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CARDIOGENIC SHOCK

FOCUS ON VENTILATORY STRATEGIES, THE ELDERLY, AND BIOMARKER-BASED RISK STRATIFICATION

Mari Hongisto

ACADEMIC DISSERTATION

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To my family

ABSTRACT

Cardiogenic shock (CS) is the most severe form of acute heart failure (HF) characterized by hypotension and systemic hypoperfusion caused by cardiac dysfunction. Prolonged hypotension provokes neurohumoral compensatory mechanisms and systemic inflammatory responses, leading to organ injury followed by multiorgan failure and poor prognosis. CS may be caused by various etiological factors, acute coronary syndromes (ACS) being the most common cause. In addition to prompt recognition of CS, the cause of shock should be treated urgently, as by means of immediate revascularization in the case of ACS-related CS. Although aggressive therapy options, such as mechanical circulatory devices and ventilatory support, may be used, this approach is demanding on the patient, carries risk for complications, and requires additional healthcare resources. Despite advanced therapy options, prognosis in CS is still very poor with a short-term mortality rate up to 40%. Appropriate risk assessment in the early stage of shock is crucial to identify patients most likely to benefit from intensive and costly treatment.

The aim of this thesis was to assess the treatment of respiratory failure in CS, focusing on the use of different ventilatory strategies and their impact on outcome; to evaluate the contemporary clinical picture, prognosis, and risk assessment of elderly (≥ 75 years) CS patients; and to investigate prognostic properties of two novel biomarkers in the early phase of CS. The study population consisted of the multinational, observational, prospective CardShock study, which included 219 patients with both ACS and non-ACS etiologies.

Study I evaluated the use of different ventilatory strategies in CS. Although most patients (63%) were treated with invasive mechanical ventilation (IMV), a fair number were successfully treated with non-invasive ventilation (NIV) (12%). The intensity of respiratory support required was dependent on the severity of shock; those treated with IMV suffered from more severe shock and had higher 90-day mortality compared with those treated with NIV (49% vs. 27%). However, after balancing the IMV and NIV groups with shock severity and clinical characteristics, the choice of ventilatory strategy itself did not influence the outcome.

Study II assessed the key features of elderly (≥ 75 years) CS patients. The elderly constituted a quarter of the population. Despite similar etiology and treatment of shock, they had a higher in-hospital mortality rate compared with younger patients (46% vs. 33%). However, those elderly patients who survived to hospital discharge had a prognosis comparable to that of the younger. The two contemporary risk prediction scores, the CardShock risk score and the IABP-SHOCK II risk score, proved to be useful in the early risk stratification in the elderly patients as well. Furthermore, by

incorporating the novel biomarkers into the scores, the risk prediction ability of the scores improved markedly.

Study III evaluated concentrations of a novel biomarker, growth differentiation factor 15 (GDF-15), in CS. GDF-15 is a stress-responsive cytokine that is expressed under acute and chronic stressful conditions and it has shown prognostic potential in various diseases. In this study GDF-15 levels were already very high at the beginning of CS and associated with markers of hypoperfusion (high lactate, low pH) and various acute organ dysfunctions (heart, renal, liver) indicating severe circulatory failure. High and increasing levels of GDF-15 were associated with a worse outcome, while low and decreasing levels were indicative of better prognosis. Furthermore, GDF-15 improved the early risk stratification of CS beyond the clinical risk score.

Study IV investigated the levels of soluble urokinase-type plasminogen activator receptor (suPAR) in the early stage of CS. suPAR is a novel biomarker secreted in response to inflammatory stimuli and thought to reflect the level of immunoactivation. suPAR has prognostic ability in many acute and chronic diseases, including cardiovascular diseases, cancer, and sepsis. In this study, suPAR levels were clearly elevated during the first days of CS. High levels were associated with both acute and chronic organ dysfunctions. suPAR had independent prognostic potential in CS and improved the risk stratification, especially in the patients with intermediate risk.

In conclusion, NIV can be used safely in the treatment of respiratory failure in suitable CS patients. The choice of ventilation strategy did not appear to influence outcome. Elderly patients constitute a considerable portion of CS patients with high mortality. Contemporary risk scores are also useful for early risk prediction in this age group. High levels of the novel biomarkers GDF-15 and suPAR are indicative of severe circulatory failure and end-organ injury, suggesting poor prognosis. These biomarkers may be new prognostic tools in the risk assessment of CS.

TIIVISTELMÄ

Sydänperäinen sokki on monitahoinen oireyhtymä, jossa sydämen akuutti toimintahäiriö aiheuttaa sen supistumiskyvyn merkittävän heikentymisen johtaen vaikeaan verenkiertovajaukseen, kudosten hapenpuutteeseen ja monielinvaurioon sekä lopulta hoitamattomana kuolemaan. Oireyhtymän patogeneesissä myös elimistön neurohumoraalisilla vasteilla sekä systeemisen tulehdusreaktion kehittymisellä on oma roolinsa. Mikä tahansa sydämen toimintaa heikentävä sairaus voi olla syynä sydänperäiseen sokkiin, useimmiten kyseessä on laaja sydäninfarkti. Hoidon kulmakivenä on sydämen toimintahäiriön aiheuttaneen syyn tunnistaminen ja välitön korjaaminen. Sokkiin liittyvää verenkierto- ja hengitysvajausta hoidetaan tarvittaessa mekaanisia tukilaitteita avuksi käyttäen tehohoito-olosuhteissa, mikä on kuitenkin potilaille raskasta, altistaa komplikaatioille ja vaatii runsaasti terveydenhuollon resursseja. Kehittyneistä hoitotoimenpiteistä huolimatta kuolleisuus sydänperäiseen sokkiin on edelleen korkea noin 40 %. Hoidossa oleellista on sokin tunnistaminen, raskaista hoidoista hyötyvien korkean riskin potilaiden tunnistaminen ja hoitotoimenpiteiden aloittaminen riittävän varhaisessa vaiheessa ennen peruuttamattomien pääte-elinvaurioiden syntymistä.

Tämän väitöskirjan tavoitteena oli selvittää sokkiin liittyvän hengitysvajauksen hoitoa keskittyen eri hengitystukimuotojen käyttöön ja niiden mahdolliseen ennustevaikutukseen sekä tutkia iäkkäiden (≥ 75-vuotiaiden) sokkipotilaiden taudin kliinistä kuvaa ja selvittää ajankohtaisten riskipisteytysmallien käyttökelpoisuutta tämän ikäryhmän ennusteen arvioimisessa. Lisäksi tavoitteena oli arvioida kahden uuden biomarkkerin käyttökelpoisuutta sydänperäisen sokin ennustearviossa. Väitöskirjan tutkimusaineisto on peräisin 219 potilasta käsittävästä monikansallisesta, havainnoivasta CardShock –tutkimuksesta.

Ensimmäisessä osatyössä tutkittiin sydänperäiseen sokkiin sairastuneiden potilaiden hengitysvajauksen hoitoa ja eri hengitystukimuotojen käyttöä keskittyen non-invasiiviseen (NIV) hengitystukihoitoon. Tutkimuksessa havaittiin, että sydänperäiseen sokkiin sairastuneiden hengitystuen tarve riippui sokin vaikeusasteesta. Suurin osa potilaista (63%) hoidettiin invasiivisella mekaanisella ventilaatiolla (IMV) keinoilmatien kera, mutta merkittävä osa (12%) pärjäsi pelkästään non-invasiivisella ventilaatiolla (NIV). IMV:lla hoidetut potilaat kärsivät vaikeammasta sokin taudinkuvasta ja heillä oli korkeampi 90 päivän kuolleisuus NIV:llä hoidettuihin verrattuna (49% vs. 27%). Hengitystukistrategian valinnalla ei kuitenkaan ollut vaikutusta ennusteeseen.

Toisessa osatyössä selvitettiin iäkkäiden (≥ 75-vuotiaiden) sydänperäiseen sokkiin sairastuneiden potilaiden kliinistä taudinkuvaa, hoitoa ja ennustearviota. Neljäsosa potilaista oli yli 75-vuotiaita. Huolimatta sokin samankaltaisesta etiologiasta ja hoidosta iäkkäiden potilaiden sairaalakuolleisuus oli selvästi nuorempia korkeampi (46% vs. 33%). Toisaalta sokista selvinneiden iäkkäiden ennuste ei eronnut nuorempien ennusteesta. Tutkimuksen mukaan sydänperäiseen sokkiin sairastuneille kehitetyt riskipisteytysmallit toimivat hyvin myös iäkkäillä ja niiden ennustearviota voidaan parantaa yhdistämällä ne biomarkkereiden kanssa.

Kolmannessa osatyössä tutkittiin biomerkkiaine GDF-15 pitoisuuksia sydänperäisen sokin alkuvaiheessa sekä niiden yhteyttä ennusteeseen. GDF-15-pitoisuuksien tiedetään nousevan elimistön erilaisissa akuuteissa sekä kroonisissa stressitilanteissa ja GDF-15 omaa ennustearvoa useissa eri sairauksissa. Tutkimuksessa havaittiin, että GDF-15–pitoisuudet olivat hyvin korkeita jo sokin ensivaiheessa. Korkeat pitoisuudet olivat yhteydessä kudosten riittämätöntä verenkiertoa kuvastaviin biomarkkereihin (korkea laktaatti ja matala pH) ja elintoimintahäiriöihin (sydän, maksa, munuaiset) sekä huonompaan ennusteeseen. Lisäksi todettiin, että nouseva GDF-15 –taso oli merkki huonosta ennusteesta, kun taas laskevat pitoisuudet kuvastivat parempaa ennustetta. Yhdistettynä kliiniseen riskipisteytysmalliin GDF-15 paransi sokkipotilaiden ennustearviota huomattavasti.

Neljännessä osatyössä määritettiin biomerkkiaine suPAR:n pitoisuuksia sydänperäisen sokin alkuvaiheessa. SuPAR on biomerkkiaine, jonka pitoisuus nousee sekä akuuttien että kroonisten tulehduksellisten tilojen yhteydessä kuvastaen elimistön immunoaktivaatiota. Sen on todettu omaavan ennustearvoa useissa eri sairauksissa, kuten syövissä, sepsiksessä sekä sydän- ja verisuonisairauksissa. Tässä tutkimuksessa suPAR-tasot olivat selvästi koholla sydänperäiseen sokkiin sairastuneilla. Korkeat pitoisuudet olivat yhteydessä eri elintoimintahäiriöihin ja suurempaan kuolemanriskiin. Tutkimuksessa todettiin, että suPAR oli itsenäinen sydänperäisen sokin ennustetekijä ja yhdistettynä kliinisen riskipisteytysmallin kanssa se paransi erityisesti keskiriskin potilaiden ennustearviota.

Yhteenvetona voidaan todeta, että sydänperäiseen sokkiin liittyvää hengitysvajausta voidaan hoitaa turvallisesti myös NIV:lla oikein valikoiduilla potilailla, eikä hengitysvajauksen hoitomuodolla ole merkitystä potilaan ennusteen kannalta. Iäkkäät muodostavat merkittävän osan sydänperäiseen sokkiin sairastuneista potilaista ja sokin ennustearvioon luodut kliiniset riskipisteytysmallit toimivat hyvin myös tässä ikäryhmässä. Tutkitut biomerkkiaineet, GDF-15 ja suPAR, kuvastavat sydänperäiseen sokkiin liittyvää vaikeaa verenkiertovajausta sekä siihen liittyviä elintoimintahäiriöitä ja voivat olla avuksi sokkipotilaiden ennustearviossa.

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Mari Hongisto

CONTENTS

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications:

I Use of noninvasive and invasive mechanical ventilation in cardiogenic shock: A prospective multicenter study. Hongisto M, Lassus J, Tarvasmaki T, Sionis A, Tolppanen H, Lindholm MG, Banaszewski M, Parissis J, Spinar J, Silva-Cardoso J, Carubelli V, Di Somma S, Masip J, Harjola VP. Int J Cardiol. 2017; 230:191-197

II Mortality risk prediction in elderly patients with cardiogenic shock: results from the CardShock study. Hongisto M, Lassus J, Tarvasmäki T, Sionis A, Sans-Rosello J, Tolppanen H, Kataja A, Jäntti T, Sabell T, Lindholm MG, Banaszewski M, Silva Cardoso J, Parissis J, Di Somma S, Carubelli V, Jurkko R, Masip J, Harjola VP; CardShock Study Investigators and the GREAT Network. ESC Heart Fail. 2021; 8(2):1398-1407

III Levels of Growth Differentiation Factor 15 and Early Mortality Risk Stratification in Cardiogenic Shock. Hongisto M*, Kataja A*, Tarvasmäki T, Holopainen A, Javanainen T, Jurkko R, Jäntti T, Kimmoun A, Levy B, Mebazaa A, Pulkki K, Sionis A, Tolppanen H, Wollert KC, Harjola VP, Lassus J; CardShock investigators. J Card Fail. 2019; 25(11):894-901

IV Soluble urokinase–type plasminogen activator receptor (suPAR) improves early risk stratification in cardiogenic shock. Hongisto M, Lassus J, Tarvasmäki T, Sans-Roselló J, Tolppanen H, Kataja A, Jäntti T, Sabell T, Banaszewski M, Silva-Cardoso J, Parissis J, Jurkko R, Spinar J, Mebazaa A, Masip J, Harjola VP; the CardShock Study Investigators and the GREAT Network. *Submitted*.

The original publications (I-III) are published with the permission of the copyright holders and are referred to in the text by their roman numerals.

*These authors contributed equally to the respective work. Publication III also appears in the dissertation of Anu Kataja, Prognostic factors in cardiogenic shock. From bench to bedside - The CardShock Study, University of Helsinki (2022).

ABBREVIATIONS

ACPE = acute cardiogenic pulmonary edema
ACS = acute coronary syndrome
AKI = acute kidney injury
ARDS = acute respiratory distress syndrome
AUC = area under the curve
BiPAP = bilevel positive airway pressure
BNP = brain natriuretic peptide
CABG = coronary artery bypass graft surgery
CI = confidence interval
CLIP score = The Cystatin C, Lactate, Interleukin-6, And N-Terminal Pro-B-Type Natriuretic Peptide score
CO = cardiac output
CO_2 = carbon dioxide
CPAP = continuous positive airway pressure
CS = cardiogenic shock
CULPRIT-SHOCK = Culprit Lesion Only PCI Versus Multivessel PCI in Cardiogenic Shock study
ECMO = extracorporeal membrane oxygenation
ESC = European Society of Cardiology
GFR = glomerular infiltration rate
GDF-15 = Growth differentiation factor 15
HF = heart failure
HFNC = high-flow nasal cannula
hs-CRP = high-sensitivity C-reactive protein
IABP = intra-aortic balloon pump
IABP-SHOCK II = Intra-Aortic Balloon Pump in Cardiogenic Shock II – study
ICU = intensive care unit
IDI = Integrated discrimination index
IL = interleukin
IQR = interquartile range
IMV = invasive mechanical ventilation
LV = left ventricular
LVEF = left ventricular ejection fraction
MCS = mechanical circulatory support
MI = myocardial infarction
MODS = multiple organ dysfunction syndrome
MV = mechanical ventilation
NIV = non-invasive ventilation
NRI = net reclassification improvement
NT-proBNP = N-terminal prohormone of brain natriuretic peptide

OR = odds ratio
PCI = percutaneous coronary angiogram
PEEP = positive end-expiratory pressure
PPV = positive pressure ventilation
ROC = receiver operating characteristic
RF = respiratory failure
RV = right ventricle
SCAI = the Society for Cardiovascular Angiography and Interventions
SD = standard deviation
SHOCK = The Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock study
SIRS = systemic inflammatory response syndrome
sST2 = Soluble suppression of tumorigenicity 2
STEMI = ST-elevation myocardial infarction
suPAR = soluble urokinase–type plasminogen activator receptor
TIMI = thrombolysis in myocardial infarction flow
uPAR = urokinase-type plasminogen activator receptor

1 INTRODUCTION

Cardiogenic shock (CS) is the most severe form of acute heart failure (HF) characterized by hypotension and systemic hypoperfusion caused by insufficient cardiac output (CO).[1] The primary insult is cardiac dysfunction most commonly caused by acute coronary syndromes (ACS) and myocardial infarction (MI). Other common etiologies are cardiomyopathies, myocarditis, valvular dysfunction, and acute exacerbation of chronic HF.[1-4] Impaired pumping function and associated insufficient CO may result in systemic hypotension, tissue hypoperfusion, and hypoxemia, and progress into multiple organ dysfunction syndrome (MODS) and eventually death.[5] CS is a complex clinical syndrome with multifaceted pathophysiology. Prolonged hypotension provokes compensatory vasoconstriction mechanisms, activation of neurohormonal cascades, and systemic inflammatory responses, all of which may be maladaptive and have further detrimental effects on the tenuous hemodynamics of shock.[5, 6] Considering the complex pathophysiology of CS, it is not surprising that the severity of the cardiac pump failure does not always correlate with the development of shock. Even very severely impaired cardiac function does not necessarily cause CS; conversely CS can develop with nearly normal left ventricular (LV) systolic function.[3, 5]

Despite improvements in the treatment of CS during recent decades, prognosis of CS remains poor with a short-term mortality up to 40%.[7-10] Prompt recognition of CS is essential, and treatment should be started before irreversible end-organ damage occurs. The cornerstone of treatment is the immediate management of the cause of shock.[11, 12] In severe circulatory failure advanced mechanical assist devices may be used to restore hemodynamics in high-risk patients; however, their use is associated with a significant risk for complications.[12-14]

The management of CS is expensive and requires healthcare resources. Nevertheless, the prognosis of survivors is favourable with a good quality of life.[5] Accurate risk stratification in the early phase of CS is essential to allocate healthcare resources and to assist in tailoring individualized treatment strategies. Traditionally, risk assessment has relied on clinical markers and it has based largely on clinical judgement, which may remain inaccurate. Clinical risk stratification scores developed specifically for prognostication of CS have emerged in recent years.

Many CS patients have markedly elevated pulmonary capillary wedge pressure due to LV dysfunction and elevated filling pressures making them prone to develop acute cardiogenic pulmonary edema (ACPE) and respiratory failure (RF), which requires ventilatory support.[15] Although the use of non-invasive ventilation (NIV) and its beneficial effects on the failing

heart is well established in acute HF, its use in CS is largely unexplored.[16-20] Hypoperfusion-related altered mental status is frequently observed and considered as a contraindication for the use of NIV. The data regarding the use of different ventilatory strategies, specifically NIV, in the treatment of RF in CS are limited.

Advanced age is associated with a higher risk for CS and mortality.[8, 21, 22] Due to aging of the population, the elderly are likely to constitute a growing proportion of CS patients.[23] Nevertheless, they are often underrepresented or even excluded from many studies.[24-27] Age-related physiological changes in the elderly diminish their physiological reserves and ability to recover from critical illness, predisposing them to treatment-related complications. On the other hand, there is remarkable individual variation among the aged in chronological and biological age, highlighting the importance of individualized risk assessment and treatment decisions. There is need for data regarding patient selection in this age group, namely identifying the elderly patients who would benefit from further intensive and costly therapy options and those for whom these life-prolonging efforts are futile and treatment should be directed towards palliative care.

Activation of neurohumoral cascades and inflammatory responses play a role in the pathogenesis of CS.[1, 5, 28] Biomarkers reflecting these pathways may be valuable in prognostication and risk stratification and may elucidate the pathophysiologic axis of CS. Growth differentiation factor 15 (GDF-15) is a stress-responsive protein that is only weakly expressed under healthy conditions but is strongly induced in response to acute and chronic stressful conditions, such as inflammation, hypoxia, oxidative stress, tissue injury, and oncogene activation.[29-32] GDF-15 levels are elevated and associated with prognosis in chronic inflammatory diseases, several cancers, and cardiovascular diseases.[31]

Soluble urokinase-type plasminogen activator receptor (suPAR) is a protein biomarker involved in many biological processes, including inflammation and immune response, coagulation, and cell signaling.[33] suPAR concentration is increased in response to inflammatory stimuli and is thought to reflect the level of immunoactivation.[33] suPAR is valuable marker in progression and prognostication in many acute and chronic diseases, such as infectious and cardiovascular diseases, cancers, and critical illness.[33-37] Additionally, elevated suPAR levels are associated with organ damage, such as development of acute kidney injury (AKI) and heart failure.[38-40]

The aim of this thesis was to assess the treatment of respiratory failure in CS, to evaluate the clinical picture and prognostication of elderly CS patients, and to investigate the prognostic role and clinical significance of two novel biomarkers, GDF-15 and suPAR, in CS by using material from the prospective, observational, multinational CardShock study.

2 REVIEW OF THE LITERATURE

2.1 Cardiogenic shock

2.1.1 Definition and classification

Cardiogenic shock (CS), the most severe form of acute heart failure (HF), is a life-threating condition characterized by inadequate tissue and end-organ perfusion due to severe cardiac dysfunction and low CO.[1] Although patients presenting with CS are critically ill, the clinical picture of shock may range from pre-shock and mild hypoperfusion to profound treatment-refractory shock. There are no generally accepted criteria for the definition of CS and thus most studies on CS have used different definitions, which make the comparison of results difficult (Table 1). The most recent suggestion for the definition of CS by the European Society of Cardiology (ESC) in the guidelines for the diagnosis and treatment of acute and chronic heart failure states CS as 'a syndrome caused by a primary cardiovascular disorder in which inadequate CO results in a life-threatening state of tissue hypoperfusion associated with impairment of tissue oxygen metabolism and hyperlactatemia which, depending on its severity, may result in multiorgan dysfunction and death'.[41] During the last decade, many studies on CS have included persistent hypotension together with clinical signs of end-organ hypoperfusion as criteria to define CS (Table 1).[2, 10, 42] There are also hemodynamic criteria for CS, which include low cardiac index (<2.2 l/min/m^2) and elevated pulmonary artery occlusion pressure (>15 mmHg) or right ventricular end-diastolic pressure (>10-15 mmHg).[5, 43] However, the importance of the clinical criteria has recently been highlighted and hemodynamic parameters are not considered mandatory in clinical practice (Table 1).[12, 44]

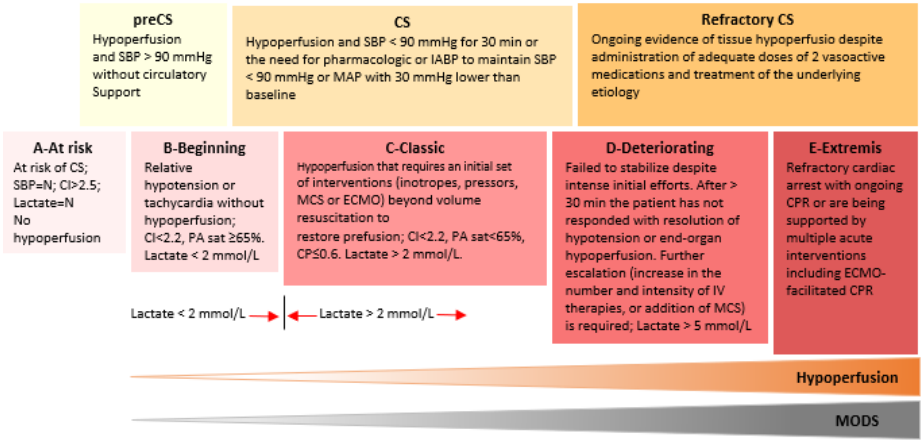
Due to a lack of uniform CS criteria, the Society for Cardiovascular Angiography and Interventions (SCAI) recently suggested a new clinical staging system for CS classification based on the expert consensus opinion.[45] The SCAI classification consists of the following five stages of CS from A to E: Stage A is 'at risk' for CS, B is 'beginning' CS, C is 'classic' CS, D is 'deteriorating' CS, and E is 'extreme' CS (Figure 1). The SCAI classification can be introduced easily at bedside by physical examination and with easily available biochemical markers to assess the signs of hypoperfusion. Further invasive hemodynamic measurements have also been implemented to the classification as well. The SCAI classification has been validated in a large unselected intensive care unit (ICU) patient cohort with good results.[46]

Table 1. Different definitions of CS used by various studies and guidelines.

Clinical study or Guidelines	Clinical criteria
SHOCK Trial (1999) [11]	• SBP < 90 mmHg for ≥ 30 min *OR* vasopressor support or IABP to maintain SBP ≥ 90 mmHg *AND* • end-organ injury (UO < 30 ml/h or cool extremities) • Hemodynamic criteria: CI ≤ 2.2 L/min/m^2 *AND* PCWP ≥ 15 mmHg
IABP-SHOCK II Trial (2012) [10] **and CULPRIT Trial (2017)** [42]	• SBP < 90 mmHg for ≥ 30 min *OR* catecholamines to maintain SBP > 90 mmHg[10]/ SBP ≥ 90 mmHg[42] *AND* • Clinical pulmonary congestion *AND* • Impaired end-organ perfusion (at least one): altered mental status, cold/clammy skin and extremities, UO < 30 mL/h, or lactate > 2.0 mmol/L
ESC Heart Failure Guidelines (2021) [41]	A syndrome caused by a primary cardiovascular disorder in which inadequate CO results in a life-threatening state of tissue hypoperfusion associated with impairment of tissue oxygen metabolism and hyperlactatemia which, depending on its severity, may result in multiorgan dysfunction and death. Diagnostic signs of hypoperfusion • clinical: cold sweated extremities, oliguria, mental confusion, dizziness, narrow pulse pressure • laboratory: metabolic acidosis, elevated serum lactate, elevated serum creatinine

CI, cardiac index; CO = cardiac output; CULPRIT = The Culprit Lesion Only PCI versus Multivessel PCI in Cardiogenic Shock Trial; ESC = European Society of Cardiology; IABP = Intra-aortic Balloon Pump; IABP-SHOCK = Intra-aortic Balloon Pump in Cardiogenic Shock Trial; PCWP = pulmonary capillary wedge pressure; SBP = systolic blood pressure; SHOCK = Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock Trial; UO = urine output

Figure 1. Clinical classifications of CS including the recent classification system by SCAI including stages A to E. Reproduced from Wiley with permission.[12]



CI, cardiac index; CP, cardiac power; CPR, cardiopulmonary resuscitation; CS, cardiogenic shock; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; IV, intravenous MAP, mean arterial pressure; MCS, mechanical assist device; MODS, multi-organ dysfunction syndrome; N, normal; PA sat, pulmonary artery saturation; SBP, systolic blood pressure

2.1.2 Etiology and epidemiology

CS can be caused by an acute ischemic or a non-ischemic cardiac event or by underlying long-standing cardiac disease. The most common cause of CS is ACS with following ventricular dysfunction, which accounts for 50-80% of the cases.[2, 3, 47] Most patients with ACS etiology present with ST-elevation myocardial infarction (STEMI), whereas acute MI-related mechanical complications, such as acute severe mitral regurgitation and ventricular septal or free wall rupture, are less frequent causes of shock (9-13%).[2, 3, 12] Other etiologies include worsening of chronic HF, acute myocarditis, valvular heart disease, cardiomyopathies (stress-induced, autoimmune, peripartal).[2, 4, 12] However, in recent studies the proportion of ACS-CS has decreased and non-ACS increased.[4, 47] As ACS is the most frequent cause of CS, most prior studies on CS have focused only on ACS-CS. [42, 43, 48-50] Contemporary data on CS with various etiologies are scarce.

CS complicates 3-13% of ACS cases depending on the definition of CS used, time of the study period, and the study population.[21, 51-54] CS can occur already in the pre-hospital phase, early during hospitalization (during the first 24 hours of hospitalization), or later (late-onset shock) during hospital stay. In most ACS-CS patients, shock is not present on hospital admission but occurs early during hospitalization.[7, 21, 55] In ACS patients, known risk factors for CS are older age, signs of HF at admission, anterior location of MI, and a history of HF, MI, coronary artery bypass grafting (CABG), or diabetes.[22, 56] STEMI doubles the risk for CS compared with non-STEMI.[21, 52, 55]

2.1.3 Pathophysiology

The pathophysiology of CS is complex (Figure 2). Despite the broad etiological spectrum of shock, the primary insult is usually severe cardiac dysfunction leading to ventricular dysfunction, inadequate CO, systemic hypotension, and end-organ hypoperfusion. This creates a vicious circle, where hypotension further reduces coronary perfusion and increases ischemia followed by an additional decrease in cardiac contractility and CO worsening end-organ hypoperfusion and dysfunction, which results in MODS and eventually in death (Figure 2).[5] Hypotension and hypoperfusion are counteracted by several compensatory mechanisms that may be maladaptive and further worsen the downward spiral of CS. Hypotension induces vasoconstriction by releasing endogenous catecholamines, which may temporarily improve cardiac contractility and peripheral blood flow but also increase myocardial oxygen consumption.[5, 6] Neurohormonal responses contribute to salt and water retention, which may improve perfusion but also worsen pulmonary edema and systemic congestion.[1, 5] Microcirculatory dysfunction in the early phase of CS may also contribute to the development of multi-organ failure and is associated with poor prognosis.[57, 58] In addition, systemic inflammatory

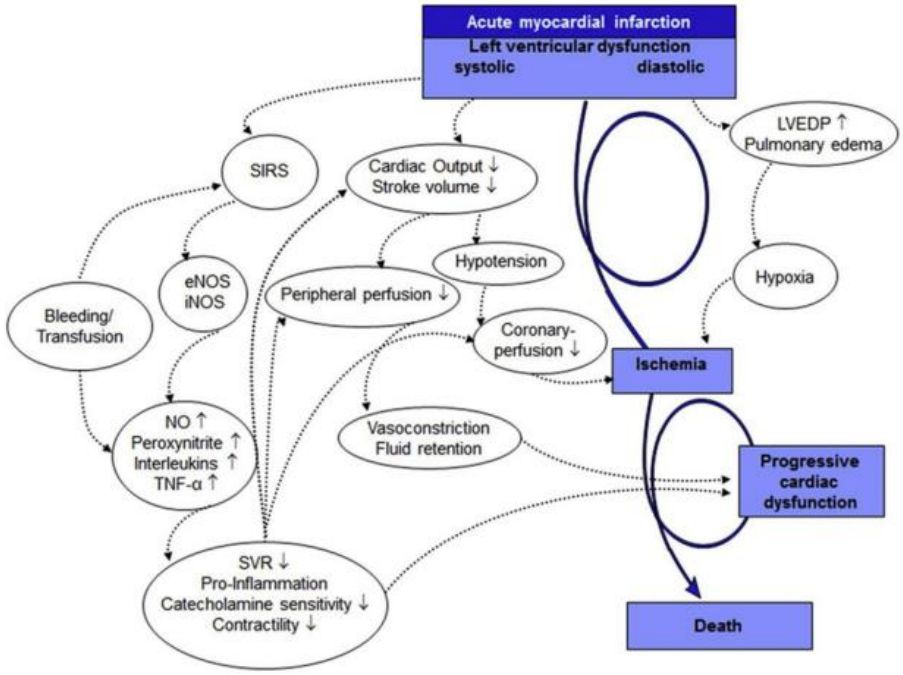
responses play a critical role in the pathophysiology of CS.[28] Prolonged hypotension triggers the activation of systemic inflammatory response syndrome (SIRS) and the related release of proinflammatory cytokines (such as interleukins and tumor necrosis factor-α).[59] This in turn induces the expression of nitric oxide synthase, leading to high levels of nitric oxide and subsequent vasodilatation of the peripheral vasculature.[60-62] Proinflammatory cytokines may also impair myocardial function and induce endothelial dysfunction, further diminishing coronary blood flow (Figure 2).[5, 63] Additionally, excess nitric oxide is a strong endogenous vasodilator and may also depress myocardial function.[63, 64] Furthermore, as a consequence of SIRS, inappropriate vasodilatation and hypotension may result in impaired perfusion of the gastrointestinal tract, enabling transmigration of bacteria leading to sepsis.[5] An extensive inflammatory response is associated with poor prognosis in CS.[65] SIRS complicates approximately 20-50% of CS cases.[28, 65] However, despite the important role of inflammatory responses in pathogenesis, attempts to modify or restrict SIRS and the consequent pathological vasodilatation with nitric oxide synthase inhibition have not been successful.[66, 67]

Interestingly, although the primary insult in the pathogenesis of CS is cardiac dysfunction, the degree of LV systolic dysfunction is not associated with severity of shock or prognosis. Severely impaired left ventricular ejection fraction (LVEF) does not necessarily cause CS, and conversely, CS can develop with nearly normal LVEF, which reflects the complex pathophysiology behind shock.[3, 5]

2.1.4 Prognosis

Despite improvements in the treatment of CS in recent decades, the mortality in CS patients is still unacceptably high, up to 40-50%.[7, 8, 12, 68-70] Although the mortality rate has declined from 80% observed in 1980[71], it has remained almost unchanged during the last 20 years.[2, 10, 21, 42, 52, 54] During these last two decades, the treatment of ACS-CS in particular has changed due to widespread use of percutaneous coronary intervention (PCI) in early revascularization. Additionally, mechanical circulatory support (MCS) devices have been introduced and increasingly used in the treatment of severe circulatory failure. Nevertheless, CS is still a leading cause of death in patients with acute MI. In general, the prognosis of patients with non-ACS-CS is better than in ACS-CS even though patients with non-ACS-CS usually have more comorbidities.[2, 4] Regardless of the high mortality related to acute phase of shock, those surviving to hospital discharge have good long-term survival and a decent quality of life.[5, 72-75]

Figure 2. The vicious downward spiral of complex pathogenesis of cardiogenic shock. Reproduced with permission from AHA Journals and Wolters Kluwer.



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; TNF-α, tumor necrosis factor-α

2.2 Management of cardiogenic shock

2.2.1 Initial assessment and general approach

Early recognition of shock, initial stabilization, and prompt evaluation for the underlying etiology are the key approaches in CS management. Electrocardiogram should be performed to detect ischemia, possible arrhythmias, and conduct disturbances. Urgent echocardiography is essential in identifying the underlying cause of shock, such as tamponade, mechanical complications of acute MI, severe left or right ventricular dysfunction, or valvular disease. All treatable causes of CS should be managed immediately. If ACS is suspected, urgent coronary angiography and revascularization should be performed, and mechanical complications of MI should be considered for immediate surgical treatment.[70, 76] Comprehensive laboratory tests and essential radiological examinations should be performed. Signs and symptoms for hypoperfusion should be carefully assessed.

All patients with CS should be transferred to a tertiary care center with full-time facilities for coronary angiography and early revascularization, immediate surgery, and a dedicated intensive or cardiac care unit with possibility for mechanical circulatory support.[12]

Patients should be monitored carefully; continuous rhythm and arterial blood pressure monitoring are recommended. Insertion of a central venous catheter is advised to assist with treatment, such as administration of vasoactive agents.[70] The use of a pulmonary artery catheter is increasingly infrequent, probably due to an unproven mortality benefit related to its use in critically ill patients in randomized controlled trials.[77-79] Nevertheless, based on expert opinion its use is recommended in selected patients with persistent hypotension and hypoperfusion.[12, 70] Instead, hemodynamic measurements are increasingly assessed by repeated echocardiography.

2.2.2 Coronary revascularization

Immediate angiography and acute revascularization are the cornerstones in the treatment of ACS-CS. The role of urgent revascularization in CS was established already two decades ago in a landmark trial of CS, 'The Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock (SHOCK)' study, which compared early revascularization and initial medical stabilization in the treatment of CS.[43, 72] The study demonstrated the benefit of early revascularization in 6-month mortality; the benefit persisted up to 6 years. Another issue is how complete the emergency revascularization should be. Current guidelines recommend culprit-lesion-only PCI instead of an immediate multivessel PCI strategy.[76] This recommendation was based on the findings in the recent randomized Culprit Lesion Only PCI Versus Multivessel PCI in Cardiogenic Shock (CULPRIT-SHOCK) study, which revealed that the culprit-lesion-only strategy was associated with better 30-day survival compared with immediate multivessel approach (mortality 43% vs. 52%, respectively).[42] In patients whose coronary anatomy in unsuitable for PCI, CABG should be considered.[44, 76, 80]

2.2.3 Hemodynamic support

Patients with CS are usually hypotensive and at least relatively hypovolemic. Fluid administration should be considered as a first-line treatment to manage hemodynamic instability if there are no signs of overt fluid overload.[81] A controlled fluid challenge should be performed and the response evaluated while avoiding excessive fluid administration, which may lead to congestion or worsen it.[82]

If hemodynamic instability persists despite initial fluid resuscitation, vasoactive medication should be administered to restore

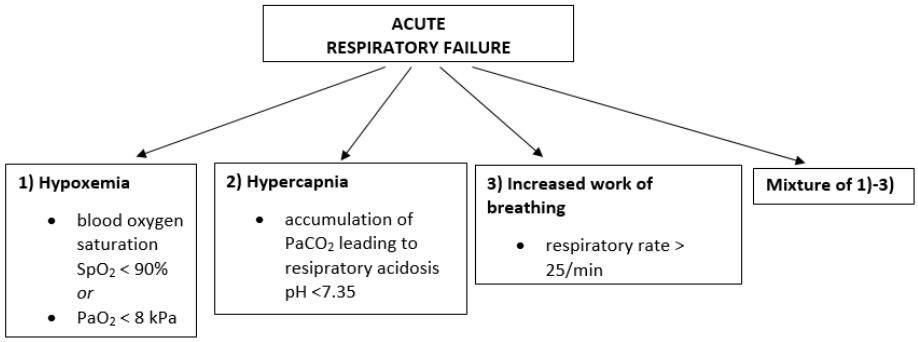
sufficient CO and tissue perfusion. Most (80-90%) CS patients require vasoactive medication.[10, 83] However, it should be noted that despite facilitating hemodynamic restoration, vasoactive medication may increase myocardial oxygen consumption and be arrhythmogenic at the same time.[84, 85] Therefore, the dose and duration of vasoactive medication should be restricted to the lowest possible level and time. Norepinephrine is the current initial vasopressor of choice in hypotension to sustain adequate perfusion pressure, with a class IIb/B recommendation in guidelines.[12, 41, 86, 87] Dobutamine is recommended as the initial inotrope of choice, with a class IIb/C recommendation.[41, 88] The routine use of other vasopressors, epinephrine and dopamine, is not recommended. According to recent studies, the administration of epinephrine is associated with a higher rate of refractory CS and increased mortality compared with norepinephrine.[89, 90] Similarly, the use of dopamine is associated with higher mortality and increased risk of arrhythmias.[91] Other inotropic agents used in the treatment of CS are levosimendan and milrinone.

