# Myocardial infarction - Risk stratification and evaluation of therapies

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2021

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

# Myocardial infarction

## Risk stratification and evaluation of therapies

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Axel Wester grew up in Uppsala and received his medical degree in 2018 from Lund University. He then completed a clinical internship at Helsingborg Hospital in parallel to his doctoral studies. The focus of his research is risk stratification and evaluation of therapies for high-risk patients with myocardial infarction, using national quality and population-based registries. Dr Wester has been granted a postdoc position at Karolinska Institutet in Stockholm.

Printed by Media-Tryck, Lund 2021 NORDIC SWAN ECOLABEL 3041 0903

LUND UNIVERSITY

FACULTY OF MEDICINE

Department of Clinical Sciences, Lund
Faculty of Medicine

Lund University, Faculty of Medicine
Doctoral Dissertation Series 2021:99
ISBN 978-91-8021-106-2
ISSN 1652-8220

# Myocardial infarction

## Risk stratification and evaluation of therapies

Axel Wester


LUND
UNIVERSITY

DOCTORAL DISSERTATION

by due permission of the Faculty of Medicine, Lund University.
To be defended at Segerfalksalen, Wallenberg Neurocentrum, BMC, Lund.

2021-10-08 at 13:00.

*Faculty opponent*
Professor Ulf Näslund, MD, PhD

Umeå University

| **Organization** | **Document name** |
|---|---|
| LUND UNIVERSITY<br>Department of Cardiology,<br>Clinical Sciences, Faculty of Medicine,<br>Lund University, Lund, Sweden | DOCTORAL DISSERTATION |
| | **Date of issue** 2021-10-08 |
| Author: Axel Wester | Sponsoring organization: None |


**Title and subtitle** Myocardial infarction – Risk stratification and evaluation of therapies


**Abstract**

**Background.** Myocardial infarction (MI) remains the leading cause of death worldwide, despite several advances in acute coronary care during the last decades. This thesis assessed different risk stratification tools and evaluated interventional and pharmacological treatment strategies in high-risk patients with MI.

**Methods.** This work comprises four studies. The first and the fourth study extracted data from national registries. The first study evaluated the prognostic value of early percutaneous coronary intervention (PCI) on mortality in 2896 patients with cardiac arrest and no signs of ST-elevation MI (STEMI) undergoing coronary angiography, while the fourth study validated the novel PRECISE-DAPT score for the prediction of post-discharge bleeding in 66295 patients with MI treated with PCI and dual antiplatelet therapy (DAPT). The second and the third study were prespecified subgroup analyses of a recent trial that randomly assigned MI patients to an anticoagulation strategy with bivalirudin or heparin during PCI in a contemporary setting, including routine radial artery access, potent P2Y12 inhibition, and rare use of glycoprotein IIb/IIIa inhibitors. The second study investigated the impact of baseline anemia on clinical outcomes in 5482 of these patients, whereas the third study compared bivalirudin to heparin monotherapy regarding clinical outcomes in 1592 elderly patients (≥75 years).

**Results.** A total of 1271 (43.9%) of resuscitated cardiac arrest patients without STEMI had severe coronary artery stenosis (≥90%) on coronary angiography, of whom 753 (59.2%) underwent PCI but experienced a higher 30-day mortality rate compared to patients undergoing only diagnostic coronary angiography (40.9% vs 32.7%; p=0.011). After adjustments for confounders, there was no association between PCI and mortality (hazard ratio [HR] 1.07; 95% confidence interval [CI] 0.84-1.36). Baseline anemia identified a subset of MI patients undergoing PCI with a higher comorbidity burden. Anemia was associated with increased 180-day rates of death (6.9% vs 2.1%; p<0.001), myocardial reinfarction (4.3% vs 1.9%; p<0.001), major bleeding (13.4% vs 8.2%), and stroke (2.0% vs 0.7%). Results were particularly evident in patients with a hemoglobin value below 100 g/L, who had a tenfold higher mortality rate, sixfold higher MI rate, and threefold higher bleeding rate, compared to patients without anemia. Results were similar after adjustments for confounders. Elderly patients (≥75 years) had a markedly increased risk of adverse outcomes within 180 days after MI and PCI compared to younger patients (<75 years). Elderly patients who received bivalirudin or heparin had similar baseline characteristics. Bivalirudin did not reveal any benefit over heparin monotherapy, regarding 180-day mortality, myocardial reinfarction, major bleeding, stroke, or stent thrombosis. A high PRECISE-DAPT score (≥25) identified a high-risk subset of MI patients with more comorbidities and higher bleeding rates during DAPT. However, the predictive performance for major bleeding was moderate (c-statistic 0.64; 95% CI 0.63-0.66). Furthermore, the discriminatory power of the score was even more limited in patients with pre-existing risk factors for bleeding, especially for patients with advanced age (c-statistic 0.57; 95% CI 0.55-0.60), low body weight (c-statistic 0.56; 95% CI 0.51-0.61), anemia (c-statistic 0.60; 95% CI 0.58-0.63), or cancer (c-statistic 0.59; 95% CI 0.53-0.66).

**Conclusion.** The reported findings in this research on risk stratification tools and therapies have potential implications for a more patient-tailored acute coronary care that may further improve outcomes for patients with MI.



**Key words:** myocardial infarction, percutaneous coronary intervention, cardiac arrest, elderly, anemia, bleeding

Classification system and/or index terms (if any)

| Supplementary bibliographical information | | **Language** English |
|---|---|---|
| **ISSN** and key title: 1652-8220 | | **ISBN:** 978-91-8021-106-2 |
| Recipient's notes | **Number of pages** 72 | Price |
| | Security classification | |




Signature  Date 2021-08-31

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ISBN 978-91-8021-106-2
ISSN 1652-8220

Printed in Sweden by Media-Tryck, Lund University
Lund 2021

*To my parents*

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# Abbreviations

| | |
|---|---|
| ACS | Acute coronary syndrome |
| ACUITY | Acute Catheterization and Urgent Intervention Triage Strategy trial |
| ADP | Adenosine diphosphate |
| BARC | Bleeding Academic Research Consortium |
| BMS | Bare-metal stent |
| CABG | Coronary artery bypass grafting |
| CAD | Coronary artery disease |
| CI | Confidence interval |
| COACT | Coronary Angiography after Cardiac Arrest trial |
| CRUSADE | Can Rapid risk stratification of Unstable angina patients Suppress Adverse outcomes with Early implementation of the American College of Cardiology/American Heart Association guidelines |
| DAPT | Dual antiplatelet therapy |
| DES | Drug-eluting stent |
| ECG | Electrocardiogram |
| EUROMAX | European Ambulance Acute Coronary Syndrome Angiography trial |
| GRACE | Global Registry of Acute Coronary Events |
| GP IIb/IIIa inhibitor | Glycoprotein IIb/IIIa receptor inhibitor |
| HORIZONS-AMI | Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction trial |
| HR | Hazard ratio |
| LDL | Low-density lipoproteins |
| MI | Myocardial infarction |

| | |
|---|---|
| NSTEMI | Non-ST-elevation myocardial infarction |
| OR | Odds ratio |
| PCI | Percutaneous coronary intervention |
| PEGASUS-TIMI 54 | Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction 54 trial |
| PLATO | Study of Platelet Inhibition and Patient Outcomes trial |
| PRECISE-DAPT | Predicting bleeding Complications In patients undergoing Stent implantation and subsequent Dual Anti Platelet Therapy |
| RCT | Randomized controlled trial |
| RIKS-HIA | The Register of Information and Knowledge About Swedish Heart Intensive Care Admissions |
| ROC | Receiver operating characteristic |
| SCAAR | Swedish Coronary Angiography and Angioplasty Registry |
| STEMI | ST-elevation myocardial infarction |
| SWEDEHEART | Swedish Web System for Enhancement and Development of Evidence-based Care in Heart Disease Evaluated according to Recommended Therapies |
| TIMI | Thrombolysis in Myocardial Infarction |
| TRITON-TIMI-38 | Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction 38 trial |
| TTM | Targeted temperature management |
| VALIDATE | Bivalirudin versus Heparin in ST-Segment and Non–ST-Segment Elevation Myocardial Infarction in Patients on Modern Antiplatelet Therapy |
| VF | Ventricular fibrillation |
| VT | Ventricular tachycardia |

# Introduction

## Historical overview

During the last 60 years, there have been several groundbreaking advances within the field of acute coronary care. The term angina pectoris was first used in 1772 by William Heberden to describe the typical chest pain caused by coronary artery disease (CAD), even though the connection between angina pectoris and CAD had not yet been established.[1] In the late 18th century, there were speculations about the relationship of the two,[2] but it was not until a century later that the pathologist Ludvig Hektoen concluded that myocardial infarction (MI) is caused by coronary thrombosis secondary to sclerotic changes in the coronary arteries, and often presents as sudden death.[3] Later on, in 1912, MI was established as its own diagnosis, separate from stable angina pectoris.[4] At that time, the standard of care for MI was bed rest, and patients were regularly found dead in their hospital beds, with an in-hospital mortality rate around 30%.[5]

One of the first major advances in acute coronary care came in the 1960s with the introduction of specialized coronary care units in the hospitals. These units had the availability of continuous electrocardiogram (ECG) monitoring to detect potentially fatal arrhythmias, closed-chest cardiac resuscitation, and external defibrillation, followed by a halving of in-hospital mortality rates.[5] During the same time, the Framingham study identified important risk factors for CAD such as hypertension and hyperlipidemia, leading the way for primary as well as secondary preventive measures.[6] Further improvements to the mortality rates following MI came with intravenous thrombolysis for ST-elevation MI (STEMI) and the introduction of aspirin in the 1980s.[7, 8] Streptokinase and aspirin were shown to reduce the odds of cardiovascular death within 1 month by 25% and 23%, respectively, and their effects were revealed to be additive demonstrated by a 42% odds reduction when both drugs were used, compared to placebo.[8]

Stemming on the work of the Nobel laureate Werner Forssman, who performed the first human cardiac catheterization in 1929, on himself,[9] and the development of coronary angiography in the 1950s to visualize vessel anatomy,[10] the first percutaneous coronary intervention (PCI) technique was presented in the late 1970s, using a distensible balloon to dilate a stenotic coronary artery.[11] Since the first trial comparing PCI to thrombolysis in the 1980s, several reports in the 1990s and the 21st century have concluded the superiority of PCI, which is now considered the

standard of care reperfusion strategy for patients with MI.[12, 13] Outcomes after MI have further improved with intracoronary stenting as well as concomitant medications such as beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, statins, anticoagulants, and P2Y12 inhibitors, resulting in a current in-hospital mortality rate around 5%.[14-24]

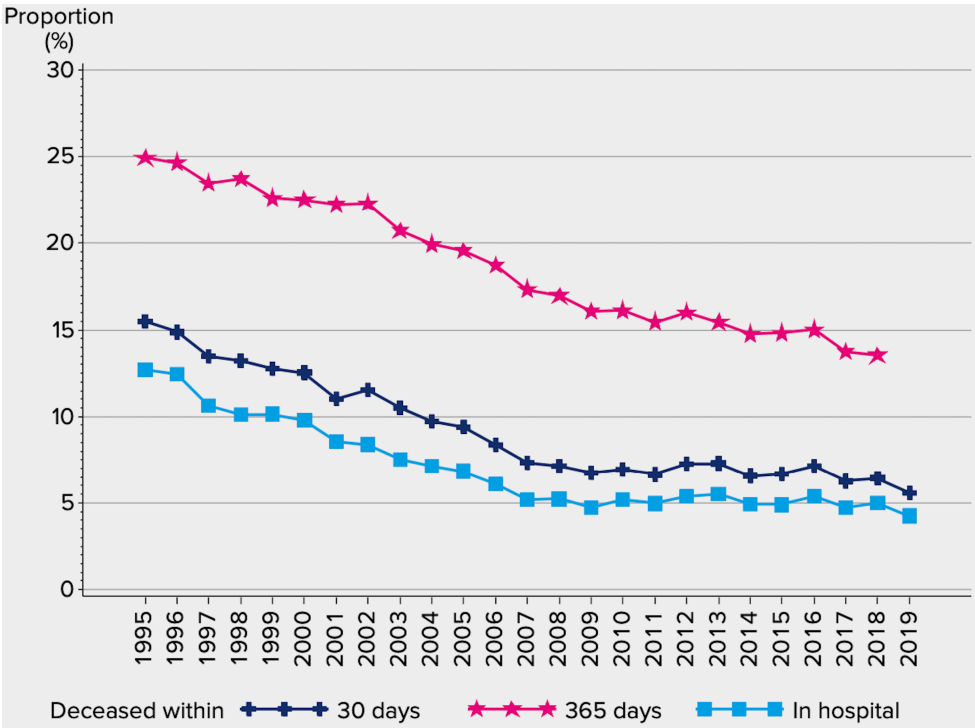


**Figure 1.**
Trend in mortality in myocardial infarction patients, 1995-2019. The reduction in mortality has ended and reached a plateau. Reprinted with permission from SWEDEHEART annual report 2019.

