Optimizing Percutaneous Coronary Intervention

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2022

Document Version:
Publisher's PDF, also known as Version of record

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Optimizing Percutaneous Coronary Intervention

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UNIVERSITY

DOCTORAL DISSERTATION

by due permission of the Faculty of Medicine, Lund University, Sweden.
To be defended at Skåne University Hospital, Lund, föreläsningssal 2.
March 18, 2022, 13:00.

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Document name
DOCTORAL DISSERTATION

Date of issue February 9, 2022

Sponsoring organization

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Abstract

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Methods: This thesis comprises five studies, three large-scale registry-based observational studies and two using dedicated imaging analysis. All studies included coronary imaging with intravascular ultrasound (IVUS), near-infrared spectroscopy (NIRS), optical coherence tomography (OCT), and/or conventional coronary angiography. Studies I–III investigated the impact of IVUS on long-term outcomes following left main PCI, analysed non-culprit lesion lipid burden and its association with future adverse events by NIRS, and used serial OCT to evaluate neointimal healing and stent-related complications relative to baseline stent edge landing zone characteristics. Study IV assessed angiographic thrombus burden and vessel occlusion in ST-segment elevation myocardial infarction (STEMI) patients receiving heparin pre-treatment, and Study V assessed the occurrence and prognosis of intra-procedural stent thrombosis (IPST).

Results: Study I found use of adjunct IVUS to be associated with a lower cumulative occurrence of the composite endpoint of all-cause mortality, restenosis, and definite stent thrombosis compared with left main PCI guided by angiography alone (HR 0.65, 95%CI 0.50–0.84, P=0.001). Study II showed presence of a non-culprit maximum lipid core burden index in a four mm segment ($maxLCBI_{4mm}$) ≥400, as detected by NIRS, to be significantly associated with the composite endpoint of all-cause mortality, acute coronary syndrome requiring revascularization, and cerebrovascular events (HR 3.67, 95% CI 1.46–9.23, P=0.006). Study III found baseline stent edge landing zone calcium, edge dissection, and myocardial bridging to be independent predictors of percent neointimal volume (%NIV) at nine months. Landing zone lipid was associated with angiographic edge restenosis (odds ratio [OR] 5.25, 95% CI 1.59–17.31, P=0.006) and inversely related to reference minimum lumen area, but showed no relationship with %NIV. Study IV demonstrated a significantly lower occurrence of intracoronary thrombus (adjusted OR 0.73, 95% CI 0.65–0.83, P<0.001) and total vessel occlusion (adjusted OR 0.64, 95% CI 0.56–0.73, P<0.001) prior to PCI in STEMI patients receiving heparin pre-treatment. Study V reported IPST in 0.9% of procedures, and showed IPST to be an independent predictor of the composite endpoint of cardiovascular death, myocardial infarction, definite stent thrombosis, and target vessel revascularization (HR 3.82, 95% CI 2.05–7.12, P<0.001).

Conclusions: The findings of this research demonstrate the value of intravascular imaging during PCI in facilitating stent implantation and stratifying patient-level risk. They support a role for heparin pre-treatment in STEMI and provide insight into mechanisms of stent-related complications, of potential importance for PCI optimization.

Key words Percutaneous coronary intervention, intravascular ultrasound, near-infrared spectroscopy, optical coherence tomography, heparin pre-treatment, intra-procedural stent thrombosis

Classification system and/or index terms (if any)

Supplementary bibliographical information — Language English

ISSN and key title 1652-8220 Optimizing PCI — ISBN 978-91-8021-189-5

Recipient's notes — Number of pages 86 — Price

Security classification

Signature  Date 2022-02-09

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Pages 1-86

Department of Cardiology
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ISBN 978-91-8021-189-5
ISSN 1652-8220
Lund University, Faculty of Medicine Doctoral Dissertation Series 2022:28

Printed in Sweden by Media-Tryck, Lund University
Lund 2022

To my family

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Paper II — **Karlsson (Bergman) S,** Anesäter E, Fransson K, Andell P, Persson J, Erlinge D. Intracoronary near-infrared spectroscopy and the risk of future cardiovascular events. Open Heart. 2019 Feb 9;6(1):e000917.

Paper III — **Bergman S,** Matsumura M, Lee S, Tam CC, Liu Y, Kong S, Mintz G, Maehara A. Coronary stent edge landing zone characteristics and their association with neointimal healing assessed by serial optical coherence tomography (manuscript).

Paper IV — **Karlsson (Bergman) S,** Andell P, Mohammad MA, Koul S, Olivecrona GK, James SK, Fröbert O, Erlinge D. Heparin pre-treatment in patients with ST-segment elevation myocardial infarction and the risk of intracoronary thrombus and total vessel occlusion. Insights from the TASTE trial. Eur Heart J Acute Cardiovasc Care. 2019 Feb;8(1):15–23.

Paper V — **Bergman S,** Mohammad MA, James SK, Angerås O, Wagner H, Jensen J, Scherstén F, Fröbert O, Koul S, Erlinge D. Clinical Impact of Intraprocedural Stent Thrombosis during Percutaneous Coronary Intervention in Patients Treated with Potent P2Y12 inhibitors – a VALIDATE-SWEDEHEART Substudy. J Am Heart Assoc. 2021 Sep 21;10(18):e022984.

Thesis overview

Study	Goals	Data source	Main Findings	Conclusions
I	To evaluate the impact of IVUS in left main PCI.	SCAAR Left main PCI 2005–2014 n=2468	Left main PCI with adjunct IVUS was associated with a lower occurrence of the composite endpoint of cardiovascular death, definite stent thrombosis, and restenosis compared with left main PCI without IVUS (adjusted HR 0.65 95% CI 0.50–0.84).	Outcome of left main PCI with adjunct IVUS was superior to that of left main PCI with angiography guidance alone. A randomized trial is needed to confirm the value of IVUS in left main PCI.
II	To study non-culprit lesions and their association with future cardiovascular events using combined NIRS-IVUS.	Lund+Danderyd NIRS-IVUS 2012–2015 n=144	Non-culprit max$LCBI_{4mm}$ ≥400 was associated with the composite endpoint of all-cause death, ACS requiring revascularization, and cerebrovascular events (HR 3.7, 95% CI 1.5–9.2).	NIRS-derived non-culprit max$LCBI_{4mm}$ ≥400 identified patients at higher risk of future cardiovascular events.
III	To evaluate the relationship of stent edge landing zone characteristics with neointimal healing using serial OCT imaging.	EGO studies 2010–2014 n=220	Neointimal healing, reference MLA, and angiographic edge restenosis at nine months differed with baseline stent edge landing zone character-istics.	Baseline landing zone characteristics predicted neointimal healing, reference MLA, and angiographic stent edge restenosis at nine months.
IV	To investigate the effect of heparin pre-treatment in patients with STEMI.	TASTE trial 2010-2013 n=7144	Heparin pre-treatment was independely associated with a lower occurrence of a visible intracoronary thrombus (OR 0.73, 95% CI 0.65-0.83) and total vessel occlusion (OR 0.64, 95% CI 0.56-0.73) prior to PCI.	Heparin pre-treatment appears safe and effective in patients with STEMI referred to primary PCI.
V	To examine the occurence and consequences of IPST in patients with MI undergoing PCI.	VALIDATE trial 2014–2016 n=6006	IPST occurred in 0.9% of procedures and was independently associated with the composite endpoint of cardiovascular death, MI, definite stent thrombosis, and target vessel revascularization (HR 3.82, 95% CI 2.05–7.12).	IPST is rare but associated with adverse outcomes, and should be routinely reported during PCI.

ACS=acute coronary syndrome, CI=confidence interval, HR=hazard ratio, IPTS=intra-procedural stent thrombosis, IVUS=intravascular ultrasound, max$LCBI_{4mm}$=maximum lipid core burden index in a four mm segment, MI=myocardial infarction, MLA=minimum lumen area, NIRS=near infrared spectroscopy, OCT=optical coherence tomography, OR=odds ratio, PCI=percutaneous coronanry intervention, SCAAR= Swedish Coronary Angiography and Angioplasty Registry, STEMI=ST-segment elevation myocardial infarction.

Abstract

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Abbreviations

ACS	Acute coronary syndrome
ARC	Academic research consortium
BARC	Bleeding academic research consortium
BMS	Bare-metal stent
CABG	Coronary artery bypass grafting
CCS	Chronic coronary syndrome
DAPT	Dual antiplatelet therapy
DES	Drug-eluting stent
ECG	Electrocardiogram
GPI	Glycoprotein IIb/IIIa-receptor inhibitor
HR	Hazard ratio
IPST	Intra-procedural stent thrombosis
IQR	Interquartile range
IVUS	Intravascular ultrasound
LAD	Left anterior descending artery
LCBI	Lipid core burden index
LCX	Left circumflex artery
LMCA	Left main coronary artery
LMWH	Low molecular weight heparin
MACCE	Major adverse cardiovascular and cerebrovascular events
$maxLCBI_{4mm}$	Highest lipid core burden index within a four mm segment
MLA	Minimum lumen area

MSA	Minimum stent area
NIV	Neointimal volume
NIRS	Near-infrared spectroscopy
Non-STEMI	Non ST-segment elevation myocardial infarction
OCT	Optical coherence tomography
OR	Odds ratio
PCI	Percutaneous coronary intervention
QCA	Quantitative coronary angiography
RCA	Right coronary artery
SCAAR	Swedish coronary angiography and angioplasty registry
STEMI	ST-segment elevation myocardial infarction
SWEDEHEART	Swedish web-system for enhancement and development of evidence-based care in heart disease evaluated according to recommended therapies
TCFA	Thin cap fibroatheroma
TIMI	Thrombolysis in myocardial infarction
UFH	Unfractionated heparin

Introduction

Historical overview

> "But there is a disorder of the breast marked with strong and peculiar symptoms, considerable for the kind of danger belonging to it, and not extremely rare, which deserves to be mentioned more at length. The seat of it and the sense of strangling and anxiety with which it is attended, may make it not improperly be called angina pectoris. Those who are afflicted with it, are seized while they are walking (more especially if it be uphill, and soon after eating) with a painful and most disagreeable sensation in the breast, which seems as if it would extinguish life if it were to increase or to continue; but the moment they stand still, all this uneasiness vanishes."[1]

This classic description of angina pectoris was published by Dr William Heberden in 1772.[1] He provided the term *angina pectoris,* referring to the strangling feeling in the chest, from the Greek *ἀγχόνη*, 'strangling,' the Latin *angina*, 'infection of the throat,' and the Latin *pectus*, 'chest.' At the time, little was known of the underlying pathophysiology.

Over the subsequent century, advances emerged in pathology, physiology, and clinical medicine. In the late 19th century, pathologists demonstrated a relationship between myocardial infarction and coronary thrombosis, and physiologists observed that coronary artery occlusions in dogs caused ventricular quivering and sudden death.[2,3] In the early 20th century, reports linking the clinical presentation of non-fatal myocardial infarction with subsequent post-mortem findings of coronary thrombosis appeared.[4] By 1919, myocardial infarction could be diagnosed by electrocardiography (ECG), but treatment options remained scarce, and patients were primarily consigned to bed rest, with accordingly high mortality rates.[5-7]

In the mid-20th century, significant findings of the pathogenesis of atherosclerosis were reported, and the concept of coronary artery disease as the cause of angina pectoris gained recognition.[8,9] To further investigate the development of cardiovascular disease, the Framingham study was initiated. Through long-term monitoring of the behaviours and lifestyles of residents of the city of Framingham, Massachusetts, the project provided fundamental knowledge of the relationships among blood pressure, blood cholesterol, and heart disease.[10] The 1960s saw the advent of dedicated coronary care units, and continuous cardiac monitoring of patients with myocardial infarction enabled early identification and defibrillation of

malignant arrhythmias, reducing in-hospital mortality from 30% to 15%.[11-13] Nevertheless, the medical community remained divided over the significance of the reported association of coronary artery thrombosis with myocardial infarction, debating whether intracoronary thrombosis is a cause or a consequence of myocardial infarction.[14] The question was settled in the late 1970s when thrombolysis was demonstrated to successfully reperfuse a thrombosed coronary artery.[15] Thrombolysis became the treatment of choice for acute myocardial infarction, and reducing time to reperfusion was established as crucial to improving outcome. A number of large-scale randomized trials investigating the efficacy of various fibrinolytic strategies followed.[15-19] While the first balloon angioplasty was conducted and gained recognition about the same time,[20] the technique was initially not applied to patients with acute myocardial infarction. In the mid-1990s, landmark studies demonstrated immediate angioplasty to be superior to thrombolytic strategies in patients with acute myocardial infarction, thus paving the way for the era of primary percutaneous coronary intervention (PCI).[21,22]

The development of percutaneous coronary intervention

Preceded by the pioneering work of Dr Werner Forssman, who performed the first cardiac catheterization in 1929, the first coronary cineangiography was conducted in 1958 when Dr F. Mason Sones, while conducting an aortogram, accidently injected contrast into the right coronary artery (RCA).[23,24] Drs Melvin Judkins and Charles T. Dotter later reported a novel percutaneous technique for dilatation of stenotic peripheral arteries.[25] In 1965, Dr Judkins arrived in Lund, Sweden, where he began to design the still-used Judkins catheters. Sweden was then, according to his spouse, considered the 'the Mecca of radiology, particularly selective arteriography.'[26] In 1977, Dr Andreas R. Grüntzig applied the dilatation technique to the coronary arteries and opened a left anterior descending (LAD) blockage with a double-lumen balloon catheter.[20] Since the first coronary balloon angioplasty over 40 years ago, PCI has expanded in a remarkable fashion, with progress in sophisticated diagnostic and therapeutic options for patients with coronary artery disease, including drug-eluting stents (DES), intracoronary imaging, and adjunct antithrombotic therapies. Accordingly, survival rates of myocardial infarction have improved dramatically.[27]

Epidemiology

Despite the success story of coronary intervention and medications improving outcomes, cardiovascular disease remains the leading cause of death worldwide, with an estimated 18.6 million deaths in 2019.[28] Alarmingly, the prevalence and burden of cardiovascular disease is still increasing in most areas outside of high-

income countries, and ischemic heart disease is the number one killer.[28] Sweden, as well as other high-income countries, has seen a steady decrease in the incidence of myocardial infarction in recent decades (Figure 1). Mortality following acute myocardial infarction is also decreasing, although at a slower pace.[29] Ischemic heart disease is, nevertheless, the most common cause of death in Sweden and worldwide,[28] and further measures to optimize treatment strategies are needed, along with primary preventive measures.

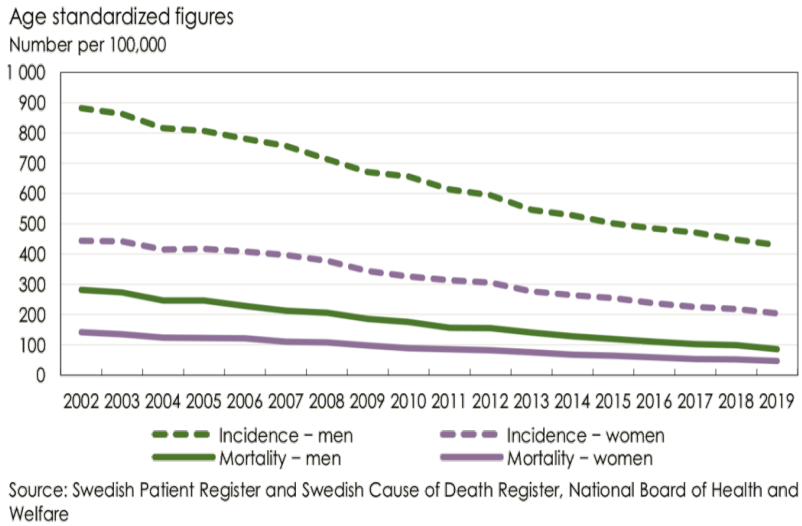

Figure 1. Acute myocardial infarction incidence and mortality per 100,000 inhabitants 20 years and older by sex 2002–2019. Reprinted with permission from the National Board of Health and Welfare in Sweden.