In refractory CS when attempts to restore hemodynamics with fluid administration and vasoactive medication fail, temporary MCS is recommended for patients considered to have a reasonable prognosis to recover from shock or to be eligible for heart transplant or durable MCS.[12, 13, 41, 70] MCS devices are used to maintain adequate perfusion pressure and to prevent end-organ hypoperfusion. However, the use of MCS is associated with a significant risk for complications such as bleeding, limb ischemia, infections, and hemolysis. Additionally, the use of MCS is expensive and requires extensive staffing. Previously, intra-aortic balloon pump (IABP) was the most commonly used MSC in CS for decades, until the randomized Intra-Aortic Balloon Pump in Cardiogenic Shock II (IABP-SHOCK II) trial reported no survival benefit regarding its use in ACS-CS.[10] Thereafter, its use has generally declined and the ESC guidelines do not recommend the routine use of IABP in CS but conclude that it may be considered in selected patients with mechanical complications (Class IIa/C).[88] Other most frequently used temporary MCS devices include Impella and extracorporeal membrane oxygenation (ECMO).[92, 93] Despite the increasing use of MCS devices in refractory CS, thus far no trial has demonstrated a distinct survival benefit. In addition, concerns regarding optimal timing, device choice, and appropriate patient selection remain.[10, 93-96] Nevertheless, contemporary ESC guidelines provide a class IIb/C recommendation for the use of MCS in refractory CS.[41, 88] At present, there are at least five ongoing randomized controlled trials evaluating whether treatment with ECMO[97-100] or Impella[101] in addition to early revascularization and optimal medical treatment is beneficial in comparison to no MCS. Four of these studies include only CS patients with ACS etiology[97, 98, 100, 101] and one study does not make a distinction regarding CS etiology.[99] These studies will hopefully elucidate the unanswered questions regarding the use of MCS in CS.

2.3 Respiratory failure in cardiogenic shock

Respiratory failure is one of the most frequent organ injuries in CS, with a reported prevalence reaching 60-80%.[11, 102] RF is a syndrome characterized by an inability of the respiratory system to manage its gas exchange function, resulting in impaired oxygenation (hypoxemia; blood oxygen saturation SpO_2 <90% or PaO_2 <8 kPa), carbon dioxide (CO_2) elimination (hypercapnia; respiratory acidosis due to accumulation of CO_2 with pH <7.35), or both or by increased work of breathing leading to disturbance of body homeostasis (Figure 3).[103] Normal values for respiratory parameters are presented in Table 2. The severity of RF may be categorized by using the classification originally created for acute respiratory distress syndrome (ARDS), which is the most severe form of lung injury due to acute RF. ARDS is categorized according to the Berlin definition criteria into the following three stages by using P/F ratio [ratio of the partial pressure of arterial oxygen (PaO_2) to the fraction of inspired oxygen (FiO_2)]: mild (200 mmHg < P/F ≤ 300 mmHg), moderate (100 mmHg < P/F≤ 200 mmHg), and severe (P/F ≤ 100 mmHg) (Table 2).[104] CS patients with RF are usually hypoxemic, complain of dyspnoea, have an elevated respiratory rate, and may experience even very severe respiratory distress. Most CS patients with RF require some ventilatory support.[105, 106] However, along with the broad spectrum of clinical presentations in CS, the degree of RF and the intensity of ventilatory support required varies between minimal supplemental oxygen and IMV. RF itself is associated with poorer outcome in CS.[105] Additionally, RF requiring mechanical ventilation (MV) is associated with higher mortality compared with cases surviving without MV.[105, 107, 108] This has been recognized and implemented in the recent CS classification schema by the SCAI, where the need for ventilatory support in CS has been considered as a marker of shock severity.[45]

Figure 3. Definition of acute respiratory failure.[103]



PaO_2, arterial partial pressure of oxygen; $PaCO_2$, arterial partial pressure of carbon dioxide; SpO_2, blood oxygen saturation

Table 2. Categorization of ARDS severity and normal values of respiratory parameters.[103, 104]

Degree of ARDS	PaO2/FiO2, mmHg	PaO2/FiO2, kPa
Mild	200-300	27-40
Moderate	100-200	13-27
Severe	<100	<13
Normal values of respiratory parameters		
PaO_2	80-100	10-13
$PaCO_2$	35-45	4.7-6
P/F ratio	≥400	≥53
pH	7.35-7.45	
SpO_2	>95%	
Respiratory rate	12-20/min	

ARDS, acute respiratory distress syndrome; FiO_2, fraction of inspired oxygen; PaO_2, arterial partial pressure of oxygen; $PaCO_2$, arterial partial pressure of carbon dioxide; P/F ratio, ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen; SpO_2, blood oxygen saturation

2.3.1 Pathophysiology of respiratory failure in cardiogenic shock

The pathophysiology behind RF in CS is multifactorial. Left ventricular dysfunction and elevated filling pressure cause a rapid increase in pulmonary capillary hydrostatic pressure, leading to ACPE.[15, 109] When transvascular fluid filtration exceeds the lymphatic interstitial drainage capacity, excessive fluid accumulates in the alveoli and interstitium, causing a significant reduction in gas exchange and accompanying shunt effect.[15] In addition, reduced lung perfusion due to global tissue hypoperfusion diminishes blood flow into some ventilated areas in the lungs, causing an increase in pulmonary dead space and thus increasing the ventilation-perfusion mismatch.[109] A concomitant inflammatory response may change vascular membrane permeability, further worsening alveolar edema.[110, 111] In addition, respiratory compensation of metabolic acidosis due to circulatory failure and tissue hypoperfusion leads to a further increase in respiratory burden.

2.3.2 Treatment of respiratory failure in cardiogenic shock

ACPE and RF require prompt evaluation and management should be initiated immediately. Due to its progressive nature, RF may proceed to cardiorespiratory collapse in hours or even minutes if treatment is not initiated at a sufficiently early stage. In recent studies, approximately 70-80% of the CS patients with RF were treated with MV.[10, 107, 112, 113] The milder forms of RF may be treated only with conventional oxygen therapy. Nevertheless,

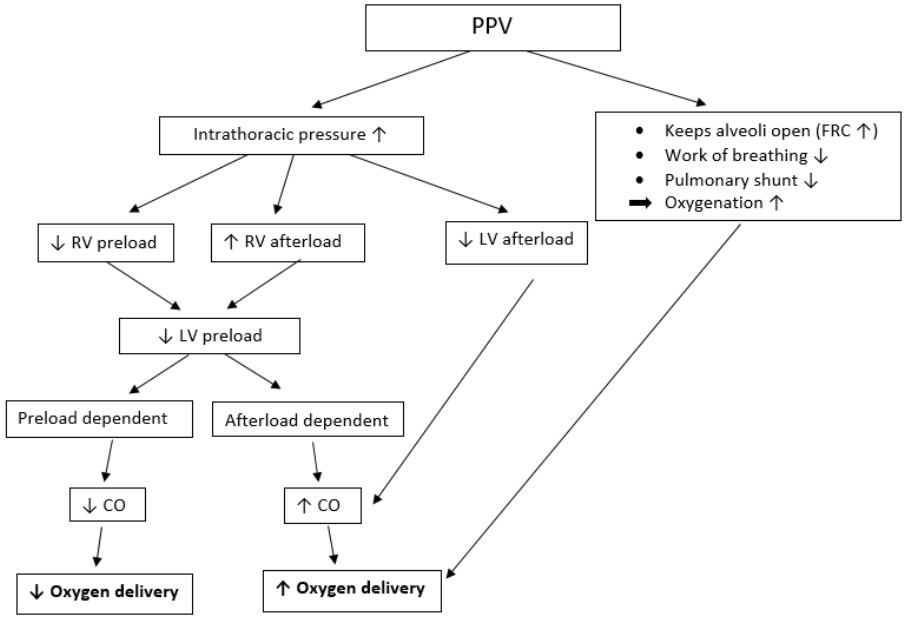
despite the severity of CS and the large number of patients requiring mechanical ventilation, there are exceptionally minimal data available on the most suitable respiratory support in this setting and the current clinical management of RF in CS is largely based on physiological principles and expert opinions.[70, 114] When choosing and applying the respiratory support modality in CS patients with RF, the delicate cardiopulmonary interactions between positive pressure ventilation and both right and left ventricle function and their effects on hemodynamics should be considered.[106, 114, 115]

Positive pressure ventilation (PPV) is a form of respiratory therapy that delivers air or a mixture of oxygen combined with other gases by positive pressure into the lungs through specific interfaces (NIV) or via an endotracheal or tracheostomy tube (IMV). When using PPV, the pressure in the alveoli at the end of expiration remains positive. This is called positive end-expiratory pressure (PEEP), which is determined as a pressure level above atmospheric pressure in the alveoli at the end of the expiration. The use of PEEP in MV treatment is universally accepted due to its several beneficial effects; it recruits collapsed alveolar units, counterbalances hydrostatic forces behind the pulmonary edema, helps maintain airway patency, improves gas exchange during the whole respiratory cycle, and decreases the work of breathing.[116]

PEEP has variable effects on CO depending on LV and right ventricle (RV) function, preload, and filling pressures. PEEP increases intrathoracic pressure, reducing both LV and RV preload and LV afterload.[117-122] In afterload-dependent situations, these changes are favourable due to consequently increased CO and enhanced perfusion. In contrast, in preload-dependent situations, the effects of PPV may be disadvantageous due to decreased CO leading to reduction in tissue perfusion and oxygen delivery. In practice, in acute decompensated HF (which is a mostly afterload-dependent state) PEEP may be helpful by unloading the LV. A decrease in preload and afterload reduces venous return, LV systolic wall stress, and thus the work of failing LV, all of which can help augment CO and tissue perfusion.[116] Instead, in RV failure or in other preload-dependent states, PEEP-induced decrease in preload and increase in afterload of RV may further worsen RV function and CO and thus deteriorate the tenuous hemodynamics and tissue oxygenation further. However, despite the large spectrum of the cardiopulmonary consequences of PEEP, the net cardiopulmonary effect of PEEP depends on the clinical scenario in which is it used (Figure 4).

Despite the well-known advantages of PEEP in acute HF, there are concerns regarding the adverse effects of PPV in CS patients. The possible deleterious effects of PPV and PEEP on CO and on delicate hemodynamics have been a cause of concern.[116]

Figure 4. Cardiopulmonary effects of positive pressure ventilation (PPV). Modified with permission from British Medical Journal Publishing Group.[116]



PPV, positive pressure ventilation; FRC, functional residual capacity, RV, right ventricle; LV, left ventricle; CO, cardiac output

2.3.2.1 Oxygenation

Due to RF, patients with CS are often hypoxemic and treated with oxygen. The goal of oxygen therapy is to maintain normal hemoglobin saturation and to ensure adequate oxygen delivery to vital organs and peripheral tissues. However, by enhancing oxidative stress and inflammation as well as inducing vasoconstriction and change in microvascular perfusion, excess oxygen supplementation may have harmful effects on pulmonary and systemic physiology.[123] Hyperoxemia may have potential adverse effects on the myocardium by reducing coronary blood flow, increasing coronary vascular resistance, and producing reactive oxygen species, contributing to vasoconstriction and reperfusion injury.[123-129] During the last decade, randomized controlled trials have shown that compared with ambient air, supplemental oxygen does not have beneficial effects on mortality or size of MI in normoxic patients with STEMI.[130-132] Accordingly, the current ESC guidelines for the management of STEMI do not recommend routine use of oxygen for patients with an oxygen saturation >90%.[88] The potential adverse effects of hyperoxemia have been observed also in critically ill patients.[128] However, the criterion for hyperoxemia has largely varied between studies

(PaO_2 ranging from 120 to 300 mmHg [16-40 kPa]) and the results have been inconsistent, making the interpretation and implementation of the results difficult.[123, 129] There are no studies on optimal oxygen level in CS. Expert recommendations have proposed blood oxygen saturations of >90% to be acceptable.[106, 133] In general, the targets of oxygen therapy should be adjusted according to patient comorbidities, such as obesity and chronic obstructive pulmonary disease.

2.3.2.2 Invasive mechanical ventilation

IMV is the most frequently used respiratory support modality in CS.[105-107] In the studies from the last decade, the use of IMV has varied between 46-83%.[4, 105, 107, 113, 134] However, despite its widespread use there are no data regarding the optimal mode, settings, or ideal timing of IMV in CS. Lung-protective ventilation with low tidal volumes (tidal volume level of 5-7 mL/kg/body weight) is recommended to prevent lung injury.[106, 135] There are potential benefits of overtaking the patient's ventilation by IMV, such as decreased sympathetic tone, setting the respiratory muscles at rest, and reduced work of breathing, which results in reduced total oxygen demand. Additionally, there are situations requiring prompt intubation and treatment with IMV, such as uncontrolled agitation, unconsciousness, severe refractory CS, and cardiac arrest.

2.3.2.3 Non-invasive ventilation

The main modalities of NIV include continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP), and more recently, high-flow nasal cannula (HFNC).

CPAP represents the simplest technique of the NIV modalities (Figure 5). CPAP delivers constant PEEP and can be applied with a separate machine (flow generator) or with a ventilator. CPAP helps to keep the airways open during the entire respiratory cycle, functionally provides the effects of PEEP on improved oxygenation, and relieves the work of breathing.

BiPAP is a more advanced modality consisting of two levels of pressures, expiratory and inspiratory pressure. The latter is obtained with pressure support, which assists inspiration. The use of BiPAP requires a ventilator. In addition to having equal beneficial effects on hypoxemia as CPAP, BiPAP can improve ventilation in patients with hypercapnia. Practically, BiPAP corresponds to CPAP with inspiratory pressure support and in contemporary ventilators this modality is often called 'CPAP with pressure support'. In current clinical practice, the term NIV often refers to both CPAP and BiPAP modalities. CPAP is mostly used with inspiratory pressure support

that mimics the function of BiPAP. Managing two pressure levels requires more experience and the respirator settings should be adjusted according to patient needs.[109]

HFNC delivers humidified and heated high flow (up to 60-80 L/min) of air and oxygen through specific nasal cannulas (Figure 5). The advantages of HFNC include constitution of a low level of PEEP (depending on the flow, approximately 0.5-1 cm H_20 per 10 L/min)[136-138], possible reduction in CO_2 level (washout in nasopharyngeal area), and reduction of upper airway resistance.[139] HFNC has beneficial effects on the weaning process from IMV and in treatment of hypoxemic RF with different etiologies.[140, 141] However, data on the use of HFNC in ACPE are scarce and further studies are needed. Recent expert recommendations propose that HFNC may be used in patients with acute HF requiring prolonged ventilation support, during weaning period, and in hypoxemic acute HF intolerant to NIV or if conventional oxygen therapy fails.[109] The role of HFNC has not been studied in the CS setting.

Figure 5. Non-invasive ventilation and high-flow oxygen therapy.

NIV has some advantages compared with IMV. NIV is easier to use and does not necessarily require admission to the ICU. With NIV, patients are allowed to breath spontaneously, communicate, and eat. NIV can be applied without sedation and the unwanted hemodynamic effects of sedative medication, risk of ventilator-associated pneumonia, and injuries related to intubation and IMV can be avoided. However, if the patient does not respond to NIV and improvement in RF is not observed, IMV should be initiated

without delay. There are some contraindications for the use of NIV which should be checked before applying this technique (Table 3).[142]

Table 3. Contraindications for NIV.[142]

Absolute	Inability to keep patent airway (altered mental status, coma, uncontrolled agitation)
	Respiratory or cardiac arrest
	Vomiting
	Anatomical abnormality (unable to fit the interface)
	Refractory hypotension
Relative	Mild agitation or poor co-operation
	Mild hypotension
	Upper gastrointestinal tract haemorrhage
	Inability to expectorate copious secretions
	Recent frail upper gastrointestinal or airway surgery
	Multiorgan failure
	Isolated right ventricular failure

Although NIV can reduce respiratory distress and intubation rate and improve hemodynamics compared to conventional oxygen therapy in ACPE, its impact on mortality is controversial.[16-20] However, a meta-analysis of randomized studies suggests that CPAP may reduce mortality rate (risk ratio 0.64; 95% CI 0.44-0.92) compared with traditional oxygen therapy.[143] Additionally, several studies have demonstrated a beneficial effect of early application of CPAP already in the pre-hospital care in ACPE patients.[144-146]

Despite the widespread use of NIV in acute HF, its use in CS remains controversial. There are currently only few studies that have assessed the use of NIV in CS.[105, 107, 113, 134] According to these studies NIV has been used in 5-11% in CS patients. Traditionally, patients with CS have not been considered suitable for this modality and the data regarding the use of NIV in CS are very limited. Frequently altered mental status may prevent the use of NIV due to inability to maintain airway patency and spontaneous breathing. In general, most of the trials that assessed the use of NIV in ACPE and acute HF excluded patients with CS.[16, 19, 147, 148] Nevertheless, recent expert recommendations have proposed that NIV could be used in selected CS patients with caution and some studies have suggested a cautious trend toward more frequent use of NIV in CS-related RF.[44, 105, 109, 149]

2.4 Cardiogenic shock in the elderly

The elderly (≥ 75 years) comprise a specific group of CS patients. Advanced age is an established risk factor for ACS-CS and for poor outcome in CS.[8, 21, 22, 150, 151] In recent registry and database studies, approximately one third of CS patients were >75 years old (Table 4).[150-152] Considering the ageing of the population in Western countries, the elderly will comprise a growing patient cohort of CS in the future.[23] Despite this, the elderly are often under-represented or even excluded from many trials, and lack of evidence-based data makes them susceptible to more conservative management than their younger counterparts.[24-26, 153-156] There are only few reports available regarding the etiology of CS in the elderly. According to a recent database study the causes of shock in this age group seem to differ from that of the younger. ACS etiology is more common among the elderly, whereas non-ACS -etiologies, mainly underlying HF, are more frequent causes of CS in the younger.[157, 158] The incidence of ACS-CS among the elderly has been decreasing but is still higher than in younger patients.[52, 112, 159]

Both short- and long-term mortality rates in elderly CS patients have been decreasing parallel with the increasing use of PCI and early revascularization. In-hospital mortality has varied between 40-66%[150-152, 160-162] and 1-year mortality between 55-67%,[52, 160, 161, 163] during the last two decades depending on the study design and period (Table 4). The pathophysiologic background for the poorer outcomes among the elderly is probably multifactorial and may include multimorbidity, frailty, reduced tissue regenerative capacity, and limited physical reserves, all of which diminish the probability of the elderly to recover from critical illness and may complicate care.[164] However, there is remarkable individual variation in the functional and cognitive reserves among the elderly, highlighting the disparity between chronological and biological age.

CS may have different presentation in the elderly than in younger patients. The elderly present with atypical and subtle ACS symptoms leading to delayed presentation and diagnosis of shock, which subsequently results in delayed transfer to coronary angiogram.[25, 165] Furthermore, compared to younger patients, elderly CS patients are more often female and have more co-morbidities, especially renal failure, hypertension, and generalized arteriosclerosis, including multivessel coronary artery disease.[152]

Table 4. Studies on CS in the elderly.

Study	Time period	Study population	N (all)	Elderly (≥ 75 years)			Observations
				N (%)	Revascularization	Mortality (in-hospital or 30-day)	
SHOCK trial [43, 166]	1993–1997	ACS-CS ERV vs. IMS	302	19 %	75% (ERV) 27% (IMS)*	75 % (ERV) 53 % (IMS)	Failed to show the benefit of ERV in the elderly
SHOCK registry [167]	1993–1997	ACS-CS	865	32 %	PCI 16 % CABG 6%	76% (ERV 48 %, no ERV 81 %)	First study that showed mortality benefit of ERV in the elderly
Gasior [162]	2003–2007	ACS-CS	5390	37 %	PCI 24 % CABG 0.3 %	66 %	Invasive strategy improved early and long-term survival in the elderly
Tommassini [160]	2003–2008	ACS-CS undergoing PCI	157	37 %	For all	55 %	PCI is feasible in the elderly, risks related are lower than in previous studies
Aissaoui [168]	1995–2010	ACS-CS	10610	32 %	PCI 51% (2010) CABG 3% (2010)	84 % (1995) 47 % (2010)	Use of PCI increased and mortality decreased during the study period
Damluji [150]	1999–2013	ACS-CS	317728	35 %	PCI 27% (1999) 56% (2013)	64% (1999) 46% (2013)	Treatment with PCI associated with significant improvement in survival
Lim [152]	2004–2007	ACS-CS undergoing PCI	143	32 %	For all	42%	Survival rates of the elderly were comparable with the younger
ALKK registry [151] Zeymer et al.	2010–2015	ACS-CS undergoing PCI	2323	33 %	For all	51%	High PCI success rate with low bleeding risk in the elderly
Kanwar [157]	2016–2019	unselected etiology (ACS 35 %, ADHF 50 %)	1412	19 % (ACS 53 %, ADHF 35 %)	Not available	40 %	Increasing age is associated with higher mortality across all SCAI stages regardless of etiology

ACS, acute coronary syndrome; ACS-CS, acute coronary syndrome related cardiogenic shock; ADHF, acute decompensated heart failure; ALKK, Arbeitsgemeinschaft Leitende Kardiologische Krankenhausärzte registry; CABG, coronary artery bypass grafting; ERV, emergency revascularization; IMS, initial medical stabilaztion; PCI, percutaneous coronary intervention; RCT, randomized controlled trial; SCAI, the Society for Cardiovascular Angiography and Interventions; SHOCK, Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock trial
*Delayed revascularization (> 54 hours) in the IMS group

2.4.1 Specific features in the treatment of cardiogenic shock in the elderly

The first report from the SHOCK trial suggested that elderly patients (≥75 years) do not benefit from early revascularization compared with initial medical stabilization. However, the number of elderly patients in the trial was limited (n=56), and only 43% (n=24) were randomized in the early revascularization group, with 75% 30-day mortality compared with 53% mortality in the initial medical stabilization group (n=32).[166, 169] Based on these results, the American College of Cardiology/American Heart Association guidelines recommended early revascularization in ACS-CS limited to those <75 years old (Class I).[170] However, re-evaluation of the SHOCK trial revealed that there were significant disparities in baseline characteristics (such as LVEF) between the early revascularization and the initial medical stabilization groups, which may have affected the lack of treatment effect in the early revascularization group.[166, 171] In addition, there were long delays from shock diagnosis to treatment and the use of stents was limited, all of which probably further contributed to the poorer outcome in the elderly revascularization group. In contrast, data from the SHOCK registry using a larger sample size revealed that selected older CS patients managed with early revascularization had lower 30-day mortality compared with initial medical stabilization (48% vs. 81%; P=0003).[167] Subsequently, the benefit of early revascularization in elderly CS patients has been demonstrated in several other trials, and contemporary guidelines do not make an age distinction regarding the recommendation for early revascularization in CS.[88, 150, 152, 172-175] Table 4 represents studies on CS in the elderly patients during the last two decades.

Compared with younger patients, the success rate of PCI in the elderly has been lower since the SHOCK registry study. The difference still exists despite advances in PCI techniques and antithrombotic therapy, which is probably due to more diffuse coronary artery disease and greater extent of calcification among the elderly.[151, 163, 169] Advanced age carries a higher risk for treatment-related complications, such as severe bleeding and stroke. Nevertheless, according to the recent prospective Arbeitsgemeinschaft Leitende Kardiologische Krankenhausärzte PCI registry study, the potential benefits of the invasive treatment strategy and revascularization seem to outweigh the PCI-related risks also in the elderly.[151]

The use of MCS, mostly ECMO, in refractory CS in the elderly has been increasing in the last two decades, though the application rate is still clearly lower than in younger patients.[176] ECMO is used mostly as a 'bridge to recovery' indication in this age group.[176, 177] There are only few mainly single-center studies that assessed the survival of elderly CS patients treated with ECMO. The results are somewhat controversial but emphasize an increasing mortality rate along with ageing.[176-178] A recent analysis of the large,

international ECMO registry found relatively poor survival rates (in-hospital mortality rate reaching almost 70%) in elderly patients with refractory CS treated with ECMO.[177] Nevertheless, the authors concluded that although the use of ECMO is associated with higher mortality in the elderly compared with younger patients and carries a substantial risk for complications, age itself cannot be an exclusion criterion and discourage the use of this advanced therapy option.[177, 179] Instead, careful patient selection by a highly specific multidisciplinary team is essential. Interestingly, the five ongoing trials assessing early support with MCS in CS have different inclusion criteria regarding patient age; one includes patients <75 years, the other includes patients aged up to 90 years, and the remaining three have not set an age limit.[97-101]

In conclusion, it is recommended that the choice of treatment strategy in an individual elderly CS patient is based on clinical judgement and evaluation of patient and family preference. In addition to the severity of shock and related possible organ failures, individualized assessment of comorbidities, frailty, prior functional and cognitive status, and possible risk factors for complications should be carefully evaluated. Along with survival, other relevant outcomes, such as quality of life, maintenance of independence, and physical function should be assessed and discussed when choosing the most optimal treatment strategy for each elderly CS patient.

2.5 Biomarkers

Biomarkers are biological measures that may provide objective information on normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention.[180] An ideal biomarker is easy and safe to measure, consistent across gender and ethnic groups, cost effective, and modifiable with treatment. In practice, biomarkers are mostly used either for diagnostic or prognostic purposes together with clinical judgement. Biomarkers are usually sampled and measured from blood or urine, but other body tissues and secretions may be used as well. Usually, biomarker samples are analysed in clinical laboratories. However, point-of-care tests, which can be performed easily and quickly at the bedside, have recently become popular in the health care system, including emergency and critical care settings.[181]

In recent last decades, there have been numerous studies evaluating potential biomarkers in cardiovascular medicine and critical illness.[182, 183] Some biomarkers have become established and routinely used in everyday clinical practice, such as troponin, natriuretic peptides, and lactate.[41, 184] From a clinical perspective, a novel biomarker should provide incremental diagnostic or prognostic information beyond the existing tests and data and should be readily available and easily analysed with a rapid turnaround time.

Most importantly, a novel biomarker should facilitate clinical decision making and aid the clinician in patient management.[185, 186] In addition to facilitating clinical decision making, a novel biomarker that provides additional information on disease pathology is also beneficial. Furthermore, biomarkers may serve as valuable tools in personalized medicine, where all decisions and practices are tailored according to individual patient needs.[187, 188]

The study of biomarkers is very popular in CS. The complex pathophysiology behind shock, including systemic inflammatory response, neurohumoral activation, oxidative stress, cardiorenal involvement, and multiorgan failure in addition to initial cardiac insult provide an almost endless field for biomarker studies.[1, 5, 189, 190] Different biomarkers reflect distinct pathogenetic cascades and pathways of CS and have been used for diagnostics, monitoring, prognostication, and for evaluating possible end-organ involvement and failure.[189, 191-193] In addition, information gained from biomarker studies have furthered understanding of the complex syndrome of CS and provided new insights into the pathophysiologic axis.[194-197] Biomarkers are also attractive for risk stratification and prognostication due to their potential to reflect pathophysiologic pathways not captured by traditional risk factors. Considering that different biomarkers represent different derangements and pathogenetic perspectives of CS, combining markers in a multimarker approach could provide substantially more information than any individual biomarker and may be particularly helpful in prognostication and risk stratification.[198] However, from a clinical perspective, biomarkers should be interpreted together with clinical judgement. Biomarkers have been acknowledged as important factors in risk stratification and many biomarkers have been incorporated in several risk scores.[199-202]

2.5.1 Growth differentiation factor-15

Growth differentiation factor-15 (GDF-15) is a promising prognostic biomarker in several diseases. It is a member of the transforming growth factor-β cytokine superfamily. GDF-15 exists in most tissues but is only minimally produced under normal circumstances except for the placenta, which is the only organ that expresses high levels of GDF-15 under healthy conditions.[29, 30] Expression of GDF-15 is strongly induced in response to different acute and chronic stressful conditions, such as inflammation, oxidative stress, hypoxia, oncogene activation, and tissue injury in organs such as liver, kidney, heart, and lung.[31, 32, 203-205] Due to its pathophysiologic nature, GDF-15 is often called a ‘stress-induced cytokine’. Cell types shown to express GDF-15 include cardiomyocytes, fibroblasts, adipocytes, macrophages, and endothelial and vascular smooth muscle cells both in healthy and diseased tissues.[205-209] On a molecular level, expression of GDF-15 is partly regulated by p53 pathway, a transcription factor that is a key regulator in tumor growth and responds to various cellular stress signals, such as hypoxia, ischemia, oxidative

stress, and inflammation.[210] Additionally, GDF-15 can also be induced independently of p53, notably by nonsteroidal anti-inflammatory agents.[211] Although knowledge on GDF-15 has notably increased during the last decade, the receptors and downstream mediators of its signaling in most tissues have not been identified.

Increased concentration of GDF-15 is associated with several pathological conditions, such as various cancers, cardiovascular diseases, autoimmune diseases, respiratory diseases, obesity, and chronic kidney diseases. Instead of being a specific diagnostic marker, GDF-15 seems to have excellent prognostic properties in different pathological conditions.[31, 212-215] However, the exact biological functions of GDF-15 in distinct clinical scenarios are not fully understood. Depending on the state and the microenvironment of cells and on disease stage, GDF-15 can have both beneficial and adverse effects on cellular processes. GDF-15 has both antitumoral and peritumoral effects. Consistent with this, GDF-15 also has opposing effects in cardiovascular diseases. Evidence exists for cardioprotective (anti-hypertrophic, anti-fibrotic, anti-inflammatory, and anti-apoptotic effects) and adverse (pro-hypertrophic, pro-fibrotic, pro-inflammatory, and pro-apoptotic) effects with high GDF-15 levels.[205, 216, 217]

By reflecting cardiometabolic risk and disease burden, GDF-15 has gained considerable attention as a promising prognostic biomarker in cardiovascular diseases.[31] GDF-15 is associated with cardiovascular risk factors, such as diabetes, obesity, smoking, ageing, and high levels of high-sensitivity C-reactive protein (hs-CRP).[218-222] Additionally, in individuals without cardiovascular disease, GDF-15 is associated with a risk of developing cardiovascular disease or events in the future.[223, 224] In healthy individuals, serum GDF-15 concentrations range between 200 and 1150 ng/L and increase with age.[225, 226] In most studies, levels < 1200 ng/L are considered normal.[31, 227] Table 5 presents studies that assessed GDF-15 in different cardiovascular settings (ACS, HF, and CS) and in sepsis.

GDF-15 levels are elevated in ACS and associate with all-cause and cardiovascular mortality and events (recurrent MI, stroke) beyond clinical predictors and other prognostic biomarkers, including troponin, N-terminal prohormone of brain natriuretic peptide (NT-proBNP), hs-CRP, and creatinine clearance.[228-231] GDF-15 has shown to improve risk stratification in ACS patients; low levels (< 1200 ng/L) associated with clearly lower 1-year mortality rate compared with elevated levels (> 1800 ng/L) (< 2% vs. 14%, respectively).[229, 232] In acute MI, GDF-15 is expressed in the ischemic myocardium probably due to ischemia and reperfusion injury.[205] However, GDF-15 levels in ACS appear to not be independently related to the extent of myocardial damage, as reflected by necrosis biomarkers or infarct size.[217, 228, 230, 232]

Increased concentrations of GDF-15 in patients with ACS but also in cardiovascular healthy individuals are indicative for developing HF.[223, 230, 233] In chronic HF, GDF-15 levels are elevated and predict disease severity,

progression, and mortality (Table 5).[234-236] Additionally, the information provided by GDF-15 is independent of established clinical risk factors (New York Heart Association class, LVEF, renal function) and cardiac biomarkers, including brain natriuretic peptide (BNP).[234, 236] GDF-15 levels seem to increase in relation to HF severity, as reflected by New York Heart Association class, increased BNP/NT-proBNP, and peripheral edema.[234, 235]

GDF-15 concentrations in patients with acutely decompensated HF seem to be higher than in chronic HF (4000 ng/L on average), as observed in the biomarker substudy of the Relaxin in Acute Heart Failure trial (RELAX-AHF) (Table 5).[237] In this study, increasing GDF-15 levels were associated with cardiovascular deaths and rehospitalizations due to HF or renal failure. Interestingly, the decrease in GDF-15 levels was faster and more pronounced in patients randomized to the studied drug (serelaxin), potentially indicating a treatment response in GDF-15 levels.

A very interesting finding is a dramatic drop in GDF-15 levels after LV assist device implantation in patients with end-stage non-ischemic HF.[238] In this study, GDF-15 concentrations were very high (on average 7000 ng/L) before implantation but dropped to nearly normal one month after the device was implanted. Moreover, GDF-15 expression in the LV was very low, suggesting peripheral sources of secretion.

GDF-15 has been studied also in critical illness. In patients with sepsis, GDF-15 levels are very high (average concentration 7000-16000 ng/L) and predict unfavourable outcome.[239, 240] Additionally, GDF-15 levels are strongly associated with organ dysfunction (kidney, liver) and hypoperfusion (lactate) in sepsis.[240]

Taken together, findings in studies assessing GDF-15 in cardiovascular diseases, specifically in acute and chronic HF, together with findings in critical illness make GDF-15 an attractive biomarker in CS. Considering the complex pathophysiology of shock and its tendency to affect multiple organ systems, GDF-15 seems to have considerable potential in providing incremental prognostic information beyond traditional biomarkers by reflecting both cardiac and extracardiac abnormalities and thus integrating information from several pathological pathways. In addition to the present study, thus far there is only one study that investigated GDF-15 levels in CS, the biomarker substudy of the IABP-SHOCK II trial by Fuernau et al.[241] This study revealed very high GDF-15 levels already at baseline (median 7600 ng/L) and GDF-15 concentrations were independently associated with higher mortality.

Table 5. Studies on GDF-15 in ACS, HF, CS, and sepsis.

	Study population	n	GDF-15, ng/L[a]	Risks associated with high GDF-15-levels[b] and specific observations
ACS	PLATO [231] NSTE-ACS or STEMI	16876	1550	All-cause mortality ++ CV mortality ++ MI ++ stroke ++ Major bleeding ++
	GUSTO [228] NSTE-ACS	2081	1499	All-cause mortality ++ GDF-15 improved risk stratification
	ASSENT-2 and ASSENT-plus [229] STEMI (treated with fibrinolysis)	741	1635	
	PROVE IT-TIMI–22 [233] NSTE-ACS or STEMI	3501	1362	All-cause mortality ++ MI ++ HF hospitalization ++
Acute HF	RELAX-AHF [237] mean LVEF 39% serelaxin + standard therapy vs. standard therapy	1088	4013	Baseline GDF-15/increase in GDF-15: CV death +/++ Rehospitalization for HF or renal failure +/++ GDF-15 levels decreased in serelaxin group
Chronic HF	Val-HeFT [234] mean LVEF 26%	1734	2040	All-cause mortality ++ Death or nonfatal HF event ++
	end-stage non-ischemic DCM undergoing LVAD implantation GDF-15 measured before and after LVAD [238]	30	7100 (prior LVAD)	Myocardial fibrosis ++ Kidney function ++ No cardiac mRNA of GDF-15 -> production outside of the heart? Dramatic drop in GDF-15 levels after LVAD implantation
	PARADIGM-HF [236] LVEF ≤ 40%, NYHA II-IV sacubitril/valsartan vs. enalapril	1935	1663	CV outcomes ++ All-cause mortality ++ Sacubitril/valsartan did not affect GDF-15 levels
CS	IABP-SHOCK II [241] ACS-CS	190	7662	All-cause mortality ++
Sepsis	patients with severe sepsis or septic shock [239]	15	16127	GDF-15 levels are very high in sepsis GDF-15 correlates with galectin-3 and sST2
	ICU patients with sepsis [240]	146	7410	Sepsis ++ Organ failure ++ Disease severity ++ All-cause mortality ++

ACS-CS, acute coronary syndrome related cardiogenic shock; ASSENT, The Assessment of the Safety and Efficacy of a New Thrombolytic Regimen; CV, cardiovascular; DCM, Dilated cardiomyopathy; GUSTO, The Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries Trial; HF, heart failure; ICU, Intensive care unit; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association class; NSTE-ACS, non- ST-elevation acute coronary syndrome; PARADIGM-HF, Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial; PCI, percutaneous coronary intervention; PLATO, Platelet Inhibition and Patient Outcomes; PROVE-IT, The Pravastatin or Atorvastatin Evaluation and Infection Therapy trial; RELAX-AHF, the Relaxin in Acute Heart Failure; STEMI, ST-elevation myocardial infarction; Val-HeFT, The Valsartan Heart Failure Trial

[a] median

[b] ++, association persists after adjustment for clinical risk predictors and other plasma biomarker(s); + association persists after adjustment for clinical risk predictors

2.5.2 Soluble urokinase-type plasminogen activator receptor

Soluble urokinase-type plasminogen activator receptor (suPAR) is the soluble form of the urokinase-type plasminogen activator receptor (uPAR), which is a membrane-bound receptor for urokinase plasminogen activator. suPAR is formed when uPAR is cleaved and released into circulation.[242] uPAR is mostly expressed on immunologically active cells (neutrophils, activated T-cells, macrophages) and on endothelial cells and smooth muscle cells.[33, 243-246] uPAR promotes invasion by neoplastic or inflammatory cells by focusing proteolysis of urokinase to the cell surface.[247] The shedding of uPAR from the cell surface is stimulated by proinflammatory cytokines.[248] In pathologic conditions suPAR is released activating cell receptors to promote chemotaxis and immune response.

