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PROGNOSTICATION IN ACUTE HEART FAILURE AND CARDIOGENIC SHOCK

FOCUS ON ELECTROCARDIOGRAPHY AND BIOMARKERS

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ABSTRACT

Acute heart failure (AHF) is a leading cause of hospitalizations in patients over the age of 65 worldwide, and is associated with high mortality. Cardiogenic shock (CS), the most severe form of AHF, is characterized by hypotension and end-organ hypoperfusion. Acute coronary syndrome (ACS) precipitates a third of all cases of AHF, and up to 80% of CS. Objective and timely risk assessment in AHF is challenging due to the heterogeneity in its pathophysiology and clinical picture. Risk assessment has traditionally relied on clinical parameters, which may remain subjective or become evident too late, after end-organ dysfunction has become irreversible. Considering the costs and possible adverse effects, application of the most aggressive therapies should be limited to those that most likely procure benefit.

The aim of this thesis is to evaluate the prognostic value of electrocardiographic changes and biomarkers in AHF and CS. The patient data come from three cohorts of AHF and two cohorts of CS. All cohorts are independent, prospective, observational, investigator-initiated European cohorts.

Study I compared the prognostic value of ventricular conduction blocks (VCB) in patients with new-onset (de novo) AHF and in patients with acutely decompensated chronic heart failure (ADCHF). RBBB was similarly common in de novo AHF and ADCHF, but RBBB was a prognosticator of poor outcome only in those with de novo AHF. LBBB and IVCD were more common in those with ADCHF, and IVCD was a predictor of poor outcome only in ADCHF. LBBB had no predictive value in either group.

Study II investigated the role of VCBs in ACS-related CS. Half the patients had a VCB in their baseline ECG, and the presence of any VCB predicted mortality independently of baseline clinical variables or angiographic findings. Interestingly, in those patients surviving until day 3, a third of the baseline VCBs had disappeared. However, those patients had the highest mortality, and a transient VCB was a strong independent predictor of poor outcome.

After myocardial infarction, activation of inflammatory responses and of neurohumoral cascades contributes to the induction, maintenance, and severity of the

shock state, providing the rationale for a biomarker approach in risk assessment of CS. Soluble ST2 (sST2) is a novel cardiovascular biomarker associated with inflammation and cardiac fibrosis, whereas N-terminal natriuretic peptide (NT-proBNP) as a natriuretic peptide is a conventional marker of myocardial dysfunction and congestion. Bioactive adrenomedullin (Bio-ADM) is a novel marker of vascular dysfunction; it is a vasoactive peptide excreted from vascular cells in response to hypoxia or sheer stress.

Study III showed that sST2 and NT-proBNP provide strong and complementary prognostic value in ACS-related CS, and can help in stratification of patients into low, intermediate and high-risk groups as early as 12 hours after detection of shock. Study IV evaluated in CS patients the prognostic value and association with haemodynamic parameters of bio-ADM compared to lactate. Whereas lactate had good prognostic value in the early phase, its levels normalized during the first 24 hours in the majority of patients, with a decreasing prognostic value thereafter. In contrast, levels of bio-ADM stayed elevated in non-survivors during the first 4 days of intensive care, and bio-ADM had good prognostic value when measured on days 2 to 4. High levels of bio-ADM were associated with low cardiac index and mean arterial pressure, and with high central venous and pulmonary artery pressures.

In conclusion, in patients with AHF or CS, electrocardiographic alterations may prove useful in early risk assessment on top of clinical parameters. In addition, biomarkers provide a novel approach in CS risk assessment.

TIIVISTELMÄ

Akuutti sydämen vajaatoiminta on yksi yleisimmistä sairaalahoitoon johtavista sairauksista, ja siihen liittyy merkittävä kuolleisuus. Sydänperäinen sokki on akuutin vajaatoiminnan vaikein muoto; sille on tunnusomaista matala verenpaine ja yleinen elimistön verenkierron vajaus. Sepelvaltimotautikohtaus on akuutin vajaatoiminnan taustalla noin kolmasosassa tapauksista, mutta jopa 80 %:ssa tapauksista sydänperäisessä sokissa. Johtuen akuutin vajaatoiminnan kliinisen kuvan ja taustalla vaikuttavien patofysiologisten mekanismien moninaisuudesta objektiivinen ja oikea-aikainen riskinarvio on haastavaa. Varhainen riskinarvio on kuitenkin tärkeää hoitomuotojen valintaa ja ajoitusta ajatellen erityisesti sokkipotilailla. Perinteisesti riskinarvio on perustunut kliinisiin löydöksiin, joiden tulkinnassa voi kuitenkin olla subjektiivisuutta ja ne voivat ilmetä sairauden liian myöhäisessä vaiheessa, kun peruuttamattomia elinvaurioita on jo ehtinyt kehittyä. Huomioiden raskaimpien hoitomuotojen, kuten sydämen apupumppujen, korkea komplikaatioriski ja hinta, niiden käyttö tulisi rajata potilaille jotka todennäköisimmin niistä hyötyvät.

Tämän väitöskirjatyön tavoitteena on määrittää sydänsähkökäyrä (EKG) – muutosten sekä uusien biomerkkiaineiden ennustearvo akuutissa sydämen vajaatoiminnassa ja sydänperäisessä sokissa. Väitöskirjatyön potilasmateriaali on peräisin kolmesta akuutin sydämen vajaatoiminnan sekä kahdesta sydänperäisen sokin potilaskohortista. Kaikki aineistot ovat eteneviä, havainnoivia, tutkijalähtöisiä eurooppalaisia potilasaineistoja.

Osatyössä I tutkittiin EKG:ssa nähtävien kammiojohtumishäiriöiden yhteyttä kuolleisuuteen potilailla joilla akuutti vajaatoiminta ilmeni ensimmäistä kertaa (de novo) verrattuna potilaisiin joilla oli kroonisen sydämen vajaatoiminnan pahenemisvaihe. Oikea haarakatkos oli yhtä yleinen molemmissa ryhmissä, mutta se ennusti itsenäisesti kuolleisuutta vain de novo akuutissa vajaatoiminnassa. Vasen haarakatkos ja määrittämätön kammiojohtumishäiriö (IVCD) olivat yleisempiä potilailla, joilla oli kroonisen vajaatoiminnan pahenemisvaihe kuin de novo -potilailla, ja IVCD ennusti itsenäisesti kuolleisuutta vain kroonisen vajaatoiminnan pahenemisvaiheessa. Vasen haarakatkos ei ennustanut kuolleisuutta kummassakaan ryhmässä.

Osatyössä II tutkittiin kammiojohtumishäiriöitä äkillisestä sepelvaltimokohtauksesta johtuvassa sydänperäisessä sokissa. Puolella potilaista alkuvaiheen EKG:ssa oli jokin kammiojohtumishäiriö, ja kammiojohtumishäiriöt ennustivat suurempaa kuolleisuutta kliinisistä piirteistä ja sepelvaltimotaudin vaikeusasteesta riippumatta. Jopa kolmasosa alkuvaiheessa nähdyistä kammiojohtumishäiriöistä väistyi kolmen päivän seurannassa, näillä potilailla oli kuitenkin korkein kuolleisuus.

Neurohumoraalisten vasteiden ja tulehduskaskadien aktivoituminen ovat tärkeässä roolissa sydäninfarktin jälkeisen sokin patogeneesissä. Biomerkkiaineet kuvastavat aktivoituneita vasteita, mikä puoltaa niiden hyödyntämistä riskinarviossa. sST2 on uusi kardiovaskulaarisairauksien biomerkkiaine, joka liittyy sydänlihaksen inflammaatioprosessiin ja fibrotisoitumiseen, ja natriureettinen peptidi NT-proBNP on perinteinen sydämen vajaatoiminnan merkkiaine. Bio-ADM on vasoaktiivinen peptidi, jota erittyy pääasiassa verisuonten seinämistä hapenpuuteessa ja mekaanisessa ärsytyksessä, ja se on uusi hemodynaamiikan ja verisuonten toimintahäiriön biomerkkiaine.

Osatyö III osoitti, että sST2:lla ja NT-proBNP:llä on vahva itsenäinen ja toisiaan tukeva ennustearvo sydänperäisessä sokissa, ja niiden yhteismäärityksellä potilaat voidaan jakaa matalan, keskisuuren ja suuren riskin ryhmiin jo 12 tuntia sokin toteamisesta. Osatyö IV määritti bio-ADM:n ennustearvoa sekä yhteyttä hemodynaamisiin muuttujiin verrattuna laktaattiin sydänperäisessä sokissa. Laktaatilla oli hyvä ennustearvo ensimmäisten 24 tunnin aikana sokin toteamisesta, mutta sen pitoisuus normaalistui valtaosalla potilaista 24 tunnissa ja sen ennustearvo väheni sen jälkeen. Korkea bio-ADM pitoisuus heijasti matalaa verenpainetta ja sydämen minuuttivoluumia sekä korkeaa keskuslaskimo- ja keuhkovaltimopainetta, ja bio-ADM:n ennustearvo oli parhaimmillaan kun se mitattiin 2.-4. päivänä sokin toteamisesta.

Yhteenvetona voidaan todeta, että EKG-muutoksia voidaan hyödyntää kliinisten muutosten rinnalla varhaisessa riskinarviossa akuuttia sydämen vajaatoimintaa tai sydänperäistä sokkia sairastavilla potilailla. Lisäksi uudet biomerkkiaineet mahdollistavat täysin uuden lähestymistavan sydänperäisen sokin riskinarviossa.

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CONTENTS

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications:

I. Ventricular conduction abnormalities as predictors of long-term survival in acute de novo and decompensated chronic heart failure. Tolppanen H, Siirila-Waris K, Harjola VP, Marono D, Parenica J, Kreutzinger P, Nieminen T, Pavlusova M, Tarvasmaki T, Twerenbold R, Tolonen J, Miklik R, Nieminen MS, Spinar J, Mueller C and Lassus J. Esc Heart Failure. 2016;3:35-43.

II. Prevalence, Temporal Evolution, and Impact on Survival of Ventricular Conduction Blocks in Patients With Acute Coronary Syndrome and Cardiogenic Shock. Tolppanen H, Javanainen T, Sans-Rosello J, Parenica J, Nieminen T, Pavlusova M, Masip J, Köber L, Banaszewski M, Sionis A, Spinar J, Harjola VP Jurkko R, Lassus J. Am J Cardiol. 2018;122(2):199-205

III. Combined Measurement of Soluble ST2 and Amino-Terminal Pro-B-Type Natriuretic Peptide Provides Early Assessment of Severity in Cardiogenic Shock Complicating Acute Coronary Syndrome. Tolppanen H, Rivas-Lasarte M, Lassus J, Sadoune M, Gayat E, Pulkki K, Arrigo M, Krastinova E, Sionis A, Parissis J, Spinar J, Januzzi J, Harjola VP, Mebazaa A, CardShock Study group and the Great Network. Crit Care Med. 2017;45(7):666-673.

IV. Adrenomedullin: a marker of impaired hemodynamics, organ dysfunction, and poor prognosis in cardiogenic shock. Tolppanen H, Rivas-Lasarte M, Lassus J, Sans-Rosello J, Hartmann O, Lindholm M, Arrigo M, Tarvasmaki T, Kober L, Thiele H, Pulkki K, Spinar J, Parissis J, Banaszewski M, Silva-Cardoso J, Carubelli V, Sionis A, Harjola VP and Mebazaa A. Annals of intensive care. 2017;7:6.

The original publications are published with the permission of the copyright holders and are referred to in the text by their roman numerals. In addition, this thesis includes some unpublished material.

ABBREVIATIONS

ACS	acute coronary syndrome
ADCHF	acutely decompensated chronic heart failure
AHF	acute heart failure
AMI	acute myocardial infarction
AUC	area under the curve
bio-ADM	bioactive adrenomedullin
BNP	brain natriuretic peptide
CABG	coronary artery bypass graft surgery
CI	confidential interval
CS	cardiogenic shock
ECG	electrocardiogram
ECMO	extracorporeal membrane oxygenation
eGFR	estimated glomerular filtration rate
ESC	European Society of Cardiology
hs-TnT	high-sensitivity troponin T
HR	hazard ratio
IL	interleukin
IQR	interquartile range
IVCD	intraventricular conduction delay
LAHB	left anterior hemiblock
LBBB	left bundle branch block
LPHB	left posterior hemiblock
LVEF	left ventricular ejection fraction
MR-proADM	mid-regional pro-Adrenomedullin
NT-proBNP	N-terminal pro-B-type natriuretic peptide
NSTEMI	non-ST elevation myocardial infarction
PCI	percutaneous coronary intervention
RAAS	renin-angiotensin-aldosterone system
RBBB	right bundle branch block
ROC	receiver operating characteristic
SBP	systolic blood pressure
SD	standard deviation
sST2	soluble suppression of tumourigenicity 2 (soluble ST2)
STEMI	ST-elevation myocardial infarction
VCB	ventricular conduction block

1 INTRODUCTION

Acute heart failure (AHF) is a leading cause of hospitalization in patients over age 65 and associates with high morbidity and mortality, leading in all Western countries to significant health care expenditure. Although chronic heart failure has been under extensive study, and modern treatment has considerably improved patient outcomes during recent decades, AHF has received less attention.

AHF can result from acute decompensation of chronic heart failure (acutely decompensated chronic heart failure, ADCHF), or it can be a new-onset disease, "de novo AHF", in individuals without previous history of heart failure. Cardiogenic shock (CS) is the most severe form of AHF, and accounts for less than 5% of AHF cases (1, 2). CS is characterized by low blood pressure and organ hypoperfusion resulting from cardiac dysfunction. Acute coronary syndromes (ACS) account for about one-third of all cases in AHF but up to 80% of cases in CS (1, 3-6). Conversely, CS complicates 5 to 8% of ST-elevation myocardial infarctions (STEMI) (7) and is largely responsible for the short-term mortality associated with myocardial infarction.

Despite early revascularization and modern intensive cardiac care survival in CS remains poor (7, 8). Haemodynamics may be restored pharmacologically with vasopressors and inotropes or with mechanical circulatory support (9), but all those treatment options have potentially detrimental side effects, and cost containment needs consideration in modern healthcare systems. Objective risk stratification tools are thus necessary to accurately select patients for advanced therapies. Currently, in the absence of established early predictors of poor outcome, risk stratification for AHF and CS are based on clinical judgment (10), and as such may remain subjective and become evident too late in the course of the disease, after end-organ dysfunction has become irreversible.

Electrocardiography (ECG) is a routine, fast and low-cost diagnostic tool available to all emergency care providers. In addition to traditional ischaemic alterations, an ECG may reveal conduction abnormalities, which have been related to poor survival in patients with chronic heart failure and acute myocardial infarction

(AMI). In patients with AHF and CS, however, there is less evidence regarding the clinical associations and prognostic value of conduction abnormalities.

After myocardial infarction, activation of inflammatory responses and of neurohumoral cascades contribute to CS induction and maintenance (11). Several biomarkers reflecting these pathways have been identified (12, 13), giving a rationale in risk assessment for a biomarker approach. Soluble suppression of tumourigenicity 2 (soluble ST2, sST2) is a marker of inflammation, cardiac stress, and adverse remodelling, and has recently shown strong prognostic value in several cardiovascular diseases, which is additive to the traditional risk markers (14-17). Adrenomedullin, an endogenous peptide with vasodilator and inotropic properties, at high levels has predicted poor survival both in cardiovascular diseases (12) and in critically ill patients (18).

This thesis aims to assess the prognostic value of 1) ventricular conduction blocks (VCBs) in AHF and CS, and 2) novel biomarkers in CS to achieve objective and easily reproducible tools for severity assessment of AHF and CS. These may support clinical decision-making in treatment of such patients.

2 REVIEW OF THE LITERATURE

2.1 HEART FAILURE

Heart failure is a clinical syndrome characterized by typical symptoms (breathlessness, ankle swelling, fatigue) that may be accompanied by clinical signs (elevated jugular venous pressure, pulmonary crackles, peripheral oedema), and results from a structural or functional cardiac abnormality, which result in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress (19). Heart failure is never a solitary disease but rather the common end-stage of structural heart diseases. Due to inadequate cardiac function and impaired circulatory capacity to provide oxygen and nutrients to other organs and muscles, heart failure is characterized by poor exercise tolerance, repeated hospitalizations, and poor prognosis. The overall prevalence of symptomatic heart failure is currently around 1 to 2%, but it increases with age to over 10% at over 70. (20, 21). The combination of progressive ageing of the population and improved cardiovascular disease survival is expected to make heart failure a new epidemic within the next few decades in the Western world (22).

Evidence of structural or functional abnormality of the heart is essential for a heart failure diagnosis. Although abnormalities in the valves, pericardium, endocardium, heart rhythm, and conduction can also cause heart failure, the main abnormality is in systolic or diastolic ventricular function, or both. The current European Society of Cardiology (ESC) guidelines divide heart failure into three categories according to left ventricular ejection fraction (LVEF), a measure of left ventricular systolic function. These categories are heart failure with preserved (LVEF $\geq$ 50%), mid-range (LVEF 40-49%), and reduced (LVEF<40%) ejection fraction (19).

Several pathological processes occur in heart failure, which may further perpetuate myocardial dysfunction after the initial insult. These include increased haemodynamic overload, ischaemia-related dysfunction, excessive neurohumoral stimulation, abnormal myocyte calcium cycling, excessive or inadequate proliferation of the extracellular matrix, leading to accelerated apoptosis, genetic alteration, and adverse ventricular remodelling (23). The neurohumonal system is activated primarily

as an adaptive mechanism to support the failing heart and restore perfusion status (24). However, when sustained, these compensatory mechanisms become maladaptive and lead to exacerbation of cardiac dysfunction. Indeed, current heart failure medications (ACE inhibitors, β-blockers, mineralocorticoid antagonists) are directed at counterbalancing those maladaptive neurohuomral mechanisms (25). With increasing understanding of the background phenomena, treatment of chronic heart failure has progressed considerably over recent decades with corresponding survival benefit.

2.2 ACUTE HEART FAILURE

AHF is defined as rapid-onset or worsening heart failure symptoms requiring immediate care, usually leading to an unplanned hospitalization (19). AHF is currently the most common cause of unplanned hospital admission in patients aged over 65, causing in all Western countries considerable health care expenditure (21, 26).

AHF may be either the first presentation of heart failure (de novo AHF) or a deterioration in previously diagnosed chronic heart failure (ADCHF). AHF onset and the worsening of symptoms may be abrupt such as in AMI, or may develop within days or even weeks. Each episode of AHF leads to deterioration in myocardial function, and AHF characterizes a patient group with a particularly poor outcome (27). Indeed, mortality risk in patients with chronic heart failure is directly associated with the number of decompensation episodes requiring medical intervention (28). After a hospitalization due to AHF, one-year mortality is up to 28 to 47%, and five-year mortality is around 60% (1, 4, 27, 29), and the rehospitalisation rate within one year after a hospitalization for AHF is over 50% (30, 31).

