Invasive treatment of coronary artery disease

Aspects on antithrombotic and percutaneous treatment options

PER GRIMFJÄRD
Abstract


The outcome after percutaneous coronary intervention (PCI) has improved considerably thanks to more effective antithrombotic treatment strategies and improved coronary stents. Stent thrombosis (ST) is a rare complication to PCI associated with considerable mortality and morbidity.

The general aim of this thesis was to add real-world evidence for antithrombotic and technical strategies in invasive treatment of coronary artery disease. Five observational studies were performed on a large, unselected, real-world population undergoing PCI. All studies were based on data from the national registry SWEDEHEART.

In 31,258 patients undergoing PCI for ST-elevation myocardial infarction (STEMI), the rate of definite early ST was low (0.84%, n=265) but ST was associated with very high mortality (21%, n=51) at one year.

Among 20,600 patients with STEMI, we compared the outcomes for those treated with heparin and those treated with bivalirudin during PCI. Rates of ST were low and similar with heparin and bivalirudin but all-cause mortality at 30 days and one year was significantly higher with heparin. We found no differences in rates of major bleeding, re-infarction and stroke.

A novel bioresorbable scaffold (Absorb), used in patients undergoing PCI for all indications, was associated with a four- to eightfold higher adjusted rate of definite ST over two years, compared with conventional modern drug-eluting stents (DES). One in four ST events occurred later than one year after PCI. Rates of in-stent restenosis were comparable with Absorb and DES. Suboptimal implantation technique and non-adherence to antiplatelet therapy guidelines was common among patients with bioresorbable scaffold thrombosis.

The novel parenteral and potent platelet inhibitor cangrelor was used nearly exclusively in STEMI (n=899), in early presenters with high-risk, often with cardiac arrest (18%) but was associated with low ST rates and no major bleeding events.

In an unselected population of 65,000 patients undergoing PCI for all indications, the Xience permanent polymer everolimus eluting stent (n=36,600) appears to be safe and effective with low event rates of ST and in-stent restenosis. Compared with a control group of other modern DES (n=167,000) including a high proportion of thinner struts and absorbable polymers, Xience exhibits similar results in all important endpoints.

All studies of this thesis provided important real-world evidence on antithrombotic and technical treatment strategies in invasive management of coronary artery disease.

**Keywords:** PCI, STEMI, stent thrombosis, bivalirudin, heparin, bioresorbable scaffold, cangrelor, drug eluting stent, DES

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List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.


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Additional Papers

The following relevant co-written papers are not included in this thesis.


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Abbreviations

ACS  Acute coronary syndromes
AF   Atrial fibrillation
ASA  Acetylsalicylic acid
BMS  Bare metal stent
BRS  Bioresorbable scaffold
CABG Coronary artery by-pass graft surgery
CCS  Chronic coronary syndromes
CVD  Cardiovascular disease
DAPT Dual antiplatelet therapy
DOAC Direct oral anticoagulant
DES  Drug eluting stent
ESC  European Society of Cardiology
GPI  Glycoprotein IIb/IIIa-receptor inhibitor
IHD  Ischaemic heart disease
ISR  In-stent restenosis
IVUS Intravascular ultrasound
MI   Myocardial infarction
NSTEMI Non ST-elevation myocardial infarction
OAC  Oral anticoagulation
OCT  Optical coherence tomography
PCI  Percutaneous coronary intervention
PPCI Primary percutaneous coronary intervention
RCT  Randomised controlled trial
ST   Stent thrombosis
STEMI ST-elevation myocardial infarction
UA   Unstable angina
UFH  Unfractionated heparin
VKA  Vitamin K-antagonist
1 Preface

Invasive treatment of coronary artery disease is a rapidly evolving field. Having worked with percutaneous coronary intervention (PCI) for more than ten years, I have witnessed an invasive strategy become increasingly common among complex patients, including the very elderly. Technical progress in wires, stents and balloon catheters has improved the treatment of complex coronary lesions and chronically occluded vessels. The use of functional assessment and intravascular imaging has increased, helping us to identify which lesions need treatment and to optimise stent implantation. Pharmacological treatment strategies have evolved, especially with regards to antithrombotic therapy. Data from national quality registries like SWEDEHEART, with its sub-registries including SCAAR, illustrates patterns in practice and allows us to monitor important outcome measures. The most important contribution of SWEDEHEART however, is to improve patient outcome by enhancing the adaptation of evidence-based therapies.\textsuperscript{1,2}
2 Introduction

2.1 Cardiovascular disease in a global perspective

The Global Burden of Disease (GBD) Study, originally an initiative of the World Bank and the World Health Organisation in 1991, repeatedly conducts systematic assessments of global health and related data.\(^3,4\) The GBD 2015 study reported that there were an estimated 420 million prevalent cases of cardiovascular disease (CVD) and 18 million related annual deaths worldwide, making CVD the global leading cause of death.\(^5\) Ischaemic heart disease (IHD) was the leading CVD subset, with 110 million prevalent cases and 9 million annual deaths, followed by stroke. Currently, IHD and stroke account for 85% of all CVD related deaths.\(^6\)

By combining sociodemographic data and trends in CVD mortality, interesting patterns are revealed. Declines in age-standardised CVD mortality were observed between 1990 and 2015 in countries of high socioeconomic standard, including Sweden where the 1-year mortality of acute coronary syndrome (ACS) was halved from 22% to 11% over the years 1995 to 2014, attributed to the implementation of pharmacological and interventional treatment strategies.\(^5,7\)

However, only a slight or no decrease of CVD mortality has been reported in low and middle-income regions, where 80% of all current global CVD related deaths occur.\(^5,8,9\) Estimates predict that global rates of IHD and stroke may even begin to rise globally for the first time since the 1970s.\(^10\) This trend primarily reflects suboptimal delivery of health care and increasing risk factors, particularly obesity and diabetes.

The burden of CVD is currently heavier in low- and middle-income countries and hence not a problem concentrated in affluent regions. Access to cardiovascular health care is more limited in countries of lower socioeconomic standard, and the variations are great.\(^8,9\) For the first time, the GBD 2017 study included data on health worker density, reporting that only half of all countries had the health-care workforce required to deliver quality health care.\(^11\)

The annual cost of cardiovascular disease in Europe is estimated to 210 billion Euro.\(^8,9\) As a comparison, the gross domestic product of Sweden for 2018 was around 500 billion Euro.\(^12\) The cost of cardiovascular disease could potentially be mitigated by relatively low-cost measures such as reorganising existing health services and prioritising measures of proven value.\(^8\)
In summary, the global burden of CVD calls for improved treatments and better implementation of effective treatments. Research and development, structural changes and appropriate policy making is mandated.

2.2 Ischemic heart disease

Ischemic heart disease refers to a spectrum of clinical entities caused by disease of coronary arteries usually but not exclusively related to atherosclerosis. This clinically heterogeneous disease entity with varied modes of management can be subclassified in chronic coronary syndromes (CCS) and acute coronary syndromes (ACS).\textsuperscript{13–15} Myocardial infarction is part of ACS and can be further subclassified.

Characteristic for ACS is acute onset or worsening of ischemic symptoms usually due to dynamic changes in coronary blood flow caused by plaque rupture, platelet activation and thrombus formation. The location and degree of coronary artery obstruction determines the extent of myocardium at risk and clinical presentation. Partial or temporary obstruction tends to result in non-ST segment elevation myocardial infarction (NSTEMI) whereas in the more acutely ill ST-segment elevation myocardial infarction (STEMI) patients, a completely blocked coronary artery is commonly found.\textsuperscript{14–16} Unstable angina (UA) refers to a clinically unstable condition with symptoms of cardiac ischemia in the absence of troponin elevation. Classically, STEMI, NSTEMI and UA are all considered part of the ACS spectrum.

The 4th universal definition of myocardial infarction (MI) was presented by the European Society of Cardiology in 2018.\textsuperscript{17} A diagnosis of MI generally requires the detection of a typical rise or fall of troponin in combination with at least one of the following: symptoms of myocardial ischemia, new ischemic ECG changes, imaging evidence of new myocardial injury/wall motion abnormality consistent with ischaemic aetiology or identification of coronary thrombus by coronary angiography. To account for different clinical scenarios leading to myocardial infarction, five subtypes of MI have been defined. Type 1 MI is caused by a plaque rupture or thrombus in the coronary artery (includes STEMI and NSTEMI). Type 2 MI is caused by a mismatch in oxygen supply and demand, common examples being severe anaemia or desaturation. Type 3 MI is considered when a patient suffers cardiac death before the collection of blood for troponin analysis, but there are symptoms, signs or autopsy findings suggestive of myocardial ischemia. Type 4 is MI related to PCI and type 5 is MI related to coronary artery by-pass graft surgery (CABG). Importantly, a situation where an elevated troponin is detected, but other basic criteria for MI are absent should be referred to as myocardial injury.\textsuperscript{17}
2.3 Risk factors for ischaemic heart disease

In general, the risk of developing IHD, or CVD correlates to the presence and severity of risk factors. Globally established modifiable risk factors for IHD are hyperlipidaemia, smoking, hypertension, diabetes, abdominal obesity, poor dietary habits, poor exercise habits and psychosocial factors. Gender and age are major non-modifiable risk factors. Furthermore, a positive family history of premature cardiovascular death is associated with increased risk of both early and lifetime coronary heart disease death.

Other conditions associated with an increased risk for IHD and CVD include chronic kidney disease, obstructive sleep apnoea syndrome, autoimmune disease, previous cancer treatment with chemo or radiotherapy, periodontitis, erectile dysfunction, pre-eclampsia, gestational hypertension and polycystic ovarian syndrome.

2.4 Estimating risk in healthy individuals

In presumably healthy individuals, European guidelines recommend using the SCORE tool to estimate the 10-year risk of fatal CVD, primarily to motivate and guide decision-making with regards to preventive measures. Generally, a SCORE of 10% or greater is considered very high risk and pharmacological treatment is often required. A SCORE of 5-10% (high risk) warrants intense life-style advice and consideration of pharmacological treatment. Low to moderate risk (<5%) generally warrants life-style advice to maintain a favourable risk status. The SCORE model has been externally validated.

A problem with all standard risk estimating tools, SCORE included, is that age is the strongest of all predictors. Consequently, individuals aged 50 or under are predicted to be at low absolute risk, regardless of other factors included (gender, systolic blood pressure, total cholesterol and smoking status, in the case of SCORE). However, there may of course be younger individuals with markedly increased relative risk. One highly important group to identify are subjects with familial hyperlipidaemia.

2.5 Pathophysiology of atherosclerosis

Atherosclerosis occurs in the subendothelial space of arteries and is generally viewed as the result of initial subendothelial retention of lipoproteins in focal areas, particularly regions where flow is altered by bends or bifurcations. A complex interplay of lipid deposition and endothelial dysfunction leads to chronic low-grade inflammation involving macrophages, other inflammatory cells and smooth muscle cells adopting myofibroblast properties. With time,
cellular, extracellular and lipid material is accumulated in the subendothelial space.\textsuperscript{24,26} Atherosclerotic lesions frequently form an overlying scar, a fibrous cap, providing a protective barrier between the prothrombotic material in the plaque and the circulating platelets.\textsuperscript{27,28} Some atherosclerotic plaques develop micro- and macrocalcification, frequently observed in lesions with large necrotic core.\textsuperscript{29}

Outward remodelling of the arterial wall and the development of collateral vessels can compensate to some extent for chronic luminal reduction caused by atherosclerosis.\textsuperscript{30} Certain lesions develop properties that can lead to plaque rupture, local thrombus formation, and acute MI. These so called vulnerable plaques tend to have a large necrotic core, thinning of the fibrous cap and more intense inflammation, although the mechanism behind plaque rupture is not fully understood.\textsuperscript{24,26}

2.6 Platelets, thrombus formation and targets for antiplatelet agents

The primary physiological role of platelets is primary haemostasis, to quickly form a thrombus acting as a plug in a damaged vascular segment in order to prevent bleeding. Primary haemostasis is complemented by secondary haemostasis, a process involving a host of circulating coagulation factors that can be activated in a sequential, cascade manner, eventually leading to the formation of insoluble strands of fibrin that interlink platelets and stabilise the thrombus. Primary and secondary haemostasis occur simultaneously in a complex interplay.

Platelets adhere to sites of vascular injury in both physiological and pathophysiological processes like ACS. Subsequent to adhesion at a ruptured atherosclerotic plaque, platelets go through set steps of activation, aggregation and stabilisation.

Platelets are non-nuclear cells with surface receptors and granules. By degranulation, various mediators are released that exert a host of biological effects. Alfa-granules contain von Willebrand factor (vWF) and glycoprotein IIb/IIIa (GpIIb/IIIa), both involved in thrombus formation; P-selectin and platelet derived growth factor (PDGF), important in inflammatory processes and angiogenesis. Dense granules contain smaller molecules like ADP and ATP, involved in platelet activation and thrombus formation.\textsuperscript{31}

Binding of ADP to platelet receptors P2Y1 and P2Y12 causes platelet activation. Commonly used antiplatelet agents clopidogrel, prasugrel and ticagrelor are P2Y12-inhibitors. Thromboxane A2 (TXA2), ligand to the TXA2-receptor is another important mediator of activation and aggregation of
platelets. Platelet synthesis of TXA2 relies on the enzyme cyclooxygenase 1 (COX-1), the target for original antiplatelet agent acetylsalicylic acid (ASA).

Once an atherosclerotic plaque ruptures, prothrombotic compounds in the extracellular matrix like vWF, collagen and tissue factor (TF) are exposed. Platelets adhere to the lesion and become activated. The first critical step in platelet adhesion and activation is the binding of the GpIb/IX/V receptor complex to vWF. The vWF and collagen bound platelets undergo further activation, change shape and secrete granules, which in turn activates other platelets.32

A critical step in platelet activation is the surface expression of GpIIb/IIIa-receptors that bind to fibrinogen and vWF to adhere to other activated platelets, allowing the formation of a close network. Glycoprotein IIb/IIIa-receptor inhibitors (GPI), studied in paper I, are potent parenteral antithrombotic agents.

Secondary haemostasis via the coagulation cascade is primarily triggered by the binding of coagulation factor VII to exposed endothelial TF, leading on to the final common pathway. In the final common pathway factor Xa is activated, prothrombin converted to thrombin and finally fibrinogen converted to insoluble fibrin.33

Apart from its central role in the common pathway, thrombin is also a powerful activator of platelets, constituting a strong feedback loop to promote thrombus formation. Bivalirudin, a recombinant, parenteral, direct thrombin inhibitor, is studied in papers I and II. Unfractionated heparin (UFH), the main comparator in papers I and II, enhances the effect of antithrombin III, which in turn inhibits thrombin and factor Xa.

