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## **Acute myocardial infarction. Short-term triggers, treatment optimisation and risk stratification.**

Mohammad, Moman

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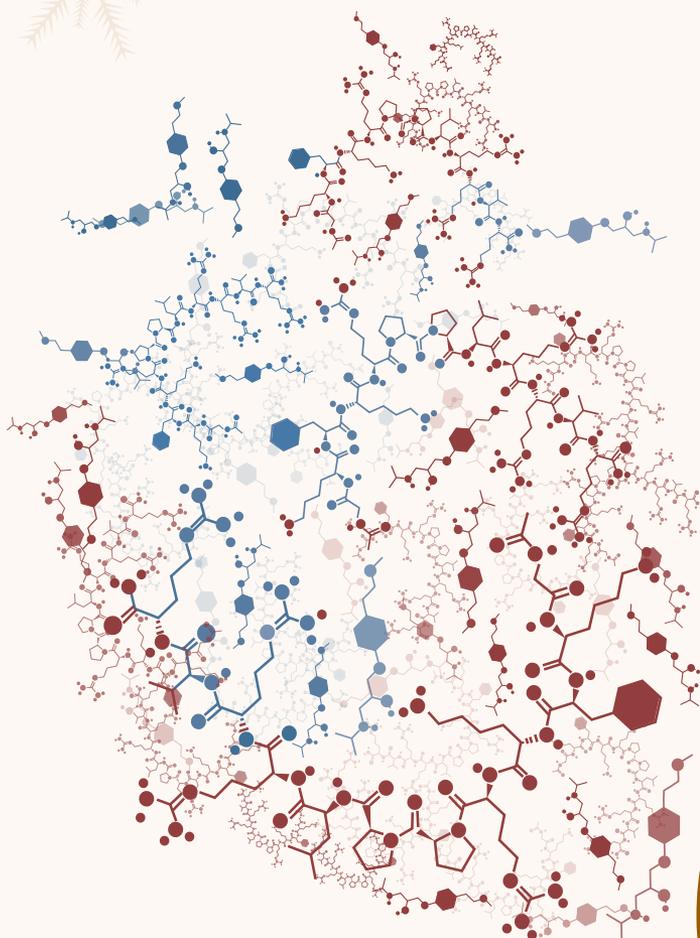


# Acute myocardial infarction

Short-term triggers, treatment optimisation and risk stratification

MOMAN A. MOHAMMAD

FACULTY OF MEDICINE | LUND UNIVERSITY





Moman A. Mohammad was born in Iraq in 1990 and moved with his family to Sweden in 1996. He studied medicine at the Medical University of Gdansk in Poland, graduating with an MD degree in 2015. He completed a clinical internship at Skåne University Hospital in Lund in 2019 while conducting research focusing on aspects of myocardial infarction. His doctoral thesis comprises five studies examining the onset of myocardial infarction, the use of intravenous beta-blocker therapy and the prognostic value of high-sensitivity troponin T as a marker of long-term systolic dysfunction in patients with ST-elevation myocardial infarction treated with percutaneous coronary intervention. Dr. Mohammad is currently a resident physician at the Department of Cardiology at Skåne University Hospital in Lund.

# Acute myocardial infarction

Short-term triggers, treatment optimisation and  
risk stratification

Moman A. Mohammad, MD



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DOCTORAL DISSERTATION

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*Faculty opponent*  
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<b>Abstract</b>  <p><b>Introduction:</b> Myocardial infarction (MI) is irreversible death of the heart muscle due to ischemia. The objectives of this research were to study factors associated with the onset of MI and evaluate treatment and prognostic approaches in patients diagnosed with ST-elevation MI (STEMI). <b>Methods:</b> This thesis comprises five studies, with Studies I-III retrieving patient data from the nationwide SWEDEHEART registry. Studies I and II investigated the risk of MI associated with selected weather conditions and temporal factors such as time of day and day of the week as well as with holidays and sporting events, periods possibly reflecting stress and/or abrupt lifestyle changes. Study III evaluated the effect of intravenous beta-blocker therapy on short-term mortality of intravenous beta-blockers in STEMI patients treated with primary PCI and dual antiplatelet therapy. Studies IV and V used data from two randomized clinical trials to compare the value of selected cardiac biomarkers in prediction of left ventricular (LV) dysfunction after STEMI to that of early morphological and function assessments obtained by cardiac magnetic resonance imaging (CMR). <b>Results:</b> In the studied population, Christmas/New Year and Midsummer holidays, as well as days with lower air temperature and atmospheric pressure, higher wind velocity, and shorter duration of sunshine were associated with a higher incidence of MI. Intravenous beta-blocker therapy in patients with STEMI treated with PCI was associated with higher short-term mortality, lower LVEF at discharge, and higher incidence of in-hospital cardiogenic shock. The peak high sensitivity cardiac troponin (hs-cTnT) value provided risk-prediction comparable in accuracy to that of early infarct size and LV ejection fraction as assessed by CMR and transthoracic echocardiography and superior to that of standardized clinical risk scores, demonstrating troponin T as an excellent prognostic marker of LV dysfunction. <b>Conclusions:</b> The reported findings have potential implications for cardiac health, as, in addition to evaluating aspects of treatment, they identify modifiable triggers of MI and strategies for estimating level of risk in post-STEMI patients.</p>		
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**MADE IN SWEDEN** 

*To my parents*

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# List of papers

This thesis is based on research reported in the following papers, referred to hereafter by their respective Roman numerals. By permission of publishers, all papers are appended at the end of this thesis. In addition to those listed, the author has published eight other articles in international peer-reviewed journals.

- I. **Mohammad MA**, Karlsson S, Haddad J, Cederberg B, Jernberg T, Lindahl B, Frobert O, Koul S, Erlinge D. Christmas, national holidays, sport events, and time factors as triggers of acute myocardial infarction: SWEDEHEART observational study 1998-2013. *BMJ* 2018;363:k4811.
- II. **Mohammad MA**, Koul S, Rylance R, Frobert O, Alfredsson J, Sahlen A, Witt N, Jernberg T, Muller J, Erlinge D. Association of Weather With Day-to-Day Incidence of Myocardial Infarction: A SWEDEHEART Nationwide Observational Study. *JAMA Cardiol* 2018;3:1081-1089.
- III. **Mohammad MA**, Andell P, Koul S, Desta L, Jernberg T, Omerovic E, Spaak J, Frobert O, Jensen J, Engstrom T, Hofman-Bang C, Persson H, Erlinge D. Intravenous beta-blocker therapy in ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention is not associated with benefit regarding short-term mortality: a Swedish nationwide observational study. *EuroIntervention* 2017;13:e210-e218.
- IV. **Mohammad MA**, Koul S, Smith JG, Noc M, Lang I, Holzer M, Clemmensen P, Jensen U, Engstrom T, Arheden H, James S, Lindahl B, Metzler B, Erlinge D. Predictive Value of High-Sensitivity Troponin T for Systolic Dysfunction and Infarct Size (Six Months) After ST-Elevation Myocardial Infarction. *Am J Cardiol* 2018;122:735-743.

- V. **Mohammad MA**, Koul S, Lønborg JT, Nepper-Christensen L, Høfsten DE, Ahtarovski KA, Bang L, Helqvist S, Kyhl K, Køber L, Kelbæk H, Vejstrup N, Holmvang L, Schoos MM, Göransson C, Engstrøm T and Erlinge D. High Sensitivity Troponin T is predictive of long-term left ventricular dysfunction after ST-Elevation Myocardial Infarction– Manuscript.

# Abbreviations

CAD	Coronary Artery Disease
CCU	Coronary Care Unit
CHILL-MI	Randomized Controlled Study of the Use of Central Venous Catheter Core Cooling Combined with Cold Saline as an Adjunct to Percutaneous Coronary Intervention for the Treatment of Acute Myocardial Infarction
DANAMI-3	The Third DANish Study of Optimal Acute Treatment of Patients with ST-segment Elevation Myocardial Infarction: Ischemic postconditioning or deferred stent implantation versus conventional primary angioplasty and complete revascularization versus treatment of culprit lesion only: Rationale and design of the DANAMI 3 trial program
EARLY-BAMI	Early Beta-blocker Administration before primary PCI in patients with ST-elevation Myocardial Infarction
IS	Infarct Size
IRR	Incidence Rate Ratio
LVEF	Left Ventricular Ejection Fraction
METOCARD CNIC	Effect of METOpolol in CARDioproteCtioN during an acute myocardial InfarCtion
MI	Myocardial Infarction
NSTEMI	Non ST-Elevation Myocardial Infarction
RIKS-HIA	Swedish Register of Information and Knowledge about Swedish Heart Intensive Care Admission

SCAAR	Swedish Coronary Angiography and Angioplasty Registry
SD	Standard Deviation
SMHI	Swedish Meteorological and Hydrological Institute
STEMI	ST-Elevation Myocardial Infarction
SWEDEHEART	Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies
TIMI	Thrombolysis in Myocardial Infarction

# Introduction

## Historical perspective

Ischemic heart disease has long been the most common cause of morbidity and mortality worldwide.<sup>1</sup> What is probably the earliest known record is a depiction of sudden cardiac death in an Egyptian tomb relief dating from 2625–2475 B.C. Dissection studies as well as a recent imaging study have shown the prevalence of atherosclerosis in Egyptian mummies.<sup>2,3</sup> However, it was not until the mid-19<sup>th</sup> century that coronary thrombosis, the term used at the time, was first identified as a cause of death: In a study dated 1859, Malmsten and von Düben described a case of a 66 year-old man with symptoms of myocardial infarction (MI) who died a week later.<sup>4</sup> Post-mortem examination showed a ruptured heart wall and a clotted anterior branch of the left coronary artery. The authors stated, ‘There is no doubt that the clot caused the heart wall rupture.’ Because this study was published in a Swedish medical journal, it did not receive international attention, and it was not until Hammer’s study in 1878 that MI was recognised as a clinical syndrome.<sup>5</sup> In the 20<sup>th</sup> century, coronary thrombosis was linked to the clinical features of MI, resulting in the recognition of MI as a disease entity.<sup>6-8</sup> Although the term myocardial infarct was introduced in 1896, ‘coronary thrombosis’ was used for many years.<sup>9</sup> In 1919 MI was captured on electrocardiogram.

Fast forward to the early 1960s when the paediatric cardiologist F.M. Sones accidentally injected contrast into the coronary arteries rather than the left ventricle, performing coronary angiography for the first time. The use of this new technique led to development of angioplasty in 1964 by Charles Dotter and was employed to treat peripheral artery disease. It was further developed for use in coronary arteries by Andreas Gruntzig. Around this same time, significant improvements in cardiac treatment were made, among them the introduction of specialised coronary care units (CCU) and the addition of early defibrillation to the two standard treatment modalities, pain relief and bed rest, resulting in significant increase in survival rate, which, at the time, was approximately 40% in hospitalised patients. Also in the

1960s, the first studies of beta-adrenergic blocking agents (beta-blocker) were conducted.<sup>10</sup> In the late 1970s, studies of fibrinolysis, showing a 50% reduction in mortality, were presented, leading to the ‘golden era’ of cardiology of the 1980s,<sup>11</sup> when some of the largest randomized trials in the history of cardiology were conducted. Results of research on fibrinolysis, beta-blockers, and aspirin came to largely shape current treatment of MI. Hjalmarson et al. showed a 36% reduction in mortality with beta-blocker therapy in the Göteborg Metoprolol trial, the first large randomized trial of beta-blockers.<sup>12 13</sup> Shortly thereafter, the MIAMI trial and the first International Study of Infarct Survival followed, both investigating the potential benefits of beta-blockers.<sup>14 15</sup>

Around this same time, results of thrombolysis in myocardial infarction (TIMI) trials showed superiority of intravenous (IV) tissue plasminogen activator (tPA) over intracoronary streptokinase, leading the way to IV administration of pharmacological reperfusion.<sup>16</sup> The antiplatelet effect of aspirin was discovered in 1971, and the role of aspirin in the treatment of acute MI was established during the late 1980s in the second International Study of Infarct Survival, which showed a 23% reduction in odds of cardiovascular mortality in the first month post-MI.<sup>17 18</sup> Both the aforementioned study and the GISSI trial, large randomized clinical trials, showed a benefit of pharmacological reperfusion with IV fibrinolysis, and the TIMI-IIa and TIMI-IIb studies explored several invasive treatments adjunctive to IV thrombolytic therapy.<sup>18-21</sup> The first reports comparing pharmacological reperfusion with angioplasty were published in the early 1990s, and, in the early 2000s, large randomized trials were conducted to evaluate the relative benefits of pharmacological and mechanical reperfusion in PCI.<sup>22-25</sup> A number of therapeutic advancements targeting biological pathways resulted in the introduction of statins, P2Y<sub>12</sub> inhibitors, and inhibitors of the renin-angiotensin system to the therapeutic arsenal in MI.

In addition to the advancements in therapeutics, measures of blood levels of cardiac enzymes in the clinical setting resulted in improved diagnostic accuracy. In 2000, the first Global MI Task Force forged a consensus document presenting a universal definition of MI as any necrosis in the setting of myocardial ischemia. This definition was refined in 2007 and 2012 and finally in 2018.<sup>26-29</sup> The advancements of recent decades have resulted in significant reduction of mortality, with in-hospital post-MI mortality decreasing from 40% during the 1960s to 13% in 1996 and approximately 5% today.<sup>30 31</sup>

## Definition and pathophysiology

The universal definition of MI classifies it into five types based on pathological, clinical, and prognostic characteristics as well as treatment strategies.<sup>29</sup> Of these, Type I, spontaneous MI, is the most common. It is caused by a spontaneous rupture of an atherosclerotic plaque resulting in platelet activation and aggregation and stimulation of the coagulation cascade, ultimately leading to thrombus formation occluding the coronary artery. As a result, blood supply to the myocardium distal to the occlusion is disrupted, and myocardial ischemia with subsequent cell death occurs. From a pathological standpoint, MI is defined as myocardial cell death due to prolonged ischemia as identified by cardiac troponin above the 99<sup>th</sup> percentile upper reference limit, making cardiac troponin level a hallmark in the diagnosis of MI. Clinically, MI is defined as acute myocardial injury due to myocardial ischemia. The diagnosis is based on a characteristic rise or fall in cardiac troponin with at least one value above the 99<sup>th</sup> percentile upper reference limit in addition to at least one of the following: symptoms characteristic of MI, new ischemic ECG changes or development of pathological Q-waves, angiographic or autopsy findings suggestive of MI, or evidence of new loss of viable myocardium in a pattern consistent with ischemia on cardiac imaging modalities.<sup>29</sup> The focus of this reported research is Type I myocardial infarction, hereafter referred to as MI.

## Epidemiology

The incidence rate of MI in Sweden is estimated at 340 per 100 000 inhabitants per year and in 2017, 25 300 MIs were recorded by the Swedish National Board of Health and Welfare.<sup>32</sup> Myocardial infarction is more common among males (64% vs. 36%), and females are, on average, 5 years older at presentation (75 vs. 70).<sup>33</sup> Approximately 30% of MIs are ST-elevation MI (STEMI).<sup>31</sup> Patients with STEMI are generally younger at presentation and predominantly male.<sup>33 34</sup> The incidence of STEMI is decreasing, whereas the incidence of non-ST-elevation MI (NSTEMI) is increasing.<sup>35 36</sup> Myocardial infarction is associated with a number of predisposing risk factors, generally classified as modifiable or non-modifiable.<sup>37</sup> The modifiable risk factors include smoking, diabetes, hypertension, hypercholesterolemia, and abdominal obesity. The non-modifiable risk factors include age, sex, and genetics. Protective factors have been identified, including physical activity and increased intake of fruits and vegetables.<sup>37</sup> In a large register study of more than half a million cases of first MI, more than 85% of patients exhibited at least one of the modifiable

risk factors or heredity for MI.<sup>38</sup> Controlling risk factors and incorporating preventive factors are important lifestyle goals to minimize cardiovascular burden.<sup>37</sup> In addition to above mentioned risk factors, a number of external factors associated with emotional stress, physical activity, and lifestyle may affect the onset of myocardial infarction by acting as short-term triggers of MI.<sup>39-41</sup> These risk factors comprise the focus of Studies I and II and are described in more detail in the following section.

