Multimodality imaging in the immediate and long-term evaluation of bioresorbable vascular scaffolds

In patients with ST-elevation myocardial infarction

Erlend Eriksen

Thesis for the degree of Philosophiae Doctor (PhD)
University of Bergen, Norway
2024

UNIVERSITY OF BERGEN

Multimodality imaging in the immediate and long-term evaluation of bioresorbable vascular scaffolds

In patients with ST-elevation myocardial infarction

Erlend Eriksen

Thesis for the degree of Philosophiae Doctor (PhD)
at the University of Bergen

Date of defense: 15.03.2024

Year: 2024

Title: Multimodality imaging in the immediate and long-term evaluation of bioresorbable vascular scaffolds

Name: Erlend Eriksen

Print: Skipnes Kommunikasjon / University of Bergen

Scientific environment

This research project was performed in the coronary intervention laboratory of the Department of Heart Disease, Haukeland University Hospital, Bergen, Norway, under the auspices of the Interventional Cardiology Research Group.

Main supervisor:

Øyvind Bleie, dr. med., Department of Heart Disease, Haukeland University Hospital, Bergen, Norway.

Co-supervisors:

Vegard Tuseth, PhD, Department of Heart Disease, Haukeland University Hospital, Bergen, Norway and Associate Professor, Faculty of Medicine, University of Bergen, Norway.

Jan Erik Nordrehaug, Professor Emeritus, Department of Clinical Science, University of Bergen, Norway. Former head of the Department of Heart Disease, Haukeland University Hospital, Norway.

The PhD programme was performed at the University of Bergen.

Funded by

The Department of Heart Disease, Haukeland University Hospital, Bergen and an unrestricted grant from St Jude Medical (now Abbott).

Acknowledgements

This thesis would not have been possible without the support of numerous collaborators and co-workers both at the Department of Clinical Sciences at the University of Bergen and at the Department of Heart Disease, Haukeland University Hospital.

To my main supervisor Øyvind Bleie, I would like to express my deepest gratitude for taking over the supervision of my project at a time when it did not seem possible to complete the task. His experience and knowledge in the field of interventional cardiology and keen eye for details in the presentation of the data, were essential for pulling through. His patience at a time when my own motivation was lost is much appreciated.

My co-supervisor Vegard Tuseth was the motivation and brain behind the initiation of the project. His combination of grand vision and down to earth mentality is unique and an inspiration. This project would not have gotten on its feet without his talent for applications and finding funding.

For my co-supervisor Professor Jan Erik Nordrehaug I have the the deepest respect. His role in establishing interventional cardiology at Haukeland University and the interventional research group at the University of Bergen cannot be underplayed. I have had the privilege of training under his supervision and his foresight in planning this project made it relevant even now, 10 years after the first protocol.

To all my colleagues at the interventional lab, thank you first of all for making our working environment a fun place to be, making it a pleasure to go to work every day(almost). A special thanks to those who helped to include patients in this study at all times of day in the stressful setting of acutely ill STEMI patients.

My colleagues at the CT lab, especially Karel Kuiper and Terje Larsen, were essential in the follow up of the patients. Thank you for always prioritizing slots for the study, your patients and for being enthusiastic about our project.

In turbulent times, Professor Jose P. Simao Henriques has been my mentor, and he has a special place in this project. His experience in conducting clinical trials is impressive, and he was more than willing to share his experience and network with me. His invitation to spend time at his laboratory in AMC and introduction to Professor Allard C van der Waal secured the pathology part of this project. A big thank you to both!

Optical coherence tomography plays an essential part in all my papers. Without the help from Niels Ramsing Holm, Omeed Neghabat and their colleagues at the core lab in Skejby, none of this would have been possible. Their experience with imaging and continuous scientific production is impressive. I am very greatful for their time and interest in my project.

Sahrai Saeed came in as a rescuing angel when trying to publish my second paper. His skills as manuscript editor and adding echocardiography as part of the results made an essential contribution to our important second paper. Without this publication, the project would likely have stalled.

Learning to utilize new software has been a time consuming task. To all those I have bothered with silly questions about software hacks, statistics and figures: you are not forgotten. Especially Cedric Davidsen is a marvel when it comes to statistics and figures. Others I would like to thank in particular are Reinhard Seifert, Erik Packer, Jon Herstad, Kjetil Løland, Iman Karaji and Magrethe Solvik.

I am grateful to the Department of Heart Disease and the Section of Interventional Cardiology for opportunity and incitement, in addition to time and practical support, to complete this thesis. Specifically, I would like to thank former and current Heads of the Department, Jan Erik Nordrehaug and Kjell Vikenes.

I would also like to thank St Jude Medical (now Abbott) for their unrestricted grant, which helped to fund the OCT core lab expences.

To my parents, Solveig and Einar: the values and ethics I have been given by you, the persistence and selfconfidence, I contribute to you. To my dear Tina I would like to say that your limitless support and belief in me holds my head high when the water is rising. And finally, to my three princesses Hana Christine, Nadja Sophie and Zara Emilia: Thank you for sharing your father with the field of coronary imaging. You all mean the world to me!

Abbreviations

3D-QCA	Three-dimensional quantitative coronary angiography
AIDA	The Amsterdam Investigator-Initiated Absorb Strategy All-Comers trial
ALA	Average lumen area
AMC	Academic Medical Centre
BMI	Body mass index
BMS	Bare metal stent
BP	Blood pressure
BRS	Bioresorbable scaffold
CABG	Coronary artery bypass grafting
CSHI	Coronary stent healing index
CX	Circumflex artery
DES	Metallic drug-eluting stent
DM	Diabetes mellitus
ECG	Electrocardiogram
GISSI	Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto
GFR	Glomerular filtration rate
Gp IIb/IIIa	Glycoprotein receptor IIb/IIIa
HT	Hypertension
ISIS	International Study of Infarct Survival
IVUS	Intravascular ultrasound
IQR	Interquartile range
LAD	Left anterior descending artery
MFA	Minimum flow area
MLA	Minimum lumen area
MMP	Matrix metalloproteinase
MSCT	Multislice computed tomography
NET	Neutrophil extracellular trap
OCT	Optical coherence tomography
PCD	Photon-counting detector
PCI	Percutaneous coronary intervention

RCA	Right coronary artery
RCT	Randomized clinical trial
ROI	Region of interest
RWMA	Regional wall motion abnormalities
SD	Standard deviation
SMC	Smooth muscle cells
STEMI	ST-elevation myocardial infarction
TAPAS	Thrombus aspiration during primary percutaneous coronary intervention
TASTE	Thrombus aspiration during ST-elevation myocardial infarction
TLF	Target lesion failure
TLR	Target lesion revascularization
TOTAL	Randomized trial of primary PCI with or without routine manual thrombectomy

List of publications

Paper I:

Eriksen E, Herstad J, Pertiwi KR, Tuseth V, Nordrehaug JE, Bleie Ø, van der Wal AC. Thrombus characteristics evaluated by acute optical coherence tomography in ST-elevation myocardial infarction.

PLoS ONE, 2022, Apr 11;17(4): e0266634

DOI: 10.1371/journal.pone.0266634

Paper II:

Eriksen E, Neghabat O, Saeed S, Herstad J, Nordrehaug JE, Tuseth V, Holm NR, Holck EN, Sejr-Hansen M, Maule CF, Barkholt TØ, Andreassen LN, Christiansen EH, Bleie Ø. Everolimus-eluting bioresorbable scaffold versus everolimus-eluting metallic stent in primary cutaneous coronary intervention of ST-segment elevation myocardial infarction: a randomized controlled trial.

Coronary Artery Disease, 2023 Jan 1;34(1):1-10.

DOI: 10.1097/MCA.0000000000001202

Paper III:

Erlend Eriksen, Omeed Neghabat, Terje H. Larsen, Sahrai Saeed, Øyvind Bleie. Long-term multimodality imaging follow-up of STEMI patients treated with bioresorbable vascular scaffold: Advantages and challenges.

Coronary Artery Disease, 2023, Sep 6:34(6):415-424

DOI:10.1097/MCA.0000000000001249

Abstract

Introduction

Emergency revascularisation by primary percutaneous coronary intervention (PCI) is the preferred strategy for patients presenting with ST-elevation myocardial infarction (STEMI). The current technique involves implanting metallic stents, which poses a continuous threat of restenosis and stent thrombosis, and also hinders further revascularization. Furthermore, slow flow after manipulating thrombi presents an unresolved issue, significantly impacting mortality. This study explores the potential of non-metallic bioresorbable scaffolds (BRS) as a response to some of these challenges, offering the added benefit of non-invasive follow-up with multislice computed tomography (MSCT). Additionally, optical coherence tomography (OCT) is investigated for its potential to provide real-time insights into thrombus management.

Materials and methods

This prospective, randomized controlled, open-label study planned to include 120 patients with STEMI, randomly assigned in a 1:1 ratio to treatment with an Absorb™ BRS or Xience™ DES (metallic drug-eluting stent). The study involved manual thrombus aspiration and OCT examination of the thrombus remnants after aspiration, measuring a light intensity ratio through the thrombus.

After primary PCI, results were evaluated by angiography and OCT at index and after 12 months. The primary endpoint was the minimum flow area (MFA) assessed at the 12-months mark. The coronary stent healing index (CSHI) was calculated from OCT images.

The BRS cohort underwent multimodality imaging and long-term follow-up with minimum lumen area (MLA) and average lumen area (ALA) assessed at 12 and 36 months post-BRS implantation with MSCT, using OCT at 12 months as reference.

Results

A total of 66 patients were included before the premature closure of the study due to safety concerns. Of the aspirates, 42 were analysable for erythrocyte content, platelet content and age. There were 11 red, 21 white and 10 mixed thrombi. Furthermore, 36

aspirates exhibited features of fresh, seven of lytic and eight of organized thrombi. No significant correlation was found between colour and age, and OCT appearance could not predict erythrocyte or platelet content. The light intensity ratios were not significantly different between fresh, lytic and organized thrombi.

Out of 66 patients, 31 received BRS and 35 received DES. Of these, 58 underwent OCT at 12 months, and 49 were included in the matched analysis. One death occurred in each group, both unrelated to the study device. MFA was 5.13 ± 1.70 mm^2 (95% CI: 4.44;5.82) in the BRS group compared to 6.30 ± 2.49 mm^2 (95% CI: 5.22;7.37) (p = 0.06) in the DES group. Non-inferiority could not be evaluated. The CSHI showed good healing response in both groups with a median score of 3.

In the BRS cohort (n=31), MLA measured by MSCT differed by only by 0.05±1.32 mm^2 (p=0.85) from OCT, but ALA was 1.32 (±2.59 mm^2, p=0.015) greater by MSCT than OCT. ALA and MLA did not change significantly from 12 to 36 months. MSCT identified all cases of restenosis, but missed one patient with huge malapposition.

Conclusions

OCT proved incapable of differentiating between red and white thrombi or determining thrombus age. The DES group performed numerically better in primary and secondary endpoints, but the CSHI showed good stent healing in both groups. Our data support the use of MSCT in the follow-up after BRS implantation, although an invasive examination should still be considered in patients with unexplained symptoms.

Contents

1. Introduction **15**

1.1 ST-elevation myocardial infarction (STEMI), the development of imaging and percutaneous coronary intervention (PCI), and current challenges *15*

1.1.1 History of coronary artery disease 15

1.1.2 History of coronary revascularization 16

1.1.3 Intravascular ultrasound (IVUS) 18

1.1.4 Optical coherence tomography (OCT) 18

1.1.5 Multislice computed tomography (MSCT) 19

1.1.6 Echocardiography 20

1.1.7 3D quantitative coronary angiography (3D-QCA) 20

1.1.8 Stent development and bioresorbable vascular scaffolds (BRS) 20

1.1.9 Current challenges in STEMI revascularization 23

1.2 Rationale for the clinical study *24*

1.2.1 General 24

1.2.2 Bioresorbable scaffolds 25

1.2.3 OCT 25

1.2.4 MSCT 26

1.2.5 Thrombus investigation 26

1.2.6 Biobank 26

2. Aims **27**

2.1 General aim *27*

2.2 Specific aims *27*

2.2.1 Thrombus investigation 27

2.2.2 Bioresorbable vascular scaffold 27

2.2.3 Long-term non-invasive follow-up 27

3. Methods **28**

3.1 Study population *28*

3.2 Thrombus collection *29*

3.3 Analysis of aspirated thrombus material *29*

3.4 OCT acquisition and imaging analysis of thrombus *30*

3.5 Study procedure PCI ... *31*

3.6 3D-QCA ... *31*

3.7 OCT analysis of the treated segment ... *32*

3.8 Echocardiography ... *33*

3.9 Study procedure MSCT follow-up ... *33*

3.10 MSCT acquisition and analysis ... *33*

3.11 Clinical events ... *37*

3.12 Statistics ... *37*

3.12.1 Sample size calculation ... 37

3.12.2 Paper I ... 37

3.12.3 Paper II ... 37

3.12.4 Paper III ... 38

4. Summary of results ... **39**

4.2 Paper 1 ... *40*

4.2.1 Flowchart ... 40

4.2.2 Thrombus composition ... 40

4.2.3 Correlations thrombus content vs imaging ... 41

4.3 Paper II ... *44*

4.3.1 Primary endpoint, minimum flow area at 12 months follow up ... 45

4.3.2 Secondary endpoints ... 48

4.3.3 Clinical events ... 48

4.4 Paper III ... *50*

4.4.1. MSCT at 12 vs. 36 months ... 50

4.4.2 OCT vs. MSCT at 12 months ... 51

4.4.3 Echocardiography ... 55

4.4.4 Clinical evaluation and events ... 56

5. Discussion ... **57**

5.1 General ... *57*

5.2 Thrombus investigation ... *57*

5.2.1 Colour and age ... 57

5.2.2 Aspiration methodology ... 58

5.2.3 OCT methodology ... 58

5.2.4 Clinical impact of thrombus age ... 59

5.2.5 Patient selection and generalizability of results 59
5.2.6 Pharmacologic treatment 60

5.3 BRS vs. DES 12 months after implantation *60*
5.3.1 Minimum flow area 60
5.3.2 Coronary stent healing index 62
5.3.3 Summary and the future of BRS 62

5.4 MSCT vs. OCT and MSCT 36 months after implantation *63*
5.4.1 MSCT compared to reference OCT 12 months after implantation 63
5.4.2 ALA, MLA and area stenosis 12 vs. 36 months after implantation 64
5.4.3 Clinical evaluation of MSCT 64
5.4.4 MSCT limitations 64
5.4.5 Stent thrombosis in BRS 65
5.4.6 Summary 68
5.4.7 Strengths and limitations 68

6. Conclusions 69

6.1 Thrombus investigation *69*

6.2 Bioresorbable vascular scaffold *69*

6.2 Long-term non-invasive follow-up *69*

7. Evaluation and future perspectives 70

7.1 Our study *70*
7.1.1 Evaluation of imaging techniques 70
7.1.2 Evaluation of study population and inclusion 70
7.1.3 Clinical impact 70
7.1.4 Learning points 71

7.2 Future perspectives *72*
7.2.1 Bioresorbable vascular scaffolds 72
7.2.2 Advances in MSCT 77
7.2.3 Thrombus burden 78

7.3 Ethical considerations *78*

8. References 81

9. Erratum 89

9.1 Missing clinical event *89*

10. Supplementary material **90**

10.1 Approval Regional Ethics Committee *90*

10.2 Patient informed consent *93*

10.3 CSHI definition *104*

1. Introduction

1.1 ST-elevation myocardial infarction (STEMI), the development of imaging and percutaneous coronary intervention (PCI), and current challenges

The topic of this thesis is to investigate the healing response of bioresorbable vascular scaffolds (BRS) as compared to metallic stents implanted in patients with ST-elevation myocardial infarction (STEMI), and to assess long-term follow-up using multislice computed tomography (MSCT). We are also interested in exploring the feasibility of intraoperative identification of thrombus content and age by optical coherence tomography (OCT).

1.1.1 History of coronary artery disease

Throughout recorded history, diseases affecting the human vascular system, especially the coronary arteries of the heart, have plagued humanity. Atherosclerosis has been found in up to a third of old mummies from different geographical regions of the world (1). Heberden first described angina pectoris in 1772, and the first article of the first issue of New England Journal of Medicine was entitled “Remarks on angina pectoris”, by John Warren, M.D. (2). Very early, “ossification” was seen as a cause of angina, and after a theory of thrombus formation was hypothesized by Rudolph Virchow (1812-1902) and associates, these two elements were finally combined by Ludvig Hektoen in 1879. He concluded that myocardial infarction is caused by “coronary thrombosis secondary to changes in coronaries” (3). By 1919 it was possible to diagnose myocardial infarction using an electrocardiogram (ECG) (4, 5). Acute occlusion of a major coronary artery typically shows elevation of the ST segment in an ECG, hence the term ST-elevation myocardial infarction (STEMI). Until today, ECG is the primary tool to select the initial treatment pathway for patients with chest pain, although myocardial infarction often presents with less specific ECG changes, or none at all (6).

Recognizing the need for more accurate diagnostic methods, a number of biomarkers for cardiac necrosis have been scrutinized. While serum levels of muscle enzymes such as creatine kinase were known to increase in myocardial infarction, they lacked the specificity for precise diagnosis. Although the first World Health

Organization definition of myocardial infarction in 1971 did not include biomarkers (7), subsequent revisions have gradualy incorporated biomarkers, and the current fourth definition of myocardial infarction (8), lays great emphasis on cardiac troponin.

1.1.2 History of coronary revascularization

The technique of introducing catheters into the heart dates back to 1929 when Werner Forssman daringly inserted a urine catheter into his own heart in 1929 via venous access. However, until the 1960s intravascular catheters had predominantly been employed for hemodynamic measurements (9).

In the early 1960s, techniques were developed for selective coronary angiography (10, 11). This coincided with experiments of surgical revascularization. Rene Favaloro is usually credited with the first successful saphenous vein graft bypass in 1967 (12). Following several breakthroughs in the late 1960s, coronary artery bypass grafting (CABG) was the first and only way to revascularize, and thus save myocardium at risk of losing blood supply. However, open heart surgery of patients presenting with STEMI carries high mortality, and was too resource- and time-consuming to be performed in an acute setting (2).

In 1979, 28-day mortality for myocardial infarction at Haukeland University Hospital was 31% and 37% for men and women respectively. The majority of these patients died from heart failure, arrhythmia and mechanical complications following large myocardial infarctions (2, 13). Saving myocardium through revascularization had demonstrated success in laboratory animals, using selective infusion of fibrinolytic agents. Fibrinolytic agents dissolve blood clots by activating plasmin, promoting fibrin degradation, and thus thrombolysis. The most common agents are streptokinase, alteplase, reteplase and tenecteplase. Human trials using selective fibrinolysis with streptokinase were conducted by 1976, but early trials failed to recognize the critical importance of rapid administration (14) (15). In clinical trials after 1980, intracoronary streptokinase was found to be most effective if administered < 3 hours and inefficient > 6 hours after onset of chest pain. Intravenous streptokinase was shown to be effective up to six hours after onset in the large first GISSI (The first Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto) trial (16), and the second international

study of infarct survival (ISIS-2) showed overall mortality reduction from 12% to 9% with intravenous administration of streptokinase, which was preferred due to the greater availability and easier administration (17).

A competing strategy to CABG in angina and pharmacological revascularisation in infarction, was mechanical intervention. In 1977, Andreas Gruntzig demonstrated the possibility of treating a stenotic coronary artery by inflating a balloon within the lesion (18), ushering in a new era of catheter-based angioplasty, now called percutaneous coronary intervention (PCI). Nevertheless, mechanical manipulation of arteries may damage the vessels causing acute closure resulting in potentially fatal myocardial infarction. Managing these acute emergencies became a pressing concern for the advancement of angioplasty as a safe therapy. Metallic scaffolds, called stents, to ensure patency of an artery at risk of acute closure was first used in 1986 and approved by the United States Food and Drug Administration in 1994 (19). These early stents, however, were bulky and technically difficult to handle. They were also prone to restenosis and thrombogenicity, causing stent thrombosis, vessel occlusion and thus large myocardial infarctions. Nonetheless, as stent platforms improved, two landmark studies in 1993 and 1994 showed that stents outperformed balloon angioplasty alone in coronary stenosis (19, 20). The introduction of dual antiplatelet therapy with acetylsalicylic acid combined with thienopyridine reduced the problem of stent thrombosis and further enhanced outcomes (21).

For STEMI patients, it became evident that time to revascularisation was the most critical predictive factor for prognosis. While pharmacological thrombolysis offered the advantage of on-site administration by prehospital emergency care teams, PCI necessitated transportation to highly specialized centres. However, PCI delivered superior revascularisation success, reduced the risk of reinfarction and was efficacy was not as time-dependent as thrombolysis. By the early 2000s, clinical guidelines reflected this dilemma, and PCI was recommended over systemic thrombolytic therapy, provided the delay to treatment was not more than 60-120 minutes, depending on time from symptom onset (22).

In addition to rapid development of stent technology, enhanced visualization of the coronary lumen, vessel wall and implanted stents became pivotal to improve

results. With the advent of better imaging modalities, criteria for stent optimization were published, and techniques continued to evolve (23, 24).

1.1.3 Intravascular ultrasound (IVUS)

In IVUS, high-frequency soundwaves ranging from 20-60 MHz pass through tissue, producing echoes that create real-time 360º transaxial visualization of the coronary artery (25). These soundwaves effortlessly penetrate fluid and soft tissue, allowing visualisation of the structure of the vessel wall as well as the lumen and its inner structures. IVUS can distinguish a diseased from a healthy artery, and differentiate between different types of tissue, such as calcium, thrombus and plaque, and it visualizes metallic stents. Consequently, IVUS enables a comprehensive understanding of coronary anatomy, the underlying pathology, and the factors contributing to acute coronary syndrome and stent failure (26). IVUS studies have demonstrated that minimum lumen diameter and cross-sectional area after PCI were predictive factors of restenosis (27, 28). Recent consensus documents have recommended the utilization of intravascular imaging to optimaze stent placement and to diagnose underlying pathology in selected patients (29, 30). Moreover, accumulating evidence suggests that intravascular imaging reduces mortality and adverse cardiovascular events (31, 32). However, it is important to note that IVUS does have certain limitations, notably relatively low axial resolution of about 150-200 μm.

1.1.4 Optical coherence tomography (OCT)

OCT is a light-based technique, and the shorter wavelength of light compared to sound achieves a higher axial resolution of 10-15 μm. First use in man was published in 2001 with the technology called time-domain OCT. Time-domain had a relatively slow acquisition, needing prolonged inflation with a balloon to empty the blood. The subsequent development of frequency-domain OCT significantly improved the speed of acquisition. Frequency-domain OCT relies on multiple light frequencies with a wavelength of 1250-1350 nm. It operates by comparing backscattered light with a light

reflected from a reference mirror, enabling the generation of detailed images. With frequency domain, only a flush of contrast is needed to empty the vessel of blood (33).

Compared to IVUS, the high resolution of OCT offers better visualization of stent struts, typically measuring 60-150 μm (34). OCT also excels in precisely determining the distance from strut surface to vessel wall and assessing the extent of neo-endothelial coverage of the struts. This also enables evaluation of other potential stent failure indicators, such as malapposition, neointimal thickness and uncovered or jailing struts (35). The details of the immediate vessel surface, such as the thickness of endothelium covering plaques and of plaque ruptures, also require the resolution of OCT. For pathology located deeper than 1-2 mm, IVUS maintains its superiority, as light penetrate solid tissue poorly. A notable limitation of OCT is its dependence on complete removal of blood from the vessel for optimal imaging.

1.1.5 Multislice computed tomography (MSCT)

Computed tomography has been a pivotal tool in medical imaging since its inception in the 1970s. However, its application in cardiology has been limited due to the perpetual motion of the heart. Originally, computed tomographies were too slow to capture still images of the organ, but the development of multiple detectors, complimented by ECG triggering, made coronary imaging possible. Initially this was achieved by synchronizing scans taken from the same phase in the cardiac cycle over several heart beats. The resolution of the first 64-slice scanners that became available in 2008 was still crude (36), but the introduction of dual sources, and doubling of the numbers of detectors to 2x128 made it possible to perform a coronary angiogram in a single heartbeat. Detector technology with increased computational power further increased the image quality (37). MSCT currently in clinical use in Haukeland University Hospital has 2x192 slices. The evolution of even more and better detectors is still ongoing, making MSCT the first choice in coronary examinations in increasingly diverse patient populations. Nevertheless, challenges persist, particularly when imaging patients previously treated with PCI. Metallic stents cast shadows creating blooming artefacts. While advances in resolution are gradually addressing this

limitation, metal present in the coronary arteries will invariably attenuate X-ray-based imaging.

1.1.6 Echocardiography

Echocardiography, a non-invasive ultrasound-based technique, is an indispensable tool for imaging the large structures of the heart. Its widespread accessibility makes it the first choice for evaluating cardiac chamber function and valve pathology, as well as identifing and monitoring complications. In STEMI, the echocardiographic evaluation of the extent of myocardial damage is an important prognostic marker (38-40).

1.1.7 3D quantitative coronary angiography (3D-QCA)

A conventional coronary angiogram provides a 2-dimensional image of the coronary lumen. By employing dedicated software to process two orthogonal views, an approximation of the 3-dimensional structure can be methodically examined. This method is readily accessible in all patients being investigated with coronary angiography, with no additional discomfort or procedural time required. However, it does not give a true 3-dimensional image and it only visualizes the lumen of the artery (38).

1.1.8 Stent development and bioresorbable vascular scaffolds (BRS)

The initial metal stents developed in the 1990s were metallic scaffolds to hold the artery open and contain any plaque rupture or dissection that might cause occlusion. Any foreign body exposed in the bloodstream is inherently thrombogenic until it becomes covered by endothelial tissue. When properly expanded against the vessel wall, stent struts are typically covered with new endothelium within weeks. However, in some cases the inflammatory response and excessive ingrowth of tissue may obstruct the lumen due to the healing process. To balance endothelialization with the inflammatory response, manufacturers started to cover the stents with cytotoxic drugs. The first available were stents covered in paclitaxel and sirolimus. The drug was embedded in a polymer to titrate the emission of the drug over time. Subsequent generations of drug-eluting stents (DES) further decreased complications and

improved outcomes with design modification, more biocompatible polymers and new antiproliferative drugs such as zotarolimus and everolimus. The largest stent study to date, NORSTENT, reported a target lesion failure of about 5% over six years in an all-comers population treated with DES (41). Strut thickness of the first DES was about 130-140 µm. With increased understanding of the importance of flow dynamics around bulky struts, newer generations now in use are typically 60-80 µm (Fig. 1) (34). Other innovations include different metal alloys, various ways of eluting the drug and duration of the polymer. Finding the optimal balance of stent properties is still a challenge, and indeed one formula may not exist for all types of lesions.

Although performance of DES continues to improve, they are all still made of metal designed to long outlast the lifetime of the patient. In patients with extensive coronary disease, complex lesions and repeated interventions, this translates into an accumulation of implanted metal. Additionally, restenosis is still a significant issue, resulting in repeated procedures and even more metal. Arteries treated with metal becomes rigid tubes, losing their natural vasomotor activity and the inherit functionality of the endothelium (42). Furthermore, later revascularization by CABG is also hindered if metal is present at the desired site of anastomosis.

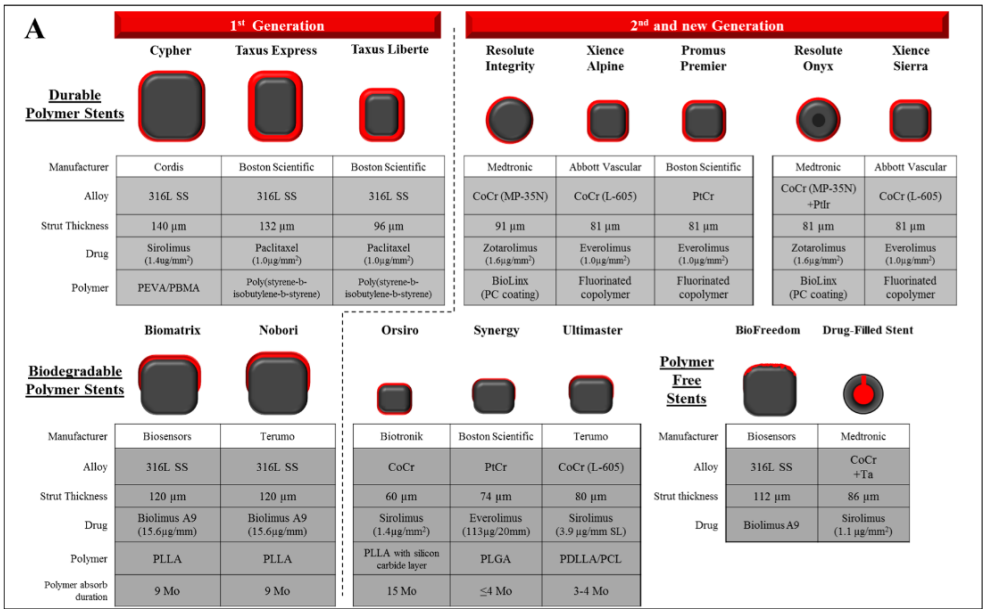
Structural support of the stent is only needed for a limited period, after which the lesion is healed and can support itself (42). The concept of a scaffold that supports the vessel for a limited time and then disappears is therefore attractive. Fully biodegradable scaffolds (BRS) could be an answer to this challenge. Early studies demonstrated the feasibility of poly L-lactide (PLLA) or magnesium-based resorbable scaffolds (43, 44).