The clinical phenotype of AHF is heterogenous, ranging from hypertensive patients with hyperdynamic ventricular function to end-stage heart failure with very poor LVEF, and also involving simultaneous conditions such as valve disorders or infections, all of which produce a distinctive clinical profile (32). About half of all AHF patients have preserved LVEF (33), and a subset of patients present with predominantly right ventricular dysfunction (34). Treatment of AHF aims at relieving

symptoms, protecting the myocardium from further damage, and resolving the haemodynamic and neurohumoral imbalance (35, 36). Contrary to the revolutionary steps seen during recent decades in the management of chronic heart failure, AHF has received little attention, and treatment options have largely remained unchanged during the last 40 years. Indeed, other than use of diuretics, treating the underlying pathophysiology (AMI, arrhythmia, infection) and initiation/up-titration of chronic heart failure management, little evidence exists on the survival benefit of therapies directed toward AHF (19). Moreover, trials on novel pharmacological agents have been consistently negative (37-41).

2.2.1 CLINICAL PROFILES AND CLASSIFICATION OF AHF

AHF may be classified in several ways, according to its clinical presentation: pulmonary oedema, hypertensive heart failure, predominantly right-sided heart failure, decompensated AHF, CS (42), or based on haemodynamic status, underlying cardiac or non-cardiac pathology, or by the precipitating factor of AHF.

Regarding selection of appropriate therapy, the patient's haemodynamic status is probably the most useful (43). Most AHF patients have normal (90-140 mmHg) or elevated (>140 mmHg) systolic blood pressure (SBP) on admission. A minority of patients present with low blood pressure (SBP < 90 mmHg), which is associated with poor prognosis. The Forrester classification (44) was introduced 40 years ago to describe the hemodynamic status of patients after myocardial infarction, and is still useful in the assessment of patients with AHF (with or without myocardial infarction). Based on bedside clinical examination, AHF patients are classified as having signs or symptoms of congestion ("wet" or "dry") and for signs or symptoms of hypoperfusion ("cold" or "warm"). The combination of these options identify four groups: warm and wet (well perfused and congested), cold and wet (hypoperfused and congested); cold and dry (hypoperfused without congestion); and warm and dry (compensated, well perfused without congestion). (19) Patients with signs of hypoperfusion are usually, but not always, also hypotensive.

2.2.2 ACS AS A PRECIPITATING FACTOR IN AHF

Identification of precipitating factors of AHF is important, as their precise pathology determines the specific treatment necessary. The precipitating factors that require urgent management include ACS, hypertensive emergencies, rapid arrhythmias or severe bradycardia, valvular causes, and acute mechanical causes (ventricular wall rupture, acute valve regurgitation, aortic dissection, pulmonary embolism) (19). Infections and lack of adherence to medications, lifestyle recommendations, or dietary restrictions are also common precipitating factors, especially in those with ADCHF.

ACS causes about one-third of all cases of AHF, most of which are de novo AHF, and up to 80% of cases of CS (1, 3-6). ACS refers to a spectrum of clinical conditions ranging from unstable angina to non-ST elevation myocardial infarction (NSTEMI) and STEMI. Diagnosis of ACS is based on symptoms, electrocardiographic changes, troponin elevations, and imaging. Coronary artery disease is the main underlying pathology, in which atherosclerotic plaques obstruct or occlude coronary arteries limiting oxygen-rich blood delivery to the myocardium, resulting in ischaemic injury, and in the case of myocardial infarction, in myocardial necrosis. In most cases, an acute atherosclerotic-plaque rupture or erosion leads to thrombus formation and thus abruptly obstructs or occludes a coronary artery, leading to ischaemia (type I myocardial infarction), which may lead to regional myocardial dysfunction. However, myocardial ischaemia may also result from a mismatch of oxygen delivery and demand resulting from changing intra-cardiac pressure conditions and neurohumoral imbalance in AHF (type II myocardial infarction and/or injury), especially in those with underlying chronic coronary artery disease (45, 46). Ischaemia may lead to both systolic and diastolic ventricular dysfunction. In addition, myocardial stunning and hibernation are common in patients with heart failure and coronary artery disease, and stunning may play a major role in the pathophysiology of CS (see section on CS) (47). Of note, mild troponin elevations caused by increased cardiac wall stress and toxic effects of circulating neurohormones such as norepinephrine are common in AHF also in the absence of concomitant ACS. This may make the diagnosis of concomitant ACS challenging, especially with the use of highly sensitive troponin assays. (45)

In coronary angiography, coronary stenoses of ≥ 50% in the left main artery or in coronary branches with a diameter of ≥1.5 mm are regarded as clinically relevant.

Traditionally, performance of coronary angiography in ACS-AHF cohorts has been rather low, with only a minority of patients being revascularized (1, 2, 48). More recently, the coexistence of ACS and AHF has been recognized as identifying a particularly high-risk population, and the latest ESC guidelines for AMI and AHF (19, 49, 50) thus recommend urgent coronary angiography with intent to perform revascularization in patients with AHF caused by ACS, irrespective of electrocardiographic or biomarker findings.

2.2.3 PATHOPHYSIOLOGY OF AHF

The pathophysiology of AHF is complex, and specific mechanisms leading to decompensation remain largely unclear. Furthermore, phenotypes of AHF and the causes of the acute decompensations, as well as comorbidities may have important roles in the pathogenesis. All in all, the key disturbance in AHF is left or right-sided ventricular dysfunction, or both, accompanied by dysfunction in the systemic and pulmonary vasculature resulting in decreased cardiac output, high filling pressures, and augmented afterload (51). In left-sided heart failure, impaired left-ventricular contractility and relaxation results in elevated left-ventricular filling pressures, which in turn lead to increased pulmonary pressure and may cause pulmonary oedema. By increasing the right-sided afterload, the initially left-sided dysfunction can also lead to biventricular failure. In addition to decreased cardiac output and hypoperfusion, congestion is currently believed to play a major role in the pathogenesis of AHF and its related end-organ dysfunction (36, 52). Congestion results from increased volume load in the venous compartment or tissues. In manifest right-ventricular failure, volume overload leads to elevated venous pressure and tissue (liver, intestines, kidney, leg) congestion. (53)

Several background phenomena occur in acute cardiac dysfunction, such as the activation of neurohumoral cascades including activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS), inflammatory reactions, endothelial dysfunction, and oxidative stress. Activation of the RAAS leads to angiotensin II production, of which the main haemodynamic effects include vasoconstriction, aldosterone secretion, vasopressin release, and adverse cardiac remodelling. (54) Recent studies indicate that the myocardium itself is a major

contributor to regulation of the endocrine response in heart failure via natriuretic- and other vasoactive-peptide pathways (55).

As in the case of chronic heart failure, the activated cascades are primarily adaptive, but when sustained become maladaptive, inducing and maintaining a vicious circle of continuing myocardial damage and cell lost. As an example, activation of the sympathetic nervous system and RAAS lead to vasoconstriction, sodium and water retention and redistribution of blood volume. Substances from the activated neurohumoral cascades and oxidative reactions are associated with cardiomyocyte hypertrophy and apoptosis, depressed myocardial contractility, increased fibrosis, and adverse remodelling. (51) These, together, lead to a further increase in left ventricular afterload and impairment of diastolic filling, which eventually leads to further decreased cardiac output. The influence of these phenomena exceeds far beyond the episode of AHF, and contributes to a steady progression of chronic heart failure with marked cardiomyocyte loss and dynamic changes in the architecture of the myocardial extracellular matrix (remodelling) and to electrical imbalance (56).

2.3 CARDIOGENIC SHOCK

CS is the most severe form of AHF and represents less than 5% of cases (1, 6, 57). It is characterized by both hypotension and end-organ hypoperfusion (cold-wet or less commonly cold-dry in the Forrester classification) (58, 59). Contemporary clinical criteria for CS are SBP < 90 mmHg for 30 minutes or need for vasoactive medication to maintain it (after correction of preload conditions), with signs of peripheral or organ hypoperfusion (cold periphery, lactataemia, confusion, oliguria) caused by cardiac dysfunction. The haemodynamic criteria of CS include reduced cardiac index (< 2.2 l/min/m^2) and elevated pulmonary artery wedge pressure (>15 mmHg) or right ventricular end-diastolic pressure (>10-15 mmHg). As the use of invasive hemodynamic monitoring with pulmonary artery catheterization has decreased significantly over the last decade (60), recent expert recommendations have relied on clinical criteria of CS (61, 62), and this approach has been used in the more recent CS studies.

CS is most commonly (about 80%) caused by an ACS and type I myocardial infarction, most commonly by a STEMI (3). Conversely, 5% to 8% of AMIs are complicated by CS, depending on the definition of CS and the characteristics of the populations studied (7, 8, 63). The shock may be caused by acute myocardial dysfunction due to AMI or more rarely by a mechanical complication (chordal rupture and severe mitral regurgitation, ventricular septal- or free-wall rupture), typically developing within a few days after the AMI. Other aetiologies of CS include myocarditis, takotsubo cardiomyopathy, valvular causes, and end-stage chronic heart failure (59). Since the majority of CS results from ACS, most published data on CS is derived from cohorts of ACS-CS patients (7, 8, 63-65), and contemporary data including CS patients of various aetiologies is scarce.

In most patients, CS occurs during the first 24 hours of hospitalization. Despite routine use of primary percutaneous coronary intervention (PCI) in AMI, the overall rate of ACS-related CS has decreased only slightly during the last 20 years. (8, 66, 67) While the incidence of pre-hospital CS (2-3% of patients with AMI) has remained rather stable, incidence of in-hospital CS has declined over time, especially for late-onset shock (developing after 24 hours of hospital admission) (8, 67). Clinical risk factors for CS development in ACS include older age, history of previous myocardial infarction, coronary artery bypass graft surgery (CABG), history of heart failure or diabetes, anterior location of the AMI, and signs of heart failure on hospital admission (68). The presence of a bundle branch block in the admission ECG is also associated with increased incidence of CS (69, 70).

Urgent revascularization has been the gold standard of treatment in ACS-related CS since the publication of Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock (SHOCK) trial, showing benefit for 6-month mortality with early revascularization compared to initial medical stabilization (64). The recent randomized Culprit Lesion Only PCI versus Multivessel PCI in Cardiogenic Shock (CULPRIT-SHOCK) study showed that the culprit-lesion-only approach was associated with a survival benefit for 30-day mortality over an immediate multivessel approach (71). The haemodynamic stabilization in CS, in addition to reperfusion therapy, can be achieved by vasoactive medication or mechanical circulatory support or both. Norepinephrine is currently the first-line vasopressor to restore blood pressure, whereas dobutamine is advised as the first-line inotropic agent in addition to vasopressor therapy if necessary (19, 59, 72). Other

vasoactive medications used in patients with CS include dopamine, adrenaline, levosimendan, and milrinone. No randomized controlled trials directly compare these agents specifically in CS, and the choice between different vasoactive agents is largely based on expert opinion and on individual preferences. However, a small, randomized trial recently showed that refractory shock develops more often after adrenaline than after noradrenaline use in patients with AMI-related CS (73). Adrenaline use was also associated with substantially higher short-term mortality than were other vasoactive medications in a recent meta-analysis of CS (74).

When medical stabilization fails in CS, the increasingly used approach is mechanical circulatory support. The intra-aortic balloon pump was standard for decades in CS, but did not improve outcome in the Intra-aortic Balloon Pump in Cardiogenic Shock II (IABP SHOCK II) trial (65), and its use largely declined thereafter. The mechanical assist devices currently used include Impella (2.5 - 5.0 L/min), Tandem Heart, and iVAC 2L, as well as extracorporeal membrane oxygenation (ECMO) (75). Short-term mechanical circulatory support is used as a bridge to recovery, or as a bridge to urgent heart transplantation or implantation of a long-term circulatory support device, or as a bridge to further decision-making. The long-term mechanical assist devices, in turn, may serve as a bridge to heart transplantation or as a destination therapy (76). No proven survival benefit from the use of short-term mechanical circulatory support has emerged, however, at least in unselected patients with CS (77, 78).

2.3.1 PATHOPHYSIOLOGY OF CS

In CS, the same regulatory cascades are activated as in AHF, such as RAAS, natriuretic peptides, vasopressin, adrenomedullin, galectin-3, and endothelial dysfunction (47, 79). However, since CS most commonly is a de novo disease with abrupt onset, the long-term adaptive mechanisms are lacking, and activation of the cascades may be delayed. In addition, hypoperfusion affects end-organ systems, resulting in the activation of various inflammatory pathways, oxidative stress, acid-base disturbances, and the release of substances from the failing organs that become involved in maintenance of the shock state following the initial insult (11, 80).

As Figure 1 illustrates, in ACS-related CS**,** a decrease in cardiac output resulting from myocardial infarction causes hypotension, which leads to decreased

coronary perfusion, which in turn perpetuates cardiac dysfunction, further reducing cardiac output and perfusion of other vital organs (59). In addition, hypotension leads to release of cathecholamines (noradrenaline, adrenaline), which temporarily enhance ventricular contractility and peripheral blood flow; but rather than interrupting the vicious circle, cathecholamines cause increased myocardial oxygen demand and afterload, and exert proarrhytmogenic and cardiotoxic effects. In addition, cathecholamines, both endogenous and as medications, promote oxidative stress, modulate inflammatory responses, and interfere with cellular energy metabolism (81).

As the majority of CS patients have multivessel coronary artery disease (3, 71), coronary blood flow may be additionally compromised due to low perfusion pressure in one or more non-culprit arteries, perpetuating myocardial dysfunction. The severity of left ventricular dysfunction is related to the extent of coronary artery disease, and to the location of the culprit lesion and its revascularization success (82). Compromised blood supply may lead to impaired contractility of viable myocardium even after successful revascularization; in such cases, the myocardial dysfunction is often reversible, and is called myocardial stunning. Hibernation is another form of reversible dysfunction of viable myocardium; it usually results from a longer period of compromised blood supply, such as in patients with severe chronic multivessel coronary artery disease. In the CS state, the detrimental effects of circulating cathecholamines and of agents from the activated neurohumoral and inflammatory cascades may further impair systolic function and maintain myocardial stunning. In addition, ischaemia-induced diastolic derangements may lead to increased filling pressures with a resultant volume and/or pressure load to the myocardium.

Degree of ventricular dysfunction seems not to be the pivotal factor in the pathogenesis of shock, however. In fact, the concept of the pathogenesis of CS has undergone a paradigm change in the era of urgent reperfusion therapies: in many cases, severe impairment of contractility has not led to shock, and conversely, in CS, LVEF may be only moderately depressed (3, 11). Indeed, although ineffective stroke volume is the inciting event, a major role is played by inadequate circulatory compensation (59). The vasoplegic state in CS is caused and maintained by various pathways, including inflammation, nitric oxide, potassium- and calcium channels, adrenomedullin, and free radicals (54); this corresponds to the systemic inflammatory response syndrome seen, for example, in sepsis.

Inflammatory reactions in CS include activation of the innate immune response, increased expression of proinflammatory mediators (such us tumour necrosis factor-α and interleukins), activation of the complement system, autoantibody production, and overexpression of major histocompatibility complex molecules, as well as of adhesion molecules (51). The inflammatory mediators may also have myocardial depressant action causing stunning, or they may induce endothelial dysfunction, leading to further diminished coronary blood flow and end-organ suffering (11). Vasoplegia results from excessively activated nitric oxide pathways which have negative inotropic effects, interfere with cathecholamine action, and carry cardiotoxic substances. (47, 54, 59) Finally, hypoperfusion and inappropriate vasodilatation of the gastrointestinal tract enables transmigration of bacteria to the blood and may lead to bactereamia and clinical sepsis. Although vasoplegia and inflammatory responses play a major role in the pathogenesis of CS, attempts to restrict the inflammatory responses with pharmacologic agents have not proven successful (83, 84).

https://www.ahajournals.org/doi/10.1161/CIR.0000000000000525

Figure 1. The current concept of the pathophysiology of cardiogenic shock. Reproduced with permission from Contemporary Management of Cardiogenic Shock: A Scientific Statement From the American Heart Association (59). SIRS = systemic inflammatory response syndrome, e/iNOS = endothelial/inducible nitric oxide synthase, LVEDP, left ventricular end-diastolic pressure; NO, nitric oxide; SIRS,

systemic inflammatory response syndrome; SVR, systemic vascular resistance; and TNF-α, tumour necrosis factor-α.

2.4 ELECTROCARDIOGRAPHIC ALTERATIONS

The ECG examines cardiac activity through electrical potentials measured from the body surface. Electrical potentials within the myocardium are altered in many pathologic circumstances, forming the basis for use of body surface ECG in the evaluation of cardiac diseases. When the heart undergoes depolarization and repolarization, under normal conditions, the action potential generated by the sinoatrial node spreads through the atria to the atrioventricular node, and to the ventricles through the bundle of His and bundle branches, up to the site of smaller fascicles and Purkinje fibres (Figure 2) at very high velocity (about 2 m/sec), producing rapid and synchronous depolarization and contraction of ventricular cardiomyocytes. Ischaemia, scar tissue due to chronic ischaemia, inflammation, fibrosis, infiltrative lesions, calcification (85, 86), or overstreching of the conduction fibres due to ventricular wall stress (87, 88) may damage the conduction network within the ventricles, resulting in slow impulse conduction through cardiomyocytes, which is seen as intraventricular conduction disturbances in the ECG.

2.4.1 ISCHAEMIC CHANGES IN ELECTROCARDIOGRAPHY

Acute ischaemia, due to compromised blood supply to the myocardium, alters the electrical properties of the myocardium, thus leading to repolarization abnormalities. The first ischaemic sign is peaking of T waves, after which, acute ischaemia resulting from complete coronary artery occlusion typically creates ST-segment elevations in the leads whose positive pole is located over the ischaemic region, and reciprocal ST segment depressions in the leads whose positive poles are oriented in the opposite direction. (89) The ischaemic ST-segment deviations are a hallmark in the diagnosis of myocardial infarction in clinical practice. When the ST-segment is elevated over a predetermined threshold value in 2 or more anatomically contiguous ECG leads, the

term used is ‘STEMI’. The term ‘NSTEMI’ (non-STEMI) is used for myocardial infarctions with all other ECG findings, such as those with lesser degree of ST-segment elevation or elevation in only one contiguous lead, with ST-segment depression, T-wave inversion, or no abnormalities at all. The magnitude and extent of ECG alterations depend on the size and location of the ischaemic/infarcted region and the relationship of this region to the spatial orientation of the particular ECG lead. By the location, extent, and degree of the ischaemic changes clinicians can estimate the affected area of the myocardium, its extent, and the coronary artery involved. The size of the region affected depends, in turn, on the site of occlusion within the coronary artery, and the presence or absence of collateral circulation. (89)

2.4.1.1 Changes in QRS duration and pattern in ischaemia

As the electrical properties of the myocardium during ischaemia change, regional ventricular conduction is slowed, resulting in changes in QRS duration and amplitude. The changes in QRS usually include enlargement of the R wave amplitude in the leads with ST segment elevation, resulting in a shift of the electrical axis. (90) The changes in the QRS axis due to ischaemia-induced slowing of conduction may present as hemiblock configuration without true injury of the conduction fibres (91, 92). Since transmural conduction time progressively increases due to transmural ischaemia, the QRS-complex alterations in addition to conventional ST-segment deviations usually indicate more severe ischaemia and faster progression of irreversible myocardial necrosis than do lone ST deviations (93, 94). Indeed, alterations in the ST segment and T wave are generally regarded as ECG signs of myocardial ischaemia, but alterations in the QRS pattern as myocardial necrosis (95). Once myocardial necrosis is present, Q waves are formed in those leads whose positive pole is located over the infarcted region as a result of absence of electrical activity.

