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Advancing Management in Coronary Care

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Advancing Management in Coronary Care

Troels Yndigegn

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DOCTORAL DISSERTATION

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Abstract:

Background
Contemporary management of coronary artery disease (CAD), particularly myocardial infarction (MI), has significantly improved patient outcomes with the introduction of new therapies and interventions. However, the plateau in mortality rates underscores the need for continued advancements in management strategies. This thesis aims to enhance coronary care by investigating the efficacy of beta-blockers, the safety of early hospital discharge post-MI, the deferral of coronary revascularization, and the prognostic value of the biomarker CA125.

Methods
The thesis is based on four studies utilizing real-world data from the SWEDEHEART registry and other clinical resources. Using both observational and trial designs, the studies assessed: the long-term efficacy of beta-blocker therapy in post-MI patients with preserved ejection fraction; the safety of early hospital discharge in low-risk STEMI patients; the safety of deferring revascularization using instantaneous wave-free ratio (iFR) and fractional flow reserve (FFR); and the prognostic value of the biomarker CA125 in predicting adverse cardiac outcomes following acute coronary syndrome (ACS).

Results
The findings from this thesis indicate: no significant reduction in mortality or recurrent MI from long-term beta-blocker therapy in patients with preserved ejection fraction; early discharge for low-risk STEMI patients did not increase the risk of major adverse cardiac events (MACE); iFR and FFR-guided deferral of revascularization were equally safe in the long term, though real-world complication rates were higher than those reported in controlled trials; and elevated CA125 levels were associated with heart failure and adverse cardiac remodeling in ACS patients, highlighting its potential as a biomarker for identifying high-risk patients.

Conclusions
Long-term beta-blocker therapy does not lower the risk of death or new MI in patients after MI with preserved ejection fraction. Early discharge for low-risk STEMI patients can be safely implemented, potentially reducing hospital costs and improving resource efficiency. Deferral of revascularization based on physiological measurements is a safe and effective strategy, though further real-world evaluation is warranted. Finally, CA125 shows potential as a prognostic biomarker for identifying ACS patients at higher risk of heart failure, contributing to more personalized and effective treatment strategies. These insights altogether may have significant implications for improving coronary care management.

Key words:

Coronary artery disease, Myocardial infarction, Beta-blockers, Early hospital discharge, Revascularization deferral, Instantaneous wave-free ratio, Fractional flow reserve, SWEDEHEART registry, CA125 biomarker, Registry-based randomized clinical trial

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Advancing Management in Coronary Care

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MADE IN SWEDEN

My father, for inspiring me to do research
My children, for teaching me to look at the world with curiosity
My wife, for sharing the ups and downs along the way

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Summary

In recent decades, there have been significant breakthroughs in the treatment of heart attacks and coronary artery disease, leading to improved survival rates and fewer complications. These discoveries have shaped global treatment guidelines, but their application varies between countries and even within regions. Despite great progress, the decline in mortality has recently begun to plateau, particularly in Sweden, indicating the need for new ways to diagnose and treat patients with coronary artery disease.

This thesis aims to improve the care of patients with coronary artery disease by providing new knowledge in the field. The thesis is based on four individual studies that were initiated, conducted, and reported during the period 2014-2024. Below is a summary of the studies forming the foundation of the thesis:

Study I: This study examined whether long-term beta-blocker therapy is still beneficial for heart attack patients with preserved heart function. The study, which included 5,020 patients from Sweden, Estonia, and New Zealand, showed that beta-blockers did not reduce the risk of death or recurrent heart attacks compared to patients who did not take them. This suggests that not all heart attack patients, especially those with milder heart damage, need long-term beta-blocker treatment.

Study II: This study used data from the SWEDEHEART registry to investigate whether it is safe for low-risk patients to be discharged from the hospital within two days after a PCI procedure (a treatment to open blocked coronary arteries) following a STEMI-type heart attack. The study showed that the PAMI-II risk score effectively identified patients with very low risk of complications, making early discharge a safe option for them.

Study III: This study, which also used data from SWEDEHEART, compared two methods of pressure wave analysis (iFR and FFR) to determine whether it was safe to forgo placing a stent in coronary arteries that did not show significant narrowing. The results indicated that both iFR and FFR were equally safe in the long term, allowing patients to avoid unnecessary treatment. However, real-world data revealed a higher rate of complications than previously reported in controlled clinical trials, underscoring the need for continuous evaluation of treatment outcomes in practice.

Study IV: This study investigated whether the biomarker CA125 could help predict future risks for heart attack patients. The research found that elevated CA125 levels in the blood at the time of illness were associated with heart problems such as impaired function, heart remodeling, and an increased risk of heart failure and death during the follow-up period. This suggests that measuring CA125 could be useful in identifying patients at high risk of complications after a heart attack.

In conclusion, these four studies, through the use of data from the quality registry SWEDEHEART, along with biomarker analyses, ultrasound data, and innovative clinical trials, have contributed new approaches to improving the care of patients with coronary artery disease. By offering new insights into how we can refine our treatment strategies, the results of the studies in this thesis may contribute to better care for coronary artery disease patients, both in Sweden and globally.

Populärvetenskaplig sammanfattning

Under de senaste decennierna har det skett stora genombrott inom behandlingen av hjärtinfarkt och kranskärlssjukdom, vilket har lett till bättre överlevnad och färre komplikationer. Dessa upptäckter har format globala behandlingsriktlinjer, men tillämpningen av dem varierar mellan länder och även inom regioner. Trots stora framsteg har minskningen av dödligheten på senare tid börjat plana ut, särskilt i Sverige, vilket visar att vi behöver nya sätt att diagnostisera och behandla patienter med kranskärlssjukdom.

Denna avhandling syftar till att förbättra omhändertagandet av patienter med kranskärlssjukdom genom att tillvägabringa ny kunskap på området. Avhandlingen baserar sig på fyra individuella studier som påbörjades, genomfördes och rapporterades under perioden 2014-2024. Här följer en sammanfattning av de studier som ligger till grund för avhandlingen:

Studie I: Denna studie undersökte om långtidsbehandling med betablockerare fortfarande är fördelaktig för hjärtinfarktpatienter med god hjärtfunktion. Studien, som inkluderade 5 020 patienter från Sverige, Estland och Nya Zeeland, visade att betablockerare inte minskade risken för död eller återkommande hjärtinfarkt jämfört med patienter som inte tog dem. Detta tyder på att inte alla hjärtinfarktpatienter, särskilt de med mildare hjärtskador, behöver långtidsbehandling med betablockerare.

Studie II: Denna studie använde data från SWEDEHEART-registret för att undersöka om det är säkert för lågriskpatienter att lämna sjukhuset inom två dagar efter en PCI-behandling (en behandling för att öppna blockerade kranskärl) vid hjärtinfarkt av typen ”STEMI”. Studien visade att riskskalan PAMI-II effektivt kunde identifiera patienter med mycket låg risk för komplikationer, vilket gör tidig utskrivning till ett säkert alternativ för dem.

Studie III: Denna studie, som också använde data från SWEDEHEART, jämförde två metoder av pulsvågsanalys (iFR och FFR) för att avgöra om det var säkert att avstå från att placerat en s k ”stent” (ett nät som håller kärlet öppet) i kranskärlen hos patienter som inte hade tydlig förträngning av kärlet. Resultaten visade att båda metoderna iFR och FFR var lika säkra på lång sikt varför patienter kan undvika onödig behandling. Data visar dock att det finns en högre komplikationsgrad än vad som tidigare rapporterats i kontrollerade kliniska studier, vilket understryker behovet av kontinuerlig utvärdering av behandlingsresultat i praktiken.

Studie IV: Denna studie undersökte om biomarkören CA125 kan hjälpa till att förutsäga framtida risker för hjärtinfarktpatienter. Forskningen fann att förhöjda CA125-nivåer i blodet vid sjukdomstillfället var kopplade till hjärtproblem som försämrad funktion, hjärtombyggnad och ökad risk för hjärtsvikt och död under uppföljningstiden. Detta tyder på att mätningen av CA125 kan vara användbart för

att identifiera patienter med hög risk att drabbas av komplikationer efter en hjärtinfarkt.

Sammanfattningsvis har dessa 4 studier genom användandet av data från kvalitetsregistret SWEDEHEART, tillsammans med biomarköranalyser, ultraljudsdata och innovativa kliniska prövningar, bidragit med nya sätt att förbättra vården för patienter med kranskärlssjukdom. Genom att ge nya insikter om hur vi kan finjustera våra behandlingsstrategier, kan resultaten av studierna i denna avhandling förhoppningsvis bidra till att förbättra omhändertagandet av patienter med kranskärlssjukdom, både i Sverige och globalt.

Abbreviations and acronyms used in the present thesis and Papers I-IV

ACS:	Acute Coronary Syndrome
ARB:	Angiotensin II Receptor Blocker
ASA:	Acetylsalicylic Acid
AU:	Arbitrary Units
CA125:	Carbohydrate Antigen 125
CABG:	Coronary Artery Bypass Grafting
CCS:	Canadian Cardiovascular Society class
CI:	Confidence Interval
CONSORT:	Consolidated Standards of Reporting Trials
ECG:	Electrocardiogram
EF:	Ejection Fraction
eGFR:	Estimated Glomerular Filtration Rate
FFR:	Fractional Flow Reserve
HF:	Heart Failure
HR:	Hazard Ratio
hsTnT:	High-Sensitivity Troponin T
iFR:	Instantaneous Wave-Free Ratio
LVEF:	Left Ventricular Ejection Fraction
MACE:	Major Adverse Cardiac Events
MI:	Myocardial Infarction
NSTEMI:	Non-ST-Elevation Myocardial Infarction
NYHA:	New York Heart Association class
n/a:	Not Applicable
ns:	Not Significant
P2Y12:	Platelet P2Y12 Receptor Antagonist
PAMI-II:	The Second Primary Angioplasty in Myocardial Infarction Risk Score
PCI:	Percutaneous Coronary Intervention
RCT:	Randomized Clinical Trial
REDUCE-AMI:	Randomized Evaluation of Decreased Usage of Beta-Blockers After Acute Myocardial Infarction
RRCT:	Registry-Based Randomized Clinical Trial

SCAAR:	Swedish Coronary Angiography and Angioplasty Registry
STEMI:	ST-Elevation Myocardial Infarction
STROBE:	Strengthening the Reporting of Observational Studies in Epidemiology
SWEDEHEART:	Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended therapies

Introduction

Management of Coronary Care in the modern era of Cardiology – a brief summary

The management of patients with coronary artery disease, particularly myocardial infarction (MI), has undergone significant evolution since the "birth of modern cardiology" in 1902 with Einthoven's description of the string galvanometer[1], the invention of the electrocardiogram (ECG), which enabled the first modern clinicopathological definitions of MI. In the early days of therapy, caffeine and camphor were used as supportive measures to alleviate hypotension, syncope, and heart block,[2] while morphine was administered to relieve pain and anxiety.[3]

By the mid-20th century, advancements in cardiovascular physiology and pharmacology paved the way for more effective interventions. In the 1950s, Sir James Black made a major breakthrough in the management of coronary artery disease by applying Alquist's theory of "sympathins" to drug development.[4] By targeting and blocking these compounds, he discovered that myocardial oxygen demand could be reduced in patients with obstructive coronary artery disease, the same time period which saw the development of the first coronary care units (see section below). Sir James Black's creation of propranolol, the first beta-blocker, marked a significant advancement in the treatment of angina pectoris.[5] Propranolol is regarded as one of the most pivotal innovations in medical history,[6] and for this achievement, Sir James Black was awarded the Nobel Prize in Medicine.

The 1970s onward marked the beginning of an era in cardiology that has systematically and critically tested the management of coronary care patients through large randomized clinical trials (RCTs).[1] Beta-blockers were among the first class of drugs for MI patients to be rigorously tested[7], parallel to the introduction of percutaneous coronary intervention (see section below), fibronolytic therapy and the use of low molecular weight heparins. Following this, secondary preventive measures such as angiotensin-converting enzyme (ACE) inhibitors were introduced, advancements included the development of antiplatelet therapies, and by the early 2000s, statins had emerged as critical agents in secondary prevention.[8]

Over the past decades, numerous successful clinical trials have demonstrated improved survival rates and reduced morbidity with the introduction of new

treatments for patients with myocardial infarction and coronary artery disease. These findings have resulted in the creation of consistent global treatment guidelines. While substantial improvements have been made, there has been a tendency towards a plateau in the reduction of mortality rates[9,10], highlighting the need for further advancements in the management of coronary care.