Magmaris™ is a magnesium-based stent, and the only other BRS specifically studied in a STEMI population (45). The study shows that although the vasomotor response for Magmaris™ at follow-up was better than the DES comparator, lumen late loss and restenosis rates were higher, leading to a target lesion revascularization (TLR) rate of 16%. Another more recent STEMI study showed a clinical event rate of 13.3% in the Magmaris™ group compared to 10.0% and 6.7% in the two control groups, mainly driven by TLR The authors hypothesize that reason might be that Magmaris™

has a relatively short period of radial support (three months), potentially leading to early recoil and collapse of the scaffold (46).

The PLLA scaffold, Absorb™ (Abbott, Illinois, USA) demonstrated in 2008 full resorbtion with return of vasomotion in the ABSORB Cohort A trial (47-50). A second generation Absorb™ with thinner struts of about 150 µm and stronger mechanical integrity was tested from 2010 in the ABSORB Cohort B trial (49) (51), showing a low rate of ischaemia-driven major adverse cardiovascular events and no difference in late lumen loss six months after implantation, compared to DES. The endothelial vasomotor function also seemed to be intact after resorption (52). Several randomized trials further established Absorb™ as a safe alternative to DES (51, 53), the largest being ABSORB III, randomizing 2008 patients, showing 7.8% target lesion failure (TLF) vs. 6.1% in the DES group (54). Absorb™ also seemed to perform well in the initial STEMI trials (55, 56). Several other bioresorbable platforms of polymeric or metallic base have reached clinical trials, but balancing the radial strength with strut thickness remains an unresolved issue (57).

Figure 1: Design characteristics of representative drug-eluting stents showing development in strut thickness and polymer and drug type and distribution. (Source: Sakamoto et al., Bioengineering 2018, 5(3)) (34)



1.1.9 Current challenges in STEMI revascularization

Current recommendations for the management of patients with STEMI are described in the European Society of Cardiology guidelines published in 2023 (58). These guidelines emphasize the benefit of rapid revascularization. Patients with less than 90 minutes delay from first medical contact to wire crossing have significantly lower in-hospital mortality, with an odds ratio (OR) of 0.57 (95% CI 0.47-0.70, P<0.0001), than patients with > 90 minutes delay. Furthermore, even with rapid revascularization, poor coronary flow after revascularization predicts more than threefold increased risk of in-hospital mortality (OR 3.632, CI 2.822-4.675, P<0.0001) (59). Achieving an optimal angiographic result with good coronary flow is perhaps the most important procedure-related challenge. Slow coronary flow, or microvascular obstruction, occurs in about two-thirds of patients, and several mechanisms may explain this phenomenon,

including distal atherothrombotic embolization, ischaemic injury, reperfusion injury and susceptibility of coronary microcirculation to injury (60).

To avoid distal embolization it makes sense to extract the occlusive thrombotic material. The TAPAS trial showed improved reperfusion after thrombus aspiration in the short term (61), and thrombus aspiration was still widely recommended at the time of our study. However, the later TASTE trial contradicted these findings (62). Finally, routine use was no longer recommended after the TOTAL trial (63, 64). Despite this, thrombus aspiration is still in use in selected cases, although no subgroups have shown to definitely benefit (65).

A different approach would be to defer stenting after achieving flow to minimize manipulation of the thrombus and unstable plaque. Unfortunately, when studied, this did not reduce the area of microvascular obstruction, and introduced added risk with a second procedure shortly after the acute infarction (66). An expert review by Giampaolo Niccoli presents a summary of other strategies investigated, concluding that there is no single pathway to address this issue (67). The mechanism is complex and the prevailing pathogenic mechanism(s) might differ in the individual patient. Knowing the composition of the specific thrombus might help the operator to tailor the treatment perioperatively.

1.2 Rationale for the clinical study

1.2.1 General

Although primary PCI has been the preferred strategy for revascularization of patients admitted with acute STEMI for more than 20 years, there are still challenges that need to be addressed to optimize treatment.

Primary PCI is done to re-establish normal flow in an occluded coronary artery. To secure such flow, we need to understand the pathology of the lesion and the thrombus at site in order to tailor treatment. Intravascular imaging may provide such information and support improving the intervention.

Metallic DES are efficient, but has limitations with accumulation of metallic struts, loss of vasomotion and restenosis. To date, there is limited documentation of BRS as

an alternative in treating STEMI patients. There are also challenges in how to follow-up such novel treatment.

We sought to explore the use of OCT to examine thrombi in primary PCI and optimizing treatment, and the use of BRS in STEMI. Also, we wanted to study the use of MSCT, as compared to OCT, in follow-up of patients treated with BRS.

1.2.2 Bioresorbable scaffolds

Although metallic stents are safe and improve outcome in STEMI, they do involve a permanent presence of inflammatory stimuli, thrombogenicity, loss of vasomotor activity and may hinder later revascularization. During a lifetime of coronary disease, some patients accumulate an extensive amount of metal in the vasculature as the disease progresses. A BRS offers an alternative, giving structural support for a limited time before being resorbed. This may give the artery a chance to heal with healthy endothelium and restored vasomotor activity. Absorb™ BRS was the first BRS to be commercially available, launched in 2012. Initial trials were promising, including smaller trials in STEMI patients. Larger trials in STEMI with long-term imaging follow-up were needed.

1.2.3 OCT

Frequency-domain OCT, such as Ilumien Optis™ (St Jude, Minnesota, USA), opened up for investigator-initiated trials. Intracoronary OCT offers instant high-resolution images of the arterial wall, lumen and inner structures during a single acquisition.

OCT visualizes the underlying pathology of STEMI such as plaque ruptures and erosions, as well as thrombus remnants. In addition, images reveal the immediate result after stenting, which may prompt further optimalization. During follow-up, OCT is an excellent imaging tool for evaluating stent malapposition, uncovered struts and other markers of a suboptimal result. As well as being an established tool for stent optimization and follow-up, OCT enables direct observation of thrombi during a procedure. By observing the intensity of the backscattered light, it might be possible to determine the content of the thrombus.

1.2.4 MSCT

Cardiac computed tomograohy with increasing numbers of detectors, improved detector technology and algorithms, has dramatically improved the resolution, to the benefit of detection and follow-up of coronary artery disease. It is a non-invasive and simple method of investigating coronary pathology with little risk for the patient. However, MSCT has limitations in arteries with metallic stents. Metal will give blooming artefacts, blurring and reduction of the resolution of the image. This often makes it difficult to determine whether the stent is open, or indeed to trace the lumen in order to measure its area and diameter. BRS on the other hand is invisible on MSCT, potentially making it feasible to follow up patients with BRS implants non-invasively. However, the resolution of MSCT of about 0.5 mm, still cannot compete with the superior resolution of OCT. There have not yet been any studies directly comparing the two modalities.

1.2.5 Thrombus investigation

The age of a thrombus impacts mortality, and perhaps the risk of embolization and slow flow after revascularization in STEMI. The age can be reliably classified according to the standard histopathological appearance of tissue decay followed by repair and organization in the aspirated material (68, 69). Ischaemic time has also been shown to be positively correlated with fibrin content, and negatively with platelet content (70, 71). Thus, if the fibrin and platelet content of the thrombus can be determined intraoperatively, this might also correlate with its age and degree of organization. The only study on OCT imaging of thrombus content has been conducted in vitro. In vivo studies are lacking.

1.2.6 Biobank

We are establishing a biobank with serum extracted from the coronary arteries during the index procedure with the aim of studying biomarkers related to thrombus type and burden.

2. Aims

2.1 General aim

Our general aim is to assess outcomes after primary PCI of STEMI using BRS with image-guided optimized PCI, and to improve follow-up after BRS implantation by using MSCT. We also seek to explore OCT as a method to determine thrombus composition in STEMI patients.

2.2 Specific aims

2.2.1 Thrombus investigation

To determine whether thrombi can be characterized according to erythrocyte content and age using OCT.

2.2.2 Bioresorbable vascular scaffold

To investigate the 12-month healing response in a STEMI population after implantation of either Absorb® BRS or Xience DES®.

2.2.3 Long-term non-invasive follow-up

To investigate the value of non-invasive follow-up with MSCT after BRS implantation.

3. Methods

3.1 Study population

The present trial is an investigator-initiated prospective randomized controlled trial. It was designed as an open-label non-inferiority study with planned inclusion of 120 patients with STEMI at Haukeland University Hospital. Patients were randomly assigned 1:1 to treatment with either Absorb™ BRS (Abbott, Illinois, USA) or Xience Pro™ DES (Abbott, Illinois, USA).

Inclusion criteria were age of 18 years or above, history of chest pain of less than 12 hours, ST segment elevation on the ECG of at least two mm in at least two contiguous precordial leads (V1–V6) and/or at least one mm in at least two contiguous standard leads (I, II, III, aVR, aVL, and aVF), and clinical decision to treat with primary PCI.

Exclusion criteria were contraindications to long-term dual antiplatelet therapy, known kidney failure with estimated glomerular filtration below 45 ml/min/1.73 m², cardiac arrest or severe cardiogenic shock with persistent systolic blood pressure below 90 mmHg despite adequate treatment, and other severe illness with life expectancy of less than 12 months.

Procedural contraindications were heavily calcified plaques, tortuous vessels, side branches with a diameter of more than 2.5 mm at the culprit lesion, inability to advance thrombus aspiration catheter and severly impaired flow after thrombus aspiration (thrombolysis in myocardial infarction flow 0–1).

Angiography with OCT of the treated vessel was performed at baseline pre- and post-PCI, and at 12-month follow-up. Echocardiography was performed before discharge from hospital at index and after 12 months. MSCT was performed at 12- and 36-month follow up.

The study was approved by the Regional Ethics Committee of Western Norway. All patients provided verbal consent during the procedure, and written informed consent within 24 h. The study was conducted according to the Declaration of Helsinki and the ICH Good Clinical Practice Guidelines. The trial protocol was registered at clinicaltrials.gov: NCT02067091.

3.2 Thrombus collection

After identifying the culprit lesion in a coronary artery by angiography, thrombus was collected with a manual aspiration catheter (Export advance™, Medtronic, Minnesota, USA) that was passed through the lesion. The aspirate was filtered through a 40 micron filter basket and the thrombus collected from the basket was fixated in 4% buffered formalin for at least 24 hours before being sent to the Academic Medical Center (AMC), Amsterdam, The Netherlands.

3.3 Analysis of aspirated thrombus material

Formalin-fixed aspirates were embedded in paraffin, cut in 5 μm sections and stained with Haematoxylin and Eosin and elastic van Gieson stains for conventional histomorphological evaluation. The adjacent sections were used for immunohistochemical staining with anti-α smooth muscle actin (Dako, Glostrup, Denmark) and anti-CD31 for smooth muscle cells and endothelial cells, respectively, to visualize the organization of thrombus. Sample size of aspirated materials was measured morphometrically on the total tissue area of HE-stained sections in mm^2.

For histological composition, the presence of thrombus material, plaque material (such as lipid-rich debris and/or foam cells) or both in each aspirate were recorded.

For thrombus composition, we discriminated between red thrombi (erythrocyte-rich in combination with fibrin and/or granulocytes) and white thrombi part (platelet aggregates in combination with fibrin and/or granulocytes). A ‘red thrombus’ was defined as erythrocyte content of > 70%, a ‘white thrombus‘ as platelet content of > 70%, and a ‘mixed thrombus’ as both erythrocyte and platelet content < 70%.

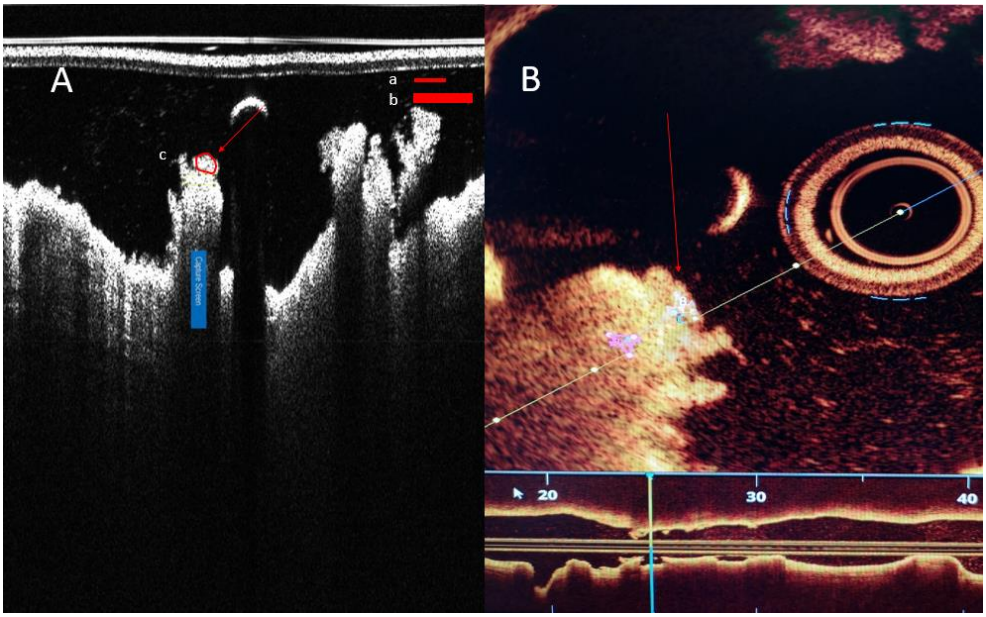
Thrombus age was determined analytically according to previously published definitions of thrombus age (53) as: 1) fresh (up to one day), composed of layered patterns of morphologically intact platelets, fibrin, erythrocytes and granulocytes, 2) lytic thrombus (1–5 days), characterized by areas of colliquative (lytic) necrosis and/or karyorrhexic granulocytes, and 3) organized thrombus (> 5 days), marked by an ingrowth of smooth muscle cells, with or without depositions of connective tissue and capillary vessel ingrowth.

The thrombotic material was processed and analysed by Professor Allard C. van der Wal of the AMC.

3.4 OCT acquisition and imaging analysis of thrombus

The Ilumien Optis™ (Abbott, Illinois, USA) OCT system was used. The Dragonfly™ (Abbott, Illinois, USA) catheter was introduced into the culprit vessel after restoring flow with a thrombus aspiration catheter. Images were taken in high resolution of about 100 frames per second, with pullback speed of 20 mm/s during contrast bolus. Thrombi were identified in the stored recordings and analysed using Ilumien Optis™ software. Raw data from the OCT recording were exported to an offline station with ImageJ™ (National Institute of Health and the Laboratory for Optical and Computational Instrumentation, Wisconsin, USA) software. An identical frame used to measure intensity with Ilumien Optis software was used with the corresponding thrombus structure. Intensity was measured using three different sized regions of interest (Fig. 2).

Figure 2: The same thrombus (arrow) as it appears on ImageJ (A) and Ilumien Optis (B) software. Thrombus protruding towards catheter appears compressed in ImageJ (A). Size of region of interest (ROI) is shown in red (a=small ROI, b= large ROI, c=freehand ROI).



3.5 Study procedure PCI

After thrombus aspiration and pre-PCI OCT, the patients were randomized 1:1 to either DES or BRS. Pre-dilatation was performed at the operator's discretion. After implantation of the stent, post-dilatation was performed if needed and followed by a post-PCI OCT scan. Any further post-dilatation was followed by an additional OCT scan. All patients were prescribed 12 months of double antiplatelet treatment with either clopidogrel or ticagrelor in addition to acetylsalicylic acid.

3.6 3D-QCA

3D-QCA analysis was performed at the core lab of Aarhus University Hospital, Skejby, Denmark. End-diastolic frames of angiography after primary PCI and at 12-month follow-up were analysed to render 3D reconstructions of the coronary artery

using a dedicated software package, QAngio XA 3D (Medis Medical Imaging Systems, Leiden, The Netherlands). Vessel contour detection was automated and corrected as needed. A reference vessel was created from non-stenotic segments proximal and distal to the lesion. Vessel dimensions were measured relative to the reference. In cases without two suitable projections available for 3D-QCA, 2D-QCA on a single projection was performed following the same steps.

3.7 OCT analysis of the treated segment

OCT was analysed at the core lab of Aarhus University Hospital, Skejby, Denmark. Images were graded based on their quality. Unanalysable recordings were excluded, while the remainder were analysed using a dedicated software package, QCU-CMS (Medis Medical Imaging Systems, Leiden, The Netherlands). Two experienced observers evaluated all frames deemed unanalysable. Corresponding OCT recordings from baseline and 12-month follow-up for each patient were matched at frame level by locating side branches and stent edges on each recording, thus accommodating for longitudinal image distortions and artefacts created by vasomotion during the cardiac cycle. Recorded frames from the in-stent segment and an additional 5 mm at the distal and proximal edge segments were analysed at a frequency of 0.5 mm at 20 mm pullback speed. The recording was calibrated to the size of the OCT catheter and set to 0.910 mm. The lumen contour was detected automatically, and manually corrected as needed. Stent struts were manually detected and used to create luminal and abluminal contours. All stent struts were characterized with predefined labels. Struts were defined as malapposed for BRS if a gap between the strut and vessel wall was identified, and for DES if the distance from the vessel wall to the centre of the strut blooming exceeded the strut thickness, plus an error margin of 20 μm. Struts were defined as jailing if located in front of a side branch with no connection to the vessel wall. In OCT recordings at follow-up, struts were defined as uncovered if visible tissue was not found on all sides of the strut of BRS or the luminal side of DES. Neointimal thickness at follow-up was measured as the shortest distance from the centre of stent struts to the lumen surface. The extra-stent lumen area was measured from the abluminal to the luminal surface edge of the stent.

3.8 Echocardiography

Standard transthoracic echocardiography was performed at baseline (index hospitalization) and at 12-month follow-up using a Vivid E9 scanner (GE Vingmed Ultrasound AS, Horten, Norway). Left ventricular wall thicknesses, chamber dimensions and ejection fraction were measured according to international guidelines for cardiac chamber quantification (38). Wall motion abnormalities were visually assessed in all myocardial segments.

3.9 Study procedure MSCT follow-up

The BRS cohort of the main study was included in the MSCT follow-up. The patients underwent an MSCT scan 12 and 36 months after index hospitalization. OCT at 12 months was used to validate baseline values.

3.10 MSCT acquisition and analysis

All MSCT examinations were performed using the in-house dual source 128 slice Siemens Somatom FLASH, and after December 2016, with the dual source 256 slice Somatom FORCE (Siemens, Erlangen, Germany) with ECG-triggering. Pretreatment with nitroglycerin is mandatory, and beta blockers were administered until heart rate < 60 beats/min was achieved. The scans were performed within one week prior to the angiography and the clinical CT investigator was blinded to the angiography results. The stented segment was graded as open, stenotic with ≥ 50% reduction in diameter or unassessable using routine clinical software (Syngo Via, Siemens, Germany). Diastolic series were uploaded to Qangio (Medis Medical Imaging, Leiden, The Netherlands) for postprocessing. Quality was graded as “poor” if the lumen contour could not be defined in three or more consecutive frames. The BRS was marked from first frame proximal to the proximal metallic marker to the first frame distal to the distal metallic marker of the BRS (Fig. 3: grey dotted line). To avoid the artefact of the metallic markers, a between-markers segment was measured from the first frame in the BRS after the visible metallic marker to the last frame before the distal metallic marker and used in further comparison with OCT (Fig. 3: blue lines). The reference area was

calculated as a regression line from points approximately 5 mm from each end of the scaffold (Fig. 3: red and green lines). An obstruction was marked at the MLA (Fig. 3: yellow line). The lumen contour was automatically traced and manually corrected where necessary (Fig. 3: top right picture). The length and volume of the segment (i.e. the whole BRS) and the lesion (i.e. BRS between metal markers) were calculated, as well as the reference area, average area, minimum area and area stenosis (Fig. 4).

Figure 3:

Left: the measurements shown in longitudinal axis.

Bottom right: area as a graph with the grey dotted lines marking the scaffold and a blue line marking the area between the metal markers. The green and red lines mark the area of interest. The reference area is a regression line between the two. The yellow line marks MLA.

Top right: automatic trace of lumen.

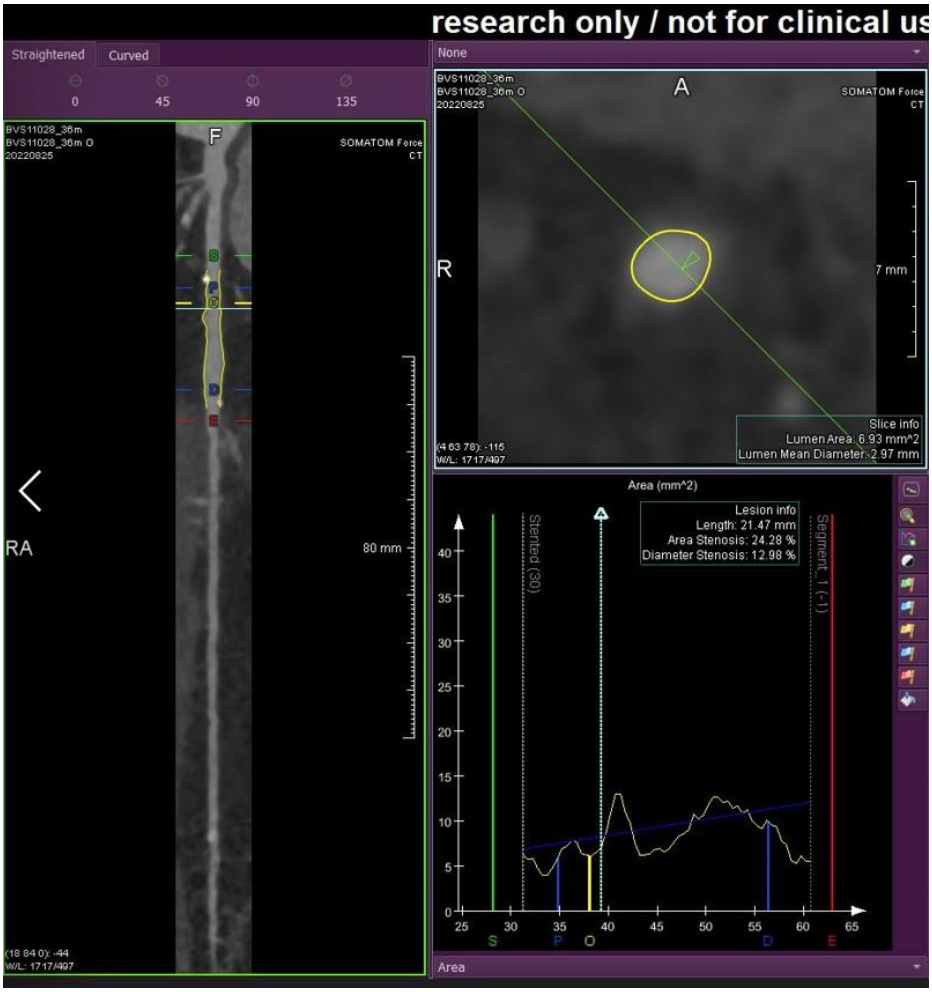
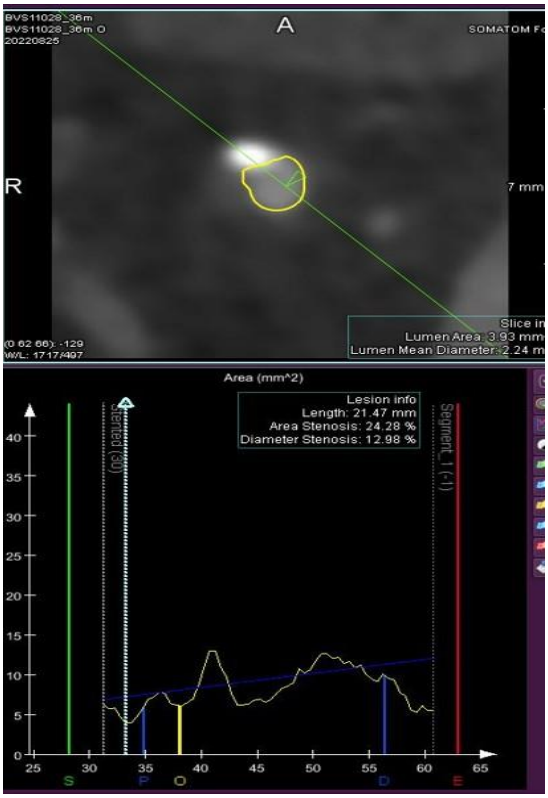


Figure 4:

Top: blooming artefact by metal marker.

Bottom: white dotted line showing the dip in lumen area due to the artefact.



3.11 Clinical events

Clinical events were recorded at visits at 12 and 36 months: total death, cardiac death, non-procedure related myocardial infarction, target lesion failure, target vessel failure, target lesion revascularisation, stent thrombosis, cerebral vascular events and hospitalization for congestive heart failure or arrhythmia.

3.12 Statistics

3.12.1 Sample size calculation

Pooled results from the Cardialysis database, Rotterdam, The Netherlands, have shown a mean MFA of 4.95 ± 1.39 mm^2 among patients with acute coronary syndrome (55, 56). A sample size of 54 patients in each arm was required (alpha = 0.05, power = 0.85, predefined non-inferiority margin = - 0.72 mm^2) to prove non-inferiority of the BRS. The non-inferiority margin of 0.72 mm^2 was chosen on the basis of a post hoc analysis of the data from the TROFI II trial (72, 73). To allow for patients being lost to follow-up, 60 patients were planned for enrolment in each arm, giving a total of 120 patients.

3.12.2 Paper I

Categorical values are presented as counts and percentages and compared using a Chi-square test or Fisher's test in cases of cell values below 5. Continuous variables are presented as means ± SD and compared by t-test if data followed a Gaussian distribution. In cases of a non-Gaussian distribution, continuous variables were compared using the Wilcoxon-Mann-Whitney U test and are presented as medians and interquartile ranges. One-way ANOVA was used to investigate correlations between categories of thrombi and lightloss measurements. Outcomes were analysed based on the principles of intention-to-treat. Statistical analysis was performed using STATA 15.0 (StataCorp LLC, College Station, Texas, USA).

3.12.3 Paper II

Categorical values are presented as counts and percentages and compared using a Chi-squared test or Fisher's test in cases of cell values below 5. Continuous variables are

presented as means ± standard deviation and compared by t-test if data followed a Gaussian distribution. In cases of a non-Gaussian distribution, continuous variables were compared by Wilcoxon-Mann-Whitney U-test and are presented as medians and interquartile ranges. Outcomes were analysed based on the principles of intention-to-treat. Statistical analysis was performed using STATA 15.0 (StataCorp LLC, USA).

3.12.4 Paper III

Statistical analysis was conducted using IBM SPSS Statistics 26 (Armonk, NY, USA). The data were checked for normal distribution using a Q-Q plot. Differences in average and minimum area in the OCT and MSCT methods were analysed with a Bland-Altman plot and by paired samples tests. The outcomes of MSCT at 12 and 36 months were analysed using a paired samples t-test.

4. Summary of results

A total of 66 patients presenting with STEMI for PPCI at Haukeland University Hospital in the period August 2014 to February 2017 were included. The study was terminated prematurely, as the Absorb™ BRS was discontinued by the manufacturer due to safety concerns. The Absorb™ arm consisted of 31 patients, while 35 received Xience™ DES. Mean age was 60.7±10.5 and 62.3±10.6, respectively. No significant difference was found between the groups.

Baseline characteristics of all included patients are presented in Table 1.

