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PREDICTORS OF ARRHYTHMIAS, CARDIAC ARREST, AND MORTALITY IN ACUTE CORONARY SYNDROME

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"All interest in disease and death is only another expression of interest in life."

Thomas Mann, The Magic Mountain (1924)

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Predictors of Arrhythmias, Cardiac Arrest, and Mortality in Acute Coronary Syndrome

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SAMMANFATTNING

Bakgrund

Patienter med akut kranskärlssjukdom (ACS) löper hög risk för allvarliga komplikationer såväl under vårdtiden som efter utskrivning från sjukhus. Syftet med detta avhandlingsarbete har varit att undersöka faktorer, som kan förutsäga risk för allvarliga händelser såsom rytmrubbningar, hjärtstopp och död vid och efter ACS. Vidare har betydelsen av kaliumrubbningar i detta sammanhang undersökts.

Metoder och resultat

Studie I: Vi använde data från det svenska hjärtsjukvårdsregistret SWEDEHEART för att undersöka möjliga prediktorer för hjärtstopp på sjukhus hos patienter med misstänkt NSTE-ACS, den form av ACS där kranskärlet vanligen bara är delvis tilltäppt. En riskalgoritm bestående av fem variabler (blodtryck, ålder, hjärtfrekvens, EKG-förändring och grad av hjärtsviktssymptom) togs fram. Denna validerades genom att använda annan patientdata från SWEDEHEART och MINAP, det brittiska hjärtinfarktsregistret.

Studie II: Genom att länka data från SWEDEHEART och det svenska pacemaker- och ICD-registret kunde vi identifiera patienter, som skrivits ut efter hjärtinfarkt, genomgått kranskärlsröntgen under vårdtiden och inte hade ICD (inopererad defibrillator). Sambanden mellan kliniska parametrar och hjärtstopp utanför sjukhus (OHCA) inom 90 dagar undersöktes genom samkörning med det svenska hjärt-lungräddningsregistret. Incidensen av OHCA var lägre (0,29%) än i tidigare studier. Sex variabler (kön, ålder, njurfunktion, grad av hjärtsviktssymptom, nyupptäckt förmaksflimmer/-fladder och LVEF, d.v.s. andel blod som pumpas ur vänster kammare vid varje hjärtslag) var oberoende associerade med OHCA. Dessa variabler predicerade också risk för död inom 90 dagar hos patienter, som inte registrerats i det svenska hjärt-lungräddningsregistret under samma tidsperiod. Ovannämnda variabler förutsade risken för OHCA bättre än endast LVEF, som enskilt fortfarande är den mest använda riskmarkören.

Studie III: Patienter som lagts in på sjukhus på misstanke om ACS och som registrerats i SWEDEHEART och SCREAM inkluderades i denna studie. SCREAM är ett register, som samlat laboratoriedata avseende njur- och saltprover från alla patienter, som genomgått dylik provtagning i Stockholm. Sambanden mellan kaliumnivå vid inskrivning och utfall under sjukhusvistelsen undersöktes. Hyperkalemi (förhöjt kalium) var associerat med risk för död medan hypokalemi (för lågt kalium) var associerat med risk för hjärtstopp och nyupptäckt förmaksflimmer-/fladder. Dessa samband påverkades inte av huvuddiagnos vid utskrivning (typ av ACS eller annan icke-ACS-diagnos) eller kliniska parametrar vid ankomst till sjukhus.

Studie IV: Även i denna studie användes data från SWEDEHEART och SCREAM. Patienter som skrivits ut efter hjärtinfarkt inkluderades. Sambanden mellan kaliumnivå vid utskrivning och diverse utfall under följande år undersöktes. Kaliumnivå och njurfunktion vid utskrivning förutsade risken för kaliumrubbningar under det följande året, vilka drabbade knappt 37% av patienterna. Ett U-format samband sågs mellan kaliumnivå vid utskrivning och risk för död inom ett år.

Slutsats

En riskalgoritm bestående av fem variabler kan underlätta riskbedömningen avseende hjärtstopp på sjukhus för patienter som inläggs på misstanke om ACS. Incidensen av OHCA inom 90 dagar efter hjärtinfarkt var i vår studie lägre än tidigare visat. Sex variabler inklusive LVEF förutsade risken för OHCA bättre än vad LVEF för sig gjorde. Kaliumrubbningar vid inkomst är associerade med allvarliga rytmrubbningar och död under sjukhustiden hos patienter som läggs in på misstanke om ACS oavsett slutdiagnos och inkomstparametrar. Kaliumrubbningar inom första året efter hjärtinfarkt är vanligt förekommande och prediceras av njurfunktion och kaliumnivå vid utskrivning, vilka också predicerar död inom ett år.

ABSTRACT

Background

Patients with acute coronary syndrome (ACS) face a high risk of lethal complications, both during the hospital course and after discharge. The aim of this thesis was to assess patient characteristics and predictors of adverse events in ACS including arrhythmias, cardiac arrest, and mortality as well as the impact of potassium disorders in this setting.

Methods and results

Study I: We used data from the Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART) to assess predictors of in-hospital cardiac arrest in patients admitted with suspected non-ST-elevation ACS (NSTE-ACS). A risk-score model was developed including five variables: systolic blood pressure <100 mmHg, age ≥60 years, heart rate <50 or ≥100 bpm, ST-T abnormalities on the admission ECG, and Killip class ≥II. The risk-score model was temporally validated in SWEDEHEART and externally validated using data from the Myocardial Ischaemia National Audit Project (MINAP).

Study II: Using SWEDEHEART and the Swedish Pacemaker and Implantable Cardioverter-Defibrillator (ICD) Registry, we identified patients without a prior ICD, who had undergone in-hospital coronary angiography and were discharged alive after myocardial infarction (MI). Associations between patient characteristics and out-of-hospital cardiac arrest (OHCA) as recorded in the Swedish Cardiopulmonary Resuscitation Registry within 90 days after discharge were assessed. The incidence of OHCA was low (0.29%) compared to previous studies. Six variables (male sex, age ≥60 years, estimated glomerular filtration rate [eGFR] <30 mL/min per 1.73 m2, Killip class ≥II, new-onset atrial fibrillation/flutter, and LVEF categorized as ≥50%, 40-49%, 30-39%, and <30%) were independently associated with OHCA and predicted OHCA as well as non-OHCA death better than an LVEF cut-off of <40% alone.

Study III: Patients admitted with suspected ACS and registered in SWEDEHEART and the Stockholm CREAtinine Measurements (SCREAM) project were included. Associations between admission plasma potassium and in-hospital outcomes were assessed. In fully adjusted models, hyperkalemia was associated with mortality, while hypokalemia was associated with cardiac arrest and new-onset atrial fibrillation. No association was observed between potassium and second- or third-degree atrioventricular block. Results were not modified by discharge diagnosis (ACS subtype or non-ACS diagnosis) or baseline characteristics.

Study IV: SWEDEHEART and SCREAM were used to identify patients discharged alive after MI. Associations between plasma potassium at discharge and outcomes within one year were assessed. Potassium and eGFR at discharge were found to be independent predictors of hyper- or hypokalemia within one year, which affected 36.5% of the patients. A U-shaped association was observed between discharge potassium and mortality within one year.

Conclusion

A five-variable risk score can be used to predict in-hospital cardiac arrest in patients admitted with suspected ACS. In a contemporary cohort of MI patients, the incidence of OHCA within 90 days after discharge was low, but compared to an LVEF cut-off alone which is routinely used, five variables in addition to LVEF predicted OHCA better. Dyskalemias at admission are associated with in-hospital arrhythmic events and mortality across all ACS/non-ACS diagnoses regardless of baseline characteristics. Potassium disorders within the first year following MI are frequently encountered and potassium level and kidney function at discharge strongly predict their occurrence as well as one-year mortality.

LIST OF SCIENTIFIC PAPERS

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A user-friendly risk-score for predicting in-hospital cardiac arrest among patients admitted with suspected non ST-elevation acute coronary syndrome - The SAFER-score.
Resuscitation. 2017;121:41-8.

II. Faxén J, Jernberg T, Hollenberg J, Gadler F, Herlitz J, Szummer K.
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Manuscript.

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Potassium levels and risk of in-hospital arrhythmias and mortality in patients admitted with suspected acute coronary syndrome.
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Dyskalemias and adverse events associated with discharge potassium in acute myocardial infarction.
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CONTENTS

LIST OF ABBREVIATIONS

ACC	American College of Cardiology
ACEi	Angiontensin-converting enzyme inhibitor
ACS	Acute coronary syndrome
AF	Atrial fibrillation
AHA	American Heart Association
APD	Action potential duration
ARB	Angiotensin II receptor blocker
AV	Atrioventricular
CA	Cardiac arrest
CCU	Coronary care unit
CI	Confidence interval
CKD	Chronic kidney disease
CPR	Cardiopulmonary resuscitation
CV	Conduction velocity
DAD	Delayed afterdepolarization
EAD	Early afterdepolarization
eGFR	Estimated glomerular filtration rate
EMS	Emergency medical service
EPS	Electrophysiology study
ESC	European Society of Cardiology
GISSI	Gruppo Italiano per lo Studio delia Sopravvivenza nell'Infarto Miocardico
GRACE	Global Registry of Acute Coronary Events
HR	Hazard ratio
ICD	Implantable cardioverter-defibrillator
LVEF	Left ventricular ejection fraction
MI	Myocardial infarction
MICE	Multiple imputation by chained equations
MINAP	The Myocardial Ischaemia National Audit Project
NSTE-ACS	Non-ST-elevation acute coronary syndrome
NSTEMI	Non-ST-elevation myocardial infarction
NYHA	New York Heart Association
OHCA	Out-of-hospital cardiac arrest
OR	Odds ratio
PEA	Pulseless electrical activity
PCI	Percutaneous coronary intervention
RAAS	Renin angiotensin aldosterone system
RCT	Randomized controlled trial
RIKS-HIA	Register of Information and Knowledge About Swedish Heart Intensive Care Admissions

SCAAR	Swedish Coronary Angiography and Angioplasty Registry
SCD	Sudden cardiac death
SCREAM	The Stockholm Creatinine Measurements project
SEPHIA	Secondary Prevention after Heart Intensive Care Admission
SWEDEHEART	The Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies
TIMI	Thrombolysis in Myocardial Infarction
UA	Unstable angina
VEST	Vest Prevention of Early Sudden Death Trial
VF	Ventricular fibrillation
VT	Ventricular tachycardia

1 INTRODUCTION

The term acute myocardial infarction (MI) defines a clinical or pathologic event consistent with acute myocardial ischemia, where there is proof of myocardial necrosis. In a clinical setting, a typical rise and/or fall in biomarkers of myocyte injury (ideally cardiac troponin) with at least one value above the 99th percentile upper reference limit is mandatory for the diagnosis[1]. Acute coronary syndrome (ACS) refers to the clinical spectrum of presentation of acute myocardial ischemia and includes ST-elevation MI (STEMI), non-ST-elevation MI (NSTEMI), and unstable angina (UA), where the latter is not accompanied by myocardial necrosis. NSTEMI and UA are jointly termed NSTE-ACS[2].

Rates of morbidity and mortality associated with ischemic heart disease have declined considerably during the last decades, much owing to the earlier and more widespread use of coronary revascularization, more aggressive antithrombotic treatment, and secondary preventive medication[3-6]. Furthermore, there has been a change in pattern of ACS with a transition from STEMI to NSTE-ACS, which has now become predominant[7]. Nevertheless, ACS is still a leading global cause of morbidity and mortality. A better understanding and reconsideration of risk factors associated with adverse events in ACS is therefore warranted[8].

The following sections outline certain aspects of risk in ACS covered in the thesis.

1.1 MECHANISMS AND TEMPORAL DISTRIBUTION OF VENTRICULAR ARRHYTHMIAS IN ACUTE CORONARY SYNDROME

In the setting of ACS, ventricular arrhythmias, including sustained ventricular tachycardia (VT) and ventricular fibrillation (VF), are a potentially life-threatening complication that can occur both in the acute phase and during the course of follow-up. Ventricular arrhythmias can be thought to result from the interaction between three basic components: substrate, trigger, and modulating factors. These components and hence the electrophysiological mechanisms of arrhythmia vary during the time course of ischemia. The functional changes within the injured myocardium set the stage for the arrhythmogenic substrate. In order for arrhythmias to become manifest, appropriate trigger factors such as ventricular premature depolarization, variations in cycle length, and heart rate must be present. Additionally, modulating factors including electrolyte abnormalities, e.g. potassium disturbances (see Section 1.2), impaired left ventricular function, and altered sympathetic nervous system activity may modify the substrate as well as the trigger[9].

Much of our knowledge about ischemia-related arrhythmia mechanisms is derived from experimental studies. A distinction is made between phase 1, the early and potentially reversible stage within 2 to 30 minutes of ischemia, and phase 2, the infarct-evolving phase starting about 1.5-5 hours after ischemia onset and lasting up to 48-72 hours. Phase 1 is further divided into phases 1A (2-10 minutes) and 1B (15-30 minutes). Phase 1A arrhythmias are thought to arise mainly from reentry that causes bursts of VT, which rarely degenerates into VF. Arrhythmias during phase 1B may involve both automatic and non-automatic ectopic excitation as well as reentry, resulting in VT and more frequently VF, as opposed to

phase 1A. It has been proposed that phase 2 arrhythmias are associated with reperfusion of ischemic areas and share mechanisms similar to those seen in phase 1B. Surviving Purkinje fibers displaying abnormal automaticity are believed to be among the specific foci underlying arrhythmia in phase 2[10]. Ventricular arrhythmias occurring beyond phase 2 (>72 hours) are usually scar mediated and give rise to monomorphic VT caused by reentry, which is facilitated by slow conduction in fibrotic areas of infarcted myocardial tissue[11]. Polymorphic VT has been reported to occur infrequently after myocardial infarction and may be associated with signs or symptoms of recurrent ischemia[12]. **Figures 1** and **2** outline temporal distribution, biochemical, and electrophysiological characteristics of ischemic ventricular arrhythmias in more depth

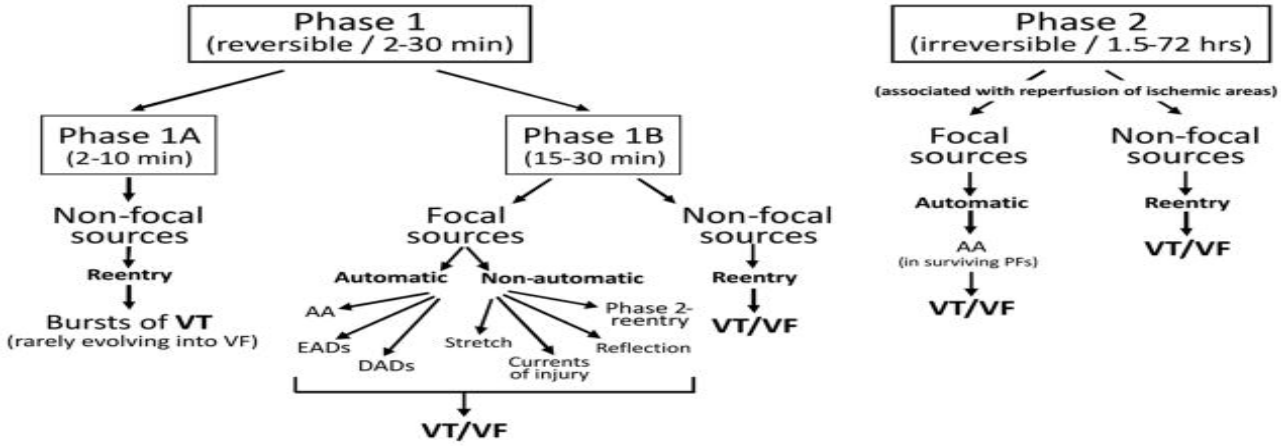

Figure 1. Temporal distribution and genesis of ischemic ventricular arrhythmias[10]. Reproduced with permission from Elsevier.
VT: ventricular tachycardia; VF: ventricular fibrillation; AA: abnormal automaticity; EADs: Early afterdepolarizations; DADs: Delay afterdepolarizations (DADs); P2R: phase 2-reentry; PFs: Purkinje fibers.