Betablockers in myocardial infarction in the reperfusion era

Beta-blockers have long been established as beneficial for patients with heart failure and reduced ejection fraction (EF), as supported by solid evidence and randomized clinical trials have demonstrated that long-term beta-blocker use improves outcomes, reducing mortality by approximately 20% in post-myocardial infarction (MI) patients.[11-13] However, these trials primarily involved patients with large infarctions and frequent left ventricular (LV) systolic dysfunction. Furthermore, most were conducted in the 1980s, preceding the widespread adoption of contemporary treatments such as high-sensitive troponins, percutaneous coronary intervention, antithrombotic agents, high-intensity statins, and renin-angiotensin-aldosterone system inhibitors. In a meta-analysis comparing pre-reperfusion and reperfusion eras, beta-blockers did not show a mortality benefit in the reperfusion era.[14]

There is a lack of investigation into the long-term effects of beta-blockers in recent, adequately powered RCTs involving patients with acute MI and preserved LV systolic function. Large-scale observational studies and meta-analyses have produced mixed findings. Some studies suggest lower mortality rates in patients receiving beta-blockers,[15], whereas other authors did not find significant associations between beta-blockers and reduced mortality in 179,810 acute MI survivors without heart failure or LV dysfunction.[16] It has been argued that there are several studies in HF pointing to a clear interaction between betablockers and LVEF[17] and indeed Joo et al. found that while beta-blockers did not reduce major cardiovascular events in patients with an EF ≥50%, they did show benefits in those with mildly reduced EF (40–49%).[18] Meta-analyses of observational studies also present conflicting results, with some suggesting beta-blockers improve survival in MI patients with preserved EF[19] while others found no mortality reduction in those with EF >40%.[20 21] A recent Cochrane review emphasized the need for new trials to assess the risks and benefits of beta-blockers in contemporary MI patients without heart failure.[22]

This uncertainty is reflected in varying guideline recommendations.[23] For patients with STEMI, the European Society of Cardiology (ESC) recommends considering beta-blockers during hospitalization and thereafter (Class IIa).[24] Meanwhile, the

American College of Cardiology (ACC) and the American Heart Association (AHA) provide a Class IA recommendation. O'Gara AHA 2013. For acute coronary syndrome without persistent ST-segment elevation, the ESC limits beta-blockers to patients with reduced LV function (EF ≤ 40%, Class IA),[25] while the AHA/ACC suggests continuing beta-blockers in patients with normal systolic function (Class IIa) despite the lack of conclusive evidence.[26]

Evaluation of generic pharmacotherapies in the contemporary era

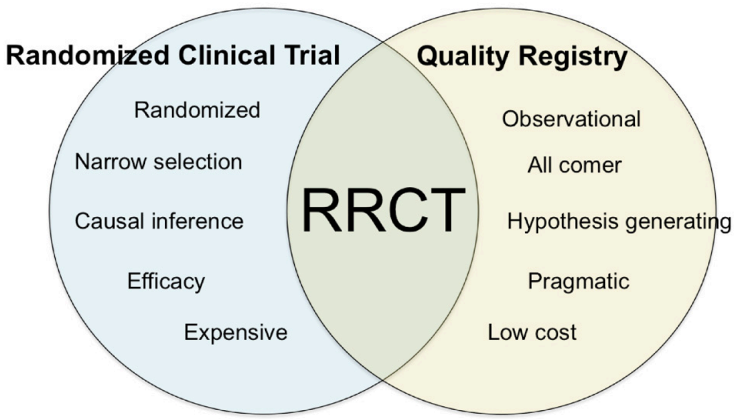

FIGURE1. Overview of RRCT. MODIFIED FROM *YNDIGEGN et al.*[27]

Since the advent of large-scale trials in cardiology in the late 70'ies – several of which have changed the landscape of care of patients with myocardial infarction[28] - randomized clinical trials (RCTs) have become the gold standard for testing clinical interventions and assessing their effectiveness. A key advantage of RCTs is their ability to use randomization to reduce selection bias and account for both known and unknown confounders, thereby providing robust evidence of treatment effects. The design and execution of RCTs face several significant challenges. One of the main issues is the increasing cost associated with bringing new medications to the market through clinical trials.[29] These costs can be influenced by factors such as disease characteristics, the frequency of events the treatment aims to prevent, and the infrastructure required—especially for multicenter trials, which tend to be more expensive. Therefore evaluations of generic drugs in contemporary patient populations are unlikely. Furthermore, legislative and administrative hurdles can further complicate the execution of RCTs.[30] Therefore

alternative RCT designs that incorporate data from quality registries have been proposed.[31-34], however only the RRCT has gained widespread acceptance as a reliable tool for the conduction of low-cost trials with a high degree of accuracy and minimal loss to follow-up.

The quality registry involves the collection of disease-specific patient data focused on medical treatments and outcomes. This data is utilized to assess and compare the quality of care delivered by participating healthcare units and to evaluate the adoption of guideline-recommended therapies.[27] Typically, these registries are established by healthcare professionals as seen in countries like Sweden and the UK. One example is SWEDEHEART, which is one of over 100 national clinical quality registries in Sweden. Funded publicly, it gathers comprehensive data on critical clinical variables throughout the entire care process for patients with myocardial infarction. (For further details, see materials and methods section below)

Dubbed "The next disruptive technology in clinical research"[35] the registry-based randomized clinical trial (RRCT) has been acknowledged as a trial design of with important impact in the possibility to conduct well-powered, timely trials. The RRCT which utilizes registry data to streamline participant recruitment, lower study costs, and maintain high scientific standards.[36] It merges the unique features of the randomized clinical trial of causal inference and leveraging this with the low-cost, pragmatic all-comer nature of the quality registry,[27] (see Figure 1). To further strengthen the quality of these trials, the CONSORT guidelines for reporting of randomized controlled trials conducted using routinely collected data in registries was recently published.[37]

A fundamental requirement for conducting an RRCT is the availability of a comprehensive quality registry that covers the population of interest. While Nordic countries have a strong tradition of maintaining such registries, many other regions do not have this infrastructure. The accuracy of RRCT data is inherently tied to the quality of the registry data. In Sweden national registry data have a high degree of accuracy across diseases and enpoints,[38,39] however a Norwegian registry review revealed early deaths were underreported by up to 28%.[40] Concerns about data quality remain a key barrier to adopting the RRCT framework. This underscores the importance of regular audits and transparent reporting to ensure completeness and validity in RRCT data. Several trials based on the RRCT platform in SWEDHEART have now been published in high impact journals proving the efficacy of the RRCT concept.[41-43]

Valid concerns should be mentioned such as the potential lack of structured follow-up, which may lead to safety risks and treatment crossover that can dilute the treatment effect.[44] Decisions to use RRCTs should therefore carefully balance cost against trial design, with some relying on hospital-based testing rather than contracted core facilities. For example, in traditional RCTs, adherence is closely

monitored through regular visits, phone calls, and pill counts. In contrast, RRCTs encourage adherence through routine care without extra visits. The SPIRRIT RRCT trial has addressed this by using prescription data to track whether patients continuously renewed and collected prescriptions, reflecting drug adherence.[45]

A significant challenge in RRCTs is capturing clinical endpoints. If registry data do not capture certain endpoints well, this could result in a type II error—missing a true effect due to an artificially low event rate. Careful consideration of sample size, follow-up duration, and event reporting is essential to mitigate this risk. Event-driven trials such as the REDUCE-AMI may offer a solution to underreporting issues.[27]

Duration of hospital stay for patients with myocardial infarction

Coined "the single most important advance" in the management of patients with acute MI[2], the coronary care unit as proposed by JULIAN in 1961[46] offered the possibility to continuously monitor patients with ECG for malignant arrhythmias and prompt delivery of the novel external cardioversion therapy could be performed[47,48] by dedicated nurses significantly reducing mortality following MI.[8] Following the seminal instructions in a 1912 paper by Herrick[49] bedrest was strictly recommended for several days and remained the mainstay through several decades.[3] Indeed when suffering a MI in 1954, president Dwight D. Eisenhower stayed in the hospital for several weeks as care focused on bedrest with limited modern interventions.[8] In contemporary care, extended hospital stay for patients with STEMI has been shown to correlate with increased healthcare costs and heightened risks of morbidity and mortality[50,51] Advancements in mechanical reperfusion techniques and the implementation of evidence-based treatment strategies have contributed to a reduction in early mortality rates and a decrease in the duration of hospital stay[52-54], however the optimal length of stay following MI is still uncertain. Several small randomized clinical trials[55], [56] [57] alongside observational studies[58,59], have aimed to determine the optimal duration of hospital stay for patients with ST-elevation myocardial infarction (STEMI). One useful clinical tool is the Second Primary Angioplasty in Myocardial Infarction (PAMI-II) risk score, which evaluates candidates for early discharge. This tool is based on a clinical trial involving 471 low-risk STEMI patients (age under 70, left ventricular ejection fraction above 45%, one- or two-vessel disease, and successful PCI without persistent arrhythmias). The trial demonstrated that early discharge could be a safe alternative to the traditional extended hospital stay.[50] Based on these findings, the European Society of Cardiology gives early discharge within 72 hours a Class IIa recommendation.[24] However, the PAMI-II score, which was

introduced in the late 1990s, has only been validated in smaller observational studies[58,59].

Deferral of invasive treatment in coronary care

The advent of percutaneous coronary intervention was done by Andreas Gruentzig on 16th September 1977 with the guidance of cine films and the use of distal pressure measurements.[60] While the immediate reperfusion by of myocardium in STEMI by PCI was a superior therapy, treating patients with PCI with moderate coronary lesions has been of topic of scrutiny. Lesions, with a visually estimated stenosis between 40-70%, can be difficult to evaluate accurately using angiography alone. Misjudging such lesions can lead to unnecessary stenting of hemodynamically insignificant stenoses, which increases the risk of complications such as stent thrombosis, restenosis, or unnecessary exposure to dual antiplatelet therapy.[61] The use of physiological assessments like fractional flow reserve (FFR) or instantaneous wave-free ratio (iFR) allows for more precise decision-making by determining whether a lesion is truly ischemia-inducing. Studies have shown that revascularization guided by intracoronary physiology significantly improves outcomes compared to angiography-guided interventions.[62] Still, it has remained a topic with controversy whether to intervene in coronary artery stenoses that appears moderate on angiography but does not show significant functional impairment as there has been raised concerns about whether deferring treatment of such a lesion is truly safe.[63,64]. The DEFER trial, with extended follow-up data[65,66] demonstrated that deferring PCI in lesions deemed hemodynamically insignificant by fractional flow reserve (FFR) is a safe strategy. Additionally, two large-scale randomized trials found that both instantaneous wave-free ratio (iFR) and FFR are equally effective in guiding revascularization decisions in cases where PCI was deferred.[67,68] Therefore it has become a standard to guide percutaneous coronary intervention by intracoronary physiology when managing patients with chronic coronary syndrome and is incorporated into the latest coronary revascularization guidelines.[69] The cumulative risk of major adverse cardiac events within one year was reported to be approximately 4% in the aforementioned trials on deferral using iFR and FFR. Randomized trials often focus on a narrow, highly selective patient population. In a study of 220 clinical trials published in 2017, only 15% could be replicated using real-world data[70] which limits the generalizability of trial outcomes to broader clinical practice[71] Thus, real-world data are essential to complement clinical trials when implementing new treatments.

CA125 and residual risk following myocardial infarction

Killip and Kimball laid the groundwork for understanding the prognostic significance of heart failure symptoms in the context of myocardial infarction with their publication of their pivotal paper in 1967 on the classification of MI patients according to the presence of heart failure symptoms and signs.[72] In this paper they stratified patients with acute MI into four classes (hence the term "Killip Class") based on the presence of heart failure and physical findings, such as rales (indicative of pulmonary congestion) and jugular venous distension. This classification system highlighted that patients with signs of heart failure (like rales) were at much higher risk of mortality following MI. While advances in myocardial infarction treatment have led to reductions in recurrent MI events and cardiovascular death [73] the incidence of HF within the first year following a STEMI has only marginally improved.[10] Identifying new disease pathways and biomarkers that can detect ACS patients at higher risk of HF and mortality is crucial for advancing management and improving post-ACS outcomes.

In the past decade, carbohydrate antigen 125 (CA125) has gained recognition as a promising biomarker for both disease severity and prognosis in HF patients.[74-76] CA125 is a membrane-associated mucin encoded by the MUC16 gene.[77] Elevated levels of CA125 have been observed in HF patients, suggesting a relationship between this biomarker, fluid overload, and increased systemic inflammation in these individuals.[75] In severe HF cases, CA125 levels have been shown to correlate with the New York Heart Association (NYHA) classification and pulmonary capillary wedge pressure.[78] Furthermore, CA125 has been associated with echocardiographic measures of both systolic and diastolic dysfunction, and with re-hospitalization rates and mortality in patients with midrange reduced left ventricular systolic function.[79,80] Also, the CHANCE-HF trial demonstrated that CA125-guided therapy could enhance outcomes in HF patients beyond standard care.[81]

Although the role of CA125 in HF is becoming more established, its utility in ACS remains less explored. Studies have indicated that elevated CA125 levels are linked to reduced left ventricular ejection fraction (LVEF), the presence of pulmonary edema during acute ischemic events,[82-84] and a higher risk of HF re-hospitalization within three months post-ACS. [83,84]. Most recently an analysis of 175 biomarkers in 1,099 MI patients identified CA125, along with tumor necrosis factor-related apoptosis-inducing ligand receptor 2 and fibroblast growth factor 23, as strong predictors of mortality.[85] Altogether these findings suggest that further research is needed to assess the potential of CA125 as a prognostic biomarker to advance management of coronary care.

Aims

The overall aim of this thesis, *Advancing Management in Coronary Care*, is to improve the care and outcomes of patients with coronary artery disease. Through the use of large-scale real-world data from quality registries in SWEDEHEART, biomarker analyses and novel trial designs, the present thesis seeks to further improve the outcome for patients following MI. By this, the thesis seeks to further advance management of coronary care.

Paper I.

The aim of this study is to evaluate the long-term efficacy of beta-blocker therapy in patients with acute MI who have a preserved left ventricular ejection fraction (LVEF ≥50%). Conducted across multiple centers in Sweden, Estonia, and New Zealand, the trial investigates whether beta-blocker treatment, compared to no beta-blocker therapy, reduces the risk of the composite primary endpoint of all-cause mortality or recurrent MI. The study focuses on determining whether beta-blockers continue to offer benefit in patients without large infarctions or reduced ejection fraction, reflecting contemporary MI management in the reperfusion era.

Paper II.

The aim of this study is to evaluate the safety of early discharge (≤2 days) in low-risk patients with STEMI who have been treated with PCI. Using data from the SWEDEHEART registry, the study assesses whether early discharge is associated with an increased risk of major adverse cardiovascular events, including death, reinfarction, stroke, or heart failure hospitalization, within one year.

Paper III.

The aim of this study is to assess the long-term safety of deferring coronary revascularization using either instantaneous wave-free ratio (iFR) or fractional flow reserve (FFR) as guidance. By analyzing a large real-world population from

the SWEDEHEART registry, the study compares long-term outcomes, specifically the incidence of major adverse cardiac events, including all-cause death, nonfatal myocardial infarction, and unplanned revascularization, between patients whose revascularization was deferred based on iFR (>0.89) versus FFR (>0.80).