SuPAR is involved in several biological processes, including the plasminogen activating pathway, inflammation and immune response, cell signaling, and cell migration.[33, 242, 247, 249, 250] Elevated suPAR levels are thought to reflect the level of immunoactivation in numerous pathological conditions.[33, 251] In contrast to many other inflammatory biomarkers, suPAR is not an acute phase reactant, but is merely thought to reflect low-grade inflammation.[252] In general populations, suPAR predicts cancer, cardiovascular disease, diabetes, kidney disease, and mortality.[38, 252] suPAR has prognostic potential in various pathological conditions. In patients with different infections, autoimmune diseases, critical illness, and cancer, high suPAR levels are associated with disease severity and poor outcome.[33, 251, 253-256]

Studies assessing the levels of suPAR in ACS, HF, critical illness, and in patients at risk of AKI are presented in Table 6. suPAR is related to the progression of renal impairment, as it plays a role in regulating the permeability of the glomerular filtration barrier in the kidneys. Circulating suPAR interacts with αvβ3 integrin on podocytes, thereby promoting podocyte dysfunction, proteinuria, and ultimately, glomerular scarring.[257] Elevated suPAR levels associating with chronic renal disease are indicative for rapid decline in glomerular infiltration rate (GFR).[38, 39, 258, 259] Additionally, high suPAR levels are associated with AKI in various settings (after coronary angiography or cardiac surgery and in critical illness).[260]

suPAR is also associated with an increased risk of cardiovascular disease. From a pathogenetic perspective, suPAR is related to impaired microcirculation, endothelium dysfunction, increased vascular stiffness, and thereby atherosclerosis.[40, 261-264] suPAR predicted new-onset HF and increased risk of coronary artery disease in the general population in a prospective population-based cohort study (the Swedish Malmö Diet and Cancer Study).[265] In patients undergoing cardiac catheterization, elevated suPAR levels associated with presence and severity of coronary artery disease.[266]

In ACS and in acute and chronic HF, higher suPAR levels predict poor outcome beyond clinical risk factors.[36, 267, 268] Furthermore, suPAR

outperformed sST2 and NT-proBNP in prognostication in HF both in the acute and chronic phase.[267, 268]

suPAR has gained considerable attention as a prognostic biomarker also in critical illness, especially in sepsis. suPAR reflects disease severity, correlates with treatment intensity required, and is a strong prognostic marker in unselected ICU patients and in patients with sepsis.[34, 256, 269] Additionally, suPAR has a close association with acute organ dysfunctions in ICU patients.[34, 256]

Compared to other inflammatory markers, suPAR levels are stable in healthy individuals and concentrations are not affected by circadian rhythms.[33] Additionally, suPAR levels also remain quite constant in acute settings, making it an attractive biomarker from a clinical perspective.[36, 256] In healthy individuals, suPAR levels are between 1 to 3 ng/mL. In contrast, suPAR levels can become multiple in critically ill patients.[34] According to the author's knowledge, the role of suPAR in CS is unknown.

Table 6. Studies on suPAR in ACS, HF, and critical illness and in patients at risk of AKI.

	study population	n	suPAR, ng/mL[a]	Risks associated with high suPAR levels [c] and specific observations
ACS	STEMI patients undergoing PCI [36]	296	4.0	All-cause mortality ++ Recurrent MI ++ suPAR remained stable after PCI
HF	Acute (STADE-HF) (LVEF 43% [a]) and chronic HF patients (NYHA ≥2) [267, 268]	95 and 319	3.7-7.6	All-cause mortality ++ suPAR outperformed sST2 and NT-proBNP in prognostication
at risk of AKI	Patients undergoing coronary angiography for suspected ischemic heart disease [260]	3827	AKI 3.9 no AKI 3.2 [b]	Postprocedural AKI ++ Combined endpoint of AKI and all-cause mortality ++ Incidence of AKI increased; in the highest Q (>4.2 ng/L) 14%, in the lowest Q (<2.5 ng/L) 4%
	Critically ill patients [260]	692	AKI 8.7 no AKI 6.6	Incidence of AKI ++ Incidence of AKI increased; in the highest Q (>9.4 ng/L) 53%, in the lowest Q (< 5.2 ng/L) 15%
Critical illness	Critically ill patients [256]	273	9.8	All-cause mortality + Correlation with disease severity and renal and hepatic function
	Patients with sepsis [269]	1914	survivors 9.3 non-survivors 14.1	Higher suPAR levels in non-survivors Combination with APACHE II score improved risk stratification

[a] median; [b] in patients with AKI or with no AKI; [c] ++ association persists after adjustment for clinical risk predictors and other plasma biomarker(s), [+] association persists after adjustment for other plasma biomarkers
ACS, acute coronary syndrome; AKI, acute kidney injury; ICU, intensive care unit; HF, heart failure; ICU, intensive care unit; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; NYHA, New York Heart Association NYHA Classification of Heart Failure, PCI, percutaneous coronary intervention; Q, quartile; sST2, Soluble suppression of tumorigenicity 2; STADE-HF, Soluble Suppression of Tumorigenesis-2 as a Help for Management of Diagnosis, Evaluation and Management of Heart Failure; STEMI, ST-elevation myocardial infarction

2.5.3 Soluble suppression of tumorigenicity 2

Soluble suppression of tumorigenicity 2 (sST2) is one of the most successful novel cardiovascular biomarkers. ST2 is a member of interleukin (IL) -1 receptor family. The ST2 entity consists of the transmembrane ST2 receptor isoform and its soluble (sST2) isoform, which are expressed in several cell types. ST2 was originally related to inflammatory processes, but further studies revealed its role in cardiac and vascular remodelling. Recently, sST2 has gained considerable attention in the cardiovascular field.[270] Together with its receptor ligand IL-33, ST2 promotes antihypertrophic, antiapoptotic, and antifibrotic effects on cardiomyocytes in response to cardiac injury.[271, 272] Circulating sST2 instead serves as a 'decoy' receptor of IL-33 and inhibits the beneficial effects of IL-33/ST2 and is a marker of cardiac stress and remodelling.[270, 273] The IL-33/ST2 combination also plays a role in the development of vascular disease by interacting with atherosclerotic plaques.[274]

Several studies have shown the independent and additive prognostic potential of ST2 in both acute and chronic HF.[275-277] Accordingly, the American College of Cardiology Foundation and American Heart Association taskforce recommend (Class IIb) measurement of sST2 for additive risk stratification in patients with acutely decompensated HF and in patients with chronic HF.[278] Currently, sST2 is the only novel biomarker that is established in national guidelines. The prognostic role of sST2 in CS is largely unknown. In a small, single-center prospective study, sST2 levels were higher in CS than in patients presenting with STEMI. However, sST2 levels did not have any prognostic value in CS.[279] Instead, according to the biomarker substudy from the CardShock trial, early risk assessment improved markedly beyond clinical variables by combining sST2 with NT-proBNP.[280]

sST2 levels depend on patient sex. The reference range for sST2 is higher in men (8.6-49.3 ng/mL) than in women (7.2-33.5 ng/mL).[281] In general, the higher the sST2 levels are, the poorer the outcome. Unlike many other biomarkers, such as natriuretic peptides, sST2 is not affected by age, renal function, or obesity.[270]

2.6 Risk assessment of cardiogenic shock

Risk stratification and individual risk assessment are essential in CS. Proper risk stratification helps to guide treatment and allocation of healthcare resources. Considering the mostly abrupt onset and progressive course of CS and the associated high early mortality, proper early risk prediction is crucial to estimate an individual patient's prognosis and to assist with patient disposition and treatment decisions, such as whether to escalate (to more advanced therapy options) or withdraw treatment. Timely treatment escalation may help to restore hemodynamics and correct CS-related end-

organ dysfunctions in the reversible phase before irreversible organ damage and MODS occur.[92] However, considering the costs and the resources required for advanced therapy options and critical care, tools for accurate risk stratification are needed to estimate the benefits regarding prognosis and cost-effectiveness of treatment.

2.6.1 Risk scores in cardiogenic shock

During the last decade, several specific risk scores have been developed to improve risk prediction of CS patients. The scores include clinical and biochemical variables that are easily available, such as prior medical history, current clinical status, laboratory tests, and success of revascularization. Together with experienced clinical judgement, risk scores may serve as valuable tools in risk prediction and appropriate patient selection regarding advanced therapy options. Additionally, considering the heterogeneity of CS patients in clinical studies, which complicates comparison of results between trials, an accurate risk prediction model could help to recruit homogenous patient populations in future studies and thus facilitate implementation of results in real-life practice. An optimal risk prediction score should be applicable on hospital admission but also later during the hospital stay.

One of the first risk scores for CS was derived from the SHOCK-trial, the Sleeper score.[282] Considering the time period when the SHOCK trial was conducted and when the Sleeper score was created, therapy options for CS have subsequently developed and more recent risk scores might be more relevant in current clinical practice. Contemporary risk prediction models are further discussed below, including the CardShock risk score, which was derived from the present CardShock Study population. The variables included in different CS risk scores are presented in Table 8.

In addition to the specific risk models created for CS, there are several risk prediction models developed to assess disease severity and organ dysfunction in critically ill patients in general, such as the Acute Physiology, Age, Chronic Health Evaluation (APACHE) II and III scores[201, 283], the Simplified Acute Physiology Score (SAPS II)[202], and the Sepsis-related Organ Failure Assessment (SOFA).[284] These scores focus largely on different organ dysfunctions (renal, hepatic, respiratory, circulatory, neurological, hematological). Despite developed for the intensive care patient population or particularly for sepsis, the performance of these scores is also acceptable in CS patients but does not achieve the performance of the specific CS sores.[285, 286] A recent study evaluated the performance of the CardShock risk score, the IABP-SHOCK II score, and the SAPS II score in the ACS-CS population derived from the CULPRIT-SHOCK trial and registry. The IABP-SHOCK II score performed best in this population.[287]

An interesting consideration is the role of serial evaluation of risk score during hospitalization. In critical care, change in risk score is associated

with outcome and there has been increasing interest on repeated risk stratification during the hospital stay. A change in SOFA score is associated with outcome in unselected ICU patient cohorts and in a more specific cohort of patients with coronavirus disease treated with MV.[288-290]

2.6.1.1 The CardShock risk score

The CardShock risk score is a risk prediction model developed for in-hospital mortality in CS patients with unselected etiology.[2] It was created from baseline clinical and biological parameters that independently predicted in-hospital mortality. The risk score consists of seven variables yielding a maximum of nine points (Table 7). Patients can be classified into low (0 - 3 points), intermediate (4 – 5 points), and high risk (6 – 9 points) groups regarding in-hospital mortality. The mortality rates in each category were 9%, 36%, and 77%, respectively. The score had excellent discrimination ability for in-hospital mortality, with an area under the curve (AUC) of 0.85 (95% CI 0.79 – 0.90). (16) The performance of the CardShock risk score has subsequently been validated in other CS study populations with good results.[199, 291]

Table 7. The CardShock risk score.

Variable	Score
Age >75 years	1
Confusion at presentation	1
Previous myocardial infarction or CABG	1
ACS etiology	1
LVEF <40%	1
Blood lactate	
<2 mmol/L	0
2-4 mmol/L	1
>4 mmol/L	2
$eGFR_{CKD-EPI}$	
>60 mL/min/1.73m^2	0
30-60 mL/min/1.73m^2	1
<30 mL/min/1.73m^2	2
Maximum	**9**

ACS, acute coronary syndrome; CABG, coronary artery bypass graft surgery; $eGFR_{CKD-EPI}$, estimated glomerular filtration rate by the Chronic Kidney Disease Epidemiology Collaboration formula; LVEF, left ventricular ejection fraction.

2.6.1.2 The IABP-SHOCK II score

The IABP-SHOCK II score is a risk prediction model derived from the IABP-SHOCK II study.[199] The study included patients with CS due to ACS undergoing PCI. The score consists of six dichotomous variables [age >73 years; prior stroke; lactate at admission > 5 mmol/L; glucose at admission >10.6 mmol/L; creatinine at admission >132.6 mmol/L; thrombolysis in myocardial infarction (TIMI) flow grade <3] that yield a maximum of 9 points (prior stroke, lactate level, and TIMI flow gives two points) (Table 8). The patients can be classified into low-risk (0–2 points), intermediate-risk (3–4 points), and high-risk (5–9 points) categories with respect to 30-day mortality. The AUC of the IABP-SHOCK II score was 0.79 [95% confidence interval (CI) 0.70-0.88]. The score has been validated internally and externally.[199, 291]

2.6.1.3 The Cystatin C, Lactate, Interleukin-6, and N-terminal pro-B-type natriuretic Peptide score

The most recent risk prediction tool, the Cystatin C, Lactate, Interleukin-6, and N-terminal pro-B-type natriuretic Peptide score (CLIP score), was developed from the CULPRIT-SHOCK study which randomly assigned patients with ACS-CS either to culprit-lesion-only PCI or immediate multivessel PCI.[42] In contrast to the earlier risk models, the CLIP score is based solely on circulating biomarkers. These are cystatin-C (reflecting renal function), lactate (reflecting global hypoperfusion), interleukin-6 (reflecting inflammation), and NT-proBNP (reflecting cardiac wall stress).[200] The CLIP score estimates the risk of 30-day mortality. Due to various biomarkers reflecting important, different, and ongoing pathways in CS pathophysiology, the CLIP score provides an integrated estimation on the state of shock. Comparison with other existing scores revealed that the CLIP score outperformed all other contemporary risk prediction models and had an AUC of 0.82 (95% CI 0.78-0.86). The CLIP score has been validated both internally and externally.[200] The challenge of the clinical utilization of the CLIP score is the requirement for a designated counter or specific application.

Table 8. Variables included in different risk scores.

	Sleeper score 2010 [282]	CardShock risk score 2015 [2]	IABP-SHOCK II score 2017 [199]	CLIP score 2021 [200]
Higher age	X	X	X	
Prior MI or CABG	X	X		
Prior stroke			X	
ACS etiology for CS		X		
Shock on admission	X			
Confusion at presentation		X		
Systolic blood pressure	X			
LVEF		X		
Clinical signs of end-organ hypoperfusion	X			
Blood lactate		X	X	X
Creatinine or eGFR	X	X	X	
Cystatin C				X
NT-proBNP				X
Interleukin-6				X
Glucose			X	
Non-inferior MI	X			
TIMI < 3 flow post-PCI			X	
Anoxic brain damage	X			

ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; CLIP score, The Cystatin C, Lactate, Interleukin-6, and N-terminal pro-B-type natriuretic Peptide score; CS, cardiogenic shock; eGFR, estimated glomerular filtration rate; IABP-SHOCK II, Intra-Aortic Balloon Pump in Cardiogenic Shock II –study; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; PCI, percutaneous coronary intervention; TIMI, thrombolysis In Myocardial Infarction flow grade

3 AIMS

The general aim of this study was to evaluate the contemporary use of different ventilation strategies in CS, to assess the key features and outcomes of CS and the performance of contemporary risk prediction scores in the elderly, and to investigate the role of two novel biomarkers for early risk stratification. In more detail, the aims were:

1) To assess the use of different ventilation strategies in CS and their impact on outcome. (I)
2) To examine the clinical picture, treatment, and outcomes of elderly (≥ 75 years) CS patients and to compare them with younger patients. This study also aimed to evaluate the performance of contemporary risk prediction models and to assess the potential incremental ability of novel biomarkers to improve early risk stratification. (II)
3) To evaluate the levels of GDF-15 in CS using serial measurements and to analyze its prognostic properties and incremental value for risk stratification in CS. (III)
4) To investigate the role of suPAR in CS using serial measurements, and to assess its association with organ dysfunction and to evaluate the prognostic ability and value of suPAR in early risk stratification in CS. (IV)

4 SUBJECTS AND METHODS

4.1 The CardShock study

All studies (I-IV) in this dissertation are based on the CardShock study (ClinicalTrials.gov identifier: NCT01374867), which was a prospective, observational, multicenter study on cardiogenic shock coordinated by the Heart Failure Study Group at Helsinki University Hospital.[2] The CardShock study was conducted in eight European countries in nine centers (Athens, Barcelona, Brescia, Brno, Copenhagen, Helsinki, Porto, Rome, and Warsaw) between October 2010 and December 2012 and enrolled a total of 219 patients.

The diagnostic criteria for CS were systolic blood pressure <90 mmHg for 30 minutes (after adequate fluid challenge) or need for vasoactive therapy to maintain adequate systolic blood pressure and at least one or more signs of hypoperfusion: confusion or altered mental status, oliguria <0.5 ml/kg/h for the previous 6 h, cool extremities, or blood lactate >2 mmol/l. Shock had to be of cardiac origin. Exclusion criteria were CS caused by hemodynamically significant arrhythmia or after cardiac or non-cardiac surgery. The etiology of CS was defined by the local investigators. Patients had to be >18 years old and enrolled within 6 hours from the identification of CS.

Comprehensive data on patients' clinical characteristics and medical history were collected. Clinical signs, biochemical findings, and hemodynamic parameters were registered at detection of shock. Furthermore, serial biochemical samples were collected and hemodynamic measurements were recorded at prespecified time points every 6 to 24 hours (0–120 h). Routine blood samples were analysed locally in each participating hospital. Creatinine, C-reactive protein, high-sensitive troponin T (Elecsys, Roche Diagnostics, Basel, Switzerland), and NT-proBNP (Elecsys, Roche Diagnostics) were measured at a central laboratory (ISLAB, Kuopio, Finland). Patients were treated according to local practice; medical and invasive treatment procedures were recorded.

Primary endpoints were all-cause 90-day mortality for study I, III, and IV, and all-cause in-hospital and 1-year mortality for study II. Vital status during follow up was determined through direct contact with the patient or next of kin, or through population and hospital registries. Three patients were lost to follow up. All patients or their next of kin provided informed consent. The CardShock study was approved by local ethics committees at the participating centers except for Copenhagen, where the study was accepted by the Danish Protection Agency due to different laws. Danish law does not necessitate ethical approval if the data are collected from existing registries. Two of the centers did not participate in the biomarker sampling. The

CardShock study was conducted in accordance with the Declaration of Helsinki.

4.1.1 Main results of the CardShock study

The characteristics of the study population and clinical picture of CS and in-hospital mortality and its predictors have been published previously.[2] In brief, mean age of the patients was 67 (standard deviation, SD 12) years and 26% were women. The most common co-morbidities were hypertension (60%), coronary artery disease (35%), and diabetes (28%). ACS was the main cause of shock (81%), 68% of the patients had STEMI, and 11% had mechanical complication of MI. Non-ACS causes accounted for 19% of the CS etiology and consisted mainly of worsening of chronic heart failure and valvular causes. In-hospital mortality was 37% in all patients, 40% in ACS patients, and 24% in non-ACS patients. Table 9 presents patient demographics, clinical presentation at baseline, and mortality of all CardShock study patients and of the patient populations used in studies III and IV. There were no significant differences between the populations.

Table 9. Patient demographics, clinical presentation at baseline, and mortality.

	Studies I, II	Study III	Study IV
N	219	177	161
Age (SD)	67 (12)	66 (12)	66 (12)
Women (%)	57 (26)	45 (25)	41 (26)
Medical history, n (%)			
Coronary artery disease	76 (35)	57 (32)	53 (33)
History of MI/CABG	70 (32)	45 (25)	40 (25)
Hypertension	132 (60)	107 (60)	100 (62)
Heart failure	36 (16)	29 (16)	27 (17)
Renal insufficiency	25 (11)	21 (12)	19 (12)
Diabetes	62 (28)	52 (29)	48 (30)
Etiology of CS, n (%)			
Acute coronary syndrome	177 (81)	142 (80)	127 (79)
STEMI	149 (68)	119 (67)	106 (66)
Presentation			
Systolic blood pressure, mmHg	78 (14)	77 (14)	77 (14)
Mean arterial pressure, mmHg	57 (11)	57 (11)	57 (11)
Heart rate, bpm	90 (28)	88 (29)	88 (28)
Sinus rhythm, n (%)	170 (78)	127 (72)	119 (74)
LVEF, %	33 (14)	33 (14)	32 (14)
Resuscitated from cardiac arrest	62 (18)	47 (27)	47 (29)
Signs of hypoperfusion, n (%)			
Cold periphery	207 (95)	169 (96)	154 (96)
Confusion	148 (68)	116 (66)	105 (65)
Oliguria	121 (55)	93 (53)	85 (53)
Lactate > 2 mml/L	155 (71)	124 (70)	112 (70)
Biochemistry			
Hemoglobin (g/L)	128 (22)	129 (23)	129 (24)
CRP (mg/L)	16 (4-54)	15 (4-53)	16 (2-75)
Creatinine (µmol/L)	104 (78-140)	103 (79-140)	101 (77-139)
eGFR (mL/min/1.73 m^2)	61 (41-87)	63 (42-88)	62 (41-87)
Arterial blood pH	7.30 (7.20-7.40)	7.30 (7.21-7.40)	7.30 (7.20-7.40)
Lactate (mmol/L)	2.8 (1.7-5.8)	2.7 (1.7-5.8)	2.7 (1.6-5.9)
hsTnT (ng/L)	2190 (388-5418)	2190 (393-5399)	1857 (365-5279)
NT-proBNP (ng/L)	2710 (585-9434)	2581 (575-9323)	2450 (565-9172)
Mortality, n (%)			
In-hospital mortality	80 (37)	66 (37)	59 (37)
90-day mortality	89 (41)	73 (41)	64 (40)

Results are presented as numbers and percentages (%), mean (SD), and median (IQR).
CABG, coronary artery bypass surgery; CRP, C-reactive protein; CS, cardiogenic shock; eGFR, estimated glomerular filtration rate; hsTnT, highly sensitive troponin T; LVEF, left ventricular ejection fraction; MI, myocardial infarction; SD, standard deviation; STEMI, ST-elevation myocardial infarction

4.2 Study populations and study outlines

4.2.1 Study I

Study I included all the 219 CardShock patients and evaluated the use of different ventilatory support strategies in CS. The patients were grouped by the maximum intensity of ventilatory support required during the first 24 hours (observation period) into the supplementary oxygen group (including patients treated with supplementary oxygen only by nasal cannula or face mask), NIV group (including both CPAP and BiPAP), and IMV group. Clinical characteristics, treatment, and outcomes of the groups were analysed. Further comparisons were made between the NIV and IMV groups. NIV failure was determined as a requirement for endotracheal intubation after NIV was used as first-line ventilatory support treatment. The need for ventilatory assistance and the choice of ventilatory mode (supplementary oxygen, NIV, or IMV) were assessed by the responsible physician in each participating hospital and based on common indications and contraindications for NIV and IMV treatment.

Arterial blood gas samples were analysed locally at baseline and at pre-specified time points. PaO_2/FiO_2 ratio was calculated using the measured PaO_2 and registered FiO_2. The degree of hypoxemia and RF were categorised according to ARDS Berlin definition criteria: mild (200 mmHg < PaO_2/FiO_2 ≤ 300 mmHg), moderate (100 mmHg < PaO_2/FiO_2 ≤ 200 mmHg), and severe (PaO_2/FiO_2 ≤ 100 mmHg).[104]

4.2.2 Study II

Study II included all the 219 CardShock patients and investigated the clinical picture, outcome, and risk prediction of CS in the elderly. The patients were grouped and compared according to age into those ≥75 years (elderly group) and <75 years (younger group). In addition, further analyses were performed that compared elderly in-hospital survivors with non-survivors.

The performance of the risk prediction models, the CardShock risk score and the IABP-SHOCK II score, and the additional ability of GDF-15 and sST2 to improve risk prediction were assessed. Cutoff values of GDF-15 (>7000 ng/L) and sST2 (>500 ng/mL) defined in separate studies were used in these analyses.[280, 292] Further information on GDF-15 is presented in section 4.2.3 Study III.

sST2 samples were available from 177 patients. The sST2 samples were frozen and stored at -80 C° until assayed. Analyses were performed at INSERM UMR-S 942 (Paris, France) utilizing a quantitative sandwich monoclonal enzyme-linked immunosorbent assay kit (Presage sST2 Assay; Critical Diagnostics, San Diego, CA, USA). In the analyses assessing the performance of the risk scores, the number of the elderly patients was limited (n=40 for the CardShock risk score and n=28 for the IABP-SHOCK II score), due to different variables included in the risk models. The IABP-SHOCK II study included only CS patients with ACS etiology undergoing PCI, whereas the CardShock study included both ACS and non-ACS etiologies.[2, 199] Consequently, the variable TIMI flow in the IABP-SHOCK II score was missing in the CardShock study patients who did not undergo coronary angiogram. In addition, GDF-15 and sST2 concentrations were not available from all patients.

The performance of the CardShock risk score was further validated in an external cohort from a single-center prospective study consisting of 262 CS patients with unselected etiology. The validation was performed in all patients and separately in the elderly (n=83) and in the younger (n=179).

4.2.3 Study III

Study III included 177 CardShock patients with available baseline GDF-15 samples and focused on assessing the kinetics and prognostic properties of GDF-15 in CS. Baseline serial plasma samples were taken at pre-specified time points (12, 24, 36, 48, 72, 96, and 120 h). Plasma aliquots were frozen and stored at -70 C° until assayed. GDF-15 samples were analysed centrally at ISLAB (Kuopio, Finland) using an electrochemiluminescence immunoassay (Roche Diagnostics). According to previous studies, GDF-15 levels <1200 ng/mL were considered normal.[31, 227]

Patients were grouped and compared according to baseline median level into GDF-15 >median and GDF-15 ≤median groups. In addition, GDF-15 levels of in-hospital survivors and non-survivors were assessed and compared.

4.2.4 Study IV

Study IV included 161 CardShock patients with available baseline suPAR samples and evaluated the kinetics and prognostic potential of suPAR in CS. After baseline, serial plasma sampling was performed at pre-specified time-points (12, 24, 36, 48, 72, and 96 h). Plasma aliquots were immediately frozen and stored at -70 C° until assayed. Samples were analysed using a

commercially available enzyme linked immunosorbent assay kit (suPARnostic®, ViroGates, Denmark).

Patients were divided and compared according to baseline median suPAR level into suPAR ≤median and suPAR >median groups. In addition, suPAR levels of in-hospital survivors and non-survivors were analysed and compared.

The values of suPAR at 12 h were used (n=138) in the analyses assessing the additional ability of suPAR to improve early risk stratification. The selection of timepoint 12 h was based on the discriminative ability of suPAR at each measured time point and on the relevance of the timepoint to early risk assessment.

4.3 Statistical analyses

Results are presented as numbers and percentages for categorical variables, and as mean with SD or median with interquartile range (IQR) for continuous variables as appropriate. Group comparisons were performed with chi-square test and Fisher's exact test for categorical variables and with Student's *t*-test and Mann-Whitney *U* test for continuous variables. Wilcoxon signed-rank test was used to determine differences in serial sampling (I, III, IV). Linear mixed modelling served to assess the differences in biomarker levels between groups over time (III, IV). Biomarkers were log-transformed due to skewed distributions to normalize the distributions and the residuals (when needed). Correlation analyses were performed by Spearman test (studies III, IV).

Kaplan-Meier survival curves were drawn to assess unadjusted survival and statistical assessment was performed using log-rank analyses. Univariate and multivariable logistic regression models were built to investigate the association of different variables with outcome. In study I, multivariable logistic regression analysis was used to determine independent risk factors of outcome. The covariates were carefully chosen from the variables known to be clinically related to outcome. The model was adjusted for the CardShock risk score variables, gender, and participating center. In studies III and IV, multivariable logistic regression analysis was used to evaluate the association of biomarker levels with outcome. In these studies, the models were adjusted for disease severity by using the CardShock risk score variables. Results from the regression analyses are presented as odds ratios (OR) with 95% confidence intervals (CI). Three patients were lost to follow-up and their cases were censored at the time of hospital discharge in survival analyses.

In study I, propensity score adjustment was performed to reduce bias and increase precision when assessing the relationship between ventilatory strategy (NIV or IMV) and mortality.[293, 294] The variables with

potential confounding effect were chosen for propensity score analyses based on their known clinical relevance and potential or known association with outcome. Multivariable logistic regression analysis was used to create a propensity score modelling the likelihood of a patient to receive either NIV or IMV using ventilatory strategy as an outcome variable and chosen covariates as predictor variables in the model. The final propensity score was estimated with the following variables: age, gender, medical history (MI, CABG, diabetes mellitus, hypertension), ACS etiology, and initial presentation (confusion, blood lactate, systolic blood pressure, non-sinus rhythm, LVEF, and estimated GFR). The score estimate was transformed into logit scale. The Kaplan-Meier method was used for unadjusted and Cox regression for the propensity score adjusted survival analyses.

The AUC of the receiver operating characteristic (ROC) curves were calculated 1) in study II to investigate the ability of the CardShock risk score and the IABP-SHOCK II score to predict outcome and to assess the additional value of GDF-15 and sST2 on the risk prediction models and 2) in studies III and IV to assess the prognostic value of the biomarkers and their ability to improve discrimination beyond the CardShock risk Score. Youden's index was used to identify the optimal cutoff value of the biomarkers from the ROC curve. The additional value of the biomarkers in the risk prediction models was assessed using the likelihood ratio test for nested models (studies II-IV).

Integrated discrimination index (IDI) analysis was performed to further evaluate the incremental discriminative ability of GDF-15 when added on top of the CardShock risk score (study III). Furthermore, net reclassification improvement (NRI) analysis was used to evaluate whether adding of GDF-15 would improve the clinical risk stratification using pre-specified categories of low (0-15%), intermediate (15-50%), and high (>50%) mortality risk that were originally defined for the CardShock risk score.[2]

P-values <0.05 were considered statistically significant. All statistical analyses were performed using SPSS versions 22.0-26.0 (IBM Corp., Armonk, N.Y., USA) except for the reclassification analyses in study III, which were performed with R version 3.4.1 using PredictABEL package.

5 RESULTS

5.1 Ventilation strategies in cardiogenic shock and their impact on outcome (I)

5.1.1 Patient characteristics and ventilation strategies

This study included all the 219 CardShock study patients. We assessed the maximum level of ventilatory support the patients required during the first 24 hours. The patients were stratified into the following groups:

1. Invasive mechanical ventilation (IMV) (n=137; 63%)
2. Non-invasive ventilation (NIV) (n= 26; 12%)
3. Supplementary oxygen (n=56; 26%)

Initially, 30 patients were treated with NIV during the observation period, of which 8 required intubation (NIV failure). Four of the NIV failures occurred during the observation period and were thus included in the IMV group. As the remaining 4 NIV failures occurred after the observation period, they were included in the NIV group.

Comparison of the IMV and NIV groups is presented in Table 10. Both groups were generally similar in baseline characteristics and shock etiology, ACS was the main cause of shock in both groups. Patients in the IMV group presented with more severe shock and hypoperfusion already at baseline; they had mental confusion, poorer metabolic acidosis, and higher lactate levels. In contrast, the clinical picture of the patients treated with NIV appeared to be more congestive. The treatment procedures were similar between the two ventilation strategy groups, except for the greater need for vasoactive medication in the IMV group. Of note, 40% of the patients in the IMV group and no patients in the NIV group were resuscitated before inclusion to the study.

Patients in the IMV group were treated with a higher oxygen fraction (75% vs. 60%; p=0.001) and lower level of PEEP (6 cm H_2O vs. 8 cm H_2O; p=0.002) at baseline compared with NIV group. The severity of RF was moderate in both groups at baseline according to P/F ratio; the P/F ratio improved in both groups during the observation period. The median duration of ventilation was more than doubled in the IMV group than in the NIV group (Table 11).

Table 10. Patient characteristics, shock etiology, clinical findings, biochemistry, and mortality in NIV and IMV groups. Reproduced with permission from Study I. [295]

	IMV (n=137)	NIV (n=26)	p-value
Age, years	66 (11)	66 (12)	0.8
Women, n (%)	31 (23)	8 (31)	0.4
Medical history, n (%)			
Coronary artery disease	51 (37)	10 (39)	0.9
Heart failure	25 (18)	3 (12)	0.6
Hypertension	85 (62)	17 (65)	0.7
Diabetes	44 (32)	6 (23)	0.4
Asthma or COPD	18 (13)	2 (8)	0.7
Etiology of CS, n (%)			
ACS	111 (81)	20 (77)	0.6
STEMI	87 (64)	18 (69)	0.6
non-ACS	26 (19)	6 (23)	0.6
CardShock risk score	4.8 (1.8)	3.4 (1.6)	0.001
Clinical findings			
Systolic blood pressure, mmHg	78 (15)	83 (10)	0.03
LVEF, %	32 (14)	33 (12)	0.7
Confusion, n (%)	113 (83)	8 (31)	< 0.001
Biochemistry at baseline			
pH	7.27 (7.17-7.34)	7.39 (7.32-7.43)	< 0.001
Arterial blood lactate (mmol/L)	3.7 (2.2-7.0)	1.7 (1.4-2.8)	< 0.001
hs-TnT (ng/L)	1597 (337-4178)	3631 (1289-10170)	0.06
NT-proBNP (pg/mL)	2367 (559-8563)	7375 (2053-17372)	0.04
Creatinine (mmol/L)	110 (87-144)	100 (69-119)	0.1
Management, n (%)			
Coronary angiography	114 (83)	23 (89)	0.8
PCI	90 (66)	19 (73)	0.5
CABG	5 (4)	3 (12)	0.1
IABP	85 (62)	16 (62)	1.0
Mortality, n (%)			
In-hospital mortality	62 (45)	5 (19)	0.01
90-day mortality	67 (49)	7 (27)	0.03

Data are presented as numbers and percentages (%), mean (SD), and median (IQR).
ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; CS, cardiogenic shock; eGFR, estimated glomerular filtration rate; hs-TnT, highly sensitive troponin T; IABP, intra-aortic balloon pump; IQR interquartile range; IMV, invasive mechanical ventilation group; LVEF left ventricular ejection fraction; NIV noninvasive ventilation group; PCI, percutaneous coronary intervention; SD, standard deviation; STEMI, ST-elevation myocardial infarction

Table 11. Ventilatory parameters during the first 24 hours. Reproduced with permission from Study I.[295]

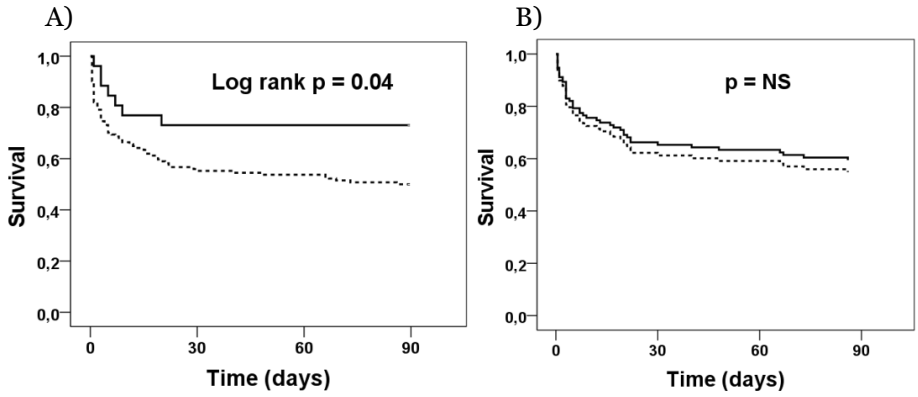
	IMV (n=137)	NIV (n=26)	p-value
PEEP (cmH_2O) at baseline	6 (5-8)	8 (7-10)	0.002
Duration of ventilation, h	94 (30-184)	41 (28-71)	0.007
AT BASELINE			
PaO_2, kPa	12.9 (10.4-18.6)	11.2 (9.9-15.0)	0.2
$PaCO_2$, kPa	5.5 (4.9-6.4)	4.5 (4.2-5.9)	0.01
FiO_2, %	76 (22)	60 (19)	0.001
P/F ratio, mmHg	141 (97-211)	167 (107-215)	0.3
200-300 mmHg, n (%)	35 (26)	7 (27)	0.9
100-200 mmHg, n (%)	54 (40)	14 (54)	0.2
<100 mmHg, n (%)	40 (29)	4 (15)	0.1
AT 24 HOURS			
PaO_2, kPa	12.1 (10.5-14.0)	11.8 (10.4-13.6)	0.5
$PaCO_2$, kPa	5.30 (4.70-5.70)	4.50 (4.20-4.90)	< 0.001
FiO_2, %	52 (18)	53 (23)	0.8
P/F ratio, mmHg	192 (138-265) [1,2]	191 (136-284) [2]	1.0
200-300 mmHg, n (%)	33 (24)	6 (23)	0.9
100-200 mmHg, n (%)	46 (34)	8 (31)	0.7
<100 mmHg, n (%)	13 (10)	3 (12)	0.7

Data are presented as numbers and percentages (%), mean (SD), and median (IQR).
FiO_2, fraction of inspired oxygen; IMV, invasive mechanical ventilation group; NIV noninvasive ventilation group; PaCO2, partial pressure of carbon dioxide in arterial blood; PaO2, partial pressure of oxygen in arterial blood; PEEP, positive end expiratory pressure; P/F ratio, PaO2/FiO2 ratio
1)the improvement during the 24 h was significant in the MV group, 2) but not between the groups

5.1.2 Ventilation strategies and mortality

In-hospital and 90-day mortality rates were lower in the NIV group (Table 10). Nevertheless, the choice of ventilation strategy did not affect 90-day mortality (OR 0.85, 95% CI 0.15–4.8; p=0.85) when adjusting for disease severity using CardShock risk score variables. This finding was not only limited to the observation period but also remained unchanged later during the study. Propensity score analysis, which was used to balance differences and covariates between NIV and IMV groups, confirmed the results; the choice of ventilation strategy was not associated with 90-day mortality (Figure 6). Additionally, further adjustment with prior resuscitation did not influence the results in the analysis.