Table 1: Baseline characteristics

	Absorb BRS (n=31)	Xience DES (n=35)	*P*-value
Age (years)	60.7 ± 10.5	62.3 ± 10.6	0.54
Male gender	24 (77.4)	25 (71.4)	0.58
BMI (kg/m^2)	28.6 ± 1.2	27.6 ± 1.2	0.44
Smoking status			
Current	11 (35.5)	16 (45.7)	
Former	10 (32.3)	11 (31.4)	
Never	10 (32.3)	8 (22.9)	0.62
Diabetes	3 (9.7)	2 (6.7)	0.66
Antihypertensive treatment	9 (29.0)	10 (28.6)	0.97
Statin treatment	7 (22.6)	5 (14.3)	0.38
Other vascular disease	2 (5.7)	2 (6.5)	1.00
Previous PCI	0	1 (2.9)	1.00
Previous CABG	0	0	–
Echocardiography results			
Interventricular septum thickness (cm)	1.2 ± 0.3	1.3 ± 0.2	0.176
Left ventricular end-diastolic diameter (cm)	5.0 ± 0.7	5.0 ± 0.7	0.667
Posterior wall thickness (cm)	1.1 ± 0.2	1.2 ± 0.2	0.319
Left ventricular ejection fraction (%)	54 ± 10	54 ± 7	0.990
Presence of RWMA at presentation (%)	27 (87.1)	29 (82.9)	0.632

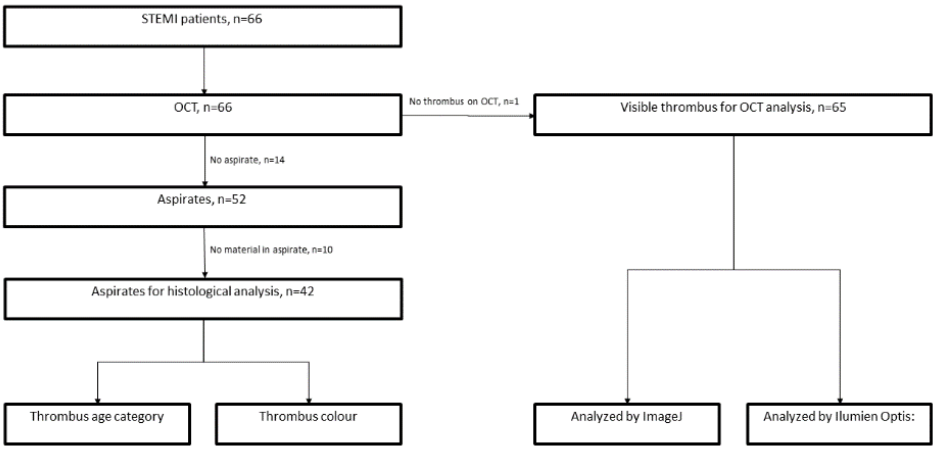
Values are presented as mean ± SD or n (%).
BMI: Body mass index; BRS: Bioresorbable scaffold; DES: Drug eluting stent; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass graft; RWMA: Regional wall motion abnormalities.

4.2 Paper 1

4.2.1 Flowchart

All 66 randomized patients were included in this paper, 52 of whom had successful thrombus aspiration. During analysis of OCT images, 65 patients had visible thrombi. Out of these, 42 could be analysed by both histology and imaging and could enter our analysis (Fig. 5).

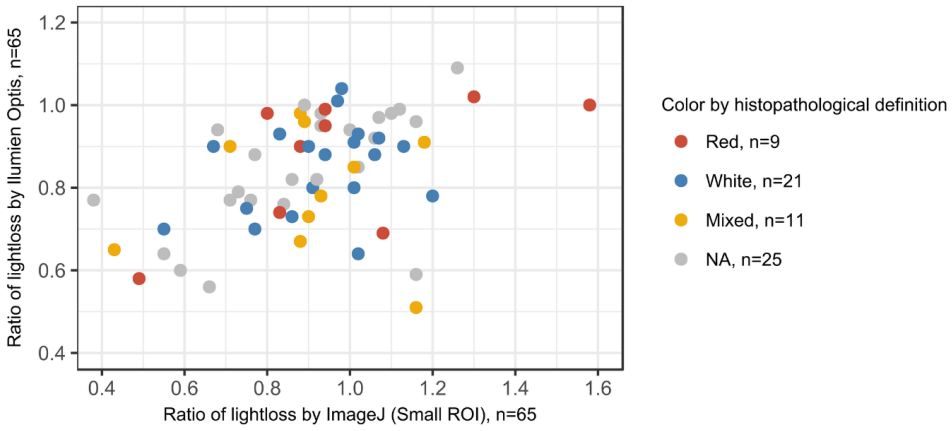
Figure 5: Flowchart.



4.2.2 Thrombus composition

We found that 36 had elements of fresh thrombi, seven had elements of lytic stage and eight had elements of an organized thrombus. In terms of erythrocyte and platelet content, 11 thrombi were classified as red, 21 as white and ten as mixed. Of the fresh thrombi 16 (44%) were classified as white and ten (28%) as red ($p = 0.27$), of the lytic thrombi two (29%) were classified as white and three (43%) were classified as red ($p = 0.46$), while of the organized thrombi five (63%) were classified as white and two (25%) were as red ($p = 0.62$). We visualized the intensity ratio using ImageJ and Ilumien Optis and compared the finding with the colour of the thrombi (Fig. 6).

Figure 6: Comparison between ratio of lightloss measured by ImageJ (x-axis) and Ilumien Optis (y-axis) softwares with a good correlation of 0.40 (p=0.0001). According to lightloss classification, red thrombi should be clustered below 0.5, and white thrombi above 0.5, on both axes. However, this is not the case.



4.2.3 Correlations thrombus content vs imaging

The histological categories of red, white and mixed thrombus showed no correlation with intensity measurements by Ilumien Optis (p = 0.41) or ImageJ, small ROI, (p = 0.48) using one-way ANOVA. The intensity ratio could not predict the content of erythrocytes (Standardized Beta -0.014, p = 0.93) or platelets (Standardized Beta 0.002, p = 0.99) (Ilumien Optis). Thrombus age was analysed by independent sample t-test, and there were no significant differences in intensity between fresh and non-fresh by Ilumien (p = 0.97) or ImageJ (p = 0.49), between organized and non-organized by Ilumien (p = 0.72) and ImageJ (p = 0.72) or lytic and non-lytic by

Ilumien ($p = 0.31$) and ImageJ ($p = 0.63$). The correlations between intensity ratio by Ilumien Optis and erythrocyte content and age are shown in Figures 7 and 8.

Figure 7: Ratio of lightloss by Ilumien Optis software in the different histopathologically defined colours. Ratio of lightloss below 0.5 is classified as red by OCT (Illumien Optis software).

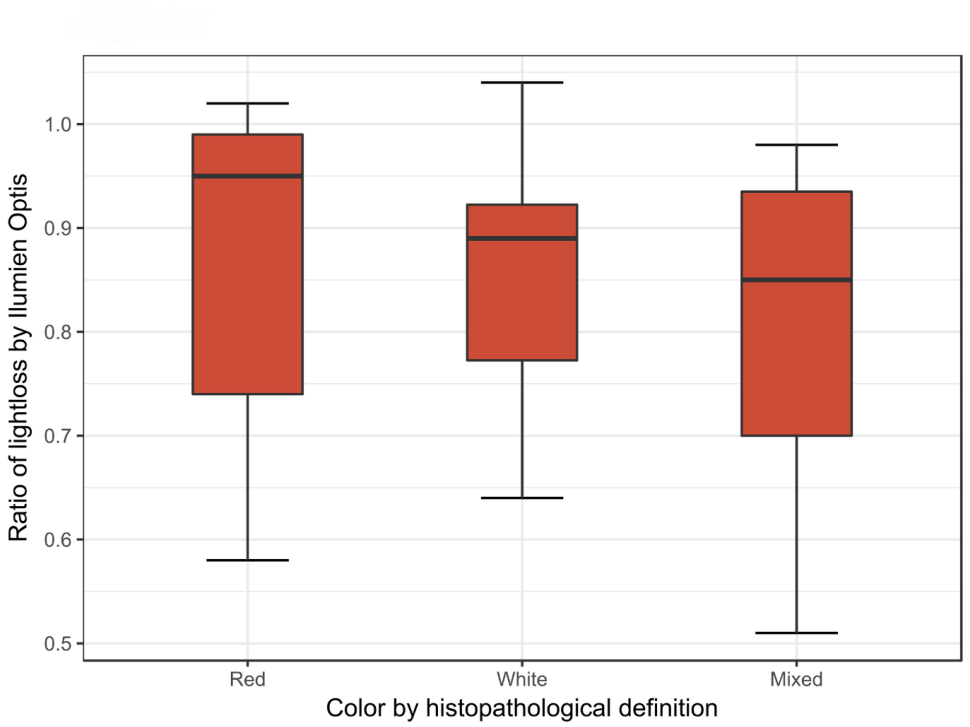
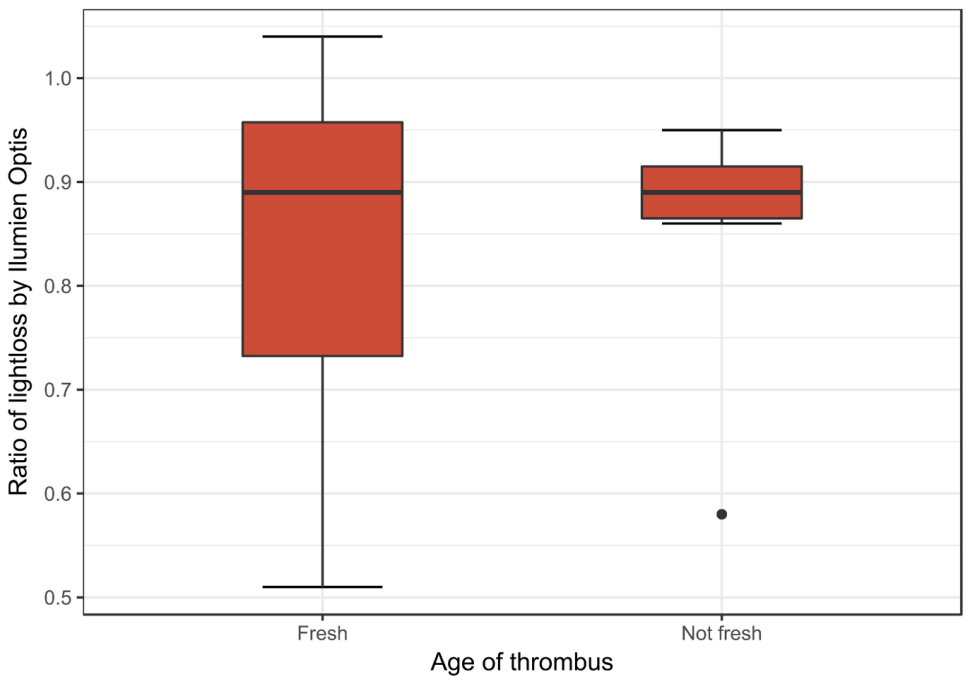


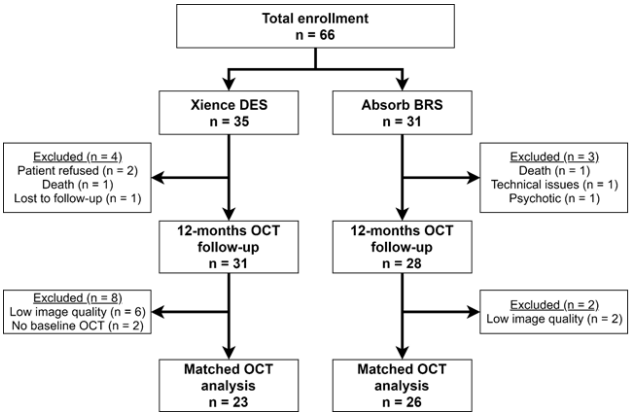
Figure 8: Ratio of lightloss by Ilumien Optis software in thrombi defined by histopathological appearance. Ratio of lightloss below 0.5 is classified as red by OCT (Illumien Optis software).



4.3 Paper II

At 12-month follow-up, 28 patients in the BRS group and 31 patients the DES group had angiography and OCT. Finally, 26 patients receiving the BRS and 22 patients receiving the DES entered quantitative OCT analysis (Figure 9).

Figure 9: Flowchart



4.3.1 Primary endpoint, minimum flow area at 12 months follow up

The results of the primary endpoint, MFA at 12 months follow-up, are presented in Table 2 and Figures 10-12. The study was underpowered for the primary endpoint of non-inferiority evaluated by MFA, which could thus not be evaluated, but there was a strong trend towards lower MFA in the BRS group (p=0.06).

Table 2: Results at 12-month follow-up

	Absorb BRS (n=26)	Xience DES (n=22)	*P*-value
OCT results			
Reference lumen diameter (mm)	3.46 ± 0.45	3.68 ± 0.50	0.11
Reference lumen area (mm^2)	9.53 ± 2.49	10.8 ± 3.09	0.12
Average stent area (mm^2)	9.25 ± 2.57	9.90 ± 2.68	0.39
Minimum stent area (mm^2)	7.27 ± 1.83	7.97 ± 2.48	0.26
Stent recoil			
Gain in average stent area (mm^2)	0.68 ± 1.11	0.93 ± 1.01	0.40
Gain in minimum stent area (mm^2)	0.10 ± 0.94	0.68 ± 0.92	0.03
Average lumen area (mm^2)	7.11 ± 2.33	8.02 ± 2.51	0.19

Minimum lumen area (mm^2)	5.13 ± 1.70	6.30 ± 2.49	0.06
Lumen late loss			
Loss in average lumen area (mm^2)	1.73 ± 0.92	1.16 ± 1.03	0.05
Loss in minimum lumen area (mm^2)	2.06 ± 1.23	1.03 ± 1.15	<0.01
Minimum flow area (mm^2)	5.13 ± 1.70	6.30 ± 2.49	0.06
Malapposed struts (%)	0 [0;0]	0 [0;0]	0.33
Average neointimal thickness (µm)	80.6 ± 30.5	162 ± 41.9	<0.01
3D-QCA Results			
Reference vessel diameter			
Baseline, post PCI (mm)	2.96 ± 0.45	3.12 ± 0.40	0.18
Follow-up (mm)	2.98 ± 0.47	3.23 ± 0.53	0.11
Mean lumen diameter			
Baseline, post PCI (mm)	2.55 ± 0.48	2.74 ± 0.32	0.08
Follow-up (mm)	2.37 ± 0.55	2.79 ± 0.54	0.02
Diameter stenosis			
Baseline, post PCI (%)	13.7 ± 10.2	11.8 ± 6.09	0.42
Follow-up (%)	20.6 ± 11.8	13.0 ± 6.09	0.01
Area stenosis			
Baseline, post PCI (%)	16.7 ± 13.7	14.6 ± 10.5	0.52
Follow-up (%)	28.4 ± 18.4	15.7 ± 10.3	0.01

Values are presented as mean ± SD or median [inter quartile range].
BRS: Bioresorbable scaffold; DES: Drug eluting stent; OCT: Optical coherence tomography; 3D-QCA: Three-dimensional quantitative coronary angiography; PCI: Percutaneous coronary intervention.

Figure 10: Minimum flow area (MFA) difference (mm2) at 12 months follow-up. The red dotted line is the predefined non-inferiority margin. MFA, minimum flow area

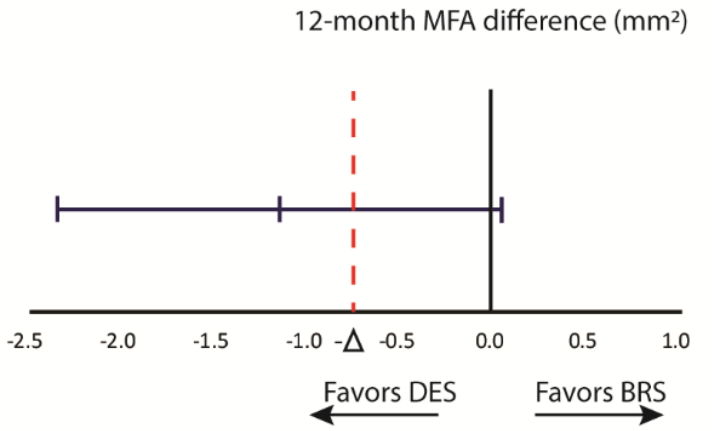


Figure 11: Boxplot of minimum flow area (MFA) at 12 months follow-up. MFA, minimum flow area.

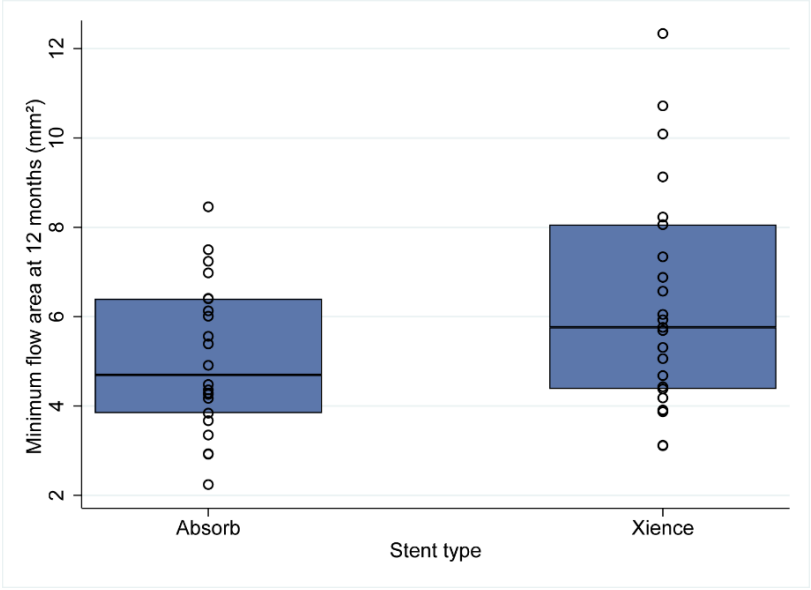
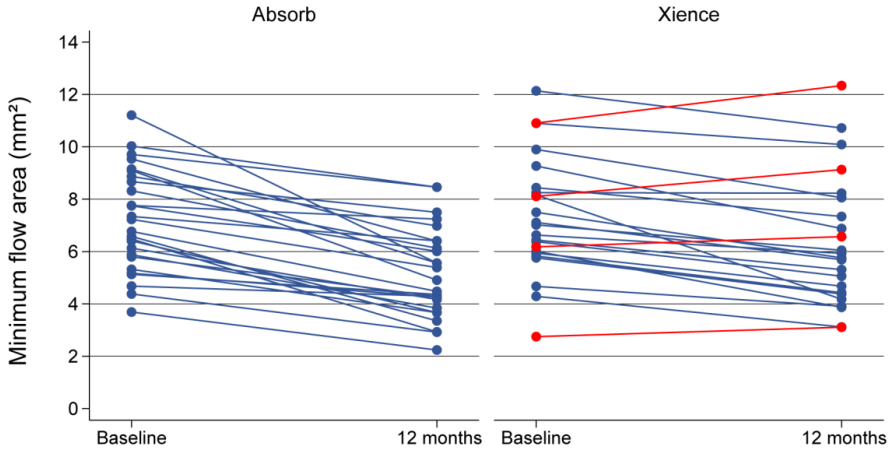


Figure 12: Individual change in MFA from baseline to follow-up. Blue = decrease in MFA. Red = increase in MFA. MFA, minimum flow area.



4.3.2 Secondary endpoints

OCT and 3D QCA results at 12-month follow-up are presented in Table 3. There were small non-significant differences in reference diameter and area in both modalities. This would impact the area and diameter stenosis calculation, which is a ratio with the reference diameter as denominator. Loss in average lumen (p=0.05) and loss in minimum area (p<0.03) were greater in the BRS group.

Average (±SD) neointimal thickness was significantly lower in the BRS group at 80.6 ± 30 µm, compared to 162 ± 41.9 µm (p < 0.01) in DES, at 12 months. Neointimal strut coverage was complete and acute strut malapposition was resolved in both groups at 12 months.

4.3.3 Clinical events

Two patients died during the 12 months of follow-up: one (1/31, 3.23%) in the BRS group and one (1/35, 2.86%) in the DES group. The patient in the BRS group suffered from a ventricular septum rupture subsequent to the index myocardial infarction. Surgery was performed four days after inclusion, but the patient died during the

procedure. The patient in the DES group was readmitted within a week due to major hematuria, subsequently resulting in sudden cardiac arrest. Autopsy revealed a recent myocardial infarction but no coronary occlusion. One patient in the DES group had a minor bleeding (hematuria) during index hospitalization and another patient in the DES group suffered an intracerebral haemorrhage eight months after index procedure.

4.4 Paper III

The BRS cohort (n=31) was included in this analysis.

4.4.1. MSCT at 12 vs. 36 months

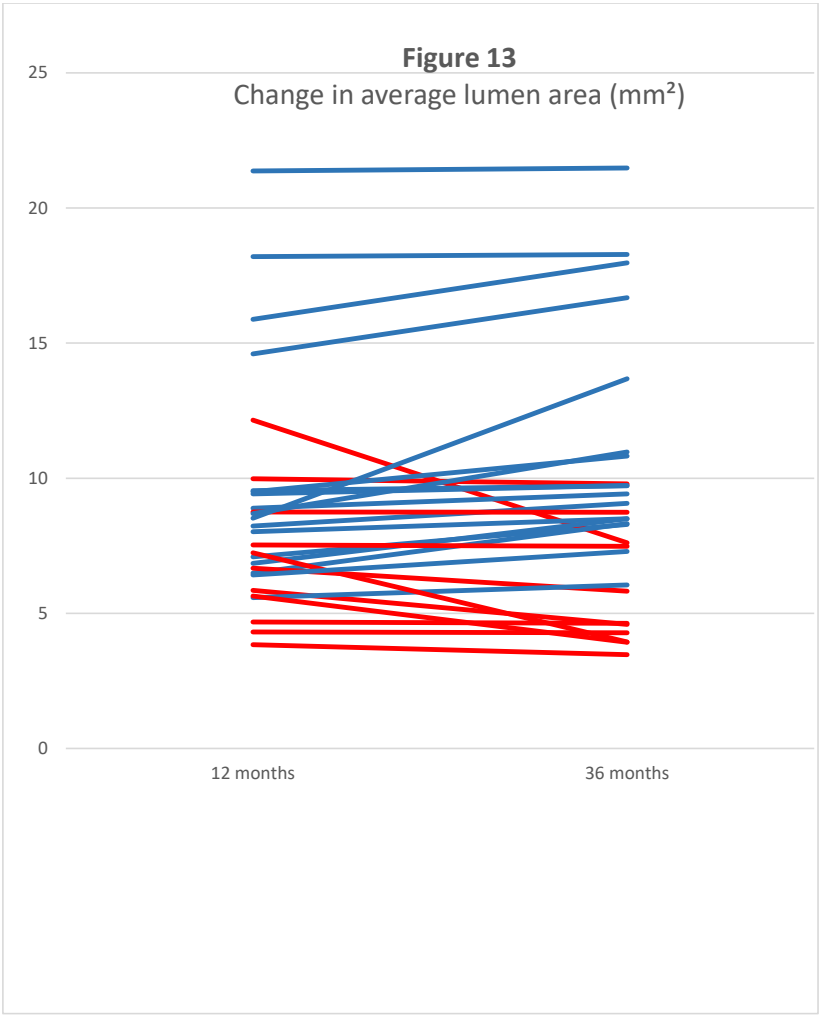
Our main results are shown in Table 3. A total of 7 (12%) scans were graded as poor at postprocessing, but could still enter the analysis. Area stenosis, reference area, average and minimum lumen area did not change significantly during the observation period, but there was a numerical increase in all lumen area measurements. There was a slightly, non-significant higher degree of area stenosis. The individual changes in average lumen between markers are shown in Figure 13.

Table 3: Multislice computed tomography at 12 and 36 months

	12 months (n=29)	36 months (n=28)	Mean difference	Paired samples t-test
Time from inclusion (months)	12.3 ± 2.2	36.7 ± 1.6		
Length between markers (mm)	19.8 ± 8.4	19.4 ± 8.6		
Stent length measured (mm)	25.3 ± 8.7	24.8 ± 9.1		
Reference vessel lumen area (mm^2)	9.04 ± 4.62	9.83 ± 5.18	0.61 ± 2.43	p=0.20
Average lumen area between markers (mm^2)	8.74 ± 4.17	9.25 ± 4.63	0.32 ± 1.79	p=0.34
Average lumen area including markers (mm^2)	8.41 ± 3.81	8.92 ± 4.22	0.35 ± 1.60	p=0.25
Minimum lumen area (mm^2±)	5.25 ± 1.84	5.66 ± 3.11	0.41 ± 2.17	p=0.33
Area stenosis (%)	38 ± 15	41 ± 18	0.02 ± 0.15	p=0.55

Values are presented as mean±SD.

Figure 13: Change in average lumen area between metal markers measured by multiclice computed tomography (MSCT) (blue = increasing lumen area; red = decreasing lumen area).



4.4.2 OCT vs. MSCT at 12 months

At 12-month follow-up, 29 patients had OCT scans, 26 of which had sufficient quality for analysis. Results are presented in Figure 14, and in detail in a previous publication (12). The reference area measured by MSCT was numerically smaller than that measured by OCT with a mean (±SD) difference of 0.95 (±2.64 mm², p=0.10). The

average lumen area between markers measured by MSCT was higher than the average area by OCT, with a mean (±SD) difference of 1.32 (±2.59 mm², p=0.015). The difference between the two imaging modalities is visualized in a Bland-Altmann plot (Fig. 15). The mean difference in average area was consistent in small lumen areas, but had two outliers in very large anatomy. The mean of the minimum lumen area differed only by 0.05±1.32 mm² (p=0.85), but the Bland-Altman plot showed a large degree of variation across the range of lumen areas (Fig. 16).

Figure 14: Reference area, average lumen area and minimum lumen area measured by MSCT and OCT 12 months after scaffold implantation. OCT = Optical coherence tomography. MSCT = Multislice computed tomography. CI = Confidence interval.

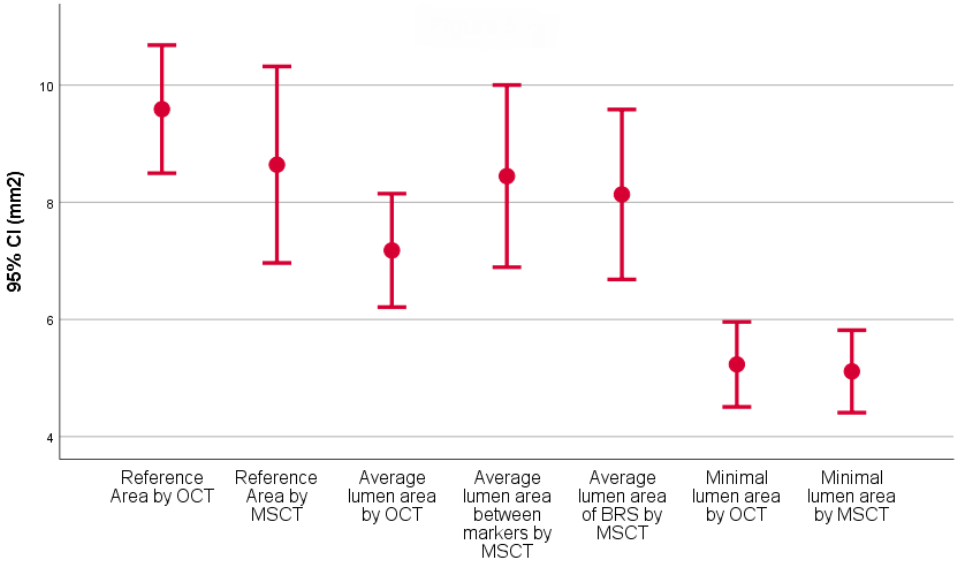


Figure 15: Bland-Altman plot of average lumen area by multislice computed tomography (MSCT) and optical coherence tomography (OCT) 12 months after scaffold implantation. The figure shows a consistently larger lumen area measured by MSCT.