2.4.1.2 Bundle branch blocks and hemiblocks

The appearance of left or right bundle branch block (LBBB or RBBB) results from an injury to the left or to the right bundle branch due to ischaemia or overstreching of the

conduction fibres (90, 96). In AMI, the appearance of a new bundle branch block is associated with poor outcome (69). Since the conduction system is more resistant to ischaemia than is the myocardium, the occurrence of a bundle branch block may relate to the amount of myocardium jeopardized after coronary artery occlusion, and may relate to extensive and on-going myocardial infarction despite revascularization (69, 97-99). As the course of the right bundle branch goes through the anterior septum, the appearance of a new RBBB may be explained by septal ischaemia from occlusion in a more proximal section of the left anterior descending artery (before the large septal branches), leading to larger infarctions and a poorer outcome than in anterior infarctions without RBBB. More extensive ischaemia and necrosis is required to produce LBBB since the left bundle branch has a varied distribution from a network of fibres (97), and this branch receives its blood supply from two or even all three of the main coronary arteries. More extensive ischaemia and necrosis is required to produce LBBB since the left bundle branch has a varied distribution from a network of fibres (100), and this branch receives its blood supply from two or even all three of the main coronary arteries. (Figure 2).

Left anterior hemiblock (LAHB) results from injury to the left anterior fascicle, which is a long, thin fascicle and thus relatively susceptible to injury. The left anterior fascicle is mainly supplied by septal branches of the left anterior descending artery, with the most proximal segment supplied by the artery to the atrioventricular node. Left posterior hemiblock (LPHB) results from a blockage of the left posterior fascicle, which is short and thick, and thus more resistant to injury. The left posterior fascicle also generally has a double blood supply from both the left anterior descending coronary artery and the posterior descending branch, which is a distal branch of the right coronary artery in most individuals (right dominant circulation) (101, 102).

The presence of LBBB makes the diagnosis of STEMI difficult, since the ST segment is altered by LBBB itself. There exist, however, specific criteria to diagnose a STEMI in the presence of LBBB (103). RBBB or a hemiblock does not impede the diagnosis of STEMI (89). In the newly updated ESC guidelines for STEMI, both RBBB and LBBB are indications for emergent revascularization in AMI, comparable to STEMI (50).

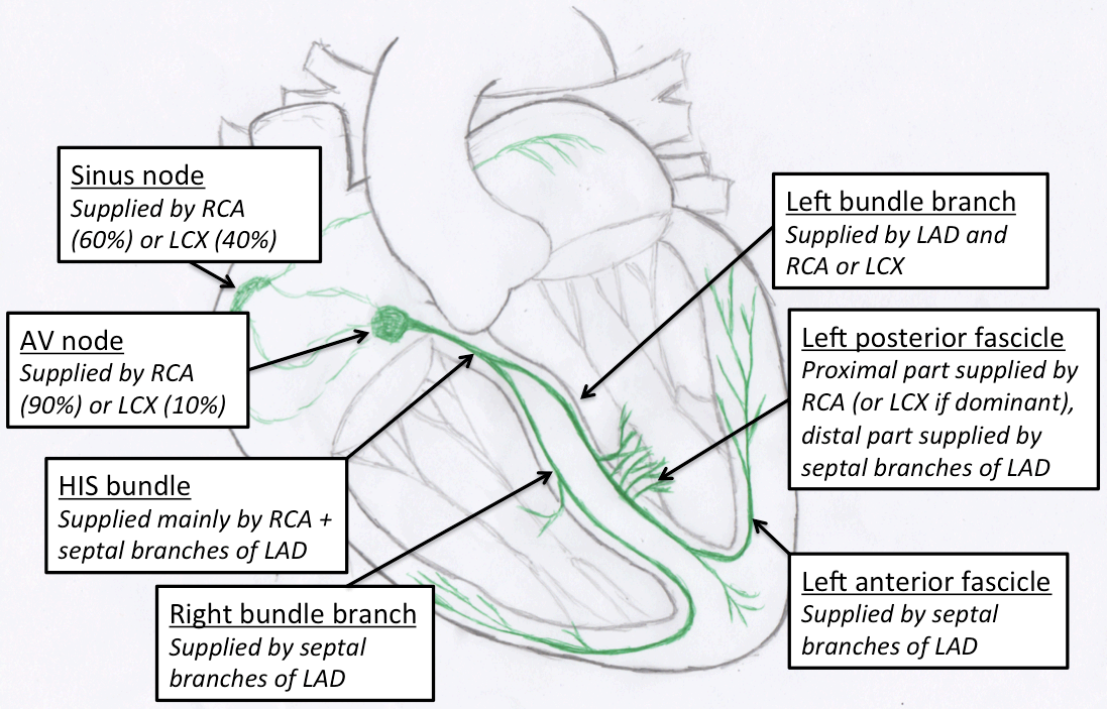

Figure 2. Conduction system and its arterial supply. AV = atrioventricular, RCA = right coronary artery, LCX = left circumflex artery, LAD = left anterior descending artery. Illustration by author.

2.4.2 DEFINITIONS OF VENTRICULAR CONDUCTION ABNORMALITIES

The term *intraventricular conduction disturbance* refers to abnormalities in the intraventricular conduction of supraventricular impulses that result in changes in the shape or duration, or both, of the QRS complex. These disturbances can be either fixed or intermittent, or they can be heart-rate dependent. They may also be functional, due to the arrival of a supraventricular impulse during the relative refractory period in a conduction system, which is called *aberrant ventricular conduction*. (90) In this thesis, ventricular conduction abnormalities refer to abnormalities in the QRS complex in the supraventricular complexes of the predominant rhythm in a patients' resting ECG. The definitions for each abnormality are in Table 1. Based on conventional criteria for LBBB, one-third of patients are suggested not to have true complete LBBB, but rather a combination of left ventricular hypertrophy and left anterior fascicular block (104, 105), possibly explaining the lack of benefit from cardiac resynchronizing therapy seen in some

patients with LBBB. Strauss criteria have been proposed as stricter criteria to diagnose "complete LBBB"; these criteria require a QRS duration ≥ 140 ms for men and ≥ 130 ms for women, along with mid-QRS notching or slurring in 2 or more lateral leads, in addition to the conventional criteria (106).

Block type	Definition
LBBB	QRS duration ≥ 120 ms Tall R, broad or notched R waves in the lateral leads (I, V5-6) Deep S waves in the right precordial leads (V1-3) Absence of septal Q waves in the lateral leads (I, V5-6)
RBBB	QRS duration ≥ 120 ms Wide or notched R wave in leads V1 or V2. Slurred S wave of greater duration than R wave in leads I and V6
LAHB	Left axis deviation (-30° to -90°) qR pattern (small q, tall R) in the lateral limb leads I and aVL rS pattern (small r, deep S) in the inferior leads II, III, and aVF QRS width <120 ms (in the absence of RBBB)
LPHB	Right axis deviation (90°-180°) rS pattern in leads I and aVL qR pattern in leads III and aVF QRS width <120ms (in the absence of RBBB)
IVCD	Definition varies depending on the source, usually QRS >110-120 ms without bundle branch blocks/hemiblocks In Study I: QRS ≥ 110 ms without bundle branch blocks In Study II: QRS ≥ 110 ms without bundle branch blocks and hemiblocks

Table 1. Definitions of ventricular conduction blocks used in this thesis. Adapted from AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: part III: intraventricular conduction disturbances (90).

2.5 BIOMARKERS

Biomarkers are biological markers usually sampled from blood or urine and serve for diagnostics or for prognostic purposes. In both cases, they always serve as adjuncts to clinical judgement. For a novel biomarker to be useful in clinical practice, its testing needs to be easily reproducible and interpretable, it needs to have significant additive value to clinical variables and to other routine tests, and needs to be cost-effective. (107, 108) Any biomarker-guided assessment should also promise some outcome benefit. The discovery of novel biomarkers provides insights into biological processes and cascades in AHF; they may serve as therapeutic targets for novel pharmacologic agents, or help in more accurate and objective patient profiling in the decision on individual therapies or design of clinical trials for novel therapies (25). In such cases, biomarkers may serve among inclusion criteria to enrich the study population with higher-risk subjects, to be a measure of drug toxicity, to act as an outcome measure, or be one means to explain efficacy of a therapeutic agent. (13, 109)

In heart failure, elevated biomarker concentrations represent various pathways of myocardial injury and the activated neurohumoral and inflammatory cascades involved in the pathogenesis (23, 110). In addition to the neurohumoral responses occurring in chronic heart failure, end-organ dysfunction resulting from congestion and hypoperfusion in AHF and CS activate further cascades with organ-specific biomarkers. In general terms, the higher the biomarker concentration, the greater the cascade activation and the poorer the prognosis. The currently recognized biomarker pathways in AHF include RAAS, natriuretic peptides, sST2, vasopressin and copeptin, adrenomedullin, galectin-3, and pathways of endothelial dysfunction, inflammation, and oxidative stress (Figure 3). (109, 111) Activated pathways that the biomarkers represent can be either maladaptive, thus exacerbating organ dysfunction (such as products of oxidative stress), or adaptive, aimed at counteracting the deranged physiology of heart failure (such as natriuretic peptides). Since the various biomarkers each represent a different pathway of cardiac stress, the prognostic value they provide may be additive, thus rendering a multimarker strategy in risk stratification particularly beneficial (17). In CS, in which the abrupt activation of neurohumoral and inflammatory cascades seems pivotal for the development,

severity, and outcome of shock, a biomarker-based approach in severity assessment seems particularly attractive.

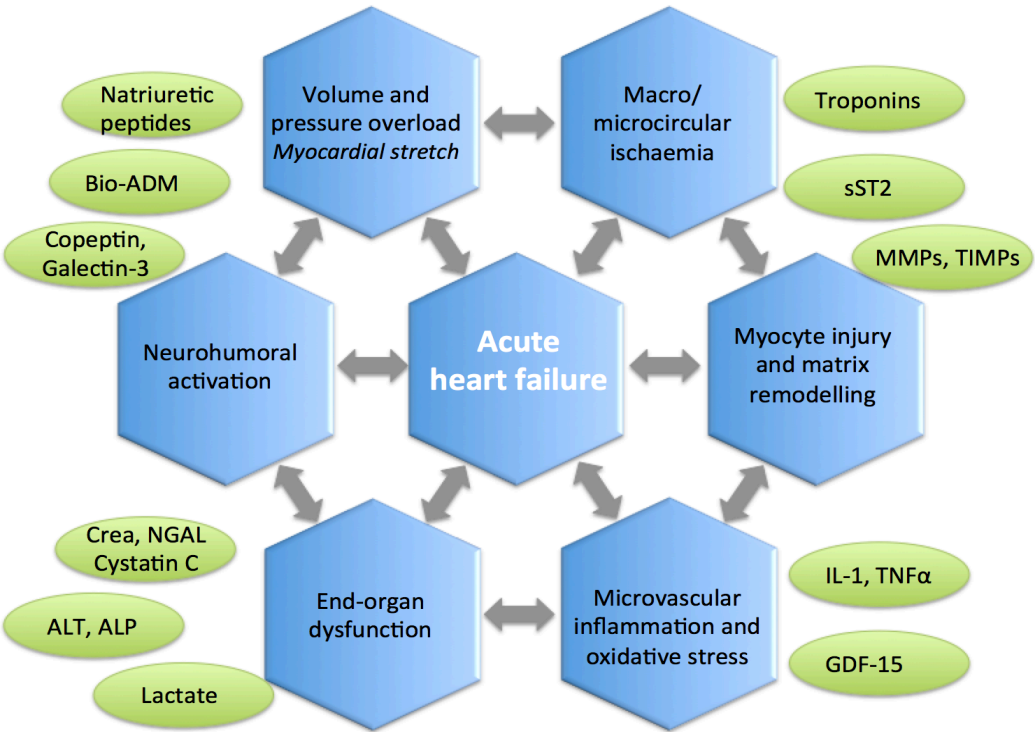

Figure 3. Pathophysiology and biomarker pathways of acute heart failure. Bio-ADM = bioactive adrenomedullin, Crea = Creatinine, NGAL = Neutrophil gelatinase-associated lipocalin, ALT = alanine aminotransferase, ALP = Alkaline Phosphatase, MMP = Matrix metallopeptidase, TIMP = tissue inhibitor of metalloproteinases, IL-1 = interleukin 1, TNFα = tumor necrosis factor α, GDF-15 = growth/differentiation factor 15. Illustration by author.

2.5.1 NATRIURETIC PEPTIDES

Natriuretic peptides are peptide proteins sampled from plasma. They are primarily produced from cardiomyocytes in the atria (atrial natriuretic peptide and mid-regional proatrial natriuretic peptide) and the ventricles (brain natriuretic peptide, BNP) in response to myocyte stretch from volume or pressure overload (112). Upon stimulation, proBNP is synthetized *de novo,* mostly from ventricular cardiomyocytes, and after several processing steps, the biologically inactive peptide N-terminal pro-B-

type natriuretic peptide (NT-proBNP) is cleaved from proBNP, resulting in mature bioactive BNP; then both parts are released to plasma.

BNP and the inactive fragment NT-proBNP are the most widely used natriuretic peptides. The biological effects of natriuretic peptides include vasodilatation, natriuresis, diuresis, reduction in the effects of activated RAAS, and reduction in myocardial stiffness and improvement of myocardial relaxation. All these effects are favourable biological responses to the derangement of physiology involved in heart failure. (112) Besides heart failure, many other cardiovascular disorders (ACS, myocarditis, pulmonary embolism, atrial fibrillation, valvular disease) and non-cardiac disorders (renal failure, anemia) raise the levels of BNP and NT-proBNP. In contrast, levels of BNP and NT-proBNP are significantly lower in obese patients (113). The effects of BNP are ultimately terminated by passive removal, by receptor clearance, by inactivation in the circulation by post-translational modifications or by degradation with catalytic enzymes such as neprilysin (114).

2.5.2 SOLUBLE ST2

sST2 is one of the most promising novel biomarkers in cardiovascular medicine and in heart failure studies. ST2 is a member of the IL-1 family proteins; the ST2 pathway consists of a transmembrane ST2 receptor (ST2L) isoform and its soluble isoform sST2 that can be detected in plasma or serum. IL-33, which is secreted by fibroblasts and myocytes under biomechanical stress, is a member of the IL-1 family of cytokines, and acts as a ligand for the ST2 receptor. IL-33/ST2L signalling regulates inflammatory responses, particularly those involving T helper type 2 (Th2) responses and production of Th2-associated cytokines (115). The soluble isoform sST2 is also released upon mechanical stimulation of cardiomyocytes and acts as a decoy receptor, thus neutralizing IL-33 and blocking the IL-33/ST2L signalling pathway (115, 116) (Figure 4). Although biomechanical stress triggers elevation in both the levels of sST2 and IL-33, in the setting of AMI, the rise in sST2 seems disproportionate compared to that of IL-33. Moreover, the response in IL-33/sST2 concentrations may be different in some patient groups, such as those with diabetes or smokers, suggesting variation in individual immunological responses to AMI. (117)

The interaction between IL-33 and transmembrane ST2L is thought to represent intramyocardial fibroblast–cardiomyocyte communication and seems to have an important favourable role in regulating myocardial response to biomechanical overload in stretched cardiac fibroblasts and cardiomyocytes (118). The IL-33 - ST2L signalling is also assumed to be protective against atherosclerosis, myocardial infarction, and myocardial fibrosis and hypertrophy (119, 120). As such, sST2 seems to serve as a marker of cardiac and vascular stress, inflammation, adverse remodelling, and fibrosis (121).

The ST2/IL-33 pathway is also involved in inflammatory processes in extracardiac tissues, particularly in those with predominant Th2 lymphocytic responses such as asthma, pulmonary fibrosis, rheumatoid arthritis, sepsis, trauma, and some malignancies (122). Due to its lack of specificity, the diagnostic value of sST2 for heart failure is low (123). By contrast, sST2 shows very strong prognostic value in AHF, as discussed further in Section 2.6.4.1.

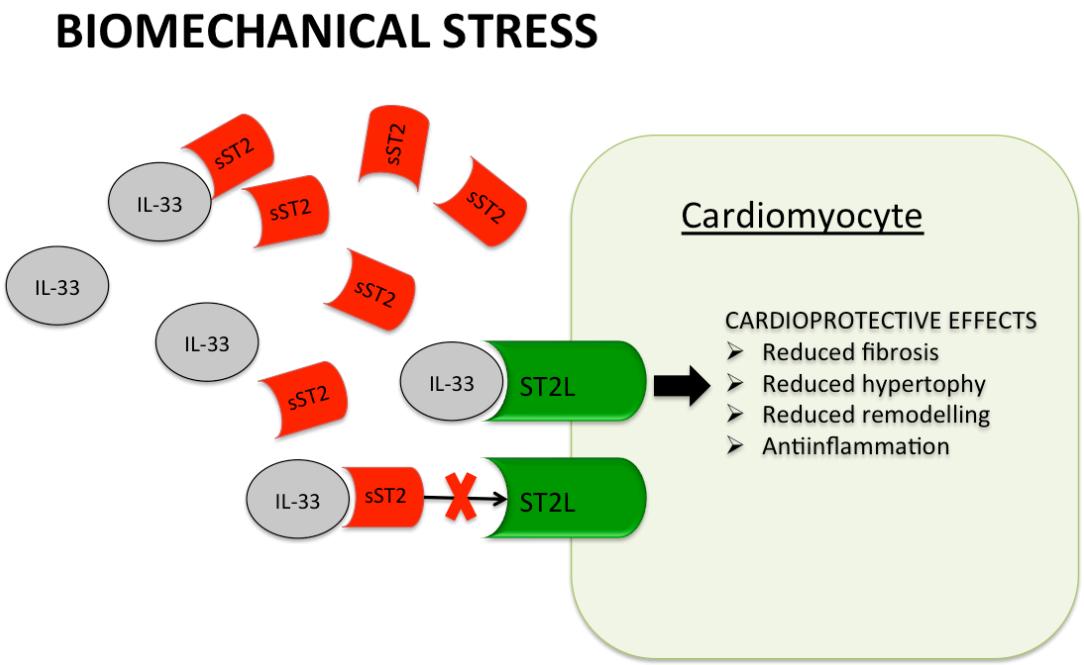

Figure 4. Schematic figure of ST2 signalling. sST2 = soluble ST2, IL-33 = interleukin 33, ST2L = ST2 ligand. In biomechanical stress, both interleukin 33 (IL-33) and soluble ST2 (sST2) concentrations are increased in circulation. sST2 blocks the cardioprotective effects of the IL-33- ST2 ligand (ST2L) interaction. Illustration by author.

2.5.3 ADRENOMEDULLIN

Adrenomedullin is a potent, long-lasting, vasodilatory peptide originally discovered in human pheochromocytoma tissue. It is secreted from various tissues, including of the heart, lungs, central nervous system, and kidneys, as well as from endothelial cells, vascular smooth muscle cells, fibroblasts and adipocytes. Adrenomedullin targets are also widely distributed across cardiovascular, pulmonary, renal, gastrointestinal, cerebral, and endocrine tissues. (124) Clinical use of adrenomedullin has been limited for some years because of its instability in vitro; to overcome such difficulties, mid-regional pro-Adrenomedullin (MR-proADM), a non-bioactive precursor of adrenomedullin, has been the choice. The most recent studies have used a novel immunoassay that allows ultrasensitive measurement of bioactive adrenomedullin (bio-ADM) peptide from a small sample volume (50 uL of plasma) (18). All of the proteins: MR-proADM, adrenomedullin, and bio-ADM reflect the same adrenomedullin pathway.