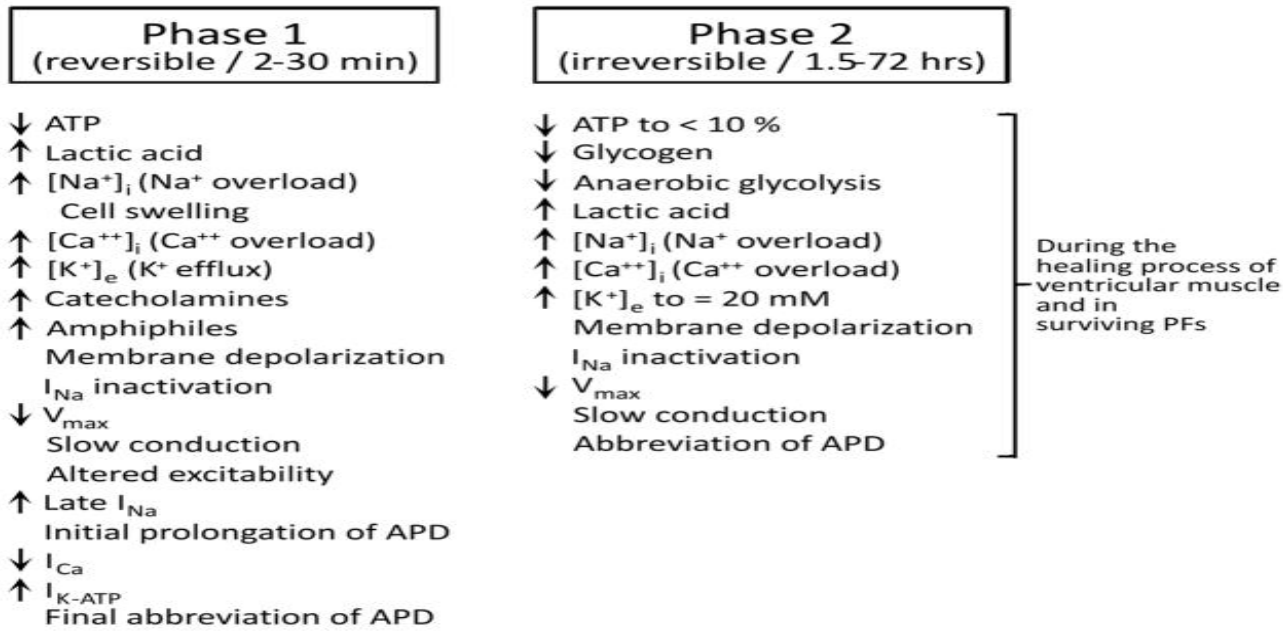

Figure 2. Biochemical and electrophysiological characteristics of Phase 1 and Phase 2 ischemia mediated ventricular arrhythmias[10]. Reproduced with permission from Elsevier .
INa: sodium channel current; Late INa: late INa; APD: action potential duration; ICa: inward calcium current; IK-ATP: ATP-sensitive potassium current.

1.2 ELECTROPHYSIOLOGICAL EFFECTS OF POTASSIUM DISORDERS

The ratio of intra- and extracellular potassium concentrations is critical for the resting membrane potential and for generating action potentials in the heart and other excitable tissues. Approximately 98% of total body potassium is distributed as an intracellular cation, whereas only a small portion is extracellular with plasma levels normally strictly maintained between 3.5 and 5.0 mmol/L[13]. Potassium derangements impact on electrophysiological properties and promote arrhythmias through the interplay between K^+, Na^+, and Ca^{2+}, and the regulation of the Na^+-K^+ ATPase and Na^+-Ca^{2+} exchange.

Hypokalemia causes hyperpolarization of the resting membrane, inhibits the Na^+-K^+ ATPase, and suppresses K^+ channel conductance. This, in turn, results in action potential duration (APD) prolongation, reduced repolarization reserve, early afterdepolarization (EAD), delayed afterdepolarization (DAD), and automaticity. EAD-mediated arrhythmias include Torsades de pointes and polymorphic VT, which may degenerate to VF. Additionally, hypokalemia enhances the proarrhythmic effect of class III antiarrhythmic drugs (K^+ channel blockers) by further suppressing K^+ channel conductance and may also increase the affinity of the drug[14].

Some observational data have suggested a possible association between hypokalemia and atrial fibrillation[15, 16]. An experimental study demonstrated that hypokalemia reduces sinoatrial node automaticity and induces triggered activity and burst firing in pulmonary veins, which may play a role in the genesis of atrial fibrillation[17].

Systemic hyperkalemia enhances K^+ channel conductance, shortens APD, and induces post-repolarization refractoriness, resulting in increased repolarization reserve. Furthermore, the resting membrane potential depolarizes, which alters conduction velocity (CV) in a biphasic manner. Initially CV accelerates but then gradually becomes slower as hyperkalemia progresses. Nonetheless, hyperkalemia causes CV restitution, i.e. the dependence of the CV of a propagating wave on the preceding diastolic interval, to accentuate. Arrhythmias resulting from hyperkalemia include asystole, heart block, and VT/VF, where reentry may be induced by several mechanisms. The severity of hyperkalemia needed to induce arrhythmias varies substantially among humans. The sinus node and sinoatrial conduction are generally less sensitive to hyperkalemia than the atrioventricular (AV) node and infranodal escape pacemakers[14].

Interstitial hyperkalemia defines a rise of interstitial [K^+] in tissue with normal [K^+] in the systemic circulation. Interstitial [K^+] increases swiftly in the central ischemic zone after acute coronary occlusion. APD shortens and the resting membrane potential depolarizes resulting in systolic and diastolic injury currents flowing across the border zone, which can reexcite nonischemic recovered tissue to generate extrasystoles promoting reentry. Additionally, phase 2 reentry (reentry not depending on circus movement, where local reexcitation is generated in a region with spatially widely dispersed repolarization[18]) may arise from the subepicardium[14]. All together, these changes set the stage for both triggers and substrates

capable of inducing ventricular ectopy, VT, and VF during phase 1 of acute myocardial ischemia[14].

1.3 IN-HOSPITAL CARDIAC ARREST AND RHYTHM MONITORING IN NON-ST ELEVATION ACUTE CORONARY SYNDROME

In patients with STEMI, in-hospital ventricular arrhythmias affect approximately 5% and most commonly occur within the first 48 hours[19-21]. In NSTE-ACS, in-hospital ventricular arrhythmias are less common. A pooled analysis of four major randomized controlled trials (RCTs) with over 26,000 patients conducted in the 1990s showed that the incidence of in-hospital ventricular arrhythmias was 2.1%. Median time to arrhythmia was approximately 78 hours and its occurrence was associated with increased mortality at 30 days and six months. Prior hypertension, chronic obstructive pulmonary disease, prior myocardial infarction, and the presence of ST-segment changes at presentation were associated with VF, and the same variables except for hypertension also predicted VT (**Table 1**)[22]. In a more recent substudy of the Early Glycoprotein IIb/IIIa Inhibition in NSTE-ACS (EARLY ACS) trial, comprising 9211 patients, in-hospital ventricular arrhythmias occurred in 1.5% and were associated with increased mortality after discharge, both at 30 days and at one year. In-hospital ventricular arrhythmias were as likely to occur after 48 hour as within 48 hours and in 38% of affected patients they occurred after revascularization. Eight factors were independently associated with in-hospital ventricular arrhythmias (**Table 1**). Higher systolic blood pressure and higher estimated creatinine clearance were associated with a lower risk of in-hospital ventricular arrhythmias. Higher white blood cell count, higher heart rate, and higher body weight were associated with higher risk of in-hospital ventricular arrhythmias as were elevated baseline troponin level, Killip class higher than I, and a history of angina[23]. A single-center study of 588 NSTEMI patients reported a 2.6% incidence of in-hospital ventricular arrhythmias where two-thirds occurred within 12 hours of onset of symptoms[24]. In a more recent single-center study of 1325 patients with NSTEMI, the incidence of in-hospital ventricular arrhythmias was 1.5% (n=21) and approximately 25% occurred after 48 hours of hospitalization[25]. This study also reported that risk stratification at admission using the Global Registry of Acute Coronary Events (GRACE) score[26, 27] and echocardiographic systolic left ventricular ejection fraction (LVEF) could identify NSTEMI patients with a higher risk for in-hospital ventricular arrhythmias[25].

Patients with ACS are also at risk for in-hospital non-VT/VF cardiac arrest, i.e. asystole and pulseless electrical activity (PEA), as well as high-degree AV block. In a pooled analysis of three large RCTs comprising nearly 30,000 patients with NSTEMI, asystole or PEA occurred in 0.7% and was more frequent beyond the first 48 hours. High-degree AV block affected 0.4% and was more common within the first 48 hours. Increasing age, higher heart rate, higher Killip class, ST-segment depression on admission, prior myocardial infarction, and prior peripheral artery disease were associated with both asystole and PEA. Older age, lower heart rate, lower blood pressure, and prior diabetes were associated with high-degree AV-

block, which was also more commonly observed in patients with right coronary artery lesions[28].

For patients admitted with confirmed or suspected NSTE-ACS, decisions have to be made regarding level of surveillance including selection of patients for and duration of continuous ECG monitoring. Current guidelines (2014) from the American College of Cardiology (ACC) and the American Heart Association (AHA) provide several clinical factors that have been found to be predictive of VT/VF (**Table 1**): heart failure signs on presentation, hypotension, tachycardia, cardiogenic shock, and poor Thrombolysis in Myocardial Infarction (TIMI) flow[29]. Current guidelines (2015) from the European Society of Cardiology (ESC) recommend monitoring in low-risk patients until revascularization or ≤24 hours, and prolonged monitoring only if intermediate/high-risk features are present (e.g. hemodynamic instability, major arrhythmias, LVEF <40%, failed reperfusion and the presence of critical stenosis or complications related to percutaneous coronary intervention [PCI])[2]. According to ESC guidelines, continuous rhythm monitoring is also recommended until the diagnosis of NSTE-ACS is established or ruled out[2] and this is supported by a consensus document from AHA with expert opinions from 2004[30].

Table 1. Predictors of in-hospital VT/VF in NSTE-ACS.

Al-Khatib et al.[22]	Piccini et al.[23]	Amsterdam et al.[29]
Prior hypertension*	Lower systolic blood pressure	Signs of HF on presentation
COPD	Lower creatinine clearance	Hypotension
Prior MI	Elevated troponin	Tachycardia
ST-changes at presentation	Killip class ≥II	Cardiogenic shock
	Higher WBC	Low TIMI flow grade
	Higher heart rate	
	Higher body weight	
	History of angina	

*Only associated with VF; COPD: chronic obstructive pulmonary disease; TIMI: Thrombolysis in Myocardial Infarction; WBC: white blood cell count; HF: heart failure.

In summary, several studies have investigated incidence, timing and prognosis of in-hospital ventricular arrhythmias and also non-VT/VF cardiac arrest in the setting of NSTE-ACS. However, the best data come from subanalyses of large multicenter trials, which refer to selected patients and do not necessarily reflect real-life clinical practice. Current guidelines suggest several risk factors associated with in-hospital ventricular arrhythmias and also provide recommendations for duration of continuous ECG-monitoring but these are mainly based on experts' opinions.

1.4 CARDIAC ARREST AND SUDDEN CARDIAC DEATH AFTER MYOCARDIAL INFARCTION DISCHARGE

Following MI, patients are at increased risk for sudden cardiac death (SCD), which is largely due to ventricular tachyarrhythmias and subsequent cardiac arrest[31]. The 30-day cumulative incidence of SCD was 1.2% in a community cohort of nearly 3000 post-MI patients between 1979 and 2005, while the event rate after 30 days declined to 1.2% per year during a median follow up of 4.7 years[32]. In a study comprising over 14,000 post-MI patients between 1998 and 2001 with LVEF ≤40% or clinical or radiologic evidence of heart failure, the risk of SCD or resuscitated cardiac arrest was 1.4% in the first month and fell to 0.14% per month after two years. Restricted to patients with LVEF ≤30%, the event rate in the first month was 2.3%. Notably, among patients with cardiac arrest within the first month and successful resuscitation, 74% were still alive at 12 months[33]. Despite the increased risk of SCD in the early phase after MI, two major randomized trials conducted between 1998 and 2007 did not, due to competing causes of death, demonstrate improved survival for patients with LVEF ≤35% and ≤30%, respectively, randomly assigned to receive an implantable cardioverter-defibrillator (ICD) within 31 to 40 days (at a mean of 18 and 13 days respectively) after MI[34, 35]. Hence, current guidelines recommend ICD for primary prevention at least 40 days after MI and 90 days after revascularization in patients with LVEF ≤35% and symptomatic heart failure, New York Heart Association (NYHA) class II-III, or LVEF ≤30%, on optimal medical therapy for ≥3 months[36, 37]. These guidelines primarily rely on two RCTs demonstrating superior long-term survival for patients who received an ICD more than 30 days after MI with LVEF ≤30%[38] or after at least three months of optimal medical therapy with symptomatic heart failure (NYHA II-III) and LVEF ≤35%[39]. Several non-invasive tests for early risk stratification, such as microvolt T-wave alternans, tests for autonomic dysfunction, or signal-averaged electrocardiogram, have been proposed but without convincing evidence[40-42]. Thus, according to current European guidelines, non-invasive tests in the early post-MI phase are not recommended (class III). Instead, LVEF should be reevaluated 6 to 12 weeks (class I) after MI to assess indication for primary prevention ICD implantation[36].

Some data support that an electrophysiology study (EPS) with no inducible sustained ventricular tachyarrhythmias early after MI in patients with LVEF ≤40% is associated with a low long-term risk of SCD[43-45]. Two fairly recent non-randomized single-center studies have also demonstrated the use of EPS to guide early ICD therapy in patients with STEMI and LVEF ≤40%. An ICD was implanted before discharge in patients with inducible VT at EPS performed at a median of 9 days after MI. ICD patients had high rates of spontaneous ventricular arrhythmias and a non-negligible proportion received appropriate therapies early post-MI: 17% within 2 months post-MI and 25% within 40 days post-MI, respectively. The non-ICD patients had a low mortality rate during follow-up (≥30 months)[46, 47]. Current European guidelines suggest that EPS with programmed ventricular stimulation may be considered early post-MI in patients with LVEF <40% but also stress that randomized trials are needed to evaluate the role of EPN in early risk stratification after MI[36].

The recently published Vest Prevention of Early Sudden Death Trial (VEST) enrolled 2302 post-MI patients with LVEF ≤35%. Participants were randomly assigned to a wearable cardioverter–defibrillator in a 2:1 ratio within 7 days after MI-discharge and followed up to 90 days. The cumulative incidences of arrhythmic death and non-arrhythmic death were 1.6% and 1.4% in the device group and 2.4% and 2.2% in the control group. The primary outcome of arrhythmic death did not differ significantly between the device and control groups[48].