# Epidemiology

Despite advances in acute coronary care, CAD still represents the leading cause of both overall and premature death globally.[25] The implementations of all aforementioned evidence-based treatments have, however, led to a decline in mortality rates following MI. In Sweden, mortality rates after STEMI decreased

between 1995 and 2010 both in-hospital (13.6% to 7.8%) and within 1 year (22.1% to 14.1%).[26] The same applies for non-ST-elevation MI (NSTEMI) patients with corresponding numbers of in-hospital mortality decreasing from 12.4% to 3.7% and 1-year mortality rates from 26.0% to 14.9%.[27] However, during the last decade, the mortality rate following MI has ceased to decline and has reached a plateau phase at approximately 14% at 1-year follow-up in 2019, highlighting the need for new treatment strategies to further improve outcomes (Figure 1).[24] Similar trends have been observed in other countries as well.[26-28]

In Europe, CAD causes around 1.8 million deaths annually, or 20% of total deaths.[29] The incidence of MI varies between countries and was reported to be 322 cases per 100 000 inhabitants in Sweden in 2018.[30, 31] The incidence of MI has decreased over time, particularly for STEMI, which accounts for about a third of all MI cases.[24, 32] The average age for MI differs between the sexes, with a mean age of 75-76 years for women and 69-70 years for men, and a mean age in the whole population of 71 years.[24] Multiple factors influence the prognosis after MI including advanced age, initial clinical presentation, ventricular dysfunction, as well as various comorbidities.[33] Ischemic complications after MI have dropped, accompanied by a substantial fall in mortality rates, thanks to invasive reperfusion strategies and secondary prevention including antithrombotic medications, but, in parallel, bleeding complications have become more frequent.[34] Major bleeding carries a significant impact on mortality rates and is associated with a reduced quality of life.[35-38]

# Pathophysiology

## Endothelial dysfunction and early atherosclerosis development

The pathophysiological mechanism of MI involves the disruption of a vulnerable atherosclerotic plaque, which takes several decades to evolve.[39] The plaque forms at specific sites of predilection in the arterial tree, such as bifurcations, due to lowered and turbulent shear stress which induces local endothelial dysfunction.[40] The endothelial dysfunction is further enhanced when subjected to stimuli from various cardiovascular risk factors such as hypertension, hyperlipidemia, diabetes, or smoking.[41] The endothelium normally carries various antithrombotic properties that inhibit platelet activation and aggregation, including the production of nitric oxide and prostacyclin, which in the setting of endothelial dysfunction are impaired.[41] The permeability over the endothelial barrier and the expression of various adhesion molecules increase due to the endothelial dysfunction, resulting in the entry of monocytes and low-density lipoproteins (LDL) into the artery wall, which plays a key role in the development of atherosclerosis.[42, 43]

## Atherosclerotic plaque formation and progression

Inside the intima of the arterial wall, the LDL undergo oxidation which promotes an inflammatory response, and the monocytes differentiate into macrophages (Figure 2).[44] Macrophages attempt to clean the intima from oxidized LDL, but eventually become overloaded and transformed into foam cells, further enhancing inflammation.[45] Smooth muscle cells are attracted from the tunica media to produce fibrous tissue such as collagen and elastin, that form the fibrous cap of the plaque.[42] However, T cells eventually impair the ability of the smooth muscle cells to maintain and repair the fibrous cap, simultaneously as macrophages produce enzymes that degrade collagen.[42] Consequently, the fibrous cap undergoes thinning and the risk of rupture increases. Macrophage and smooth muscle cell apoptosis as well as impaired clearance of dead cells form the lipid-rich necrotic core of the advancing atherosclerotic plaque.[46, 47] Eventually, the atherosclerotic plaque also undergoes calcification.[48] The rupture prone atherosclerotic plaque, termed the vulnerable plaque, is characterized by a thin fibrous capsule, large lipid core, and high degree of inflammation, as opposed to a stable plaque.[49]

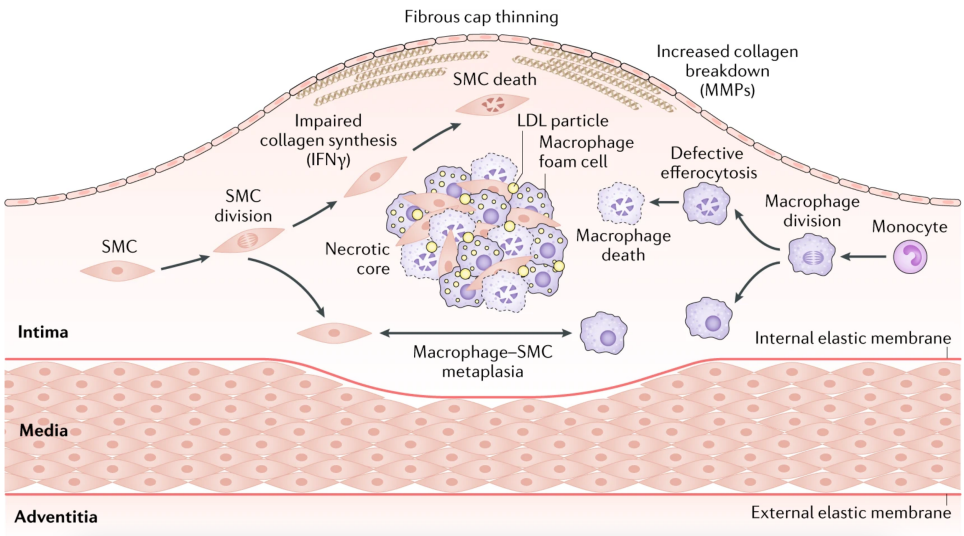


**Figure 2.**
Progression of an atherosclerotic plaque in the artery wall. IFNγ, interferon γ; LDL, low-density lipoprotein; MMP, matrix metalloproteinase; SMC, smooth muscle cell. Reprinted with permission from Libby P, Buring JE, Badimon L, Hansson GK, Deanfield J, Bittencourt MS, Tokgozoglu L and Lewis EF. Atherosclerosis. *Nat Rev Dis Primers*. 2019;5:56.

### Plaque rupture

Rupture of the atherosclerotic plaque exposes its prothrombotic interior to the blood compartment and can trigger thrombosis.[50] Collagen and von Willebrand factor within the plaque stimulate platelets to release adenosine diphosphate (ADP) and thromboxane A2, which activate additional platelets.[51] Glycoprotein IIb/IIIa receptors on the platelets subsequently bind circulating fibrinogen and von Willebrand factor to cross-link with adjacent platelets and thus cause platelet aggregation.[51] Simultaneously, following plaque rupture, tissue factor within the atherosclerotic plaque initiates the coagulation cascade, where factor Xa promotes the generation of thrombin, which further activates platelets as well as cleaves fibrinogen to fibrin to finalize thrombus formation.[52] The thrombus interrupts blood flow to the affected myocardium, thereby creating an imbalance between oxygen supply and demand, leading to ischemia and ultimately necrosis.[53]

## Definition of myocardial infarction

Cardiomyocyte death results in an outflow of cardiac specific enzymes that can be measured in blood samples, most commonly troponins.[54] MI is clinically defined as a dynamic rise and/or fall of cardiac troponin, with at least one value above the 99$^{th}$ percentile upper reference limit in combination with symptoms suggestive of MI, new ischemic ECG changes, imaging indicating myocardial death, or coronary artery thrombosis identified by angiography or autopsy.[54] The classical MI, resulting from rupture or erosion of an atherosclerotic plaque, is designated as type 1 MI and is further divided into STEMI and NSTEMI for treatment strategy reasons.[33, 55] The ST-elevation on ECG that characterizes STEMI typically reflects a total or subtotal occlusion of the affected coronary artery.[56] NSTEMI, on the other hand, can present with an ECG showing ST-depression, transient ST-elevation, T-wave abnormalities, or a normal ECG.[55]

STEMI and NSTEMI, together with unstable angina, constitute the acute coronary syndrome (ACS).[54] Unstable angina, however, is caused by a thrombus that only temporarily limits blood flow, resulting in ischemia but no cell death, and holds a substantially more favorable prognosis than does NSTEMI or STEMI.[57] As a result of the development of more sensitive cardiac-specific troponin assays, cardiomyocyte death is more easily detected and ACS patients previously considered to suffer from unstable angina are now instead diagnosed with NSTEMI, which has reduced the relevance of unstable angina as a separate entity.[58] Accordingly, this thesis will mainly focus on enzyme-positive ACS (that is, MI). Type 2 MI is the result of a non-thrombotic related discrepancy between oxygen supply and demand, such as severe anemia, coronary artery dissection, respiratory failure, hypotension, or tachyarrhythmias.[54] Type 3 MI denotes a setting of cardiac arrest, where symptoms and ECG changes are suggestive of MI, but where troponin

levels have not been measured before death ensued, while type 4 and 5 reflects PCI and coronary artery bypass grafting (CABG) related MI, respectively.[54]

# Percutaneous coronary intervention

## Strategies for STEMI

The effect of PCI on the outcome after MI has been extensively evaluated. A systematic review and meta-analysis of 23 randomized trials found that PCI reduced the odds of death, myocardial reinfarction, or stroke, by 47% compared to thrombolysis in patients with STEMI.[13] Time is a critical factor for patients presenting with STEMI, who often bypass the emergency department for immediate transfer to the catheterization laboratory to undergo PCI.[59] If PCI cannot be performed within the recommended timeframe of 120 minutes from diagnosis, for example due to long transportation distances in remote geographical areas, intravenous thrombolysis is recommended.[60] The use of emergency CABG for revascularization may be indicated in selected STEMI patients with a coronary anatomy unsuitable for PCI.[33]

Primary PCI should be directed against the culprit lesion.[33] However, multivessel disease is present in approximately half of STEMI patients.[61] The timing of revascularization for non-infarct related significant coronary artery stenoses (immediate or staged) is unclear, although recent guidelines recommend that it should be performed before hospital discharge.[33] For patients with MI and cardiogenic shock, a recent trial showed that a strategy of PCI for the culprit vessel only with the option of staged revascularization of other coronary arteries reduced the risk of death within 30 days compared to immediate multivessel PCI.[62]

## Strategies for NSTEMI

An invasive management is the main strategy also for patients with NSTEMI,[63] but the optimal timing of PCI is highly dependent on the risk profile of the patient.[64, 65] NSTEMI patients deemed at very high risk should undergo immediate PCI, analogously to STEMI patients.[55] Among factors considered to indicate very high risk are cardiogenic shock, potentially fatal arrhythmias, or recurrent chest pain despite medical treatment. Other patients with an established NSTEMI diagnosis should be subject for an invasive approach within 24 hours.[55] For patients with NSTEMI and multivessel disease, one trial found that single-stage PCI was associated with reduced cardiovascular and cerebrovascular events, primarily driven by a lower rate of target vessel revascularization at 1-year follow-up, compared to initial culprit vessel-only PCI with delayed revascularization of non-infarct related

arteries.[66] Due to the limited amount of evidence, however, the exact revascularization strategy should be individualized based on factors such as functional relevance of the coronary stenoses, the general condition of the patient, and left ventricular function.[55]

The optimal revascularization modality in patients with NSTEMI is uncertain as the inclusion of these patients has been rare in trials comparing CABG and PCI, which mainly have included patients with unstable angina.[67] Complex cases should be subject for a multidisciplinary team discussion, but, in general, factors such as multivessel disease, left main stenosis, and the presence of diabetes favor the choice of CABG in analogy to the recommendations for stable angina.[67-69]

### Intracoronary stenting and vascular access route

PCI with the placement of a bare-metal stent (BMS) reduces the rate of restenosis by half compared to plain balloon angioplasty.[70] Intracoronary stenting techniques have subsequently been refined by the advent of stents coated with cytostatic drugs to prevent restenosis, commonly referred to as drug-eluting stents (DES).[71] However, early-generation DES were shown to increase the rate of stent thrombosis, a rare but potentially fatal complication after PCI, beyond 1 year of the PCI procedure compared to BMS.[72, 73] Subsequently, a second generation of DES have evolved and demonstrated a lower risk of stent thrombosis than both first-generation DES and BMS and are therefore currently considered the default choice of stent.[15, 74, 75]

Both major bleeding unrelated to the access site during PCI as well as bleeding at the access site are related to increased mortality.[76] Vascular access through the radial artery has been shown to reduce major bleeding and increase survival compared to the femoral artery approach.[77, 78]

## Cardiac arrest

The incidence of out-of-hospital cardiac arrest treated by emergency medical services has been estimated to be 38 per 100 000 person-years in Europe.[79] MI is the main cause of both out-of-hospital and in-hospital cardiac arrest and clinical presentation with either of these entities is associated with a poor prognosis.[79-81] In Sweden, the 30-day mortality rate was estimated to be 89% for out-of-hospital and 63% for in-hospital cardiac arrest in 2019,[82] which is in line with international reports.[79] Cardiac arrest is divided into different categories depending on the observed initial rhythm on ECG assessment: sustained ventricular tachycardia (VT), ventricular fibrillation (VF), asystole, or pulseless electrical activity.[83] Mortality rates have decreased over the years for VT and VF, while it remains high for asystole and pulseless electrical activity.[84] Key factors for survival are summarized in “the

chain of survival" and include prompt cardiopulmonary resuscitation as well as defibrillation for shockable rhythms (VT and VF).[85] In fact, delaying bystander cardiopulmonary resuscitation and defibrillation decreases the odds of survival by 26% and 11% each minute, respectively.[86] During the first 4 minutes after cardiac arrest, defibrillation alone may be sufficient for return of spontaneous circulation.[87] However, between 4 and 10 minutes after the arrest, chest compressions are necessary to regain the possibility of successful defibrillation, while the chance of survival rapidly declines beyond 10 minutes after cardiac arrest.[87]