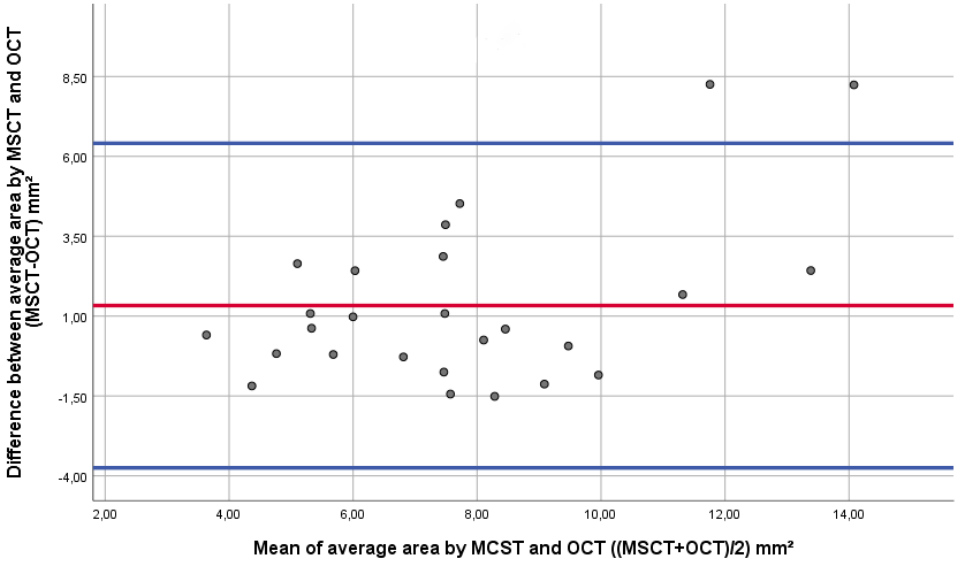
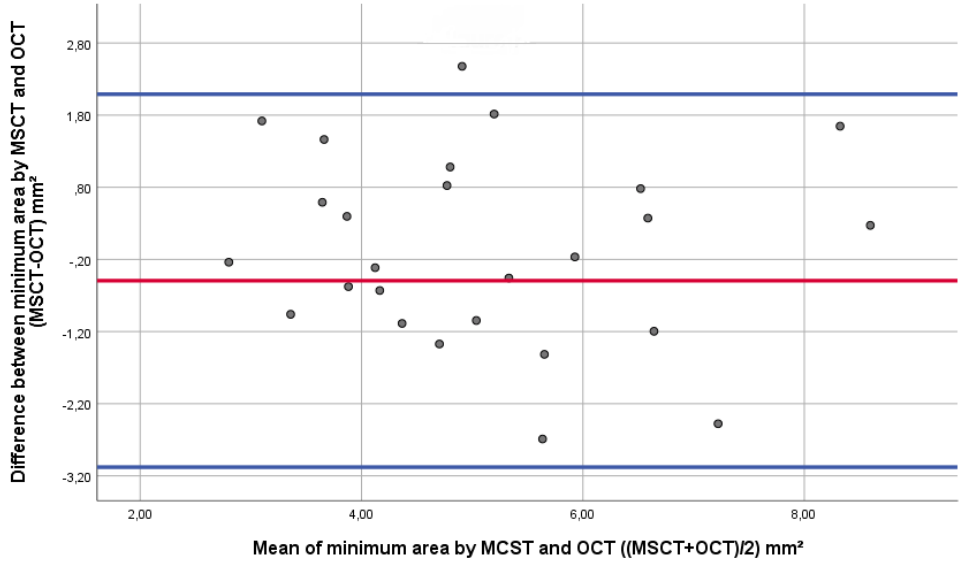


Figure 16: Bland-Altman plot of minimum lumen area by MSCT and OCT 12 months after scaffold implantation. The figure shows little difference in the mean, but the individual measurements have large deviations from the mean.



4.4.3 Echocardiography

Echocardiography showed a significant improvement in LV ejection fraction from index to 12-month follow-up. The proportion of patients with regional wall motion abnormalities (RWMA) decreased from 87% to 40% (p<0.001) (Table 4). Similarly, LV wall thicknesses also decreased significantly.

Table 4: Echocardiographic data at 0 and 12 months post-STEMI

	0 months (n=31)	12 months (n=30)	P-value
Interventricular septum thickness (cm)	1.2 ± 0.3	1.1 ± 0.2	p=0.001
Left ventricular end-diastolic diameter (cm)	5.0 ± 0.7	4.9 ± 0.7	p=0.639
Posterior wall thickness (cm)	1.1 ± 0.2	1.0 ± 0.1	p=0.001
Left ventricular ejection fraction (%)	54 ± 10	58 ± 6	p=0.002
Presence of RWMA (%)	27 (87)	12(40)	p<0.001

RWMA, regional wall motion abnormalities.

Values are presented as mean ± SD or n(%).

4.4.4 Clinical evaluation and events

In 24 (77%) of 29 patients who underwent MSCT at 12-month follow-up, the BRS was assessed as open. One of these was post-dilated due to massive malappositon shown by OCT. This patient later developed stent thrombosis. In two (7%) patients the BRS was assessed as stenosed by MSCT, but only one of these was considered stenosed and treated with PCI after invasive angiography and OCT. In three (10%) patients the stented segments were unassessable, but none of these needed intervention on the basis of clinical presentation. At 36-month follow-up, 28 patients underwent MSCT, out of which 20 (71%) of the BRSs were assessed as open by MSCT. In four (14%) the BRS was described as stenosed. Three of these had invasive angiography performed, two of whom had an instantaneous wave-free ratio value >0.90, while the third was treated with PCI. Four (14%) scans were unassessable, and one of these had a clinical indication for invasive angiography but no intervention was needed. Thus, out of a total of 57 MSCT scans, 50 (88%) were assessable, and six (11%) were described as stenosed, while three (5%) patients had an indication for intervention.

5. Discussion

5.1 General

In this study we included 66 STEMI patients, with 59 (31 and 28 in the BRS and DES group respectively) patients completing 12 months of follow-up. In the BRS group, 29 patients also completed the 36-month follow-up. Due to slow initial inclusion, and early termination due to safety concerns about the study device, we could only include 66 of the planned 120 patients. Consequently, we did not have sufficient power to evaluate our primary endpoint of non-inferiority. However, the almost complete set of imaging data from index to 12 months, and for BRS, 36 months, still provides valuable information on the performance of BRS in a STEMI population.

The power calculation was based on a non-inferiority design. This design is based on an assumption of how large a difference in an endpoint can be accepted before it poses a clinical disadvantage for the study device. Our calculations were based on MFA registry data from another publication (72). As we have explored in our study, MFA alone may be insufficient in describing performance and healing of BRSs.

A matched histological and imaging sample of 42 cases is unique, and provides important insights into the peroperative evaluation of thrombi in STEMI.

5.2 Thrombus investigation

5.2.1 Colour and age

We did not find any correlation between intensity ratio measured by OCT and thrombus content of red blood cells or platelets. The variances in colour between the different histological stages were not significant. Furthermore, OCT could not distinguish between the different histologically defined thrombus stages: fresh, lytic or organized. Fresh thrombi tended to have a shorter ischaemic time, although this was not significant. Paradoxically, ischaemic time was shortest for red thrombi. This difference was also not significant.

5.2.2 Aspiration methodology

Our method of thrombus aspiration was to use an off-the-shelf aspiration catheter. The Export Advance™ catheter was chosen as this comes with a 40 micron filter basket. Other methods for extracting thrombus and for intracoronary imaging such as a larger mother-and-child catheter or angioscopy are not feasible in this population due to the acute setting.

We characterized thrombus composition by histology, contrary to Kume et al (74) who characterized the colour by macroscopic visual appearance. In our view, histological examination is a more accurate way to determine thrombus composition. On the hand, Kume et al. could be certain that they studied the same sample by OCT and histology. We studied the aspirate and compared it to the remnants in the vessel. The age and composition of the abluminal parts of the thrombi left behind after aspiration could potentially differ from than the aspirates. As 36 out of 42 aspirates contained elements of fresh thrombus and 21 out of 42 were classified as white, we at least knew that the luminal parts of the thrombus were mostly fresh and to a large extent white. The remnants were only studied by imaging, and were exclusively red, as defined by OCT. If the first formed abluminal part of the thrombus matures after being formed, this would explain why the remnants were all red, and could explain the discrepancy with the ex vivo study. However, the latter seems unlikely, as Silvain et al. showed that fibrin content increases with ischaemic time in aspirated thrombi (71). Previous aspiration studies have also shown that the formation of thrombus is somewhat complex with a layered appearance, rather than a continuous platelet-rich to erythrocyte/fibrin-rich gradient from the vessel wall to the lumen (75).

5.2.3 OCT methodology

OCT has important limitations. Because data are collected in a tomographic pattern, the amount of echoed information will greatly decrease as the distance from the light source increases. This means that the backscattered data from structures close to the catheter will produce more detailed pictures than those further away. The ratio between two fixed points will also be influenced. The Optis Ilumien software

compensates for this by using an algorithm to fill in the missing information (76). The data are also logarithmically transformed. Although we sought to determine whether this online system could be used clinically, we also analysed the raw data using the ImageJ offline system. Kume et al. used NIH Image™ (National Institute of Health, Wisconsin, USA), a previous version of ImageJ. Choosing the size of ROI poses a challenge using ImageJ software. The computation performed in Optis Ilumien is visualized in Figure 2, where structures furthest away from the catheter are extended to form a circular image.

5.2.4 Clinical impact of thrombus age

The age of a thrombus can be classified reliably according to the standard histopathological appearance of tissue decay followed by repair in the aspirated materials. The presence of an older age thrombus has been shown to correlate to higher mortality (74, 77), although the underlying mechanism is uncertain. A longer period of thrombus formation and lysis could result in a prolonged period of ischaemic myocardial damage. The process of clotting and lysis could result in more distal embolization, which would compromise the microvascular bed of the myocardium. The increased mortality could also be a result of confounding patient factors, such as sensitivity to chest pain and how urgently the patients seek medical help. We know now that the formation and fate of thrombi are much more complex than Virchow's theory. Smooth muscle cells and neutrophil granulocytes play a specific and complex role, with expression of cytokines such as matrix metalloproteinases and creation of neutrophil extracellular traps. The expression of matrix metalloproteinases and the amount of neutrophil extracellular traps varies with thrombus age (78-80). As well as promoting thrombogenicity, this could also affect the healing of the implanted stent (78, 81-84). Finding an optimal treatment strategy is therefore more complex than we can hope to visualize with intracoronary imaging alone.

5.2.5 Patient selection and generalizability of results

We chose to study thrombi from STEMI patients. This is a relatively homogenous group presenting with a similar clinical picture and with a clear ECG indication for a

coronary intervention. In most cases, the presence of coronary thrombi can be assumed, and thrombus aspiration was, at the time of submitting the protocol, routine practice (85). Our cohort represents a selection of STEMI patients. Patients with complex lesions, tortuous anatomy and heavy calcifications were excluded. Our findings cannot be generalized without some considering these factors. However, the selection was made in order to aspirate thrombus and obtain the best quality OCT images. We do believe that including all STEMI patients would have clouded the data with poorer quality of OCT images and fewer thrombi would have been aspirated. It is also an investigation of methodology, transferring findings in a standardized laboratory setting to an acute clinical scenario.

5.2.6 Pharmacologic treatment

All patients received a loading dose of acetylsalicylic acid and either ticagrelor or clopidogrel before angiography. All were given 5000 IU to 7500 IU of heparin at the start of the procedure. This reflects clinical practice, but could alter the coagulation state and thrombus appearance. No patients were given Glycoprotein IIb/IIIa (Gp IIb/IIIa) inhibitors or Bivalirudin before thrombus aspiration and OCT.

5.3 BRS vs. DES 12 months after implantation

The main findings 12 months after implantation can be summarized as follows: 1) The primary endpoint of non-inferiority could not be evaluated, but there was a strong tendency towards lower MFA in the BRS group. 2) OCT and 3D QCA endpoints showed favourable outcomes for the DES group. 3) The CSHI showed similar healing patterns in both groups 12 months after implantation. 4) There were four clinically serious adverse events, including two deaths. Three of the events were related to bleeding, all in the DES group. There were no stent-related clinical endpoints.

5.3.1 Minimum flow area

Mean values of MFA in this study were comparable to reports from previous trials (72, 73). In comparison to Xience™ DES, the Absorb™ BRS has thicker struts causing significant obstructing of the lumen, which would result in a lower flow area. Due to

safety concerns regarding the Absorb™ BRS, the present study was terminated after inclusion of 66 patients and thus did not reach the calculated sample size of 120 patients calculated to investigate the pre-defined non-inferiority margin of a difference in mean MFA of less than 0.72 mm^2. Large clinical trials comparing DES and BRS reported three-year results with higher rates of target lesion failure with BRS, mainly driven by target vessel myocardial infarction and stent thrombosis (86, 87). Hence, the Absorb™ BRS was subsequently withdrawn from the market. The steering committee therefore deemed it unethical to continue the study.

The average and minimum lumen area decreased during follow-up, and thus there was a net lumen late loss. However, the average and minimum stent area seemed to increase in both groups. This indicates that stent recoil was not a contributor to lumen late loss. The average neointimal thickness measured seemed to contradict a larger lumen area in the DES group, but as neointima is measured from the luminal edge of the struts, the thicker struts of the BRS must be taken into account.

The presence of intraluminal mass, such as thrombus, cannot explain the difference in MFA at follow-up. The MLA and MFA are identical at 12 months, showing that there are no significant intraluminal masses visible on OCT. This concurs with other reports (88), and is reassuring as implantation of the Absorb™ BRS in the STEMI setting has been of concern due to a potentially more thrombogenic environment. In a porcine model, the Absorb™ BRS showed 21.8% acute platelet coverage by immunostaining compared to 3.0% in the Magmaris™ BRS (Biotronik, Germany) ($p = 0.03$) and 4.6% in the Orsiro™ DES (Biotronik, Germany) ($p = 0.06$) (89). A meta-analysis of seven randomized trials comparing Absorb™ BRS and DES showed higher cumulated two-year incidence of stent thrombosis in the BRS group with relative risk at 3.35 (95% CI: 1.96;5.72, $p < 0.001$), compared to the DES (86). Hence, the Absorb™ BRS has been deemed more thrombogenic than regular DES due to its acute and long-term mechanical properties, bulky struts and acidity during degradation. The lack of agreement between our study and the above-mentioned data could be due to the strict antithrombotic treatment before the intervention, whereas published literature heavily relies on stable patients with less aggressive pre-treatment. Notably, the low sample size does not allow for detection of rare clinical events, such as stent thrombosis.

5.3.2 Coronary stent healing index

The CSHI at 12-month follow-up was numerically in favour of the BRS arm. However, the numbers are too small to draw any firm conclusions. The difference was mainly driven by more uncovered jailing struts in the DES group. Retrospectively, this element of the score is troublesome, as a single uncovered jailing strut generates a very high score, and thus a worse healing response even if only a few jailing struts are present. Rationally, uncovered material located in front of a side branch will lead to a higher risk of thrombosis. However, stent healing scores have yet to be clinically validated and no consensus has been reached on which parameters to include. Uncovered struts, stent malapposition, and neoatherosclerosis have been proven to be associated with higher rates of stent thrombosis (90-93). The value of combining many clinically relevant factors into a single score is attractive but remains theoretical. The TROFI II trial used a different healing score with four components: intraluminal mass (4 points), presence of both malapposed and uncovered struts (3 points), presence of uncovered struts alone (2 points), presence of malapposed struts alone (1 point). Here, the Absorb™ BRS had a non-inferior healing score compared the DES after six months (73). This was mainly driven by uncovered and malapposed struts in the DES arm. Our study showed complete coverage of struts in both groups after 12 months. Delayed arterial healing has previously been reported in a STEMI population, where uncovered struts, fibrin deposition and inflammation were significantly higher than in patients treated under stable conditions (93).

5.3.3 Summary and the future of BRS

Overall, our study presents a near-complete healing response after 12 months in both groups, but secondary endpoints are numerically in favour of the DES group. No stent-related clinical events were observed in this trial during the 12-month follow-up period. Clinical endpoints after short-term (94, 95) and long-term (96) follow-up of BRS implantation in a STEMI population were reported in the PRAGUE-19 study. Low rates of mortality and of cardiac and stent-related events were observed and were comparable to five-year results of BRS implantation in stable patients (97).

The BRS platforms have suffered a setback due to increased rates of stent thrombosis. Selecting the most suitable subgroups for future platforms will be important in the next generations of BRS. The lower neointimal thickness and similar healing response based on the CSHI in BRS compared with DES at 12-month follow-up, suggest that incomplete healing with malapposed and uncovered struts play an inferior role, and that other underlying causes of scaffold failure should be evaluated.

The inflammatory and thrombogenic environment in STEMI patients did not correspond to a worse outcome up to 12 months than in stable patients in our study, and a STEMI population with soft plaques and short lesions might serve as the ideal target for future BRS platforms. New BRS devices of different composition and with thinner struts than the Absorb™ BRS are currently in development. Further study of these devices will be needed in order to clarify the role of BRS in the STEMI setting.

5.4 MSCT vs. OCT and MSCT 36 months after implantation

This substudy of BRS in STEMI demonstrates that 12 months after primary PCI with BRS, the mean LV function significantly improved, and the number of patients with RWMA decreased. The mean average lumen area was larger measured by MSCT than by OCT, and did not change significantly from 12 to 36 months. MSCT identified all cases of restenosis, but missed one case of malapposition.

5.4.1 MSCT compared to reference OCT 12 months after implantation

We established that mean average lumen area measured by MSCT was larger than by OCT. This difference was consistent except for some outliers in patients with large anatomies (Fig. 6). As a complete match of measurements derived from different modalities is not feasible, our opinion is that MSCT can be used to assess the average area in a coronary artery treated with BRS (98-100). Metallic markers could potentially generate artefacts when the average lumen area is calculated, but in our study, this had little impact. The minimum lumen area as measured by MSCT showed more deviation from OCT measurements (Fig. 7). Consequently, using minimum lumen area from MSCT in the follow-up after BRS implantation carries a higher degree of uncertainty than OCT. An explanation for this may be that the lumen shown

by MSCT can be difficult to trace in some frames, and sometimes must be averaged based on adjacent frames. The reference lumen area is calculated differently by the two imaging techniques, and cannot be compared directly. Despite this, the mean values did not differ greatly. We used a regression line as reference lumen area value for MSCT because this gives a more accurate value for area stenosis.

5.4.2 ALA, MLA and area stenosis 12 vs. 36 months after implantation

The ALA, MLA and area stenosis did not change significantly between 12 and 36 months, and there was a numerical increase in average and minimum area in the scaffold. As the reference area also increased, there was a numerical higher degree of area stenosis. However, we do not consider this slight increase as clinically important.

5.4.3 Clinical evaluation of MSCT

Although it is reassuring for the concept of BRS that mean lumen areas did not change significantly over time, some individual differences can be found. As shown in Figure 4, there is a loss in average lumen area in some patients. Importantly, MSCT managed to identify all patients with restenosis, but out of six patients assessed as stenosed, only two had an indication for an intervention. Therefore, specificity was in line with previous MSCT studies of DES using 64-slice scanners (101). Our study was performed with a more modern dual source MSCT scanner, and we therefore expected higher diagnostic accuracy. Comparison with previous studies on BRS, however, is difficult as these studies presents no restenosis in their cohorts, and there is an overlap in the definition of unassessable and stenosed BRS in relation to ours. In our study, the use of physiology with instantaneous wave-free ratio to exclude functional stenosis may in part explain the low need for intervention even with anatomic stenosis on imaging (37). Using non-invasive fractional flow reserve might improve the usefulness of MSCT of BRS in the future (102).

5.4.4 MSCT limitations

The seven unassessable MSCT scans were mostly due to heavy calcification in the stented area or poor contrast filling of the vessel. The limitations of MSCT in heavily

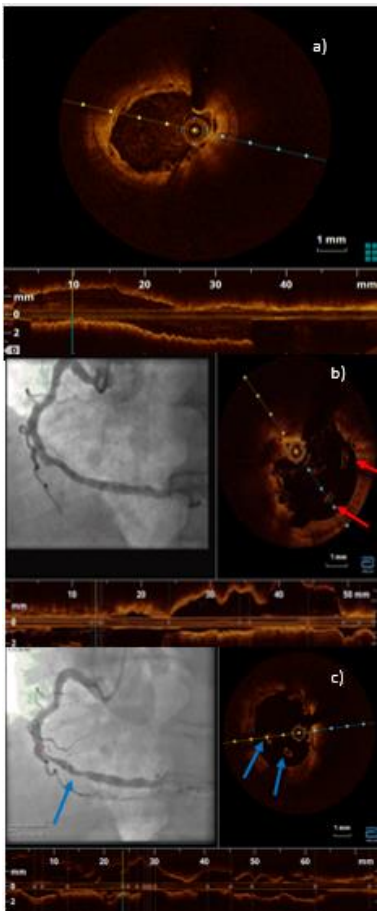
calcified vessels are well known, as are the limitations related to arrhythmia and stented vessels. The range of patients assessable by MSCT is continuously increasing with improved technology, starting from the early 64-slice MSCT and the dual 128- and 192-scanners used in our study, to the photon-counting detectors now available (103). The high sensitivity and safety of current technology makes it likely that MSCT will replace conventional coronary angiography as the primary imaging modality in a majority of patients with suspected coronary artery disease, and in the follow-up after revascularization (104).

5.4.5 Stent thrombosis in BRS

The one case where MSCT did not detect a need for intervention was a patient with massive malapposition where much of the scaffold was not in contact with the vessel wall (Fig. 17). The fact that the BRS is translucent on X-ray, this is an inherent limitation of MSCT. Moreover, this indicates one possible mechanism for stent thrombosis in BRS. If the scaffold fails to be completely embedded in the vessel wall, it can collapse into the lumen as it is being resorbed and loses its structural strength. In our case, a likely cause is positive remodelling, with the vessel wall retracting from the scaffold, contrary to the more common reaction of neointimal hyperplasia which grows to cover the struts. It is difficult to predict this interaction between implant and vessel wall, and it might be that exposed metallic struts of a DES are more forgiving than collapsing BRSs in terms of thrombogenicity (89). This case also demonstrates that MSCT was unable to detect this potential problem, yet neither did conventional coronary angiography (Fig 17b). Intravascular imaging should therefore be mandatory where mechanical problems are suspected in all coronary implants. Although malapposition and positive remodelling are known underlying causes of stent thrombosis (88), there is no certain knowledge of what degree of suboptimal scaffold or stent healing should be treated in asymptomatic patients, or indeed how to solve it. We postdilated the scaffold with a non-compliant balloon and extended the dual antiplatelet treatment, but unfortunately this patient later presented with a non-ST-elevation myocardial infarction 31 months after implantation. OCT showed a collapse of the distal part of the scaffold with visible thrombi attached to the scaffold (Fig.

17c). We cannot exclude that our post-dilatation at 12-months actually caused the structural failure of the scaffold and worsened the outcome. Our patient had no further clinical events after the stent thrombosis was treated with implantation of a DES.

Figure 17: Patient with scaffold thrombosis 31 months after BRS implantation. a) OCT immediatly after implantation showing well expanded BRS without malapposed struts. b) OCT at 12 months follow-up with malapposition (red arrows). c) OCT at 31 months with collapsed scaffold and thrombus (blue arrows).



5.4.6 Summary

In summary, the ALA measured by MSCT is clinically useful in the follow-up after BRS implantation, although significantly higher than that measured by OCT. The MLA measurement by MSCT differed from OCT, but MSCT still had excellent sensitivity for restenosis. Area stenosis, average and minimum lumen area did not change significantly from 12 to 36 months. However, MSCT could not identify malapposition of the BRS struts. Despite this, our data supports MSCT as the first choice for coronary imaging after BRS implantation.

5.4.7 Strengths and limitations

Although data from long-term follow-up after Absorb™ implantation has been published from several cohorts (86, 87, 94, 105), these did not include MSCT imaging. In addition, our measurements can be directly compared to OCT at the same time point. It is also the largest BRS cohort to date to be evaluated by both MSCT and OCT. However, STEMI patients are a subgroup with different characteristics from other patients with coronary disease, in e.g. age, gender, urgency and presence of thrombus. Further, our cohorts were selected based on the ability to perform thrombus aspiration. We did not perform OCT of the aspirated thrombi, and we cannot exclude that the aspirated thrombi we analyzed by histology had different composition than the thrombi remnants we imaged with OCT. Invasive angiography at 36-month follow-up was not part of the study, and thus the true sensibility of MSCT was not confirmed by angiography.

6. Conclusions

6.1 Thrombus investigation

In our study, OCT could not determine erythrocyte content, nor predict whether the thrombi contained fresh, organized or lytic elements. Thus, we have not been able to reproduce previous findings characterizing thrombus content by loss of light intensity by OCT or establishing an association between erythrocyte content and thrombus age. This calls for caution in tailoring treatment according to thrombus characterization using OCT.

6.2 Bioresorbable vascular scaffold

In the present study, a strong tendency towards lower MFA and corresponding measurements was observed in the BRS group, compared to DES. The healing response did not explain the difference, which suggests that the thicker struts of the BRS are an important explanation for the poorer performance. However, the study was underpowered and could not investigate the primary endpoint of MFA by OCT at 12 months follow-up after implantation of Absorb™ BRS in patients with STEMI.

6.2 Long-term non-invasive follow-up

Our data supports the use of contemporary MSCT as the first choice of imaging in clinical and investigational follow-up after BRS implantation. There are, however, limitations in specificity, especially in calcified vessels, and a potential to miss important complications of BRS, calling for caution in symptomatic patients.

7. Evaluation and future perspectives

7.1 Our study

7.1.1 Evaluation of imaging techniques

Our objective was to assess outcomes after primary PCI of STEMI by leveraging the latest advances in imaging technology, with a specific focus on BRS. We successfully employed OCT in an acute setting, obtaining highly detailed images of thrombi and immediate post-PCI results, as well as monitoring the subsequent healing process. The utilization of MSCT for follow-up evaluation proved to be patient-friendly, with a high level of patient compliance, and most importantly, it delivered sufficient high-quality images for BRS assessment. The pathology aspect of our study presented certain complexities. Firstly, the number of specimens suitable for analysis was relatively low. Moreover, assessing the degree of organization posed challenges, as many specimens exhibited elements at various stages of organization. However, establishing the erythrocyte and platelet content, thus the colour of the thrombi by our definition, did not pose a problem.

7.1.2 Evaluation of study population and inclusion

We aimed to study a STEMI population with simple lesions to optimize image quality. The included patients were selected based on this criterion, resulting in a specific subset within the STEMI population. This approach excluded more patients than initially anticipated, and was one reason for the slower than expected inclusion rate. Nevertheless, the patients included fitted the population we targeted.

7.1.3 Clinical impact

Firstly, we have established some strengths and weaknesses in using MSCT for coronary imaging. MSCT is increasingly becoming the preferred choice for coronary imaging in patients with suspected coronary disease, also in those with previous PCI or CABG. Our research underscores that in future investigation of BRS, evaluation with MSCT is a good alternative to invasive methods.

Secondly, we have revealed that MSCT lacks the resolution to detect mechanical complications of BRS. Currently, only intracoronary imaging can reveal complications arising at the micron level. Despite the withdrawal of Absorb™ due to increased risk of stent thrombosis, and the absence of commercially available BRS at the moment, upcoming BRS platforms are under development. However, these will require rigorous evaluation before becoming clinically accessible.

Thirdly, even with the detailed images made possible by OCT, we emphasize the need for caution in interpreting OCT images. The images are highly computed and distorted from the raw data, as our findings have demonstrated. Therefore, drawing conclusions about thrombus content based on OCT should be approached judiciously.

7.1.4 Learning points

The choice of conducting a non-inferiority study can be debated. The selection of non-inferiority margin is a critical point, and often difficult to establish. We looked to other large studies and databases, but cannot argue strongly for the MFA margin we chose. To compensate we included several other secondary endpoints including the CSHI score, fully aware that the score was not validated against hard clinical endpoints. It would also pose problems to design for superiority, as we did not expect BRS to outperform DES. Another option is an equivalence trial, but true equivalence is hard to achieve, and would likely have forced us to discuss retrospectively if the difference in MFA was clinically meaningful.

The inability to establish thrombus content using OCT came as a surprise to the study group. Originally, we wanted to investigate if OCT could predict stent-healing properties based on thrombus appearance using imaging. As OCT imaging could not predict any of the properties investigated, we did not pursue this track. In retrospect, we could have included OCT of the aspirated material ex vivo to validate OCT as a method to establish thrombus content.

Overall, the inclusion rate at our centre proceeded more slowly than anticipated, and despite our efforts, we were unable to recruit additional centres. We implemented various measures to expedite patient recruitment, including 24/7 availability of the principal investigator and suspending serum collection for the biobank. Despite these

initiatives, study inclusion was delayed, and after 2.5 years the study device was withdrawn from the market before inclusion could be completed.

Additionally, the presentation of our results was delayed due to several unforeseen events. Conducting a comprehensive randomized clinical trial with limited resources presented a significant challenge.