In summary, the risk of ventricular tachyarrhytmias and subsequent SCD is markedly increased in the early period following MI. However, current evidence only supports primary-preventive ICD implantation at least 40 days after MI. Several non-invasive tests for early risk stratification have been suggested but not been proven useful. Further studies are needed to support the use of EPN in this setting. Current knowledge and guidelines are mainly based on studies conducted in the late 1990s and early 2000s even though demographics and treatment of MI-patients have changed.

1.5 POTASSIUM IMBALANCE AND IN-HOSPITAL OUTCOMES IN ACUTE CORONARY SYNDROME

A number of older observational studies have reported an association between hypokalemia and ventricular arrhythmias in patients with acute MI[49-57] or suspected but not confirmed MI[51, 56]. However, these studies were all conducted before beta-blockers and reperfusion therapy were routinely used and results were mainly based on unadjusted analyses of small case series. Hypokalemia was most often defined as serum potassium below 3.6 or 3.5 mEq/L[49-57].

Data from the Gruppo Italiano per lo Studio delia Sopravvivenza nell'Infarto Miocardico-2 (GISSI-2) trial, a multicenter, randomized, open trial comparing two thrombolytic agents, where all patients without contraindications were treated with intravenous beta-blockers, was used to investigate incidence, prognosis and predictors of in-hospital VF. This study comprised 9720 patients with STEMI. Multivariate logistic regression analyses, including serum potassium level, systolic blood pressure, smoking status, number of ECG leads with ST elevation, age, infarct site, admission heart rate, sex, and a history of previous angina, showed that serum potassium <3.6 mEq/L was independently associated with early (within the first 4 hours) VF (odds ratio [OR] 1.97, confidence interval [CI] 95% 1.51-2.56)[58].

Based on the above mentioned knowledge, guidelines and expert recommendations from the early 2000s suggested maintaining serum potassium at a level greater than or equal to 4.0 mEq/L[59, 60] or even above 4.5 mEq/L[61] in the setting of MI. These recommendations remained unquestioned for several years but were challenged by Goyal and colleagues in 2012[62].

Goyal et al. investigated the association between serum potassium levels, in-hospital mortality, and the composite of in-hospital VF or cardiac arrest. The cohort comprised 38,689 patients with MI from 67 US hospitals between 2000 and 2008. A U-shaped relationship between mean post-admission serum potassium level and mortality was observed. Potassium

levels <3.5 and ≥4.5 mEq/L were associated with increased mortality. This association remained after multivariable adjustment including demographics, comorbidities, first measurement during hospitalization of several laboratory values including estimated glomerular filtration rate (eGFR) and potassium, presence of cardiogenic shock and acute respiratory failure on admission, interventional procedures during hospitalization, and medication during hospitalization. When considering serum potassium level at admission only, the association was attenuated. After multivariable adjustment, admission potassium levels <3.0 and ≥5.0 mEq/L were significantly associated with increased in-hospital mortality. For the composite of VF and cardiac arrest, the relationship with mean post-admission serum potassium level was flatter. Increased rates of VF or cardiac arrest were only observed at post-admission serum potassium levels <3.0 and ≥5.0 mEq/L. For serum potassium at admission, increased rates of VF or cardiac arrest were only observed at potassium levels <3.5 mEq/L[62].

Another study based on the same cohort of MI-patients specifically addressed hyperkalemia during hospitalization. Hyperkalemic events (any serum potassium ≥5.0 mEq/L during hospitalization) were common and affected 22.6% of patients on dialysis and 66.8% of patients not on dialysis. In-hospital mortality surpassed 15% when maximum potassium was ≥5.5 mEq/L. The association between higher maximum potassium level and increased in-hospital mortality remained after multivariable adjustment. In-hospital mortality also increased with the number of hyperkalemic events[63].

A number of studies after Goyal et al. have demonstrated that both hypo- and hyperkalemia are associated with adverse outcomes, primarily increased mortality, in the setting of ACS. Choi et al. reported an association between mean serum potassium levels >4.5 and <3.5 mEq/L during hospitalization and increased long-term mortality (up to three years) in patients with MI[64]. Another study also demonstrated that serum potassium >4.5 and <3.5 mEq/L at admission was associated with increased long-term mortality in patients with ACS[65]. Additionally, several studies have showed that potassium imbalance during hospitalization is associated with worse outcome in cohorts of patients with NSTE-ACS and STEMI exclusively[66, 67].

A recent meta-analysis included twelve studies to assess associations between serum potassium concentrations and short and long-term mortality as well as ventricular arrhythmias. Short and long-term mortality were defined as all-cause mortality within or beyond 6 months. Using serum potassium 3.5-<4.0 mEq/L as the reference category, pooled results demonstrated a significantly increased risk for both short and long-term mortality in patients with serum potassium concentrations of <3.5 mEq/L and ≥4.5 mEq/L. Moreover, serum potassium <3.5 mEq/L was significantly associated with the risk of ventricular arrhythmias. Additional analyses were conducted separating studies using admission and mean serum potassium concentrations. Both groups of studies showed a significant association between serum potassium <3.5 mEq/L and ventricular arrhythmias. However, for serum potassium ≥5.0 mEq/L, a significantly increased pooled OR was only seen in studies

with a mean serum potassium measurement. In contrast, studies with admission serum potassium measurement showed a significantly decreased pooled OR.Since several studies used different effect sizes or reference categories, unadjusted, instead of confounder-adjusted, estimates were used from some of the studies in the meta-analyses. Hence, and as also stressed by the authors, the pooled effects may have been overestimated[68].

In summary, potassium imbalance has been associated with in-hospital ventricular arrhythmias and mortality in the setting of ACS. Although this has been shown for ACS in general as well as for NSTE-ACS and STEMI separately, no direct comparison between different subtypes of ACS has been performed. Furthermore, prior studies have not considered important baseline characteristics such as blood pressure, heart rate, or Killip class.

1.6 POTASSIUM IMBALANCE AND OUTCOMES AFTER MYOCARDIAL INFARCTION DISCHARGE

Potassium imbalance is a common clinical problem and is associated with the risk of adverse events. Hyperkalemia is more prevalent among patients with chronic kidney disease (CKD), diabetes, cardiovascular disease, heart failure, and users of medication such as renin angiotensin aldosterone system (RAAS) inhibitors and non-steroidal inflammatory drugs[69]. Hypokalemia is most frequently caused by drugs, primarily diuretic therapy[70]. A US study comprising over 15,000 individuals from the general population aged 44 to 66 years with eGFR of at least 60 mL/min/1.73 m^2, reported that nearly 5% had serum potassium values of <3.5 or ≥5.5 mmol/L in blood samples drawn at baseline between 1987 and 1989. Compared to those with normokalemia, a majority of individuals with hypokalemia were taking potassium-wasting diuretics (17.7% vs. 9.9%). The use of angiontensin-converting enzyme inhibitors (ACEi) did not differ between individuals with normokalemia and potassium imbalance[71]. A retrospective analysis with data from laboratory visits of nearly 16,000 patients with cardiovascular disease defined as heart failure and hypertension treated with antihypertensive drugs showed that 24.5% had hyperkalemia (serum potassium ≥5.0 mEq/L). There were no differences in the use of ACEi, angiotensin II receptor blockers (ARBs), or potassium-sparing diuretics between normokalemic and hyperkalemic patients. Diabetes, CKD stage, coronary artery disease, and peripheral vascular diseased were predictors of hyperkalemia. Hyperkalemia was associated with increased all-cause mortality and hospitalization[72].

Patients with MI have multiple risk factors for potassium imbalance given a high burden of comorbidities such as diabetes, hypertension, heart failure, and CKD. In addition, recommended treatment after MI includes medication that may alter potassium levels, primarily RAAS inhibitors and diuretics.

Data on post-discharge potassium levels and associated outcomes following MI are scarce. Major randomized clinical trials on treatment with RAAS inhibitors after MI have provided

little information about potassium disorders. Furthermore, patients with renal failure, not uniformly defined, were often excluded.

GISSI-3 and the International Study of Infarct Survival-4 (ISIS-4) investigated the effects of short-term ACEi therapy (4-6 weeks) after MI but did not report data on potassium levels[73, 74]. Neither did the Survival and Ventricular Enlargement (SAVE) trial nor the Acute Infarction Ramipril Efficacy (AIRE) trial, two large RCTs on long-term ACEi treatment following MI with heart failure, present information about potassium disturbances[75, 76]. The Trandolapril Cardiac Evaluation (TRACE) trial, another study where patients with heart failure after MI were assigned long-term ACEi therapy, reported that hyperkalemia (not defined in terms of specific biochemical values) occurred in 4.9% compared to 2.6% in the placebo group[77]. The Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan (OPTIMAAL) compared ACEi to ARB treatment in patients after MI associated with heart failure. Data on potassium disorders were not reported but serum potassium differed significantly between baseline and study end (mean follow-up 2.7 years) in the two treatment arms with an increase by approximately 0.2 mmol/L[78]. In the VALIANT trial, patients with heart failure after MI were assigned to ACEi, ARB, or both. Hyperkalemia was not specified but was reported to result in dose reduction in 0.9-1.3% in the three treatment arms whereas hyperkalemia resulting in permanent discontinuation occurred in 0.1-0.2%[79]. The EPHESUS trial investigated the effects of eplerenone, a mineralocorticoid receptor antagonist (MRA) vs. placebo when added to optical medical therapy including ACEi/ARB (87%), beta-blockers (75%), and diuretics (60%) in patients with heart failure following MI. Mean follow-up was 16 months. Serious hypokalemia defined as serum potassium <3.5 mmol/L was observed in 8.4% in the eplerenone group and 13.1% in the placebo group. Serious hyperkalemia defined as serum potassium ≥6.0 mmol/L was observed in 5.5% in the eplerenone group and in 3.9% in the placebo group[80].

A Danish registry-based study of 2596 patients receiving diuretics following hospitalization for MI reported increased all-cause mortality at 90 days for those with serum potassium <3.5 mmol/L and >5.0 mmol/L post-discharge. Increased mortality was also observed for serum potassium levels within the lower and upper normal ranges (3.5-3.8 and 4.6-5.0 mmol/L). These associations remained after multivariable adjustment including comorbidities and medication (RAAS inhibitors included). However, the models were not adjusted for renal function and patients with CKD before index MI were excluded from the study[81].

Table 2 summarizes the abovementioned trials.

In summary, comorbidities and medication are contributing risk factors to potassium disorders after MI discharge. Potassium levels and associated outcomes have rarely been reported in the major RCTs on RAAS inhibitors post-MI and real-world data on this matter are also lacking.

Table 2. Major randomized controlled trials on renin-angiotensin-aldosterone system inhibitors following myocardial infarction.

Trial	Intervention drug	Exclusion for renal impairment	Method of K measurement	Hypokalemia	Hyperkalemia
EPHESUS[80] N=6642. AMI within 3-14 days. LVEF <40% after index MI. Symptoms of HF or non-symptomatic if concomitant diabetes. Mean follow-up 16 months.	Eplerenone vs. placebo added to optical medical therapy: ACEi/ARBs (87%), beta-blockers (75%), diuretics (60%).	Serum creatinine > 220 µmol/L (2.5 mg/dL)	Serum potassium	Severe hypokalemia (<3.5 mmol/L): Eplerenone (8.4%), Placebo (13.1%)	Serious hyperkalemia (≥6.0 mmol/L): Eplerenone (5.5%), Placebo (3.9%)
VALIANT[79] N=14,703. AMI within 0.5-10 days. Clinical or radiological signs of HF, LVEF <35% (TTE) or <40% (nuclear imaging). Mean follow-up 24.7 months.	Valsartan or valsartan + captopril vs. captopril alone. Beta-blockers (70%), potassium-sparing diuretics (9%), other diuretics (50%).	Serum creatinine > 221 µmol/L (2.5 mg/dL)	Hyperkalemia, increased blood potassium level, was investigator-reported and not defined in terms of specific biochemical values.	Not specified	Resulting in dose reduction: valsartan (1.3%), valsartan+ captopril (1.2%), captopril (0.9%) Resulting in permanent discontinuation: Valsartan (0.1%), valsartan+ captopril (0.2%), captopril (0.1%)
OPTIMAAL[78] N=5477. AMI during the acute phase (new anterior Q-wave AMI, any AMI with previous anterior Q-waves, or any AMI with heart failure). Mean follow-up 2.7 years.	Captopril vs. losartan. Beta-blockers (78.6%), diuretics (63.8%), digitalis (11.2%).	Not specified	Serum potassium	Not specified	Not specified. A significant difference between baseline and study end was observed (increase of 0.19-0.22 mmol/L).
ISIS-4[74] N=58,050. Suspected AMI (92% confirmed) with symptom onset within 24 h. 5-week follow-up.	Captopril vs. placebo	Not specified	Not specified	Not specified	Not specified

Table 2. Major randomized controlled trials on renin-angiotensin-aldosterone system inhibitors following myocardial infarction (continued).

Trial	Intervention drug	Exclusion for renal impairment	Method of K measurement	Hypokalemia	Hyperkalemia
GISSI-3[73] N=18,895. AMI with symptom onset within 24 h. 6-week follow-up.	Lisinopril vs. controls.	Serum creatinine > 177 μmol/L, proteinuria >500 mg per 24 h, or both. Bilateral stenosis of the renal arteries.	Not specified	Not specified	Not specified
TRACE[77] N=1749. AMI within 3-7 days. LVEF ≤35%. 24-50 months of follow-up.	Trandolapril vs. placebo. Beta-blockers (16%), diuretics (66%), digoxin/ digitalis (27%).	Serum creatinine ≥ 200 μmol/L (2.3 mg/dL)	Not specified	Not specified	Trandolapril (4.9%), placebo (2.6%)
AIRE[76] N=2006. AMI within 3-10 days. Clinical evidence of heart failure. Mean follow-up 15 months.	Ramipril vs. placebo. Beta-blockers (22%), diuretics (60%), digoxin (12%).	Not specified	Not specified	Not specified	Not specified
SAVE[75] N=2231. AMI within 3-16 days. LVEF ≤40% without overt heart failure or symptoms of myocardial ischemia. Mean follow-up 42 months.	Captopril vs. placebo. Beta-blockers (36%), diuretics (35%), digitalis (26%).	Serum creatinine > 221 μmol/L (2.5 mg/dL)	Not specified	Not specified	Not specified

EPHESUS: Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study; AMI: acute myocardial infarction; LVEF: left ventricular ejection fraction; HF: heart failure; VALIANT: Valsartan in Acute Myocardial Infarction; TTE: transthoracic echocardiography; OPTIMAAL: Optimal Therapy in Myocardial Infarction with the Angiotensin II Antagonist Losartan; ISIS-4: The Fourth International Study of Infarct Survival; GISSI-3: The Third Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-2) trial; TRACE: Trandolapril Cardiac Evaluation; AIRE: Acute Infarction Ramipril Efficacy; SAVE: Survival and Ventricular Enlargement; ACEi: angiontensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker.

2 AIMS

The overall aim of the thesis was to assess patient characteristics and predictors of adverse events in ACS including arrhythmias, cardiac arrest, and mortality. Furthermore, we sought to investigate the impact of potassium disorders in this setting.

2.1 SPECIFIC AIMS

Study I: To find possible predictors of in-hospital cardiac arrest in patients admitted with suspected NSTE-ACS and further to develop and validate a user-friendly risk-score for this purpose.

Study II: To find possible predictors of out-of-hospital cardiac arrest early after MI within the time window where primary preventive ICD is not routinely recommended.

Study III: To study the impact of potassium disorders at admission and associations to adverse in-hospital outcomes in patients admitted with suspected ACS.