Paper IV.

The aim of this study is to evaluate the prognostic value of carbohydrate antigen 125 in patients with acute coronary syndrome investigating its association with long-term risks of heart failure hospitalization and mortality. The study seeks to determine whether elevated CA125 levels at the time of an acute coronary event are predictive of adverse outcomes, including cardiac remodeling and loss of function as determined by echocardiography as well as subsequent hospitalization for HF and the risk of death.

Material and Methods

The SWEDEHEART registry

SWEDEHEART was formed in 2009 through the merger of four Swedish health registries: the national registry of acute cardiac care (RIKS-HIA), the Swedish coronary angiography and angioplasty registry (SCAAR), the Swedish heart surgery registry, and the national registry of secondary prevention (SEPHIA). The earliest cardiovascular care registries in Sweden were RIKS-HIA, established in 1990, and the Swedish heart surgery registry, started in 1992. RIKS-HIA became a national quality registry in 1995, with SEPHIA added in 2005 to track secondary prevention in patients with acute myocardial infarction. SCAAR was created in 1998 by merging national angioplasty and coronary angiography registries, both of which originated in the early 1990s. Since 2009, three more registries have joined SWEDEHEART: SWENTRY (the Swedish transcatheter cardiac intervention registry) in 2008, SwedeHF (the Swedish Heart Failure Registry) in 2001, and the Swedish National Cardiogenetic Registry, which is still developing but has begun registering adults with familial hypercholesterolemia in recent years (Suppl. appendix, Yndigegn et al.). [86]

SWEDEHEART collects data from patients hospitalized for suspected ACS and those undergoing coronary procedures or heart surgery. The registry records about 80,000 cases annually, including 20,000 MI, 10,000 unstable angina, and 40,000 coronary procedures. It follows 6,000 MI patients under 75 for 12-14 months for secondary prevention. Data is entered online by caregivers and securely transferred to a central server. SWEDEHEART tracks over 106 variables, including patient demographics, risk factors, treatments, and outcomes. Follow-up data on smoking, blood pressure, and quality of life is collected for MI patients. For coronary procedures, 150 variables are recorded, detailing angiographic findings, stents, and complications. The registry is linked with other national databases, such as the National Cause of Death Register and the National Drug Prescription Registry, allowing for comprehensive patient tracking. The National Board of Health and Welfare conduct data merges with ethical approval, and patient identities are removed during these processes. Uppsala Clinical Research Centre provides support and monitors data accuracy. See Table 1 for data correctness at the latest internal monitoring (before Covid-19). Regular audits

ensure high data quality and SWEDEHEART captures virtually 100% of patients undergoing coronary procedures in Sweden.[38]

SWEDEHEART registry	No. of patients	No. of variables	No. of hospitals	Overall data correctness
RIKS-HIA	30	63	72	97.1%
SCAAR	30	104	30	98.2%
SEPHIA	20	29	74	94.8%

TABLE 1. SWEDEHEART Data accuracy during 2017-2018. Table expressing number of paitents, variables and hospitals monitored for each sub-registry within the SWEDEHEART framework. Table modified from Supplentary appendix Yndigegn et al. [86]

Study population, treatments and procedures

Paper I

The REDUCE-AMI trial was designed as a prospective, open-label, randomized parallel trial and conducted across Sweden (38 centers, utilizing the SWEDEHEART registry), Estonia (1 center), and New Zealand (6 centers, using the ANZAQS-QI registry). Adult patients who provided written informed consent between 1 to 7 days after experiencing a myocardial infarction, and who had undergone both coronary angiography and echocardiography showing a preserved left ventricular ejection fraction (defined as LVEF ≥50%), were eligible to participate. Additionally, patients needed to have obstructive coronary artery disease, evidenced by coronary angiography (defined as ≥50% stenosis, fractional flow reserve ≤0.80, or an instantaneous wave-free ratio ≤0.89 in any coronary segment) at any time before randomization. Exclusion criteria included any clear indication for or contraindication to beta-blocker therapy. For further details on inclusion and exclusion criteria for the REDUCE-AMI trial, please see Table 2. To ensure proper follow-up, only residents of the three participating countries were eligible for randomization. In Sweden, randomization was carried out through an online web-based system linked to the electronic data capture system, where treatment prescriptions, initial doses, and target doses was recorded. In New Zealand and Estonia, randomization was performed using a separate web application. Randomization was stratified by center with permuted block randomization. In Sweden, the trial was approved by the Ethical Review Board in Stockholm and the Swedish Medical Products Agency (MPA), and data linkages subsequently approved by the National Board of Health and Welfare. In New

Zealand, the study received approval from the National Health and Disability Ethics Committee as well as from the respective hospital research review committees. In Estonia, the Research Ethics Committee of the National Institute for Health Development granted approval. [23]

INCLUSION CRITERIA

1. Age ≥ 18 years.
2. Day 1–7 after MI as defined by the universal definition of MI, type 1.
3. Coronary angiography performed during hospitalization.
4. Obstructive coronary artery disease documented by coronary angiography, i.e. stenosis ≥ 50%, FFR ≤ 0.80, or iFR ≤ 0.89 in any segment at any time point before randomization.
5. Echocardiography performed after the MI showing a normal ejection fraction defined as EF ≥ 50%.
6. Written informed consent obtained.

EXCLUSION CRITERIA

1. Any condition that may influence the patient's ability to comply with study protocol.
2. Contraindications for beta-blockade.
3. Indication for beta-blockade other than as secondary prevention according to the treating physician.

TABLE 2. Inclusion and exclusion criteria. Modified from Yndigegn et al. [23]

Patients who were randomly allocated to the beta-blocker group were treated with either metoprolol (preferred option) or bisoprolol (alternative option) during their hospital stay. Upon discharge, they were prescribed to continue using the same medication. Physicians were advised to target a daily dosage of at least 100 mg for metoprolol or 5 mg for bisoprolol. Patients were encouraged to remain on beta-blockers after discharge unless a contraindication developed. For patients in the no–beta-blocker group, the use of beta-blockers was discouraged unless there was another clear indication beyond secondary prevention following a myocardial infarction. For blood pressure management, medications other than beta-blockers were recommended according to the relevant guidelines. If a patient was already taking beta-blockers before enrollment and was assigned to the no–beta-blocker group, a gradual reduction of the beta-blocker over 2 to 4 weeks was necessary. The significance of maintaining the assigned treatment (whether beta-blockers or no beta-blockers) was documented in each patient's medical records. Additionally, patients were given written information emphasizing the importance of adhering to their assigned treatment unless new contraindications or indications for beta-

blocker use arose. They were also provided with a summary of this information in a card-sized format to carry with them for use in medical consultations.[23]

Paper II and Paper III

Both studies were conducted as non-randomized comparisons on all-comer level in prospective included patients from the SWEDHEART registry. Statistical methods to count for possible confounders are described below. **Paper II** and **paper III** utilized data from the SWEDEHEART registry to form two separate observational cohorts for hypothesis testing. The selection of patients to form the cohorts was determined by the subject of interest. In **Paper II** the aim was to evaluate the safety of early discharge following STEMI according to the PAMI-II Criteria. An overview of the selection can be seen in Figure 2: All patients diagnosed with STEMI from January 2009 to April 2017 were included. Only the initial admissions during this timeframe were considered, while patients who presented with cardiogenic shock or those who had experienced a resuscitated cardiac arrest were excluded; only patients treated with PCI and who underwent transthoracic echocardiography were included in the analysis. A total of 8,092 patients were identified as low-risk based on the PAMI-II risk score, which formed the final study cohort. Seven patients had incomplete data, preventing the calculation of their PAMI-II risk score, and were therefore excluded. The low-risk patients were then divided into two groups based on the duration of their hospital stay: those discharged within ≤2 days (early discharge group, left-censored at 0 days) and those discharged after ≥2 days (late discharge group, right-censored at a given time).

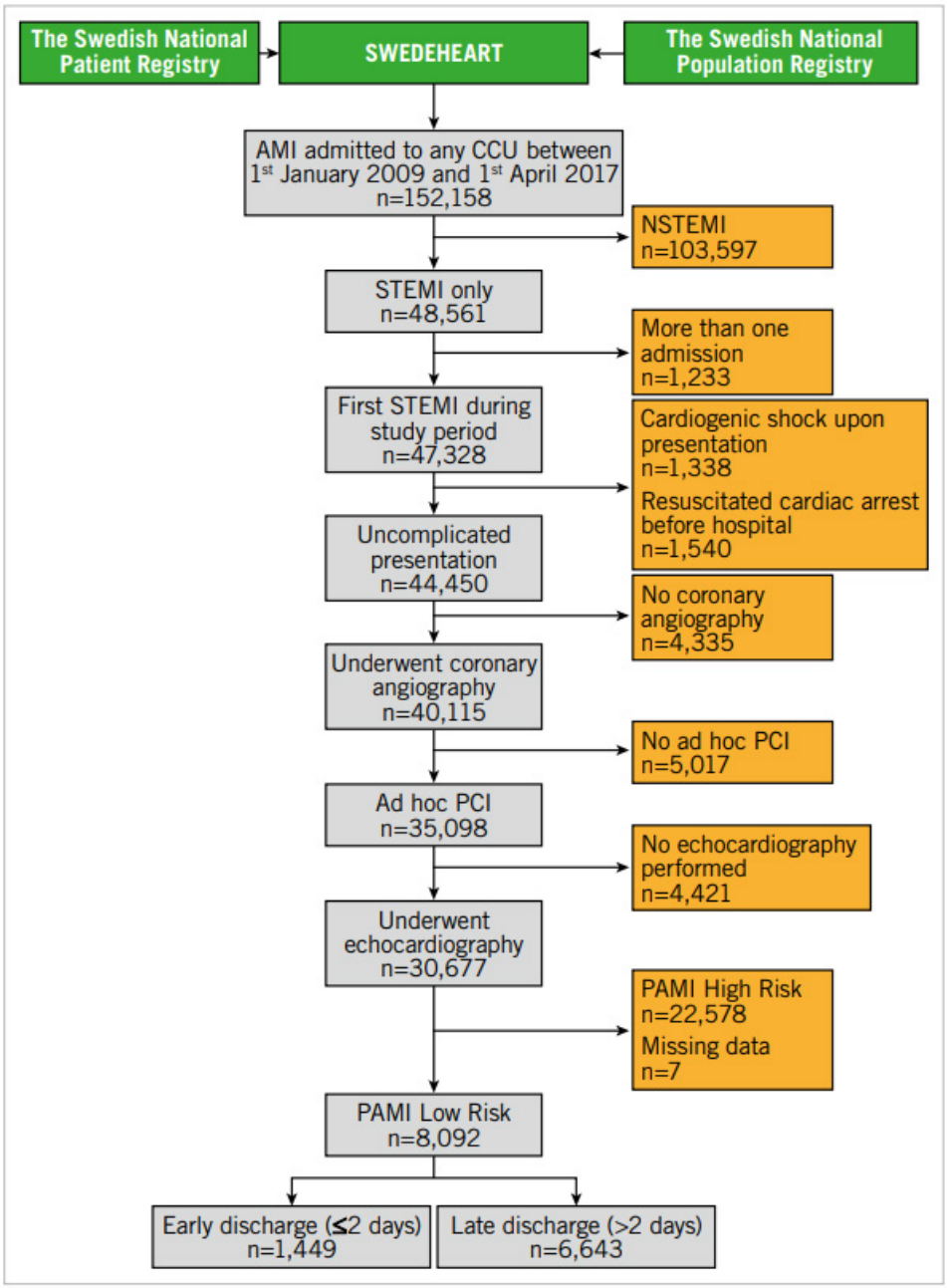

FIGURE 2. SHOWING Selection of patients in the study (Modified from Yndigegn et al.(Yndigegn, 2023 #69)

In **Paper III** the aim was to evaluate the outcome of deferral of intervention of intermediate coronary lesions using iFR or FFR. As the physiology module in SCAAR was not introduced until June 2013, patients could not be included before this time point. However from this time point all consecutive cases were included until the end of data-period. 2013 to 2017, the SWEDEHEART registry (SCAAR) documented 201,933 coronary angiography procedures. Of these, 11,324 patients met the study's inclusion criteria, with 1,998 patients assigned to the iFR group and 9,326 to the FFR group. Patients were eligible for inclusion in the study if they underwent coronary angiography, during which a decision was made to perform physiological assessment (index procedure), regardless of the initial indication. Patients who did not undergo intracoronary physiology or had both iFR and FFR measurements were excluded. The final analysis included all patients in the SWEDEHEART registry who had at least one deferred coronary lesion during the index procedure, defined as a lesion considered appropriate for physiological assessment with an iFR value greater than 0.89 or an FFR value greater than 0.80, without subsequent ad hoc or planned revascularization. An overview of the inclusion can be seen below (Figure 3).