7.2 Future perspectives

7.2.1 Bioresorbable vascular scaffolds

The field of vascular intervention has long been dominated by the implantation of metallic structures to ensure that the vasculature remains open. In coronary interventions, the current success of the DES will be difficult to emulate, but it is far from flawless. The DES impedes vasomotion, provokes inflammatory responses and still has a significant incidence of restenosis and stent thrombosis (106). While these DES-related complications are largely manageable, they are often treated with additional DES, contributing to a cumulative burden of metal in the coronary arteries over a patient's lifetime. This accumulation can hinder endovascular and surgical revascularization. Although BRS lost traction after Absorb™ was withdrawn by Abbott, the technique of permanently lining the vascular lumen with metal is likely to be succeeded by more modern materials. From the individual patient perspective, the notion of restoring the vasculature without metal is indeed attractive (Fig. 18). Some evidence suggests that the real benefit of BRS will be evident only in the very long term (105). In a five-year analysis of the AIDA trial, adverse events seemed to plateau after four years (107). There are also subsets of patients and procedures where BRS might be particularly useful, such as in side branches (108) (109).

PLLA scaffolds like Absorb™ are essentially plastic, consisting of long chains of lactic acid. One challenge with polymeric stents is making them strong enough without increasing strut thickness. Techniques to enhance strength include using higher-molecular-weight polymers, improving the crystallinity, altering the interior structure of the polymer chain, reinforcing the polymer with fibres or incorporating nanoparticles. Shape-memory self-expandable materials offer a different approach, but face challenges in adapting to the clinical environment due to long expansion time in

the 37°C in vivo environment. There are also concerns that they might be susceptible to bacterial colonization. There have been some improvements in this concept, such as incorporating polyurethane nanohybrids. Another approach is to 3D print individualized polymer scaffolds to suit the anatomy of each patient. It is, however, difficult to imagine 3D printing to be plausible in clinical practice with the high volume of patients currently being treated, some with great urgency.

Polymers are not the only way to make biodegradable materials. Stents made of metallic ions, such as Mg2+, have shown promise in in-vitro studies. These salt-based stents have great radial strength, but are prone to rapid and uncontrollable degradation, not lasting quite long enough for the vasculature to be restored. In-vitro studies have also shown that ions released during degradation might be detrimental to neo-endothelium formation. Even so, the Magmaris™ magnesium scaffold has recently presented data with from more than 2000 patients in the BIOSOLVE-IV registry, that showed only 0.8% stent thrombosis, and TLF of 6.8 % during 24 months follow-up (110).

Iron-based stents have greater biocompatibility, and do not have the same impact on neo-endothelium formation. However, they are more prone to form corrosion products with oxygen. Fe^{2+} ions are mainly removed by macrophages, causing inflammation even in distant lymph nodes. A first-in-man trial with an ultrathin (70 μm) iron scaffold (IBS; Biotyx Medical, Shenzhen, China, previously developed at Lifetech Scientific Company) was published this year, with TLF of 6.7% after three years and no scaffold thrombosis (111).

Zn^{2+}-based stents do not seem to elicit the same inflammatory response, and degrade at an appropriate rate. However, current models do not have the tensile strength to mechanically support the vessel.

Improvements being tested out on these salt-based materials include alloys to enhance strength and coatings to control degradation (57).

Regardless of platform, extensive testing in animal models remains imperative for future scaffolds. Common animal models are rabbit iliac or aortic models, or pig coronary artery models. In these tests, scaffolds are meticulously implanted under image guidance in non-atherosclerotic uniform size arteries. In

clinical practice, a perfect implant in all patients is not possible. The atherosclerotic artery often has positive remodelling, crypts, recesses and side branches. Consequently, some struts will have delayed or possibly no endothelial healing. Furthermore, as we have demonstrated, the interaction between scaffold and vessel wall is unpredictable, and a seemingly perfect implantation can still leave struts permanently exposed in the lumen. Future platforms need to take account of this problem, and demonstrate that exposed struts do not pose a thrombogenic risk during resorption (Fig. 19).

Figure 18

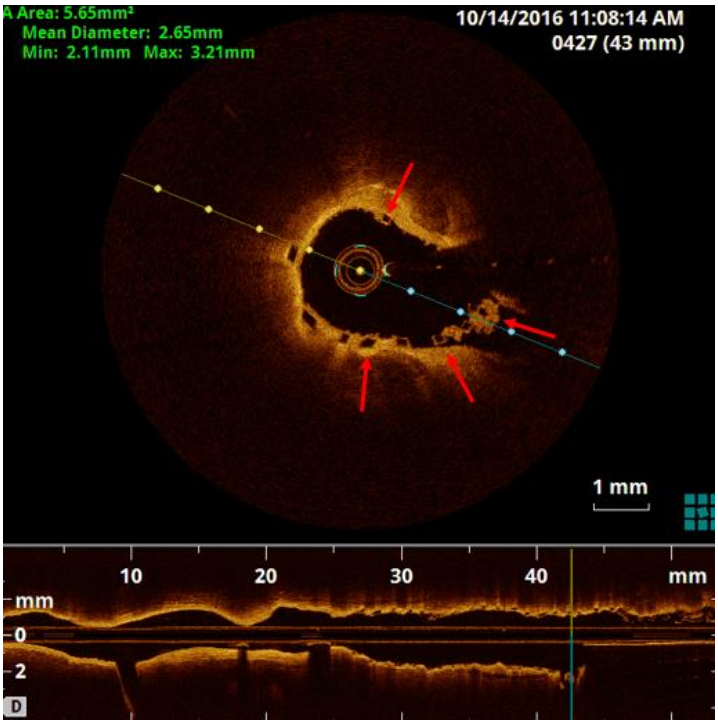
OCT images showing Absorb™ 3.0/23 implanted in mid LAD.

A: Immediately after implantation with visible struts (red arrows show examples)

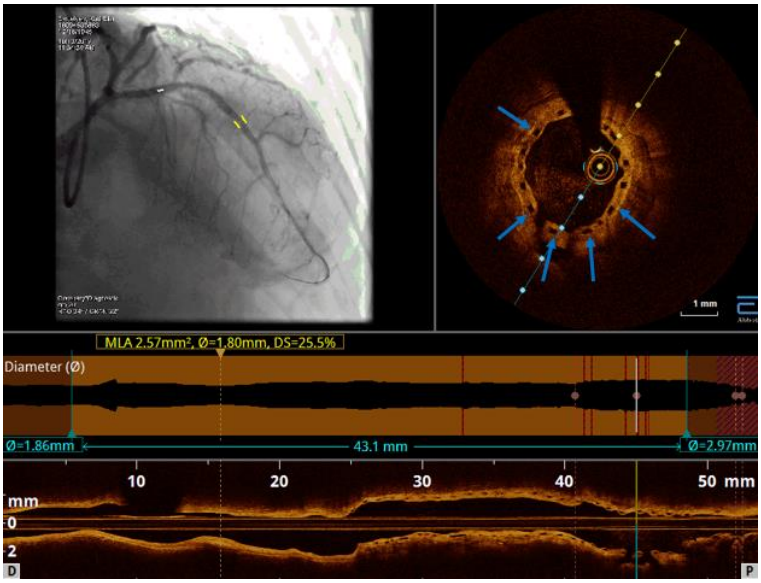
B: 12 months after implantation. Struts (blue arrows show examples) are completely covered in neo-endothelium with struts covering a sidebranch (jailing struts).

C: Six years after implantation. Struts completely resorbed with no jailing struts.

A:



B:


1 mm
MLA 2.57mm², Ø=1.80mm, DS=25.5%
Diameter (Ø)
Ø=1.86mm
43.1 mm
Ø=2.97mm
10
20
30
40
50 mm
mm
0
2
D
P

C:

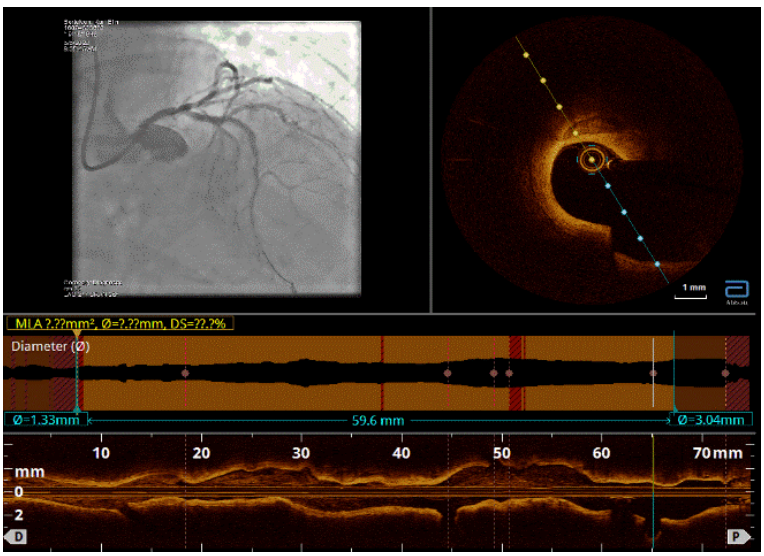
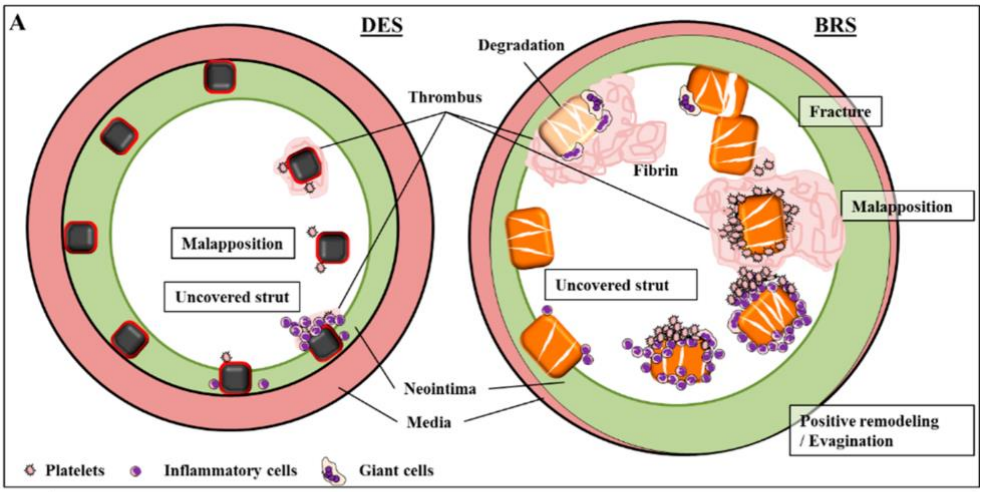

1 mm
MLA ?.??mm², Ø=?.??mm, DS=??.?%
Diameter (Ø)
Ø=1.33mm
59.6 mm
Ø=3.04mm
10
20
30
40
50
60
70 mm
mm
0
2
D
P

Figure 19

A: Various mechanisms of late stent thrombosis (ST) in drug eluting stents (DES) (left) and bioresorbable scaffolds (BRS) (right) illustrating the thrombogenic environment surrounding uncovered struts being resorbed.

B: The impact of each factor and its relationship to thrombosis in different devices (Source: Sakamoto et al, Bioengineering 2018, 5(3)) (34)



B

Cause of very late ST	BMS	1st DES	2nd DES	BRS
Malapposition	(+)	(++)	(+)	(+++)
Fracture / discontinuity	(+)	(++)	(+)	(+++)
Uncovered strut	(-)	(++)	(+)	(+++)
Edge-related disease	(+)	(+)	(+)	(+)
Rupture from neoatherosclerosis (Very late)	(++)	(+++)	(++)	(?)
Inflammation	(++)	(++)	(+)	(+++)
Hypersensitivity	(±)	(+++)	(+)	(?)

7.2.2 Advances in MSCT

The MSCT scanners used in our study were based on energy-integrating detectors. Stated simply, these detectors convert photons to visible light before being absorbed in a semiconductor to produce an electrical signal. Photon-counting detectors (PCD) skip this stage, absorbing photons directly in a thick semiconducting layer producing an electrical signal for each photon. This reduces electrical noise and potentially increases the amount of information from each photon, thus reducing the necessary radiation dose. To accommodate the large amount of information from PCD, the individual

detectors are made smaller in size, theoretically increasing the spatial resolution from 0.5x0.5 mm²2 up to 0.07x0.07 mm². The improvement in resolution might not be quite as great in real life, but it is nevertheless a dramatic improvement. Blooming artefacts will likely be reduced, and specificity greatly improved (112). The first PCD scanner became available for patient care in 2021, and is expected to be the technology of choice as current scanners are being replaced (113).

7.2.3 Thrombus burden

Large thrombus burdens in patients with STEMI present a clinical problem, and the optimal management remains a subject of debate. While routine use of thrombus aspiration is not recommended, it is still used in selected cases in the absence of good alternatives. Standard treatments include heparin and antiplatelet agents, but infusion of agents such as bivalirudin, tirofiban, abciximab and pro-urokinase have not proven beneficial in studies (114-118). These agents target different aspects of thrombus formation, inhibiting either platelet aggregation, fibrin formation or the coagulation cascade. Given the diverse nature of thrombi and the trade-off with bleeding complications when multiple components of the coagulation system are inhibited, it is unlikely that a single agent will suffice for all cases.

To better tailor treatment approaches, it would be useful to gain further insight into thrombus characteristics. Unfortunately, our attempt to identify thrombus content based on OCT did not succeed. To advance our understanding of thrombus characteristics and facilitate more personalized treatments, we believe imaging alone may not provide a comprehensive solution. One potential approach could be to aspirate the thrombus for live examination in the interventional laboratory. To make this feasible, it would be useful to develop of a rapid test, e.g. of the fibrin content.

7.3 Ethical considerations

New and promising devices are continuously becoming available to the field of interventional cardiology. Many of these are to the benefit of the patient, involving either an easier and safer procedure or better long-term results. Some new developments, however, are found to be inadequate after more extensive testing or

larger studies. It is ethically challenging to decide when to use newly developed devices in routine clinical practice. Therefore, the most ethical way to take up new technology is in a randomized trial.

Randomizing the patients in a trial involves informing them that it is new technology that is not yet fully investigated. The safety and benefit of the device will be monitored, and criteria set for the endpoints being studied. The trial will need approval by an ethics committee, and the results must be published and made available to the scientific community.

One disadvantage of being in a trial is the additional follow-up usually required. In our case this meant an additional invasive examination with intracoronary imaging, and up to two extra MSCT scans. The possibility of complications of an invasive examination, radiation and contrast is a risk the patient must be willing to bear. However, patients are at liberty to refuse these additional examinations, and indeed some did. Most patients did, however, see these examinations as a comforting follow-up procedure.

To obtain informed consent from a patient in the setting of an acute STEMI is challenging. There is no time for the patient to read and understand an extensive informed consent. We solved this by only asking the patient for oral consent after the flow of the coronary artery had been re-established. There was then time to provide the most basic information, and for the patient to ask questions. The written consent could, however, only be signed after the procedure. In our view, this is the most ethical way to obtain consent from a patient in an acute setting.

Our trial was terminated early, due to increasing concern about rates of stent thrombosis in BRS. The decision was based on several trials, but the final blow was the Amsterdam Investigator-initiated Absorb Strategy (AIDA) trial. This emphasizes the need for industry-independent trials, and re-evaluation of ongoing trials if new information becomes available. We believe it would have been unethical to continue to include patients in our trial, taking this new knowledge into account.

Overall, our view is that new devices should be tried out in investigator-initiated trials, also in STEMI patients. Obtaining initial oral consent is the only practical way for the patient to consent perioperatively, and it is always made clear to

patients that they can refuse the additional burden of follow-up procedures, should they change their mind.

8. References

1. Thompson RC, Allam AH, Lombardi GP, Wann LS, Sutherland ML, Sutherland JD, et al. Atherosclerosis across 4000 years of human history: the Horus study of four ancient populations. Lancet. 2013;381(9873):1211-22.
2. Nabel EG, Braunwald E. A tale of coronary artery disease and myocardial infarction. The New England journal of medicine. 2012;366(1):54-63.
3. Kumar DR, Hanlin E, Glurich I, Mazza JJ, Yale SH. Virchow's contribution to the understanding of thrombosis and cellular biology. Clin Med Res. 2010;8(3-4):168-72.
4. JB H. Certain clinical features of the sudden obstruction of coronary arteries. JAMA. 1912;59:2015-20.
5. Idem. Thrombosis of the coronary arteries. JAMA. 1919;72:389-90.
6. Khurana KV, Ranjan A. ST-Segment Elevation in Conditions of Non-cardiovascular Origin Mimicking an Acute Myocardial Infarction: A Narrative Review. Cureus. 2022;14(10):e30868.
7. Rosalki SB, Roberts R, Katus HA, Giannitsis E, Ladenson JH, Apple FS. Cardiac biomarkers for detection of myocardial infarction: perspectives from past to present. Clin Chem. 2004;50(11):2205-13.
8. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, et al. Fourth universal definition of myocardial infarction (2018). European heart journal. 2019;40(3):237-69.
9. Chokkalingam Mani B, Chaudhari SS. Right Heart Cardiac Catheterization. StatPearls. Treasure Island (FL)2022.
10. Abrams HL. Selectivity in the study of the cardiovascular system. Calif Med. 1962;96(3):149-55.
11. Sones FM, Jr., Shirey EK. Cine coronary arteriography. Mod Concepts Cardiovasc Dis. 1962;31:735-8.
12. Bakaeen FG, Blackstone EH, Pettersson GB, Gillinov AM, Svensson LG. The father of coronary artery bypass grafting: Rene Favaloro and the 50th anniversary of coronary artery bypass grafting. J Thorac Cardiovasc Surg. 2018;155(6):2324-8.
13. Langorgen J, Igland J, Vollset SE, Averina M, Nordrehaug JE, Tell GS, et al. Short-term and long-term case fatality in 11 878 patients hospitalized with a first acute myocardial infarction, 1979-2001: the Western Norway cardiovascular registry. Eur J Cardiovasc Prev Rehabil. 2009;16(5):621-7.
14. Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI). Lancet. 1986;1(8478):397-402.
15. Kennedy JW. Streptokinase for the treatment of acute myocardial infarction: a brief review of randomized trials. Journal of the American College of Cardiology. 1987;10(5 Suppl B):28B-32B.
16. Long-term effects of intravenous thrombolysis in acute myocardial infarction: final report of the GISSI study. Gruppo Italiano per lo Studio della Streptochi-nasi nell'Infarto Miocardico (GISSI). Lancet. 1987;2(8564):871-4.
17. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Lancet. 1988;2(8607):349-60.
18. Gruntzig AR, Senning A, Siegenthaler WE. Nonoperative dilatation of coronary-artery stenosis: percutaneous transluminal coronary angioplasty. The New England journal of medicine. 1979;301(2):61-8.
19. Fischman DL, Leon MB, Baim DS, Schatz RA, Savage MP, Penn I, et al. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. Stent Restenosis Study Investigators. The New England journal of medicine. 1994;331(8):496-501.
20. Serruys PW, de Jaegere P, Kiemeneij F, Macaya C, Rutsch W, Heyndrickx G, et al. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with

coronary artery disease. Benestent Study Group. The New England journal of medicine. 1994;331(8):489-95.
21. Schomig A, Neumann FJ, Kastrati A, Schuhlen H, Blasini R, Hadamitzky M, et al. A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery stents. The New England journal of medicine. 1996;334(17):1084-9.
22. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. Lancet. 2003;361(9351):13-20.
23. Parise H, Maehara A, Stone GW, Leon MB, Mintz GS. Meta-analysis of randomized studies comparing intravascular ultrasound versus angiographic guidance of percutaneous coronary intervention in pre-drug-eluting stent era. Am J Cardiol. 2011;107(3):374-82.
24. Buccheri S, Franchina G, Romano S, Puglisi S, Venuti G, D'Arrigo P, et al. Clinical Outcomes Following Intravascular Imaging-Guided Versus Coronary Angiography-Guided Percutaneous Coronary Intervention With Stent Implantation: A Systematic Review and Bayesian Network Meta-Analysis of 31 Studies and 17,882 Patients. JACC Cardiovascular interventions. 2017;10(24):2488-98.
25. Marrocco CJ, Jaber R, White RA, Walot I, DeVirgilio C, Donayre CE, Kopchok G. Intravascular ultrasound. Semin Vasc Surg. 2012;25(3):144-52.
26. Hodgson JM, Graham SP, Savakus AD, Dame SG, Stephens DN, Dhillon PS, et al. Clinical percutaneous imaging of coronary anatomy using an over-the-wire ultrasound catheter system. Int J Card Imaging. 1989;4(2-4):187-93.
27. McDaniel MC, Eshtehardi P, Sawaya FJ, Douglas JS, Jr., Samady H. Contemporary clinical applications of coronary intravascular ultrasound. JACC Cardiovascular interventions. 2011;4(11):1155-67.
28. Schiele F, Meneveau N, Seronde MF, Deforet MF, Gupta S, Bassand JP. Predictors of event-free survival after repeat intracoronary procedure for in-stent restenosis; study with angiographic and intravascular ultrasound imaging. European heart journal. 2000;21(9):754-62.
29. Raber L, Mintz GS, Koskinas KC, Johnson TW, Holm NR, Onuma Y, et al. Clinical use of intracoronary imaging. Part 1: guidance and optimization of coronary interventions. An expert consensus document of the European Association of Percutaneous Cardiovascular Interventions. EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology. 2018;14(6):656-77.
30. Johnson TW, Raber L, Di Mario C, Bourantas CV, Jia H, Mattesini A, et al. Clinical use of intracoronary imaging. Part 2: acute coronary syndromes, ambiguous coronary angiography findings, and guiding interventional decision-making: an expert consensus document of the European Association of Percutaneous Cardiovascular Interventions. EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology. 2019;15(5):434-51.
31. Zhang YJ, Pang S, Chen XY, Bourantas CV, Pan DR, Dong SJ, et al. Comparison of intravascular ultrasound guided versus angiography guided drug eluting stent implantation: a systematic review and meta-analysis. BMC Cardiovasc Disord. 2015;15:153.
32. Lee JM, Choi KH, Song YB, Lee JY, Lee SJ, Lee SY, et al. Intravascular Imaging-Guided or Angiography-Guided Complex PCI. The New England journal of medicine. 2023;388(18):1668-79.
33. Parviz Y, Shlofmitz E, Fall KN, Konigstein M, Maehara A, Jeremias A, et al. Utility of intracoronary imaging in the cardiac catheterization laboratory: comprehensive evaluation with intravascular ultrasound and optical coherence tomography. Br Med Bull. 2018;125(1):79-90.
34. Sakamoto A, Jinnouchi H, Torii S, Virmani R, Finn AV. Understanding the Impact of Stent and Scaffold Material and Strut Design on Coronary Artery Thrombosis from the Basic and Clinical Points of View. Bioengineering (Basel). 2018;5(3).
35. Tearney GJ, Regar E, Akasaka T, Adriaenssens T, Barlis P, Bezerra HG, et al. Consensus standards for acquisition, measurement, and reporting of intravascular optical coherence tomography studies: a report from the International Working Group for Intravascular Optical

Coherence Tomography Standardization and Validation. Journal of the American College of Cardiology. 2012;59(12):1058-72.
36. Boogers MJ, Schuijf JD, Kitslaar PH, van Werkhoven JM, de Graaf FR, Boersma E, et al. Automated quantification of stenosis severity on 64-slice CT: a comparison with quantitative coronary angiography. JACC Cardiovasc Imaging. 2010;3(7):699-709.
37. Nielsen LH, Ortner N, Norgaard BL, Achenbach S, Leipsic J, Abdulla J. The diagnostic accuracy and outcomes after coronary computed tomography angiography vs. conventional functional testing in patients with stable angina pectoris: a systematic review and meta-analysis. European heart journal cardiovascular Imaging. 2014;15(9):961-71.
38. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. European heart journal cardiovascular Imaging. 2015;16(3):233-70.
39. van Loon RB, Veen G, Baur LH, Kamp O, Bronzwaer JG, Twisk JW, et al. Improved clinical outcome after invasive management of patients with recent myocardial infarction and proven myocardial viability: primary results of a randomized controlled trial (VIAMI-trial). Trials. 2012;13:1.
40. van Loon RB, Veen G, Baur LH, Twisk JW, van Rossum AC. Long-term follow-up of the viability guided angioplasty after acute myocardial infarction (VIAMI) trial. International journal of cardiology. 2015;186:111-6.
41. Bonaa KH, Mannsverk J, Wiseth R, Aaberge L, Myreng Y, Nygard O, et al. Drug-Eluting or Bare-Metal Stents for Coronary Artery Disease. The New England journal of medicine. 2016;375(13):1242-52.
42. Cornelissen A, Vogt FJ. The effects of stenting on coronary endothelium from a molecular biological view: Time for improvement? J Cell Mol Med. 2019;23(1):39-46.
43. Erbel R, Di Mario C, Bartunek J, Bonnier J, de Bruyne B, Eberli FR, et al. Temporary scaffolding of coronary arteries with bioabsorbable magnesium stents: a prospective, non-randomised multicentre trial. Lancet. 2007;369(9576):1869-75.
44. Tamai H, Igaki K, Kyo E, Kosuga K, Kawashima A, Matsui S, et al. Initial and 6-month results of biodegradable poly-l-lactic acid coronary stents in humans. Circulation. 2000;102(4):399-404.
45. Sabate M, Alfonso F, Cequier A, Romani S, Bordes P, Serra A, et al. Magnesium-Based Resorbable Scaffold Versus Permanent Metallic Sirolimus-Eluting Stent in Patients With ST-Segment Elevation Myocardial Infarction: The MAGSTEMI Randomized Clinical Trial. Circulation. 2019;140(23):1904-16.
46. de Hemptinne Q, Xaplanteris P, Guedes A, Demeure F, Vandeloo B, Dugauquier C, et al. Magmaris resorbable magnesium scaffold versus conventional drug-eluting stent in ST-segment elevation myocardial infarction: 1-year results of a propensity score matching comparison. Cardiovasc Revasc Med. 2022.
47. Ormiston JA, Serruys PW, Regar E, Dudek D, Thuesen L, Webster MW, et al. A bioabsorbable everolimus-eluting coronary stent system for patients with single de-novo coronary artery lesions (ABSORB): a prospective open-label trial. Lancet. 2008;371(9616):899-907.
48. Ormiston JA, Webster MW, Armstrong G. First-in-human implantation of a fully bioabsorbable drug-eluting stent: the BVS poly-L-lactic acid everolimus-eluting coronary stent. Catheter Cardiovasc Interv. 2007;69(1):128-31.
49. Serruys PW, Onuma Y, Ormiston JA, de Bruyne B, Regar E, Dudek D, et al. Evaluation of the second generation of a bioresorbable everolimus drug-eluting vascular scaffold for treatment of de novo coronary artery stenosis: six-month clinical and imaging outcomes. Circulation. 2010;122(22):2301-12.
50. Serruys PW, Ormiston JA, Onuma Y, Regar E, Gonzalo N, Garcia-Garcia HM, et al. A bioabsorbable everolimus-eluting coronary stent system (ABSORB): 2-year outcomes and results from multiple imaging methods. Lancet. 2009;373(9667):897-910.
51. Serruys PW, Chevalier B, Dudek D, Cequier A, Carrie D, Iniguez A, et al. A bioresorbable everolimus-eluting scaffold versus a metallic everolimus-eluting stent for ischaemic heart disease

caused by de-novo native coronary artery lesions (ABSORB II): an interim 1-year analysis of clinical and procedural secondary outcomes from a randomised controlled trial. Lancet. 2015;385(9962):43-54.
52. Brugaletta S, Heo JH, Garcia-Garcia HM, Farooq V, van Geuns RJ, de Bruyne B, et al. Endothelial-dependent vasomotion in a coronary segment treated by ABSORB everolimus-eluting bioresorbable vascular scaffold system is related to plaque composition at the time of bioresorption of the polymer: indirect finding of vascular reparative therapy? European heart journal. 2012;33(11):1325-33.
53. Puricel S, Arroyo D, Corpataux N, Baeriswyl G, Lehmann S, Kallinikou Z, et al. Comparison of everolimus- and biolimus-eluting coronary stents with everolimus-eluting bioresorbable vascular scaffolds. Journal of the American College of Cardiology. 2015;65(8):791-801.
54. Ellis SG, Kereiakes DJ, Metzger DC, Caputo RP, Rizik DG, Teirstein PS, et al. Everolimus-Eluting Bioresorbable Scaffolds for Coronary Artery Disease. The New England journal of medicine. 2015;373(20):1905-15.
55. Kajiya T, Liang M, Sharma RK, Lee CH, Chan MY, Tay E, et al. Everolimus-eluting bioresorbable vascular scaffold (BVS) implantation in patients with ST-segment elevation myocardial infarction (STEMI). EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology. 2013;9(4):501-4.
56. Wiebe J, Mollmann H, Most A, Dorr O, Weipert K, Rixe J, et al. Short-term outcome of patients with ST-segment elevation myocardial infarction (STEMI) treated with an everolimus-eluting bioresorbable vascular scaffold. Clin Res Cardiol. 2014;103(2):141-8.
57. Zong J, He Q, Liu Y, Qiu M, Wu J, Hu B. Advances in the development of biodegradable coronary stents: A translational perspective. Mater Today Bio. 2022;16:100368.
58. Byrne RA, Rossello X, Coughlan JJ, Barbato E, Berry C, Chieffo A, et al. 2023 ESC Guidelines for the management of acute coronary syndromes. European heart journal. 2023.
59. Scholz KH, Maier SKG, Maier LS, Lengenfelder B, Jacobshagen C, Jung J, et al. Impact of treatment delay on mortality in ST-segment elevation myocardial infarction (STEMI) patients presenting with and without haemodynamic instability: results from the German prospective, multicentre FITT-STEMI trial. European heart journal. 2018;39(13):1065-74.
60. Ndrepepa G, Tiroch K, Keta D, Fusaro M, Seyfarth M, Pache J, et al. Predictive factors and impact of no reflow after primary percutaneous coronary intervention in patients with acute myocardial infarction. Circulation Cardiovascular interventions. 2010;3(1):27-33.
61. Svilaas T, Vlaar PJ, van der Horst IC, Diercks GF, de Smet BJ, van den Heuvel AF, et al. Thrombus aspiration during primary percutaneous coronary intervention. The New England journal of medicine. 2008;358(6):557-67.
62. Frobert O, Lagerqvist B, Olivecrona GK, Omerovic E, Gudnason T, Maeng M, et al. Thrombus aspiration during ST-segment elevation myocardial infarction. The New England journal of medicine. 2013;369(17):1587-97.
63. Jolly SS, Cairns JA, Yusuf S, Meeks B, Gao P, Hart RG, et al. Stroke in the TOTAL trial: a randomized trial of routine thrombectomy vs. percutaneous coronary intervention alone in ST elevation myocardial infarction. European heart journal. 2015;36(35):2364-72.
64. Jolly SS, Cairns JA, Yusuf S, Rokoss MJ, Gao P, Meeks B, et al. Outcomes after thrombus aspiration for ST elevation myocardial infarction: 1-year follow-up of the prospective randomised TOTAL trial. Lancet. 2016;387(10014):127-35.
65. Moxham R, Dzavik V, Cairns J, Natarajan MK, Bainey KR, Akl E, et al. Association of Thrombus Aspiration With Time and Mortality Among Patients With ST-Segment Elevation Myocardial Infarction: A Post Hoc Analysis of the Randomized TOTAL Trial. JAMA Netw Open. 2021;4(3):e213505.
66. Belle L, Motreff P, Mangin L, Range G, Marcaggi X, Marie A, et al. Comparison of Immediate With Delayed Stenting Using the Minimalist Immediate Mechanical Intervention Approach in Acute ST-Segment-Elevation Myocardial Infarction: The MIMI Study. Circulation Cardiovascular interventions. 2016;9(3):e003388.

