion coverage, geographic miss, tissue protrusion and residual thrombus (87-92). Incomplete endothelialisation of stents has been associated to late and very late ST in histological studies, and is now considered a surrogate marker for risk of LST (10, 93). Unfortunately, the resolution of IVUS does not allow the assessment of stent endothelialisation.

2.1.3 Coronary angioscopy

Coronary angioscopy was the first invasive intracoronary imaging modality introduced in clinical practice in the 80's (94-96). It is based on the reflection of light from the vessel wall. The fibre-optic imaging catheter consists of illumination and collection fibres and a lens at the distal end of the catheter (97). This technology allows visualization of the surface of the vessel wall and it has been applied in the assessment of lesion morphology (67, 98-102) and in the assessment of stents (103, 104). A serial angioscopic study showed changes in plaque colour and morphology after statin therapy (105). However, coronary angioscopy has remained an instrument used for research purposes due to the several shortcomings of this technology, limiting its more widespread use in clinical practice. These include the large diameter of the catheter, making it unable to pass significant stenoses, the requirement to clear the lumen of blood with the infusion of saline and the limited capability to evaluate proximal segments of the vessel. Angioscopy does not provide information on the deeper structures of the vessel wall and the accurate analysis of the images requires experience. (97)

2.1.4 Near-infrared spectroscopy

Spectroscopy quantifies the interaction between electromagnetic radiation and molecules by detecting the spectrum of light reflected from the tissue. Intracoronary near-infrared spectroscopy (NIRS) uses a source emitting near-infrared light with wavelengths from 1000 to 2400 nm. Amount of light remitted from the vessel wall is measured allowing the absorbance to be calculated. The chemical composition of the vessel wall can be evaluated by applying special algorithms. (97)

The method has been validated in animal and ex-vivo histological studies with special focus for the identification of unstable plaques (106-110). The method has been shown

to detect different features of unstable plaques including lipid pools, inflammatory cells and thin fibrous caps (108). In an in-vivo validation study, spectral data obtained from coronaries of patients were similar to those obtained from autopsy specimens and the imaging procedure was shown to be feasible for the detection of lipid-rich plaques with no procedure-related complications (111). The advantage of the method is that blood in the coronaries does not affect image acquisition and thus flushing of coronaries with saline or contrast medium is not needed. In order to combine the information on the chemical composition of the vessel wall provided by NIRS with anatomical information by IVUS, a dual catheter has also been developed incorporating both imaging modalities with simultaneous image acquisition (112).

2.1.5 Optical coherence tomography

2.1.5.1 Introduction

OCT has previously been used in ophthalmology in the imaging of the retina (11). Coronary OCT is a novel intravascular imaging modality, in which cross-sectional images of the coronary artery are produced by the introduction of an imaging catheter inside the coronary artery in an analogical way as in IVUS (113). Automated pull-back of the rotating imaging catheter enables acquisition of serial cross-sectional images of the desired segment of the coronary artery. The imaging is based on the reflection of near-infrared light from the structures of the vessel wall (113). The wavelength used in current OCT systems is approximately 1300 nm (12). This enables an axial resolution of 10 – 20 μm, which is only one tenth of that of IVUS and allows visualization of coronary anatomy and pathology with unforeseen detail. However, this technology also sets a limit to the tissue penetration, which is only 1 to 3 mm with OCT when compared to 4 to 8 mm with IVUS (12). Some features of FD-OCT and IVUS are compared in Table 1.

The image acquisition is based on backscattering of light from the vessel wall. The distance travelled by the backscattered light cannot be directly measured due to the high speed of light and small distances measured. Therefore, interferometry is applied. There are currently two basic technologies, the first-generation time-domain OCT (TD-OCT) and second-generation FD-OCT systems. The original TD-OCT uses a light source transmitting low-coherent near-infrared light. The light beam is divided by a fibre-optic coupler into two arms: the measurement arm and the reference arm. Light in the measurement arm is transmitted via imaging catheter at the vessel wall, and light in the reference arm into a moving mirror. The movements of the mirror are calibrated, so that for any given position of the mirror, the distance that the reflected light has travelled is known. When light reflected from the vessel wall and the reference arm is combined, interference occurs when the light in both arms arrives at the same time, having travelled the same optical distance. The intensity of interference is detected by a detector, and is translated after processing into an intensity map and a visual image. (113)

Table 1. Comparison of IVUS and FD-OCT.

	FD-OCT	IVUS	References
Technical specifications			
Axial resolution	12 – 15 μm	100 – 200 μm	(12-14, 116, 117)
Lateral resolution	20 – 40 μm	200 – 300 μm	
Tissue penetration	1.0 – 2.5 mm	10 mm	
Scan diameter	9.7 mm	15 mm	
Pullback speed	20 mm/s	0.5 – 1 mm/s	
Frame rate	100 frames/s	30 frames/s	
Contrast medium required	yes	no	
Advantages	High resolution allows assessment of intima, detection of plaque rupture, dissection, measurement of TCFA thickness, stent endothelialisation and apposition, detection of thrombus Calcified lesions Fast image acquisition	No need for contrast medium Validated for the guidance of stent deployment Validated for the assessment of stenosis severity Better tissue penetration allows the assessment of media and adventitia Quantification of lipid pools and lipid burden	(13, 14, 43, 75, 116, 117)
Limitations	Inability to assess aorto-ostial lesions Need for contrast medium Limited tissue penetration Lipid plaques cause signal attenuation Inadequate blood displacement causes artefacts Limited data on OCT-guided PCI on outcomes	Inadequate resolution to assess intima or stent endothelialisation Limited capability to detect thrombi Calcified lesions Relatively slow image acquisition	
Clinical use according to guidelines			
Characterisation of lesions in stable CAD			(72, 84)
AHA	*No recommendation*	*Reasonable for LM (IIa, B), may be reasonable for non-LM (IIb, B)*	
ESC	*May be considered (IIb), B*	*May be considered (IIb), B*	
To improve stent deployment			
AHA	*No recommendation*	*May be considered, particularly for LM (IIb, B)*	
ESC	*May be considered (IIb), B*	*May be considered (IIb), B*	

FD-OCT, frequency-domain opticalcoherence tomography; IVUS, Intravascular ultrasound;LM, left main coronary artery; PCI, percutaneous coronary intervention; TCFA, thin-cap fibroatheroma

As the near-infrared light does not penetrate red blood cells, blood must be cleared off from the imaged vessel during image acquisition by manual or automatic infusion of saline or contrast medium. The original TD-OCT image acquisition technique required occlusion of the vessel proximal to the region of interest with a special over-the-wire balloon catheter while flushing the occluded vessel during image acquisition. This limited the imaging of proximal lesions (12). Later, non-occlusive technique was developed (114, 115).

The FD-OCT system resembles TD-OCT, but the light-reflecting mirror is fixed, the frequency of the light source is varied and the interference of light in the measurement and reference arms oscillates according to the frequency difference. All echo delays are acquired simultaneously in the FD-OCT system. This significantly increases the speed of image acquisition. Due to the faster image acquisition, proximal balloon occlusion is not needed and the required dose of contrast medium for flushing the vessel is smaller when compared to TD-OCT. (12)

2.1.5.2 Assessment of stenosis severity

There is good correlation with luminal dimensions measured by OCT and IVUS, albeit OCT measurements appear to give somewhat smaller values (118). When the proximal balloon occlusion technique was used with the older TD-OCT technology, luminal dimensions appeared to be underestimated when compared to FD-OCT or IVUS (119). In a study comparing FD-OCT to IVUS and QCA on 100 patients with coronary heart disease, the MLD measured by FD-OCT was significantly larger when compared to measurements by QCA and significantly smaller when compared to measurements by IVUS (120). The MLA was also significantly smaller with FD-OCT than with IVUS. FD-OCT measurements also showed less inter-observer variability than IVUS, and by using phantom models of vessels with known dimensions, the researchers showed that FD-OCT could reliably measure the true dimensions of the lumen while IVUS measurements exaggerated the luminal dimensions and were less reproducible.

In contrast to IVUS, there has been paucity of studies to validate OCT-derived luminal measurements in the assessment of haemodynamic significance of angiographically intermediate stenoses. Pawlowski et al used TD-OCT with the non-occlusive technique to study 71 angiographically intermediate stenoses with diameter stenosis (DS) of 40-70% on 48 patients and found an MLA < 2.05 mm^2 to best predict a lesion with FFR < 0.80 with a sensitivity of 75%, specificity of 90% and diagnostic accuracy of 87% (121). Best cut-off for MLD was < 1.28 mm (sensitivity 71%, specificity 84% and accuracy 87%). Similarly as reported earlier for IVUS-derived measurements, the cut-off values for OCT-derived luminal measurements correlated with the size of the affected vessel, leading to larger cut-off values in larger vessels.

In another study by Gonzalo et al evaluated the ability of FD-OCT and IVUS to detect a haemodynamically significant lesion with FFF < 0.80 in 61 angiographically intermediate (DS 40-70%) lesions on 56 patients (122). OCT-derived cut-off for MLA of 1.95 mm^2 was found to predict a lesion with FFR < 0.80 with a sensitivity of 82% and a specificity of 63%. Optimal cut-off value for OCT-derived MLD was 1.34 mm (sensitivity 82%, specificity 67% and accuracy 73%). The cut-off value for IVUS-derived MLA was 2.36 mm^2 (sensitivity 67%, specificity 65%). The diagnostic efficiency of OCT was slightly better when compared to IVUS (AUC 0.70 vs. 0.63), but the difference was not statistically significant (p=0.19). However, OCT was superior to IVUS in the assessment of the haemodynamic significance of stenoses in small vessels with a diameter < 3 mm (AUC 0.77 vs. 0.63, respectively, p=0.04). MLA cut-off values for were 1.62 mm^2 for OCT (sensitivity 80%, specificity 83%, accuracy 82%) and 2.36 mm^2 for IVUS (sensitivity 72%, specificity 62%, accuracy 68%). The diagnostic efficacy of both OCT- and IVUS-derived AS was low. A lower threshold of FFR < 0.75 was applied by Shiono et al, who used TD-OCT with the occlusive technique to study 62 intermediate lesions in 59 patients (123). They found that OCT-derived MLA <1.91 mm^2 (sensitivity 93.5%, specificity 77.4%), MLD <1.35 mm (sensitivity 90.3%, specificity 80.6%) and percent AS >70.0% (sensitivity 96.8%, specificity 83.9%) to be the best cut-off values to predict a haemodynamically significant stenosis with FFR <0.75.

2.1.5.3 Characterization of plaques and identification of the culprit lesion

Of all the currently clinically widely available imaging modalities, OCT provides best resolution and near-anatomic view of intracoronary structures. Its major drawbacks are the limited tissue penetration and the need to clear blood off the lumen during image acquisition. Thick lipid-rich plaques also cause signal attenuation, which limits visualization of these structures. OCT can reliably distinguish calcium and lipid-rich components of coronary plaques, the fibrous cap and especially the intimal layer of the vessel. Dissections in the intima are clearly visible. Red and white thrombi are detected. Dimensions and area of coronary lumen, stents, neointimal layer, plaques and thrombi can be measured. (13)

Based on histologic studies, the atherosclerotic lesions of patients with stable CAD are typically fibrotic, have thick fibrous caps, small necrotic cores, little or no overlaying thrombus and few inflammatory cells. Culprit lesions of patients with ACSs present with different features with a rupture or tear in the thin fibrous cap, large cholesterol-rich necrotic core with macrophage and neutrophil infiltrates, neo-vascularization, intra-plaque haemorrhage and thrombosis. (124, 125)

The universal definition classifies MI into five categories (126). The commonest is type 1 MI, which is considered to be caused by a disruption, erosion or dissection of a lipid-rich coronary-plaque. Type 2 MI is associated to imbalance between myocardial oxygen supply and demand. Type 3 MI denotes cardiac death due to MI and types 4 and 5 are

reserved for PCI- and CABG-related MI. In patients with confirmed diagnosis of MI, 72% had type 1 MI and 26% type 2 (127).

Plaques with thin fibrous cap are thought to be vulnerable, unstable plaques. The thickness of the fibrous cap can be easily measured which helps to recognize unstable plaques. Acute plaque ulceration or rupture can be detected by OCT as a discontinuation in the contour of the thin fibrous cap overlaying a lipid-rich plaque. Thrombus attached to the ruptured plaque corroborates the identification of a culprit lesion in ACS, but evidence of thrombosis is not always seen, especially after thrombolysis or potent antithrombotic drug therapy. (128)

In the first in-man OCT study on coronary plaque morphology in patients with different clinical presentations, Jang et al showed that TCFAs were more frequently observed in patients with ACS when compared to those with stable CAD (129). Different features in plaque characteristics between diabetic and non-diabetic patients with UAP have also been detected by OCT (130). It has also been shown that OCT-measured thickness of the fibrous cap significantly increased after statin therapy for 9 months after AMI (131).

Sealing of OCT-detected TCFAs with a special self-expanding stent has been shown to be feasible in a small pilot study, but data from randomized trials powered for clinical end-points to support this practice is lacking (132).

Current ESC guidelines state that OCT as well as IVUS may be considered (IIb) for the characterization of lesions (72). However, there is no evidence to support PCI of lesions with high-risk features in stable CAD when they are not hemodynamically significant.

2.1.5.4 Optical coherence tomography guided percutaneous coronary intervention

In situations where optimal stent deployment is essential, such as in the PCI of bifurcation lesions or the left main, IVUS has been used to measure lumen dimensions for appropriate stent sizing and to confirm stent apposition after PCI.

When compared to IVUS, OCT provides more detailed information after PCI on edge dissections, thrombus formation and tissue prolapse (133). The incidence and predictors of stent edge dissections was evaluated in 90 lesions of 73 diabetic patients by Reith el al (134). Stent edge dissections were present in 41.1% of lesions. Placement of the stent edge on the diseased segment, the eccentricity of the lumen at the stent edge, and mismatch of stent and lumen size were associated with stent edge dissections. The incidence of stent edge dissections was 37.8% in another retrospective study of a group of 230 patients with 249 lesions, in whom OCT was performed after PCI (135). 84% of these edge dissections were not visible on angiography. Additional stenting was performed in 22.6%. However, there was no difference in MACE between patients with or without stent edge dissections. In line with this finding, angiographically silent OCT-detected stent edge dissections did not increase the incidence of ST or restenosis during one-year follow-up in another study (136). Furthermore, in a study of 35 patients with 40

DES, Kawamori et al showed that most cases of stent malapposition with a strut-to-wall distance ≤ 260 μm, thrombus, tissue prolapse, or minor stent edge dissection improved during a follow-up of 8 months (137).

Porto et al searched for OCT features associated with periprocedural MI and found that the presence of TCFA before PCI, intrastent thrombus and intrastent dissection after PCI predicted this complication (138). Imola et al showed that implantation of stent edge on a lipid pool detected by OCT was more frequently observed in a group of patients with postprocedural MI than the control group, suggesting that incomplete stent coverage of lipid pool detected by OCT is associated with postprocedural MI after PCI (139).

In a retrospective analysis, the use of OCT in pre-PCI evaluation of ambiguous lesions lead to PCI in 60% of patients and unnecessary PCI was avoided in 40%, while OCT imaging after stenting lead to an additional intervention in 32 % of cases (140). In another study, OCT-guided strategy was compared to standard angiographic guidance in a retrospective registry of 670 patients undergoing PCI (141). OCT identified additional procedural issues requiring an additional intervention in 34.7% of patients. OCT-guided strategy significantly reduced the risk of the primary combined end-point of cardiac death or MI after propensity-score adjusted analysis (OR=0.49 [0.25-0.96], p=0.037). OCT findings leading to additional interventions with balloon dilatation (22.1%) or stenting (12.6%) included stent edge dissections, reference lumen narrowing, stent under-expansion, stent malapposition and thrombus.

When FD-OCT was compared to IVUS in the guidance of PCI on 70 patients, 35 per group, with de-novo CAD, FD-OCT-guidance was associated with smaller stent expansion and more frequent residual segment stenosis than IVUS-guidance (142). The reference method for determining lumen dimensions and residual stenosis for both groups in this study was IVUS. As it has been shown that OCT-derived lumen measurements tend to be smaller than IVUS-derived, the use of IVUS as a reference method could favour IVUS over OCT when residual stenosis is considered (120). In another study, FD-OCT was more accurate than IVUS in measuring the actual length of implanted coronary stents (143).

DES implanted in distal left main were evaluated by OCT in a small pilot study, showing that malapposed and uncovered stent struts were more often present in the proximal segments of the stents (144). Despite the use of high-pressure balloon dilatation techniques, the incidence of acute malapposition in the proximal segment was as high as 13.9% after PCI, and acute malapposition also often lead to persistent malapposition. In another small study comparing FD-OCT to IVUS in PCI of unprotected left main stenosis, similar lumen and stent dimensions were reported with both imaging modalities (145). FD-OCT appeared safe and feasible in this indication. FD-OCT was more often successful to reveal stent edge dissections and malapposition than IVUS. However, complete imaging of the left main was less often successful with FD-OCT when compared to IVUS.

Postprocedural OCT imaging of the main vessel was performed in a small series of patients undergoing bifurcation stenting (146). Malapposed stent struts were commonly observed at the side-branch ostium and a single-stent strategy was associated with less strut malapposition, while OCT-guided stent implantation lead to further improved results in this regard. Use of 3-dimensional FD-OCT with special algorithm may be useful to assess the relation between stent struts and the jailed side branch and to aid in wire re-crossing (147).

Deferral of stenting in patients presenting with ST-elevation myocardial infarction (STEMI), without significant stenosis after thrombus aspiration and with intact fibrous cap on OCT, was shown to be feasible in a small series of patients (148). A small pilot study assessed the use of OCT to defer balloon angioplasty and stenting on 100 patients presenting with STEMI (149). After thrombus aspiration, the patients had to be symptom-free with a TIMI flow-grade of 2-3 of the affected vessel. Balloon angioplasty and stenting was deferred for angiographically significant (>50%) stenoses if the lesion was considered mostly thrombotic by OCT. 20 patients were treated with thrombus aspiration only, without major adverse cardiovascular events during a follow-up of 12 months or significant residual stenosis on angiography or OCT performed after 1 week and 9 months from the primary procedure. OCT findings in this study revealed TCFA (thickness of fibrous cap < 65 μm) and thrombus in all cases. Plaque rupture was identified in 75% of patients treated with thrombus aspiration only and 78% of patients treated with balloon angioplasty or stenting. After one week, the coronary angiogram was normal, while OCT revealed no thrombus but plaque rupture still present in all 20 patients treated with thrombus aspiration only.