Risk factors contributing to the development and progression of coronary artery disease can be modifiable or non-modifiable. Non-modifiable risk factors include greater age, male sex, and a family history of early-onset coronary artery disease. Males typically present with disease at a younger age compared with females and more often experience acute myocardial infarction (Figure 1). Modifiable factors include hyperlipidaemia, hypertension, diabetes, obesity, and aspects of lifestyle including diet, physical activity, tobacco use, alcohol consumption, and psychosocial factors. While older age represents a strong non-modifiable risk factor, most cardiovascular disease and death can be attributed to a small number of modifiable risk factors, emphasizing the importance of preventative measures.[30]

Definitions and classification

Coronary artery disease can be categorized according to its clinical presentation, biochemical markers, ECG alterations, or pathologic features.[31-33] Central chest discomfort is the most commonly described symptom at onset, although clinical presentation varies widely, ranging from self-limiting symptoms to sudden cardiac death. Criteria for the diagnosis of myocardial infarction include the manifestations of myocardial injury as detected by a dynamic rise and/or fall in cardiac marker levels, together with clinical evidence of acute myocardial ischemia including at least one of the following: ischemic symptoms, new ischemic ECG-changes or development of a pathological Q-wave, imaging evidence consistent with ischemia, or the presence of an intracoronary thrombus.

The Fourth Universal Definition of Myocardial Infarction comprises five subtypes.[34] Type 1 is defined as myocardial infarction resulting from acute coronary atherothrombosis, usually a consequence of plaque rupture or erosion. Type 2 is myocardial infarction related to a mismatch in oxygen supply and demand, that is unrelated to acute atherothrombosis, and includes spontaneous coronary artery dissection, embolism, vasospasm, and extra-cardiac causes such as anaemia, hypotension, and blood oxygen desaturation. Type 3 refers to sudden cardiac death in conjunction with symptoms indicating myocardial ischemia before the possibility of troponin analysis. Types 4 a–c are defined as myocardial infarction related to PCI, stent thrombosis, and restenosis, respectively, and type 5 is myocardial infarction linked to coronary artery bypass grafting (CABG). The term *myocardial injury* is used in cases of elevated cardiac marker levels without evidence of myocardial ischemia. Based on ECG changes, myocardial infarctions are classified as ST-segment elevation myocardial infarction (STEMI) or non-ST-segment elevation myocardial infarction (non-STEMI), and, together with unstable angina and sudden cardiac death, constitute the acute coronary syndromes (ACS).[31-33]

Pathophysiology

Atherosclerosis

As a systemic, multifactorial, immune-inflammatory disease driven by the interaction of lipids and inflammatory cells, atherosclerosis is recognized as the major cause of coronary artery disease.[35] Beginning early in life, low-density lipoprotein particles enter the innermost layer of the arteries, the intima, and undergo oxidative modifications.[36] Chemoattractant cytokines promote the migration of monocytes into the intima where they are transformed into lipid-laden macrophage foam cells that accumulate to form fatty streaks, also known as *intimal xanthomas*.[37]

Intimal xanthomas are typically present from an early age and are often reversible.[38] Pathologic intimal thickening represents the earliest progressive atherosclerotic lesion, consisting of smooth muscle cells, extracellular matrix, and lipid pools.[39] Continuous inflammation, macrophage recruitment, apoptosis, and secondary necrosis lead to the formation of a fibroatheroma with an acellular lipid-rich necrotic core.[40] A fibrous cap composed of collagen, proteoglycans, and smooth muscle cells overlies the plaque and its highly thrombogenic core. Continuing inflammation, macrophage activation, proteinases, and, possibly, impaired healing can lead to thinning of the cap, making the plaque increasingly prone to rupture.[41-44] Common cardiovascular risk factors are known to accelerate the atherosclerotic process, and vascular segments with low shear stress may be particularly vulnerable.[36,45] As coronary lesions increase in size, the vessel expands outward, preserving luminal diameter, a mechanism referred to as positive remodelling.[46] Thus, large plaques can be obscured in the vessel wall, initially without luminal stenosis. As the plaque burden grows beyond 40%, the luminal area typically begins to decrease as the plaque burden increases.

While coronary plaque can impair cardiac flow and cause angina, atherosclerosis per se is rarely fatal.[47] Instead, it is the sudden formation of a thrombus on a ruptured or eroded coronary plaque that is the most common source of the devastating event of acute myocardial infarction.[47]

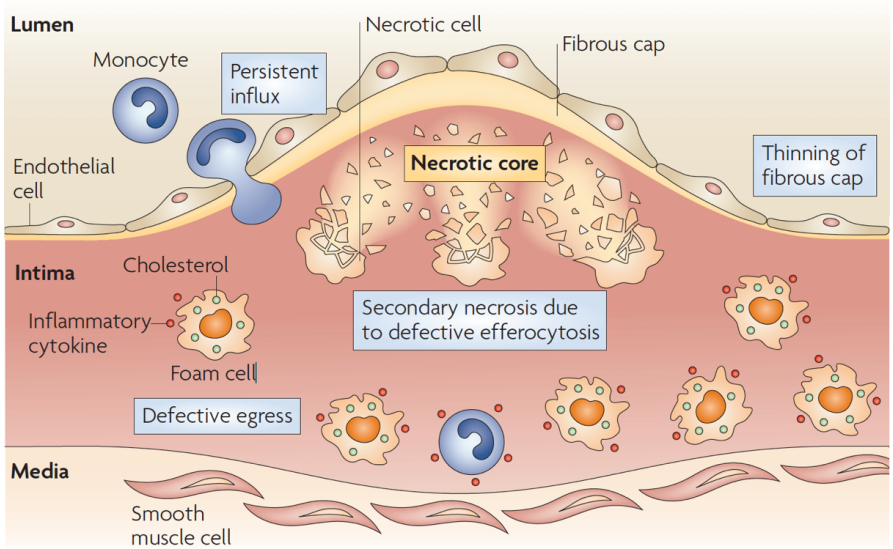

Figure 2. Formation of an atherosclerotic plaque. Mononcytes enter the intima, engulfing the lipids while transforming into lipid-laden macrophages known as foam cells. Persistent influx of monocytes, defective egress, macrophage apoptosis, and secondary necrosis contribute to the formation of a necrotic core. Reprinted with permission of Nat Rev Immunol. 2010;10(1):36-46.

Coronary lesions

Based on autopsy studies of individuals succumbing to sudden cardiac death, the morphology of three lesion types associated with intraluminal thrombosis have been decribed.[39] The most common cause of coronary thrombosis is plaque rupture, characterized by the disruption of a thin inflamed fibrous cap covering a lipid-rich and highly thrombogenic necrotic core. As the necrotic core is exposed, an intraluminal thrombus rapidly forms. Plaque rupture is the predominant cause of acute myocardial infarction and is particularly frequent in males.[47,48] The second most common cause of intracoronary thrombosis is plaque erosion. The mechanisms of plaque erosion are not fully understood. The endothelium is typically missing at the site of erosion, but the fibrous cap remains intact.[39] Plaque erosions are believed to represent an increasingly important cause of ACS worldwide, possibly a consequence of the growth in statin therapy.[49,50] Finally, coronary thrombosis can stem from a calcified nodule, a less common condition primarily observed in the elderly with tortuous and heavily calcified arteries.[47]

While a gradual increase in coronary stenosis is more likely to induce exertional symptoms, rapid thrombus formation resulting in partial or total vessel occlusion plays a central role in myocardial infarction. The development and severity of myocardial ischemia and subsequent infarction depend on the degree and duration of vessel obstruction, presence and efficacy of collateral flow, and the extent of myocardium at risk.[51] Prolonged ischemia causes cardiomyocyte death, with the first cellular changes starting as early as 10 to 15 minutes following ischemia onset, although timing varies depending on the pre-conditioning status and sensitivity of the myocytes.[52,53]

Small mural thrombi may undergo spontaneous lysis, and plaque ruptures can occur without overt clinical symptoms. Such recurrent plaque ruptures and healing may cause gradual build-up of plaque, eventually compromising the lumen with or without accompanying symptoms.[36] Importantly, a previously silent atherosclerotic plaque can, at any time, trigger luminal thrombosis and acute ischemia. The formerly used term ‘stable angina’ has therefore been replaced by ‘chronic coronary syndrome’ (CCS), to better describe this chronic and dynamic disease.[33] Why some lesions remain stable over time, some gradually increase, and others result in acute-onset symptoms is not fully understood.

Vulnerable plaques and vulnerable patients

The thin cap fibroatheroma (TCFA) displays features similar to those of a ruptured plaque: a large lipid-rich necrotic core with a thin, inflamed, but intact, fibrous cap. Based on the similarities, TCFAs have been suggested to be precursors of ruptured plaques and are often described as rupture-prone or vulnerable plaques.[54] The ability to identify these lesions before they rupture and cause myocardial infarction has

been a goal of cardiologists since 1989 when the concept of vulnerable plaques was first introduced.[55] Recent developments in intravascular imaging technology providing excellent in vivo visualization of coronary lesions, have intensified the pursuit of vulnerable plaques, but the topic is not without controversy.[56] As mentioned, a plaque rupture does not always result in a clinical event, and the fate of a ruptured or eroded plaque is not necessarily determined solely by the morphology of the lesion itself. Patient-level variables including endogenous fibrinolytic and haemostatic capacity, inflammation, comorbidities, and medical therapies are likely contributors to the occurrence or inhibition of a clinical event.[56-58] Thus, increased interest in identifying vulnerable plaques *in vulnerable patients* has emerged to better predict susceptibility to adverse outcomes.[56-58] Whether the identification of vulnerable plaques in vulnerable patients can be of prognostic value, guide treatment strategies, and ultimately improve outcome remains to be established.

Percutaneous coronary intervention

The preferred revascularization strategy for patients with coronary artery disease depends on clinical presentation, disease distribution, co-morbidities, and the available treatment options.[59] For STEMI, immediate primary PCI with adjunct antithrombotic medication is recommended. If primary PCI is not available within 120 minutes, thrombolysis should be considered.[31] For patients with non-STEMI or unstable angina, timely, but not necessarily immediate, PCI is recommended.[32] Clinical presentation, along with risk factors, should guide the urgency of the procedure. In patients with CCS, guideline-directed medical therapy is recommended to halt atherosclerosis and alleviate symptoms. Coronary revascularization may be considered in addition to pharmaceutical treatment, taking into account patient risk-benefit as detailed in current guidelines.[33] In a subset of patients, CABG may be preferred, as determined by a dedicated multidisciplinary heart team.[59]

Percutaneous coronary intervention has undergone considerable advancement since the first balloon angioplasty was conducted in 1977. The Achilles heel of balloon angioplasty was the substantial risk of acute vessel closure and subsequent constrictive restenosis,[60,61] spurring the development of the bare metal stent (BMS). The BMS eliminated acute vessel closure and late constrictive remodelling but brought the complication of subacute stent thrombosis and in-stent restenosis.[62,63] The use of dual antiplatelet therapy (DAPT) was demonstrated to reduce the rate of stent thrombosis,[64] but in-stent restenosis with neointimal hyperplasia lingered as a major limitation of BMS use.[65] To address the issue, a metallic stent with a polymer coating that releases immuno-suppressant or cytotoxic drugs was launched in the early 2000s, initiating the era of drug eluting stents (DES). Large-scale randomised

trials demonstrated a consistent reduction in target lesion revascularization with DES compared with BMS, although DES resulted in higher rates of late stent thrombosis.[66] Since its introduction, several improvements have been made in DES, including refinements of the stent platform, polymer, and drugs.[67-70] As the first polymers used were found to provoke a hypersensitivity reaction, delay arterial healing, and increase the risk of stent thrombosis, polymer biocompatibility has been improved, and biodegradable polymers and polymer-free stents have been developed.[71,72] While current DESs are more effective and safer compared with prior generations of stents, stent-related complications remain a critical issue in PCI.[73]

Stent-related complications

In-stent restenosis

Angiographically defined as luminal narrowing with diameter stenosis ≥50% of a stented segment or its adjacent 5 mm proximal or distal reference segment, in-stent restenosis mainly results from neointimal hyperplasia.[74,75] Mechanisms underlying its development are likely to be multifactorial, with biological, mechanical, and technical components.[76] The principal biological factor is local inflammation, and the most important mechanical issues include stent under-expansion and, less frequently, stent fracture.[76] Technical risk factors include incomplete lesion coverage with residual plaque in the reference segment and barotrauma outside the stented segment.[76,77] Although the rate of in-stent restenosis related to neointimal hyperplasia has decreased significantly since the introduction of the DES, it still occurs, predominantly presenting with a focal pattern. The stent edge segment moreover represents an area of concern. Stent edge restenosis may be attributed to neointimal proliferation, negative remodelling, and/or disease progression in the reference segment.[76,78] In addition, neo-atherosclerosis is recognized as an increasing cause of in-stent restenosis, especially in late DES failure.[79,80] Patients with diabetes and chronic kidney disease may be particularly vulnerable.[81]

Currently, both DES and drug-coated balloons are recommended for treating DES and BMS restenosis.[59] In patients experiencing recurrent restenosis, CABG may be considered. Establishing the root cause of restenosis is of clinical importance, as treatment strategies may differ. Current guidelines emphasize the benefit of intravascular imaging to ascertain underlying mechanisms.[59,82] Treatment can be challenging, requiring special cutting or scoring balloons, adjunctive athero-ablative devices, intravascular lithotripsy, or vascular brachytherapy.[83,84]

Stent thrombosis

Although rare, stent thrombosis represents a severe complication following PCI. Symptom onset is typically acute, and the condition is associated with poor outcome.[85,86] The papers included in this thesis defined stent thrombosis according

to the Academic Research Consortium (ARC) criteria,[87] which classify stent thrombosis according to time of event post-PCI: *early* (within 30 days), *late* (1–12 months), and *very late* (after 1 year). Early events are sub-categorized as acute (<24 hours) and sub-acute (24 hours–30 days). The classification also includes event adjudication: definite, probable and possible. *Definite* stent thrombosis denotes acute clinical presentation with stent thrombosis verified by angiography or autopsy. *Probable* stent thrombosis includes any unexplained death sooner than 30 days following stent implantation or acute myocardial infarction corresponding to the stented vessel, but without angiographic confirmation of thrombosis. *Possible* stent thrombosis is defined as any unexplained death occurring 30 or more days post-implantation.

Dual antiplatelet therapy is currently recommended following stent implantation to counteract the risk of stent thrombosis, although the accompanying increased risk of bleeding is a concern.[88] Research to identify predictors of stent thrombosis has been extensive.[89-91] Discontinuation of antithrombotic medications and stent under-expansion are the most often identified sources of early stent thrombosis,[89-91] while late stent thrombosis is more frequently related to delayed arterial healing, uncovered stent struts, and malapposition.[92-96] Acute malapposition can be a contributing factor, but late-acquired malapposition is believed to be of greater relevance. Diabetes, smoking, ACS presentation, and use of longer stents are additional risk factors for stent thrombosis.[97]

Intra-procedural stent thrombosis

The ARC criteria of stent thrombosis define events occurring after PCI, thus excluding thrombotic events taking place during the procedure.[87] Research has defined intra-procedural stent thrombosis (IPST) as the formation of a new or an expanding thrombus in or adjacent to the implanted stent, partially or completely occluding the lumen, during the PCI procedure.[98-100] It occurs most often in patients with STEMI and has a prognosis similar to that of ARC-defined out-of-lab stent thrombosis.[98] In recent ARC-2 criteria, IPST is mentioned as an optional additional classification.[101] Nevertheless, IPST is not widely recognized by interventional cardiologists. The occurrence and clinical relevance of IPST is addressed in **Study V**.

Further PCI optimization is crucial to improve prognosis and reduce long-term dependence on antiplatelet therapy. Intravascular imaging can play a key role in revealing processes contributing to stent-related complications, guiding treatment strategies, and minimizing the occurrence of restenosis and stent thrombosis, especially in complex lesions at increased risk of complications.