2.7 The contact activation system and its clinical implications

In addition to the principal activation by TF, there is an alternative trigger of the common pathway, also eventually resulting in fibrin formation. This alternative trigger is called the contact activation system (CAS). As the name implies, a surface can trigger and generate thrombus. The physiological role of CAS is not fully understood but it is probably less important than the TF pathway in physiological haemostasis and atherothrombosis. However, invasive procedures and medical devices carry a risk of triggering CAS, which may cause complications like catheter-induced thrombus, stent thrombosis or prosthetic heart valve thrombosis.34 Mechanistic studies imply that factor XII activation is important in CAS triggering. Antithrombotic agents vary in their capacity to inhibit CAS. In vitro and in rabbit, heparin is an effective inhibitor of CAS, in contrast to fondaparinux, a parenteral factor X inhibitor.35 In clinical practice, heparin inhibits catheter-induced thrombus more effectively than
In analogy, dabigatran, a direct oral thrombin inhibitor, does not sufficiently inhibit catheter-induced thrombosis in vitro. Consistently, dabigatran is inferior to warfarin in preventing thrombotic complications in patients with mechanical heart valves.\textsuperscript{34,37}

In summary, mechanistic and clinical data indicates that efficient prevention of medical device induced thrombus requires not only thrombin inhibition, but also inhibition of coagulation enzymes above the level of factor Xa.\textsuperscript{34}

Bivalirudin (a direct thrombin inhibitor) with an added small dose of heparin has been associated with a lower incidence of stent thrombosis in PCI, compared with bivalirudin monotherapy.\textsuperscript{38}

2.8 Coronary revascularisation in ACS

Coronary revascularisation is a fundamental part of contemporary ACS management. In STEMI, European and American guidelines favour primary PCI over pharmacological thrombolysis given that PCI can be performed within reasonable time, defined in most patients as 90 minutes from first medical contact.\textsuperscript{15,39} Primary PCI has markedly increased in Swedish STEMI patients of all ages. Even in octogenarians, primary PCI is currently performed in around 65\% of patients (Figure 1a). Among patients discharged alive, nearly all are subject to an invasive strategy, including octogenarians (Figure 1b). Currently in Sweden, thrombolysis is exclusively used in regions with long delays due to geographical challenges.

Figure 1a. Proportion of primary PCI in Swedish STEMI patients, by gender and age group, 1995-2018. Adopted from the SWEDHEART Annual Report 2018, with permission.
In NSTEMI, coronary revascularisation is recommended early but not necessarily immediately, depending on clinical presentation.\textsuperscript{14,40} The 2018 coronary revascularisation guidelines by the ESC suggest that NSTEMI patients with at least one high-risk feature should undergo coronary angiography within 24 hours of diagnosis (Class 1A recommendation).\textsuperscript{40} Some NSTEMI-patients with symptoms and/or signs of ongoing ischemia such as persisting chest pain, ST-segment depression, overt heart failure or ventricular arrhythmia likely benefit from a more urgent invasive strategy. Clinical decision-making is not always easy, necessitating a more liberal strategy towards early angiography in some NSTEMI patients, which is well described in the 2017 ESC STEMI Guidelines and a reflection of the fact that not all patients with a blocked coronary artery have ST-elevation on the ECG.\textsuperscript{15} An invasive approach is chosen for most NSTEMI patients in Swedish hospitals, and the fraction has increased strongly over the last two decades. There is however a considerable difference in rates of invasive management among octogenarians compared with younger patient groups (Figure 2). In Swedish ACS patients it is very rare to choose CABG rather than PCI as mode of revascularisation. There is a role for CABG primarily in CCS.
2.9 Antithrombotic therapy in ACS

This chapter aims to discuss antithrombotic therapy in ACS in a general perspective. Details of parenteral agents GPI, UFH, bivalirudin and cangrelor, all of particular interest for this thesis, are presented in separate chapters.

2.9.1 Benefit of antithrombotic therapy

Antithrombotic therapy is the mainstay pharmacological component of ACS management and includes two distinct modes of action: platelet inhibition and anticoagulation. Antithrombotic treatment reduces thrombotic activity locally in the coronary circulation, which improves or at least counteracts further reduction of coronary flow in the acute setting. Antithrombotic therapy prevents catheter thrombosis and embolisation during PCI, prevents stent thrombosis and reduces rates of reinfarction. Antithrombotic therapy is associated with improved outcome in ACS, both in a short and long perspective. Hence, all ACS patients receive both antiplatelet agents and anticoagulants before and/or during PCI.

2.9.2 Parenteral anticoagulation in ACS

In NSTEMI, current European guidelines recommend Fondaparinux, a parenteral factor X inhibitor, to be administrated from diagnosis until revascularisation, Class 1 A. In STEMI, unfractionated heparin (UFH) is the recommended parenteral anticoagulant (Class 1C). UFH is commonly administered prehospitaly in Swedish STEMI patients. Alternative anticoagulants,
currently not as strongly recommended for routine use, include enoxaparin and bivalirudin, the latter discussed in detail below.

2.9.3 Anticoagulating agents after revascularisation in ACS
Parenteral anticoagulants are usually discontinued after the ACS patient has undergone a coronary angiogram and revascularisation if appropriate. There is RCT evidence supporting oral anticoagulation with low-dose factor X inhibitor rivaroxaban (2.5 mg twice daily) in combination with single or dual antiplatelet therapy after ACS, but this therapeutic option is not well established in Sweden. In analogy, there is RCT evidence supporting rivaroxaban 2.5 mg twice daily in combination with ASA for high risk CCS patients, particularly those with coexisting peripheral artery disease and reduced ejection fraction.

2.9.4 Choice of oral antiplatelet agent in ACS
Acetylsalicylic acid (ASA) in combination with one of the two potent P2Y12-inhibitors ticagrelor or prasugrel is recommended unless contraindicated in all STEMI and NSTEMI patients, based on landmark studies proving superior net clinical benefit compared with clopidogrel. Ticagrelor is a direct acting, reversible P2Y12-agonist, while prasugrel needs conversion to an active metabolite before binding irreversibly to the same receptor. Both compounds have a more prompt, potent and predictable platelet inhibitory effect than clopidogrel.

Clopidogrel, also a prodrug, with irreversible binding to the ADP-binding site of the P2Y12-receptor, has a markedly reduced effect in poor metabolisers, predominately patients who carry two non-functional copies of the CYP2C19 gene. Approximately 2-14% of patients are classified as poor metabolisers, depending on ethnic background. In patients with one functional copy of the CYP2C19 gene, intermediate metabolisers, the effectiveness of clopidogrel is reduced to a lesser extent. Genetic variations of converting enzymes do not have a relevant impact on prasugrel effect. Ticagrelor is used in a majority of Swedish ACS patients (Figures 3a and 3b).
A recent open-label study randomising ACS patients to either ticagrelor or prasugrel found that prasugrel was superior to ticagrelor.\textsuperscript{45} Despite being a head to head comparison with a clear result, methodological flaws like the open label design, low power, and the marked inconsistency with blinded RCT results of ticagrelor vs clopidogrel and prasugrel vs clopidogrel respectively, makes the study results difficult to judge. Prasugrel being superior to ticagrelor in terms of thrombotic endpoints, and non-inferior with regards to bleeding.
suggests compliance inequality between treatment groups. The fact that prasugrel is not indicated in patients bound for non-invasive management, contraindicated in patients with prior stroke and unsuitable in patients older than 75 years are important practical limitations regardless.

Clopidogrel in combination with ASA is recommended in CCS after PCI and in patients with ACS and an indication for oral anticoagulation (OAC).  

2.9.5 Timing of oral antiplatelet loading

For STEMI, guidelines recommend oral loading with ASA and a potent P2Y12-inhibitor as early as possible after diagnosis. Ticagrelor is the most commonly used potent P2Y12-inhibitor in Sweden, and prehospital loading is common (Figure 3a). Interestingly, prehospital (30 min) ticagrelor loading compared to hospital loading increased the pharmacological response but did not increase ST resolution and infarct vessel patency at angiography in a large RCT. Among prehospitaly loaded patients there were no definite ST-events within 24 hours, compared with 0.8% among in-hospital ticagrelor loaded patients. Observational studies have not been able to detect an association between prehospital ticagrelor loading in STEMI and improved outcome, compared with in-hospital loading. A meta-analysis based on 7 RCT:s including a total of 9,600 patients did however indicate an advantage with prehospital loading, including lower rates of MI, fewer main adverse cardiovascular events, less GPI use and improved coronary perfusion before PCI but no increase in major bleeding.

Prasugrel loading before knowing the coronary anatomy is not recommended in NSTEMI, as an RCT showed excess bleeding and no reduction in thrombotic events with such an approach, using a reduced 30 mg prasugrel loading dose. In contrast, ticagrelor loading at the time of NSTEMI diagnosis may be used, based on the PLATO trial. In Sweden, ticagrelor is used in a majority of NSTEMI cases and loading at the time point of diagnosis, before coronary angiography, is common (Figure 3b).

2.9.6 Duration of antiplatelet therapy in ACS

After ACS, dual antiplatelet therapy (DAPT) with ASA and a P2Y12-inhibitor is generally recommended for a minimum of 12 months. If increased bleeding risk is considered a greater concern than thromboembolic risk, the DAPT course may be shortened. After a period of DAPT, single antiplatelet therapy with ASA is usually recommended life-long. An important exception is patients on chronic oral anticoagulation (OAC) for other indications such as atrial fibrillation (AF), where guidelines generally recommend discontinuation of all antiplatelet agents one year after ACS.

A recent large double-blind RCT of patients undergoing PCI, for ACS in 2/3 of cases, randomised patients after 3 event-free months of DAPT (ASA +
ticagrelor) to either continue with ticagrelor monotherapy or continue with ASA + ticagrelor for another 9 months. Patients who stopped ASA after 3 months had a 44% relative risk reduction in clinically relevant bleeding events (Bleeding Academic Research Consortium type 2, 3 or 5) compared with patients randomised to DAPT for 12 months. No differences in ischaemic events were detected, but power was limited.52,53

Quite illustrative of how complex the issue of DAPT duration is, one year after ACS, prolonged DAPT with ASA and low dose ticagrelor (60 mg twice daily) may be considered for up to three years in high-risk patients without bleeding events up to one year, supported by a large RCT.54 This does not apply to patients on OAC.

In patients undergoing PCI for CCS, a 6-12 month DAPT course of clopidogrel + ASA is generally recommended.13,40

2.9.7 Oral antiplatelet agents less predictable in STEMI
The risk of periprocedural thromboembolic complications such as distal embolisation and acute stent thrombosis (ST) is more prominent in STEMI than in NSTEMI.55 The thrombotic burden reflects MI severity with more pronounced platelet and procoagulant activity in STEMI than NSTEMI.56 Some STEMI patients vomit and many have impaired gastrointestinal absorption, partly due to the underlying clinical condition, often enhanced by opioid analgesics, making oral platelet inhibitor response delayed and less predictable. One major problem is that stent placement in a situation of inappropriate platelet inhibition poses a risk for acute ST. This over-all rare complication to stent implantation, discussed in detail below, carries substantial morbidity and mortality.57 Cangrelor, discussed in detail below, is a parenteral P2Y12-inhibitor that may be used in such patients where oral loading is not feasible or desirable.

2.10 Thromboembolic risk versus bleeding risk
All antithrombotic treatment strategies aim to optimally balance the benefit of reducing thromboembolic events with the corresponding disadvantage of increased bleeding risk. Bleeding complications adversely impact outcome, increasing both mortality and ischemic events. Bleeding after PCI occurs more frequently after STEMI than NSTEMI, and less often after PCI for CCS.58,59

Access site bleeding is currently a diminishing issue, seldom causing discontinuation of DAPT post PCI. Less access-site bleeding of serious consequence is attributed to routine use of radial access, endorsed by guidelines.40 Currently, bleeding events posing a clinical problem are predominantly gastrointestinal.60
Thromboembolic risk is high in most ACS patients. Recurrent MI is common, can occur in any coronary segment but more often the new culprit is located in a previously non-stented rather than stented segment.\(^6^1\) In contrast to recurrent MI, ST is a rare but often serious complication to stenting. The location of a stent is known and the impact of a theoretical ST can be estimated. A left main stent is more problematic than a peripheral stent in a non-major coronary artery, if the patient suffers ST.

Estimating bleeding risk can be challenging. Risk-scores have been developed to aid decisions on DAPT-duration after PCI. The DAPT score guides decisions on DAPT duration after coronary stenting by simultaneously predicting ischemic and bleeding risk.\(^6^2\) The DAPT score has been questioned due to its inability to adequately discriminate ischemic and bleeding risk and its clinical usefulness debated.\(^6^3\)

The PRECISE-DAPT score was introduced in the 2017 ESC focused update on dual antiplatelet therapy and is based on a collaborative study of 14,900 patients undergoing PCI for all indications.\(^6^4\) The predictive performance of the score was validated in the original cohort, and externally validated in both the PLATO trial cohort and the Bern PCI registry. The DAPT and the PRECISE-DAPT scores have not been prospectively tested in randomised clinical trials.\(^5^1\)

Baseline anaemia before PCI for ACS is associated with a markedly increased risk of both ischemic events, bleeding events and mortality.\(^6^5\) A contemporary registry study of 6,200 consecutive patients undergoing PCI found that increasing age, previous gastrointestinal bleed, history of malignancy, smoking and triple antiplatelet therapy were independent predictors of gastrointestinal bleeding after PCI. Bleeding was associated with at least a three-fold increase in all-cause mortality at one year.\(^6^0\)

The most difficult situations with regards to DAPT duration arise with a co-existing indication for oral anticoagulation (OAC), a scenario discussed in detail below. There is currently no clear consensus on how to manage these patients in detail, and the DAPT or PRECISE-DAPT scores do not apply. Further studies are clearly warranted.

2.11 Dual platelet inhibition with oral anticoagulation: triple therapy

A particularly challenging and quite frequent scenario is finding the optimal strategy in patients with ACS (DAPT indication) combined with an indication for OAC, most commonly AF. The combination of DAPT and OAC is termed triple therapy. Patients undergoing PCI have a high risk for thromboembolic events such as ST or MI, and AF poses a risk of thromboembolic stroke. However, both platelet inhibition and OAC, particularly triple therapy, increases
the bleeding risk. Coexistence of ACS and AF is rather common. According to Swedish national data around 15% of all ACS patients have OAC prescribed when discharged after MI. Data from SWEDEHEART also shows that patients with AF and MI are managed with great variation, illustrating that this is a complicated topic.66

The ESC has issued a focused update on DAPT including patients where OAC is indicated.51 Triple therapy for 1-6 months is recommended, depending on the clinical situation. A North-American expert consensus also provides clinical guidance, with a more liberal approach towards OAC + single antiplatelet therapy already after hospital discharge, however also stressing individual tailoring of strategy.67

ASA and clopidogrel are primarily recommended as part of a triple therapy regime, rather than ASA + more potent agents ticagrelor or prasugrel. Currently there is an ongoing debate on if and for how long a patient should be subject to triple therapy. Direct oral anticoagulants (DOAC), formerly known as NOAC, are however clearly recommended rather than vitamin K antagonists (VKA), in triple therapy.

Four randomised clinical trials have been conducted on AF patients undergoing PCI, treated with DOAC agents apixaban, rivaroxaban, edoxaban and dabigatran. All trials studied the outcome of various pharmacological strategies, particularly P2Y12-inhibition in combination with a DOAC, compared to triple therapy with a VKA.68–71 Only one trial studied whether the addition of ASA per se to clopidogrel and DOAC/VKA is beneficial or not, applying a 2x2 factorial design.68 All studies support the use of DOAC rather than VKA in the setting of PCI and AF due to lower bleeding incidence, however only in one trial were VKA and DOAC “evenly” compared with ASA-free arms of both VKA and apixaban.68 One clear conclusion from this study was that rates of major or clinically relevant nonmajor bleeding were roughly doubled with the addition of ASA (Hazard Ratio 1.89). All four trials were underpowered with regards to thrombotic endpoints. A meta-analysis of the four studies showed that single antiplatelet therapy + OAC is associated with an increased risk of MI and ST, compared with triple therapy, but also a clearly reduced bleeding risk.72 The four studies contain rather few patients with potent agents like ticagrelor, so no conclusions can be drawn on however they are safe to use in triple therapy.