In the presence of calcified lesions, OCT may be able to select patients who benefit from rotational atherectomy (128). When calcified lesions were assessed by OCT, the circumferential extent of superficial calcification was found to be associated with stent strut malapposition while the depth of calcification did not play a role (150).

Currently, there are no data from randomized prospective trials to support the use of OCT to guide PCI. A randomized prospective trial on the value of OCT to optimize results of PCI on patients presenting with non-ST-elevation myocardial infarction (NSTEMI) is currently recruiting patients (151). The primary end-point is functional result of the procedure as assessed by FFR and secondary end-points include percentage of patients with sub-optimal result of PCI revealed by OCT, change in procedural strategy based on OCT, safety of OCT in ACS and adverse cardiac events at 6 months.

According to ESC guidelines on the management of stable CAD, OCT or IVUS can be considered (IIb) to improve stent deployment (72).

2.1.5.5 Optical coherence tomography in evaluation of vascular healing after stenting

In the development of new stent technologies, OCT is now commonly used to evaluate the interaction between the stent and the vessel wall. Due to its superior resolution over IVUS, OCT is more accurate and reproducible in the assessment of stent strut tissue coverage (152). In a cross-sectional OCT frame, metallic stent struts appear as bright spots, which are caused by reflection of light from the luminal edge of the stent strut (13, 14). The luminal edge of the stent strut is considered to be located in the middle of this blooming effect. As light does not penetrate metallic stent struts, only the leading edge of the stent strut is visualised creating a shadowing effect behind the blooming effect. For bioresorbable vascular scaffolds (BVSs), the full thickness of the strut can usually be visualized. Stent strut coverage can be assessed by evaluating whether any tissue is visible on the luminal edge of the strut, classifying the struts as covered or uncovered. The thickness of this neointimal hyperplasia (NIH) can be measured. However, even the 10 μm axial resolution of FD-OCT is insufficient to allow detection of the thickness of a single layer of endothelial cells. This may lead to underestimation of stent strut coverage especially in the assessment of very early stent endothelialisation, when the neointima is thin. On the other hand, normal neointima and thrombus overlaying a stent strut cannot be reliably distinguished from each other in the early phase of stent healing, which again may lead to overestimation of stent strut endothelialisation in the early phase of vascular healing after stenting. Due to the shadowing effect of metallic struts, only the luminal coverage of malapposed struts can be assessed.

If neointimal growth is excessive, it can lead to restenosis. In OCT analysis lumen cross-sectional area (CSA) can be readily measured by tracing the lumen contour manually or automatically using software provided by the manufacturer (13, 14, 116). MLA and MLD can be measured. Stent CSA can also be measured by connecting the strut reflections manually or semiautomatically. NIH area can be assessed per frame by subtracting lumen CSA from stent CSA. Percentage of NIH area of stent CSA can be used to assess neointimal AS. In a small study on 27 patients, the ability of OCT to identify haemodynamically significant restenotic lesions was compared to FFR (153). The study suggested that the best cut-off values for OCT-based minimal luminal diameter (MLD) and minimal luminal area (MLA) to detect a lesion with FFR $\leq$ 0.80 were 1.77 mm (sensitivity 74% and specificity 78%) and 2.54 mm^2 (sensitivity 71% and specificity 84%), respectively. The correlation of maximum neointimal AS measured by OCT with FFR $\leq$ 0.80 was poor in this study.

OCT evaluation of restenotic lesions showed some morphological differences between lesions treated with first-generation DES (PES and SES) and BMS (154). NIH layer of restenotic lesions was classifies as layered, homogenous or heterogenous. The layered appearance was predominant in DES-treated restenotic lesions, while BMS-treated lesions were usually homogenous. The reduction of NIH area after plain old balloon angioplasty (POBA) was greater in layered and heterogenous than homogenous types.

Based on another study, the assessment of restenotic lesions with OCT might help to select patients who benefit from drug-eluting balloon dilatation over POBA (155). The different appearances of NIH detected by OCT correlated with specific histological findings in a swine model of restenosis (156).

Intra-stent neoatherosclerosis has also been reported, which is defined as the presence of lipid or calcification in the neointima (157). In a restrospective study of 152 restenotic lesions, most of which were initially treated with DES, neoatherosclerosis was present in 35.5%. Neoatherosclerosis was more common with older stents, when first-generation DESs were used and in patients with hypertension. Thickness of NIH has been associated with lipid deposition in the intima (158). In a small study where patients with symptomatic restenotic lesions were evaluated, neoatherosclerosis was more commonly observed on patients treated with DES when compared to BMS (159). In a small observational study the features of neoatherosclerosis of restenotic stents were studied after DES and BMS implantation (160). In stents developing restenosis in the early (< 9 months) or intermediate (9 – 48 months) phase, the prevalence of lipid-rich neointima was higher in DES than in BMS. In those presenting with restenosis after 48 months, most lesions had lipid-rich neoatherosclerosis and there was no difference between DES and BMS. OCT evaluation of 33 patients, with 27 DES- and 6 BMS-treated lesions, presenting with VLST, neoatherosclerosis and neointimal rupture appeared to be the most common finding, present in 70% of cases (161). When early and late ISR after SES implantation was evaluated by OCT, neointima of patients with late ISR more often presented features of neoatherosclerosis, such as lipid accumulation and TCFA-like features (162).

The apposition status of stent struts can be assessed by OCT (163). Stent struts can be classified as apposed, if the distance from the luminal edge of the strut to the edge of the lumen border is less than the thickness of the strut (plus polymer, if present). If measurement is made from the luminal edge of the blooming effect, half of the measured blooming effect thickness has to be added. The measurement can also be made from the centre of the blooming effect – the presumed location of the luminal edge of the strut. If the distance of the leading edge of the stent strut exceeds the thickness of the strut plus possible polymer, the strut is classified as malapposed. The classification of apposition status of metallic struts thus requires information on the strut and possible polymer thickness of the specific stent type studied. In some studies, apposed struts are also further divided into embedded and protruding struts. ISA or stent malapposition may be acute, related to initial suboptimal deployment of the stent, late-persistent and also late-acquired, which has been reported with first-generation DES. Im et al. evaluated the incidence, predictors and clinical outcomes of ISA on 351 patients who underwent immediate post-PCI and follow-up OCT examinations (164). Overlapping DESs were excluded. Acute stent malapposition was common after PCI, occurring in 62 % of lesions. Acute stent malapposition was more common in severe and calcified lesions and was associated with the use of long stents. 72 % of acute stent malapposition was seen in the edges of the stent, whereas late-acquired malapposition more commonly affected the central part of the stent. Predictors of late-

persistent stent malapposition included the location of acute stent malapposition in the edges of the stent and the volume of acute stent malapposition. The incidence of late-acquired stent malapposition was 15%. Late stent malapposition was not associated with adverse clinical events during an average follow-up of 29 months.

Coronary evaginations, defined as outward bulges in the luminal contour between stent struts detected by OCT, have been reported after DES implantation (165, 166). These evaginations were associated with positive vessel remodelling, stent strut malapposition, uncovered struts and thrombus. Intrastent dissection during the procedure and use of first-generation DES increased the likelihood of detecting these evaginations. Stented lesions with coronary artery aneurysms on coronary angiography after DES implantation were more frequently associated with OCT-detected incomplete stent strut coverage and malapposition when compared to lesions without aneurysms (167). Acquired incomplete stent strut coverage was also observed in this small study in association with coronary artery aneurysm formation. Coronary artery aneurysms were associated with increased risk for ischemic events. The length of the aneurysms was associated with the risk of cardiac events. Long-term OCT follow-up after first-generation DES implantation has revealed a heterogenous vascular response, with clustering of malapposed and uncovered stent struts and coronary evaginations in some lesions (168).

Signs of incomplete vascular healing, including uncovered and malapposed stent struts, are more often detected by OCT after first-generation DES implantation on ACS patients when compared to patients with stable CAD (169, 170). The impact on vascular healing may be persistent as differences have been detected after up to five years from stent implantation (171). Several mechanisms for this phenomenon have been postulated. Higher lipid content of the unstable plaque than the more fibrotic stable plaque may lead to increased concentration of the lipophilic drug in the vessel wall and higher amount of thrombus may reduce drug wash-out leading to prolonged effect of the drug. Fewer smooth muscle and endothelial cells are observed in unstable plaques with large necrotic lipid cores than stable plaques, which could impair vascular healing. Lysis of jailed thrombus between the stent and the vessel wall has also been proposed as a mechanism behind late-acquired malapposition. Overlapping stents may show signs of incomplete vascular healing. The implantation of overlapping DES was associated with incomplete stent strut coverage and generally lower NIH thickness in the overlapping segments in a follow-up of 9-13 months, but the vascular response was heteregenous sometimes leading to exaggerated neointimal growth (172).

Uncovered stent struts have been associated with ST (15). OCT was used to search for stent-related features behind ST in a small case–control study, which enrolled six patients with subacute and 17 patients with late or very late ST and respective controls (16). Patients with subacute ST had smaller minimum stent area at the thrombus site (2.1 mm^2 vs. 2.9 mm^2, p=0.05) and more uncovered (26.2% vs. 13.9%, p=0.001) and malapposed (18.8% vs. 15.2%, p=0.001) stent struts when compared to controls. Patients with late/very late ST had more uncovered (23.6% vs. 5.2%, p=0.001) and malapposed (12.1% vs. 2.8%, p=0.001)

struts and a larger maximum malapposition distance (0.45 mm vs. 0.12 mm, p=0.01) than controls. All patients with ST had also previously discontinued DAPT or showed high residual platelet reactivity on clopidogrel therapy. There are some small studies suggesting that incomplete vascular healing may be associated with impaired endothelial function (173), but the results have been conflicting and this association has not been found in other studies (174). Won et al aimed to determine a cut-off value for the percentage of uncovered stent struts that would predict adverse outcomes in 489 patients, in whom OCT examination had been performed within 6-18 months after DES implantation (175). A cut-off value of ≥ 5.9% for uncovered stent struts predicted the combined end-point of cardiovascular death, MI and ST with a sensitivity of 83.3% and a specificity of 70.3%.

Findings of some recent OCT studies after implantation of different stents at short-term (< 4 months), mid-term (4 – 12 months) and long-term (> 12 months) follow-up are summarized in Table 2. There are very few studies on the very early vascular healing after PCI. Vascular healing after *Endeavor*™-ZES was evaluated in a small study with 27 patients, who were divided into five groups undergoing OCT examination after 2, 4, 6, 8 and 10 weeks (176). The binary stent strut coverages at these time points were 2.3, 70.4, 67.9, 86.0, and 99.2%, respectively; and the respective mean NIH thicknesses were 40.2, 52.1, 48.1, 86.5, and 146.2 μm. There is also little OCT data on vascular healing after BMS implantation, as most of the studies have been performed on different types of DES. OCT findings appear to be associated with the duration of follow-up, as NIH thickness tends to increase and percentage of uncovered stent struts decrease over time, reflecting vascular healing process. However, the percentage of malapposed stent struts does not seem to be associated with the duration of follow-up after stenting. In a small study with OCT follow-up after 9 months and 2 years from DES implantation, the thickness of neointima increased and stent strut coverage improved during follow-up, while no change was seen in the rate of malapposed stent struts and thrombus (177).

There is remarkable variability in OCT findings between different studies of the same stent type. Differences in baseline characteristics of patients, such as percentage of patients with ACS or diabetes, may partly explain these differences. Furthermore, some investigators have reported strut-level data while others have used different statistical methods to account for the so called clustering effect. If a stent strut is uncovered or malapposed, the adjacent struts of the same stent are also more likely to share the same qualities and thus the apposition status and endothelial coverage of the struts of the same stent are not truly independent variables. As the number of analysed struts per stent is generally rather large when compared to the number of analysed stents, this can lead to overestimation of the incidence of malapposed and uncovered stent struts. Stent platform of first-generation stent may also have an effect on vascular healing properties. For PES, the newer stent platform was associated with greater and more homogeneous reduction of NIH when compared to the older stent platform despite same drug and polymer (178).

BVS show different healing properties than durable stents. *Absorb*™BVS is composed of fully bioresorbable poly-L-lactide polymer, which is gradually hydrolysed and replaced

by matrix of proteoglycan. BVS strut coverage and apposition can be assessed by OCT as for permanent implanted coronary stents, but the bioresorption process cannot be accurately evaluated by OCT due to inability of OCT to discriminate the poly-L-lactide polymer from the proteoglycan. A multimodality follow-up study applying OCT and IVUS showed that struts still recognizable on OCT at 2 years had a 99% neointimal coverage, with increase in the NIH area from 6 months to 2 years (179). There were also signs of biodegradation and increase in the mean scaffold area evaluated by both IVUS and OCT during the follow-up. After a follow-up of 3 years, OCT showed increase in the count of strut cores, suggesting dismantling of the scaffold (180).

Table 2. OCT findings after implantation of different stents.

Stent type	Follow-up (months)	NIH thickness (μm)	Uncovered struts (%)	Malapposed struts (%)	References
BMS	6	186	2.0	0.15	(181)
	70	220	4.0	0.4	(182)
PES	6 – 12	153 – 240	1.5 – 9.9	1.1 – 6.0	(183-189)
	34 – 60	110 – 157	1.0 – 20.8	0.7 – 2.6	(168, 188, 190)
SES	3 – 4	45 – 191	2.8 – 14.3	0.0 – 2.2	(191-194)
	6 – 12	57 – 178	0.5 – 17.3	0.0 – 15.0	(183-185, 188, 192, 193, 195-198)
	14 – 60	110 – 152	0.9 – 16.5	0.2 – 1.9	(168, 188, 190, 192, 196)
EES	3 – 4	59 – 75	4.7 – 22.9	0.7 – 2.3	(194, 199, 200)
	7 – 12	70 – 132	0.7 – 4.9	0.3 – 1.3	(189, 198, 200, 201)
	13	117 – 142	1.0 – 5.8	0.1 – 1.4	(202)
ZES	3	74 – 154	0.1 – 18.5	0.2 – 1.4	(199, 200, 203)
	6 – 12	192 – 333	0.0 – 6.4	0.0 – 1.1	(184, 186, 195, 199, 204)
	13	116	7.4	1.8	(205)
BES	3	34	14.7	0.1	(193)
	7 – 12	50 – 63	0.5 – 10.7	0.0 – 1.6	(193, 197, 201)
	69	170	8.7	0.6	(182)

BES, biolimus-eluting stent; BMS, bare metal stent;EES, everolimus-eluting stent; NIH, neointimal hyperplasia; OCT, optical coherence tomography;PES, paclitaxel-eluting stent; SES, sirolimus-eluting stent; ZES zotarolimus-eluting stent

2.2 Coronary flow and pressure measurements

2.2.1 Coronary flow reserve

Even a relatively severe stenosis in a coronary artery has little effect on coronary blood flow velocity in the resting state (206). Gould and co-workers measured coronary flow at rest and during pharmacologically induced maximal hyperaemia in the same coronary

artery in dogs. They showed that severe stenosis caused a blunted flow velocity response to hyperaemic stimulus. The concept of CFR was introduced in 1974, defined as the ratio of coronary flow during hyperaemia to baseline flow at resting conditions (206). Initially CFR was measured with a thermodilution method, requiring repeated intracoronary injections of saline boluses to calculate transit times. Boluses of saline could also affect resting hemodynamic conditions. Later, a catheter utilizing pulsed-wave Doppler crystal was introduced for coronary flow measurements, which allowed CFR to be measured more easily during coronary angiography (207).

Three levels in the coronary arterial tree are involved in regulation of coronary flow and vascular resistance. First, the large epicardial coronary arteries and their branches usually contribute little to the coronary arterial resistance. Second, most of the vascular resistance arises from the arterioles, which also play a major role in the autoregulation of coronary flow. Third, the capillaries contribute little to the arterial resistance. (208)

Epicardial stenosis limits maximal coronary flow and decreases CFR (206, 209). CFR < 2.0 has been shown to detect a haemodynamically significant coronary stenosis (210-214) and it has been shown to be associated with increased risk of cardiac death (215). Factors that affect epicardial and microcirculatory resistance also influence maximal coronary flow and CFR. These factors include haemodynamic state, age, left ventricular hypertrophy and diabetes (213, 216-219). This limits its use in the assessment of stenosis severity.

CFR can be measured non-invasively by positron emission tomography (PET) (220, 221). CFR can also be measured by single-photon emission computed tomography (SPECT), which has been validated by comparison to intravascular Doppler and PET (222, 223). Measurement of CFR by transthoracic echocardiography (TTE) is also possible (224). The advantages of TTE are that it does not expose the patient to ionising radiation and it can be performed as a bed-side examination.

TTE measurement of CFR is performed by using B-mode and colour Doppler to identify the distal coronary artery. Coronary flow velocities are measured during baseline and adenosine infusion with pulsed-wave Doppler. CFR is calculated as the hyperaemic-to-baseline ratio of the mean diastolic flow velocity of repeated measurements. (225)

TTE has been validated for measuring CFR for LAD and RCA with invasive Doppler-wire CFR (226, 227). In patients with a lesion in LCX, a transthoracic CFR < 2.0 showed a good correlation with a reversible perfusion defect detected by SPECT (228). TTE-measured CFR correlated to CFR measured by invasive thermodilution method after implantation of DES, although TTE measurements were less reproducible (229). The advantages of the transthoracic CFR measurement include avoidance of ionising radiation and risks of invasive procedure, but otherwise it has the same limitations as invasive Doppler CFR. The need for good transthoracic acoustic window is also a limitation of this method, making it also less reproducible when compared to other

modalities. Transthoracic CFR measurement is most often successful in the LAD, while RCA and LCX remain more challenging, with reported success rates of 98%, 66% and 43% respectively (230).

2.2.2 Fractional flow reserve

The concept of measuring FFR for the assessment of hemodynamic severity of a coronary epicardial stenosis by utilizing intra-coronary pressure wire was first introduced and validated in an animal model in 1993 (231) and later in human studies (232, 233). An FFR value of 0.74 was first proposed as a threshold for ischemia-inducing coronary stenosis by Pijls (234). Later the method was validated against multiple non-invasive imaging modalities and FFR was shown to reliably detect ischemia-inducing coronary stenosis when a threshold of < 0.75 was used (235). Deferral of PCI of functionally non-significant lesions with FFR > 0.75 appeared to be safe and improve prognosis in a retrospective follow-up study (236). This was confirmed by the prospective randomized DEFER trial, in which deferral of PCI for lesions with an FFR > 0.75 was associated with reduced frequency of adverse cardiac events during 24 months of follow-up (35). FFR was demonstrated to be useful method for the assessment of procedural success and prognosis after POBA (237) and after stenting when compared to IVUS (238). Validation studies for the assessment of serial stenoses followed (239, 240). FFR during maximal hyperemia is dependent on the mass of viable myocardium perfused by the diseased artery, and in the presence of scar tissue after MI, the FFR values for a similar stenosis are higher, and a cut-off point of 0.75 can be used is this circumstance as well (241). FFR has also been shown to be feasible in the assessment of equivocal left main stenoses (242).