Intravascular imaging

While coronary angiography is the most commonly used diagnostic tool for evaluation and treatment-guidance of coronary artery disease worldwide, it has several well-recognized limitations.[102] First and foremost, coronary angiography depicts the contrast-filled lumen as opposed to the atherosclerotic disease in the coronary vessel wall, hence providing scant information of coronary lesions that do not obstruct coronary flow. Indeed, Mintz et al.[103] found fewer than 10% of angiographically 'normal' reference segments to be identified as normal by intravascular imaging. Eccentric lesions, foreshortening, and vessel overlap may also interfere with angiographic interpretation.[104] Supplemental intravascular imaging can counteract these limitations. Intravascular imaging modalities currently available for commercial use include intravascular ultrasound (IVUS), near-infrared spectroscopy (NIRS), and optical coherence tomography (OCT), along with hybrid imaging systems such as the combined NIRS-IVUS catheter used in **Study II** of this thesis.

Intravascular ultrasound

Preceded by the innovation of echocardiography by Edler and Hertz in 1953,[105] Dr Paul Yock invented the catheter-based intravascular ultrasound (IVUS) in 1988.[106] The IVUS catheter is advanced distally through the target vessel, and cross-sectional images are generated as the catheter scans the vessels during an automated or manual pullback. While not without risk, reported rates of adverse events caused by imaging catheters have been low.[107,108]

Grayscale ultrasound images are generated as sound waves reflect off the arterial wall layers, allowing visualization of the vessel wall, its dimensions, and the presence of plaque (Figure 3). Two types of IVUS catheters are available: the solid-state (digital) and the mechanical (rotational).[102] The solid-state catheter generates cross-sectional images by sequential firing of small transducer elements positioned around the circumference of the catheter tip. Mechanical catheters consist of a single transducer on a flexible drive shaft rotating within a monorail imaging sheath. Available transducer frequencies range from 20 MHz to 60 MHz high-definition devices and imaging catheters are currently available from a number of manufacturers.

Near-infrared spectroscopy

The NIRS catheter uses near infrared light to identify organic molecules by their unique optical structure. Validated by histology in autopsy studies, NIRS accurately detects coronary lipid accumulations.[109,110] As the catheter is automatically pulled

back along the artery, a colour-coded chemogram illustrating the presence and location of lipids within the vessel wall is constructed (Figure 3). The x-axis represents the vessel length and the y-axis the vessel circumference. Yellow pixels signify a probability of lipid presence exceeding 0.6, whereas red pixels indicate a probability of lipid 0.6 or less. A lipid core burden index (LCBI) ranging from 0–1000, representing the proportion of yellow pixels (lipid) in any region of interest, is automatically reported (yellow pixels divided by number of all analysed pixels multiplied by 1000). The highest LCBI in a four mm segment, designated $maxLCBI_{4mm}$, is also automatically reported. Because NIRS alone does not provide anatomical data of vessel structures, NIRS and IVUS technologies have been combined in a dual-modality catheter, enabling both chemical and structural assessment of the investigated coronary arteries (Figure 3).

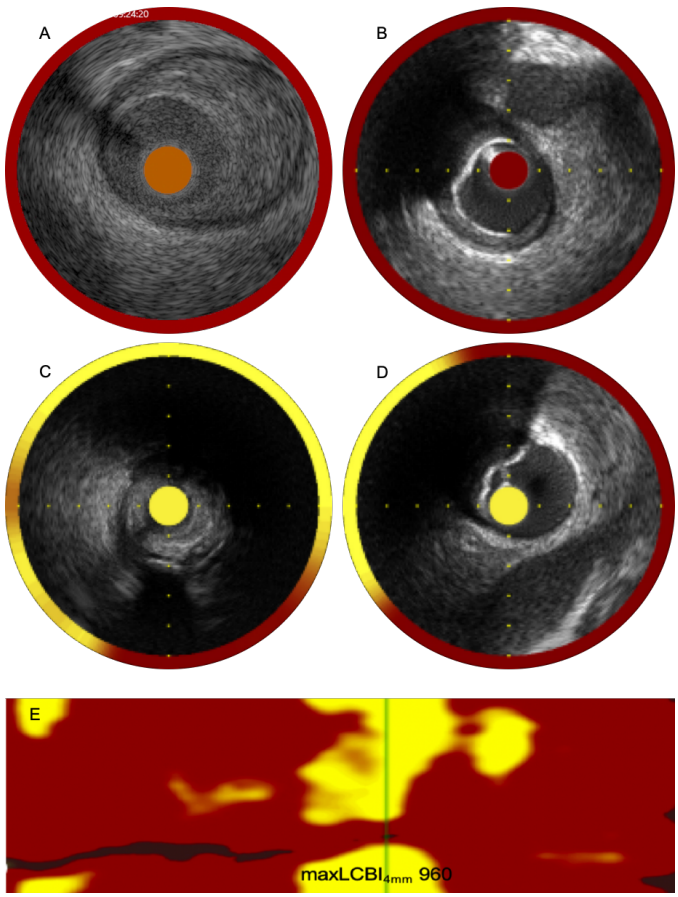

Figure 3. Combined intravascular ultrasound and near-infrared spectroscopy images. (A) fibrotic lesion (B) calcified lesion, (C) lipid-rich lesion, (D) calcified lipid-rich lesion, (E) Chemogram of a large, nearly circumferential, lipid accumulation, $maxLCBI_{4mm}$=960. $maxLCBI_{4mm}$=highest lipid core burden index in a four mm segment.

Optical Coherence Tomography

Optical coherence tomography (OCT) is a more recent innovation than IVUS. Using near-infrared light instead of ultrasound, OCT generates images with superior axial resolution but lower depth of penetration than IVUS.[111] Imaging with OCT moreover requires blood clearance, as red blood cells will scatter the light. The high resolution of OCT, approximately 10-fold that obtained with IVUS, permits detailed analysis of plaque composition (Figure 4) and stent and luminal characteristics, while vessel outer borders and plaque burden are more difficult to determine.[111]

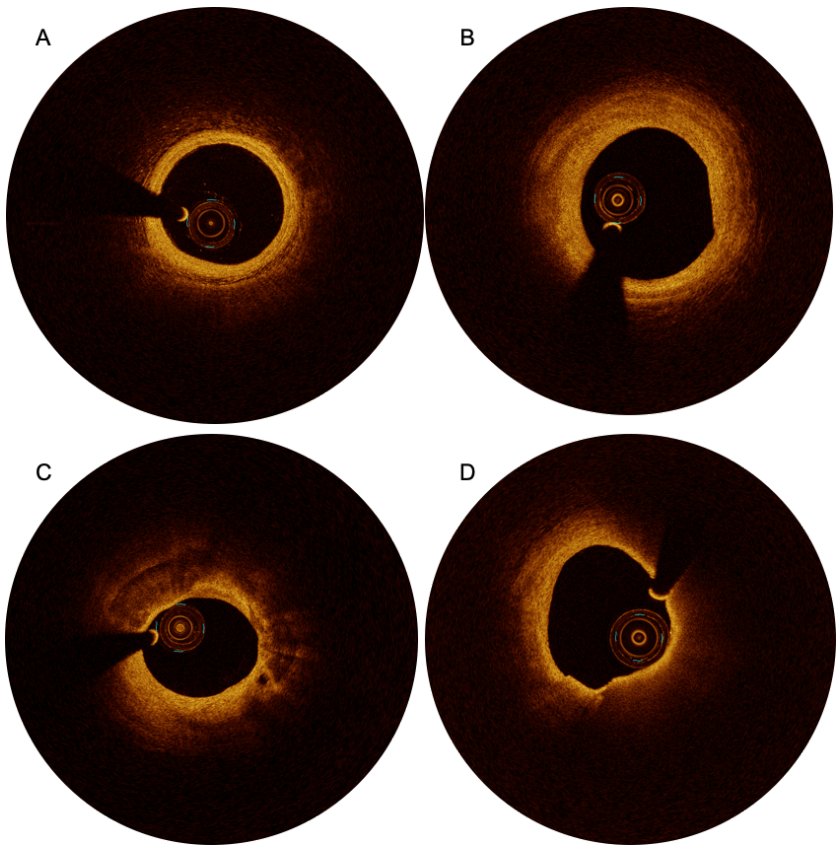

Figure 4. Optical coherence tomography images. Optical coherence tomography images of (A) a normal vessel, (B) a fibrotic lesion, (C) a calcified lesion, and (D) a lipid-rich lesion.

Intravascular imaging in clinical practice

Current European guidelines state that "IVUS or OCT should be considered in selected patients to optimize stent implantation" (Class IIa level of evidence B).[59] Several algorithms defining procedural guidance by intravascular imaging have been proposed.[82,102,112-114] Ideally, imaging is performed prior to, during, and after PCI. For left main coronary artery (LMCA) PCI, this includes imaging to confirm the necessity of intervention and for planning the procedure with respect to lesion preparation and stent strategy, sizing, and positioning. Post-PCI imaging should confirm optimal results or the need for further intervention through evaluation of stent expansion and lesion coverage, checking for severe proximal malposition, side branch compromise, dissections, and other procedural complications.[115] Angiographic assessment of LMCA stenoses can be challenging, and low agreement among experienced investigators in estimation of LMCA level of stenosis based on angiography has been reported.[116] Thus, intravascular imaging may be of particular value in LMCA PCI, as addressed in **Study I** of this thesis.

Antithrombotic medication

The use of antithrombotic medications including parenteral anticoagulation and oral antiplatelet agents are essential in patients undergoing PCI.[31,32] The recommended combination of drugs depends on clinical presentation, co-morbidities, and concomitant medications.

Antiplatelet Therapy

Current guidelines recommend the use of aspirin in combination with a P2Y12-inhibitor for most patients undergoing PCI, unless contraindicated.[31,32] Aspirin accomplishes its antiplatelet effect by suppressing production of the pro-thrombotic thromboxane A2, whereas P2Y12 inhibitors decrease platelet activity by blocking the adenosine diphosphate receptor. A number of oral P2Y12 inhibitors are available, including clopidogrel and the newer generation ticagrelor and prasugrel. Advantages of ticagrelor and prasugrel compared with clopidogrel include their rapid onset of action and more potent platelet inhibition. Dedicated randomized trials have demonstrated superior clinical outcome with ticagrelor and prasugrel compared to clopidogrel in patients with ACS, leading to their recommendation in current ACS guidelines.[31,32,117-119] A single parenteral P2Y12-inhibitor, cangrelor, is available in clinical practice. Cangrelor shows rapid onset with a powerful and constant effect during infusion. A similarly rapid cessation, with the return of platelet function within 30–60 min, is observed when the infusion is halted. Thus, cangrelor offers an appealing, albeit costly, alternative to patients not adequately

pre-treated with a P2Y12-inhibitor and those with a high thrombus burden or otherwise complex presentation.[31] Glycoprotein IIb/IIIa-receptor inhibitors (GPI) impede platelet aggregation by blocking glycoprotein IIb/IIIa receptors and preventing fibrinogen binding. Currently, use of GPI is primarily consigned to bail-out treatment in patients with high thrombus burden or procedural thrombotic complications, although randomized data supporting this strategy is lacking.[31,32]

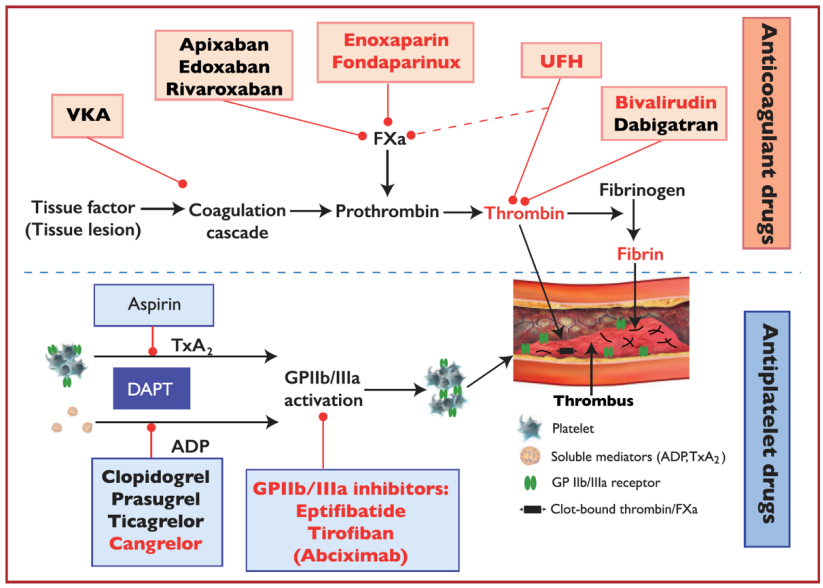

Figure 5. Antithrombotic therapies and pharmacological targets. Black letters represent drugs with oral administration, and red shows drugs with preferred parenteral administration. ADP=adenosine diphosphate; DAPT=dual antiplatelet therapy; FXa=factor Xa; GP=glycoprotein; TxA2=thromboxane A2; UFH=unfractionated heparin; VKA=vitamin K antagonist. Reprinted with permission of Eur Heart J 42, 1289-1367 (2021).

Anticoagulation

A parenteral anticoagulant is required during PCI, and unfractionated heparin (UFH) and bivalirudin represent the most commonly used agents worldwide.[59] Unfractionated heparin has been used in clinical practice since the 1930s and is highly familiar and readily available to health care professionals throughout the world. The anticoagulation effect is via the activation of antithrombin III, and the inactivation of both factor Xa and thrombin. Protamine sulphate can be used to reverse its effect. Adequate monitoring of activated clotting time is essential, as the response is unpredictable.[120] Heparin-induced thrombocytopenia, while uncommon, can be a devastating complication.[121]

Bivalirudin is a direct and reversible thrombin inhibitor, originally created as a synthetic alternative to UFH. Advantages over UFH include a shorter half-life and more predictable antithrombotic response. Studies have indicated a clinical benefit

of bivalirudin over UFH, primarily driven by lower rates of bleeding,[122] although at an apparently higher risk of acute stent thrombosis.[122,123] Recently, the VALIDATE-SWEDHEART trial concluded UFH and bivalirudin to be equally effective and safe in patients with myocardial infarction undergoing PCI with potent antiplatelet agents, GPI restricted to bail-out administration, and primarily radial access.[124] Thus, UFH is currently the recommended procedural anticoagulant in clinical guidelines, while bivalirudin may be considered in selected cases.[59]

Antithrombotic pre-treatment

Antithrombotic pre-treatment of STEMI patients, when the coronary anatomy is still unknown, is a topic of debate.[125] While early treatment with aspirin is recommended, the optimal timing of P2Y12 inhibitor administration is less clear. Early administration of an antithrombotic drug may reduce thrombotic activity and favour endogenous fibrinolysis, halting further clot formation and facilitating spontaneous reperfusion. Antithrombotic medication, however, comes at the price of increased risk of bleeding, and early administration can be detrimental, especially if the initial STEMI diagnosis is in error, e.g., in patients with aortic dissection or cardiac tamponade, or if acute or subacute CABG is required. Over the timeframe of the research comprising this work, recommendations have changed, and pre-hospital loading doses of ticagrelor for STEMI are now less common. However, UFH pre-treatment is still a frequent component of STEMI protocols, usually administered in the ambulance, despite the lack of conclusive data of its benefit.

Bleeding risk

While potent antithrombotic medications have improved outcomes of ischemia, bleeding following PCI is a major concern, representing the most frequently reported non-cardiac complication of PCI, with prognosis comparable to that of an adverse ischemic event. The increased use of radial access in PCI has minimized serious access site related bleeding complications,[126] but gastrointestinal bleeding remains problematic.[127] Both ischemia and bleeding significantly influence mortality during and after PCI,[128] and balancing the risk-benefit of medications to control thrombotic complications versus bleeding remains a clinical challenge.[59]

Aims and objectives

This thesis considered aspects of PCI including culprit and non-culprit lesion evaluation, stent implantation, pre-procedural anticoagulation, and thrombotic complications assessed by intravascular imaging and conventional coronary angiography, with the overall aim of optimizing PCI.

Study-specific objectives were

I. To ascertain long-term outcome in patients undergoing LMCA PCI with versus without the use of IVUS adjunctive to angiography.

II. To characterize lipid burden in culprit and non-culprit coronary segments by NIRS and to analyse the association of large lipid-rich non-culprit lesions, as detected by combined NIRS-IVUS, with subsequent clinical events.

III. To analyse the influence of stent edge landing zone vessel characteristics on stent edge neointimal healing, as revealed by serial OCT imaging.

IV. To evaluate heparin pre-treatment in patients with STEMI and its impact on thrombus burden and vessel patency prior to PCI.