2.12 Cangrelor

Cangrelor, the only parenteral P2Y12-inhibitor, approved by the European Medicines Agency in 2015, was not in clinical use in Sweden when this PhD project started. Cangrelor is indicated for use in conjunction with ASA in patients undergoing PCI, who have not received oral P2Y12-inhibition and in
whom oral loading with a P2Y12-inhibitor is not feasible or desirable. In European 2017 STEMI guidelines, cangrelor was given a Class IIb recommendation, level of evidence A.\textsuperscript{15} Compared with oral P2Y12-inhibitors, cangrelor has clear pharmacokinetic advantages of adequate platelet inhibition within minutes, and a very short half-life allowing return of complete platelet function within 60 minutes of discontinuation.\textsuperscript{73}

The pivotal randomised trials\textsuperscript{74–76} were pooled in an analysis showing that cangrelor in combination with ASA, compared with clopidogrel + ASA, reduced the relative risk of a primary composite endpoint of death, MI, ischemia driven revascularisation or ST by 19\%, whereas the incidence of minor bleeds was significantly higher with cangrelor.\textsuperscript{77} Cangrelor remained superior to clopidogrel across major subgroups such as gender, CCS, ACS and STEMI. There was no mortality benefit seen with cangrelor and the positive result in the primary composite endpoint was mainly driven by a reduction in acute ST.

A detailed core lab analysis of the CHAMPION-PHOENIX trial showed that periprocedural adverse events after PCI are correlated to lesion complexity, defined as a number of high-risk features, concluding that the absolute benefit of cangrelor compared with clopidogrel would be greater in complex PCI cases.\textsuperscript{78}

Cangrelor is a useful antiplatelet agent in patients with cardiac arrest and intubation, or repeated vomiting. In patients with suspected ACS but with an unclear diagnosis, oral loading with ticagrelor may be reasonable to postpone. In such cases, rapid platelet inhibition may be achieved with cangrelor after confirmation of a blocked artery, before placing a stent.

There is no RCT data on the added benefit of cangrelor on a background of more potent oral P2Y12-inhibitors like ticagrelor. Importantly, the trials of cangrelor were performed in an era of clopidogrel, a P2Y12-inhibitor that can only be administered to patients after cessation of the cangrelor infusion, due to a risk of extensive elimination of clopidogrel’s active metabolite while receptors are occupied by cangrelor.

Somewhat illogical, the practice of clopidogrel loading after cessation of cangrelor may leave a window of opportunity for ST formation - all oral agents have some delay before adequate platelet inhibition is achieved. In this respect ticagrelor is theoretically a more suitable complement to cangrelor, allowing administration before cangrelor discontinuation, and with a more prompt, predictable onset.

In Sweden, cangrelor is used nearly exclusively in STEMI, and nearly exclusively in combination with ticagrelor. This practice is at variance with RCT evidence but supported by several smaller clinical and pharmacodynamic studies.\textsuperscript{79–82} Furthermore, there is randomised evidence that cangrelor gives more potent platelet inhibition compared with crushed oral ticagrelor, in STEMI patients undergoing primary PCI.\textsuperscript{83}
2.13 Glycoprotein IIb/IIIa-receptor inhibitors

Three GPI agents have been studied extensively, all parenteral. Abciximab is a monoclonal antibody targeting the GpIIb/IIIa-receptor while tirofiban and eptifibatide are non-antibody receptor inhibitors. By preventing fibrinogen from binding to activated platelets, GPI inhibits aggregation. Antiplatelet therapy with GPI has been studied in settings of ACS, and in patients undergoing PCI, originally in an era of single oral antiplatelet therapy with ASA.84–92 GPI is more effective in conjunction with UFH based on randomised evidence of a reduction in thrombotic events/reinfarction compared with only UFH.85

Originally marketed in the late 1990s, these agents became widely used. Broadly, with the arrival of DAPT including a P2Y12-inhibitor, the importance of GPI has decreased. Unfortunately, all GPI agents are associated with an increased bleeding risk.93,94 Preplanned GPI in STEMI was still very common in 2009 but was gradually replaced by bivalirudin (Figure 4). This shift was based on pivotal bivalirudin trials, further discussed below. Some evidence suggests GPI may be more beneficial in STEMI patients presenting early.95 However, current clinical guidelines recommend GPI use only in bailout situations with a large thrombus burden, a situation that usually arises in STEMI patients.14,15

![Figure 4. Patterns of use for GPI, bivalirudin and UFH in STEMI, 2008-2018. Adopted from the SWEDEHEART annual report 2018, with permission.](image)

2.14 Unfractionated heparin

UFH is the oldest and most widely used anticoagulant globally and remains an animal-derived product. Despite having been used clinically since the
1930s, the understanding of this polysaccharide is still incomplete. UFH indirectly inhibits coagulation by binding with antithrombin III and thereby facilitating the inhibitory effect of antithrombin on thrombin and activated factor X (factor Xa). Only polysaccharides of >17 sequences can exert an action on thrombin. Shorter UFH fragments can inhibit factor Xa if they contain a certain pentasaccharide.

The action of UFH is unpredictable and requires monitoring. Some UFH chains bind to other plasma proteins with potential side effects including osteoporosis and heparin induced thrombocytopenia. Low molecular weight heparins (LMWH) were engineered in the 1970s, to render a more predictable action and less adverse reactions. The improved safety profile and more predictable action enabled outpatient administration and thus LMWH replaced UFH in many clinical scenarios. In ACS however, UFH is still the agent of choice due to its suppression of CAS and a greater reversibility with protamine sulphate.

2.15 Bivalirudin

Bivalirudin, a synthetic, direct, reversible thrombin inhibitor with a short half-life, was originally introduced as an alternative to heparin during PCI. In 1995, a randomised, blinded trial was performed that compared bivalirudin with a high dose UFH (bolus of 175 U/kg) in patients undergoing PCI for unstable angina or post-infarction angina, with superior results for bivalirudin. The study was repeated with more contemporary endpoints in 2001, and the results were positive for bivalirudin, but the UFH dose was high, affecting the bleeding results.

The ACUITY-trial of 13,800 ACS-patients with an early invasive approach (excluding STEMI) compared three antithrombotic strategies: bivalirudin monotherapy, GPI + UFH and bivalirudin + GPI. Among these patients, 9200 underwent a second randomisation where routine upstream GPI administration was compared with deferred or selective GPI administration. Roughly 7800 patients underwent PCI. The 30-day results showed similar rates of ischemic endpoints with bivalirudin monotherapy and GPI + UFH, but less major and minor bleeding events with bivalirudin monotherapy, in patients undergoing PCI. Deferred GPI use in patients undergoing PCI resulted in less major bleeding, but a small increase in ischemic events could not be excluded. At one-year follow up, no differences in ischemic endpoints or mortality could be found with the three basic strategies being compared, and no difference in ischemic endpoints between upstream vs deferred GPI therapy.

The HORIZONS-AMI trial published in 2007 showed that bivalirudin was superior to UFH + GPI in patients with STEMI undergoing primary PCI. This included a reduction in bleeding rates and a reduction in all-cause mortality. Results were consistent at one-year follow up. There was however an early
signal of excess acute stent thrombosis with bivalirudin monotherapy.\textsuperscript{100,101} In the 2012 ESC STEMI guidelines, bivalirudin with restricted bailout GPI use was recommended over UFH + GPI, Class 1B.\textsuperscript{102}

Consequently, bivalirudin was commonly used in Swedish STEMI-patients, in 2012 and 2013 (Figure 4). Several clinical trials were however published, comparing bivalirudin with UFH in ACS, with diverging results.\textsuperscript{103–106} Several authors suggested the diverging results were caused by different GPI use in the bivalirudin and UFH arms. With more GPI in the UFH arm, there was a tendency to better outcome with bivalirudin, largely driven by less bleeding.\textsuperscript{107}

Several RCTs and meta-analyses have shown increased rates of ST with bivalirudin compared to UFH/GPI treatment.\textsuperscript{100,103,104,106,108,109}

Due to the puzzling body of evidence, and the lingering concern of excess acute ST with bivalirudin, there was an ongoing debate on optimal pharmacological strategy in STEMI at the time this PhD project was commenced. Real-world data was scarce, making papers I and II very relevant at the time.

Administration of bivalirudin is started with a bolus followed by an infusion with a maintenance dose during PCI. The infusion may be continued at PCI dose for a maximum of 4 hours post PCI. There is an option to continue thereafter with a reduced dose, 12 hours post PCI, if needed. There was a discussion on whether prolonged infusion with bivalirudin after PCI could mitigate the increased risk of acute ST, postulated as an explanation for the lack of excess ST in one major RCT of bivalirudin vs UFH.\textsuperscript{105} In another RCT of bivalirudin vs UFH, ST risk was not affected by prolonged infusion but an exploratory analysis of the same trial suggested that dose during prolonged infusion could affect ST risk.\textsuperscript{106} Finally, a post hoc analysis of another RCT suggested that prolonged infusion at PCI dose attenuates ST risk.\textsuperscript{103,110}

Furthermore, there was a discussion on the importance of co-administering a small dose of UFH with bivalirudin. Using bivalirudin without any UFH had been linked to increased risk of ST in both RCTs and registries.\textsuperscript{101,103,104,111}

During this PhD project, important insights regarding routine antithrombotic strategy in STEMI have been achieved with the VALIDATE-SWEDE-HEART trial proving UFH monotherapy as safe and effective as routine bivalirudin + UFH in both NSTEMI and STEMI-patients undergoing PCI in a setting of potent P2Y12-inhibitors and no planned use of GPI.\textsuperscript{112} VALIDATE-SWEDEHEART contributed to a downgrading for routine use of bivalirudin in STEMI and PPCI to a Class IIb-recommendation in ESC revascularisation guidelines.\textsuperscript{40} Details and remaining uncertainties are further analysed in the discussion section.

Also discussed below are the methodological strengths and limitations of paper II in relation to this matter.
2.16 Development of modern drug eluting stents

In 1977 Andreas Grünzig performed the first PCI using a simple balloon mounted on a wire. Balloon angioplasty was adopted slowly by the medical profession due to unpredictable results, need for thoracic surgery standby and early vessel recoil reported in at least 30% of patients. Coronary bare metal stents (BMS), introduced in the 1980s, minimised acute recoil and abrupt vessel closure caused by dissection, leading to improved outcomes. In-stent restenosis (ISR), described in detail below, emerged as the key limitation with BMS. The first-generation DES was introduced in the early 2000s. By combining a stainless-steel stent, a drug carrier and an antiproliferative agent, rates of ISR and need for revascularisation were significantly reduced compared with BMS.

The technology of DES has since been refined with improved metal alloys, thinner struts, improved antiproliferative drugs and carriers. In addition to improved deliverability, modern DES are safer and more effective than both BMS and first-generation DES, in terms of reduced rates of ISR and ST. However, ISR remains the key limitation. Stent-related (as well as non-stent related) events continue to occur at a steady rate beyond one year and up to five years post-PCI, as recently reported in a large meta-analysis.

The newest modern DES available in Sweden have even thinner metal struts and absorbable polymers carrying the antiproliferative agent. Polymer carriers ensure controlled release of the antiproliferative drug. Once the drug is completely released, the carrier is obsolete and may contribute to low-grade inflammation and ISR. Absorbable polymers are now commonly used to improve outcome, and some modern DES are even polymer free. It remains to be proven whether these devices are associated with less ISR, ST, repeat vascularisation or MI, compared with other modern DES with thicker struts and permanent polymers. In paper V this matter is discussed in detail.

2.17 Bioresorbable scaffolds

The bioresorbable scaffold (BRS) constitutes the latest extensively tested novel concept in PCI. A BRS may provide vessel support for a limited time meanwhile eluting an antiproliferative drug, and eventually be completely absorbed in a predictable manner.

Compared with a metallic stent that will infinitely cage the coronary artery, a BRS may theoretically have several advantages. A BRS may limit the problem of ISR and ST after complete resorption. Moreover, it has been postulated that caging of the artery per se may negatively impact outcome by altering normal vessel dynamics. A resorbable device may allow positive remodelling over time, i.e. increased lumen area of the diseased vessel, which is obviously not possible with an inert, metallic stent. A BRS treated vessel may be the
later target for a surgical anastomosis, in contrast to a permanently stented vessel. Finally, complete resorption may allow less intensive antiplatelet therapy.

The first BRS platform extensively tested in randomised trials was Absorb (Abbott Vascular, Santa Clara, CA, USA), an everolimus-eluting polylactate scaffold with a strut thickness of 156 μm, clearly bulkier than modern DES with strut thickness in the range of 60-85 μm. Several other BRS devices have been studied clinically, but none nearly as extensively as Absorb.

At the start of this PhD project it was not clear whether the theoretical advantages of Absorb would translate to improved clinical outcome compared with modern DES. There were signals of increased rates of late ST and target vessel revascularisation with Absorb and our real-world study was highly interesting (paper III). Below are some key findings of Absorb RCT: s and meta-analyses that have been published to date.

The first disappointing news for Absorb came with the 3-year results of the Absorb II trial, comparing the Absorb BRS to the Xience everolimus eluting DES (Abbott Vascular, Santa Clara, CA, USA). The vasodynamics were similar and there was a significantly higher rate of target vessel MI and target vessel revascularisation with Absorb.

Several disappointing results followed. The Absorb Japan trial 2-year results showed numerically higher target lesion failure with Absorb compared to DES and very late ST events were noted only with Absorb, a worrying signal. An investigator initiated RCT of 1,845 patients reported significantly higher rates of ST with Absorb compared to Xience DES at a median of two years follow up.

There was a hope that Absorb would perform better with optimal implantation technique, and the manufacturer stressed predilatation, adequate sizing and postdilatation. Intravascular imaging was encouraged to ensure apposition.

The 3 year-results of the Absorb III trial, published in 2017, showed significantly higher adverse events with Absorb compared to DES, largely driven by target vessel MI and scaffold thrombosis. The four-year results of the Absorb II trial showed consistent results.

A meta-analysis of seven RCT: s, with a total of 5,500 patients compared the outcome of PCI with Absorb and Xience DES. Rates of target lesion failure and rates of early, late and very late ST were significantly higher with Absorb compared to DES.

A serial multimodality imaging, 3-year analysis of the Absorb Japan trial was recently published, offering an explanation for the excess very late ST reported with Absorb in numerous trials. In addition to luminal dimensions on average being smaller in Absorb compared to DES treated vessels, intraluminal scaffold dismantling was observed in a substantial proportion of cases.
at 3 years, in some cases developing at 2 years. Strut discontinuities were detected in all cases of very late ST that were examined by optical coherence tomography (OCT) immediately before the re-intervention.

The 5 year-results of the Absorb III trial, published in December 2019 finally brought some positive news for Absorb. Although cumulative adverse event rates were significantly higher with Absorb through 5 years compared to DES, the period of excess risk for Absorb ended at 3 years, which coincided with complete resorption of the scaffold.\textsuperscript{126}

The Absorb device is no longer commercially available, due to the proven disadvantages. The concept of BRS is however still interesting, and new devices may perform better, as expanded on in the discussion section.