67. Niccoli G, Cosentino N, Spaziani C, Minelli S, Fracassi F, Crea F. New strategies for the management of no-reflow after primary percutaneous coronary intervention. Expert Rev Cardiovasc Ther. 2011;9(5):615-30.
68. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, et al. 2015 ACC/AHA/SCAI Focused Update on Primary Percutaneous Coronary Intervention for Patients With ST-Elevation Myocardial Infarction: An Update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention and the 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. Circulation. 2016;133(11):1135-47.
69. van der Wal AC, Becker AE. Atherosclerotic plaque rupture--pathologic basis of plaque stability and instability. Cardiovascular research. 1999;41(2):334-44.
70. Beygui F, Collet JP, Nagaswami C, Weisel JW, Montalescot G. Images in cardiovascular medicine. Architecture of intracoronary thrombi in ST-elevation acute myocardial infarction: time makes the difference. Circulation. 2006;113(2):e21-3.
71. Silvain J, Collet JP, Nagaswami C, Beygui F, Edmondson KE, Bellemain-Appaix A, et al. Composition of coronary thrombus in acute myocardial infarction. Journal of the American College of Cardiology. 2011;57(12):1359-67.
72. Onuma Y, Thuesen L, van Geuns RJ, van der Ent M, Desch S, Fajadet J, et al. Randomized study to assess the effect of thrombus aspiration on flow area in patients with ST-elevation myocardial infarction: an optical frequency domain imaging study--TROFI trial. European heart journal. 2013;34(14):1050-60.
73. Sabate M, Windecker S, Iniguez A, Okkels-Jensen L, Cequier A, Brugaletta S, et al. Everolimus-eluting bioresorbable stent vs. durable polymer everolimus-eluting metallic stent in patients with ST-segment elevation myocardial infarction: results of the randomized ABSORB ST-segment elevation myocardial infarction-TROFI II trial. European heart journal. 2016;37(3):229-40.
74. Kume T, Akasaka T, Kawamoto T, Ogasawara Y, Watanabe N, Toyota E, et al. Assessment of coronary arterial thrombus by optical coherence tomography. Am J Cardiol. 2006;97(12):1713-7.
75. Kramer MC, van der Wal AC, Koch KT, Ploegmakers JP, van der Schaaf RJ, Henriques JP, et al. Presence of older thrombus is an independent predictor of long-term mortality in patients with ST-elevation myocardial infarction treated with thrombus aspiration during primary percutaneous coronary intervention. Circulation. 2008;118(18):1810-6.
76. Huang D, Swanson EA, Lin CP, Schuman JS, Stinson WG, Chang W, et al. Optical coherence tomography. Science. 1991;254(5035):1178-81.
77. Li X, de Boer OJ, Ploegmaker H, Teeling P, Daemen MJ, de Winter RJ, van der Wal AC. Granulocytes in coronary thrombus evolution after myocardial infarction--time-dependent changes in expression of matrix metalloproteinases. Cardiovascular pathology : the official journal of the Society for Cardiovascular Pathology. 2016;25(1):40-6.
78. Li X, Kramer MC, van der Loos CM, Koch KT, de Boer OJ, Henriques JP, et al. A pattern of disperse plaque microcalcifications identifies a subset of plaques with high inflammatory burden in patients with acute myocardial infarction. Atherosclerosis. 2011;218(1):83-9.
79. Mangold A, Alias S, Scherz T, Hofbauer M, Jakowitsch J, Panzenbock A, et al. Coronary neutrophil extracellular trap burden and deoxyribonuclease activity in ST-elevation acute coronary syndrome are predictors of ST-segment resolution and infarct size. Circulation research. 2015;116(7):1182-92.
80. Riegger J, Byrne RA, Joner M, Chandraratne S, Gershlick AH, Ten Berg JM, et al. Histopathological evaluation of thrombus in patients presenting with stent thrombosis. A multicenter European study: a report of the prevention of late stent thrombosis by an interdisciplinary global European effort consortium. European heart journal. 2016;37(19):1538-49.
81. Johnson C, Galis ZS. Matrix metalloproteinase-2 and -9 differentially regulate smooth muscle cell migration and cell-mediated collagen organization. Arteriosclerosis, thrombosis, and vascular biology. 2004;24(1):54-60.

82. Li X, van der Meer JJ, van der Loos CM, Ploegmakers HJ, de Boer OJ, de Winter RJ, van der Wal AC. Microvascular endoglin (CD105) expression correlates with tissue markers for atherosclerotic plaque vulnerability in an ageing population with multivessel coronary artery disease. Histopathology. 2012;61(1):88-97.
83. Newby AC. Dual role of matrix metalloproteinases (matrixins) in intimal thickening and atherosclerotic plaque rupture. Physiological reviews. 2005;85(1):1-31.
84. Newby AC. Matrix metalloproteinases regulate migration, proliferation, and death of vascular smooth muscle cells by degrading matrix and non-matrix substrates. Cardiovascular research. 2006;69(3):614-24.
85. Vlaar PJ, Svilaas T, van der Horst IC, Diercks GF, Fokkema ML, de Smet BJ, et al. Cardiac death and reinfarction after 1 year in the Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction Study (TAPAS): a 1-year follow-up study. Lancet. 2008;371(9628):1915-20.
86. Ali ZA, Gao R, Kimura T, Onuma Y, Kereiakes DJ, Ellis SG, et al. Three-Year Outcomes With the Absorb Bioresorbable Scaffold: Individual-Patient-Data Meta-Analysis From the ABSORB Randomized Trials. Circulation. 2018;137(5):464-79.
87. Kereiakes DJ, Ellis SG, Metzger C, Caputo RP, Rizik DG, Teirstein PS, et al. 3-Year Clinical Outcomes With Everolimus-Eluting Bioresorbable Coronary Scaffolds: The ABSORB III Trial. Journal of the American College of Cardiology. 2017;70(23):2852-62.
88. Tousek P, Kocka V, Maly M, Lisa L, Budesinsky T, Widimsky P. Neointimal coverage and late apposition of everolimus-eluting bioresorbable scaffolds implanted in the acute phase of myocardial infarction: OCT data from the PRAGUE-19 study. Heart Vessels. 2016;31(6):841-5.
89. Waksman R, Lipinski MJ, Acampado E, Cheng Q, Adams L, Torii S, et al. Comparison of Acute Thrombogenicity for Metallic and Polymeric Bioabsorbable Scaffolds: Magmaris Versus Absorb in a Porcine Arteriovenous Shunt Model. Circulation Cardiovascular interventions. 2017;10(8).
90. Adriaenssens T, Joner M, Godschalk TC, Malik N, Alfonso F, Xhepa E, et al. Optical Coherence Tomography Findings in Patients With Coronary Stent Thrombosis: A Report of the PRESTIGE Consortium (Prevention of Late Stent Thrombosis by an Interdisciplinary Global European Effort). Circulation. 2017;136(11):1007-21.
91. Cuesta J, Rivero F, Bastante T, Garcia-Guimaraes M, Antuna P, Alvarado T, et al. Optical Coherence Tomography Findings in Patients With Stent Thrombosis. Rev Esp Cardiol (Engl Ed). 2017;70(12):1050-8.
92. Guagliumi G, Sirbu V, Musumeci G, Gerber R, Biondi-Zoccai G, Ikejima H, et al. Examination of the in vivo mechanisms of late drug-eluting stent thrombosis: findings from optical coherence tomography and intravascular ultrasound imaging. JACC Cardiovascular interventions. 2012;5(1):12-20.
93. Nakazawa G, Finn AV, Joner M, Ladich E, Kutys R, Mont EK, et al. Delayed arterial healing and increased late stent thrombosis at culprit sites after drug-eluting stent placement for acute myocardial infarction patients: an autopsy study. Circulation. 2008;118(11):1138-45.
94. Tousek P, Kocka V, Maly M, Kozel M, Robert P, Hajsl M, et al. Two-year follow-up after bioresorbable vascular scaffold implantation in STEMI patients - Results from PRAGUE-19 study. International journal of cardiology. 2016;209:20-1.
95. Widimsky P, Petr R, Tousek P, Maly M, Linkova H, Vrana J, et al. One-Year Clinical and Computed Tomography Angiographic Outcomes After Bioresorbable Vascular Scaffold Implantation During Primary Percutaneous Coronary Intervention for ST-Segment-Elevation Myocardial Infarction: The PRAGUE-19 Study. Circulation Cardiovascular interventions. 2015;8(12):e002933.
96. Tousek P, Kocka V, Maly M, Kozel M, Petr R, Hajsl M, et al. Long-term follow-up after bioresorbable vascular scaffold implantation in STEMI patients: PRAGUE-19 study update. EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology. 2016;12(1):23-9.

97. Serruys PW, Ormiston J, van Geuns RJ, de Bruyne B, Dudek D, Christiansen E, et al. A Polylactide Bioresorbable Scaffold Eluting Everolimus for Treatment of Coronary Stenosis: 5-Year Follow-Up. Journal of the American College of Cardiology. 2016;67(7):766-76.
98. Gutierrez-Chico JL, Serruys PW, Girasis C, Garg S, Onuma Y, Brugaletta S, et al. Quantitative multi-modality imaging analysis of a fully bioresorbable stent: a head-to-head comparison between QCA, IVUS and OCT. Int J Cardiovasc Imaging. 2012;28(3):467-78.
99. Mazhar J, Shaw E, Allahwala UK, Figtree GA, Bhindi R. Comparison of two dimensional quantitative coronary angiography (2D-QCA) with optical coherence tomography (OCT) in the assessment of coronary artery lesion dimensions. Int J Cardiol Heart Vasc. 2015;7:14-7.
100. Toutouzas K, Chatzizisis YS, Riga M, Giannopoulos A, Antoniadis AP, Tu S, et al. Accurate and reproducible reconstruction of coronary arteries and endothelial shear stress calculation using 3D OCT: comparative study to 3D IVUS and 3D QCA. Atherosclerosis. 2015;240(2):510-9.
101. Carrabba N, Schuijf JD, de Graaf FR, Parodi G, Maffei E, Valenti R, et al. Diagnostic accuracy of 64-slice computed tomography coronary angiography for the detection of in-stent restenosis: a meta-analysis. J Nucl Cardiol. 2010;17(3):470-8.
102. Tonet E, Cossu A, Pompei G, Ruggiero R, Caglioni S, Mele D, et al. Coronary Computed Tomography Angiography for the Assessment of Sirolimus-Eluting Resorbable Magnesium Scaffold. Life (Basel). 2022;12(10).
103. Decker JA, O'Doherty J, Schoepf UJ, Todoran TM, Aquino GJ, Brandt V, et al. Stent imaging on a clinical dual-source photon-counting detector CT system-impact of luminal attenuation and sharp kernels on lumen visibility. Eur Radiol. 2022.
104. Narula J, Chandrashekhar Y, Ahmadi A, Abbara S, Berman DS, Blankstein R, et al. SCCT 2021 Expert Consensus Document on Coronary Computed Tomographic Angiography: A Report of the Society of Cardiovascular Computed Tomography. J Cardiovasc Comput Tomogr. 2021;15(3):192-217.
105. Simsek C, Karanasos A, Magro M, Garcia-Garcia HM, Onuma Y, Regar E, et al. Long-term invasive follow-up of the everolimus-eluting bioresorbable vascular scaffold: five-year results of multiple invasive imaging modalities. EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology. 2016;11(9):996-1003.
106. Jinnouchi H, Torii S, Sakamoto A, Kolodgie FD, Virmani R, Finn AV. Fully bioresorbable vascular scaffolds: lessons learned and future directions. Nat Rev Cardiol. 2019;16(5):286-304.
107. Kerkmeijer LSM, Renkens MPL, Tijssen RYG, Hofma SH, van der Schaaf RJ, Arkenbout EK, et al. Long-term clinical outcomes of everolimus-eluting bioresorbable scaffolds versus everolimus-eluting stents: final five-year results of the AIDA randomised clinical trial. EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology. 2022;17(16):1340-7.
108. Erglis A, Narbute I, Sondore D, Jegere S, Kumsars I, Dombrovskis A, et al. Four-Year Outcomes of Left Main Percutaneous Coronary Intervention with a Bioresorbable Scaffold in the Circumflex Ostium. J Interv Cardiol. 2022;2022:7934868.
109. Stone GW, Biensock SW, Neumann FJ. Bioresorbable coronary scaffolds are ready for a comeback: pros and cons. EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology. 2023;19(3):199-202.
110. Wlodarczak A, Montorsi P, Torzewski J, Bennett J, Starmer G, Buck T, et al. One- and two-year clinical outcomes of treatment with resorbable magnesium scaffolds for coronary artery disease: the prospective, international, multicentre BIOSOLVE-IV registry. EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology. 2023;19(3):232-9.
111. Gao RL, Xu B, Sun Z, Guan C, Song L, Gao L, et al. First-in-human evaluation of a novel ultrathin sirolimus-eluting iron bioresorbable scaffold: 3-year outcomes of the IBS-FIM trial. EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology. 2023;19(3):222-31.

112. Willemink MJ, Persson M, Pourmorteza A, Pelc NJ, Fleischmann D. Photon-counting CT: Technical Principles and Clinical Prospects. Radiology. 2018;289(2):293-312.
113. Rajendran K, Petersilka M, Henning A, Shanblatt ER, Schmidt B, Flohr TG, et al. First Clinical Photon-counting Detector CT System: Technical Evaluation. Radiology. 2022;303(1):130-8.
114. Zhang Z, Li W, Wu W, Xie Q, Li J, Zhang W, Zhang Y. Myocardial reperfusion with tirofiban injection via aspiration catheter : Efficacy and safety in STEMI patients with large thrombus burden. Herz. 2020;45(3):280-7.
115. James S, Koul S, Andersson J, Angeras O, Bhiladvala P, Calais F, et al. Bivalirudin Versus Heparin Monotherapy in ST-Segment-Elevation Myocardial Infarction. Circulation Cardiovascular interventions. 2021;14(12):e008969.
116. Han Y, Guo J, Zheng Y, Zang H, Su X, Wang Y, et al. Bivalirudin vs heparin with or without tirofiban during primary percutaneous coronary intervention in acute myocardial infarction: the BRIGHT randomized clinical trial. JAMA. 2015;313(13):1336-46.
117. Cao M, Wang Z, Meng X, Xu Z, Gao J, Zhu W, et al. Effects of intracoronary low-dose prourokinase administration on ST-segment elevation in patients with myocardial infarction and a high thrombus burden: a randomized controlled trial. J Int Med Res. 2022;50(12):3000605221139723.
118. Bikdeli B, Erlinge D, Valgimigli M, Kastrati A, Han Y, Steg PG, et al. Bivalirudin Versus Heparin During PCI in NSTEMI: Individual Patient Data Meta-Analysis of Large Randomized Trials. Circulation. 2023;148(16):1207-19.

9. Erratum

9.1 Missing clinical event

In paper II we reported no stent related clinical events during first 12 months follow-up. When working on paper III, we discovered that one patient had an occluded scaffold at coronary angiography. The patient was asymptomatic, thus was not recorded as an event at the pre-angio clinical visit.

10. Supplementary material

10.1 Approval Regional Ethics Committee

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK vest	Arne Salbu	55978498	19.12.2013	2013/2006/REK vest
			Deres dato:	Deres referanse:
			05.11.2013	

Vår referanse må oppgis ved alle henvendelser

Erlend Eriksen
Haukeland universitetessykehus
Bergen

2013/2006 Sammenligning av resorberbar stent med stent av metall ved hjerteinfarkt

Forskningsansvarlig: Helse Bergen HF
Prosjektleder: Erlend Eriksen

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK vest) i møtet 28.11.2013. Vurderingen er gjort med hjemmel i helseforskningsloven (hfl.) § 10, jf. forskningsetikklovens § 4.

Prosjektomtale
Pasienter med akutt hjerteinfarkt med ST hevning i EKG trenger akutt behandling med revaskularisering og innsetting av stent. Studien ønsker å sammenligning av tradisjonell metallsten med resorberbar polymer-basert stent. Begge typer stenter er godkjent for bruk i klinisk praksis. Deltakerne vil være pasienter med akutt hjerteinfarkt som trenger primær perkutan koronar intervensjon. Det planlegges å inkludere 120 pasienter i alt randomisert til 60 i hver arm. Selve innsettingen av stenten følger vanlig prosedyre og er lik for begge alternativene. Tillegg som følge av deltakelse i studien: 1) Blodprøver 4, 8, 12 og 24 timer etter akuttbehandling, 2) CT etter 12 og 24 måneder, 3) Angiografi etter 12 måneder. Det søkes om opprettelse av spesifikk forskningsbiobank STEMI med ansvarshavende Erlend Eriksen.

Vurdering

Dette er en velbegrunnet studie med et klart potensiale for å kunne fremskaffe ny og viktig kunnskap. Deltagelse i studien vil imidlertid medføre noen prosedyrer (angiografi og OCT-undersøkelser) som potensielt kan medføre alvorlige komplikasjoner. Søknaden og informasjonsskrivet inneholder en god drøfting av risiko-nytte ved å delta i studien. Komiteen anser prosjektet som forsvarlig å gjennomføre og har ingen innvendinger til forskningsprotokollen.

Forskningsbiobank
Det søkes om opprettelse av spesifikk forskningsbiobank STEMI med ansvarshavende Erlend Eriksen. Imidlertid sies i forespørsel til deltakerne Kapittel B at materialet kun kan brukes etter godkjenning fra REK. Slik dette er formulert, søker man da om en generell biobank og ikke en spesifikk biobank (se helseforskningsloven § 25).

REK Vest antar at formuleringen i kapittel B er kommet til ved en inkurie og at det faktisk er en spesifikk forskningsbiobank man søker om. REK Vest legger denne forståelsen til grunn i saksbehandlingen.

REK Vest vil godkjenne oppretting av den prosjektspesifikke forskningsbiobank STEMI med Erlend

Besøksadresse: Haukeland Universitetssykehus, Sentralblokken, 2. etg, Rom 4617
Telefon: 55975000
E-post: rek-vest@uib.no
Web: http://helseforskning.etikkom.no/

Eriksen som ansvarshavende. Vi forutsetter da at opplysningene om biobanken blir korrekt forklart i forespørselen til deltakerne, herunder at materialet ikke kan benyttes i senere prosjekter.

Tidsramme
Prosjektet er planlagt å gå over syv år. Etter dette ønsker en å beholde avidentifiserte data i 10 år, for så å slette dem. Grunnkravet i helseforskningsloven § 38 er at det ikke skal forekomme unødig lagring, men for etterkontroll kan REK kreve lagring i fem år. REK Vest ser ingen grunn til å fravike dette og ber om at dataene oppbevares i fem år etter innlevert sluttrapport for etterkontroll. Da må de anonymiseres eller slettes.

Datasikkerhet
Helseopplysninger som ønskes registrert vil være direkte personidentifiserbare på personnummer. REK Vest krever at opplysningene skal lagres avidentifisert hvor opplysninger og koblingsnøkkel holdes adskilt.

Forespørsel/samtykkeerklæring
Informasjonsskrivet må revideres og tittel på prosjektet må oversettes til norsk. Videre må skrivet ta utgangspunkt i at pasienten muntlig har sagt seg villig til å delta (fått en stent) og nå skal ta stilling til om han/hun skal delta videre. Siden første samtykke ble innhentet i en nødsituasjon er det økt aktsomhet i forhold til at forsøksdeltager ikke skal føle seg presset til å delta videre i studien. Dersom forsøksdeltager ikke ønsker å delta videre - et tilbakekall av det muntlige samtykke – betyr under slike omstendigheter at det biologiske materialet destrueres, at helseopplysninger innsamlet til forskningsformål slettes og at nye opplysninger ikke samles inn. Dette bør tydeliggjøres.

Samtykkeerklæringen er mangelfull. Her må studiens tittel (på norsk) settes som overskrift sammen med REK-nummer. Innholdet i samtykket bør være: Jeg har mottatt skriftlig og muntlig informasjon om studien og sier meg villig til å delta.

Vilkår

- Helseopplysninger må oppbevares avidentifisert slik at koblingsnøkkel holdes adskilt fra opplysningene.
- Informasjonsskriv og samtykkeerklæring må rettes i samsvar med komiteens anvisninger.
- Helseopplysninger skal ikke oppbevares lengre enn det som er nødvendig for å gjennomføre prosjektet, men dokumenter som er nødvendig for etterkontroll av prosjektet, skal oppbevares i fem år etter sluttmelding er sendt REK.

Vedtak

1. *REK Vest godkjenner prosjektet på betingelse av at ovennevnte vilkår tas til følge.*
2. *REK Vest godkjenner opprettelse av den prosjektspesifikke forskningsbiobanken STEMI med Erlend Eriksen som ansvarshavende.*

Sluttmelding og søknad om prosjektendring
Prosjektleder skal sende sluttmelding til REK vest på eget skjema senest 30.06.2021, jf. hfl.
12. Prosjektleder skal sende søknad om prosjektendring til REK vest dersom det skal gjøres vesentlige endringer i forhold til de opplysninger som er gitt i søknaden, jf. hfl. § 11.

Klageadgang
Du kan klage på komiteens vedtak, jf. forvaltningslovens § 28 flg. Klagen sendes til REK vest. Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK vest, sendes klagen videre til

Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering.

Med vennlig hilsen

Ansgar Berg
Prof. Dr.med
Komiteleder

Arne Salbu
rådgiver

Kopi til: postmottak@helse-bergen.no

10.2 Patient informed consent

Forespørsel om deltakelse i forskningsprosjektet

«Sammenligning av resorberbar stent med stent av metall ved hjerteinfarkt»

Tittel på engelsk: "Performance of bioresorbarble scaffold in primary percutaneous intervention of ST-elevation myocardial infarct"

Bakgrunn og hensikt

Du har allerede etter muntlig informasjon samtykket muntlig til å delta i en forskningsstudie hvor vi undersøker en ny generasjonen medikamentavgivende stenter med resorberberbart skjelett ved akutt hjerteinfarkt. Denne sammenlignes med dagens praksis hvor man bruker en stent med skjelett av metall. Dette er en skriftlig forespørsel om det samme med utfyllende informasjon. På slutten av dokumentet er det en samtykkeerklæring med signaturfelt som må signeres før vi kan inkludere deg i studien.

Hva innebærer studien?

Du har nå blitt behandlet for et akutt hjerteinfarkt. Vi har åpnet blodåren som hadde gått tett, og som var årsaken til infarktet. Etter åpning av åren, satte vi inn en stent for at den skal holde seg åpen. Dette er den medisinsk anbefalte behandlingen. I studien sammengligner vi to typer stenter. Hvilken type stent du får blir avgjort vilkårlig, og hverken legen eller andre kan påvirke hvilken type stent du får.

I forbindelse med studien bruker vi en teknikk som heter optical coherence tomography (OCT) til å ta bilder av stenten inne i blodåren. Denne undersøkelsen ønsker vi å gjenta etter 12 mnder for å avgjøre hvilken stent som gir det beste resultatet. Dette medfører en ny hjertekateterisering.

En del av studien innebærer analyse av blodproppmateriale. Blodpropper vi henter ut fra kransåren din vil derfor bli sendt til et laboratorium i Amsterdam.

Vi ønsker også å ta en CT undersøkelse av hjertet etter 12 mnder og 36 mnder.

Vi vil også innkalle til kontroll hos en studiemedarbeider etter 12 mnder.

Deretter ønsker vi å kontakte deg telefonisk etter 2, 3 og 5 år. For ytterligere detaljer, se vedlegg kapittel A.

Mulige fordeler og ulemper

Et metallskjelett blir værende i blodåren for alltid. En absorberbar stent vil forsvinne helt etter 1-2 år. At stentskjelettet forsvinner helt har flere teoretiske fordeler som lavere risiko for sene innsnevringer i det stentede området, mulighet for fremtidig bruk av de nyere hjertebildeteknikkene CT og MR, mindre sjanse for at sidegrener med tiden går tett, samt mulighet for å sy på nye årer i det stentede området ved behov for en eventuell bypassoperasjon i fremtiden. Resorberbare stenter er noe mindre robust og mindre utprøvd.

Å delta i studien innebærer som nevnt en kontrollhjertekateterisering etter 12 måneder. Dette er ikke standardoppfølgning etter et hjerteinfarkt. Da det er en liten risiko for komplikasjoner ved alle hjertekateteriseringer, vil det å delta i studien altså medføre en viss økt komplikasjonsrisiko. De viktigste komplikasjonene ved hjertekateterisering er hjerneslag, hjerteinfarkt og større blødninger. Dette inntreffer i < 0,5% av tilfellene. Mindre blødninger på innstikkstedet er vanlig. Dette kan være plagsomt, men sjelden farlig.

CT av hjertet etter 12 og 24 mnder medfører en noe strålebelastning, men vi bruker en nye generasjon av CT maskin som gir betydelig mindre stråling enn eldre modeller.

Resultatene fra studien kan bidra til å forbedre behandlingen av akutt hjerteinfarkt generelt. Vi anser den minimalt økte risikoen for komplikasjoner som etisk forsvarlig. Studien er godkjent av regional komitè for medisinsk og helsefaglig forskningsetikk. Se kapittel A for utfyllende informasjon om nytte og risiko.

Hva skjer med prøvene og informasjonen om deg?

Blodprøvene tatt av deg oppbevares i en biobank. Disse prøvene og informasjonen som registreres om deg skal kun brukes slik som beskrevet i hensikten med studien. Alle opplysningene og prøvene vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. En kode knytter deg til dine opplysninger og prøver gjennom en navneliste. Samarbeidspartnere utenfor studiegruppen vil kun ha tilgang til avidentifisert informasjon.

Det er kun autorisert personell knyttet til prosjektet som har adgang til navnelisten og som kan finne tilbake til deg. Tidspunkt for sletting av informasjonen som lagres er 31.12.2026 .Det vil ikke være mulig å identifisere deg i resultatene av studien når disse publiseres. Se vedlegg kapittel B for ytterligere informasjon.