FFR was shown to be applicable in multivessel disease to guide PCI (243), which was later confirmed in the randomized FAME trial (33). In the FAME trial, patients with multivessel CAD were randomized into FFR-guided or angiography-guided PCI groups. FFR-guided strategy with deferral of stenting of lesions with FFR > 0.80 proved to be superior when compared to angiography-guided strategy in terms of composite end-point of death, MI or repeat revascularization after one-year (33) and the results remained similar after follow-up of two years (244). A concept of functional SYNTAX score has been presented, which is calculated in a similar way as traditional SYNTAX score, but only for stenoses with FFR ≤ 0.80 (245). In the FAME study population of patients with multi-vessel CAD undergoing PCI, the functional SYNTAX score was superior to traditional SYNTAX score in the stratification of risk of adverse events (245).

FFR measured with an intracoronary pressure wire is a valuable tool in invasive cardiology. It is relatively simple to perform and to interpret and it allows the assessment of functional significance of coronary stenoses. It also takes into account coronary collateral circulation and myocardial scars and has proved to be very useful in assessing the need for coronary revascularization. Different cut-points have been used in the initial validation studies and the more contemporary studies, creating a “grey zone” when FFR

is between 0.75 and 0.80. In this population, clinical judgement and information on other invasive and non-invasive imaging modalities should be used.

2.2.3 Instantaneous wave-free ratio

Instantaneous wave-free ratio (iFR) was introduced in 2012 (246). Like FFR, it is calculated as the ratio of the distal transstenotic pressure to the proximal aortic pressure. FFR is measured as an average of several cardiac cycles and adenosine is used to induce maximal vasodilatation of the microcirculation to minimize the effect of microcirculatory resistance. Unlike FFR, iFR is measured during a specific diastolic wave-free period in a single cardiac cycle when resistance of coronary microvasculature is thought to be most stable and minimized. Thus, adenosine infusion is not needed. At present, there is no evidence to show that iFR-guided PCI would improve clinical outcomes.

2.2.4 Discordance of coronary flow reserve and fractional flow reserve

On some instances, CFR and FFR produce conflicting results when performed in the same coronary artery in the same patient. Johnson et al showed that the extent of focal and diffuse disease in the coronary vasculature explains discordant PET-measured CFR and invasive FFR values (247). CFR measures maximal increase in coronary flow during adenosine infusion, while FFR measures the pressure drop caused by a focal stenosis during adenosine-induced maximal coronary flow. Both epicardial and microvascular disease affect CFR measurements while FFR is thought to reflect the haemodynamic significance of a focal epicardial stenosis. FFR can be abnormal despite normal CFR when microvascular or diffuse disease is limited and coronary autoregulation is preserved. On the other hand, FFR can be normal but CFR abnormal when severe epicardial stenosis and severe microvascular disease co-exist. The flow velocity achieved during adenosine infusion may not increase enough for an epicardial stenosis to have a significant FFR-value.

van de Hoef et al showed by measuring FFR and CFR in the same coronary artery, that patients with normal FFR but abnormal CFR appeared to have worse prognosis when compared to either those with normal CFR and FFR, or those with normal CFR and abnormal FFR (248). Patients with abnormal FFR but normal CFR appeared to have good prognosis. The potential explanation for this could be that the compensatory vasodilatation of the microvasculature is sufficient to counteract the effect of the epicardial stenosis on myocardial blood flow in these patients. The study can be criticised by the small number of patients with normal FFR and abnormal CFR, but it is evident that FFR has limitations when microvascular disease is present.

The simultaneous measurement of coronary blood flow velocity and pressure gradient enables taking the microvascular resistance into account. The measurement of index of microvascular resistance (IMR) is possible with a pressure-wire catheter using the thermodilution method (249). Measuring IMR together with FFR provides complementary

data on coronary microcirculatory function and may be useful to overcome some of the above-mentioned limitations of FFR-measurement.

2.3 Coronary artery stents in percutaneous coronary intervention

2.3.1 Bare-metal stents

Coronary artery stents were developed to treat abrupt vessel occlusion due to dissection after balloon angioplasty and their potential to prevent restenosis also soon became evident (2, 250, 251). The implantation of intra-coronary stents led to remarkably improved results when compared to POBA by halving the rate of restenosis, occurring in up to 40 per cent in the first year after POBA (252-254). The first stents used in PCI were bare-metal stents (BMS) made of stainless steel. The early stents had high metallic density, relatively thick struts and limited deliverability. These features resulted in high incidence of sub-acute ST and frequent failure in deployment and embolization (255). Advances in stent design have made modern BMS more deliverable with thinner struts and different alloys are used to improve deliverability and biocompatibility and to reduce restenosis while maintaining radial strength. Modern BMS are usually made of cobalt-chromium or platinum-chromium alloys (255).

DESs have largely replaced the use of BMS especially when patient or lesion characteristic suggest increased risk of restenosis, namely small-calibre vessels and long lesions, diabetics. BMS are still widely used and are a good option for patients with low risk of restenosis and a contraindication for prolonged DAPT.

2.3.2 Drug-eluting stents

2.3.2.1 Early-generation drug-eluting stents

DESs were developed in order to reduce ISR commonly seen after implantation of BMSs (3). The first DESs were stainless steel stents coated with a durable polymer-bound anti-proliferative drug. The function of the polymer was to mediate controlled release of the drug. First anti-proliferative drugs used were sirolimus, also known as rapamycin, and paclitaxel. The sirolimus-eluting stent (SES; *Cypher*™, Cordis, Miami Lakes, USA) and PES (*Taxus*™, Boston Scientific, Natick, Massachusetts, USA) were shown to reduce late luminal loss, ISR and target-vessel revascularization (TVR) when compared to BMS (4, 256). However, no mortality benefit was observed in a meta-analysis of trials comparing SES or PES with BMS (6).

A large meta-analysis of 38 trials with 18023 patients confirmed the effectiveness of SES and PES in reducing target-lesion revascularization (TLR) when compared to BMS with hazard ratio (HR) of 0.30 (95% CI 0.24-0.37; $p<0.0001$) and 0.42 (0.33-0.53; $p<0{\cdot}0001$), respectively. The NNT for SES and PES to prevent TLR when compared

to BMS were 7 and 8 respectively. SES was more effective than PES in reducing TLR (HR 0.70, 0.56-0.84; p=0.0021). No difference in mortality was observed, while SES was associated with fewer MIs when compared to BMS or PES (HR 0.81, 0.66-0.97, p=0.030 and 0.83, 0.71-1.00, p=0.045, respectively). The risk of LST was greater with PES when compared to BMS or SES (HR 2.11, 1.19-4.23, p=0.017 and 1.85, 1.02-3.85, p=0.041, respectively). (257)

With the increased use of DES, concerns of their long-term safety arose (258, 259). In two large registries, an increased risk of LST was observed (8, 260). In a pooled analysis from four double-blind trials with 1748 patients, there was a trend of higher 4-year rates of ST for DES when compared to BMS (1.2% for SES vs. 0.6% for BMS, p=0.20 and 1.3% for PES vs. 0.9% for BMS, p=0.30) (9). However, after 1 year, the risk of ST became statistically significant with five episodes of ST in patients with SES versus none in patients with BMS (P=0.025) and nine episodes in patients with PES versus two in patients with BMS (P=0.028) (9).

Delayed vascular healing after DES implantation, with pronounced inflammatory reaction with eosinophilic infiltrates, negative vascular remodelling leading to late acquired malapposition, delayed endothelialisation and fibrin deposition has been associated with the increased risk of late and very late ST in post-mortem studies (10, 93, 261). There is evidence that the polymer-coating of DESs or the drug itself can trigger a hypersensitivity reaction leading to delayed healing and predisposing to LST (262, 263). This has led to the attempts to improve the bio-compatibility of stent platforms, polymers and anti-proliferative agents.

2.3.2.2 Newer-generation drug-eluting stents

Everolimus, a sirolimus-analogue, has been used as an anti-proliferative agent in newer-generation of DESs (*Xience*™, Abbot Vascular, California, USA; and *Promus*™, Boston Scientific, California, USA). The use everolimus-eluting stents (EES) has been shown to reduce the rates of repeat revascularization, MI, and ST when compared to PES (264, 265) and to be non-inferior to SES (266-268). However, in the subgroup of diabetic patients, no difference in end-points between EES and PES was found (264, 265). The rate of ST at 2-year follow-up among patients implanted with EES was significantly lower when compared to SES (0.2% vs. 0.9%, p = 0.02) (266). In a large network meta-analysis, EES was associated with lower risk of ST when compared to BMS, PES, SES and zotarolimus-eluting stents (ZESs) (269).

Zotarolimus is another sirolimus-analogue designed spesifically for use in stents. *Endeavor*™ (Medtronic, California, USA) ZESs have been shown to reduce restenosis when compared to similar BMS platform (270) and similar efficacy but better safety profile when compared to PES (269, 271, 272). In the PROTECT-trial, *Endeavor*™ ZES was compared to SES on 8791 for three years patients with no difference in the primary end point of definite or probable ST and the rates of death and MI were similar (273).

Among secondary end points there was a higher risk of repeat revascularization and lower risk of VLST with ZES when compared to SES. The other commercially available ZES, *Resolute*™ (Medtronic, California, USA) has been shown to be non-inferior to EES in two trials (274, 275).

2.3.2.3 Drug-eluting stents with biodegradable polymer

Increased risk of LST after implantation of early-generation DES has been associated with incomplete stent endothelialisation (10). Although the cause of delayed endothelialisation of DES is not known, plausible stent-related factors could be either the cytostatic drug itself or the polymer coating to which it is bound. Cytostatic drugs inhibit smooth muscle cell proliferation and neointimal hyperplasia formation, but could also inhibit endothelialisation of the stent. The durable polymer coatings could cause inflammatory reactions leading to impaired vascular healing after stenting. Possible other explanations could include the use of DES in more complicated and high-risk lesions when compared to BMS. The possible deleterious effect of durable polymer coatings on stent endothelialisation has led to the development of DESs with biodegradable polymer coatings or totally polymer-free DES.

Biolimus is a sirolimus-derivative developed for use in DES. The biolimus-eluting stent (BES; *Biomatrix*™, Biosensors Europe SA, Switzerland) with biodegradable polymer performed non-inferior to SES after 4-years follow-up in a study with 1707 patients and 2472 lesions regarding the primary composite endpoint of MACE (276). There were significantly fewer definite stent thromboses, especially between years 1 and 4, in the BES group, which is consistent with the theory that at least some durable polymer coatings may interfere with vascular healing and predispose to VLST.

The *Synergy*™ stent (Boston Scientific, Massachusetts, USA) is an everolimus-eluting platinum chromium stent which has an abluminal coating of biodegradable poly(lactic-co-glycolic acid) (PLGA), which resorbs in three to four months. The Synergy stent, with two different doses of everolimus, was compared to durable polymer EES in the EVOLVE I trial in 1:1:1 fashion, and the biodegradable polymer EES with both doses were shown to be non-inferior to durable polymer EES considering the primary end-point of late lumen loss (LLL) at 6 months follow-up. (277)

The *Orsiro*™ stent (Biotronik, Germany) is another application using cobalt chromium stent releasing sirolimus from biodegradable poly-L-lactic acid (PLLA) polymer coating (278). The stent is also coated with a layer of silicon carbide to reduce corrosion. The polymer degrades in a period of less than two years. Initial promising results of a non-inferiority trial comparing Orsiro stent to durable polymer EES were presented at the EuroPCR 2013.

The *Mistent*™ (Micell Technologies, North Carolina, USA) has a cobalt chromium platform with biodegradable PLGA polymer releasing sirolimus (279). The polymer

degrades in a period of two months. In a pilot study of 30 patients the LLL after 18 months follow-up was 0.08 mm, and the percentages of uncovered stent struts by OCT after 4 and 18 months were 7.3 % (range 0.4 % – 46.3 %) and 0 % (0 % – 3.4 %) respectively (280). Positive initial results of a non-inferiority trial comparing Mistent to durable-polymer ZES have been presented at TCT 2012.

The *Desyne BD*™ (Elixir, California, USA) is a cobalt chromium stent with biodegradable poly-D-L-lactic acid (PDLLA) coating releasing novolimus, which is another sirolimus analogue. The polymer degrades in 6 to 9 months. It has been compared to durable polymer ZES in a non-inferiority trial and positive intial reports have been presented at TCT 2011 and EuroPCR 2013 (278). The *Ultimaster*™ stent (Terumo, Japan) is another cobalt chromium stent coated with PDLLA and polycaprolactone copolymer releasing sirolimus. The polymer degrades in 3-4 months. Initial yet unpublished data suggest good endothelialisation and low LLL (278).

2.3.2.4 Polymer-free drug-eluting stents

The *Yukon Choice PF*™ (Translumina, Germany) is a stainless steel stent with microporous surface and coated with sirolimus and probucol combined with a shellac resin. It has been compared to durable-polymer SES and ZES in the ISAR-TEST 2 trial, which showed the superiority of *Yukon Choice PF*™ over ZES and similar outcomes with SES regarding binary restenosis at 6 to 8 months follow-up (11.0 % vs. 19.3 %, p=0.002; and 11.0 % vs. 12.0 %, p=0.68 respectively) (281). After 2 years follow-up, binary restenosis rates were 13.9 %, 20.9 % and 18.6 %, respectively (p=0.047). In the ISAR-TEST 3 trial, the *Yukon Choice PF*™ was compared to a similar stent with durable biodegradable coating (*Yukon Coice PC*™) and durable-polymer SES but the *Yukon Choice PF*™ stent failed to show non-inferiority regarding LLL when compared to SES at 6-8 months follow-up (282). However, after 2-year follow-up, there was no difference in LLL between these stents (281).

The *Biofreedom*™ (Biosensors, Switzerland) BES has a stainless steel platform with microstructured surface alteration on the abluminal side. It showed favourable healing properties in a porcine model when compared to SES, with reduced neointimal proliferation, inflammation and delayed vascular healing at 180 days follow-up (283). The BIOFREEDOM study compared *Biofreedom*™ stent with standard and low doses of biolimus to PES in 1:1:1 fashion on 182 patients. The primary end-point of LLL is evaluated at 4 and 12 months in two cohorts. Presented in the TCT 2009, the unpublished data suggest non-inferiority of standard-dose *Biofreedom*™ stent when compared to PES at while the low-dose stent failed to show non-inferiority at 12 months. The ongoing LEADERS FREE trial is designed to compare *Biofreedom*™ with BMS on 2456 patients with high risk of bleeding and only 1 months DAPT (284).

The *Cre8*™ stent (CID, Italy) has a cobalt chromium platform with abluminal reservoirs to store amphilimus and has a passive carbon coating. The Cre8 stent was compared to

PES in a non-inferiority trial with 323 patients (162 *Cre8*™ and 161 PES) (285). The stent succeeded to show superiority over PES regarding the primary end-point of in-stent LLL, which was 0.14 ± 0.36 mm for Cre8 and 0.34 ± 0.40 mm for PES (p for both non-inferiority and superiority <0.0001).

Other polymer-free stents currently in clinical trials include *Vestasync*™ (MIV Therapeutics, Georgia, USA) cobalt chromium stent with hydroxyapatite surface coating releasing sirolimus and *Amazonia Pax*™ (Minvasys, France) cobalt chromium stent releasing paclitaxel (278).

2.3.3 Alternative stent technologies

2.3.3.1 The bio-active stent

The bio-active stent (BAS; *Titan2*™, Hexacath, Paris, France) is a stainless steel stent coated with TITANOX by reactive physical vapour deposition in a vacuum chamber (17). Titanium is widely used in prostheses as it is biologically inert and in contrast to stainless steel does not induce a foreign body reaction. TITANOX coating of coronary stents has been shown to reduce neointimal hyperplasia in pigs when compared to uncoated stainless steel stents (17). In the preliminary randomized trial with 92 human patients with *de novo* coronary lesions, TITANOX coated stents were superior to similar uncoated stainless steel stents by reducing the binary restenosis rate at six months from 33 % to 15 % (p=0.07) while the occurrence of MACE was 7 % in the BAS group and 27 % in the BMS group (p=0.02) (286). After five years, BAS remained superior to BMS with MACE rates of 16 % and 39 %, respectively (p=0.03), mainly driven by the reduced need for TLR (9 % vs. 25 %, p=0.05) (18).

Progressive registries confirmed the safety and feasibility of BAS in routine clinical practise with good procedural success and MACE rates of 0 – 1.6 % at 30 days, 6.0 – 7.6 % at 6 months and 9 10.4 % at 9 months (287-289). A rate of 8.3 % for TVR was reported at 9 months (287). A French registry including 356 patients with a total of 420 lesions implanted with BAS with a follow-up of one year, the incidence of MACE was only 7.2 %, death 1.2 %, MI 1.5 %, TLR 5.1 % and ST 0.3 % (290). In a registry of 311 patients with BAS implanted in lesions in small (2.0 – 2.75 mm) coronary arteries, low incidence of MACE (6.9 %) was reported during an average follow-up of 8 months (291). A progressive registry on 156 diabetic patients treated with BAS reported 6-month MACE of 10.3 %, with no cases of ST (292).

In a comparison of two progressive registries including all patients with de novo CAD treated with a BAS (n = 201) or PES (n = 204) in a single centre, there were more MACE at 30 days (0 % vs. 4.9%, p = 0.001) with significantly more frequent TVR (0 % vs. 2.9 %, p = 0.014) and ST (0 vs. 3.4 %, p=0.008) (293). After 1 year, the difference in MACE was no longer significant (10.9 % vs. 13.7 %, p = 0.40), but the rate of MI was lower in the BAS group (4.5 % vs. 10.3 %, p = 0.025) and the rate of TVR (8 % vs. 6.9 %; p =

0.67) was similar between the two groups. After 3 years of follow-up, the rate of MACE in the BAS group was significantly lower (13.9 % vs. 23.5 %, p=0.006) and the incidence of MI higher (7.5 % vs. 19.1%, p<0.001) (294). The recently published five-year results reported similar results, with cumulative incidence of MACE of 16.9% in the BAS group and 26 % in the PES group (p = 0.03), MI 9.5 % vs. 20.6 % respectively, (p = 0.002) and ST in 7.8 % of patients in the PES group versus none in the BAS group (19).