2.18 In-stent restenosis

In-stent restenosis is a process characterised by chronic inflammation and hyperplasia of the neo-intima in a stented segment, potentially leading to compromise of lumen and flow. It has been postulated that vascular damage, stretching and dissection during PCI induces several processes resulting in inflammation and intimal hyperplasia. Further, the presence of a metallic stent and polymer may contribute to a low-grade inflammatory reaction. ISR was observed early after the introduction of BMS.\textsuperscript{127} Clinically, ISR can lead to CCS or ACS, as flow is compromised beyond a certain point.\textsuperscript{128}

Contrary to ST, ISR is not counteracted by platelet inhibition or anticoagulation. Antiproliferative agents of DES limit intimal hyperplasia and ISR by attenuating inflammation.

Several predictors of ISR have been reported, including age, diabetes, long/complex lesions, calcified lesions, stents with a diameter of <2.5 mm, long stents/lesions, multivessel disease at index PCI, stent type and length, significant atherosclerosis adjacent to stented segment and malapposition/undersizing. All these are intuitive, since more extensive disease at the index PCI tends to result in more events and adversely impact prognosis. Intravascular imaging has increased our understanding of the reasons for stent failure, including ISR.\textsuperscript{129}

Neo-atherosclerosis of a stented segment, another cause of ISR, is increasingly recognised as more frequent use of intravascular ultrasound (IVUS) and OCT allow for more detailed pathophysiological information than what can be appreciated in the coronary angiogram.\textsuperscript{130} The process of neo-atherosclerosis is not affected by antithrombotic treatment but rather reflects aggressive atherosclerotic disease progression.

Technically, IRS can be revascularised by PCI with balloon angioplasty, drug-coated balloon (DCB) or placement of another DES. European guidelines give both DES and DCB a Class 1A recommendation in the treatment of ISR, regardless of whether the original stent was BMS or DES. It is further
stated that the use of IVUS and/or OCT should be considered (Class IIa recommendation, level of evidence C) to detect stent-related mechanical problems in cases of ISR.40

2.19 Stent thrombosis

Stent thrombosis is a rare but severe complication to coronary stenting associated with substantial mortality.131 Clinically, ST frequently results in vessel closure and STEMI. To compare rates of ST across trials and registries, a standard definition was proposed in 2007 and updated in 2018.132,133 Accordingly, definite ST relies on angiographic or post mortem confirmation of a thrombus in or adjacent to (<5mm) a stented segment, in the context of ACS. Probable ST is currently defined as any MI related to documented acute ischemia in the territory of the implanted stent, without angiographic confirmation of ST, and in the absence of another obvious cause. Possible ST was originally proposed as a measure to report in patients with unexplained death beyond 1 year of PCI.132 This category has been excluded due to excessive uncertainty. Incidental finding of ST without symptoms or signs of ischemia is not considered ST.133

Early ST refers to an event within days 0-30 post implantation. Late ST occurs beyond 30 days and very late ST beyond 365 days after implantation. Early ST is often further divided in acute (day 0-1) and subacute (days 1-30 post implantation).

In a large RCT of STEMI patients undergoing PCI with DES and BMS, definite or probable ST occurred in 4.4% of patients within 2 years.38 A large meta-analysis of studies with DES implantation for any indication reported that definite, probable or possible ST had occurred in 2.4% of patients over a median of 22 months.134

Mechanisms of ST are multiple, and several predictors have been identified.135,136 Antiplatelet therapy discontinuation is the strongest predictor of ST according to virtually all studies. Other frequently reported predictors are undersizing of coronary stents, residual moderate stenosis adjacent to a stented segment, bifurcation or ostial lesions, diabetes, extent of coronary artery disease, renal failure, stent length and smoking status. Stent or BRS material is also important, as expanded in paper III on Absorb BRS which has a clear tendency towards increased ST, related to the physical properties of the device. Modern DES are associated with reduced rates of ST, compared with BMS and first-generation DES, discussed in detail above.

European guidelines state that the use of IVUS and/or OCT should be considered (Class IIa recommendation, level of evidence C) to detect stent-related mechanical problems in cases of ST.40

Both BMS and DES cause platelet adhesion, and potentially subsequent thrombus formation. Hence, effective antiplatelet therapy is crucial after stent
implantation. Stents are gradually covered with endothelial cells, which do not attract platelets and the need for antiplatelet therapy decreases. Antiproliferative drugs used in DES limit inflammation and ISR but also delay endothelialisation.\textsuperscript{137} High-resolution visualisation of implanted stents with OCT has established the presence of uncovered stent struts as a factor associated with late ST after DES implantation.\textsuperscript{138} As discussed earlier, the risk of ST is lower after PCI for NSTEMI than for STEMI, and even lower for CCS.

Another factor logically related to ST is platelet reactivity. In routine patient care this rarely alters the way patients are treated, but rather represents a clinical observation that prothrombotic states such as thrombocytosis, inflammation and ongoing infection are associated with increased risk of MI and possibly also increased risk of ST.\textsuperscript{139–141} Recently, chronic obstructive pulmonary disease has been observed as an independent risk factor for ST.\textsuperscript{142}

After primary PCI for STEMI there is often some element of chest pain and ECG abnormalities lingering, complicating the assessment of symptoms and making decisions difficult on the need for re-angiography due to suspected acute ST or other acute complications such as a coronary artery dissection.

### 2.20 Swedish national quality registries

A national quality registry (NQR) contains person-based details related to a problem, the actions taken and results within health-care. The National Steering Group for Quality Registers certifies and monitors all NQR: s. The purpose of all NQR: s is to support health-care providers in delivering evidence-based treatments. The registers provide feedback and the opportunity to compare different institutions in terms of treatments and results. Sweden has more than 100 NQR: s.

### 2.21 SWEDEHEART

SWEDEHEART, a NQR, was created in 2009 by the merging of four large registries: the national registry of acute cardiac care RIKS-HIA (established in 1995); the national registry of secondary prevention SEPHIA; the Swedish coronary angiography and angioplasty registry SCAAR (established in 1998); and the Swedish Cardiac Surgery Registry (established in 1992).\textsuperscript{66,143} Several sub-registries have later been incorporated (Figure 5).
All sites in SWEDEN caring for ACS patients or performing coronary angiography or PCI enter data for all patients with a Swedish citizenship. Patients are informed of the data collection and have the right to decline. An abundance of data is published publicly in an annual report, where hospitals are ranked according to a score of predefined quality measures, and there are regular publications on the performance of commonly used coronary stents.

### 2.21.1 Leadership and funding

The leadership of SWEDEHEART is a steering board consisting of the chairmen of each sub-registry working group plus representatives from the Swedish Heart Association and the Swedish Society of Cardiac Nurses.

The Uppsala region health care provider (Region Uppsala) is legally responsible for the data and the national registry center is Uppsala Clinical Research Center (UCR). Technical infrastructure, legal and management support, monitoring, quality controls and statistical reports are provided by UCR. The registry is funded by the Swedish government, the association of local regions (SKR) and the Swedish Heart and Lung Foundation. All work related to the registry at the local Swedish hospitals is supported by local budgets i.e. there are no reimbursements to hospitals or doctors.

### 2.21.2 Patient registration and data

Patients admitted to a Swedish hospital with suspected ACS, and patients undergoing coronary angiography, PCI, transcatheter or open-heart surgery are registered in SWEDEHEART. Currently 80,000 cases are enrolled annually: 30,000 cases of ACS, 40,000 cases of angiography or PCI and around 7,000 patients undergoing heart surgery.
Local health care professionals enter all data directly on-line, and data is continuously transferred to a central server. The central server communicates with the Swedish National Population Registry, to enable updated access to personal data and deaths.

More than 100 variables are entered for an ACS patient, including demographics, logistical parameters, medical history including risk factors, biomarkers, additional clinical features and investigations, pharmacological treatment before and during admission, interventions, hospital outcome including complications, discharge medications and diagnoses. Patients with ACS younger than 80 years old are offered secondary prevention outpatient follow-up visits at 6-10 weeks and 12 months, where more than 75 new variables are entered.

For any patient undergoing a coronary angiogram or PCI for any indication, more than 150 additional variables are entered covering coronary anatomy, technical PCI data, intracoronary diagnostics, stent specifications, complications and pharmacological treatment before and during PCI. For STEMI-patients, important time points are registered like symptom start, diagnostic ECG, start of cath and PCI guide-wire passage through the culprit lesion. Data on clinical features like cardiac arrest and cardiogenic shock are also registered.

2.21.3 Consistency with source data
Instructions, manuals and support for registry users are provided by UCR. There are automated checks for inconsistencies within the registry. Annual monitoring visits to 20 selected hospitals are performed. At each hospital, 30-40 random patients are selected and source data compared to data entered in the registry. An extensive check of data consistency involving patients from all participating centres was performed in 2015-2016 and a 97% agreement was found (data not published).

2.21.4 Completeness of data
One limitation of SWEDEHEART is that patients not admitted to coronary care units are not registered, but a total of 90% of all ACS patients are captured, with higher numbers among younger patients and STEMI-patients. Many patients not captured are subjects diagnosed with ACS in a state of life/health where they are not admitted to a coronary care unit.¹⁴³

2.21.5 Aims of SWEDEHEART
The main purpose of SWEDEHEART, like any NQR, is to support the development and implementation of evidence-based therapy, specifically in acute and chronic ischemic heart disease and catheter based or surgical interventions
on coronary arteries, valves and structural heart disease. SWEDHEART also provides a base for research. Of particular interest, SWEDHEART serves as a platform for registry based randomised clinical trials (RRCT) including large numbers and proportions of patients. Long-term goals are to contribute to reduced mortality and morbidity and increased cost-effectiveness in health care.

SWEDHEART is also a procedure- and surgery-related registry gathering relevant information on patients and procedures, medical/technical products, treatments and complications. Comparisons can be made between hospitals and a single operator can compare his/her results with average results of the working unit or average national results.

2.21.6 Merging of data
Merging of SWEDHEART data with information from other national registries enables complete follow-up regarding death, myocardial infarction and other diseases. Every merging of registries demands approval from the Swedish Ethical Review Authority and the National Board of Health and Welfare.

2.22 Patient identification
After birth or immigration, all inhabitants are assigned a unique personal identity number by the Swedish Tax Agency. This number is used for many purposes in Swedish society such as identification for memberships and subscriptions, taxation, medical records, banking purposes etc. The personal identity number is the way all individuals are identified in mandatory registries and NQR: s, enabling merging of data.

2.23 Swedish mandatory registries
The National Board of Health and Welfare (Socialstyrelsen, SoS) is a government agency in Sweden under the Ministry of Health and Social Affairs. SoS administers a number of registries to analyse and monitor trends in health care and social services. Below is a brief description of selected registries kept by SoS, of importance for medical research.

2.23.1 The National Cause of Death Register
The purpose of this registry is to provide official statistics about causes of death in Sweden. The data is also used to describe population health status, to guide health-care decisions and serve research purposes.
2.23.2 The National Patient Register
Since 1984, participation in The National Patient Register (NPR) is mandatory for all county councils and from 1987 NPR includes all in-patient care in Sweden. From 2001 the registry also covers outpatient visits and care from both private and public health-care providers, except primary care. Information to the register is delivered to the SoS once a month from each county council. Under-reporting for inpatient data has been estimated to less than 1%. Control is performed on the submitted data, checking for quality and validity of personal identification number, hospital, main diagnosis etc. Incorrect data over a certain threshold generates new data request.

The NPR contains four main types of data:

1. Patient data: personal identity number, gender, age and place of residence.
2. Geographical data: county council, hospital/clinic, department.
3. Administrative data: inpatient admission and discharge dates, length of stay, planned/unplanned admission, referring unit, discharge destination, corresponding outpatient data.
4. Medical data: main diagnosis, secondary diagnosis, external cause of injury, poisoning and procedures.

2.23.3 The Swedish Population Register
This register is administered by the Swedish Tax Agency. Birth and death certificates are sent to local tax agencies and data is entered to a central database. Many other registries are updated continuously with data from the Population Register.

2.23.4 Legislations surrounding the use of registry data
Many government agencies and other organisations keep registries as part of their services. Researchers can access data, if laws regarding personal integrity protection and personal data handling are followed, and ethical permission has been granted. Ethical rules surrounding research are based on international conventions. Data should always be anonymous and de-identified to protect the individual.
3. Aims

The overall aim of this thesis was to add real-world evidence to several areas of uncertainty, with regards to pharmacological and technical strategies in invasive treatment of coronary artery disease. The main aims of the individual papers of the thesis were the following:

I. To report the crude, unadjusted incidence of early ST (day 0-30) in a contemporary, complete, real-world primary PCI (PPCI) population stratified on antithrombotic treatment with bivalirudin, UFH alone or GPI. To report the temporal distribution of early ST in the different antithrombotic therapy subgroups. Further to report crude all-cause mortality at 1 year in patients suffering ST, regardless of antithrombotic therapy (paper I).

II. To compare the outcome of PPCI, in real-world patients treated with UFH monotherapy or bivalirudin. To compare the incidence of early, definite ST in UFH vs bivalirudin treated PPCI patients. Further to compare the incidence of all-cause death, reinfarction, stroke or major bleeding in UFH vs bivalirudin treated PPCI patients (paper II).

III. To compare the device-related outcome of patients treated with the Absorb BRS in a contemporary, national, real-world population of patients undergoing PCI to the outcome of PCI using modern (metallic) DES. The primary outcome measures reported were rates of ST and ISR. Further to report on background and procedural data in the Absorb BRS treated patients, and how these differed from corresponding data for patients treated with modern DES. Further to analyse cases of ST in Absorb BRS treated patients with regards to procedural and pharmacological information of importance to the risk of ST (paper III).

IV. To study and describe the first two years of clinical routine use of cangrelor in a national, complete population of patients undergoing PCI. To evaluate whether contemporary use was in accordance with clinical trial evidence. Further to specifically study patient selection, choice of concomitant antithrombotic drugs and temporal aspects (paper IV).

V. To compare the outcome of PCI using the Xience DES vs the outcome of PCI using other modern DES, in a contemporary, real-world population. The primary individual level outcome measure was a combination of all-cause death, MI and revascularisation with PCI. The primary stent level outcome measures were ISR and definite ST (paper V).
4. Methods

4.1 Data sources and patient populations

All papers in this thesis were retrospective, observational studies based on data from the prospective SWEDEHEART registry, described in detail above. The population captured by SWEDEHEART is a complete, national, real-world, unselected population with 100% follow up for mortality via the Swedish Population Register. Follow up is 100% for repeat coronary angiography and interventions taking place in Sweden. Subsequent myocardial infarctions are covered to a very high degree, as described above in the designated SWEDEHEART chapter.

Papers I, II and IV focused on pharmacological treatment of STEMI-patients. Papers III and V included patients with both ACS and CCS, focusing on the performance of one bioresorbable scaffold (Absorb BRS) and one drug eluting stent (Xience) respectively.

For paper II, additional data on outcome measures not captured in SWEDEHEART such as bleeding events after hospital discharge, was obtained from the national patient register (NPR).

In paper III, we compared the outcome of PCI using the Absorb BRS (n=810) with the outcome of PCI using a set of commonly used modern DES (n=67,099), by the same operators, in the same hospitals, in the same time period. Mean follow-up time was two years and the main outcome measure was definite ST. Secondary outcome measures were ISR, all-cause mortality at one year and re-infarction (any vessel) within one year.

In addition, detailed angiographical and patient chart data was obtained for Absorb BRS ST events by contacting the sites performing both the original PCI and the re-interventions. Images of angiography and PCI-procedures were reviewed locally. PCI-related factors analysed were dilatation pressures, intravascular imaging data and evidence of BRS/vessel size mismatch, factors that have been brought forward as important for successful BRS implantation and patency. Data on antithrombotic therapy was gathered.

