The relationship between the use of loop diuretics, congestion and heart failure outcome

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THE RELATIONSHIP BETWEEN THE USE OF LOOP DIURETICS, CONGESTION AND HEART FAILURE OUTCOME:

2022

IN SEARCH OF NOVEL TOOLS OF CONGESTION DETECTION AND GRADING

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ISBN: 978-94-6423-918-8

Cover design: Rokas Petreikis

Printed in Lithuania

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DISSERTATION

to obtain the degree of Doctor at the Maastricht University,
on the authority of the Rector Magnificus, Prof. dr. Pamela Habibović
in accordance with the decision of the Board of Deans,
to be defended in public on

Friday 30th of September 2022 at 10.00 hours

by

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CHAPTER 1

INTRODUCTION

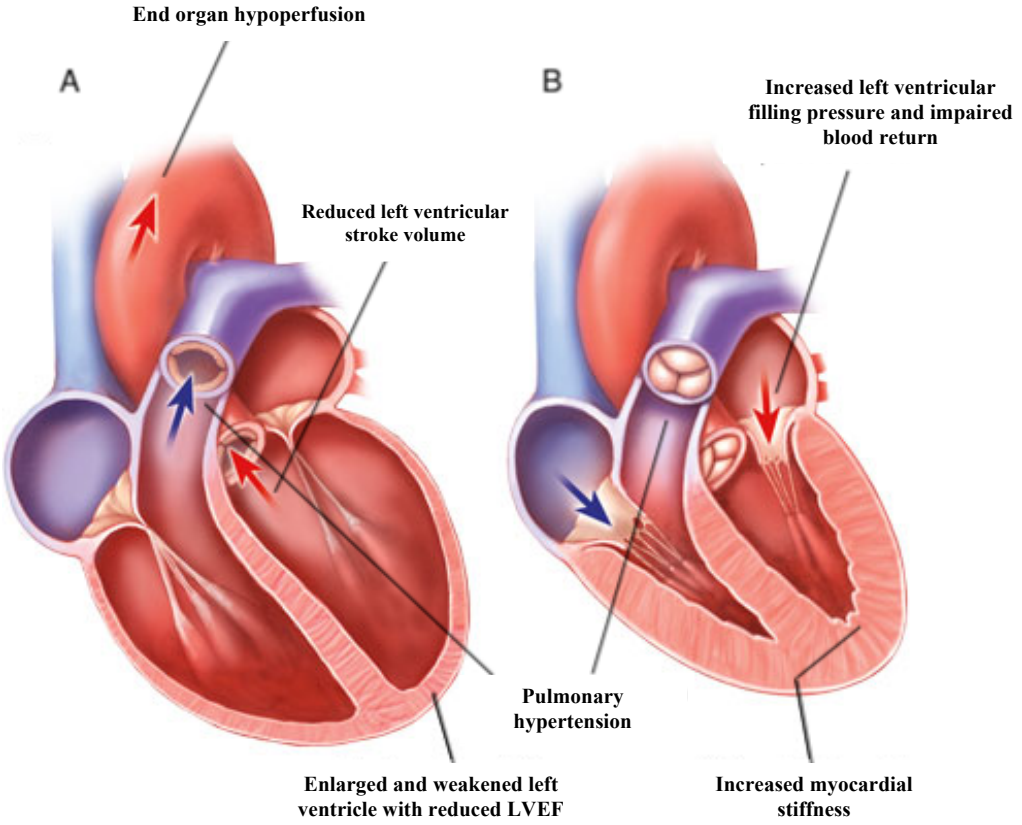
Heart failure (HF) is a clinical syndrome characterised by typical signs and symptoms caused by structural and/or functional abnormalities of the heart[1]. The condition is diagnosed in 1-2% of people in Western countries, meaning that it affects more than 60 million people globally[2,3]. In some specific populations the prevalence may even be higher. For instance, up to 10% of people older than 70 years of age suffer from HF[4]. The absolute number of yearly new cases of HF is increasing in the developed countries, meaning that the number of people living with the disease is continuously rising[5]. This phenomenon may be attributed to many factors; the most important of which are the improvement of treatment of myocardial infarction and better survival of patients with post-myocardial infarction cardiomyopathy and increasing proportion of elderly patients in the modern societies. The prevalence of comorbidities leading to HF, including atrial fibrillation, diabetes, and obesity is also rising. Although there is a modest decrease in mortality among HF patients, the rates remain unacceptably high and reach 32% in the first year after an incident HF diagnosis is established[6]. Apart from that, the absolute number of HF-related hospitalizations is also rising, making it the leading cause of disease-related hospitalisations[7]. One out of two HF patients is repeatedly hospitalized after an episode of acute decompensation withing a year and there is no tendency towards the reduction of repeated hospitalisations in a real-world setting[8]. The cost of inpatient treatment accounts for 44-96% of total HF expenses and the financial burden is rising[9,10]. It is generally accepted that decompensation leading to hospitalisation is primarily determined by progressing congestion[11]. Even more, congestion is closely associated with worse survival[12]. Therefore, advances in its detection, grading, and management can potentially reduce hospitalization rates, decrease HF-attributed financial burden, and improve survival of patients living with HF.