In a pooled analysis of three studies comparing BAS to PES on 1774 patients, BAS significantly reduced the risk of recurrent MI (2.7 % vs. 5.6 %, p = 0.004) and MACE (8.9 % vs. 12.6 %, p = 0.02) during a follow-up of 12 months (295). In contrast, in another study with propensity-matched analysis comparing BAS with SES on 319 pairs of patients and BAS with PES on 337 pairs, the superiority of BAS over SES or PES could not be demonstrated during a follow-up of three years, while the cumulative incidence of MACE for BAS, SES and PES were 20%, 19% and 23% respectively (296).

In the TITAX-AMI trial comparing BAS to PES in 425 patients with acute myocardial infarction (AMI), there was no statistically significant difference in the primary composite end-point of MI, target lesion revascularisation (TLR) or death from cardiac causes during one-year follow-up (10.3 % vs. 12.8 %, p=0.5) (297). In addition, the incidence of ST was significantly lower in the BAS group than the PES group (0.9 % vs. 4.3 %, p=0.03). After 2 years of follow-up, a significantly lower rate of primary end-point was observed in the BAS group compared with the PES group (11.2 % vs. 21.8 %, p=0.004), a difference driven by a reduced rate of MI (5.1 % vs. 15.6%, p<0.001) and cardiac death (0.9 % vs. 4.7 %, p=0.02) (20). The incidence of definite ST continued to be significantly lower in the BAS group (0.5 % vs. 6.2 %, p=0.001). After 5 years of follow-up BAS remained superior to PES considering the clinical end-points of MACE (16.4 % vs. 25.1 %, p=0.03), cardiac death (1.9 % vs. 5.7 %, p=0.04) and recurrent MI (8.4 % vs. 18.0 %, p=0.004) while there was no difference in ischemia-driven TLR (11.2 % vs. 10.9 %, p=0.92) (298). The cumulative incidence of definite ST remained significantly more frequent in patients treated with PES (0.9 % for BAS vs. 7.1 % for PES, p=0.001).

In the BASE-ACS trial, 827 patients with ACS were randomized to receive either BAS or EES in 1:1 fashion. There was no difference in the incidence of the primary end-point of MACE (cardiac death, non-fatal MI or ischaemia-driven target lesion revascularisation (TLR)) at 12-month follow-up (9.6 % for BAS vs, 9.0 % for EES, HR 1.04, CI 0.81-1.32, p=0.81) and BAS proved to be non-inferior to EES in this regard (p for non-inferiority =0.001) (299). The rates of cardiac death and ischaemia-driven TLR were similar between the groups (1.9 % vs. 1.0 %, p=0.39, and 6.5 % vs. 4.9 %, p=0.37, respectively), while non-fatal MI occurred less frequently in patient treated with BAS than EES (2.2 % vs. 5.9 %, p=0.007). In a post hoc analysis of the 2-year results, no significant difference was observed in the stent-oriented composite end-point (cardiac death, target vessel-related non-fatal MI, or ischemia-driven TLR) nor in the patient-oriented composite end-point (all-cause death, any non-fatal MI, or any revascularization); with the cumulative

incidences of 10.1 % for BAS versus 11.2 % for EES (p=0.53) and 16.3 % versus 19.8 %, respectively (p=0.2) (300).

In an assessor-blind non-inferiority study comparing BAS with ZES (*Endeavor*™, Medtronic, Minneapolis, Minnesota, USA) on 302 patients undergoing PCI, BAS failed to achieve the pre-specified non-inferiority margin for the primary end-point of in-stent late loss (0.64 ± 0.61 mm vs. 0.47 ± 0.48 mm, difference: 0.16, upper 1-sided 95 % confidence interval: 0.26; p for noninferiority = 0.54) during a follow-up of one year (301). However, this difference in the angiographic end-point did not reflect as a difference in the secondary clinical end-points of death (0.7 % vs. 0.7 %; p = 1.00), MI (5.3 % vs. 6.7 %; p = 0.60), or MACE (21.1% vs. 18.0%, hazard ratio: 1.19, 95% CI: 0.71 to 2.00; p = 0.50), nor in the rates of definite or probable ST (0.7% vs. 0%; p = 0.51) at one-year follow-up. The incidence of MACE at 12 months in this study was remarkably higher than reported in many of the previous studies, mainly driven by the relatively high incidence of clinically indicated TVR, which was 17.8 % in the BAS group and 13.3 % in the ZES group. In this study, revascularization of the target lesion and vessel were regarded as clinically indicated if the DS on any target lesion or vessel was at least 50 % on QCA in the presence of recurrent angina or objective signs of ischemia, or if the DS was at least 70 % even in the absence of ischemic signs and symptoms. The routine angiographic follow-up in the study protocol mandated by the primary end-point may account for the higher incidence of TVR in contrast to the purely clinically indicated TVR reported in other studies without angiographic follow-up. Interestingly, the incidence of MI was non-significantly lower in the BAS group. Based on this study, BAS appears inferior to ZES in the prevention of neointimal hyperplasia on angiographic follow-up, while the comparison regarding clinical end-points remains an area warranting further research.

2.3.3.2 Endothelial progenitor cell capturing stent

The endothelial progenitor cell (EPC)-capturing stent (*Genous*™, OrbusNeich) is coated with polysaccharide matrix containing antibodies that are directed against the human CD34 antigen, which is a cell surface marker found on circulating EPCs. These antibodies attract circulating EPCs on the surface of the stent, thus promoting stent endothelialisation and inhibiting ST and ISR (21, 302, 303). The multicentre HEALING-II study has shown promising results in patients treated with EPC stent for de-novo CAD (304). No acute or late angiographic ST was observed despite of only one month of DAPT. Several singe-centre prospective studies have shown EPC stent to be safe and effective in unselected population with low risk of ST in up to 2 years follow-up (23, 305-309). The 12 month results of the international e-Healing registry in real-world population of patients treated with EPC stent showed good clinical outcomes with low rates of repeat revascularization and ST (310). In diabetic patients of the e-Healing registry, the mortality was higher than in non-diabetics and the incidence of TLR was higher in diabetics requiring insulin (311). EPC-capturing stent has also been reported to be safe and effective on patients treated for STEMI (312-314).

The advantage of the EPC stent is rapid endothelialisation permitting shorter DAPT, which is desirable e.g. in patients who require urgent non-cardiac surgery or who are on oral anticoagulant therapy. In a study of Piscione et al., patients requiring undeferrable non-cardiac surgery were implanted with EPC stent and treated with only two weeks of DAPT (309). Major non-cardiac surgery was performed after three weeks of stent implantation with no cardiac events during the perioperative period or 30-days' follow-up. One-month DAPT after EPC-capturing stent implantation has also successfully been used on patients taking oral anticoagulant therapy, with no evidence of ST at 14 months' follow-up (308).

EPC-capturing stent has been compared with BMS in a study including patients with bifurcation lesions. EPC-capturing stent showed favourable outcomes but the reduction in the cumulative rate of cardiac death, MI, or TLR was not statistically significant. (315)

In a registry study comparing the two-year results of EPC stent, BMS and SES with bio-absorbable polymer, EPC stent showed comparable results with the BMS (316). On high-risk patients treated for de novo coronary lesions, EPC stent showed comparable results when compared to PES, with non-significant higher rate of the composite end-point of target-vessel-failure (317). There were four cases of ST in the PES-group and none in the EPC-capturing stent group. However, in the high-risk arm of the TRIAS trial, the EPC-capturing stent failed to show non-inferiority as compared with the DES, and the high-risk arm of the study was prematurely terminated because of a higher incidence of target vessel failure in the EPC-capturing stent group (318). The results of the low-risk arm of the TRIAS trial, which was designed to show superiority of EPC-capturing stent over BMS, have not yet been published.

The disappointing results of the TRIAS trial have led to the development of the *Combo*™ stent, combining stainless steel stent platform with abluminal BP releasing sirolimus with anti-CD34 antibody coating to attract circulating EPCs (319). Pre-clinical animal study proposed that endothelialisation could be advanced and neointimal formation and inflammation reduced when compared to bare EPC-capturing stent or durable-polymer SES. Non-inferiority of the Combo stent when compared to durable polymer PES was shown in the REMEDEE trail randomizing 183 patients to receive the Combo stent or durable-polymer PES in 2:1 fashion, with LLL 0.39 ± 0.45 mm and 0.44 ± 0.56 mm respectively (p for non-inferiority = 0.0012) and comparable clinical end-points (320).

2.3.3.3 Bioresorbable vascular scaffolds

After coronary stenting, the stent is covered on the luminal side by endothelial cells, after which migration and proliferation of smooth muscle cells create a neointimal layer on the luminal side of the stent. As is long acknowledged, excessive neointimal growth sometimes leads to ISR, phenomenon which the DESs were designed to counteract on. Allergic or immunological reactions to stent components or durable polymers can also lead to delayed vascular healing, which predisposes to ST. Permanent caging of the vessel may also have an effect on arterial remodelling and vasomotor function and stent struts

may occlude side branch ostia. To overcome these issues, fully bioresorbable stents, or scaffolds, have been introduced. These devices are made of bioresorbable polymeric materials or metals.

The everolimus-eluting bioresorbable vascular scaffold (*BVS*™, Abbot Vascular, California, USA) consists of a PLLA core which is coated with PDLLA matrix releasing everolimus (321). After 6 months from implantation on 30 patients the angiographic in-stent late lumen loss (LLL) was 0.44 ± 0.35 mm. The luminal area measured by IVUS was reduced by 16.8%, which was primarily due to reduction of the stent area by 11.8% while the neointimal area was small (0.30 ± 0.44] mm^2), with a minimal area obstruction of 5.5%. One MI occurred during 1 year of clinical follow-up. After 2 years, there was no significant change in the angiographic in-stent LLL (0.48 ± 0.28 mm) and no additional major cardiac events occurred (322). Multiple imaging by OCT, IVUS and IVUS virtual histology was used to confirm apposition and bioapsorption of the BVS. There was a reduction of 34.5% of visible stent struts by OCT during the follow-up of two years. Improvement of vasomotion of the stented segment was also noted after infusion of ergometrine or acethlycholine. However, the shrinkage of the first version of the BVS suggested that it could lack radial strength to oppose recoil of the vessel and a new design of the device, the ABSORB BVS (Abbott Vascular, Santa Clara, California, USA) was developed. After 12 months from implantation of 57 ABSORB scaffolds on 56 patients the scaffold area remained unchanged, when measured with IVUS and OCT (323). The radiofrequency backscattering and the echogenicity of the struts decreased and the strut core area on OCT decreased as well by 11.4%. Pharmacologically induced vasomotion was restored. The angiographic LLL was 0.27 ± 0.32 mm with an IVUS relative decrease in MLA of 1.94%, without significant changes in mean lumen area. 96.69% of the struts were covered by OCT and malapposition, which was initially present in 18 scaffolds, was only observed at follow-up in 4 scaffolds. Two MIs and two repeat procedures occurred, with a MACE rate of 7.1%. The ongoing trials will show its feasibility and efficacy on wider variety of patients including also ACSs.

The AMS-1 scaffold (Biotronik, Germany) is composed of an alloy with 93% of magnesium and 7% of rare metals (324). 71 stents were implanted on 63 patients with good procedural success. Resolution of the stents at 4 months was confirmed by IVUS. However, after four months follow-up, the in-stent late loss was 1.08 ±0.49 mm and ischemia-driven target lesion revascularisation rate 23.8%; and after 1 year the overall target lesion revascularisation rate was 45%. Upgraded version of the scaffold has been developed to address these issues, the AMS-2, which has with thinner struts, improved radial strength and slower resorption (278). Results on the feasibility of AMS-2 have not yet been reported. However, the DREAMS stent, which uses a platform of AMS-2 coated with biodegradable PLGA polymer coating releasing paclitaxel has been studied on 46 patients with 47 lesions (325). The procedural success was 100% and primary composite end-point of cardiac death, target vessel MI and clinically driven target lesion revascularisation occurred in 4% and 7% at 6 and 12 months respectively.

The Desolve scaffold (Elixir Medical, California, USA) consists of PLLA and releases novolimus. It resolves in 1 to 2 years. The results of the DESolve Nx study with 126 patients have been presented at EuroPCR 2013. After 6 months follow-up, the angiographic in-stent LLL was 0.21±0.34 mm and binary restenosis 3.5 %. The percentage of volume obstruction at 6 months on IVUS was low, 5.1±4.2% as was the neointimal thickness by OCT (0.10±0.03 mm). The percentage of covered struts was as high as 98.8%. (278)

2.4 Antiplatelet therapy after percutaneous coronary intervention

2.4.1 Introduction

PCI induces mechanical plaque disruption and platelet activation, which leads to local thrombus formation and distal embolization of platelet thrombi into the microcirculation (326). Implantation of coronary stents increases the risk of thrombus formation, as the stent as a foreign body activates platelets. In the early years of interventional cardiology, antiplatelet therapy with aspirin and dipyridamole was shown to reduce ischemic events after PCI (327, 328). At that time, subacute ST was a rather frequent complication of PCI (250, 252, 253). Antithrombotic therapy during that period included antiplatelet therapy with aspirin and dipyridamole and unfractioned heparin until systemic anticoagulation was achieved with warfarin. This led to increased bleeding complications and prolonged hospital stay for patients treated with stents.

Since the introduction of ticlodipine, DAPT replaced the oral anticoagulation with warfarin. A randomized multicentre trial showed that DAPT with 6 weeks of ticlodipine plus aspirin indefinitely was superior to 6 weeks of warfarin treatment plus aspirin indefinitely in patients treated with coronary stenting regarding the primary end-point of bleeding or peripheral vascular complications, which occurred in 14% in the antiplatelet group and in 21% in the anticoagulation group (p=0.03) (329). The composite secondary end-point of death, infarction, or stent occlusion also occurred less frequently in electively stented patients in the antiplatelet group than in the anticoagulation group (2.4% vs. 9.9%, p=0.01). In a trial comparing three antithrombotic regimens, DAPT with aspirin plus ticlodipin resulted in lower rate of ST when compared to aspirin alone or combination of aspirin and warfarin (330).Since then, ticlodipin has largely been replaced by clopidogrel, and more recently prasugrel and ticagrelor on ACS patients.

The risk of ST is highest during the first month after PCI, and uninterrupted DAPT is crucial during this period (331, 332). ST is a relatively rare event with newer-generation DES and modern antithrombotic therapy. For cobalt-chromium EES, 2-year rate of ST was only 0.74%. However, in a large pooled analysis of 11219 patients, the 2-year incidence of ST was as high as 4.95% in a group of patients in whom DAPT was interrupted during the first 30 days after PCI (333). In a study with *Resolute*™ ZES, interrupted DAPT was only associated with increased risk of ST during the first month after PCI, with one-year incidence of ST 3.6% in this patient group (334).

2.4.2 Aspirin

Aspirin, or acetylsalicylic acid, inhibits platelet aggregation by irreversibly inhibiting cyclo-oxygenase-1 (COX-1), an enzyme facilitating the production of thromboxane A_2, which again promotes platelet aggregation via conformational activation of GPIIb/IIIa receptor on platelet surface. An oral loading dose of 150 – 300 mg of chewed aspirin is recommended and a daily maintenance dose of 75 – 100 mg is sufficient to prevent thrombotic events after PCI (335). Different doses of aspirin were compared in 2658 patients undergoing PCI in the CURE trial, showing that the dosage of aspirin (<100 mg, 100-199 mg or ≥200 mg) as a part of DAPT with clopidogrel did not effect the incidence of cardiovascular death, MI or stroke, but the rate of major bleeding events was doubled in the high-dose aspirin group when compared to the low-dose group (336).

2.4.3 $P2Y_{12}$ receptor antagonists

Adenosine diphosphate (ADP) mediates platelet aggregation via the $P2Y_{12}$ receptor on the cell membranes of platelets. $P2Y_{12}$ or ADP receptor antagonists inhibit this ADP-mediated platelet aggregation. Ticlodipine, clopidogrel and prasugrel are thienopyridine pro-drugs that require conversion to an active metabolite which irreversibly binds to the $P2Y_{12}$ receptor, whereas ticagrelor belongs to a new family of cyclopentyl-triazolo-pyrimidines, binding directly and reversibly to the receptor, facilitating more rapid and potent inhibition of platelet activity when compared to clopidogrel. The conversion of clopidogrel to its active metabolite requires at least two CYP-dependent steps mediated mainly by CYP1A2, CYP3A4/5 and CYP2C19 enzymes, while the formation of the active metabolite of prasugrel requires only one CYP-dependent step. Ticagrelor is not a pro-drug and does not require CYP-dependent metabolism to be active. Thus the onset of action and efficacy of platelet inhibition of ticagrelor should not be affected by CYP-related genetic polymorphisms and drug interactions, while clopidogrel is more susceptible these to than prasugrel. (337)

2.4.3.1 Ticlodipine

DAPT with ticlodipine and aspirin proved to be superior to treatment with warfarin and aspirin on patients treated with stenting (329). Ticlodipine was the first $P2Y_{12}$ antagonist, but due to its hematologic side effects, including neutropenia and thrombotic thrombocytopenic purpura and other adverse effects such as allergic exanthema and diarrhoea, it was soon replaced by clopidogrel, which also appeared to be more efficient than ticlodipine (338).

2.4.3.2 Clopidogrel

In the subset of 2658 patients in the CURE trial with non-ST-elevation acute coronary syndrome (NSTE-ACS) treated with PCI were randomly assigned to double-blind treatment with clopidogrel (n=1313) or placebo (n=1345) (339). Patients were pretreated

with aspirin and study drug for a median of 6 days before PCI during the initial hospital admission, and for a median of 10 days overall. After PCI, most patients (>80%) in both groups received open-label clopidogrel for about 4 weeks, after which study drug was restarted for a mean of 8 months. The primary composite endpoint of cardiovascular death, MI, or urgent TVR within 30 days of PCI occurred in 4.5% of patients in the clopidogrel group and 6.4% in the placebo group (p=0.03). Long-term administration of clopidogrel after PCI was associated with a lower rate of cardiovascular death, MI, or any revascularisation (p=0.03), and of cardiovascular death or MI (p=0.047).