Study IV: To study the impact of potassium disorders at and after discharge and associations to adverse outcomes following MI

3 THESIS AT A GLANCE

Study	**I**	**II**	**III**	**IV**
Design	Cohort study	Cohort study	Cohort study	Cohort study
Data source	SWEDEHEART, MINAP	SWEDEHEART, the Swedish CPR Registry, the Swedish Pacemaker and ICD Registry	SWEDEHEART, SCREAM	SWEDEHEART, SCREAM
Time of data collection	2008-2014 (derivation cohort), 2005-2007 (temporal validation cohort), 2008-2013 (external validation cohort)	2009-2017	2006-2011	2006-2011
Study population	Cases admitted with suspected NSTE-ACS	Cases, which had undergone coronary angiography and were discharged alive after MI without previous ICD	Patients admitted with suspected ACS	Patients with MI discharged alive
Numbers included in analyses	N=242,303 (derivation cohort); N=126,073 (temporal validation cohort) N=276,109 (external validation cohort)	N=121,379	N=32,955	N=4861
Follow-up time	During hospitalization	90 days post-discharge or December 31, 2017	During hospitalization	1 year post-discharge
Outcomes	In-hospital cardiac arrest	Out-of-hospital cardiac arrest	In-hospital mortality, cardiac arrest, new-onset AF, and 2nd- or 3rd-degree AV-block	Hyperkalemia, hypokalemia, mortality, reinfarction, heart failure, new-onset AF within 1 year
Main statistical analyses	Logistic regression	Cox regression, Fine-Gray regression	Logistic regression	Logistic regression, Cox regression, Fine-Gray regression
Conclusion	A simple risk-score model including five easily accessible variables predicts the risk of in-hospital cardiac arrest for patients admitted with suspected NSTE-ACS.	The incidence of OHCA at 90 days was low. Six clinical variables including LVEF more accurately predicted OHCA as well as non-OHCA death than an LVEF cut-off of <40% alone.	Hyperkalemia at admission is associated with in-hospital mortality and hypokalemia is associated with cardiac arrest and new-onset atrial fibrillation in patients admitted with suspected ACS.	Hyperkalemia and hypokalemia are common within the first year after MI discharge. Potassium level and eGFR at discharge strongly predict their occurrence, as well as mortality at one year.

4 METHODS

4.1 DATA SOURCES

All studies (**Studies I-IV**) were conducted using data from the Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART). In **Study I**, additional data from the Myocardial Ischaemia National Audit Project (MINAP) was used. **Study II** was made possible by merging data from SWEDEHEART, the Swedish Cardiopulmonary Resuscitation Registry, and the Swedish Pacemaker and ICD Registry. To carry out **Studies III-IV**, SWEDEHEART was enriched with data from the Stockholm CREAtinine Measurements (SCREAM) project.

4.1.1 SWEDEHEART

SWEDEHEART was developed in December 2009 after consolidation of the Register of Information and Knowledge About Swedish Heart Intensive Care Admissions (RIKS–HIA), the Swedish Coronary Angiography and Angioplasty Registry (SCAAR), the Swedish Heart Surgery Registry, and the Secondary Prevention after Heart Intensive Care Admission (SEPHIA)[82]. RIKS-HIA was launched as a regional registry in the early 1990s and developed into a national quality register in 1995 with the addition of SEPHIA in 2005. Swedish hospitals performing coronary angiography started a national angioplasty registry and a coronary angiography registry in the beginning of the 1990s and these were merged to form SCAAR in 1998. The Swedish Heart Surgery Registry was launched in 1992[82].

SWEDEHEART includes patients hospitalized because of symptoms suggestive of ACS and patients undergoing coronary angiography/ PCI or cardiac surgery for any reason. All Swedish hospitals providing coronary care participate and except for secondary prevention (SEPHIA), the coverage is 100%. For patients admitted with suspected ACS, some 100 variables are collected prospectively. Variables include demographics, prior medical history, admission logistics, medication before admission, presentation characteristics including clinical and electrocardiographic features, laboratory data, treatments and interventions during hospitalization, hospital outcomes, discharge diagnoses, and medication at discharge. In addition, SWEDEHEART is regularly merged with the National Cause of Death Register, which provides information about vital status of all Swedish citizens, the National Patient Registry, providing diagnoses at discharge for all hospital stays in Sweden, and with the Swedish Prescribed Drug Register, where all drug prescriptions in Sweden are recorded[82].

All patients are informed about their entry and follow-up in the registry and have the right to opt-out. A majority of variables are mandatory in order to ensure a high degree of completeness. To ensure data correctness, randomly assigned monitor visits to approximately 25% of participating hospitals take place yearly, where registry-recorded data and information in patients' records are compared. An agreement of over 95% has been reported[82].

According to the National Board of Health and Welfare, 86.6% of acute MIs in Sweden 2015 were captured by SWEDEHEART and there has been a slight improvement of coverage since 2011. According to the same report, almost 100% of PCIs and about 96% of cardiac surgery procedures performed in 2015 were captured by SWEDEHEART[83].

The RIKS-HIA registry forms of 2018 are shown in **Figures 3-5**. The present thesis is based on SWEDEHEART data collected from 2006 and onwards. The variables used in the analyses have not changed up to 2018.

4.1.2 MINAP

MINAP was founded in 1998. Since 2002 all acute hospitals in England and Wales are part of the registry[84]. The National Institute for Cardiovascular Outcomes Research (NICOR) which includes the MINAP database (Ref: NIGB: ECC 1-06 (d)/2011) has support under section 251 of the National Health Service Act 2006 to use patient information for medical research without consent. Hospitals are requested to register all patients admitted with ACS. However, under-reporting has been observed, in particular for NSTEMI, with over 40% of cases estimated to be missing. Over 100 variables are collected including demographics, prior medical history, prior drug treatment, admission method, clinical features and investigations, drug treatment in hospital, interventional treatments, hospital outcome, complications, discharge diagnosis, and discharge treatment. Additionally, MINAP is regularly linked to the Office for National Statistic's registry to assess patients' vital status. Participating hospitals are recurrently monitored regarding validation and completeness of entered data[84].

4.1.3 The Swedish Cardiopulmonary Resuscitation Registry

The Swedish Cardiopulmonary Resuscitation Registry was started in 1990. Registration coverage has increased considerably over time and is now almost 100% as all Swedish emergency medical service (EMS) stations participate. All patients with out-of-hospital cardiac arrest (OHCA) where attempted resuscitation by EMS personnel and/or a bystander has been performed are eligible for inclusion except for cases where cardiopulmonary resuscitation (CPR) was initiated by a bystander but not continued by EMS personnel because of definite signs of death. Registry reporting is made in two steps. First, EMS personnel register baseline data including time and date of OHCA, treatment, initial rhythm, and outcome. If applicable, a local CPR coordinator with access to in-hospital medical records, registers in-hospital treatments, outcomes, and diagnoses. Cardiac arrest survivors are informed about their entry in the registry and may choose to opt out. Non-survivors are included without consent[85].

4.1.4 The Swedish Pacemaker and ICD Registry

The Swedish Pacemaker Registry was started in 1989. Since 2004 data on ICD implants are also reported. The registry covers almost 100% of the total pacemaker and ICD implanting activity in Sweden with 44 centers reporting data. Informed consent is required for data entry by the ethics committee of individual participating hospitals. Reported variables include

patient demographics, clinical indication for implantation, etiology, surgical procedural data, perioperative and postoperative complications, number of implants or replacements per center, and technical information on generators and leads[86].

4.1.5 SCREAM

SCREAM is a repository of laboratory data of residents of the Stockholm County, who had a valid personal identifying number, were at least 18 years old, and underwent creatinine testing between 2006 and 2011[87]. The cohort comprises data from 1,118,507 individuals. Laboratory data was provided from Aleris, Unilabs, and Karolinska University Hospital Laboratory, the three laboratories performing nearly all laboratory tests within the Stockholm region. Inter- and intra-laboratory variation was considered to be negligible as laboratory quality and harmonization is regularly monitored by Equalis, a national provider of external quality assessment for clinical laboratory investigations in Sweden. All creatinine tests analyzed within the time period were included in addition to other routine laboratory measurements, such as electrolytes, glucose, and hemoglobin. Each provided test included date, method used, and units of measurement. The SCREAM dataset was further enriched with data from the regional administrative health data register (Vårdanalysdatabasen, VAL; Stockholm Regional Healthcare Data Warehouse) including demographics and information (date, center and medical department, clinical diagnoses, and therapeutic procedures) on all healthcare visits in primary and secondary care, as well as hospitalizations. Additionally, the SCREAM dataset was linked to the Swedish Population Registry, the Swedish Prescribed Drug Registry, the Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA by Swedish acronym), and the Swedish Renal Registry. The SCREAM project is approved by the Ethical Committee of Stockholm[87].

4.2 DEFINITIONS

All variables were defined according to each respective registry. In SWEDEHEART, in-hospital cardiac arrest is defined as cardiac arrest requiring defibrillation and/or CPR. This variable is categorized as “VT/VF”, “other causes of cardiac arrest”, or “no cardiac arrest”. In order to overcome possible misclassification of type of cardiac arrest, we used a dichotomized variable defined as in-hospital cardiac arrest “yes” or “no” in **Studies I** and **III**.

In **Studies III-IV**, hypokalemia was defined as plasma potassium <3.5 mmol/L. Hyperkalemia was defined as plasma potassium ≥5.0 mmol/L in **Study III** and as plasma potassium >5.0 mmol/L in **Study IV**.

4.3 STUDY POPULATION

4.3.1 Study I

A derivation cohort was developed using data from SWEDEHEART between January 1, 2008 and December 31, 2014. All registered patients admitted with symptoms suggestive of NSTE-ACS were eligible for entry. Patients were eligible for entry more than once if they were admitted multiple times during the study period. Exclusion criteria included cardiac

arrest before admission or missing data on cardiac arrest before admission or during hospitalization. The same inclusion and exclusion criteria were applied for selection of a temporal and an external validation cohort. The temporal validation cohort comprised patients registered in SWEDEHEART between January 1, 2005 and December 31, 2007. The external validation cohort included patients registered in MINAP between January 1, 2008 and December 31, 2013.

4.3.2 Study II

All patients registered in SWEDEHEART, who were discharged alive after an acute MI between January 1, 2009 and December 31, 2017, and had undergone in-hospital coronary angiography were eligible for entry. Patients, who had an ICD implanted prior to admission, during the hospital course, or during follow-up, as registered in the Swedish Pacemaker and ICD Registry, were excluded. Patients could enter the study multiple times if a new MI admission was more than 90 days apart from the last preceding MI discharge date.

4.3.3 Study III

All consecutive patients admitted with symptoms suggestive of ACS and registered in SWEDEHEART and SCREAM between January 1, 2006 and July 1, 2011 were eligible for entry. Patients who did not have a potassium test available at admission or had cardiac arrest before admission were excluded.

4.3.4 Study IV

All consecutive patients discharged alive after an acute MI and registered in SWEDEHEART and SCREAM between January 1, 2006 and December 31, 2010 were eligible for entry. Patients who did not have a potassium test and/or a creatinine test available at discharge date (± one day) were excluded as were patients undergoing hemodialysis or peritoneal dialysis during index hospitalization.

4.4 STATISTICS

Categorical data are expressed as number (n) and proportion (%) of patients. Continuous data are presented as median with interquartile range (IQR) or mean with standard deviations (SD). In all analyses, a p-value of <0.05 was considered statistically significant. Statistical analyses were performed with Stata version 13.1 (**Study I**), Stata version 15.1 (**Study II)**, and Stata version 14.0 (**Studies III-IV**) (Stata Corporation, College station, Texas, USA). In **Study I**, additional statistics were performed using R version 3.1.0 (R Foundation for Statistical Computing, Vienna, Austria).

4.4.1 Study I

Multivariable regression models were used to assess associations between 26 candidate baseline variables and in-hospital cardiac arrest. Using backward selection, variables were selected for inclusion in a risk-score model, which was developed according to the points system described by Sullivan et al.[88] Internal, temporal, and external validations including an

additional model adjusting for underlying risk were assessed by graphically determining the calibration curves and calculating the area under the receiver operating characteristic (ROC) curves. Missing data was imputed using multiple imputation by chained equations (MICE)[89]. For the purpose of sensitivity analyses, risk-score model performance was assessed using complete-case data only as well as using first-time admissions only, i.e. unique patients.

4.4.2 Study II

Cox proportional hazard models were used to assess the association between 24 candidate variables and the occurrence of OHCA within 90 days after discharge. Patients who died during follow-up without having OHCA registered were censored. A prediction model was developed using backward selection. In the final model, interaction terms were tested for all variables. Furthermore, we constructed a simple risk-score model, where the included variables were assigned points approximately corresponding to the hazard ratios. As a sensitivity analysis, all candidate variables were tested and a predictive model was developed using Fine-Gray models with mortality in the non-OHCA group as the competing event. Only complete-case analyses were used for this study.

4.4.3 Study III

We assessed the associations between admission plasma potassium categories (reference 3.5-<4.0 mmol/L) and in-hospital outcomes: mortality, cardiac arrest, new-onset atrial fibrillation/ flutter, and second- or third-degree AV block. Multivariable adjustment with logistic regression was applied using three models, adjusting for an increasing number of covariates (24 in total). Associations between exposure (plasma potassium per mmol/L) and outcomes were also graphically modeled using cubic spline logistic regression, adjusting for all covariates. Interaction terms were tested for a subset of covariates. Missing data was imputed using MICE.

4.4.4 Study IV

The odds of hyperkalemia or hypokalemia at discharge were assessed using multivariable logistics regression and adjusting for 21 covariates. Multivariable Cox proportional hazard models were used to assess associations between discharge plasma potassium categories (reference 4.0-<4.5 mmol/L) and hyperkalemia or hypokalemia within one year (with a blanking period of two weeks post-discharge) as well as mortality within one year. Fine-Gray regression models were used to assess associations between discharge plasma potassium categories and hospitalization due to reinfarction, hospitalization due to heart failure, or new-onset atrial fibrillation/ flutter within one year, where death was the competing event. In the above mentioned time-dependent regression analyses, 19 covariates were included. Associations between discharge plasma potassium and outcomes were also assessed using restricted cubic splines. There were no missing data on variables used in the regression models.