The last link in "the chain of survival" highlights the importance of post-resuscitation care.[85] During cardiac arrest, with no blood flow, the whole body is subjected to ischemia and metabolites are no longer removed.[88] When spontaneous circulation and organ perfusion returns, a systemic inflammatory response is activated with high levels of various cytokines and risk of subsequent multiorgan failure.[89] This state, called the post cardiac arrest syndrome, is characterized by brain damage and myocardial dysfunction and carries a substantial mortality rate.[88, 90] Damage to the brain is the most common death cause beyond day 3 after cardiac arrest and neurological outcome in survivors varies from full recovery to a vegetative state.[91] In 2002, two studies found that targeted temperature management (TTM) with induced hypothermia to 32-34°C for 12-24 hours increased survival and improved neurological outcomes compared to normothermia.[92, 93] The results from these studies have however been questioned and another study revealed that the time to initiation of TTM and the time to reach the target temperature had no effect on outcome.[94] In 2013, the TTM trial randomized patients with resuscitated cardiac arrest of presumed cardiac cause to hypothermia with a target temperature at either 33°C or 36°C and found no difference regarding survival or neurological function.[95] Although induced hypothermia may offer neuroprotection, it is also associated with various harmful complications such as hyperglycemia, reduced cardiac output, arrhythmias, impaired coagulation, and higher risk of infections.[88] To bring clarity to this matter, another trial is currently comparing hypothermia at 33°C with normothermia and early fever control.[96]

The post cardiac arrest syndrome may also include myocardial dysfunction, which is present in two thirds of resuscitated out-of-hospital cardiac arrest patients.[97] The myocardial dysfunction normally starts to improve within 24 hours and is responsible for most deaths the first 3 days after cardiac arrest.[91, 98] The clinical assessment of resuscitated cardiac arrest patients includes an ECG evaluation to identify the cause of the cardiac arrest.[99] The ECG may display ST-elevation, ST-depression, left bundle branch block, unspecific ST-T changes, or be normal.[100] Normal diagnostic criteria for MI, such as presence of chest pain, troponin levels, and ischemic ECG changes might be difficult to assess immediately after the return of spontaneous circulation.[101, 102] Signs of ST-elevation on the ECG appears to have a high positive predictive value for recent coronary artery lesions and these patients should undergo emergent coronary angiography and PCI if indicated according to current guidelines.[33, 99, 103] However, the negative predictive value of ST-elevation

is low and approximately a third of resuscitated cardiac arrest patients without STEMI also have acute coronary artery lesions.[103, 104] Furthermore, the role of coronary angiography with the option of PCI to improve outcomes in cardiac arrest patients without STEMI and no obvious non-coronary cause of the arrest has been investigated in several observational studies showing conflicting results.[105-108] Therefore, randomized controlled trials (RCT) to investigate this matter further are warranted.[109]

# Platelet inhibition

Platelet inhibition is a cornerstone in the treatment of MI and necessary in all patients who undergo PCI and stent implantation to avoid recurrent thrombotic events. The key agent to accomplish this is aspirin.[110] It exerts its effect by irreversibly blocking the cyclooxygenase-1-mediated thromboxane A2 production in the platelets and should be initiated at the time of diagnosis and maintained indefinitely after MI at a low dose.[111-113] Furthermore, dual antiplatelet therapy (DAPT), consisting of aspirin in combination with an inhibitor of the ADP-receptor P2Y12, blocks both the thromboxane A2 mediated and the ADP mediated route to platelet activation and aggregation, and was shown to be superior to aspirin alone (Figure 3).[21, 114, 115] Clopidogrel is an oral irreversibly binding pro-drug that blocks the P2Y12 receptor and thereby prevents glycoprotein IIb/IIIa mediated platelet aggregation.[116] It was long considered the standard P2Y12 inhibitor for MI patients undergoing PCI,[117] until the advent of more potent P2Y12 inhibitors. First, the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction (TRITON–TIMI) 38 trial revealed that prasugrel, a P2Y12 inhibitor with a more rapid onset, reduced ischemic events compared to clopidogrel, but increased the risk of major bleeding.[22] Second, ticagrelor, an oral reversibly binding direct-acting P2Y12 inhibitor with rapid onset, demonstrated a reduced risk of ischemic events and death, but a higher risk of non-CABG related major bleeding, compared to clopidogrel in the Study of Platelet Inhibition and Patient Outcomes (PLATO).[23] Although both prasugrel and ticagrelor increase the risk of major bleeding, their risk-benefit ratios were advantageous, with a number needed to treat to avoid ischemic events of 46 and 53, respectively, while the number needed to harm for Thrombolysis In Myocardial Infarction (TIMI) non-CABG related major bleeding was 167 for both drugs.[22, 23, 118] Thus, international guidelines recommend DAPT with ticagrelor or prasugrel for MI patients undergoing PCI, unless there are contraindications.[118] Another alternative that may be considered for P2Y12-naïve MI patients undergoing PCI is the intravenous agent cangrelor.[119]

For patients with STEMI, the timing of P2Y12 inhibitor treatment initiation has been a matter of debate and clinical practice varies between different countries.[33, 120]

The use of P2Y12 inhibitor pretreatment (before the diagnosis has been verified by coronary angiography) may offer better ischemic protection at the time of PCI, but could be deleterious in the setting of mechanical complications or differential diagnoses such as aortic dissection.[121] Patients with NSTEMI should generally not be treated with P2Y12 inhibition until the time of PCI.[55, 122] For patients with MI who have been treated with PCI, secondary antithrombotic prevention with DAPT is generally recommended for 12 months.[23, 117, 123]

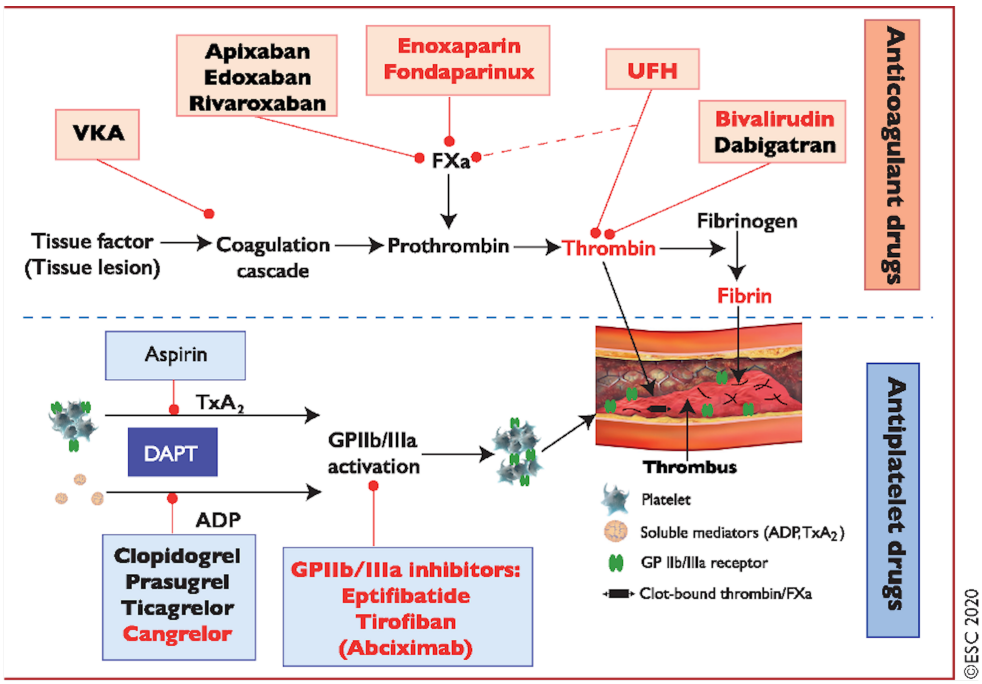


**Figure 3.**
Antiplatelet and anticoagulant drugs and their pharmacological targets. ADP, adenosine diphosphate; DAPT, dual antiplatelet therapy; GP, glycoprotein; $TxA_2$, thromboxane A2; UFH, unfractionated heparin; VKA, vitamin K antagonist. Reprinted with permission from Collet JP, Thiele H, Barbato E, Barthelemy O, Bauersachs J, Bhatt DL, Dendale P, Dorobantu M, Edvardsen T, Folliguet T, et al. 2020 European Society of Cardiology Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. 2020;42:1289-1367.

# Periprocedural anticoagulation

Periprocedural anticoagulant therapy is recommended for all MI patients undergoing PCI and the preferred agent is unfractionated heparin.[20, 68] Heparin was discovered over a century ago and there is an extensive clinical experience of using it.[124] The drug is a potent anticoagulant, as it inhibits both factor Xa and thrombin, by binding the cofactor antithrombin III (Figure 3).[125] In the pre-DAPT era, despite

the use of periprocedural heparin, abrupt vessel reclosure during or soon after PCI was a major problem, that was resolved with the addition of a glycoprotein IIb/IIIa receptor inhibitor (GP IIb/IIIa inhibitor).[126, 127] A decade later, after the advent of routine DAPT with predominantly clopidogrel, the direct thrombin inhibitor bivalirudin was compared to heparin plus routine GP IIb/IIIa inhibition in two large trials. In the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial, similar ischemic and bleeding event rates were found using either bivalirudin or heparin in NSTEMI patients, both in combination with GP IIb/IIIa inhibition, while patients allocated bivalirudin monotherapy had a lower risk of major bleeding.[128] Next, the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial showed that bivalirudin lowered mortality for STEMI patients undergoing PCI, compared to heparin with GP IIb/IIIa inhibition, primarily driven by a reduction in major bleeding.[129] Subsequent trials that also had more frequent use of GP IIb/IIIa inhibitors in the heparin arms mostly supported these results.[130-132] However, in the current potent P2Y12 inhibitor era, routine GP IIb/IIIa inhibitors are not recommended anymore due to their associated excess bleeding risk, other than for bail-out use in the setting of thrombotic complications or evidence of no-reflow during PCI.[68] Therefore, a number of trials compared bivalirudin to heparin without routine GP IIb/IIIa inhibitor use, showing conflicting results.[133-135]

To determine to optimal anticoagulation strategy in MI patients undergoing PCI according to contemporary practice, with routine potent P2Y12 inhibition as well as routine radial artery access during PCI, and without routine GP IIb/IIIa inhibitors, the Bivalirudin versus Heparin in ST-Segment and Non-ST-Segment Elevation Myocardial Infarction in Patients on Modern Antiplatelet Therapy in the Swedish Web System for Enhancement and Development of Evidence-based Care in Heart Disease Evaluated according to Recommended Therapies registry (VALIDATE-SWEDEHEART) trial was conducted.[136] The specifics of VALIDATE-SWEDEHEART are outlined in the methods section. The trial demonstrated that bivalirudin was neutral compared to heparin monotherapy, followed by a downgrade for bivalirudin in international guidelines and a recommendation of primarily using heparin as the anticoagulant of choice for PCI.[68] The use of bivalirudin in Sweden has fallen dramatically during recent years, in favor of heparin.[24] Furthermore, a meta-analysis supported the results of VALIDATE-SWEDEHEART by showing that the decreased risk of major bleeding with bivalirudin as compared to heparin was related to unbalanced use of GP IIb/IIIa inhibitors across treatment groups and when GP IIb/IIIa inhibitor use was balanced between groups, an association of lower bleeding rates when using bivalirudin could not be seen.[137] Importantly, bivalirudin is a lot more expensive than heparin.[138] However, due to bivalirudin's more predictable pharmacodynamic profile (direct inhibition of thrombin) and shorter off-set of action in case of bleeding (half-life 25 minutes compared to the dose-dependent half-life of heparin), bivalirudin might be preferable to heparin for patients at high risk of bleeding, such as the elderly.[139-141]

# Ischemic versus bleeding risk

Considering the trade-off between ischemic (for example, myocardial reinfarction, stent thrombosis, or ischemic stroke) and bleeding risk, the ultimate aim of antiplatelet and anticoagulant therapy is to balance these to minimize mortality and patient suffering.[142] On the one hand, although the risk of ischemic events is highest early after MI, it remains high even beyond 12 months after the index event.[22, 23, 143] On the other hand, the risk of major bleeding is related to the duration of DAPT and has an association with mortality equal to that of reinfarction during the first year after MI.[36, 144] However, Bleeding Academic Research Consortium (BARC) type 2 and 3a bleeding have a more favorable prognosis than MI, whereas BARC 3b has an equivalent prognosis as MI, and BARC 3c has a worse prognosis than MI (Table 1).[37, 145] To decide on the optimal antithrombotic treatment that offers maximal ischemic protection while minimizing the risk for bleeding complications, it is recommended to use an individualized approach, that identifies those at high ischemic or bleeding risk, and tailor the treatment according to the patient's ischemic versus bleeding risk profile.[118] To this end, risk scores may be utilized.[146]

**Table 1.**
Bleeding academic research consortium (BARC) definition of bleeding.

| | |
|---|---|
| Type 1 | Bleeding that does not cause the patient to seek treatment |
| Type 2 | Any overt bleeding requiring evaluation, intervention, or hospitalization |
| Type 3a | Overt bleeding in combination with either blood transfusion or a hemoglobin drop of 30-50 g/L |
| Type 3b | Overt bleeding with a hemoglobin drop of at least 50 g/L, cardiac tamponade, or bleeding requiring surgery or vasoactive agents |
| Type 3c | Intracranial bleeding, or intraocular bleeding compromising vision |
| Type 4 | Coronary artery bypass grafting-related bleeding |
| Type 5 | Fatal bleeding |