Figure 6. A) Unadjusted (Kaplan Meier) and B) propensity score adjusted (Cox regression) survival curves for the use of IMV (dashed line) and NIV (solid line) in CS. Reproduced with permission from Study I. [295]



5.2 Cardiogenic shock in the elderly (II)

5.2.1 Patient characteristics and treatment

The elderly constituted a quarter of the patients (26%; n=56). Compared with the younger group, the elderly were more likely to be women and more often had underlying arteriosclerosis-related comorbidities and renal insufficiency. Shock etiology was mainly ACS in both groups (Table 12). The distribution of non-ACS etiologies did not differ between the groups; chronic HF was present in 9% in the elderly group and 11% in the younger group. The treatment of CS in the elderly group did not differ from that of the younger group except for the use of IABP, which was more common in the younger group (Table 13). The severity of coronary artery disease in the elderly group (one-vessel disease 20%; multivessel disease 59%; and left main disease 11%) was not greater when compared with the younger group. Similar proportions of patients were resuscitated before study inclusion in both groups.

5.2.2 Outcome of the elderly cardiogenic shock patients

The elderly group had poorer short-term and long-term outcomes than the younger group; in-hospital mortality rates were 46% vs. 33% (p=0.08) and 1-year mortality rates 52% vs. 41% (p=0.17), respectively. Interestingly, the prognosis of the elderly hospital survivors was favourable and similar to the younger hospital survivors (Figure 7, Table 13).

Table 12. Clinical characteristics, CS etiology, and biochemical and clinical findings at baseline in elderly and younger groups and separately in elderly in-hospital survivors and non-survivors. Reproduced with permission from study II.[296]

	ELDERLY n= 56 (26%)	YOUNGER n = 163 (74%)	p-value	ELDERLY SURVIVORS n = 30 (54%)	ELDERLY NON-SURVIVORS n = 26 (46%)	p-value
Age, years	81 (4)	62 (9)	< 0.001	81 (5)	81 (4)	0.7
Female, n (%)	23 (41)	34 (21)	0.003	13 (43)	10 (39)	0.6
MEDICAL HISTORY, n (%)						
Hypertension	39 (70)	93 (57)	0.10	21 (70)	18 (69)	1.0
History of MI/CABG	19 (34)	38 (23)	0.12	7 (23)	12 (46)	0.07
PAD	11 (20)	10 (6)	0.003	3 (10)	8 (31)	0.05
Chronic heart failure	7 (13)	29 (18)	0.4	2 (7)	5 (19)	0.2
Renal insufficiency	11 (20)	14 (9)	0.03	4 (13)	7 (27)	0.2
SHOCK ETIOLOGY, n (%)						
ACS	47 (84)	130 (80)	0.5	25 (83)	22 (85)	1.0
STEMI	37 (66)	112 (69)	0.7	21 (70)	16 (62)	0.5
CLINICAL PRESENTATION AT BASELINE						
Systolic blood pressure, mmHg	78 (11)	77 (15)	0.7	81 (10)	75 (11)	0.08
LVEF, %	36 (15)	32 (14)	0.12	41 (15)	31 (13)	0.03
Confusion, n (%)	44 (79)	104 (64)	0.06	21 (70)	23 (89)	0.09
Oliguria, n (%)	35 (63)	86 (53)	0.19	11 (37)	24 (92)	< 0.001
BIOCHEMICAL FINDINGS						
Creatinine, µmol/L	121 (96-159)	96 (73-138)	0.004	116 (92-137)	127 (106-173)	0.3
Peak hs-TnT, ng/L	3680 (1270-14281)	3849 (927-12585)	0.8	3521 (1194-8036)	4291 (1345-16665)	0.4
NT-proBNP, ng/L	4322 (1599-16786)	2367 (400-8082)	0.02	4965 (838-18786)	3706 (1609-16547)	0.9
Arterial pH	7.29 (7.18-7.37)	7.32 (7.21-7.39)	0.2	7.31 (7.25-7.41)	7.23 (7.10-7.31)	0.02
Lactate, mmol/L	2.8 (2.0-7.9)	2.9 (1.6-5.3)	0.16	2.3 (1.6-3.3)	6.4 (2.8-8.6)	< 0.001
GDF-15, ng/L *at 12h* (n=154)	10871 (6562-30074)	8440 (3846-16033)	0.05	6912 (3901-13309)	29647 (9775-42406)	< 0.001
sST2, ng/mL *at 12h* (n=154)	602 (372-1244)	633 (343-1028)	0.6	482 (311-923)	907 (543-1574)	0.2
suPAR, ng/mL *at 12h* (n=141)	4.7 (4.0-8.3)	4.2 (3.1-7.5)	0.4	4.3 (3.6-4.8)	7.7 (4.8-9.2)	0.004

ACS, acute coronary syndrome; CABG, coronary artery bypass graft surgery; GDF-15, growth differentiation factor 15; hs-TnT, high sensitivity troponin; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NT-proBNP, N-terminal piece of pro-BNP; PAD, peripheral artery disease; STEMI, ST-elevation myocardial infarction; sST2, soluble suppression of tumorigenicity 2; suPAR, soluble urokinase–type plasminogen activator receptor

Table 13. Treatment of shock and outcomes in elderly and younger groups and separately in elderly in-hospital survivors and non-survivors. Reproduced with publisher's permission from study II. [296]

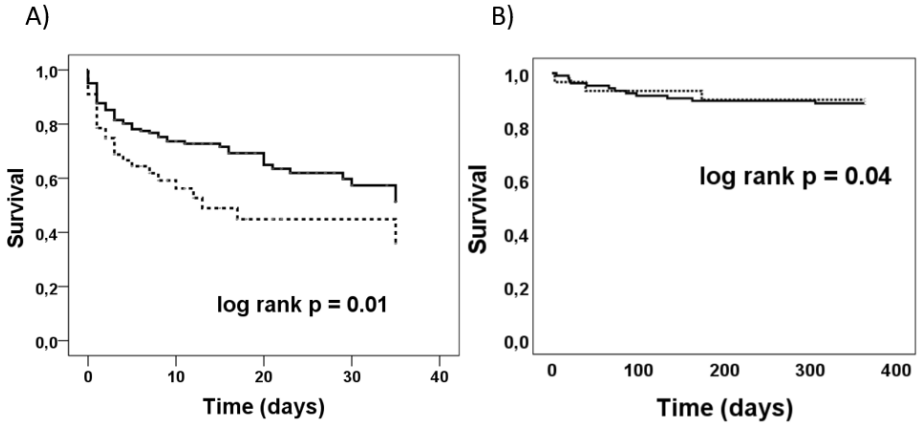
	ELDERLY n= 56 (26%)	YOUNGER n = 163 (74%)	p-value	ELDERLY SURVIVORS n = 30 (54%)	ELDERLY NON-SURVIVORS n = 26 (46%)	p-value
TREATMENT, n (%)						
Angiogram	45 (80)	137 (84)	0.2	28 (93)	17 (65)	0.009
PCI[a]	39 (87)	110 (80)	0.3	23 (82)	16 (94)	0.2
IABP	22 (39)	100 (61)	0.004	10 (33)	12 (46)	0.3
IMV	31 (55)	106 (65)	0.2	11 (37)	20 (77)	0.003
NIV	6 (11)	20 (12)	0.9	3 (10)	3 (12)	0.7
USE OF VASOACTIVE MEDICATION, n (%)						
Noradrenaline	40 (71)	124 (76)	0.5	19 (63)	21(81)	0.15
Dobutamine	25 (45)	84 (52)	0.4	10 (33)	15 (58)	0.07
Adrenaline	13 (23)	33 (20)	0.6	3 (10)	10 (39)	0.01
CARDSHOCK RISK SCORE	5.6 (1.5)	4.0 (1.8)	<0.001	4.9 (1.1)	6.4 (1.4)	<0.001
IABP-SHOCK SCORE	4.8 (1.4)	3.2 (1.4)	<0.001	4.4 (1.2)	5.6 (1.3)	0.009
OUTCOMES, n (%)						
In-hospital mortality	26 (46)	54 (33)	0.08			
1-year mortality	29 (52)	67 (41)	0.17			
1-year mortality[b]	3 (10)	13 (12)	1.0			

IABP, intra-aortic balloon pump; IMV, invasive mechanical ventilation; NIV, non-invasive mechanical ventilation; PCI, percutaneous angiogram

Data are presented as numbers and percentages (%) and means (SD).

a) Proportion of those who underwent angiogram, b) among hospital survivors (n=139)

Figure 7. Kaplan-Meier survival curves for all-cause mortality in the elderly (≥75 years old) (dashed line) and the younger (<75 years old) (solid line) group patients with cardiogenic shock. (A) In-hospital mortality including all patients. (B) 1-year mortality for those surviving hospitalization. Reproduced with publisher's permission from Study II.[296]



5.2.3 Risk prediction and performance of the risk scores in the elderly

The elderly group exhibited higher risk scores according to both risk models when compared with the younger group (CardShock risk score 5.6 [SD 1.5] vs. 4.0 [1.8], p<0.001; IABP-SHOCK score 4.8 [SD 1.4] vs. 3.2 [1.4], p<0.001). In addition, both risk models categorized the elderly group more frequently into intermediate and high-risk groups than into the low-risk group. The higher the risk category was, the poorer the outcome (Figure 8).

The discriminative ability of the risk models to predict in-hospital mortality in the elderly was reasonable. The AUC values were 0.75 for the CardShock risk score and 0.71 for the IABP-SHOCK II score; the corresponding values for the younger group were 0.82 and 0.73, respectively. In the elderly, GDF-15 and sST2 improved the discrimination of both risk models when added separately on top of the scores. Interestingly, adding both biomarkers at the same time did not improve the discrimination compared to adding only one biomarker at a time (Table 14).

The CardShock risk score was further validated in a cohort consisting of CS patients with unselected etiology from a Spanish single-center prospective study. In this validation cohort, the CardShock risk score had an AUC of 0.75 (95% CI 0.69–0.80) for all patients (n=262), 0.77 (95% CI 0.67–0.87) for patients ≥75 years old (n=83), and 0.75 (95% CI 0.68–0.82) for patients <75 years old.

Figure 8. Distribution of patients and in-hospital mortality of the elderly and younger groups according to A) the CardShock score and B) the IABP-SHOCK II score. Modified with publisher's permission from study II. [296]

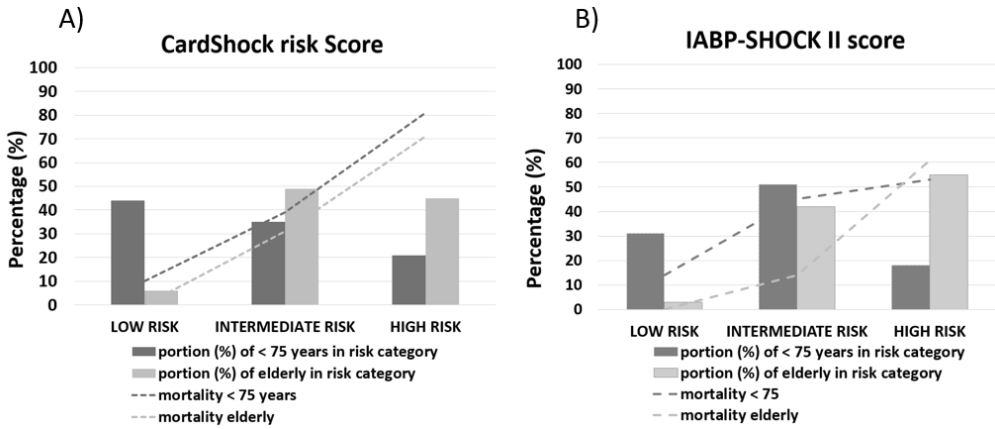


Table 14. Discriminative ability of the CardShock risk score and the IABP-SHOCK score to predict in-hospital mortality in the elderly and the additional value of GDF-15 and sST2 to improve discrimination. Reproduced with publisher's permission from study II. [296]

Model	ELDERLY AUC (95 %CI)	χ^{2*}	p-value*
CardShock risk score (n=40)	0.75 (0.60–0.91)		
+ GDF-15	0.82 (0.69–0.95)	4.92	0.03
+ sST2	0.80 (0.66–0.93)	2.56	0.1
+ GDF-15 + sST2	0.81 (0.68–0.94)	5.76	0.06
IABP-SHOCK II score (n=28)	0.71 (0.47–0.94)		
+ GDF-15	0.84 (0.69–0.99)	8.78	0.003
+ sST2	0.78 (0.59–0.96)	5.14	0.02
+ GDF-15 + sST2	0.83 (0.68–0.98)	9.56	0.008

AUC, area under the curve; CI, confidence interval; GDF-15, growth differentiation factor-15; sST2, soluble ST2.
*χ2- and P-values are shown for comparison of nested models.

5.2.4 Comparing elderly survivors and non-survivors

Elderly survivors and non-survivors were similar regarding age and shock etiology. Non-survivors tended to have more underlying diseases, specifically generalized arteriosclerosis. Evaluation of the clinical picture at baseline revealed that non-survivors suffered from more severe shock and hypoperfusion already at inclusion, as reflected by the greater requirement for hemodynamic and respiratory support (Tables 12 and 13).

Assessing the performance of the risk models separately in the elderly survivors and non-survivors revealed that the survivors had a markedly lower risk profile according to both risk models (CardShock risk score 4.9 vs. 6.4, p<0.001; IABP-SHOCK II score 4.4 vs. 5.6, p=0.009). In addition, the survivors were more frequently categorized into the intermediate-risk group (64% vs. 32%; p=0.02) in contrast to non-survivors, who were mostly categorized into the high-risk group (68% vs. 25%; p=0.002).

5.3 Novel biomarkers in cardiogenic shock (III, IV)

5.3.1 Growth differentiation factor-15 (III)

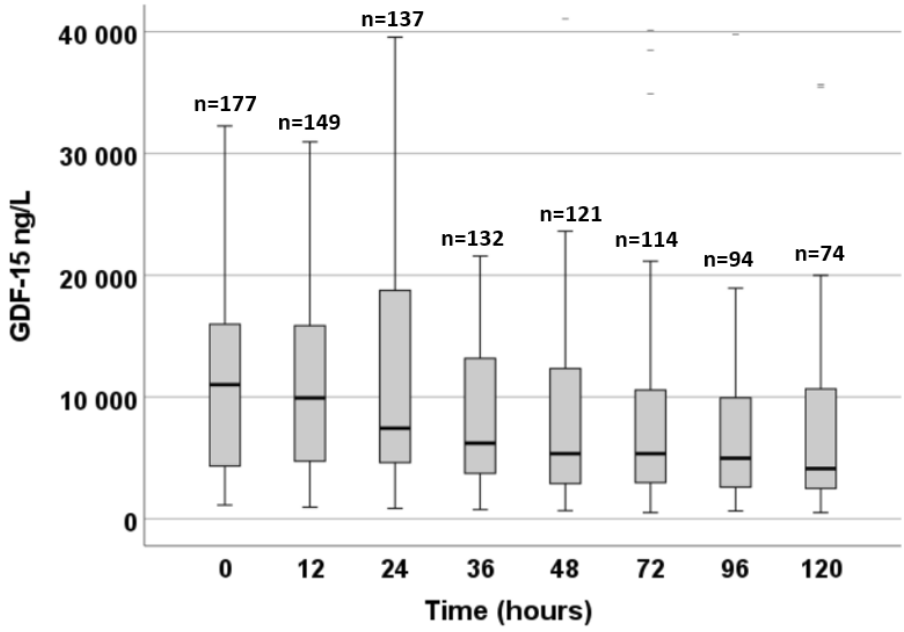
5.3.1.1 Kinetics and serial sampling of GDF-15

This study included 177 patients. The levels of GDF-15 were strongly elevated in CS at all measured time points. The median level of GDF-15 was highest at baseline (9647 ng/L, IQR 4500-19270 ng/L) and decreased thereafter (Figure 9). Baseline GDF-15 levels above median were associated with acidosis, hyperlactatemia, congestion, liver injury, and renal dysfunction (Figure 10, Table 15). GDF-15 levels correlated significantly at baseline with NT-proBNP (ρ=0.38, p<0.001), lactate (ρ=0.47, p<0.001), and eGFR (ρ=-0.45, p<0.001).

According to serial measurements, non-survivors had significantly higher GDF-15 levels at all timepoints compared with survivors. Furthermore, GDF-15 levels in survivors decreased. In contrast, GDF-15 levels in non-survivors remained stable or even increased in the early course of shock (Figure 9).

Figure 9. A) Median levels of GDF-15 in all patients and B) GDF levels in 90-day survivors (white) and non-survivors (grey).

A)



B)

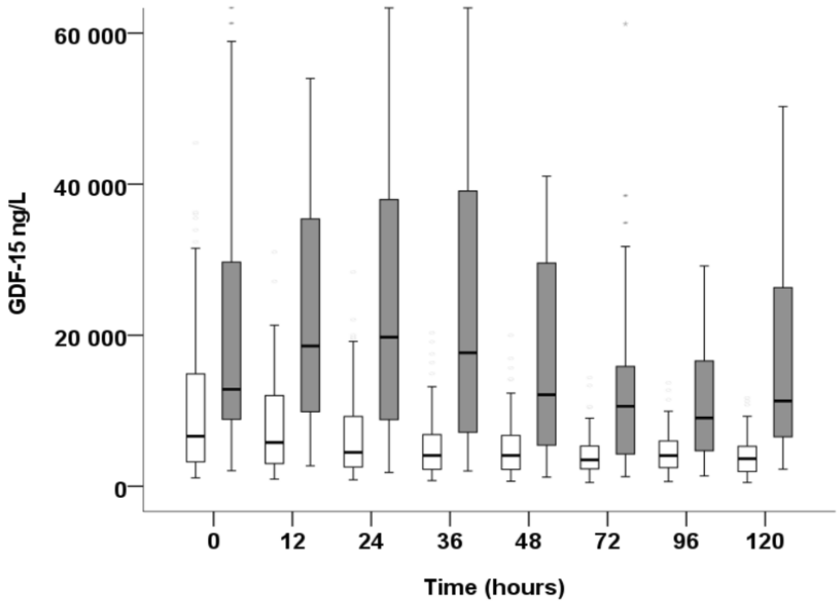
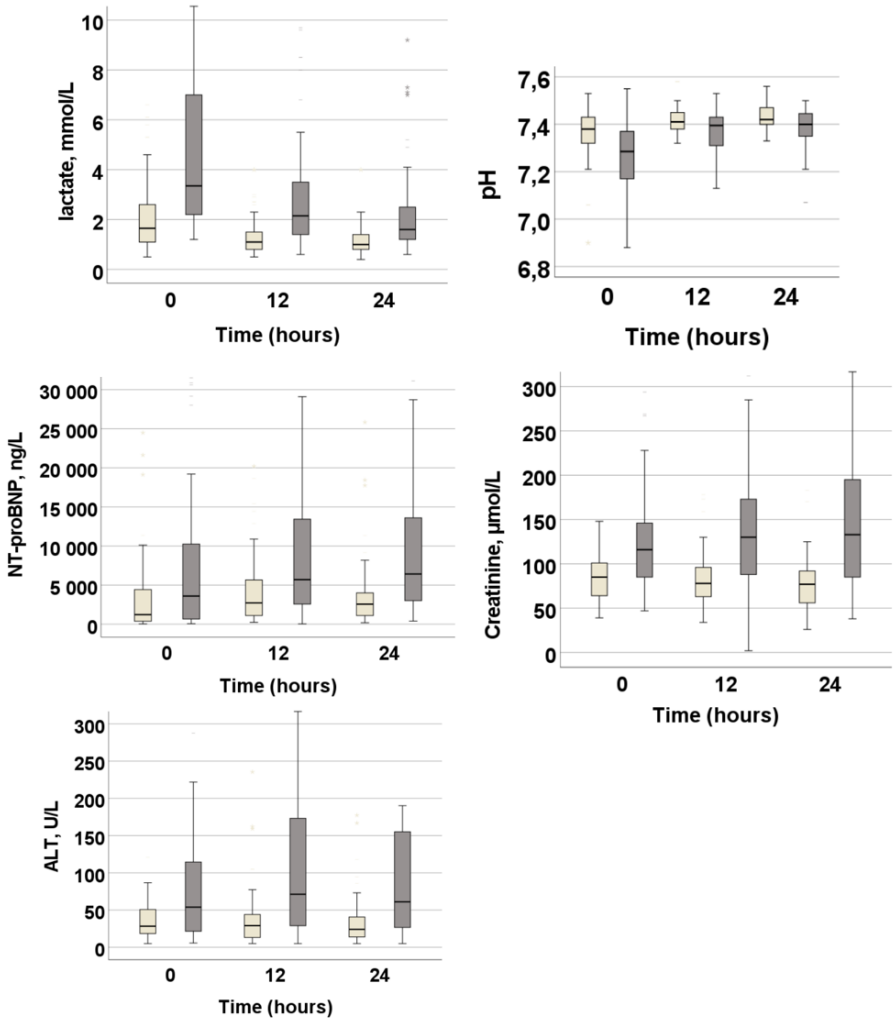


Figure 10. Biomarkers reflecting end-organ damage and hypoperfusion during the first 24 hours in patients with GDF-15 over (grey) or below (beige) 7000 ng/L at 12 h (all p<0.05).

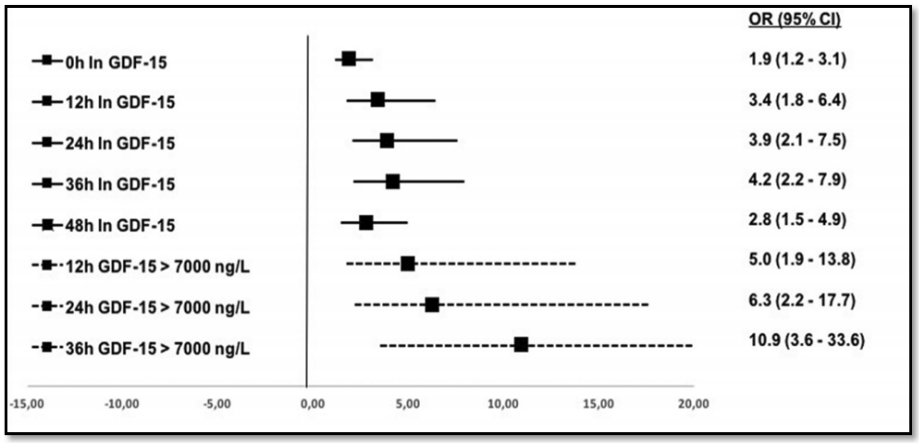


5.3.1.2 GDF-15 and outcome

In-hospital and 90-day mortality rates were higher among those with baseline GDF-15 levels > median compared with those with GDF-15 levels ≤ median (50% vs 25%, p=0.001; 56% vs 28%, p<0.001).

The unadjusted OR for 90-day mortality at baseline for lnGDF-15 was 2.1 (95% CI 1.5-2.9; p<0.001). After adjusting the model with the CardShock risk score variables, GDF-15 remained an independent 90-day outcome predictor with an OR of 1.9 (95% CI 1.2–3.1; p=0.008). Furthermore, GDF-15 was also a strong and independent predictor of 90-day mortality at later time points (Figure 11).

Figure 11. Forest plot for association of ln GDF-15 (solid line) and GDF-15 > 7000 ng/L (dashed line) at various time points with 90-day mortality (all p<0.05). The model is adjusted for the CardShock risk score variables. Reproduced with publisher's permission from study III.[292]



5.3.1.3 GDF-15 in risk prediction

The prognostic ability of GDF-15 to predict 90-day mortality was highest at 12-36 h (AUC range 0.81-0.84). We selected GDF-15 at 12 h for further analyses. The optimal cutoff value of 7000 ng/L for GDF-15 at 12 h was derived from the ROC curve with a sensitivity of 86% and a specificity of 62%. Adding this cutoff to the CardShock risk score improved the discrimination compared with the CardShock risk score alone, with an increase in AUC from 0.83 to 0.85 (χ^2=10.6, p=0.001; IDI 0.053, 95% CI 0.012–0.094, p=0.01). Furthermore, adding the cutoff to the CardShock risk score improved the re-classification specifically among survivors (NRI 0.18, 95% CI 0.06–0.30; p=0.003). Improvement in re-classification was observed until 36 hours.

The prognostic value of GDF-15 at 12 h > 7000 ng/L for 90-day mortality was independent from the CardShock risk score variables. The result remained unchanged using the same cutoff of 7000 ng/L at 24 h and 36 h (Figure 11).

Table 15. Clinical characteristics and presentation, shock etiology, baseline biochemistry, and outcomes in patients according to median GDF-15 and suPAR. Modified with permission from studies III and IV.[292]

	GDF-15 ≤ median (n=89)	GDF-15 > median (n=88)	p-value	suPAR ≤ median (n= 81)	suPAR > median (n= 80)	p-value
Age, years (SD)	65 (12)	67 (13)	0.4	66 (11)	66 (12)	1.0
Female, n (%)	20 (23)	25 (28)	0.4	21 (26)	20 (25)	0.9
Shock etiology, n (%)						
ACS	71 (80)	71 (81)	0.9	71 (88)	56 (70)	0.006
STEMI	61 (69)	58 (66)	0.7	65 (80)	41 (51)	<0.001
Medical history, n (%)						
Diabetes	20 (22)	32 (36)	0.04	21 (26)	27 (34)	0.3
Coronary artery disease	21 (24)	36 (41)	0.014	21 (26)	32 (40)	0.06
Heart failure	11 (12)	18 (20)	0.15	7 (9)	20 (25)	0.005
Renal insufficiency	7 (8)	14 (16)	0.1	1 (1)	18 (23)	<0.001
Clinical presentation (at baseline)						
Systolic BP; mmHg	77 (12)	77 (16)	1.0	75 (12)	80 (15)	0.05
HR, beats/min	87 (28)	89 (29)	0.6	86 (26)	90 (29)	0.4
LVEF; %	35 (14)	31 (14)	0.10	35 (14)	29 (13)	0.006
CardShock risk score	3.6 (1.9)	5.0 (1.6)	<0.001	3.9 (1.9)	4.7 (1.9)	0.008
Biochemistry						
CRP; mg/L	7 (4-40)	26 (5-75)	0.01	6 (2-25)	41 (9-89)	<0.001
Creatinine; µmol/L	91 (68-116)	125 (88-157)	<0.001	88 (69-114)	127 (91-168)	<0.001
ALT; U/L	29 (17-52)	82 (33-152)	<0.001	44 (23-79)	50 (20-141)	0.2
Lactate; mmol/L	2.1 (1.3-3.7)	3.7 (2.3-6.7)	<0.001	2.6 (1.5-4.9)	3.0 (1.7-6.8)	0.1
NT-proBNP; ng/L	1360 (373-6627)	5029 (1581-12300)	<0.001	1077 (253-3589)	6726 (2088-16786)	<0.001
hs-TnT; ng/L	1581 (347-4083)	2629 (441-8716)	0.06	1885 (446-5365)	1733 (208-5110)	0.6
In-hospital mortality, n (%)	22 (25)	44 (50)	0.001	23 (28)	36 (45)	0.03
90-day mortality, n (%)	24 (28)	49 (56)	<0.001	25 (31)	39 (49)	0.02

Data are presented as numbers and percentages (%), means (SD), or medians (interquartile range), as appropriate.
ACS, acute coronary syndrome; ALT, alanine aminotransferase; BP, blood pressure; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HR, heart rate; hs-TnT, high sensitivity troponin; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal piece of pro-BNP; SD, standard deviation; STEMI, ST-elevation myocardial infarction

5.3.2 Soluble urokinase–type plasminogen activator receptor (IV)

5.3.2.1 Kinetics and serial sampling of suPAR

Study IV included 161 patients from the CardShock study population. Clinical characteristics of the patients are presented in Table 15. The baseline median suPAR level was 4.4 (IQR 3.2-6.6) ng/mL. In contrast to the kinetics of GDF-15, suPAR levels were lowest at the beginning of shock and increased thereafter. According to serial sampling, the median level of suPAR remained fairly stable during the first 24 hours and increased thereafter, reaching maximum at 96 h (5.6 [IQR 4.1-9.4] ng/mL) (Figure 12).

Baseline suPAR levels above median were associated with a history of heart failure and renal insufficiency and with the biomarkers reflecting these derangements. Furthermore, C-reactive protein levels were higher in patients with baseline suPAR > median (Table 15).

5.3.2.2 suPAR and outcome

Baseline suPAR levels above median were associated with higher in-hospital (45% vs 28%; p=0.03) and 90-day mortality (49% vs 31%; p=0.02).

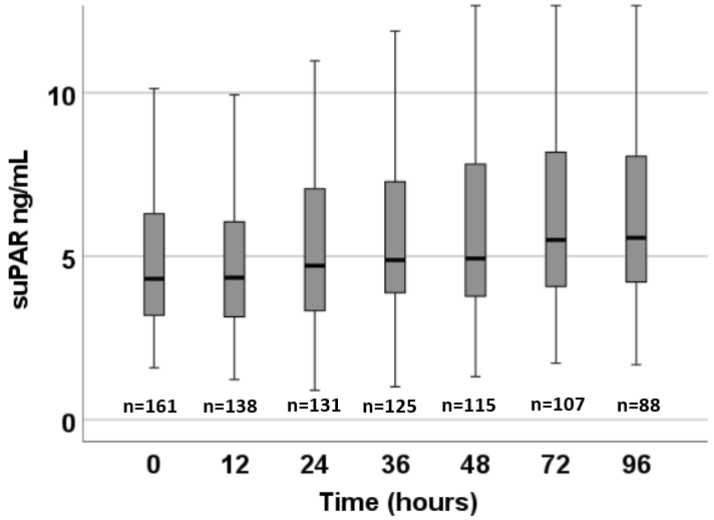
Serial measurements revealed that survivors had significantly lower suPAR levels at all timepoints than non-survivors. Furthermore, suPAR concentrations remained stable in survivors but increased in non-survivors (Figure 12).

5.3.2.3 suPAR in risk prediction

SuPAR at 12 hours was selected for further analyses to assess the additional prognostic role of the biomarker in risk stratification. A cutoff value of 4.4 mg/mL was derived from the ROC curve with a sensitivity of 77% and a specificity of 64%. The prognostic ability of the cutoff value for 90-day mortality was independent of the CardShock risk score variables (adjusted OR 5.6 [95% CI 2.0-15.5]; p=0.001). Adding the cutoff value to the CardShock risk score improved risk prediction for 90-day mortality compared with the risk score alone (AUC 0.87 vs. 0.84, χ^2=14.2; p<0.001). Furthermore, dividing each CardShock risk category by the cutoff into two subgroups (low/intermediate/high risk category + suPAR 12h above or below cutoff) improved the risk stratification, particularly in patients with intermediate risk (Figure 13).

Figure 12. A) Median suPAR levels in all patients and B) suPAR levels in 90-day survivors (white) and non-survivors (grey).

A)



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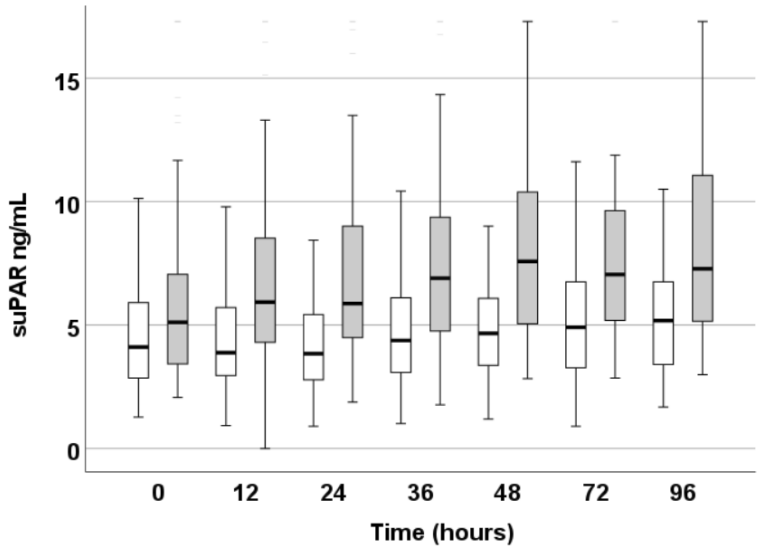
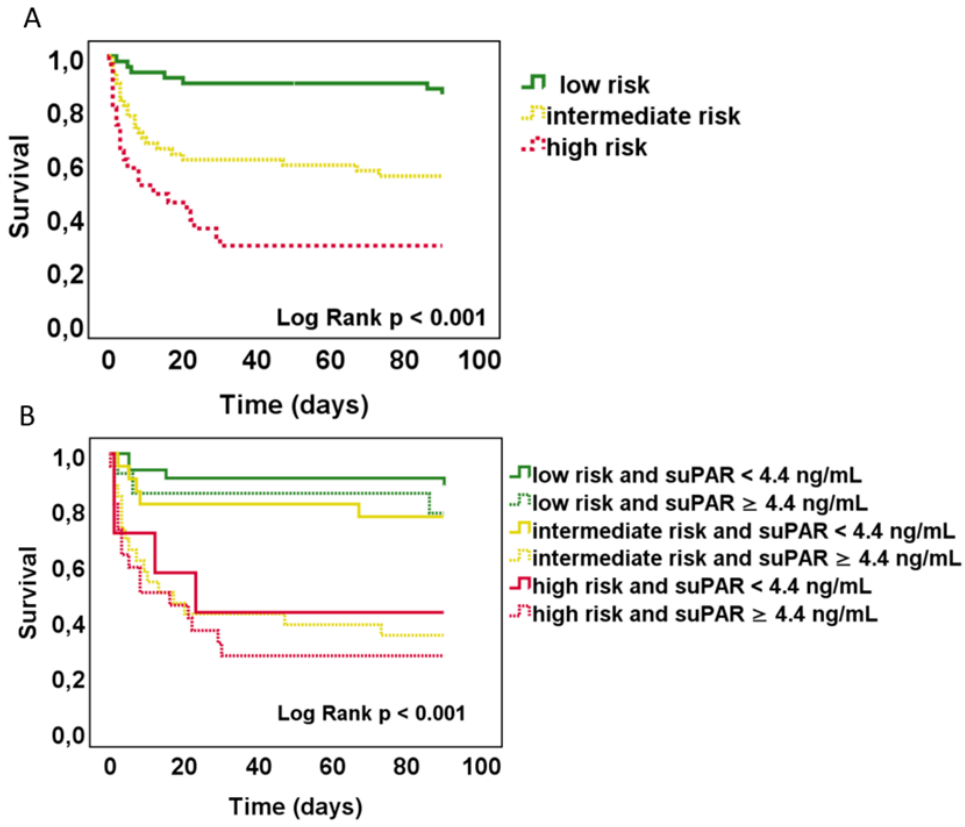


Figure 13. 90-day mortality A) in different CardShock risk categories (low/intermediate/high risk) and B) in CardShock risk score categories (low/intermediate/high risk) divided by the suPAR cutoff 4.4 ng/mL at 12 h into two subgroups.



6 DISCUSSION

6.1 Ventilation strategies in cardiogenic shock

In this study, we evaluated the use of different ventilation strategies in CS and focused on the use of NIV. Reflecting the wide spectrum of the clinical picture of shock, presentations ranging from from mild hypoperfusion to treatment-refractory shock, the distribution of the ventilatory modalities used in our study was also broad. One fourth of the patients managed only with conventional oxygen therapy and the remainder were treated with MV. Twelve percent were treated with NIV and 63% with IMV. In prior studies, the use of MV, NIV, and IMV in CS patients varied between 40-85%[10, 105, 107, 112, 113, 134], 4-11%[105, 107, 113, 134], and 46-83%[105, 107, 113, 134], respectively, depending on the study design and population. In two quite recent randomized controlled studies on CS, with patient populations that quite closely resemble our study population (the IABP-SHOCK II study and the CULPRIT study), on average 80% of the patients were treated with MV, which corresponds with our findings.[10, 107] Nevertheless, in this study the use of NIV was higher than in previous studies. Overall, the use of NIV in CS has been increasing in the last two decades, probably due to more advanced techniques and because NIV devices have become more readily available.[105]

Closer examination revealed that the NIV and IMV groups did not differ regarding previous medical history or shock etiology. Rather, the clinical picture of patients treated with NIV seemed to be congestive, whereas those treated with IMV tended to suffer from more severe shock already at baseline. In addition, 40% of the patients in the IMV group were resuscitated, which may have contributed to the choice of IMV. Interestingly, the degree of RF in terms of P/F ratio did not differ between the NIV and the IMV groups, and improvement in the P/F ratio was similar between the groups. This may also suggest indications other than only RF for intubation, such as altered mental status or refractory shock.

Although the use of NIV is well established and recommended in acute HF, its role in CS is largely unexplored.[41, 297, 298] Many studies assessing ventilation strategies, especially NIV, in acute HF excluded patients presenting with shock, STEMI, or a need for urgent revascularization.[16, 19, 147, 148] There are safety concerns regarding the use of NIV in CS patients; the possible deleterious effects of PPV on tenuous hemodynamic and frequently altered mental status do not necessarily ensure correct spontaneous breathing and preservation of the upper airway.[109, 116] In our study, only few patients in the NIV group were intubated, and the number was insufficient to draw definite conclusions on safety and efficacy. Nevertheless, most of the patients initially treated with NIV managed with this ventilatory modality and avoided intubation. Furthermore, the choice of ventilation strategy (NIV vs. IMV) did

not affect mortality. In comparison, in the CULPRIT study (n=683), 8% of the patients were treated with NIV, of which 22% failed and required intubation.[107] The outcome of those with failed NIV was very poor with mortality rate over 80%.

Mortality in the IMV group was markedly higher than in the NIV group. The higher risk profile was also reflected by the higher CardShock risk scores in the IMV group. Poorer outcome was most likely explained by the more severe shock in the IMV group. However, 90-day mortality was similar in both groups after balancing the NIV and IMV groups for medical history, shock etiology, age, gender, and severity of shock.