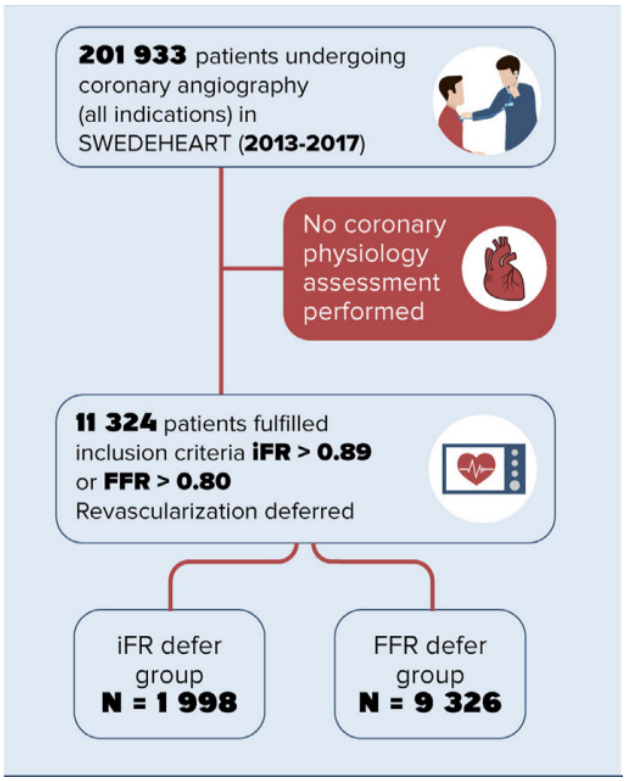

FIGURE 3: Overview of inclusion of patients for the iFR/FFR cohort in Paper III (Modified from Yndigegn et al.(Yndigegn, 2023 #69)

The study described in **Paper IV** was designed as a prospective single-center study. The initial study population consisted of 605 consecutive patients admitted to the Coronary Care Unit at Skåne University Hospital Malmö for suspected ACS between October 2008 and December 2012. Patients were recruited on weekdays during regular hours by a research nurse and were required to provide written informed consent. The definition of ACS included unstable angina (UA) or MI, diagnosed based on the universal definition of MI. UA was characterized by recent onset angina symptoms with normal elevated troponin. Fifty patients were excluded for not meeting ACS diagnostic criteria, and 31 were excluded due to missing samples, leaving a final cohort of 524 patients: 180 with STEMI (34.4%), 294 with NSTEMI (56.1%), and 50 with UA (9.5%). All patients were part of the correlation analysis of plasma CA125 levels at the time of the acute event and the long-term risk of heart failure hospitalization and mortality. A subgroup of 107 patients, who had baseline CA125 measurements and echocardiography data available one year post-ACS, was further evaluated to determine whether baseline CA125 was associated with cardiac remodeling and functional decline based on echocardiography. Additionally, in another subgroup of 115 patients with plasma samples available six weeks post-ACS, the study explored whether elevated CA125 levels during follow-up were linked to an increased risk of HF and death.

Paper IV

Plasma sampling and CA125 measurements

Plasma samples were collected from all study participants within 24 hours of admission. Portions of the plasma were used for CA125 analysis, while the remaining samples were sent to the certified clinical laboratory at Skåne University Hospital in Malmö for high-sensitivity troponin T (hsTnT) measurements, which served as a surrogate marker for infarct size. Additionally, cystatin C (CystC) was analyzed to assess kidney function. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula, incorporating CystC, age, and gender. A second plasma sample was collected six weeks later from 115 elderly patients (aged 75 and above). CA125 was analyzed using the Proximity Extension Assay (PEA) technique at the Science for Life Laboratory in Uppsala, Sweden. This method involved oligonucleotide-labeled antibody probes binding to their specific targets in the plasma samples. Upon the addition of DNA polymerase, the oligonucleotides were extended and joined to form a PCR template. The resulting DNA sequences were then pre-amplified using universal primers and quantified via real-time quantitative PCR using a microfluidic chip. Data were normalized using a preprocessing procedure with Olink Wizard for GenEx software, and therefore the results are presented in arbitrary units (AU).

Echocardiography

Baseline echocardiograms were routinely conducted during the initial hospital stay for all participants. One of the study's objectives, as outlined in the study protocol, was to identify factors that predict long-term cardiac function in elderly survivors of acute coronary syndrome. Patients aged 75 and older were invited to undergo a follow-up echocardiogram one year after their inclusion in the study. A total of 111 patients with baseline CA125 measurements completed the follow-up. All echocardiograms were performed by trained sonographers and analyzed offline using Xcelera software (Philips) by a single examiner (the first author) who was blinded to the clinical data. Four echocardiograms had missing data, leaving 107 available for analysis. Reliable left ventricular ejection fraction measurements were possible for 97 patients; the remaining 10 were excluded. LVEF was determined using the Simpson's biplane method in both apical four-chamber and two-chamber views, based on left ventricular end-systolic volume (LVESV) and left ventricular end-diastolic volume (LVEDV). Changes in LVEF (delta LVEF) were calculated by subtracting the baseline LVEF from the LVEF measured at one year. Chamber quantification, diastolic function assessments, and filling pressure measurements were performed in line with international guidelines and local procedures. The criteria used to identify left ventricular diastolic dysfunction included a mitral valve deceleration time (MVDT) of less than 0.130 seconds, a mitral valve E/A ratio of less than 0.7 or greater than 1.5, and an E/e′ ratio above 15.

Endpoints and events

Paper I

The REDUCE-AMI had a composite primary endpoint of death from any cause or new (non-fatal) myocardial infarction. Secondary end points were the individual components of the primary endpoint, death from cardiovascular causes, hospitalization for atrial fibrillation or heart failure (primary diagnosis). Safety end points were related to concerns for bradycardia, hypotension, syncope, asthma or COPD and stroke. Patient reported symptoms of Angina pectoris (according to Canadian Cardiovascular Society class) and dyspnea (according to New York Heart As sociation class) after 6 to 10 weeks and after 11 to 13 months were also end points. The complete list can be seen in Table 3.

Primary Composite Outcome
1. All-cause death or new MI
Secondary Outcomes
1. All-cause death 2. Cardiovascular Death (ICD 10 codes: I00-I99) 3. New MI 4. Heart failure hospitalization (ICD 10 code: I50, primary diagnosis) 5. Atrial fibrillation hospitalization (ICD 10 code: I48, primary diagnosis)
For those followed in the secondary prevention part of SWEDEHEART (in Sweden):
1. Dyspnea (NYHA-class) 2. Angina (CCS-class) 3. Health related quality of life (EQ-5D) 4. Health care costs
Safety Outcome
Hospitalization due to 1. Bradycardia (ICD 10 codes: R00.1, I49.5), AV-block II-III (ICD 10 codes: I44.1-3), Hypotension (ICD 10 code: I95), Syncope (ICD 10 codes: R55.9, T67.1) or Need for pacemaker (ICD 10 codes: FPE00-26, FPF00-20, TFP00) 2. Asthma (ICD 10 codes J45-46, primary diagnosis) or COPD (ICD 10 code: J44, primary diagnosis) 3. Stroke (ICD 10 codes: I60-64)

TABLE 3. Primary, secondary and safety outcomes in the REDUCE-AMI trial. Modified from Supplementary appendix YNDIGEGN NEJM 2024.

Paper II and Paper III

For **Paper II** The primary outcome measured was the occurrence of a major adverse cardiac event within one year, defined as the first incidence of one of the following all-cause mortality; myocardial infarction treated with PCI; hospitalization due to decompensated heart failure or stroke. For **Paper III** the primary outcome was a composite of all-cause death, non-fatal myocardial infarction or unplanned revascularization at any time during the study period. Secondary outcomes were individual components of the composite primary outcome. For both **Paper II and Paper III** information on PCI-treated MI was sourced directly from the SWEDEHEART registry, identified as a subsequent hospital entry with a discharge diagnosis of MI treated with PCI. Similarly as describer for Paper I, mortality status was attained via the National Population Registry and linkages between registries were used to determine rates of stroke and HF admissions from the National Patient Registry. Secondary analyses explored the relationship between early discharge and each individual component

of the main outcome. Follow-up began on the day of admission, with outcomes tracked through 2018 ensuring full follow-up for all participants.

Paper IV

The cohort was followed prospectively, with the primary outcomes being the first occurrence of hospitalization due to heart failure or death during the follow-up period. These outcomes similarly to Paper I-III were identified using data from the Swedish National Patient Registry and the Swedish Cause of Death Register. The last follow-up for heart failure incidents was on 31 December 2012, and for mortality, it was 31 December 2013. Data on causes of death were available until 31 December 2012.

Data sources

The baseline data for **Paper I** were collected from the randomization module and the SWEDEHEART registry. For **Paper II and III** only data from the SWEDEHEART registry was used for baseline data. Data on death was collected from the Swedish population registry. Data on MI during the index hospital stay and during follow-up was collected via the SWEDEHEART registry. In **Paper I**, all MI events were validated by the principal investigator in REDUCE-AMI to ensure correctness of data according to a pre-specified checklist. Death from cardiovascular causes was collected from the cause-of-death registry and data on atrial fibrillation and HF was collected from the national patient registry according to ICD-codes that are mandatory for all Swedish hospital to complete. Symptoms were collected for those patients who attended the follow-up visits in the SWEDEHEART outpatient registry SEPHIA at 6-10 weeks of follow-up and 11-13 months of follow-up. For **Paper IV** data was obtained by the use of electronic data records at the hospital including imaging, SWEDEHEART registry data and data from the National Patient Registry and the Cause of Death registry.

Statistical analyses and considerations

Paper I: Prior to the trial, it was estimated that the annual event rate of death from any cause or new myocardial infarction would occur in 7.2% in the no–beta-blocker group. A risk reduction of 16.7% in the beta-blocker group, equating to a 1.2 percentage-point reduction in absolute risk, was considered the smallest meaningful difference to detect. However, during the trial, the actual blinded event rate was observed to be around 3% per year. Following discussions between the sponsor, steering committee, and patient representatives, it was decided that a 25%

relative risk reduction corresponding to a 0.9 percentage-point reduction in absolute risk, would remain a clinically relevant threshold. Consequently, the trial protocol was amended at the earliest possible time point. To detect a hazard ratio of 0.75 with 80% power at a 5% significance level, a total of 379 primary endpoint events were calculated to be necessary. As the trial was event-driven, it was expected to be possible to achieve by enrolling approximately 5000 patients. All patients who were randomized were included in the intention-to-treat analyses, which accounted for all events occurring from randomization until the end of follow-up. These analyses presented the endpoints, excluding symptom-related outcomes, as cumulative incidence plots and frequency tables, with Cox proportional hazards regression used for comparisons between groups. To account for competing risks, such as non-cardiovascular deaths, cause-specific hazard ratios were estimated for cardiovascular-specific endpoints and other outcomes. Post hoc analyses were conducted if any deviations from the proportional hazards assumption were suspected, including assessments using restricted mean survival time. Patients who withdrew or emigrated were censored on the day of withdrawal or emigration. For endpoints excluding all-cause mortality, patients who died before reaching an endpoint were censored at their time of death. The primary analysis did not adjust for adherence to the treatment protocol, but secondary "on-treatment" analyses were conducted for those with available data. Sensitivity analyses for competing risks and multiple testing were outlined in the statistical analysis plan.

For **Paper II**, continuous variables were presented as medians with interquartile ranges, while categorical variables were expressed as counts and percentages. Group comparisons for continuous variables were analyzed using the Mann-Whitney U test, and categorical variables were evaluated with the chi-squared test. Kaplan-Meier estimates were employed to calculate the incidence of MACE and other outcomes. The relationship between early and late discharge and the risk of MACE was assessed using Cox proportional hazards models, adjusted with propensity scores and supplemented with bootstrap resampling to provide hazard ratios (HR) and 95% confidence intervals (CI). To mitigate confounding, both a propensity score-adjusted Cox model and an inverse probability weighting approach were used to estimate average treatment effects, with variables such as age, sex, creatinine levels, diabetes, and coronary artery disease history included in the models. Missing creatinine values (3.1%) were not imputed due to the low percentage of missing data.

For **Paper III**, continuous variables were similarly presented as medians (interquartile range), and categorical variables as counts with percentages. Kaplan-Meier curves were used to illustrate failure rates, with the log-rank test applied for group comparisons. A Cox proportional hazards model, adjusted for factors including age, sex, smoking status, procedure indication, and the year of the index procedure, was used to compare outcomes between the iFR and FFR groups.

Sensitivity analyses were conducted by excluding patients who underwent PCI during the index procedure and those treated for non-coronary indications. Prespecified subgroups, including age, sex, hypertension, diabetes, and smoking status, were tested for potential interactions with FFR and iFR outcomes.

In **Paper IV** between-group comparisons for continuous variables were conducted using the Mann–Whitney U test. Dichotomous variables were compared using Pearson's χ^2 test or Fisher's exact test when appropriate. Correlations were assessed through Spearman's rank test. The incidence of heart failure hospitalization and mortality across baseline CA125 tertiles was examined using Kaplan–Meier analysis with log-rank tests. Multivariate Cox proportional hazards models were applied to determine hazard ratios for outcomes based on baseline and follow-up CA125 levels. Skewed variables underwent logarithmic transformation before analysis.

Three statistical models were used: Model 1 adjusted for age and sex; Model 2 additionally adjusted for established prognostic factors such as diabetes, smoking, hypertension, previous ACS, heart failure, stroke, and revascularization; Model 3 further adjusted for eGFR, a significant post-ACS prognostic factor. Binary logistic regression was used to assess the relationship between baseline CA125 and LVEF decline in ACS patients discharged with normal LVEF, defined as greater than 50%. LVEF deterioration was considered a decrease of at least 5% between baseline and the one-year follow-up.

Unadjusted binary logistic regression (Model 1) was employed initially, with further adjustments for age and sex (Model 2), and additional adjustments for age, sex, diabetes, smoking, and hypertension (Model 3). Statistical significance was defined as a P value less than 0.05.

Results

Paper I

Baseline characteristics

Between September 2017 and May 2023, 5020 patients were enrolled in a clinical trial, with 95.4% of them being from Sweden. At baseline, patient characteristics were well balanced between groups. The median age was 65 years, and 22.5% of participants were women. Risk factors included hypertension (46.2%) and diabetes (14.0%). At the time of admission, 11.6% of patients were already on beta-blocker therapy. Coronary angiography results showed that 55.4% had one-vessel disease, and 95.5% underwent percutaneous coronary intervention (PCI). After discharge, most patients received aspirin (97.4%), a P2Y12 receptor blocker (95.8%), and a statin (98.5%). The baseline table can be viewed in the original paper attached to this thesis.