4.5 ETHICAL CONSIDERATIONS

All studies were approved by the regional ethical review board in Stockholm and conducted in accordance with the declaration of Helsinki[90]. Data were only analyzed on a group level and the results cannot be linked back to an individual patient

SWEDEHEART – 2018 PatientID:

START – RIKSHIA (1/2) (* = obligatorisk)

Överflyttad patient*						
Överflyttad från	0 Nej	1 Omdirigerad ambulans	2 Annat sjukhus	3 Annan vårdenhet inom sjukhuset		4 Ej registrerande enhet
Ange sjukhus /enhet (om 1-4)						
Beslutsgrundande EKG och ankomststatus*						
EKG rytm	1 Sinus	2 Förmaksflimmer/-fladder				8 Övrigt
EKG QRS	1 Normalt	2 Pacemaker	3 Vänster-grenblock	4 Patol Q-våg	5 Höger-grenblock	8 Övrigt
Vänstergrenblock	0 Tidigare känt	1 Ej tidigare känt				
EKG STT	1 Normalt	2 ST-höjning	3 ST-sänkning	4 Patologisk T-våg		8 Övrigt
Hjärtfrekvens		/min				
Blodtryck Syst/diast		/				
Lungrassel	0 Nej	1 Basala rassel	2 Mer än halva lungorna	3 Lungödem		
Cardiogen chock vid ankomst	0 Nej	1 Ja				
Prehospitala uppgifter*						
Intagningsorsak	1 Bröstsmärta	2 Dyspné	3 Cirkulationsstillestånd			8 Övrigt
Symtomdebut	Datum		Kl			
Ambulans	0 Nej	1 Ja, till Akuten		2 Ja, till HIA/PCI-lab		
Prehospitalt EKG Tidpunkt	Datum		Kl			
HLR före sjukhus	0 Nej	1 Ja				
Prehospital trombolys	0 Nej	1 Ja				
Preh trombolys läkemedel			3 Rapilysin	4 Metalyse		
Preh trombolys tidpunkt	Datum		Kl			
Ankomstuppgifter*						
Ankomst till akuten	Datum		Kl			
Avresa till PCI-sjukhus	0 Nej	1 Ja				
HIA/AVD/PCI-lab	Datum		Kl			
Klinisk bakgrund*						
Längd	_____ cm					
Vikt	_____ kg					
Sysselsättning	1 Arbete	2 Sjukskrivning /sjukersättning	3 Arbetslöshet	4 Ålderspensionär	5 Studerar/Övrigt	
Riskfaktorer						
Rökning*	0 Aldrig rökare		1 Ex rökare > 1 mån	2 Rökare		
Snusning*	0 Aldrig varit snusare		1 Ex snusare > 1 mån	2 Snusare		
Skörhet	1 Mycket vital	2 Vital	3 Klarar sig bra	4 Sårbar	5 Lindrigt skör	
	6 Måttligt skör	7 Allvarligt skör	8 Mycket allvarligt skör	9 Terminalt sjuk		

Figure 3A. RIKS-HIA registry form. Data collected on admission.

SWEDEHEART – 2018

PatientID:

START – RIKSHIA (2/2)

Tidigare hjärtsjukdom*						
Tidigare hjärt-infarkt	0 Nej	1 Ja				
Känd nedsatt vänsterkammar-funktion	0 Nej	2 Ja, lätt nedsatt (40-49%)	3 Ja, måttligt nedsatt (30-39%)	4 Ja, kraftigt nedsatt (<30%)	5 Ja, men okänd grad	
Tidigare PCI	0 Nej	1 Ja				
Tidigare hjärt-kirurgi (avser ej pacemaker)	0 Nej	1 CABG	2 Annan hjärtkirurgi			
Tidigare sjukdomar*						
Diabetes	0 Nej	1 Ja				
Hypertoni	0 Nej	1 Ja				
Tidigare stroke (ej TIA)	0 Nej	1 Ja				
Medicin vid ankomsten*						
ACE-hämmare	0 Nej	1 Ja				
A2-blockerare	0 Nej	1 Ja	2 ARB + Neprilysin			
Antikoagulantia	0 Nej	1 Waran		3 Dabigatran (Pradaxa)	4 Rivaraoxaban (Xarelto)	5 Apixaban (Eliquis)
ASA	0 Nej	1 Ja				
Övriga trombocyt-hämmare	0 Nej	1 Clopidogrel (Plavix)	2 Tiklopidin (Ticlid)	3 Prasugrel (Efient)	4 Ticagrelor (Brilique)	8 Övrigt
Betablockerare	0 Nej	1 Ja				
Ca-hämmare	0 Nej	1 Ja				
Diabetesbe-handling insulin	0 Nej	1 Insulin				
Diabetesbehand-ling per oral	0 Nej	1 Tablettbehandlad				
Digitalis	0 Nej	1 Ja				
Diuretika	0 Nej	1 Ja				
Aldosteron-blockad	0 Nej	1 Spironolakton (Aldactone)	2 Eplerenon (Inspra)			8 Övrigt
Statiner	0 Nej	1 Ja				
Ezetimibe (Ezetrol)	0 Nej	1 Ja				
Övriga lipid-sänkare	0 Nej	1 Ja	Om Ja:			
			2 Fibrater	3 PCSK9-antikroppar	4 Lipoproteinaferes	8 Övrigt
Nitroglycerin långverkande	0 Nej	1 Ja				
Kommentarer						

Figure 3B. RIKS-HIA registry form. Data collected on admission (continued).

SWEDEHEART – 2018 PatientID:

VÅRD – RIKSHIA (* = obligatorisk)

Ankomst HIA/Avd/PCI-lab*	Datum			KI	
Revaskularisering*					
Reperfusionsbehandling	0 Nej	1 Trombolys	2 Primär PCI	3 Akut CABG	4 Akut cor.ai utan åtgärd
Trombolys	0 Nej	1 Streptokinas	2 Actilyse	3 Rapilysin	4 Metalyse
Trombolys kontraindikation	0 Nej	1 Ja			
Trombolys tidpunkt	Datum		KI		
Reperfusionsgrundande EKG = Prehospitalta EKG	0 Nej	1 Ja			
Reperfusiongrundande EKG Tid	Datum		KI		
Medicinering*					
iv/sc Antikoagulantia	0 Nej	1 iv Heparin	2 sc Fragmin/Klexane	3 Arixtra	
iv Betablockerare	0 Nej	1 Ja			
iv Diuretika	0 Nej	1 Ja			
iv Inotropa	0 Nej	1 Ja			
iv Nitroglycering	0 Nej	1 Ja			
Utredningar och behandlingar*					
Typ av stresstest	0 Ej utfört	1 Myocardscint	2 Stress EKO	3 Arbetsprov	
Resultat av stresstest		1 Normalt	2 Patologiskt	3 Ej bedömbart	
Vänsterkammar-funktion mätt		1 Ekokardiografi	2 LV-angio	3 Annan metod	
Vänsterkammarfunktion (LVEF)		1 Normalt (≥50%)	2 Lätt nedsatt (40-49%)	3 Måttligt nedsatt (30-39%)	4 Kraftigt nedsatt (<30%)
CABG	0 Nej	1 Ja, akut CABG	2 Ja, under vårdtillfället	3 Planerad efter utskrivning	
PM/ICD	0 Nej	1 PM permanent	2 ICD	4 CRT	5 ICD+CRT
CPAP	0 Nej	1 Ja			

Laboratorieuppgifter									OBS! Ankomstprover: Hb, CRP, Krea och P-Glucos	
Infarktmarkör	0 Ej utfört	1 Trop T (µg)	2 Trop I	3 CKMB	5 HS Trop T (ng)	6 HS Trop I (ng)				
Maxvärde infarktmarkör										
Kolesterol		Triglycerider		HDL		ApoB		ApoA1		
LDL direktmätt:										
P-Glucos		HbA1c		Prov 2				Prov 3		
Kreatinin*		Dat	KI	Dat	KI			Dat	KI	
CRP		Dat	KI	Dat	KI			Dat	KI	
Hb		Dat	KI	Dat	KI			Dat	KI	

Komplikationer					
Reinfarkt under vårdtillfället*	0 Nej	1 Ja			
Blödning under vårdtillfället*	0 Nej	1 Dödlig	2 Cerebral	3 Krävande op/transfusion	
HLR/Defibrillering under vtf*	0 Nej	1 VT/VF		8 Övrigt	
Cardiogen chock*	0 Nej	1 Ja			
AV-block*	0 Nej/AV-I	1 AV-II-III			
Nytt förmaksflimmer*	0 Nej	1 Ja			
Mekanisk komplikation	0 Nej	1 Fri väggruptur	2 VSD	3 MI (Akut allvarlig MI)	
Överföring utskrivning*					
Överförs till vårdenhet/sjukhus					

Figure 4. RIKS-HIA registry form. Data collected from the hospital course.

SWEDEHEART – 2018

PatientID:

SLUT – RIKSHIA

(* = obligatorisk)

Ankomst HIA/Avd/PCI*	Datum					
Avliden*						
Avliden	0 Nej	1 Ja				
Medicinering*						
ACE-hämmare	0 Nej	1 Ja				
A2-blockerare	0 Nej	1 Ja	2 ARB + Neprilysin			
Antikoagulantia	0 Nej	1 Waran	3 Dabigatran (Pradaxa)	4 Rivaroxaban (Xarelto)	5 Apixaban (Eliquis)	8 Annat
ASA	0 Nej	1 Ja				
Planerad behandlingstid		1 1 mån	2 3 mån	3 6 mån	6 >=12 mån	
Övriga trombocythämmare	0 Nej	1 Clopidogrel (Plavix)	2 Tiklopidin (Ticlid)	3 Prasugrel (Efient)	4 Ticagrelor (Brilique)	8 Övrigt
Planerad behandlingstid		1 1 mån	2 3 mån	3 6 mån	6 >=12 mån	5 tillsvidare
Betablockerare	0 Nej	1 Ja				
Ca-hämmare	0 Nej	1 Ja				
Diabetesbeh insulin	0 Nej	1 Insulin				
Diabetsbeh per oral	0 Nej	1 Tablettbeh				
Digitalis	0 Nej	1 Ja				
Diuretika	0 Nej	1 Ja				
Aldosteronblockad	0 Nej	1 Spironolakton (Aldacton)	2 Eplerenon (Inspra)			8 Övrigt
Statiner	0 Nej	1 Ja				
Ezetimibre (Ezetrol)	0 Nej	1 Ja				
Övriga lipidsänkare	0 Nej	1 Ja Om Ja:	2 Fibrater	3 PCSK9-antikroppar	4 Lipoprotein-aferes	8 Övrigt
Nitroglycering långv	0 Nej	1 Ja				
EKG*						
EKG-rytm	1 Sinus		2 Förmaksflimmer/-fladder			8 Övrigt
Diagnos*						
Infarkttyp	0 Ej infarkt	1 STEMI	2 NSTEMI			
Subklass. av hjärtinfarkt		1 Typ-1	2 Typ-2	3 Typ-3	4 Typ-4a	5 Typ-4b 6 Typ-5
Diagnos 1	Diagnos 3		Diagnos 5			
Diagnos 2	Diagnos 4		Diagnos 6			
Utskrivning*						
Utskrivningsdatum						
Planerad koronarangio efter utskrivning	0 Nej	1 Ja				
Planerad PCI efter utskrivning	0 Nej	1 Ja				
Planerad CABG efter utskrivning	0 Nej	1 Ja				
Uppföljning	0 Nej	1 Kardiologi/Medicin	2 VC	3 Annan		
Uppföljande sjukhus/enhet						

Figure 5. RIKS-HIA registry form. Data collected at discharge.

5 RESULTS

5.1 STUDY I

In the derivation cohort (n=242,303), 2077 (0.9%) cases of in-hospital cardiac arrest were registered. Restricted to patients with a final diagnosis of NSTE-ACS (42%), in-hospital cardiac arrest accounted for 1365 (1.3%) cases. The corresponding number among patients with a non-ACS diagnosis was 712 (0.5%). **Figure 6** depicts the incidence of in-hospital cardiac arrest by year and final diagnosis (NSTE-ACS and non-ACS) for the derivation cohort, as well as for the temporal validation and external validation cohorts.

Overall in the derivation cohort, patients with in-hospital cardiac arrest tended to be older and have a higher burden of comorbidities. They were also more prone to have electrocardiographic ST-T-abnormalities, lower systolic blood pressure and eGFR, higher heart rate, Killip class and blood glucose level.

A points-based risk score with a maximal sum of seven points was developed. The included variables were: age ≥60 years (1 point), ST-T abnormalities (2 points), Killip Class >1 (1 point), heart rate <50 or ≥100 bpm (1 point), and systolic blood pressure <100 mmHg (2 points). Estimated risk of in-hospital cardiac arrest by sum of points in the risk score ranged from 0.18% to 11.94%.

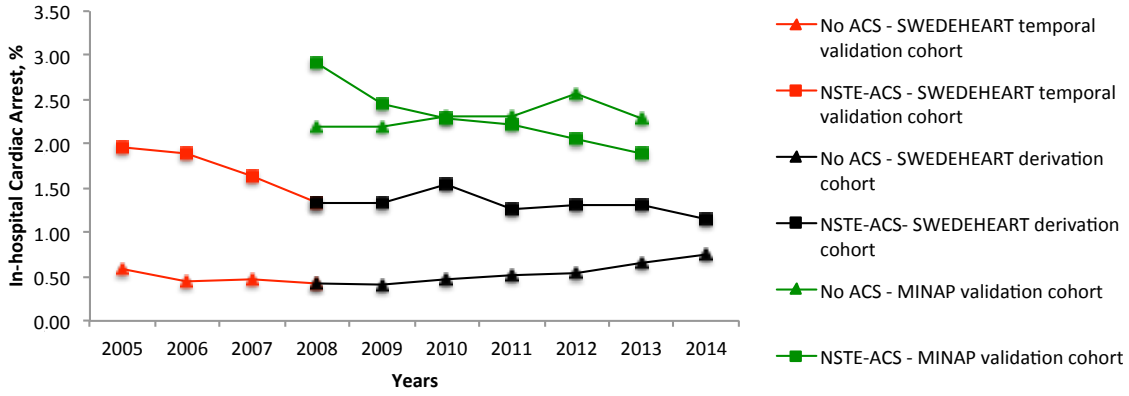

Figure 6. Incidence of in-hospital cardiac arrest by year and final diagnosis in SWEDEHEART and MINAP.

Internal validation showed good discrimination with a *c*-statistic of 0.72 (95% CI, 0.71–0.73). The calibration plot demonstrated reasonable agreement but there was a tendency towards overestimation of risk with a higher sum of score points (**Figure 7A**). The risk score performed similarly in the temporal validation cohort (n=126,073) with respect to discrimination (*c*-statistic 0.74 [95% CI, 0.73–0.76]) and calibration but instead there was a tendency towards overestimation of risk with a higher sum of score points (**Figure 7B**).

In the external validation cohort (n=276,109) from MINAP there were 6388 (2.3%) cases of in-hospital cardiac arrest. The incidence was equal in patients with NSTE-ACS (87%) and patients with a non-ACS diagnosis. Baseline characteristic differences between cardiac arrest

and non-cardiac arrest cases were comparable to the derivation cohort. The external validation demonstrated moderate discrimination (*c*-statistic 0.65 [95% CI, 0.65–0.66]). The calibration plot showed a general underestimation of risk (**Figure 7C**). A separate model adjusting for underlying risk demonstrated good discrimination in the lower range of sum of points but a general overestimation of risk with an increasing sum of points.