In heart failure, adrenomedullin production is upregulated in cardiac myocytes in response to pressure/volume overload and ventricular wall stretching. In addition to vasodilatation, adrenomedullin has inotropic and natriuretic properties. The primary effects of adrenomedullin are proposed to be protective, lowering both preload and afterload as well as reducing hypertrophy, adverse remodelling, and fibrosis. (125) In CS, the excess adrenomedullin is believed to originate from both cardiomyocytes and from vascular endothelial and smooth muscle cells. Catecholamines, angiotensin II, and aldosterone, all of which are elevated in heart failure and CS, are potent stimulators of adrenomedullin production (126). In addition, inflammatory cytokines such as interleukins and tumour necrosis factor-α have also been suggested to stimulate adrenomedullin secretion (127). In patients with septic shock, adrenomedullin is depicted as a double-edged sword for its primarily protective mechanisms, but upon release in abundant quantities, adrenomedullin is associated with inappropriate vasoplegia and organ dysfunction (54). Adrenomedullin mediates its vasodilatory and natriuretic properties through cyclic adenosine 3',5'-monophosphate, nitric oxide, and the renal the prostaglandin system. (128) As with natriuretic peptides, concentrations of adrenomedullin are affected by age, renal function, and body mass. Women also appear to have higher concentrations than men. (124) Due to its lack of specificity to the heart, the diagnostic value of the

adrenomedullin cascade for heart failure is low (123).

2.5.4 OTHER BIOMARKERS

The other biomarkers recognized as risk markers in AHF listed below are not discussed in further detail here. Copeptin is a novel biomarker that represents the activated arginine vasopressin / antidiuretic hormone pathway in AHF, which is up-regulated in response to decreased plasma volume and results in fluid retention (111, 129). Galectin-3 is produced in abundance by macrophages in AHF, resulting in the proliferation of cardiac fibroblasts and in collagen deposition. Galectin-3 is thus also a marker of adverse remodelling and cardiac fibrosis, but its predictive value in heart failure is lower than that of sST2 (130). Matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) are matrix-degrading enzymes up-regulated in the failing heart and also influencing left ventricular remodelling (131). Elevated troponin levels in the absence of concomitant ACS in AHF are associated with the myocardial injury caused by elevated wall pressure and direct cardiotoxic effects of circulation cathecholamines, thus associating with poor outcome (45). Growth/differentiation factor 15 (GDF-15) is a strong prognostic marker in AHF, but it is not cardiac specific. Its production is strongly induced in response to acute stressors including inflammation, oxidative stress, hypoxia, and tissue injury (132). Procalcitonin is produced from neuroendocrine cells of the lungs, intestines, and peripheral mononuclear cells in response to bacterial endotoxins, and is useful in detecting an underlying bacterial pulmonary infection in AHF patients. Cystatin C and neutrophil gelatinase-associated lipocalin (NGAL) are biomarkers of renal failure and cardiorenal syndrome. (111)

2.6 RISK ASSESSMENT

Accurate patient profiling and risk stratification are needed to guide the therapeutic decisions of patients with AHF and CS, in efforts to improve outcomes such as repeated hospitalizations and mortality, and save health care resources. Due to high early mortality, accurate and early risk assessment is particularly important in CS,

where timely application of advanced therapies may halt the progression of irreversible end-organ dysfunction. Indeed, many of the pathophysiological derangements in CS may be reversible, and those surviving the acute phase may expect good long-term survival with good quality of life (11). Risk assessment in AHF and CS is traditionally based on clinical parameters and routine laboratory measurements (133).

2.6.1 CLINICAL RISK MARKERS IN AHF

Several clinical parameters have been recognized as predictors of poor outcome in AHF. These include: advanced age, history of diabetes mellitus, arrhythmia, previous myocardial infarction or stroke, lower SBP on admission, elevated heart rate, and poorer left ventricular function (133, 134). Of the conventional biochemical measures, low haemoglobin, high serum creatinine and blood urea nitrogen (reflecting kidney injury), elevated liver enzymes (reflecting liver injury), and hyponatremia are associated with poor outcome (133-135). Red-cell distribution width is a marker available in a routine blood count that was recently shown to be an accurate risk marker (136), as is iron deficiency, defined by plasma levels of hepcidin and transferritin receptor (137). Several scores for risk stratification in AHF include clinical markers that associate with poor survival, most of them being well validated in large international cohorts (133, 138-143).

2.6.2 CLINICAL RISK MARKERS IN CS

As in AHF, older age and previously diseased myocardium (previous myocardial infarction or revascularization), as well as previous stroke, are associated with poor CS outcome (10, 144). Baseline clinical characteristics that reflect severe shock, ones such as low blood pressure, high arterial lactate, poor left ventricular function, and ischaemic brain injury are also predictive of poor outcome (145, 146). High plasma glucose, especially in those without diabetes (146), and poor renal function are also associated with increased mortality (147). As urgent revascularization is crucial in CS management, unsuccessful revascularization is strongly associated with increased mortality (64, 144, 145), as is also the extent of coronary artery disease (82).

There are several scores for risk stratification in CS that include the clinical characteristics associated with poor survival, the newer ones also including revascularization success (10, 144, 148). These scores are designed to be easily applicable, usually with parameters available at baseline such as patient history, baseline clinical profile, or routine laboratory findings. The most recent score, the IABP score (144), was developed from the IABP-SHOCK II trial in patients with ACS-related CS, and includes dichotomous parameters such as age over 73 years, history of stroke, increased glucose and creatinine, and arterial lactate > 5 mmol/L, and the final Thrombolysis In Myocardial Infarction (TIMI) flow grade < 3 after revascularisation as the strongest variables. The applicability of this score has been validated both internally and externally. Clinical scores used for sepsis, or in general with intensive care patients, which reflect the severity of shock state or end-organ damage, such as Acute Physiology, Age, Chronic Health Evaluation (APACHE) II and III scores (149, 150), the Sepsis-related Organ Failure Assessment (SOFA) score (151), and the Simplified Acute Physiology Score (SAPS II) (152), also accurately predict survival in patients with CS (153).

2.6.3 VENTRICULAR CONDUCTION BLOCKS AS RISK MARKERS

The role of ventricular conduction abnormalities in chronic heart failure is well established (143, 144), and QRS duration and morphology play an important role in determining candidates for cardiac resychronizing therapy (19). However, few studies concern ventricular conduction abnormalities in AHF and CS. Delayed activation of the myocardium shortens the duration of the diastolic ventricular filling period of either left or right ventricle, which in turn reduces stroke volume and cardiac output. Systolic and diastolic ventricular dyssynchrony also worsen already depressed cardiac output and favour further ventricular volume remodelling in heart failure. (154, 155) As these findings originate from the setting of chronic heart failure, the exact role of ventricular conduction abnormalities in the pathogenesis and mechanism of AHF is less clear.

2.6.3.1 Bundle branch blocks

In the few clinical studies of AHF, the prevalence of LBBB is around 14 to 16%, and the prevalence of RBBB around 7 to 10%, depending on characteristics of the patient cohorts (156-158). In a study of 403 patients with severe AHF, those with LBBB more frequently had dilated cardiomyopathy, more cardiac comorbidities, and lower LVEF, and more often AHF resulting from an unidentified precipitating factor than did those without LBBB (156). In that study, LBBB was an independent predictor of increased 1-year mortality. In another study, involving 9082 patients hospitalized for AHF (157), both LBBB (present in 16%) and RBBB (present in 7%) were associated with older age, cardiomegaly, and poorer renal function. LBBB was associated with ischaemic heart failure aetiology, whereas patients with RBBB were often men and diabetes sufferers. That study found both bundle branch blocks to associate with significantly higher short- and long-term mortality, but only LBBB was independently predictive of mortality. Another study involving 1888 patients hospitalized for heart failure with reduced or mid-range ejection fraction (LVEF<50%) (158), 14% of patients had LBBB; they were older and had lower LVEF and more often chronic heart medication than did those without LBBB. Patients with RBBB (10%) were less often women and tended to have higher pulmonary artery pressures than those without RBBB. In that analysis, only RBBB predicted mortality, which appeared to be pronounced in those with more advanced left ventricular dysfunction (LVEF<30%).

In CS, in a subanalysis of the SHOCK trial (159), LBBB was present in 6% and RBBB in 20%, but their independent association with increased mortality was not reported. In a more recent study of 358 patients with CS complicating AMI, 11% had LBBB and 13% had RBBB (with or without hemiblock) at baseline. Patients with RBBB more often had the left main artery as the infarct-related artery than did those with STEMI without bundle branch block. In that study, RBBB, but not LBBB, was an independent predictor of mortality (70). Finally, in a small study of 25 patients with CS caused by myocardial infarction due to left main coronary artery disease, 48% of patients had RBBB, and RBBB was associated with significantly increased short-term mortality (160). Further, in patients with AMI, the presence of a bundle branch block is associated with higher incidence of both AHF (161) and CS (70).

2.6.3.2 Hemiblocks and IVCD

Hemiblocks are a relatively common finding in patients with heart disease, particularly in those with prior myocardial infarction (101), but their exact role in AHF and CS has not been defined. The definition of IVCD varies in the heart failure literature, including QRS durations of ≥110 ms to ≥120 ms and including or excluding bundle branch blocks or hemiblocks, or both. The prevalence of IVCD in AHF ranges from 27% to 44% based on the characteristics of the studied populations and on the definition, with most studies including bundle branch blocks in the IVCD group (162, 163). Prolonged QRS has been independently associated with increased mortality in chronic heart failure (164, 165) – also when LVEF is preserved (166), and in AHF (162, 163). In the SHOCK trial, 11% of the patients had QRS duration >115 ms without a bundle branch block. Increasing QRS duration, independently of age and the presence of a bundle branch block, was a predictor of mortality (159).

2.6.3.3 Temporal evolution of blocks

Changes in QRS morphology during acute ischaemia may be transient (96, 167). Other than patients with AMI, the data on block evolution during episodes of AHF is scarce. In studies of myocardial infarction, definitions used for temporal evolution of the ventricular conduction abnormalities have been heterogeneous. In most studies, patients who died during follow-up period (usually the index hospitalization) were regarded as having a persistent block, although a repetitive ECG was not necessarily documented (70, 161, 168). In the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO-1) trial, of the 26,003 AMI patients during the thrombolytic era, incidence of complete block resolution was 12% and for partial block resolution 12% (69). Later, in 5570 AMI patients (161) with an overall LBBB incidence of 13%, 27% of these were confirmed to be of new onset, and 60% of the new-onset LBBBs were transient. The overall incidence of RBBB was 11%, of which 36% were confirmed to be of new onset, and 65% of the new-onset RBBBs were transient.

In AMI, persistent blocks have been associated with higher mortality than are transient blocks (69, 161, 168, 169). However, the increase in mortality risk

associated with persistent blocks appeared mainly to apply to very early in-hospital death; after discharge, the long-term mortality was even lower in those with persistent compared to transient block (161). In a study of 358 patients with AMI-related CS (70), 62% to 66% of bundle branch blocks were persistent, while 13% to 15% were transient. One third of bundle branch blocks were new-onset blocks, while 21% of LBBB and 46% of RBBBs were confirmed as old findings. The relationship between block evolution and survival was not reported.

2.6.4 BIOMARKERS IN RISK STRATIFICATION

Biomarkers associated with myocyte stress (troponin, natriuretic peptides, sST2, matrix metalloproteinases), activated neurohumoral cascades (natriuretic peptides, sST2, copeptin, adrenomedullin), reflecting organ dysfunction (creatinine, cystatin C, NGAL, liver transaminases) have been associated with poor outcomes in AHF and CS, and can be useful in risk stratification (Figure 3) (135, 147, 170-172). In addition, markers reflecting inflammatory state or iron deficiency (137) are prognosticators of poor outcome. Finally, a multimarker approach, as reflecting different cascades of the derangements associated with AHF, may provide additional prognostic information to single-biomarker measurements (17).

2.6.4.1 Natriuretic peptides and ST2

The roles of BNP and NT-proBNP are well established both for diagnostic and prognostic purposes in both chronic heart failure and AHF (19, 173-175). Use of natriuretic peptides in assessment of patients with suspected AHF has proven both cost-effective and beneficial to outcomes (176, 177). In addition to a single measurement, variation in BNP or NT-proBNP levels during hospitalization is strongly associated with outcome; failure to reduce their levels following treatment of AHF is associated with both increased rehospitalizations and mortality (178). In CS, high levels of NT-proBNP predicted short-term death in a composite patient population of cardiogenic and septic shock (174) and in a small population of patients with CS (179), and higher levels of BNP in ACS-related CS (180).

sST2 also has shown very strong prognostic value in AHF (181, 182). In comparison to other biomarkers including natriuretic peptides, sST2 has provided the best reclassification for one-year mortality in AHF, beyond clinical variables (17). Higher levels of sST2 in AHF are associated with more severe left ventricular remodelling, lower LVEF, worse diastolic compliance, and higher pulmonary artery pressures (183). Similar to natriuretic peptides, dynamic changes in sST2 levels during hospitalization and in response to therapies add prognostic value to a single measurement (181, 184). Moreover, sST2 levels may predict specific benefit from disease-modifying heart failure therapies (185, 186). In CS, levels of sST2 have been significantly higher than in those with STEMI and no CS, but that study failed to show any prognostic value of sST2 in CS, possibly due to a small number of patients (187).

Since information provided by sST2 is fundamentally different from that provided by natriuretic peptides, the two biomarkers together provide additive prognostic information (12). The Pro-Brain Natriuretic Peptide Investigation of Dyspnea in the Emergency Department (PRIDE) study showed in 593 patients with suspected AHF that the combination of results of sST2 and of NT-proBNP provided multiplicative prognostic value as compared to either of the two biomarkers alone (188). Similar results emerged from 1239 STEMI patients: when both sST2 and NT-proBNP were added to a model containing traditional clinical predictors, risk stratification for both heart failure and mortality were significantly improved (189).

2.6.4.2 Adrenomedullin

The prognostic value of adrenomedullin in AHF or suspected AHF has been strong in several studies (190-192), especially for short-term mortality. In the setting of AMI, high adrenomedullin levels are associated with impaired left ventricular function and death (193, 194). The adrenomedullin pathway has shown prognostic value in CS as well. In a study of 42 patients with ACS-related CS, higher concentrations of MR-proADM, a precursor protein of adrenomedullin, at 24 hours after onset of CS were associated with higher 1-year mortality. In another small study of 41 patients with refractory CS with ECMO support, the levels of proadrenomedullin were steadily elevated but did not differ in respect to weaning success (79). In addition to its

prognostic value for mortality, high levels of adrenomedllin have reflected hemodynamic derangements and instability. In patients with AMI, levels of adrenomedullin have correlated positively with capillary wedge pressure (195), and in patients with septic shock higher plasma adrenomedullin levels have been associated with lower arterial pressure and increased need of vasopressor therapy (18).

3 AIMS

The main aims of this thesis were to assess the prognostic value of QRS abnormalities on the electrocardiogram in patients with AHF and CS, and in CS to explore novel biomarkers for risk stratification. More precisely, the objectives were as follows:

1) To evaluate in patients with AHF the prevalence, associated clinical parameters, and impact on mortality of VCBs

2) To evaluate in patients with ACS-related CS the prevalence, temporal evolution, associated clinical parameters, and impact on mortality of VCBs

3) To evaluate in patients with ACS-related CS the kinetics and prognostic value of sST2 and NT-proBNP

4) To evaluate in patients with CS the kinetics, prognostic value, and association with haemodynamic measures of bio-ADM and lactate

4 METHODS

4.1 STUDY COHORTS

4.1.1 ACUTE HEART FAILURE STUDY (STUDY I)

The analyses of Study I were performed in a cohort of 982 AHF patients (derivation cohort), with the main findings validated in an independent validation cohort of 1511 AHF patients. The derivation cohort was combined from two independent prospectively collected populations of AHF patients. The Finnish Acute Heart Failure Study (FINN-AKVA) was a prospective, national multicentre study, enrolling 620 consecutive patients with AHF in 2004 in Finland (196). Admission ECG was available for 595 (96%) patients. The B-type Natriuretic Peptide for Acute Shortness of Breath EvaLuation V (BASEL V) study recruited patients presenting to Swiss emergency departments with a chief complaint of shortness of breath in 2006-2007 (197). For the present analysis, only the 387 patients with an adjudicated diagnosis of AHF were included, in all of whom the admission ECG was available. The final AHF diagnosis in both cohorts was confirmed by local investigators based on all clinical, laboratory, and imaging information. Data on echocardiography were available for 622 (63%) patients. The mean follow-up was 3.9 years (95% CI 3.7–4.0 years); median follow-up was 5 years.

Data for the validation cohort originated from University Hospital Brno, a centre participating in the Czech Acute Heart Failure Database (AHEAD) registry (198) with available data of baseline ECG on 1511 patients. Patient data were prospectively collected between 2006 and 2009. AHF diagnosis was based on ESC guidelines of heart failure from 2005 (199). Data on echocardiography were available for 1421 (94%) patients. The mean follow-up was 5.9 years (95% CI 5.8–6.1 years, range 0.0–8.0 years).

The primary end-point in both cohorts was all-cause mortality. The study protocols were approved by local Ethics Committees in each study centre, and conducted in accordance with the Declaration of Helsinki. Written consent was obtained from the patients or next of kin.

4.1.2 CARDSHOCK STUDY (STUDIES II, III, IV)

The CardShock study was a prospective European multicentre cohort study of CS coordinated from Helsinki University Hospital. A total of 219 patients with CS were recruited from nine centres in eight countries between October 2010 and December 2012. The study centres were in Helsinki, Barcelona, Copenhagen, Brno, Athens, Warsaw, Porto, Rome, and Brescia. Diagnosis of CS was based on contemporary clinical criteria: SBP <90 mmHg for 30 minutes despite fluid administration or need for vasoactive therapy to maintain SBP, and one or more signs of organ hypoperfusion (cool extremities, confusion or altered mental status, oliguria <0.5 ml/kg/h for the previous 6 hours, or blood lactate >2 mmol/l), and cardiac origin of the state of hypoperfusion. Exclusion criteria were age below 18, CS caused by persistent arrhythmia, and CS after cardiac or non-cardiac surgery.

Enrolment in the study was required to be within the first 6 hours of the detection of shock. The aetiology of CS was determined by local investigators. ACS aetiology was defined as shock caused by myocardial infarction. Electrocardiography and echocardiography were performed per protocol at study entry and on day three. Routine laboratory samples were taken and analysed locally in the participating centre. Serial plasma sampling was performed at eight time-points, and aliquots frozen at -80°C stored for centralized laboratory analyses. The study plasma samples were available for 178 patients from the eight centres participating in serial sampling. Patients were treated according to local practise, with treatment and procedures registered. Primary endpoints were all-cause in-hospital, 90-day, and one-year mortalities. Vital status during follow-up was determined through direct contact with the patient or next of kin, or through population- and hospital registers. The cause of death was determined by the local investigators based on clinical findings with or without autopsy findings. The study was approved by local ethics committees and conducted in accordance with the Declaration of Helsinki.