Beta-blockers after MI with preserved EF and outcome

Follow-up and adherence to treatment were monitored; with 4388 Swedish patients being invited to the SWEDEHEART registry follow-up visits. In the beta-blocker group, 62.2% were treated with metoprolol and 37.8% with bisoprolol. The majority of these patients (90.6%) were still on beta-blockers 6 to 10 weeks after the event, though this dropped to 81.9% after 11 to 13 months. In contrast, 11.3% of patients in the no-beta-blocker group were using beta-blockers at the 6 to 10 week mark, increasing slightly to 14.3% at 11 to 13 months.

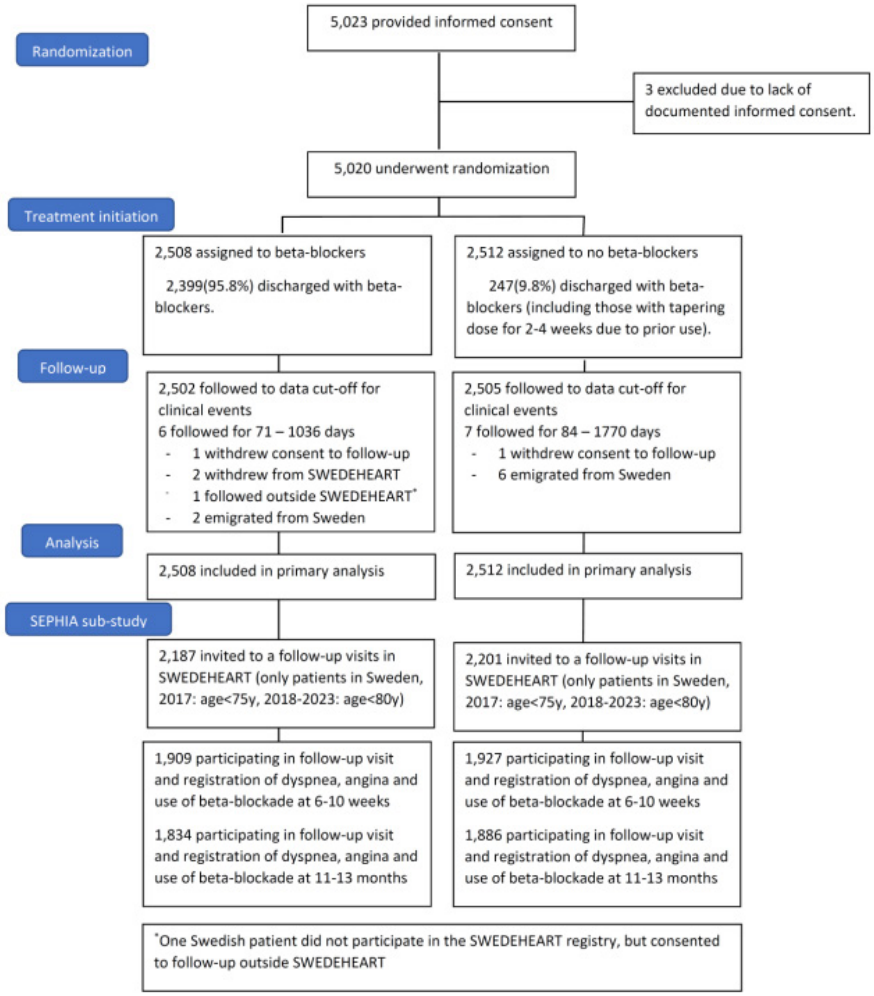

FIGURE 4. Showing the inclusion of patients in the REDUCE-AMI study. Modified from appendix Yndigegn et al.[86]

The median follow-up period was 3.5 years (interquartile range, 2.2 to 4.7). Of the total participants, 2508 were assigned to the beta-blocker group and 2512 to the no-beta-blocker group. A primary end-point event, such as death from any cause or a new myocardial infarction, occurred in 7.9% of the beta-blocker group and 8.3% of the no-beta-blocker group, with no significant difference between the groups (hazard ratio 0.96; 95% CI, 0.79 to 1.16; P=0.64).

No significant difference in secondary end points, such as death from cardiovascular causes, hospitalization for atrial fibrillation, or heart failure, was found between the two groups. The incidence of safety end points, such as hospitalization for bradycardia or stroke, was also 3similar across the groups. A restricted mean survival time analysis was conducted due to non-proportional hazards for stroke-related hospitalizations, but it did not alter the overall findings. Additionally, adjusting for variables like age, diabetes, and previous myocardial infarction did not significantly impact the primary outcomes

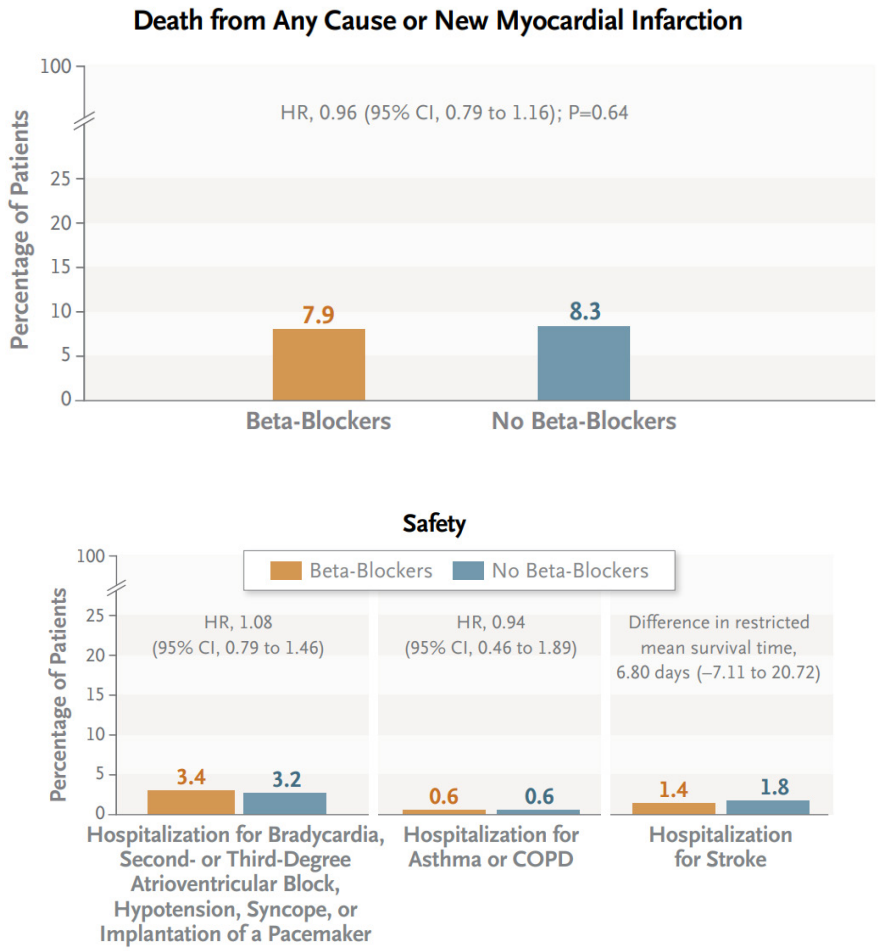

Figure 4a and 4b. modified from Yndigegn NEJM 2024. Showing primary and safety outcome in REDUCE-AMI trial.

Analyses of the pre-specified subgroups showed consistent results with primary outcome. Apart from patients who whad betablocker on admission, where a tendency was seen towards a better outcome when allocated to no betablocker. See Table 4.

Subgroup analyses for the primary outcome, ITT

Subgroup	Beta−block N	Beta−block N / 100 years	No beta−block N	No beta−block N / 100 years	Hazard ratio (95% CI)
Beta−blockers on admission					
Yes	42/269	4.85	34/302	3.26	1.48 (0.94, 2.33)
No	152/2199	2.08	173/2170	2.44	0.85 (0.69, 1.06)
Resting heart rate					
>= 70	128/1576	2.46	136/1535	2.65	0.93 (0.73, 1.18)
< 70	70/913	2.3	71/960	2.28	1.01 (0.73, 1.4)
Sex					
Female	47/563	2.55	61/568	3.19	0.8 (0.55, 1.17)
Male	152/1945	2.35	147/1944	2.31	1.02 (0.81, 1.28)
Age					
>= 75	72/489	4.79	68/495	4.45	1.08 (0.77, 1.5)
< 75	127/2019	1.87	140/2017	2.07	0.9 (0.71, 1.15)
Hypertension					
Yes	121/1155	3.21	110/1163	2.91	1.1 (0.85, 1.43)
No	78/1352	1.72	96/1346	2.14	0.81 (0.6, 1.09)
Diabetes					
Yes	46/346	4.14	52/354	4.72	0.88 (0.59, 1.31)
No	153/2159	2.13	156/2154	2.17	0.98 (0.78, 1.22)
Previous MI					
Yes	31/165	5.66	29/192	4.63	1.23 (0.74, 2.03)
No	168/2338	2.17	178/2315	2.33	0.93 (0.75, 1.15)
Infarct type					
STEMI	65/877	2.24	80/892	2.76	0.81 (0.59, 1.13)
NSTEMI	134/1623	2.49	124/1597	2.33	1.07 (0.84, 1.36)
Revascularized					
Yes	194/2449	2.4	202/2442	2.5	0.96 (0.79, 1.17)
No	3/42	1.91	5/54	2.86	0.68 (0.16, 2.83)
Complete revascularization					
Yes	126/1875	2.04	146/1876	2.38	0.86 (0.68, 1.09)
No	47/400	3.53	36/389	2.65	1.33 (0.86, 2.05)
Chronic kidney disease (eGFR < 60)					
Yes	36/226	5.02	47/229	6.64	0.76 (0.49, 1.17)
No	161/2273	2.13	161/2276	2.13	1 (0.8, 1.24)
Previous atrial fibrillation					
Yes	3/21	4.1	6/23	9.24	0.45 (0.11, 1.81)
No	196/2481	2.39	201/2481	2.45	0.97 (0.8, 1.19)
Country					
Estonia and New Zeeland	9/116	3.4	5/116	1.86	1.82 (0.61, 5.44)
Sweden	190/2392	2.36	203/2396	2.53	0.93 (0.77, 1.14)

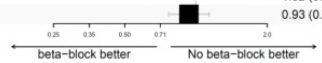

TABLE 4. Pre-specified subgroups in the REDUCE-AMI trial for the primary outcome of death or new MI. Adapted from Yndigegn et al. [86]

Paper II

Baseline characteristics

In the screened cohort of 30,677 patients with uncomplicated STEMI who underwent primary PCI and transthoracic echocardiography, the modified PAMI-II risk score identified 8,092 patients (26.4%) as low risk. The main reasons for not being classified as low risk included: Aged 70 or older (58.3%), LVEF below 50% (67.4%), persistent arrhythmia (7.6%), multivessel disease (26.8%), or unsuccessful PCI (<1%). Those not classified as low risk had a significantly higher incidence of MACE within a year (22.0% compared to 4.1% in the low-risk group; unadjusted HR 6.00, 95% CI: 5.36-6.70, $p<0.001$).

Among the low-risk group, 1,449 patients (17.9%) were discharged within two days (early discharge group), while 6,643 patients (82.1%) had a longer hospital stay (late discharge group). The groups were well balanced with early discharge being more common in the latter years of the study (se Table 5). Both groups had similar comorbidities and presentation medications, although a radial vascular approach was more frequently used in the early discharge group (83.9% vs. 72.4%, $p<0.001$).