For paper IV, we excluded hospitals without cangrelor use, tailoring time frames from first cangrelor use per hospital. Thereafter, patients treated with cangrelor (n=899) were compared with those not receiving cangrelor treatment (n=4,614). Reported measures were baseline characteristics, angiographical and PCI-related data, co-administered antithrombotic agents and data on proportion of patients receiving cangrelor in different time delay strata.
(diagnostic ECG to start of PCI). To indicate the level of risk, crude 30-day and 1-year all-cause mortality was reported for both groups, as were crude rates of definite ST. A separate analysis was performed for patients with STEMI and cardiac arrest (n=273).

All papers shared a focus on ST, which at the time of the start of this PhD project was a major concern with bivalirudin, and later became a particular concern with the Absorb BRS. For cangrelor and Xience DES, studied in papers IV and V respectively, ST was likewise an important parameter.

4.2 Descriptive versus comparative studies

Papers I and IV were purely descriptive without any adjusted comparisons. In papers II, III and V, outcomes were compared for different treatment strategies, using adjustments to account for baseline differences in the treatment groups.

4.3 Individual level versus stent level analyses

Papers I, II, and IV included only individual level analyses. Papers III and V included stent and individual level analyses. In a patient receiving several stents, the study database allowed us to follow all stents individually and generate an outcome event like ISR.

4.4 Definitions

Myocardial infarction is defined in SWEDEHEART in accordance with the 4th universal definition.17

Definite, angiographically proven ST, reported in papers I-V, is largely in accordance with the ARC-2 definition of definite ST: angiographical evidence of a thrombus in a setting of ACS.133 However, the ARC-2 definite ST also includes post-mortem evidence of ST, which we are unable to capture in SWEDEHEART. Probable ST is not reported in any of the papers included in this thesis, neither captured in SWEDEHEART.

The SWEDEHEART definition of ISR is a re-stenosis with at least 70% lumen diameter reduction in a previously stented segment, or a re-stenosis with a fractional flow reserve (FFR) measurement of <0.80, alternatively the documented cut-off used for iFR or other flow indices.

Bleeding endpoints were only reported in papers II and IV. For paper II, major bleeding was defined as any major bleeding reported in the NPR as a hospital discharge diagnosis of: intracerebral, subarachnoidal or subdural hematoma, GI tract bleeds including oesophageal, gastric, duodenal, lower GI
tract and rectal bleeds, hematemesis or melena. For paper IV, index admission in-hospital major bleeding was reported using a corresponding definition, with the data source being SWEDEHEART.

4.5 Statistical methods

A full description of the statistical methods used can be found in the respective papers.

Papers II, III and V were all registry studies aiming to compare different treatment strategies. Since patients were not randomised to the different strategies, the compared groups were unbalanced with respect to important baseline characteristics and procedural factors that affect outcome. Hence, the unadjusted outcome could not be used to evaluate the treatment efficacy. Therefore statistical adjustment models were used to enable comparisons. Despite adjustments there may be residual bias due to factors not taken into account.

To strengthen the results, sensitivity analyses were performed on different populations selected within the cohorts or by applying different statistical models on the same cohorts. Sensitivity analyses were included in papers II, III and V.

In paper V, sensitivity analyses were completed for patients receiving only one DES per PCI, and for PCI using only small/medium/large diameter DES.

4.6 Propensity score

Propensity scores are tools to estimate the effect of a treatment compared to another or no treatment, when randomisation is not possible. A propensity score is a conditional probability of an individual having a certain treatment given the values for a defined set of variables, in that individual. Cases with identical propensity score will be comparable with respect to the variables used to calculate the score. Different treatment in two individuals with the same propensity score is thereby comparable to that of chance or randomisation, with respect to the variables included.

To calculate the propensity score, a logistic regression model is fitted with the treatment received as dependent variable. The logistic regression measures the change in likelihood of a dependent variable, given a set of independent variables. A propensity score is provided for each research subject and summarises the information about all variables chosen.

Confounders are variables other than the treatments or effects being measured that change the relationship between the treatment and the effect. Confounding effects can be minimised in observational studies using propensity score techniques.
Variables can be confounders or not. In an adjusted analysis one will attempt to include all possible relevant confounders. There will always be a chance of additional confounders not identified or included in the propensity score model, constituting residual bias. As an example, frailty in a patient is not recorded or registered in SWEDEHEART. A frail patient may affect choice of antithrombotic treatment and be associated with poor outcome, making frailty a confounder that is not accounted for in the adjustment model.

Propensity scores were used in different ways in the comparative papers. Below are some examples of conceptually different use.

In paper II, all analyses were carried out on individual level. Propensity scores were used in two ways:

- Propensity scores were added as covariates in Cox regression models used for the adjusted outcome analyses (described below). Additional covariates were added based on clinical relevance.
- To create propensity-matched cases, which were later compared using adjusted Cox regression models: a propensity matched analysis.

In papers III and V, different propensity scores were created for stent and individual level analyses. Complete lists of variables can be found in the manuscripts. The propensity scores were then used in different ways in papers III and V:

- Added as covariates in two different Cox regression models for stent and individual level analyses. The additional covariates in the Cox model were chosen based on clinical relevance and the fact that they occurred after the selection of BRS/DES.
- To create a propensity matched analysis.

4.7 Cox regression

Survival analysis refers to statistical approaches used to study time passed for an event of interest to occur. The event of interest may be death or non-fatal. A commonly used model for survival analysis is the Cox proportional hazards regression (Cox regression). This model is used to relate several variables known as covariates, simultaneously, to survival time and can be used to compare treatment groups, despite multiple differences in factors considered to affect outcome.

The measure of effect is the hazard rate, corresponding to the risk of an event to occur, given that a subject has survived a particular time. When the
objective is to compare groups with respect to their hazards, a hazard ratio can be estimated.

Cox regression models were used in the comparative papers II, III and V. In order to obtain adjusted analyses, a selection of covariates was included in a number of models.

In paper V, differences in outcome on individual level were analysed using a Cox model adjusted for age, gender, index year and indication. In addition, for the main stent level analysis, a full Cox model was used. This model included all the following covariates: gender, age, admission year, hospital, smoking status, indication for PCI, treatment of RCA, treatment of LAD, treatment of LCX, treatment of left main, chronic occlusion, treatment of restenosis, number of stents in PCI, minimum stent diameter, total stent length, diabetes, hyperlipidaemia, hypertension, previous CABG, previous MI, anticoagulation before PCI, ASA before PCI, OAC before PCI, any P2Y12i before PCI. Results were presented as Hazard Ratios (HR) with 95% confidence intervals.
5. Results

5.1 Paper I

This analysis was part of the preparation for the registry-based randomised clinical trial (R-RCT) VALIDATE-SWEDEHEART.112 There had been randomised clinical trial signals of excess early ST with bivalirudin, compared with UFH/GPI-treatment, making this purely descriptive real-world study an important complement to the overall safety assessment of bivalirudin.

Incidence of early ST within 30 days was low, regardless of bivalirudin, UFH alone or GPI treatment. Temporal distribution was similar in the antithrombotic strategy subgroups (Table 1).

Table 1. Incidence of early, definite stent thrombosis, per antithrombotic treatment subgroup, also reported as acute and subacute (days 0-1 and days 2-30 post PCI, respectively).

<table>
<thead>
<tr>
<th></th>
<th>Bivalirudin</th>
<th>UFH</th>
<th>GPI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=16,860</td>
<td>n=3,182</td>
<td>n=11,216</td>
</tr>
<tr>
<td>ST day 0-30</td>
<td>0.84% (n=142)</td>
<td>0.94% (n=30)</td>
<td>0.83% (n=93)</td>
</tr>
<tr>
<td>ST day 0-1</td>
<td>0.33% (n=55)</td>
<td>0.28% (n=9)</td>
<td>0.21% (n=23)</td>
</tr>
<tr>
<td>ST day 2-30</td>
<td>0.53% (n=87)</td>
<td>0.68% (n=21)</td>
<td>0.64% (n=70)</td>
</tr>
</tbody>
</table>

UFH, unfractionated heparin; GPI, Glycoprotein IIb/IIIa-inhibitor; n, number of patients or events.

Mortality was reported for all patients, regardless of antithrombotic treatment. All-cause mortality at one year was 20.7% for all ST patients (n=265), compared with 9.1% in patients without ST (n=31286) (p<0.001) (Table 2).

Table 2. All-cause mortality at one year in patients with and without early stent thrombosis.

<table>
<thead>
<tr>
<th></th>
<th>All-cause mortality at one year</th>
</tr>
</thead>
<tbody>
<tr>
<td>ST day 0-30 (n=265)</td>
<td>20.7% (n=51) (CI 0.16-0.26)</td>
</tr>
<tr>
<td>No ST (n=31286)</td>
<td>9.1% (n=2,548) (CI 0.088-0.094)</td>
</tr>
<tr>
<td></td>
<td>p&lt;0.001</td>
</tr>
</tbody>
</table>

n, number of patients or events; CI, 95% confidence interval.
Patients with ST day 2-30 had numerically higher all-cause mortality at one year compared to patients with ST day 0-1 (23% vs 16%, p=0.20) (Table 3).

**Table 3. All-cause mortality at one year in patients with stent thrombosis day 2-30 and day 1 post PCI, respectively.**

<table>
<thead>
<tr>
<th>All-cause mortality at one year</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ST day 2-30 post PCI (n=178)</td>
<td>23% (n=38)</td>
</tr>
<tr>
<td>ST day 0-1 post PCI (n=87)</td>
<td>16% (n=13)</td>
</tr>
<tr>
<td>p</td>
<td>0.204</td>
</tr>
</tbody>
</table>

n, number of patients or events.

5.2 Paper II

*In this study we compared the outcome of PPCI in 20,614 patients treated with UFH monotherapy vs bivalirudin. The bivalirudin treatment group contained both patients with and without concomitant UFH, reflecting a variation in clinical practice across Swedish hospitals. All patients with GPI or OAC treatment were excluded.*

At baseline, UFH only treated patients were older, more often female and generally at higher risk with more prior MI, PCI, CABG and longer time delays to PPCI. On the other hand, they were less often smokers and tended to have less complicated lesions. Propensity score matching with imputed datasets generated similar groups.

The primary outcome measure of early ST (within 30 days of PCI) occurred at low and similar crude rates in UFH only and bivalirudin treated patients, 0.9% vs 0.8% (Figure 6). Adjusted analyses for early ST showed similar rates for UFH and bivalirudin treated patients (Table 4).

The Kaplan-Meier plot for deaths within 30 days of PPCI is showed in Figure 7.
Figure 6. Kaplan-Meier curve of definite stent thrombosis (ST) within 30 days of primary PCI for STEMI. UFH: unfractionated heparin monotherapy (red plot). Bivalirudin (black plot). X-axis: number of days post PCI. Y-axis: proportion of individuals with ST.

Figure 7. Kaplan-Meier curve of all-cause deaths within 30 days of primary PCI for STEMI. UFH: unfractionated heparin monotherapy (red plot). Bivalirudin (black plot). X-axis: number of days post PCI. Y-axis: proportion of individuals who died.
All-cause death at 30 days occurred in 6.9% vs 5.4% of patients (adjusted HR 1.23, 95% CI 1.05-1.44) and within 365 days in 12.1% vs 8.9% (adjusted HR 1.34, 95% CI 1.19-1.52), significantly higher in UFH only compared with bivalirudin treated patients. Results were similar with PS matched groups (Table 4). The incidence of major bleeding within 30 days was numerically higher for UFH only but did not reach statistical significance. The incidence of re-infarction within 365 days and stroke within 30 days was similar in UFH only and bivalirudin treated patients (Table 4).

Table 4. Outcome of primary PCI patients treated with UFH only vs bivalirudin.

<table>
<thead>
<tr>
<th></th>
<th>UFH % (n)</th>
<th>Bivalirudin % (n)</th>
<th>Unadjusted HR (95% CI)</th>
<th>Adjusted HR (95% CI)</th>
<th>PS matched (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=3,721</td>
<td>n=16,891</td>
<td>n=20,612</td>
<td>n=20,612</td>
<td>n=5,942</td>
</tr>
<tr>
<td>Early ST</td>
<td>0.91% (34)</td>
<td>0.78% (131)</td>
<td>1.19 (0.82-1.74)</td>
<td>1.08 (0.7-1.65)</td>
<td>1.03 (0.54-1.94)</td>
</tr>
<tr>
<td>ST day 0–1</td>
<td>0.32% (12)</td>
<td>0.29% (49)</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>ST day 2–30</td>
<td>0.61% (22)</td>
<td>0.50% (82)</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>All-cause death at 30 days</td>
<td>6.93% (256)</td>
<td>5.43% (916)</td>
<td>1.29 (1.12 - 1.48)</td>
<td>1.23 (1.05 - 1.44)</td>
<td>1.2 (0.97-1.49)</td>
</tr>
<tr>
<td>All-cause death at 365 days</td>
<td>12.1% (415)</td>
<td>8.94% (1,472)</td>
<td>1.37 (1.23 - 1.53)</td>
<td>1.34 (1.19 - 1.52)</td>
<td>1.35 (1.07 - 1.72)</td>
</tr>
<tr>
<td>MI at 365 days</td>
<td>3.05% (101)</td>
<td>2.41% (377)</td>
<td>1.27 (1.02 - 1.58)</td>
<td>1.14 (0.88 - 1.46)</td>
<td>1.04 (0.73 - 1.48)</td>
</tr>
<tr>
<td>Stroke at 30 days</td>
<td>1.17% (41)</td>
<td>1.02% (165)</td>
<td>1.16 (0.82–1.63)</td>
<td>1.08 (0.73-1.59)</td>
<td>1.12 (0.62-2.02)</td>
</tr>
<tr>
<td>Major bleeding at 30 days</td>
<td>0.8% (28)</td>
<td>0.62% (100)</td>
<td>1.31 (0.86–1.98)</td>
<td>1.54 (0.97-2.45)</td>
<td>1.40 (0.72–2.69)</td>
</tr>
<tr>
<td>Death, MI, stroke at 365 days</td>
<td>16.9% (568)</td>
<td>12.6% (2065)</td>
<td>1.37 (1.25-1.5)</td>
<td>1.34 (1.2-1.49)</td>
<td>1.27 (1.07-1.5)</td>
</tr>
</tbody>
</table>

UFH: unfractionated heparin; HR: hazard ratio; n: number of events, CI: confidence interval. Early ST: stent thrombosis day 1-30 post PCI; MI: myocardial infarction. Hazard ratio displayed is for UFH vs bivalirudin treatment. * Not calculated.
5.3 Paper III

At the time of this study, randomised clinical trials had indicated higher rates of ST and target lesion failure (TLF) for the Absorb BRS compared with modern drug eluting stents (DES). Our real-world data were a valuable contribution and complement to RCT data.

Absorb BRS was implanted in a younger (median 59 vs 68 years), lower-risk population with less diabetes, less previous MI and previous PCI compared with modern DES treated patients. Full background and procedural data are presented in paper III.

There were 12 cases of definite ST (12/810) in Absorb BRS compared with 406/67,099 for modern DES. Absorb BRS was associated with a higher incidence of ST in the main stent level analysis and all three sensitivity analyses. The adjusted risk of ST was increased fourfold to nearly eightfold with Absorb BRS compared with modern DES (Table 5).

Table 5. Stent thrombosis.