Our findings indicate that the choice of ventilatory strategy itself does not have an effect on the outcome in CS. Although NIV may be used safely and successfully in the treatment of RF in CS, careful patient selection for NIV is necessary. The use of NIV and PPV requires experience and knowledge regarding the cardiopulmonary effects of PPV. NIV should be considered in patients who require oxygen and ventilatory support but are not in immediate need for intubation. After application of NIV, treatment response should be carefully monitored; IMV should be started immediately if treating RF with NIV fails. In general, the need for MV and IMV are related to poorer prognosis in CS.[134] This has been acknowledged and incorporated in some general risk scores and more recently in the new classification of CS by the SCAI.[45, 202, 284]

6.2 Cardiogenic shock in the elderly

Although elderly patients are the fastest growing age group of the Western population and constitute a continuously increasing proportion of CS patients, this age group is often underrepresented or even excluded in clinical trials. Age-related changes have multiple physiological effects that lead to uncertainty on the efficacy and safety of some treatment strategies, which highlights the need for contemporary data on real-life elderly CS patients.

This study revealed several novel findings on a contemporary cohort of elderly CS patients and early risk prediction in this age group. The elderly consisted of a quarter of the CS patients. In previous studies, the proportion of elderly CS patients varied between 19-37%, depending on the study design.[52, 152, 157, 162] The present study was conducted in tertiary hospitals with revascularization facilities, which may have affected patient selection; elderly patients with a heavy burden of comorbidities and very poor prognosis were probably not transferred to tertiary centers for treatment. In line with the present study, a recent Danish retrospective registry study on ACS-CS patients admitted to tertiary care reported that 29% of patients were ≥75 years old.[299]

Shock etiology was similar between the age groups in our study. Unsurprisingly, ACS was the most common cause. However, the spectrum of non-ACS etiologies did not differ between the groups. The treatment

procedures were similar in the elderly and the younger groups, although there was more frequent use of IABP in the younger group. In general, elderly patients are less likely to receive evidence-based treatment and they have a risk for longer pre-hospital delay. This may be partly due to delayed symptoms but there is also suspicion of age-related nihilism regarding the treatment choice.[25, 156, 299, 300] In the present study, coronary angiogram was performed in 80% of the elderly and PCI in 87% of those who underwent an angiogram. Considering the etiology of shock in this age group (ACS in 84% and STEMI in 66%), we can conclude that the revascularization rate was very reasonable and actually higher than in previous studies.[52, 162] Interestingly, in the aforementioned Danish study, the elderly were less likely to be referred to a tertiary center or undergo a revascularization attempt compared with younger patients.[299]

Elderly CS patients may be considered a double-edged sword. As they are at the highest risk for poor outcome, these patients would benefit most from treatment. However, they are also more susceptible to treatment-related complications. In the elderly, age-related decline in physiological and functional reserves reduces the likelihood of recovery from critical illness. However, depending on risk factors, comorbidities, and lifelong health habits, among other considerations, persons of the same age may have different risk profiles and thus prognosis, which emphasizes the need for proper risk stratification.

6.2.1 Prognosis of cardiogenic shock in the elderly

The elderly had poorer outcomes in our study than the younger patients. Among those elderly who survived to hospital discharge, 1-year survival rate was similar compared with the younger. Our findings are consistent with previous studies, which reported comparable long-term survival rates (33-45%) among the elderly.[52, 160, 161, 163] Furthermore, quality of life in survivors has been reported to be good.[5] Overall, survival among the elderly has improved markedly since the SHOCK-study, which reported 75% mortality in those treated with early revascularization two decades ago. In contrast, the recent Danish study reported 30-day mortality of 73% in elderly CS patients, which is clearly higher than in our study and previous studies.[299] In general, differing survival rates in different studies are due to various study designs and populations, which makes comparison of results challenging. Most CS studies have focused on ACS-CS patients and been based on populations undergoing PCI.[151, 152, 160, 163, 173, 299, 301]

We assessed the differences between the elderly survivors and non-survivors. The non-survivors were characterized by a more severe degree of shock already at baseline, with higher lactate levels and acidosis along with greater need for vasoactive medication and IMV. The non-survivors were less likely to undergo a revascularization attempt, which highlights the importance

of well-balanced treatment decisions based on clinical judgement instead of nonselective use of early revascularization and futile life-prolonging efforts in hopeless situations.

6.3 Risk prediction of cardiogenic shock

Early and accurate risk stratification is essential in CS. Considering the progressive nature of CS with its complex pathophysiology, early recognition of shock and prompt treatment may help to stop shock progression and prevent irreversible end-organ failure. Although the available evidence for the use of advanced therapy options (such as MCS devices) in the early stages of CS is limited, it appears beneficial to start such therapies at the early phase rather than as a last resort.[92] The ability of MCS to improve prognosis is limited if applied when overt multiorgan failure has already occurred. Proper risk stratification can help recognize shock at the early stage, identify patients with the highest risk, and help select the correct treatment for the appropriate patient.

6.3.1 Performance of the risk prediction scores in the elderly

We evaluated the performance of the two contemporary risk prediction scores (the CardShock risk score and the IABP-SHOCK score) in the elderly. Although both scores performed satisfactorily, their discriminative ability did not reach that of the younger. Additionally, we performed a further external validation of the CardShock risk score in an unselected CS population; the results corresponded to those we observed in our study.

Both risk scores categorized most elderly patients into intermediate and high-risk groups. Additionally, most non-survivors were categorized into the high-risk group according to both scores. Nevertheless, both scores classified a substantial number of survivors in the intermediate-risk group and even into the high-risk group. As age is one of the variables in both scores (one point is given to elderly patients automatically), the elderly were more likely to receive higher scores and thus had less score dispersion, which reduces the discriminative ability of the risk prediction tools. In a cohort of >10 000 cardiac intensive-care patients, the performance of the illness severity scores was less accurate in patients >70 years compared with younger patients.[302]

Recently, the concept of frailty syndrome has drawn attention in critical care and it may be beneficial in the risk assessment of CS as well.[303-305] In practice, the entities behind frailty syndrome (such as independence, cognitive function, comorbidities) are currently estimated individually in each patient. However, staging frailty state by a common frailty categorization may

help to standardize care and may also be useful in future trials to recruit more homogenous cohorts and to compare results. Frailty may be the missing link between age and mortality that is not reflected in the current risk scores. Although the performance of the scores in our results seems to be reasonable in the elderly, further improvement in their discriminative ability would be preferred. In comparison, according to the Danish study by Ratcovich et al, most of the elderly CS patients were categorized into low- and intermediate-risk groups (45% and 42%, respectively) by the IABP-SHOCK score even though the mortality of the elderly in that study was as high as 73%, which suggests unsatisfactory performance of the risk model.[299]

6.4 Biomarkers in cardiogenic shock and their role in early risk stratification

Optimal risk prediction tools are reproducible, easy to use, and consist of readily available variables that collectively provide objective guidance in risk assessment and resource allocation. However, risk prediction tools, including mainly clinical variables, are inaccurate and more individualized tools are needed. Biomarkers that reflect distinct pathogenetic pathways in CS may bring incremental prognostic information beyond clinical data when combined with risk scores.

We evaluated the prognostic role of two novel biomarkers, GDF-15 and suPAR, in early risk stratification. We found that despite the differing and partly opposing kinetics, high levels of both biomarkers were associated with higher mortality in CS. Additionally, we investigated the potential of GDF-15 and sST2 to improve risk prediction in the elderly.

Contemporary risk prediction scores for CS include variables that are not necessarily immediately available in the emergency setting (such as TIMI flow), may be difficult to obtain due to the patient's critical illness (such as previous medical history from an intubated patient), or may be subjective (such as LVEF and confusion).[2, 199] These limit the objectivity and usefulness of these scores. A recent biomarker-based risk score, the CLIP score, offers an interesting alternative tool for risk prediction.[200] Based on different biomarkers, each of which reflect various pathogenetic pathways in CS (renal, inflammation, hypoperfusion, and cardiac stress), the score integrates information not captured by traditional markers and provides an objective view for risk assessment. Additionally, the score may offer a modern tool for repeated risk stratification during the hospital stay. However, use of the CLIP score requires a separate application or a designated counter, making its use challenging in clinical practice.

6.4.1 GDF-15

Study III evaluated the kinetics and the prognostic role of GDF-15 in CS. We found that GDF-15 levels were markedly elevated at each measured time point and concentrations reached maximum already at baseline, indicating a very rapid rise in the expression of GDF-15 in response to stressors caused by CS. GDF-15 was associated with markers reflecting hypoperfusion (lactate, acidosis) and end organ dysfunction (heart, kidney, liver). Our findings support data from previous studies that assessed GDF-15 levels in two different systemic hypoperfusion conditions, end-stage HF and severe sepsis.[238, 239] These studies also revealed high GDF-15 levels and their association with hypoperfusion-related markers. Additionally, GDF-15 has shown to associate with different organ failures.[240] Altogether, these results highlight the potential of GDF-15 as a prognostic marker in CS; by mirroring several pathophysiological pathways and systems activated in shock with a rapid response, GDF-15 seems to simultaneously collect information from distinct pathogenetic pathways already in the early phase of shock, thus offering a novel means to improve risk assessment. Furthermore, the observed very rapid rise in GDF-15 concentration in response to shock increases its attractiveness and usefulness when compared with traditional biomarkers, such as creatinine, the concentration of which increases relatively slowly in acute situations and may lead to delayed detection of organ failure.

We observed that high and increasing GDF-15 levels were associated with poorer prognosis, whereas decreasing concentrations were associated with a more favourable outcome. These findings are consistent with a previous study that revealed that decreasing GDF-15 levels were associated with better outcome in patients with ACS-CS, whereas high levels were associated with refractory shock and poorer outcome.[89] Furthermore, as described previously, implantation of an MCS device in patients with advanced HF decreased GDF-15 levels to nearly normal, probably by unloading the failing heart.[238] Considering these results together with our findings, decreasing GDF-15 levels may be indicative of a favourable response to treatment and thus better prognosis.

In this study, we showed that GDF-15 is a strong and independent prognostic marker not only at the beginning of shock but also later during the hospital course. However, the discriminative ability of GDF-15 was best at the early stage of shock, a finding that is very relevant from a clinical perspective. Incorporating the defined cutoff of GDF-15 at 12 h to the CardShock risk score improved the discrimination and early risk stratification significantly. Appropriate risk stratification in the early phase of shock is a cornerstone of CS treatment. Risk stratification can assist in timing of therapy options and allocating resources and thereby improve prognosis. Application of advanced therapies, such as mechanical circulatory devices, should be started early before irreversible end-organ damage occurs.[92]

6.4.2 suPAR

In study IV we assessed the kinetics of suPAR and its potential in prognostication. In contrast to GDF-15, we found that suPAR levels were quite stable at the early phase of shock. However, suPAR concentrations tended to increase thereafter. The stability of suPAR levels in the early phase of shock increases its potential from a clinical perspective. This feature of suPAR has been utilized in risk stratification in emergency care. Certain suPAR cutoff values are useful for identification of patients at low risk of serious illness who can be discharged safely from the emergency department.[306]

SuPAR is known to reflect the level of immunoactivation and has been shown to have prognostic potential in several inflammatory conditions, ranging from sepsis to chronic inflammatory diseases.[252, 256, 307] Additionally, suPAR has a close correlation with impaired renal function and heart failure.[38, 260, 267, 268] Inflammation and renal and heart failure play important roles in the complex pathogenesis of CS. However, suPAR levels in our study were markedly lower than in other critically ill patient populations (such as sepsis) and rather corresponded with the levels measured in chronic HF and STEMI.[36, 256, 268, 308] One potential explanation may be that although inflammation is closely related to the pathogenesis of CS, the degree of inflammation is probably not as high in CS as in sepsis. Actually, a study that assessed the inflammatory responses in ACS-CS and sepsis revealed that inflammatory responses in CS were lower than in septic shock.[65] Nevertheless, although suPAR levels in our study were lower when compared with other critically ill patients, suPAR was an independent and strong predictor of outcome. Its prognostic potential may reflect its ability to integrate information from different pathogenetic pathways, such as inflammation, organ failure, and underlying comorbidities.

High suPAR levels were clearly related to poorer prognosis and non-survivors presented higher biomarker levels when compared with survivors. The ideal cutoff for suPAR defined in this study at 12 hours improved risk stratification, especially in the patients originally categorized in the intermediate risk group by the CardShock risk score. This is an important finding from a clinical perspective. In the early phase of shock, which can be regarded as a turning point in the management of patients with CS (almost all of whom are revascularized as indicated), suPAR provides additional prognostic information beyond clinical variables and the recently developed risk score in CS.

The main challenge in the treatment of CS patients is recognition of high-risk patients who may benefit most from advanced treatment options, such as mechanical circulatory devices, before irreversible end-organ injury occurs. The finding of the present study regarding the ability of suPAR to restratify patients with intermediate risk into high- and low-risk categories offers a promising tool for clinicians treating these patients and struggling with the decision whether to proceed into more advanced therapy options or

not. Although treatment decisions may be more straightforward in patients with low or high risk, such decisions for patients with intermediate risk are more challenging and additional treatment guidance is needed. Our results indicate that by combining suPAR with the clinical risk stratification model, discrimination and early risk prediction may be markedly improved. This may facilitate identification of the highest-risk patients who may benefit most from further treatments.

6.4.3 GDF-15 and sST2 in risk assessment in the elderly

In elderly non-survivors with severe shock and hypoperfusion, GDF-15 levels were very high, over 4-fold greater than those of survivors. The numerical levels of sST2 were also clearly higher in elderly non-survivors, although the difference did not reach statistical significance when compared with survivors.

We evaluated the additional value of GDF-15 and sST2 in risk prediction in the elderly CS patients. We found that both biomarkers substantially improved early risk prediction. Surprisingly, adding both biomarkers at the same time in addition to the risk prediction models did not improve risk prediction compared with adding one biomarker at a time. This may be due to the small sample size.

6.5 Limitations

This study had some limitations. First, although the overall number of patients included in this study is reasonable, the number of the patients in certain subgroups (I, II) was limited, which created some uncertainty in statistical between-group comparisons. Thus, caution is required in interpretating these results. However, this is a common problem in studies regarding CS and critical illness in general.

Second, there was a lack of centralized adjudication of diagnoses (I-IV) in this study. Nevertheless, all diagnoses were set by the local experienced investigators, with a high rate of accordance to international guidelines.

Third, as this was an observational study, the management of CS was not guided per protocol, and all treatment decisions were at the discretion of the responsible physician. Our trial lacked randomization and confounding by indication is a possible bias when comparing different treatment modalities (I). However, we used advanced statistical methods to minimize this bias. Furthermore, this study reflects real-life practice in European tertiary care hospitals, and the choice of treatment strategy was made after careful evaluation based on each individual patient's global health and clinical presentation by an experienced clinician.

Finally, one of the main limitations in our study was the lack of external validation in biomarker studies (II-IV). However, this was one of the largest cohorts of biomarker studies in CS and provides the most current knowledge in this field and a good basis for further studies.

6.6 Clinical implications and future perspectives

The CardShock study is one of the largest contemporary study cohorts on CS. The study provides unique data on the clinical picture, treatment, biochemistry, and prognostication of CS. There are several strengths of the CardShock study, such as the prospectively recruited cohort with unselected CS etiology, multinational enrolment, including patients from nine European tertiary centers, and extensively collected data regarding serial plasma sampling.

This thesis and its results provide several clinical implications and open new perspectives for future research. The results from study I are supportive for the use of NIV in CS in properly selected patients. The spectrum of the clinical picture of RF in CS patients is wide; a quarter were managed only with conventional oxygen therapy, whereas over half of the patients were treated with IMV. Accordingly, it seems that some CS patients with RF may be managed with NIV. More detailed research is warranted regarding the optimal ventilation mode and settings for CS and which oxygen therapy and targets would have the most favourable physiologic responses and clinical outcomes. Furthermore, the use of HFNC in milder forms of CS-related RF and the weaning process should be evaluated.

The results from study II support the use of the contemporary risk scores also in elderly CS patients. Although short-term mortality was higher in the elderly, the prognosis of the elderly patients who survived to hospital discharge was comparable with the younger patients, underlining the importance of appropriate patient selection and accurate risk assessment. Furthermore, the outcome of the elderly patients categorized into low and intermediate risk groups was actually better compared with their younger counterparts, indicating that elderly CS patients with low-intermediate risk, whose overall situation warrants aggressive therapy, should be treated as actively as younger patients with the same risk profile. Considering the ageing of the population, the risk prediction scores may serve as valuable tools not only currently but also increasingly in the future. However, the risk prediction tools based only on clinical variables may not necessarily perform ideally in the elderly. Another important aspect regarding the outcome of the elderly CS patients is the quality of life, which was not assessed in this study and would be essential to evaluate in future trials.

Third, the novel biomarkers GDF-15 and suPAR open new perspectives regarding their association with pathogenetic mechanisms and

prognostic properties in CS. The strength of this study is serial sampling, which allowed investigation of the kinetics of these biomarkers. The observed rapid rise in their concentrations in response to shock and their association with hypoperfusion and organ dysfunction suggest that these biomarkers reflect severe circulatory failure already in the early phase of shock. This suggests their use in providing early warning to initiate interventions to stop the downward spiral of shock and prevent end organ failure. Furthermore, from a clinical perspective, a recently introduced point-of-care test for suPAR enhances its attractiveness in emergency and critical care settings.

From practical perspective, both biomarkers could serve as valuable tools and provide incremental value in early risk stratification of CS. Estimation of the individual patient's prognosis in the early phase of shock is crucial for decision-making regarding further treatment strategies (such as MCS) or treatment withdrawal because of futility. Both biomarkers have potential to improve early risk assessment beyond the existing clinical risk scores. Most risk scores are developed for use at baseline and consist mostly of constant variables (such as age and medical history) and thus do not capture potential changes in clinical status or response to treatment. Biomarkers and changes in their concentration over time may help in re-evaluating the risk of an individual patient during the hospital stay and help in treatment decision making. The divergent kinetics of GDF-15 among survivors and non-survivors supports its use in monitoring treatment response; decreasing levels may indicate favourable response to treatment.

Finally, the major challenge in the future is how to improve the prognosis of CS patients. Despite improved techniques and generalized availability of advanced therapies, the mortality rate in CS patients is still unacceptably high. CS patients comprise a heterogeneous population with various clinical pictures and underlying etiologies. Furthermore, the pathogenesis of shock is not fully understood. A better understanding of the complex pathogenetic pathways behind shock and the role of different biomarkers may facilitate development of new, more personalized therapy options or provide guidance in the use of existing treatment options. GDF-15 has already been investigated as a treatment target in animal studies of cardiometabolic diseases and obesity; several pharmaceutical companies are currently conducting clinical testing of GDF-15 analogues.[309] Additionally, by combining different biomarkers that reflect various pathogenetic pathways of shock, a multimarker strategy could improve the prognostication and risk stratification of CS. In future studies, the use of more uniform criteria and classification of CS would enable recruitment of more homogeneous patient populations, allow more individualized and targeted treatment, and facilitate comparison of results.

6.7 Conclusions

This thesis investigated the contemporary use of different ventilation strategies in CS and their impact on outcome and described the clinical characteristics and prognostication of elderly CS patients. This thesis also provides new relevant insights and tools into early risk stratification of CS by introducing two novel biomarkers that are associated with the complex pathogenesis and prognosis of CS. These findings may assist in treatment decision making and in allocating healthcare resources in clinical practice.

Study I assessed the application of the different ventilation strategies in unselected CS population and revealed that varying ventilatory modalities were used depending on RF severity. While most patients were treated with IMV, a fair number received NIV or were managed only with conventional oxygen therapy. We focused on the use on NIV and our results indicate that NIV can be used safely in the treatment of RF in suitable CS patients. Ventilation strategy did not influence outcome.

According to the results from study II, elderly CS patients have higher in-hospital mortality compared with younger patients despite similar treatment strategies. However, the elderly patients that survive to hospital discharge had a prognosis comparable to that of their younger counterparts. The contemporary risk prediction scores were useful for early risk prediction in the elderly. Interestingly, the novel biomarkers GDF-15 or sST2 improved risk stratification beyond the clinical scores.

This thesis introduced two novel biomarkers, GDF-15 and suPAR, in the setting of CS (III, IV). High levels of these biomarkers were indicative of severe circulatory failure and end-organ dysfunction and associated with poor prognosis. The kinetics of these biomarkers between survivors and non-survivors was diverse, with survivors exhibiting decreasing and non-survivors increasing levels. Additionally, both biomarkers improved the early risk stratification beyond the contemporary clinical risk scores; suPAR especially improved the risk assessment of patients with intermediate risk.

Taken together, the findings of this thesis may be utilized in clinical practice to facilitate treatment decision making and early risk assessment of CS patients.

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Use of noninvasive and invasive mechanical ventilation in cardiogenic shock: A prospective multicenter study

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ABSTRACT

Background: Despite scarce data, invasive mechanical ventilation (MV) is widely recommended over noninvasive ventilation (NIV) for ventilatory support in cardiogenic shock (CS). We assessed the real-life use of different ventilation strategies in CS and their influence on outcome focusing on the use of NIV and MV.
Methods: 219 CS patients were categorized by the maximum intensity of ventilatory support they needed during the first 24 h into MV ($n = 137$; 63%) , NIV ($n = 26$; 12%), and supplementary oxygen ($n = 56$; 26%) groups. We compared the clinical characteristics and 90-day outcome between the MV and the NIV groups.
Results: Mean age was 67 years, 74% were men. The MV and NIV groups did not differ in age, medical history, etiology of CS, PaO_2/FiO_2 ratio, baseline hemodynamics or LVEF. MV patients predominantly presented with hypoperfusion, with more severe metabolic acidosis, higher lactate levels and greater need for vasoactive drugs, whereas NIV patients tended to be more often congestive. 90-day outcome was significantly worse in the MV group (50% vs. 27%), but after propensity score adjustment, mortality was equal in both groups. Confusion, prior CABG, ACS etiology, higher lactate level, and lower baseline PaO_2 were independent predictors of mortality, whereas ventilation strategy did not have any influence on outcome.
Conclusions: Although MV is generally recommended mode of ventilatory support in CS, a fair number of patients were successfully treated with NIV. Moreover, ventilation strategy was not associated with outcome. Thus, NIV seems a safe option for properly chosen CS patients.

1. Introduction

Cardiogenic shock (CS) is defined as a state of critical end-organ hypoperfusion due to reduced cardiac output often resulting in multiorgan failure. The most frequent cause of CS is acute myocardial infarction (AMI), but also other cardiac emergencies can lead to shock [1,2]. Despite remarkable advancement in pharmacological and interventional treatment of AMI over the last decades, mortality in CS remains unacceptably high at 40% to 50% [3,4]. Even though patients presenting with CS are critically ill, their clinical picture can range from mild hypoperfusion to profound treatment-refractory shock. CS patients frequently have significantly elevated pulmonary capillary wedge pressure and

Abbreviations: CS, cardiogenic shock; AMI, acute myocardial infarction; MV, invasive mechanical ventilation; NIV, noninvasive ventilation; APE, acute cardiogenic pulmonary edema; STEMI, ST-elevation myocardial infarction; ACS, acute coronary syndrome; ARDS, acute respiratory distress syndrome; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MI, myocardial infarction; CABG, coronary artery bypass grafting; SD, standard deviation; IQR, interquartile range; OR, odds ratio; CI, confidence interval; PCI, percutaneous coronary intervention; ARF, acute respiratory failure.

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consequently are prone to pulmonary oedema and respiratory distress. Most CS patients need some ventilatory support to provide adequate gas exchange and to relieve the work of breathing. Depending of the severity of ventilatory disturbance, some patients may be managed only with supplementary oxygen, whereas those suffering from profound circulatory shock are intubated as a rule.

The majority of guidelines and reviews recommend mechanical ventilation (MV) in CS [5,6]. However, this recommendation is essentially based on expert opinion rather than on scientific data. The role of noninvasive ventilation (NIV) is well established and studied in acute cardiogenic pulmonary edema (APE). It has been shown to reduce respiratory distress and the rate of endotracheal intubation [7–9], but despite several studies and meta-analyses, its impact on mortality is still a matter of debate [10–12]. On one hand, patients presenting with symptoms of shock or ST segment elevation myocardial infarction (STEMI) and those who need urgent coronary revascularization have been excluded from most of these studies [7,8,11,13]. On the other hand, NIV has been formally contraindicated in patients with CS because it may worsen hypotension, and the frequently altered mental status does not ensure adequate spontaneous ventilation. Little is known about the use of different ventilatory support strategies in the treatment of CS. To the best of our knowledge, there are no data comparing the use of NIV and MV in CS. The aim of our study was to analyze the use of different ventilatory support strategies and their impact on 90-day outcome in a large cohort of CS patients.

2. Patients and methods

The CardShock study (ClinicalTrials.gov identifier NCT01374867, registered on 9 June 2011) was conducted at nine European tertiary care hospitals in eight countries between October 2010 and December 2012. The study population, which comprised 219 prospectively enrolled patients with CS, has been described previously [1].

2.1. Inclusion criteria and data collection

Adult patients were enrolled within 6 h from the detection of CS. In addition to an acute cardiac cause, the inclusion criteria were: systolic blood pressure had to be <90 mm Hg (after adequate fluid challenge) for 30 min OR need for vasopressor therapy to maintain SBP > 90 mm Hg AND signs of hypoperfusion (confusion, cold periphery, oliguria <0.5 mL/kg/h for the previous 6 h, or blood lactate >2 mmol/L). Exclusion criteria were shock caused by ongoing hemodynamically significant arrhythmias or shock after cardiac or non-cardiac surgery. The etiology of shock was classified as acute coronary syndrome (ACS) or non-ACS, and the diagnosis was set by the local investigators. Baseline characteristics, medical history, clinical findings and hemodynamic parameters were recorded at detection of shock. Biochemical and hemodynamic data as well as treatment and procedures were registered at baseline and at predefined time points until 96 h after inclusion. Patients were treated according to local clinical practice. Written informed consent was obtained from each patient or a close person or a relative if the patient was unable to give the consent on admission.

Assessing the need for ventilatory assistance and the choice of ventilatory mode (room air, supplementary oxygen, NIV or MV) were at the discretion of the physician in charge and based on common indications and contraindications for NIV and MV treatment. Arterial blood gas samples were analyzed locally at baseline and at pre-specified time points thereafter. PaO_2/FiO_2 ratio was calculated using the measured PaO_2 and reported FiO_2. The degree of hypoxemia and respiratory failure was classified according to Berlin definition ARDS (acute respiratory distress syndrome) criteria: mild (200 mm Hg < PaO_2/FiO_2 ≤ 300 mm Hg), moderate (100 mm Hg < PaO_2/FiO_2 ≤ 200 mm Hg), and severe (PaO_2/FiO_2 ≤ 100 mm Hg) [14]. Estimated glomerular filtration rate (eGFR) was calculated from creatinine values using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation [15].

We categorized the patients by the maximum intensity of ventilatory support during the first 24 h in three groups: invasive MV group, NIV group (including both continuous positive airway pressure and bilevel positive airway pressure) and supplementary oxygen group (including patients treated with supplementary oxygen only by mask or nasal cannulas). We analyzed their clinical characteristics, treatment and outcome. The supplementary oxygen therapy group was not included in further comparisons. Patients who died during the first 24 h were included if they received NIV or MV treatment. The primary endpoint was all-cause 90-day mortality; three patients were lost to follow up. NIV failure was defined as requirement for endotracheal intubation after NIV as a first line ventilatory support mode. Vital status during follow-up was determined through direct contact with the patient or next of kin, or through population and hospital registers. The study was approved by local ethics committees (detailed later after discussion) and conducted in accordance with the Declaration of Helsinki.

2.2. CardShock risk Score

The CardShock risk Score is a risk prediction model for in-hospital mortality in CS that has been created by using the variables which independently associated with all-cause death in the CardShock study [1]. The Score consists of seven parameters [age >75 years, eGFR, blood lactate, confusion on admission, left ventricular ejection fraction (LVEF) <40%, previous myocardial infarction (MI) or coronary artery bypass grafting (CABG), and ACS etiology] giving a maximum of nine points. Patients can be classified according to the risk Score into low, intermediate, and high risk groups regarding in-hospital mortality.

2.3. Statistical analysis

Results are presented as numbers (n) and percentages (%) for categorical variables, and for continuous variables as mean and standard deviation (SD) or median and interquartile range (IQR), as appropriate. Chi-squared test and Fisher's exact test were used to compare categorical variables, and Student's *t*-test, Wilcoxon signed rank test and Mann–Whitney *U* test were used for continuous variables, as appropriate. Multivariable logistic regression analysis was used to determine independent risk factors for 90-day mortality. In order to avoid model over-fitting, independent predictors of 90-day mortality were identified from selected variables known to be clinically related to outcome. The model was also adjusted for CardShock Risk Score variables, age, gender, and participating center. Results from the regression analyses are presented as odd ratios (OR) with 95% confidence intervals (CI).

Propensity score adjustment was used to diminish bias and increase precision in analyses assessing the relationship between ventilatory treatment and mortality [16]. Propensity score was created using logistic regression modeling the likelihood of a patient receiving either NIV or MV. Variables were chosen based on clinical relevance and on potential or observed association with outcome [1]. The final propensity score was estimated with the following variables: age, gender, medical history (myocardial infarction, coronary artery bypass graft surgery, diabetes mellitus, hypertension), acute coronary syndrome etiology, and initial presentation (confusion, blood lactate, systolic blood pressure, non-sinus rhythm, left ventricular ejection fraction, and estimated glomerular filtration rate (CKD-EPI)). The score estimate was transformed into logit scale [17]. The Kaplan-Meier method was used for unadjusted and the Cox regression for adjusted survival analyses; the assumption of proportional hazards was checked with parallelism of log-log survival curves. The variables included in the propensity score adjustment analysis are stated below the Fig. 1. A two-sided *p*-value <0.05 was regarded as statistically significant. All statistical analyses were performed with SPSS 22.0 statistical software (IBM Corp, Armonk, NY, USA).

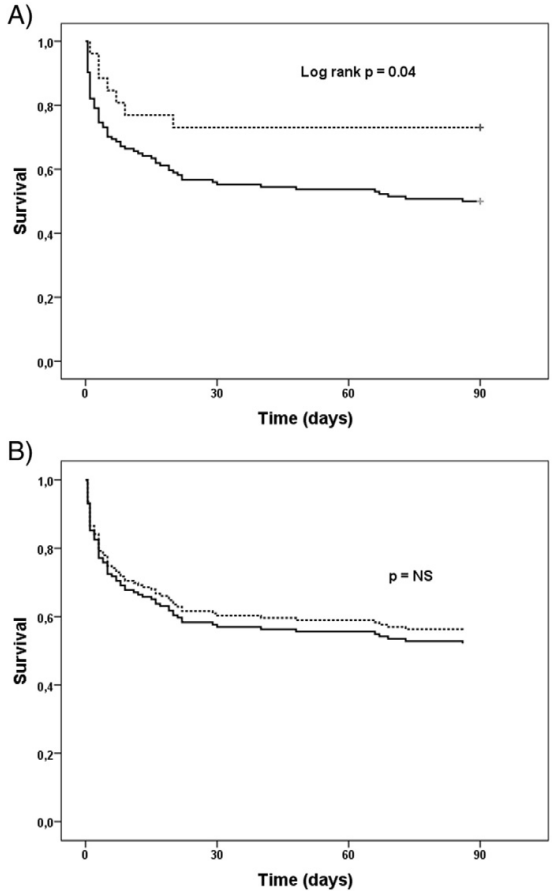

Fig. 1. A) Unadjusted (Kaplan Meier) and B) propensity score adjusted (Cox regression) survival curves for the use of MV (solid line) and NIV (dashed line). MV, invasive mechanical ventilation group; NIV, noninvasive ventilation group. Adjusted for logit of the propensity score, which was estimated with the following variables: age, gender, medical history (myocardial infarction, coronary artery bypass graft surgery, diabetes mellitus, hypertension), acute coronary syndrome, and initial presentation (confusion, blood lactate, systolic blood pressure, non-sinus rhythm, left ventricular ejection fraction, and estimated glomerular filtration rate (CKD-EPI)).

3. Results

3.1. Study population

A total of 219 patients were included in the study. The main characteristics of the study population are summarized in Table 1. Briefly, the mean age was 67 (SD 12) years, and 26% were women. ACS was the most frequent cause of CS (81%, $n = 177$). At baseline, the blood pressure was on average 78/40 mm Hg and heart rate 90 beats per minute. Median length of hospital stay was 12 (IQR 7–25) days, and 90-day mortality was 41%.

3.2. Mechanical ventilation (MV) and noninvasive ventilation (NIV)

During the first 24 h, 30 patients were initially treated with NIV. Eight of these patients had to be intubated (NIV failure). Half of the failures occurred during the first 24 h, and the rest later during the subsequent 24 to 96 h. Those four patients initially treated with NIV and shifted to MV during the first 24 h have been included in the MV group. In comparing ventilation modes, 63% ($n = 137$) of the patients were classified as treated with MV, and 12% ($n = 26$) with NIV. Clinical characteristics and baseline information of the patients who required oxygen only by mask or nasal cannula ($n = 56$; 26%) are presented in Tables 1-3 as a "Supplementary oxygen group". Because this group differs from the NIV and the MV groups, especially with regard to the severity of the respiratory failure (Table 3), it was not included in further comparisons.

Clinical characteristics between the MV and the NIV groups are compared in Table 1. There were no significant differences between the groups in age, gender, or medical history. In both groups, over 50% of the patients were smokers or ex-smokers, but few had a diagnosed chronic lung disease. The proportion of patients with ACS etiology of CS was similar in both groups. Clinical presentation and biochemistry at baseline are shown in Tables 1 and 2. The NIV group had slightly higher systolic blood pressure, but the groups did not differ otherwise in hemodynamic parameters or LVEF at baseline. Patients in the MV group were more often confused (83% vs. 31%, $p < 0.001$) and had higher lactate levels (3.7 vs. 1.7 mmol/L, $p < 0.001$). MV patients also received vasoactive medication more frequently (norepinephrine 88% vs. 69%, $p = 0.03$; dobutamine 61% vs. 27%, $p = 0.001$), with the exception of levosimendan (22% vs. 58%, $p < 0.001$) that was administered more often to patients in the NIV group. Noninvasively ventilated patients had higher hs-TnT (3631 vs. 1597 ng/L; $p = 0.06$) and NT-proBNP (7375 vs. 2367 ng/L; $p = 0.04$) levels (Table 2). Revascularization rates did not differ between the groups. Forty percent of MV patients had been resuscitated before inclusion into the study.

3.3. Ventilatory parameters and mortality

Ventilatory parameters at baseline and at 24 h are presented in Table 3. Patients treated with MV suffered from metabolic acidosis more often and were treated with higher oxygen fraction at baseline compared with NIV group. The MV group had also slightly higher PaO_2 and $PaCO_2$ levels. In terms of PaO_2/FiO_2 ratio, the degree of respiratory failure was moderate in both groups at baseline but improved with both respiratory modalities during the first 24 h. The level of positive end-expiratory pressure (PEEP) ranged in the NIV group from 5 to 12 cmH_2O with a median level of 8 cmH_2O (IQR 7.5–10) and in the MV group from 4 to 14 cmH_2O with a median level of 6 cmH_2O (IQR 5–8), respectively. The duration of the ventilation was significantly longer in the MV group.

Outcome and length of stay for each group are shown in Table 2. In-hospital mortality was 45% in the MV group and 19% in the NIV group ($p = 0.01$), and 90-day mortality was 49% and 27% ($p = 0.03$), respectively. However, after adjustment for severity of disease using variables of the CardShock risk Score, ventilation strategy had no influence on the 90-day outcome. The results remained unchanged when ventilation strategy was analyzed up to 96 h. Interestingly, higher PaO_2 at baseline was independently associated with better outcome. Whether the patient was resuscitated or not did not have an effect on outcome when tested in multivariable analysis. Adjusted ORs for variables associated with 90-day mortality are shown in Table 4. The propensity score adjustment analysis confirmed that ventilation strategy did not influence the mortality rate (Fig. 1). We performed an additional propensity score analysis excluding the resuscitated patients but this did not affect the results (Supplementary material online, Fig. S1).

4. Discussion

To our knowledge, this prospective multinational study is the first to provide information about contemporary use of different ventilation modalities in CS. First, we found that while the majority of patients were intubated and mechanically ventilated, one fourth did not need ventilatory support at all. Second, NIV treatment was used successfully

Table 1
Patient characteristics and etiology of cardiogenic shock.

	All ($n = 219$)	MV ($n = 137$)	NIV ($n = 26$)	p-Value*	Supplementary oxygen ($n = 56$)
Age, years	67 (12)	66 (11)	66 (12)	0.8	68 (13)
Women, n (%)	57 (26)	31 (23)	8 (31)	0.4	18 (32)
BMI	26.9 (4.2)	27.4 (3.9)	26.4 (4.3)	0.3	25.8 (4.5)
Medical history, n (%)					
Coronary artery disease	76 (35)	51 (37)	10 (39)	0.9	15 (27)
Previous MI	54 (25)	35 (26)	8 (31)	0.6	11 (20)
Prior CABG	16 (7)	11 (8)	4 (15)	0.3	1 (2)
Heart failure	36 (16)	25 (18)	3 (12)	0.6	8 (14)
Hypertension	132 (60)	85 (62)	17 (65)	0.7	30 (54)
Diabetes	62 (28)	44 (32)	6 (23)	0.4	11 (20)
Asthma or COPD	25 (11)	18 (13)	2 (8)	0.7	5 (9)
Smoker or ex-smoker	135 (62)	95 (69)	14 (54)	0.2	26 (47)
Etiology of cardiogenic shock, n (%)					
ACS	177 (81)	111 (81)	20 (77)	0.6	46 (82)
non-ACS	42 (19)	26 (19)	6 (23)	0.6	10 (18)
STEMI	148 (68)	87 (64)	18 (69)	0.6	43 (77)
Resuscitated, n (%)	62 (28)	55 (40)	0		7 (13)

Data are presented as numbers and percentages (%), mean (SD), and median (IQR).
* p-Values are for the difference between MV and NIV group. MV, invasive mechanical ventilation group; NIV noninvasive ventilation group; BMI, body mass index; SD, standard deviation; MI, myocardial infarction; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; ACS, acute coronary syndrome; STEMI, ST-elevation myocardial infarction.

in 12% of patients. Third, most important find, was that NIV was not associated with increased mortality even after adjustment for severity of disease. Fourth, higher PaO_2 on admission was associated with better prognosis.