## **Short-term risk-factors**

The multifactorial nature of MI is complex, involving short-term risk factors as potential precipitators of MI.<sup>1 37 42</sup> These can be categorized as host-related (e.g. depression, influenza, emotional distress, stress) and external risk factors such as weather and air pollution. The first recorded observations of short-term risk factors as triggers of MI date from the earliest related publications. The patient described by Malmsten and von Düben in 1859 was deeply mourning the loss of his wife, which occurred three months prior to his suffering the MI.<sup>4</sup> Several studies have shown an association of depression with risk of MI, and numerous patient interview studies have identified emotional distress preceding an MI event. The earliest studies of season and weather associations were published in the 1920s, in which most cases were observed during winter and consequently correlated with air temperature.<sup>43 44</sup> In 1932, Collins et al. described the relationship of influenza to organic heart disease with highest incidence corresponding to the peak of the influenza pandemic.<sup>45</sup> Recently, influenza was shown to be associated with a six-fold increase in MI.<sup>46</sup> The interest in MI triggers expanded following the report by Muller et al. of circadian variation in its incidence, peaking at around 09.00, correlated to time of awakening.<sup>47-50</sup> A large number of potential triggers have been identified, including cold weather exposure, air pollution, earthquakes, hurricanes, war, sporting events, and stock market volatility.<sup>37 40 41 46 51-60</sup> Studies have shown that cardiac mortality in the western world consistently peaks on Christmas and New Year holidays and during Islamic holidays in countries where that religion predominates.<sup>61-64</sup> The variation in characteristics of short-term triggers suggests that they may induce MI by initiating rupture of an atherosclerotic plaque through different mechanisms. Because MI is the product of a lifelong atherosclerotic process in the coronary arteries, the external factors do not cause MI but precipitate the event.

# Treatment

Therapy guidelines for STEMI and NSTEMI differ. Since this research is focussed on STEMI, treatment strategies for NSTEMI will not be discussed. The cornerstone of STEMI treatment is prompt diagnosis and early reperfusion to reduce infarct size and improve survival.<sup>35</sup> Pharmacological therapy in the acute phase targets pain relief with morphine and nitro-glycerine and alleviation of hypoxemia in patients with blood oxygen saturation  $\leq 90\%$ . Important time guidelines have been established by the European Society of Cardiology (ESC): Time from initial medical contact to ECG and diagnosis should be  $\leq 10$  minutes, and maximum time from diagnosis to primary PCI should be  $\leq 120$  minutes, or fibrinolysis should be considered and initiated within 10 minutes of initial contact, as studies have shown that risk of adverse outcome is increased after 60 minutes.<sup>65</sup> Anticoagulant therapy with unfractionated heparin is recommended in addition to antiplatelet therapy with aspirin at a loading dose of 150–300 mg together with a more potent P2Y<sub>12</sub> inhibitor in the peri-procedural phase unless contraindicated.<sup>35</sup> The role of intravenous beta-blockers is a topic of this thesis and is discussed in more detail below. Following reperfusion, the patient should be admitted to a coronary care unit with continuous monitoring, evaluation of cardiac function and risk factors, and initiation of appropriate long-term pharmacological treatment.<sup>35</sup>

## Early intravenous beta-blockers

In the absence of contraindications, guidelines state that beta-blocker therapy should be initiated in all STEMI patients within 24 hours and up-titrated during and after hospitalisation as tolerated.<sup>35 66</sup> When started early post-MI, beta-blockers have been shown to improve survival rate.<sup>35 67</sup> The suggested mechanisms of the observed benefit of beta-blockers includes a reduction in myocardial oxygen demand and fewer and less malignant arrhythmias.<sup>68 69</sup> Beta-blocker therapy in the setting of MI has been studied for nearly 50 years, with the first large randomized trials conducted in the early 1980s laying the groundwork for their use in clinical practice. A number of trials were conducted before and during the era of pharmacological reperfusion therapy, investigating initial IV beta-blocker followed by long-term oral treatment compared to placebo. The trials showed in general a beneficial effect in the pre-fibrinolysis era and inconsistent results during the fibrinolysis era.<sup>13-15 69-72</sup> The effect of IV beta-blocker alone has therefore never been investigated until recently, in the present era of primary PCI, as nearly all patients receive standard oral beta-blocker therapy today. Current guidelines recommend the consideration of early administration of IV beta-blocker at time of presentation in hemodynamically stable

patients undergoing PCI (Class IIa, level of evidence A).<sup>35</sup> The level of evidence for use in conjunction with primary PCI is not convincing. To date, four randomized clinical trials have been conducted on the administration of IV beta-blockers in patients with STEMI undergoing primary PCI. The trials were small and showed inconsistent results (Table 1).<sup>73-76</sup> Two of the studies administered esmolol and landiolol, beta-blockers rarely used in clinical practice and of which, one evaluated post-reperfusion IV beta-blockers, and none of the four studies was powered for hard clinical endpoints. Two of the four trials assessed IS by cardiac magnetic resonance imaging (CMR)<sup>74 76</sup>; one measured peak troponin T as a surrogate of IS<sup>75</sup>; and one assessed LVEF measured with left ventriculography<sup>73</sup>, a procedure not widely used in clinical practice. The randomized Effect of Metoprolol in Cardioprotection During an Acute Myocardial Infarction (METOCARD-CNIC) trial provided promising results with regard to IS reduction and improved LVEF in patients with anterior STEMI. However, the results were not replicated in the Early-BAMI trial with unselected STEMI patients, furthering the uncertainty around the effectiveness of IV beta-blockers in patients undergoing primary PCI and treated with potent platelet inhibition.<sup>74 76</sup>

The paucity of studies and uncertainty regarding IV beta-blocker benefits translates to a high variation in their clinical use. The use of IV beta-blockers ranges from 2% to 40% in Swedish hospitals, with the majority administering it to fewer than 20% of MI patients.<sup>33</sup> The uncertainty is further reflected in the steady decline in the use of IV beta-blockers.<sup>33</sup>

**Table 1. Randomized trials of IV beta-blockers in patients with STEMI treated with PCI**

Trial	Year	Design	Inclusion criteria	Beta-blocker	Sample size	Endpoint	Result	LVEF
Hanada et al. <sup>73</sup>	2012	Single-center, open, no placebo	Killip class I or II, HR $\geq$ 50bpm, SBP $\geq$ 90mmHg	Landiolol 24h weight-based continuous infusion after PCI	96	Arrhythmias, cardiac death, left ventriculography at 2 weeks and 6 months	No difference in any endpoint	Increased LVEF
METOCARD-CNIC <sup>74</sup>	2013	Multi-center (Spain), open, blinded endpoint, no placebo	Killip class I or II, anterior STEMI only, SBP $\geq$ 120mmHg, HR $\geq$ 60bpm, no previous per os beta-blockers	Metoprolol Three bolus doses of 5mg 2 min apart.	270/220	Infarct size (CMR) at 5-7 days and 6 months	Smaller infarct size. No difference in clinical endpoint	Increased LVEF
BEAT-AMI <sup>75</sup>	2016	Single-center, single-blinded, placebo-controlled. IV beta-blocker administration after PCI.	Killip class I or II, HR $>$ 60bpm, MAP $>$ 65 mmHg	Esmolol 24h weight-based continuous infusion	100	Troponin T and TTE on day 1, after 6 weeks and 6 months	Lower peak TnT	No difference
EARLY-BAMI <sup>76</sup>	2016	Multi-center (Spain & Netherlands), double-blinded, placebo-controlled	Killip class I or II, HR $\geq$ 60bpm, SBP $\geq$ 100mmHg, no history of previous MI	Metoprolol Two bolus doses of 5 mg each	683/342	Infarct size (CMR) at 1 month $\pm$ 10 days	No difference in primary endpoint or enzyme release. Less malignant arrhythmias.	No difference

BEAT-AMI = The BEta-Blocker Therapy in Acute Myocardial Infarction Trial; CMR = Cardiac Magnetic Resonance Imaging; EARLY-BAMI = Early Beta-blocker administration before primary PCI in patients with ST-elevation myocardial infarction trial; IV = Intravenous; LVEF = Left Ventricular Function; METOCARD-CNIC = Effect of METOProlol in CARDioproteCtioN during an acute myocardial InfarCtion.

## Risk assessment post-STEMI

Risk factors do not only influence the incidence of MI, but also impinge upon outcome of the event. According to The National Board of Health and Welfare, mortality rate due to MI in Sweden was 76 per 100 000 population in 2017.<sup>32</sup> A number of high-risk factors that contribute to determining outcome post-MI have been identified. These include the type of MI; treatment delay; previous comorbidities such as anaemia, chronic kidney disease, peripheral artery disease, atrial fibrillation, and heart failure; extent of coronary artery involvement; levels of various biomarkers; Killip class; and left ventricular function as well as complications due to the MI.<sup>77-80</sup> The Killip classification system is used to classify patients from I–IV according to their signs and symptoms of heart failure and is a strong prognostic factor.<sup>81</sup> In addition, a number of signs and symptoms associated with large infarcts are associated with adverse outcome. These include hypotension (SBP  $\leq$ 100 mmHg), tachycardia, and ECG characteristics as well as presenting features such as cardiogenic shock and cardiac arrest.<sup>82-84</sup>

Guidelines recommend that patients with STEMI should be assessed to determine risk of further adverse events upon admission and at discharge.<sup>35</sup> Early risk assessment serves a means of identifying patients at high risk of death during hospitalisation. The use of validated risk scores based on the presence of predictors of outcome is recommended for this purpose.<sup>35 66</sup> The assessment of long-term risk prior to discharge includes evaluating LVEF and LV dysfunction, key prognostic factors of long-term outcome.<sup>35</sup> Routine transthoracic echocardiography (TTE) is recommended after primary PCI in all STEMI patients before discharge or earlier if indicated. In addition to the evaluation of LVEF at discharge, assessment of severity of coronary artery disease (CAD) and degree of revascularization, metabolic risk profile, renal function, and comorbidities are also recommended. The extent of infarcted myocardium has been shown to be a predictor of long-term mortality and heart failure after STEMI, as it is inversely related to left ventricular function and positively correlated to malignant arrhythmias.<sup>85-90</sup> A number of predictors of infarct size are known and include coronary artery territory, TIMI flow before PCI, and time from symptom onset to reperfusion as well as the release of cardiac enzymes.<sup>91</sup> A strong correlation between IS and circulating levels of cardiac troponins provides predictive information and is the focus of Studies IV and V in this research.

The following introduces the prognostic procedures employed in Studies IV and V.

## Cardiac magnetic resonance imaging

Infarct size can be quantified non-invasively using radiologic examination. In the past, single-photon emission computed tomography was used, but has been replaced by late gadolinium enhanced CMR as the gold standard technique due to high spatial resolution and greater sensitivity for smaller infarctions.<sup>92</sup> Cardiac magnetic resonance imaging allows accurate measurements of IS in grams, as percentage of left ventricular mass (LVM), or as percentage of myocardium at risk, with high reproducibility and low inter-observer variation. It quantifies microvascular obstruction as well as myocardial function (LVEF/RVEF), LV volume, and LVM. Morphological and function assessments by CMR have been shown to provide strong prognostic information post-STEMI.<sup>85-89</sup> An inverse relationship exists between IS and LVEF. However, high cost and limited availability and applicability, due to logistics and contraindications, precludes the routine use of CMR as a prognostic tool in STEMI patients and has yet to become standard in the clinical setting.

## Cardiac biomarkers

Cardiac biomarkers play a crucial role in the diagnosis of MI. In the past, levels of creatine kinase, creatine kinase isoenzyme-MB (CK-MB), myoglobin, and lactate dehydrogenase were measured but have been largely replaced by cardiac-specific troponin (cTn) assays. Currently, 5<sup>th</sup> generation high-sensitivity assays based on monoclonal antibodies targeting cardiac-specific epitopes are the preferred biomarkers for diagnosis of acute coronary syndrome (ACS).<sup>93</sup> Biomarkers in the setting of MI are not only useful for their diagnostic properties but also provide strong prognostic information.<sup>94-99</sup> Troponin is a protein complex consisting of three subunits and make up integral components of the contractile apparatus in myocytes. Each subunit plays a specific role in muscle contraction, and three isoforms of troponin T and troponin I are identified based on their presence in slow- and fast-twitch skeletal muscle or cardiac muscle.<sup>100</sup> In comparison, two isoforms of troponin C have been identified, one in fast-twitch skeletal muscle and one in both cardiac and slow-twitch skeletal muscle.<sup>93</sup> <sup>100</sup> The majority of troponin is located on the contractile apparatus, making up what is termed the structural pool, with a small fraction reported to occur unbound in the cytoplasm.<sup>100-102</sup> The precise mechanism behind the release of cTn into blood is unknown, and whether reversible ischemia causes release of cTn into the bloodstream is controversial. However, it is generally accepted that release occurs secondary to myocardial necrosis with rupture of the cell membrane and proteolytic degradation of the contractile apparatus. The initial increase in the blood level is thought to represent early release from the cytoplasmic

pool, whereas the observed plateau phase, with elevated cTn detectable up to two weeks post-MI, is suggested to be the result of damage in the structural pool.<sup>101</sup> In the setting of MI, and in particular STEMI, studies have confirmed a strong correlation between the quantity of cTn released into the bloodstream and IS, translating to strong prognostic value.

## **Risk scores**

Standardized clinical risk assessments are intended as easy-to-use clinical tools for early risk evaluation post-MI. Over the years, numerous risk scores have been developed from large datasets using multiple predictors of outcome and regression models. Current ESC and American Heart Association guidelines recommend the two most widely used for early risk assessment, the Global Registry of Acute Coronary Events (GRACE) score and Thrombolysis in Myocardial Infarction (TIMI) risk score.<sup>35 66</sup> They have been directly compared in patients with STEMI with regard to several outcome measures in small studies.<sup>103 104</sup> Important differences between the two exist. The GRACE assessment is based on an international ACS registry that included real-world patients with STEMI as well as NSTEMI and unstable angina.<sup>105</sup> The TIMI risk score was developed using a population from a randomized clinical trial, including STEMI patients eligible for thrombolysis.<sup>106</sup> The GRACE score was developed to predict in-hospital mortality and later modified to include six-month mortality, while the TIMI predicts 30-day mortality. Variables included in the risk scores are presented in Table 2.

### *Global Registry of Acute Coronary Events Risk Score (GRACE)*

The GRACE risk score is recommended by ESC STEMI guidelines.<sup>35</sup> It is derived from the GRACE international ACS registry, a collaboration of 94 hospitals in Argentina, Australia, Austria, Belgium, Brazil, Canada, France, Germany, Italy, New Zealand, Poland, Spain, the United Kingdom, and the United States designed to study outcomes of ACS in unselected patients.<sup>105</sup> Three publications have given rise to the GRACE risk score: Granger et al. developed a model to assess risk of in-hospital mortality based on 11 389 patients enrolled in the registry from April 1999 through March 2001.<sup>105</sup> Approximately 35% of included patients were diagnosed with STEMI. The model was based on a multivariable stepwise logistic regression model and was validated on an external dataset of 3972 patients from the GRACE registry and 12 142 patients from the Global Use of Strategies to Open Occluded Coronary Arteries IIb (GUSTO-IIb) trial dataset. The model obtained a C-statistic of 0.84 in the GRACE validation dataset and 0.79 in the GUSTO-IIb dataset. It was updated to include the prediction of six months post-discharge all-cause mortality

and reinfarction in larger datasets.<sup>107 108</sup> The most recent version, GRACE 2.0, is available as an online tool (<https://www.mdcalc.com/grace-acs-risk-mortality-calculator>) and derived from 32 037 patients enrolled from January 2002 through December 2007 and was validated in a French nationwide registry of 2959 patients.<sup>109</sup> It predicts one-year mortality, one-year all-cause mortality/MI, and three-year all-cause mortality.<sup>109</sup> Variables included in the model are presented in Table 2. In the validation dataset, C-statistics of 0.83 and 0.84 were obtained for all patients and for STEMI patients only, respectively, with regard to one-year all-cause mortality. Similar estimates were obtained for the simplified models.<sup>109</sup> The GRACE risk model has been externally validated.<sup>110</sup>

### *TIMI-risk score*

The TIMI risk score was developed as a bedside tool to assess risk of 30-day all-cause mortality in patients with STEMI eligible for reperfusion therapy with fibrinolysis.<sup>106</sup> The model was developed using the patient population from the randomized clinical trial Intravenous nPA for Treatment of Infarcting Myocardium Early II dataset including 14 114 patients from the TIMI-II database. A logistic regression model was used and was externally validated by a dataset from the TIMI-9 trial including 3 687 patients. The model is an additive model with a scoring system of 0-14 points. It obtained C-statistic values of 0.78 in the original dataset and 0.75 in the external dataset with respect to 30-day mortality, and 0.765 for one-year mortality. The model has been externally validated.<sup>111</sup>

**Table 2. Variables included in GRACE and TIMI risk score**

GRACE risk score	TIMI risk score
Age	Age ≥75 years – 3 points
Killip class	Age 65–74 years – 2 points
SBP	History of DM, HTN or angina – 1 point
HR	SBP <100mmHg – 3 points
ST-segment deviation	HR >100bpm – 2 points
Cardiac arrest at presentation	Killip class II–IV – 2 points
S-creatinine	Weight <67kg – 1 point
Elevated cardiac enzymes	Anterior STEMI/LBBB – 1 point
	Time to reperfusion >4hrs – 1 point

DM = Diabetes mellitus; HR = Heart rate; LBBB = Left bundle branch block; SBP = Systolic blood pressure.