1.1 Classification of heart failure

Some classifications of HF are available[13,14]. Each of them provides useful information about the disease and helps to classify the patients according to a parameter of interest. Still, the most widely accepted classification is based on left ventricular ejection fraction (LVEF). The European Society of Cardiology (ESC) and the American College of Cardiology/American Heart Association guidelines distinguish HF with reduced ejection fraction (HFrEF), when LVEF is $\leq 40\%$[1,15]. The recent ESC guidelines suggest classifying the remaining HF patients to HF with mildly reduced LVEF (HFmrEF, LVEF 41-49%) and HF with preserved LVEF (HFpEF, LVEF $\geq 50\%$) patients[1]. The differences in morphological and functional changes of the heart between HFrEF and HFpEF are explained in **Figure 1**. LVEF-based classification has two major advances: 1) it describes – at least in part – HF pathophysiology; 2) it

differentiates candidates to guidelines-directed evidence-based medical therapy (i.e. HFrEF) from patients for whom medical therapy is less investigated but probably helpful (i.e. HFmrEF) and those where most therapeutic interventions have not been proven to improve outcome (i.e. HFpEF). In spite of different aetiology and pathogenesis, all groups of patients develop similar degree and extent of congestion[16], which has been shown to be an important target for treatment[17,18]. Therefore, congestion management remains the same for the entire spectrum of HF cases.

Figure 1. Morphological and functional changes of the heart in heart failure with reduced (A) and preserved (B) left ventricular ejection fraction



In heart failure with reduced ejection fraction (HFrEF, A) the left ventricle loses its ability to effectively contract during systole. This is represented by the left ventricular ejection fraction (LVEF), and results in reduced left ventricular stroke volume, in turn leading to systemic end organ hypoperfusion. These changes are often accompanied by pronounced left ventricular dilation and eccentric remodelling. In contrast, in patients with heart failure with preserved ejection fraction (HFpEF, B), the systolic function is normal or only mildly impaired (LVEF ≥ 50%), but the diastolic component is disturbed by an increase in myocardial stiffness. This impairs left ventricular diastolic filling, which in turned leads to increased left atrial filling pressure. Concentric left ventricular hypertrophy is often found in HFpEF, but its absence does not exclude the condition. Both, HFrEF and HFpEF can induce postcapillary pulmonary hypertension and lead to right ventricular dysfunction. Patients with heart failure with mildly reduced LVEF exhibit a combination of functional and morphological changes found in HFrEF and HFpEF patients.