		Total 8,092 (100.0%)	Early discharge 1,449 (17.9%)	Late discharge 6,643 (82.1%)	*p*-value
Variable	Age, years	59.0 (53.0-65.0)	59.0 (53.0-65.0)	59.0 (53.0-65.0)	0.69
	Body mass index	27.1 (24.7-30.0)	27.1 (24.7-29.9)	27.2 (24.7-30.1)	0.54
	Men	6,254 (77.3%)	1,129 (77.9%)	5,125 (77.1%)	0.53
	Women	1,838 (22.7%)	320 (22.1%)	1,518 (22.9%)	0.53
Smoking status	Never smoked	2,313 (30.0%)	401 (28.6%)	1,912 (30.3%)	0.32
	Ex-smoker	2,068 (26.8%)	370 (26.4%)	1,698 (26.9%)	0.32
	Current smoker	3,339 (43.3%)	630 (45.0%)	2,709 (42.9%)	0.32
Inclusion period*	≤2010	1,870 (100%)	260 (13.9%)	1,610 (86.1%)	<0.001
	2011-2014	4,006 (100%)	677 (16.9%)	3,329 (83.1%)	<0.001
	≥2015	2,216 (100%)	512 (23.1%)	1,704 (76.9%)	<0.001
Past medical history	Diabetes	1,223 (15.1%)	194 (13.4%)	1,029 (15.5%)	0.04
	Hypertension	2,893 (35.8%)	500 (34.5%)	2,393 (36.0%)	0.28
	Hyperlipidaemia	1,494 (18.8%)	269 (18.8%)	1,225 (18.8%)	0.99
	History of CAD	806 (10.0%)	166 (11.5%)	640 (9.6%)	0.04
	History of MI	709 (8.8%)	148 (10.2%)	561 (8.4%)	0.03
	History of PCI	538 (6.6%)	112 (7.7%)	426 (6.4%)	0.07
	History of CABG	48 (0.6%)	14 (1.0%)	34 (0.5%)	0.04
	CHF	92 (1.1%)	12 (0.8%)	80 (1.2%)	0.22
	Stroke	231 (2.9%)	37 (2.6%)	194 (2.9%)	0.44
	Renal failure	83 (1.0%)	16 (1.1%)	67 (1.0%)	0.74
Past medications	ACE inhibitors	917 (11.5%)	160 (11.2%)	757 (11.5%)	0.72
	Angiotensin receptor blockers	831 (10.4%)	147 (10.3%)	684 (10.4%)	0.89
	Beta-blockers	1,315 (16.4%)	226 (15.8%)	1,089 (16.6%)	0.47
	Aspirin	1,009 (12.6%)	184 (12.8%)	825 (12.5%)	0.75
	Statins	1,286 (16.0%)	229 (16.0%)	1,057 (16.0%)	0.94
	Diuretics	527 (6.6%)	77 (5.4%)	450 (6.8%)	0.04
	Oral anticoagulants	87 (1.1%)	10 (0.7%)	77 (1.2%)	0.12
In-hospital characteristics	Heart rate, bpm	72 (61-84)	71 (62-84)	72 (61-84)	0.98
	SBP, mmHg	144 (126-163)	145 (127-165)	143 (126-163)	0.17
	Serum creatinine, µmol/L	75 (65-87)	75 (66-87)	75 (65-87)	0.91
	eGFR-CK Depi, mL/min/1.73 m²	93 (80-101)	93 (80-101)	93 (80-100)	0.43
	Haemoglobin, g/L	144 (134-153)	143 (135-153)	144 (134-153)	0.70
Admission ECG	AF/AFL	117 (1.4%)	13 (0.9%)	104 (1.6%)	0.053
Office/duty hours	Planned - office hours	55 (0.7%)	5 (0.4%)	50 (0.8%)	0.14
	Acute - office hours	2,465 (31.3%)	451 (31.7%)	2,014 (31.2%)	0.14
	Acute - duty hours	4,885 (62.1%)	897 (63.0%)	3,988 (61.8%)	0.14
	Subacute - office hours	383 (4.9%)	55 (3.9%)	328 (5.1%)	0.14
	Subacute - duty hours	84 (1.1%)	16 (1.1%)	68 (1.1%)	0.14
	Symptoms to PCI, min	177.0 (116.0-330.0)	180.0 (120.0-339.0)	176.0 (115.0-329.0)	0.34
	FMC to PCI, min	70.0 (49.0-108.0)	70.0 (50.0-110.0)	70.0 (48.0-107.0)	0.34
Vascular approach	Femoral artery	1,786 (22.1%)	186 (12.8%)	1,600 (24.1%)	<0.001
	Radial artery	6,025 (74.5%)	1,216 (83.9%)	4,809 (72.4%)	<0.001
	Combined/other	281 (3.5%)	47 (3.2%)	234 (3.5%)	<0.001
Angiographic findings	1-vessel disease not LM	5,465 (67.5%)	1,010 (69.7%)	4,455 (67.1%)	0.22
	2-vessel disease not LM	2,597 (32.1%)	435 (30.0%)	2,162 (32.5%)	0.22
Culprit vessel PCI	LM	13 (0.2%)	3 (0.2%)	10 (0.2%)	0.33
	LAD	2,374 (29.3%)	424 (29.3%)	1,950 (29.4%)	0.33
	LCx	745 (9.2%)	142 (9.8%)	603 (9.1%)	0.33
	RCA	3,534 (43.7%)	604 (41.7%)	2,930 (44.1%)	0.33
	Branches	1,425 (17.6%)	276 (19.0%)	1,149 (17.3%)	0.33
	Procedure with stent implanted	7,805 (96.5%)	1,408 (97.2%)	6,397 (96.3%)	0.10
Other in-hospital treatments	CPAP	48 (0.6%)	10 (0.7%)	38 (0.6%)	0.60
	IV inotropes	77 (1.0%)	19 (1.3%)	58 (0.9%)	0.12
	IV nitroglycerine	598 (7.4%)	83 (5.7%)	515 (7.8%)	0.008
	IV diuretics	295 (3.6%)	34 (2.3%)	261 (3.9%)	0.004
	Complication in lab or ward	297 (3.7%)	48 (3.3%)	249 (3.7%)	0.42

Percentages are calculated on complete case data. *Percentage in rows. CABG: coronary artery bypass graft; CHF: chronic heart failure; CPAP: continuous positive airway pressure; LAD: left anterior descending artery; LCx: left circumflex artery; LM: left main artery; MI: myocardial infarction; PAD: peripheral artery disease; RCA: right coronary artery

TABLE 5.. Showing baseline variables between the early discharge group and the late discharge group.

Early vs. late discharge and outcome

A comparison of early and late discharge revealed that, after adjustment, there was no significant difference in the one-year MACE rate between the two groups (4.3% vs 3.2%; adjusted HR 1.31, 95% CI: 0.92-1.87, p=0.14). Similarly, no significant differences were observed in all-cause mortality, reinfarction, hospitalization for heart failure, or stroke between the two discharge groups (See Figure 5). After inverse probability weighting and adjustment there were no difference in outcome between the early and late discharge group.

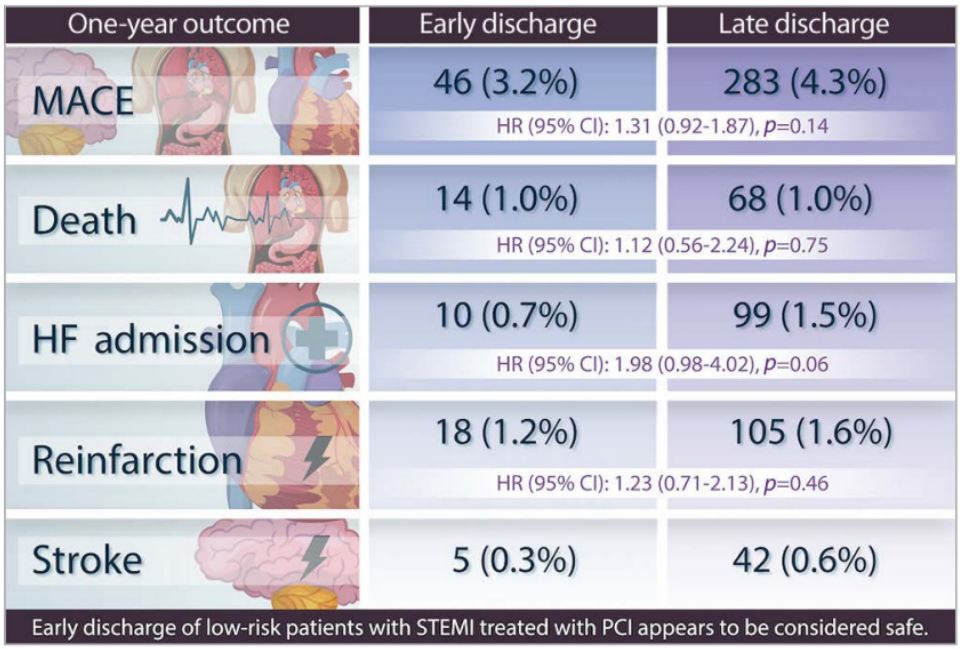

FIGURE 5. Showing adjusted Hazards ratios (HR) between early and late discharge. Modified central illustration from Yndigegn et al.[87]

Additionally subgroup and sensitivity analyses were consistent across different subgroups, and early discharge did not lead to a higher rate of MACE in landmark analyses at discharge or after 30 days.

Paper III

Baseline characteristics

The median age was 68 years in the iFR group and 69 years in the FFR group (P = 0.30). The proportion of male patients was similar between the two groups, with 69.8% in the iFR group and 68.6% in the FFR group (P = 0.29). Both groups had a median creatinine level of 81 µmol/L (P = 0.29). The indications for physiological assessment were similar, including stable angina pectoris (46.9% for iFR vs. 48.6% for FFR), unstable angina or non-ST-elevation myocardial infarction (37.7% vs. 33.1%), ST-elevation myocardial infarction (1.9% vs. 1.6%), and other indications (12.5% vs. 15.7%, P = 0.001). Most patients had angiographically non-significant lesions or one- or two-vessel disease without left main involvement. Minor dissimilarities were seen for tobacco status, antiplatelets, the use of concomitant anticoagulants as well as puncture site (see Table below).

Table 1. Baseline characteristics

	iFR (n = 1998)	FFR (n = 9326)	*P*	% Missing
Male sex	1394 (69.8)	6393 (68.6)	.286	0
Age, y	68 (61-75)	69 (61-75)	.295	0
Creatinine, µmol/L	81 (70-94)	81 (69-94)	.289	9.6
Indication			<.001	1
Stable angina	936 (46.9)	4530 (48.6)		
STEMI	37 (1.9)	153 (1.6)		
Other	250 (12.5)	1461 (15.7)		
NSTEMI/unstable angina	754 (37.7)	3088 (33.1)		
Year			<.001	0
2013	52 (2.6)	914 (9.8)		
2014	291 (14.6)	1667 (17.9)		
2015	597 (29.9)	2000 (21.5)		
2016	490 (24.5)	2326 (24.9)		
2017	568 (28.4)	2419 (25.9)		
Smoking			<.001	3.4
Never	750 (37.5)	3767 (40.4)		
Previous smoker	915 (45.8)	4019 (43.1)		
Current smoker	306 (15.3)	1187 (12.7)		
Unknown	27 (1.4)	353 (3.8)		
Diabetes	452 (22.6)	2224 (23.9)	.112	0.9
Hypertension	1498 (75.0)	7018 (75.3)	.842	1.4
Hyperlipidemia	1384 (69.3)	6416 (68.8)	.439	1.4
Previous myocardial infarction	688 (34.4)	3027 (32.5)	.225	0
Previous PCI	788 (39.4)	3614 (38.8)	.660	0
Previous coronary artery bypass grafting	95 (4.8)	504 (5.4)	.538	0
Aspirin before procedure	1818 (91.0)	8443 (90.5)	.731	0.1
Ticagrelor before procedure	983 (49.2)	3488 (37.4)	<.001	0.1
Bivalirudin during procedure	58 (2.9)	101 (1.1)	<.001	0.1
Heparin during procedure	1875 (93.8)	8345 (89.5)	<.001	0.1
Artery approach			.006	0.8
Femoral	216 (10.8)	1182 (12.7)		
Radial	1774 (88.8)	8063 (86.5)		
PCI during index procedure			.008	0
Yes	420 (21)	1721 (18.4)		
No	1578 (78)	7605 (81.6)		

TABLE 6. Showing baseline variables for iFR and FFR groups. Adapted from Yndigegn et. al [88]

iFR vs. FFR and outcome

The median follow-up period was two years for both the iFR and FFR groups. At one year, the cumulative MACE risk was 9.4% for iFR and 9.9% for FFR (P = 0.51). At the end of the study, the cumulative MACE risk was 26.7% for iFR and

25.9% for FFR (P = 0.27). Kaplan-Meier curves revealed no significant difference in long-term outcomes between the two groups. Adjusted survival analysis also showed no significant difference in MACE hazard ratios (adjusted HR: iFR vs. FFR, 0.947; 95% CI: 0.84-1.08; P = 0.39). Furthermore, the risk of mortality, myocardial infarction, or unplanned revascularization was similar across both groups in the long term.

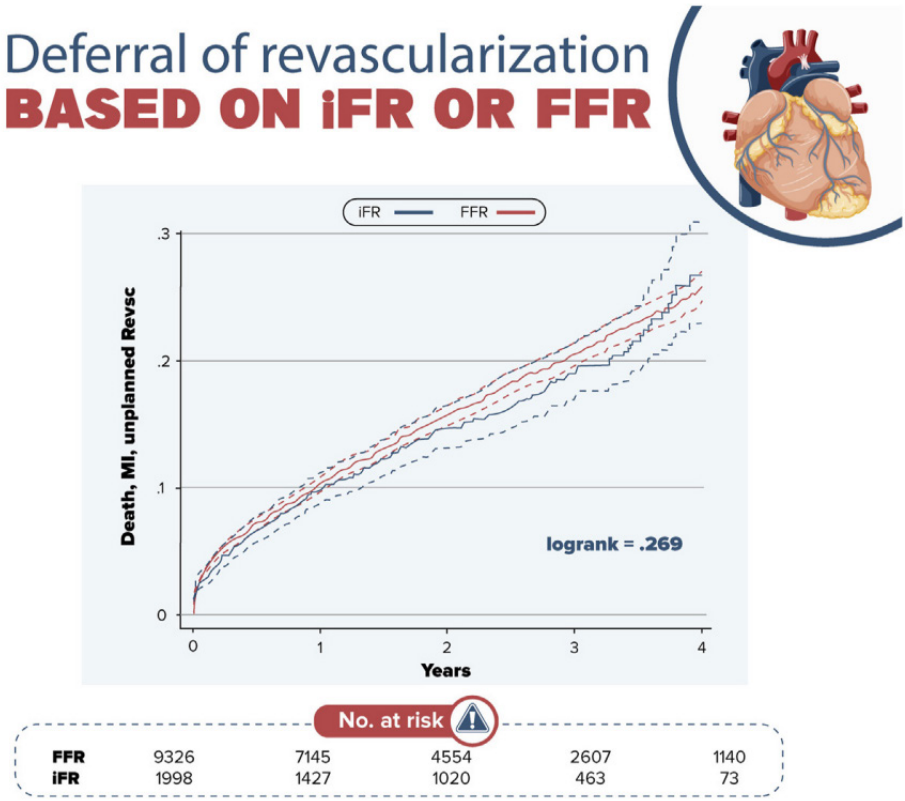

FIGURE 6. Kaplan-Meier failure curves for the primary composite endpoint of death, myocardial infarction or unplanned revascularization. Modified from Yndigegn et. al [88]

Sensitivity analyses supported these findings, with an adjusted MACE hazard ratio of 0.907 (95% CI: 0.79-1.05; P = 0.19) when excluding patients who underwent PCI during the index procedure. Subgroup analyses revealed no significant interactions, with results consistent across all groups, including those with stable angina. An exploratory analysis of stable angina patients found no significant difference in outcomes, with an adjusted hazard ratio for the composite endpoint of 0.835 at four years (P = 0.088).