V. To assess the occurrence and prognosis of IPST in patients with myocardial infarction undergoing PCI with contemporary antithrombotic medications.

Methods

This section presents an overview of the methods used in the reported research. Table 1 provides information of study populations, imaging technology, and primary endpoints. Full details of materials and methods of each study are available in the attached papers.

Table 1. Method overview

Study	Study Population	Imaging	Imaging Analysis	Primary Endpoints
I	Left main PCI in SCAAR n=2468	IVUS + Angiography	Use of IVUS (yes/no)	Composite of cardiovascular death, definite stent thrombosis, and restenosis.
II	Lund+Danderyd NIRS-IVUS n=144	NIRS-IVUS + Angiography	Lipid burden, Plaque burden	Composite of all-cause death, ACS requiring revascularization, and cerebrovascular event.
III	EGO-Studies n=220	OCT + Angiography	Stent edge landing zone characteristics, percent neointimal volume, MLA, MSA, and serial QCA assessment.	OCT-assessed %NIV.
IV	TASTE trial n=7144	Angiography	Thrombus burden, TIMI flow	Angiographic thrombus burden and TIMI flow prior to PCI.
V	VALIDATE trial n=6006	Angiography	Intra-procedural stent thrombosis, Thrombus burden, TIMI flow	Composite of cardiovascular death, MI, definite stent thrombosis, and target vessel revascularization.

ACS=acute coronary syndrome, IVUS=intravascular ultrasound, MI=myocardial innfarction, MLA=minimum lumen area, MSA=minimum stent area, NIRS=near infrared spectroscopy, OCT=optical coherence tomography, PCI=percutaneous coronary intervention, SCAAR=Swedish Coronary Angiography and Angioplasty Registry,TIMI=thrombolysis in myocardial infarction, QCA=quantitative coronary angiography, %NIV=percent neointimal volume.

Study populations

National Registries

The Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART) registry is a Swedish nationwide quality-of-care registry initiated

Figure 6. Location of hospitals participating in SWEDEHEART. Reprinted with permission from the SWEDEHEART Annual Report 2019, issued 2020.

to monitor and improve evidence-based cardiac care in Sweden with the long-term goal of reducing mortality and morbidity and maximizing cost-effectiveness. The registry was created in 2009 with the merging of four existing registries.[129] The Swedish Register of Information and Knowledge about Swedish Heart Intensive Care Admission (RIKS-HIA), established in 1995, collects hospital-stay data of patients admitted to any of the coronary care units in Sweden. Data include baseline patient information, medications, test results, and diagnoses. The Swedish Coronary Angiography and Angioplasty Registry (SCAAR), established in 1998, records procedural details of all coronary angiographies and interventions conducted in Sweden. Procedural data are reported at the coronary segment level and include peri-procedure medications, angiographic findings, use of intravascular imaging, coronary physiology, the intervention conducted, type and size of stents and balloons, post-dilatation, and adjunct therapeutic devices. The National Registry of Secondary Prevention after Heart Intensive Care Admission (SEPHIA) follows patients <80 years of age throughout the year following acute myocardial infarction, and the Swedish Heart Surgery Registry holds data of heart surgeries performed in the thoracic surgery centres in Sweden. The SWEDEHEART registry currently also includes the Swedish Transcatheter Cardiac Intervention Registry (SWENTRY) and The Swedish National Cardiogenetic Register. The Swedish personal identification number enables data in nationwide registers to be merged or cross-referenced with that of other registries of interest. Cross-referencing patient data with the Swedish National Population Registry and Swedish National Cause of Death registry provides information on mortality and cause of death, while the National Patient Registry and the Swedish Prescribed Drugs Registry lists concomitant diagnoses

and prescribed drugs. The nationwide coverage, the high rate of participation, and the potential to cross-reference information from other nationwide registries, make the SWEDEHEART registry an ideal platform for medical research. Data from the SWEDEHEART sub-registries were used in **Studies I**, **IV**, and **V** of this thesis.

Study I included patients who underwent unprotected LMCA PCI with stent implantation from 2005 through 2014 as registered in SCAAR. The National Patient Registry was used to access data of comorbidities, and the National Cause of Death registry provided data of vital status and date of death.

Studies IV and **V** were based on data from two registry-based randomized clinical trials (R-RCT) conducted within the SWEDEHEART registry.[124,130]

Registry-based clinical trials

The Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia (TASTE) study was a prospective multicentre controlled open-label R-RCT conducted within the SWEDEHEART registry from 2010 through 2013.[130] In total, 7244 patients were randomized to either PCI preceded by manual thrombus aspiration or to PCI alone. Antithrombotic therapy was administered according to current guidelines and local protocols. The study found no difference in the primary endpoint of 30-day all-cause mortality in patients with versus without thrombus aspiration, nor in the secondary endpoints of rehospitalization for myocardial infarction or stent thrombosis at 30 days. The study was the first in a series of R-RCTs conducted within the SWEDEHEART registry, providing proof of concept for this design of randomized trial.[131] **Study IV** included all subjects from the TASTE trial with the exception of 100 for whom data of heparin pre-treatment, thrombus burden, or thrombolysis in myocardial infarction (TIMI) flow was not available or who had withdrawn consent, thus generating a study population of 7144 STEMI patients.

The Bivalirudin versus Heparin in ST-Segment and Non-ST-Segment Elevation Myocardial Infarction in Patients on Modern Antiplatelet Therapy in the Swedish Web System for Enhancement and Development of Evidence-based Care in Heart Disease Evaluated according to Recommended Therapies Registry Trial (VALIDATE-SWEDEHEART) was, similar to the TASTE trial, an R-RCT conducted within the SWEDEHEART registry from 2014 through 2016.[124] The aim was to evaluate the efficacy and safety of bivalirudin as compared with heparin in 6006 patients with myocardial infarction undergoing primary PCI. The administration of a potent P2Y12 inhibitor was a condition of enrolment, and use of GPI was restricted to bail-out. Before arrival at the catheterization laboratory, patients were allowed to receive up to 5000 units of intravenous heparin. The study found no significant difference in the primary endpoint of all-cause death, myocardial infarction, or major bleeding at 30 days. **Study V** included all patients

from the VALIDATE-SWEDEHEART trial, thus comprising 6006 subjects with myocardial infarction, including STEMI (n=3005) and non-STEMI (n=3001).

NIRS-IVUS study population

Consecutive patients from Skåne University Hospital, Lund, Sweden and Danderyd Hospital, Stockholm, Sweden undergoing PCI with combined NIRS-IVUS imaging from 2012 through 2015 were screened for inclusion in **Study II**. Inclusion criteria were age >18 years, coronary angiography to investigate suspected ischaemic coronary artery disease, and combined NIRS-IVUS imaging of the culprit segment along with at least 10 mm of a non-culprit segment in a native coronary artery. Baseline, procedural, and follow-up data were obtained by review of medical records. One-hundred-sixty-eight patients were eligible for inclusion, 24 of whom were eventually excluded because of incomplete follow-up, referral for CABG, or uninterpretable NIRS-IVUS images, generating a study population of 144 patients.

OCT study population

Study III was based on data from the EGO-COMBO, EGO-ORION, and EGO-BIOFREEDOM studies.[132-134] The EGO studies were prospective, open-label, single centre studies conducted at Queen Mary Hospital, University of Hong Kong. The studies employed serial OCT imaging to evaluate stent strut coverage and neointimal healing, as previously described.[132-134] **Study III** pooled data of the EGO series studies to include all stent edges for which baseline and nine-month follow-up OCT data of the landing zone segment (stent edge and 5 mm reference segment) were available. The final study population comprised 220 patients with 296 lesions and 583 stent edges.

Image acquisition and analysis

The five studies making up this work included application of coronary imaging to evaluate stent implantation, lesion characteristics, neointimal healing, coronary flow, thrombotic burden, and IPST. Study-specific imaging analyses are described here and in detail in the relevant papers.

Study I obtained imaging status with respect to use of IVUS from the SCAAR registry. Whether IVUS was used, image interpretation, and its level of influence on the procedure were at the discretion of the interventional cardiologist performing the procedure, and no IVUS-specific data were available in the SCAAR registry.

Study II obtained combined NIRS-IVUS imaging data using the TVC Imaging System, Infraredx (Burlington, Massachusetts, USA). Imaging was performed pre-

and/or post-PCI, at the discretion of the physician conducting the procedure. Imaging analysis assessed the plaque burden, LCBI, and max$LCBI_{4mm}$. Plaque burden was measured by manual outlining of the vessel and lumen contours and calculated as the vessel area minus lumen area, divided by the vessel area. Measurements of the segment of interest were made at 1 mm intervals, and the maximum plaque burden was recorded. The LCBI and the max$LCBI_{4mm}$ were automatically generated by the NIRS software. Measurements were recorded within the culprit segment, defined as the segment treated with balloon angioplasty and/or stent implantation, and in adjacent continuous 10 mm non-culprit segments of the investigated artery, excluding previously stented segments. The non-culprit segments were screened for previously reported high-risk features including plaque burden ≥70% and max$LCBI_{4mm}$ ≥400.[135-137]

Study III obtained serial OCT imaging from the EGO studies that performed OCT at baseline, post-implantation, and after a nine-month follow-up period. The images were acquired using the Dragonfly imaging catheter and the C7-XR OCT Intravascular Imaging System (Abbott Vascular, CA, USA). The stent edge landing zone was defined as the stent border plus the 5 mm reference segment. Baseline OCT images were reviewed to determine landing zone morphology and features, including presence of calcium, lipid, edge dissection, and myocardial bridging as well as lumen and stent dimensions, in accordance with consensus definitions.[138,139] The nine-month follow-up OCT images were reviewed for stent and lumen dimensions of each millimetre of the 5 mm stent edge segment inside the stent border, calculating the neointimal area (stent area minus lumen area), stent edge neointimal volume, and stent edge percent neointimal volume (%NIV) defined as neointimal volume divided by stent volume. Minimum lumen area (MLA) was measured at the stent border and in the 5 mm reference segment. Serial quantitative coronary angiography (QCA) analysis was also conducted. Analyses were conducted at the Cardiovascular Research Foundation Core Laboratories, New York, New York.

Study IV recorded TIMI flow and thrombus burden prior to PCI, as reported by the interventional cardiologist performing the procedure. TIMI flow grade 0 was defined as the absence of antegrade flow and grade 1 as partial flow beyond the obstruction with incomplete filling distally. Grade 2 was defined as flow patency with delayed filling or washout of contrast, and grade 3 as normal coronary flow.[140] The thrombus burden was classified according to TIMI criteria, with the possibility of reclassification after flow restoration in cases of initial total vessel occlusion, as suggested by Sianos et al.[141] Grade 0 was defined as no features of thrombus present; grade 1, possible thrombus, i.e., angiographic findings suggestive, but not diagnostic, of thrombus; grade 2, definite thrombus with largest dimension less the vessel diameter; grade 3, definite thrombus with largest dimension greater than the vessel diameter but less than twice the vessel diameter; grade 4, definite thrombus

with the largest dimension more than twice the vessel diameter; grade 5, total occlusion, i.e. thrombus size cannot be determined.

Study V evaluated TIMI flow and thrombus burden, as described above, along with occurrence of IPST, defined as a new, reappearing or worsening thrombus related to a stent deployed during the procedure, partially or totally occluding the vessel. Angiographic assessment was made by the interventional cardiologist at the time of the procedure and reported as stipulated in the VALIDATE-SWEDEHEART study protocol.

Endpoints

Study I analysed long-term clinical outcome following LMCA PCI, as obtained from the national registries. The primary composite endpoint was all-cause mortality, restenosis, and definite stent thrombosis. Secondary endpoints included the individual components of the primary composite endpoint as well as probable stent thrombosis, defined as unexplained death within 30 days.[87]

Study II recorded clinical endpoints following PCI over the available follow-up period, a minimum of one year. Events were recorded by review of medical records and adjudicated by study investigators. The primary composite endpoint of major adverse cardiovascular and cerebrovascular events (MACCE) was defined as all-cause mortality, non-culprit related ACS requiring revascularisation, and cerebrovascular events (transient ischaemic attack or stroke).

Study III analysed OCT-detected endpoints at a nine-month follow-up. The primary endpoint was %NIV, and secondary endpoints were edge and reference MLA. Exploratory endpoints included angiographic binary stent edge restenosis ≥50% at nine months and clinical edge-related revascularization over a follow-up period of five years, adjudicated by the study investigators.

Study IV recorded angiographic thrombus burden and TIMI flow prior to PCI as reported by the interventional cardiologist at the time of the procedure. The primary endpoints were visible intracoronary thrombus (grades 2–5) and total vessel occlusion (TIMI 0) prior to PCI. Secondary endpoints included in-hospital major bleeding (Bleeding Academic Research Consortium [BARC] type 2, 3, or 5),[142] stroke, and 30-day all-cause mortality, obtained from national health registries.

Study V analysed clinical outcome at 30 days post-PCI, as reported and adjudicated in the VALIDATE-SWEDEHEAT trial. The primary endpoint was a composite of cardiovascular death, myocardial infarction, out-of-laboratory definite stent thrombosis, and target vessel revascularization. Secondary endpoints included the individual components of the primary endpoint and major bleeding (BARC type 2, 3, or 5). The composite primary endpoint was also assessed at 180 days post-PCI.

Statistical analyses

Baseline information is expressed as numbers and percentages, mean and standard deviation, or median and interquartile range. Differences between groups were analysed by the chi-square test, Student t-test, or Mann-Whitney U test, as appropriate. Normality was determined by histograms and the Kolmogorov-Smirnov test. Receiver operating characteristic (ROC) analysis with c-statistic (area under the ROC curve) was conducted, plotting the sensitivity against 1–specificity for various thresholds to illustrate diagnostic accuracy. Time-to-event data were illustrated by Kaplan-Meier curves, with the log-rank test for significance testing. Unadjusted and adjusted hazard ratios (HR) and odds ratios (OR) with 95% confidence intervals (CI) were calculated by univariable and multivariable Cox regression and logistic regression, respectively. Variables in the multivariable models were selected to fit the data based on medical plausibility and differences among groups. Clustered data related to multiple lesions within a vessel and/or patient were accounted for by hierarchical mixed-model analyses. Propensity score matching was used to balance baseline differences in non-randomized observational data. A propensity score of 0–1 was calculated by mixed-effects logistic regression, with the exposure of interest (IVUS guidance in **Study I**) as the dependent variable. Patients were matched based on their propensity score using the caliper method, with a single control for each case. Kappa-statistics were calculated to test inter- and intra-observer variation. Subgroup analyses included the assessment of p-values for interaction. A two-sided $P<0.05$ was considered significant. Statistical analyses were performed in STATA v.14 (Stata Corp, College Station, TX, USA), SPSS v.22–26 (IBM Corp.; Armonk, NY, USA) or R v.3 (R Foundation for Statistical Computing; Vienna, Austria).

Ethics

All studies were approved by local ethics committees, and patients included in the TASTE trial, VALIDATE-SWEDEHEART, and the EGO-series studies provided written informed consent. Registry data was anonymized and subjects were assigned unique study identification numbers. As the SWEDEHEART registry is a national quality-of-care registry for health care improvement, written informed consent is not mandatory for patient registration. All patients are informed of their participation in the registry and the ongoing right to opt out. Approval of the National Board of Health and Welfare, the Swedish Data Inspection Board, and an ethics committee is required for merging of SWEDEHEART data with other nationwide registries holding sensitive patient information.

Results

Study I

Baseline Characteristics

Of 5067 patients undergoing LMCA PCI from 2005 through 2014, we excluded from the analysis 1747 patients with previous CABG, 217 with Killip class 3–4, 195 with procedure complications or death, 120 based on the size of the implanted stent, and 266 readmissions. The final study population consisted of 2468 individuals, with IVUS used in 621 (25.2%). Patients undergoing LMCA PCI with IVUS were younger and generally healthier with lower rates of heart failure and prior myocardial infarction than those not having IVUS. Conversely, a greater proportion of patients without IVUS underwent PCI because of ACS, and procedures not employing IVUS were more often performed outside regular office hours. The number and size of stents, fluoroscopy time, volume of contrast medium, and the use of post-dilatation were greater in procedures that utilized IVUS than in those without, and revascularization was more often considered complete at the end of the procedure. The propensity score model generated 340 with/without IVUS pairs with well-matched baseline characteristics, with the exception of larger stent diameters in the IVUS group.