Among several scores for ischemic risk stratification, the Global Registry of Acute Coronary Events (GRACE) score is one of the most used scores, which calculates the risk of death or MI and has been implemented in current guidelines.[147-149] Furthermore, it has been reported that objective risk estimation using the GRACE score is superior compared to subjective physician assessment alone.[150] Likewise, the risk for bleeding during the hospital stay can be estimated using different scores, where the Can Rapid risk stratification of Unstable angina patients Suppress Adverse outcomes with Early implementation of the American College of Cardiology/American Heart Association guidelines (CRUSADE) score has shown the best discriminatory performance.[151, 152] In-hospital bleedings have decreased over the years, with the introduction of radial artery access and less use of GP IIb/IIIa inhibitors, whereas later bleeding events have increased with the advent of

more potent P2Y12 inhibition for secondary antithrombotic prevention.[34] To avoid these later bleeding events, international guidelines state that discontinuation of DAPT after 3 or 6 months should be considered for patients deemed at high bleeding risk.[55, 118, 153, 154] On the contrary, patients who have been treated with DAPT for 12 months without bleeding complications and who are considered at high ischemic risk, may instead be subject for an extended DAPT course beyond 12 months to mitigate this risk.[33, 55, 155-157] The Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction (PEGASUS-TIMI) 54 trial compared a prolonged DAPT duration using ticagrelor with placebo on a basis of aspirin in patients with a myocardial infarction 1 to 3 years previously who had at least one additional high ischemic risk feature: age ≥65 years, diabetes, a second prior MI, multivessel CAD, or kidney dysfunction.[155] Patients were excluded if they had a history of intracranial or gastrointestinal bleeding the last 6 months before enrollment. The trial found that patients allocated a low dose of ticagrelor had reduced risk of cardiovascular death, MI, or stroke, and an increased risk of major bleeding at 3 years compared to placebo.[155] The DAPT trial enrolled MI patients who had been treated with DAPT for 12 months without any major bleeding complications and compared a prolonged DAPT duration, using clopidogrel or prasugrel, with placebo for an additional 18 months.[156] The study found a decreased risk of ischemic events but more bleeding in the prolonged DAPT arm. The DAPT score was subsequently developed from the DAPT trial to identify patients who would experience a lowered ischemic risk with only a small increase in bleeding risk when DAPT is prolonged as well as patients who would not benefit from an extended treatment.[158] The score has been validated in a retrospective setting.[159] While the DAPT score may be used to find patients suitable for a continued DAPT course after the standard 12 months, the Predicting bleeding Complications In patients undergoing Stent implantation and subsequent Dual Anti Platelet Therapy (PRECISE-DAPT) score has demonstrated the ability to identify patients where a shortened treatment duration might be beneficial.[153]

**Table 2.**
The 4-item PRECISE-DAPT score multivariable model for 1-year out-of-hospital TIMI major or minor bleeding. Age was truncated below 50 years. Hemoglobin at baseline was truncated above 12 g/dL and below 10 g/dL. Creatinine clearance was truncated above 100 mL/min.

| | Hazard ratio (95% confidence interval) | p-value |
|---|---|---|
| Age (for each increase of 10 years) | 1.23 (1.01-1.59) | 0.012 |
| Previous bleeding | 4.13 (1.19-14.37) | 0.026 |
| Hemoglobin (for each increase of 1 g/dL) | 0.67 (0.53-0.84) | 0.001 |
| Creatinine clearance (for each increase of 10 ml/min) | 0.90 (0.82-0.99) | 0.001 |

The original PRECISE-DAPT score uses 5 components (age, creatinine clearance, hemoglobin, previous bleeding, and white blood cell count) to predict major bleeding during the first 12 months after PCI with stent placement. Patients with a high score (≥25) had a lowered bleeding risk when ending their DAPT treatment

after 3 or 6 months without an increased risk of ischemic events, whilst patients with a non-high score (<25) did not show this characteristic.[153] The PRECISE-DAPT score has been validated by several investigators using a retrospective design and has revealed a moderate or good discriminatory power for major bleeding.[160-162] However, large real-world validation studies as well as prospective evaluations of the score are lacking. Furthermore, a simplified 4-item version of the score (without white blood cell count) might be more user-friendly and has revealed similar predictive qualities as the original score (Table 2).[163]

# Advanced age

The proportion of elderly is growing worldwide and so is the mean age of patients treated with PCI.[164, 165] To balance ischemic and bleeding events in the elderly is challenging, as they are at increased risk of both.[149, 166] As part of normal ageing, an increased collagen/elastin ratio and calcification is seen in the vessel walls, with consequential loss of the windkessel effect, resulting in hypertension and increased cardiac demand.[167] While the systolic blood pressure increases with age, the diastolic blood pressure eventually declines, leading to a decreased coronary perfusion.[168] Moreover, advanced age is associated with platelet hyperreactivity, increased blood viscosity, more multivessel disease, as well as higher levels of various coagulation factors which may lead to an increased ischemic risk.[169, 170] The increased bleeding risk that the elderly also suffer from can be explained by age-related hyperfibrinolysis and altered drug metabolism that may lead to excess dosing of antithrombotic medications.[169, 171] Moreover, the high comorbidity burden of the elderly also contributes to their overall high risk.[172, 173]

Due to their high ischemic risk, the elderly may derive the greatest benefit from PCI, which is the preferred reperfusion strategy in these patients.[174, 175] However, the PCI procedure requires antithrombotic medications. To tailor the optimal antithrombotic treatment for the elderly might be difficult (due to their bilateral risk profile), but crucial to improve outcomes.[176, 177] Furthermore, elderly patients are frequently excluded from clinical trials and evidence-based treatments have often been established based on studies of younger and healthier individuals, which makes extrapolation to the high-risk elderly population difficult.[178]

# Anemia

Anemia indicates a low blood concentration of hemoglobin, defined as <120 g/L for women and <130 g/L for men according to the World Health Organization definition.[179] The prevalence of anemia at the time of hospital admission in MI

patients has been reported to be nearly 20%, which is comparable to the prevalence of anemia in the normal population who are older than 80 years.[180, 181] Iron deficiency is the most common cause of anemia and is often a result of blood loss (for example, occult gastrointestinal bleeding).[182] Another frequent cause is anemia secondary to chronic disease, such as malignancy, kidney dysfunction, or other inflammatory disorders.[183] Anemia in chronic disease may result from entrapment of iron inside macrophages in the setting of inflammation or from reduced production of erythropoietin in the case of kidney dysfunction.[184] Other causes of anemia include vitamin B12 or folic acid deficiency, hemolysis, hypothyroidism, and bone marrow disorders.[183]

For patients with MI, those who have anemia are older and have higher frequencies of comorbidities such as diabetes, kidney dysfunction, heart failure, malignancy, peripheral artery disease, a history of MI, and prior major bleeding, compared to patients without anemia.[180, 185-187] Anemia in patients with MI is associated with higher mortality as well as higher risk of both major bleeding and recurrent MI.[180, 185] The underlying mechanisms for these association are not entirely clear, but anemia may have both direct consequences that affect outcome and work as a biomarker for a less favorable prognosis.[188] However, this increased risk does not seem to be mitigated by a liberal transfusion strategy, which seem to increase mortality and myocardial reinfarction rates,[189, 190] possibly explained by side effects such as transfusion reactions or increased platelet reactivity.[191] According to international guidelines, a restrictive blood transfusion strategy for MI patients with anemia may be considered using hemoglobin below 80 g/L as threshold.[55] Given the high bleeding risk profile of MI patients with anemia, it is key to apply bleeding avoidance strategies such as radial artery access and adequate antithrombotic therapy dosing according to body weight and kidney function in these patients, as well as new-generation DES that are safe with a short DAPT duration strategy (if DAPT has to be discontinued because of major bleeding).[55, 188, 192] Available studies that have investigated the relationship between anemia and outcomes in MI are mostly based on data from patients not treated with potent P2Y12 inhibitors and often treated with GP IIb/IIIa inhibitors as well as rare radial artery access.[187] Using the radial route eliminates access related bleeding to a high degree.[78] The role of baseline anemia in the setting of MI treated with contemporary pharmacology and PCI techniques has not been adequately studied.

# Aims

The general aims of this thesis were to explore risk stratification strategies to identify myocardial infarction patients at high risk for adverse outcomes as well as to evaluate therapies in such high-risk patients. The specific aims for each paper are outlined below.

I. To describe the demographics, angiographic findings, mortality rate and prognostic value of percutaneous coronary intervention, and identify factors associated with a severe coronary artery stenosis (≥90%), in resuscitated cardiac arrest patients without ST-elevation myocardial infarction.

II. To evaluate the prognostic value of baseline anemia in myocardial infarction patients undergoing percutaneous coronary intervention with contemporary pharmacology and intervention techniques, including routine radial artery access, potent P2Y12 inhibition, and only bail-out glycoprotein IIb/IIIa inhibition.

III. To compare the effect of bivalirudin to that of unfractionated heparin monotherapy on outcomes in elderly (≥75 years) myocardial infarction patients undergoing percutaneous coronary intervention according to modern practice, with routine radial artery access, potent P2Y12 inhibition, and only bail-out glycoprotein IIb/IIIa inhibition.

IV. To investigate the predictive ability of the 4-item PRECISE-DAPT score for rehospitalization with major bleeding during dual antiplatelet therapy the first 12 months after myocardial infarction and percutaneous coronary intervention in a nationwide real-world cohort.

# Methods

The following is a summary of the databases and methods used in this research. The specifics of each study can be found in the individual papers appended to this thesis. All studies were approved by Lund University ethical committee.

## Study populations

### National registries

The SWEDEHEART registry comprises several sub-registries that hold data on consecutive patients from all Swedish hospitals that provide acute coronary care or cardiac interventions.[193] The Register of Information and Knowledge About Swedish Heart Intensive Care Admissions (RIKS-HIA) was initiated in 1991 and established as a national quality registry in 1995. The registry records data from all acute coronary care units in Sweden (a total of 74 hospitals) and covers 88% of all myocardial infarction patients.[24] The Swedish Coronary Angiography and Angioplasty Registry (SCAAR) was formed in 1998 and collects data on all coronary angiographies and PCI procedures in Sweden at a total of 30 PCI centers. In 2009, after merging RIKS-HIA and SCAAR together with other national registries, SWEDEHEART was launched.[193] SWEDEHEART is linked to the Swedish National Population Registry for information on death. As the SWEDEHEART registry is a national quality registry for health care improvements, informed consent is not required according to Swedish law, but participants are informed about registration and have the right to deny partaking at any moment. Every year, SWEDEHEART is merged by the National Board of Health and Welfare with the National Cause of Death Registry, the National Patient Registry, and the National Prescribed Drugs Registry, which is possible thanks to the Swedish personal identification number system. Patients are anonymized and given a unique SWEDEHEART identification number, and thereafter, data are available for principal investigators to use for prespecified research projects approved by the SWEDEHEART steering committee and local ethical committees. The National Patient Registry contains data on International Classification of Disease codes from electronic healthcare records while the National Prescribed Drugs Registry carries data on all dispensed drugs at any pharmacy in Sweden.[194, 195] The SWEDEHEART

registry was utilized in paper I and IV for study inclusion. Paper I included all cardiac arrest patients who underwent coronary angiography in Sweden between 2005 and 2016. Paper IV retrieved data on all MI patients treated with PCI between 2008 and 2017, and thereafter excluded patients who were on treatment with oral anticoagulants, who were not prescribed DAPT, did not dispense DAPT from the pharmacy, or who had missing values for any variable in the 4-item PRECISE-DAPT score (age, creatinine clearance, hemoglobin, previous bleeding).[163]

## VALIDATE-SWEDEHEART

The VALIDATE-SWEDEHEART trial was a multicenter, prospective, randomized, registry-based, controlled, and open-label clinical trial that evaluated the efficacy and safety of bivalirudin compared to unfractionated heparin monotherapy in the era of routine radial artery access (90.3%).[136] Patients were eligible for inclusion if they presented with STEMI or NSTEMI within 24 hours from symptom onset and urgent PCI of the culprit lesion was planned. Furthermore, potent P2Y12 inhibition was mandatory (ticagrelor 94.9%, prasugrel 2.1%, or cangrelor 0.3%) and only bail-out GP IIb/IIIa inhibition (2.6%) was allowed.[136] Exclusion criteria included pre-existing terminal disease with life expectancy <1 year, known ongoing bleeding, uncontrolled hypertension, known subacute bacterial endocarditis, severe renal or liver dysfunction, thrombocytopenia, more than 5000 U of heparin given before arrival at the catheterization laboratory or more than 3000 U given in the laboratory but before coronary angiography.[196] Bivalirudin was administered intravenously at a bolus dose of 0.75 mg/kg as soon as the decision to perform PCI was made, followed by a 1.75 mg/kg/h infusion. The bivalirudin group received bivalirudin alone or in combination with a low dose of heparin within the boundaries of abovementioned exclusion criteria. The heparin arm patients were recommended a 70-100 U/kg dose. If the activated clotting time was <250 seconds, a second bolus of the assigned anticoagulant drug was given.