## *Echocardiography*

Guidelines recommend the routine use of TTE to assess LVEF in all patients with STEMI before discharge. Initial improvement in LVEF is often seen after STEMI and occurs partially due to myocardial stunning in the acute phase of STEMI as well as to newly administered drugs, e.g. ACE-inhibitors and beta-blockers.<sup>35</sup> Patients with LVEF  $\leq 40\%$  should be re-evaluated within 6 –12 weeks following optimal medical therapy and complete revascularization to assess the need for an implantable cardioverter defibrillator (ICD).<sup>35 66</sup> In addition to LVEF assessment, TTE is capable of detecting structural heart problems such as valvular heart disease, hypertrophy, and LV and LA dilation. Advantages over CMR include low cost, rapidity, and widespread availability. Factors making it inferior to CMR include suboptimal image quality in obese patients and inter-observer variability.

## Registries and datasets used in this research

This chapter briefly describes the registries and trial datasets that were used in this thesis.

### **SWEDEHEART**

Although the significant improvements in outcome of MI achieved in recent decades have been due to improvement in diagnosis and the introduction of novel therapies, registries and data sources have enabled us to continuously monitor and evaluate their effectiveness. The nationwide Swedish Web-system for Enhancement and Development of Evidence-based care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART) is perhaps one of the most comprehensive CAD registries worldwide and an invaluable source of research material. Its exceptionality lies in its lack of recruitment bias, including all patients admitted to a CCU in Sweden, thereby reflecting a real-world MI patient population.<sup>112</sup> The SWEDEHEART registry comprises four national registries of CAD: the Swedish Register of Information and Knowledge about Swedish Heart Intensive Care Admission (RIKS-HIA), the Swedish Coronary Angiography and Angioplasty Registry (SCAAR), the National Registry of Secondary Prevention, and the Swedish Heart Surgery Registry. The RIKS-HIA was originally a regional registry established in the early 1990s and became a national quality register in

1995. The SCAAR was established in 1998 by merging two registries, the angiography registry and the angioplasty registry. The four registries merged in 2009, establishing SWEDEHEART as a national registry of all patients admitted due to ACS or undergoing coronary or valvular intervention.<sup>112</sup> Each of the four registries serves a distinct purpose, and all hospitals in Sweden participate with prospective web-based data collection. Inter-hospital agreement has been estimated at 96%. Each Swedish citizen has a unique personal identification number allowing data collection from the National Patient Registry and National Population Registry. Only RIKS-HIA and SCAAR were used in this research.

#### *Register of Information and Knowledge about Swedish Heart Intensive Care Admission (RIKS-HIA)*

All consecutive patients with symptoms suggestive of ACS admitted to a CCU are recorded in the RIKS-HIA. Background information such as age, body mass index; smoking status; electrocardiographic findings; past medical history; and previous examinations, interventions, and complications is collected. The registry includes ~50 000 admissions to any of the 74 CCUs in Sweden annually. Of these, an average of 18 000 admissions are discharged with a diagnosis of MI.

<sup>112</sup> Nationwide, the registry includes ~70% of all MIs when compared to numbers from the National Board of Health and Welfare based on the ICD-10 codes only.<sup>31</sup>

<sup>32</sup>

#### *Swedish Coronary Angiography and Angioplasty Registry (SCAAR)*

All coronary angiographies with subsequent interventions in the 29 catheterization laboratories in Sweden are recorded in the SCAAR database for complete coverage of angiographies and interventions in Sweden. Data capture is on a procedural level as well as intra-procedural, with data pertaining to each coronary artery segment and phases of intervention collected. Data of indication, peri- and post-procedural pharmacotherapy, previous comorbidities, anatomical location of stenosis or occlusion, degree of stenosis for each coronary segment, adjunct therapies, anti-platelet therapies, primary and secondary decisions after angiography, invasive diagnostic imaging modalities, and PCI variables are collected.

## **CHILL-MI**

The CHILL-MI trial ([www.clinicaltrials.gov](http://www.clinicaltrials.gov); identifier NCT01379261) was a randomized, endpoint-blinded, international multicentre study aimed to investigate the cardioprotective effects of hypothermia as adjunctive therapy to PCI.<sup>113</sup> One-hundred-twenty patients with STEMI treated with PCI were randomized to hypothermia induced by rapid infusion of cold saline and endovascular cooling or

to standard care. Patients with cardiac arrest, history of MI/PCI or cardiac artery bypass graft (CABG), known heart failure, end-stage kidney disease or hepatic failure, recent stroke, coagulopathy, pregnancy, or Killip class II – IV at presentation were excluded. Hypothermia was induced by forced infusion of 4°C saline solution and maintained for one hour after reperfusion, followed by spontaneous rewarming or continued until the completion of the procedure if the procedure took more than one hour, resulting in a mean body temperature at reperfusion of 34.7±0.6°C. The primary endpoint was IS/myocardium at risk (MaR) assessed by CMR on day 4±2. The primary endpoint was not significantly reduced (relative reduction 13%,  $p = 0.15$ ). The study concluded that, although hypothermia did not reduce IS, it is feasible and safe, resulting only in a delay of 9 min.

### **DANAMI-3**

The DANAMI-3 trial ([www.clinicaltrials.gov](http://www.clinicaltrials.gov); identifier: NCT01435408) encompassed three randomized investigator-initiated trials in a multicentre setup. The trial programme was designed to evaluate ischemic post-conditioning (DANAMI-3-iPOST), deferred stenting (DANAMI-3-DEFER), and PCI in culprit lesion only vs. fractional flow reserve (FFR) guided complete revascularization (DANAMI-3-PRIMULTI) in patients with STEMI. The study design for the DANAMI-3 trial has been previously published.<sup>114</sup> Patients were randomized from all centres in Denmark performing primary PCI in an open blinded endpoint design. Inclusion criteria for the DANAMI-3 trial included age  $\geq 18$  years with onset of chest pain  $< 12$  hours and ST-segment elevation  $\geq 0.1$  mV in two or more contiguous leads or newly developed left bundle branch block. Exclusion criteria were pregnancy; known intolerance to aspirin, P2Y12 inhibitors, heparin, and/or contrast agent; inability to understand the presented information or provide informed consent; unconsciousness; cardiogenic shock; PCI deemed unfeasible; indication for CABG; stent thrombosis; haemorrhagic disorder; or known coagulopathy. A total of 2239 patients were included. DANAMI-3-PRIMULTI determined that complete FFR-guided revascularisation reduced the risk of future adverse events after primary PCI procedure, largely driven by fewer repeat revascularizations. DANAMI-3-DEFER and DANAMI-3-iPOST did not show an effect of deferred stenting or mechanical post-conditioning. A CMR sub-study was conducted as part of the DANAMI-3 trial program at Rigshospitalet, Copenhagen University Hospital, one of the centres involved in the clinical trial. After revascularization, and within 48 hours of index admission, patients without contraindications were offered a CMR scan with CMR-specific exclusion criteria applied.<sup>115</sup> The CMR was performed using a 1.5 Tesla scanner (Avanto scanner; Siemens, Erlangen, Germany) and a six-channel body array coil.

# Project Description and Aims

The research presented in this thesis assessed aspects of myocardial infarction ranging from external triggers of MI to assessment of current treatment strategies and outcome prediction, with emphasis on STEMI.

The general aim of the research was to increase knowledge in these areas, targeting improvement in the management of patients with MI. In Study I, we analysed association of national holidays, major sporting events, and aspects of circadian rhythm with incidence of MI. Study II investigated the relationship of weather to risk of MI. In Study III, the effect of intravenous beta-blockers in the acute phase of STEMI was determined. Study IV analysed the correlation of clinical biomarkers to long-term IS/LVEF and LV dysfunction after STEMI. In Study V, we repeated the design of Study IV in a larger, external STEMI cohort.

*Specific aims:*

- The aim of Study I was to determine the comparative risk of MI during periods of possible emotional stress, increased physical activity, and/or abrupt lifestyle changes such as national holidays and sports events and to assess that risk relative to circadian cycles.
- The aim of Study II was to determine whether selected weather parameters show an effect on risk of myocardial infarction.
- The aim of Study III was to investigate the effect of IV beta-blocker therapy on short-term mortality and in-hospital cardiac events in patients with STEMI treated with modern antiplatelet therapy and PCI.
- The aim of Study IV was to determine the predictive value of hs-cTnT, CK-MB, and NT-proBNP with respect to long-term IS/LVEF and LV dysfunction compared to that of early IS and LVEF assessed by CMR at 4±2 days post-STEMI.

- The aim of Study V was to validate the results of hs-cTnT in a larger cohort by comparing it to early CMR-assessed IS/LVEF, discharge TTE-assessed LVEF, and standardized clinical risk scores with regard to long-term LV dysfunction.

# Methods

This chapter presents an overview of the materials and methods used in the research. The details of each study can be found in the papers appended to this manuscript.

## Study designs and populations

Research subjects were retrieved from three sources: Studies I, II, and III comprised patients from the SWEDEHEART registry. For Studies IV and V, data from two randomised clinical trials were used, the CHILL-MI (Study IV) and DANAMI-3 (Study V). Studies I and II comprised data of all MI events resulting in admittance to a CCU in Sweden from 1998 through 2013 reported to the SWEDEHEART registry. Studies III, IV, and V included only patients with STEMI undergoing primary PCI. A summary of retrieval source and study population, sample size, and purpose of the studies is shown in Table 3.

**Table 3. Sources of data for this research.**

Paper	Study population	Retrieval source	Sample size	Purpose
I	All MI events 1998–2013 admitted to any CCU in Sweden	SWEDEHEART-RIKSHIA	283 014	Identify potential short-term triggers and temporal risk of MI
II	All MI events 1998–2013 admitted to any CCU in Sweden with available data on weather at symptom onset available.	SWEDEHEART-RIKSHIA	274 029	Determine association of weather and MI
III	STEMI patients treated with primary PCI and DAPT 2006–2013	SWEDEHEART-RIKSHIA+SCAAR	16 909	Evaluate IV beta-blocker treatment in STEMI
IV	STEMI patients treated with primary PCI	CHILL-MI trial	86	Determine predictive value of hs-cTnT
V	STEMI patients treated with primary PCI	DANAMI-3 trial	578	Determine predictive value of hs-cTnT

BB = Beta-Blockers; CCU = Coronary Care Unit; DAPT = Dual Antiplatelet Therapy; hs-cTnT = High Sensitivity-Cardiac Troponin T; IV = Intravenous.

## **Study I**

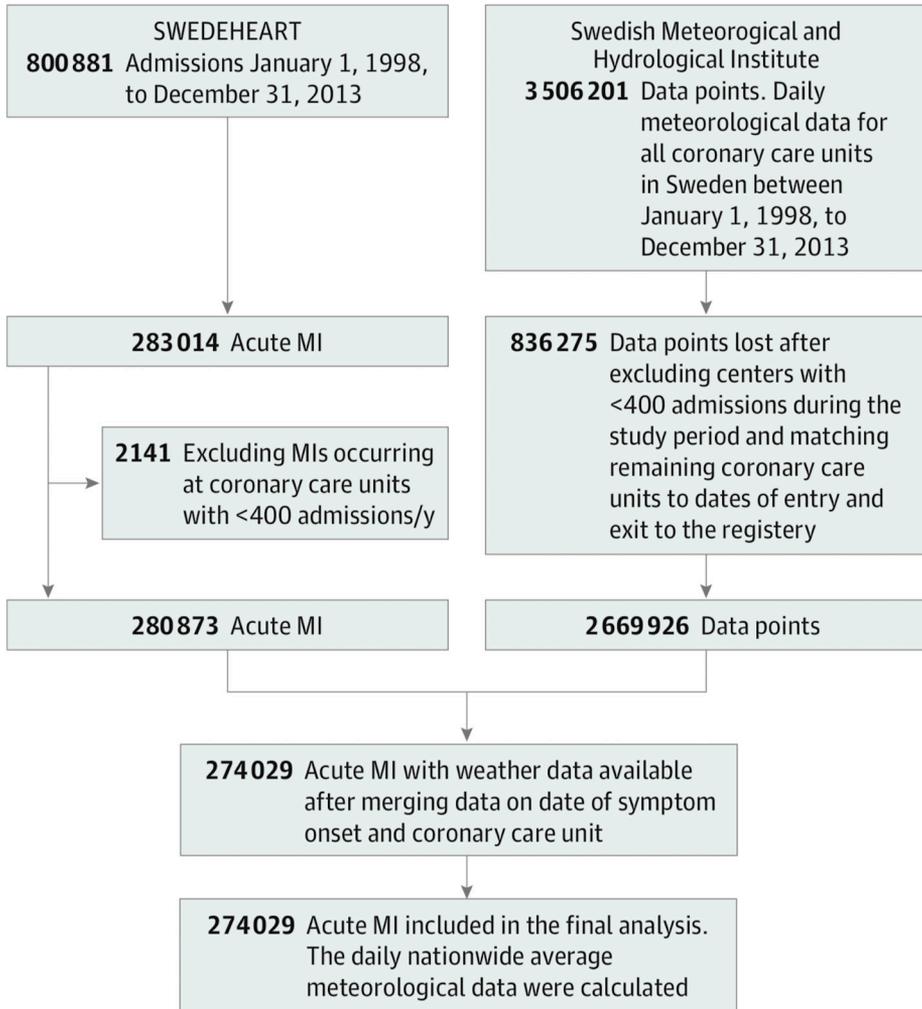
Study I comprised data of all cases of MI admitted to a CCU in Sweden and reported to RIKS-HIA from 1998–2013. Using information of date and time of symptom onset, cases with symptom onset on national holidays including Christmas Eve, Christmas Day, Boxing Day, New Year’s Eve, New Year’s Day, Epiphany, Easter Eve, Easter Sunday, Easter Monday, Midsummer Eve, and Midsummer Day (St. John’s Day) were identified. A period consisting of the fourteen days prior to and following the holiday, excluding any other holidays occurring within this period, was selected as a control, and all MIs occurring within this time frame were identified. In addition, all MIs that occurred on the Fédération Internationale de Football Association (FIFA) World Cup, Union of European Football Association (UEFA) European Championship, and winter and summer Olympic games during the study period were identified. For sport events, the control period was designated as the same time period in the years immediately previous to, and following, the event. Time of symptom onset was available for 88% of MI events, allowing us to study circadian and circaseptan variation. For temporal analyses, Sunday and 00.00 were set as the reference day and hour to which remaining days of the week and hours were compared. The primary outcome was daily count of MI, with STEMI and NSTEMI calculated independently as secondary outcome measures.

## **Study II**

Data from the Swedish Meteorological and Hydrological Institute (SMHI) were used to investigate the association of selected weather parameters with the incidence of MI. The SMHI is a government agency operating under the Ministry of Environment and Energy and collects data from 132 active weather stations in Sweden. The data is readily available through the website [www.smhi.se/en](http://www.smhi.se/en). A map of Sweden from the SMHI website showing active weather stations reporting air temperature is presented in Figure 1. Daily data of air temperature, minimum air temperature, maximum air temperature, wind, sunshine duration, atmospheric pressure, relative humidity, and precipitation were extracted from the SMHI database for each city with a CCU in Sweden during the studied period, 1998-2013. Daily variation in air temperature was calculated from maximum and minimum temperature. Effective air temperature, which is the perceived temperature taking into account wind velocity was calculated using the Osczevski and Bluestein equation available on the SMHI website. Relative humidity, atmospheric pressure, wind velocity, and sunshine duration were available as hourly data and converted to a 24h mean for each city. Weather data for each city were combined into a



NSTEMI. A variety of additional analyses were conducted including analyses at regional, seasonal, and subgroup levels.

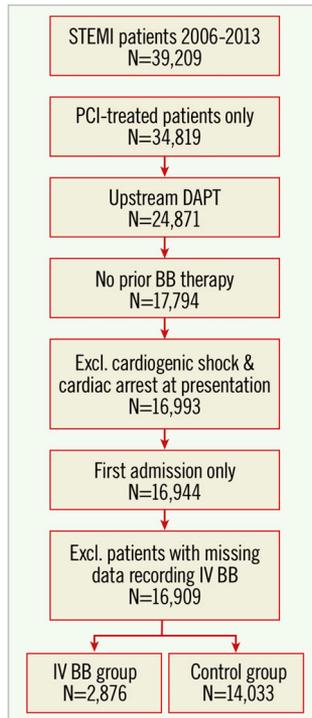


**Figure 2. Flowchart depicting data management in Study II.**

Represents all MI events entered from 1998 through 2013. Weather data were merged with MI data of date of symptom onset and coronary care unit.