<table>
<thead>
<tr>
<th>Analysis / Cohort</th>
<th>Absorb BRS Events/N</th>
<th>DES Events/N</th>
<th>Unadjusted HR (95% CI)</th>
<th>Unadjusted P value</th>
<th>Adjusted HR (95% CI)</th>
<th>Adjusted P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total stent</td>
<td>12/810 (1.5%)</td>
<td>406/67,099</td>
<td>2.38 (1.28-4.45)</td>
<td>0.006</td>
<td>4.34 (2.35-8.00)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Single stent</td>
<td>8/336 (2.4%)</td>
<td>120/20,996</td>
<td>3.96 (1.94-8.10)</td>
<td>&lt;0.001</td>
<td>7.88 (3.53-17.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Individual level</td>
<td>10/460 (2.2%)</td>
<td>320/38,097</td>
<td>2.50 (1.33-4.69)</td>
<td>0.004</td>
<td>4.44 (2.25-8.77)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PS matched</td>
<td>12/790 (1.5%)</td>
<td>23/6,405</td>
<td>*</td>
<td></td>
<td>4.22 (2.02-8.82)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>


Rates of ISR did not differ between Absorb BRS and DES treated patients. Results were consistent in all analyses (Table 6).
Crude all-cause mortality at one year was calculated for both Absorb BRS and DES groups (1.0 vs 5.0 %). Crude rates of re-infarction (any vessel) at one year were 3% in Absorb BRS and 3.8% in DES treated patients. These findings reflect the markedly lower risk at baseline in Absorb BRS treated patients.

Non-compliance with dual antiplatelet therapy (DAPT) guidelines was noted in 6 out of 12 BRS ST-events and 3 out of 12 devices were undersized in retrospect. Three very late ST events occurred with the Absorb BRS (Figure 8).

<table>
<thead>
<tr>
<th>Analysis / Cohort</th>
<th>Absorb BRS Events/N</th>
<th>DES Events/N</th>
<th>Unadjusted HR (95% CI)</th>
<th>Unadjusted P value</th>
<th>Adjusted HR (95% CI)</th>
<th>Adjusted P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total stent</td>
<td>11/810 (1.4%)</td>
<td>1005/67,099 (1.5%)</td>
<td>0.88 (0.41-1.92)</td>
<td>0.752</td>
<td>1.04 (0.44-2.44)</td>
<td>0.930</td>
</tr>
<tr>
<td>Single stent</td>
<td>3/336 (0.9%)</td>
<td>312/20,996 (1.5%)</td>
<td>0.58 (0.19-1.82)</td>
<td>0.355</td>
<td>0.62 (0.19-2.05)</td>
<td>0.435</td>
</tr>
<tr>
<td>Individual level</td>
<td>6/460 (1.3%)</td>
<td>779/38,097 (2.0%)</td>
<td>0.61 (0.27-1.37)</td>
<td>0.233</td>
<td>0.91 (0.40-2.08)</td>
<td>0.818</td>
</tr>
<tr>
<td>PS matched</td>
<td>11/790 (1.4%)</td>
<td>74/6,405 (1.2%)</td>
<td>*</td>
<td></td>
<td>1.22 (0.54-2.74)</td>
<td>0.635</td>
</tr>
</tbody>
</table>

Figure 8. Timing of Absorb BRS stent thrombosis (ST) events and antithrombotic pharmacological treatment. X-axis shows time elapsed from index percutaneous coronary intervention (PCI) to stent thrombosis (ST) event (blue bars). + marks ST event. The duration of antithrombotic drug treatment in days is printed at end of bars. Y-axis shows the different ST events. * marks duration of dual antiplatelet therapy (DAPT) < 12 months (as noted in six out of eleven ST events). Failure of initiation of DAPT was noted in three cases. At the top of the panel the blue arrows indicate time intervals for early, late and very late ST. BRS: Absorb bioresorbable scaffold.

5.4 Paper IV

The aim of this study was to analyse the first two years of routine clinical use of cangrelor in all Swedish patients treated with PCI. There was and is still a paucity of real-world data on how cangrelor has been incorporated into clinical practice, making our study important.

Cangrelor-use in primary PCI varied greatly between analysed hospitals (4-36%, mean 16%) and was more frequent the earlier the patients presented after diagnostic ECG. In contrast to patient populations studied in randomised tri-
als, cangrelor was used nearly exclusively in STEMI (>98%), often with cardiac arrest (18%). Cangrelor was used more frequently in high-risk patients: left main PCI, thrombus aspiration and cardiac arrest, compared with non-cangrelor treated patients. Median time-delays were shorter in cangrelor-treated patients (Table 7).

Table 7. Co-administered antithrombotic agents

<table>
<thead>
<tr>
<th></th>
<th>Cangrelor treated (n=899)</th>
<th>Non-cangrelor treated (n=4,614)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender, % (n)</td>
<td>72 (646)</td>
<td>72 (3,313)</td>
</tr>
<tr>
<td>Age, mean (years)</td>
<td>67.2</td>
<td>67.6</td>
</tr>
<tr>
<td>Hypertension, % (n)</td>
<td>47 (421)</td>
<td>49 (2,257)</td>
</tr>
<tr>
<td>Diabetes with insulin, % (n)</td>
<td>6.3 (57)</td>
<td>6.7 (308)</td>
</tr>
<tr>
<td>Diabetes w/o insulin, % (n)</td>
<td>9.7 (87)</td>
<td>9.5 (439)</td>
</tr>
<tr>
<td>Previous MI, % (n)</td>
<td>12.9 (116)</td>
<td>14.7 (680)</td>
</tr>
<tr>
<td>Previous PCI, % (n)</td>
<td>12.1 (109)</td>
<td>13.2 (607)</td>
</tr>
<tr>
<td>Previous CABG, % (n)</td>
<td>2.1 (19)</td>
<td>3.2 (147)</td>
</tr>
<tr>
<td>Current smoker, % (n)</td>
<td>22.9 (206)</td>
<td>25.7 (1,186)</td>
</tr>
<tr>
<td>Creatinine, median (µg/L)</td>
<td>83</td>
<td>79</td>
</tr>
<tr>
<td>Indication for PCI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>STEMI, % (n)</td>
<td>82.0 (737)</td>
<td>96 (4,426)</td>
</tr>
<tr>
<td>STEMI + Cardiac arrest, % (n)</td>
<td>17.8 (160)</td>
<td>2.4 (75)</td>
</tr>
<tr>
<td>STEMI/rescue PCI, % (n)</td>
<td>0.2 (2)</td>
<td>1.6 (113)</td>
</tr>
<tr>
<td>Puncture site radial, % (n)</td>
<td>78 (699)</td>
<td>88 (4,050)</td>
</tr>
<tr>
<td>Puncture site femoral, % (n)</td>
<td>22 (194)</td>
<td>11 (526)</td>
</tr>
<tr>
<td>Extent of coronary disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 vessel, LM not involved, % (n)</td>
<td>49.6 (446)</td>
<td>51.9 (2,393)</td>
</tr>
<tr>
<td>2 vessel, LM not involved, % (n)</td>
<td>29.1 (262)</td>
<td>27.3 (1,260)</td>
</tr>
<tr>
<td>3 vessel, LM not involved, % (n)</td>
<td>14.2 (128)</td>
<td>15.2 (702)</td>
</tr>
<tr>
<td>LM disease, % (n)</td>
<td>6.5 (58)</td>
<td>4.7 (215)</td>
</tr>
<tr>
<td>LAD treated, % (n)</td>
<td>52.5 (472)</td>
<td>47.1 (2,174)</td>
</tr>
<tr>
<td>LCX treated, % (n)</td>
<td>19 (167)</td>
<td>20 (930)</td>
</tr>
<tr>
<td>RCA treated, % (n)</td>
<td>38 (337)</td>
<td>41 (1,875)</td>
</tr>
<tr>
<td>LM treated, % (n)</td>
<td>5.2 (47)</td>
<td>2.6 (120)</td>
</tr>
<tr>
<td>Vein graft treated, % (n)</td>
<td>0.7 (6)</td>
<td>1.5 (69)</td>
</tr>
<tr>
<td>Thrombectomy performed, % (n)</td>
<td>17 (151)</td>
<td>9 (434)</td>
</tr>
<tr>
<td>Time delays (hours:minutes)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECG* to PCI, median</td>
<td>0:59</td>
<td>1:12</td>
</tr>
<tr>
<td>ECG* to PCI, mean</td>
<td>1:35</td>
<td>2:27</td>
</tr>
<tr>
<td>ECG* to PCI, mean, 5% trimmed</td>
<td>1:08</td>
<td>1:27</td>
</tr>
</tbody>
</table>


Cangrelor was combined with ticagrelor in two thirds of patients, among which >50% had prehospital ticagrelor (Table 7).
Table 7. Co-administered antithrombotic agents

<table>
<thead>
<tr>
<th></th>
<th>Cangrelor treated (n=899)</th>
<th>Non-cangrelor treated (n=4,614)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ticagrelor before PCI, % (n)</td>
<td>33.4 (300)</td>
<td>70.6 (3,258)</td>
</tr>
<tr>
<td>Ticagrelor during PCI, % (n)</td>
<td>31.9 (287)</td>
<td>23.9 (1,105)</td>
</tr>
<tr>
<td>Prasugrel before PCI, % (n)</td>
<td>0 (0)</td>
<td>0.3 (12)</td>
</tr>
<tr>
<td>Prasugrel during PCI, % (n)</td>
<td>0 (0)</td>
<td>0.02 (1)</td>
</tr>
<tr>
<td>Clopidogrel before PCI, % (n)</td>
<td>1.3 (12)</td>
<td>4.0 (183)</td>
</tr>
<tr>
<td>Clopidogrel during PCI, % (n)</td>
<td>1.2 (11)</td>
<td>1.3 (62)</td>
</tr>
<tr>
<td>Bivalirudin during PCI, % (n)</td>
<td>17.8 (160)</td>
<td>24 (1,107)</td>
</tr>
<tr>
<td>GPI before PCI, % (n)</td>
<td>0 (0)</td>
<td>0.1 (6)</td>
</tr>
<tr>
<td>GPI during PCI, % (n)</td>
<td>4.2 (38)</td>
<td>10.4 (479)</td>
</tr>
<tr>
<td>Warfarin before PCI, % (n)</td>
<td>1.2 (11)</td>
<td>1.7 (77)</td>
</tr>
<tr>
<td>DOAC before PCI, % (n)</td>
<td>2.9 (26)</td>
<td>3.5 (160)</td>
</tr>
</tbody>
</table>

More than 98% of patients received heparin i.v. PCI: percutaneous coronary intervention, GPI: Glycoprotein IIb/IIIa inhibitor, DOAC: direct oral anticoagulant.

Despite cangrelor being used in higher-risk patients, crude definite ST rates at 30 days were low in both cangrelor (0.7%) and non-cangrelor treated patients (0.8%). Any bleeding during the entire hospital stay was noted in 2.3% of cangrelor treated patients, and 2.8% of non-cangrelor treated. Major bleeding did not occur in any of the cangrelor treated patients, and in 0.1% of non-cangrelor treated patients.

Among a total of 273 patients presenting with cardiac arrest STEMI, nearly 60% (n=160) received cangrelor, indicating that this is an established strategy.

In summary, cangrelor was used at variance with the protocols of pivotal clinical trials, nearly exclusively in STEMI, often with ticagrelor and often in patients with cardiac arrest.

5.5 Paper V

*Xience has generally been regarded the best in class modern DES and is one of the most commonly implanted stents worldwide. Data on the outcome of PCI using Xience in large, unselected populations is limited. We aimed to compare the outcome of PCI using Xience with the outcome of PCI using other modern DES. A complete list of stents included is found in paper V.*

For the individual level analysis, we included all patients undergoing PCI in the specified time (n=180,054). We excluded patients with a previous PCI, those with no DES in the procedure, those with BMS and DES in the same procedure and those with infrequently used DES or older DES. Finally, patients with more than one type of Xience stent in the procedure were excluded. The final individual level data set contained 65,110 individuals (Figure 9).
For the stent level analysis, we excluded procedures with simultaneous implantation of BMS and infrequently used or older DES. The final data-set contained 203,760 stents (Figure 9).

Crude rates of the primary outcome measure, a combination of all-cause mortality, MI and revascularisation with PCI were 31.9% and 28.2% for Xience and other DES, respectively.

Secondary outcome measures were all-cause mortality, MI and revascularisation with PCI. Crude rates for all secondary outcome measures were similar in Xience and other DES treated patients. Kaplan-Meier plots for the reported outcomes are displayed in Figure 10.
Figure 10. Kaplan-Meier curves for individual level outcome measures, matched data set. A: the combination of all-cause mortality, myocardial infarction and revascularisation. B: all-cause mortality. C: Myocardial infarction. D: Revascularisation with PCI.

The adjusted hazard ratio for the primary endpoint was 0.99 (95% CI 0.95-1.03), with consistent results in both sensitivity analyses. Results were similar for Xience and other DES in all secondary outcomes analysed (Table 8).
Table 8. Clinical outcome, Xience vs other DES, individual level.

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted HR 95% CI</th>
<th>Adjusted HR 95% CI</th>
<th>PS matched HR 95% CI</th>
<th>One stent adjusted HR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death/MI/Revasc</td>
<td>0.928 0.90-0.96</td>
<td>0.992 0.95-1.03</td>
<td>1.05 0.99-1.11</td>
<td>1.014 0.96-1.07</td>
</tr>
<tr>
<td>Death</td>
<td>0.869 0.82-0.92</td>
<td>0.958 0.90-1.02</td>
<td>1.055 0.96-1.16</td>
<td>1.006 0.93-1.09</td>
</tr>
<tr>
<td>MI</td>
<td>1.077 1.00-1.17</td>
<td>1.054 0.97-1.15</td>
<td>1.067 0.95-1.20</td>
<td>1.061 0.95-1.18</td>
</tr>
<tr>
<td>Revasc</td>
<td>0.950 0.91-0.99</td>
<td>0.999 0.95-1.05</td>
<td>1.051 0.98-1.12</td>
<td>1.009 0.95-1.07</td>
</tr>
</tbody>
</table>

HR: hazard ratio, CI: confidence interval, MI: myocardial infarction, Revasc: revascularisation with PCI, PS: propensity score. Adjusted: A Cox regression model was applied adjusting for age, gender, index year and indication. PS matched: After PS matching, a Cox regression model was applied adjusting for age, gender, index year and indication. One stent adjusted: this analysis included procedures with one single stent implanted. A Cox regression model adjusting for age, gender, index year and indication was applied.

Crude rates of ISR were 2.9% vs 2.1% over 4.3 and 2.9 years respectively, for Xience vs other DES. Corresponding crude rates of definite ST were 0.9% vs 0.7%. Kaplan-Meier plots for ISR and definite ST are displayed in Figure 11.