4.1.3 ELECTROCARDIOGRAPHY IN CS (STUDY II)

For the ECG analyses in CS, the patients with ACS aetiology of CS from the CardShock study with baseline ECG available were included. Additional ECG and clinical data came from 45 patients with CS caused by ACS from the University

Hospital of Brno, Czech Republic. Patients with only paced QRS complexes or those with idioventricular rhythm were excluded from both cohorts. Patients from the University hospital of Brno were recruited between 2005 and 2012. Criteria of CS were the same as for the CardShock cohort, but the Czech cohort included only patients with ACS as the aetiology of shock (200). Echocardiography was performed at baseline in all patients. Serial NT-proBNP samples were locally analysed. Written informed consent forms were obtained from the patients either before their participation in the study, or after regaining consciousness. For patients who failed to regain consciousness, anonymous data were utilized with the consent of a relative. The study protocol was approved by the local ethics committee of the University Hospital of Brno, and it was conducted in accordance with the Declaration of Helsinki.

4.2 ELECTROCARDIOGRAPHIC ANALYSES

4.2.1 ECG ANALYSES IN STUDY I

Baseline ECG was analysed in all participating patients. The ECGs in each of the AHF study cohorts were analysed by one to three researchers (medical doctors) specially trained for and assigned to the task. Rhythm and bundle branch blocks were manually analysed. QRS duration was analysed with the aid of an automatized computer program; in cases with a discrepancy in data, the priority was in manual assessment. RBBB and LBBB were identified by standard international criteria, (90). Intraventricular conduction delay (IVCD) was defined as QRS duration ≥110 ms without fulfilling the criteria of either bundle branch block (201).

4.2.2 ECG ANALYSES IN STUDY II

ECGs at baseline and on day 3 underwent analysis for the study on ventricular conduction abnormalities in CS. In cases with multiple ECG recordings at baseline, the closest ECG to the detection of shock with intrinsic (not paced) ventricular complexes was the preference. Complete LBBB and RBBB were identified by

standard criteria (90). LAHB was defined as QRS axis between -45 and -90 degrees; qR/R in leads I and aVL, rS in lead II, III and aVF, and QRS <120 ms if without concomitant RBBB. LPHB was defined as QRS axis >90 degrees, qR in lead III and rS complex in lead I; and as QRS duration <120 ms, if without concomitant RBBB. IVCD was defined as QRS duration ≥110 ms not fulfilling the criteria of either complete bundle branch block or hemiblock. Group comparisons were performed and pairwise comparisons were assessed using as a reference group those with no VCB. Temporal evolution of conduction pattern (appearance, resolution, or change of block) from baseline to day 3 was assessed and group comparisons performed, with those who had no block at baseline and on day 3 (=never block) considered as the reference group. Patients who died before day 3 or in whom the day-3 ECG was unavailable were excluded from analyses of the temporal evolution of blocks. A retrospective search of the patients' previous ECG was performed to investigate the pre-existence of the block. The search was restricted to patients with a VCB in baseline the ECG from the three largest study centres (Helsinki, Brno, Barcelona). A previous ECG was available in 42% (30 of 72) of these patients.

4.3 BIOMARKER SAMPLING (STUDIES III, IV)

Study plasma samples (EDTA and heparin plasma) in the CardShock study were taken at eight time-points: at baseline (0 hours), at 12 hours, 24 hours, 36 hours, 48 hours, 72 hours, 96 hours, and on the last day of cardiac / intensive care unit stay between days 5 to 10 (labelled 5-10 days). Aliquots of plasma were immediately frozen and stored at −80◦C. Blood lactate was locally analysed from arterial blood samples. NT-proBNP, high-sensitivity troponin T (hs-TnT), creatinine, C-reactive protein, and liver enzymes were centrally analysed from the frozen plasma samples in ISLAB, Kuopio, Finland. NT-proBNP and hs-TnT analyses were performed on a Cobas 6000 analyser with Elecsys Roche Diagnostics electrochemiluminescent sandwich immunoassays. Estimated glomerular filtration rate (eGFR) was calculated from creatinine values by use of the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation. sST2 was measured from EDTA plasma at INSERM UMR-S 942 (Paris, France) utilizing a quantitative sandwich monoclonal

enzyme-linked immunosorbent assay (Presage sST2 Assay; Critical Diagnostics, San Diego, CA, USA). The Bio-ADM measurement was performed with a one-step sandwich-coated tube chemiluminescence immunoassay in the laboratories of Sphingotec GmbH, Hennigsdorf, Germany; this is a novel immunoassay capable of reliable ultrasensitive measurement of bio-ADM peptide from small sample volume (50 uL of plasma) (202).

4.4 STATISTICAL ANALYSES

Characteristics of the study populations were assessed, and patients were categorized as considered appropriate for each study. Well-established statistical methods were used in all analyses, (Studies I-IV). Results are in numbers and percentages (%), as means with standard deviation (SD), or as medians with interquartile range (IQR) for variables not normally distributed. Dichotomous variables were compared with chi-square analysis, and continuous variables with Student's t-test or the Mann-Whitney U, or Wilcoxon rank-sum test, as appropriate. Multigroup comparisons were performed with one-way ANOVA or Kruskal-Wallis tests by Dunnett's method or with Bonferroni corrections. Correlations were assessed with Spearman's correlation coefficients.

4.4.1 BIOMARKER ANALYSES

For biomarker analyses in Studies III-IV, receiver operating characteristic (ROC) curves were generated with area under the ROC curve (AUC) testing to assess prognostic performance of the biomarkers for mortality, as well as to define optimal cut-off values in terms of sensitivity and specificity for categorizations of biomarkers. The cut-off values for sST2 and NT-proBNP in Study III were rounded to the closest figures. Sensitivity and specificity of the chosen cut-off values were reported.

For analyses of the associations of biomarker levels and haemodynamic variables in Study IV, the median value of each biomarker or each haemodynamic parameter during the study period (i.e. 0-96 hours or 48-96 hours) for each patient was used. Dichotomization of lactate levels was based on 1.63 mmol/L: the median

value of each patient's median lactate level during the first 96 h. Dichotomization of bio-ADM levels was based on 55.7 mg/ml, the optimal cut-off with highest sensitivity and specificity for 90-day mortality when measured at 48 h, and similar to the median values of bio-ADM during the first 96 hours (range of medians at 0–96 hours, 54.5–59.9 pg/ml).

4.4.2 MORTALITY ANALYSES

Mortality analyses were performed with Kaplan-Meier curves with Log-Rank testing and with Cox Proportional Hazard Ratios (HRs) with 95% confidence intervals (95% CI). Biomarkers were entered either as continuous values or as categorical variables after categorization by their median value or by a predefined cut-off value according to ROC curve analyses. Logarithmic transformation of biomarker levels was performed if necessary. Logistic regression with predicted probabilities of death were calculated and entered into AUC analyses to assess the prognostic value of combinations of continuous variables (i.e. biomarkers) in Studies III and IV. Incremental discrimination improvement allowed assessment of addition of prognostic value of sST2 and NT-proBNP to clinical variables in Study III. The time-dependent Cox model served to assess the independence of clinical variables of the predictive value of serial measurement of lactate and bio-ADM, and Wald statistics assessed the prognostic value of each biomarker and their combination at each time-point in Study IV. In Study I, the patients were censored at the time of last contact to the study centre in the time-dependent mortality analyses. Three patients in the CardShock study cohort were lost to follow-up; in the mortality analyses their cases were censored at the time of hospital discharge.

The multivariable models were built with variables a priori of clinical interest or that were associated with increased mortality in each sub-study. In Study I, the multivariable model in the derivation group included age, gender, history of hypertension, coronary artery disease, previous myocardial infarction, or chronic obstructive pulmonary disease, as well as smoking and renal function at baseline. A separate analysis including NT-proBNP results (available for 64% of patients) was performed. Multivariable analysis of the validation cohort was built with the same variables but replacing NT-proBNP (available only in few patients) with LVEF. In

Study II, two separate multivariable models served to evaluate the independent association of ventricular conduction abnormalities with mortality. Model 1 included baseline variables: age, gender, history of hyperlipidaemia, chronic obstructive pulmonary disease, previous PCI or CABG, SBP, LVEF, and renal function. Model 2 included findings in coronary angiography: three-vessel disease, infarct-related artery (left main/ left anterior descending or its main branches/ left circumflex or its main branches/ right coronary artery or its main branches). Both models were constructed applying a Cox Regression backward selection approach. In the biomarker analyses (Studies III-IV) the previously published CardShock risk score (203) was used as a continuous variable in the multivariable models. The score consists of seven baseline variables (Table 2) that were associated with increased in-hospital death in the CardShock cohort. In patients with ACS-related CS, peak value of hs-TnT was an independent predictor of mortality, and it was used in the multivariable model together with CardShock risk score in Study III. The tests were two-sided with a statistical significance level of 0.05. Statistical analyses were performed with SPSS, Stata, and R-program.

Variable	CardShock risk score
Age >75 years	1
Confusion at presentation	1
Previous MI or GABG	1
ACS etiology	1
LVEF <40%	1
Blood lactate	
<2 mmol/L	0
2-4 mmol/L	1
>4 mmol/L	2
eGFR	
>60 ml/min/1.73m2	0
30-60 ml/min/1.73m2	1
<30 ml/min/1.73m2	2
Maximum points	9

Table 2. CardShock risk score. ACS = acute coronary syndrome, CABG = coronary artery bypass grafting, MI = myocardial infarction, eGFR = estimated glomerular filtration rate by the Chronic Kidney Disease Epidemiology Collaboration formula, LVEF = left ventricular ejection fraction. Reproduced with permission from *Clinical picture and risk prediction of short-term mortality in cardiogenic shock* (203).

5 RESULTS

5.1 PATIENT CHARACTERISTICS

5.1.1 DERIVATION AND VALIDATION COHORTS IN STUDY I

For baseline characteristics of the derivation (n=982) and validation (n=1511) cohorts in Study I see Table 3. These patients were divided into two groups according to whether hospitalization for AHF was for new-onset heart failure (de novo AHF) or whether for a decompensation of previously diagnosed chronic heart failure (ADCHF). In the derivation cohort, 52% of the patients had de novo AHF; these patients were younger (75±11 years vs. 77±10 years, $P<0.001$) and less often had a history of coronary artery disease or atrial fibrillation, and had higher LVEF (47 ±15% vs. 43±17%, $P<0.001$) than those with ADCHF. In the validation cohort, 65% had de novo AHF, and 35% had ADCHF; validation cohort patients were younger, were more often men, and had more cardiovascular comorbidities than those in the derivation cohort. AHF resulted from ACS more often (49% vs. 24%; $P<0.001$), and CS was more common (14% vs. 2%, $P<0.001$) in the validation cohort than in the derivation cohort.

	AHF Derivation (n= 982)	AHF Validation (n=1511)	CardShock biomarkers all (Bio-ADM) (n=178)	CardShock biomarkers ACS (sST2) (n= 145)	CardShock + Brno, ACS (ECG) (n=199)
Age, years	76 ±11	70 ±12	66 ±12	68 ±12	67 ±11
Women	474 (48)	636 (42)	41 (23)	30 (21)	49 (25)
Hypertension	613 (62)	1046 (71)	110 (62)	93 (64)	119 (60)
Diabetes	304 (31)	741 (49)	53 (30)	48 (33)	66 (33)
Hyperlipidemia	NA	NA	85 (48)	75 (52)	106 (53)
Smoker	140 (14)	306 (45)	71 (40)	64 (44)	86 (43)
Previous CAD	494 (50)	986 (65)	59 (33)	46 (32)	62 (31)
Previous MI	254 (26)	439 (30)	45 (25)	35 (24)	45 (23)
Previous HF	476 (48)	533 (35)	29 (16)	12 (8)	14 (7)
COPD	177 (18)	207 (14)	14 (8)	11 (8)	12 (6)
ACS	235 (24)	741 (49)	142 (80)	145 (100)	199 (100)
Cardiogenic shock	21 (2)	214 (14)	178 (100)	145 (100)	199 (100)
Cardiac arrest	NA	NA	47 (26)	43 (30)	62 (31)
Acute AF	234 (24)	72 (5)	26 (15)	19 (13)	25 (13)
LVEF, %	45 ±16	41 ±15	33 ±14	34 ±14	35 ±14
LVEF <40%	241 (39)	667 (47)	112 (63)	87 (60)	110 (55)
eGFR, mL/min/1.73 m²	60 ±29	60 ±24	62 ±30	63 ±28	62 ±28
RBBB	74 (8)	130 (9)	18 (10)	17 (12)	28 (14)
LBBB	126 (13)	167 (11)	9 (5)	5 (3)	8 (4)
IVCD (incl. hemibl.)	165 (18)	161 (11)	47 (26)	38 (26)	47 (24)

Table 3. Characteristics of patient cohorts in Study I (AHF derivation and validation cohorts) and in Studies II-IV (cardiogenic shock). Mean ± standard deviation (SD), or n (%). AHF = acute heart failure, CAD = coronary artery disease, MI = myocardial infarction, HF = heart failure, COPD = chronic obstructive pulmonary disease, AF = atrial fibrillation, LVEF = left ventricular ejection fraction, eGFR = estimated glomerular filtration rate, RBBB = right bundle branch block, LBBB = left bundle branch block, IVCD = intraventricular conduction delay (includes also hemiblocks for Study II), NA = not available.

5.1.2 CARDSHOCK COHORT (STUDIES II, III, IV)

The total CardShock cohort comprised 219 patients with CS. ACS was the most common aetiology of CS (N=177, 81%); other aetiologies included chronic heart failure, valvular causes, Takotsubo cardiomyopathy, and myocarditis. The majority (n=148) of ACS patients presented with STEMI, and 19 had a mechanical complication of AMI. The mean age of the patients in the whole CardShock cohort was 67 years; 74% were men. Hypertension was present in 60% of the patients, but only a minority of patients had previous manifestations of coronary heart disease or heart failure. Table 3 shows the baseline characteristics of the three subcohorts of CardShock used in the analyses of this thesis.

In the CardShock cohort, patients were hypotensive (mean arterial pressure, MAP, 57±11 mmHg) with a mean heart rate of 90 (±28) BPM at baseline. Signs of hypoperfusion were prevalent: 95% had cold periphery, 68% had altered mental status, 55% had oliguria, and 71% high blood arterial lactate. Mean LVEF was 33±14%. Vasopressors and/or inotropes were administered to 94%; noradrenaline was the most common vasopressor (75%), and dobutamine the most common inotropic agent (in 49%). Urgent PCI was performed in 82% of all patients and in 89% of those with ACS-related CS. Urgent CABG was performed in 5% of patients. Half the patients (56%) were treated with an intra aortic balloon pump and 6% with another mechanical assist device or ECMO. Most patients (63%) were mechanically ventilated. One third (n=82, 37%) had pulmonary artery catheter, and additional 19% had central venous pressure monitoring.

Shock was already present at hospital admission in 24%, developed within their first 24 hours of hospitalization in 62% of patients, and developed after 24 hours of hospitalisation for 15%. The proportions were similar in those with ACS-related CS. The 30-day mortality was 37% (80 deaths) in the whole CardShock study cohort and 40% (70 deaths) for those with ACS-related CS. The 90-day mortality was 41% (43% for ACS-related CS), and one-year mortality was 43% (46% in ACS-related CS). Patients dying early (within the first 48 hours of shock) numbered 35 (16%), and 60 (27%) died later (between days 3 and 365). According to the local investigators, the earlier deaths tended to occur more often due to myocardial infarction (68% vs. 50%, *P*=0.10) than did the later deaths. Conversely, the later-occurring deaths were more often described as being due to worsening heart failure (41% vs. 20%, *P*=0.041)

or being related to infection (23% vs 0%, *P*=0.003), renal failure (15% vs. 0%, *P*=0.017), or stroke (6% vs. 0%, *P*=NS).

5.2 VENTRICULAR CONDUCTION BLOCKS IN AHF (STUDY I)

The prevalences of ventricular conduction abnormalities in AHF (derivation + validation cohort) and CS are shown in Figure 5. RBBB prevalence was similar in de novo AHF and ADCHF (8% vs. 8%, *P*=0.34), and in those with AHF caused by ACS or non-ACS aetiology (8% vs. 9%, *P*=0.37). LBBB was more prevalent in those with ADCHF than with de novo AHF (16% vs. 9%, *P*<0.001) and in those with non-ACS than ACS aetiology (14% vs. 8%, *P*<0.001), and IVCD was more common in the ADCHF than in de novo AHF (18% vs. 10%, *P*<0.001).

In the derivation cohort in Study I, the patients with RBBB (79±9 years) and LBBB (78±9 years) were older than those either with IVCD or without conduction abnormality (75±11 years in both groups, *P*=0.013). Each of the three conduction abnormalities was more common in men than in women (RBBB 10% vs. 5%; *P*=0.001, LBBB 15% vs. 10%; *P*=0.01, and IVCD 22% vs. 14%; *P*=0.003). Patients with LBBB and IVCD more often had a history of coronary artery disease and lower LVEF than did those with RBBB or without a block (LVEF 37±16% in LBBB, 41±16% in IVCD, 48±16% in RBBB, 47±16% in those without a block, *P*<0.001).

Overall mortality during the 5 years of follow-up in the derivation cohort was 62% (497 deaths); it was significantly higher in patients with ADCHF than in those with de novo AHF (76% vs. 47%, *P*<0.001). Patients with any VCB had higher mortality than those without a VCB (72% vs. 55%, *P*<0.001), and any VCB was an independent predictor of mortality (adjusted HR 1.4, 95% CI 1.1–1.8, *P*=0.004). Of the different types of VCBs, RBBB and IVCD were independent predictors of mortality in the whole patient cohort. The predictive value of RBBB applied for those with de novo AHF, while the predictive value of IVCD applied for those with ADCHF. These findings were confirmed in the validation cohort (Figure 6). The effects on mortality of RBBB in de novo AHF and of IVCD in ADCHF were pronounced in patients with impaired systolic function (LVEF<40%) in both the

derivation and validation cohorts.

In an exploratory analysis in joined cohorts (derivation + validation cohort, 2493 patients in total), the impact of RBBB on mortality mainly applied to those with ACS aetiology of AHF, ACS aetiology being more common in the de novo AHF group compared to ADCHF group (204). A trend appeared towards higher incidence of CS in patients with RBBB (14%) and ICVD (11%) than in those with LBBB (8%) or no VCB (9%, *P*=0.06).