The VALIDATE-SWEDEHEART trial utilized a hybrid registry-based RCT design, using active endpoint screening and registry acquisition of baseline characteristics, compared to a pure registry-based RCT that uses a registry for both these purposes.[196] Research nurses contacted participants or a first-degree relative by telephone after 7 and 180 days to screen for endpoints. If contact had not been made after several telephone calls and a mailed letter, endpoint information was acquired from hospital records. If suspicion of an event arose, electronic healthcare records were subjected to central blinded adjudication to verify the event and determine the time of the event. Active screening for events included the primary endpoint (180-day all-cause death, MI, or major bleeding), the individual components of the primary endpoint, and stroke. Other endpoints were gathered by using the SWEDEHEART registry, the National Patient Registry, or the Swedish National Population Registry. MI was defined according to the third universal definition and major bleeding as type 2, 3, or 5 on the BARC scale.[145, 197] The

registry RCT design has several advantages over a conventional RCT. A large number of patients can be randomized in a short amount of time and the costs are substantially lower, which allows for a more all-comer study population that is more representative of real-world patients. The VALIDATE-SWEDEHEART trial enrolled 6006 patients admitted to one of the 25 participating PCI centers between 2014 and 2016 and showed that an anticoagulation strategy with bivalirudin was neutral compared to heparin monotherapy in the era of routine radial artery access, potent P2Y12 inhibition and only bail-out GP IIb/IIIa inhibition. Paper II and III in this thesis are prespecified analyses of VALIDATE-SWEDEHEART. Paper II utilized the advantage of adjudicated endpoints and routine radial artery access, which substantially decreases access site bleeding rates, to determine the prognostic value of baseline anemia in current clinical practice. Paper III compared bivalirudin to heparin monotherapy in an elderly population (≥75 years), who might derive a greater benefit from bivalirudin, due to their high bleeding risk profile.[140]

# Endpoints

## Paper I: Cardiac arrest

Endpoints in this study included the probability of a severe coronary artery stenosis of at least 90%, and the probability of receiving PCI when having such a stenosis, for cardiac arrest patients without STEMI. Furthermore, 30-day all-cause mortality was assessed in patients with cardiac arrest without STEMI compared to cardiac arrest with STEMI. Within the group of patients without STEMI, 30-day mortality was compared for those with versus without a severe coronary artery stenosis (≥90%). For cardiac arrest patients without STEMI who had a stenosis of at least 90%, 30-day all-cause mortality was evaluated for those who underwent PCI versus those who only underwent diagnostic coronary angiography.

## Paper II: Anemia

The primary endpoint was 180-day all-cause death. Secondary endpoints included myocardial reinfarction, major bleeding, definite stent thrombosis, and stroke within 180 days from the index MI.

## Paper III: Elderly

The primary endpoint was a composite of all-cause mortality, myocardial reinfarction, or major bleeding at 180 days. Secondary endpoints included a composite of the primary endpoint or stroke, as well as 180-day rates of several

individual endpoints: death, myocardial reinfarction, major bleeding, BARC 2 bleeding, BARC 3 or 5 bleeding, access site bleeding, stroke, and stent thrombosis.

### Paper IV: The PRECISE-DAPT score

The primary endpoint was the c-statistic for the PRECISE-DAPT score regarding prediction of rehospitalization with major bleeding during DAPT after MI and PCI. Secondary endpoints included the rate of major bleeding for patients with a high PRECISE-DAPT score (≥25) versus those with a non-high score (<25) as well as the c-statistic for the PRECISE-DAPT score among subgroups of patients with pre-existing risk factors for bleeding (elderly, underweight, women, patients with anemia, kidney dysfunction, or cancer).

## Statistics

Parametric continuous variables were compared using the independent samples *t*-test while non-parametric continuous variables were compared by means of the Mann-Whitney *U* test. Categorical variables were compared using the chi-square test. Univariable or multivariable logistic regression was used to compare the odds of time-independent binary outcomes. For time-to-event endpoints, crude estimates were calculated with the Kaplan-Meier method and compared using the log-rank test, while unadjusted hazard ratios (HR) with their 95% confidence interval (CI) were computed using univariable Cox regression. Furthermore, multivariable Cox regression models were fit to adjust for potential confounders in paper I and paper II. To avoid overfitting, a rule of thumb suggests that there should be at least 10 outcome events per covariate included in a Cox regression model, although it has been suggested that this rule might be too conservative.[198] The specific covariates included in each Cox regression model are outlined in the respective papers appended to this thesis. All covariates were identified a priori. For paper II, propensity score matching was used as a supplemental method to control for confounding.[199] Multivariable logistic regression was used to calculate the propensity score (probability that a study subject belongs to the exposed group). Included covariates to do this are outlined in paper II. Thereafter, exposed subjects were matched with unexposed control subjects with a 1:1 ratio using the nearest neighbor method.[200] Univariable Cox regression was subsequently used to compare outcomes between groups. Moreover, paper II and paper IV used multiple imputation to handle missing data, which were assumed to be missing at random.[201] In Paper IV, receiver operating characteristic (ROC) curves were plotted to calculate the c-statistics (defined as the area under the ROC curve). A two-tailed p-value below 0.05 was considered statistically significant. Statistical analyses were executed using SPSS (version 24-25; IBM Corp.; Armonk, NY, USA), Stata

(version 14-15; Stata Corp.; College Station, TX, USA), R (version 3.4.4; R Foundation for Statistical Computing; Vienna, Austria), or GraphPad Prism (version 8.0.2; GraphPad Software; San Diego, CA, USA).

# Results

## Paper I: Cardiac arrest

### Demographics and angiographic findings

This study included 4308 resuscitated cardiac arrest patients who underwent coronary angiography, of whom 1412 (33%) had STEMI and 2896 (67%) did not show signs of STEMI. Patients without STEMI more often had relevant comorbidities such as a history of diabetes, hypertension, hyperlipidemia, previous MI, CABG, or PCI, compared to those with STEMI. Cardiac arrest patients without STEMI more often had normal coronary arteries (no stenosis ≥50%) compared to patients with STEMI (36.4% versus 5.7%, respectively). Severe significant coronary artery stenosis (≥90%) was present in 43.9% (1271 of 2896) of cardiac arrest patients without STEMI and in 80.1% (1131 of 1412) of patients with STEMI. In patients with cardiac arrest without STEMI who had a coronary artery stenosis of at least 90%, 753 of 1271 (59.2%) patients underwent PCI, while the corresponding number for cardiac arrest with STEMI was 92.6% (1047 of 1131).

### 30-day mortality

All-cause crude mortality rates within 30 days were lower for cardiac arrest patients without STEMI (35.9%) compared to those with cardiac arrest and STEMI (41.1%; $p<0.001$), but substantially higher than for patients with ACS without cardiac arrest (2.8%). After adjustments for confounders, mortality rates for cardiac arrest patients with or without STEMI were similar (HR 0.98; 95% CI 0.87-1.10; p=0.72). The presence of a significant coronary artery stenosis (≥90%) in cardiac arrest patients without STEMI did not significantly affect mortality rates (37.5% versus 34.6%; p=0.11; HR 1.04; 95% CI 0.89-1.22). For patients with cardiac arrest without STEMI who had a coronary artery stenosis of at least 90%, PCI was associated with a higher crude mortality rate (40.9%) than only diagnostic coronary angiography (32.7%; p=0.011; Figure 4). This difference completely vanished after adjustments for confounders (HR 1.07; 95% CI 0.84-1.36; p=0.57). Of these patients treated with PCI, 80.2% underwent coronary angiography on their admission day, and 11.3% on the day after.

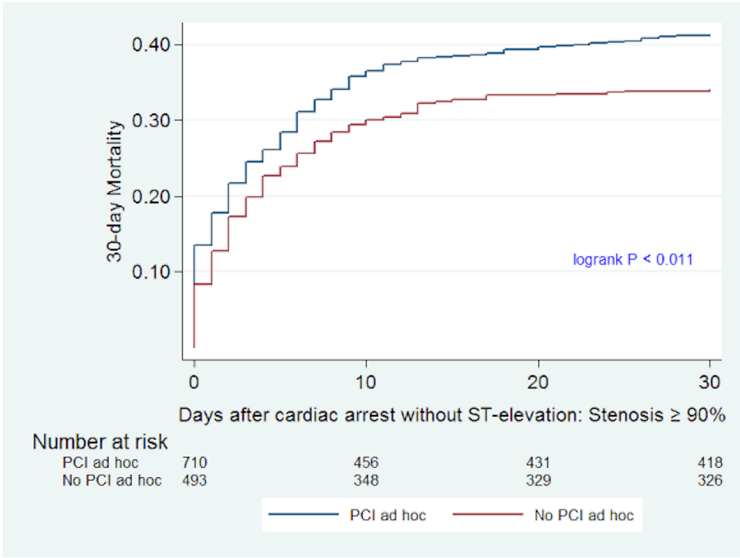


**Figure 4.**
Kaplan-Meier failure function for 30-day mortality in resuscitated cardiac arrest patients without ST-elevation myocardial infarction, who had at least one significant coronary artery stenosis (≥90%) at coronary angiography. Patients are stratified into those who were treated with percutaneous coronary intervention (blue line) and those who only underwent diagnostic coronary angiography (red line).

### Explanatory model for coronary artery stenosis (≥90%)

The strongest explanatory factor in multivariable analysis for the presence of coronary artery stenosis (≥90%) in cardiac arrest patients without STEMI was previous MI (odds ratio [OR] 3.58; 95% CI 2.79-4.60; p<0.001). Other factors were advanced age, male sex, hypertension, diabetes, and current smoking, while previous PCI was a protecting factor (OR 0.54; 95% CI 0.41-0.71; p<0.001).

## Paper II: Anemia

### Baseline characteristics

All patients enrolled in VALIDATE-SWEDEHEART without missing values for hemoglobin were included (n=5482) of whom 792 (14.4%) had anemia at baseline. Patients with anemia were older, more often women, and had lower body weight compared to patients without anemia. Furthermore, patients with anemia more frequently had relevant comorbidities such as kidney dysfunction, hyperlipidemia, hypertension, diabetes, heart failure, and a history of coronary artery disease, or

stroke. Baseline anemia was associated with lower prescription rates of aspirin, potent P2Y12 inhibitors, beta-blockers, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, and statins at hospital discharge.

## Unadjusted outcomes

Patients with MI and anemia at baseline had a higher risk of death from any cause at 180 days of follow-up compared to patients with MI and normal hemoglobin values (6.9% versus 2.1%; p<0.001). Patients with anemia were also at higher risk of myocardial reinfarction (4.3% versus 1.9%), major bleeding (13.4% versus 8.2%), and stroke (2.0% versus 0.7%), within 180 days compared to patients without anemia (p<0.001). Rates of stent thrombosis did not differ between groups. Outcomes were gradually worse for lower hemoglobin values (Figure 5). Hemoglobin values below 100 g/L were associated with a 10 times higher mortality rate, 6 times higher myocardial reinfarction rate, and a 3 times higher major bleeding rate, compared to normal hemoglobin values.

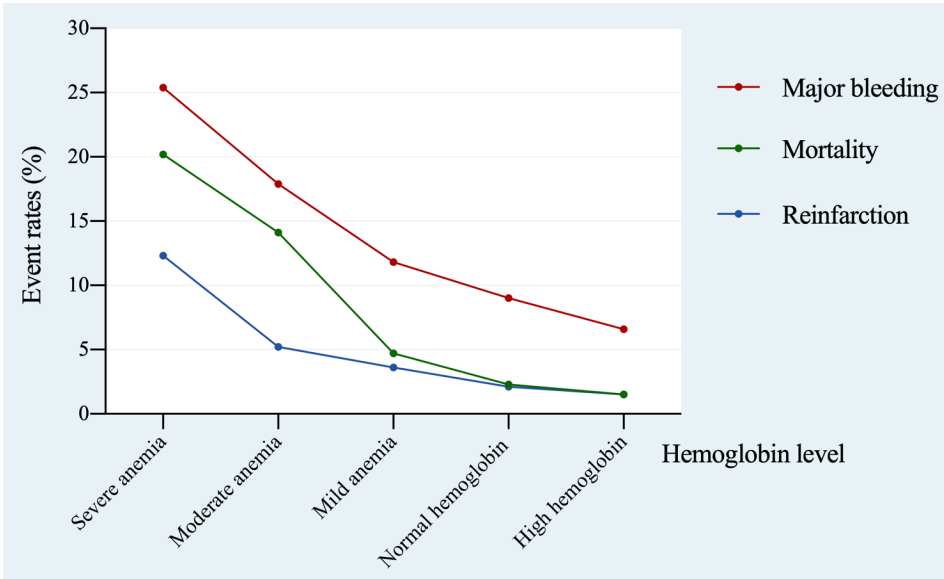


**Figure 5.**
Event rates at 180 days for mortality (green), reinfarction (blue), and major bleeding (red), stratified by hemoglobin level categories in acute coronary syndrome patients: severe anemia (hemoglobin <100 g/L); moderate anemia (hemoglobin 100–109 g/L); mild anemia (hemoglobin 110–129 g/L for men and 110–119 g/L for women); normal hemoglobin (130–150 g/L for men and 120–150 g/L for women); and high hemoglobin (>150 g/L).

### Adjusted outcomes

After multiple imputation for missing values and adjustments for numerous confounders, anemia was still associated with an increased risk of death (HR 1.9; 95% CI 1.3-2.7; p<0.001), myocardial reinfarction (HR 1.7; 95% CI 1.1-2.7; p=0.013), and major bleeding (HR 1.3; 95% CI 1.0-1.6; p=0.041). Results were consistent when adjustments were made without prior multiple imputation as well as when using propensity score matching.