There are scarce data available on the use of different respiratory modalities in CS. In the AHEAD (Acute Heart Failure Database) registry study, 8% of the subgroup of CS ($n = 600$) were treated with NIV and 56% with MV [18]. Only 11.6% of these CS patients underwent coronary angiography, suggesting a different patient population compared to the patients in our study, in whom coronary angiography was performed in 83%. In another British study assessing the outcome of CS patients undergoing percutaneous coronary intervention (PCI), only 28.4% were treated with MV [19]. This contrasts with the IABP-SHOCK II trial, in which 80% of patients were mechanically ventilated [20]. A recent French registry study reported that in intensive care units 75% of CS patients were treated with MV and 7% with NIV [21]. Contrary to this study we recruited patients from emergency departments, cardiac and intensive care units, as well as catheter laboratories, and thus included probably also milder forms of shock which can account for the smaller need for MV in our study. In addition, the shock was caused by AMI in only 12% of the patients differing clearly from our population. Our multinational, multicenter study shows that the majority of CS patients indeed are treated with ventilatory support, mostly with MV, but also with NIV with success.

The overall mortality of 41% observed in our study is comparable with other recent studies on CS [4,19,22,23]. The 90-day mortality was

Table 2
Physiologic parameters at baseline, mortality, and length of ICU/CCU and hospital stay.

	All ($n = 219$)	MV ($n = 137$)	NIV ($n = 26$)	p-Value*	Supplementary oxygen ($n = 56$)
Clinical findings					
Systolic blood pressure, mmHg	78 (14)	78 (15)	83 (10)	0.03	75 (11)
Heart rate, beats per minute	90 (28)	91 (29)	87 (23)	0.2	89 (29)
LVEF, %	33 (14)	32 (14)	33 (12)	0.7	36 (17)
Confusion, n (%)	148 (68)	113 (83)	8 (31)	<0.001	26 (46)
Biochemistry					
Blood hemoglobin, g/L	128 (22)	130 (23)	125 (22)	0.3	124 (24)
Arterial blood lactate, mmol/L	2.8 (1.7–5.8)	3.7 (2.2–7.0)	1.7 (1.4–2.8)	<0.001	2.3 (1.6–3.5)
hsTnT, ng/L	2190 (388–5418)	1597 (337–4178)	3631 (1289–10,170)	0.06	2427 (418–7459)
NT-proBNP, pg/mL	2710 (585–9434)	2367 (559–8563)	7375 (2053–17,372)	0.04	1860 (511–8976)
Creatinine, mmol/L	104 (78–140)	110 (87–144)	100 (69–119)	0.1	107 (84–140)
eGFR, mL/min/1.73 m^2	61 (41–87)	64 (30)	67 (28)	0.6	59 (28)
CRP, g/L	16 (4–54)	15 (4–49)	37 (6–79)	0.2	15 (4–48)
Management, n (%)					
Coronary angiography	182 (83)	114 (83)	23 (89)	0.8	45 (80)
PCI	149 (68)	90 (66)	19 (73)	0.5	40 (71)
CABG	9 (4)	5 (4)	3 (12)	0.1	1 (2)
IABP	122 (56)	85 (62)	16 (62)	1.0	21 (38)
Mortality, n (%)					
In-hospital mortality	80 (37)	62 (45)	5 (19)	0.01	13 (23)
90-day mortality	89 (41)	67 (49)	7 (27)	0.03	15 (27)
ICU/CCU length of stay, days	5 (2 − 10)	6 (2 − 11)	4 (2–8)	0.2	3 (1–7)
In-hospital length of stay, days	12 (7–25)	17 (10–27)	12 (7–27)	0.2	8 (4–18)

Data are presented as numbers and percentages (%), mean (SD), and median (IQR).
* p-Values are for the difference between MV and NIV groups. MV, invasive mechanical ventilation group; NIV noninvasive ventilation group; LVEF; left ventricular ejection fraction; hsTnT, highly sensitive troponin; eGFR, estimated glomerular filtration rate; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; IABP, intra-aortic balloon pump; ICU, intensive care unit; CCU, cardiac care unit.

Table 3
Arterial blood gas values, ventilatory parameters at baseline and at 24 h, and duration of ventilation.

	MV (n = 137)	NIV (n = 26)	p-Value*	Supplementary oxygen (n = 56)
At baseline				
pH	7.27 (7.17–7.34)	7.39 (7.32–7.43)	<0.001	7.38 (7.30–7.44)
PaO_2, kPa	12.9 (10.4–18.6)	11.2 (9.9–15.0)	0.2	13.40 (9.2–16.8)
$PaCO_2$, kPa	5.5 (4.9–6.4)	4.5 (4.2–5.9)	0.01	4.9 (3.9–5.6)
HCO_3, mmol/L	19.6 (15.9–21.5)	22.0 (20.5–24)	0.001	21.9 (16.7–23.4)
FiO_2, %	76 (22)	60 (19)	0.001	32 (26)
P/F ratio, mm Hg	141 (97–211)	167 (107–215)	0.3	311 (200–358)
200–300 mm Hg, n (%)	35 (26)	7 (27)	0.9	7 (13)
100–200 mm Hg, n (%)	54 (40)	14 (54)	0.2	7 (13)
<100 mm Hg, n (%)	40 (29)	4 (15)	0.1	0
At 24 h				
pH	7.40 (7.35–7.43)	7.42 (7.38–7.46)	0.05	7.43 (7.40–7.46)
PaO_2, kPa	12.1 (10.5–14.0)	11.8 (10.4–13.6)	0.5	11.1 (10.0–13.1)
$PaCO_2$, kPa	5.30 (4.70–5.70)	4.50 (4.20–4.90)	< 0.001	4.8 (4.3–5.5)
HCO_3, mmol/L	24 (21.3–26.3)	23 (21–25)	0.2	24 (21–25)
FiO2, %	52 (18)	53 (23)	0.8	27 (17)
P/F ratio, mm Hg	192 (138–265) [1,2]	191 (136–284) [2]	1.0	302 (239–396)
200–300 mm Hg, n (%)	33 (24)	6 (23)	0.9	7 (13)
100–200 mm Hg, n (%)	46 (34)	8 (31)	0.7	3 (5)
<100 mm Hg, n (%)	13 (10)	3 (12)	0.7	0
Duration of ventilation, h	94 (30–184)	41 (28–71)	0.007	

Data are presented as numbers and percentages (%), mean (SD), and median (IQR).
MV, invasive mechanical ventilation group; NIV noninvasive ventilation group; PaO_2, partial pressure of oxygen in arterial blood; $PaCO_2$, partial pressure of carbon dioxide in arterial blood, FiO_2, fraction of inspired oxygen; P/F ratio, PaO_2/FiO_2 ratio.
* p-Values are for the difference between MV and NIV groups. 1) the improvement during the 24 h was significant in the MV group, 2) but not between the groups.

higher in the MV group. After accounting for the possible imbalance of multiple covariates and baseline characteristics by using propensity score method, the ventilation strategy did not have an effect on outcome. The outcome of patients treated with NIV was better in our study than in the AHEAD study, which showed a 62.7% in-hospital mortality in the NIV group, and an even worse prognosis for those treated with MV, whose in-hospital mortality was 71.8% [18].

Compared to patients treated with NIV, those requiring MV were more often confused, had metabolic acidosis, higher lactate levels, and greater need for vasoactive drugs indicating a more severe tissue hypoperfusion and shock, whereas the NIV group had higher NT-proBNP levels, possibly indicating a greater distension of the ventricles and elevated filling pressure. In terms of PaO_2/FiO_2 ratio, the degree of acute respiratory failure (ARF) at baseline was moderate in both groups and improved equally during the first 24 h with both respiratory modalities. Since the degree of respiratory failure improved equally with both ventilation strategies, probably the more severe shock and hypoperfusion accounted for the longer duration of the ventilation in the MV group.

In general, there are no specific recommendations concerning indications for NIV or intubtion and MV in CS except in isolated right ventricular failure, where caution is advised due to possible undesirable effect of positive end-expiratory pressure on right ventricular afterload and function. Our study suggests that CS patients with congestion and mild-to-moderate respiratory failure, able to co-operate, and without signs of severe hypoperfusion can be safely treated with NIV. Success rate of NIV during the first 24 h was 87%, which is higher than in previous studies assessing the use of NIV in ARF in intensive care units [24–26]. However, patients who do not improve with NIV treatment should be promptly intubated, and NIV trial should not delay intubation and mechanical ventilation when needed. It is also crucial to start the NIV treatment in a very early phase of respiratory failure, preferably already in the out-of hospital setting [27,28].

There are several advantages in NIV compared with MV. NIV allows patients to communicate, eat, move at least to some extent, and breathe spontaneously. By avoiding endotracheal intubation and invasive MV, the risks of nosocomial infections, ventilator-associated pneumonia and injuries related to the intubation procedure itself are diminished [29,30]. By using NIV instead of MV, the administration of complete sedation with loss of vasomotor tone can be avoided. This might be especially beneficial in patients presenting with symptoms of shock, in whom the sedatives may increase hypotension.

Higher PaO_2 at baseline predicted improved outcome independently. This is striking, since studies assessing the impact of hyperoxemia on outcome during critical illness have demonstrated excess oxygen to be harmful [31]. Arterial hyperoxia has been shown to induce vasoconstriction and reduce cardiac output, which may impair blood flow to the organs at risk [32]. Indeed, these effects could be considered especially harmful in CS. However, there are several important differences between these studies assessing the role of hyperoxemia on outcome and the present one. First, the previous studies have focused only on certain patient populations, e.g. patients with cardiac arrest, traumatic brain injury or stroke, and thus probably cannot be generalized into general intensive care unit population. Second, the level of hyperoxemia among the studies has varied and has in some of the trials been 40 kPa (300 mm Hg) or even more [33], which is clearly higher than the average PaO_2 level in our study. Furthermore, some of the studies excluded patients presenting with hypoxemia [(PaO_2/FiO_2 ratio <27 kPa (200 mm Hg) or PaO_2 <8 kPa (60 mm Hg)] [33], whereas most of the patients in our study had PaO_2/FiO_2 ratio below 27 kPa (200 mm Hg). However, there are preliminary data indicating that by inducing peripheral vasoconstriction, hyperoxemia may prevent shock-induced hypotension and decrease the need for use of vasopressor and thus help to stabilize hemodynamics in vasodilatory shock [34]. In the present

Table 4
Multivariable regression analysis for 90-day mortality.*)

Variable	Adjusted OR (95% CI)	p-Value
Age > 75 years	1.62 (0.45–5.86)	0.47
Confusion	5.22 (1.30–21.00)	0.02
Prior CABG	25.57 (1.57–417.76)	0.02
ACS etiology	4.69 (1.13–19.46)	0.03
Ventilation mode**)	0.85 (0.15–4.80)	0.85
eGFR (per 10 mL/min/1.73 m^2 increase)	0.96 (0.78–1.19)	0.72
LVEF (per 10% increase)	0.79 (0.50–1.25)	0.31
Lactate (per mmol/L increase)	1.47 (1.17–1.84)	0.001
PaO_2 (per kPa increase at baseline)	0.93 (0.88–0.99)	0.02

OR, odds ratio; CI, confidence interval; CABG, coronary artery bypass grafting; ACS, acute coronary syndrome; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction.
* The mode included also variable accounting for participating center and sex.
** The reference factor is NIV.

study, the severity of shock and underlying cardiovascular status were clearly the main determinants of prognosis, whereas the ventilation strategy did not have an effect on outcome.

Guidelines do not recommend using NIV in patients presenting with ACS or APE and suffering from shock or low blood pressure, or requiring urgent coronary revascularization [5,6,35]. In many studies regarding the use of NIV in APE or ARF, the presence of low blood pressure, need for vasoactive medication or shock have been considered as exclusion criteria or as criteria for intubation [7,8,13,36,37]. In our experience, NIV is feasible during angiography and PCI, and the study results suggest that NIV can be safely used in patients presenting with severe hemodynamic impairment treated with vasoactive drugs. Our findings are also supported by a recently published propensity-based analysis, which demonstrated that presence or absence of shock did not have an effect on mortality in APE patients treated with CPAP [38].

4.1. Limitations

There are some limitations to be acknowledged. First, although the CardShock study was prospective and included a reasonable number of patients, the limited number of patients treated with NIV decreased the statistical power in between-group comparisons. Second, the choice of ventilation strategy was at the discretion of the physician in charge. However, the study reflects real life practice in European tertiary care hospitals. Third, the study lacks randomization and confounding by indication is a possible bias. We used regression and propensity score methods to minimize this bias, and though differences in some unmeasured confounding variables cannot be excluded, the results regarding the safety of NIV use were consistent. Finally, the number of patients in the NIV group from whom a complete serial blood gas data was available was limited, and caution in the interpretation of the results is advocated.

5. Conclusions

In this observational multicenter study, we observed that NIV can be safely used in properly selected patients in cardiogenic shock. Ventilation strategy did not affect outcome. In conclusion, it seems that in highly skilled centers, NIV can be used in the treatment of respiratory failure in CS. However, appropriate patient selection and close monitoring during the treatment are crucial, and NIV trial should not delay intubation and mechanical ventilation when indicated.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcard.2016.12.175.

Ethics committees

Athens: Ethics Committee of Attikon University Hospital; Barcelona: Health Research Ethics Committee of the Hospital de Sant Pau; Brescia: Ethics Committee of the Province of Brescia; Brno: Ethic committee of University hospital Brno; Helsinki: The Ethics Committee, Department of Medicine, The Hospital District of Helsinki and Uusimaa; Porto: Ethics committee of S. João Hospital Center/Porto Medical School; Rome: Ethical Committee Sant'Andrea Hospital; Warsaw: Local Bioethics Committee of the Institute of CardiologyCopenhagen: By Danish law (https://www.retsinformation.dk/forms/r0710.aspx?id=137674) scientific projects only using information from existing registries does not require approval from a scientific ethical committee. Thus, Ethical approval and informed consent was not required from the Danish Ethical Committee since this study was conducted in a public organization using encrypted personal data. The study was approved by the Danish Protection Agency with reference number GEH-2014-013; I-Suite number: 02731.

Competing interests

V.-P.H. has served on advisory boards for Bayer, BMS/Pfizer, Boehringer-Ingelheim, Roche Diagnostics, Novartis, and Servier, and received lecture fees from Bayer, Orion Pharma, Resmed, and Roche Diagnostics. J.L. has received consulting and/or lecture fees from Boeringer-Ingelheim, Roche Diagnostics, Novartis, Orion Pharma, Pfizer, Servier, and Vifor Pharma. A.S. has served on advisory board for Orion Pharma, and received lecture fees from Astra-Zeneca, Bayer, Menarini, Novartis and Servier. V.C. has received an unrestricted research grant from CVie Therapeutics Limited and consulting honoraria from Servier. J.P. received honoraria for lectures from Orion Pharma and Novartis International. J.M. has received speaker fees and travel grants from Novartis, Menarini, Orion, and Thermo Fisher, and consulting honoraria from Cardiorentis. M.H., T.T., J.S., H.T., M.B., and M.G.L. reported having no disclosures.

Authors' contributions

MH analyzed and interpreted the data and drafted the manuscript. TT assisted analyzing the data. V-PH, JL, TT and JM helped interpreting the results and contributed substantially to the development of the manuscript. All the authors revised the manuscript critically and read as well as approved the final manuscript.

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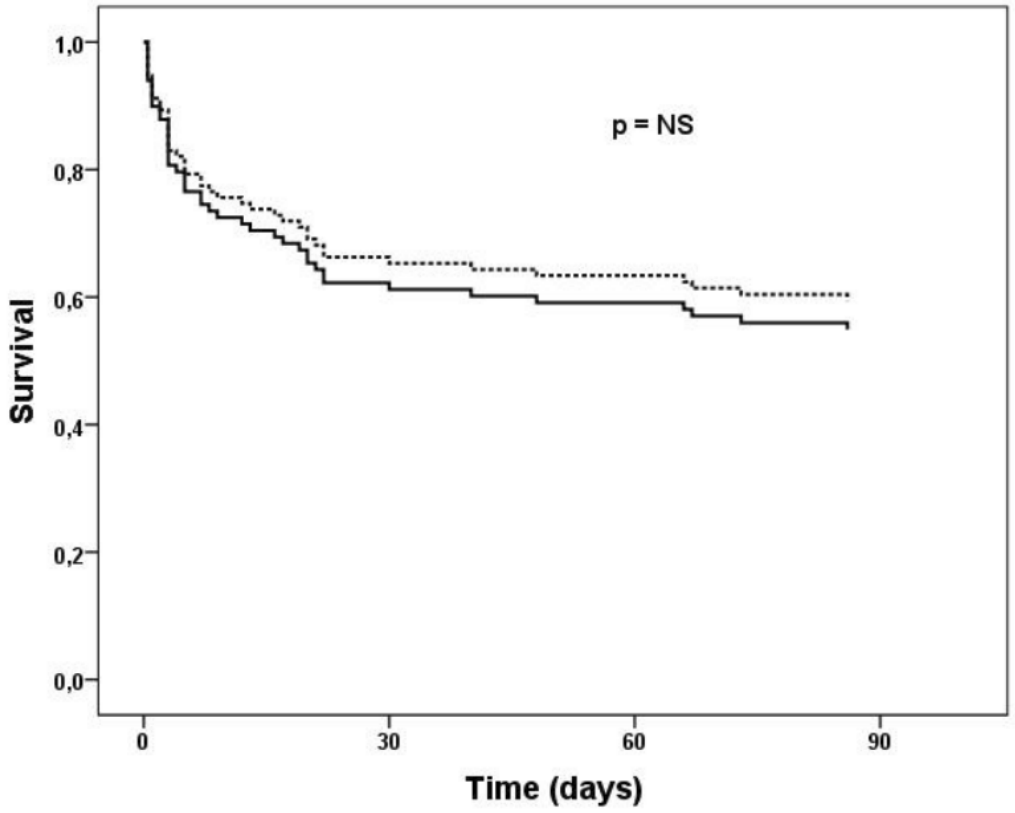
Supplmetary figure 1. Propensity score adjusted (Cox regression) survival curves for the use of MV (solid line) and NIV (dashed line), resuscitated patients excluded.



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ORIGINAL RESEARCH ARTICLE

Mortality risk prediction in elderly patients with cardiogenic shock: results from the CardShock study

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Abstract

Aims This study aimed to assess the utility of contemporary clinical risk scores and explore the ability of two biomarkers [growth differentiation factor-15 (GDF-15) and soluble ST2 (sST2)] to improve risk prediction in elderly patients with cardiogenic shock.

Methods and results Patients (n = 219) from the multicentre CardShock study were grouped according to age (elderly ≥75 years and younger). Characteristics, management, and outcome between the groups were compared. The ability of the CardShock risk score and the IABP-SHOCK II score to predict in-hospital mortality and the additional value of GDF-15 and sST2 to improve risk prediction in the elderly was evaluated. The elderly constituted 26% of the patients (n = 56), with a higher proportion of women (41% vs. 21%, $P < 0.05$) and more co-morbidities compared with the younger. The primary aetiology of shock in the elderly was acute coronary syndrome (84%), with high rates of percutaneous coronary intervention (87%). Compared with the younger, the elderly had higher in-hospital mortality (46% vs. 33%; P = 0.08), but 1 year post-discharge survival was excellent in both age groups (90% in the elderly vs. 88% in the younger). In the elderly, the risk prediction models demonstrated an area under the curve of 0.75 for the CardShock risk score and 0.71 for the IABP-SHOCK II score. Incorporating GDF-15 and sST2 improved discrimination for both risk scores with areas under the curve ranging from 0.78 to 0.84.

Conclusions Elderly patients with cardiogenic shock have higher in-hospital mortality compared with the younger, but post-discharge outcomes are similar. Contemporary risk scores proved useful for early mortality risk prediction also in the elderly, and risk stratification could be further improved with biomarkers such as GDF-15 or sST2.

Keywords Cardiogenic shock; Elderly; Risk prediction; Biomarker; GDF-15; sST2

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[Correction added on 11 February 2021, after first online publication: The name of the author Jordi Sans Roselló has been corrected in this version.]

Introduction

The management of cardiogenic shock (CS) in the elderly poses a clinical challenge. On one hand, the elderly are at the highest risk for adverse outcomes and therefore have the greatest potential to benefit from treatment, but, on the other hand, they are vulnerable to treatment-related complications. Furthermore, there is remarkable individual variation in functional and cognitive reserves among this age group, presenting a hurdle to the objective evaluation of the prognosis in acute settings.

Early assessment of shock severity is crucial in order to single out patients at high risk of death. Accurate risk stratification could guide the treatment and help in the allocation of clinical resources, through identification of patients most likely to benefit from the highly intense and costly treatment options. Age itself elevates the risk of myocardial infarction-related CS, and advanced age is an additional known risk factor for CS mortality.[1,2] Risk prediction models have been introduced to facilitate risk assessment and the prediction of mortality in the acute phase of CS. Two risk prediction scores, the CardShock risk score and the IABP-SHOCK II score, have been developed specifically for CS and have shown good performance in both early risk stratification and prediction of short-term mortality.[1,3,4] However, the utility of these risk score models in the elderly remains unclear. Biomarkers have become significant prognostic tools in many cardiovascular diseases.[5,6] Most recently, growth differentiation factor-15 (GDF-15) and soluble ST2 (sST2) have been found to be valuable in risk stratification in heart failure and CS,[7–10] but data on elderly patients with CS in the contemporary era remain scarce.

We examined the clinical picture, management, and outcomes of patients aged ≥75 years in a prospective, multicentre study on CS. Our aim was to compare the key features between survivors and non-survivors and to assess the performance of the contemporary risk prediction scores in the elderly. Finally, we investigated the ability of GDF-15 and sST2 to improve early risk stratification in this age group.

Methods

The CardShock study (NCT01374867 at https://www.ClinicalTrials.gov is a prospective, observational, multicentre study on CS, including both acute coronary syndrome (ACS)-related and non-ACS-related aetiologies. Nine tertiary hospitals in eight European countries participated between October 2010 and December 2012, enrolling 219 patients. The detailed design and the primary results of the study have been published elsewhere.[1]

Inclusion criteria and data collection

Besides an acute cardiac cause, the inclusion criteria consisted of systolic blood pressure <90 mmHg (after adequate fluid challenge) for 30 min, or need for vasopressor therapy to maintain systolic blood pressure >90 mmHg, and signs of hypoperfusion (altered mental status/confusion, cold periphery, oliguria <0.5 mL/kg/h for the previous 6 h, or blood lactate >2 mmol/L). The exclusion criterion was shock caused either by ongoing hemodynamically significant arrhythmias or by cardiac or non-cardiac surgery. Patients had to be over 18 years old, and they had to be included within 6 h of the identification of the shock.

Baseline characteristics and previous medical history were recorded. Biochemical and clinical findings, as well as haemodynamic parameters, were documented at detection of shock and at pre-specified time points until 96 h after inclusion. Patients were treated according to local practice in each hospital, and treatment procedures were registered. The primary outcome was all-cause in-hospital mortality. In addition, 1 year mortality was assessed. After hospital discharge, three patients were lost to follow-up. In the mortality analyses, their cases were censored at the time of hospital discharge. Written informed consent was obtained from the patient or, according to local regulations, from a close person or a relative. Vital status during follow-up was determined through direct contact with the patient or next of kin or through population and hospital registers. The study was approved by the following local ethics committees: Athens: Ethics Committee of Attikon University Hospital; Barcelona: Health Research Ethics Committee of the Hospital de Sant Pau; Brescia: Ethics Committee of the Province of Brescia; Brno: Ethics Committee of University Hospital Brno; Helsinki: The Ethics Committee, Department of Medicine, The Hospital District of Helsinki and Uusimaa; Porto: Ethics Committee of São João Hospital Center/Porto Medical School; Rome: Ethical Committee Sant'Andrea Hospital; Warsaw: Local Bioethics Committee of the Institute of Cardiology; and Copenhagen: the study was approved by the Danish Protection Agency with reference number GEH-2014-013 and I-Suite number 02731. The study was conducted in accordance with the Declaration of Helsinki.

Serial blood sampling was performed at baseline and thereafter at 12 h intervals up to 48 h, and plasma samples were stored in aliquots frozen at −80 (−70)°C until assayed. Creatinine, C-reactive protein, high-sensitivity troponin T (hsTnT), N-terminal pro-B-type natriuretic peptide (NT-proBNP), and GDF-15 (Roche Diagnostics, Basel, Switzerland) were analysed centrally at ISLAB (Kuopio, Finland). sST2 was measured at INSERM UMR-S 942 (Paris, France) using a quantitative sandwich monoclonal enzyme-linked immunosorbent assay (Presage sST2 Assay; Critical Diagnostics, San Diego, CA, USA). Arterial blood lactate and pH were analysed locally. Estimated glomerular filtration rate (eGFR) was calculated from creatinine values using the Chronic Kidney Disease Epidemiology Collaboration equation.[11] Acute kidney injury was defined and staged according to the Kidney Disease: Improving Global Outcomes criteria based on creatinine value.[12]

Risk prediction models

We assessed the ability of two published risk prediction models, the CardShock risk score and the IABP-SHOCK II score, to predict in-hospital mortality in the elderly.

The CardShock risk score consists of seven variables measured at admission in patients with CS of various aetiologies (age >75 years; eGFR; blood lactate; confusion on admission; left ventricular ejection fraction <40%; previous myocardial infarction or coronary artery bypass grafting; and ACS aetiology) with a maximum of 9 points. The score categorizes the patients into low-risk (0–3 points), intermediate-risk (4–5 points), and high-risk (6–9 points) groups.[1]

The IABP-SHOCK II score is derived from the Intra-aortic Balloon Pump in Cardiogenic Shock II (IABP-SHOCK II) study in patients with CS due to ACS who are undergoing percutaneous coronary intervention (PCI). It consists of six variables (age >73 years; prior stroke; glucose at admission >10.6 mmol/L; creatinine at admission >132.6 mmol/L; thrombolysis in myocardial infarction flow grade <3 after PCI; and arterial blood lactate at admission >5 mmol/L) giving a maximum of 9 points. The patients can be classified according to the points into low-risk (0–2 points), intermediate-risk (3–4 points), and high-risk (5–9 points) categories.[3]

Statistical analysis

We categorized the patients by age into (i) ≥75 years old (elderly group) and (ii) <75 years old (younger group). Elderly patients were further compared with respect to their in-hospital survival status (survivors vs. non-survivors). Results are presented here as number (*n*) and percentage (%); mean with standard deviation (SD); or median with inter-quartile range, as appropriate. Group comparisons were performed using the χ^2 test and Fisher's exact test for categorical variables and Student's *t*-test and Mann–Whitney *U* test for continuous variables. The Kaplan–Meier method was used to elucidate the timing of events during 30 day and 1 year follow-up in relation to age group, and statistical assessment was performed using the log-rank test.

To assess the ability of the CardShock risk score and IABP-SHOCK II score to predict in-hospital mortality in the elderly, and to evaluate the additional value of GDF-15 and sST2 on the risk prediction models, receiver operating characteristic curve analysis was performed. We used previously defined cut-off values of the biomarkers (GDF-15 > 7000 ng/L and sST2 > 500 ng/mL) for this analysis.[7,8] The distribution of the elderly patients and observed mortality within risk categories of both risk prediction models were calculated. The additional value of the biomarkers in mortality prediction was assessed via the likelihood ratio test for nested models. For comparison, the CardShock risk score was further validated in an external cohort of patients with CS with unselected aetiology from a single-centre prospective study. The validation was performed in all patients as well as separately in the elderly (≥75 years) and the younger (<75 years) patients. Logistic regression was used to investigate the interaction between age and risk prediction models. A two-sided *P*-value <0.05 was regarded as statistically significant. All statistical analyses were performed with SPSS 22.0 statistical software (IBM Corp., Armonk, NY, USA).

Results

Clinical characteristics, presentation, and treatment of cardiogenic shock in the elderly

Table 1 outlines the baseline characteristics of the elderly and the younger patients. The elderly constituted 26% (*n* = 56) of the patients, with a mean age of 81 ± 4 years. They were more frequently female (41% vs. 21%, *P* = 0.003) and had more co-morbidities overall, with generalized arteriosclerosis being particularly high compared with younger patients. Overall, ACS (81%) was the principal aetiology of shock, and its frequency did not differ between the age groups.

The two age groups were largely similar with respect to clinical presentation and biochemical findings, as summarized in *Table 2*, except for a few differences. Compared with the younger group, the elderly were less likely to have sinus rhythm at baseline, and a higher proportion of them had left ventricular ejection fraction >40%. The elderly group had worse renal function (creatinine and eGFR) at admission but with a similar incidence of acute kidney injury as the younger patients. Biomarker levels of congestion/cardiac stress (NT-proBNP) were higher in the elderly, whereas the extent of myocardial injury as measured by hsTnT did not differ between the groups [peak hsTnT 3680 (1270–14 281) ng/L in the elderly vs. 3849 (927–12 585) ng/L in the younger; *P* = 0.8]. The extent of coronary artery disease assessed by coronary angiogram in the elderly (one-vessel disease 20%; multivessel disease 59%; and left main disease 11%) was comparable with that of the younger group.

The management of CS, including invasive assessment by coronary angiography and coronary interventions, mechanical ventilation, and use of vasoactive pharmacotherapy, was similar between the age groups, as shown in *Table 3*. The use of intra-aortic balloon pump was more common in the younger group (61% vs. 39%, *P* = 0.004). No differences in the prescription of antithrombotic medication were observed between the age groups (data not shown).

Outcomes and comparing elderly survivors and non-survivors

The elderly had numerically higher in-hospital (46% vs. 33%, *P* = 0.08) and 1 year (52% vs. 41%; *P* = 0.17) mortality. Kaplan–Meier survival curves for in-hospital mortality for all patients and 1 year mortality for those surviving hospitalization stratified by the age group are shown in *Figure 1*. Of

Table 1 Clinical characteristics, medical history, and shock aetiology

	≥75 years n = 56 (26%)	<75 years n = 163 (74%)	P-value	Elderly survivors n = 30 (54%)	Elderly non-survivors n = 26 (46%)	P-value
Age (years)	81 (4) 80 (78–83)	62 (9) 63 (57–69)	<0.001 0.003	81 (5)	81 (4)	0.7
Female, n (%)	23 (41)	34 (21)	0.003	13 (43)	10 (39)	0.6
BMI (kg/m^2)	26 (5)	27 (4)	0.2	26 (5)	26 (4)	0.9
Resuscitated, n (%)	16 (29)	46 (28)	1.0	7 (23)	9 (35)	0.4
Medical history, n (%)						
Hypertension	39 (70)	93 (57)	0.10	21 (70)	18 (69)	1.0
Diabetes	17 (30)	44 (27)	0.6	8 (27)	9 (35)	0.5
History of MI/CABG	19 (34)	38 (23)	0.12	7 (23)	12 (46)	0.07
Prior stroke/TIA	8 (14)	12 (7)	0.12	4 (13)	4 (15)	1.0
PAD	11 (20)	10 (6)	0.003	3 (10)	8 (31)	0.05
Chronic heart failure	7 (13)	29 (18)	0.4	2 (7)	5 (19)	0.2
History of AF	11 (20)	21 (13)	0.2	4 (13)	7 (27)	0.2
Renal insufficiency	11 (20)	14 (9)	0.03	4 (13)	7 (27)	0.2
Smoking history	24 (43)	111 (68)	<0.001	14 (47)	10 (39)	0.6
Shock aetiology, n (%)						
ACS	47 (84)	130 (80)	0.5	25 (83)	22 (85)	1.0
STEMI	37 (66)	112 (69)	0.7	21 (70)	16 (62)	0.5

ACS, acute coronary syndrome; AF, atrial fibrillation; BMI, body mass index; CABG, coronary artery bypass grafting; MI, myocardial infarction; PAD, peripheral artery disease; STEMI, ST-elevation myocardial infarction; TIA, transient ischaemic attack.
Data are presented as numbers and percentages (%), means (SD), and median (inter-quartile range).

note, among patients discharged alive, 1 year survival was comparable between the age groups (*Figure 1* and *Table 3*). Causes of death did not differ between the groups (Supporting Information, *Table S1*). In addition, an exploratory analysis of the patients with ACS aetiology undergoing PCI (n = 142) showed no difference in in-hospital (41% vs. 38%, P = 0.7) and 1 year (44% vs. 46%, P = 0.8) mortality rates between the elderly and the younger groups.

Elderly survivors and non-survivors were largely similar with respect to age, sex, medical history, and shock aetiology (*Table 1*). In contrast, the non-survivors suffered from more severe shock already at baseline, requiring more intense respiratory and haemodynamic support, as depicted in *Tables 2* and *3*. Interestingly, non-survivors had significantly higher GDF-15 levels compared with survivors (*Table 2*). Survivors were more likely to undergo coronary angiogram (93% vs. 65%, P = 0.009). The revascularization rate was, however, still very high (94% had PCI) among non-survivors undergoing angiogram (*Table 3*).

Performance of risk scores for prediction of in-hospital mortality in the elderly

Compared with the younger patients, the CardShock and IABP-SHOCK II risk scores more frequently categorized the elderly patients into the intermediate-risk and high-risk groups and less frequently into the low-risk group (*Figure 2*). Both scores were useful for mortality risk prediction in the elderly; in the low-risk category, the outcome was favourable, and the mortality increased with higher risk category (*Figure 2*). The elderly demonstrated a higher CardShock risk score [5.6 (SD 1.5) vs. 4.0 (1.8); $P < 0.001$] and IABP-SHOCK II score [4.8 (SD 1.4) vs. 3.2 (1.4); $P < 0.001$] compared with the younger. The difference remained significant even after excluding the age variable from the model [CardShock risk score 4.6 (1.4) vs. 4.0 (1.8); P = 0.01 and IABP-SHOCK II score 3.8 (1.4) vs. 3.2 (1.4); P = 0.02].

The elderly survivors had a lower risk profile than non-survivors according to both risk models (CardShock risk score 4.9 vs. 6.4; $P < 0.001$ and IABP-SHOCK II 4.4 vs. 5.6; P = 0.009). While both risk models categorized the majority of the non-survivors (65% in CardShock risk score and 85% in IABP-SHOCK II) into the high-risk group, a significant proportion of the elderly survivors were classified as intermediate-risk patients (*Figure 3*). Age did not have an effect on the ability of the CardShock risk score or the IABP-SHOCK II score to predict outcome ($P_{\text{interaction}}$ 0.82 and 0.47, respectively).

Among the elderly, the CardShock risk score had an area under the curve (AUC) of 0.75 (vs. 0.82 in the younger group) and the IABP-SHOCK II score an AUC of 0.71 (vs. 0.73 in the younger group) for prediction of in-hospital mortality. Each of the biomarkers increased the discrimination of both the CardShock and IABP-SHOCK II risk scores (*Table 4*). Adding the combination of GDF-15 and sST2 to the risk prediction models did not improve discrimination compared with adding only one biomarker at a time (*Table 4*).

For comparison, the CardShock risk score had an AUC of 0.75 [95% confidence interval (CI) 0.69–0.80] for all patients (n = 262), 0.77 (95% CI 0.67–0.87) for patients ≥75 years old (n = 83), and 0.75 (95% CI 0.68–0.82) for patients <75 years old (n = 179) for predicting in-hospital mortality in the validation cohort.

Table 2 Clinical presentation and biochemical findings at baseline

	≥75 years n = 56 (26%)	<75 years n = 163 (74%)	P-value	Elderly survivors n = 30 (54%)	Elderly non-survivors n = 26 (46%)	P-value
Systolic blood pressure (mmHg)	78 (11)	77 (15)	0.7	81 (10)	75 (11)	0.08
Heart rate (b.p.m.)	86 (31)	92 (27)	0.2	78 (29)	93 (33)	0.10
Sinus rhythm, n (%)	30 (54)	128 (79)	0.001	20 (67)	11 (42)	0.09
Left ventricular ejection fraction (LVEF) (%)	36 (15)	32 (14)	0.12	41 (15)	31 (13)	0.03
LVEF < 40%, n (%)	28 (50)	107 (66)	0.03	13 (43)	15 (58)	0.3
Confusion, n (%)	44 (79)	104 (64)	0.06	21 (70)	23 (89)	0.09
Oliguria, n (%)	35 (63)	86 (53)	0.19	11 (37)	24 (92)	<0.001
Biochemical findings						
Haemoglobin (g/L)	124 (21)	130 (23)	0.12	124 (19)	123 (21)	0.6
CRP (mg/L)	19 (3–65)	14 (5–49)	0.9	19 (5–74)	8 (2–65)	0.3
Creatinine (μmol/L)	121 (96–159)	96 (73–138)	0.004	116 (92–137)	127 (106–173)	0.3
eGFR (mL/min/1.73 m^2)	44 (32–62)	70 (45–95)	<0.001	44 (32–66)	35 (30–56)	0.3
ALT (U/L)	37 (20–86)	46 (20–101)	0.4	29 (19–71)	50 (22–90)	0.4
Glucose (mmol/L)	12.7 (9.0–15.6)	10.3 (7.6–16.1)	0.3	11.2 (7.9–14.4)	12.7 (9.4–19.0)	0.9
hsTnT (ng/L)	1568 (358–4174)	2307 (403–5418)	0.7	1479 (212–6249)	1568 (441–4140)	0.9
Peak hsTnT (ng/L)	3680 (1270–14 281)	3849 (927–12 585)	0.8	3521 (1194–8036)	4291 (1345–16 665)	0.4
NT-proBNP (ng/L)	4322 (1599–16 786)	2367 (400–8082)	0.02	4965 (838–18 786)	3706 (1609–16 547)	0.9
Arterial pH	7.29 (7.18–7.37)	7.32 (7.21–7.39)	0.2	7.31 (7.25–7.41)	7.23 (7.10–7.31)	0.02
Lactate (mmol/L)	2.8 (2.0–7.9)	2.9 (1.6–5.3)	0.16	2.3 (1.6–3.3)	6.4 (2.8–8.6)	<0.001
Lactate >5 mmol/L, n (%)	20 (36)	44 (27)	0.2	5 (17)	15 (58)	0.001
GDF-15 (ng/L at 12 h) (n = 154)	10 871 (6562–30 074)	8440 (3846–16 033)	0.05	6912 (3901–13 309)	29 647 (9775–42 406)	<0.001
sST2 (ng/mL at 12 h) (n = 154)	602 (372–1244)	633 (343–1028)	NS	482 (311–923)	907 (543–1574)	0.2

ALT, alanine aminotransferase; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; GDF-15, growth differentiation factor-15; hsTnT, high-sensitivity troponin T; NS, not significant; NT-proBNP, N-terminal pro-B-type natriuretic peptide; sST2, soluble ST2.
Data are presented as numbers and percentages (%), means (SD), and median (inter-quartile range).