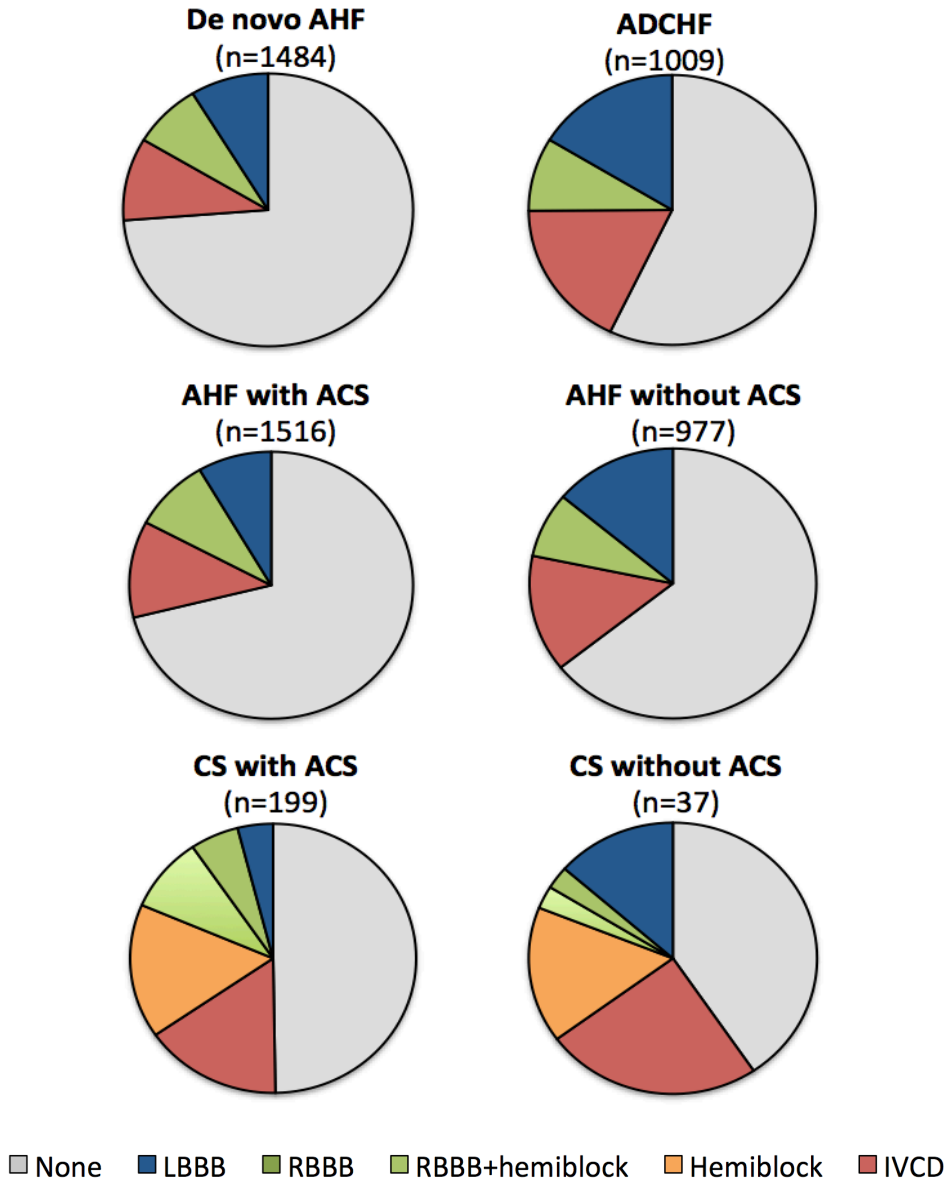

Figure 5. Proportion of ventricular conduction blocks in patients with AHF (Study I, two upper rows) and CS (Study II, lowest row). Hemiblocks were not registered in patients with AHF (Study I); they are included in IVCD group, if QRS width was ≥110 ms.

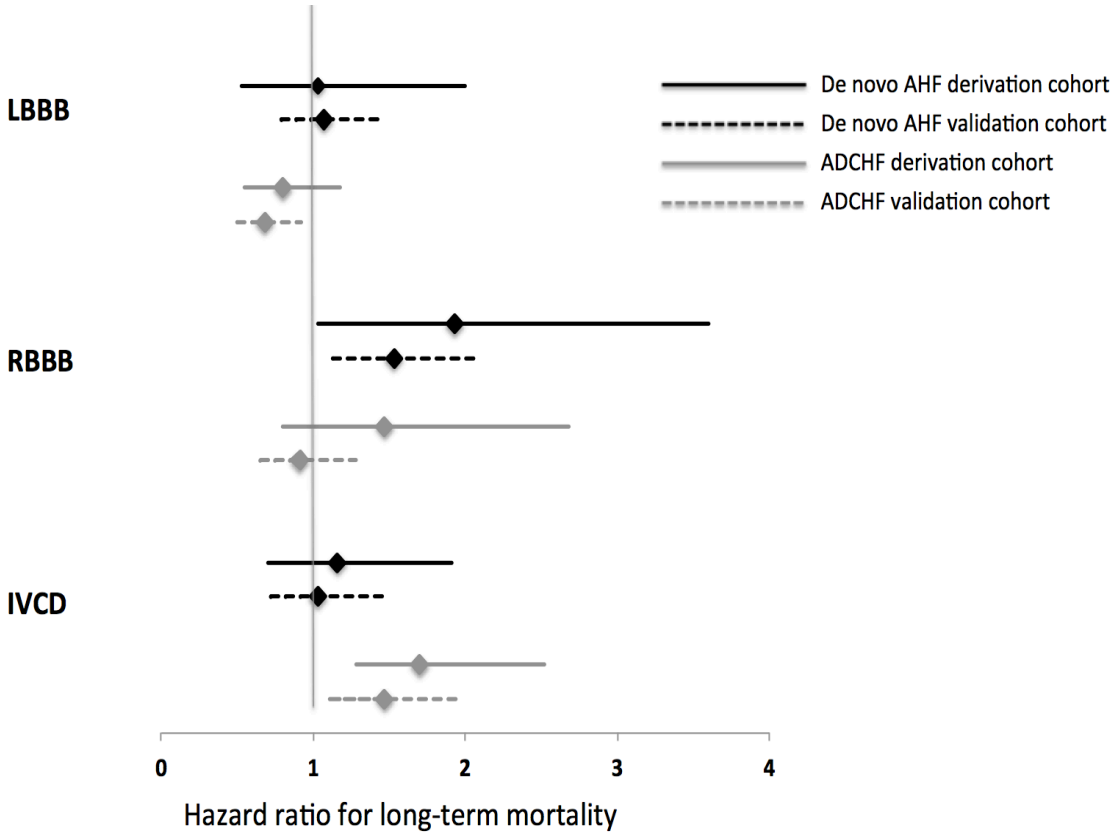

Figure 6. Hazard ratios (♦) with 95% confidential intervals (lines) for increased long-term mortality of ventricular conduction blocks in de novo AHF and in ADCHF in the derivation and validation cohorts of Study I.

5.3 VENTRICULAR CONDUCTION BLOCKS IN ACS-RELATED CS (STUDY II)

5.3.1 VENTRICULAR CONDUCTION BLOCKS IN BASELINE ECG

In the 199 patients with ACS-related CS, half (100 patients) had a VCB in their baseline ECG (Figure 5). Patients with a VCB were older (69±11 vs. 65±11 years, P=0.007), had lower LVEF (33±14% vs. 38±14%, P=0.021), and had more often the left main artery as the infarct-related artery (20% vs. 4%, P=0.001) than did patients without a VCB. Patients with a VCB in their baseline ECG had over two-fold higher 1-year mortality than did those without VCB (68% vs. 32%, P<0.001). Having any VCB in baseline ECG was a predictor of mortality independent of baseline variables

(adjusted HR 2.01, 95% CI 1.25–3.23, *P*=0.004) and of coronary angiography findings (adjusted HR 1.97, 95% CI 1.21–3.21, *P*=0.006). Each type of VCB in baseline ECG was associated with increased one-year mortality in univariate analyses, with borderline significance (*P*<0.10) in the two multivariable models, except for IVCD when adjusted for coronary angiogram findings (Figure 7).

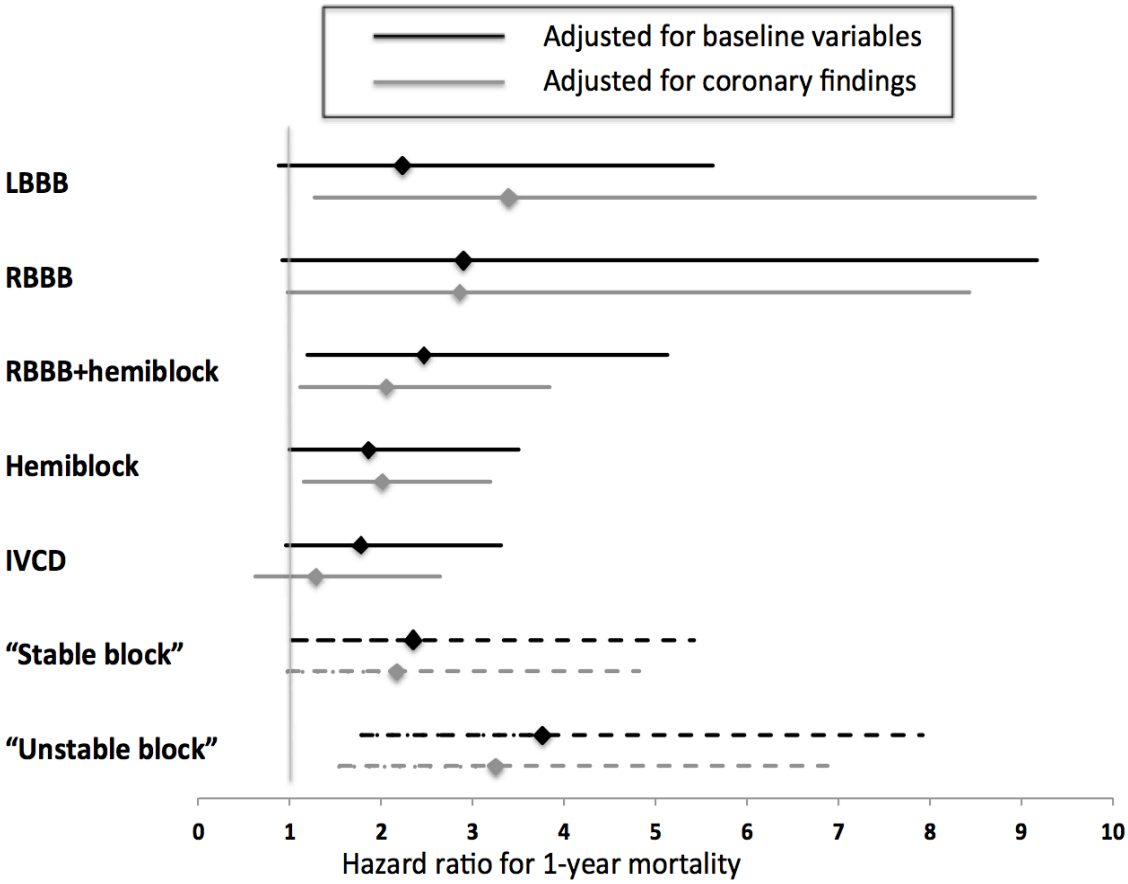

Figure 7. In patients with ACS-related CS (Study II), hazard ratios (♦) with 95% confidential intervals (lines) for increased 1-year mortality association with each type of ventricular conduction block in the baseline electrocardiogram (ECG) (top 5 rows) and of the block evolution from baseline to day 3 ECG (stable and unstable block). Modified with permission from Study II (205).

5.3.2 TEMPORAL EVOLUTION OF VENTRICULAR CONDUCTION BLOCKS

Deaths within the first 3 days of CS numbered 32 (16%). Of the 132 patients alive on the third day, 60 (45%) had no VCB either at baseline or in day-3 ECG (=never block); in 33 (25%) the same type of VCB was present in the baseline ECG and in day-3 ECG (=persistent block), while in 26 (19%), the block present at baseline had disappeared at day 3, and in 10 patients (8%) the block present in baseline ECG had changed to another type of block. In other words, of all the 100 patients having a VCB in their baseline ECG, only one third had the same block in the day-3 ECG, and in another third of patients the VCB seen in the baseline ECG had either disappeared or changed (Figure 8). The remaining 20% of patients died before day 3, or had no day-3 ECG available.

Compared to patients who had no block (at baseline nor at day 3 ECG), the patients with a persistent block were older (70±11 vs. 64±10 years, P=0.037) and had higher peak NT-proBNP levels, whereas patients with a transient block had less frequent comorbidities, higher prevalence of left main as the infarct-related artery, and particularly high peak hs-TnT and sST2 levels. Interestingly, one-year mortality was higher in those with a transient block (69%) and in those the block changed (60%), compared with those with persistent (42%) or no block (20%, P<0.001). An "unstable block" (block that disappeared or changed) was a strong independent predictor of one-year mortality (Figure 7). According to the investigator-reported cause of death three sudden cardiac deaths occurred during one year of follow-up. All of the three patients had a VCB in their baseline ECG. One patient died before day 3, the other two had the same block in the day-3 ECG as in baseline ECG.

The baseline block was present in the retrospectively searched previous ECG (available in 42% of searched patients) in 40% (4/10) of those with persistent block, in 20% (1/5) in those in which the block changed, and in none (0/10) of those with a transient block.

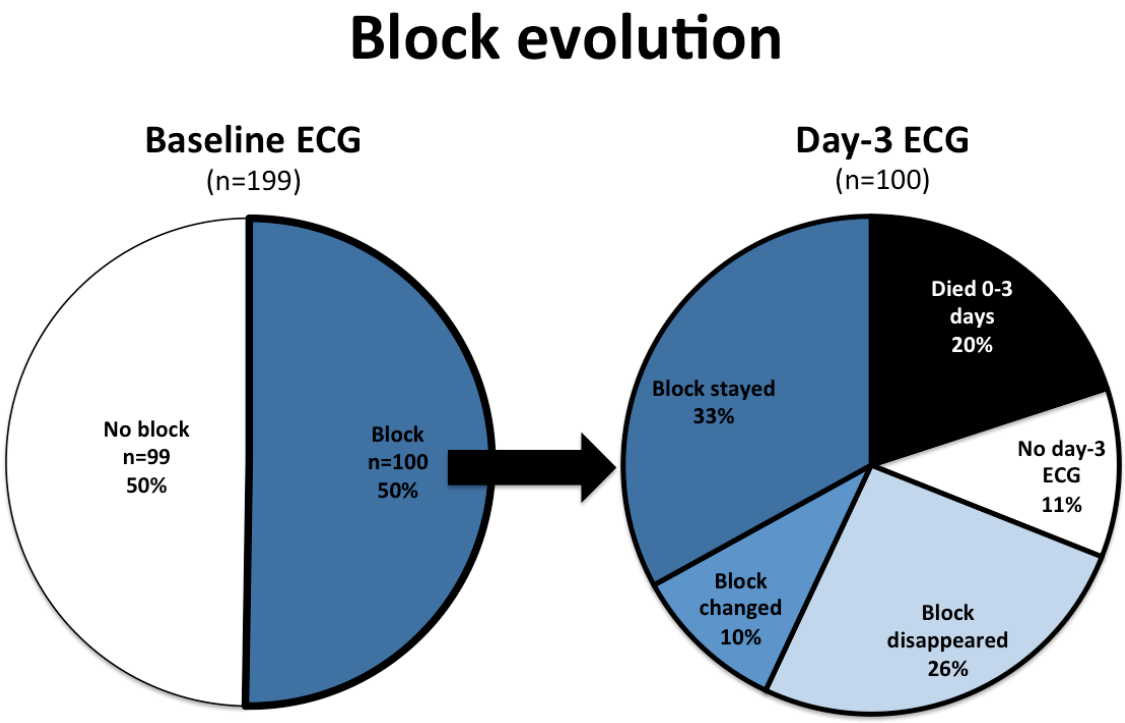

Figure 8. Evolution of ventricular conduction blocks from baseline to day-3 electrocardiogram (ECG) in cardiogenic shock caused by acute coronary syndrome (Study II).

5.4 BIOMARKERS IN CS (STUDIES III, IV)

5.4.1 SOLUBLE ST2 AND NT-PROBNP

Plasma levels of sST2 and NT-proBNP were higher in non-survivors than in survivors during the whole study period (Figure 9). Peak levels of sST2 were observable at 12 hours, and peak levels of NT-proBNP at 36 hours. Decreasing levels of both biomarkers after 12 hours were associated with better survival. sST2 levels were moderately correlated with NT-proBNP levels (ρ=–0.34; P<0.001). Both sST2 and NT-proBNP levels measured at 12 hours showed an at least moderate correlation (ρ>0.3*)* with higher lactate levels and with worse renal function at 12 hours. In addition, higher sST2 correlated (ρ>0.3) with higher hs-TnT, higher C-reactive protein, higher liver enzymes levels, higher central venous pressure, and lower

cardiac index, whereas NT-proBNP correlated with older age and higher pulmonary artery pressures, and weakly ($0.2<\rho<0.3$) with lower LVEF and with lower albumin concentrations.

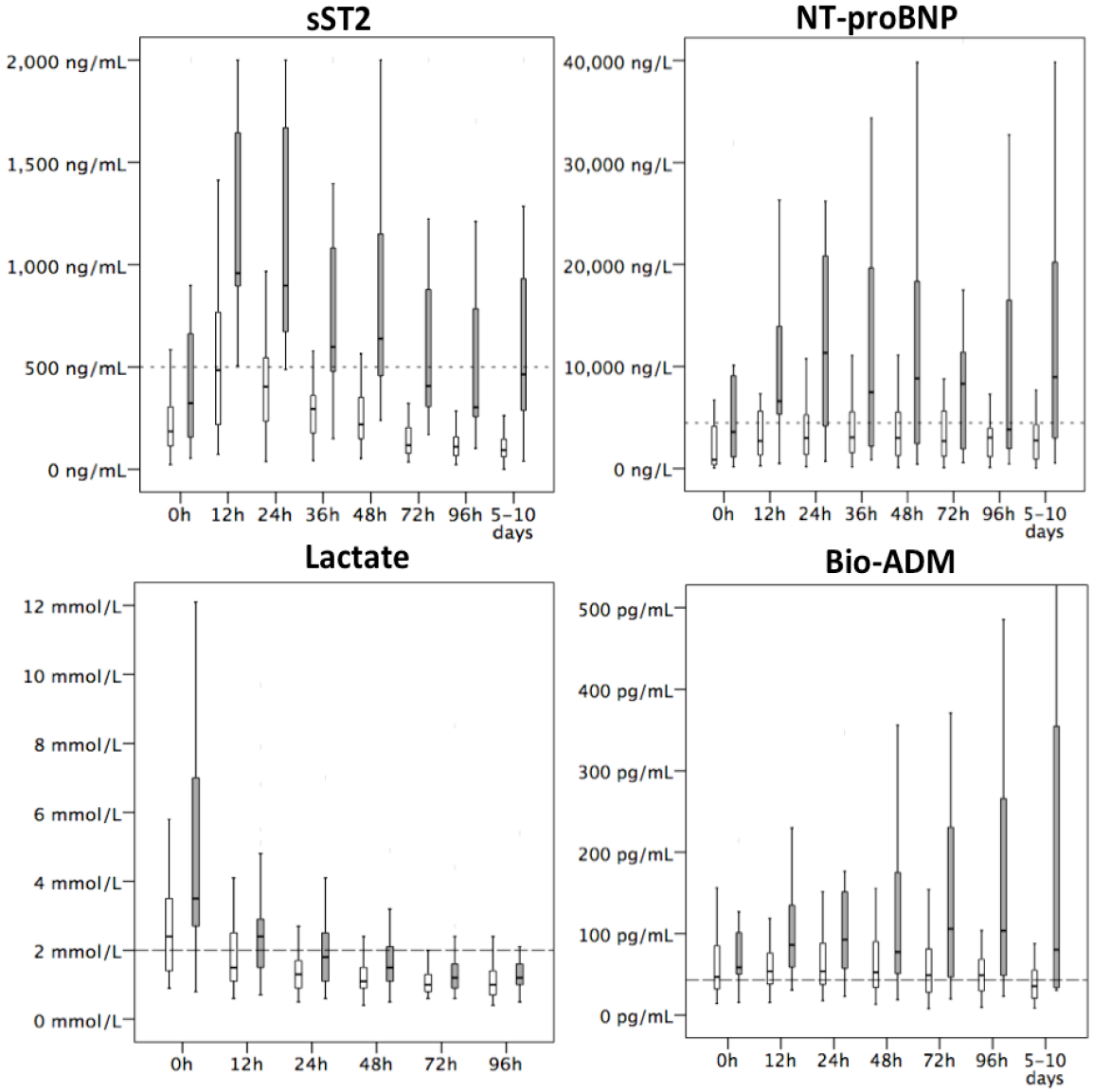

Figure 9. Kinetics of sST2, NT-proBNP, lactate, and Bio-ADM in survivors (white boxes) and non-survivors (grey boxes) during the study period. Reproduced with permission from Studies III and IV(206, 207). In the top two boxes, a dotted line depicts the chosen cut-off value for high- and low-risk groups for sST2 (500 ng/mL) and NT-proBNP (4500 ng/L), in the lower boxes, the dashed line depicts the upper normal limit of lactate (2 mmol/L) and bio-ADM (43 pg/mL).