## Study III

Patients with STEMI treated with upstream dual antiplatelet therapy (DAPT) and primary PCI and enrolled in RIKS-HIA from 2006 through 2013 were included in this study. We applied a number of inclusion and exclusion criteria to minimize confounding (Figure 3). Patients receiving regular beta-blocker therapy at time of hospitalisation and patients presenting with cardiac arrest or cardiogenic shock were excluded. A total of 16 909 patients constituted the final study population and were divided into two groups based on whether they received IV beta-blockers during hospitalisation. A total of 2 876 patients were treated with IV beta-blockers during the study period, while the non-beta-block group consisted of 14 033 patients. The primary endpoint was all-cause mortality within 30 days of admission. Secondary endpoints included in-hospital events (mortality, cardiogenic shock) and LVEF <40% shown on discharge echocardiogram. In-hospital clinical outcomes, such as cardiogenic shock and LVEF at discharge, were obtained from RIKS-HIA, and data of death was obtained from the National Population Registry. Data on comorbidities were obtained from the National Patient Registry. Cardiogenic shock was defined as one of the following: 1) systolic blood pressure (SBP) <90mm Hg for >30 minutes after hypovolemia had been excluded, 2) signs of hypo-perfusion in at least one organ system, or 3) IV inotropic drugs or intra-aortic balloon pump needed to maintain SBP >90mm Hg for >30 minutes.



**Figure 3. Flowchart of subject inclusion, Study III.**

Patients with STEMI treated with upstream DAPT and undergoing PCI during the study period were included. The numbers of patients remaining after each inclusion and exclusion criteria are shown.

BB = beta-blocker; DAPT = Dual antiplatelet therapy.

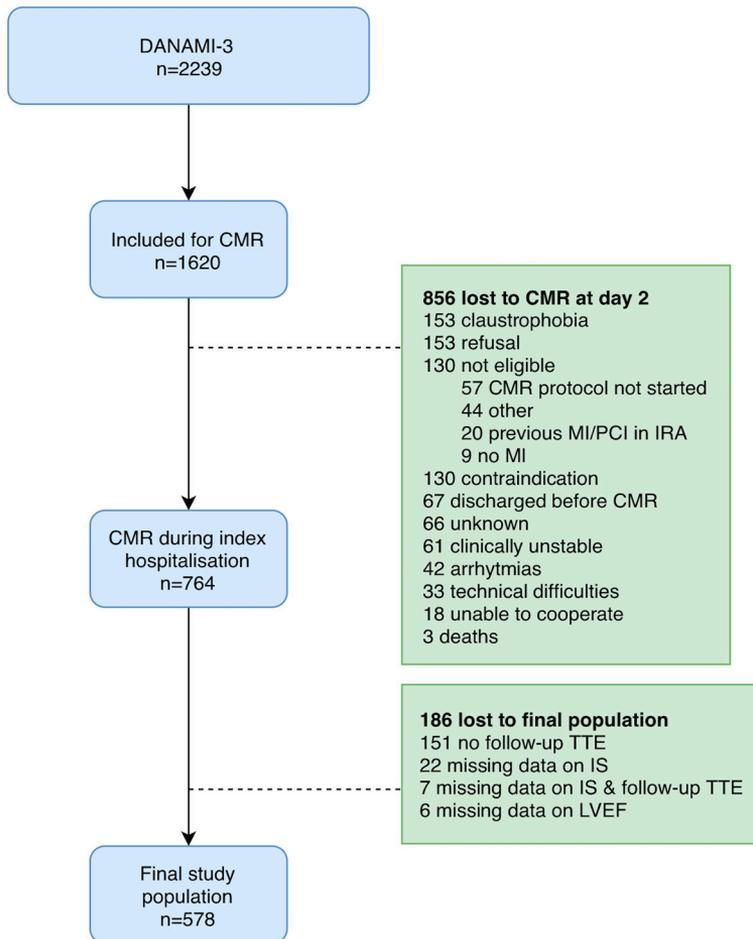
## Study IV

The CHILL-MI trial provided data of IS and LVEF for 101 patients at  $4 \pm 2$  days and for 86 patients at six months post-STEMI. Biomarker data collected from peripheral vein puncture at baseline, 6, 24, and 48 hours post-PCI was available for all patients. Biomarkers in heparinized plasma samples were analysed (Elecsys Troponin T high sensitivity assay, Roche Diagnostics; Elecsys CK-MB assay, Roche Diagnostics; Elecsys NT-proBNP, Roche Diagnostics) and their correlation to long-term IS/LVEF was compared to IS/LVEF in the acute phase of STEMI assessed by CMR during index hospitalisation ( $4 \pm 2$  days). In addition, the predictive value of the biomarkers was assessed with regard to LV systolic function, with dysfunction

defined as LVEF  $\leq$ 40%. The CMR protocol has been published elsewhere.<sup>113</sup> All CMR analyses were performed by a core lab (Imacor AB, Lund, Sweden) using post-processing software (Segment, v.1.9 R3084; <http://segment.heiberg.se>) by blinded observers.

## Study V

The primary objective of Study V was to compare the predictive value of hs-cTnT to those of early CMR-assessed IS and LVEF, discharge LVEF assessed by TTE, and GRACE and TIMI-risk scores, with regard to long-term LV dysfunction. The study population consisted of the subset of patients (n=764) in the DANAMI-3 CMR substudy. Data of IS and LVEF was available for 731 and 757 patients, respectively. A flowchart presenting CMR exclusion and patient selection criteria is presented in (Figure 4). A total of 578 subjects (79.3%) underwent TTE one-year post-STEMI and comprised the final study population (Figure 4). The primary outcome of LV systolic dysfunction was defined as TTE-assessed LVEF  $\leq$ 40% at one year. Blood samples were collected at baseline using the introducer sheath for PCI, and at 6 and 12 hours post-admission as part of the original trial. Heparinized plasma samples were analysed for hs-cTnT (Elecsys Troponin T high sensitivity assay, Roche Diagnostics) and CK-MB (Elecsys CK-MB assay, Roche Diagnostics), and peak values were identified. An additional aim was to validate the rule-in ( $\geq$ 13 000 ng/L) and rule-out ( $<$ 3500 ng/L) hs-cTnT cut-offs for prediction of long-term systolic dysfunction determined in Study IV.



**Figure 4. Flowchart of subject inclusion, Study V.**

Flowchart showing the number of patients lost to CMR and follow-up TTE. A total of 578 patients were included in the final analysis.

## Statistical analyses

This section presents as an overview of the statistical methods used; complete details can be found in the papers appended to this thesis. Continuous parametric variables are displayed as means with 95% confidence intervals (CI) and differences between groups tested using Students t-test. Continuous non-parametric variables are displayed as medians with interquartile range and comparison between groups assessed using Mann-Whitney U-test. Categorical variables are presented as counts and percentages. Differences among groups were calculated with the Chi-squared test. All analyses were performed using STATA v.14.1 for Macintosh (StataCorp, Texas, USA). The following is a brief summary of paper-specific statistical analyses.

### *Study I*

Incidence rate ratio (IRR) for major holidays, sport events, day of the week, and hour of symptom onset were calculated using univariable Poisson regression. Analyses were conducted on complete case data. The only variables with a considerable quantity of missing data were time of symptom onset and smoking status, which were not available for 12% and 9% of subjects, respectively. Family-wise error rate using the Hochberg method was applied to control for type I errors potentially occurring due to multiple testing.

### *Study II*

We generated a univariable binomial regression model with each weather parameter as a continuous variable as well as a multivariable model adjusted for air temperature, precipitation, relative humidity, atmospheric pressure, wind velocity, change in air temperature, and sunshine duration. The daily totals of MI and MI subtypes were set as outcome variable. Results of regression analyses were reported as IRR and interpreted as change in MI for each SD change in a given weather parameter. Smoothed conditional mean plots were drawn for visual assessment of the relationship between weather variable and incidence of MI. Family-wise error rate using the Hochberg method was applied to control for type I errors potentially occurring due to multiple testing.

The following enables the conversion of results in incidence rates per day to incidence rate per 100 000 population per year by reversing the formula for incidence rate calculation:  $\text{Incidence rate} = \text{Number of new events}/\text{time at risk}$ .

### 1) Incidence rate of MI at minimum temperature of 0°C:

New MIs on days of mean minimum temperature 0°C = 14 297.

Days with 0°C = 299.

Incidence rate per day:  $14297/299=47.81$  MI per day of 0°C.

Patients at risk = 5 848 828 [mean population aged  $\geq 30$  years in Sweden during the study period (Statistics Sweden: [www.scb.se/en](http://www.scb.se/en))].

Incidence rate per 100 000 inhabitants per day:  $(47.81/5848828)*100000 = 0.82$

This translates to  $0.82*365 = 299$  MI per 100 000 persons per year if the mean minimum temperature was 0°C for 365 days.

### 2) Incidence rate of MI at minimum temperature of 10°C:

New MIs on days of mean minimum temperature 10°C = 13861

Days with 10°C = 308

Incidence rate per day:  $13861/308=45.0$  MI per day at 10°C.

Incidence rate per 100 000 inhabitants per day:  $(45.0/5848828)*100000=0.77$ .

This translates to  $0.77*365= 281$  MIs per 100 000 inhabitants if the mean minimum temperature was 10°C for 365 days.

### 3) Incidence Rate Ratio:

The incidence rate ratio between 10°C and 0°C:  $299/281 = 1.064$ .

### *Study III*

Unadjusted mortality event rates were calculated with Kaplan-Meier estimates, and hazard ratios (HR) with 95% CI were calculated using Cox proportional regression. Remaining secondary endpoints were calculated using logistic regression and presented as odds ratios (OR) and 95% CI. Confounders in the multivariable analyses were identified *a priori*. Covariates included in the multivariable analysis were age, heart rate, and systolic blood pressure (all divided into quartiles); sex, comorbidities (diabetes, hypertension, congestive heart failure, peripheral artery disease, chronic obstructive pulmonary disease, previous MI, previous stroke, previous PCI, previous coronary artery bypass grafting), culprit vessel, vascular approach (radial vs. femoral puncture site), atrial fibrillation on ECG, P2Y12 inhibitor (ticagrelor vs. clopidogrel), system delay (time from first ECG to PCI)  $\leq 2$  hours vs.  $>2$  hours, and inclusion year. The PCI centre (29 centres in Sweden) was adjusted for as random effect. Propensity score (PS) was calculated by entering all covariates as predictors into a logistic regression model with IV beta-blocker therapy as the dependent variable, and the resulting score was used to match cases with controls using PS matching. Matching was conducted via the calliper method, assigning one control to each case. Individuals for whom values were missing (7.2%) were excluded from the primary analyses.

### *Studies IV and V*

In Study IV we used linear regression models with bootstrap resampling with 10 000 replications as the primary analysis model. The residuals were checked visually as well as with tests for homogeneity of variance. The area under the receiver operating characteristics (ROC) curve was used to evaluate predictive value (C-index) with regard to LVEF  $\leq 40\%$ . The size of the area under the ROC curve was compared with observations as dependent samples. Cut-offs for ruling in and ruling out LVEF  $\leq 40\%$  were assessed from the ROC tables in Study IV. Similarly, in Study V, the area under the ROC curve was used to evaluate predictive value (C-statistic). To simplify interpretation of negative associations in C-statistics, they were converted to 1-AUC. The size of area under ROC was compared with observations as dependent samples. Youden's index was determined for both outcome measures as a means of identifying the optimal dichotomous cut-off. All analyses were conducted on complete case data.



# Results

## Study I

A total of 283 014 MIs were reported to the SWEDEHEART registry and included in this study. Of these, 95 176 patients were diagnosed with STEMI. Patient characteristics are presented in Table 4. We observed a peak incidence of MI on calendar week 52, more pronounced for NSTEMI (Figure 5). Higher incidence of MI was observed over the entire period of Christmas and Midsummer holidays. Specifically, Christmas Eve, Christmas Day, Boxing Day, New Year's Day, and Midsummer were associated with a higher incidence of MI, but not New Year's Eve or Epiphany (Figure 6). Over the Christmas/New Year holiday period, there was a 15% higher risk of MI (IRR = 1.15; 95% CI, 1.12 – 1.19,  $p < 0.001$ ). The day of the year with the highest incidence of MI was Christmas Eve (IRR = 1.37; 95% CI, 1.29 – 1.46,  $p < 0.001$ ). This translated to approximately 20 more MIs on Christmas Eve as compared to a random day in December/January. Important differences in MI subtypes were apparent with ECG stratification, with a higher risk of NSTEMI on Christmas Eve (IRR = 1.48; 95% CI, 1.38 – 1.59,  $p < 0.001$ ). The Easter holiday was not associated with higher IRR of MI, in contrast to the Midsummer holiday (IRR = 1.12; 95% CI, 1.07 – 1.18,  $p = 0.001$ ). After stratification, this risk was observed only for NSTEMI (IRR = 1.16; 95% CI, 1.09 – 1.23,  $p < 0.001$ ). Periods of sporting events did not show a higher incidence of total MI or subtypes of MI. An explorative analysis including only days on which Sweden played in FIFA World Cup or UEFA European Championship did not show an associated risk. A circaseptan variation in incidence of MI was observed, with higher occurrence on Mondays, and a significant difference in incidence of MI was observed in the analysis of hour of symptom onset, peaking at 08.00. However, this was not the case for Christmas Eve, for which the incidence peaked at 22.00.

**Table 4. Patient baseline characteristics, Studies I and II**

	<b>Study I</b>	<b>Study II</b>
	N = 283 014	N = 274 029
STEMI	95 176 (33.6%)	92 044 (33.6%)
NSTEMI	187 838 (66.4%)	181 985 (66.4%)
Age mean±SD	71.7±12.2	71.7±12.2
BMI mean±SD	26.7 ± 5.9	26.7±5.8
Male	180 205 (63.7%)	174 576 (63.7%)
Female	102 809 (36.3%)	99 453 (36.3%)
Current Smoker	55 673 (21.5%)	53 980 (19.7%)
Past Medical History		
Diabetes	61 955 (21.9%)	60 134 (21.9%)
Hypertension	123 436 (43.6%)	119 799 (43.7%)
CAD	100 638 (35.6%)	97 403 (35.5%)
MI	91 283 (32.3%)	88 325 (32.2%)
PCI	32 846 (11.6%)	32 131 (11.7%)
CABG	23 971 (8.5%)	23 273 (8.5%)
Chronic HF	3 373 (1.2%)	31 858 (11.6%)
Stroke	17 116 (6.0%)	16 721 (6.1%)
Previous Medications		
Beta-blockers	120 904 (42.7%)	117 207 (42.8%)
Calcium Antagonists	51 107 (18.1%)	49 613 (18.1%)
Aspirin	123 647 (43.7%)	119 672 (43.7%)
ACE Inhibitor	88 592 (31.3%)	86 057 (31.4%)
Statins	75 381 (26.6%)	73 271 (26.7%)
Diuretics	87 367 (30.9%)	84 416 (30.8%)

ACE-Inhibitor = Angiotensin-Converting Enzyme Inhibitor; BMI = Body Mass Index; CABG = Coronary Artery Bypass Graft; CAD = Coronary Artery Disease; HF = Heart Failure.

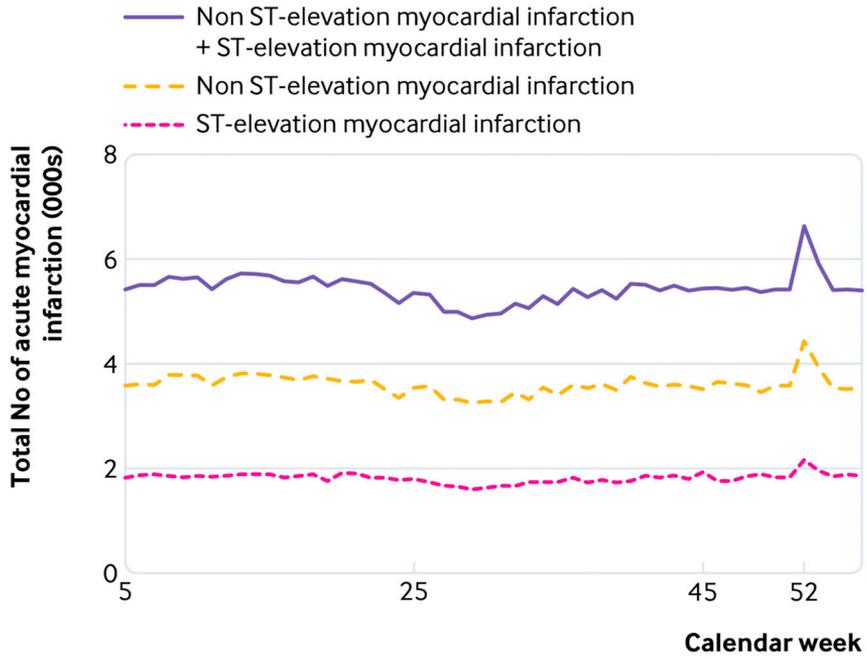
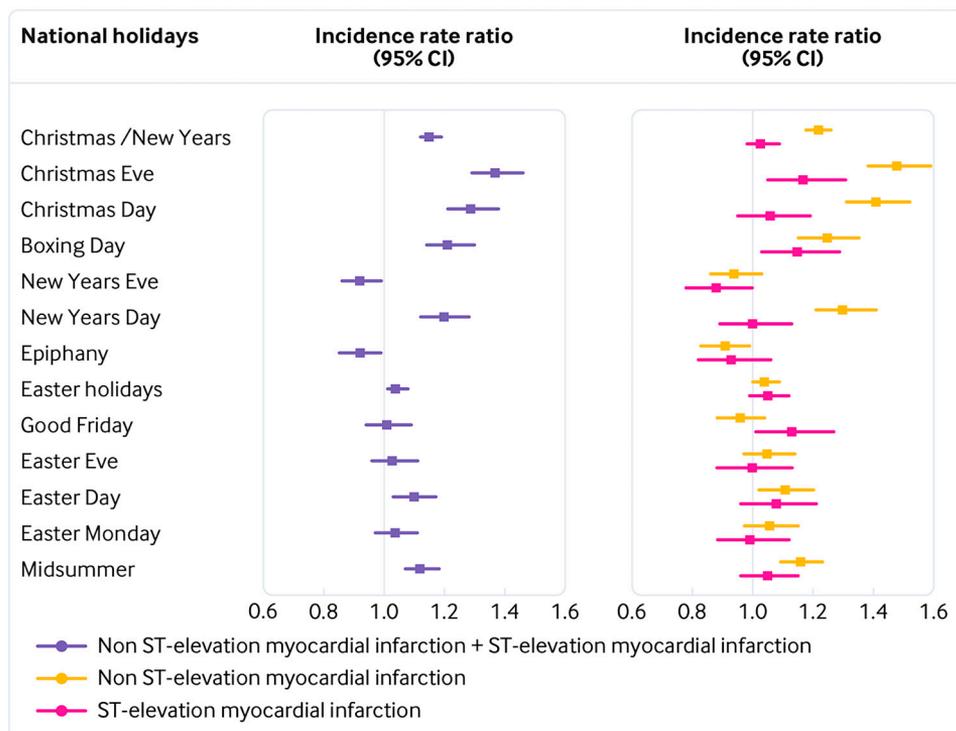


Figure 5. Myocardial Infarct relative to calendar week.