In the randomized placebo-controlled CREDO trial, prolonged DAPT with 12 months administration of clopidogrel with a loading dose of 300 mg prior PCI was superior to standard therapy of 28 days of DAPT without a loading dose, resulting in a 26.9% relative reduction in the combined risk of death, MI, or stroke in a population of 2116 patients who were to undergo elective PCI or were deemed at high likelihood of undergoing PCI (340). In the subgroup analyses, prolonged DAPT appeared to be beneficial among patients with or without ACS or stent implantation.

2.4.3.3 Prasugrel

The efficacy of prasugrel in the reduction of the incidence of the combined endpoint of cardiovascular death, MI or stroke when compared to clopidogrel was shown in the TRITON-TIMI 38 trial (341). 13608 patients were randomized to receive prasugrel with a 60 mg loading dose and a 10 mg maintenance dose or clopidogrel with a 300 mg loading dose and a 75 mg maintenance dose for 6 – 15 months. The combined primary endpoint occurred in 9.9% of patients receiving prasugrel and 12.1% of patients receiving clopidogrel, with a hazard ratio of 0.81 (CI 0.73 to 0.90). The risk of major bleeding was significantly increased in the prasugrel group (2.4% vs. 1.8%, p=0.03). Prasugrel was superior to clopidogrel in subanalysis on stented patients irrespective of stent type, with reduced rates of ST (342). On subanalyses on diabetic and STEMI patients, prasugrel was superior over clopidogrel without increase in non-CABG-related TIMI major bleeding (343, 344). Prasugrel was associated with harm among patients with previous TIA or stroke for the composite end-point of death, MI, stroke, or non–CABG–related TIMI major bleeding (hazard ratio 1.54, CI 1.02-2.32) and was not beneficial among patients aged 75 years or older or with weight less than 60 kg (341).

2.4.3.4 Ticagrelor

Ticagrelor differs from the other $P2Y_{12}$ inhibitors in that it is a direct-acting antagonist that binds reversibly to the receptor (337). Ticagrelor with a loading dose of 180 mg followed by 90 mg twice daily maintenance dose was compared to clopidogrel with a 300 to 600 mg loading dose followed by 75 mg daily thereafter for the prevention of cardiovascular events in 18,624 patients with ACS in the PLATO trial (345). After 12 months follow-up, the primary composite end-point of cardiovascular death, MI,

or stroke occurred in 9.8% of patients receiving ticagrelor as compared with 11.7% of those receiving clopidogrel (hazard ratio 0.84; CI 0.77 - 0.92; p<0.001). When compared to clopidogrel, ticagrelor was also associated with a higher rate of non–CABG-related major bleeding, but also dyspnea and bradycardia were more common.

In a subanalysis on patients with planned invasive strategy, ticagrelor was superior to clopidogrel regarding the incidence of the primary composite end-point (9.0% vs. 10.7%, hazard ratio 0.84) without statistically significant difference in GUSTO major bleeding (346). In another subanalysis on 3237 patients with chronic kidney disease, defined as creatinine clearance <60 mL/min, ticagrelor was superior to clopidogrel in reducing the primary end-point (17.3% vs. 22.0%, hazard ratio 0.77) with an absolute risk reduction greater than that of patients with normal renal function (347). Ticagrelor also reduced total mortality in this patient group (10.0% vs. 14.0%; HR, 0.72). In the subgroup of patients undergoing CABG within 7 days after the last study drug intake, no statistically significant difference in the occurrence of primary composite end-point was seen between patients receiving ticagrelor or clopidogrel (10.6% vs. 13.1% respectively; HR 0.84 [CI 0.60 - 1.16]; p = 0.29), while total and cardiovascular mortality were reduced (348). There was a statistically significant difference in the timing of the pre-operative discontinuation of the study drug between clopidogrel and ticagrelor groups. The patients in the clopidogrel group had also lower BMI and a more frequent history of previous CABG. There was no difference in bleeding events between the two groups. In another subgroup analysis of patients with NSTE-ACS, the benefit of ticagrelor over clopidogrel was seen regardless of whether revascularization was actually performed or not (349).

2.4.4 Current recommendations for antiplatelet therapy after stenting

2.4.4.1 Stable coronary artery disease

According to recent 2013 guidelines of the European Society of Cardiology (ESC) on the treatment of stable CAD, single anti-platelet therapy with aspirin, or clopidogrel for aspirin-intolerant patients, is recommended indefinitely for all patients. DAPT is recommended for at least 1 month after implantation of BMS and for 6 to 12 months after implantation of second-generation DES for patients presenting with stable CAD. DAPT may be used for more than 1 year in patients at high ischemic risk and low bleeding risk. In patients at high risk of bleeding, with undeferrable surgery or concomitant anticoagulant therapy, DAPT for 1 to 3 months may be used after DES implantation. Clopidogrel is recommended for elective stenting. Prasugrel or ticagrelor should be considered in patients with ST on clopidogrel without treatment interruption. Prasugrel or ticagrelor may be considered in specific high-risk situations of elective stenting and are not recommended in low risk elective stenting. (72)

The 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guidelines for the diagnosis and management of patients with stable ischemic heart disease or 2011 ACCF/AHA/SCAI

PCI guidelines do no give recommendations on the use of prasugrel or ticagrelor on patients with stable CAD (84, 350). The ACC/AHA/SCAI guidelines for PCI recommend DAPT with aspirin and clopidogrel after PCI. Aspirin is recommended indefinitely and clopidogrel for at least 12 months after DES implantation in patients without high risk of bleeding, for a minimum of 1 month and preferably 12 months after BMS implantation, unless the patient has increased risk of bleeding when the recommended duration of DAPT is 2 weeks after BMS implantation (84).

2.4.4.2 Myocardial infarction with ST-segment elevation

For stenting in STEMI, the 2012 guidelines of the ESC recommend DAPT with aspirin combined with prasugrel or ticagrelor over DAPT with aspirin and clopidogrel. DAPT should be continued for up to 12 months, with a minimum of 1 month for patients receiving BMS and 6 months for patients receiving DES. (351)

2013 ACCF/AHA guidelines state that DAPT with aspirin and a $P2Y_{12}$ receptor antagonist should be used for 12 months and options include clopidogrel, prasugrel or ticagrelor. (352)

2.4.4.3 Acute coronary syndromes without ST-segment elevation

The 2011 guidelines of the ESC recommend DAPT for patients with ACS without ST-segment elevation for 12 months unless there is excessive risk of bleeding. Ticagrelor is recommended for all patients at moderate-to-high risk of ischemic events regardless of treatment strategy. Prasugrel is recommended for P2Y12-naïve patients who are proceeding to PCI unless there is a high risk of life-threatening bleeding or other contraindications. Clopidogrel is recommended for other patients. A higher maintenance dose of clopidogrel should be considered for the first 7 days in patients managed with PCI without increased bleeding risk. (353)

In the ACCF/AHA guidelines on the treatment of patients with UAP or NSTEMI, updated in 2012, DAPT is recommended for 12 months. Again, in contrast to ESC guidelines, the recommendations for the use of novel $P2Y_{12}$ receptor antagonists are more conservative than ESC guidelines and prasugrel and ticagrelor are not favoured over clopidogrel. The use of glycoprotein IIb/IIIa inhibitors is more strongly recommended, as it is stated that they should be used in PCI-treated UAP/NSTEMI patients. (354)

2.5 Optical coherence tomography and the assessment of vascular healing after stenting – gaps in evidence

Most OCT studies have been performed for research purposes on small selected cohorts of patients to evaluate mid- or long-term stent healing. There is accumulating data on its use also in the assessment of ambiguous lesions and to guide PCI procedures. However,

robust evidence of its potential to improve patient outcomes is lacking, limiting its more widespread use in clinical practise. Yet, there are some active centres employing the method for clinical purposes, while data on the feasibility and safety of unrestricted use of OCT on real-life ACS patients is limited

There is little OCT data on early vascular healing after stenting. Early endothelialisation of the EPC-capturing stent or BAS had not been studied with OCT on human subjects. Delayed endothelialisation after PES has been recognised, but there are few OCT studies on long-term vascular healing after PES implantation. The long-term endothelialisation of BAS and PES has not been compared before. There is also no data on vascular response after implantation of BAS when compared to EES on ACS patients.

3. AIMS OF THE STUDY

First, the present work aims to evaluate the safety and feasibility of second-generation FD-OCT based on experiences from a single centre. Second, the study aims to evaluate vascular healing and stent endothelialisation using FD-OCT after implantation of different types of stents at different points of follow-up. The specific aims are:

1. To evaluate the safety, feasibility and clinical implications of all FD-OCT examinations performed at the Satakunta Central Hospital between August 12th 2009 and February 9th 2011.

2. To evaluate early vascular healing after 30 days from implantation of the EPC-capturing stent.

3. To evaluate early vascular healing after 30 days from implantation of BAS.

4. To compare vascular healing after 9 months from implantation of BAS and EES.

5. To compare long-term vascular healing after implantation of BAS and PES.

4. MATERIALS AND METHODS

4.1 Study population

In study I, we analysed retrospectively all OCT examinations performed in Satakunta Central Hospital (Pori, Finland) between August 12th 2009 and February 9th 2011 (18 months period) including examinations for patients with stable angina pectoris as well as those with ACS, who underwent diagnostic or interventional coronary procedures. This included some cases with clinical entities other than CAD; for instance, takotsubo cardiomyopathy. Indications to perform OCT examination included pre-PCI lesion evaluation, immediate post-PCI evaluation, remote post-stent healing evaluation, late stent failure, and research purposes.

In study II, we enrolled 20 consecutive patients who underwent successful coronary stenting with EPC-capturing stent in a single native lesion in the proximal or mid-segment LAD at Satakunta Central Hospital in Pori, Finland. Multiple stenting in the same lesion was allowed only as bailout. Patients with ACS as well as stable angina pectoris were included. We excluded patients with unprotected left main disease, aorto-ostial lesions, a contraindication to aspirin, clopidogrel or heparin, and those with life expectancy of less than 12 months. Stenting of possible lesions in vessels other than the LAD was performed during separate procedures based on clinical judgment. Informed written consent was obtained from each patient and a control visit including OCT and CFR studies was scheduled at 30 days after the index procedure. The primary endpoint was binary stent strut coverage at 30 days. Secondary endpoints included percentage of malapposed stent struts, NIH thickness, and CFR at 30 days. Major adverse cardiovascular events (MACEs), including MI, TVR, and death, were also recorded during follow-up.

For the purpose of study III, we prospectively enrolled 20 consecutive patients with symptomatic CAD amenable for PCI, who received TITANOX-coated BAS (Titan2®, Hexacath, Paris, France). We considered patients eligible for enrollment if they were above 18 years, with at least one significant coronary lesion (defined as at least 50% DS by visual estimation) in a native coronary artery. The main exclusion criteria included diabetes mellitus, unprotected left main or aorto-ostial lesions, ISR, required stent length >28 mm, and contraindication to aspirin, clopidogrel or heparin. All patients underwent follow-up coronary angiography with OCT examination of the index vessel. Treatment of more than one vessel was permissible.

The study IV is a substudy of the BASE-ACS trial (randomized comparison of TITANOX-coated bioactive stents with everolimus-eluting stents in acute coronary syndrome) , which is a prospective multi-centre single-blinded randomized controlled clinical trial, with the chief aim to evaluate non-inferiority in clinical outcome of Titan2® (Hexacath, Paris, France) BAS as compared with Xience V (Abbott Vascular,

Santa Clara, California, USA) EES in patients presenting with the whole spectrum of ACS (299). The study enrolled a total of 827 patients above 18 years, presenting with ACS, with at least one significant de novo lesion (defined as at least 50% DS by visual estimation) in a native coronary artery or coronary bypass graft. Main exclusion criteria were limited to unprotected left main disease or aorto-ostial lesions, intolerance to the study medications, planned surgery within 12 months of the index procedure, and life expectancy less than 12 months. Enrolled patients were randomly assigned in a 1:1 fashion to receive either BAS or EES.The current substudy was conducted at two of the 14 BASE-ACS sites (Satakunta Central Hospital, Pori, Finland, n=24 and Turku University Hospital, Turku, Finland, n=4). All consecutive patients who had lesion treated in the left anterior descending coronary artery during the index procedure, and who agreed on undergoing follow-up angiography were eligible for the study (we enrolled 28 out of 36 eligible patients). Exclusion criteria included diabetes mellitus and a new de novo stenosis >50% in the stented vessel. Quantitative coronary analysis was performed before and immediately after the index procedure, and at follow-up using the same angiographic projection.

The study V is a substudy of the TITAX-AMI trial, which is a prospective, randomized, multicentre trial comparing the effectiveness and long-term effects of BAS and PES (Taxus Liberte, Boston Scientific, Calway, Ireland) in patients presenting with AMI (20, 297). A total of 425 patients were enrolled and randomly assigned in a 1:1 fashion. Exclusion criteria included unprotected left main disease, ostial or restenotic lesions, contraindication to aspirin, clopidogrel or heparins, life expectancy of less than a year and need for a stent longer than 28 mm. The primary endpoint was a composite of MI, target lesion revascularisation and cardiac death. For the purpose of study V, the 180 patients participating in the TITAX-AMI trial at one of the centres, the Satakunta Central Hospital, were screened from the patient records and those who were free of major adverse cardiac events (MACEs, primary end point of the TITAX-AMI trial) and ISR and the follow-up time was at least 36 months were identified. These patients were contacted by telephone and a total of 20 eligible patients were willing to participate in the study after giving their written informed consent. Two patients had to be later excluded from the analyses because of inadequate OCT image quality leaving 18 patients, 9 in both groups. A quantitative coronary angiogram (QCA) and an OCT image acquisition of the primary culprit lesion were performed at the follow-up. The primary end point of the study was the difference of binary stent strut coverage (%) between BAS and PES. Co-primary end points were mean NIH thickness and stent strut malapposition.

Before inclusion, an informed written consent was obtained from all patients after full explanation of the study protocol. The study protocol was reviewed and approved by our Institutional Human Research Committee and it conforms to the ethical guidelines of the 1964 Declaration of Helsinki, as revised in 2002.

4.2 Methods

4.2.1 Coronary angiography

Coronary angiography and PCI were performed in a standard fashion employing radial or femoral artery access. Quantitative coronary angiography (QCA) was performed off-line using appropriate software (Philips Medical Systems, Eindhoven, Netherlands). Measurements were made in the same two orthogonal image projections before and after the procedure and at the follow-up visit. Reference vessel diameter, minimum luminal diameter and lesion length were obtained.

4.2.2 Optical coherence tomography

OCT images were obtained with the C7-XR FD-OCT system (St. Jude Medical Inc., St. Paul, MN, USA) employing the non-occlusive technique via a radial or femoral approach. All non-ACS patients received intravenous enoxaparine at a dose of 0.75 mg/kg before the OCT image acquisition. ACS patients were treated with DAPT and bivalirudin or enoxaparin according to the local standard protocol. A 0.014-inch guidewire was introduced into the vessel through a 6F guiding catheter and an optical imaging catheter (Dragonfly, St. Jude Medical Inc., St. Paul, MN, USA) was positioned distal to the region of interest. A motorized pullback system was used at a speed of 20 mm/s and OCT images were acquired at a rate of 100 frames per second. Manual injection of iso-osmolar contrast medium through the guiding catheter was used to replace blood from the field of view. During image acquisition, a segment length of 54 mm was visualized and images were stored digitally for subsequent analysis. Before image analysis, the Z-offset was calibrated in order to obtain accurate measurements.

In study I, all OCT pullbacks were assessed for image quality and whether any portion of the region of interest was out of the screen; or if the image had poor quality caused by residual blood, or artefact. Image quality of a pullback was graded on a predefined four-category scale in a similar way as previously described (355). In the classification, pullback quality was categorized as grade 0, if < 10% of cross-sections in a pullback were analysable; grade 1, if 10% to 50% of cross-sections were analysable; grade 2, if 50% to 90 % of cross-sections were analysable and grade 3, if ≥ 90% of cross-sections were analysable. Rotational artefact was defined as misalignment of the image contours due to rapid axial movement of the imaging catheter during the scanning rotation (Study I, Figure 1). Decentration artefact was defined as eccentric position of the imaging catheter so that images are distorted and/or part of the lumen is not visible (Study I, Figure 2). Caliber artefact was used to describe the situation when the large size of the vessel hampered the visualization of whole vessel lumen (Study I, Figure 3) and blood artefact was defined as inadequate clearing of blood from the lumen causing an artefact (Study I, Figure 4).

Success of an examination was evaluated qualitatively based on patient records and analysis of the image quality in OCT pullbacks. Examination was considered successful

if image acquisition could be adequately performed and image quality in at least one pullback was graded as 2 or 3. Examination was considered unsuccessful if image acquisition could not be performed due to technical or anatomical problems, the region of interest could not be reliably assessed, or image quality in all pullbacks was graded as 0. Examination was considered partially successful if image quality in at least one pullback was graded as 1, and at least a part of the region of interest could be assessed, or if multiple regions of interest were evaluated with some being successful and others not. Change of access site was defined as the need to change arterial access site between radial and femoral access after angiography in order to obtain a successful OCT examination (e.g. because of complex anatomy or inadequate guide support to successfully advance the OCT imaging catheter and perform image acquisition). Impact on diagnosis was assigned based on patient records by assessing whether OCT imaging provided additional information over plain angiography that could alter or specify the diagnosis (for instance, plaque rupture not clearly evident on coronary angiography or detection of uncovered stent struts and thrombus in suspected ST). OCT leading to intervention was assigned if PCI was performed based on OCT evaluation.

In study I, information on possible complications and symptoms during the image acquisition was collected from the patient records. Major bleeding was defined according to the criteria used in the GRACE registry (356). Minor bleeding was defined as any bleeding or hematoma noted in the patient records not meeting the criteria of major bleeding. Myocardial ischemia was defined as the occurrence of ischemic ECG changes (ST segment elevation or depression, or T-wave inversion) during the procedure.

In studies II to V, OCT images were analysed off-line independently by two investigators. Stent strut coverage, stent malapposition, NIH and possible thrombosis were evaluated at 1 mm intervals (every fifth frame) in cross-sectional images. Visible stent struts were classified into five groups: a. Apposed to the vessel wall and covered with neointima, b. Apposed to the vessel wall and uncovered, c. Malapposed and covered, d. Malapposed and uncovered and e. Stent struts over a side branch. Binary stent strut coverage was reported as percentage of covered struts of all analysed struts in categories a. to d. Struts overlaying a side branch (e.) were not classified in terms of apposition and coverage and were excluded from these calculations.