1.2 The burden of congestion

Congestion is highly prevalent in a contemporary HF setting, often leading to HF-related hospitalisation. The IMPACT-HF registry showed that progressive volume overload with or without pulmonary oedema was the reason for hospital admission in 56% of cases, whereas low cardiac output was adjudicated as the main reason in only 1% of patients[19]. The ADHERE registry indicates that most acute HF cases are due to exacerbation of chronic HF with dyspnoea, rales, and oedema as the main signs / symptoms at presentation[20]. A high volume OPTIMIZE-HF registry showed that most patients exhibit variable degree of congestion at admission, which is closely related to the length of in-hospital stay[21]. Data from the DOSE-AHF and CARESS-HF trials show that nearly half of patients are discharged with persistent clinical congestion, and even in case of clinical decongestion, two-thirds of decongested patients relapse within 60 days[22]. Both congestion at admission and persistent congestion at discharge lead to post discharge events[11,12,23]. Another retrospective analysis of the DOSE-AHF database showed that incomplete decongestion on discharge determines poor outcome and is probably the key driver of hospital readmission[24]. Congestion not only determines repeated hospitalizations and increases the risk of death, but also significantly reduces the quality of life, whereas the reduction in congestion is related to an improvement in the quality of life in a chronic HF setting[25].

1.3 Congestion pathophysiology

From a mechanical point of view, the heart acts as a pump, ensuring blood circulation in the human body. To ensure the blood flow, the pump must fulfil two simplified conditions: 1) be able to accommodate the blood that enters the heart chambers from venous circulation and 2) be able to pump the required volume of blood out of the heart chambers to the arterial circulation (**Figure 1**). These functional components are called systolic and diastolic function, respectively. Both, systolic and diastolic dysfunctions cause distinct haemodynamic derangements, leading to fluid accumulation in the human body. Importantly, significant systolic dysfunction itself is often accompanied with diastolic dysfunction, reflected by a significant increase in left ventricular filling pressure[26,27]. Therefore, congestion development in HFrEF is determined by systolic and diastolic components, meanwhile in patients with HFpEF diastolic dysfunction is primarily responsible for fluid retention.

Reduced stroke volume is a typical feature of HFrEF. When a failing left ventricle is no longer capable to ensure arterial blood demand, this underfilling is sensed by the baroreceptors in the vasculature, primarily in the carotid sinus and the aortic arch[28]. This leads to sympathetic

activation and increased norepinephrine release. This reflex primarily serves as a compensatory response because sympathetic activation increases the heart rate, induces vasoconstriction, and promotes myocardial contractility. However, vasoconstriction as a systemic effect also involves the afferent arteriole of the nephron, hereby reducing glomerular blood flow in the kidneys[29]. This renal haemodynamic change is sensed by the juxtaglomerular apparatus in the vascular pole of the nephron, which is responsible for maintaining adequate glomerular filtration. In an attempt to restore adequate renal perfusion, juxtaglomerular apparatus releases renin that enters the systemic circulation[30]. Renin binds angiotensinogen in the blood stream and angiotensinogen is hydrolysed to angiotensin I. Angiotensin I is further hydrolysed by the endothelial-bound angiotensin-converting enzyme to angiotensin II. Angiotensin II is a strong vasoactive agent, further inducing vasoconstriction by acting directly on the smooth muscles of the vasculature[31]. Importantly, angiotensin II plays a central role in sodium and water retention in the setting of HF. Firstly, it acts in the zona glomerulosa of adrenal glands and promotes the release of aldosterone[31,32], which acts on the mineralocorticoid receptors in the distal tubules and the collecting ducts of the nephron. Aldosterone induces sodium reabsorption from the tubular fluid in exchange to potassium excretion into the tubular lumen[32]. Sodium retention leads to water accumulation and increased blood plasma volume. Secondly, angiotensin II acts in the central nervous system to increase the production of vasopressin in the hypothalamus region[33]. Vasopressin is then released into systemic circulation from posterior pituitary gland and increases free water permeability in the distal and collecting tubules of the nephron via V2 receptors[34]. Such sodium-unrelated free water movement increases the osmolarity of the urine and in turn leads to plasma volume increase. Moreover, vasopressin also acts as a vasoconstrictor, further increasing vascular resistance[34]. Thirdly, angiotensin II also increases thirst sensation by acting on the area postrema and subfronical organ in the central nervous system[35]. Therefore, HF patients are prone to be thirsty and consume more fluid, which is likely to accumulate if cardiorenal mechanisms are outbalanced. The present mechanisms take place in parallel to each other and finally lead to intravascular congestion which is represented by gradually increasing right and left heart filling pressures.