Frivillig deltakelse

Det er frivillig å delta i studien. Du kan når som helst og uten å oppgi noen grunn trekke ditt samtykke til å delta i studien. Dette vil ikke få konsekvenser for din videre behandling. Dersom du allerede nå trekker tilbake ditt samtykke, vil alt biologisk materiale og opplysninger om deg bli slettet. Dersom du senere ønsker å trekke deg vil vi be om din tillatelse til å beholde de data og biologisk materiale som allerede er samlet inn. Om du ikke samtykker til dette, vil data slettes og biologisk materiale destruert.
Tilbaketrekking av samtykke vil ikke ha konsekvenser for din videre behandling hos oss.
Dersom du ønsker å delta, undertegner du samtykkeerklæringen på siste side. Dersom du senere ønsker å trekke deg eller har spørsmål til studien, kan du kontakte studieansvarlige leger Erlend Eriksen eller Jon Herstad ved Hjerteavdelingen Haukeland Universitetssykehus på 55972220.

- **Ytterligere informasjon om studien finnes i kapittel A** – *utdypende forklaring av hva studien innebærer.*
- **Ytterligere informasjon om biobank, personvern og forsikring finnes i kapittel B** – *Personvern, biobank, økonomi og forsikring.*
- **Samtykkeerklæring følger etter kapittel B**

Kapittel A – utdypende forklaring av hva studien innebærer

Kriterier for deltakelse

Deltakere kan inkluderes i studien om de har et akutt hjerteinfarkt med symptomvarighet mindre enn 12 timer, er over 18 år, ikke har noen kontraindikasjoner mot dobbel platehemmende behandling (blodfortynnende) og om de har samtykket til deltakelse etter muntlig, og i etterkant skriftlig, informasjon.
Pasienter kan ikke delta i studien om de har kontraindikasjoner mot dobbel platehemmende behandling, om de har nyresykdom med GFR < 45 (nyrefunksjonsprøve), om det foreligger

hjertestans eller kardiogent sjokk (betydelig lavt blodtrykk grunnet sviktende hjertefunksjon), om det ikke er mulig å forbehandle den tette blodåren med trombesug (kateter som suger ut blodpropp), om det ikke er god nok blodstrøm i blodåren etter trombesug (TIMI 0-1), om det er en betydelig forkalket slyngete blodåre eller en stor sidegren i relasjon til fortetningen på blodåren. Om det foreligger annen alvorlig sykdom med forventet levetid under 12 måneder kan pasienter heller ikke delta i studien.

Bakgrunnsinformasjon om studien

Vi vet at det ved behandling av akutt hjerteinfarkt med tradisjonelle stenter med metallskjelett, er bedre å sette stenten direkte inn, enn å forbehandle åren med ballongblokking først. Vi vet også at den nye generasjonen medikamentavgivende stent med absorberbart skjelett er like god som den nåværende generasjonen stent med metallskjelett ved behandling av kransårer i situasjoner hvor det ikke foreligger akutt infarkt.
Det er så langt ikke studert om absorberbare stenter er like bra som stenter med metallskjelett ved akutt infarkt. Det er heller ikke studert om det like bra å sette absorberbare stenter direkte inn ved akutt infarkt, eller om det er best å forbehandle åren med ballongblokking først.
60 pasienter med akutt hjerteinfarkt (STEMI) vil bli inkludert i studien. Legen som utfører behandlingen forsikrer seg om at du oppfyller kriteriene for å delta (se kritereier for deltakelse). Om du fyller kriteriene, vil det vilkårlig ble avgjort hvilken type stent du får.

Alternative prosedyrer eller behandling pasienten får dersom personen ikke velger å delta i studien

Pasienter som ikke ønsker å delta i studien vil bli behandlet etter etablerte retningslinjer for behandling av akutt hjerteinfarkt. Som regel vil dette innebære stenting av den aktuelle blodåren med en medikamentavgivende stent med metallskjelett. Videre oppfølgning og kontrollopplegg skreddersys på vanlig måte ut fra totalsituasjonen etter hjerteinfarktet.

Undersøkelser, blodprøver og annet den inkluderte må gjennom

Under akuttbehandlingen

Etter at muntlig samtykke til deltakelse i studien er gitt, utføres en loddtrekning for å avgjøre hvilken stent vi skal bruke. Deretter gjøres en OCT (optical coherence tomography) -

undersøkelse for å fremstille innsiden av blodåren med et optisk kamera med høy oppløsning. Dette hjelper oss bl.a. med å bestemme rett størrelse på stenten. Etter stenting gjør vi en ny OCT for å vurdere resultatet og ev.t. behov for ytterligere ballongblokking (tilpassing) av stenten i blodåren. Vi tar også blodprøver for lagring i biobank i forbindelse med denne akuttbehandlingen.

Undersøkelser nær akuttbehandlingen

Nye blodprøver inkludert vanlige hjertemarkører tas 4, 8, 12 og 24 timer etter akuttbehandlingen, disse vil ikke bli lagret til senere bruk. Annen standardoppfølgning etter hjerteinfarkt (som ikke inngår i studieprotokollen) som ultralyd av hjertet og lignende, vil også gjøres ut fra vanlige retningslinjer.

Senere kontroller

Kontroll hos lege med angiografi og OCT etter 12 mnder.

Kontroll med CT etter 12 og 24 mnder.

Deretter vil alle bli kontaktet pr. telefon etter 2, 3 og 5 år for videre oppfølgning.

Studieresultater

Alle OCT-undersøkelsene (optisk høyoppløsningsfilm av blodåre og stent) vil bli nøye analysert ved et billedanalyselaboratorium ved Århus Universitetshospital, Skejby, Danmark. Vi vil ut fra dette vurdere resulatatet etter implantasjon av resorberbar i forhold til metall stent. Sammenligningen er primært basert på vurderingen av eventuelle nye innsnevringer i det stentede området, andre tegn til sviktende stentfunksjon som for eksempel brudd i stenten, samt forekomsten av eventuell ny betydelig karsykdom i oppfølgningsårene.

Mulige fordeler

Et metallskjelett blir som beskrevet værende i blodåren for alltid. En absorberbar stent vil forsvinne helt etter 1-2 år. Studier tyder på at risikoen for ny innsnevring i det stentede området er lav etter 9-12 måneder, og at det sannsynligvis ikke er nødvendig med et forsterkende skjelett som fysisk holder åren åpen lengre enn dette. Studier tyder også på at et stentskjelett med medikamentavgivende polymer (som nåtidens medikamentavgivende stenter med metallskjelett har) kan være årsak til en lavgradig, kronisk betennelsestilstand som kan gi sene innsnevringer (etter flere år) i det stentede området. At metallskjelettet blir værende i åreveggen for alltid kan også bidra til at mindre sidegrener med tiden går tett, til

at en ikke får adekvate bilder ved nyere hjertebildeteknikker som CT (computed tomography) og MRI (magnetic resonance imaging), samt at en i fremtiden ikke kan sy på nye årer i det stentede området ved et eventuelt behov for en bypassoperasjon.
En kontrollhjertekateterisering etter 12 måneder er ikke et ledd i standardoppfølgning etter et hjerteinfarkt, og potensielle ulemper beskrives nedenfor. Potensielle fordeler med dette er at vi får sjekket resultatet etter akuttbehandlingen, og ev.t. kan fange opp annen kransåresykdom i utvikling. Samme argument gjelder også for studiekontrollopplegget etter 6 og 12 måneder, samt 2, 3 og 5 år. Ved å delta i studien kan du bidra med å forbedre behandlingen av akutt hjerteinfarkt på verdensbasis.

Mulige bivirkninger/ubehag/ulemper

Å delta i studien innebærer altså en kontrollhjertekateterisering etter 12 måneder. Dette er ikke standardoppfølgning. Da det er en liten risiko for komplikasjoner ved alle hjertekateteriseringer, vil det å delta i studien altså medføre en viss økt komplikasjonsrisiko. Hovedkomplikasjonen ved hjertekateterisering er blødning ved stikkstedet (håndledd eller lyske). Mer alvorlige komplikasjoner er svært sjeldne. I et materiale basert på 59792 pasienter er forekomsten av alvorlige komplikasjoner ved hjertekateterisering som følgende: død 0,11 %; hjerteinfarkt 0,05 %; hjerneslag/»drypp» 0,07 %; hjerterytmeforstyrrelse 0,38 %; karskade 0,43 %; allergisk reaksjon på røntgenkontrast 0,37 %; sirkulasjonsforstyrrelse 0,26 %; perforasjon av hjertekammer 0,28 %; andre komplikasjoner 0,28 %. Totalforekomst av alvorlige komplikasjoner blir til sammen 1,70 %. Samtidig er det vist at risikoen for komplikasjoner betydelig lavere i en planlagt og velkontrollert situasjon, enn ved behov for akutt hjertekateteriserinig i en mer ukontrollert situasjon.
En ekstra hjertekateterisering vil også medføre økt total stråledose. Vi anser denne tilleggsrisikoen for liten. Estimert risiko for utvikling av en dødelig kreftsykdom grunnet strålingen ved en hjertekateterisering er ca. 0,5 ‰. Til sammenligning har vi amerikanske tall for annen estimert livstidsrisiko for død: naturlig utviklet dødelig kreft 212 ‰; radongass-utløst dødelig kreft 3 -21 ‰; bilulykke 11,9 ‰; fotgjengerulykke 1,6 ‰; drukning 0,9 ‰; sykkelulykke 0,2 ‰; lynnedslag 0,013 ‰.
OCT-undersøkelser medfører bruk av 15-20 ml ekstra røntgenkontrast, dette er en liten dose og gir ikke økt risiko for nyreskade så lenge nyrefunksjonen i utgangspunktet er relativt normal med GFR > 45. OCT medfører at vi må ut i den aktuelle blodåren med en wire, dette

gir en teoretisk økt risiko for å skade blodåren, men studier har ikke vist sikkert økt forekomst av betydningsfulle blodårekomplikasjoner ved slike undersøkelser. OCT medfører at hjertekateteriseringen vil vare 10-20 minutter lengre.
Da absorberbare stenter ikke har et skjelett av metall (men en biologisk nedbrytbar polymer) er det en teoretisk økt risiko for skade av stenten sammenlignet med stenter med metallskjelett (som vi vet tåler relativt mye mekanisk manipulasjon). Tradisjonelt har en derfor argumentert for at blodårer bør forbehandles med ballongblokking før en setter inn en absorberbar stent. Dette er ikke vitenskapelig undersøkt, og er noe av det vi ønsker å studere i denne studien.
Vi anser at den økte risikoen for komplikasjoner er etisk forsvarlig. Studien er godkjent av regional komitè for medisinsk og helsefaglig forskningsetikk.

Pasientens/studiedeltakers ansvar
Full deltakelse inkludert oppmøte til alle kontroller er avgjørende for studiens kvalitet.

Informasjonsplikt
Studiedeltakeren vil bli orientert så raskt som mulig dersom ny informasjon blir tilgjengelig som kan påvirke deltakers villighet til å delta i studien. Studiedeltakeren vil opplyses om beslutninger og situasjoner som gjør at deres deltakelse i studien kan bli avsluttet tidligere enn planlagt.

Eventuell kompensasjon til og dekning av utgifter for deltakere
Du vil ikke ha utgifter eller inntekter i forbindelse med denne studien.

Kapittel B – Personvern, biobank, økonomi og forsikring

Personvern
Opplysninger som registreres om deg er blant annet alder, risikofaktorer for hjertesykdom (høyt blodtrykk, diabetes, familiær opphopning av hjertesykdom, høyt kolesterol, røyk, vekt, mosjon), eventuelle tidligere sykdommer, resultater av aktuelle undersøkelser i akuttforløpet som evaluering av hjertets pumpeevne ved ultralyd, hjertemarkører i blod, blodprosent, nyrefunksjonsprøver og lignende. I tillegg vil vi nøye registrere alle data fra

OCT-undersøkelsene (optisk filming av innsiden av blodåren og implantert stent med høyoppløsningskamera), da det er statistisk analyse av disse dataene som er hovedmålet med studien. Det er ikke planlagt noen personidentifiserende koblinger opp mot andre registre eller institusjoner. Blodprøver som bli oppbevart i en biobank vil kun bli brukt til formålet beskrevet i denne studien.
Som beskrevet tidligere skal prøvene tatt av deg og informasjonen som registreres om deg kun brukes som beskrevet i studieprotokollen. Alle opplysningene og prøvene vil bli behandlet anonymisert. Det er kun autorisert personell knyttet til prosjektet som har adgang til navnelisten og som kan finne tilbake til deg via bruk av kode. Tidspunkt for sletting av informasjonen som lagres er som nevnt 30.12.2026. Alt biologisk materiale vil også bli destruert på dette tidspunkt. Det vil ikke være mulig å identifisere deg i resultatene av studien når disse publiseres.
Data kan bli inspisert av representanter fra offentlige instanser som kontrollerer forskningsvirksomhet, men da i anonymisert form og i samråd med studiepersonell. Formålet er da å kontrollere at studieopplysningene stemmer overens med tilsvarende opplysninger i din journal. Alle som får innsyn har taushetsplikt.
Fastlegen din informeres om at du deltar i studien.
Helse-Bergen, hjerteavdelingen ved administrerende direktør Kjell Vikenes er databehandlingsansvarlig.

Biobank

Blodprøvene som blir tatt i forbindelse med studien vil bli lagret i en forskningsbiobank ved Haukeland Universitetssykehus. Hvis du sier ja til å delta i studien, gir du også samtykke til at det biologiske materialet og analyseresultater inngår i biobanken. Erlend Eriksen er ansvarshavende for forskningsbiobanken. Det biologiske materialet kan bare brukes til formålet som et beskrevet i dette skrivet. Regional komité for medisinsk og helsefaglig forskningsetikk (REK) har godkjent oppretting av biobank.

Utlevering av materiale og opplysninger til andre

Hvis du sier ja til å delta i studien, gir du også ditt samtykke til at alle OCT-bildene vil bli nøye analysert ved et uavhengig billedlaboratorium ved Århus Universitetshospital, Skejby,

Danmark. Før overføring av bildene til Skejby vil alle pasientopplysninger bli fjernet og bildene vil bli anonymisert og kodet.

Rett til innsyn og sletting av opplysninger om deg og sletting av prøver

Hvis du sier ja til å delta i studien, har du rett til å få innsyn i hvilke opplysninger som er registrert om deg. Du har videre rett til å få korrigert eventuelle feil i de opplysningene vi har registrert. Dersom du trekker deg fra studien, kan du kreve å få slettet innsamlede prøver og opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner.

Økonomi og firmaet St Judes rolle

Studien og biobanken får forskningsmidler fra ST Jude. For øvrig finansiert av Hjerteavdelingen Haukeland Universitetssykehus i sin helhet. .

Forsikring

Alle pasienter er forsikret via norsk pasientskadeerstatning.

Informasjon om utfallet av studien

Deltakere har rett på å bli informert om utfallet/resultatet av studien.

Samtykkeerklæring for studien:

Sammenligning av resorberbar stent med stent av metall ved hjerteinfarkt.

MedRek: 2013/2006

Samtykke til deltakelse i studien

Jeg har mottat skriftlig og muntlig informasjon om studien og sier meg villig til å delta:

Navn:	Signatur:	Dato (dag/måned/år):

Jeg samtykker i at biologisk materiale (blodprøve) oppbevares i en biobank:

Navn:	Signatur:	Dato (dag/måned/år):

Jeg bekrefter å ha gitt informasjon om studien

Navn og rolle i studien:	Signatur:	Dato (dag/måned/år):

Pasient eksemplar

Samtykkeerklæring for studien:

Sammenligning av resorberbar stent med stent av metall ved hjerteinfarkt.

MedRek: 2013/2006

Samtykke til deltakelse i studien

Jeg har mottat skriftlig og muntlig informasjon om studien og sier meg villig til å delta:

Navn:	Signatur:	Dato (dag/måned/år):

Jeg samtykker i at biologisk materiale (blodprøve) oppbevares i en biobank:

Navn:	Signatur:	Dato (dag/måned/år):

Jeg bekrefter å ha gitt informasjon om studien

Navn og rolle i studien:	Signatur:	Dato (dag/måned/år):

Studieeksemplar

10.3 CSHI definition

Coronary Stent Healing Index (CSHI) definition:

1) **Uncovered struts:**
   2% =1 – 5% =2 – 10% =3 - 15% =4 – 20% =5 – 25% =6 – 30% =7 – 35% =8 – 40% =9

2) **Uncovered struts in fornt of side branch on acquired or persistent malapposed struts.**
   10% =1 – 20% =2 – 30% =3 etc… til 100%=10
3) **Persistent malapposition: ≥2 adjacent struts length of at least:**
   1 mm =1 ; ≥2mm=3 ; ≥3 mm = 3
4) **Acquired malapposition:**
   ≥2 adjacent struts of at least 1 mm length =2 ; ≥2mm=4 ; ≥3 mm = 6
5) **Neointimal thickness in one frame**
   >200 =1 - >300 =2 - >400 =3 or diameter stenosis >50% =4 - > 75% =5
6) **Cumulated extra stent lumen increase in match cross sectional analysis:**
   (average area measurement): ≥0.2mm2 =1 ; ≥0.4 mm2 = 2; ≥0.6mm2=3 ; ≥0.8 mm2 = 4 ; ≥1.0 mm2=5 ; ≥1.2 mm2 = 6

Results for individual components of CSHI:

The cumulated results of CSHI at 12-month follow-up are: for the BRS group, the median score was 3 (IQR = [2;3]) and for the DES group, the score was 3 (IQR = [3;5]) ($p < 0.01$). Each component of the CSHI was analyzed separately and presented in figure X. Median score for uncovered jailing struts was 0 (IQR = [0;0]) and 0 (IQR = [0;2]) for the BRS and DES group, respectively ($p = 0.04$). Median score for maximum neointimal thickness was 3 (IQR = [1;0]) and 3 (IQR = [0;0]) for the BRS and DES group, respectively ($p = 0.01$). No differences were found between the treatment groups regarding uncovered struts, persistent and acquired malapposition, and extra-stent lumen enlargement.

PLOS ONE

RESEARCH ARTICLE

Thrombus characteristics evaluated by acute optical coherence tomography in ST elevation myocardial Infarction

Erlend Eriksen[1,2]*, Jon Herstad[1], Kartika Ratna Pertiwi[3¤], Vegard Tuseth[1,2], Jan Erik Nordrehaug[2], Øyvind Bleie[1☯], Allard C. van der Wal[3☯]

1 Department of Heart Disease, Haukeland University Hospital, Bergen, Norway, **2** Department of Clinical Science, University of Bergen, Bergen, Norway, **3** Department of Pathology, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands

☯ These authors contributed equally to this work.
¤ Current address: Department of Biology Education, Faculty of Mathematics and Natural Science, Yogyakarta State University, Yogyakarta, Indonesia
* eeer@helse-bergen.no

OPEN ACCESS

Citation: Eriksen E, Herstad J, Pertiwi KR, Tuseth V, Nordrehaug JE, Bleie Ø, et al. (2022) Thrombus characteristics evaluated by acute optical coherence tomography in ST elevation myocardial Infarction. PLoS ONE 17(4): e0266634. https://doi.org/10.1371/journal.pone.0266634

Editor: R. Jay Widmer, Baylor Scott and White, Texas A&M College of Medicine, UNITED STATES

Received: November 17, 2021

Accepted: March 23, 2022

Published: April 11, 2022

Peer Review History: PLOS recognizes the benefits of transparency in the peer review process; therefore, we enable the publication of all of the content of peer review and author responses alongside final, published articles. The editorial history of this article is available here: https://doi.org/10.1371/journal.pone.0266634

Data Availability Statement: Minimal data set has been uploaded as Supporting Information

Funding: The author(s) received no specific funding for this work.

Abstract

Aims

ST elevation myocardial infarction (STEMI) is caused by an occlusive thrombosis of a coronary artery. We wanted to assess if the thrombus can be characterized according to erythrocyte content and age using intravascular optical coherence tomography (OCT) in a clinical setting.

Methods and results

We performed manual thrombus aspiration in 66 STEMI patients. OCT was done of the thrombus remnants after aspiration. A light intensity ratio was measured through the thrombus. Forty two of the aspirates had thrombus which could be analyzed histomorphologically for analysis of erythrocyte and platelet content, and to determine the age of thrombus as fresh, lytic or organized. There were 11 red, 21 white and 10 mixed thrombi. Furthermore, 36 aspirates had elements of fresh, 7 of lytic and 8 of organized thrombi. There was no correlation between colour and age. OCT appearance could not predict erythrocyte or platelet content. The light intensity ratios were not significantly different in fresh, lytic or organized thrombi.

Conclusion

OCT could not differentiate between red and white thrombi, nor determine thrombus age.

Introduction

ST-elevation myocardial infarction (STEMI) is a life-threatening situation with mortality of about 10% even after successful primary percutaneous coronary intervention (PPCI) [1]. Time

Competing interests: The authors have declared that no competing interests exist.

Abbreviations: STEMI, ST elevation Myocardial Infarction; OCT, Optical Coherence Tomography; PPCI, Primary Percutaneous Coronary Intervention; PCI, Percutaneous Coronary Intervention; DAPT, Dual Antiplatelet therapy; GFR, Glomerulus Filtration Rate; ROI, Region of Interest; HE, Hematoxylin and Eosin; EvG, Elastic van Gieson; SMA, Smooth Muscle Actin; SMC, Smooth Muscle Cells; CD, Cluster of Differentiation; NET, Neutrophil Extracellular Trap; MMP, Matrix Metallo Proteinase; HT, Hypertension; DM, Diabetes Mellitus; BP, Blood Pressure; IVUS, Intravascular Ultrasound; AMC, Academisch Medisch Centrum; LAD, Left Anterior Descending artery; RCA, Right Coronary Artery; CX, Circumflex artery; GpIIb/IIIa, Glycoprotein receptor IIb/IIIa.

from onset to revascularization is an important prognostic factor. The underlying cause of the coronary occlusion is often a ruptured lipid rich plaque, leading to thrombus formation and coronary occlusion. In PPCI coronary flow is restored mechanically, and the plaque rupture is sealed with a stent [2, 3].

Identifying the age of the thrombus in real time, could potentially highlight the mechanism of disease, impact treatment and improve outcome.

Previous intracoronary studies have shown that an acute STEMI is often preceded by a longer period of thrombus formation and lysis. More than 50% of the thrombi showed evidence of age $>$ 1 day, with 9% showing evidence of being $>$ 5 days old. Thrombus age of $>$ 1 day predicts worse outcome [4, 5]. The mechanisms have not been evaluated.

A previous post mortem ex vivo study has demonstrated that thrombus colour, a macroscopic evaluation of erythrocyte content, can be predicted by Optical Coherence Tomography (OCT). The study compared the macroscopic colour of thrombi with the OCT image in a standardized ex vivo model [6, 7].

Our study is a substudy of "Perfomance of Bioresorbable Scaffold in Primary Percutaneous Intervention of ST Elevation Myocardial Infarction". Manuscript of this study has been submitted. We wanted to assess if OCT can predict the erythrocyte content and age of thrombi aspirated from STEMI patient.

Methods

Aim of study

The primary endpoint was the loss of backscattered light through the coronary thrombi measured as a light intensity ratio by OCT. This enable us to differentiate between erythrocyte rich thrombi (red) and platelet rich thrombi (white) [7]. The relative distribution of thrombocytes, erythrocytes and fibrin changes with ischemic time [8]. We therefore hypothesize that OCT can differentiate between fresh, lytic and organized thrombi. This could have prognostic and treatment relevance.

Patient selection

All patients >18 years presenting for PPCI with STEMI were eligible for inclusion. Important exclusion criteria were contraindications to long-term dual antiplatelet therapy (DAPT), known renal failure (Glomerulus filtration rate (GFR) $<$ 45), cardiac arrest or persistent cardiogenic shock. Procedural contraindications were severely calcified or tortuous vessel, large side branch ($\geq$2.5 mm) at culprit lesion or unable to advance aspiration catheter past the occlusion. The study was conducted in accordance with the protocol, applicable regulatory requirements and the ethical principles of the Declaration of Helsinki as adopted by the 18th World Medical Assembly in Helsinki, Finland in 1964 and subsequent versions. The study was approved by the Regional Ethics Committee of Norway, Region West (2013/2006) and registered at www.clinicaltrials.gov (NCT02067091). All patients signed a written informed consent.

Collection of thrombus

After identifying culprit lesion in a coronary artery by angiography, collection of thrombus was performed with a manual aspiration catheter (Export advance©, Medtronic, Minnesota, USA) passed through the lesion. The aspirate was filtered through a 40 micron filter basket and fixated in 4% buffered formalin for at least 24 hours before shipment. Further investigation of the thrombus was done at the Department of Pathology laboratory, Academisch Medisch Centrum (AMC), University of Amsterdam, The Netherlands.

Imaging

Ilumien Optis© (Abbott, Illinois, USA) OCT system was used. The Dragonfly© (Abbott, Illinois, USA) catheter was introduced into the culprit vessel after restoring flow with thrombus aspiration catheter. Further balloon dilatation before imaging was discouraged, but sometimes necessary to achieve images. Images were taken in high-resolution with pullback speed of 20 mm/s, using automatic trigger for the first run (automatic injection speed 4 ml/s, max 18 ml). If more runs were needed, adjustments were made at operators discretion. Thrombi were identified in the stored recordings in co-operation with the OCT core lab at Aarhus University Hospital, Skejby, Denmark.

OCT Ilumien Optis software

The OCT images were analyzed using Ilumien Optis© software. Manual calibration was performed. Thrombus was defined as irregular intraluminar structure visible over several consecutive images. An area of definite thrombus $>$ 0,25 mm in depth was identified in the pre percutaneous coronary intervention (PCI) images. If this was missing or of poor quality, post PCI images were scrutinized for thrombus remnants. If more than one area of thrombus were identified, the one with least backscattering (i.e. most "red" looking) was selected. Images were analyzed using 2x zoom. Thrombus not immediately adjacent to the catheter was preferred. The 0 mm region of interest (ROI) was marked at the luminal edge. A 0,25 mm marker was measured in an axial direction from center. The 0,25 mm ROI was then marked immediately distal to the 0,25 mm mark. A ratio of light intensity loss through the thrombus was then calculated. Two investigators at Haukeland University Hospital performed the measurements individually.

OCT ImageJ software

Raw data from the OCT recording was exported to an off-line station with ImageJ© (National Institute of Health and the Laboratory for Optical and Computational Instrumentation, Wisconsin, USA) software. The image stack was converted to 8-bit, otherwise no manipulation was done. As thrombus cannot be intuitively distinguished in Image J, the identical frame used to measure intensity by Ilumien Optis software was used with the corresponding thrombus structure. The Image was calibrated using the OCT catheteter circumference. Intensity was measured using 1) a small rectangular ROI (Region of interest), 2) a large rectangular ROI, and 3) a freehand representative ROI. Luminal (0 mm) ROI was placed as close to the luminal edge as possible. A distance of 0.25 mm in a straight line from center of catheter was measured for the distal (0.25 mm) ROI. A ratio of lightloss through the thrombus was then calculated based on these measurements.

Histology

Formalin-fixed aspirates were embedded in paraffin, cut in 5 μm sections and stained with Haematoxylin and Eosin (HE) and elastic van Gieson (EvG) stains, respectively, for conventional histomorphological evaluation. The adjacent sections were used for immunohistochemical staining with anti-α smooth muscle actin (SMA, clone 1A4, Dako, GLostrup, Denmark) and anti-CD31 for smooth muscle cells (SMC) and endothelial cells, respectively, to visualize the organization of thrombus.

Analysis of tissue sections

Sample size of aspirated materials were measured morphometrically on the total tissue area of HE-stained sections in mm^2. For histological composition, the presence of thrombus material, plaque material (such as lipid rich debris and/ or foam cells) or both in each aspirate were

recorded. For thrombus composition, we discriminated between red thrombus part (erythrocyte rich in combination with fibrin and/or granulocytes) and white thrombus part (platelet aggregates in combination with fibrin and/or granulocytes). A 'red thrombus' was defined as erythrocyte content of $\geq$ 70%, a 'white thrombus' was defined as platelet content of $\geq$ 70%, and a 'mixed thrombus' was defined as both erythrocyte and platelet content $<$ 70%. Thrombus age was determined analytically according to previously published definitions of thrombus age [5] as:1) fresh (up to 1day), composed of layered patterns of morphologically intact platelets, fibrin, erythrocytes and granulocytes; 2) lytic thrombus (1–5 days), characterized by areas of colliquation (lytic) necrosis and/or karyorrhexis granulocytes; and 3) organized thrombus ($>$ 5 days), marked by an ingrowth of SMCs, with or without depositions of connective tissue and capillary vessel ingrowth.