A stent strut was defined as covered, if there was a visible layer of tissue covering it. The thickness of the neointimal layer over each covered strut was measured. The ISA distance was measured for protruding struts as the perpendicular distance from the endoluminal surface of the strut reflection to the border of the vessel lumen. A stent strut was classified as apposed, if the ISA distance exceeded 110 µm for BAS, 100 µm for EPC-capturing stent, 110 µm for EES and 130 µm for PES. Strut malapposition was defined as previously described, and 18 µm was used as a correction for half of the blooming effect (12). As the strut thickness of the BAS (*Titan2*™) is 91 µm, this equals 109 µm, which was rounded up to full ten microns taking account the axial resolution (10-20 µm) of FD- OCT. Similarly, for the EPC-capturing stent (*Genous CoCr stent*™)

a margin of 18 µm was added to the strut thickness of 81 µm and the sum of 99 µm was rounded up to 100 µm. For PES (*Taxus Liberte*™), we added the strut thickness of 97 µm and thickness of the polymer (16 µm) and 18 µm for blooming effect to get malapposition distance of 131 µm, again rounded up to 130 µm. As for EES (*Xience V*™), the strut thickness (79 µm) + thickness of polymer (16 µm) + blooming effect (18 µm) equals 113 µm, rounded to 110 µm.

The existence of a side branch in a cross section was recognized by evaluating previous and subsequent cross sections as needed. If the image quality of a cross section was inadequate to allow reliable measurements, a subsequent cross section with adequate quality was used for measurements. Stent CSA and lumen CSA were traced manually or semi-automatically. NIH area was calculated by subtracting lumen CSA from stent CSA and percent NIH area was calculated by dividing the NIH area by the stent CSA multiplied by 100. If the lumen or stent CSA were not measurable, they were omitted. A percentage of uncovered struts more than 5% was considered abnormal.

4.2.3 Coronary flow reserve

In papers II and IV, transthoracic echocardiography (TTE) was used to measure CFR. Assessment by TTE was carried out with a Siemens Acuson Sequoia C 512 mainframe (Siemens AG, Munich, Germany) employing a 4.0 MHz transducer. Echocardiographic dimensions, wall motion abnormalities and valves were assessed using standard methods. Subjects were instructed to avoid caffeine, alcohol, large meals, and tobacco for 12 hours before the study. B-mode and colour Doppler mapping were used to identify the distal LAD as previously described (225, 357). Baseline coronary flow velocities were measured with pulsed-wave Doppler; an average of at least three cardiac cycles was obtained. Hyperaemia was induced by intravenous infusion of adenosine, which was continued until the maximal increase in flow velocity was seen. In offline analysis, the mean diastolic velocity (MDV) was measured at baseline and during the maximal response to adenosine infusion. CFR was calculated as the hyperaemic-to-baseline ratio. Heart rate and blood pressure were monitored at baseline and during adenosine infusion to detect possible hemodynamic changes that could affect the measurements. All coronary flow velocity measurements were carried out at the follow-up visit before coronary angiography, and analysed by an experienced investigator blinded to clinical data. Intra- and inter-observer variabilities for CFR measurements (coefficient of variation) in our laboratory were 2.6 ± 4.0% and 8.6 ± 9.8%, respectively (225, 357).

4.2.4 Statistical analyses

Continuous variables were presented as mean ± standard deviation. However, continuous variables such as stent area, lumen area and NIH area were estimated as medians, due to the limited number of measurements. Categorical variables were described with absolute and relative frequencies (percentage). Independent samples t-test was used to compare

continuous variables, that were normally distributed. Percentages of malapposed stent struts and binary stent strut coverage were also analysed at stent level and presented as median and interquartile range. Comparison of these variables in studies IV and V was performed with Mann–Whitney U test, since the variables were not normally distributed. Chi-square test or Fisher's exact test was used to compare categorical variables. All tests were two-sided and a p value of < 0.05 was considered statistically significant. Inter-observer variability was assessed by evaluating 50 random cross-sectional images by two independent investigators.

In study II, patients were divided into two groups according to the CFR response in off-line analysis: normal (CFR >2.5) and abnormal (CFR ≤2.5). The population was also classified according to the percentage of malapposed and uncovered stent struts (cut-off 5%) according to the classification previously used in the assessment of the determinants of uncovered stent struts. Spearman correlation was used to test the association between percentage of uncovered and malapposed stent struts and CFR class.

Statistical analysis was performed using the IMB SPSS statistical software (version 20.0.0 in study I, version 17.0 in study II and version 16.0.1 in studies III - V, IMB Corp., Armonk, New York, USA). In studies III and IV, pooled analysis was performed using Meta-analyst Beta 3.13 software (http://tuftscaes.org/meta_analyst/) in order to account for clustering and hence to get a better estimation of NIH thickness as derived by a large number of measurements obtained by OCT.

The results of pooled analysis were expressed as pooled proportions (%). Because heterogeneity was anticipated in observational studies, it was assessed a priori by a random effects model (DerSimonian−Laird). Meta-regression analysis was used to estimate the difference between the study groups in study IV.

In paper IV, the primary endpoints of the study were binary stent strut coverage and CFR. For OCT data, it was assumed that an average number of 150 struts per patient will be analysed, and therefore we estimated that inclusion of 12 patients in each study group will show 5% difference in binary stent strut coverage between BAS and EES (power β=80%, two-sided type I error of α=0.05). For CFR data, a sample size of 17 subjects was calculated for each group with a known SD of 0.7 for CFR and an assumed difference of 0.7 between the interventions (α=0.05, β=0.80). Co-primary endpoints were the mean NIH thickness and stent strut malapposition.

5. RESULTS

5.1 Feasibility and safety of optical coherence tomography (I)

A total of 230 OCT examinations were performed in 210 patients. 523 pullbacks were attempted with 519 of them being successful. On average, a single (1.1±0.4) vessel was examined requiring two (2.3±1.1) pullbacks. In a little less than half of the cases (44%), PCI was also performed. Most of the subjects were male and mean age was 66 years. Image acquisition was performed in most cases via radial artery (70%). In one third of cases, OCT findings lead to additional intervention. Indications for OCT examinations were research purposes (45%), evaluation of vascular healing after stenting and stent failure assessment (23%), assessment of ambiguous lesions (18%) and assessment of stent deployment (14%). One patient died of heart failure later after PCI for AMI. No cases of major bleeding, MI, contrast-induced nephropathy, or pericardial tamponade were encountered. Chest pain occurred in 10.9% of examinations, minor bleeding in 4.8%, and myocardial ischemia in 2.6%. Femoral access was associated with fewer blood and decentration artefacts and a trend towards better image quality when compared to radial access, with no difference in complications. After the first 50 examinations, there appeared to be fewer artefacts in the subsequent examinations. Examination was considered successful in 88%, partially successful in 10% and unsuccessful in 1.7% of cases. The main results of the study are presented in tables 3 and 4.

Table 3. Success and implications of OCT examinations.

Variable	Total	First 50	Subsequent	p
Success of examinations				0.26
Successful	202 (87.8)	41 (82.0)	161 (89.4)	
Partially successful	24 (10.4)	8 (16.0)	16 (8.9)	
Unsuccessful	4 (1.7)	1 (2.0)	3 (1.7)	
Technical problem	2 (0.9)	0 (0.0)	2 (1.1)	1.00
Patient-related problem	9 (3.9)	2 (4.0)	7 (3.9)	1.00
Impact on diagnosis	26 (11.3)	7 (14.0)	19 (10.6)	0.46
OCT leading to intervention	79 (34.4)	18 (36.0)	61 (33.9)	0.90

Variables are presented as frequency (percentage).
OCT, optical coherence tomography
Adapted from Lehtinen et al. Int J Cardiovasc Imaging. 2013;29:997-1005 (I).

Table 4. Image quality of the successful pullbacks.

Variable	Total	First 50	Subsequent	p
Successful pullbacks	519	124	395	
Image quality[1]				0.75
3	293 (56.5)	70 (56.5)	223 (56.5)	
2	155 (29.9)	34 (27.4)	121 (30.6)	
1	53 (10.2)	15 (12.1)	38 (9.6)	
0	18 (3.5)	5 (4.0)	13 (3.3)	
Artefacts				
Blood artefacts	176 (34.0)	37 (29.8)	139 (35.4)	0.28
Decentration artefacts	130 (25.1)	46 (37.1)	84 (21.4)	0.001
Caliber artefacts	67 (13.0)	27 (21.8)	40 (10.2)	0.002
Rotational artefacts	29 (5.6)	12 (9.7)	17 (4.3)	0.04

Variables are presented as frequency (percentage).
[1] Image quality was graded as 0, if < 10% of cross-sections analysable; grade 1, if 10% to 50% of cross-sections analysable; grade 2, if 50% to 90 % of cross-sections analysable and grade 3, if ≥ 90% of cross-sections analysable.
Adapted from Lehtinen et al. Int J Cardiovasc Imaging. 2013;29:997-1005 (I).

5.2 Early vascular healing after endothelial progenitor cell capturing stent implantation (II)

Baseline and procedural characteristics of patients are presented in Table 5. Most treated lesions had complex features, and 60% of patients presented with ACS. The mean follow-up was 32 days (range, 25-47 days). No MACEs or angiographic restenosis occurred during follow-up. The results of OCT measurements are presented in Table 6. The binary stent strut coverage was 95%, and no thrombi were detected. The thickness of NIH and percentage of NIH area were low. The percentage of malapposed stent struts was 2.4%. There were 7 patients (35%) with more than 5% of uncovered struts. The average CFR was 2.4 ± 0.7 and 13 patients (65%) had abnormal (≤2.5) CFR, but none of them had hemodynamically significant stenosis. The number of patients who had more than 5% of uncovered struts was 2 (28.5%) in the group with normal CFR and 5 (38.5%) in the group with abnormal CFR (p=1.00). There was no difference in the number of patients with more than 5% of malapposed struts (0 [0%] vs 2 [15.4%], respectively; P=.52). CFR ≤2.5 tended to be associated with the percentage of stent struts which were uncovered and malapposed (R=-0.43; p=.066), but there was no statistically significant difference in the distribution of stent strut categories between the two groups or in the total percentage of malapposed or uncovered struts. There was also no statistically significant difference in the mean NIH thickness between these two groups (99 ± 28 μm vs 109 ± 64 μm; p=.69).

5.3 Early vascular healing after implantation of the bio-active stent (III)

Baseline and procedural characteristics of patients are presented in Table 5. A total of 20 patients underwent OCT examination at an average of 30.5 ± 5.7 days following BAS

implantation. No clinical events were observed during the period from stent implantation to the time of follow-up. Results of OCT measurements are presented in Table 6. Binary stent strut coverage was 97.2%, and the frequency of malapposed struts was 3.2%. No thrombi were detected by OCT at this stage. On average, NIH thickness was 109.7 ± 83.6 μm; NIH area, 0.86 ± 0.46 mm2; and the percent NIH area 14.2 ± 8.2%. Pooled analyses showed that the mean NIH thickness was 103 μm (95% CI, 85-125). Inter-observer variability of the same cross-section measurements of NIH thickness was 6 ± 9 μm.

Table 5. Baseline and procedural characteristics in studies II and III.

	EPC-capturing stent (II) (n=20)	BAS (III) (n=20)
Age (years)	65 ± 9	65 ± 13
Male (%)	95	85
Diabetes (%)	10	0
Hypertension (%)	45	70
Current smoking(%)	30	25
Hypercholesterolaemia (%)	60	70
Previous MI (%)	10	10
Previous CABG (%)	0	15
Previous PCI (%)	10	10
Clinical presentation		
UAP	25	35
NSTEMI	25	40
STEMI	10	5
LAD (%)	100	60
LCx (%)	0	15
RCA (%)	0	25
B/C type lesion (%)	90	100
Bifurcation (%)	65	55
Thrombus (%)	15	15
Thrombectomy (%)	5	10
Postdilatation (%)	70	60
RVD (mm)	3.06 ± 0.29	3.05 ± 0.38
Lesion length (mm)	11.8 ± 3.5	12.5 ± 6.0
Stent diameter (mm)	3.18 ± 0.29	3.13 ± 0.38
Stent length (mm)	15.3 ± 2.2	18.2 ± 8.5
Stents per lesion	1.15 ± 0.37	1.2 ± 0.4

Continuous variables are presented as mean ± standard deviation, while categorical variables are presented as frequency (percentage).

BAS, bio-active stent; CABG, coronary artery by-pass grafting; EPC, endothelial progenitor cell; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; MI, myocardial infarction; NSTEMI, non-ST-segment-elevation myocardial infarction; PCI, percutaneous coronary intervention; RCA, right coronary artery; RVD, reference vessel diameter; STEMI, ST-elevation myocardial infarction; UAP, unstable angina pectoris

Modified from Lehtinen et al, J Invasive Cardiol. 2012;24:631-5 (II) and Annala et al, J Invasive Cardiol. 2013;25:186-9 (III).

Table 6. Results of OCT measurements in studies II and III.

	EPC-capturing stent (II) (n=20)	BAS (III) (n=20)
Follow-up (days)	31.8 ± 5.3	30.5 ± 5.7
Cross-sections analysed	336	441
Number of struts analysed	3183	3780
Mean stent CSA (mm^2)	7.57 ± 1.60	7.15± 1.83
Mean lumen CSA (mm^2)	7.02 ± 1.51	6.28 ± 1.99
Mean NIH area (%)	8.9 ± 7.4	14.2 ± 8.2
Mean NIH thickness (μm)	107.9 ± 96.4	109.7 ± 83.6
Binary strut coverage (%)	95.1	97.2
Malapposed struts (%)	2.4	3.2
Presence of thrombi (%)	0	0

Continuous variables are presented as mean ± standard deviation, while categorical variables are presented as frequency (percentage).
CSA, cross-sectional area; NIH, neointimal hyperplasia; OCT, optical coherence tomography
Modified from Lehtinen et al, J Invasive Cardiol. 2012;24:631-5 (II) and Annala et al, J Invasive Cardiol. 2013;25:186-9 (III).

5.4 Vascular healing after implantation of the bio-active and everolimus-eluting stents in acute coronary syndromes (IV)

A total of 13 patients were included in the BAS group (2033 struts); 15 in the EES group (2898 struts). Baseline clinical characteristics are presented in Table 7 and procedural characteristics in Table 8. Patients in EES group were older than those in the BAS group, but otherwise the populations did not show significant differences. Results of OCT measurements are presented in Table 9. Binary stent strut coverage was higher and malapposed struts lower with BAS versus EES (99.4% versus 89.2%, and 0.2% versus 4.6%, respectively, $p<0.001$ for both). Neointimal hyperplasia thickness was greater with BAS versus EES (274.2 μm versus 100.1 μm, respectively, $p<0.001$). CFR was lower with EES versus BAS (2.2 ± 0.8 versus 3.0 ± 0.5, respectively, $p=0.001$). Abnormal CFR (<2.5) were detected in 10 patients in the EES group versus one in the BAS group ($p=0.002$).

Table 7. Baseline clinical characteristics in study IV.

	BAS (n=13)	EES (n=15)	p
Age (years)	61 ± 9	69 ± 6	0.01
Male gender	10 (76.9)	13 (86.7)	0.51
Risk factors			
Hypertension	4 (30.1)	6 (40.0)	0.62
Hypercholesterolemia	7 (53.8)	6 (40.0)	0.47
Current smoking	3 (23.1)	2 (13.3)	0.51
Medical history			
Myocardial infarction	0	0	
PCI/CABG	0	0	
Medications at discharge			
Aspirin	13 (100)	15 (100)	1.0
Clopidogrel	13 (100)	15 (100)	1.0
ACE-inhibitor/ARB	7 (53.8)	4 (26.7)	0.15
Beta-blocker	13 (100)	15 (100)	1.0
Nitrate	1 (7.7)	1 (6.7)	0.92
Statin	12 (92.3)	15 (100)	0.28
Indication for PCI			
Unstable angina	0	2 (13.3)	0.18
NSTEMI	8 (61.5)	9 (60.0)	0.94
STEMI	5 (38.5)	4 (26.7)	0.51

Continuous variables are presented as mean ± standard deviation, while categorical variables are presented as frequency (percentage).

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BAS, bio-active stent;CABG, coronary artery by-pass grafting; EES, everolimus-eluting stent; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction

Adapted from Karjalainen et al, Int J Cardiovasc Imaging. 2013;29:1693-703 (IV).

Table 8. Lesion and procedural characteristics in study IV.

	BAS (n=13)	EES (n=15)	p
Lesion type			
A	1 (7.7)	2 (13.3)	
B1 / B2	9 (69.2)	11 (73.3)	
C	3 (23.1)	2 (13.3)	
Bifurcation lesion	7 (53.8)	6 (40.0)	0.47
Calcified lesion	8 (61.5)	6 (40.0)	0.26
Thrombus	8 (61.5)	6 (40.0)	0.26
Stent diameter (mm)	3.10 ± 0.38	3.12 ±0.35	0.88
Stent length (mm)	15.8 ± 5.1	18.7 ± 5.9	0.18
Pre-procedural TIMI flow grade	1.4 ± 1.3	2.1 ± 1.4	0.14
Post-procedural TIMI flow grade	3.0 ± 0.0	3.0 ± 0.0	1.0
Radial access	10 (76.9)	9 (60.0)	0.35
Thrombus aspiration	4 (30.8)	4 (26.7)	0.81
Pre-dilatation	7 (63.6)	11 (73.3)	0.29
Post-dilatation	4 (30.8)	7 (46.7)	0.40
Pre-Intervention			
Reference vessel diameter (mm)	3.00 ± 0.37	3.04 ± 0.35	0.79
Lesion length (mm)	12.4 ± 5.2	13.9 ± 4.6	0.41
Minimal lumen diameter (mm)	0.11 ± 0.07	0.21 ± 0.16	0.08
Diameter stenosis (%)	96.2 ± 4.5	92.9 ± 8.3	0.22
Post-Intervention			
Minimal lumen diameter (mm)	2.90 ± 0.31	2.93 ± 0.32	0.81
Diameter stenosis (%)	3.4 ± 5.3	3.6 ± 5.6	0.76
Acute gain (mm)	2.79 ± 0.39	2.73 ± 0.42	0.42
Follow-up, months	10.1 ± 2.2	9.8 ± 2.0	0.69
Duration of clopidogrel treatment (months)	6.9 ± 2.3	7.6 ± 2.8	0.49
Minimal lumen diameter (mm)	2.41 ± 0.38	2.74 ± 0.44	0.06
Diameter stenosis (%)	17.4 ± 14.2	6.6 ± 8.5	0.003
Late loss (mm)	0.49 ± 0.34	0.19 ± 0.24	0.001

Continuous variables are presented as mean ± standard deviation, while categorical variables are presented as frequency (percentage).