Clinical outcomes

Over a follow-up period of <10 years, the primary composite endpoint of all-cause mortality, restenosis, and definite stent thrombosis occurred at a significantly lower rate in patients with IVUS plus angiography guidance than in those with angiography guidance alone (Table 2). Kaplan Meier failure estimates, stratified by IVUS status, are presented in Figure 7. Multivariable regression analysis demonstrated the use of IVUS during LMCA PCI to be significantly and independently associated with a lower cumulative occurrence of the primary composite endpoint (HR 0.65; 95% CI 0.50–0.84; P=0.001). The results were consistent in the propensity score–matched population (unadjusted HR 0.54; 95% CI 0.37–0.80; P=0.002).

The occurrence of the secondary endpoint of all-cause mortality was also lower in patients with procedures that included IVUS than in those that did not (HR 0.62; 95% CI 0.47–0.82; P=0.001). In-stent restenoses and definite stent thromboses were numerically lower with IVUS, but did not differ significantly (Table 2). Subgroup and sensitivity analyses yielded overall consistent results.

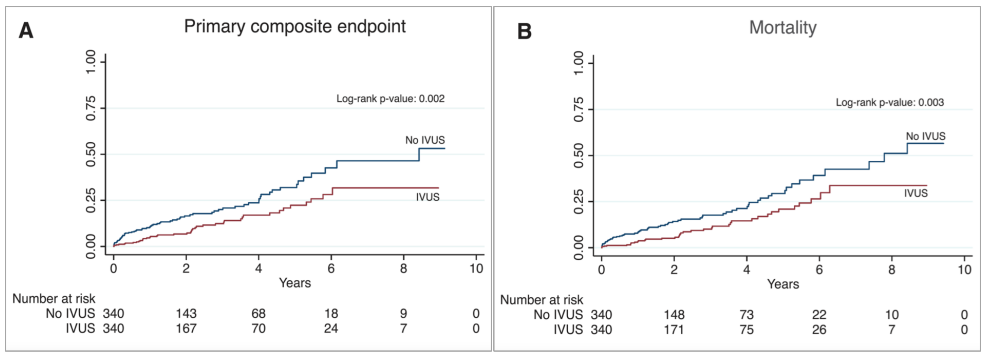

Figure 7. Primary and secondary endpoints in the propensity score–matched population. Kaplan Meier failure estimates in the propensity score–matched population (n=680) stratified by the use of intravascular ultrasound (IVUS) during the procedure. The IVUS group exhibited significantly lower occurrence of the primary composite endpoint (A) and the secondary endpoint of all-cause mortality (B).

Table 2. Primary and secondary endpoints in patients with versus without IVUS

Endpoint	No IVUS events/procedures (Kaplan-Meier event rates)	IVUS events/procedures (Kaplan-Meier event rates)	Univariable HR (95% CI)	Multivariable HR (95% CI)
Total study population				
Primary composite endpoint	541/1847 (62.5)	86/621 (33.5)	0.47 (0.37-0.58)*	0.65 (0.50-0.84)*
Mortality	509/1847 (62.1)	75/621 (32.5)	0.44 (0.34-0.56)*	0.62 (0.47-0.82)*
Restenosis	54/1847 (4.1)	14/621 (2.9)	0.72 (0.40-1.29)	NA
Definite stent thrombosis	8/1847 (1.7)	0/621 (0.0)	NA	NA
Probable stent thrombosis	90/1847 (4.9)	6/621 (1.0)	0.19 (0.09-0.44)*	NA
PS-matched population				
Primary composite endpoint	68/340 (53.2)	41/340 (31.8)	0.54 (0.37-0.80)†	NA
Mortality	63/340 (56.6)	37/340 (33.7)	0.54 (0.36-0.81)†	NA
Restenosis	10/340 (5.3)	6/340 (2.4)	0.55 (0.20-1.52)	NA
Definite stent thrombosis	1/340 (1.9)	0/340 (0.0)	NA	NA
Probable stent thrombosis	6/340 (1.8)	3/340 (0.9)	0.50 (0.12-1.98)	NA

Number of events/number of procedures and Kaplan-Meier event rates throughout the available follow-up period. Multivariable model adjusted for age, sex, diabetes mellitus, heart failure, previous myocardial infarction, previous stroke, previous PCI, chronic kidney disease stage, enrolment year, indication, time of day, urgency, upstream dual antiplatelet therapy, aspirin, ticagrelor, bivalirudin, low-molecularweight heparin, GPIIbIIIa inhibitor, other concomitantly diseased coronary vessels, ACC/AHA lesion classification, drug-eluting stent vs. bare-metal stent, number of stents implanted, number of stented segments, with/without complete revascularization, and PCI-centre. Propensity score matching was performed using the same covariates. CI=confidence interval; HR=Hazard Ratio; IVUS=intravascular ultrasound; NA=not applicable (few events or irrelevant model); PS=propensity score.*P≤0.001, †P<0.01.

Study II

Baseline characteristics

The analysis included 144 subjects, mean age 66.5 years and 70.8% male. The indications for PCI were STEMI (43.8%), non-STEMI (24.3%), unstable angina (13.9%), and CCS (18.1%). Culprit arteries included LAD (66.0%), LCX (12.5%), and RCA (21.5%).

Imaging findings

Imaging data were available for a median vessel length of 60.0 mm (47–75) and median non-culprit LCBI was 65 (9–119). Thirty-six patients exhibited a non-culprit segment maxLCBI$_{4mm}$ ≥400, and 13 had a non-culprit segment with plaque burden ≥70%. Baseline characteristics were similar among patients with and without the high-risk features of LCBI ≥median, maxLCBI$_{4mm}$ ≥400, and plaque burden ≥70%, with only hypertension significantly more common in patients with non-culprit LCBI <65, and high-density lipoprotein cholesterol levels lower among patients with a non-culprit maxLCBI$_{4mm}$ ≥ 400.

Culprit versus non-culprit lesion discrimination

Culprit segments exhibited significantly higher maxLCBI$_{4mm}$ values than did non-culprit segments (425 vs. 74, P<0.001). The ROC curve analysis showed maxLCBI$_{4mm}$ to discriminate culprit from non-culprit segments, c-statistic 0.85, 95% CI 0.81–0.89 (Figure 8).

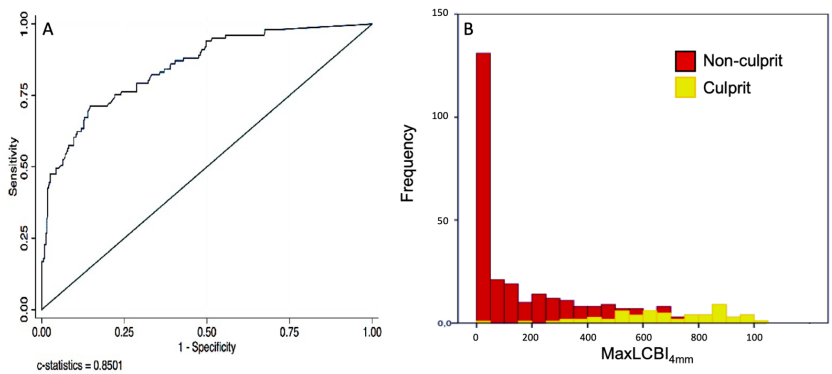

Figure 8. Discrimination of culprit vs. non-culprit segments by maxLCBI$_{4mm}$. ROC curve and histogram of culprit vs. non-culprit segments demonstrating culprit segments to present with higher maxLCBI$_{4mm}$ values compared with non-culprit segments. maxLCBI$_{4mm}$=highest lipid core burden index in a 4mm segment; ROC=receiver operating characteristics.

Clinical outcomes

Over a median follow-up period of 2.9 years, 19 observed MACCEs included ten all-cause deaths, seven cases of ACS requiring revascularisation, and two cerebrovascular events. Unadjusted event rates for patients with and without a non-culprit segment maxLCBI$_{4mm}$ ≥400 are presented in Figure 9. The occurrence of MACCE was significantly higher in patients with NIRS-identified non-culprit maxLCBI$_{4mm}$ ≥400 (HR 3.67, 95% CI 1.46–9.23; P=0.006) and non-culprit LCBI ≥median (HR 3.08, 95% CI 1.11–8.56; P=0.031). Non-culprit plaque burden ≥70% showed no significant relationship with MACCE. Segment-level analysis was not feasible.

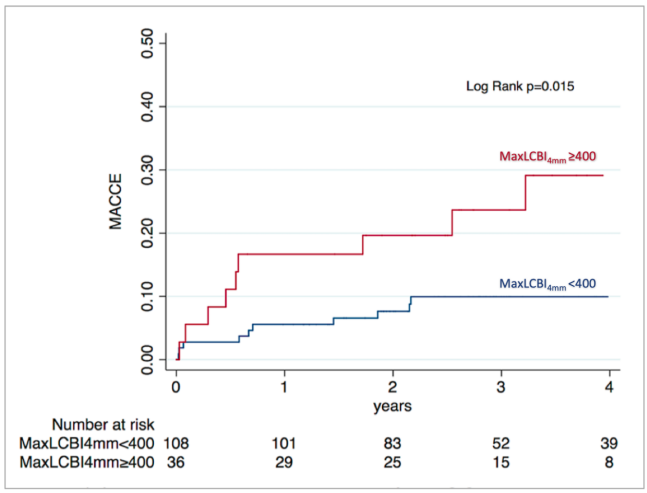

Figure 9. Kaplan-Meier failure estimates for major adverse cardiovascular or cerebrovascular events including all-cause mortality, acute coronary syndrome requiring revascularization, and cerebrovascular events, stratified by the presence of a non-culprit maxLCBI$_{4mm}$ ≥400. An NIRS-detected non-culprit segment with maxLCBI$_{4mm}$ ≥400 was associated with a higher rate of adverse events. MACCE=Major adverse cardiovascular or cerebrovascular events; maxLCBI$_{4mm}$=highest lipid core burden index in a 4mm segment; NIRS=Near-infrared spectroscopy.

Study III

Baseline characteristics

Landing zone characteristics were described for 583 stent edges in 296 lesions in 220 patients at baseline, immediately post-implantation, and at nine months. The study population had a mean age of 63 years, 82.7% were male, 37.3% had diabetes, 61.8% hypertension, and 19.5% had previously undergone PCI. Included vessels were the LAD (43.6%), LCX (27.4%), and RCA (29.1%). Median lesion length was

18.5 (13.6–25.4) mm. Stents used were the BioFreedom (Biolimus A9, Biosensors Europe SA, Morges, Switzerland) in 35.5%, the Combo (OrbusNeich Medical, Fort Lauderdale, FL) in 24.7%, the Resolute Integrity (Zotarolimus, Medtronic, Minneapolis, Minnesota) in 20.3%, and the BioMatrix NeoFlex (Biolimus A9, Biosensors International, Singapore) in 19.3%.

Imaging findings

Baseline and follow-up images of stent edge landing zone characteristics and %NIV are presented in Figure 10. At baseline, calcium was detected in 37.0% of landing zones (median calcium arc 62º [42–100]), lipid in 23% (median lipidic arc 92º [74–113]), medial dissection >60° in 5.5%, and a myocardial bridge in 5.1%. At nine months, stent edge %NIV was 11.6 (6.50–17.0), reference MLA was 5.52 (3.76–7.38) mm^2, and stent edge MLA was 5.75 (4.22–7.45) mm^2.

Multivariable hierarchical regression analysis showed landing zone calcium, edge dissection, and myocardial bridging to be independent predictors of %NIV at nine months. Adjusted correlation coefficients were calcium -1.84, 95% CI -3.02, -0.66, P=0.002; edge dissection 3.27, 95% CI 0.68, 5.85, P=0.01; and myocardial bridging 4.79, 95% CI 2.09, 7.50, P=0.001. Landing zone lipid arc showed no correlation with %NIV but was an independent predictor of reference MLA (adjusted correlation coefficient -0.34, 95% CI -0.57, -0.11, P=0.004) and was associated with angiographic stent edge restenosis at nine months (OR 5.25, 95% CI 1.59–17.31 per 90° increase in lipid arc, P=0.006), which was reported in four patients. Lipidic plaque arc >180º was present in landing zone segments of two patients at baseline, both of whom presented with angiographic stent edge restenosis after nine months. Correlation of baseline stent edge minimum stent area (MSA) with follow-up MLA was stronger than that of %NIV with follow-up MLA (Figure 11).

Clinical outcomes

Clinically indicated edge-related revascularization was performed at nine stent edges, seven of which were the proximal edge. Baseline OCT-detected characteristics did not show a significant relationship with clinically indicated edge-related revascularization.

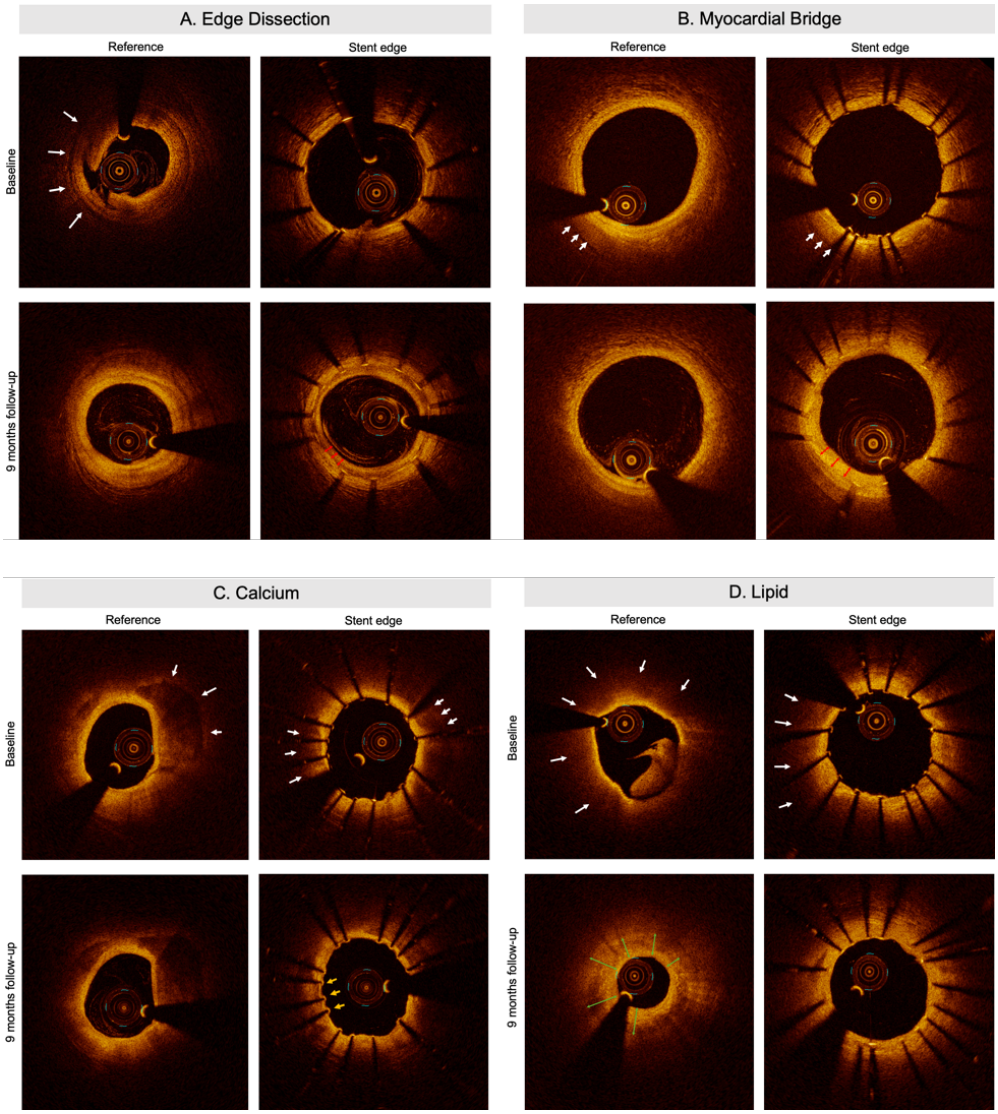

Figure 10. Baseline and nine-month follow-up OCT images of the stent edge at the landing zone segment. Stent edge dissection, myocardial bridging, and calcium were independent predictors of %NIV, whereas lipid was not. (A) White arrows demonstrate edge dissection, (B) myocardial bridge, (C) calcium, and (D) lipid. Landing zone segments with edge dissections and myocardial bridging showed a greater %NIV (red arrows) than did those without, whereas segments with calcium had a lower %NIV (yellow arrows). Lipid was an independent predictor of reference MLA, but not %NIV. %NIV=percent neointimal volume; MLA=minimum lumen area; OCT=Optical coherence tomography.