5.4.2 PROGNOSTIC VALUE OF SOLUBLE ST2 AND NT-PROBNP

The prognostic value of sST2 in the time-course of the study period differed from that of NT-proBNP (Figure 10). Whereas the strongest association of NT-proBNP with 30-day mortality occurred at 24 hours, the prognostic value of sST2 increased in a stepwise manner over the study period. The combination of sST2 and NT-proBNP had the strongest prognostic value relative to any of the biomarkers alone. The prognostic value of hs-TnT was not superior to that of sST2 or NT-proBNP at any time point (10).

The patients were categorized into three risk categories according to optimal cut-off values for sST2 and NT-proBNP defined by ROC-curve analysis (500 ng/mL for sST2 with a sensitivity of 0.80 and specificity of 0.55; 4,500 ng/L for NT-proBNP with a sensitivity of 0.67 and specificity of 0.70). Risk categories were: both biomarkers high (above cut-off level, high-risk group), either biomarker high (one of the biomarkers above cut-off level, intermediate-risk group), or both biomarkers low (below cut-off level, low-risk group). Based on biomarker levels measured at 12 hours, 25% of patients were in the low-risk group, 46% in the intermediate risk group, and 29% in the high-risk group. This categorization, with its fixed cut-off values of 500 ng/mL for sST2 and 4,500 ng/L for NT-proBNP, showed good discrimination for 30-day mortality when the biomarkers were measured at 12 hours, or at any time-point thereafter (Figure 11).

The prognostic value provided by this categorization was independent of the CardShock risk score and of peak value of hs-TnT (adjusted HR 2.0; 95% CI, 1.2–3.5; P=0.01) when biomarkers were measured at 12 hours, and at almost all time-points thereafter. When added to the CardShock risk score, the patient categorization based on levels of sST2 and NT-proBNP at 12 hours significantly improved the risk-classification of patients (integrated discrimination improvement of 11%).

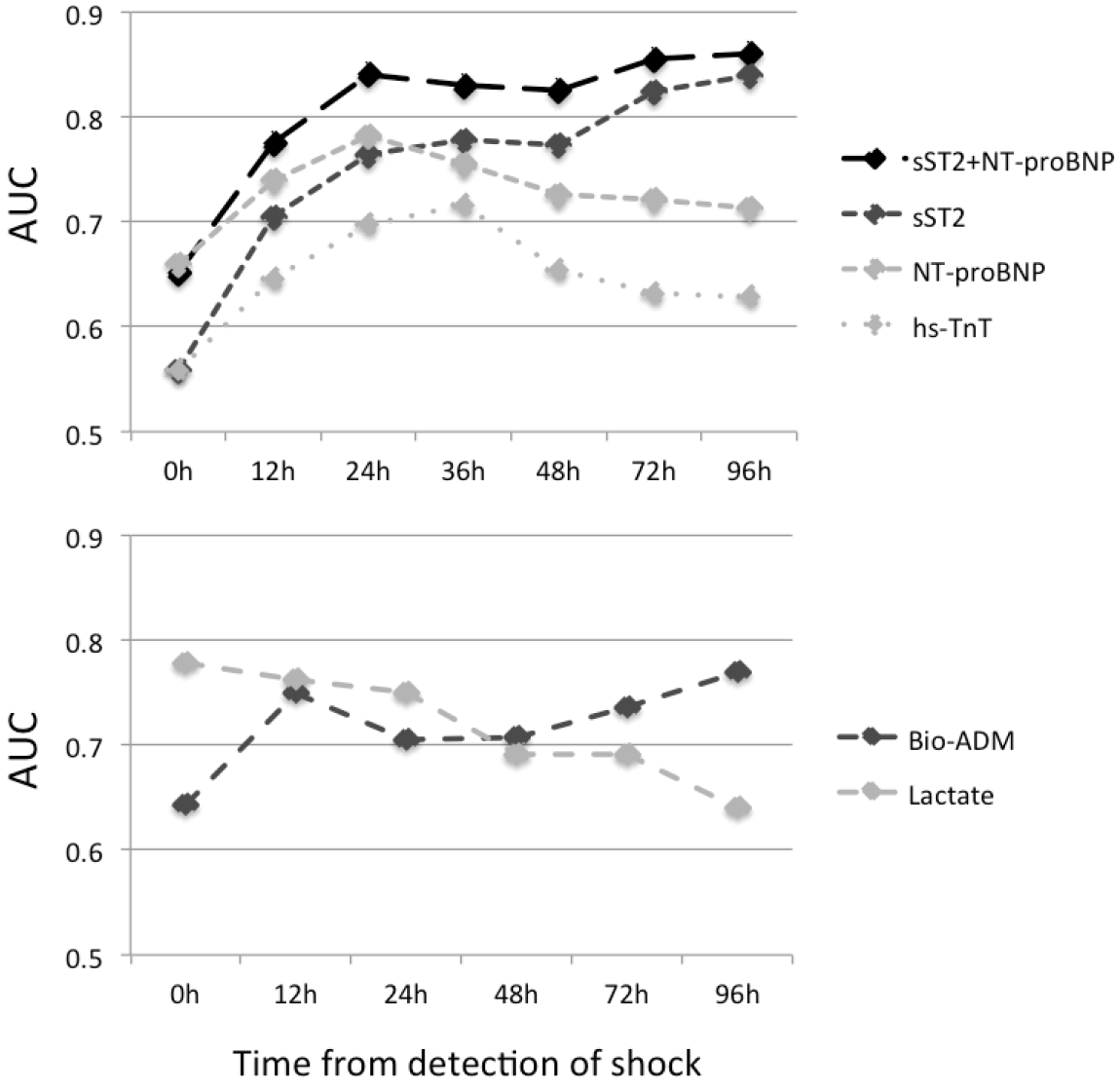

Figure 10. Time-course of the prognostic value of each of the biomarkers or their combination for increased short-term mortality in cardiogenic shock. Reproduced with permission from (206) and (207) (Studies III and IV). AUC = area under receiver operating characteristics curve, for predicting short-term mortality.

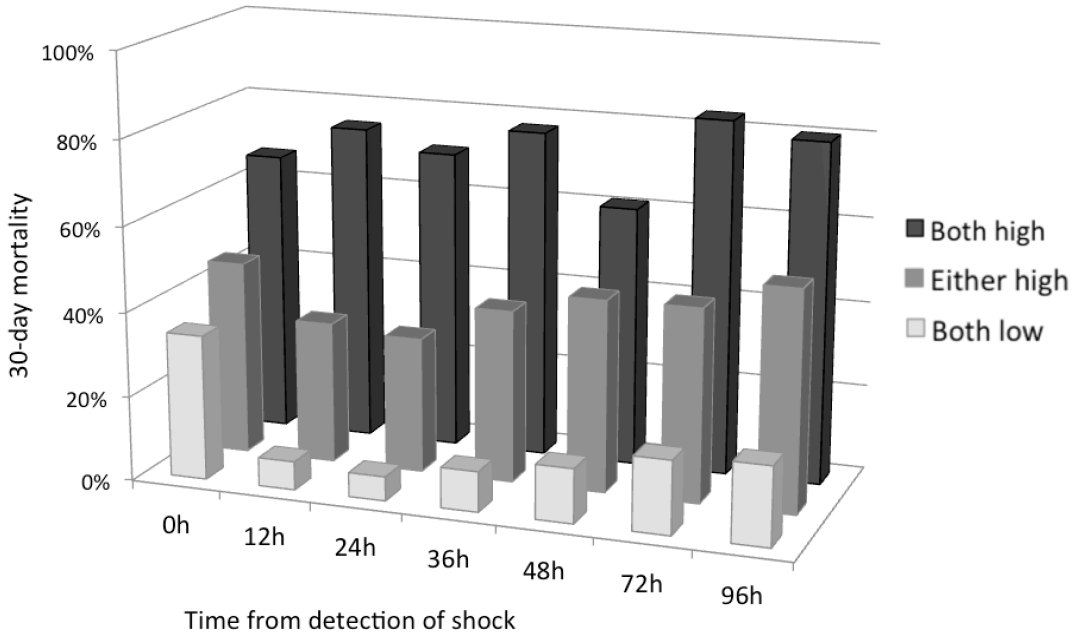

Figure 11. Thirty-day mortality based on levels of sST2 and NT-proBNP when measured 0-96 hours from the detection of cardiogenic shock. Reproduced with permission from Study III (206).

5.4.3 BIO-ADRENOMEDULLIN AND LACTATE

Levels both of plasma bio-ADM and of arterial blood lactate were higher in non-survivors than in survivors during the whole study period (Figure 9). The highest lactate levels occurred at baseline both in survivors and non-survivors (2.2 and 5.0 mmol/L, $P<0.0001$). Median levels of lactate returned to normal values within 12 hours in survivors and within 24 hours in non-survivors, so that at 24 hours the majority of all patients had normal lactate levels. In contrast, bio-ADM levels continued to be highly elevated during the whole study period in non-survivors, but remained close to the upper normal limit (43 pg/mL) in survivors. Normalization of the levels of both lactate and bio-ADM was associated with a decrease in mortality risk, while a continuing high concentration or increasing concentrations were associated with high mortality risk. Both serial bio-ADM and serial lactate measures were associated with increased 90-day mortality independently of the CardShock risk score in time-dependent Cox Proportional Hazard analysis ($P<0.001$ for both).

Reflecting the kinetics, the prognostic value of lactate and bio-ADM were divergent in their time-course. Lactate was of high prognostic value (AUC 0.78 to 0.75 for mortality) during the first 24 hours, but its prognostic value rapidly decreased thereafter, whereas the prognostic value of Bio-ADM began increasing at 48 hours. When measured at 48 hours, patients with high levels of bio-ADM (>55.7 pg/mL) had significantly higher 90-day mortality than did those with low levels (49% vs. 21%, P=0.001)

High levels of bio-ADM (>55.7 pg/mL) during the study period were associated with impaired systemic and intracardiac pressures (lower mean arterial pressure, lower cardiac index, higher central venous pressure, and higher systolic pulmonary artery pressure, whereas high lactate levels were significantly associated only with lower mean arterial pressure and lower cardiac index (Figure 12). In addition, high bio-ADM levels at 48-96 hours, were associated with persistently impaired systemic haemodynamics (lower cardiac index, higher CVP) as well as liver and kidney dysfunction. Patients with high levels of lactate during the study period had more frequently use of adrenaline than did those with low levels of lactate (30% vs. 8%, P<0.001). Patients with high levels of bio-ADM during the study period also more likely had use of adrenaline (29% vs. 5%, P<0.001) as well as use of three or more vasopressors (34% vs. 13%, P=0.001) than did those with low levels of Bio-ADM.

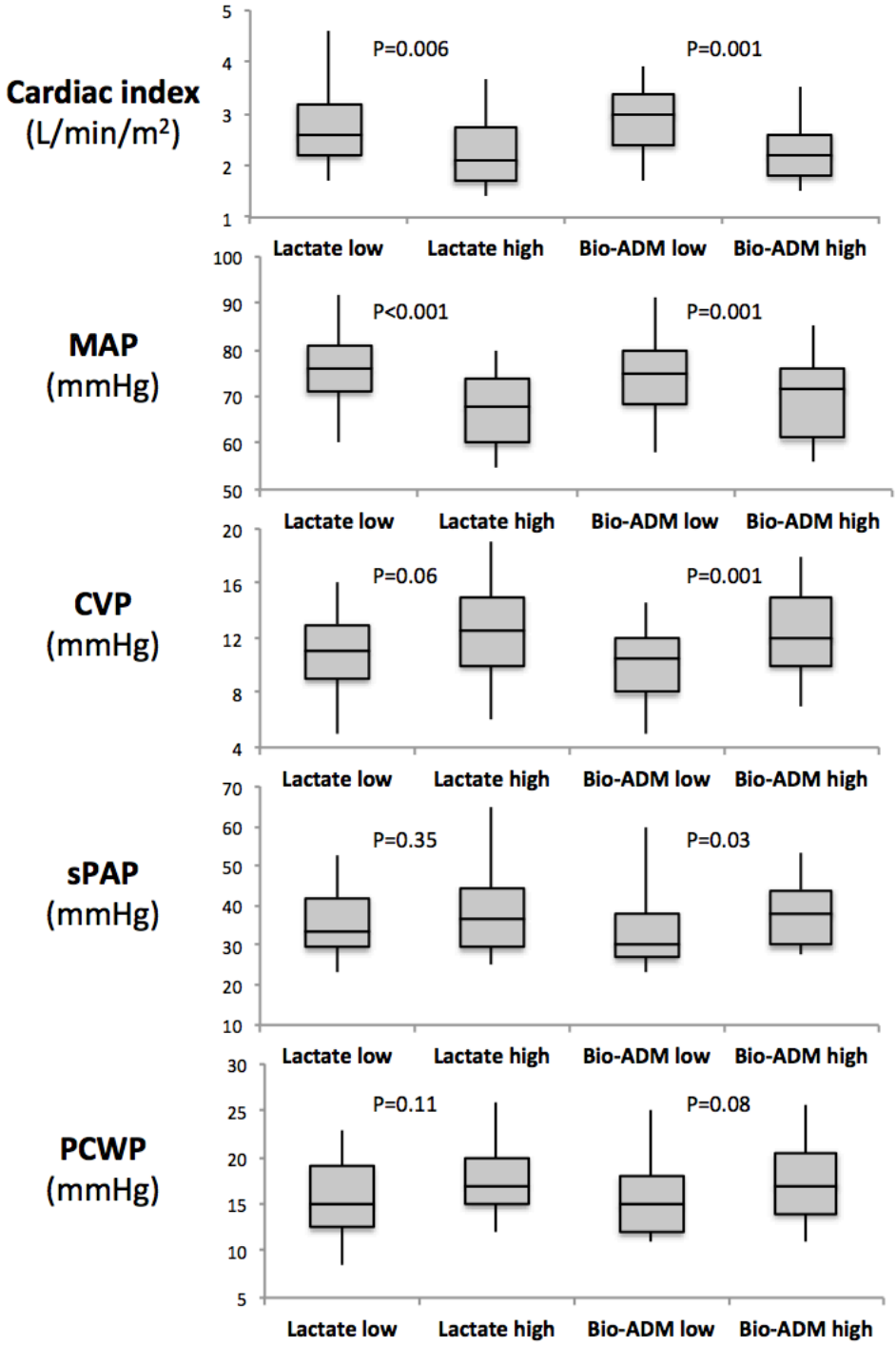

Figure 12. Haemodynamic parameters of patients with low or high lactate and bio-ADM levels during the study period (0-96 hours). MAP = mean arterial pressure, CVP = central venous pressure, sPAP = systolic pulmonary artery pressure, PCWP = pulmonary capillary wedge pressure.

5.5 MULTIMARKER TESTING IN CS

By reflecting differing pathological processes, the prognostic markers evaluated here conferred additive prognostic information. In an exploratory analysis of the whole CardShock study cohort, categorizing patients according to the number of prognostic markers presented here (a VCB at baseline, baseline lactate >2.8 mmol/L, sST2 level >500 ng/mL at 12 hours, NT-proBNP >4500 ng/L at 12 hours, and median bio-ADM level >55.7 pg/mL during the study period), one-year mortality increased in a step-wise manner with increasing number of prognostic markers (Figure 13). Distribution of patients with differing combinations of risk markers was well balanced, the largest groups being those including a VCB and elevated sST2 or lactate (5-6% of all patients in each group; data not shown).

Table 4 shows baseline characteristics and the therapeutic approach in patients identified as high-risk by each single marker. Mean age, CardShock risk score, and left ventricular function in patients of each high-risk group were similar. Patients with high baseline lactate levels or high levels of bio-ADM were aggressively treated (vasoactives, mechanical support, and mechanical ventilation commonly used). Patients with high levels of NT-proBNP relatively often had comorbidities.

	A VCB (n=81)	High Lactate (n=72)	High sST2 (n=90)	High NT-proBNP (n=74)	High bio-ADM (n=79)
Mean age, years	68 (11)	69 (11)	68 (11)	70 (11)	69 (11)
Men, %	78	76	76	70	72
Hypertension, %	67	69	67	68	66
Diabetes, %	33	38	30	38	34
Previous MI, %	26	28	24	34	27
Previous HF, %	21	20	17	26	20
ACS, %	75	81	78	72	76
STEMI, %	62	71	66	58	65
CardShock risk score, mean (SD)	5 (2)	5 (2)	5 (2)	5 (2)	5 (2)
LVEF at baseline, mean (SD)	31 (13)	31 (12)	31 (13)	31 (14)	31 (12)
LVEF on day, mean (SD)	34 (13)	33 (11)	34 (13)	33 (13)	33 (11)
3-vessel disease, %	29	36	26	40	35
Culprit LM or LAD, %	59	53	53	67	56
Final TIMI <3, %	41	35	34	33	44
Epinephrine use, %	18	22	18	13	24
Vasoactives ≥3, %	26	28	26	24	32
IABP, %	56	58	61	58	54
LVAD or ECMO, %	5	4	4	3	5
Invasive ventilation, %	70	72	72	60	68

Table 4. Characteristics of patients from the CardShock cohort with each high-risk marker. Mean (standard deviation, SD) or percentage of patients for dichotomous variables. MI = myocardial infarction, HF = heart failure, LM = left main, IABP = intra aortic balloon pump, LVAD = left ventricular assist device, ECMO = extracorporeal membrane oxygenation.