Myocardial infarct events with STEMI and NSTEMI subtypes 1998 – 2013, stratified according to calendar week, peaking at calendar week 52.

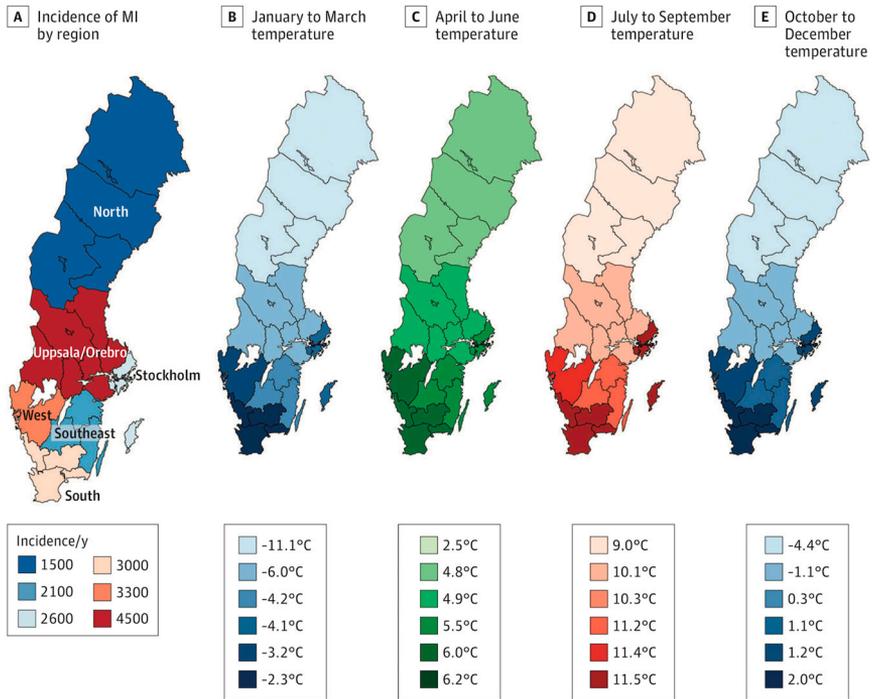


**Figure 6. Incidence rate ratio for risk of MI during national holidays.**  
Risk of MI and its subtypes STEMI and NSTEMI expressed as incidence rate ratios for major national holidays.

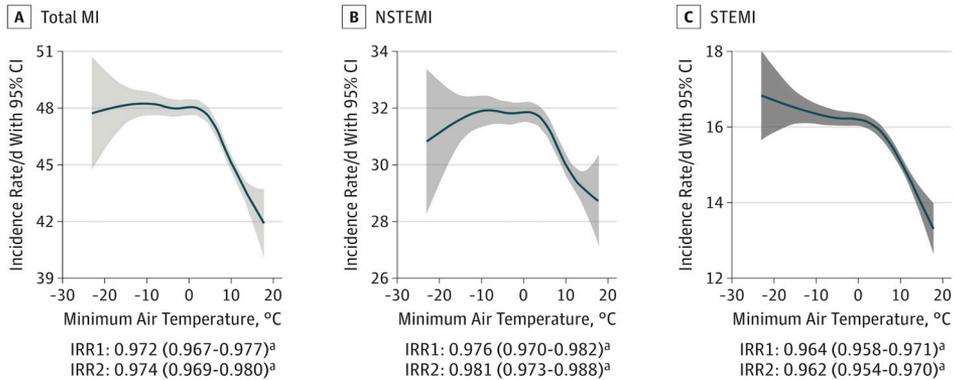
## Study II

Merging the weather database with RIKS-HIA yielded 274 029 (97.6%) patients for whom weather data was available and that were included in the study. A total of 92 044 (33.6%) of patients were diagnosed with STEMI. The mean age of MI was  $71.7 \pm 12$  years. Patient baseline characteristics are presented in Table 4. A map of Sweden and its six healthcare regions with mean minimum air temperature for each season and healthcare region is presented in Figure 7. Air temperature showed a significant negative association with incidence of MI (Figure 8). In addition, days of lower atmospheric pressure, higher wind velocity, and shorter sunshine duration were associated with higher incidence of MI (Figure 9). The most pronounced correlation was observed for air temperature, with one standard deviation increase

(7.4°C) associated with a 2.8% reduction in MI events (unadjusted IRR = 0.972, 95% CI, 0.967–0.977,  $p < 0.001$ ) (Figure 8).



**Figure 7. Mean temperature and MI incidence in the six health care regions of Sweden.** Figure 7. Annual incidence of MI per healthcare region. Figure 7B-E. Mean air temperature for healthcare region and season.

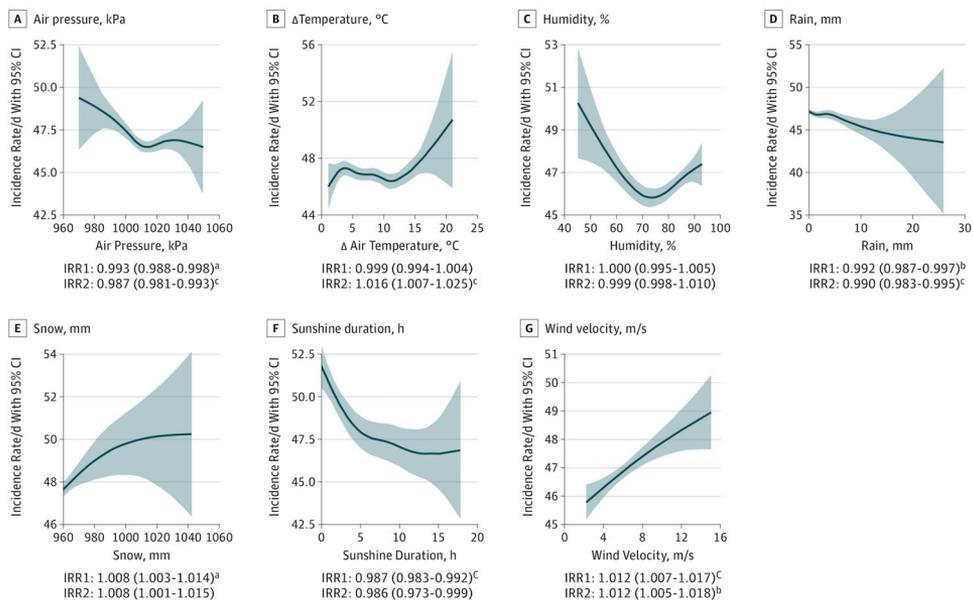


**Figure 8. Daily nationwide incidence of MI and minimum air temperature.**

Smoothed conditional mean plots depicting the relationship of nationwide daily incidence of MI with 95% CI to air temperature. Unadjusted and adjusted incidence rate ratio (IRR) and 95% CI are reported below each graph and interpreted as difference in MI incidence per standard deviation difference in temperature (7.4°C). IRR1 indicates univariable model; IRR2, multivariable model. <sup>a</sup>p < .001

Air temperature was negatively associated with risk of STEMI and NSTEMI across a broad range of subgroups and in all healthcare regions except in the north. With the exception of coldest season (January–March), consistent results were observed with greatest impact seen in July–September, at which time the highest associated risk was observed in STEMI, translating to a 9.5% reduction in incidence rate of STEMI for each SD (3.1°C) increase in air temperature (adjusted IRR = 0.905; 95% CI, 0.873-0.938, p<0.001). In contrast, winter showed a positive association between air temperature and MI in the multivariable analysis, with higher rates of NSTEMI.

Precipitation and atmospheric pressure were negatively associated with STEMI, with a minor increase in risk of MI in both univariable and multivariable analyses (Figure 9). A significant positive association was observed for wind velocity, with a small increase in IRR. Multivariable analyses showed change in air temperature to be associated with increased risk of overall MI and NSTEMI, but not STEMI (Figure 9). Wind velocity and precipitation in the form of snow were the only weather parameters associated with higher risk of MI, NSTEMI, and STEMI in the northern healthcare region, with wind velocity and risk of NSTEMI having the greatest correlation [(unadjusted IRR = 1.077; 95% CI, 1.055–1.098, p<0.001).

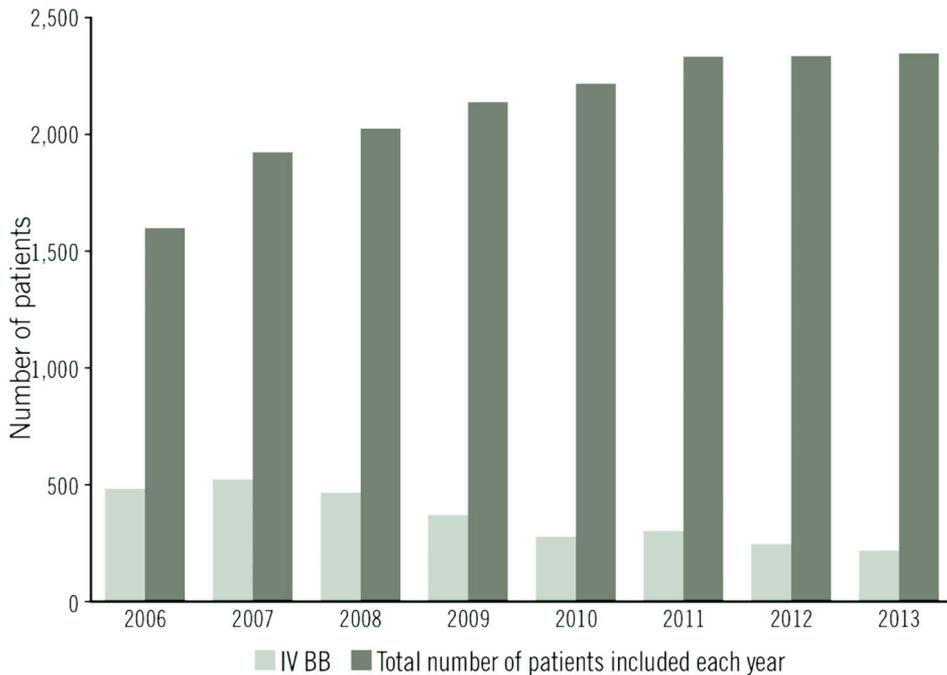


**Figure 9. Daily nationwide incidence of MI and mean minimum air temperature, atmospheric pressure, temperature, humidity, precipitation, sunshine duration, and wind velocity.** Smoothed conditional plots show the relationship of daily nationwide incidence of MI with 95% CI to weather parameters. Unadjusted and adjusted incidence rate ratio (IRR) and 95% CI are reported below each graph and interpreted as difference in MI incidence per standard deviation change in weather parameter. One SD air pressure = 10.9 kPa; Δ temperature = 3.4°C; humidity = 9.6%; rain = 2.6 mm; snow = 0.25 mm; sunshine duration = 4.2 hours; wind velocity = 1.9 m/s. IRR1 indicates univariable model; RR2, multivariable model. <sup>a</sup>p <0.05. <sup>b</sup>p <0.01. <sup>c</sup>p <0.001.

## Study III

After application of inclusion and exclusion criteria, 16 909 patients were included in the study, of whom 2 876 (17.0%) received treatment with an intravenous beta-blocker in the acute phase of STEMI. A significant decline in use of IV beta-blockers was observed over the course of the study period, from 30% to 9% (Figure 10). Important baseline differences existed between the group that received IV beta-blockers vs. controls, with the beta-blocker group being two years younger on average and having a longer system delay, higher heart rate at presentation [80 (68–95) vs. 73 (62–85)], higher blood pressure [SBP 150 (130–170) vs. 140 (121–160)], and more frequent atrial fibrillation in the presenting ECG. The IV beta-blocker group presented with LAD infarctions at higher frequency than the control group

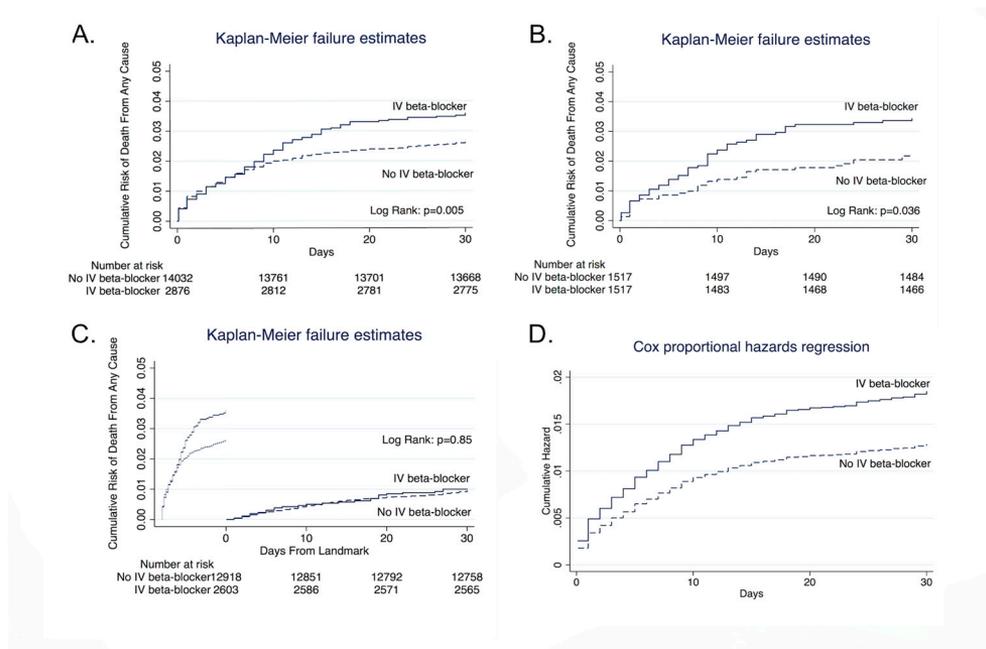
(55.8% vs. 41.6%), translating to higher peak cardiac enzyme values. After PS matching, 1517 cases and 1517 controls remained, and the majority of baseline differences were neutralized.



**Figure 10. Trend in the use of intravenous beta-blockers (IV BB) during the study period.** A decline from 30% to 9% was observed throughout the study period.

The Kaplan-Meier event rate for the primary endpoint of all cause-mortality within 30 days was significantly higher in patients treated with IV beta-blocker (3.6% compared to 2.6% (unadjusted HR = 1.37; 95% CI, 1.10–1.70) and remained elevated after adjusting for confounders in multivariable and PS-matched analyses (Figure 11, Table 5). We observed significantly higher rates of in-hospital mortality in the IV beta-blocker group [Kaplan-Meier event rates: 2.7% vs. 2.0% (unadjusted HR = 1.13; 95% CI, 0.88–1.46)], in-hospital cardiogenic shock [1.9% vs. 1.3% (unadjusted OR = 1.45; 95% CI, 1.07–1.95)], and higher rates of patients with LVEF <40% at discharge [31.4% vs. 18.1%, (unadjusted OR = 2.07; 95% CI, 1.88–2.29)]

(Table 5). Results of the secondary endpoints remained significant after adjustment for confounders, except for cardiogenic shock (Table 5). Analyses revealed consistent results across a wide range of subgroups with a p-value for interaction  $<0.05$  observed for patients with heart rate  $\geq 100$  bpm at presentation, translating to greater hazard in patients with higher heart rate. To address potential residual confounding, a landmark analysis of patients surviving 30 days after index hospitalisation showed no additional association with mortality days 31–60 in those receiving IV beta-blocker therapy (unadjusted HR = 1.02; 95% CI, 0.66–1.56,  $p = 0.94$ ) (Figure 11). Two sensitivity analyses including patients receiving beta-blocker therapy prior to admission and patients not pre-treated with DAPT showed a positive association of IV beta-blocker use with 30-day mortality when compared with control groups in both analyses.