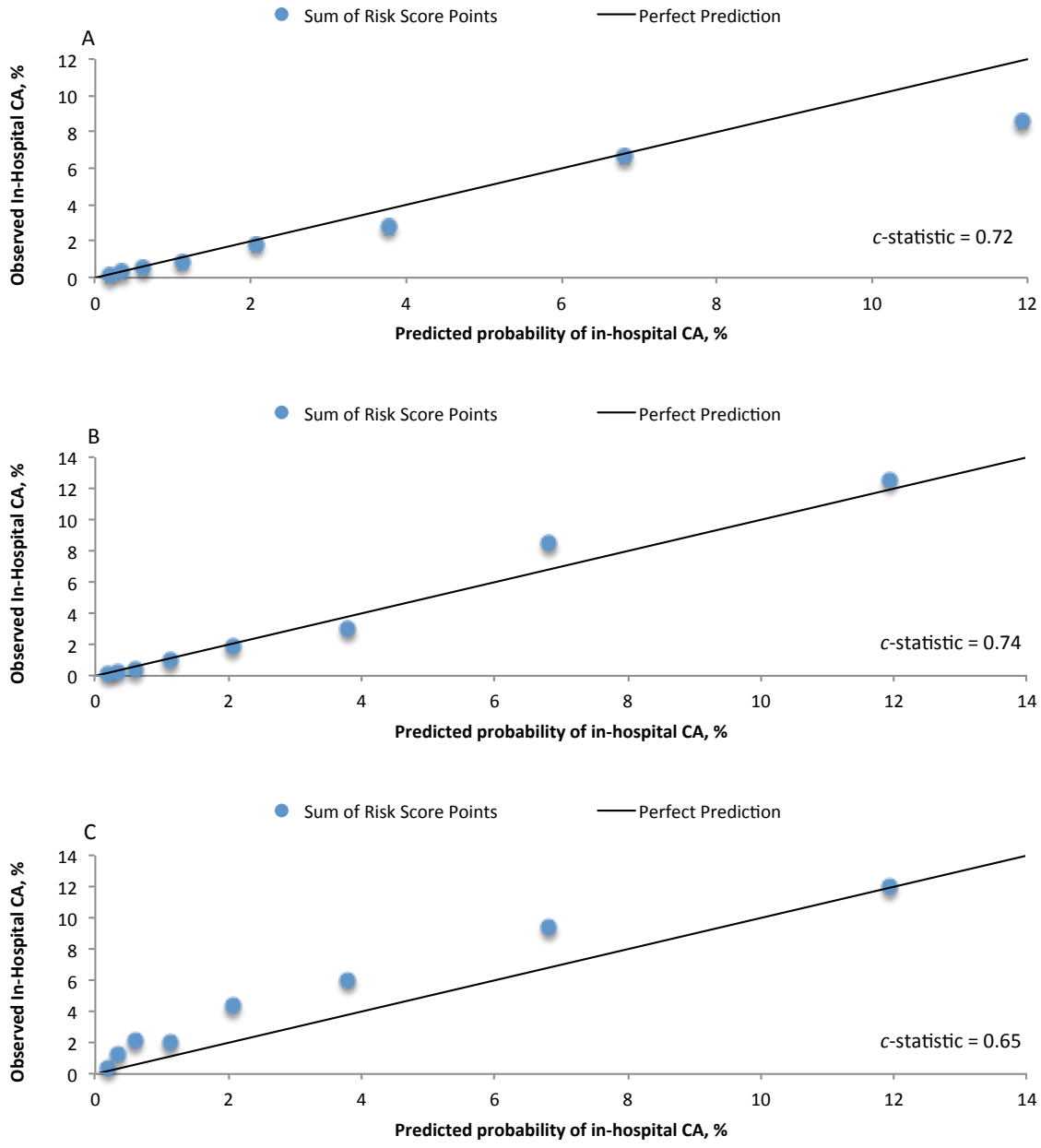

Figure 7. Calibration plot for the SWEDEHEART derivation cohort 2008-2014 (A), the SWEDEHEART temporal validation cohort 2005-2007 (B), and the MINAP validation cohort 2008-2013 (C).

5.2 STUDY II

Among the 121,379 include cases in the cohort, there were 349 (0.29%) OHCA recorded in the Swedish Cardiopulmonary Resuscitation Registry within 90 days after discharge. Among non-OHCA cases, 2194 (1.8%) died during the follow-up period (**Figure 8**).

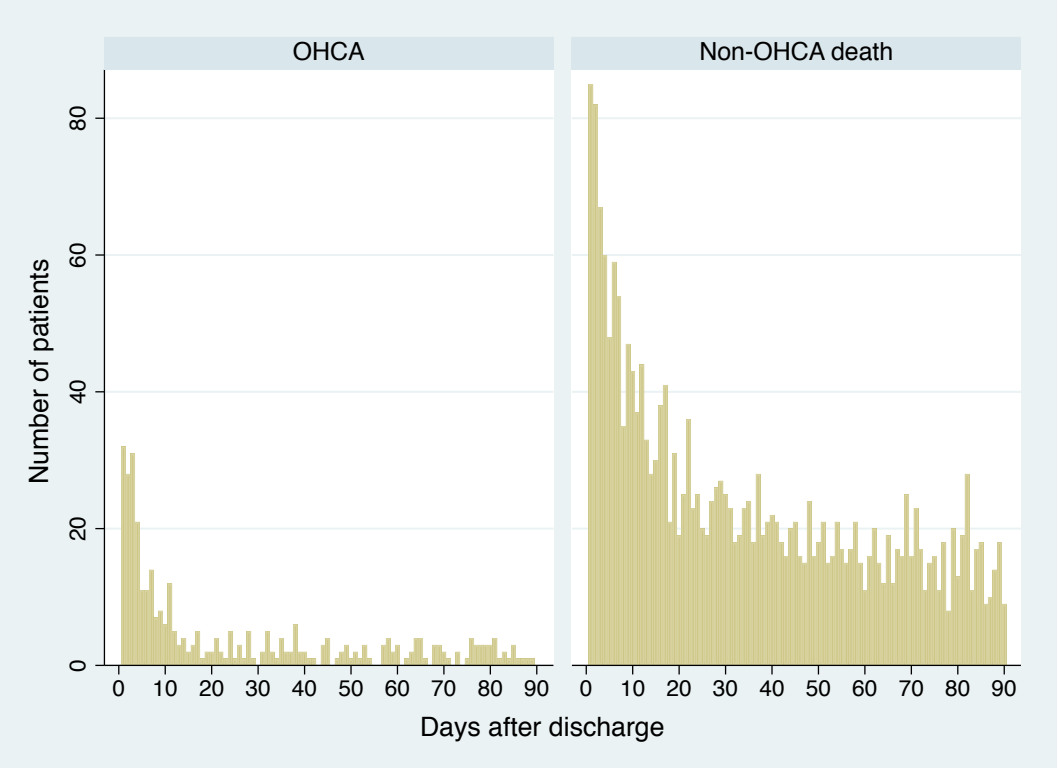

Figure 8. Frequencies of OHCA and non-OHCA death within 90 days after discharge.

Compared to non-OHCA cases, patients with OHCA were older, more likely to be male, have a history of diabetes and heart failure, and a lower eGFR on admission. Patients with OHCA were also more likely to have STEMI (as opposed no NSTEMI), multivessel and/or left main coronary artery disease, a more complicated hospital course, and a lower LVEF assessed during hospitalization.

Compared to patients with OHCA, those with non-OHCA death were more likely to be female, have three-vessel and/or left main coronary artery disease, and a lower eGFR and hemoglobin on admission.

Eight variables were independently associated with OHCA in multivariate Cox analyses. The two variables diabetes and STEMI had the weakest associations and were excluded from the final prediction model, which comprised six variables: male sex, age ≥60 years, eGFR <30 mL/min per 1.73 m^2, Killip class ≥II, new-onset atrial fibrillation/flutter, and LVEF categorized as ≥50% (reference), 40-49%, 30-39%, and <30% (**Table 3**). In the sensitivity analysis, using Fine-Gray models with death in the non-OHCA groups as competing risk, the same variables were independently associated with OHCA.

Table 3. Variables associated with OHCA within 90 days after MI discharge in multivariate Cox models and points assigned for stratification.

Variable	HR (95% CI)	*P*-value	Points
Male sex	1.75 (1.31-2.33)	<0.001	1
Age ≥60 years	1.56 (1.09-2.25)	0.016	1
eGFR <30 mL/min per 1.73 m^2	2.42 (1.57-3.72)	<0.001	2
Killip class ≥II	2.20 (1.64-2.95)	<0.001	2
New-onset atrial fibrillation/flutter	1.67 (1.13-2.47)	0.01	1
LVEF 40-49% (ref ≥50%)	2.74 (2.00-3.76)	<0.001	2
LVEF 30-39% (ref ≥50%)	4.21 (3.04-5.83)	<0.001	3
LVEF <30% (ref ≥50%)	6.24 (4.25-9.17)	<0.001	4

HR: hazard ratio; CI: confidence interval; eGFR: estimated glomerular filtration rate; LVEF: left ventricular ejection fraction.

The six variables were assigned points approximately corresponding to their hazard ratios (HRs) (**Table 3**). For further simplicity, sum of points were grouped into four categories, where the incidence of OHCA ranged from 0.11% to 2.2% and non-OHCA death from 0.65% to 11.5% Stratified by LVEF <40% alone, the incidence of OHCA was 0.20% and 0.76% and for non-OHCA death 1.1% and 4.9% (**Figure 9A-D**).

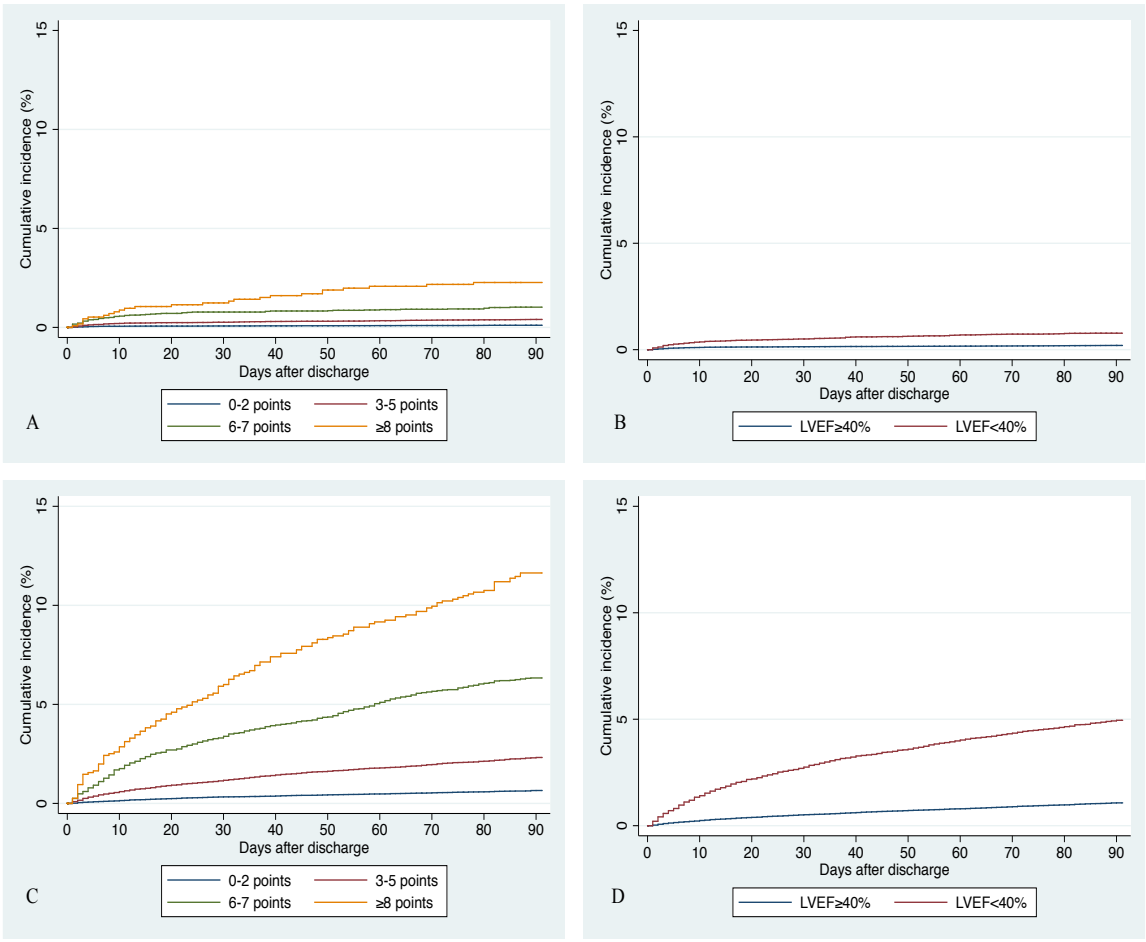

Figure 9. Kaplan-Meier estimates of the rate of OHCA (A, B) and non-OHCA death (C, D) stratified by sum of points and an LVEF cut-off of <40% respectively,

5.3 STUDY III

The cohort comprised 32,955 patients, of whom 44.6% had confirmed ACS and NSTE-ACS accounted for 70.3%. Mean admission plasma potassium was 4.0±0.5 mmol/L. The proportion of patients within each potassium stratum were: <3.0 mmol/L (1%), 3.0-<3.5 mmol/L (9%), 3.5-<4.0 mmol/L (39%), 4.0-<4.5 mmol/L (38%), 4.5-<5.0 mmol/L (10%), 5.0-<5.5 mmol/L (2%), and ≥5.5 mmol/L (1%). Overall, patients with higher potassium levels tended to be older, have more comorbidities, and a lower eGFR.

Figure 10 illustrates crude proportions of outcomes according to potassium strata stratified by final diagnosis (STEMI, NSTE-ACS, and non-ACS). During hospitalization, 886 (2.7%) patients died. A U-shaped association between admission plasma potassium and in-hospital mortality was observed. This association remained after adjusting for age, sex, and additionally eGFR strata, comorbidities, main diagnosis, and medication on admission. However, after further adjustment for presentation characteristics, only plasma potassium ≥5.0 mmol/L was significantly associated with in-hospital mortality (**Table 4**).

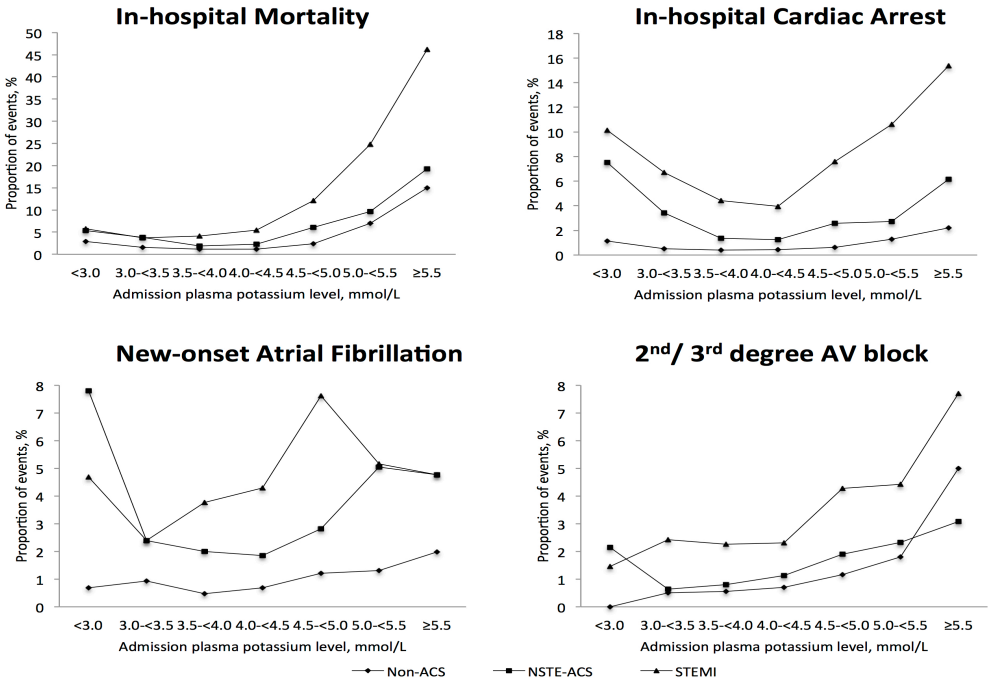

Figure 10. Proportions of outcomes by plasma potassium categories and final diagnosis.

There were 494 (1.5%) cases of in-hospital cardiac arrest registered. Also here, a U-shaped association to admission plasma potassium was observed. This association remained after adjusting for sex, age, eGFR strata, comorbidities, main diagnosis, and medication on admission. After adjusting for all covariates including presentation characteristics, only plasma potassium <3.5 mmol/L was significantly associated with in-hospital cardiac arrest (**Table 4**).