## Paper III: Elderly

### Baseline and periprocedural characteristics

A total of 1592 patients who were at least 75 years old and 4406 patients younger than 75 years were included in this study. Patients older than 75 years were divided into those who had been randomly assigned to receive heparin (n=793) or bivalirudin (n=799). The treatment groups were similar regarding baseline characteristics, such as age, previous comorbidities, and clinical presentation. Periprocedural characteristics such as time delays to PCI, the use of radial artery access, and angiographic findings were comparable between groups.

### Outcomes in the elderly

Assignment to heparin as compared to bivalirudin resulted in similar rates of the composite primary endpoint of death, myocardial reinfarction, or major bleeding at 180 days of follow-up (20.7% versus 21.0%; p=0.936) in elderly patients (Figure 6). The individual components of the primary endpoint as well as the rates of stroke, bleeding according to severity (BARC 2, or BARC 3 or 5), access-site bleeding, and stent thrombosis, occurred equally often in the different treatment groups. Results were consistent across subgroups of elderly STEMI and NSTEMI patients as well as elderly women.

### The elderly compared to younger patients

Elderly patients more often had NSTEMI and baseline anemia compared to their younger counterparts. The elderly had a higher comorbidity burden as well as more multivessel disease. All outcome measures occurred at least twice as often in elderly patients, including death, myocardial reinfarction, major bleeding, and stroke (all p<0.001), but not stent thrombosis.

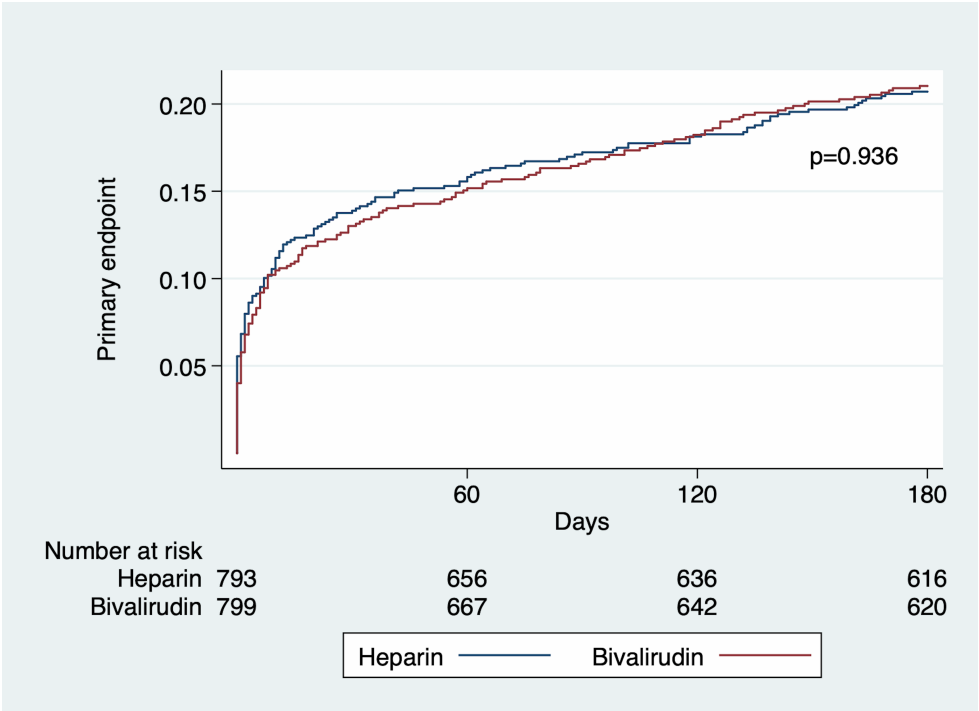


**Figure 6.**
Kaplan-Meier failure function for the primary endpoint (death, myocardial reinfarction, or major bleeding) within 180 days in 1592 elderly (≥75 years) patients with myocardial infarction undergoing percutaneous coronary intervention stratified by treatment with heparin or bivalirudin.

# Paper IV: The PRECISE-DAPT score

## Study population

A total of 66295 patients with a median PRECISE-DAPT score of 14 (interquartile range 7-23) met study criteria. Patients with a high PRECISE-DAPT score (≥25; n=13894) were significantly older (mean age 78 versus 63 years), more frequently underweight or women, and had a higher comorbidity burden, including anemia, kidney dysfunction, and cancer, compared to patients with a non-high PRECISE-DAPT score (<25; n=52401).

## Bleeding outcomes

During a median of 365 days of follow-up, 526 (3.9%) patients with a high PRECISE-DAPT score were rehospitalized with major bleeding compared to 891

(1.8%) patients with a non-high score (HR 2.2; 95% CI 2.0-2.5; p<0.001). The median time to major bleeding was 77 days (interquartile range 34-188). Patients with at least one pre-existing risk factor for bleeding also had higher rehospitalization rates with major bleeding when criteria for a high PRECISE-DAPT score were met (≥25), including patients with advanced age (≥75 years; 3.8% versus 3.0%; p=0.003), women (3.3% versus 1.8%; p<0.001), patients with anemia (5.3% versus 3.2%; p<0.001), or kidney dysfunction (3.6% versus 2.4%), although with lower absolute risk differences than for the total study population. Underweight (body weight <60 kg) patients also had a numerically higher estimated risk for major bleeding when the PRECISE-DAPT score was high, but it did not reach statistical significance (4.1% versus 3.3%; p=0.236).

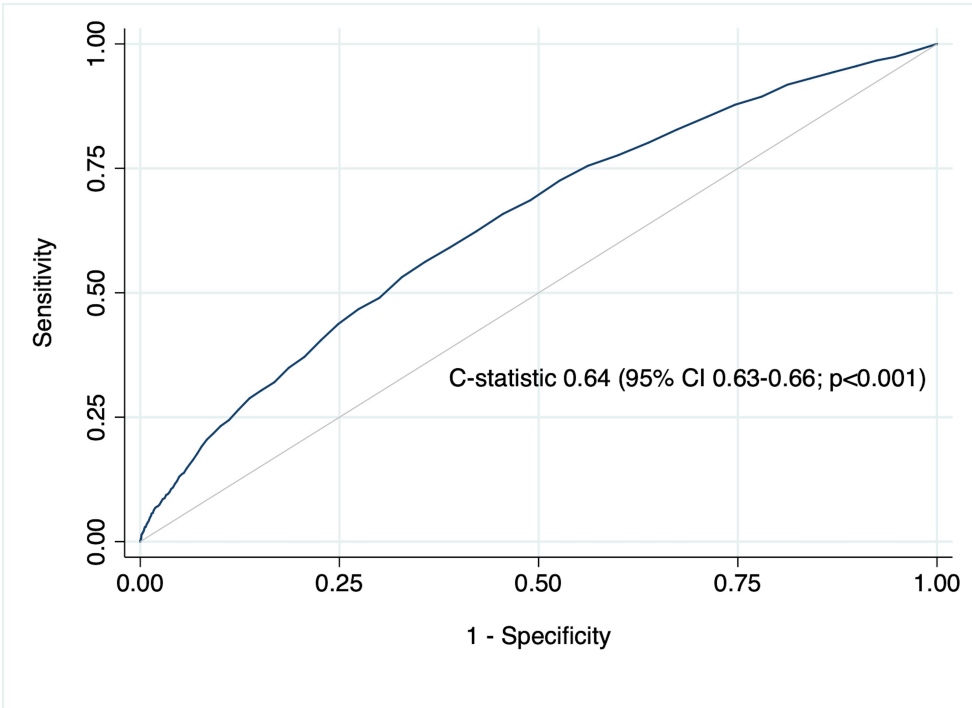


**Figure 7.**
Receiver operating characteristic curve for the PRECISE-DAPT score regarding rehospitalization with major bleeding the first year after myocardial infarction that was treated with percutaneous coronary intervention and subsequent dual antiplatelet therapy (n=66295). The figure displays the c-statistic with a 95% confidence interval (CI).

## Score discrimination

The c-statistic for the PRECISE-DAPT score regarding prediction of rehospitalization with major bleeding during DAPT in the total study population was 0.64 (95% CI 0.63-0.66; Figure 7). The PRECISE-DAPT score exhibited

moderate or poor discrimination for elderly patients (c-statistic 0.57; 95% CI 0.55-0.60), underweight patients (c-statistic 0.56; 95% CI 0.51-0.61), women (c-statistic 0.62; 95% CI 0.60-0.65), patients with anemia (c-statistic 0.60; 95% CI 0.58-0.63), kidney dysfunction (c-statistic 0.61; 95% CI 0.58-0.64), or cancer (c-statistic 0.59; 95% CI 0.53-0.66).

# Discussion

Myocardial infarction remains a major cause of mortality and morbidity worldwide. Outcomes following MI have improved over the years, but the trend of declining mortality rates ended a decade ago and has been replaced by a plateau phase. Along with the decreasing risk of recurrent ischemic events after MI through invasive management and potent antithrombotic treatment, the occurrence of bleeding has emerged as a major clinical problem with a substantial impact on mortality. Tailoring of the invasive and pharmacological treatment according to the individual patient's predicted risk of death, thrombosis, or bleeding, rather than using a one-size-fits-all approach, may further improve outcomes, especially for high-risk patients who contribute to the majority of the total mortality burden in the MI population. This thesis evaluated hemoglobin and the novel PRECISE-DAPT score for the purpose of such risk stratification. Furthermore, the research in this thesis investigated the prognostic value of early PCI in the high-risk population of resuscitated cardiac arrest patients without STEMI, as well as the optimal anticoagulation strategy for the high-risk group of elderly MI patients. The primary results of each study are discussed in the respective dedicated sections below.

## The role of PCI for cardiac arrest without STEMI

A landmark study published in 1997 reported that successful PCI was an independent predictor of hospital survival in resuscitated cardiac arrest patients.[101] Immediate coronary angiography and PCI have subsequently become routine in the management of cardiac arrest with STEMI, but results have been conflicting regarding the role of early coronary angiography and PCI for patients without signs of STEMI on the post-resuscitation ECG.[105-108] In paper I, the role of PCI for cardiac arrest without STEMI was studied in a large nationwide real-world cohort of patients undergoing coronary angiography. The principal findings were that almost two thirds of these patients had a significant coronary artery stenosis of at least 50%, while 43.9% had a severe coronary artery stenosis (≥90%). Furthermore, PCI was performed in 59.2% of patients with a severe coronary artery stenosis but was not associated with improved 30-day survival compared to only diagnostic coronary angiography.

Since the publication of paper I, several additional studies have tried to define the role of coronary angiography and PCI in the setting of cardiac arrest without STEMI. One study linked the SWEDEHEART registry to the Swedish Registry for Cardiopulmonary Resuscitation and compared the use of coronary angiography (with PCI if indicated) within 24 hours to deferred or no angiography in 799 unconscious out-of-hospital cardiac arrest patients with a shockable initial ECG rhythm.[202] The authors found that patients who underwent early coronary angiography had lower 30-day and 1-year mortality rates than those who did not. Another recent observational study supported these results (that an early invasive approach is associated with lower death rates) but found no survival benefit from PCI among patients who underwent coronary angiography, which may suggest indication bias or other unknown confounding.[203] An observational study design does preclude any certain conclusions about causal associations.

The Coronary Angiography after Cardiac Arrest (COACT) trial was an open-label, multicenter RCT that assigned 552 out-of-hospital cardiac arrest patients without STEMI and without cardiogenic shock to either an immediate (<2 hours) or delayed invasive strategy (generally after neurologic recovery).[204] Patients who were conscious at the time of return to spontaneous circulation or who had an initial non-shockable rhythm were excluded from the trial. The median time to TTM was slightly longer in the immediate angiography arm (5.4 versus 4.7 hours). Analogously to what was found in paper I, that PCI did not offer any survival benefit for patients who underwent coronary angiography, the COACT trial investigators reported that there was no difference regarding 90-day mortality between the immediate invasive approach and the delayed strategy.[204] Results were robust and similar at 1-year follow-up.[205] A recent meta-analysis, that included the results from COACT, supported the conclusion that unselected early coronary angiography with the option for PCI does not increase survival in patients with cardiac arrest without STEMI.[206]

Early revascularization should by intuition have the potential to improve hemodynamics and cardiac function to prevent recurrence of cardiac arrest as well as perfusion of the brain to improve neurologic recovery, and thereby improve the prognosis in resuscitated patients with MI. There are several possible explanations for the neutral finding of early PCI in paper I and of early coronary angiography and PCI in COACT. In paper I, an in-depth discussion is provided of potential over- or underdosing of DAPT due to multiorgan failure in patients undergoing PCI after cardiac arrest which could lead to bleeding or stent thrombosis, as well as inherent potential selection bias in observational studies where patients who receive PCI might have worse hemodynamics but a more favorable neurologic outcome. In COACT, there were no statistically significant differences in bleeding frequencies between treatment arms.[204] Moreover, the major death cause of resuscitated patients with cardiac arrest is neurological injury, which might mask a potential positive effect of coronary revascularization to prevent cardiac death causes.[91, 204] Notably, acute coronary occlusions were present in only 5% of patients in COACT, which is

much lower than in paper I and in other reports.[202] Patients without STEMI are a more heterogenous group than those with STEMI, with a higher prevalence of non-cardiac causes of the arrest. The performance of coronary angiography could delay the initiation of TTM as well as treatment of the precipitating cause of the arrest for patients without MI. Furthermore, the transportation of cardiac arrest patients between or within hospitals early after return of spontaneous circulation to perform expeditious coronary angiography and PCI might also be risky.