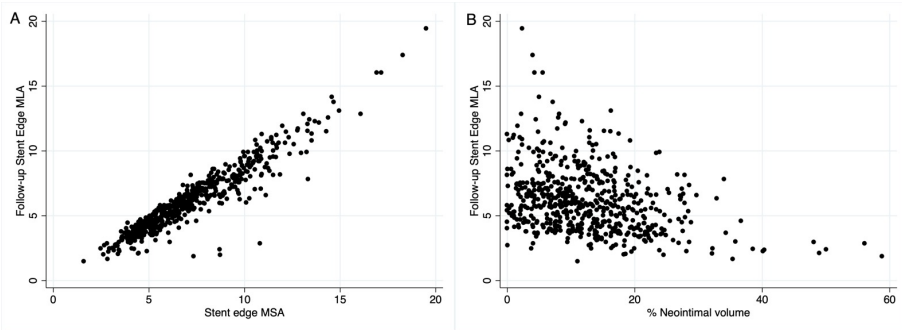

Figure 11. Correlation plots. Correlation plots of the relationship of baseline stent edge minimum stent area (MSA) to follow-up minimum lumen area (MLA) (A). Correlation of percent neointima volume (%NIV) with follow-up MLA (B).

Study IV

Baseline Characteristics

The study included 7144 patients with STEMI from the TASTE trial; 2898 (41%) received UFH pre-treatment and 4246 (59%) did not. The groups were similar in baseline variables of age, sex, and the majority of comorbidities, although hypertension was more prevalent among patients without UFH pre-treatment, and smoking rates were higher in patients with UFH pre-treatment. Patients with UFH pre-treatment more often received pre-treatment with aspirin plus ticagrelor. A greater proportion of those not receiving UFH pre-treatment were taking warfarin or a P2Y12 inhibitor at the time of admission and a greater proportion were pre-treated with antithrombotics other than UFH.

Imaging findings

The TIMI flow and thrombus burden in patients with and without UFH pre-treatment are presented in Figure 12. The proportion of patients with visible intracoronary thrombus (61.3% vs. 66.0%, $p<0.001$) and total vessel occlusion (62.9% vs. 71.6%, $p<0.001$) prior to PCI was lower with heparin pre-treatment than without. Multivariable regression analysis showed heparin pre-treatment to be significantly and independently associated with lower occurrence of a visible thrombus (multivariable OR 0.73, 95% CI 0.65–0.83; $P<0.001$) and total vessel occlusion (multivariable OR 0.64, 95% CI 0.56–0.73; $P<0.001$).

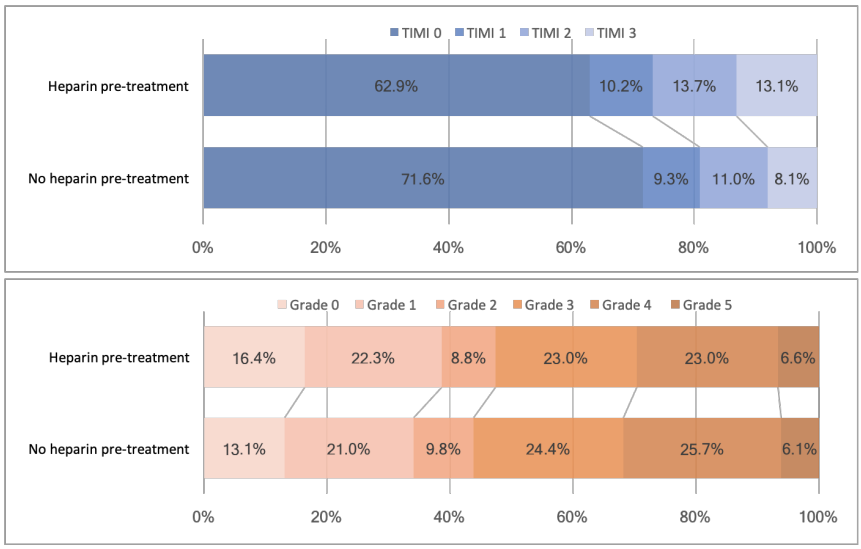

Figure 12. Thrombolysis in myocardial infarction (TIMI) flow and thrombus burden in patients with and without heparin pre-treatment. The proportion of patients presenting with each TIMI flow and thrombus burden grade prior to percutaneous coronary intervention relative to heparin pre-treatment.

There was no significant difference in the occurrence of the secondary endpoints of in-hospital bleeding (OR 0.84, 95% CI=0.55–1.27), in-hospital stroke (OR 1.17, 95% CI=0.48–2.82), and 30-day all-cause mortality (HR 0.88, 95% CI=0.60–1.30) between those with and without UFH pre-treatment. The results were consistent across subgroups with a single exception: UFH pre-treatment did not show reduced risk of total vessel occlusion in patients who did not receive pre-procedure DAPT. A sensitivity analysis excluding patients pre-treated with low molecular weight heparin (LMWH), warfarin, fondaparinux, or thrombolysis demonstrated comparable results.

Study V

Baseline Characteristics

The VALIDATE study included 6006 patients with STEMI (n=3005) and non-STEMI (n=3001). Intra-procedural stent thrombosis was reported by the interventional cardiologist in 55 (0.9%) patients. A higher proportion of patients with IPST presented with STEMI, Killip class ≥2, and TIMI flow 0–1 at the time of admission than did those without IPST. Stent length was greater in patients with IPST, and they showed higher rates of post-dilatation and more antithrombotic

medications, including bailout GPI and additional heparin, than those without IPST. Finally, TIMI flow grade 3 was less likely to be obtained in patients with IPST.

Clinical outcomes

The occurrence of the primary composite endpoint of cardiovascular death, myocardial infarction, definite stent thrombosis, and target vessel revascularization at 30 days was significantly higher in patients with IPST (Figure 13) (unadjusted HR 4.87, 95% CI 2.66–8.90; P<0.001), and the relationship remained after adjustment in the multivariable model (adjusted HR 3.82, 95% CI 2.05–7.12; P<0.001). Intra-procedural stent thrombosis was also associated with higher rates of the composite endpoint components cardiovascular death (adjusted HR 3.33, 95% CI 1.32–8.41; P=0.011), target vessel revascularization (adjusted HR 4.86, 95% CI 2.09–11.3, P<0.001), and ARC-defined definite stent thrombosis (unadjusted HR 8.48, 95% CI 2.0–35.7, P=0.004), although the low number of events did not allow for multivariable adjustments in the latter. No relationship was observed with myocardial infarction or major bleeding. Findings at 180 days were similar. The association of IPST with adverse events was consistent among subgroups, including the patients showing TIMI flow grade 3 at the end of the procedure.

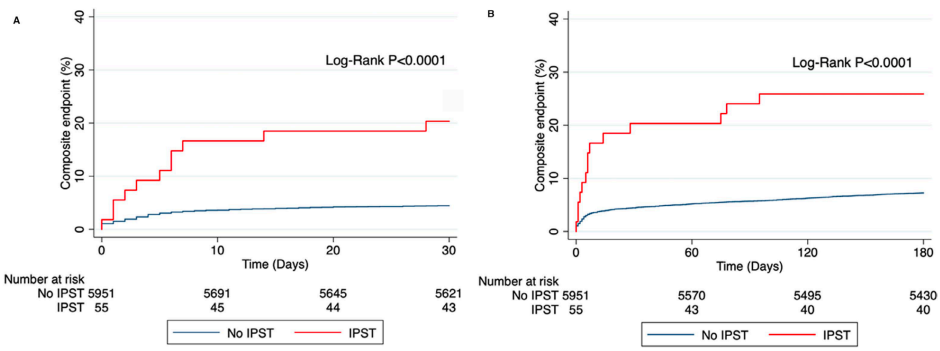

Figure 13. Kaplan-Meier failure estimates for the composite primary endpoint in patients with myocardial infarction undergoing primary percutaneous coronary intervention, stratified by the occurrence of intra-procedural stent thrombosis. Intra-procedural stent thrombosis was associated with a higher risk of adverse outcome over 30 (A) and 180 days (B) follow-up. IPST=intra-procedural stent thrombosis.

Discussion

In spite of major advances in interventional cardiology, ischemic heart disease remains the predominant cause of death and a major contributor to disability worldwide.[28] While procedural success rates of PCI are exceptional, patients not rarely return to the catheterization laboratory with stent-related issues or de-novo disease progression, despite secondary prevention medications.[73,143] The reduction in mortality following acute myocardial infarction seen in recent decades has moreover appeared to plateau.[144] Thus, measures are needed to further optimize PCI and improve clinical outcomes.

The research of this thesis considered diagnostic, technical, and pharmacological strategies in PCI. The studies share a focus of invasive coronary imaging, including conventional angiography and the adjunct intravascular imaging modalities IVUS, NIRS, and OCT, and identify potentially valuable contributions to PCI optimization with respect to procedure guidance, risk stratification, treatment evaluation, and insight into mechanisms of stent-related complications.

Left main coronary artery imaging

Coronary artery bypass grafting was previously the preferred revascularization strategy for LMCA disease. As outcomes following PCI have improved, LMCA PCI has become a viable option, especially in patients at high surgical risk and with low or intermediate anatomical complexity.[145-148] Current guidelines encourage consensus of a dedicated heart team to establish the revascularization strategy optimal for the individual patient.[59] A potential benefit of IVUS guidance has been suggested for patients with LMCA disease referred to PCI.[115] However, data have not been conclusive, and the implementation of IVUS in LMCA PCI is still limited worldwide.[149,150]

Although LMCA PCI has been proven a feasible option to CABG, it undeniably presents a clinical challenge.[151-153] The anatomy of the LMCA, with natural vessel tapering, possible lack of proximal reference, and atherosclerosis often involving the distal bifurcation, make the procedure technically complex. The large proportion of myocardium at risk further emphasizes the necessity of a meticulous stent

strategy to achieve results comparable to those of CABG. Hence, IVUS guidance may be of particular benefit in this coronary segment.

Study I aimed to evaluate the clinical impact of IVUS in LMCA PCI based on data from the nationwide SCAAR registry.[154] Occurrence of the primary composite endpoint of all-cause mortality, restenosis, and definite stent thrombosis as well as of all-cause mortality alone was significantly lower following procedures using IVUS. While residual confounders in a non-randomized observational study cannot be ruled out, the association was consistent across subgroups and in all applied statistical models adjusted for baseline differences.

Mechanisms of improved outcome

While the nationwide SCAAR registry records a large number of procedural factors in PCI, reports of imaging data are limited. At the time of **Study I**, the registry did not provide data of imaging timing (before and/or after stent implantation) or how imaging data was used to guide the procedure. In addition, no information of imaging-detected dimensions of MLA, plaque burden, or reference vessel diameter was available in the SCAAR registry. The mechanisms explaining the better clinical outcome in patients undergoing LMCA PCI with IVUS in **Study I** are therefore difficult to ascertain. Still, some differences in procedure data merit consideration, although any causal relationship is hypothetical. Stent length and diameter were greater in patients who had IVUS, and they were more likely to receive multiple stents and post-dilatation than were those without IVUS. Hence, a greater rate of more appropriately-sized and expanded stents with adequate lesion coverage could have been the source of the favourable outcome in the IVUS group. In contrast, small and, especially, under-expanded stents are recognized as risk factors for stent thrombosis.[89] Given the critical position of the LMCA, acute stent thrombosis is likely to be a catastrophic event and possibly a factor contributing to the higher mortality rate among patients without IVUS.

Although patients with unstable haemodynamics and advanced disease represent a group in which imaging guidance may be particularly beneficial, IVUS was less often used in these patients. Thus, we recognize the possibility of unfavourable outcome in the non-IVUS group secondary to selection bias. To address this issue, patients presenting with Killip class ≥3 were excluded from the analysis. Patients receiving stents smaller than 3.0 mm in diameter, indicating a small vessel in which imaging may not have been feasible, were also excluded. In the remaining study population, both hierarchical multivariable regression models and propensity score–matching were conducted to, as far as possible, adjust for other baseline differences between groups. With all applied statistical models, the use of IVUS remained significantly associated with lower rates of the primary composite endpoint.

Data in support of imaging-guided PCI

Since the publication of **Study I**, data derived from registries of other geographic areas have supported the use of IVUS in LMCA PCI,[155,156] and meta-analyses have produced similar results.[157,158] However, the significantly lower occurence of all-cause mortality with IVUS-guided LMCA PCI, with no clear evidence of the underlying mechanisms, has raised concern regarding unmeasured residual confounders,[82] an issue that cannot be ruled out despite adjustments in statistical models. Thus, randomized trials are needed to confirm our observations and establish the role of IVUS imaging in LMCA PCI.

Randomized trials of IVUS have been conducted in non-LMCA interventions. The randomized IVUS-XPL demonstrated IVUS-guided PCI in long lesions to result in a significantly lower rate of adverse outcome compared with angiography guidance alone.[159] While the benefit of IVUS guidance in an all-comers population might be less pronounced than in individuals with lengthy or otherwise complex lesions, the randomized ULTIMATE trial demonstrated a significantly lower rate of target vessel failure in all-comer patients randomized to IVUS guidance. The benefit of IVUS was even more pronounced in patients meeting criteria of optimal IVUS-guided PCI (MLA >5.0 mm^2 or 90% of distal reference area, residual reference plaque burden <50%, and no media edge dissection >3 mm in length).[160] Similarly, de la Torre Hernandez recently demonstrated LMCA PCI guided by a pre-specified IVUS optimization protocol to be associated with a lower rate of adverse events compared with angiography guidance, whereas no statistical difference was observed between angiography and IVUS guidance without these pre-specified criteria.[161] Indeed, the imaging catheter in and of itself does not improve outcome. Adequate image interpretation and actions in response to the findings are, along with technical skills, crucial to optimizing PCI and ultimately improving outcome.

Imaging in clinical practice – nice to have or necessary?