All adjusted analyses including sensitivity analyses for ISR showed similar outcome for PCI using Xience vs other DES. All adjusted analyses for definite ST showed similar outcome for Xience vs other DES (Table 9).
<table>
<thead>
<tr>
<th></th>
<th>Crude rates</th>
<th>Full adjusted</th>
<th>Adjusted</th>
<th>PS matched</th>
<th>One stent adjusted</th>
<th>One stent PS matched</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR 95% CI</td>
<td>HR 95% CI</td>
<td>HR 95% CI</td>
<td>HR 95% CI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISR</td>
<td>2.9% 0.926</td>
<td>0.81-1.06</td>
<td>0.954 1.04</td>
<td>0.928 1.03</td>
<td>0.988 1.11</td>
<td>0.953 1.14</td>
</tr>
<tr>
<td></td>
<td>vs 2.1%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ST</td>
<td>0.9% 1.067</td>
<td>0.82-1.39</td>
<td>1.091 1.28</td>
<td>1.064 1.29</td>
<td>1.135 1.40</td>
<td>1.357 1.85</td>
</tr>
<tr>
<td></td>
<td>vs 0.7%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ISR: in-stent restenosis, ST: stent thrombosis, HR: hazard ratio, CI: confidence interval, PS: propensity score. The crude rates do not consider differences in follow-up time, nor baseline differences. The full adjusted analysis applied a Cox regression model using an extensive number of co-variates. The adjusted analysis applied a Cox regression model adjusting for age, gender, index year and indication. In the PS matched groups adjusted analysis the groups were matched based on PS. After matching the groups, a Cox regression model was applied adjusting for age, gender, index year and indication. The one stent per procedure analysis included procedures with one single stent implanted. One stent adjusted analysis applied a Cox model adjusting for age, gender, index year and indication. One stent PS matched: After PS matching, a Cox regression model adjusting for age, gender, index year and indication was applied. Crude rates for ISR and ST are displayed as cumulative incidence for Xience DES vs other DES, not accounting for differences in follow up time.
6 Discussion

Modern invasive treatment of coronary artery disease is a field where pharmacological and technical strategies must be combined appropriately to achieve the best patient outcome. Hence, the context needs to be considered when analysing results of trials, whether they involve stents or pharmacological agents. As an illustration, in paper III the rates of definite ST are more informative thanks to the in-depth analysis of antithrombotic treatment and details of implantation technique. As another illustration, the outcome of PCI using bivalirudin depends not only on bivalirudin, but the baseline risk, the access route, the combination of bivalirudin with oral agents, UFH and GPI, technical aspects and success of PCI, downstream management and drug compliance etc.

Papers I-V all share a focus on ST. Papers I, II and IV all share a focus on STEMI and PPCI, whereas papers III and V include patients with ACS and CCS.

The field of interventional cardiology is rapidly evolving, and new treatment strategies are adopted early. The fundamental RCT evidence for new strategies needs external validation in unselected populations. All papers of this thesis are all examples of real-world evidence as a complement to randomised trials.

6.1 Bivalirudin or UFH in primary PCI

Paper II compared outcomes in UFH and bivalirudin-treated patients undergoing PPCI for STEMI. The study was performed in a setting different from today’s evidence.

Many previous trials of bivalirudin vs UFH had suffered from asymmetric GPI use in the groups compared. Particularly the lower bleeding rates reported with bivalirudin were influenced by GPI imbalance. At the time of planning paper II, the use of GPI was already considered primarily a bailout option, and the main question was if bivalirudin was a better routine anticoagulant than UFH in PCI for ACS.

There was recent evidence suggesting bivalirudin was inferior to UFH in PPCI for STEMI with the publication of the open label, single center RCT HEAT-PPCI. In this trial, 1,800 PPCI patients were randomised to bivalirudin monotherapy or UFH monotherapy. By protocol, GPI use was only bailout
and did balance between groups. Bivalirudin was used without any concomitant UFH and infusions were not prolonged beyond PCI. Rates of early ST in HEAT PPCI were strikingly high for bivalirudin, 3.4% vs 0.9% for UFH. Rates of new or recurrent MI were significantly higher for bivalirudin, as were rates of unplanned revascularisation. No differences were reported for major bleeding and all-cause death. These results, published in 2014, were clearly negative for bivalirudin and sparked further debate on what was the optimal anticoagulation strategy in PCI for ACS.

In paper II, UFH treatment was associated with significantly higher all-cause mortality at 30 and 365 days, compared with bivalirudin. In contrast to findings in several RCTs of bivalirudin vs UFH/GPI100,103,104,106 there was no excess early ST with bivalirudin. Neither did we find any differences in major bleeding rates, consistent with the results of RCTs with balanced GPI use.104,105

The low rates of early ST with bivalirudin in paper II were likely due to a combination of frequent prehospital ticagrelor loading, frequent concomitant UFH with bivalirudin and optional prolonged bivalirudin infusion at PCI dose. Prolonged infusion was perceived as rather common, although infusion times are not recorded in SWEDEHEART so no data exists.

The VALIDATE-SWEDEHEART RRCT was designed with these parameters in mind, to give bivalirudin optimal chances to perform well.112 The trial randomised 3,000 STEMI and 3,000 NSTEMI patients with potent P2Y12-inhibitors, no planned GPI use and predominantly radial access PCI to either bivalirudin including a small UFH bolus dose or UFH monotherapy. The trial, published in 2017, was neutral for the primary combined endpoint of death, MI or major bleeding. There were further no differences in the secondary endpoints of death, MI, major bleeding or definite ST. The trial results contributed to a downgrading of bivalirudin in the 2018 European guidelines on myocardial revascularisation to the current class IIb recommendation during PCI for STEMI and NSTEMI, whereas UFH is recommended as routine anticoagulant.40

Hence, the results of paper II must be analysed in light of VALIDATE. Our conclusion is that in paper II, a complete all-comer, higher risk population was included and despite adjustments for baseline differences, there may be residual bias favouring bivalirudin, with respect to all-cause mortality.

We note however that the absence of excess ST with bivalirudin in paper II was confirmed by VALIDATE. Early ST (within 30 days) in paper II was 0.78% and 0.91% for bivalirudin and UFH, respectively. In the VALIDATE STEMI substudy, with 3,000 patients, recently published as an abstract, rates of definite ST within 180 days were significantly lower for bivalirudin compared to UFH, 0.5% vs 1.3%, HR 0.42, 95% CI 0.18-0.96.144

In paper II, all-cause mortality at 30 days was 5.43% vs 6.93%, for bivalirudin and UFH respectively. In the VALIDATE STEMI substudy, all-cause death at 180 days was markedly lower, 3.9% in both groups. These mortality
differences show that although VALIDATE had a very high inclusion rate, the average risk in randomised patients was lower than in an unselected population. The fact that all-cause death at 180 days was similar for bivalirudin and UFH, contrary to the finding in paper II, further contributes to the indication of residual bias in paper II. Both paper II and the VALIDATE STEMI substudy reported similar major bleeding rates for bivalirudin and UFH.

In summary, despite efforts to adjust, paper II likely suffers from residual selection bias, pushing the results in favour of bivalirudin. With the results of VALIDATE, our conclusion is that routine use of bivalirudin in PCI for ACS is not supported by evidence. There may however still be subgroups of patients where bivalirudin is superior to UFH, for example female patients, as reported in another recent VALIDATE substudy.\textsuperscript{145} This finding may relate to the generally higher bleeding rates observed after PCI in female patients.\textsuperscript{146,147} A large individual level meta-analysis including 8 RCTs of bivalirudin vs UFH is under way.\textsuperscript{148} This analysis will hopefully provide informative insights from a large population and selected subgroups.

6.2 Absorb and other resorbable devices

The results with the Absorb BRS were disappointing as follow up times reached beyond 1-2 years. Paper III was consistent with the totality of RCT evidence as we found markedly increased risk of ST, including very late events, but no reduction in ISR. Our study added detailed information about timing of ST cases.

When the problem of late ST became apparent with Absorb, a strong focus on intravascular imaging followed. Several publications reported that optimal implantation technique could reduce adverse events.\textsuperscript{149,150} A detailed summary however suggested that only about half of all BRS ST-events might be avoidable by meticulous implantation technique.\textsuperscript{151} Paper III showed that among all index PCI procedures with Absorb BRS (n=460), OCT was used in 7.4% and IVUS in 5.7%. The corresponding figures for modern DES were lower: 1.3% and 3.8% respectively.

With regards to paper III we note that SWEDHEART (with the SCAAR sub registry for angiography and PCI-procedures) only records limited data on implantation technique. Recorded parameters for each implanted stent or BRS include: brand and dimensions, anatomical location, grade and classification of stenosis, predilatation yes/no, post-dilatation yes/no, maximum dilatation pressure, maximum dilatation diameter, and finally if PCI was generally successful or not. Use of OCT or IVUS during the procedure is recorded but without details on vessel diameter, minimum lumen areas, stent or scaffold apposition etc.

Therefore, in paper III, an in-depth analysis on BRS ST events was performed, including information from medical records and angio/PCI films.
This provided a deeper insight and showed that many ST events were associated with suboptimal use (undersizing) and non-adherence to DAPT recommendations.

We can speculate that the rates of BRS ST may well have been lower if more intravascular imaging had been used. However, a device that performs worse despite the evident more frequent use of costly imaging to ensure a perfect implantation is obviously not going to be a success. It must be noted that an absorbable device has a very strong comparator, as modern DES have excellent performance, which is shown in paper V. Compared to Absorb, modern DES are more forgiving and predictable from a technical perspective.

The key issue with Absorb BRS seems to be the dismantling of the scaffold during its rather slow resorption. As described in the introduction it seems that the excess risk for adverse events with Absorb ends beyond three years, coinciding with complete resorption. This renders hope for newer devices with prompter, more predictable resorption, without pro-thrombotic properties.

There are around 20 clinically available CE-marked resorbable devices at present, and more than ten devices with thinner struts than Absorb’s 156 µm, down to below 100 µm. The one magnesium-based sirolimus eluting bioresorbable device has markedly shorter resorption and seems promising in terms of thrombogeneity. To our knowledge there is presently no routine clinical use of any BRS in Sweden. Magnesium-based sirolimus eluting scaffolds are implanted in clinical trial settings. A meaningful SWEDEHEART analysis of safety and efficacy is not yet possible for devices other than Absorb, due to the low number of implantations.

6.3 Increased focus on intravascular imaging

Although the development of Absorb did not result in a successful device, the trial program contributed to the current strong focus on intravascular imaging, particularly with OCT. Increased understanding thanks to imaging will likely be beneficial for stent-related outcome in a broader PCI-perspective. Present European guidelines state that for general optimisation, in selected patients undergoing PCI, IVUS or OCT should be considered (Class IIa C). Further, the use of IVUS and/or OCT should be considered (Class IIa C) to detect stent-related mechanical problems in cases of stent failure like ISR or ST.

In recent years there has been a growing interest in intravascular imaging with bifurcation techniques involving more than one stent, to ensure a good technical result. It is important to remember that provisional main branch stenting only is generally recommended for bifurcation lesions (Class I A). Exceptions to this rule, where planned two-stent techniques may be preferable, include true left main bifurcations. In such cases, DK crush may be the preferred technique (Class IIb B). There is an ongoing multinational
clinical trial, of 1,200 patients investigating whether an OCT-guided compared to angiography-guided strategy during PCI of complex bifurcation lesions leads to superior outcome at two years.\textsuperscript{158} Currently it is clear that intravascular imaging provides information impossible to obtain from angiography alone. Some of the information obtained does however not necessarily warrant action, so this is a complicated field to study. It remains to be proven that routine intravascular imaging translates to better outcome in PCI.

6.4 The role of cangrelor in PCI

Paper IV showed that the clinical use of cangrelor is at variance with RCT evidence for this novel agent. The combination of cangrelor with more potent platelet inhibitor ticagrelor is reasonable and supported by mechanistic data as well as smaller clinical studies.\textsuperscript{79–83} The main drawback with clopidogrel and cangrelor is the pharmacological interaction leading to restrictions on the timing of clopidogrel in relation to the cangrelor infusion. By following the instructions and loading the patient with clopidogrel after stopping the cangrelor infusion, a potential gap in platelet inhibition may follow. Ticagrelor may be administered before stopping the cangrelor infusion and has a faster, more predictable onset than clopidogrel.

It has not been studied in a randomised setting however, if the combination of cangrelor and ticagrelor leads to increased bleeding, compared to only ticagrelor. With more potent platelet inhibition, an expected trade-off would be more bleeding events. In the CHAMPION trial program, increased rates of mild GUSTO bleeding were noted with cangrelor.\textsuperscript{77} In paper IV, with the observed use of cangrelor in many high-risk patients including 18\% with cardiac arrest STEMI, reassuringly the rates of bleeding were not higher than in non-cangrelor treated patients. No major bleeding events were reported in cangrelor treated patients. As a caution, there are obviously many layers of bias present. There was an initial selection of the highest risk patients never reaching hospital, and after circulatory stabilisation and PCI there were likely patients to have recurrent episodes of circulatory instability with fatal ending. Bleeding complication as a potential reason for deterioration is likely underdiagnosed in such a setting.

Another main finding in paper IV was that cangrelor was used nearly exclusively in STEMI. The main advantage of using cangrelor is to limit thromboembolic adverse events by effective, prompt platelet inhibition. The greater ST and thromboembolic risk in STEMI, and the fact that STEMI patients are not loaded with platelet inhibitors in a controlled, timely manner as in planned PCI or most cases of NSTEMI, makes it very logical to use cangrelor in PPCI for STEMI. The issue of delayed resorption, discussed in the introduction, gives an advantage for parenteral agents. With the formation of better STEMI networks, delays from diagnostic ECG to revascularisation can be reduced.
Shorter delay means less time for absorption of prehospital oral antiplatelet agents, a potential window where cangrelor could be an attractive treatment option.

If there were no increased cost with cangrelor compared to oral agents, the drug might well be used in most patients undergoing PPCI based on its pharmacokinetic advantages. Cangrelor enables a more controlled way of inhibiting platelets in a setting where bleeding risk is sometimes hard to estimate. In NSTEMI the use of cangrelor is not intuitively as beneficial, particularly with the common practice of ticagrelor loading at the time of NSTEMI diagnosis in Swedish hospitals, resulting in adequate platelet inhibition before PCI. It can be argued however that deferred oral loading may be advantageous in certain NSTEMI patients. As an example, when urgent CABG is the preferred treatment option, oral loading may delay open heart surgery.

6.5 Xience and strategies to improve stent related outcome

As paper V concluded, Xience is a modern DES with similar performance to a pool of other modern DES with a large proportion of thinner strut stents and absorbable polymers.

Stent manufacturers have engineered resorbable polymers to improve DES performance, as permanent polymers may contribute to low-grade inflammation and IRS or even neo-atherosclerosis. To date, RCTs and meta-analyses have not been able to show a clinical advantage with resorbable polymers.

Strut thickness has been reduced with the newest modern DES compared to Xience, and an ultra-thin sirolimus eluting DES with absorbable polymer has been compared head to head with Xience in two randomised trials of both ACS and CCS patients, showing lower rates of target lesion revascularisation with the ultra-thin DES. A longer follow up RCT comparing the ultrathin sirolimus eluting DES with Xience reported no differences in target lesion failure but an unexplained higher mortality associated with the ultrathin DES. A thinner strut DES may enable more rapid endothelialisation, which should reduce the risk of late ST. A thinner strut DES may also enable more flexibility and deliverability. There may however be a breaking point, where a thinner DES loses radial strength and becomes more sensitive to vessel recoil, mechanical distortion by protruding catheters or other manipulation during the PCI procedure. In that sense, a J-shaped curve for stent related outcome in relation to strut thickness is intuitively what to expect.
7 Strengths and limitations

7.1 Limitations of observational studies

The most important limitation of this thesis is common to all observational data, in relation to RCT data. A blinded RCT is the only way to eliminate bias when comparing two different treatment strategies.

Observational studies attempting to compare safety and efficacy of different treatment strategies will always suffer from some degree of residual confounding, despite efforts to adjust. Therefore, observational data constitutes lower level evidence compared with RCT data.