Statistical analysis

IBM SPSS 24© (IBM, New York, USA) was used for all calculations. Chi Square test was used for comparing thrombus age and colour. For comparison of ratios by measured by different software, we used Pearson's correlations coefficient. For comparing intensity in different colour thrombus, we used One-Way ANOVA. For comparing fresh, lytic and organized elements, we used independent sample T-test. Linear regression was used for predicting erythrocyte and platelet content. For ischemic time we used a two tailed non-parametric test to compare means.

Interobserver variability

The two investigators were in full agreement on the categorical variable red or white thrombus using a ratio of 0.5 as cut off value.

Results

Thrombus colour and age

66 patients (Table 1) were included in the study, of which 52 had successful aspirates of thrombus which were analyzed histologically. During image analysis, definite thrombus was found in 65 patients, but only 42 matched pairs were available in which thrombus could be analyzed by both histology and imaging (Fig 1). Of these, 36 had elements of fresh thrombi, 7 had elements of lytic stage and 8 had elements of an organized thrombus. Looking at erythrocyte and platelet content, 11 were classified as red, 21 as white and 10 as mixed. Out of the fresh thrombi 16 (44%) were classified as white and 10 (28%) as red (p = 0.27), of the lytic thrombi 2 (29%) were classified as white and 3 (43%) were classified as red (p = 0.46) and of the organized thrombi 5 (63%) was classified as white and 2 (25%) were classified as red (p = 0.62).

Ischemic time

Ischemic time, defined as time from debut to reperfusion, was 200 (±28) min for white, 188 (±27) min for mixed and 167 (±21) min for red thrombi (p = 0.66). Thrombi characterized as fresh had shorter ischemic time than not-fresh; 179 (±14) min vs 249 (±79) min (p = 0.39).

Intensity ratio by Illumien Optis and ImageJ software

Measured intensity ratio by small ROI (N = 65) and freehand ROI (N = 66) by Image J were highly correlated (0.91, p <0,0001) and slightly less with large ROI (N = 43) (0.80, p <0.0001). Intensity ratio measured by Ilumien Optis software was weakly correlated to ImageJ small ROI measurements (0.40; p = 0.001). Further statistics were therefore performed with both Ilumien Optis measurements and small ROI ImageJ measurements (Fig 2).

Table 1.

Table (N = 66)			
Age mean(SD)		years	61(10.5)
Sex (female)		%	26
Body Mass Index mean(SD)		kg/m^2	28.2(6.4)
Hypertension		%	29
Diabetes Mellitus		%	8
Statin use		%	19
Smoking		%	42
Previous PCI		%	2
BP systolic mean(SD)		mmHg	142(25)
BP diastolic mean(SD)		mmHg	87(19)
Ischemic time mean(SD)		min	194(109)
Procedure time mean(SD)		min	59(24)
X-ray contrast volume mean(SD)		ml	182(58)
Acetylisalicylic acid		%	100
Ticagrelor		%	48.5
Clopidrogel			51.5
GpIIb/IIIa inhibitor		%	68
Culprit vessel	LAD	%	41
	RCA	%	42
	CX	%	14
	Other	%	3
OCT runs (SD)			1.3(0.7)

SD = Standard deviation, PCI = Percutaneous Coronary Intervention, BP = Blood Pressure, GPIIb/IIIa = Glycoprotein receptor IIb/IIIa, LAD = Left Anterior Descending artery, RCA = Right Coronary Artery, CX = Circumflex artery

https://doi.org/10.1371/journal.pone.0266634.t001

Erythrocyte content

The histological categories red, white and mixed thrombus showed no correlation with intensity measurements by Ilumien Optis (p = 0.41) or ImageJ Small ROI (p = 0,48) by One-Way ANOVA. Intensity ratio could not predict the content of erythrocytes (Standardized Beta -0.014, p = 0.93) or platelets (Beta 0.002, p = 0.99) (Ilumien) (Fig 3).

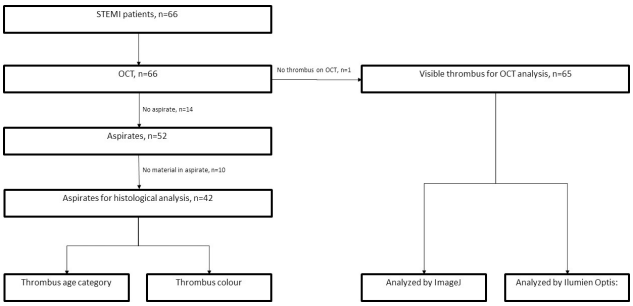


Fig 1. Flowchart.

https://doi.org/10.1371/journal.pone.0266634.g001

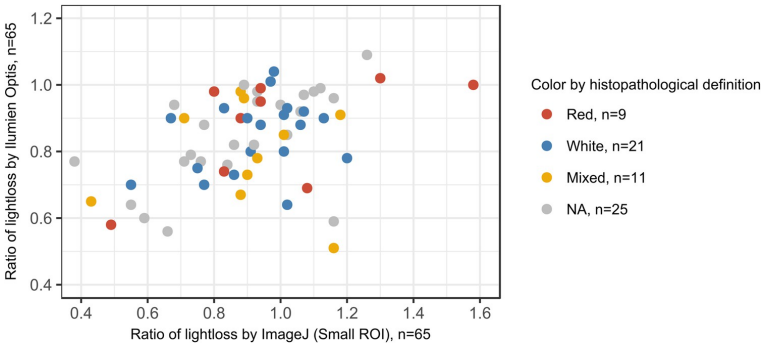


Fig 2. Comparison between ratio of lightloss measured by Ilumien Optis and ImageJ softwares with correlation 0,40 (p = 0,0001).

https://doi.org/10.1371/journal.pone.0266634.g002

Thrombus age was analyzed by independent sample T-Test, and there were no significant difference in intensity between fresh and non-fresh by Ilumien (p = 0.97) or ImageJ (p = 0.49), between organized and non-organized by Ilumien (p = 0.72) and ImageJ (p = 0.72) or lytic and non-lytic by Ilumien (p = 0.31) and ImageJ (p = 0.63) (Fig 4).

Discussion

We did not find any correlation between intensity ratio measured by OCT and thrombus content of red blood cells or platelets. The variances in colour between the different histological stages were not significant. Furthermore, OCT could not distinguish between the different

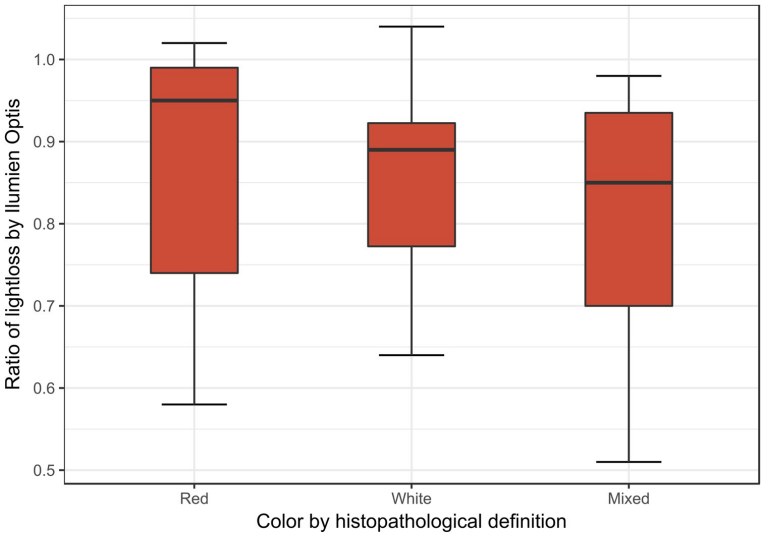


Fig 3. Ratio of lightloss by Ilumien Optis software in the different histopathological defined colours.

https://doi.org/10.1371/journal.pone.0266634.g003

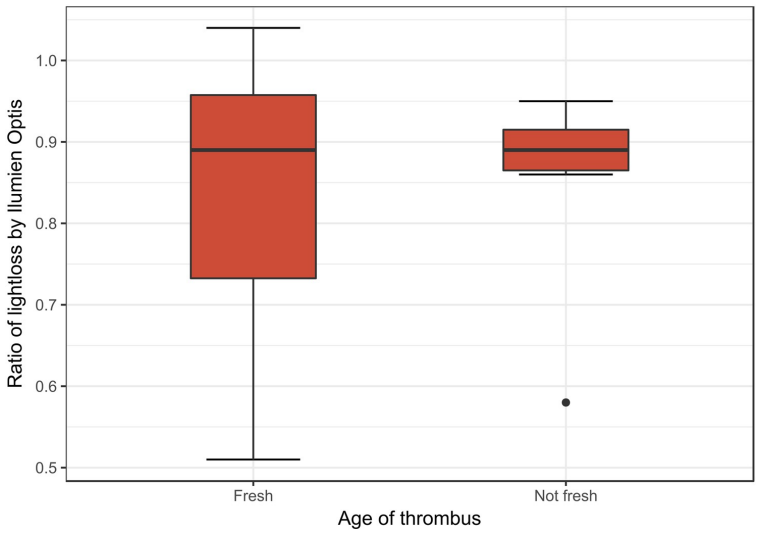


Fig 4. Ratio of lightloss by Ilumien Optis software in thrombi defined by histopathological appearance.

https://doi.org/10.1371/journal.pone.0266634.g004

histologically defined thrombus stages: fresh, lytic or organized. Fresh thrombi tended to have a shorter ischemic time, though not significant. Paradoxically, ischemic time was shortest for red thrombi. This difference was also not significant.

Our findings contradicts previous workers reporting that red and white thrombi have different appearance on OCT images [6]. The presence of larger thrombi can be established with a conventional coronary angiogram. Using intra vascular ultrasound (IVUS), even smaller volumes of thrombi can be detected. However, only OCT gives images with sufficiently high resolution to potentially evaluate the content of each individual thrombus [9].

OCT uses infrared light and measure the echo time delay from nearby structures giving a distance, and signal intensity, which reveals the optical properties of the structures. During acquisition, the catheter spins around collecting data in a circular or tomographic pattern. This means that structures that are behind objects impenetrable to infrared light will not be visible. Red blood cells are impenetrable to light, meaning that blood must be cleared from the lumen by injecting contrast. Thrombi containing a high proportion of red blood cells will be less penetrable to light than those with less red blood cells. Kume et al [7] used this principle to show that in a macroscopic red thrombus the light intensity decreased more rapidly than in a macroscopic white thrombus with increasing distance from the catheter. A cut of value of $>$ 50% intensity loss over a distance of 0.25 mm was found to correlate with a macroscopic red thrombus with a sensitivity of 90% and specificity of 88%. Our study has a different design than Kume et al. We characterized thrombus composition by histology. In our view, histological examination is a more direct way to determine thrombus composition. Kume et al studied the exact same thrombus sample by OCT and histology, however their OCT study was performed ex vivo on 40 human cadavers and compared to histologic examination post mortem. In our clinical study, OCT was performed in vivo and we compared thrombus remnants in the patient with the histology of aspirated materials. The age and composition of the abluminal parts of the thrombi left behind after aspiration could potentially be more white and platelet

rich, and the luminal aspirated part more red and erythrocyte/fibrin rich. As 36 out of 42 aspirates contained elements of fresh thrombus and 21 out of 42 where classified as white, we at least know that the luminal parts of the thrombus are mostly fresh and to a large extent white. The remnants were only studied by imaging, and were as defined by OCT exclusively red. If the first formed abluminal part of the thrombi matures after it is formed, this would explain that the remnants are all red, and could explain the discrepancy with the ex vivo study. However, it seems unlikely as Silvain et al showed that fibrin content increases with ischemic time in aspirated thrombi [8]. Previous aspiration studies have also shown that the formation of thrombus is more complex with a layered appearance, rather than a continuous gradient of platelet rich to erythrocyte/fibrin rich gradient from the vessel wall to the lumen [5].

OCT has important limitations. Because data are collected in a tomographic pattern, the amount of echoed information will greatly decrease as the distance from the light source increases. This means that the backscattered data from structures close to the catheter will produce more detailed pictures than those further away. The ratio between two fixed points will also be influenced. The Optis Ilumien software compensates for this with by using an algorithm to fill in the missing information [10]. The data are also logarithmically transformed. Although we sought to evaluate if this on-line system could be used clinically, we also analyzed the raw data using the off-line system ImageJ. Kume et al used NIH Image© (National Institute of Health, Wisconsin, USA), a previous version of ImageJ. Choosing size of ROI poses a challenge using ImageJ software. A fixed sample size will cover a much larger anatomical structure further away from the catheter than close to it. The dilemma is therefore whether to include the same number of pixels or an anatomical area of the same size. Structures close to the catheter will appear more compressed (Figs 5 and 6), making it more difficult to identify anatomical structures. Also, a large geometrical ROI, such as a large rectangle, will not fit the irregular structure of a thrombus. We therefore chose to identify thrombi with Ilumien Optis and use the same frame for measurements with ImageJ. We used three different ROIs; two different sizes of fixed rectangular ROI, and one freehand ROI to trace the irregular surface of the

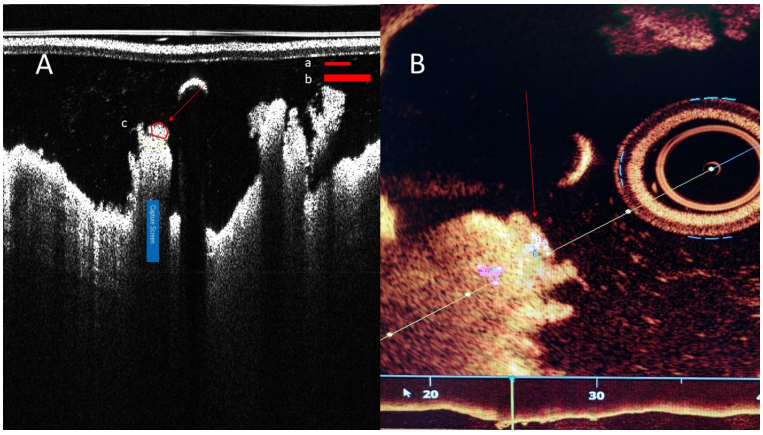


Fig 5. The same thrombus (arrow) as it appears on ImageJ (A) and Ilumien Optis (B) softwares. Thrombus protruding towards catheter appears compressed in ImageJ (A). Size of ROI (Region of Interest) showed in red figures (a = small ROI, b = large ROI, c = freehand ROI). Ratio of lightloss in these images was 1.02 by ImageJ and 0.64 by Ilumien Optis. Diameter of catheter is 0.914 microns.

https://doi.org/10.1371/journal.pone.0266634.g005

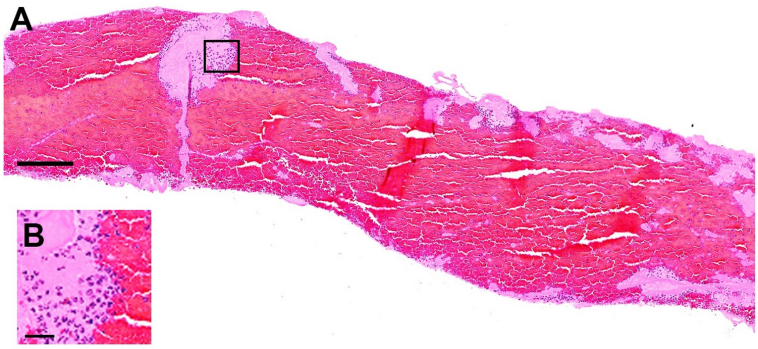


Fig 6. Representative image of fresh thrombus, classified as a red thrombus (in this case 80% of erythrocytes) in HE staining (A), red area represents erythrocytes; Inset: a higher magnification image (B) showing the interface of small area of platelet aggregates (pale pink staining) with red blood cells and granulocytes (dark purple nucleated cells). Images are from the same patient as Fig 5. Bar scale in A: 200 μm and in B: 25 μm.

https://doi.org/10.1371/journal.pone.0266634.g006

thrombus. The size of small rectangular ROI was chosen so that all images could be analyzed. Using large rectangular ROI, 23 out of 66 images could not be analyzed. All the three different ROIs were highly correlated, so we compared only the fixed small rectangular ROI with measurements from Ilumien Optis.

Our histopathological analysis used a set-up validated by other thrombus aspirations studies at AMC [4, 5]. Rudolf Virchow (1821–1902) first described the mechanism of thrombus formation (150 years ago), which became later known as "Virchow Triad". He divided thrombi into two types: arterial (white) thrombi consisting of platelet aggregates and venous (red thrombi) consisting of mainly red blood cells and fibrin. His theory was that arterial thrombi first forms through activation of platelets, and thus platelet aggregation, leading to stasis and fibrin formation with trapping of erythrocytes transforming the thrombus to red in colour over time. This would mean that red thrombi tend to be older than white thrombi. The timespan in which red thrombus is formed is obviously highly variable, because it depends on diverse factors that evoke significant stasis of blood at the site of the culprit vessel. This theory is supported by modern evidence. Ischemic time is positively correlated with fibrin content, and negatively with platelet content [8, 11]. From clinical experience we know that thrombi behaves very differently in the individual STEMI patient. Problems with high thrombus burden, distal embolization and no-flow situations are well known. If the age and content of a thrombus could be determined peroperatively, this could give the operator a better understanding of the thrombus at hand.

The age of a thrombus can be classified reliably according to standardized histopathological appearance of tissue decay followed by repair in the aspired materials. The presence of older age thrombus has been showed to correlate to higher mortality [5, 12]. The mechanism is uncertain. A longer period of thrombus formation and lysis could result in a prolonged period of ischaemic myocardial damage. A process of clotting and lysis could result in more distal embolization, which would compromise the microvascular bed of the myocardium. The increased mortality could also be a result of patient confounding factors, such as sensitivity to chest pain and at what urgency the patients seeks medical help. We know presently that the formation and fate of thrombi are much more complex than Virchow's theory. Smooth muscle cells and neutrophil granulocytes play a specific and complex role, with expression of cytokines

such as matrix metalloproteinase (MMP) and creating neutrophil extracellular traps (NETs). The expression of MMPs and the amount of NETs varies with thrombus age [12–14]. As well as promoting thrombogenicity, this could also affect the healing of the implanted stent [15–19]. Finding an optimal treatment strategy is therefore more complex than what we can hope to visualize with intracoronary imaging alone.

Patient selection and generalizability of results

We chose to study thrombi from STEMI patients. This is a relatively homogenous group presenting with similar clinical picture and with a clear ECG indication for intervention. In most cases the presence of coronary thrombi can be assumed, and thrombus aspiration was, at the time of submitting the protocol, routine practice [20]. Our cohort represents a selection of STEMI patients. Patients with complex lesions, tortuous anatomy and heavy calcifications were excluded. Our findings cannot be generalized without some considerations. However, the selection was done in order to be able to aspirate thrombus and to get the best quality OCT images. We do believe that including all STEMI patients would cloud the data with poorer quality of OCT images and fewer thrombi aspirated. It is also an investigation of methodology, transferring findings in a standardized laboratory setting to an acute clinical scenario.

Aspiration method

Our method for thrombus aspiration was using an off the shelf aspiration catheter. Export Advance catheter was chosen as this comes with a 40 micron filter basket. Other methods for extracting thrombus and for intracoronary imaging such as larger mother-and-child catheter or angioscopy are not feasible in this population due to the acute setting.

Medication

All patients received loading dose of acetylic salisylic acid and either ticagrelor or clopidrogel before angiography. All were given heparin at dose of 5000 IU to 7500 IU at the start of the procedure. This reflects clinical practice, but could alter the coagulation state and thrombus appearance. None were given GpIIb/IIIa inhibitors before thrombus aspiration and OCT.

Limitations

Our study is limited by having a small number of subjects, and limited number of paired subjects with both histological and imaging. The thrombus aspiration was performed before imaging, so the aspirated content might be different from the remnants analyzed by OCT

Conclusion

The consensus document for OCT measurements states that thrombus composition can be predicted by measuring light intensity in thrombus relying on only one reference article using post mortem thrombus analysis. We have not been able to reproduce these findings in a clinical setting, either by use of online llumien Optis software or the offline software ImageJ. We have not found a relationship between erythrocyte content and thrombus age. In our study OCT could not predict whether the thrombus contains fresh, organized or lytic elements. One reason for this could be the limitations in the OCT system itself.

Supporting information

S1 File. Supporting data.
(DAT)

S1 Text.
(DOCX)

Acknowledgments

Special acknowledgments to Niels Ramsing Holm and Omeed Neghabat at the OCT core lab at Aarhus University Hospital for help with OCT analysis, and to Kjetil Løland and Cedric Davidsen at Haukeland University Hospital for help statistics and figures.

Author Contributions

Conceptualization: Erlend Eriksen, Vegard Tuseth, Jan Erik Nordrehaug, Øyvind Bleie, Allard C. van der Wal.

Data curation: Erlend Eriksen.

Formal analysis: Erlend Eriksen, Jon Herstad, Øyvind Bleie, Allard C. van der Wal.

Funding acquisition: Erlend Eriksen, Jan Erik Nordrehaug, Øyvind Bleie.

Investigation: Erlend Eriksen, Jon Herstad, Øyvind Bleie, Allard C. van der Wal.

Methodology: Erlend Eriksen, Jon Herstad, Øyvind Bleie, Allard C. van der Wal.

Project administration: Erlend Eriksen.

Resources: Erlend Eriksen.

Software: Erlend Eriksen.

Supervision: Øyvind Bleie, Allard C. van der Wal.

Validation: Erlend Eriksen, Jon Herstad.

Writing – original draft: Erlend Eriksen.

Writing – review & editing: Jon Herstad, Kartika Ratna Pertiwi, Vegard Tuseth, Jan Erik Nordrehaug, Øyvind Bleie, Allard C. van der Wal.

References

1. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). European heart journal. 2018; 39(2):119–77. https://doi.org/10.1093/eurheartj/ehx393 PMID: 28886621
2. George JC, Dangas GD, American Heart A, American College of C. 2009 Focused updates to guidelines in ST-elevation myocardial infarction and percutaneous coronary intervention: application to interventional cardiology. JACC Cardiovascular interventions. 2010; 3(2):256–8. https://doi.org/10.1016/j.jcin.2010.01.004 PMID: 20170887
3. van der Wal AC, Becker AE. Atherosclerotic plaque rupture—pathologic basis of plaque stability and instability. Cardiovascular research. 1999; 41(2):334–44. https://doi.org/10.1016/s0008-6363(98)00276-4 PMID: 10341833
4. Rittersma SZ, van der Wal AC, Koch KT, Piek JJ, Henriques JP, Mulder KJ, et al. Plaque instability frequently occurs days or weeks before occlusive coronary thrombosis:a pathological thrombectomy study in primary percutaneous coronary intervention. Circulation.2005; 111(9):1160–5. https://doi.org/10.1161/01.CIR.0000157141.00778.AC PMID: 15723983
5. Kramer MC, van der Wal AC, Koch KT, Ploegmakers JP, van der Schaaf RJ, Henriques JP, et al. Presence of older thrombus is an independent predictor of long-term mortality in patients with ST-elevation myocardial infarction treated with thrombus aspiration during primary percutaneous coronary

intervention. Circulation. 2008; 118(18):1810–6. https://doi.org/10.1161/CIRCULATIONAHA.108.780734 PMID: 18852369

6. Tearney GJ, Regar E, Akasaka T, Adriaenssens T, Barlis P, Bezerra HG, et al. Consensus standards for acquisition, measurement, and reporting of intravascular optical coherence tomography studies: a report from the International Working Group for Intravascular Optical Coherence Tomography Standardization and Validation. Journal of the American College of Cardiology. 2012; 59(12):1058–72. https://doi.org/10.1016/j.jacc.2011.09.079 PMID: 22421299
7. Kume T, Akasaka T, Kawamoto T, Ogasawara Y, Watanabe N, Toyota E, et al. Assessment of coronary arterial thrombus by optical coherence tomography. Am J Cardiol. 2006; 97(12):1713–7. https://doi.org/10.1016/j.amjcard.2006.01.031 PMID: 16765119
8. Silvain J, Collet JP, Nagaswami C, Beygui F, Edmondson KE, Bellemain-Appaix A, et al. Composition of coronary thrombus in acute myocardial infarction. Journal of the American College of Cardiology. 2011; 57(12):1359–67. https://doi.org/10.1016/j.jacc.2010.09.077 PMID: 21414532
9. Porto I, Mattesini A, Valente S, Prati F, Crea F, Bolognese L. Optical coherence tomography assessment and quantification of intracoronary thrombus: Status and perspectives. Cardiovasc Revasc Med. 2015; 16(3):172–8. https://doi.org/10.1016/j.carrev.2015.01.007 PMID: 25681257
10. Huang D, Swanson EA, Lin CP, Schuman JS, Stinson WG, Chang W, et al. Optical coherence tomography. Science. 1991; 254(5035):1178–81. https://doi.org/10.1126/science.1957169 PMID: 1957169
11. Beygui F, Collet JP, Nagaswami C, Weisel JW, Montalescot G. Images in cardiovascular medicine. Architecture of intracoronary thrombi in ST-elevation acute myocardial infarction: time makes the difference. Circulation. 2006; 113(2):e21–3. https://doi.org/10.1161/CIRCULATIONAHA.105.551705 PMID: 16418443
12. Li X, de Boer OJ, Ploegmaker H, Teeling P, Daemen MJ, de Winter RJ, et al. Granulocytes in coronary thrombus evolution after myocardial infarction—time-dependent changes in expression of matrix metalloproteinases. Cardiovascular pathology: the official journal of the Society for Cardiovascular Pathology. 2016; 25(1):40–6. https://doi.org/10.1016/j.carpath.2015.09.007 PMID: 26490693
13. Mangold A, Alias S, Scherz T, Hofbauer T, Jakowitsch J, Panzenbock A, et al. Coronary neutrophil extracellular trap burden and deoxyribonuclease activity in ST-elevation acute coronary syndrome are predictors of ST-segment resolution and infarct size. Circulation research. 2015; 116(7):1182–92. https://doi.org/10.1161/CIRCRESAHA.116.304944 PMID: 25547404
14. Riegger J, Byrne RA, Joner M, Chandraratne S, Gershlick AH, Ten Berg JM, et al. Histopathological evaluation of thrombus in patients presenting with stent thrombosis. A multicenter European study: a report of the prevention of late stent thrombosis by an interdisciplinary global European effort consortium. European heart journal. 2016; 37(19):1538–49. https://doi.org/10.1093/eurheartj/ehv419 PMID: 26761950
15. Johnson C, Galis ZS. Matrix metalloproteinase-2 and -9 differentially regulate smooth muscle cell migration and cell-mediated collagen organization. Arteriosclerosis, thrombosis, and vascular biology. 2004; 24(1):54–60. https://doi.org/10.1161/01.ATV.0000100402.69997.C3 PMID: 14551157
16. Newby AC. Matrix metalloproteinases regulate migration, proliferation, and death of vascular smooth muscle cells by degrading matrix and non-matrix substrates. Cardiovascular research. 2006; 69(3):614–24. https://doi.org/10.1016/j.cardiores.2005.08.002 PMID: 16266693
17. Newby AC. Dual role of matrix metalloproteinases (matrixins) in intimal thickening and atherosclerotic plaque rupture. Physiological reviews. 2005; 85(1):1–31. https://doi.org/10.1152/physrev.00048.2003 PMID: 15618476
18. Li X, Kramer MC, van der Loos CM, Koch KT, de Boer OJ, Henriques JP, et al. A pattern of disperse plaque microcalcifications identifies a subset of plaques with high inflammatory burden in patients with acute myocardial infarction. Atherosclerosis. 2011; 218(1):83–9. https://doi.org/10.1016/j.atherosclerosis.2011.04.032 PMID: 21605863
19. Li X, van der Meer JJ, van der Loos CM, Ploegmakers HJ, de Boer OJ, de Winter RJ, et al. Microvascular endoglin (CD105) expression correlates with tissue markers for atherosclerotic plaque vulnerability in an ageing population with multivessel coronary artery disease. Histopathology. 2012; 61(1):88–97. https://doi.org/10.1111/j.1365-2559.2011.04166.x PMID: 22463585
20. Vlaar PJ, Svilaas T, van der Horst IC, Diercks GF, Fokkema ML, de Smet BJ, et al. Cardiac death and reinfarction after 1 year in the Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction Study (TAPAS): a 1-year follow-up study. Lancet. 2008; 371(9628):1915–20. https://doi.org/10.1016/S0140-6736(08)60833-8 PMID: 18539223

Graphic design: Communication Division, UiB / Print: Skipnes Kommunikasjon AS

uib.no

ISBN: 9788230847367 (print)
9788230858448 (PDF)