Although the use of intravascular imaging during PCI in Sweden is generally limited, recent data from the SWEDEHEART registry show a substantial increase in use of IVUS and OCT in LMCA PCI (Figure 14).[144] Recent data from the British Cardiovascular Intervention Society demonstrated a similar increase in imaging use in LMCA PCI, along with a concomitant reduction in procedural complications, in-hospital adverse events, and 30-day and 12-month mortality rates.[155]

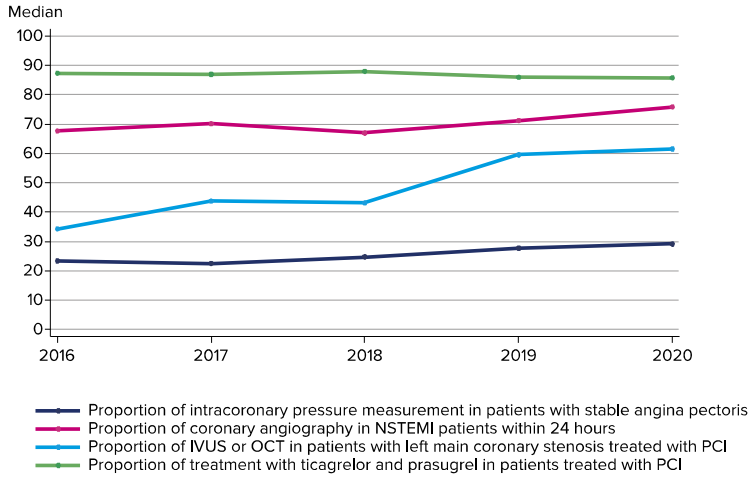

Figure 14. Proportion of procedures with use of intracoronary imaging and pressure measurements, 2016–2020. The proportion of patients (%) with left main coronary stensosis undergoing PCI with intravascular imaging (IVUS or OCT). Reprinted with permission of the SWEDEHEART Annual Report 2020, issued 2021. IVUS=intravascular ultrasound; OCT=optical coherence tomography; PCI=percutaneous coronary intervention

While data of OCT use in LMCA PCI are limited, studies addressing its potential benefits are underway.[162] The high resolution OCT images that provide accurate information of lesion morphology and detection of procedural complications may be of particular benefit in distal LMCA lesions, although technical challenges of OCT imaging in larger vessels and ostial disease present possible limitations.[111]

While randomized trials are needed to establish the optimal imaging modalities for LMCA PCI, our data, along with that of others, suggest a potential hazard of relying on angiography alone.[157,158]

Vulnerable patients and vulnerable plaques

Lesions causing ACS have been well-defined by autopsy studies, and intravascular imaging modalities now enable in-vivo characterization of these, often lipid-containing, lesions.[163,164] An imaging tool that can identify lesions causing acute myocardial infarction will hypothetically be able to prospectively detect lesions at risk of initiating future events. Addressing this topic, **Study II** investigated the in-vivo appearance of culprit and non-culprit coronary segments by NIRS and analysed the relationship of large lipid-rich non-culprit segments detected by combined NIRS-IVUS with clinical outcome.[165]

The NIRS analysis found greater quantities of lipid in culprit vs. non-culprit segments and showed that $maxLCBI_{4mm}$ discriminates culprit from non-culprit

segments, especially accurately in patients with STEMI. As previously obtained data have suggested $maxLCBI_{4mm}$ ≥400 to be a signature of lesions causing myocardial infarct and plaque burden ≥70% to be associated with adverse cardiovascular events, we screened the non-culprit segments for these features.[135,137,166]

Thirty-six non-culprit segments in 36 patients had a $maxLCBI_{4mm}$ ≥400, one of which led to confirmed ACS requiring revascularization within the study follow-up period. However, the most frequently recorded endpoint in **Study II** was all-cause death without available angiography or post-mortem examination, and the lesion responsible for these events could not be determined. In addition, the majority of lesions requiring revascularization for which follow-up angiography was available occurred in coronary segments not imaged at baseline. Thus, lesion-level analysis of the relationship of baseline imaging findings with adverse cardiovascular events was not possible. However, a significant association of $maxLCBI_{4mm}$ ≥400 with subsequent patient-level MACCE was observed. As baseline characteristics and co-morbidities were found to be poorly correlated with lipid burden, NIRS-derived measurements of lipidic burden could provide supplemental information regarding a patient's cardiovascular risk.

The significance of plaque burden

While an IVUS-detected plaque burden ≥70% has been demonstrated to be a marker of adverse outcome risk,[135] non-culprit plaque burden ≥70% was not found to increase risk of the composite primary endpoint in **Study II**. Although large plaques do not always lead to clinical events, the role of a substantial plaque burden in causing adverse events was again confirmed in the recent PROSPECT II trial.[167] The small study population and consequently low number of non-culprit segments with plaque burden ≥70% in Study II is a possible explanation for the lack of an observed relationship of plaque burden ≥70% with future events in our study. The fact that the chemogram was not blinded to the physician conducting the procedure could also have affected results, amplifying the estimated ability of NIRS to discriminate culprit from non-culprit segments, as it is possible that a longer stent (defining the culprit segment) was selected to fully cover the NIRS-revealed lipid.

At the time of publication of **Study II**, limited data regarding the implications of NIRS-detected atherosclerotic burden, vulnerable plaques, and vulnerable patients were available. Our results corroborated those of previous studies and supported ongoing prospective trials.[136,168-170] To date, data from two large-scale studies have confirmed the value of NIRS in identifying plaques that confer high risk of cardiovascular events.[167,171] Similar findings with respect to OCT-detected vulnerable plaques have been reported,[172,173] and the question of whether myocardial infarction can be predicted and ultimately prevented has been revived.

The Holy Grail or a fools' errand?

While studies have linked features detected by IVUS, NIRS, and OCT with an elevated risk of adverse events at both patient and lesion level, the positive predictive value is low and their clinical relevance debated.[174] Considering atherosclerosis as a systemic disease with frequent plaque ruptures and healing only occasionally leading to symptoms, systemic therapy options may be preferred over focal detection and treatment. Nevertheless, patients receiving optimal medical treatment still experience recurrent events.[175] In a pilot study randomizing patients with a non-culprit segment exhibiting an IVUS-detected plaque burden ≥65% to either optimal medical treatment or optimal medical treatment plus a bioresorbable vascular scaffold, the scaffold group showed larger MLA at follow-up than seen in the medically treated group.[175] While the study was not powered for hard clinical endpoints, a trend of favourable outcome was observed.

Whether high-risk patients with high-risk lesions will benefit from identification, intensified systemic treatment, preventive stenting strategies, or some other intervention remains to be elucidated. Ongoing trials are in the process of further assessing features of vulnerable plaque and the possible benefit of preventative stent implantation (NCT02316886, NCT03857971).

Stent edge landing zone characteristics

Stenting typically aims to connect a 'normal to a normal' coronary segment. A completely unaffected reference segment may, however, be difficult to locate. As long and overlapping stents are linked to stent thrombosis and restenosis,[176] it may be necessary to tolerate some degree of landing zone disease in order to avoid implanting excessively long or overlapping stents. The level of acceptable reference segment disease, as detected by OCT, is poorly defined, and the relevance of landing zone morphology is not well understood. Pooling of serial OCT data from the EGO-series studies provided a unique database for investigation of stent edge landing zone features and analysis of their relationship with stent edge healing and edge-related complications over time. **Study III** found several OCT-defined characteristics, assessed at the time of the index procedure, to show a relationship with %NIV at nine months post-PCI.

Landing zone morphology

Imaging studies using serial IVUS have demonstrated stent edge restenosis to result from negative remodelling, neointima hyperplasia, and/or lesion progression in the reference segment,[78] and have identified residual plaque burden in the reference segment as a strong risk factor for stent-related complications.[77] While OCT does

not permit accurate assessment of vessel remodelling or plaque burden, it offers excellent visualization of the morphology and innermost structures of the vessel, including luminal borders, stent struts, and level of neointimal proliferation.

As residual reference segment plaque burden identified by IVUS presents a well-known risk of stent edge restenosis,[77] an association of advanced landing zone disease by OCT with high %NIV could be expected. However, we observed no association between lipidic landing zones and %NIV and found calcific landing zones to be negatively associated with %NIV at nine months. The limited vascularization and small quantity of fibrous tissue in calcified lesions could contribute to the low degree of neointimal proliferation, and similar findings have been reported in autopsy studies.[177,178] Malapposed stent struts, often observed in calcific lesions, could also have influenced the results.[94]

Lack of association between landing zone lipid and %NIV can possibly be attributed to the variation in neointimal response at lipidic stent edge segments, which ranged from extensive asymmetric neointima to poorly covered stents. Landing zone lipid arc, however, showed a significant negative correlation with reference MLA, as well as a positive association with angiographic stent edge restenosis at nine months, although such events were scarce. Hence, we speculate that stent edge restenosis following stent implantation at landing zones with residual lipidic plaque may be attributed to disease progression in the reference segment, rather than to neointimal hyperplasia at the stent edge per se. Of note, the majority of landing zone disease observed in **Study III** was mild to moderate, and whether more extensive disease might have led to increased neointimal proliferation cannot be concluded from our data. Both patients with landing zone lipidic arc >180º exhibited angiographic stent edge restenosis at nine months, supporting the prudence of avoiding landing zones with lipid arc ≥185º, as suggested by Ino et al.[179]

Stent edge dissection and myocardial bridging

The clinical relevance of OCT-detected stent edge dissection has been debated, as many dissections appear to heal uneventfully.[180-182] In **Study III**, no clinical adverse event was attributable to an index stent edge dissection, although the significant association of edge dissection with higher %NIV could represent an enhanced healing response following medial injury, hypothetically posing a risk of restenosis. Detailed characterization of these medial edge dissections and their healing pattern in the reference segment could be of value in defining edge dissections not associated with adverse clinical events. Such investigation was not a component of **Study III**, which dealt primarily with stent edge %NIV.

Landing zone myocardial bridges are well defined by IVUS, but less so by OCT.[183-186] Although typically considered a benign finding, unintentional stenting of a myocardial bridge has been associated with adverse outcome.[184] **Study III** found

landing zone segments with a myocardial bridge to show significantly higher %NIV at nine months than segments without a myocardial bridge, substantiating prior IVUS-derived data suggesting that neointimal hyperplasia plays an important role in restenosis of stented myocardial bridge segments.[185] Again, clinical adverse events were few in **Study III**, and none arose from a stented myocardial bridge segment. Thus, the clinical relevance of these observations needs further evaluation.

Baseline stent edge MSA was strongly and positively associated with stent edge MLA at nine months. Thus, baseline MSA may be clinically more important than the identification of predictors of degree of neointimal healing, as %NIV correlated less strongly with follow-up MLA.

Study III aimed to assess neointimal volume based on repeat OCT. However, thin fibrin deposits or thrombus can be difficult to discriminate from true neointima. Subclassification of neointimal morphological patterns were moreover not included in our analysis. In addition, the influence of landing zone plaque burden, vessel remodelling, culprit lesion morphology, tissue protrusion, and malapposed stent struts were not addressed in the study.

Antithrombotic therapy and thrombotic complications

Guidelines mandate antithrombotic medications in contemporary PCI, and balancing the risk of thrombotic events against bleeding complications is a clinical challenge. As therapeutics, procedural techniques, and equipment evolve, including use of more potent antithrombotic agents, newer generations of DES, and the increased use of radial-access, the PCI scene is constantly changing. Thus, ongoing research to address both ischemia and bleeding complications is needed.

Antithrombotic pre-treatment

While time to reperfusion is a critical prognostic factor in patients with STEMI, some delay from symptom onset to PCI is inevitable. Current STEMI guidelines present pros and cons of early administration of antiplatelet therapies, but the timing of anticoagulation is not specified. Accordingly, clinical practice with respect to anticoagulation pre-treatment for STEMI varies considerably. A pre-treatment drug should be easy to administer, show rapid onset of effect, and preferably be reversible. In this context, UFH represents an attractive option, being highly familiar to health care professionals, with quick onset, short duration of effect, and with an available antidote (protamine). While UFH pre-treatment is common in STEMI protocols in Sweden as well as in other countries, data of randomized trials supporting the strategy are scarce. **Study IV** showed UFH pre-treatment to be associated with a lower thrombus burden and better TIMI flow prior to PCI

compared with patients not pre-treated with UFH. These favourable angiography-indicated endpoints were consistent across the majority of subgroups, without increased in-hospital bleeding complications. A similar study from a group in Australia recently published findings corroborating our results.[187]

The benefit of pre-treatment with antithrombotic medications including bivalirudin, LMWH, GPI, and P2Y12 inhibitors has been investigated with inconsistent results.[188-191] As the timing of initiation of pre-treatment, concomitant drugs, and dosage differed among studies, direct comparisons are difficult. In **Study IV**, the specific timing of administration and dose of heparin was not available, although 5000 units of intravenous UFH administered in the ambulance is a common recommendation in UFH pre-treatment protocols. Hypothetically, antithrombotic medication is most effective when administered early, when the thrombus is newly formed. Results of a study indicating a time-dependent effect of UFH pre-treatment were recently published.[192]

Notwithstanding the observed favourable impact of UFH pre-treatment on the primary endpoints of thrombus burden and TIMI flow in **Study IV,** UFH pre-treatment showed no impact on the secondary endpoint of 30-day all-cause mortality. While a single UFH dose might not reduce 30 day all-cause mortality, both thrombus burden and TIMI flow have been demonstrated to be associated with clinical outcome.[193] A reduction in thrombus burden and improved vessel patency could hypothetically reduce infarct size and halt microvascular injury and subsequent development of ischemic heart failure.[194] A longer clinical follow-up, monitoring infarct size and development and progression of ischemic heart failure, may better quantify the clinical benefit of UFH pre-treatment. However, a retrospective observational study including over 10 000 subjects from the TOTAL study revealed, similar to our findings, a significant association of UFH pre-treatment with lower thrombus burden and improved vessel patency, but showed no significant differences in death, stroke, reinfarction, or heart failure at 12 months.[195]

In general, current data demonstrate UFH pre-treatment to be beneficial, and without major risk of bleeding complications.[187,192,195,196] Whether UFH pre-treatment improves vessel patency and, ultimately, clinical outcome, needs to be investigated in a sufficiently powered randomized trial.

Clinical importance of intra-procedural stent thrombosis

Stent thrombosis is a feared complication of PCI, but the clinical relevance of stent thrombosis occurring during the procedure, IPST, is not universally recognized. The aim of **Study V** was to estimate the occurrence and evaluate the outcome of IPST in a contemporary setting using data from the VALIDATE-SWEDEHEART study.[197] We found IPST reported in 0.9% of patients, along with an associated poor prognosis. As the number of cases was small, multivariable analysis to identify

predictors of IPST was not possible. However, several pre-procedural and procedural variables differed in patients with and without IPST. Although causality of such associations cannot be determined, some factors deserve consideration: The higher rate of STEMI-presentation, poor TIMI flow, and higher Killip class among patients with IPST could have contributed both to its occurrence and its adverse outcome, and the higher rate of long stents and post-dilatation may represent both risk factors and treatment strategies for IPST. Some of these factors have been demonstrated to pose an increased risk of ARC-defined out-of-lab stent thrombosis,[198] supporting the association of IPST with subsequent ARC-defined definite stent thrombosis observed in **Study V**.

There are several possible reasons for the lack of recognition of IPST among interventional cardiologists, despite previously reported poor prognosis following IPST.[98] First and foremost, IPST is rare, occurring in fewer than 1% of patients with myocardial infarction, and less often in patient without ACS.[99] Second, previous studies of IPST have been based on retrospective analyses conducted in dedicated core laboratories, and **Study V** represents the first evaluation of the applicability of IPST detection to clinical practice in the contemporary era of potent P2Y12 inhibitors.

Although the clinical relevance of a procedural thrombotic event that is immediately detected and treated could be in question, the poor prognosis of IPST, even in patients with adequate final epicardial flow, highlights the importance of recognizing this event regardless of final PCI results. Normal epicardial flow does not ensure adequate myocardium perfusion, and residual thrombi, distal embolization, vasoconstriction, and microcirculatory injury and/or dysfunction, possibly associated with IPST, can all contribute to a poor outcome. Re-evaluation of the reported IPST cases in **Study V** could be of value in identifying the mechanisms fundamental to IPST and its associated adverse outcome and is a topic for future investigation.

Treatment options for IPST include bailout GPI, frequently observed in our study. No patient treated with cangrelor during the procedure developed IPST. While this group of patients was small, the observation is in agreement with data from the CHAMPION PHOENIX trial, which reported lower rates of stent thrombosis with the use of cangrelor versus clopidogrel, with a particularly low risk of IPST.[99] Although several aspects of the development of IPST remain to be elucidated, our results support routine reporting of IPST in PCI and its inclusion in definitions of acute stent thrombosis, allowing further studies to investigate its causes, treatment options, and possible prevention.[98,100]

Strengths and limitations

Post-hoc registry-based studies

While registry-based observational studies have some evident limitations, they provide the opportunity to enrol and follow a large number of patients representative of real-world populations in real-world clinical practice, as opposed to RCTs that often comprise a highly selected population of younger and healthier individuals, with specific study protocols and potentially limited external validity.[199] Hypotheses generated by registry-based observational studies can also be of value as a prelude to more demanding, time-consuming, and costly randomized trials. The innovation of R-RCTs conducted within a nationwide registry has introduced a feasible option for clinical trials, taking advantage of the benefits of existing registries from real-world clinical practice, while adequately evaluating randomized treatment allocation.[131]

Core laboratory versus site-assessed analysis

While independent core laboratory analysis of coronary imaging is the gold standard to ensure optimal inter- and intra-observer agreement and blinded evaluation of treatment strategies, it may not always be available, feasible, or necessary. Thus, while we recognize the limitations conferred by lack of core-laboratory verification of some of the imaging-based analyses conducted in this research, the valuable insights provided by site-assessment of imaging data should not be overlooked. In particular, this thesis demonstrates the applicability of imaging to clinical practice and the possibility of real-time image-assessment by the physician performing the procedure.