Real-world evidence is however an important complement, based on the limitations of many RCTs, as expanded below.

7.2 Limitations of randomised clinical trials

Randomised data is the foundation of new treatments. However, once an RCT has been performed and a new drug is incorporated in routine practice, the population receiving the treatment often differs from the RCT population.

Patients in RCTs tend to be younger, disproportionately often male and at lower risk of adverse events. Further they are subject to more frequent visits to healthcare professionals and generally receive a better, more evidence-based treatment. Patients with complicating co-morbidities, too advanced age, contraindications or inability to give consent or fulfil a study protocol are excluded. This results in idealised conditions and generalisability issues, also known as reduced external validity.

Time and cost, limiting sample size and power, are issues of many RCTs, due to the rigorous protocols needed to ensure internal validity. Real-world studies based on registries often have larger sample sizes and thus the appropriate power to find differences in rare outcome events, like ST. Observational studies may also be informative in clinical areas/topics impossible to study in RCTs, for example on patient populations where consent is difficult, like cardiac arrest STEMI.

The time needed to complete an RCT may be a problem, as practice patterns change with time, and trial protocols may not reflect current practice once the trial is finished. A good example is the CHAMPION trial program.
for cangrelor, performed in an era of clopidogrel, followed by approval in an environment of the more potent platelet inhibitor ticagrelor.77

A registry-based randomised clinical trial (RRCT) is a prospective randomised trial that uses a clinical registry for one or several major components of trial conduct and reporting of outcome events.168 By including randomisation for common treatment decisions in large clinical registries with unselected consecutive enrolment, the advantages of a prospective randomised trial can be combined with the strengths of large-scale registries.

7.3 Strengths and limitations of the SWEDEHEART registry
The long established, high quality, complete, national, real-world nature of the data is the main strength of SWEDEHEART. Additionally, SWEDEHEART mirrors a health system with overall high adherence to evidence-based therapies, which is the main purpose of SWEDEHEART.143 Data would be less valuable with generally poor quality of care. The large sample sizes of studies I, II and V are important strengths. Papers III and IV naturally have limited sample sizes since they are focusing on newly introduced treatment modalities. The cardiac arrest STEMI subgroup treated with cangrelor in paper IV is however to our knowledge the largest cohort studied in this very high-risk patient group.

A limitation of SWEDEHEART and other public registries is the absence of adjudication of outcome events.

Mortality, the most important outcome event, is automatically followed up 100% via merging of data from the national population register. Definite ST is likely captured at a high rate, since mandatory questions arise at a subsequent coronary angiogram for every previously implanted stent. ISR data is also collected through the same mandatory questions. Myocardial infarction is captured at a high rate as discussed in the introduction, but not 100% like re-vascularisation or re-PCI in a Swedish facility. Patients with MI treated in hospital units other than acute cardiac care-units are not entered in SWEDEHEART/Riks-HIA, meaning that some cases of MI can only be identified in the National Patient Registry, NPR. Bleeding events are probably underreported in SWEDEHEART like other registries, and only in-hospital events are recorded. Additional bleeding data can be collected from the NPR. Underreporting of bleeding events is likely a problem in all patients, regardless of treatment strategy.

Drug dosage and duration is not recorded in SWEDEHEART, and it is unknown whether a pharmacological treatment was planned or bailout. All events recorded in SWEDEHEART are clinically driven, i.e. there is no
planned safety surveillance performed to actively look for asymptomatic events like ISR.

7.4 Specific limitations for the respective papers

Papers I and II. Drug dosages are unknown; hence we do not know if bivalirudin was given as a prolonged infusion or not. Activated clotting time measurements are unknown. Further we cannot distinguish whether bivalirudin (or GPI for paper I) use was a planned or bailout strategy. Underreporting of ST is a potential limitation and only definite, angiographically proven ST is included. In paper II, the exclusion of GPI treated patients is a potential limitation, as we may introduce a bias.

Papers II, III and V contain comparisons of different treatment strategies. Although we use adjustment models, there may be residual confounding due to factors not accounted for in the models like frailty, signs of advanced disease/poor prognosis or even degree of thrombus burden, all of which are unknown factors that may influence choice of treatment strategy and outcome.

A clear limitation of paper III is the relatively small cohort of Absorb devices (n=810), and the low number of ST events (n=12). Since the BRS and DES groups are vastly different there is probably residual bias after adjustments. However, residual bias should if anything contribute to a relatively better outcome for Absorb BRS compared with DES. Suboptimal implantation technique may have influenced outcome. We have not analysed the DES ST-events in detail, so DAPT duration and technical data are not known in detail, as for BRS ST-events.

The relatively small number of patients treated with cangrelor limits paper IV. There is no data on the details of pharmacological strategy, i.e. was cangrelor initial strategy or used as bailout. There is no data on what time oral P2Y12-inhibitors were administered, only before arriving at the cath-lab or during PCI. There is no data on vomiting or parenteral opioid analgesic administration. There is no data on orotracheal intubation or circulatory support, which would have been interesting in the cardiac arrest group. Further there is no detailed data on cardiac arrest, duration or quality of CPR, number of defibrillations etc.
8 General conclusions

The overall aim of this thesis was to add real-world evidence to several areas of uncertainty, with regards to pharmacological and technical strategies in invasive treatment of coronary artery disease. Based on the findings of the papers of this thesis, we can conclude the following:

I In a real-world, unselected population of patients undergoing PPCI for STEMI, the incidence of early ST was low, regardless of antithrombotic treatment strategy (0.83-0.94%). We could not confirm the earlier reported excess early ST with bivalirudin, compared to UFH/GPI. Early ST was associated with a crude all-cause mortality of 21% at one year, compared to 9% in patients without ST. The temporal distribution of early ST was similar for patients treated with bivalirudin, UFH and GPI.

II In a real-world, unselected PPCI population, there were low and similar early definite ST-rates in UFH only and bivalirudin treated patients. All-cause mortality at 30 days and one year was significantly higher in UFH only compared with bivalirudin treated patients. Rates of major bleeding, re-infarction and stroke were similar in UFH only and bivalirudin treated patients.

III In a real-world, unselected population of patients undergoing PCI for all indications, the rates of definite ST were significantly higher (four- to eightfold) with the Absorb BRS compared with frequently used modern DES. One fourth of all BRS ST events occurred later than one year after implantation. Rates of ISR were similar for Absorb BRS and modern DES. Patients treated with Absorb BRS were significantly younger and at lower baseline risk, compared to patients treated with modern DES. Suboptimal implantation technique and non-compliance with DAPT guidelines were commonly associated with BRS ST events.

IV Clinical use of cangrelor in Sweden was at variance with the protocols of pivotal cangrelor RCT: s. The use of cangrelor in PPCI for STEMI varied greatly between hospitals, 4-36%. Cangrelor was used nearly exclusively in PPCI STEMI patients and with ticagrelor in 2/3 of cases, 50% of which was administered prehospitaly. Cangrelor was used more often in early presenters. STEMI with cardiac arrest was the indication for PCI in 18% of cangrelor
treated patients. Despite being used in very high-risk patients, cangrelor treatment was associated with low definite ST rates. No major bleeding events were reported in cangrelor treated patients.

V In a real-world, unselected population, Xience is a safe and effective DES with low event rates of ISR and ST. Compared with a control group containing a large proportion of thinner strut DES with absorbable polymers, Xience exhibits similar results in all important endpoints.
9 Clinical implications and future perspectives

The papers of this thesis all add real-world evidence for the various treatment strategies. Paper II was important for the planning of the VALIDATE study, which in turn did result in a major change of clinical practice. An upcoming meta-analysis may shed new light on certain subgroups of patients undergoing PCI, where bivalirudin may be beneficial compared with UFH.

Paper III confirmed RCT evidence of excess ST events with Absorb and added valuable clinical information on ST event timing, and factors associated with these events. There are other resorbable scaffolds studied in clinical trials, as the idea of avoiding permanent caging is still appealing. Intravascular imaging will gain even more focus, especially if clinical trials can prove that routine use leads to improved outcome in broad PCI populations.

Paper IV provided unique clinical information on how cangrelor was used during the first two years of routine clinical practice. Importantly, we found that physicians use cangrelor nearly exclusively in STEMI and combine cangrelor with ticagrelor in most cases. Despite cangrelor being used in a very high-risk population, we found no excess risk of ST, and no excess bleeding, compared to non-cangrelor treated patients.

Paper IV also identified that in patients with cardiac arrest STEMI, cangrelor is already an established treatment strategy. This patient group would be interesting to study more in detail, and incorporate information not recorded in SWEDHEART, like duration of cardiopulmonary resuscitation, information on initial rhythm, number of defibrillations if any, important time points and delays etc. With time, larger cohorts may enable a more detailed analysis on bleeding and thromboembolic adverse events.

Increased use of cangrelor would not be surprising, considering the pharmacokinetic advantages compared with oral antiplatelet agents.

Regarding innovations in metallic DES, there will be more evidence of the performance of thinner strut stents in relation to thicker struts, and more information on types of polymers, possibly also with new antiproliferative drugs or metallic alloys with improved radiopacity, strength and reduced thrombogenicity.

Complex PCI and broader use of intravascular imaging will increase the identification of various specific lesion characteristics. Tailoring of technical approach may enable better stent results and better outcome. One example is thorough lesion preparation for circumferential calcium to achieve better stent
expansion and apposition. Long term outcome data for recently introduced lesion preparation alternative intracoronary lithotripsy will be important.\textsuperscript{169}

Finally, there will likely be new tools to individually tailor treatment, including antithrombotic strategies in different scenarios. A one-size fits all concept clearly does not work well in real-world patients, as baseline risk varies greatly for both thromboembolic and bleeding complications. There will likely be scoring tools combining clinical information with biomarkers to enable more individualised intensity and duration of antithrombotic therapy before, during and after PCI. There will likely be new pharmacological agents with improved net clinical benefit, by targeting more specific steps of the coagulation cascade or platelet activation process.
Invasiv behandling av kranskärlssjukdom med PCI (perkutan kranskärlsinter-vention) innebär ballongvidgning och implantation av stent i hjärtats kranskärl. Ingreppet utförs via slangar och vajrar som förs till hjärtats kranskärl via en artärpunctio från huden, oftast vid handleden. Målet med behandlingen är att vidga och förbättra blodflödet i förträngda kranskärl.

Kranskärlssjukdom orsakas i de flesta fall av åderförkalkning och kan yttra sig i både kroniska och akuta tillstånd, däribland hjärtinfarkt. Vid hjärtinfarkt är den vanligaste genosen att ett åderförkalkat kärlsegment täpps till av en blodpropp som uppstår akut, till följd av plackruptur och aktivering av blodplättar och andra koagulationsfaktorer som cirkulerar i blodet.

I de flesta fall kan PCI minska omfattningen av hjärtinfarkt och begränsa/förhindra följdpromblem vilket leder till bättre prognos. PCI är en mycket etablerad metod och i Sverige görs ca 20000 ingrepp årligen på 28 sjukhus. Alla ingrepp registreras i det nationella kvalitetsregistret SWEDEHEART, liksom extensiv information kring patienter med hjärtinfarkt, deras behandlingar, läkemedel, tekniska data kring kranskärlsanatomi och PCI-ingrepp, utfall, komplikationer, tidsangivelser, labprover etc. Syftet med SWDEDEHEART är att utveckla och förbättra hjärtsjukvården, samt tjäna som bas för medicinsk forskning. SWEDEHEART innehåller en bred, oselekterad population av patienter som genomgår rutinmässig behandling av hjärtsjukdomar. Patienterna inkluderas i registret lokalt på respektive sjukhus där utredningar och behandlingar genomförs.

Vid kranskärlssjukdom och PCI är blodförtunnande läkemedel en central del av behandlingen, för att minska tendensen till proppbildning. Resultaten av PCI har förbättrats avsevärt tack vare förbättrade stent och effektivare blodförtunnande läkemedel. Idag används i första hand metallstent indränkta med läkemedel (drug eluting stent, DES). Det sker en snabb utveckling och under tiden för denna avhandling har behandlingsrekomendationer ändrats bland annat gällande intravenösa blodförtunnande läkemedel vid PCI.

Akut blodpropp i ett kranskärlsstent (stenttrombos, ST) är en ovanlig komplikation efter PCI, associerad med hög dödlighet. Ett annat problem efter PCI är inflammationsorsakad långsam restenosering, att kärlet åter blir förträngt på platsen för stentet. Läkemedel i moderna DES har effektivt reducerat tendensen till denna så kallade in-stent restenos (ISR). ST och ISR är två mycket
viktiga utfallsmått att studera hos patienter som genomgått PCI-behandling. Läkemedel och tekniska egenskaper hos stent, liksom patientrelaterade faktorer har betydelse.

Syftet med denna avhandling var att studera olika blodförtunnande läkemedelsstrategier och olika tekniska strategier (typer av stent) vid PCI. Fem registerstudier genomfördes, alla baserade på data från SWEDHEART.

I den första studien undersöktes 31258 patienter som behandlats med PCI för den mest akuta typen av hjärtinfarkt, ofta med helt tilltäpt kranskärl (ST-höjningsinfarkt, STEMI). Andelen som drabbades av ST efter PCI var låg (0,84 %) men ST var förenat med mycket hög dödlighet inom ett år (21 %). Andelen ST var ungefär lika oavsett typ av intravenöst blodförtunnande läkemedel som använts vid PCI.

I studie II undersökte 20600 patienter med STEMI som genomgått PCI. Vi jämförde utfallet hos patienter som behandlats med heparin respektive bivalirudin, två intravenösa blodförtunnande läkemedel. Andelen patienter som drabbades av ST var låg i båda grupperna. Risken för död var högre bland patienter som behandlats med heparin. Förekomst av ny hjärtinfarkt, stroke eller allvarlig blödning var lika i båda grupperna.


I studie IV undersöktes användningen av cangrelor, ett nytt, potent intravenöst blodförtunnande läkemedel med snabb effekt. I studien kartlades de första två åren av rutinmässig användning på svenska sjukhus. Vi fann att cangrelor används uteslutande vid PCI för STEMI, ofta hos patienter som kommit till sjukhus tidigt efter symptomdebut, ofta hos patienter med hög risk, komplicerade kranskärlsproblem och ofta i samband med STEMI som kompliceringsårsak av hjärtstillestånd. Trots att läkemedlet används hos svårt sjuka patienter sågs inga allvarliga blödningar och låg förekomst av ST.

I studie V undersöktes utfallet hos 65000 patienter som genomgått PCI med ett av världens mest använda läkemedelsstent (DES) av metall (produktetnamn Xience). Jämförelsegrupp var en rad andra moderna DES. Vi fann att Xience är ett säkert och effektivt DES med låg förekomst av ST samt restenos. Jämfört
med en kontrollgrupp som innehåller flera nyare DES med tunnare metalltrådar och mer modern design visade Xience lika bra resultat i alla viktiga utfallsmått.


Sammanfattningsvis har denna avhandlings fem studier bidragit med viktig kunskap från rutinsjukvård gällande blodförtunnande läkemedel och tekniska strategier vid invasiv behandling av kranskärlssjukdom.
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12. References


A doctoral dissertation from the Faculty of Medicine, Uppsala University, is usually a summary of a number of papers. A few copies of the complete dissertation are kept at major Swedish research libraries, while the summary alone is distributed internationally through the series Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine. (Prior to January, 2005, the series was published under the title “Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine”.)