Paper IV

Baseline characteristics

The baseline table can be viewed in the original paper attached to this thesis. The median age of the cohort was 67 years. A total of 41 patients (7.8%) experienced HF hospitalization during a median follow-up of 27.3 months (IQR 14.8–40.3). Patients who developed HF were generally older, with poorer kidney function, and had higher rates of comorbidities such as hypertension, diabetes, previous HF, ACS and stroke. Additionally, these patients were less likely to have been prescribed statins at discharge. Their baseline plasma CA125 levels were significantly elevated compared to those without HF. The median follow-up time for mortality was 39.5 months (IQR: 27.4–52.2), during which 63 patients (12.0%) died, with 31 deaths (5.9%) attributed to cardiovascular causes. Patients who died were older, had worse kidney function, and more often had a history of hypertension, diabetes, HF, and ACS, but a lower smoking prevalence. They were also less likely to have been revascularized or treated with ACE inhibitors, aspirin, or statins. Elevated CA125 levels were observed in these patients as well.

CA125 and incident HF and mortality

Baseline CA125 levels were associated with the risk of developing HF even after adjusting for all relevant confounding factors (Figure 7 (A) and Table 2, Models 1–3). In the fully adjusted analysis, each 1-standard deviation (SD) increase in baseline CA125 was linked to a hazard ratio (HR) of 1.46 for incident HF [95% confidence interval (CI): 1.10–1.93; P = 0.009].

We also observed an association between baseline CA125 levels and mortality during the follow-up period (Figure 7 (B) and Table 7). However, after adjusting for cardiovascular risk factors such as diabetes, smoking, hypertension, previous ACS, heart failure, stroke, as well as revascularization and renal function, this relationship lost statistical significance (Table 7; Models 2 and 3). However, in a smaller subgroup of 115 elderly patients, persistently elevated CA125 during follow-up independently predicted mortality.

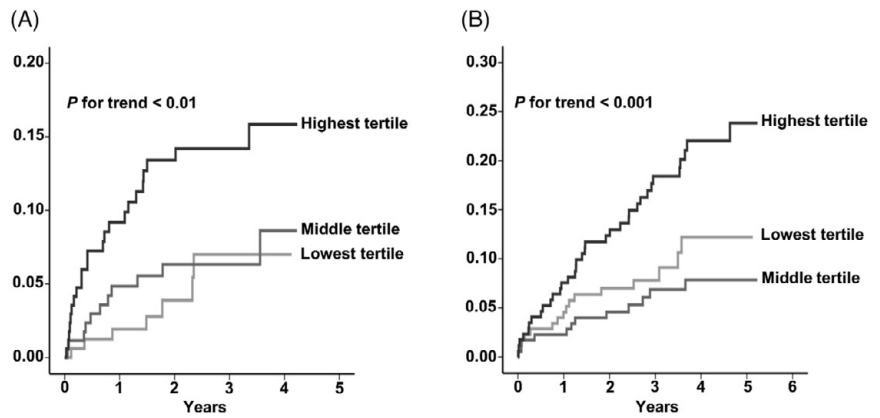

FIGURE 7. Incident heart failure and mortality by tertiles of plasma carbohydrate antigen 125 (CA125) at the index coronary event. (A) Kaplan– Meier 1-minus event-free survival plot of the association between CA125 tertiles at the index acute coronary syndrome event and the incidence of HF hospitalization during follow-up (N = 41 events). (B) Kaplan–Meier 1-minus event-free survival plot of the association between CA125 tertiles at the index ACS event and all-cause mortality during follow-up (N = 63 events). The P values for trend are calculated using the log-rank test.

Biomarkers	Model	HF (*N* = 41)			Mortality (*N* = 63)		
		HR	CI	*P*	HR	CI	*P*
CA125 [a]	1	1.68	1.29–2.19	<0.001	1.37	1.09–1.71	0.006
	2	1.56	1.18–2.07	0.002	1.23	0.97–1.56	0.082
	3	1.46	1.10–1.93	0.009	1.22	0.96–1.54	0.100

Note: Cox proportional hazards analyses of the relationships between CA125 at baseline and outcomes in the entire cohort (*N* = 524).

Abbreviations: CA125, carbohydrate antigen 125; CI, confidence interval; HF, heart failure; HR, hazard ratio.

[a] HR expressed per 1-SD increase in baseline CA125. Model 1: age and sex. Model 2: age, sex, diabetes, smoking, hypertension, prevalent acute coronary syndrome (ACS), prevalent HF, prevalent stroke and revascularization. Model 3: age, sex, diabetes, smoking, hypertension, prevalent ACS, prevalent HF, prevalent stroke, revascularization and estimated glomerular filtration rate.

TABLE 7. showing associations between plasma CA125, incident HF and mortality. Adapted from Yndigegn et al. [89]

CA125 and cardiac structure and function during follow-up

Baseline CA125 levels were significantly associated with cardiac structure and function one year after the ACS index event in a subgroup of 107 patients who had available CA125 data and follow-up echocardiography results. Specifically, higher baseline CA125 levels were strongly correlated with indicators of LV dysfunction and cardiac remodeling. These included association with reduced LVEF as a measure of systolic function. Additionally, elevated CA125 was positively linked to increased LV e3nd-systolic volume, LV end-diastolic volume and left atrial volume, all of which indicators of LV and left atrial dilation. See table below. These findings suggest that higher baseline CA125 is a marker of adverse cardiac remodeling post-ACS. Given that CA125 was linked to lower LVEF one year after the initial event we explored whether baseline CA125 could be used to identify ACS patients with normal LV systolic function at discharge who were at risk of LVEF deterioration over time. This analysis focused on the 44 ACS patients who had a normal LVEF (defined as 50% or above) at baseline and a valid echocardiogram after one year. None of the patients had a prior history of heart failure. Among these patients, only 25 (56.8%) maintained normal LVEF at the one-year mark, while 19 (43.2%) experienced a significant reduction in LVEF, with an average decrease of 14.5% (95% CI: -10.2% to -18.7%). Patients who exhibited LVEF decline had significantly higher baseline CA125 levels compared to those who maintained normal LVEF [54.95 (IQR 30.06–133.44) vs. 36.76 (IQR 19.70–48.86); P = 0.006] suggesting that higher baseline CA125 may help identify ACS patients at risk for future LVEF decline, even if they initially present with normal systolic function.

	Parameter	r	P[a]
Cardiac structure	IVSd	−0.004	ns
	LVIDd	0.098	ns
	PWd	−0.068	ns
	LVMi	0.092	ns
	LVEDVi[b]	0.329	<0.001
	LVESVi[b]	0.391	<0.001
	LAVi	0.320	<0.001
LV systolic function	LVEF[b]	−0.373	<0.001
LV diastolic function	MVE	−0.004	ns
	MVDT	−0.075	ns
	e′	−0.185	ns
	E/A of <0.7 or >1.5	n/a	ns[c]
	E/e′ > 15	n/a	ns[c]
	MVDT < 130 ms	n/a	ns[c]

Abbreviations: E/A, ratio between MVE and MVA (MV late Doppler velocity); E/e′, ratio between E and e′; e′, early mitral annulus tissue Doppler velocity; IVSd, interventricular septum in end-diastole; LAVi, left atrial volume indexed to body surface area; LV, left ventricular; LVEDVi, LV end-diastolic volume indexed to body surface area; LVEF, LV ejection fraction; LVESVi, LV end-systolic volume indexed to body surface area; LVIDd, LV inner diameter in end-diastole; LVMi, LV mass indexed to body surface area; MVDT, mitral valve early Doppler deceleration time; MVE, mitral valve early Doppler velocity; n/a, not applicable; ns, not significant; PWd, posterior wall thickness in end-diastole; *r*, Spearman's correlation coefficient.

[a]Spearman's correlation analysis between continuous echocardiographic variables and baseline carbohydrate antigen 125 levels ($N = 107$).

[b]LVEDVi, LVESVi and LVEF ($N = 97$).

[c]The Mann–Whitney *U*-test comparing patients with normal diastolic function and patients who met the following echocardiographic criteria for diastolic dysfunction: E/A either <0.7 or >1.5; E/e′ > 15; and MVDT < 130 ms.

TABLE 8. showing plasma CA125 and the time of the index event and cardiac function at 1 year after the index coronary event. from Yndigegn et al. [89]

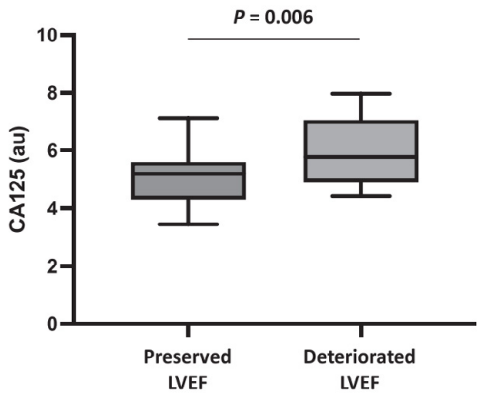

FIGURE 8. CA125 levels in patients with preserved LVEF at follow-up and those with LVEF deterioration. Modified from Yndigegn et al. [89]

Baseline carbohydrate antigen 125 (CA125) and deterioration of systolic cardiac function in patients discharged with a left ventricular ejection fraction (LVEF) > 50% after the index coronary event. Box plots of baseli3ne plasma CA125 in patients with preserved LVEF and patients with reduced LVEF at 1 year after acute coronary syndrome. All patients considered for this analysis (N = 44) had a normal LVEF at the time of the acute ischaemic event. The P value for the difference between groups is calculated using the Mann-Whitney U-test. AU: arbitrary units

Discussion

The papers presented in the present thesis addresses several important aspects of coronary care: the efficacy of beta-blockers in MI patients in the contemporary era; the safety of early discharge in low-risk patients post-STEMI; long-term outcomes of deferred revascularization and the prognostic value of the novel biomarker CA125 in MI patients. The studies collectively aim to refine clinical practice in the management of coronary care. Below follows a discussion of the individual papers.

Beta-blocker therapy after myocardial infarction with preserved ejection fraction

In the REDUCE-AMI trial conducted as an open-label, randomized, registry-based trial across 45 centers, early initiation of oral beta-blockers in patients with acute myocardial infarction and preserved left ventricular ejection fraction did not result in a reduced cumulative incidence of death or recurrent myocardial infarction, which formed the composite primary endpoint. Furthermore, there were no significant differences between the two groups in the analyses of secondary efficacy and safety outcomes. After one year, the severity and occurrence of symptoms appeared similar in both groups. The lack of an observed effect (beneficial of detrimental) of beta-blocker therapy on the incidence of death or myocardial infarction was consistent across all predefined subgroups. Utilizing a novel concept of randomization within a quality registry, it is estimated that the trial during 5.7 years recruited more than 50% of all eligible patients according to the emulated study group[90] underscoring the all-comer, pragmatic potential of the RRCT concept. Indeed, baseline characteristics of the trial participants were representative of the broader population of myocardial infarction patients with preserved ejection fraction in the participating countries making the trial highly representative. These patients generally had a low risk for future cardiac events and were well-managed with early revascularization procedures, along with a high degree of evidence-based medications at discharge. Thus the annual rates of the primary endpoint, 2.4% in the beta-blocker group and 2.5% in the no-beta-blocker group, were lower than initially anticipated. The trial was designed as a superiority study, aiming to detect a 25% reduction in the risk of death or myocardial

infarction with beta-blocker therapy, which would have translated to a 0.7 percentage-point lower risk per year based on the observed event rates. While the neutral outcome does not entirely rule out a small beneficial or harmful effect, the similar time-to-event curves during follow-up and consistent findings across all prespecified subgroups and secondary outcomes suggest that a clinically significant difference is unlikely. Furthermore these findings align with results from several large observational studies and meta-analyses of such studies.[16,18,20,21] The potential indication of harm in the subgroup of patients already on beta-blockers at admission remains uncertain and is likely a chance finding a one would speculate the effect to be opposite based on other interruption studies.

Some apprehension was raised as to the dosages recommended in the trial (Steg NEJM, editorial) as these were lower than equivalent target doses in the landmark trials [12,91]. However the trial mirrored actual doses given in contemporary practices[92] and there was no interaction with the prescribed dosages in the study. Also a previous study did not find a clear effect of the dosage of beta-blockers on outcome following myocardial infarction.[93] The REDUCE-AMI trial included omitted patients with a mid-range LVEF (40-49%) whereas upcoming studies (REBOOT, DANBLOCK, BETAMI) have decided to include these patients. During the planning stages, several potential investigators expressed reluctance to include patients with a mid-range LVEF, which led us to maintain a more homogeneous study population. This decision was made to minimize any interaction between treatment subgroups of varying LVEF, which could complicate the interpretation and generalization of the trial outcomes. Also a meta-analysis of clinical trials, has suggested that beta-blockers may provide benefits in patients with mid-range LVEF and a large registry study from Korea indicated that beta-blockers is indeed beneficial following a myocardial infarction in this population. 7,17

The trial has noteworthy limitations. Our study has several limitations. First, it was conducted as an open-label trial, as blinding was not considered feasible. This however would have only limited effect on the hard clinical endpoint of death or new MI, albeit caution is needed when interpreting results related to more subjective outcomes like symptom reporting. Clinical outcomes were derived from the SWEDEHEART and Swedish Population registries without central adjudication, but this was mitigated as investigators cross-checked electronic health records to ensure that new myocardial infarctions recorded in SWEDEHEART met the diagnostic criteria, and any misclassification would likely have been evenly distributed between the two treatment groups.

Second, only safety endpoints related to hospitalization were assessed. Third, as with any pragmatic trial involving standard clinical therapies, the possibility of treatment crossover exists. Despite efforts to minimize this, approximately 14% of patients in the no–beta-blocker group were taking beta-blockers after one year of follow-up. The observed adherence to beta-blocker therapy reflected patterns

typical in routine clinical settings.[94] However, we cannot completely rule out the possibility that beta-blocker use in the no–beta-blocker group may have influenced the neutral outcome of the trial.