**Figure 11. Mortality analyses in Study III.**

A) Failure estimates for the entire population. B) Failure estimates for the propensity score matched population. C) Landmark analysis of all-cause mortality days 31–60. D) Cumulative hazard based on Cox proportional regression model.

**Table 5. Results of primary and secondary endpoints.**

	<b>IV beta-blocker Group</b>	<b>Control Group</b>	<b>Unadjusted HR (95% CI)</b>	<b>Multivariable adjusted HR (95% CI)</b>	<b>PSM adjusted HR (95% CI)</b>
<b>Primary endpoint</b>					
<b>30 day mortality</b>	103 (3.6%)	368 (2.6%)	1.37 (1.10–1.70)**	1.44 (1.14–1.83)**	1.59 (1.02–2.45)*
<b>Secondary endpoints</b>					
<b>In-hospital mortality</b>	77 (2.7%)	272 (2.0%)	1.13 (0.88–1.46.)	1.23 (0.93–1.61)	1.43 (0.82–2.47)
<b>LVEF &lt;40%</b>	743 (31.4%)	2138 (18.1%)	2.07 (1.88–2.29)***	1.70 (1.51–1.92)***	1.72 (1.43–2.08)***
<b>Cardiogenic shock</b>	56 (1.9%)	189 (1.3%)	1.45 (1.07–1.95)*	1.53 (1.09–2.16)*	1.62 (0.90–2.94)

\*p<0.05; \*\*p<0.01; \*\*\*p<0.001.

PSM = Propensity score matched.

<sup>1</sup> Adjusted for age, heart rate, and systolic blood pressure (all divided into quartiles), sex, comorbidities (diabetes, hypertension, congestive heart failure, peripheral artery disease, chronic obstructive pulmonary disease, previous MI, previous stroke, previous PCI, previous coronary artery bypass grafting, culprit vessel, radial vs. femoral puncture site, atrial fibrillation on ECG, P2Y12 inhibitor ticagrelor vs. clopidogrel, system delay ≤2 hours vs. >2 hours, and inclusion year). PCI-centres were adjusted for as random effect.

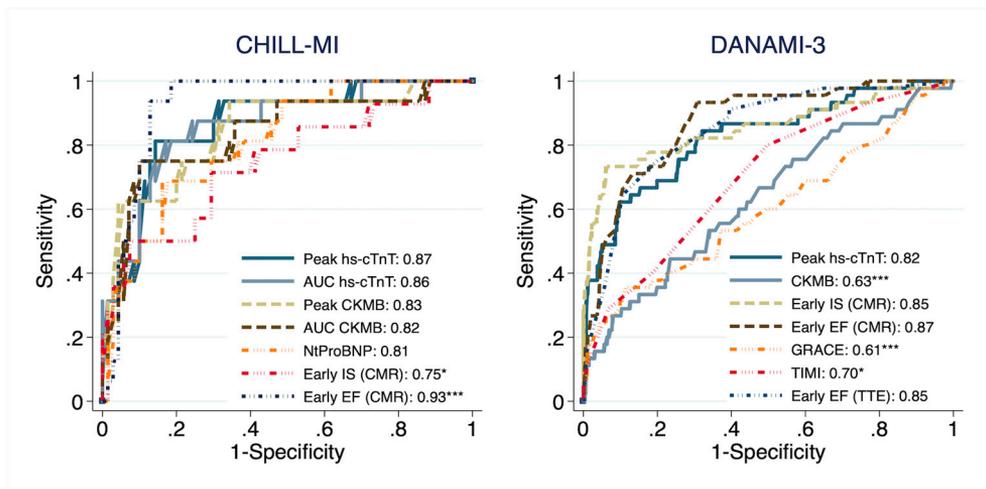
## Study IV

Eighty-six patients who underwent follow-up CMR were included in the final analysis of the study. Patient characteristics, biomarker values, and CMR measures are presented in Table 6.

<b>Table 6. Patient baseline characteristics for Studies IV and V</b>			
	<b>Danami-3</b>	<b>Chill-MI</b>	
<b>Variable</b>	n=578	n=86	p-value
<b>Age</b>	59.1±10.5	58.4±10.1	0.71
<b>Sex</b>			
<b>Male</b>	461 (79.8%)	75 (87.2%)	<0.001
<b>Female</b>	117 (20.2%)	11 (12.8%)	
<b>BMI</b>	27.0±4.0	27.3±3.7	0.51
<b>Smoking</b>	296 (51.2%)	35 (40.7%)	0.07
<b>Diabetes</b>	44 (7.6%)	8 (9.3%)	0.59
<b>Hypertension</b>	188 (32.6%)	26 (30.2%)	0.66
<b>Myocardial infarction</b>	16 (2.8%)	0 (0%)	<0.001
<b>Time from symptom onset to PCI, min</b>	167 (122–265)	145 (121–194)	0.003
<b>TIMI flow before PCI</b>			
<b>0-1</b>	364 (63.0%)	74 (86.0%)	<0.001
<b>2-3</b>	214 (37.0%)	12 (14.0%)	
<b>TIMI flow grade 3 after PCI</b>	555 (96.0)	82 (95.4%)	0.52
<b>PCI main vessel</b>			
<b>LAD</b>	253 (43.8%)	33 (38.4%)	0.35
<b>LCx</b>	93 (16.1%)	10 (11.6%)	0.29
<b>RCA</b>	263 (45.5%)	42 (48.8%)	0.56
<b>Biomarkers</b>			
<b>Peak hs-cTnT</b>	2 945 (1 190–5 910)	6 693 (3 412–9 644)	<0.001
<b>CMR during index hospitalisation</b>			
<b>Infarct size (% of LVM)</b>	15.9 (8.1–24.8)	17.1 (9.7–24.5)	0.50
<b>Infarct size (g)</b>	21 (9–34)	22.3 (11.7–31.1)	0.73
<b>Ejection fraction (%)</b>	50.8±9.7	48.0±8.4	0.01
<b>Myocardium at risk (%)</b>	32.7±11.5	36.6±10.2	0.004
<b>CMR at follow-up</b>			
<b>Infarct size (% of LVM)</b>	11.0 (4.3–18)	10.4 (6.7–15.5)	0.6
<b>Infarct size (g)</b>	13.0 (5.0–23.0)	11.0 (6.9–16.5)	0.23
<b>Ejection fraction (%)</b>	57.9±9.3	51.4±9.7	<0.001

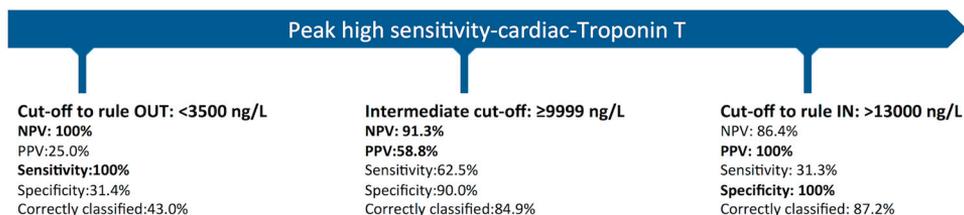
BMI = Body mass index; CMR = cardiac magnetic resonance imaging; LAD = left anterior descending artery; LCx = left circumflex artery; LVM = left ventricular mass; RCA = right coronary artery; TIMI = thrombolysis in myocardial infarction

A number of correlation analyses showed a strong correlation of hs-cTnT with IS and LVEF. However, early IS and LVEF were slightly more strongly correlated to long-term IS and LVEF than were the biomarkers. Sixteen patients showed LVEF <40% at 6 months. The area under the ROC curve of hs-cTnT (0-48hrs) for prediction of long-term LVEF  $\leq$ 40% was 0.86 and slightly higher for peak hs-cTnT, AUC = 0.87, with no significant difference between curves ( $p = 0.75$ ). Infarct size as % of LVM at  $4\pm 2$  days had higher discriminatory value than peak hs-cTnT for prediction of LVEF  $\leq$ 40%,  $p = 0.04$ . The AUC for peak CK-MB was 0.83 and 0.81 for NT-proBNP (Figure 12). Based on ROC tables, the optimal cut-off to rule out long-term LVEF  $\leq$ 40% for peak hs-cTnT was <3500 ng/L (Figure 13). This cut-off yielded an NPV of 100% in 31% true negative individuals. Accordingly, a peak hs-cTnT of >13 000 ng/L identified 31% true positive individuals (100% positive predictive value), and all individuals with a positive test showed an LVEF  $\leq$ 40% after 6 months (Figure 13).



**Figure 12. Receiver Operating Characteristic analyses, Studies IV and V.**

ROC results in Study IV for prediction of LVEF  $\leq$ 40% are presented in the left graph. The right graph presents ROC results of Study V for prediction of left ventricular dysfunction, defined as LVEF  $\leq$ 40% at one year as assessed by TTE. Test of equality of ROC areas evaluated all variables against hs-cTnT as referenced in both studies. \*\*\* =  $p < 0.001$ ; \* =  $p < 0.05$



**Figure 13. Optimal peak hs-cTnT cut-offs for rule-in and rule-out LVEF <40% at 6 months post-STEMI.**

Proposed cut-offs for peak hs-cTnT for rule-in and rule-out of LVEF  $\leq 40\%$  at 6 months with sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV).

## Study V

Data of IS and LVEF was available for 731 and 757 patients, respectively, from the DANAMI-3 trial. Follow-up data on TTE one-year post-admission was available for 578 (79.3%) of the CMR subgroup of patients and constituted the basis of the final analysis. Patients who underwent CMR were younger, more frequently male, and showed lower prevalence of hypertension and myocardial infarction compared to non-CMR participants. Median peak hs-cTnT was 2945 ng/L (IQR, 1190–5910), and mean time from symptoms to PCI was 167 minutes (IQR, 122–265 minutes). A total of 364 (63.0%) showed TIMI flow 0–1, and, in 53 (43.8%), the LAD was the culprit vessel.

Five (7.8%) patients exhibited LVEF  $\leq 40\%$  on TTE examination at one-year post-inclusion. The ROC analyses showed no difference between hs-cTnT and early IS or LVEF in predicting subsequent LVEF  $\leq 40\%$  (Figure 12). The area under the ROC curve of peak hs-cTnT for prediction of LVEF  $\leq 40\%$  was 0.82. The AUC values for other indicators were IS, 0.85 ( $p = 0.22$ ); LVEF, 0.87 ( $p = 0.23$ ); TTE-assessed LVEF, 0.85 ( $p = 0.45$ ); CK-MB, 0.63 ( $p < 0.001$ ); GRACE risk score, 0.61 ( $p < 0.001$ ); and TIMI risk score, 0.70 ( $p = 0.02$ ) (Figure 12). Youden's index was calculated as peak hs-cTnT of 6550 ng/L, correctly classifying 81.8% of patients, with NPV of 96.7%, PPV of 24.2%, and sensitivity and specificity of 66.7% and 82.4%, respectively. The pre-specified cut-off to rule out LVEF  $\leq 40\%$  (hs-cTnT  $\leq 3500$  ng/L) showed specificity of 59.9% and NPV of 98.2%. The cut-off to rule in LV dysfunction (hs-cTnT  $\geq 13\ 000$  ng/L) demonstrated sensitivity of 37.8% with PPV of 50.0% and a positive likelihood ratio of 11.8.

**Table 7. ROC cut-offs to rule in and rule out LVEF  $\leq$ 40%.**

	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)	LR (+)	LR (-)	Correctly classified (%)
<b>Youden's index - hs-cTnT <math>\geq</math>6550 ng/L</b>	66.7	82.4	96.7	24.2	3.8	0.4	81.4
<b>Cut-off to rule out: hs-cTnT <math>&lt;</math>3500 ng/L</b>	86.7	59.9	98.2	15.4	2.2	0.22	62.0
<b>Intermediate cut-off: hs-cTnT <math>\geq</math>9999 ng/L</b>	46.7	94.9	95.5	43.8	9.2	0.56	91.2
<b>Cut-off to rule in: hs-cTnT <math>\geq</math>13000 ng/L</b>	37.8	96.8	94.9	50.0	11.8	0.64	92.2

LVEF = left ventricle ejection fraction; hs-cTnT = high-sensitivity cardiac Troponin T; NPV = negative predictive value; PPV = positive predictive value.

# Discussion

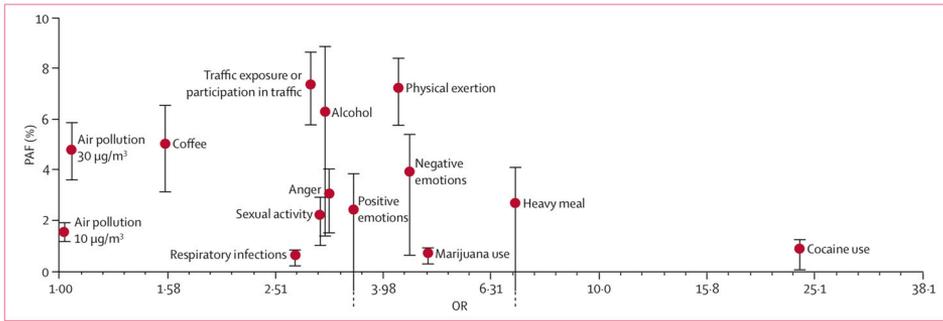
The research reported in this thesis investigated the risk of MI relative to selected weather conditions and temporal factors associated with emotional stress, physical activity, and possible lifestyle changes using date and time of symptom onset of MI in a large, nationwide registry. The effectiveness of IV beta-blockers in patients with STEMI treated with PCI and dual antiplatelet therapy was investigated in a nationwide setting. Finally, we evaluated the accuracy of high-sensitivity troponin T, a surrogate marker of infarct size, in predicting long term LV dysfunction post-STEMI. The primary findings were that, in the studied population, Christmas/New Year and Midsummer holidays, as well as days with lower air temperature and atmospheric pressure, higher wind velocity, and shorter duration of sunshine, were associated with a higher incidence of MI. Intravenous beta-blocker therapy in patients with STEMI treated with PCI was not associated with short-term benefit, and high sensitivity cardiac troponin T was demonstrated to be an excellent prognostic marker of LV dysfunction following STEMI.

## Short-term triggers of MI

The most striking finding of Studies I and II was the significantly higher incidence of MI on Christmas Eve with incidence rate of MI 37% higher compared to a random day in December and January, making Christmas Eve the most hazardous day of the year from a myocardial perspective. Not only was Christmas associated with a higher risk of MI, but, whereas the incidence of MI generally peaks in the morning, the peak on Christmas Eve was observed around 22.00. Combined, Christmas Eve, Christmas Day, Boxing Day, and New Year's Day accounted for 54 additional MIs per annum. Whether these MIs are avoidable is unknown, but the increase in incidence is indicative of how its risk can be modified externally, most probably secondary to activity, emotion, or short-term lifestyle changes. This is further supported by results of Study II demonstrating the non-linear association of weather parameters and incidence of MI, with the most prominent correlation

observed for air temperature. A higher incidence of MI was recorded on days with low air temperature, low atmospheric pressure, high wind velocity, or shorter sunshine duration. For each increase of one standard deviation in mean minimum air temperature (7.4°C) the incidence of MI decreased by 2.8%, and by 3.6% for STEMI. Although the co-linearity among the assessed variables renders the results difficult to interpret, multivariable analyses showed independent associations. Studies I and II are distinguished from other studies of this topic by the inclusion of ECG and biomarker-positive MI data retrieved from a validated nationwide registry and by date and time of symptom onset documented to the nearest minute, in contrast to surrogate variables of MI retrieved from administrative data or ICD codes.<sup>112 116</sup> Both studies are exceptional in terms of sample size and study duration, including nearly 280 000 MIs over a 16-year study period.

Differences in results of the studies exist, the most notable of which relate to the difference in effect estimates for the studied triggers. In Study I, categorical variables were analysed, as opposed to the continuous weather variables that yielded smaller effect estimates in Study II. However, as weather is inescapable, even a small increase in effect may have a great magnitude from a public health standpoint, as exposure occurs in 100% of the population. This is in contrast to traditional risk factors, experienced by only subgroups. In a comparative risk assessment of external triggers of MI, Nawrot et al. ranked triggers of MI from highest to lowest according to their odds ratios in the following order: use of cocaine, eating a heavy meal, smoking marijuana, experiencing negative emotions, heavy physical activity, strong positive emotions, alcohol, anger, sexual activity, traffic exposure, respiratory infections, coffee, and air pollution.<sup>41</sup> However, when ranking the factors according to their population attributable fraction (PAF), a widely used measure in public health defined as the fraction of all cases in a population that can be attributed to a specific exposure, trigger, or degree of exposure, cocaine and marijuana resulted in the lowest risk due to their minimal prevalence as exposures. The factors with highest PAF were those with high prevalence of exposure such as traffic and air pollution. The relationship of the odds ratios with PAF is illustrated in Figure 14.