New-onset atrial fibrillation/flutter was observed in 804 (2.4%) patients during hospitalization. Only plasma potassium <3.0 mmol/L was significantly associated with new-

onset atrial fibrillation/flutter after adjusting for all covariates (**Table 4**). A total of 361 (1.1%) patients experienced in-hospital second- or third-degree AV-block. After adjusting for age, sex, gender, eGFR strata, comorbidities, main diagnosis, and medication on admission, plasma potassium ≥5.5 mmol/L was significantly associated with second- or third-degree AV-block. This association did not remain after additional adjustment for presentation characteristics (**Table 4**).

No significant interactions were found between admission plasma potassium strata and final diagnosis (STEMI, NSTE-ACS or non-ACS), eGFR strata, sex, presentation characteristics, or medication.

Table 4. Odds ratios (OR) and 95% confidence intervals (CI) for in-hospital outcomes by plasma potassium level on admission.

				Model 1 Adjusted for age, sex		**Model 2***		**Model 3****	
Plasma potassium level on admission, mmol/L	No. Of patients	No. Of events	Event rate, %	OR	(95 % CI)	OR	(95 % CI)	OR	(95 % CI)
In-hospital mortality									
<3.0	335	14	4.18	2.25*	[1.28,3.96]	1.98	[1.11,3.52]	1.60	[0.89,2.88]
3.0-<3.5	2,908	75	2.58	1.41*	[1.07,1.84]	1.29	[0.98,1.69]	1.15	[0.86,1.52]
3.5-<4.0	12,711	225	1.77	1.00	[1.00,1.00]	1.00	[1.00,1.00]	1.00	[1.00,1.00]
4.0-<4.5	12,630	263	2.08	0.95	[0.79,1.14]	0.89	[0.74,1.07]	0.91	[0.75,1.10]
4.5-<5.0	3,276	165	5.04	1.74***	[1.41,2.15]	1.30	[1.04,1.63]	1.22	[0.97,1.54]
5.0-<5.5	759	80	10.54	3.49***	[2.65,4.60]	1.98***	[1.47,2.67]	1.83***	[1.34,2.49]
>=5.5	336	64	19.05	6.29***	[4.58,8.64]	3.05***	[2.16,4.32]	2.27***	[1.57,3.27]
In-hospital cardiac arrest									
<3.0	335	16	4.78	4.27***	[2.52,7.25]	3.21***	[1.86,5.54]	2.72***	[1.56,4.74]
3.0-<3.5	2,908	71	2.44	2.10***	[1.58,2.80]	1.83***	[1.37,2.44]	1.63**	[1.21,2.19]
3.5-<4.0	12,711	152	1.2	1.00	[1.00,1.00]	1.00	[1.00,1.00]	1.00	[1.00,1.00]
4.0-<4.5	12,630	142	1.12	0.84	[0.67,1.06]	0.83	[0.66,1.05]	0.85	[0.67,1.08]
4.5-<5.0	3,276	73	2.23	1.48*	[1.11,1.98]	1.20	[0.89,1.61]	1.11	[0.82,1.50]
5.0-<5.5	759	24	3.16	2.03**	[1.30,3.16]	1.27	[0.80,2.03]	1.20	[0.75,1.92]
>=5.5	336	16	4.76	2.93***	[1.72,5.00]	1.87*	[1.05,3.33]	1.41	[0.78,2.55]
New-onset atrial fibrillation (n=29,307)									
<3.0	286	10	3.50	2.66*	[1.38,5.11]	2.22	[1.14,4.32]	1.93	[1.00,3.76]
3.0-<3.5	2,576	41	1.59	1.18	[0.83,1.67]	1.07	[0.75,1.52]	0.98	[0.69,1.40]
3.5-<4.0	11,592	156	1.35	1.00	[1.00,1.00]	1.00	[1.00,1.00]	1.00	[1.00,1.00]
4.0-<4.5	11,237	172	1.53	0.98	[0.79,1.22]	0.96	[0.76,1.19]	0.96	[0.77,1.21]
4.5-<5.0	2,738	74	2.70	1.43*	[1.07,1.90]	1.23	[0.91,1.65]	1.18	[0.87,1.58]
5.0-<5.5	601	19	3.16	1.54	[0.95,2.52]	1.15	[0.69,1.91]	1.05	[0.63,1.75]
>=5.5	277	9	3.25	1.47	[0.74,2.93]	1.14	[0.56,2.36]	0.88	[0.42,1.83]
2nd /3rd degree atrioventricular block									
<3.0	335	3	0.9	1.09	[0.34,3.45]	0.89	[0.28,2.84]	0.70	[0.22,2.29]
3.0-<3.5	2,908	26	0.89	1.07	[0.70,1.65]	0.96	[0.62,1.48]	0.85	[0.55,1.31]
3.5-<4.0	12,711	108	0.85	1.00	[1.00,1.00]	1.00	[1.00,1.00]	1.00	[1.00,1.00]
4.0-<4.5	12,630	131	1.04	1.05	[0.81,1.36]	1.05	[0.81,1.36]	1.03	[0.80,1.35]
4.5-<5.0	3,276	60	1.83	1.55**	[1.12,2.14]	1.37	[0.98,1.92]	1.20	[0.86,1.69]
5.0-<5.5	759	18	2.37	1.88*	[1.13,3.14]	1.37	[0.80,2.32]	1.18	[0.70,2.04]
≥5.5	336	15	4.46	3.35	[1.91,5.86]	2.44	[1.344.48]	1.54	[0.82,2.90]

*Model 2 adjusted for age, sex, eGFR strata (≥60, 30-59, <30), comorbidities (hypertension, diabetes, prior myocardial infarction, history of heart failure, prior stroke, peripheral vascular disease), main diagnosis (non-ACS, NSTE-ACS, STEMI), and medication on admission (ACEI/ARB, DAPT, beta-blocker, calcium channel blocker, statins, diuretics, aldosterone antagonist and nitrates).

**Model 3 further adjusted for systolic blood pressure, heart rate category (<50 or >100 bpm), presenting chest pain, Killip≥2, ECG rhythm (sinus rhythm, atrial flutter/ fibrillation, other), ECG ST-T changes (no, ST elevation, ST depression, T-wave changes, or other).

Abbreviations: OR, Odds ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate; ACS, acute coronary syndrome; NSTE, non-ST elevation; STEMI, ST-elevation myocardial infarction; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; DAPT, dual antiplatelet therapy; bpm, beats per minute; ECG, electrocardiography; * p<0.05 ** p<0.01 ***p<0.001

5.4 STUDY IV

There were 4861 patients with confirmed acute MI included in the cohort. NSTEMI accounted for 70% of all MI cases. Mean plasma potassium at discharge was 4.0±0.4 mmol/L. While most patients were discharged with plasma potassium within normal range, 8.1% had potassium <3.5 mmol/L and 1.5% had potassium >5.0 mmol/L. A higher burden of comorbidities and a lower eGFR were more common among patients with elevated potassium at discharge. After multivariable adjustment, a strong association between lower eGFR strata and hyperkalemia (>5.0 mmol/L) at discharge was observed. Hyperkalemia was also associated with a prior diagnosis of diabetes and prior use of ACEi. Hypokalemia (<3.5 mmol/L) at discharge was significantly associated with older age, female sex, a prior diagnosis of hypertension, treatment with intravenous diuretics during hospitalization, and non-invasive treatment of MI during the hospital course (**Table 5**).

Table 5. Cross-sectional logistic regression analyses identifying factors associated with hypokalemia and hyperkalemia at discharge.

	Discharge Hypokalemia K<3.5 mmol/L		Discharge Hyperkalemia K>5.0 mmol/L	
	OR	**95%CI**	**OR**	**95%CI**
eGFR strata, ml/min/1.73m²				
90+	1.00	[1.00,1.00]	1.00	[1.00,1.00]
60-89	0.96	[0.68,1.36]	2.13	[0.59,7.72]
45-59	0.82	[0.54,1.26]	4.68*	[1.21,18.06]
30-44	0.62	[0.39,1.01]	9.95***	[2.58,38.34]
<30	0.44**	[0.25,0.77]	17.08***	[4.39,66.55]
Demographics				
Age, per 10 years	1.18**	[1.04,1.33]	0.94	[0.72,1.22]
Male sex	0.78*	[0.63,0.98]	0.89	[0.55,1.45]
Comorbid history				
Diabetes mellitus	0.95	[0.74,1.21]	1.74*	[1.06,2.86]
Hypertension	1.43**	[1.12,1.83]	1.20	[0.71,2.03]
Myocardial infarction	0.84	[0.62,1.13]	0.73	[0.40,1.32]
Heart failure	0.75	[0.55,1.03]	1.48	[0.82,2.67]
Peripheral vascular disease	1.01	[0.68,1.49]	0.63	[0.26,1.52]
Stroke	0.99	[0.72,1.36]	0.73	[0.37,1.46]
Chronic obstructive pulmonary disease	0.95	[0.67,1.36]	1.63	[0.84,3.15]
Cancer (3 years)	0.78	[0.43,1.40]	1.09	[0.38,3.14]
Known Atrial fibrillation	1.34	[0.99,1.83]	0.89	[0.46,1.74]
Hospital course characteristics				
Killip≥2	1.06	[0.83,1.37]	1.49	[0.86,2.56]
STEMI (vs. NSTEMI)	1.09	[0.84,1.41]	1.31	[0.73,2.36]
PCI	0.75*	[0.58,0.98]	0.79	[0.42,1.48]
CABG	1.01	[0.63,1.63]	2.10	[0.83,5.30]
In-hospital new-onset atrial fibrillation	1.03	[0.66,1.59]	1.20	[0.46,3.10]
Intravenous diuretic use	2.07***	[1.63,2.63]	0.68	[0.40,1.17]
Medication on admission				
ACEi	1.01	[0.77,1.33]	1.93*	[1.15,3.26]
ARB	0.92	[0.67,1.27]	1.26	[0.67,2.35]
β-blocker	1.02	[0.81,1.30]	1.18	[0.71,1.98]
Diuretics	1.49**	[1.16,1.92]	1.36	[0.79,2.34]

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Within one year following the index hospitalization, hyperkalemia was observed in 784 (16.1%) patients. After multivariable adjustment, lower eGFR and higher discharge potassium were the two factors most strongly associated with a hyperkalemic event. Hypokalemia within one year was observed in 991 (20.4%) patients. Lower discharge potassium was the factor most strongly associated with a hypokalemic event (**Table 6**).

Table 6. Multivariable hazard ratios (HR) for first hyperkalemic or hypokalemic event within 1 year post discharge.

	Hypokalemia K<3.5 mmol/L		Hyperkalemia K>5.0 mmol/L	
	HR	**95%CI**	**HR**	**95%CI**
Potassium at discharge, mmol/L				
<3.5	3.13***	[2.59,3.77]	0.83	[0.63,1.10]
3.5-<4.0	1.43***	[1.23,1.67]	0.63***	[0.53,0.76]
4.0-<4.5	1.00	[1.00,1.00]	1.00	[1.00,1.00]
4.5-5.0	0.97	[0.77,1.23]	1.73***	[1.43,2.09]
>5.0	0.95	[0.57,1.58]	2.40***	[1.71,3.37]
eGFR strata, ml/min/1.73m²				
90+	1.00	[1.00,1.00]	1.00	[1.00,1.00]
60-89	0.88	[0.72,1.09]	1.72***	[1.26,2.35]
45-59	0.76*	[0.58,0.99]	2.79***	[1.97,3.94]
30-44	0.98	[0.74,1.29]	4.35***	[3.04,6.22]
<30	1.24	[0.92,1.67]	7.20***	[4.99,10.38]
Demographics				
Age, per 10 years	1.07	[1.00,1.16]	0.99	[0.91,1.07]
Male sex	0.81**	[0.71,0.93]	1.04	[0.89,1.21]
Medical history				
Diabetes mellitus	0.97	[0.84,1.12]	1.54***	[1.32,1.79]
Hypertension	1.46***	[1.26,1.68]	0.89	[0.75,1.04]
Myocardial infarction I	1.03	[0.88,1.21]	1.04	[0.88,1.23]
Heart failure [a]	1.20*	[1.03,1.40]	1.47***	[1.23,1.75]
Peripheral vascular disease	1.20	[0.97,1.47]	1.29*	[1.03,1.61]
Stroke	1.03	[0.86,1.23]	0.99	[0.80,1.22]
Chronic obstructive pulmonary disease	1.20	[0.99,1.45]	1.41**	[1.15,1.74]
Cancer (3 years)	1.43*	[1.09,1.89]	2.11***	[1.60,2.79]
Atrial fibrillation [b]	1.31***	[1.12,1.52]	1.08	[0.91,1.29]
STEMI	0.94	[0.80,1.12]	1.10	[0.92,1.31]
PCI	0.59***	[0.50,0.70]	0.70***	[0.59,0.84]
CABG	1.51**	[1.17,1.94]	1.28	[0.94,1.75]
Medication at discharge				
ACEi	0.89	[0.77,1.02]	1.00	[0.85,1.18]
ARB	0.91	[0.75,1.11]	1.00	[0.80,1.25]
β-blocker	0.85	[0.70,1.03]	1.08	[0.85,1.37]
Diuretics	1.35***	[1.15,1.57]	1.27**	[1.07,1.51]

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

a History of heart failure defined as previous heart failure history, or Killip≥2 or intravenous diuretic use during the index hospitalization.
b History of atrial fibrillation defined as the previous atrial fibrillation history or development of atrial fibrillation during the index hospitalization.

Mortality within one year of discharge was 14.8% (n=718). A U-shaped association between potassium at discharge and 1-year mortality was observed. This association remained after multivariable adjustment and was significant for plasma potassium strata <3.5 mmol/L and ≥4.5 mmol/L. Within one year of discharge, 633 (13.0%) patients were hospitalized due to reinfarction, 1045 (21.5%) were hospitalized due to heart failure, and 247 (6.0%) had a new diagnosis of atrial fibrillation/flutter. After multivariable adjustment, no significant associations between discharge potassium and the latter three outcomes were observed with one exception; patients with discharge potassium between 3.5-<4.0 mmol/L had lower odds (OR 0.80, 95% CI 0.69-0.92) of becoming hospitalized because of heart failure (**Table 7**).

Table 7. Multivariable hazard ratios (HR) for potassium categories at discharge and the risk of death and cardiovascular outcomes within 1 year.

	Death		**Myocardial re-infarction**		**Heart failure**		***De novo* Atrial fibrillation (n=4109)**	
	HR	**95%CI**	**HR**	**95%CI**	**HR**	**95%CI**	**HR**	**95%CI**
Potassium at discharge, mmol/L								
<3.5	1.50***	[1.18,1.89]	1.07	[0.80,1.43]	0.98	[0.79,1.21]	1.11	[0.72,1.70]
3.5-<4.0	0.88	[0.74,1.06]	0.98	[0.81,1.18]	0.80**	[0.69,0.92]	0.77	[0.58,1.04]
4.0-<4.5	1.00	[1.00,1.00]	1.00	[1.00,1.00]	1.00	[1.00,1.00]	1.00	[1.00,1.00]
4.5-5.0	1.25*	[1.00,1.56]	0.98	[0.75,1.27]	1.01	[0.83,1.22]	0.66	[0.42,1.05]
>5.0	1.51*	[1.00,2.27]	1.21	[0.71,2.06]	1.11	[0.76,1.64]	0.80	[0.32,1.99]

* p < 0.05, ** p < 0.01, *** p < 0.001

a Adjusted for age, sex, history of diabetes mellitus, hypertension, myocardial infarction, heart failure, peripheral vascular disease, stroke, chronic obstructive pulmonary disease, cancer, atrial fibrillation, STEMI, non-STEMI, PCI, CABG and medication at discharge (ACEi, ARB, β-blocker and diuretics); History of heart failure defined as previous heart failure history, or Killip≥2 or intravenous diuretic use during the index hospitalization; History of atrial fibrillation defined as the previous atrial fibrillation history or development of atrial fibrillation during the index hospitalization.