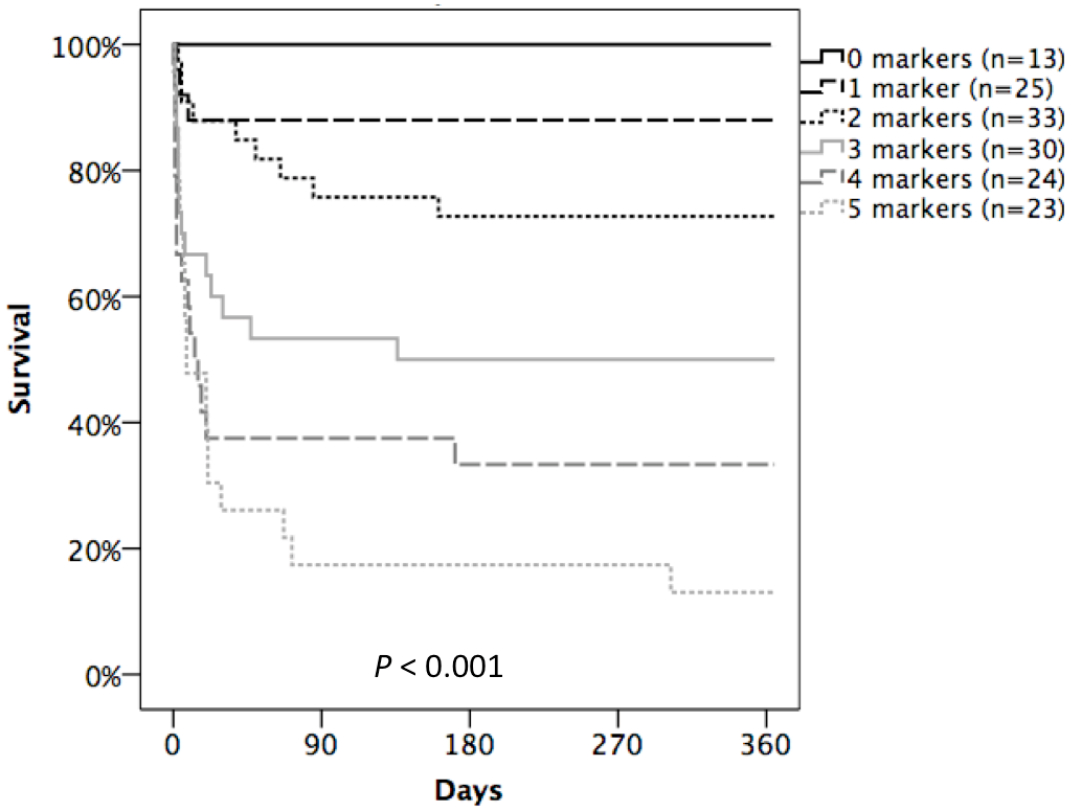

Figure 13. One-year mortality of patients from the CardShock cohort with 0 to 5 of the prognostic markers. Markers: Lactate >2.8 mml/L (median) at baseline, any conduction block at baseline, sST2>500 ng/mL at 12 hours, NT-proBNP>4500 ng/L at 12 hours, median Bio-ADM>55.7 pg/mL during the study period.

6 DISCUSSION

The results presented here highlight several novel prognostic markers in AHF and particularly in CS, the most severe form of AHF. Studies I and II showed that ventricular conduction abnormalities are predictors of poor outcome both in AHF and ACS-related CS. Studies III and IV presented two novel biomarkers, sST2 and bio-ADM that show prognostic value beyond clinical risk markers in patients with CS, and they may aid in risk stratification and patient profiling.

Accurate patient profiling and risk stratification are essential to guide therapeutic decisions of patients with AHF and CS, in efforts to improve outcomes (repeated hospitalizations, mortality) and save health care resources. Recognition of markers that associate with specific clinical scenarios, or portend poor outcome may support timely choice of specific therapies to halt maladaptive and self-nourishing cascades leading to further cardiomyocyte loss and end-organ dysfunction. Although few therapies in AHF have proven to bring survival benefit, high-risk patients may benefit from more intensive surveillance (cardiac or intensive care unit setting), and follow-up after hospitalization. Correct risk stratification of AHF patients may also improve allocation of resources, avoiding overtreatment of low-risk subjects and early/inappropriate discharge of high-risk patients.

Early risk stratification is particularly important in CS. Although CS is associated with very high early mortality, many of its pathophysiological derangements may be reversible, with those surviving the acute phase often having long-term survival with good quality of life (11). It seems that to increase survival, advanced therapies, such as circulatory support devices should be started early, prior to irreversible end-organ dysfunction (75, 208). Thus, objective and easily reproducible tools are vital to guide and support clinical decisions concerning advanced therapies in early-phase CS. Moreover, recognition of markers that identify advanced stages of shock, stages when restoring cardiac function may not reverse end-organ failure, can help more objectively to guide clinicians in the difficult process of limiting therapeutic effort.

6.1 ELECTROCARDIOGRAPHIC PREDICTORS OF MORTALITY IN AHF

Although VCBs are common in heart failure, there have been surprisingly few studies of VCBs in AHF, and their role with regard to outcome has been inconsistent (156-158). This heterogeneity probably stems, at least in part, from the differences in the characteristics of the studied patient population and in duration of follow-up. Specifically, our analysis showed in a large multinational cohort of AHF that the impact of VCB on mortality differed considerably between patients with de novo AHF and those with ADCHF. We showed that RBBB in the baseline ECG was associated with an almost two-fold increase in long-term mortality in patients with de novo AHF but had neutral impact in ADCHF; whereas IVCD was associated with an almost 30% mortality increase in patients with ADCHF but had a neutral effect in those with de novo AHF.

Characteristics of patients with de novo AHF differ from those with ADCHF (209) with, for instance, impairment of left ventricular function raising mortality rates only in ADCHF and not in de novo AHF (210). Nevertheless, in our study, the impact on mortality of RBBB in de novo AHF was pronounced in those with poor left ventricular function (LVEF < 40%). Furthermore, the effect of RBBB mainly applied to those with ACS aetiology. In chronic heart failure, RBBB has been associated with increased pulmonary artery pressure (211) and right ventricle dysfunction (155). Right ventricular failure is recognized as an independent prognostic marker in both chronic heart failure (212) and in AHF (213). RBBB in manifest left ventricular failure may, therefore, serve as a marker of more severely impaired left ventricular function, or biventricular failure through a left-right ventricular coupling mechanism, with constantly high pulmonary pressures that negatively impact long-term prognosis. Following our publication, an association of RBBB with increased mortality in AHF patients was also reported in an Asian cohort (214). Study I also showed that LBBB and IVCD were significantly more prevalent in patients with ADCHF than in those with de novo AHF. Our findings of IVCD as an independent predictor of mortality in ADCHF – predominantly in those with severely impaired left ventricular function – are in line with the well-established fact that QRS prolongation associates with increased mortality in chronic heart failure with reduced LVEF (164).

6.2 ELECTROCARDIOGRAPHIC PREDICTORS OF MORTALITY IN CS

In Study II, as many as half the patients with ACS-related CS presented with a VCB, in line with the CS literature (70, 159), but was considerably higher than in AHF or in populations with AMI (215). Our prevalence of hemiblocks and IVCDs was particularly high, which is a novel finding in CS. Most of the RBBBs coexisted with a hemiblock; an isolated RBBB or LBBB was rather uncommon. The relation of bundle branch blocks, particularly of RBBB, to increased mortality in CS has been recognized (159, 160). Study II confirmed that finding and extended it to apply to all types of VCBs. Study II showed that patients presenting with any type of VCB had an over two-fold one-year mortality compared to the mortality of those without a VCB. Patients with a VCB were older, more frequently had left main disease, and had poorer left ventricular function than did those without a VCB. However, the predictive value of a VCB was independent of baseline variables, of angiographic findings, and of revascularization success.

In patients surviving until day 3, one-third of the VCBs seen at baseline had converted to normal conduction, and an additional 15% had evolved into another morphology. In addition to direct ischaemic injury, ventricular wall stress may cause intraventricular conduction defects by overstretching the conduction fibres or by ischaemia at microvascular level (87, 88). Both these conditions occur in CS, which may explain the high prevalence of the transient VCBs. Interestingly, mortality was highest in patients with an “unstable” block. Data are scarce on block evolution and its effect on survival in CS, but in revascularized AMI patients, persistent conduction blocks have been associated with higher mortality than transient blocks have (69, 161, 169). However, the excess mortality associated with persistent blocks seemed to influence only the very early in-hospital mortality. In our study, block evolution was only recorded after 3 days from baseline, thus allowing more time for block reversal, and those that died before day 3 were excluded from the analyses; this may explain, at least in part, the discrepancy with studies in patients with AMI (69, 161, 169). Furthermore, the independent association of VCBs with disease severity and poor outcome in AMI mainly applied to new-onset blocks (98, 215). Since blocks of recent onset are more likely to revert to normal conduction than do pre-existing blocks (168,

216), the transient VCBs in our cohort probably were of new onset, thus reflecting the severity of acute-phase myocardial damage. This assumption is supported by particularly high peak troponin and sST2 levels in those patients with a transient block who were also relative young with rather few comorbidities. Furthermore, none of the transient blocks were present in the few previous ECGs that were available.

Since concomitant QRS complex alterations indicate more severe ischaemia and faster progression of irreversible myocardial necrosis than do lone ST deviations (93, 94), the negative effect on survival of VCBs, even if transient, may be explained by more severe and extensive ischaemia. In addition to infarct localization, poor collateral circulation and lack of preconditioning probably affect the degree of damage to the myocardium and to the conduction system, despite active and timely revascularization of the infarct-related artery. The ischaemic scars create regions of slowed ventricular conduction and provide a substrate for re-entrant post-infarction arrhythmias (85, 92, 217). Patients with heart failure in general are at high risk for sudden death due to ventricular arrhythmias; after myocardial infarction, remodelling of the left ventricle is related to cardiac electrical instability, which predicts sudden death (56, 218, 219). In Study II, patients with a VCB, and particularly those with an unstable VCB, had high levels of sST2, which is also associated with adverse remodelling and scar-tissue formation (220, 221). The findings of Study II in ACS-related CS thus suggest that VCBs, stable or unstable, may prove to be markers of extensive myocardial injury and adverse remodelling that both lead to scar tissue formation and poor prognosis.

6.3 BIOMARKER-BASED RISK ASSESSMENT IN CS

We showed that high levels of sST2, NT-proBNP, bio-ADM, and lactate are all associated with increased mortality in CS. Each of these biomarkers was associated with different clinical manifestations, reflecting differing pathological processes and differing risk profiles. High levels of sST2 correlated with large infarctions and inflammatory markers, NT-proBNP was associated with congestion, lactate reflected hypoperfusion, and high bio-ADM levels were associated with persisting haemodynamic instability and high filling pressures. All of these factors:

hypoperfusion, congestion, and inflammation, are major contributors to the perpetuation of cardiac and end-organ dysfunction in CS (36), providing a rationale for their synergistic association with poor outcome.

6.3.1 BIOCHEMICAL PATHWAYS OF CARDIAC STRESS - SOLUBLE ST2 AND NT-PROBNP

Study III showed that high levels of both sST2 and NT-proBNP were predictive of mortality, and the predictive value of each was additive to that of the other. The kinetics of sST2 was similar to that of troponin, rising sharply after the onset of shock with a peak value at 12 hours and then decreasing, whereas the peak value of NT-proBNP occurred later, at 36 hours. Starting at 12 hours, the combined measurement of sST2 and NT-proBNP had very strong prognostic value for short-term mortality. Based on the levels of these two biomarkers, patients could be stratified into three risk categories with markedly distinct outcomes. Furthermore, a lack of a decrease in concentration of both sST2 and NT-proBNP during the study period was associated with poor prognosis, in line with findings in AHF and chronic heart failure (182, 188). The predictive value of sST2 has complemented the predictive value provided by natriuretic peptides in studies with AHF (188) and AMI (189). After myocardial infarction, even after successful revascularization, the degree of cardiac structural remodelling is a major determinant of later outcome (222, 223). Myocardial infarction triggers an inflammatory response in the infarcted area, leading to collagen formation and deposition that result in scarring of the ischaemic zone (222). sST2 levels seem to reflect the degree of structural remodelling mediated by active processes of inflammation, fibrosis, and cardiomyocyte cell death occurring over the weeks and months after myocardial infarction (220, 221). Natriuretic peptides are another marker of remodelling after myocardial infarction and a surrogate of ventricular wall stress; they are powerful predictors of later left ventricular dilation (224). In Study III on ACS-related CS, high sST2 levels were associated with inflammatory markers, high troponin, and markers of end-organ dysfunction (impaired renal function and high liver enzymes), whereas high NT-proBNP levels were associated with markers of congestion and volume overload (higher pulmonary pressure and lower serum albumin concentration), as well as with lower LVEF. These

findings together support the concept that, in patients with ACS-related CS, sST2 and NT-proBNP reflect distinct pathways of cardiac stress and of end-organ dysfunction, explaining the strong and additive prognostic value of these biomarkers.

6.3.2 HAEMODYNAMIC ALTERATIONS AND BIOMARKES

The prognostic value provided by lactate in CS (225), when measured during the first 24 hours, was confirmed in Study IV. At 24 hours, however, most patients had a normal lactate level irrespective of later outcome, and the prognostic value of lactate decreased significantly thereafter. In contrast, levels of bio-ADM remained elevated in non-survivors during the whole study period, and bio-ADM was of increasing prognostic value starting at 48 hours after onset of shock. Patients with high levels of bio-ADM at 48 hours had over two-fold higher mortality compared to those with lower levels; higher levels also reflected haemodynamic instability, high filling pressures, and need for aggressive vasoactive medication in line with experimental studies (128) and findings in patients with septic shock (18, 226). Adrenomedullin is secreted mainly by vascular cells in response to cytokines and activated neurohumoral cascades. Although adrenomedullin production is primarily an adaptive mechanism in heart failure, when excessively produced in refractory cardiogenic or septic shock, with its vasodilatatory and negative inotropic effects, adrenomedullin may contribute to maintenance of the vasoplegic state (54). Indeed, its depiction as a double edged sword in septic shock may reflect its role in CS as well. In a conclusion, results of Study IV suggest that bio-ADM serves as both a prognostic and a haemodynamic marker in CS, with a temporal and hemodynamic profile differing from that of lactate.

6.4 CLINICAL IMPLICATIONS

The prognostic markers presented in this thesis have several clinical implications. Firstly, ventricular conduction disturbances, in general, have already received increasing attention in AHF and ACS since the publication of Study I, as bundle branch blocks (both LBBB and RBBB) were upgraded as an indication for urgent revascularization in patients presenting with ACS, equivalent to STEMI, in the latest ESC guidelines for myocardial infarction in 2017 (50). Since all patients with CS are treated with emergency revascularization, the information provided by baseline blocks in CS may have few implications for revascularisation decisions. However, the fact that block reversal was prevalent and was associated with the highest risk of death may call for specific attention to conduction disturbances on the ECG. Evaluation of repeated ECG recordings and comparison to findings on ECG at admission is necessary, in particular when the patient's previous ECG is not available for the attending clinician, as is often the case in tertiary care centres where CS patients are treated. Patients with reversible ventricular conduction disturbances should be candidates for closer monitoring; we advocate evaluating those patients in greater detail before discharge.

Secondly, the novel biomarkers presented here may provide objective tools useful in addition to clinical assessment in risk stratification of patients with CS; and moreover, in tailoring a patient-specific therapeutic approach. To restore haemodynamics impaired due to both cardiac dysfunction and a vasodepressive state in CS, fluid resuscitation, vasoactive medication and mechanical circulatory support are used. Current vasoactive medications (vasopressors and inotropes) have, however, detrimental side-effects in particular with prolonged use (74, 81), and little guidance is available for the choice or timing of therapies. Current CS guidelines and consensus papers advise use of vasopressors and inotropes in their lowest therapeutic dose for the shortest possible time (19, 43, 59). In cases refractory to medical stabilization, short-term mechanical circulatory support is increasingly the choice, although their definitive benefit has not been confirmed (76). Such advanced therapies should be considered when initial treatment fails to stabilize haemodynamics, before irreversible end-organ dysfunction occurs (59). Due to lack of objective measures of disease severity, the decision to escalate therapy, in clinical practice, remains challenging. In the early stages of shock, recognition of VCBs or high levels of sST2 and NT-

proBNP may help to identify patients at a particularly high mortality risk who may benefit from an early aggressive therapeutic approach, such as mechanical circulatory support. Further, evaluation of bio-ADM levels during intensive care may help to identify patients developing systemic inflammatory responses leading to a vasoplegic state that may require multiple vasopressor therapy or may be refractory to medical stabilization (54). Thus, measurement of bio-ADM levels may aid in guiding the therapeutic approach in patients with sustained CS after the early phase of management, either for escalation of therapy to prevent development of irreversible end-organ injury, or for supporting the difficult process of limiting therapeutic effort and the transition to palliative care.

6.5 FUTURE DIRECTIONS

Further research is essential for validation in other cohorts of AHF and CS of the prognostic markers presented here, and to further test whether these markers in risk stratification is associated with improved therapy allocation and survival.

In addition to the prognostic yield of the biomarkers presented here, the recognized biomarker pathways in the pathogenesis of AHF and CS may come to serve as therapeutic targets in future. Interestingly, patients with transient blocks had the highest levels of sST2, a marker of fibrosis, which in turn is known to be associated with higher mortality, particularly from arrhythmic causes in AMI patients. More research should focus on patients with dynamic conduction abnormalities, discovering whether those patients are at higher risk of experiencing sudden arrhythmic death, even if left ventricular function improves in follow-up. These observations may, in future, have an impact on the evaluation of candidates for antiarrhythmic therapies such as implantable or wearable ICDs, of which criteria are currently under review; new tools are needed for more accurate prediction of arrhythmic events to attain the potential benefit of those devices (227, 228).

As sST2 appears as a marker of adverse remodelling and a predictor of myocardial fibrosis, elevated levels of sST2, particularly if sustained, may reveal a therapeutic window for treatment directed against myocardial fibrosis. As a marker of the vasodilatative state, the levels of bio-ADM may help in guiding therapy with

vasoactive agents. Currently, human studies on patients with septic shock involve infusion of new humanized antiadrenomedullin antibody Adrecizumab, which may counteract the negative effects on haemodynamic instability of the disproportionately up-regulated adrenomedullin axis (Clinical Trials NCT03085758). Whether this proves safe and beneficial, it is plausible that patients with refractory CS could benefit from a similar approach.

Finally, more objective risk stratification may also improve patient profiling for design of trials of advanced therapies, both novel medications and mechanical circulatory support devices, with regards to improving response rate and achieving novel therapies that show evidence of survival benefit.

7 CONCLUSIONS

This thesis identified markers associated with poor outcome in AHF and CS. These markers may aid in guiding patient management in clinical practice. Assessment of ventricular conduction abnormalities on the ECG is routinely available in patients presenting with AHF or CS. RBBB and IVCD were associated with increased mortality in patients with AHF; RBBB particularly in those with de-novo AHF, and IVCD in those with ADCHF. In patients with ACS-related CS, ventricular conduction abnormalities were surprisingly common, and each was associated with poor outcome. CS patients with a transient block had the highest mortality; those patients also had the highest levels of troponin and of sST2, a marker of remodelling and fibrosis.

Our biomarker studies evaluated novel biomarkers in the setting of CS. Earlier observations on the additive prognostic value of sST2 to NT-proBNP in AHF and AMI were now, to our knowledge, demonstrated for the first time, in ACS-related CS. These two biomarkers could stratify patients into three risk categories with markedly different 30-day outcomes when measured at 12 hours after shock onset, or later. Furthermore, the prognostic value of sST2 and NT-proBNP was additive to that provided by troponin and by clinical variables. Bio-ADM had independent prognostic value in CS, with a time profile differing from that of lactate. Although in routine use in clinical practice, the prognostic value of lactate decreased significantly after the first 24 hours, and the association of bio-ADM with impaired haemodymics outperformed that of lactate. These findings suggest that measurement of these novel biomarkers, sST2 and bio-ADM, could be added to CS evaluation in clinical practice to support clinical decision-making regarding the therapeutic approach. Whether risk estimation based on ventricular conduction abnormalities, sST2, NT-proBNP, and bio-ADM levels helps to optimize therapies and improve outcomes requires further investigation.

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