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Table 3 Treatment of the shock, length of hospital stay, and outcomes

	≥75 years *n* = 56 (26%)	<75 years *n* = 163 (74%)	*P*-value	Elderly survivors *n* = 30 (54%)	Elderly non-survivors *n* = 26 (46%)	*P*-value
Treatment, *n* (%)						
Angiogram	45 (80)	137 (84)	0.2	28 (93)	17 (65)	0.009
PCI[a]	39 (87)	110 (80)	0.3	23 (82)	16 (94)	0.2
TIMI flow <3 prior PCI (*n* = 167)	38 (95)	114 (90)	0.5	22 (92)	15 (100)	0.5
CABG[a]	1 (2)	8 (6)	0.5	1 (4)	0	—
IABP	22 (39)	100 (61)	0.004	10 (33)	12 (46)	0.3
Invasive mechanical ventilation	31 (55)	106 (65)	0.2	11 (37)	20 (77)	0.003
Use of vasoactive medication, *n* (%)						
Noradrenaline	40 (71)	124 (76)	0.5	19 (63)	21 (81)	0.15
Dobutamine	25 (45)	84 (52)	0.4	10 (33)	15 (58)	0.07
Adrenaline	13 (23)	33 (20)	0.6	3 (10)	10 (39)	0.01
Levosimendan	12 (21)	41 (25)	0.6	7 (23)	5 (19)	0.7
Outcomes						
Incidence of AKI, *n* (%) (*n* = 154)	15 (36)	32 (29)	0.4	1 (4)	14 (74)	<0.001
Length of hospital stay (days)[b]	10 (5–18)	14 (8–27)	0.07			
In-hospital mortality, *n* (%)	26 (46)	54 (33)	0.08			
One year mortality (*n* = 216), *n* (%)	29 (52)	67 (41)	0.17			
One year mortality (among hospital survivors, *n* = 139), *n* (%)	3 (10)	13 (12)	1.0			

AKI, acute kidney injury; CABG, coronary artery bypass grafting; IABP, intra-aortic balloon pump; PCI, percutaneous coronary angiogram; TIMI, thrombolysis in myocardial infarction flow.
Data are presented as numbers and percentages (%), means (SD), and median (inter-quartile range).
[a]Proportion of those who underwent angiogram.
[b]Reported only for those who survived to hospital discharge.

Discussion

Within this prospective, multicentre study on CS with unselected aetiology, the elderly constituted one-fourth of the population. They had a higher in-hospital mortality rate compared with the younger, despite active revascularization. However, those surviving to hospital discharge had a favourable long-term prognosis. Contemporary CS risk prediction scores showed good ability for mortality risk stratification also in the elderly. The discriminative performance of the scores could be further improved by biomarkers such as GDF-15 and sST2.

The elderly constituted 26% of the patients with CS in this study. In prior studies, the proportion of the elderly has varied between 29% and 37%.[2,13,14] In our study, both the clinical presentation and management strategies were similar in the elderly and the younger patients with CS. Considering the predominance of ACS aetiology also in the elderly, the PCI rate was very reasonable; indeed, it was higher than in previous studies. The PCI rate among the elderly patients with CS in previous studies varied between 26% and 51% depending on the study period and the study design including hospital facilities.[2,14] The elderly had 40% higher in-hospital mortality compared with the younger. However, the outcome at 1 year in the elderly hospital survivors was surprisingly good and comparable with the younger. Other studies have reported similar rates of short-term and 1 year mortality in the elderly.[2,13,15]

All the centres in our study were tertiary hospitals with an on-site catheterization laboratory, which might have had an influence on patient profiles. The most frail elderly patients judged to have poor prognosis may not have been transferred to tertiary centres. Consequently, mortality in all elderly patients may be higher than we found in our study. The decision whether to transfer the patient or not is made by the physician in charge, often based on the patient's clinical condition.

Accurate risk prediction is essential in the critically ill and in the elderly in particular. Considering the complex pathophysiology and clinical picture of CS especially in the elderly, tools for objective risk stratification are needed to help treatment decisions at all levels of care. The favourable prognosis in discharged elderly patients with CS highlights the importance of well-balanced treatment decisions early during the in-hospital phase. We evaluated two contemporary risk scores developed specifically in CS and found satisfactory performance in the elderly. Both scores have recently been externally validated in patients with CS.[4,16,17] Furthermore, according to our additional validation, CardShock risk score performed well in the elderly in the study population cohort as well. The risk scores are easy to use, and they can be applied early in the management of patients with CS. These risk scores could serve as useful tools for clinicians taking care of elderly patients with CS in their daily practice. In addition, they provide objective risk stratification and may therefore be an aid in allocating resources adequately.

In the current study, the discriminative ability of the risk scores was, however, somewhat lower in the elderly compared with the younger. Age is included as a variable in both scores, and certain other variables, such as renal function and

Figure 1 Survival in patients with cardiogenic shock by the age group. Kaplan–Meier survival curves for all-cause mortality in the elderly (≥75 years old) (dashed line) and the younger (<75 years old) (solid line) patients with cardiogenic shock. (A) In-hospital mortality (46% in the elderly and 33% in the younger) for all patients. (B) One year mortality (10% in the elderly and 12% in the younger) for those surviving hospitalization.

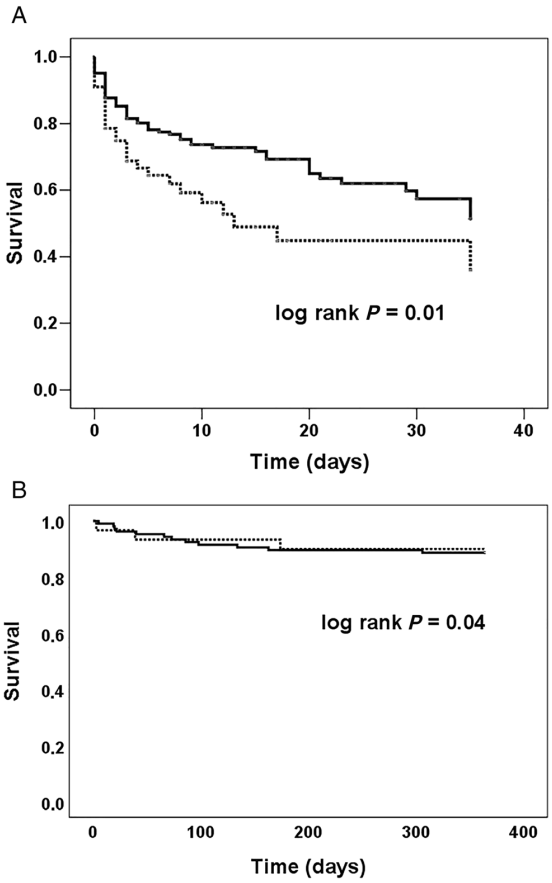
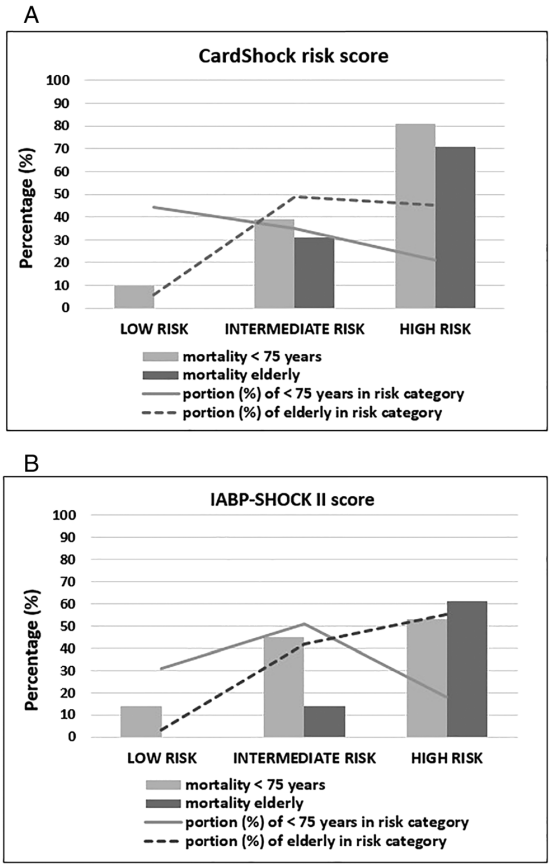


Figure 2 In-hospital mortality by the risk categories in the elderly and the younger with cardiogenic shock. Distribution of the patients (%; bars) and in-hospital mortality (%, dashed lines) according to the risk category (low, intermediate, and high) in the elderly (≥75 years) and in the younger (<75 years) patients with cardiogenic shock in (A) CardShock risk score and (B) IABP-SHOCK II score.



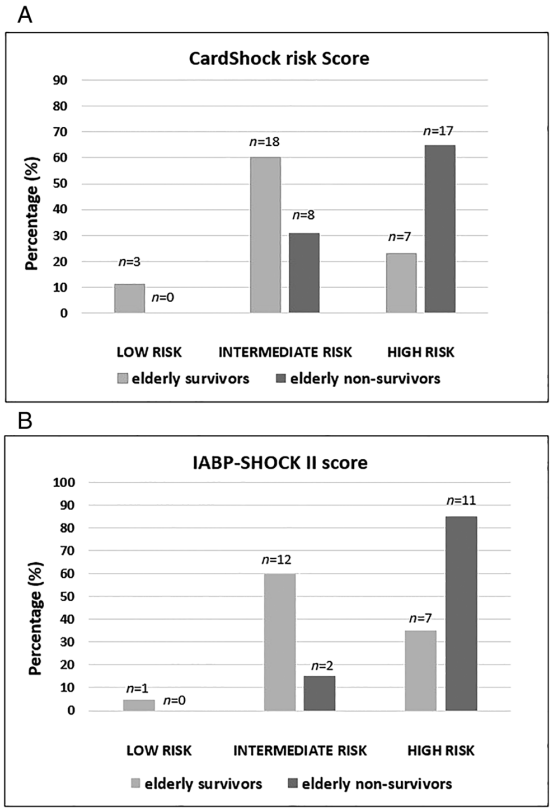
prior manifestation of atherosclerosis, reflect the greater underlying burden of diseases in the elderly. Consequently, most elderly patients are classified into intermediate-risk or high-risk groups. Although the majority of the non-survivors were appropriately categorized as high risk, many elderly survivors were in the intermediate-risk group, leaving room for improved risk classification.

We found that incorporating biomarkers into the risk prediction improved mortality risk discrimination in the elderly. Considering the complex pathophysiology of CS biomarkers such as GDF-15, a marker of oxidative stress and associating with biomarkers of hypoperfusion in CS,[8] and sST2, a marker of cardiac stress and inflammation,[18] likely provide additional prognostic information related to CS that is not captured by traditional risk score variables, which could be particularly useful in the elderly. In view of the ageing population, more studies on accurate risk stratification and the optimal management of elderly patients with CS seem warranted.

Limitations

There are some limitations to be acknowledged. First, although the number of the patients in the prospective CardShock study was reasonable, the proportion of elderly was limited, creating some statistical uncertainty in between-group comparisons. This is a common problem for

Figure 3 Elderly survivors and non-survivors and the risk model categories. Distribution (%) of the elderly (≥75 years) in-hospital survivors and non-survivors in different risk categories in (A) CardShock risk score (n = 53) and (B) IABP-SHOCK II score (n = 33). Numbers above the bars indicate the number of the patients in each category.



most studies in CS.[19] Nevertheless, only a small number of patients were included in the analyses of the risk scores' performance and biomarkers. The number of the patients available differed between the CardShock and the IABP-SHOCK II risk scores. This is mostly due to the variable thrombolysis in myocardial infarction flow in the IABP-SHOCK II score, which was missing in patients who did not undergo coronary angiogram (e.g. non-ACS aetiology). Only a few patients were excluded for other missing variables. Furthermore, GDF-15 and sST2 concentrations were not available from all patients limiting the number of the patients included in the analyses assessing the additional prognostic value of the biomarkers. Secondly, age is one of the variables in both scores giving one point to the elderly automatically. This may contribute to higher score levels and lesser dispersion of the scores among the elderly potentially diminishing the predictive capability of the risk models. Thirdly, having been developed in this study population (patients with CS with different aetiologies), CardShock risk score will perform better in this patient population compared with IABP-SHOCK II score, which was developed in a different patient population (patients with CS due to ACS). Nevertheless, IABP-SHOCK II score performed well in this study population as well. Finally, all treatment decisions were at the discretion of the physician in charge. Nevertheless, this study reflects real-life practice in European tertiary care hospitals, and the choice of treatment strategy was made after careful evaluation based on each individual patient's global health and clinical presentation.

Conclusions

A quarter of patients with CS are elderly. Despite being similar to younger patients in terms of clinical presentation and active revascularization, elderly patients have a higher in-hospital mortality rate. Those surviving to hospital discharge, however, were comparable with younger discharges in having a good long-term prognosis. Contemporary mortality risk prediction scores are useful for risk stratification also in the elderly. The added value of biomarker-based risk

Table 4 AUC for the CardShock risk score and for the IABP-SHOCK II score in combination with GDF-15 or sST2 or both biomarkers to discriminate between in-hospital survivors and non-survivors in the elderly (≥75 years old) and in the younger (<75 years old)

Model	≥75 years AUC (95% CI)	χ^{2a}	P^a	<75 years AUC (95% CI)	χ^{2a}	P^a
CardShock risk score	0.75 (0.60–0.91) (n = 40)			0.82 (0.74–0.90) (n = 106)		
+GDF-15	0.82 (0.69–0.95)	4.92	0.03	0.85 (0.78–0.92)	4.67	0.03
+sST2	0.80 (0.66–0.93)	2.56	0.1	0.83 (0.76–0.91)	1.08	0.3
+GDF-15 + sST2	0.81 (0.68–0.94)	5.76	0.06	0.85 (0.78–0.93)	4.76	0.09
IABP-SHOCK II score	0.71 (0.47–0.94) (n = 28)			0.73 (0.61–0.84) (n = 81)		
+GDF-15	0.84 (0.69–0.99)	8.78	0.003	0.81 (0.71–0.90)	8.64	0.003
+sST2	0.78 (0.59–0.96)	5.14	0.02	0.79 (0.69–0.89)	4.75	0.03
+GDF-15 + sST2	0.83 (0.68–0.98)	9.56	0.008	0.81 (0.72–0.90)	9.42	0.009

AUC, area under the curve; CI, confidence interval; GDF-15, growth differentiation factor-15; sST2, soluble ST2.
[a]χ^2 and P-values are shown for comparison of nested models.

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stratification in elderly patients with CS needs to be confirmed in larger, prospective cohorts.

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Conflict of interest

J.L. has received fees for lectures and advisory board meetings from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Novartis, Pfizer, Roche Diagnostics, and Vifor Pharma. J.P. received honoraria for advisory meetings and lectures from Orion Pharma and Roche Diagnostics. V.C. received consulting honoraria from CVie Therapeutics Limited, Servier, and Windtree Therapeutics. All other authors have no conflicts to declare.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Causes of death as reported by local investigators. Note: more than 1 cause of death per patient was accepted.

Figure S1. Distribution of the age in the elderly. Histogram of the distribution of the age in the elderly patients.

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Supplementary Table 1. Causes of death as reported by local investigators. Note: more than 1 cause of death per patient was accepted.

	≥ 75 years n= 29 (52%)**	**< 75 years n = 67 (41%)****
Myocardial infarction	15	36
Worsening heart failure	11	18
Pulmonary embolism	0	1
Witnessed arrhythmic (VT/VF)sudden death	2	1
Stroke	2	1
Infection	2	10
Renal failure	3	5
Other cause	2	11

*) Data are presented as numbers
**) 1-year mortality
P-value for comparison between the groups is NS for all

III

Levels of Growth Differentiation Factor 15 and Early Mortality Risk Stratification in Cardiogenic Shock

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ABSTRACT

Background: The aim of this study was to assess the levels, kinetics, and prognostic value of growth differentiation factor 15 (GDF-15) in cardiogenic shock (CS).

Methods and Results: Levels of GDF-15 were determined in serial plasma samples (0−120 h) from 177 CS patients in the CardShock study. Kinetics of GDF-15, its association with 90-day mortality, and incremental value for risk stratification were assessed. The median $GDF\text{-}15_{0h}$ level was 9647 ng/L (IQR 4500−19,270 ng/L) and levels above median were significantly associated with acidosis, hyperlactatemia, renal dysfunction, and higher 90-day mortality (56% vs 28%, $P < .001$). Serial sampling showed that non-survivors had significantly higher GDF-15 levels at all time points ($P < .001$ for all). Furthermore, non-survivors displayed increasing and survivors declining GDF-15 levels during the first days in CS. Higher levels of GDF-15 were independently associated with mortality. A $GDF\text{-}15_{12h}$ cutoff >7000 ng/L was identified as a strong predictor of death (OR 5.0; 95% CI 1.9−3.8, $P = .002$). Adding $GDF\text{-}15_{12h}$ >7000 ng/L to the CardShock risk score improved discrimination and risk stratification for 90-day mortality.

Conclusions: GDF-15 levels are highly elevated in CS and associated with markers of systemic hypoperfusion and end-organ dysfunction. GDF-15 helps to discriminate survivors from non-survivors very early in CS. (*J Cardiac Fail 2019;25:894−901*)

Key Words: Cardiogenic shock, growth differentiation factor 15 (GDF-15), prognosis, biomarkers.

Cardiogenic shock (CS) is a state of emergency determined by severe systemic hypoperfusion due to cardiac dysfunction. Despite remarkable advances in the treatment of myocardial infarction and intensive care, mortality in CS remains unacceptably high.[1,2] A systemic inflammatory response and multiorgan injury contribute to the high fatality rates in CS. Therapy options like advanced circulatory support are invasive, highly intense, and costly. Recently, clinical risk scores for predicting outcome have been put forward in CS.[3,4] Biomarkers have shown good potential for prognostic risk stratification in cardiovascular disease and could eventually be helpful in classifying patients eligible for specific therapeutic strategies in CS.[5,6]

Growth differentiation factor 15 (GDF-15), a member of the transforming growth factor-β cytokine superfamily, has emerged as a strong prognostic biomarker in cardiovascular

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disease.[7] GDF-15 is weakly expressed in most tissues under physiological circumstances but may be strongly induced in response to acute stressors including inflammation, oxidative stress, hypoxia, and tissue injury.[7,8] GDF-15 has been shown to provide independent prognostic information beyond traditional clinical risk factors and established biomarkers in acute coronary syndromes (ACS), including ST-elevation myocardial infarction, and in heart failure.[9–16] However, GDF-15 is not a cardiac-specific biomarker. In advanced heart failure, GDF-15 appears to be mainly derived from peripheral tissues reflecting systemic and extra cardiac pathologies.[17] Stress-induced expression, through p53-mediated pathways, of GDF-15 in macrophages, vascular smooth muscle, and endothelial cells makes it a potential marker of vascular injury.[5,6] Data on GDF-15 in critically ill patients are still scarce. Based on its association with systemic and vascular abnormalities, GDF-15 may be of particular interest in CS.

The aim of our study was to assess the levels of GDF-15 in CS using serial measurements and to analyze its prognostic properties and incremental value for risk stratification in CS.

Methods

The CardShock study (NCT01374867 at ClinicalTrials.gov) is a prospective, observational, multicenter study on CS. The overall aim of the CardShock study was to investigate the aetiology, clinical and biochemical characteristics, and to describe management and prognosis in contemporary CS. Specific aims were to identify novel prognostic risk markers in this medical emergency. Patients (n=219) were recruited in 8 European countries at 9 tertiary hospitals between October 2010 and December 2012. A detailed description of the study population, treatments, and overall mortality has been previously published.[3]

Inclusion Criteria and Data Collection

Patients had to be >18 years old and enrolled within 6 hours from the identification of CS. In addition to an acute cardiac cause (both ACS and non-ACS patients were included), the inclusion criteria required systolic blood pressure to be <90 mmHg despite adequate fluid challenge or need for vasopressor therapy to maintain systolic blood pressure >90 mmHg and signs of hypoperfusion (altered mental status/confusion, cold periphery, oliguria <0.5 mL/kg/h for the previous 6 hours, or blood lactate >2 mmol/L). Patients presenting with hemodynamically significant cardiac arrhythmia or shock after cardiac or non-cardiac surgery were excluded from the study. Baseline characteristics, medical history, and clinical findings were recorded at the time of detection of the shock. Biochemical and hemodynamic data as well as treatment and procedures were registered at baseline and until 120 hours after inclusion at prespecified time points. Patients were treated according to local clinical practice. Written informed consent was obtained from the patient or next of kin if the patients were unable to give the consent on admission. The study was approved by local ethics committees and conducted in accordance with the Declaration of Helsinki. The primary outcome was 90-day all-cause mortality.

Blood Sampling and Laboratory Analyses

Serial blood sampling was performed at baseline (0 h), 12, 24, 36, 48, 72, 96, and 120 hours, and plasma aliquots were stored at −70 C° until assayed. All patients with available baseline plasma samples (n=177) were included in this study. Creatinine, C-reactive protein, alanine aminotransferase, high-sensitivity troponin T (hsTnT), N-terminal pro−B-type natriuretic peptide (NT-proBNP), and GDF-15 (all assays from Roche Diagnostics) were analyzed at a central laboratory (ISLAB, Kuopio, Finland). GDF-15 levels <1200 ng/L were considered normal (the 90th percentile in a study on healthy elderly adults).[7,18] Arterial blood lactate and pH were analyzed locally. Estimated glomerular filtration rate (eGFR) was calculated from creatinine values using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation.[19]

Statistical Analysis

Descriptive data are presented as numbers (n) and percentages (%) for categorical variables, and as mean and standard deviation (SD) or as median and interquartile range (IQR) for continuous variables, as appropriate. Patients were dichotomized according to the median baseline GDF-15 level. Between groups comparisons were performed using Chi-squared test for categorical variables, and Student's *t* test, Mann−Whitney *U* test, or Wilcoxon signed rank test for continuous variables, as appropriate. Correlation analyses were performed by Spearman test.

To investigate the changes in GDF-15 levels and their impact on the outcome we created a delta-variable (ΔGDF 0−48 h) by calculating the largest change in the biomarker level between two samples ≥ 24 hours apart during the first 48 hours. The adequate number of samples required for calculation was available from 146 patients. We categorized the delta-variables into 3 groups regarding the change in the biomarker level 1) no change (≤30% increase or decrease), 2) >30 % increase, and 3) >30 % decrease.

Kaplan−Meier curves were used to illustrate the timing of events during follow-up between the groups and statistical comparison was performed using the log rank test. Univariate and multivariable logistic regression analyses were used to evaluate the association of GDF-15 levels with 90-day mortality. The model was adjusted with the CardShock risk score variables.[3] The CardShock risk score is a 9-point risk prediction tool for in-hospital mortality consisting of seven clinical parameters that are readily available on admission (age, eGFR, blood lactate, confusion on admission, left ventricular ejection fraction [LVEF], previous myocardial infarction or coronary artery bypass grafting, and ACS etiology). Results from the logistic regression analyses are presented as odds ratios (ORs) with 95% confidence intervals (CIs). Differences in GDF-15 levels

between survivors and non-survivors over time were analyzed with linear mixed modeling. Due to skewed distribution GDF-15 values were log-transformed to normalize the distribution and the residuals.

To assess whether GDF-15 improves discrimination beyond the CardShock risk Score, the area under the curve (AUC) of the receiver operating characteristic (ROC) curves were calculated. Youden's index was used to identify the optimal cutoff value of GDF-15 from the ROC curve. The added value of GDF-15 in the risk prediction model at different time points was assessed using the likelihood ratio test of nested models. Discrimination was also assessed by the integrated discrimination index (IDI). Improvement in clinical risk stratification was assessed by calculating net reclassification improvement (NRI) using prespecified categories of low (0%−15%), intermediate (15%−50%), and high (>50%) mortality risk as previously defined for the CardShock risk score.[3] A two-sided P value <.05 was regarded as statistically significant. All statistical analyses were performed with SPSS 22.0 software (IBM, Armonk, NY) with the exception of the reclassification analyses which were performed with R version 3.4.1 using PredictABEL package.

Results

The characteristics of the patient population (n=177) are shown in Tables 1 and 2. In brief, the mean age was 66 years (SD 12), and 75% were men. Mean arterial blood pressure at enrolment was 57 mmHg (SD 11) and median level of blood lactate was 2.7 mmol/L (IQR 1.7−5.8). ACS was the cause of CS in 80% of cases. Seventy-three patients (41%) died during follow-up.

GDF-15 Levels in Cardiogenic Shock

The median level of GDF-15 in patients with CS was highest at baseline (GDF-15 9647 ng/L; IQR 4500−19,270), with individual values ranging from 1123 to 115,660 ng/L (levels <1200 ng/L are considered normal). In serial sampling, the median GDF-15 levels were 8500 ng/L (IQR 4171−17,654) at 12 hours, 6642 ng/L (IQR 3428−19,010) at 24 hours, 5846 ng/L (IQR 2821−15,253) at 36 hours, and 5034 ng/L (IQR 2714−12,281) at 48 hours.

Patient characteristics, medical history, and mortality of patients stratified by median GDF-15 level at baseline are shown in Table 1. The groups did not differ with regard to age, gender, body mass index, or etiology (ACS/non-ACS) of shock. However, there was a significantly higher prevalence of comorbidities, ie, diabetes mellitus and previous history of coronary artery disease, in patients with baseline GDF-15 level above median.

The clinical presentation and biochemistry at baseline stratified according to baseline GDF-15 median level are shown in Table 2. Systolic blood pressure, heart rate, and LVEF at baseline echocardiography were similar in patients with baseline GDF-15 above and below median. Patients with baseline GDF-15 above median had significantly higher levels of blood lactate, NT-proBNP, creatinine, alanine aminotransferase, and C-reactive protein, and lower arterial pH, blood hemoglobin concentration, and eGFR.

There were significant correlations between baseline GDF-15 and baseline NT-proBNP ($\rho = 0.38$, $P < .001$) and lactate ($\rho = 0.47$, $P < .001$) with a negative correlation observed with eGFR ($\rho = -0.45$, $P < .001$). Weaker correlations were observed between baseline GDF-15 and alanine aminotransferase ($\rho = 0.29$) and C-reactive protein ($\rho = 0.26$; $P = .001$ for both). We found no significant correlation with hsTnT either at baseline or at later time points.

Baseline GDF-15 Levels and Mortality

Higher levels of baseline GDF-15 were associated with mortality both in univariate (ln$GDF\text{-}15_{0h}$ OR 2.1; 95% CI 1.5−2.9, $P < .001$) and multivariable (ln$GDF\text{-}15_{0h}$ OR 1.9; 95% CI 1.2−3.1, $P = .008$) logistic regression analyses (Fig. 1). Patients with baseline GDF-15 levels > median had

Table 1. Clinical Characteristics, In-Hospital, and 90-Day Mortality Stratified by Baseline GDF-15

	All (n=177)	GDF-15 ≤ Median (n=89)	GDF-15 > Median (n=88)	*P* Value
Age, years (SD)	66 (12)	65 (12)	67 (13)	.4
Female, n (%)	45 (25)	20 (23)	25 (28)	.4
BMI (SD), kg/m^2	27 (4)	27 (4)	27 (4)	.25
ACS etiology, n (%)	142 (80)	71 (80)	71 (81)	.9
STEMI, n (%)	119 (67)	61 (69)	58 (66)	.7
Resuscitated, n (%)	47 (27)	24 (27)	23 (26)	.9
Medical history, n (%)				
Hypertension	107 (60)	50 (56)	57 (65)	.2
Diabetes mellitus	52 (29)	20 (22)	32 (36)	.04
Coronary artery disease	57 (32)	21 (24)	36 (41)	.014
Prior CABG	11 (6)	1 (1)	10 (11)	.005
Heart failure	29 (16)	11 (12)	18 (20)	.15
Atrial fibrillation	26 (15)	13 (15)	13 (15)	1.0
Renal insufficiency	21 (12)	7 (8)	14 (16)	.1
Smoking	107 (60)	53 (60)	54 (61)	.9
In-hospital mortality, n (%)	66 (37)	22 (25)	44 (50)	.001
90-day mortality, n (%)	73 (41)	24 (28)	49 (56)	<.001

ACS, acute coronary syndrome; BMI, body mass index; CABG, coronary artery bypass surgery; SD, standard deviation; STEMI, ST-elevation myocardial infarction.

Table 2. Clinical Presentation, Treatment, and Biochemistry on Admission

	All (n=177)	GDF-15 ≤ Median (n=89)	GDF-15 > Median (n=88)	*P* Value
Systolic BP; mmHg (SD)	77 (14)	77 (12)	77 (16)	1.0
MAP; mmHg	57 (11)	57 (10)	57 (12)	.8
HR, beats/min	88 (29)	87 (28)	89 (29)	.6
LVEF; %	33 (14)	35 (14)	31 (14)	.10
Sinus rhythm, n (%)	127 (72)	73 (82)	54 (61)	.001
Atrial fibrillation, n (%)	26 (15)	8 (9)	18 (20)	.03
Confusion, n (%)	116 (66)	57 (64)	59 (67)	.7
Oliguria, n (%)	93 (53)	38 (43)	55 (63)	.015
Cold periphery, n (%)	169 (96)	85 (96)	84 (96)	1.0
Lactate > 2 mmol/L at inclusion, n (%)	124 (70)	47 (53)	85 (96)	<.001
Mechanical ventilation, n (%)	97 (55)	43 (48)	54 (61)	.08
Biochemistry				
Hemoglobin; g/L	129 (23)	133 (24)	124 (21)	.008
Leukocytes; E9/L	14.0 (5.5)	13.5 (4.9)	14.6 (5.9)	.20
CRP; mg/L	15 (4−53)	7 (4−40)	26 (5−75)	.01
Creatinine; μmol/L	103 (79−140)	91 (68−116)	125 (88−157)	<.001
eGFR; mL/min/1.73 m^2	63 (29)	73 (28)	53 (27)	<.001
ALT; U/L	45 (20−93)	29 (17−52)	82 (33−152)	<.001
Arterial pH	7.30 (7.21−7.40)	7.35 (7.26−7.40)	7.30 (7.20−7.38)	.004
Lactate; mmol/L	2.7 (1.7−5.8)	2.1 (1.3−3.7)	3.7 (2.3−6.7)	<.001
hsTnT; ng/L	2190 (393−5399)	1581 (347−4083)	2629 (441−8716)	.06
NT-proBNP; ng/L	2581 (575−9323)	1360 (373−6627)	5029 (1581−12,300)	<.001
GDF-15; ng/L	9647 (4500−19,270)	4503 (2598−6779)	19,270 (13,178−34,605)	<.001

ALT, alanine aminotransferase; BP, blood pressure; CRP, C-reactive protein; HR, heart rate; MAP, mean arterial pressure.

a significantly higher in-hospital (50% vs 25%, $P = .001$) and 90-day (56% vs 28%, $P < .001$) mortality compared with those with GDF-15 ≤ median (Table 1). The Kaplan−Meier survival curves in patients stratified by median GDF-15 levels are shown in Fig. 2 (log rank $P < .001$). After multivariable adjustment, baseline GDF-15 > median remained independently associated with 90-day mortality (OR 2.6; 95% CI 1.2−5.9, $P = .02$).

Serial Measurements of GDF-15 and Outcome

GDF-15 was an independent predictor of 90-day mortality at all measured time points (Fig. 1). The AUC of GDF-15 for 90-day mortality was 0.70 (95% CI 0.62−0.77, $P < .001$) at baseline, further increased at 12 hours (AUC 0.81; 95% CI 0.74−0.88, $P < .001$), and remained high during the following days (Fig. 3).

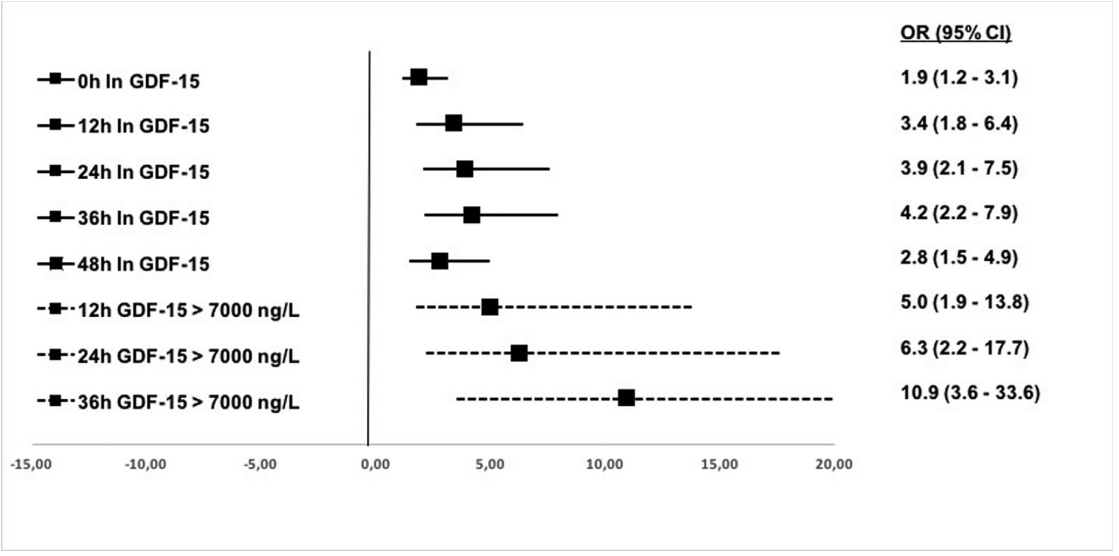

Fig. 1. Forest plot for the association of lnGDF-15 (solid line) and GDF-15 > 7000 ng/L (dashed line) at various time points with 90-day mortality. $P < .05$ for all. The number of patients having GDF-15 >7000 ng/L was 88 (57%) at 12 hours, 67 (49%) at 24 hours, and 58 (44%) at 36 hours.

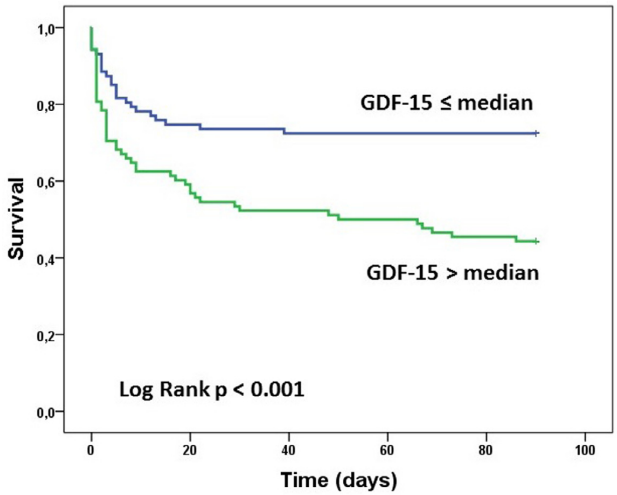

Fig. 2. Kaplan−Meier survival curves for 90-day mortality stratified by the median level of baseline GDF-15.

Serial measurement revealed that the non-survivors had significantly higher GDF-15 levels at all time points compared with the survivors (Fig. 4; $P < .001$ for between-group comparisons and $P < .001$ for all pairwise comparisons). Interestingly, there was a statistically significant decrease of the GDF-15 levels during the first 24 hours in 90-day survivors (median 6640 [IQR 3248−14,896] at baseline vs 4499 [2477−9272] ng/L at 24 h, $P < .001$), whereas the GDF-15 levels remained very high or even tended to increase (12,847 [8795−29,753] ng/L at baseline vs 19,742 [8815−38,240] ng/L at 24 h, $P = .14$) in patients who subsequently died (Fig. 4). Evolution of GDF over time between the survivors and the deceased at 90 days was significantly different ($P < .001$ for time−group interaction).