Altogether beta-blockers were not associated with a lower risk of the composite outcome of death or MI, when given early after myocardial infarction in this registry-based, prospective, open-label parallel group trial for patients that underwent early angiography with preserved EF. Most recently the Abyss-study examining the interruption of beta-blockers was presented. The study randomized 3698 patients on beta-blocker therapy with preserved EF and no recent cardiac events to either interruption of continuation of beta-blocker therapy.[95] While the study did not meet is primary endpoint of non-inferiority, there was no difference in the "hard" clinical endpoints of myocardial infarction or death. The primary endpoint was driven by a larger proportion of patients undergoing coronary angiography (with no intervention) and also a smaller proportion of patients admitted due to angina. While it is indeed prudent to await the upcoming trials [96,97] [98]before abandoning beta-blocker therapy, indeed the results of the REDUCE-AMI trial seem to have put beta-blockers "on injured reserve" [99]for patients with preserved ejection fraction in the reperfusion era.

Safety of early discharge following uncomplicated STEMI

The study examined the use of the PAMI-II criteria in a nationwide real-world setting to examine the outcome of early discharge in uncomplicated STEMI-patients. Approximately a quarter were identified as low-risk by the PAMI-II risk score, and early discharge in these patients did not lead to an increased risk of short- or long-term adverse outcomes. Thus, the findings serve as a real-world validation of the PAMI-II risk score.[50] It is the largest study to evaluate the safety of early discharge in low-risk STEMI patients, corroborating prior evidence from smaller observational studies[58,59] and randomized clinical trials[55] that support the safety of early discharge.

In our cohort, low-risk patients showed very low rates of adverse events, such as death, reinfarction, stroke, or hospitalization for heart failure within the first year. Importantly, no significant differences were observed between those with shorter hospital stays and those with longer stays. The low mortality rate of 1% further underscores the safety of early discharge. To account for potential confounders we employed propensity score analyses and inverse probability weighting. Both landmark analyses indicated minimal residual confounding, supporting the robustness of our results.

An early indication of heart failure is the use of diuretics and indeed, patients who stayed longer in the hospital were more likely to have been treated with intravenous diuretics and prescribed diuretics at discharge. Although a trend toward more heart failure hospitalizations was noted in this group, the results were not statistically significant in any adjusted analysis, though they were in unadjusted analyses. As such, there might be a small subset of low-risk patients—those requiring intravenous diuretics, heart rate management due to atrial fibrillation/flutter, or those unable to undergo radial artery access—who may need longer hospital stays. However, this subgroup does not explain the substantial inter-hospital variation in hospital stay length observed in Sweden, which we attribute more to local hospital practices than to patient risk profiles.

This variation also leads to uneven hospital costs for STEMI patients across Swedish hospitals. Adopting the PAMI-II risk score more consistently could help reduce costs. Our findings suggest that around 1,000 STEMI patients in Sweden could be eligible for early discharge each year, potentially saving approximately 1,700 care days annually if they are discharged within two days. Even limiting early discharge to patients with hospital stays of 3-5 days could save around 1,200 care days. In larger countries with higher STEMI incidences, more efficient use of hospital resources could result in significant cost savings and improved access to cardiac care.

A concern with early discharge is the potential for compromised patient education and information retention. However, when coronary care staff provides early follow-up care, this concern diminishes, and patients may better understand medication and lifestyle changes outside of the acute care environment.

The study has some limitations. The definition of low-risk features differed slightly from the original PAMI criteria due to the constraints of the available data. However, we believe our definitions more accurately reflect contemporary clinical practice. As an observational study there will be inherent potential for residual confounding and indication bias, though the consistency between unadjusted and adjusted analyses suggests a low likelihood of significant confounding. Nonetheless, as also noted above, some patients identified as low-risk may have required longer hospital stays, as indicated by their higher use of intravenous diuretics.

Deferral of revascularization guided by iFR of FFR

This study evaluated the safety of deferring coronary revascularization based on intracoronary physiology measurements in a large, unselected patient cohort with long-term follow-up using either iFR or FFR. The DEFER trial initially demonstrated that deferring PCI in patients with intermediate coronary lesions and

no ischemia, as shown by FFR, was safe.[66] Further a meta-analysis involving 3,097 patients supported these findings. [100] When the iFR-SWEDEHEART and DEFINE-FLAIR trials were completed demonstrating the non-inferiority of iFR-guided revascularization compared to FFR, there was a higher proportion of patients in which revascularization was deferred based on iFR rather than FFR [67,68] potentially giving cause to future coronary events. While both trials observed a numerically higher but non-significant number of excess deaths in the iFR group, the safety of deferring PCI based on iFR has therefore been scrutinized.[101] A pooled analysis of deferred patients from both trials (N = 2,130; 1,117 in the iFR group and 1,013 in the FFR group) showed no difference in safety between the two approaches over a one-year follow-up period. [102] and 5-year outcomes from the iFR-SWEDEHEART trial also did not differences between iFR- and FFR-based revascularization strategies.[103]

The study with 11.324 patients with coronary physiology registration performed in Sweden represents the largest cohort of patients deferred from revascularization. Revascularization was deferred based on iFR (>0.89; n = 1,998) or FFR (>0.80; n = 9,326). Data from all 30 PCI centers in Sweden, covering hospitals of various sizes and affiliations, were pooled, ensuring an all-comer population. With a follow-up extending that of iFR-SWEDEHEART and DEFINE-FLAIR, these findings suggest the equal outcome of deferring revascularization whether based on iFR or FFR in the long-term. In our study, the outcomes of iFR- and FFR-based deferral strategies aligned with the aforementioned trials, though our patient population showed a higher cumulative MACE risk in both groups. Prior trials reported ~4% cumulative MACE risks in deferred patients with one-year follow-up, with higher risks in patients presenting with ACS compared to stable angina.[102] In our study, the cumulative MACE risk was more than double, at 9%-10% at one year, likely due to the older age (median 69 years) and higher prevalence of ACS (~40%) compared to DEFINE-FLAIR and iFR-SWEDEHEART, which had younger cohorts and fewer ACS patients (~20%). Other factors contributing to these discrepancies remain uncertain, and further follow-up from clinical trials is needed to assess long-term deferral risks.

Concerns over the performance differences between iFR and FFR have been mentioned in studies suggesting that factors like sex, vessel size, and diabetes mellitus might influence the outcomes of these measurements.[104] We found no interaction between age, sex, hypertension, hyperlipidemia, diabetes, smoking, or procedure indication with the use of FFR or iFR. While an exploratory analysis indicated potentially better outcomes with iFR deferral in patients with s angina, adjusted analyses did not confirm this hypothesis. Additionally, this study included patients with conditions other than stable angina or ACS, such as heart failure, arrhythmias, and heart valve disease, highlighting the heterogeneous nature of our study population.

In conclusion, current guidelines recommend using pressure-derived ischemia measurements to guide revascularization in intermediate angiographic lesions.[69] Despite two large randomized trials showing iFR's noninferiority to FFR, questions about the safety of deferring revascularization with iFR have remained. Consistent with findings from DEFINE-FLAIR and iFR-SWEDEHEART, this study of a large real-world population demonstrates that deferring revascularization based on iFR appears to have equal outcome when compared to FFR, even with follow-up extending to four years. However, the higher cumulative MACE risks observed in this study, compared to clinical trials, should be considered when deferring revascularization, particularly in ACS settings.

Several limitations should be noted. This study only included patients who underwent invasive coronary physiology, likely excluding those with heavily calcified or tortuous vessels. Continuous pressure measurements were converted into a binary variable for guiding revascularization, and other factors influencing deferral decisions may not have been accounted for. Although robust statistical methods were used to adjust for known confounders, residual confounding cannot be ruled out due to the observational nature of registry data. Although it has now been added to the SCAAR database, information on left ventricular ejection fraction was unavailable, as it is was not recorded in SWEDEHEART for patients undergoing coronary angiography in an out-patient setting.

Prognostic implications of plasma CA125 levels in patients with myocardial infarction

The final study in thesis examined CA125 as a novel prognostic biomarker following ACS. We identified several correlations between plasma CA125 levels and long-term incidences of HF and all-cause mortality. The association between baseline CA125 and HF remained significant in the adjusted analysis. Additionally, higher CA125 levels at the time of ACS were linked to LV dilation and reduced LVEF at one year, known indicators of poor prognosis in MI patients.[105] Notably, CA125 independently predicted a decline in LV systolic function among ACS patients discharged with normal LVEF. Furthermore, persistently elevated CA125 levels during follow-up were associated with increased mortality, regardless of other confounding factors. There was no significant relationship between CA125 and cancer-related deaths, ruling out cancer as a confounding factor.

Since the initial study by Nägele that highlighted CA125's relevance in HF severity for patients awaiting heart transplants,[78] there has been growing interest in CA125's prognostic role in HF patients. The CHANCE-HF trial further supported the value of CA125-guided therapy in reducing HF readmissions and death within

one year.[81] In the context of ACS, Eggers identified CA125 as one of the strongest predictors of total mortality in a cohort of 1,099 MI patients.[85] However, the relationship between baseline CA125 and mortality lost significance after adjusting for confounders. Our study builds on these findings, extending the evidence to a mixed cohort of ACS patients. Similar to Eggers et al., we observed that elevated CA125 in the acute phase after ACS was associated with a higher mortality risk, but it was not an independent predictor when adjusting for established risk factors. In contrast, persistently elevated CA125 during follow-up independently predicted mortality, albeit in a smaller subgroup of 115 elderly patients, which warrants cautious interpretation.

Perhaps the most intriguing finding of our study is that elevated baseline CA125 appear to independently predict long-term LV systolic dysfunction, cardiac remodeling, and the onset of HF. While prior studies have shown a relationship between CA125 and HF, one of the most common complications following ACS, only a few small studies have explored this in ACS patients. Two studies involving 70 and 47 patients respectively found that CA125 correlated with reduced LVEF and clinical indicators of acute HF, such as Killip class and pulmonary edema, at the time of ACS [82,84] Another study, with a 3-month follow-up of 40 ACS patients, reported positive associations between CA125 and the risk of HF and death.[83] Our findings build on these observations, showing that the trend of increased HF hospitalizations continues long-term in patients with elevated CA125 levels and remains significant after adjusting for confounders.

While our study found associations between elevated CA125 levels and several indicators of cardiac remodeling post-ACS, the pathophysiological role of CA125 remains unclear; Whether CA125 plays an active role in this remodeling or merely reflects underlying processes: Mechanical strain on cardiac cells following ischemic injury is a key component of remodeling.[106] It is plausible that elevated CA125 production may result from inflammatory and mechanical stress on serosal cells through the c-Jun N-terminal kinase pathway.[107] Additionally, circulating CA125 has been shown to correlate with pericardial expansion in patients with pericardial effusions [108] suggesting that elevated CA125 in ACS patients may partly reflect mechanical stress on the serosal cells of the pleura, pericardium, and peritoneum due to increased filling pressure and neurohormonal activation.[109]

The fact that CA125 was elevated even in patients with normal cardiac function at baseline who later experienced a significant LVEF decline is particularly noteworthy. These patients, typically considered low risk, may not receive the same aggressive treatment or monitoring as those with reduced LVEF. Identifying elevated CA125 in these individuals could justify follow-up echocardiography at six months to detect early signs of HF. In this context, CA125 may reflect other underlying pathological mechanisms unrelated to acute HF. CA125 has been linked to systemic inflammatory responses, correlating with inflammatory cytokines like TNF-α, IL-6, IL-10, and IL-1β, which are also involved in post-MI

cardiac remodeling.[110,111] Furthermore, in vitro studies have shown that CA125 secretion by serosal cells is enhanced by stimulation with TNF-α and IL-1β.[112] This suggests that elevated CA125 during ACS may reflect heightened intra-cardiac and systemic immune activation, identifying patients at risk of excessive remodeling, progressive myocardial dysfunction, and eventual HF.

Several limitations should be acknowledged. The size of the cohort and the number of patients experiencing HF or death were moderate, and our single-center design may limit the generalizability of our findings. Nevertheless, our results align with those of Eggers et al. from larger MI cohort, which strengthens the validity of both studies. These two studies are among the largest to date examining CA125 as a prognostic biomarker post-ACS. We were unable to establish definitive CA125 cutoff values or directly compare concentrations with other studies, as CA125 was measured in arbitrary units. Additionally, only patients aged 75 or older underwent six-week follow-up and one-year echocardiography, so the association between six-week CA125 and mortality, and the correlation with echocardiographic findings, should be interpreted with caution, especially extrapolating to patients below this age. However, the association between baseline CA125 and HF risk was observed across the entire cohort, regardless of age. Finally, as an observational study, we cannot confirm a causal role for CA125 in cardiac remodeling and HF development post-ACS.

Conclusion

The present thesis has sought to advance the management of coronary care through evaluation of a novel biomarker in ACS, the integration of real-world data from the SWEDEHEART registry in observational studies and finally with an innovative trial design namely the RRCT. Several key conclusions can be drawn from the studies presented. Paper I, a randomized controlled registry-based trial involving 5,020 patients, found that among those with acute myocardial infarction who underwent early coronary angiography and had preserved left ventricular function (≥50%), long-term beta-blocker therapy did not reduce the risk of death or recurrent MI compared to no beta-blocker use. It also did not affect any of the secondary and safety outcomes as well as symptoms. Paper II, a large-scale observational non-randomized comparison from the SWEDEHEART registry, demonstrated that the PAMI-II risk score effectively identified STEMI patients with very low risk of short- and long-term adverse outcomes, suggesting that early discharge within two days may be considered safe. Paper III, another large-scale observational non-randomized comparison from the SWEDEHEART registry, showed that deferral of revascularization has similar long-term safety whether guided by iFR or FFR, aligning with findings from recent trials and current guidelines. However, real-world data suggested an incidence of MACE well above that from previous randomized trials. Finally, Paper IV, a single-center prospective study utilizing biomarker measurements and echocardiography, reported independent associations between elevated CA125, left ventricular dysfunction, cardiac remodeling, incident heart failure, and mortality post-ACS, suggesting CA125 as a potential biomarker for risk stratification and management of ACS patients during both acute events and follow-up. Collectively, these findings may contribute to advancing coronary care management for the benefit of patients worldwide.

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