Image-derived surrogate endpoints

Surrogate endpoints are essential to medical research, and imaging-derived surrogates have played a central role in the development, evaluation, and implementation of coronary intervention, assessing the efficacy and safety of new devices, pharmaceuticals, and technologies. Replacing undesirable and less common clinical endpoints, surrogates are chosen based on their expected prognostic value with respect to the endpoint of interest. Thus, a surrogate endpoint

typically allows for a smaller study population and a shorter follow-up period, resulting in less expensive, less time-consuming, and logistically simpler clinical trials. However, caution is required: As an intervention can cause undesirable side effects beyond the measured surrogate outcome, a positive effect of the intervention on the surrogate endpoint does not guarantee a net beneficial impact. In **Study IV**, the surrogate endpoints of TIMI flow and thrombus burden were analysed to evaluate the effect of heparin pre-treatment. Although heparin pre-treatment was significantly associated with a lower risk of the surrogate endpoints, and although the surrogate endpoints were significantly associated with hard clinical outcome, heparin pre-treatment did not show direct correlation with clinical outcome. The neutral effect on mortality, despite a beneficial effect on the primary endpoints, could be explained by a link between heparin and other, less favourable, outcomes, for example, higher risk of bleeding. In **Study IV**, however, bleeding rates were not found to be higher in patients receiving heparin, and a positive clinical outcome might have been observed with longer follow-up and expanded clinical endpoints.

Conclusions

The findings of this research demonstrate the value of imaging during PCI in facilitating stent implantation, stratifying patient-level risk, defining a role for heparin pre-treatment in STEMI, and providing insight into mechanisms of stent-related complications, of potential importance for PCI optimization.

Study-specific conclusions:

I. The use of adjunct IVUS in LMCA PCI was associated with a significantly lower occurrence of adverse outcomes compared with LMCA PCI guided by angiography alone. Our findings support the use of IVUS in LMCA PCI to optimize stent implantation and outcome, although a randomized trial is needed to confirm the role of IVUS in LMCA PCI.

II. Near-infrared spectroscopy accurately differentiated culprit from non-culprit coronary segments, confirming significantly higher values of $maxLCBI_{4mm}$ in culprit vs. non-culprit segments. The rate of adverse outcomes was greater in patients exhibiting non-culprit segments with $maxLCBI_{4mm} \geq 400$, supporting the value of NIRS in identifying patients at higher risk of future cardiovascular events.

III. Stent edge landing zone characteristics, as revealed by OCT at the time of stent implantation, showed significant relationships with neointimal healing, reference MLA, and angiographic stent edge restenosis, providing insight into the mechanisms of the healing response following DES implantation.

IV. STEMI patients pre-treated with heparin exhibited significantly lower rates of visible thrombi and vessel occlusion prior to PCI, with no increased risk of bleeding. Although a randomized trial is needed to confirm these findings and to demonstrate a clinical benefit of heparin pre-treatment, our observations indicate that heparin pre-treatment is effective and safe in STEMI patients referred to primary PCI.

V. Intra-procedural stent thrombosis remains a rare but severe complication of PCI even with potent P2Y12 inhibitors. The poor outcome observed in patients experiencing IPST emphasizes the importance of routine reporting of IPST, regardless of final TIMI flow.

Future perspectives

Despite the high success rate of PCI, with impressively safe and effective stents, target lesion failures related to in-stent restenosis, stent thrombosis, and neo-atherosclerosis continue to occur. When the large number of coronary stents implanted annually is considered, the occurrence of stent-related complications is not negligible.[200] While there is no single explanation of, or solution for, these stent-related events, intravascular imaging can play a role in their detection, treatment, and prevention. Dedicated randomized trials with pre-specified imaging guidance criteria are needed to confirm the contribution of coronary imaging to optimizing PCI and improving stent-related outcome.

While intravascular imaging technologies have been commercially available for several decades, their clinical implementation remains low, and use varies substantially among operators and countries.[149,150] Although modern imaging devices are more efficient and user-friendly than earlier models, their modest clinical use is often blamed on the time requirement, together with cost and lack of expertise in both image acquisition and interpretation.[149] Sceptics refer to minimal data supporting the utility of intravascular imaging in clinical practice despite a wealth of available evidence including randomized trials, registry-based trials, and meta-analyses.[159] Advances in imaging technology, including development of faster and more user-friendly software, artificial intelligence/machine learning to assist in image interpretation, as well as increased funding for imaging catheters may expand its implementation in clinical practice. Numerous randomized studies investigating imaging-guided PCI in a range of clinical scenarios are ongoing and may further support the implementation of imaging in clinical practice.[201-204]

Adverse events following PCI can also arise from non-culprit coronary segments. Contemporary data demonstrate angiographically non-stenotic non-culprit lesions to be responsible for the majority of recurrent adverse cardiac events following an index myocardial infarction.[167] High-risk lesion features have been described, including a large lipid burden as suggested in Study II. Best practice treatment for these high-risk plaques and patients remains to be established. Systemic pharmacological approaches are of utmost importance, and the feasibility of local plaque sealing with preventive stenting is currently being evaluated.

Importantly, sudden cardiac death remains an occasional devastating initial manifestation of coronary artery disease. If trials can demonstrate effective

pacifying strategies, primary prevention may be feasible. Hypothetically, high-risk patients can be subjected to non-invasive coronary imaging. Those found at highest risk could then be referred for invasive coronary angiography with intravascular imaging to tailor medical and/or interventional treatment strategies. The value of individual tailoring of interventions and pharmacotherapies before, during, and following PCI, as opposed to a one-size-fits-all strategy, is increasingly recognized in contemporary clinical practice.

Sammanfattning (in Swedish)

Idag finns effektiv behandling för den som drabbas av hjärtinfarkt. Trots detta är hjärtinfarkt den vanligaste dödsorsaken i både Sverige och världen. Studierna i denna avhandling belyser olika aspekter av perkutan kranskärlsintervention, den vanligaste typen av behandling vid hjärtinfarkt, med det övergripande målet att optimera behandlingen.

Åderförfettning, eller åderförkalkning i hjärtats kärl finns i någon grad hos nästan alla människor och är den vanligaste underliggande orsaken till kranskärlssjukdom. Vissa har en tendens att bilda fler och farligare fettinlagringar, så kallade plack. Åderförfettning med plack kan göra att det blir trångt i hjärtats kärl. Den kroniska formen av kranskärlssjukdom utmärks av att hjärtats blodtillförsel då kan bli otillräcklig, framförallt när hjärtats behov av blodtillförsel ökar. Central bröstsmärta vid ansträngning, som lättar efter en kort stund i vila, är den klassiska symptombilden vid kärlkramp. Akut kranskärlssjukdom med hjärtinfarkt orsakas oftast av att ett fettrikt plack spricker. På det spruckna placket bildas en blodpropp som abrupt stänger av blodflödet i kärlet. Hjärtats celler nedströms om avstängningen drabbas då av akut syrebrist, ett livshotande tillstånd. För att minska skadans utbredning är snabb behandling av akut hjärtinfarkt viktigt.

Den vanligaste metoden för att återställa blodflödet i ett trångt eller stängt kranskärl är perkutan kranskärlsintervention, ofta kallat PCI från engelskans: percutaneous coronary intervention. Proceduren börjar med en kranskärlsröntgen för att avbilda kranskärlen och aktuella förträngningar. När en förträngning är identifierad kan den vidgas med hjälp av en ballong som blåses upp inuti kärlet. För att kärlet skall hålla sig öppet sätts ett metallnät in, ett så kallat stent. Blodförtunnande mediciner är av största vikt både under och efter PCI, för att minska risken för proppbildning i stentet och för att minska risken för framtida hjärtinfarkt.

Utöver den standardmässigt utförda kranskärlsröntgen finns kateterburna bilddiagnostiska undersökningsmetoder för att studera kranskärlssjukdom inifrån kärlen, så kallad intravaskulär bilddiagnostik. Med hjälp av ultraljud – intravascular ultrasound (IVUS), och ljusvågor – Near-infrared spectroscopy (NIRS) och optical coherence tomography (OCT) skapas tvärsnittsbilder av kranskärlen, visualiserade från insidan. Metoderna erbjuder överlägsen upplösning av kranskärlväggens utseende, inklusive eventuella plack som inte är bedömbara på vanlig kranskärlsröntgen. Intravaskulär bilddiagnostik kan därför vara av värde som tillägg

till vanlig kranskärlsröntgen, och kan då förbättra bedömning av kranskärlsplack, guida val av stent och stentplacering, och identifiera komplikationer.

Studie I: Vänster huvudstam är det kranskärlssegment som försörjer störst del av hjärtat med blod. PCI i detta segment kräver därför yttersta noggrannhet. Att använda IVUS vid PCI mot vänster huvudstam har därför föreslagits vara av särskild nytta. I studie I inkluderades 2468 patienter som genomgått PCI med insättning av stent i vänster huvudstam från det svenska nationsomfattande kranskärlsregistret SCAAR. IVUS användes vid ca 25% av procedurerna. I studien sågs en klart minskad risk för död och stentkomplikationer efter PCI som genomförts med hjälp av IVUS, jämför med PCI utan IVUS. Resultaten stödjer användning av IVUS vid PCI mot vänster huvudstam, men måste bekräftas i en randomiserad studie.

Studie II: Från histologiska studier vet vi hur de plack som orsakat hjärtinfarkt och plötslig hjärtdöd ser ut, och att de flesta av dessa plack innehåller stora fettansamlingar. NIRS är en relativt ny kateterburen undersökningsmetod som kan detektera fett i kranskärlen hos levande människor. NIRS kan därför vara av värde för att hitta fettrika plack med en misstänkt ökad risk att orsaka framtida hjärtinfarkt. Studie II studerade kranskärlsplack med fokus på fettinlagring och plackstorlek med hjälp av kombinerad NIRS och IVUS. Studien inkluderade 144 patienter och visade att kranskärlsplack som orsakar kliniska besvär (kärlkramp eller hjärtinfarkt) innehåller mer fett än övriga kranskärlssegment. Hos 36 patienter fanns stora fettinlagringar, detekterade med NIRS, även i kranskärlssegment som såg friska ut på kranskärlsröntgen. Dessa 36 patienter hade en signifikant högre risk att drabbas av kardiovaskulära händelser under uppföljningstiden i studien. Studien drog slutsatsen att NIRS kan vara av värde vid bedömning av en patients kardiovaskulära risk.

Studie III: Vid PCI med insättning av stent är målet att täcka hela det sjuka kranskärlssegment med stent, så att de båda stentkanterna når fram till friska kärlsegment. Helt friska kärlsegment kan dock vara svårt att hitta och ett acceptabelt område för stentet får ofta godtas. Studie III undersökte hur kärlets morfologi kring stentkanterna påverkar hur stentet läker in i kärlväggen över tid, samt risken att utveckla stent-relaterade komplikationer. Studien inkludera 220 patienter med 583 stentkanter, undersökta med OCT då stentet sattes in, samt igen efter 9 månader. Studien visade att kärlets morfologi har betydelse för läkningen vid stentkanten och för risken att drabbas av stent-relaterade komplikationer, kunskap som kan vara av värde för PCI-operatören vid val av stent och stentplacering.

Studie IV: Patienter med hjärtinfarkt ges blodförtunnande mediciner både under och efter PCI för att minska risken för ytterligare blodproppar. Eftersom snabb behandling är viktigt vid hjärtinfarkt har det föreslagits att behandling med blodförtunnande mediciner även innan PCI kan vara av värde. Den optimala timingen och kombinationen av blodförtunnande läkemedel att ge innan PCI har visat sig vara en komplicerad fråga, där risk för proppbildning måste ställas mot risk

för blödning. Det blodförtunnande läkemedlet heparin ges i Sverige och andra delar av världen ibland redan i ambulansen till patienter med akut hjärtinfarkt, men klar evidens för denna strategi saknas. Studie IV inkluderade 7144 patienter med akut hjärtinfarkt och undersökte nyttan av förbehandling med heparin. Studien visade att patienter som fått heparin innan PCI hade bättre flöde i kärlet och mindre ofta en synlig tromb, utan att någon ökad risk för blödning kunde observeras. Förbehandling med heparin tycks således vara säkert och effektivt att ge till patienter med akut hjärtinfarkt under transport till PCI.

Studie V: Proppbildning i ett insatt kranskärlsstent, så kallad stenttrombos, är en ovanlig men fruktad komplikation, förknippad med dålig prognos. Stenttrombotisering kan ske redan under PCI och kallas då för procedur-relaterad stenttrombos, (intra-procedural stent thrombosis – IPST). Studie V undersökte förekomst av och prognos efter IPST hos patienter med hjärtinfarkt behandlade med moderna, potenta blodförtunnade mediciner. Studien inkludera 6006 patienter och bara 55 patienter (0.9%) drabbades av IPST. Dessa patienter hade en klart sämre prognos än patienter utan IPST. Studien drog slutsatsen att IPST är en ovanlig men allvarlig komplikation vid PCI, som bör rapporteras rutinmässigt.

Sammantaget belyser avhandlingen olika aspekter av PCI samt hur intravaskulär bilddiagnostik kan användas för att guida stent-implantation, bedöma en patients kardiovaskulära risk och förstå mekanismer som bidrar till stent-relaterade komplikationer, kunskap som kan vara av värde för att optimera PCI.

Acknowledgements

My greatest gratitude to all who helped and supported me throughout the work of this thesis. It would not have been possible without you.

A special thank you to

Professor David Erlinge, my brilliant supervisor, for giving me the opportunity to conduct medical research, for welcoming me to the Department of Cardiology in Lund, and for sending me off to New York on the experience of a lifetime. Thank you for your expertise and generosity and for always encouraging prompt submissions.

Dr Pontus Andell, my co-supervisor, for inspiring me to engage in medical research, guiding me in the world of medical statistics and for great travel company during cardiology conferences across the US.

Dr Sasha Koul, my co-supervisor, for much appreciated and thoughtful input throughout the research of this thesis.

Dr Akiko Maehara, for training in intravascular imaging analysis and for all our late-night discussions at the CRF core lab. You are truly an extraordinary woman.

Dr Moman Mohammad, for your great knowledge and high ambition and for your endless willingness to help me out.

Professor Stefan James, Professor Ole Fröbert, and other co-authors for great collaboration, appreciated input, and reviewing of my work.

Dr Göran Olivecrona and Dr Matthias Götberg, co-authors and excellent interventional cardiologists, for always being genuinely friendly and taking the time to discuss interventional cardiology with a PhD student researching PCI without having ever performed one.

Rebecca Rylance, for help with statistics and for the nice coffee breaks with Frukostklubben.

Lena Lindén and Monica Magnusson, for your assistance in whatever situation arose, for tears and laughter, and for always having my back.

Friends and colleges at the Department of Cardiology in Lund, it is a pleasure working with all of you.

To all my friends, for always being there and for bearing with me while finishing this thesis.

Lena and Per Karlsson, Mum and Dad, thank you for your unconditional love and support, no matter the mood I might be in.

Johan and Fredrik Karlsson, my brothers, for making sure that medical discussions at family events are limited. You are the best.

Agnes, my beloved daughter. Thank you for giving life a greater meaning. You mean the world to me and I am so genuinely proud to be your mother.

Erik, my husband, no words can ever describe the support and love that you bring me. I love you. You're next.

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Printed by Media-Tryck, Lund 2022 NORDIC SWAN ECOLABEL 3041 0903

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Sofia Bergman (Karlsson) was born in 1991 and received her medical degree from Lund University in 2016. She entered the PhD program later the same year, conducting research in interventional cardiology. She completed a guest research fellowship at Columbia University and the Cardiovascular Research Foundation, New York, 2018 through 2019, focusing on intracoronary imaging, and a clinical internship with research profile at Skåne University Hospital, Lund in 2021. This thesis comprises five studies assessing aspects of percutaneous coronary intervention, aiming to optimize the procedure. Dr Bergman is currently working as a resident physician at the Department of Cardiology at Skåne University Hospital in Lund.

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Lund University, Faculty of Medicine
Doctoral Dissertation Series 2022:28
ISBN 978-91-8021-189-5
ISSN 1652-8220