GDF-15 levels increased >30% in 43 (30%), decreased >30% in 83 (57%), and remained stable (≤30% increase or decrease) in 20 (14%) patients during the first 48 hours. Patients with >30% increase in GDF-15 level had worse 90-day survival than patients with stable or declining levels (Supplementary Fig. 1). However, the association with mortality of an increase in GDF-15 >30% (compared with stable/decrease) did not reach statistical significance after

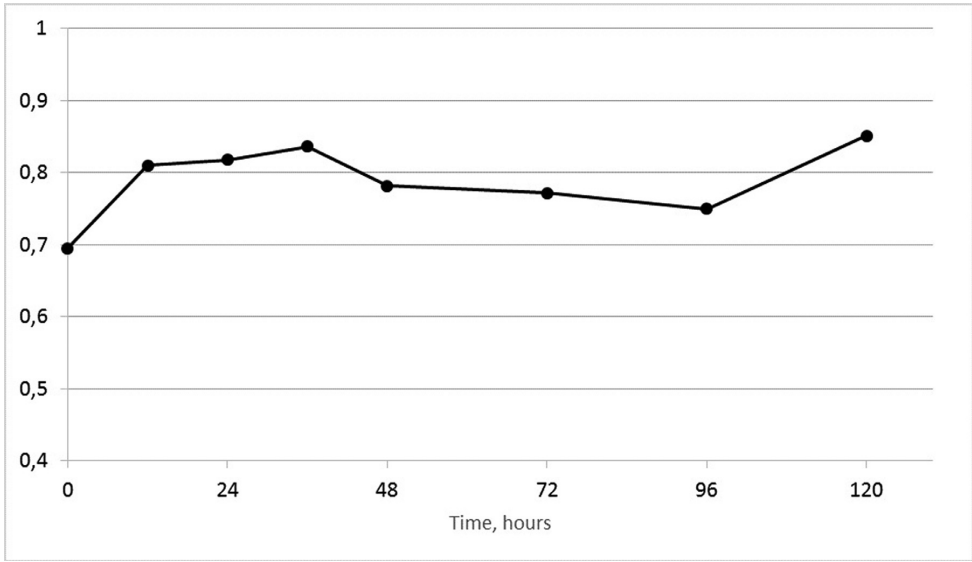

Fig. 3. AUC of GDF-15 to discriminate between 90-day survivors and non-survivors at each time point.

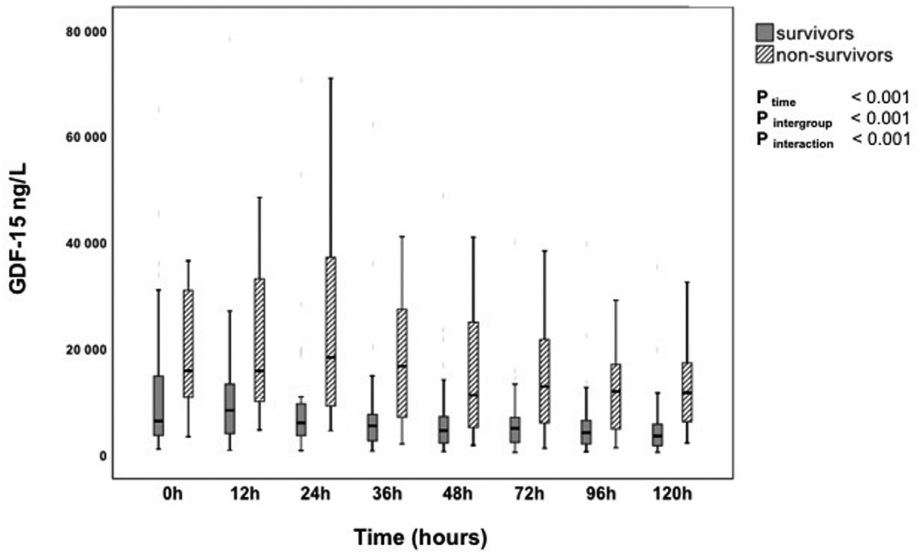

Fig. 4. GDF-15 levels 0−120 hours in survivors and non-survivors.

adjustment for the variables in the CardShock risk score (OR 2.3 [95% CI 0.9−5.8], $P = .07$)

GDF-15 for Risk Stratification in CS

For early risk stratification in CS and based on the AUC values at each time-point, GDF-15 at 12 hours ($GDF\text{-}15_{12h}$) was selected for further analyses. The $GDF\text{-}15_{12h}$ cutoff 7000 ng/L was derived from the ROC curve (Supplementary Fig. 2) and used as a binary variable in discrimination and reclassification analyses. The adjusted OR of $GDF\text{-}15_{12h} >$ 7000 ng/L for 90-day mortality was 5.0 (95% CI 1.9−13.8, $P < .002$) (Fig. 1). Adding $GDF\text{-}15_{12h} > 7000$ ng/L to the prediction model improved discrimination compared with the CardShock risk score alone (AUC 0.85 vs AUC 0.83; χ^2=10.6, $P = .001$ for comparison of nested models; and IDI 0.053 [95% CI 0.012 − 0.094]; $P = .01$). Adding $GDF\text{-}15_{12h} > 7000$ ng/L to the CardShock risk score also improved risk classification (NRI 0.18 [95% CI 0.06−0.30; $P = .003$]), especially among the survivors (Table 3; Supplementary Table 1). Sensitivity analyses were performed using the GDF-15 cutoff of 7000 ng/L also at 24 and 36 hours (Fig. 1). Clinically meaningful improvement in discrimination and reclassification was observed at any time point between 12 and 36 hours after CS detection (Table 3).

Discussion

In this prospective study with serial GDF-15 sampling in CS patients, we report 3 main findings. First, although GDF-15 levels are markedly elevated in CS already at baseline, there are marked differences in the levels and temporal trends of GDF-15 between survivors and non-survivors. Second, GDF-15 is an independent predictor of mortality in CS, with strong predictive value early during hospitalization and throughout the hospital course. Finally, we propose a GDF-15 cutoff of 7000 ng/L that provides excellent discriminative properties for early risk stratification beyond the clinical CardShock risk score.

GDF-15 Levels in CS

In this population with CS, patients presented with extremely high levels of circulating GDF-15 at the time of detection of the shock. Virtually all patients had GDF-15 levels above the previously defined upper limit of normal

Table 3. AUC, NRI, and IDI Values for 90-Day Mortality Assessing the Capability of GDF-15 >7000 ng/L to Improve the Discrimination and risk stratification of CardShock Risk Score (CSS) at 12, 24, and 36 hours

	CSS	CSS + $GDF\text{-}15_{12h}$	CSS + $GDF\text{-}15_{24h}$	CSS + $GDF\text{-}15_{36h}$
AUC (95% CI)	0.83 (0.77−0.89)	ΔAUC 0.02*	ΔAUC 0.01*	ΔAUC 0.01*
NRI (95% CI), %†	—	18.3 (6.1−30.5)	27.1 (7.4−46.8)	34.6 (13.6−55.6)
IDI (95% CI)†	—	0.053 (0.012−0.094)	0.08 (0.028−0.133)	0.14 (0.071−0.20)

*P value <.01 for comparison of the model to CardShock risk Score alone.
†P value <.01 for all NRI and IDI values compared with CardShock risk Score alone.

(1200 ng/L) and the median GDF-15 level was two to five-fold higher than the levels previously described in patients with acute heart failure or ST-elevation myocardial infarction without CS.[15,16,20] GDF-15 elevations of similar magnitude were previously found in CS patients in the biomarker substudy of the IABP-SHOCK II trial.[21] Together with our results, these highly elevated levels of GDF-15 within the first 6−12 hours from onset of CS suggest a very rapid rise in the expression of GDF-15 in response to shock. The time between the onset of CS and blood sampling should therefore be taken into consideration, when interpreting GDF-15 levels in early course of CS.

In cardiogenic shock, the sources of GDF-15 are most likely to be diverse. Ischemia and reperfusion injury induce the expression of GDF-15 in cardiomyocytes during acute myocardial infarction.[22] However, despite high circulating GDF-15 concentrations, cardiac mRNA and protein expression levels of GDF-15 in end-stage non-ischemic dilated cardiomyopathy were very low suggesting other sources of secretion.[17] In our study, no correlation between GDF-15 and myocyte necrosis (hsTnT) was observed. In contrast, GDF-15 was associated with multiple biochemical markers of systemic hypoperfusion (hyperlactatemia, acidosis) and end-organ dysfunction (cardiac, renal, hepatic). GDF-15 is expressed in almost every tissue and strongly upregulated in acute injury and chronic stressful situations. High GDF-15 levels are known to be related to different types of organ failure (heart, liver, and kidney). Similarly to CS, very high levels of circulating GDF-15 have been detected in a small study on patients with sepsis (median GDF-15 level: 16,000 ng/L), another state of systemic hypoperfusion.[23] Taken together, these results suggest GDF-15 to be a marker of systemic hypoperfusion severity and multiorgan injury and dysfunction in CS.

GDF-15 Levels in Survivors and Non-Survivors

Differences in GDF-15 levels between survivors and non-survivors were observed already at the time of detection of shock, in line with a previous report from the IABP-SHOCK II-trial.[21] Our study shows that GDF-15 levels further diverge during hospitalization between survivors and non-survivors. Our results thus suggest that stable or decreasing GDF-15 levels may be a marker of early response to treatment among patients who will survive, whereas increasing levels of GDF-15 at 24 hours despite adequate treatment are indicative of a dismal prognosis.

In addition to our study, baseline GDF-15 levels were shown to have prognostic value in CS patients also in the IABP-SHOCK II-study.[21] The results from our study indicate that although baseline levels of GDF-15 associated with outcome, the prognostic capability for mortality prediction of GDF-15 is even stronger at 12−36 hours. Considering the management during the early phase of CS (urgent revascularization, stabilization of hemodynamic, and other treatment procedures), this time frame can be regarded even more important for risk assessment and prognostication from a clinical point of view.

GDF-15 for Risk Prediction in Cardiogenic Shock

Our study demonstrates that GDF-15 possesses prognostic value beyond clinical risk prediction models for mortality in CS. There is a call for personalized medicine in general and particularly in heart failure.[6] More personalized therapeutic approaches could be based on enhanced risk stratification algorithms that incorporate biomarkers. Recently, GDF-15 has been used in the ABC risk scores in atrial fibrillation,[24−26] supporting clinical applicability of this biomarker. Personalized and precision medicine may be of particular value in the critically ill, and we believe that biomarkers may help address the persistently high mortality of patients with CS. We show that in CS, GDF-15 improves the ability to predict 90-day mortality both in terms of discrimination and reclassification in clinically useful risk categories. Although the suggested cutoff (7000 ng/L) was derived from levels measured at 12 hours, its utility was not limited by strict timing. On the contrary, GDF-15 can be assessed in a clinically relevant time window of 12−36 hours.

Limitations

The main limitation of our study is the lack of external validation, which should be taken into account when using the suggested cutoff. However, this is the first study to show the temporal trends of GDF-15 in CS and provides a solid basis for future studies. In addition, since the optimal cutoff value of GDF-15 was derived from the prospectively collected data in our study, in another dataset this cutoff level may overestimate the predictive capability of the biomarker causing bias. Nevertheless, our study is one of the largest cohorts of biomarker studies in CS and thus the results represent the most recent and contemporary knowledge available in the field.

Conclusions

Levels of circulating GDF-15 are very high early in CS, reflecting systemic hypoperfusion and end-organ dysfunction. Higher GDF-15 levels are independently associated with mortality, with non-survivors displaying further increase in GDF-15, whereas levels of GDF-15 in survivors decline during the first days in CS. At the proposed 7000 ng/L threshold, GDF-15 possesses the ability to add value to the CardShock risk prediction score for early discrimination (12−36 h after detection of shock) between survivors and non-survivors in CS, which makes it an important biomarker for risk stratification in CS.

Disclosures

KC. Wollert holds patents and licensing contract with Roche Diagnostics, both related to GDF-15. V.-P. Harjola: Advisory board fees from Roche Diagnostics, research grant from Abbott, speaker fees from Orion, all outside the present work. J. Lassus: Speakers bureau and consultancy fees: Astra-Zeneca, Bayer, Boehringer-Ingelheim, Novartis, OrionPharma, Pfizer, Roche Diagnostics, and ViforPharma,

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cardfail.2019.07.003.

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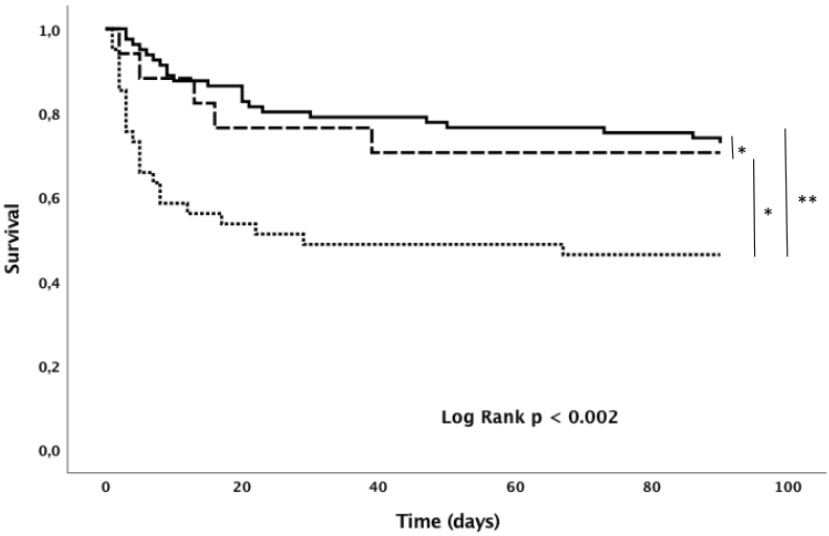
Supplemental Table 1. Net Reclassification Improvement (NRI) for 90-day mortality comparing model with CSS alone to model with CSS variables and GDF-15_{12h} >7000.

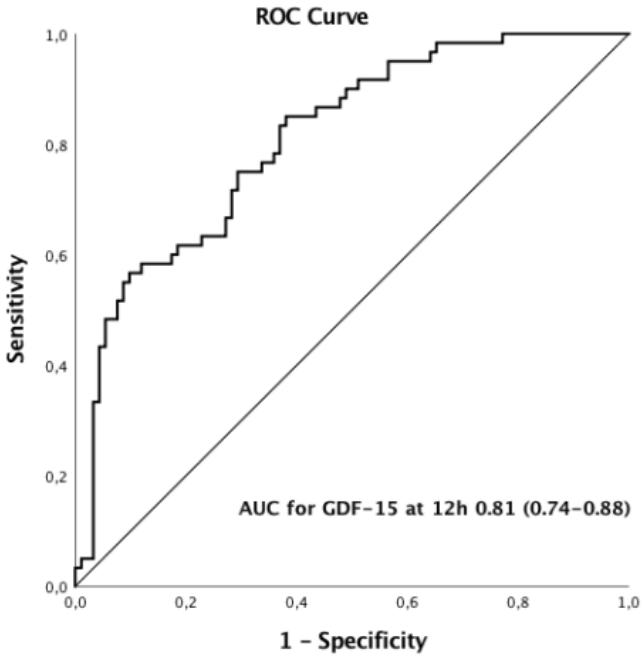
		CSS + GDF-15_{12h}>7000 ng/L			
SURVIVORS n=84	**CSS**	0 - 15%	15 - 50%	50 - 100%	**NRI (95 % CI)**
	0 - 15%	25	0	0	
	15 - 50%	11	22	0	
	50 - 100%	0	12	14	
NON-SURVIVORS n=55		**CSS + GDF-15_{12h}>7000 ng/L**			18 % (6-30 %) p = 0.003
	CSS	0 - 15%	15 - 50%	50 - 100%	
	0 - 15%	1	0	0	
	15 - 50%	2	13	0	
	50 - 100%	0	3	36	

CSS= CardShock risk Score. Green areas denote correct reclassification of survivors to lower risk categories and non-survivors to higher risk categories by adding GDF-15 to the CSS. Red areas represent survivors reclassified to higher risk and non-survivors to lower risk categories (undesirable).

Supplementary Figure 1. Kaplan-Meier survival curves for 90-day mortality according to the delta-variable (ΔGDF 0-48h) groups: no change (≤ 30% increase or decrease) (*dashed line*), > 30% increase (*dotted line*), > 30% decrease (*solid line*). Pairwise comparisons are presented with asterisks: * log-rank P=NS, ** log-rank P < 0.001



Supplementary Figure 2. ROC curve for GDF-15 at 12h.



Soluble urokinase-type plasminogen activator receptor (suPAR) improves early risk stratification in cardiogenic shock

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ABSTRACT

Aim: Soluble urokinase-type plasminogen activator receptor (suPAR) is a biomarker reflecting the level of immune activation. It has been shown to have prognostic value in acute coronary syndrome and heart failure, as well as in critical illness. Considering the complex pathophysiology of cardiogenic shock (CS), we hypothesized suPAR might have prognostic properties in CS as well. The aim of this study was to assess the kinetics and prognostic utility of suPAR in CS.

Methods and Results: SuPAR levels were determined in serial plasma samples (0–96h) from 161 CS patients in the prospective, observational, multicentre CardShock study. Kinetics of suPAR, its association with 90-day mortality, and additional value in risk stratification were investigated.

The median suPAR-level at baseline was 4.4, interquartile range (IQR) 3.2–6.6 ng/mL. SuPAR levels above median were associated with underlying comorbidities, biomarkers reflecting renal and cardiac dysfunction, and higher 90-day mortality (49% vs 31%; $P = 0.02$). Serial measurements showed that survivors had significantly lower suPAR levels at all time points compared with non-survivors. For risk stratification, suPAR at 12h ($suPAR_{12h}$), with a cut-off of 4.4 ng/mL, was strongly associated with mortality, independently of established risk factors in cardiogenic shock: OR 5.6 (95% CI 2.0–15.5; $P = 0.001$) for death by 90 days. Adding $suPAR_{12h} > 4.4$ ng/mL to the CardShock risk score improved discrimination, identifying high-risk patients originally categorized in the intermediate-risk category.

Conclusion: SuPAR is a strong and independent predictor of mortality in CS and improves risk stratification beyond known risk factors in CS patients.

Keywords: cardiogenic shock, suPAR, risk stratification, biomarker, CardShock risk score

Introduction

Cardiogenic shock (CS) is the most life-threating manifestation of acute heart failure (HF) characterized by systemic hypoperfusion due to severe cardiac dysfunction, often leading to multi-organ failure. In addition, the activation of systemic inflammatory responses plays a central role in the complex pathogenesis of CS.[1]

Soluble urokinase plasminogen activator receptor (suPAR) is the soluble form of the membrane-bound urokinase plasminogen activator receptor.[2, 3] SuPAR is thought to reflect the level of immune activation.[3] It has been shown to have excellent prognostic properties in several acute and chronic inflammatory states, including infectious diseases, cancer, organ failures, critical illnesses, and cardiovascular diseases.[4–9] High suPAR levels are known to associate with worse outcome in acute and chronic kidney disease, as well as in HF.[7,9,10]

Biomarkers have proved to be helpful in risk stratification and prognostication in cardiovascular diseases. We hypothesized that suPAR could serve as a biomarker reflecting multi-organ dysfunction as well as the severity of the systemic inflammatory response involved in CS pathogenesis, and be valuable in risk prediction in CS.

The aim of this study was to investigate the role of suPAR in CS using serial measurements, to assess its association with organ dysfunction, and to evaluate the prognostic ability and value of suPAR in early risk stratification in CS.

Methods

This was a biomarker substudy of the CardShock study. The CardShock study (ClinicalTrials.gov identifier: NCT01374867) was a prospective, observational, multicentre study on cardiogenic shock conducted in nine tertiary centres in eight European countries between

October 2010 and December 2012. A detailed description of the study design and main results have been previously published.[11]

Inclusion criteria and data collection

Patients (n = 219) aged over 18 years were included within 6 hours from the detection of shock. In addition to an acute cardiac cause, the inclusion criteria required a systolic blood pressure (SBP) of < 90 mmHg for 30 min (despite adequate fluid administration), *or* the need for a vasopressor to maintain SBP > 90 mmHg *and* at least one sign of hypoperfusion (altered mental status, cold periphery, oliguria < 0.5 mL/kg/h for the previous 6 hours, or blood lactate > 2 mmol/L). Exclusion criteria included shock caused by ongoing haemodynamically significant arrhythmia and shock after cardiac or non-cardiac surgery. The aetiology of CS [acute coronary syndrome (ACS) or non-ACS] was defined by the local investigators, and the patients were treated according to local clinical practice. Medical history, baseline characteristics, clinical signs, and treatment and procedures were recorded. The primary endpoint was 90-day all-cause mortality. Written informed consent was obtained from each patient or next of kin if the patient was unable to give the consent on admission. The study was approved by local ethics committees and conducted in accordance with the Declaration of Helsinki.

Blood sampling and laboratory analyses

Serial plasma samples were collected at seven pre-specified time points: at baseline (0h), 12h, 24h, 36h, 48h, 72h, and at 96h. Plasma aliquots were immediately frozen and stored at –70 °C until assayed. Patients with available study plasma samples at baseline were included in this substudy (n = 161); two centres did not participate in the biomarker substudy. Creatinine, C-reactive protein, alanine aminotransferase, high-sensitivity troponin T (hsTnT), and N-terminal pro–B-type natriuretic peptide (NT-proBNP) were analysed using assays from Roche Diagnostics

(Basel, Switzerland) whereas suPAR was analysed using a commercially available enzyme-linked immunosorbent assay, suPARnostic® AUTO Flex ELISA kit (ViroGates, Denmark). All these biomarkers were analysed at a central accredited lab (ISLAB, Kuopio, Finland). Arterial blood lactate and pH were analysed locally. Estimated glomerular filtration rate (eGFR) was calculated from creatinine values using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation.[12]

Statistical analyses

Results are presented as numbers (n) and percentages (%) for categorical variables, and as means and standard deviations (SD), or as medians and interquartile ranges (IQR) for continuous variables, as appropriate. Patients were categorized by the baseline median suPAR into two groups:1) above median; and 2) median or less. Between-group comparisons were performed using Chi-squared tests or Fisher's exact tests for categorical variables and Student's t-tests or Mann-Whitney U-tests for continuous variables, as appropriate. Wilcoxon signed rank tests were used to determine differences in serial suPAR measurements. Spearman tests were used for correlation analyses, which were performed on samples taken at 12h. Differences in suPAR levels between survivors and non-survivors over time were analysed with linear mixed modelling; due to skewed distribution, suPAR values were log-transformed to normalize the distribution and the residuals.

Kaplan-Meier curves were used to examine the 90-day survival and log-rank tests were used for group comparisons. A multivariate logistic regression model was used to evaluate the association of suPAR with 90-day mortality. The model was adjusted with the CardShock risk score, a nine-point risk prediction tool for in-hospital mortality consisting of seven clinical parameters: age, eGFR, blood lactate, confusion on admission, left ventricular ejection fraction (LVEF), previous myocardial infarction or coronary artery bypass grafting, and ACS aetiology.[11]

Results from the regression analyses are presented as odds ratios (OR) with 95% confidence intervals (CI).

To evaluate the prognostic value of suPAR and its capability to improve discrimination beyond the CardShock risk score, receiver operating characteristic (ROC) curves were generated and the areas under the curves (AUC) were calculated. The Youden index was used to determine the optimal cut-off value for suPAR at 12h from the ROC curve. The additional value of suPAR in the risk prediction model was assessed using the likelihood ratio test for nested models. A two-sided P value <.05 was regarded as statistically significant. All statistical analyses were performed with SPSS 25.0 software (IBM, Armonk, NY).

Results

This study included 161 patients with a mean age of 66 (12) years; 26% were women, and ACS was the main cause of shock (79%). All-cause mortality at 90 days was 40%. The clinical characteristics of the study population are presented in Table 1.

Study population in this substudy did not differ from the patient population in the whole CardShock study (supplementary Table 1).

SuPAR levels in cardiogenic shock

Baseline suPAR level measurements were available from 161 patients, with a median of 4.4 (IQR 3.2–6.6) ng/mL. In serial sampling, the median level of the biomarker remained relatively stable during the first 12 hours [4.4 (IQR 3.3–7.5) ng/mL at 12h] but tended to increase from then on, reaching a maximum at 96h with a median of 5.6 (IQR 4.1–9.4) ng/mL.

Table 1 outlines the clinical characteristics and presentation, biochemistry at baseline, and treatment, stratified by the baseline median suPAR level. The prevalence of comorbidities, particularly HF, atrial fibrillation, and renal failure, was significantly higher among those with a baseline suPAR above median, as were the levels of creatinine, NT-proBNP, and CRP. ACS aetiology was more common in patients with suPAR ≤ median.

Correlation of suPAR with other biomarkers

SuPAR correlated moderately with markers reflecting renal function (Creatinine ρ = 0.44, $P < 0.001$; and estimated GFR ρ = –0.46; $P < 0.001$), congestion/cardiac stress (NT-proBNP ρ = 0.41, $P < 0.001$), and CRP (ρ = 0.38; $P < 0.001$). Conversely, suPAR did not correlate with hs-TnT and its correlation with age was modest (ρ = 0.26; $P = 0.003$).

Outcome and serial sampling of suPAR

Clinical outcomes, stratified by the baseline median suPAR level, are presented in Table 1. Mortality at 90 days was significantly higher in those having baseline suPAR above median (49% vs 31%; $P = 0.02$). According to serial measurements, survivors had significantly lower suPAR levels at all time points compared with non-survivors (Figure 1; $P < 0.001$ for between-group, and $P < 0.001$ for all pairwise comparisons). Furthermore, suPAR levels remained fairly stable during the first 24 hours among survivors 4.15 (IQR 2.85–5.95) ng/mL at baseline vs 3.84 (IQR 2.80–5.46) ng/mL at 24 h; $P = 0.84$. In contrast, in non-survivors suPAR levels increased from 5.11 (IQR 3.36–7.13) ng/mL at baseline to 5.90 (IQR 4.49–9.32) ng/mL at 24h; $P < 0.001$. Changes in suPAR levels differed significantly between survivors and non-survivors during the whole study period ($P_{interaction} < 0.001$) (Figure 1).

SuPAR in risk prediction

To assess the ability of suPAR for early risk stratification in CS, we selected suPAR at 12 hours ($suPAR_{12h}$) for further analysis (n = 138). When analysed as a continuous variable, $SuPAR_{12h}$ had an AUC of 0.72 for 90-day mortality. According to the Youden index, the optimal cut-off value for suPAR at 12 hours to predict outcome was 4.4 ng/mL. Patients with $suPAR_{12h}$ > 4.4 ng/mL had a 90-day mortality of 56% compared with 19% for those with $suPAR_{12h} \leq$ the cut-off ($P < 0.001$). After adjustment for the CardShock risk score variables, $suPAR_{12h}$ remained an independent predictor for 90-day mortality, OR 5.6 (2.0–15.5); $P = 0.001$.

As a binary variable partitioned by the cut-off value, $SuPAR_{12h}$ improved discrimination compared to CardShock risk score alone (AUC 0.87 vs. 0.84; $\chi^2 = 14.2$ for 90-day mortality prediction; $P < 0.001$ for comparison of nested models) (Figure 2).

Kaplan-Meier analysis showed that, by dividing each CardShock risk category by the $suPAR_{12h}$ cut-off into two subgroups (low/intermediate/high risk category + $suPAR_{12h}$ above or below cut-off), risk stratification improved, especially in the intermediate risk group (Figure 3).

Discussion

This is the first study to assess suPAR in the context of CS and its association with outcome. We report three main findings. First, suPAR levels in CS are elevated and associate with comorbidities and acute organ dysfunctions. Secondly, higher suPAR levels are associated with worse outcomes, and suPAR is a strong and independent predictor of mortality in CS. Finally, measuring suPAR at 12 hours from baseline with a cut-off of 4.4 ng/mL improves early risk stratification.

The suPAR levels in our study were clearly higher than previously defined upper limit of normal healthy individuals (3 ng/mL), but remained markedly lower than suPAR levels reported in other critically ill patients.[6] In sepsis, suPAR has been reported to be as high as 9–11 ng/mL, and, in acute severe pancreatitis, the biomarker has been shown even to reach 17 ng/mL.[5,13,14] In contrast, the suPAR levels in this study more closely resemble those reported in populations with ST-elevation myocardial infarction and chronic HF (3.5–4 ng/mL).[9,15] The differences in suPAR concentrations between CS and sepsis or pancreatitis may be due to a higher degree of inflammation and a greater amount of inflammatory cells observed in the latter critical illnesses. This can be related to two findings. First, shedding of urokinase-type plasminogen activation receptor (uPAR) from activated neutrophils has been shown to represent a main source of suPAR in serum and plasma in systemic inflammation and in patients with sepsis[16] Secondly, although inflammation has a remarkable role in the complex pathophysiology in CS, the degree of inflammation has shown to be much lower in CS than in septic shock.[17]

SuPAR was associated with a previous history of renal insufficiency and HF, and correlated positively with markers reflecting these derangements. This is not surprising, considering that suPAR is known to be related to the pathogenesis and development of chronic kidney disease, and it was recently shown to be associated with a risk of acute kidney injury as well.[7,10] In addition, suPAR has been shown to predict mortality in chronic HF.[9] It remains unclear whether suPAR is a specific, prognostic biomarker for CS or merely reflects the severity of underlying chronic as well as acute renal dysfunction and HF, both related to worse prognosis in CS. However, SuPAR was shown to be a strong and independent predictor of mortality in CS. The incremental prognostic potential of suPAR in CS may be due to its capability to reflect and integrate information from underlying comorbidities, incident acute organ failures, and the complex pathophysiology of CS.

We found that an optimal cut-off of 4.4 ng/mL for suPAR at 12 hours strongly predicted mortality and improved early risk stratification when added to the CardShock risk score,

especially in the patients with intermediate risk. This is an important finding, considering the acute setting of CS and the importance of identifying high-risk patients who would benefit most from further intensive and costly treatment options, such as mechanical circulatory support. Evaluation of the patients with intermediate risk with traditional clinical tools may remain imprecise and potentially delay implication of further life-saving interventions. Using suPAR as a “warning bell”, in combination with mainly clinical variables in the CardShock risk score, could identify patients at high risk more accurately, and thus guide the treatment intensity after the initial phase of CS.

Limitations

This study has some limitations to be acknowledged. First, blood samples were not available from all the 219 patients of CardShock study and at all time points. However, this is one of the largest biomarker cohorts in CS. Secondly, since this was the first study to explore the prognostic role of suPAR in CS, the determined cut-off value needs to be validated in further studies. Thirdly, as with other observational studies, there may be residual unidentified confounders which could have led to an overestimation of the independent association of suPAR with mortality.

Conclusions

Circulating suPAR levels are elevated in CS and associate with multiple acute and chronic organ impairments. Higher suPAR levels are independently associated with mortality in CS patients. Finally, suPAR improves early risk stratification, especially in patients initially categorized into intermediate risk class by the CardShock risk score.

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Conflict of interest

JP received honoraria for lectures from Orion Pharma, Roche Diagnostics, Novartis, Astra and Servier. Dr. Mebazaa reports personal fees from Orion, Servier, Otsuka, Philips, Sanofi, Adrenomed, Epygon and Fire 1 and grants and personal fees from 4TEEN4, Abbott, Roche and Sphyngotec. All other authors have no conflicts to declare.

Table 1. Clinical characteristics and presentation, biochemistry, treatment of the shock, and outcome.

	All **n = 161**	**suPAR ≤ median** **n = 81**	**suPAR > median** **n = 80**	***P*-value**
Age, years (SD)	66 (12)	66 (11)	66 (12)	1.0
Female, n (%)	41 (26)	21 (26)	20 (25)	0.9
BMI (SD), kg/m^2	27 (4)	27 (4)	27 (4)	0.8
Aetiology of the shock, n (%)				
ACS	127 (79)	71 (88)	56 (70)	0.006
STEMI	106 (66)	65 (80)	41 (53)	< 0.001
Medical history, n (%)				
Hypertension	100 (62)	47 (58)	53 (66)	0.3
Diabetes	48 (30)	21 (26)	27 (34)	0.3
Coronary artery disease	53 (33)	21 (26)	32 (40)	0.06
Heart failure	27 (17)	7 (9)	20 (25)	0.005
Atrial fibrillation	25 (16)	6 (7)	19 (24)	0.004
Renal insufficiency	19 (12)	1 (1)	18 (23)	< 0.001
Clinical presentation (at baseline)				
Systolic BP; mmHg	77 (14)	75 (12)	80 (15)	0.05
HR, beats/min	88 (28)	86 (26)	90 (29)	0.4
LVEF; %	32 (14)	35 (14)	29 (13)	0.006
CardShock risk score	4.3 (1.9)	3.9 (1.9)	4.7 (1.9)	0.008
Biochemistry (at baseline)				
Hemoglobin; g/L	129 (24)	132 (20)	125 (26)	0.05
CRP; mg/L	16 (2–75)	6 (2–25)	41 (9–89)	< 0.001

Creatinine; µmol/L	101 (77–139)	88 (69–114)	127 (91–168)	< 0.001
eGFR; ml/min/1.73 m^2	62 (41–87)	71 (55–96)	48 (30–70)	< 0.001
ALT; U/L	46 (21–96)	44 (23–79)	50 (20–141)	0.2
Lactate; mmol/L	2.7 (1.6–5.9)	2.6 (1.5–4.9)	3.0 (1.7–6.8)	0.1
NT-proBNP; ng/L	2450 (565–9172)	1077 (253–3589)	6726 (2088–16786)	< 0.001
hs-TnT; ng/L	1857 (365–5279)	1885 (446–5365)	1733 (208–5110)	0.6
Treatment, n (%)				
Coronary angiogram	132 (82)	75 (93)	57 (71)	< 0.001
PCI*	109 (83)	66 (88)	43 (75)	0.1
CABG*	6 (5)	2 (3)	4 (7)	0.4
In-hospital mortality, n (%)	59 (37)	23 (28)	36 (45)	0.03
90-day mortality, n (%)	64 (40)	25 (31)	39 (49)	0.02

Data are presented as numbers and percentages (%), means (with SD), or medians (with interquartile range), as appropriate.
SD=standard deviation, BMI=body mass index, ACS=acute coronary syndrome, STEMI=ST-elevation myocardial infarction, BP=blood pressure, HR=heart rate, LVEF=left ventricular ejection fraction, CRP=C-reactive protein, eGFR=estimated glomerular filtration rate, ALT=alanine aminotransferase, PCI=percutaneous coronary intervention, CABG=coronary artery bypass surgery
*) proportion of those who underwent angiogram

Figure 1. SuPAR 0–96h levels in survivors vs. non-survivors. SuPAR levels during 0–96 h in survivors (green) and non-survivors (red). SuPAR median levels at each time point are presented below the figure.

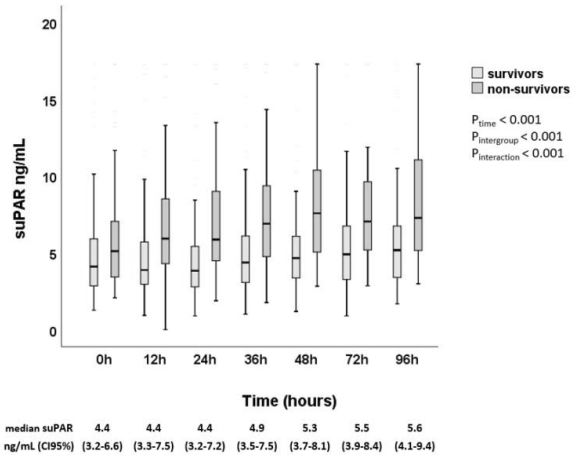


Figure 2. ROC curves for predicting 90-day mortality. ROC curves for 90-day mortality prediction for a) suPAR at 12h, b) CardShock risk score, and c) CardShock risk score + $suPAR_{12h}$ > 4.4 ng/mL.

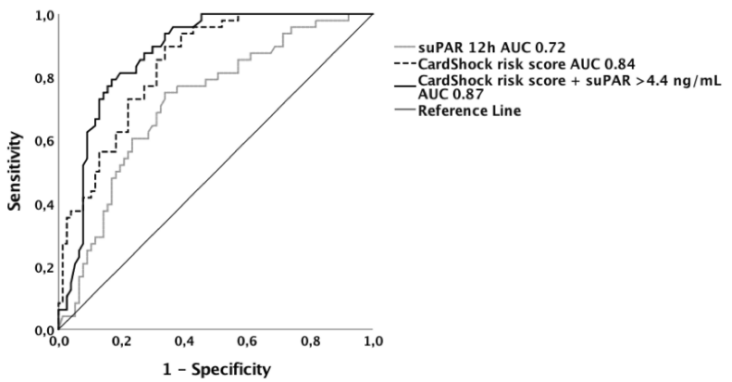
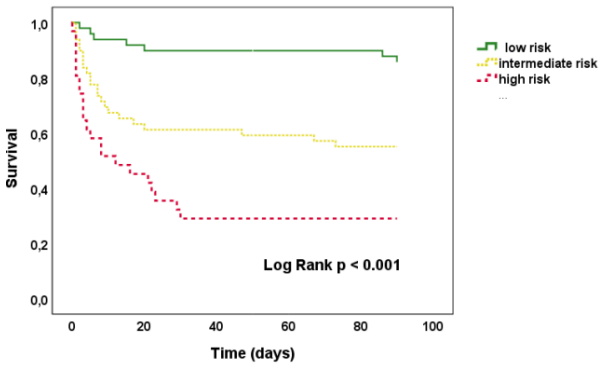
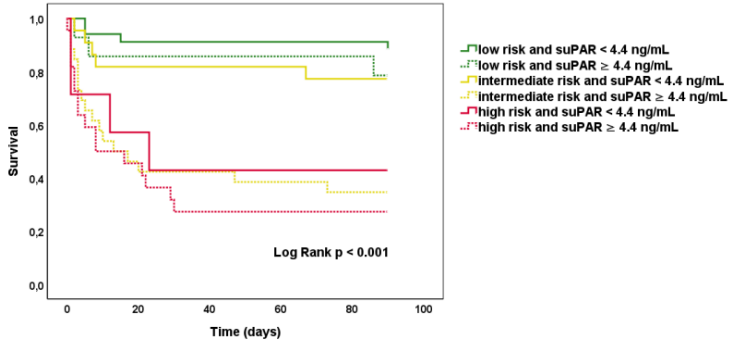


Figure 3. Kaplan Meier survival curves for 90-day mortality stratified by the CardShock risk score categories and suPAR above or below the cut-off-value 4.4 ng/mL at 12h. Panel a) comparison of survival curves according to the CardShock risk score categories (low/intermediate/high risk), b) comparison of survival curves according to the CardShock risk score categories (low/intermediate/high risk) divided by the suPAR cut-off 4.4 ng/mL at 12h into two subgroups.

A)



B)



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