BAS, bio-active stent; EES, everolimus-eluting stent;TIMI, thrombolysis in myocardial infarction

Adapted from Karjalainen et al, Int J Cardiovasc Imaging. 2013;29:1693-703 (IV).

Table 9. Optical coherence tomography measurements in study IV.

	BAS (n=13)	EES (n=15)	p
Cross sections analysed	214	284	
Total number of struts analysed	2033	2898	
Struts per cross-section	9.5 ± 2.8	10.2± 3.1	0.83
NIH thickness (μm)	274.2 ± 168.3	100.1 ± 101.0	<0.001
Stent CSA (mm^2)	6.7 ± 2.0	6.8 ± 2.3	0.92
Lumen CSA (mm^2)	4.7 ± 1.6	6.2 ± 2.5	<0.001
NIH area (mm^2)	2.0 ± 1.1	0.6 ± 0.8	<0.001
% NIH area	29.7 ± 12.3	10.8 ± 16.2	<0.001
Strut analysis			
Binary stent strut coverage (%)	99.4	89.2	<0.001
Apposed and uncovered	10 (0.5)	213 (7.3)	<0.001
Malapposed and covered	1 (0.05)	31 (1.1)	<0.001
Malapposed and uncovered	3 (0.1)	101 (3.5)	<0.001
Strut over a side branch	56 (2.8)	76 (2.6)	0.66
Uncovered stent struts	13 (0.6)	314 (10.8)	<0.001
Cross-sections with uncovered struts	10 (4.7)	105 (37.0)	<0.001
Malapposed stent struts	4 (0.2)	132 (4.6)	<0.001
Cross-sections with malapposed struts	3 (1.4)	37 (13.0)	<0.001
Presence of thrombus	0 (0)	1 (6.7)	0.67

Continuous variables are presented as mean ± standard deviation, while categorical variables are presented as frequency (percentage).

BAS, bio-active stent; CSA, cross-sectional area; EES, everolimus-eluting stent; NIH, neointimal hyperplasia

Adapted from Karjalainen et al, Int J Cardiovasc Imaging. 2013;29:1693-703 (IV).

5.5 Long-term healing after implantation of the bio-active and paclitaxel-eluting stents in acute myocardial infarction (V)

Patient and procedural characteristics are presented in Tables 10 and 11, respectively. All patients were male and the mean age was 62 years in the BAS group and 58 years in the PES group. Traditional cardiac risk factors were similar in both groups. One patient in the BAS group had a history of MI and two patients had previously undergone PCI. Stents in the PES group were slightly longer than in the BAS group, but the difference was of borderline significance (18.7 ± 5.7 vs. 13.7 ± 2.4, p=0.054). The mean follow-up was approximately four years in both groups. Results of OCT measurements are presented in Table 12. A total of 305 cross-sections and 3141 stent struts were analysed. The number of analysed cross sections and struts in the PES group was greater which is probably due to longer stented segments in the PES group and differences in the stent structure. The mean stent area was similar in both groups. There was a significant difference in the NIH thickness in favour of the PES group (265.8 ± 165.5 μm for BAS and 126.3 ± 126.4

μm for PES (p<0.001). Binary stent strut coverage was 99.6 % for BAS and 89.2 % for PES in the strut level analysis. When analysed on patient level, the results were similar (99.4 % vs. 89.3 %, p=0.001). Stent strut malapposition was also more common in the PES group (0.28 % and 13.8 % respectively). On patient level analysis, the difference remains similar, but less pronounced (0.1 % vs. 10.6 %, p=0.001). There was marked heterogeneity in the PES group and two patients had over 30 % of analyzed stent struts classified as malapposed accounting for 217 of the total 271 malapposed struts in the whole PES group. A visible thrombus was seen in two patients (22.2 %) in the PES group but not in the BAS group.

Table 10. Patient and procedural characteristics in study V.

	BAS (n=9)	PES (n=9)	p
Age, (years)	62 ± 6	58 ± 10	0.35
Male sex, n (%)	9 (100)	9 (100)	1.0
Diabetes, n (%)	2 (22)	2 (22)	1.0
Family history of CAD, n (%)	1 (11)	2 (22)	0.54
Hypertension, n (%)	5 (56)	5 (56)	1.0
Hypercholesterolemia, n (%)	5 (56)	3 (33)	0.36
Current smoking, n (%)	4 (44)	3 (33)	0.32
Myocardial infarction, n (%)	1 (11)	0 (0)	0.32
PCI, n (%)	2 (22)	0 (0)	0.15
NSTEMI, n (%)	5 (56)	4 (44)	0.65
STEMI, n (%)	4 (44)	5 (56)	0.65
Duration of clopidogrel treatment	6.3 ± 2.4	11.3 ± 2.0	< 0.001
Stent diameter, mm	3.41 ± 0.45	3.08 ± 0.40	0.14
Stent length, mm	13.7 ± 4.4	18.7 ± 5.7	0.054
Predilatation, n (%)	5 (56)	7 (78)	0.33
Postdilatation, n (%)	3 (33)	4 (44)	0.64
Thrombus aspiration, n (%)	1 (11)	1 (11)	1.00

Continuous variables are presented as mean ± standard deviation, while categorical variables are presented as frequency (percentage).

BAS, bio-active stent; CAD, coronary artery disease; NSTEMI, non-ST-segment elevation myocardial infarction; PES, paclitaxel-eluting stent; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction

Adapted from Lehtinen et al, Int J Cardiovasc Imaging. 2012;28:1859-66 (V).

Table 11. Quantitative coronary angiographic measurements in study V.

	BAS (n=9)	PES (n=9)	p
Pre-intervention			
Reference vessel diameter, mm	3.06 ± 0.38	3.05 ± 0.36	0.78
Lesion length, mm	12.1 ± 4.1	12.4 ± 5.0	0.64
Minimal lumen diameter, mm	0.18 ± 0.11	0.22 ± 0.13	0.34
Diameter stenosis, %	94.2 ± 4.6	93.9 ± 8.5	0.26
Post-intervention			
Minimal lumen diameter, mm	2.94 ± 0.31	2.94 ± 0.32	0.88
Diameter stenosis, %	3.8 ± 5.6	3.6 ± 6.2	0.48
Acute gain, mm	2.76 ± 0.42	2.72 ± 0.54	0.52
Follow-up, months	49 ± 5	44 ± 5	0.03
Minimal lumen diameter, mm	2.48 ± 0.34	2.66 ± 0.40	0.21
Diameter stenosis, %	15.6 ± 7.6	9.5 ± 9.5	0.06
Late loss, mm	0.46 ± 0.36	0.28 ± 0.18	0.04

Variables are presented as mean ± standard deviation.
BAS, bio-active stent; PES, paclitaxel-eluting stent
Adapted from Lehtinen et al, Int J Cardiovasc Imaging. 2012;28:1859-66 (V).

Table 12. Optical coherence tomographic measurements in study V.

	BAS (n=9)	PES (n=9)	p
Cross sections analysed, n	123	182	
Total number of struts analysed, n [1]	1171	1970	
Struts per cross section, n	9.5 ± 2.9	10.8 ± 3.1	0.42
NIH thickness, μm	265.8 ± 165.5	126.3 ± 126.4	< 0.001
Stent area, mm^2	9.06 ± 2.37	8.83 ± 1.79	0.41
Lumen area, mm^2	6.54 ± 1.73	8.56 ± 2.41	< 0.001
NIH area, mm^2	2.45 ± 1.50	0.59 ± 1.14	< 0.001
% NIH area	26.2 ± 12.7	7.6 ± 13.5	< 0.001
Strut level analysis			
Binary stent strut coverage, % [2]	99.6	89.2	< 0.001
Uncovered stent struts, n (%)	5 (0.4)	212 (10.8)	< 0.001
Cross sections with uncovered struts, n (%)	4 (3.3)	85 (46.7)	< 0.001
Malapposed stent struts, n (%)	2 (0.2)	271 (13.8)	< 0.001
Cross sections with malapposed struts, n (%)	1 (0.8)	73 (40.1)	< 0.001
Presence of thrombi, n (%)	0 (0.0)	2 (22.2)	0.15
Patient level analysis			
Binary stent strut coverage, % [2]	99.4 ± 0.9	89.3 ± 9.3	0.001
Percentage of uncovered struts (%)	0.6 ± 0.9	10.6 ± 9.3	0.001
Percentage of malapposed struts (%)	0.1 ± 0.4	10.6 ± 13.1	0.001

Continuous variables are presented as mean ± standard deviation, while categorical variables are presented as frequency (percentage).
[1] Including struts over a side branch
[2] Struts over a side branch excluded
BAS, bio-active stent; NIH, neointimal hyperplasia; PES, paclitaxel-eluting stent
Adapted from Lehtinen et al, Int J Cardiovasc Imaging. 2012;28:1859-66 (V).

6. DISCUSSION

6.1 Feasibility and safety of optical coherence tomography (I)

In study (I) we explored the feasibility and safety of second-generation FD-OCT based on retrospective analysis of the patient data and OCT image quality of the first consecutive 230 OCT examinations performed between August 12th 2009 and February 9th 2011 at the Satakunta Central Hospital in Pori, Finland. Of the 230 examinations performed, 88% were successful, while 10% of examinations provided at least some clinically useful information, and failure rate was 2%. Success rates of 81-92% for the imaging of the target segments with the first-generation TD-OCT have previously been reported (355, 358). FD-OCT was used to assess stents in 50 patients in another study, and the primary endpoint of obtaining at least 24 mm of clear-image length was successful in 94% of patients (359). A study on the use of OCT-guidance of PCI procedures reported a technical success rate of 99% for FD-OCT imaging (140). There are differences in the definitions of success between these studies and our study (I) and the reported success rates are thus not directly comparable. The study populations are also different. It is worth to note that our study population included not only selected stable patients with scheduled imaging for research purposes, but also 55% of real-life patients with various clinical indications for OCT imaging, and 27% of patients presented with ACS (I). According to the best of our knowledge, study (I) was at the time the largest study to demonstrate that the clinical application FD-OCT imaging on a wide range of patients is feasible.

Transient chest pain or ischemic ECG changes have frequently been reported during image acquisition with the first-generation TD-OCT. Ischemia is most probably related to the proximal balloon occlusion of the imaged artery and the relatively long image acquisition time during which blood in the artery is replaced by injection of contrast medium or saline. In a study with 468 patients undergoing TD-OCT, where over half of the examinations were performed with the non-occlusive technique, 48% of patients experienced transient chest pain and ischemic ECG changes were reported in 46% of them (360). In this study, ventricular fibrillation occurred in 1.1% of the cases, air embolism in 0.6%, and vessel dissection in 0.2%. In another study employing exclusively the non-occlusive TD-OCT technique, ischemic ECG changes were still present in 35% of the cases, and ventricular premature complexes in 10% (361). The pullback speed of FD-OCT is approximately ten-fold higher than that of TD-OCT (typically 20 mm/s vs. 1 – 3 mm/s) and thus imaging a segment of similar length lasts only one tenth of the time with FD-OCT when compared to TD-OCT. This is probably the main reason for the much lower incidence of chest pain (10.9%) or myocardial ischemia (2.6%) in our study (I). Another contributing factor may be the smaller diameter of the FD-OCT catheter when compared to TD-OCT catheter, especially when imaging severely narrowed segments.

In line with our findings, in another study with FD-OCT examinations performed on 50 patients, transient chest discomfort occurred in 10.6% of patients and bradycardia in 2.1%, while no serious complications were encountered (359). Another small study compared the feasibility and safety of FD-OCT with TD-OCT, both performed consecutively on the same 14 patients (358). In this study, all 14 patients reported chest oppression or pain during TD-OCT imaging while only one patient reported these symptoms during FD-OCT image acquisition (358). Transient ST-segment elevation, ventricular ectopy or bradycardia were also relatively frequently reported with TD-OCT and absent during FD-OCT (358). The frequency of major cardiovascular adverse events, including one death and three occurrences of TIA in the study (I) are most probably associated to the treated condition itself than the OCT image acquisition itself as most of these complications occurred when the OCT imaging was performed for clinical purposes. Naturally, in the absence of a control group, the contribution of the OCT imaging to the occurrence of adverse events in addition to other factors such as coronary angiography, PCI, and patient-related factors, can only be speculated.

The incidence of artefacts related to incomplete clearing of blood from the vessel lumen was higher than that reported for TD-OCT, while the frequency of other artefacts was similar (355). This is probably related to the use of proximal balloon occlusion with the TD-OCT imaging. The higher pullback speed of FD-OCT should reduce the incidence of rotational artefacts. In line with this reasoning, Takarada et al reported rotational (or sew-up) artefacts in 16.9% of cases with TD-OCT when compared to only 2.7% with FD-OCT, when image acquisition was performed on the same 14 patients consecutively with both methods (358). The incidence of rotational artefacts in study (I) was 5.6%. In the current study, the occurrence of blood, decentration, and caliber artefacts was related to vessel size leading often to unsatisfactory image in left main. The imaging of the left main coronary artery remains a challenge because of the large calibre of the vessel and difficulty in completely clearing the blood from the proximal part of the vessel lumen. The occurrence of blood artefacts did not diminish after the first 50 examinations, while there were significantly fewer rotational, calibre and decentration artefacts in the subsequent examinations. The more frequent imaging of the left main coronary artery in the latter group may partly explain these results.

Although not reaching statistical significance, there appeared to be a learning curve with the subsequent examinations being more successful than the initial 50. The incidence of artefacts was reduced over time. This is not surprising, as OCT image acquisition is an invasive procedure and the differences in the outcomes are probably due to the accumulation of operator experience and technical skill. Also, the patient selection for OCT imaging may have evolved over time with increasing experience and awareness of the advantages and limitations of the method. However, we found no major differences in the clinical or procedural characteristics between the groups. In general, good seating of the guiding catheter and adequate flush with a contrast bolus is mandatory in order to obtain good quality images. Imaging of large calibre vessels as the left main and

ostial lesions remains a challenge. Tortuosity of the vessel also often leads to eccentric positioning of the imaging catheter causing artefacts. There were significantly more blood artefacts and decentration artefacts when using the radial approach. This could be due to the more tortuous route when using the radial access which may lead to eccentric positioning of the guidewire and the imaging catheter.

The challenges of OCT technology remain the limited penetration depth and the inability to penetrate through blood. This also limits the use of OCT in the imaging of the ostial segments of the left main and right coronary arteries, as the clearing of blood from the ostial parts of the vessel is virtually impossible.

Our findings were based on a single centre study, thus the conclusions based on these findings should be taken with caution. Additionally, the lack of a control group is an obvious limitation when evaluating the complications of the OCT examination and distinguishing them from plain coronary angiography and PCI, which were often performed in conjunction with OCT imaging in the present study. Due to the retrospective nature of the study, there may be some inconsistency in recording of the symptoms and signs during the procedure. As there was no systematic follow-up or controlling of laboratory parameters after the procedure, the incidence of complications may be underestimated. Additionally, the requested data was not always available in the patient records underscoring the need for a prospective registry for quality control purposes.

6.2 Early vascular healing after percutaneous coronary intervention (II and III)

6.2.1 Optical coherence tomography findings (II and III)

According to our knowledge, study II was the first to assess early vascular healing after an EPC-capturing stent implantation on human subjects (II). In study (III), a similar analysis was performed for the BAS (III). Both stents showed near-complete endothelialisation after one month from implantation, with the binary stent strut coverage of 95.1 % for the EPC-capturing stent and 97.2 % for the BAS after follow-up of 31.8 ± 5.3 vs. 30.5 ± 5.7 days, respectively. The thickness of the neointimal layer after 30 days from stenting was similar between the two stents (107.9 ± 96.4 μm for EPC-capturing stent and 109.7 ± 83.6 μm for BAS). There were fewer malapposed struts (2.4 %) with the EPC-capturing stent in study II when compared to 3.2 % with BAS in study III.

Comparing the results of the two stents in these two independent studies can naturally be hypothesis-generating only, and robust data could only be achieved by randomized double-blinded setting. There are three major differences in the inclusion criteria between these two studies. First, study II with EPC-capturing stent only included patients with a lesion in the LAD, while 40 % of patients in study III had lesion in other vessel than the LAD. Second, diabetic patients were excluded from study II while 10 % of patients

in study III had diabetes. Third, study III included only patients treated for ACS, while 40 % of patients in study II had stable CAD. In other respects the patient and procedural characteristics between the two studies appear similar. It is obvious that these two small study populations are selected and do not represent the whole spectrum of patients with CAD; e.g. women and diabetics are underrepresented.

The concept of the EPC-capturing stent is to promote endothelialisation by attracting circulating EPCs to the stent surface. The BAS on the other hand is coated with TITANOX to improve the biocompatibility of the stent. It has been shown that the levels of circulating EPCs in the blood are elevated during ACS and one could expect that the mechanism of the EPC-capturing stent would work better on ACS patients, while in only 60 % of patients in study II the indication for PCI was ACS (362). On the other hand, based on previous studies, patients treated for ACS generally have a higher likelihood of suboptimal vascular healing after stenting due to thrombus and healing properties of the vulnerable plaque (184). This may offer one explanation for the higher incidence of malapposed stent struts with BAS in study III when compared to EPC-capturing stent in study II. Use of DES has been shown to be associated with improved outcomes when compared to BMS in diabetic patients. The absence of diabetics in study II could also favour EPC-capturing stent over BAS, but the number of diabetic patients in study III was rather small, only 2 (10%), and the significance of this difference in the early stent endothelialisation is probably negligible.

Most of the previous OCT studies on stent endothelialisation have been performed later after stent deployment. The binary stent strut coverage of various DES has varied between 84 % to 99 % after a follow-up of 3 to 13 months (181, 185, 186, 197, 203, 363, 364) and from 98 % to 99 % for BMS after a follow-up of 6 to 13 months (181, 364). There are currently only few small OCT studies evaluating early stent healing after PCI. Prati et al. studied very early stent healing at 3 to 7 days after stent implantation (365) in 15 patients with a total of 28 stents implanted. In this small series, binary stent strut coverage was 89 % for BMS and 87 % for DES (365). In the light of these findings, both EPC-capturing stent (II) and BAS (III) performed well and endothelialisation was nearly complete at 30 days.