For these reasons, it is essential to identify those patients who have the highest likelihood of benefiting from early PCI. In paper I, a history of MI, hypertension, and diabetes, as well as current smoking, high age, and male sex, were independently associated with a severe coronary artery stenosis of at least 90%. Furthermore, patients with multiple unfavorable factors, such as initial non-shockable rhythm, long time to return of spontaneous circulation, severe acidosis, or irreversible anoxic brain damage, are unlikely to derive benefit from revascularization.[207, 208] Ultimately, only a third of patients who underwent coronary angiography in paper I were treated with PCI, and in another study only a fourth of patients with non-shockable rhythms who underwent coronary angiography received PCI.[209] To identify this minority of cardiac arrest patients without STEMI who might benefit from PCI remains challenging and requires further studies. Several additional ongoing randomized trials are testing the hypothesis that an early invasive procedure will improve survival in selected patient cohorts.[210-213] Recent pilot studies seem to concur with the neutral findings of the COACT trial.[214-216]

# Hemoglobin as a prognostic biomarker

Anemia has been associated with increased risk of death in both the general population and in patients with MI.[185, 217] In line with the widely implemented use of radial artery access and restrictive use of GP IIb/IIIa inhibitors for MI patients undergoing PCI, the rate of in-hospital bleedings has declined, while the rate of out-of-hospital bleeding has increased since the advent of potent P2Y12 inhibitors.[34] In this new landscape of modern pharmacology and PCI techniques, the prognostic role of anemia has not been established. For this reason, paper II was a prespecified analysis of VALIDATE-SWEDEHEART that aimed to study the association between anemia and hard clinical outcomes in a population of MI patients treated according to contemporary practice with routine use of radial access and potent P2Y12 inhibition as well as rare GP IIb/IIIa inhibitor use. The main findings were the following. The presence of anemia at the time of hospital admission for MI identified a sicker patient group who were less frequently prescribed evidence-based secondary preventive medications at hospital discharge. Furthermore, patients with anemia had a markedly increased risk of death, major bleeding, myocardial reinfarction, and stroke, within 180 days from the index MI. Event rates were

particularly high for patients with severe anemia (hemoglobin <100 g/L), with a 10 times higher mortality rate, 6 times higher rate of myocardial reinfarction, and 3 times higher rate of major bleeding, compared to patients with normal hemoglobin values.

These results raise some important questions with potential clinical impact. What are the underlying mechanisms for these associations and how can the prognosis for these patients be improved? First, there might be a causal relationship between anemia and mortality. The transportation of oxygen through the circulatory system depends on oxygen saturation in the blood, the blood concentration of hemoglobin, and cardiac output (heart rate times stroke volume). Low hemoglobin levels result in a decreased transportation capacity for oxygen, which the body attempts to compensate for by an increased heart rate to achieve a higher cardiac output. However, this reduces coronary perfusion by decreasing the share of the cardiac cycle spent in diastole and by leading to an increased myocardial oxygen demand, further enhancing the oxygen supply-demand mismatch in the setting of MI. These mechanisms constitute a potential rationale for blood transfusion in the setting of concomitant anemia and MI, which is currently being evaluated in a large RCT (identifier NCT02981407). A potential causal relationship between anemia and outcomes is consistent with the finding in paper II that despite adjustments for multiple confounders using different statistical methods, anemia remained associated with higher risk of adverse events. This possible causal link remains of course only speculative, due to the observational design of paper II. Second, it was found in paper II that patients with anemia more seldom received secondary preventive medications at hospital discharge such as aspirin, ticagrelor, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, beta-blockers, and statins, which also has been reported elsewhere.[218] The lower prescription rate of antiplatelet therapy, which is probably a reflection of bleeding concerns, may result in higher rates of downstream ischemic events. Furthermore, during follow-up, even BARC type 1 bleedings, which are common but lack association with mortality, may cause discontinuation of antiplatelet therapy with consequentially increased risk of future ischemic complications.[37, 219, 220] Of note, one study found that as much as a fifth of patients with anemia at baseline were no longer using aspirin a year after their index MI, compared to a tenth at hospital discharge.[221] Third, baseline anemia is associated with higher frequencies of comorbidities that in turn may lead to worse outcomes. These include cardiovascular risk factors such as advanced age, diabetes, or kidney dysfunction, as well as malignancies that can cause anemia through bleeding or inflammation.[186]

In line with this wide range of potential mechanisms for the association between anemia and adverse events, a low hemoglobin level was associated with higher risk of death from both cardiovascular causes and bleeding, as well as non-cardiovascular/non-bleeding causes, in paper II. Furthermore, regardless of whether the association between low hemoglobin and worse outcomes is explained by 1) direct physiological mechanisms, 2) an antithrombotic treatment that is too modest

(causing ischemia) or too aggressive (causing bleeding), 3) anemia being indicative of a sicker patient group, or 4) a combination thereof, hemoglobin measured at baseline in patients with MI can be viewed as a biomarker for a poor prognosis to identify a patient group at particularly high risk that might benefit from a more personalized approach in the management of MI. This includes bleeding avoidance strategies with radial artery access and correct dosing of antithrombotic agents, second-generation DES for ischemic protection, as well as careful evaluation of the optimal duration of DAPT.

# Anticoagulation therapy for the elderly

The number of people older than 60 years in the world is currently estimated to be around 1 billion but has been projected to be approximately 1.4 billion in 2030, and 2.1 billion in 2050.[164] Likewise, the proportion of patients admitted for PCI who were at least 75 years old increased in Sweden from 5.8% in the beginning of the 1990s to 28.4% in 2010.[165] This large proportion of patients undergoing PCI is frequently underrepresented in clinical trials and their management is instead guided from studies of younger and healthier patients. Therefore, paper III was a prespecified analysis of VALIDATE-SWEDEHEART, comparing bivalirudin to heparin monotherapy in elderly patients (≥75 years) with MI who underwent PCI with almost 90% transradial access, potent P2Y12 inhibitors in more than 97%, and GP IIb/IIIa inhibitors in less than 2% of patients. The main finding of this study was that there was no difference between the treatment arms regarding a composite of all-cause mortality, myocardial reinfarction, or major bleeding, within 180 days. No differences were seen for the individual endpoints of death, myocardial reinfarction, major bleeding, stent thrombosis, or stroke. Furthermore, elderly patients had a more than doubled risk of all endpoints, except stent thrombosis, compared to their younger counterparts.

The results of paper III concur with what was found in the general MI population in the VALIDATE-SWEDEHEART trial, but not with two previous reports of anticoagulation therapy in the elderly population.[139, 140] In a prespecified analysis of the ACUITY trial, the authors found that bivalirudin was associated with a lower risk of major bleeding regardless of age compared to heparin and that the number needed to treat with bivalirudin to avoid a major bleeding was lowest among patients older than 75 years.[139] Likewise, in a pooled analysis of the HORIZONS-AMI trial and the European Ambulance Acute Coronary Syndrome Angiography (EUROMAX) trial, patients older than 65 years had a higher rate of major bleeding when receiving heparin instead of bivalirudin.[140] However, these trials were carried out more than a decade ago when potent P2Y12 inhibitors and radial access were seldom used and GP IIb/IIIa inhibitors were markedly imbalanced to the advantage of bivalirudin. Furthermore, two large studies of more than a million patients with

MI showed with a quasi-experimental design that the potential bleeding reduction associated with bivalirudin is negligible when PCI is performed via the radial artery and without the use of GP IIb/IIIa inhibitors, in accordance with contemporary practice.[222, 223] However, bivalirudin does offer some theoretical benefits over heparin. Its effect is more predictable as it directly and reversibly inhibits both circulating and clot-bound thrombin, compared to heparin that is dependent on antithrombin III and can only inhibit circulating thrombin.[224] Bivalirudin has a short half-life and, unlike heparin, does not bind to other plasma proteins than thrombin, further contributing to the more predictable antithrombotic effect of bivalirudin.[224] Moreover, heparin therapy carries a small risk of induced thrombocytopenia.[125] Despite these potential benefits with bivalirudin therapy, the results of paper III indicate that bivalirudin and heparin are similar in terms of hard clinical outcomes, even in elderly patients.

It has been suggested that there still might be a role for bivalirudin in patients with an increased baseline risk of bleeding, such as the elderly, and that the choice of periprocedural anticoagulant agent in patients with MI undergoing PCI should be tailored according to such predicted bleeding risk.[225] In paper III, the elderly population in VALIDATE-SWEDEHEART were shown to be a clear high-risk subgroup with a nearly 4 times higher mortality rate and a more than 2 times higher rate of major bleeding than younger patients. However, despite this high risk, paper III showed that bivalirudin was neutral compared to heparin monotherapy in elderly patients with MI undergoing PCI according to current pharmacology and PCI techniques, including potent P2Y12 inhibition, rare GP IIb/IIIa inhibition, and routine radial artery access. It may therefore be suggested that systematic use of heparin monotherapy is as safe and efficient as bivalirudin, in not only the general MI population, but also in the subset of high-risk elderly patients, who constitute a substantial part of patients with MI in everyday clinical practice. In addition, heparin is considerably cheaper than bivalirudin with substantial cost-savings if used routinely.[138]

# Prediction of major bleeding to tailor antiplatelet therapy

The 4-item PRECISE-DAPT score utilizes both hemoglobin and age, in conjunction with creatinine clearance and previous bleeding (and white blood cell count in the 5-item version) to predict the risk of major bleeding during DAPT after MI treated with PCI and the implantation of an intracoronary stent.[153] The PRECISE-DAPT score version with 4 variables has demonstrated similar predictive qualities as the 5-item version and might be more practical, as white blood cell count is not routinely measured in many hospitals treating MI patients.[163] However, neither score has been validated in a large study with unselected MI patients that resemble those in clinical practice. Furthermore, in patients with pre-existing risk factors for bleeding, usage

of the PRECISE-DAPT score to further stratify bleeding risk might be of limited value. In paper IV, the aim was to validate the 4-item PRECISE-DAPT score using a nationwide cohort of patients with MI undergoing PCI with subsequent DAPT. The main findings were as follows. The PRECISE-DAPT score identified a subgroup of MI patients with more comorbidities and worse bleeding outcomes. However, the PRECISE-DAPT score demonstrated only a moderate discriminative ability for rehospitalization with major bleeding. In patients with a pre-existing risk factor for bleeding, the score was of even more limited value in further stratifying bleeding risk. Notably, patients with a non-high PRECISE-DAPT score (<25) and advanced age, low body weight, anemia, or cancer, had an absolute risk of major bleeding that was similar to that of patients with a high PRECISE-DAPT score (≥25) in the total study cohort.

The PRECISE-DAPT score was first validated for TIMI major or minor bleeding using data from PLATO (c-statistic 0.70) and the Bern PCI registry (c-statistic 0.63).[153] Subsequently, several studies have validated the score, the largest of which demonstrated a c-statistic of 0.65 for the prediction of BARC 3 or 5 bleedings in 4424 patients with ACS.[161] Paper IV was the largest study so far on this subject including a total of 66295 patients with MI and revealed a c-statistic for rehospitalization with major bleeding during DAPT of 0.64. There is no definite answer to what value of the c-statistic that represents a valid prediction. However, Hosmer and Lemeshow suggest a rule of thumb that declares that a c-statistic above 0.90 represents an outstanding discrimination, 0.80-0.90 is excellent and 0.70-0.80 is acceptable, but 0.50-0.70 is considered poor and not much better than a coin toss.[226] Considering this, the c-statistic of 0.64 for the PRECISE-DAPT score in paper IV is not impressive. However, the exact value of the c-statistic must be interpreted in the light of its intended purpose. A test that is supposed to be diagnostic, such as troponin analyses for patients presenting with chest pain, requires a high discriminatory power,[227] whereas risk prediction models, such as the $CHA_2DS_2$-VASc score for atrial fibrillation/flutter, can be clinically valuable despite a lower discriminatory power.[228] The purpose of the PRECISE-DAPT score is to make risk predictions that may guide clinical practice.

It has been found that patients with a high PRECISE-DAPT score (≥25) have a lower risk of major bleeding when treated with a shorter (3-6 months) DAPT course, with only a minor increase in the risk of recurrent thrombosis. Inversely, patients with a non-high score (<25) did not show improved bleeding outcomes when using a short DAPT strategy, but experienced higher rates of ischemic complications compared to when they received a standard or prolonged treatment with DAPT (12-24 months).[153, 162, 163] Based on this, the use of the PRECISE-DAPT score for bleeding risk stratification to guide clinicians in selecting patients appropriate for a shortened DAPT duration of 3 or 6 months, has been endorsed by the European Society of Cardiology guidelines.[55, 68, 118] However, it was shown in paper IV that among real-world MI patients undergoing PCI with subsequent DAPT, a majority of bleedings happen the first 3 months and almost 75% of all bleeding events occur

before 6 months. This finding is in line with a large systematic review that found that most bleeding events happen the first 1-3 months after ACS,[220] as well as with a large registry study and the PRECISE-DAPT score derivation study that both found the median time to bleeding to be within 6 months.[153, 229] Considering these data, that bleeding usually occurs during the early months after MI, simply shortening the duration of DAPT to 6 months would not help these early bleeders, but only the minority of patients who develop bleeding at later time points. Other ways of individualizing DAPT might be more effective,[230] such as aspirin discontinuation after 1-3 months followed by P2Y12 inhibitor monotherapy, or a strategy with initial potent P2Y12 inhibition followed by de-escalation to clopidogrel.[231]

In paper IV, it was found that the discriminatory power of the PRECISE-DAPT score for patients with a pre-existing risk factor for bleeding was lower than for the general MI population. The PRECISE-DAPT score may not add much value in patients already deemed at higher risk of bleeding by conventional risk stratification, since the risk of bleeding for risk groups was similar regardless of PRECISE-DAPT score status. Examples of risk groups include high age or low body weight. Furthermore, patients with anemia or cancer in combination with a non-high PRECISE-DAPT score had a risk of major bleeding that was comparable to, or higher, than that of patients with a high PRECISE-DAPT score in the general MI population, whereas the risk of bleeding for patients with anemia or cancer and a high PRECISE-DAPT score was particularly high, indicating that these comorbidities are high bleeding risk traits regardless of the PRECISE-DAPT score. These data suggest that the clinical usefulness of the PRECISE-DAPT score in patients with pre-existing bleeding risk factors to further stratify bleeding risk is limited.