**Figure 14. The relationship between odds ratio and population attributable fraction.** Scheme demonstrates how small odds ratios can translate to high attributable risks. Reprinted with permission of The LANCET.

## Comparisons with other studies

The results of Study I confirm what has been reported with respect to circadian and circaseptan variation in MI by previous research using administrative data.<sup>47 49 117 118</sup> In agreement with other studies, we found a peak in incidence of MI on Christmas day and New Year's Day.<sup>62-64</sup> A recent study by Wallert et al. addressed this topic using data from SWEDEHEART,<sup>119</sup> examining periods with presumed increased stress, such as Christmas and New Year holidays, compared with other days. They observed the period from 15 December through 6 January to be associated with a higher incidence of MI (adjusted IRR = 1.07; 95% CI, 1.04 – 1.09,  $p < 0.001$ ). In contrast to the previous studies, the results of Study I showed no higher risk of MI during sport event periods.<sup>57 120</sup> Previous meta-analyses have shown that acute episodes of anger, anxiety, sadness, grief, and stress increase the risk of MI.<sup>40 41</sup> The INTERHEART study found psychosocial factors to account for a PAF of 7% in MI.<sup>37</sup> Patients were asked about psychosocial risk factors through questionnaires before discharge post-MI. Stress at work or home (defined as feeling irritable, filled with anxiety, or as having sleeping difficulties due to work or at situations at home) accounted for a PAF of 8 – 9%.<sup>54</sup> The PAF for general stress was estimated at 12%, for financial stress, 11%; stressful life events, 10%; and feeling depressed (defined as feeling sad, blue, or depressed for  $\geq 2$  consecutive weeks) at 9%.<sup>54</sup> Nawrot et al. reported that the PAF for MI was highest for traffic exposure followed by heavy physical activity (6%), alcohol (5%), coffee (5%), negative emotions (4%), anger (3%), eating a heavy meal (3%), and strong positive emotions (2%) within the hours preceding MI. These risk factors may alone, or in combination, explain the higher incidence of MI that is observed in Study I during national holidays.

With regard to weather, a systematic review and a meta-analysis have addressed the topic of temperature and risk of MI.<sup>121 122</sup> Both comprised 42 studies using various measures of MI including ICD codes, hospitalisation due to MI, and PCI due to MI. An additional meta-analysis investigated temperature and risk of cardiovascular hospitalisation, including MI.<sup>123</sup> A direct comparison of the present research with previous studies is problematic due to inconsistencies in study design, statistical methods, and geographic location. However, a summary of results of selected studies having relevance to Study II and with similar design and statistical methods is presented in Table 8. The combined population of all cited studies was 270 192 MI events, with geographic areas comprising Asian and European countries. Ten of 13 studies showed a negative association of air temperature to risk of MI with results of the remaining four being neutral (Table 8). Effect-size estimates similar to our study were calculated despite the geographic and cultural/social differences among populations. These comparable results, combined with the fact that our study included all CCU-treated MIs nationwide, strongly support the negative association of air temperature with MI.

In a study of 500 patients hospitalised with ACS over two consecutive winters in Canada, 7% of admissions occurred following shovelling snow.<sup>124</sup> Auger et al. showed a linear association of snowfall in Canada and hospital admissions due to MI.<sup>125</sup> Cold temperature per se causes coronary vasoconstriction in patients with coronary artery disease.<sup>126</sup> Cold also triggers systemic vasoconstriction, which results in increased afterload and higher cardiac workload, exacerbating effects of strenuous exertion in possibly infrequent exercisers.<sup>126</sup> The greater oxygen demand resulting from increased cardiac workload cannot be met when atherosclerotic plaques limit blood flow, ultimately resulting in a mismatch of oxygen supply and demand, perhaps explaining the association of snow shovelling, cold, and MI. Cold has also been shown to alter plasma viscosity and platelet aggregation, potentially contributing to the observed effects.<sup>127</sup> Finally, a number of conditions that have been associated with the risk of MI are more prevalent during colder seasons, among them infections and influenza, season-dependent behavioural patterns such as changes in physical activity, dietary changes, depression, blood pressure, and vitamin D and cholesterol levels.<sup>46 51 54 128-135</sup> Because both Studies I and II are observational, causality cannot be established and hidden confounding related to behaviour cannot be ruled out. These behavioural aspects are difficult to identify, but patients may be more likely to seek healthcare more often during colder and darker days or when influenced by family visiting during holidays. Time of symptom onset is often poorly defined in patients presenting with NSTEMI and, hence, less reliable for this group of patients, but should hypothetically be less prone to bias related to delay in seeking care than is time and date of admission, as these can be influenced by clinic business hours.

**Table 8. Studies of air temperature and risk of MI**

Study (year)	Country (city)	Study period	Sample size	Statistics	Outcome	Temperature range	Change in °C	Effect estimate
Messner et al. (2002) <sup>136</sup>	Sweden (Norrbotten & Västerbotten)	1985–1992	3322	Poisson	AMI and death	mean: -38–30	1°C increase	RR: 0.99 (0.99–1.01)
Wichmann et al. (2013) <sup>137</sup>	Sweden (Gothenburg)	1985–2010	28215	Poisson	AMI hospitalisation	app: -8–30	IQR (7°C) increase Apr–Sept	RR: 0.96 (0.89–1.02)
Versaci et al. (2019) <sup>138</sup>	Italy (Latina, Campobasso, Rome)	2012–2017	4132	Poisson	AMI hospitalisation	mean: -22–26	IQR (11°C) increase	OR: 0.97 (0.93–1.02)
Radisauskas et al. (2013) <sup>139</sup>	Lithuania (Kaunas)	2000–2007	8527	Poisson	AMI hospitalisation	mean: 12–20	1°C increase	OR: 0.99 (0.99–1.000)
Wichmann et al. (2012) <sup>140</sup>	Denmark (Copenhagen)	1999–2006	14456	Poisson	AMI hospitalisation	mean: -18–24	5°C increase	RR: 0.97 (0.96–0.98)
Wolf et al. (2009) <sup>141</sup>	Germany (Augsburg)	1995–2004	9801	Poisson	AMI and death	app: -8–30	IQR (6°C) increase Oct–Mar	RR: 0.91 (-0.86–0.97)
Lee et al. (2010) <sup>142</sup>	South Korea (Daegu)	2005–2007	2136	Poisson	AMI hospitalisation	min: -20–20	10°C decrease	RR: 1.07 (1.02–1.12)
Bhaskaran et al. (2010) <sup>143</sup>	England & Wales (15 conurbations)	2003–2006	84010	Poisson	AMI hospitalisation	min: -2.5–24	5°C decrease	RR: 1.06 (1.04–1.09)
Vasconcelos et al. (2013) <sup>144</sup>	Portugal (Lisbon & Oporto)	2003–2007	-	Poisson	AMI	mean: -3–27°C	1°C decrease	RR: 1.02 (1.01–1.03)
Danet et al. (1999) <sup>145</sup>	France (Nord district)	1985–1994	3314	Poisson	AMI and death	-	1°C decrease	RR: 1.02 (1.01–1.03)
Goggins et al. (2013) <sup>146</sup>	Hong Kong	2000–2009	49524	Poisson	AMI hospitalisation	mean: -15–28	5°C decrease	RR: 0.94 (0.91–0.96)
Chaveys et al. (2015) <sup>52</sup>	Taiwan (Taipei)	2000–2009	25720	Poisson	AMI hospitalisation	mean: 15–30	1°C decrease	RR: 1.04 (1.03–1.04)
Caussin et al. (2015) <sup>147</sup>	Taiwan (Kaohsiung)	2000–2009	9084	Poisson	AMI hospitalisation	mean: 14–31	1°C decrease	RR: 1.03 (1.02–0.04)
	Belgium	2006–2009	15964	Poisson	AMI hospitalisation	mean: 18–30	1°C decrease	RR: 1.04 (1.02–1.06)
	France (Paris)	2003–2008	11987	Poisson	AMI hospitalisation	mean: -7–28	10°C decrease	IRR: 0.93 (0.91–0.96)
					PCI due to STEMI	min: -8–26	10°C decrease	ERR: 1.06 (1.02–1.10)

AMI = acute myocardial infarction; cor = coronary; hosp = hospitalisation; app = Apparent temperature

## The effect of IV beta-blockers in ST-Elevation MI

The goal of Study III was to determine the effectiveness of IV beta-blocker therapy in patients with STEMI treated according to guidelines with modern antiplatelet reperfusion therapy with PCI. No evidence of benefit was observed with the use of IV beta-blockers relative to short-term patient survival or other in-hospital clinical outcomes. A number of strategies were applied to address confounders, including carefully selected inclusion and exclusion criteria, adjusted regression models, and subgroup stratification as well as PS matching. Regardless, all-cause mortality within 30 days of hospitalisation was higher in patients treated with IV beta-blockers compared to non-treated. In addition, in-hospital death, cardiogenic shock, and LVEF <40% at discharge showed higher incidence in the IV beta-blocker group. Whether these results represent a causative association cannot be confirmed, due to the observational nature of this study. As with all observational studies, hidden confounding may have affected the results, and, despite the efforts to limit confounding by indication, we cannot rule out bias in our results related to the individual indication for use of IV beta-blockers. High-risk patients were omitted using a core set of exclusion criteria, and patients treated with IV beta-blockers were younger, exhibited comorbidity patterns comparable to the non-treated, and received ACE-inhibitors, beta-blockers, and platelet inhibitors to the same degree at discharge, minimizing the possibility that a more frail patient group receiving beta-blockers would explain the higher short-term mortality. Higher rates of AF and LAD infarctions were observed in those receiving IV beta-blockers, possibly conferring indication bias. Lastly, despite neutralisation of most of the baseline variation with PS matching, some differences remained. Thus, there is a possibility that Study III overestimates the potential hazard of IV beta-blockers. Nonetheless, no evidence of benefit could be observed in any investigated endpoint, sensitivity analysis, or subgroup analysis.

The mechanism behind the suggested benefit of beta-blockers is their negative chronotropic and inotropic effects in addition to reducing BP, consequently resulting in decreased cardiac afterload and workload and ultimately reducing oxygen demand during ischemia. Studies conducted prior to widespread use of reperfusion showed improved survival and reduced IS with administration of IV and oral beta-blockers.<sup>12 14 68 69 148</sup> In the era of pharmacological reperfusion, studies with similar design have shown inconsistent results.<sup>70-72</sup> The effect of IV-only beta-blockers in conjunction with reperfusion has not been investigated until recently in

the PCI era, as essentially all patients currently undergoing PCI receives oral beta-blocker therapy.

## Results of recent randomised studies

In recent years, four randomized trials have investigated the effect of IV beta-blockers in patients with STEMI treated with PCI.<sup>73-76</sup> One study randomized patients to a short acting IV beta-blocker not routinely used in clinical practice to target heart rate control with a goal of 60 bpm, and demonstrated a significant reduction in the primary endpoint, peak troponin T.<sup>75</sup> Intravenous beta-blocker administration in the subacute phase after the patient has stabilised may have potential, particularly as it could result in smaller infarctions without the risk associated with early IV beta-blockers.<sup>75</sup> However, animal studies have shown that the cardioprotective effect of IV beta-blockers is restricted to administration before reperfusion.<sup>149</sup> In a single-centre study by Hanada et al. (n = 96), randomization to infusion with landiolol resulted in improved LVEF after six months compared to after two weeks.<sup>73</sup> No difference was observed in the control group, and no additional differences were observed in any outcome measure. However, the small sample size, unusual treatment strategy (landiolol), and assessment of LVEF by left ventriculography reduced the external validity of this study in a real-world setting.

The METOCARD-CNIC (n = 220) and EARLY-BAMI trials (n = 683) are the largest trials assessing the effect of early IV beta-blocker administration on IS in patients with STEMI treated with PCI.<sup>74 76</sup> The METOCARD-CNIC showed that the use of pre-procedural IV beta-blockers reduced IS assessed with CMR at five to seven days (adjusted difference = -6.5%; 95% CI, -11.4% to -1.8%). The study included patients with anterior Killip class II or lower STEMI, and the effect of IV beta-blocker was greater in patients with TIMI flow grade 0–1 prior to PCI, with no impact observed in patients with TIMI flow grade 2–3 before PCI. Patients allocated IV beta-blockers also showed improved LVEF. No significant differences were observed with regard to the composite clinical endpoint of death, malignant arrhythmia, cardiogenic shock, AV-block, and reinfarction at 24 hours. The results of the METOCARD-CNIC trial are limited by several factors: First, the trial design was open (although endpoint-blinded to evaluators) and lacked a placebo; 2) only anterior STEMIs were included; and 3) a trend towards greater MaR was observed in the control group. Taken together, these factors might have influenced the results or generalizability of the study. The EARLY-BAMI trial was an improvement in terms of study design. Unlike the METOCARD-CNIC trial, EARLY-BAMI was double-blinded, placebo-controlled, and not restricted to anterior STEMI, but included a more general Killip class I or II STEMI population. The EARLY-BAMI was not able to replicate the results of the METOCARD-CNIC trial, and pre-

procedural IV beta-blocker did not show a reduction in the primary endpoint IS or result in lower cardiac enzyme release, improvement in LVEF, or difference in major adverse cardiovascular events (MACE).<sup>76</sup> Patients receiving intravenous beta-blockers did show a reduction in the secondary endpoint of ventricular arrhythmias.<sup>76</sup>

Differences between the METOCARD-CNIC and EARLY-BAMI trial included the administration of two 5 mg boluses in the EARLY-BAMI trial instead of the three doses in METOCARD-CNIC trial, which was possibly insufficient to demonstrate a benefit. Another source of the discrepancy is the timing of CMR. Studies have shown that early post-STEMI CMR overestimates IS by approximately 30-40%.<sup>150</sup> <sup>151</sup> Whereas IV beta-blocker was associated with reduced IS in the METOCARD-CNIC trial in the early phase (although higher LVEF was recorded in patients treated with IV beta-blocker), no difference in final IS was observed by CMR six months post-admission.<sup>152</sup> In the EARLY-BAMI trial, patients underwent CMR at 30±10 days as opposed to in the acute phase, showing a recovery of infarct as reflected in the observed differences in IS of the two studies, 21.2% vs. 15.3% in METOCARD-CNIC and EARLY-BAMI, respectively.<sup>74</sup> <sup>76</sup> Accordingly, IS on follow-up CMR in the METOCARD-CNIC trial was comparable to EARLY-BAMI, 15.7% vs. 15.3%.<sup>76</sup> <sup>152</sup> Finally, patients with on-going beta-blocker treatment were not excluded from the EARLY-BAMI trial, possibly influencing the results.

## **Why does IV beta-blocker therapy currently not show benefit?**

To date, the only method confirmed to reduce infarct size is early reperfusion, as time is positively correlated to infarct size and negatively correlated to myocardial salvage. In the pre-fibrinolysis era, beta-blockers were given as mono-therapy, and infarcts reached their final size with no myocardium salvaged except through the administration of beta-blockers.<sup>127</sup> <sup>128</sup> With reperfusion, extensive myocardium is salvaged, resulting in smaller infarcts. Earlier administration or larger doses of IV beta-blockers may therefore be needed to achieve greater salvage.<sup>153</sup> In addition, the larger infarcts seen prior to the fibrinolysis era translated to post-MI congestive heart failure, estimated at approximately 40% at that time, as opposed to 2-4% today.<sup>30</sup> <sup>154-156</sup> In this context, the benefits of beta-blocker therapy after MI observed in the pre-fibrinolysis era may have been due primarily to its beneficial effect on heart failure, which was largely unknown at that time. In fact, the use of beta-blockers in heart failure was contraindicated, possibly resulting in the focus on the concept of beta-blockers reducing infarct size and ventricular arrhythmias in the acute phase of MI.<sup>69</sup> Regardless, for IV beta-blocker treatment to be employed in cardio-protection, large trials powered for clinical endpoints are needed to establish numbers needed

to treat as well as numbers needed to harm. Although IS is strongly correlated to survival after STEMI, the early administration of IV beta-blockers may not necessarily translate into clinically relevant benefit for the patient, due to the early associated risk. In spite of the lower risk for ventricular arrhythmias seen with the use of IV beta-blockers, their negative effect on myocardial contractility in the acute early phase of STEMI may result in higher rates of cardiogenic shock, as was shown in the large CIOpidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT) trial.<sup>70</sup> While the control group in the COMMIT trial received a placebo, nearly all patients currently receive oral beta-blockers in the sub-acute phase, minimizing the risk of ventricular arrhythmias. The early risk of cardiogenic shock, bradycardia, or hypotension may be more detrimental once established, potentially conferring more harm than benefit to the patients. This is particularly true if IV beta-blockers were to be given without careful patient selection. An adequately-sized randomized clinical trial would therefore be necessary to resolve this matter. The prospect for such a trial is uncertain.