6.2.2 Coronary flow reserve measurements (II)

Measuring CFR with TTE allowed us to analyze the recovery of coronary microcirculation and endothelial function. Vasodilation response was abnormal (CFR<2.5) in 65 % of patients. In the absence of stenosis, CFR depicts the vasodilator capacity of the coronary microcirculation. The potential explanations for this finding include other diseases or states that cause microcirculatory dysfunction (diabetes, smoking), transmural MI or endothelial dysfunction. Only two patients had diabetes, and there were no transmural infarctions in either group. Therefore, factors other than endothelial dysfunction are unlikely to have a major contribution to the abnormal CFR response. Seven patients with abnormal CFR had malapposed and uncovered stent struts. This may reflect that

epicardial vessel wall was not healed appropriately in terms of OCT findings in these patients and contribute to the impaired vasoreactivity. Supporting this hypothesis, one previous report demonstrated that incomplete stent endothelialisation detected by OCT was associated with abnormal vasomotor response (366). In another study however, this was not confirmed (174).

CFR findings in study II indicate that functional healing of the stented segment after EPC-capturing stent implantation is not complete at one month. We have assessed serial CFR response post PCI (data not shown). It appears that the rate of patients with normal (CFR>2.5) functional healing increases from one to 6 months follow-up. The clinical implications of this finding are to be clarified. It is possible that poor vasodilation is associated with increased platelet activity and/or increased neoatherosclerosis of the stented segment. One possible explanation is that although struts are covered with tissue they are not covered with functional endothelium but fibrin or thrombus, and thus, vasodilation is abnormal.

Advantages of TTE methodology in the assessment of CFR include avoiding the need for arterial access, fluoroscopy or iodinated contrast agents. Pitfalls of this methodology include all the inherent pitfalls of CFR measurement using any method. Baseline flow can be affected by hemodynamic status, blood pressure and heart rate. Achieving maximal hyperaemia is of particular importance. It is also important to carry out the assessment exactly in the same segment of the coronary tree in the same patient. These issues were carefully taken into account when performing the assessment. No major hemodynamic changes were detected despite the expected decrease in diastolic blood pressure. Flow velocity tracings were continuously measured to be able to detect the highest response during adenosine infusion. TTE has been used in CFR investigations by several independent laboratories (227, 367-370), and TTE measurements have been found to correlate closely with measurements carried out with an intracoronary flow wire (227, 368), MRI (369) and PET (370). Previously, the feasibility of transthoracic Doppler echocardiography in the detection of coronary flow in the LAD has been 95–100% (230, 368). In this study, the feasibility was 100%.

6.2.3 Duration of dual antiplatelet therapy

Accumulating evidence supports the role of vascular neointimal healing in the prevention of ST following PCI, a fatal complication of real-life clinical practice. Stent struts directly exposed to the blood stream provide a favourable substrate for the occurrence of ST, a fact supported by pathological studies that unveiled deficient tissue healing in cases of late ST associated with DES (10, 371). Additionally, exposed struts, particularly malapposed ones, may probably result in flow disturbance that would, in turn, create a pro-thrombotic milieu (372). An issue of immense clinical interest is the occurrence of late and very late (after one year) ST, well beyond the time covered by DAPT as recommended by the most recent guideline updates (373). In this context, a meta-analysis performed by Stone et al, pooled data from 9 randomized trials (5261 patients) comparing DES versus BMS.

They reported an incidence of ST almost identical between the two stent types during the first year of follow-up (0.6%). Nevertheless, between 1 and 4 years, that incidence was much higher with DES than BMS (0.5% versus 0.1% per year, respectively) (9).

Previous data supports the regimen of short DAPT with the EPC-capturing stent. The HEALING-II study showed promising results in patients treated with an EPC-capturing stent for de novo coronary lesions despite only one months' DAPT (304). Several single-centre prospective studies have shown EPC-capturing stents to be safe and effective in unselected populations indicating low risk for ST at long-term follow-up (up to 2 years) (23, 305-309). The multi-centre e-Healing registry showed low rates of ST and repeat revascularization with the EPC-capturing stent at 12 months follow-up (310). However, the mortality of diabetic patients was higher than in non-diabetics, and the incidence of TLR was higher in insulin-treated diabetics (311). EPC-capturing stents have also been successfully used in STEMI patients (312-314). Short (2 weeks to 1 month) DAPT following the EPC-stent implantation has also successfully been used on patients requiring undeferrable non-cardiac surgery or long-term oral anticoagulant therapy (308, 309).

As stent strut coverage has been proposed as a surrogate for risk of ST (10), our studies (II, III) suggest that short DAPT with either EPC-capturing stent or BAS could be feasible in situations where prolonged DAPT should preferably be avoided due to increased bleeding risk or need for elective surgery shortly after PCI. Naturally, this hypothesis requires confirmation from larger, randomized trials powered for clinical end-points, comparing shorter DAPT to standard therapy. Furthermore, there are several other factors affecting the risk of ST, such as the coverage of side branch struts, which was not analysed at the present study. The role of endothelial dysfunction reported after PCI with the EPC-capturing stent remains unclear and warrants further larger studies.

6.3 Vascular healing after implantation of the bio-active and everolimus-eluting stents in acute coronary syndromes (IV)

Study IV was a substudy of the BASE-ACS trial, which demonstrated similar clinical outcomes in ACS patients treated with BAS or EES at 12-month follow-up (299). In study IV, the EES showed a significantly higher frequency of uncovered stent struts than BAS after at OCT follow-up 9 months from stent implantation. Additionally, TTE-derived CFR was more often abnormal on patients treated with EES when compared to BAS. NIH thickness and angiographic LLL were significantly thicker with BAS, which was expected, as EES is specifically designed to prevent ISR.

The percentage of uncovered struts in previous OCT studies on EES with a follow-up of 7 – 12 months has been 0.7 – 4.9 % (189, 198, 199, 201). In study IV, the percentage of uncovered struts with EES was 10.8 % in strut-level analysis, and 5.9 % when analysed on stent-level. This is higher than reported in previous studies for EES. In recent OCT

studies, statistical methods to are used to account for the so called clustering effect, and thus the results of the stent-level analysis may be more comparable to those reported in other studies. For BAS, the frequency of uncovered struts was 0.6 % in both strut- and stent-level analysis. The frequency of uncovered stent struts in the BAS group was similar to that reported for ZES (Table 2).

The percentage of malapposed struts was considerable in the EES group. Other OCT studies on EES have found 0.3 – 1.3 % of struts to be malapposed, which is considerably less than 4.6 % found in study IV (189, 198, 199, 201). However, in stent-level analysis, the median percentage of malapposed struts for EES was 1.5 %, which is comparable to results reported in other studies. Differences in statistical methods used to account for clustering effect may thus partly explain this difference. As immediate post-PCI OCT imaging was not performed, we can only speculate whether the late stent malapposition detected in the EES group was due to persistent acute malapposition or late-acquired. In the BAS group, malapposition was virtually absent, which can be attributed to the correction of the acute malapposition by the thicker NIH layer or due to better vascular healing properties of BAS. A recent meta-analysis demonstrated that the risk of late stent malapposition was significantly higher with DES than bare-metal stents (92). Studies utilizing IVUS have shown that late stent malapposition may be due to positive vessel remodelling and plaque or thrombus resolution (374). Late stent malapposition was more common with PESs than BMSs in STEMI (375). However, late stent malapposition in these analyses was not associated with adverse clinical events. Our results indicate that late stent malapposition was rather common in patients treated for ACS with EES and absent when BAS was used.

In other OCT studies on EES, the NIH thickness has been 70 – 132 μm with a follow-up of 7 – 12 months, which is comparable to our results (100 ± 101 μm, follow-up 9.8 ± 2.0 months) (189, 198, 199, 201). NIH thickness in BAS group (274 ± 168 μm) was significantly higher than in the EES group, and higher than usually reported for SES or PES, but comparable to that reported for ZESs in previous studies with a similar duration of follow-up (Table 2).

The functional healing was assessed using CFR measurement. Our study protocol attempted to minimize the effects of the major confounding factors in CFR assessment. Hemodynamically significant epicardial stenosis, or in the absence of stenosis, dysfunction of the coronary microcirculation can decrease CFR (225). Restenosis and de novo stenosis were ruled out by angiography. Diabetics, who are prone to coronary microvascular dysfunction, were excluded from the study and none of the patients had transmural infarcts in either group. Older age is known to attenuate CFR response by increasing baseline flow, but it is unlikely that the small difference in age could explain the marked CFR difference between the two groups (376).

Based on meta-analyses, EES appeared to be the safest stent with the lowest risk of ST at 2 years when compared to BMS, PES, SES and ZES (269, 377). Duration of

DAPT as short as 3 months has been approved for new EES. Considering our findings, the benefit in reducing neointimal hyperplasia appears to come with a price of delayed stent endothelialisation and possible disturbance in the function of microcirculation. Interestingly, Won et al showed that ≥ 5.9% of uncovered stent struts detected by OCT after 6 – 18 months from DES implantation was associated with the combined end-point of cardiovascular death, MI and ST (175). Our findings of incomplete stent endothelialisation with EES at 9 months on ACS patients may indicate that interruption of DAPT at this time point may not be safe.

Study IV has several limitations. The sample size was relatively limited and therefore the results should be interpreted cautiously, and the study is naturally underpowered to correlate clinical end-points with OCT findings. Furthermore, the current OCT technology cannot detect tissue coverage <10 μm, and thus cannot differentiate ultra-thin layers of neointima. OCT data before and immediately after the index procedure were not available. Larger studies are needed to address the clinical implications of these results.

6.4 Long-term healing after implantation of the bio-active and paclitaxel-eluting stents in acute myocardial infarction (V)

In study V we demonstrated the very different long-term healing properties of BAS and PES. As expected, BAS had thicker NIH (265.8 ± 165.5 μm vs 126.3 ± 126.4 μm) and larger LLL when compared to PES. However, BAS was superior to PES regarding stent strut coverage (99.6 % vs 89.2 %) and the frequency of malapposed stent struts (0.28% vs. 13.8%). This is consistent with our findings from studies II and IV, indicating a favourable and a predictable pattern of vascular healing after BAS implantation (Table 13). DES have the benefit of inhibiting neointima growth, but this appears to lead to suboptimal vascular healing with uncovered and malapposed stent struts, and the pattern of vascular healing is more variable and unpredictable. In study V, the incidence of malapposed and uncovered stent struts was rather high when compared to previously reported data. In previous OCT studies performed 6 to 13 months after implantation, the rate of uncovered or malapposed struts for PES have varied between 4 % to 11.9 % and 0.5 % to 2.3 % respectively (184-187, 363, 364, 378). There are some differences in the definitions and classification of stent strut apposition and coverage, as well as in statistical analysis of the data, between these studies and study V. Due to the small sample size and clustering effect, the incidence of malapposed and uncovered struts on strut-level analysis is pronounced. As the apposition and endothelialisation status of an individual stent strut is not independent of the status of the other struts of the same stent, different statistical methods to account for this clustering effect have been widely used in OCT studies, as was done in study IV. Another option is to evaluate endothelialisation and malapposition percentages on stent or patient-level as in study V. Stent strut coverage was similar in patient-level

analysis (99.4% for BAS vs. 89.3% for PES) and in strut-level analysis (99.6% vs. 89.2%, respectively), and the difference was statistically significant. The difference in the frequency of malapposed struts was less pronounced in patient-level analysis (0.1% for BAS vs. 10.6% for PES) when compared to strut-level analysis (0.28% vs. 13.8%, respectively), but also remained highly statistically significant.

Table 13. Clinical characteristics and OCT findings after BAS implantation in studies III, IV and V.

	Study III	Study IV	Study V
Number of patients	20	13	9
Acute coronary syndrome (%)	16 (80)	13 (100)	9 (100)
Diabetes (%)	0 (0)	0 (0)	2 (22)
Lesion location			
LAD	12 (60)	13 (100)	7 (78)
LCx	3 (15)	0 (0)	1 (11)
RCA	5 (25)	0 (0)	1 (11)
RVD (mm)	3.05 ± 0.38	3.00 ± 0.37	3.06 ± 0.38
Lesion length (mm)	12.5 ± 6.0	12.4 ± 5.2	12.1 ± 4.1
Stent diameter (mm)	3.13 ± 0.38	3.10 ± 0.38	3.14 ± 0.45
Stent length (mm)	18.2 ± 8.5	15.8 ± 5.1	13.7 ± 4.4
Follow-up duration	30.5 ± 5.7 d	10.1 ± 2.2 m	49 ± 5 m
Binary stent strut coverage (%)	97.2	99.4	99.6
Uncovered struts (%)	2.8	0.6	0.4
Malapposed struts (%)	3.2	0.2	0.2
NIH thickness (μm)	109.7 ± 83.6	274.2 ± 168.3	265.8 ± 165.5

Continuous variables are presented as mean ± standard deviation, while categorical variables are presented as frequency (percentage).

BAS, bio-active stent; LAD, Left anterior descending coronary artery; LCx, left circumflex coronary artery; NIH, neointimal hyperplasia; OCT, optical coherence tomography; RCA, right coronary artery; RVD, reference vessel diameter

Our findings of delayed vascular healing with PES are consistent with the previously reported association of incomplete vascular healing of DES and LST in histological studies (10, 93, 261), and the epidemiological findings of the steady yearly incidence of VLST after first-generation DES implantation (8, 9, 260). Our results do not diminish the concern that has arisen on the long-term safety of the first-generation DES. The development of more biocompatible newer-generation DES appears to have at least partly overcome this issue (269). Our findings underline the need for careful clinical consideration on whether the potential benefits of DES implantation outweigh the long-term risks the suboptimal healing may ensue, especially when using first-generation DES, such as PES. BAS provides a good option with predictable healing properties and is suitable in situations where prolonged DAPT is not desired and risk of restenosis is not increased.

6.5 Limitations of the study

Study I is a retrospective study with all inherent limitations. Since the documentation of procedures, possible minor complications and clinical follow-up of patients was not done in a uniform structured form, there remains some variation on reporting these aspects in patient records. This may lead to underreporting of some minor periprocedural complications or symptoms. There was no routine follow-up of laboratory parameters after the procedures, which may have limited the ability of the study to detect anaemia or renal dysfunction not leading to hospitalisation.

Studies II to V have a limited sample size. Studies II and III are descriptive studies on two specific stent technologies applied in selected patients. In studies IV and V the primary end-point was binary stent strut coverage at the strut level, and the power calculations were based on this. As has been discussed before, the coverage or apposition status of struts in the same stent cannot be considered strictly independent variables, and these studies may be underpowered to detect differences in stent endothelialisation. The incidence of uncovered or malapposed struts may be exaggerated as the number of studied stents was limited. In study V, the analysis of OCT images was not blinded, which may cause bias. Studies IV and V were not designed to detect differences in clinical end-points and there was no follow-up after OCT imaging. The optimal duration of DAPT after stenting cannot be determined based on these studies. Considering these limitations, the results of the studies IV and V must be considered to be hypothesis-generating only. Larger randomised studies are warranted to address these issues.

6.6 Clinical implications and future aspects

Study I showed that OCT imaging performed on group of unselected patients undergoing coronary angiography for variable indications is safe and associated with a low risk of procedure-related complications (I). The use of OCT to guide PCI in currently under research (151) and large prospective studies are needed to show, whether OCT-guidance of PCI leads to improved clinical outcomes.

While EPC-capturing stent and BAS had nearly complete strut coverage after one month, the optimal duration of DAPT after implantation of these stents on ACS patients cannot be concluded (II and III). This would require a randomised study design powered for clinical end-points. The disappointing results of the EPC-capturing stent TRIAS trial have shifted the interest to the *Combo*™ stent, which combines EPC-capturing technology with abluminal biodegradable sirolimus-eluting polymer (318, 319).

The clinical significance of OCT-detected suboptimal stent healing after EES and PES implantation warrants further research (IV and V). Stent thrombosis, while often fatal, is a rare event. The increased risk of VLST after first-generation DES was not noticed until enough clinical data had accumulated from registries and randomised trials. Pathological studies have confirmed that VLST is associated with suboptimal stent strut coverage

(10, 93). The results of study V show that suboptimal stent healing is present after PES implantation and that the vascular response is heterogenic (V). Naturally, the clinical association of these OCT findings and risk of VLST cannot be concluded as the substudy only included patients free of clinical adverse events during the follow-up and there was no prospective follow-up after OCT imaging. To determine the possible association of OCT-detected stent endothelialisation and risk of VLST would require a prospective randomised trial powered for clinical end-points.

As the durable polymer of early-generation DES has been proposed as a culprit of delayed vascular healing after stenting, a multitude of stent designs with durable or absent polymer has been developed. At present, there is no data to show that these stents would be superior to newer-generation DES with durable polymer. EES appeared to be superior to other stents when safety end-points were assessed in a large meta-analysis (269). Determining the clinical significance of our findings of suboptimal endothelialisation of EES at 9 months in study IV warrants further larger studies. It is worth to note that current guidelines recommend DAPT for 12 months after implantation of DES on a patient with ACS. Longer-term OCT follow-up would be needed to show, whether stent strut endothelialisation of EES improves over time.

We found an association of impaired CFR and vascular healing after stenting on EES in study IV while there appeared to be no such association for EPC-capturing stent in study II. It is uncertain whether suboptimal stent healing could affect the vasodilatation response of the vessel. Further studies are needed to show the possible association and of stent endothelialisation and function of the microvasculature.

7. CONCLUSIONS

Based on the present investigation, following conclusions can be made:

1. FD-OCT is feasible, with infrequent complications in daily clinical practice when performed on a variety of patients with both research and clinical indications.

2. Endothelialisation of the EPC-capturing stent was nearly complete after 30 days from implantation. However, vasodilation response of the microcirculation of the stented coronary artery was normal in only one-third of patients.

3. In a cohort of unselected non-diabetic patients with CAD, the bio-active stent showed favourable healing properties with good endothelialisation and low prevalence of malapposed stent struts evaluated at 30 days follow-up.

4. In patients presenting with ACS, the implantation of BAS resulted in improved strut neointimal coverage when compared to EES at 9-month follow-up. Additionally, EES was associated with reduced coronary vasodilator function.

5. In a cohort of patients treated with PCI for AMI, bio-active stents were nearly completely healed with good apposition and endothelial coverage, while 10% of struts of PESs had remained uncovered 4 years after implantation.

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