6 DISCUSSION

6.1 MAJOR FINDINGS

In **Study I**, we found that incidence of in-hospital cardiac arrest in NSTE-ACS ranges from 1.3% to 2.3%. For the purpose of risk stratification, we developed a user-friendly risk score that may be used to estimate the risk of in-hospital cardiac arrest for patients admitted with suspected NSTE-ACS. The risk score comprises five dichotomous variables easily accessible at admission: systolic blood pressure <100 mm Hg, age ≥60 years, hear rate <50 or ≥100 bpm, ST-T abnormalities on the admission ECG, and Killip class ≥II.

In **Study II**, comprising a contemporary cohort of MI cases, the incidence of OHCA within 90 days after discharge was low (0.29%). Six variables (male sex, age ≥60 years, eGFR <30 mL/min per 1.73 m^2, Killip class ≥II, new-onset atrial fibrillation/ flutter, and LVEF categorized as ≥50%, 40-49%, 30-39%, and <30%) predicted OHCA as well as non-OHCA death better than an LVEF cut-off of 40% alone.

For patients admitted with suspected ACS, results from **Study III** showed that, potassium disorders at admission are associated with adverse in-hospital outcomes regardless of presentation characteristics or final diagnosis. After multivariable adjustment, plasma potassium ≥5.0 mmol/L was associated with in-hospital death, plasma potassium <3.5 mmol/L was associated with in-hospital cardiac arrest, and plasma potassium <3.0 mmol/L was associated with new-onset atrial fibrillation/flutter during hospitalization.

In **Study IV**, we found that potassium disorders within the first year of discharge after MI are frequent. In our study cohort, hyperkalemia within one year was observed in 16.1% and was strongly associated with a lower eGFR and higher potassium level at discharge. Hypokalemia affected 20.4% of patients within one year and was strongly associated with lower potassium at discharge. Additionally, a U-shaped association between discharge potassium level and mortality within one year was observed and remained after multivariable adjustment.

6.2 WHO AND WHERE TO MONITOR IN SUSPECTED NSTE-ACS?

The coronary care unit (CCU) was introduced in the beginning of the 1960s and enabled continuous heart rhythm monitoring with rapid detection and treatment of life-threating arrhythmias by trained personnel. In the treatment of acute MI, the CCU has been considered the single most important advance of the 20th century[91]. However, given the development and improvement of care and outcome in ACS, the need and cost effectiveness for low-risk patients to be admitted to the CCU have been disputed[92]. Current European guidelines recommend that according to clinical presentation after established NSTE-ACS diagnosis, UA patients do not require rhythm monitoring and NSTEMI patients at low risk for arrhythmias may be monitored in a CCU or an intermediate care unit likewise. Low risk is defined as the absence of the following criteria: hemodynamically unstable arrhythmias, left ventricular ejection fraction below 40%, failed reperfusion, additional critical coronary stenoses of major vessels, or complications related to percutaneous revascularization[2]. Still,

patients with uncomplicated NSTE-ACS are commonly observed in the CCU. A Canadian study reported that among nearly 8000 patients with stable NSTE-ACS, almost two-thirds were admitted to a CCU. Compared to those admitted to a cardiology telemetry ward, clinical outcome did not differ[93].

At admission, the diagnosis of NSTE-ACS may not necessarily have been established. Additionally, several of the abovementioned criteria to define patients at low risk for arrhythmias may not be known. Hence, for patients admitted with suspected NSTE-ACS, the risk score proposed in **Study I** may aid in targeting those suitable for monitoring in a telemetry ward or a CCU. For patients at lowest risk according to the risk score, the estimated risk of in-hospital cardiac arrest was 0.18%. The corresponding observed incidence was 0.17% in the derivation cohort, 0.19% in the temporal validation cohort, and 0.38% in the external validation cohort. Hence, using the risk score, it was not possible to find a group of patients at truly low risk for in-hospital cardiac arrest without need for rhythm monitoring.

6.3 SCD EARLY AFTER MI, HOW AND WHICH PATIENTS TO CAPTURE?

In **Study II**, the incidence of OHCA early after MI was substantially lower than reported in previous studies[32,32]. Importantly, we only included patients, who had undergone coronary angiography during the hospital course. Patients, for whom a non-invasive approach is chosen, are likely to be more fragile and at higher risk for adverse events. We hypothesized that this group of patients may not be of primary interest when risk stratification for arrhythmic death and possible ICD implantation is warranted because of competing causes of death. Still, considering that a majority of trials and registry studies were conducted in the 1990s and early 2000s, our data may indicate that the incidence of SCD early after MI has declined in recent years, at least for patients for whom SCD preventive strategies may be most beneficial.

Over 90% of SCD cases occur out-of-hospital[94]. However, SCD does not equal arrhythmic death. Based on autopsy findings, it has been reported that only slightly over 50% of SCDs are caused by arrhythmias[94, 95]. The problem of capturing arrhythmic death is also illustrated by the recent VEST trial. Five out of nine patients with a wearable cardioverter–defibrillator worn at time of death and adjudicated arrhythmic death (as determined by an expert panel blinded to the group assignments) did in fact not have ventricular arrhythmias[48].

Two landmark studies did not demonstrate a benefit of ICD therapy early after MI in patients with LVEF ≤35% or ≤30% because of competing causes of death[34, 35]. These studies were partly conducted in an earlier therapeutic era with lower rates of revascularization and less aggressive antithrombotic treatment. Furthermore, ICD implantation was performed within 31 to 40 days after MI, whereas the risk of SCD has been shown to be highest within the first 30 days.

Neither did the VEST trial show an advantage of a wearable cardioverter-defibrillator over medical therapy alone in patients with LVEF ≤35% early after MI[48]. The authors have raised questions whether the trial was sufficiently powered and whether possible misclassification

may have further reduced the power. Nevertheless, based on the aforementioned trials, using LVEF as a standalone risk predictor of arrhythmic death is not sufficient in the early phase after MI.

6.4 ADMISSION POTASSIUM LEVELS AND IN-HOSPITAL ADVERSE EVENT IN ACS

Results from **Study III** are consistent with prior observations that normokalemia on admission is associated with the lowest risk of in-hospital adverse events in ACS[62, 66, 67]. In contrast to previous studies, we included a broader population comprising patients admitted with not only confirmed but also suspected ACS. Additionally, we adjusted for subtype of ACS and presentation characteristics as well as renal function. Relative risks were not modified by final diagnosis. However, it is worth noting that for patients with STEMI and admission potassium 5.0-<5.5 mmol/L, in-hospital mortality reached almost 25%. In-hospital cardiac arrest affected 10% of patients with STEMI accompanied by admission potassium <3.0 or 5.0-<5.5 mmol/L.

Compared to the U.S. registry-based study by Goyal et al., which included only patients with confirmed MI, event rates in **Study III** were lower (6.9% vs. 2.7% for in-hospital mortality and 4.4% vs. 1.5% for in-hospital cardiac arrest)[62]. Goyal and colleagues reported that after multivariable adjustment, admission serum potassium <3.0 and ≥5.0 mEq/L were associated with in-hospital mortality and admission serum potassium <3.5 mEq/L was associated with the composite of in-hospital ventricular arrhythmias and cardiac arrest[62]. Our results are largely in agreement with these results but suggest that hyperkalemia at admission may be an even stronger predictor of in-hospital mortality than hypokalemia as this association remained after adjusting for important presentation characteristics. SWEDEHEART reports cardiac arrest only when CPR and/or defibrillation have been attempted. Patients with hyperkalemia were generally older and more diseased, which may have influenced CPR decisions. Furthermore, patients with hypokalemia and associated cardiac arrest may have had a more favorable outcome.

Our finding that plasma potassium <3.0 mmol/L was associated with new-onset atrial fibrillation, gives further support to a possible linkage between hypokalemia and the occurrence of atrial fibrillation.

6.5 THE IMPACT OF DYSKALEMIA FOLLOWING MI

The incidence of dyskalemia following hospitalization for MI has not been frequently reported. Neither have RCTs on RAAS inhibitor treatment after MI provided much data on potassium levels during the course of follow-up. Findings from **Study IV** suggest that potassium imbalance within 1 year following MI is common, affecting almost 37% of patients, with potassium level and renal function at discharge being the strongest predictors. Since all laboratory data were extracted from actual healthcare visits, the reported incidence is, if anything, an underestimation. Over 90% of the patients were normokalemic at

discharge. Given the commonness of dyskalemia during follow up, concerns may be raised whether a subgroup of patients would attain benefit from closer monitoring after discharge.

We found a U-shaped relationship between discharge potassium level and mortality within one year, which is in line with previous observational studies[64, 67, 96]. Mortality risk was already increased for potassium within the upper normal range (4.5-5.0 mmol/L), which has also been demonstrated before[62, 64].

Although associations between dyskalemia and adverse events have been repeatedly demonstrated in observational studies, no causal relationships have been established. Whether hypokalemia and hyperkalemia are in fact risk factors or merely risk markers remain unknown. In heart failure, Lund and Pitt argue that hyperkalemia may primarily be a risk marker resulting in the underuse of RAAS inhibitors, which in turn is causative of worse outcome[97]. Whether this may hold true for the MI population, which in many ways overlaps the heart failure population, is not clear.

6.6 LIMITATIONS

All studies were derived from large-sized cohorts, which reduces but does not eliminate the possibility of random errors. As for systematic errors, both selection and information biases are likely to be present in registry studies. The nation-wide SWEDEHEART registry includes the majority, but not all, of patients admitted with symptoms suggestive of ACS. Cross-linkage with the National Cause of Death Register minimizes loss to follow-up. For other predefined outcomes, validity relies solely on collected data. In order to enable imputation of missing values, data was assumed to missing at random, which may not hold true. Finally, confounding possesses a major source of bias in non-randomized cohort studies. Although, multivariable adjustment and stratification were assessed, residual confounding may still be present.

Specific limitations of the individual studies are discussed in brief below.

6.6.1 Study I

Our reported incidence of in-hospital cardiac arrest in NSTE-ACS is in agreement with previous studies. However, it is uncertain how well the true incidence of in-hospital cardiac arrest was captured considering the definition of the outcome variable and possible underreporting as well as missing data for in-hospital cardiac arrest and cardiac arrest prior to admission. The reported incidence may therefore be underestimated or overestimated. No data on timing of cardiac arrest or temporal relationships to revascularization were available. Neither were cardiac troponin measurements nor LVEF on admission available.

The risk score did not perform optimally in the MINAP cohort. Adjusting for underlying risk or including complete cases only did not improve the performance. Compared to SWEDEHEART, the overall incidence of in-hospital cardiac arrest was higher in MINAP and notably patients with a non-ACS diagnosis as compared to NSTE-ACS were at equal or

higher risk for in-hospital cardiac arrest. In addition, one of the five variables in the risk score, Killip class, was missing in 70% of patients in MINAP. Although multiple imputation was performed, its validity may be questioned.

6.6.2 Study II

Comparing our results to studies using SCD, most often ascertained by reviewing medical records and death certificates, as an endpoint may be problematic. Moreover, not all cases of SCD occur out-of hospital and OHCA does not necessarily equal SCD. We chose to include only patients who had undergone coronary angiography during the hospital course. Hence, our reported results do not represent the true OHCA incidence. Furthermore, the Swedish Cardiopulmonary Resuscitation Registry only captures cases of OHCA, which were treated by EMS.

Data was missing for several variables, most notably for the key variable LVEF. Only complete-case analyses were performed, and hence selection biases may have been introduced. Although coronary angiographic findings were evaluated in multivariable analyses, detailed data regarding specific PCI procedures were not available and hence not adjusted for. We did not have information on hospital readmissions within the follow-up period other than cases of reinfarction registered in SWEDEHEART, which were excluded.

6.6.3 Studies III-IV

In **Studies III-IV**, potassium concentration was measured in plasma, whereas most prior studies in the field were based on measurement of serum potassium. Serum potassium is generally slightly higher than plasma potassium[98]. A mean difference of 0.18 mmol/L has been reported[99]. Hence, our results are not directly comparable to prior studies reporting serum potassium measurement. Furthermore, **Studies III-IV** were restricted to patients residing in the Stockholm County, which could be a source of bias.

In **Study III**, no temporal relationships between admission potassium measurement and outcomes were available. In addition, data did not allow a distinction between different types of diuretics at admission, e.g. loop diuretics and MRA.

In **Study IV**, follow-up was based on potassium tests available within one year. Hence, selection bias, particularly detection bias, is likely to be present. Although we adjusted for medication at discharge, data on continuation or discontinuation of medical therapy during follow-up were not taking into account except for MRA.

6.7 FUTURE PERSPECTIVES

The risk score presented in **Study I** may help the clinician to assess risk of in-hospital cardiac arrest and level of surveillance needed for patients admitted with suspected NSTE-ACS. Still, further validation in different populations is needed. Additionally, temporal distribution of in-hospital cardiac arrest warrants further investigation. Future research is called for to develop a risk-score model identifying patients at truly low risk for in-hospital cardiac arrest.

Reliable risk stratification tools for SCD early after MI are lacking and further studies are indeed warranted. LVEF has not been proven a useful stand-alone predictor. As shown in **Study II**, five clinical variables in addition to LVEF predict OHCA but also non-OHCA death better than LVEF alone. An ideal risk stratification test would identify patients at high risk for arrhythmic death and low risk for non-arrhythmic death so that preventive strategies (e.g. ICD or wearable cardioverter–defibrillator) may safely and cost-effectively be implemented.

Results from **Studies III-IV** confirm that potassium imbalance is associated with adverse outcomes. Our findings suggest that patients admitted with suspected ACS or discharged after MI and who have concomitant potassium imbalance should be closely monitored. However, whether dyskalemia represents a risk factor or merely a risk marker remains unclear. Large interventional trials taking the full range of potassium disturbances into account and randomizing patients to different potassium targets will never be conducted. Still, several studies, including our own, have demonstrated an association between mild hyperkalemia or even potassium in the upper normal range and adverse events. Randomized trials in this setting might be feasible. Furthermore, novel potassium binders have recently been introduced and warrant further investigation[100, 101].

7 CONCLUSIONS

A simple points score comprising five variables readily available on admission (systolic blood pressure, age, heart rate, ST-T changes on ECG, and Killip class) may be used to predict in-hospital cardiac arrest in patients admitted with suspected ACS.

In our cohort of MI patients, six variables (sex, age, eGFR, Killip class, new-onset atrial fibrillation/ flutter, and LVEF) predicted OHCA as well as non-OHCA death within 90 days after discharge better than an LVEF cut-off alone.

Hyperkalemia at admission is associated with in-hospital mortality and hypokalemia is associated with in-hospital cardiac arrest and new-onset atrial fibrillation/flutter in patients admitted with suspected ACS irrespective of baseline characteristics or final diagnosis.

Within the first year following MI, hyperkalemia and hypokalemia are frequently encountered. Potassium level and eGFR at discharge strongly predict their occurrence as well as one-year mortality.

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"Prediction can be very difficult, especially about the future."
Danish saying