## Risk stratification with troponin

The objective of Study IV was to determine the correlation of the cardiac biomarkers hs-cTnT, CK-MB, and NT-proBNP, along with early IS and LVEF, to long-term IS and LVEF post-STEMI. In addition, their predictive value with regard to LV dysfunction was compared. Not surprisingly, hs-cTnT was strongly correlated to long-term IS/LVEF and provided LV dysfunction predictive value comparable to early CMR, although early LVEF showed a higher C-statistic (0.87 vs. 0.93,  $p < 0.001$ ). Cut-off values to rule in and rule out long-term dysfunction were suggested from ROC tables and validated in conjunction with LVEF assessed by TTE and recommended clinical risk scores by Study V in a larger independent STEMI population treated with PCI. This expanded the generalizability of the study, as CMR is not routinely performed. Study V showed that hs-cTnT provides accurate predictive value comparable to early IS/LVEF assessed by both CMR and by TTE at discharge. In addition, C-statistics for hs-cTnT were significantly higher than for GRACE and TIMI risk scores. The diagnostic value of the pre-specified cut-offs showed high accuracy, particularly the rule out cut-off of hs-cTnT  $< 3500$ ng/L. Studies IV and V demonstrated similar ROC for hs-cTnT, 0.83 and 0.87, respectively, confirming results of previous studies with LV dysfunction as endpoint that report area under the ROC curve values of 0.82–0.86 despite differing definitions of LV dysfunction.<sup>157-159</sup>

Multiple studies have addressed the correlation of cardiac biomarkers, especially cardiac troponins, to IS post-STEMI.<sup>157-165</sup> The cited studies have shown strong correlation of cardiac troponins to IS and LVEF, suggesting their use in post-STEMI risk assessment. Hallen et al. demonstrated, using an older troponin assay method, an independent association of cTnI with large IS assessed by CMR at four months post-STEMI, adjusted for IS on days five through seven.<sup>161</sup> Nguyen et al. assessed the predictive value of hs-cTnT assay in 201 patients with STEMI treated with PCI and observed an independent association of hs-cTnT with MACE after adjusting for IS as assessed by CMR.<sup>161</sup> Although a small (n=1260) single-centre study did not show prognostic benefit of hs-cTnT assay in patients with STEMI treated with PCI when controlling for traditional predictors of outcome, the majority of studies have confirmed its accuracy in predicting clinical outcomes.<sup>94-99 166</sup> Despite this evidence, little has been done to implement hs-cTnT use in evaluating prognosis in clinical practice, possibly due to availability of other risk stratification tools in the absence of comparison studies.

## **Study IV vs. Study V**

Important discrepancies exist between Studies IV and V including treatment randomisation and differences in patient characteristics. Because the original source material, the CHILL-MI trial and the DANAMI-3 DEFER substudy, showed neutral results, we disregarded these differences.<sup>113 115</sup> However, the difference observed in peak hs-cTnT values needs to be addressed. Peak hs-cTnT values in the patient population from the CHILL-MI trial (Study IV) were nearly twice that observed in Study V. The time from symptom onset to PCI in the study population in Study V was greater, and could be assumed to produce higher hs-cTnT values. The finding may possibly be attributed to the significantly fewer patients in Study V presenting with TIMI-flow grade 0–1 compared to in Study IV (Table 6). However, the similarity in early and final IS in the two study populations (final IS in study IV vs. study V: 11.0% vs. 10.4%) strongly reflects sampling time difference. This did not alter the predictive value of hs-cTnT, but could have affected the prognostic/diagnostic value of the pre-specified cut-off assessment. Although the cut-off to rule out LV dysfunction showed nearly 100% NPV, the cut-off to rule in LV dysfunction underperformed when compared with results of Study IV and the lower PPVs obtained for the rule in cut-off could be explained by failure to capture the true peak in the DANAMI-3 study population. Previous studies have shown differences in peak hs-cTnT values: Cediël et al. reported a median peak hs-cTnT of 3052 ng/L (1142 – 6392) in 1224 patients with STEMI in samples obtained at admission and 12 and 24 hours post-admission.<sup>166</sup> A study comprising 66 STEMI patients with blood samples obtained at baseline, 6, 12, and 24 hours showed a mean

peak hs-cTnT of  $6284 \pm 3943$  ng/L.<sup>159</sup> Similar values were obtained by Reindl et al. with a median peak hs-cTnT of 5464 ng/L (2337 – 8574).<sup>158</sup> In 201 STEMI patients undergoing PCI, median peak hs-cTnT determined from blood samples at baseline and at 6 and 12 hour increments within the first 24 hours was 3783 ng/L (1912 – 7204), similar to our results in Study III of a median peak hs-cTnT of 2235 ng/L (642 – 5260).<sup>157</sup> Taken together, the peak values reported in Study V are more consistent with findings of earlier studies. Finally, although the external validation of Study IV presented in Study V provides promising results, it should be considered hypothesis-generating, as type II error cannot be ruled out.

## **Relevance and future challenges**

The predictive values of the magnitude that have been observed for hs-cTnT should generate discussion regarding its implementation in clinical practice. For comparison, in large validation studies, the CHADS-VASC risk score, used to predict thromboembolic events in patients with atrial fibrillation, achieves a C-statistic of 0.67.<sup>167</sup> Despite this comparatively low value, it is widely used in clinical practice as decision support for anticoagulation therapy. With respect to post-STEMI risk assessment, considerable information is available to clinicians before patient discharge: Guidelines suggest the use of TTE during hospitalisation to stratify patient risk. Cardiac troponin levels reflect extent of myocardial damage, and, when combined with patient age and physical findings, may be more effective in predicting risk than are tools for predicting thromboembolic events in patients with atrial fibrillation.

Current practice utilizes a similar follow-up regime for all patients regardless of risk. A risk-stratified follow-up approach could improve the management of patients with STEMI by better allocation of healthcare resources, expanding access to specialised service to those at higher risk of long-term morbidity. As an alternative to follow-up in a specialised outpatient department, a secondary prevention programme with a trained nurse to educate patients about lifestyle changes and rehabilitation measures and to monitor therapeutics may be adequate for low-risk patients. This could be of primary importance in countries with fewer healthcare resources. An intriguing question is whether troponin, alone or in combination with other risk stratification tools, may provide the basis for selecting candidates for primary prophylactic ICD during index hospitalisation, possibly resulting in lower rates of patients suffering malignant arrhythmias and sudden cardiac death while awaiting evaluation at three months after MI, as is current common practice. For such a plan to be implemented in clinical practice, larger prospective studies are needed to confirm the prognostic role of hs-cTnT in patients surviving STEMI compared to currently available standard risk stratification tools. This will require

the standardisation of hs-cTnT values. Although evidence suggests that the peak hs-cTnT value provides accurate predictions and offers a convenient approach, capturing peak values can be challenging. Some studies have suggested that the plateau phase of troponin leakage may provide optimal data for reflecting net myocardial damage.<sup>157 160 168</sup> Although this is hard to argue against, we are moving towards shorter hospitalisations in low-risk patients, with length of stay down to three days in patients with STEMI.<sup>31</sup> With c-TnI, standardisation might be an issue, although no relevant differences have been observed in AUC in previous studies using older assays. A recent small study (n=29) of STEMI patients suggested better correlation between hs-cTnT and IS for hs-cTnT AUC than for the peak value.<sup>160 169</sup> Whether this is of clinical relevance is yet to be established. Finally, with the introduction of point of care tests, a prehospital troponin value can be obtained in just 10-20 minutes. This information could offer advantages when assessing patient clinical status, for example, identifying patients at potential risk of adverse reaction to reperfusion who may benefit from tailored PCI with additional LV support.

# Conclusions

The research presented in this thesis investigated the associated risk of MI with various external triggers, the use of IV beta-blockers with regard to short-term outcome after STEMI in a contemporary patient population, and the predictive value of hs-cTnT. The reported findings have potential implications for cardiac health, as, in addition to evaluating aspects of treatment, they identify modifiable triggers of MI and strategies for estimating level of risk in post-STEMI patients.

- The incidence of MI culminates on calendar week 52. A higher incidence of MI is observed during the Christmas and New Year holidays and Midsummer holiday in Sweden. The day with highest incidence of MI is Christmas Eve. More MIs occur on Mondays, with the daily peak occurring at 08.00. Days with lower air temperature, low air pressure, fewer hours of sunshine and higher wind velocity are associated with higher incidence of MI in Sweden with the most evident association observed for air temperature. The association of air temperature was stronger during warmer seasons and in southern regions. Together, results of Studies I and II indicate that the risk of MI is dynamic with abrupt short-term shifts occurring daily, confirming the hypothesis of external factors acting as precipitators of MI.
- The use of IV beta-blocker in patients with STEMI treated with primary PCI and modern antiplatelet therapy was not associated with benefit to short-term survival rates. The use of IV beta-blockers was associated with higher short-term mortality, lower LVEF at discharge, as well as a higher risk of in-hospital cardiogenic shock. Results were consistent across a range of subgroups and sensitivity analyses. The routine use of IV beta-blocker in patients with STEMI is questionable and should be reserved for carefully selected patients until more evidence is available.

- Peak high-sensitivity cardiac troponin T accurately predicts long-term LV dysfunction defined as LVEF  $\leq$ 40% in patients with STEMI treated with PCI. The predictive value of hs-cTnT is higher than that of widely used clinical risk scores with regard to the studied endpoint and equivalent to predictive values of early infarct size and LVEF assessed with CMR and TTE. Due to its general availability, low cost, and accuracy, hs-cTnT may be an optimal tool in the risk assessment arsenal for patients surviving STEMI.

# Swedish summary (Populärvetenskaplig sammanfattning)

Denna avhandling syftar till att öka kunskapen kring sambandet mellan yttre faktorer som kan framkalla en hjärtinfarkt, studera betydelsen av intravenös beta-blockad i akutskedet av en ST-höjningsinfarkt och hur man kan använda en diagnostisk hjärtskademärkare som kan mätas i blodet i samband med hjärtinfarkt, Troponin till att identifiera högriskpatienter med sämre prognos efter hjärtinfarkt.

En hjärtinfarkt är resultatet av en mångårig komplicerad åderförkalkningsprocess i de kärl som försörjer hjärtmuskeln med syre, kranskärlen. Vid en hjärtinfarkt stängs blodflödet av i ett eller flera av dessa kranskärl på grund av en skada i det cellager som täcker kranskärlens insida, vilket leder till en proppbildande process. Resultatet av denna process blir syrebrist och, hjärtmuskelceller dör. Vid ett totalt stopp får man en allvarligare hjärtinfarkt, som benämns som ST-höjningsinfarkt efter de karaktäristiska förändringar som kan ses på EKG, och, vid en mindre hjärtinfarkt är dessa EKG-förändringar frånvarande varför dessa benämns icke-ST-höjningsinfarkter. I Sverige uppskattas incidensen av hjärtinfarkt till 25 300 per år eller 340 per 100 000 invånare per år enligt Socialstyrelsen. En majoritet av dessa vårdas på hjärtintensivvårdsavdelningar runt om i landet och ingår i det stora riksomfattande hjärtregistret SWEDEHEART som använts i tre av fem delstudier i denna avhandling.

Allra sedan de första studierna om hjärtinfarkt har man misstänkt att yttre faktorer kan provocera fram hjärtinfarkter genom att agera som trigger. I denna avhandling har Studie I och II dedikerats till att försöka studera dessa faktorer genom att använda data från SWEDEHEART-registret. Alla hjärtinfarkter mellan åren 1998–2003 inkluderades och genom registret kunde vi identifiera symptomdebut ned till närmaste minut. Incidensen av hjärtinfarkt studerades vid olika tider på dygnet, veckodagar, dagar på året och stora högtider såsom jul- och midsommarhelgerna. Genom en unik sammanslagning av hjärtregistret till data från Svenska Meteorologiska och Hydrologiska Institutets väderdata kunde vi studera vilka väderförhållanden som rådde i den stad den dagen varje patient insjuknade i sin hjärtinfarkt och därigenom studera incidensen av hjärtinfarkt under olika väderförhållanden. Närmare 280 000 hjärtinfarkter ingick i studierna, vilket gör de till de största studierna av sitt slag. I Studie I såg vi att antalet hjärtinfarkter var som

högst på året under vecka 52 samt ett samband mellan Julafton, Juldagen, Annandag Jul och Nyårsdagen och en högre risk för hjärtinfarkt jämfört med andra dagar. Ett liknande samband sågs även för Midsommarhelgen. Utav alla dagar så var Julafton den dag som var kopplad till högst antal hjärtinfarkter under året och motsvarande i snitt 37 % fler hjärtinfarkter jämfört med andra dagar. I Studie II såg vi att fler hjärtinfarkter sker på kalla dagar jämfört med varma dagar, dagar med lågt lufttryck, dagar med få antal soltimmar och blåsiga dagar. Sambandet var starkast för lufttemperatur där varje sänkning i lufttemperatur med 7 grader motsvarade en ökning med 3 % i insjuknandet i hjärtinfarkt. Sammanfattningsvis talar resultaten från Studie I och II för att risken för hjärtinfarkt är dynamisk och kan modifieras av yttre faktorer.

I Studie III studerades användningen av intravenös beta-blockad i akutskedet av en ST-höjningsinfarkt. Beta-blockerare har visat sig förbättra överlevnad efter hjärtinfarkt men det vetenskapliga evidensläget för användningen av läkemedlet i intravenös form i det akuta skedet hos patienter med hjärtinfarkt som genomgår kranskärlsintervention (PCI) och erhåller behandling med modern blodförtunnande läkemedel är begränsat. Genom att använda oss av data från SWEDEHEART-registret identifierade vi 16 909 patienter som mellan åren 2006–2013 varit aktuella för sådan behandling. Av dessa erhöll 2 876 patienter beta-blockad intravenöst. I studien såg vi att användningen av denna behandling sjönk kraftigt under studieperioden och att användningen av denna behandling inte kunde kopplas till några fördelar för patienterna. Tvärtom såg vi ett samband mellan behandling med intravenös betablockad och sämre korttidsöverlevnad, sämre hjärtfunktion uppskattad vid utskrivning och med mer av det fruktade tillståndet kardiogen chock, vilket är ett tillstånd som kan vara svårt att häva och omfattas av hög dödlighet. Resultaten var genomgående för hela studien och kunde säkerställas statistiskt i en rad olika patientgrupper samt efter kontroll för orsaksfaktorer. Eftersom detta inte var en randomiserad klinisk prövning utan en observationsstudie så måste resultaten tolkas med försiktighet. Vår slutsats blev således att vi inte kan se någon klar nytta med användningen av beta-blockerare i intravenös form utan att man bör invänta nyare data. Under tiden bör man fortsätta med beta-blockerare i tablettform enligt gängse riktlinjer.

I studie IV och V studerades det prognostiska värdet av hjärtskademarkören Troponin som läcker ut i blodet vid en hjärtmuskelskada. Idag används högkänsliga metoder som mäter koncentrationen av Troponin. I tidigare studier har man sett att mängden Troponin i blodet efter en ST-höjningsinfarkt korrelerar väldigt starkt med storleken på hjärtskadan, vilken kan kvantifieras med avancerade bildiagnostiska undersökningar såsom magnetkameraundersökning av hjärtat. Detta gör Troponin till en utmärkt prognostisk markör för att kategorisera patienter i olika riskgrupper

då den har goda prognostiska egenskaper, är lättillgänglig och tas på alla patienter. Få studier har dock jämfört hur bra Troponin kan riskkategorisera patienter jämfört med andra kliniska verktyg för detta ändamål. I Studie IV studerade vi hur väl Troponin korrelerar med storleken av hjärtskadan efter en ST-höjningsinfarkt när hjärtmuskeln fått läka i 6 månader och risken för utveckling av hjärtsvikt efter hjärtinfarkt. Vi jämförde dessa kvaliteter mot kvantifiering av infarktstorlek och hjärtfunktion under akutskedet av en hjärtinfarkt. Studien visade på att högkänsligt Troponin korrelerar starkt med hjärtinfarktens storlek, och mängden Troponin i blodet kunde kategorisera de patienter som utvecklar nedsatt hjärtfunktion med hög sannolikhet. I Studie V validerades resultaten i en större, extern patientpopulation som i tillägg även jämförde Troponin mot etablerade kliniska riskskalor och hjärtfunktion uppmätt med ultraljud av hjärtat, vilken är standardmetoden för att studera hjärtats pumpförmåga. Resultaten från Studie V bekräftade resultaten från Studie IV och visade på att högkänsligt Troponin innehar prognostiska egenskaper som är bättre än etablerade riskskalor och att dessa egenskaper är jämförbara med det prognostiska värdet av en magnetkameraundersökning och ultraljud av hjärtat under vårdtillfället för en ST-höjningsinfarkt. Dock är studierna relativt små vilket begränsar resultaten som får ses som hypotesgenererande och bekräftas i större studier.



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