# Conclusions

This thesis examined different risk stratification methods and evaluated therapies in high-risk MI patients referred for invasive treatment with PCI. Several conclusions can be drawn based on this research. First, early PCI did not improve survival in resuscitated cardiac arrest patients without STEMI as compared to only diagnostic coronary angiography. Unselected early coronary angiography for these patients may therefore not be reasonable. Future research is required to confirm or refute these findings and to identify subsets of patients who are most likely to benefit from PCI. Second, anemia remains a strong prognostic marker for MI patients undergoing PCI in the setting of contemporary practice with bleeding avoidance strategies such as radial artery access and only bail-out GP IIb/IIIa inhibitors as well as ischemic protection with potent P2Y12 inhibitors and second-generation DES. A low hemoglobin value, especially one below 100 g/L, identified a subgroup in the MI population who are at particularly high risk and may benefit from more personalized medicine. Third, elderly patients with MI constitute a high-risk patient group with markedly increased risk of death, myocardial reinfarction, major bleeding, and stroke, and may benefit from a more patient-tailored approach. However, a periprocedural anticoagulation strategy during PCI with bivalirudin instead of heparin monotherapy did not present any benefit. Heparin monotherapy may therefore be considered for systematic use in not only the general MI population but also in the high-risk subset of elderly MI patients undergoing PCI. Fourth, the PRECISE-DAPT score could be used for risk stratification to assist the treating cardiologist in tailoring the DAPT duration after MI in the general population, but its usefulness to further stratify bleeding risk in patients with a pre-existing bleeding risk factor seems limited. More powerful risk stratification tools regarding post-discharge bleeding are warranted. In total, the findings from this thesis have potential implications for a more personalized approach in acute coronary care that may further improve outcomes following MI.

# Popular science summary in Swedish

Hjärtinfarkt är den vanligaste orsaken till förtida död globalt. I Sverige vårdas årligen ungefär 21 000 personer på sjukhus för hjärtinfarkt, varav cirka en av sju dör inom ett år. Flera viktiga framsteg i behandlingen av hjärtinfarkt har lett till en markant minskning av dödligheten, men de senaste tio åren har denna minskning avstannat och upphört. Hjärtinfarkt föranleds av en långvarig biologisk process i det innersta lagret av väggarna i de blodkärl som försörjer hjärtmuskulaturen med syre (kranskärlen), vilken resulterar i bildandet av aterosklerotiska plack, även kallat åderförkalkning eller åderförfettning. Om ett aterosklerotiskt plack spricker, bildas blodproppar som riskerar att stänga av blodflödet, med syrebrist och celldöd i hjärtmuskulaturen som följd.

Den vanligaste behandlingen för hjärtinfarkt är att vidga upp det förträngda kärlet, ofta med efterföljande insättning av kärlprotes (stent) som ska hålla kärlet fortsatt öppet. Denna behandling kallas perkutan kranskärlsintervention (PCI) och utförs med hjälp av en uppvidgningsbar ballong som förs in i hjärtats kranskärl via en kateter som sticks in i en artär i underarmen eller ljumsken. Ytterligare behandling inkluderar blodförtunnande mediciner, vilka tillsammans med PCI har medfört stora överlevnadsvinster. Dock har risken för blödningskomplikationer ökat, vilket också medför ökad risk att dö. Fastän denna behandling på populationsbasis gör mer nytta än skada, finns ett ökat intresse för mer skräddarsydda behandlingar baserade på den enskilda patientens uppskattade risk för död, ny hjärtinfarkt, eller blödning, för att ytterligare förbättra prognosen efter hjärtinfarkt. Denna avhandling syftade till att utvärdera metoder för att uppskatta sådan risk samt undersöka olika behandlingsalternativ hos högriskpatienter.

Avhandlingen är indelad i fyra delstudier. Den första studien analyserade värdet av PCI hos patienter med hjärtstopp avseende överlevnad. Den vanligaste orsaken till att hjärtat stannar är hjärtinfarkt, vilket kan identifieras med hjälp av elektrokardiografi (EKG) efter att hjärtat återfått pulsbärande rytm. Andra orsaker inkluderar bland annat annan strukturell hjärtsjukdom och lungsjukdom. Tidigare forskning har visat att många av de patienter som saknar tydliga tecken på hjärtinfarkt på EKG ändå har hjärtinfarkt som bakomliggande orsak till hjärtstoppet. Det har dessutom rapporterats om att tidig kranskärlsröntgen för att diagnosticera en eventuell hjärtinfarkt, med samtidig PCI-behandling ifall det finns förträngningar, är förenat med ökad överlevnad för denna grupp av patienter med hjärtstopp utan tydliga EKG-tecken. Det har därför föreslagits att alla patienter med hjärtstopp där någon uppenbar bakomliggande orsak inte har identifierats ska

undersökas med tidig kranskärlsröntgen och behandlas med PCI vid kranskärlsförträngningar. Förekommande studier på detta område har dock inkluderat relativt få studiedeltagare. Denna avhandlings första delarbete syftade därför till att undersöka detta på nationell nivå. Med hjälp av det svenska registret för hjärtsjukdomar (SWEDEHEART) identifierades 2896 patienter med hjärtstopp utan tydliga EKG-tecken på hjärtinfarkt som alla hade undersökts med kranskärlsröntgen, av vilka 1271 hade mycket täta kranskärlsförträngningar vilka kan ha orsakat hjärtstoppet. Av dessa 1271 patienter behandlades 753 med PCI, men denna behandling medförde ingen överlevnadsvinst inom 30 dagar jämfört med kranskärlsröntgen utan PCI.

I den andra studien undersöktes vad anemi (lågt blodvärde) har för betydelse för prognosen efter hjärtinfarkt. Anemi har visats identifiera en extra sjuk undergrupp av patienter med hjärtinfarkt med högre risk för död, ny hjärtinfarkt, och blödning. Detta har dock inte studerats hos patienter med modern behandling, vilket inkluderar PCI via underarmen istället för ljumsken för att minska risk för blödning samt blodförtunnande medicinering som bättre balanserar risken för ny hjärtinfarkt med risken för blödning. Data från en stor klinisk prövning (VALIDATE-SWEDEHEART) som jämförde två blodförtunnande mediciner hos patienter med en sådan modern behandling användes för att inkludera 5482 patienter. De 792 patienter som hade anemi var äldre och hade fler bakomliggande sjukdomar, så som högt blodtryck, njursvikt, och hjärtsvikt, än patienter utan anemi. Patienter med anemi hade ökad risk för död, ny hjärtinfarkt, blödning, samt stroke inom 180 dagar från den initiala hjärtinfarkten. Detta samband var extra tydligt hos de patienter som hade svår anemi med ett särskilt lågt blodvärde, vilka hade en tiofaldigt högre risk för död, sexfaldigt högre risk för ny hjärtinfarkt, och trefaldigt högre risk för blödning jämfört med patienter utan anemi.

Den tredje studien använde också data från den kliniska prövningen VALIDATE-SWEDEHEART. I samband med PCI ges en typ av blodförtunnande läkemedel direkt i blodet. I VALIDATE-SWEDEHEART jämfördes de vanligaste sådana läkemedlen, bivalirudin och heparin, och det visades att risken för död, ny hjärtinfarkt, eller blödning, inte skiljde sig åt beroende på vilket läkemedel som användes. Detta fynd hade bland annat viktiga hälsoekonomiska vinster eftersom bivalirudin är flerfaldigt dyrare än heparin. En del forskare har dock argumenterat för att bivalirudin är förenat med fördelar så som lägre risk för blödning hos patienter som har särskilt hög risk för detta, till exempel äldre patienter. Den tredje studien i denna avhandling var en subgruppsanalys av VALIDATE-SWEDEHEART vars syfte var att jämföra bivalirudin och heparin hos 1592 patienter äldre än 75 år. Äldre patienter visade sig ha åtminstone dubbelt så hög risk för död, ny hjärtinfarkt, blödning, och stroke, jämfört med patienter yngre än 75 år. Bivalirudin medförde dock inga fördelar avseende minskad risk för död, ny hjärtinfarkt, blödning, eller stroke hos denna äldre högriskgrupp med hjärtinfarkt.

Avhandlingens fjärde studie utvärderade en ny matematisk modell för att förutsäga risken för blödning hos patienter med hjärtinfarkt som behandlas med PCI

och blodförtunnande tablettbehandling. Denna tablettbehandling består av så kallad dubbel blodförtunning, som dels inkluderar livslång behandling med acetylsalicylsyra och dels med ytterligare ett blodförtunnande medel de första tolv månaderna efter infarkten. Syftet med denna matematiska modell är att kunna erbjuda patienter med hög risk för blödning en kortare behandlingstid med dubbla blodförtunnande läkemedel om tre eller sex månader istället för tolv, för att på så vis minska risken för blödning. Europeiska Kardiologföreningen rekommenderar att den matematiska modellen används i detta syfte, men evidensen för hur väl den presterar är bristfällig. I denna studie användes data från SWEDEHEART-registret, patientregistret, samt läkemedelsregistret på totalt 66 295 patienter. Med hjälp av denna matematiska modell kunde patienter identifieras som hade en ökad risk för blödning under tiden de behandlades med dubbel blodförtunning det första året efter en hjärtinfarkt. Modellen gav dock en svag förutsägelse av vilka enskilda patienter som drabbades av blödning under behandlingen. Modellen presterade särskilt svagt i patientgrupper med kända riskfaktorer för blödning, framförallt hos äldre, underviktiga, och patienter med anemi eller cancer. Denna studie visade även att de flesta blödningar sker tidigare än tre månader efter en hjärtinfarkt, varför en kortare behandlingstid om tre eller sex månader endast har potential att vara fördelaktig för den minoritet av patienter som drabbas av senare blödningar.

Sammanfattningsvis bidrog denna avhandling med ett flertal viktiga fynd med potentiell betydelse för behandlingen av hjärtinfarkt. För det första var patienter med hjärtstopp utan tydliga tecken på hjärtinfarkt på EKG på gruppnivå inte betjänta av tidig PCI, vilket nyligen styrktes i en klinisk prövning. Ytterligare forskning behövs för att identifiera vilka enskilda patienter i denna grupp som kan ha nytta av tidig PCI. För det andra visade sig anemi hos patienter med hjärtinfarkt identifiera en subgrupp med särskilt hög risk som möjligen kan dra fördel av en mer skräddarsydd behandling. För det tredje medförde behandling med bivalirudin inga fördelar jämfört med heparin hos högriskgruppen av patienter äldre än 75 år, varför heparin bör kunna användas systematiskt även hos äldre med potentiella hälsoekonomiska vinster. Slutligen visades att värdet av en ny matematisk modell som införts i internationella kliniska riktlinjer har begränsat värde, framförallt för patienter med kända riskfaktorer för blödning.

# Acknowledgements

I would like to thank everyone who has helped or supported me throughout this thesis.

A special thank you to my brilliant main supervisor Dr Sasha Koul for excellent guidance in the fields of research, statistics, and cardiology. Thank you for believing in me, for your never-ending enthusiasm, and for great friendship.

Professor David Erlinge, my co-supervisor, for your invaluable input and support throughout this thesis.

Dr Moman Mohammad, my co-supervisor, for your patience when I first learned SPSS, careful review of my syntax code, and dedication to help me refine my papers until publication.

Dr Pontus Andell and Dr Nazim Isma, my co-supervisors, for great scientific input, support, and encouragement.

Rebecca Rylance, for aiding me in completing the more advanced statistical analyses of paper I and for introducing me to Stata.

Co-authors Dr Rubina Attar, Professor Stefan James, Professor Elmir Omerovic, Dr Josef Dankiewicz, Professor Hans Friberg, Dr Robin Hofmann, Dr Jens Jensen, Dr Karolina Szummer, Dr Göran Olivecrona, Dr Jasminka Holmqvist, and Dr Troels Yndigegn, for great research collaborations.

Monica Magnusson for administrative support.

Professor Pyotr Platonov for inviting me to various research meetings that have contributed to my scientific maturity.

Professor Åke Lernmark, for first igniting my interest in striving for a research career seven years ago.

All the staff at coronary care units and catheterization laboratories in Sweden who provide data to the SWEDEHEART registry and to everyone who participated in the VALIDATE-SWEDEHEART collaboration.

Finally, I would like to thank my family and friends for all your support.

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