Increased left ventricular filling pressure at rest and/or during exercise is characteristic for all groups of HF patients. When the pressure in the left atrium increases beyond a certain critical threshold, pulmonary venous return becomes impaired. This causes postcapillary pulmonary hypertension and in turn leads to pulmonary venous congestion. Rising hydrostatic pressure in the pulmonary circulation eventually causes an accumulation of extravascular lung water in the interstitial space, potentially leading to interstitial pulmonary oedema. Moreover, different

pathophysiological mechanisms including progressing pulmonary hypertension gradually lead to right ventricular dysfunction[36,37], that is a recognised trigger of systemic venous congestion[36].

Systemic venous fluid accumulation plays a key role in congestion pathophysiology. Veins contain two-thirds of the total body volume[38], and even more in the setting of HF. The venous system is highly compliant and acts as a capacitance vessel network, ensuring optimal fluid distribution in the human body. In fact, high capacitance determines low venous pressure change in response to significant venous volume increase[39]. The splanchnic veins are characterized by the largest blood volume capacity and very high sensitivity to α-adrenergic stimulation, which induces robust venous vasoconstriction[40–42]. This mechanism of vasoconstriction of a large blood reservoir is potentially lifesaving, e.g. in case of haemorrhagic shock or hypovolemia. However, in case of HF-mediated systemic venous congestion and sympathetic activation, splanchnic vasoconstriction can lead to a sudden blood volume shift from visceral compartment to the central vein, inducing an increase in central venous pressure. Such haemodynamic shift leads to an acute intravascular congestion, followed by increased intracardiac filling pressure which can potentially lead to acute pulmonary oedema. Therefore, not only fluid accumulation, but also fluid redistribution in the human body plays its role in the pathophysiology of HF-induced congestion. The role of fluid redistribution is nicely illustrated by the fact that the commonly used weight gain rule (≥ 2 kg over 48-72 hours) has a sensitivity of only 9% to predict HF decompensation[43], again revealing the complexity of congestion pathophysiology in HF. Moreover, only half of HF patients develop any weight gain before HF decompensation, meaning that chronic volume build-up explains only part of the mechanism of congestion-related decompensation[44].

Intravascular congestion leads to continuously increasing hydrostatic pressure in the capillary system. Increasing hydrostatic pressure leads to water and subsequent sodium shift from the vasculature to the interstitial space. At first, a strong interstitial network of glycosaminoglycans attach the excessive sodium and water molecules and the lymphatic drainage is increased. For a short period, this compensatory response to dysregulation in transcapillary oncotic and hydrostatic pressures prevents the interstitium from free water build-up[45]. If the process of tissue congestion and tissue sodium retention continues, the tissue loses its ability to compensate the accumulating sodium and water. The structural network of glycosaminoglycans is then destroyed and free water starts building up in the interstitial compartment[46]. A clinical manifestation of this process is peripheral and pulmonary congestion. Since 75% of total extracellular sodium is stored in the interstitial compartment,

and only 25% in the intravascular space, the interstitium accommodates nearly ¾ of the accumulating fluid in congestion[47]. These mechanisms also play their role in the process of fluid accumulation inside serous spaces, such as pleural or pericardial cavities[48].

HF is a recognised pro-inflammatory state[49]. Inflammation further contributes to vascular dysfunction and progressing congestion via mechanisms related to fluid exchange between the interstitial compartment and the vasculature[50]. In particular, inflammation triggers fluid reabsorption and promotes endothelial permeability, potentially contributing to the formation of interstitial oedema[51]. The inflammatory effect of congestion has been elegantly proven in an experimental model by Colombo et al.[52].

About 50% of HF subjects suffer from chronic kidney disease with impaired renal filtration capacity. The two conditions share similar risk factors and at the same time are the precursors of one another, given the complex interplay between the heart and the kidney[53–55]. Also, progressing venous congestion leading to renal venous hypertension further promotes renal dysfunction, as previously demonstrated by Mullens et al.[54]. Cardiorenal interaction-mediated renal failure also contributes to congestion progression due to the loss of renal filtration and tubular functions[51,56]. An experimental model was used to demonstrate that intravascular congestion in the coronary sinus induces left ventricular oedema, resulting in an increased stiffness of the left ventricular chamber, probably further contributing to progressing systemic congestion[57].

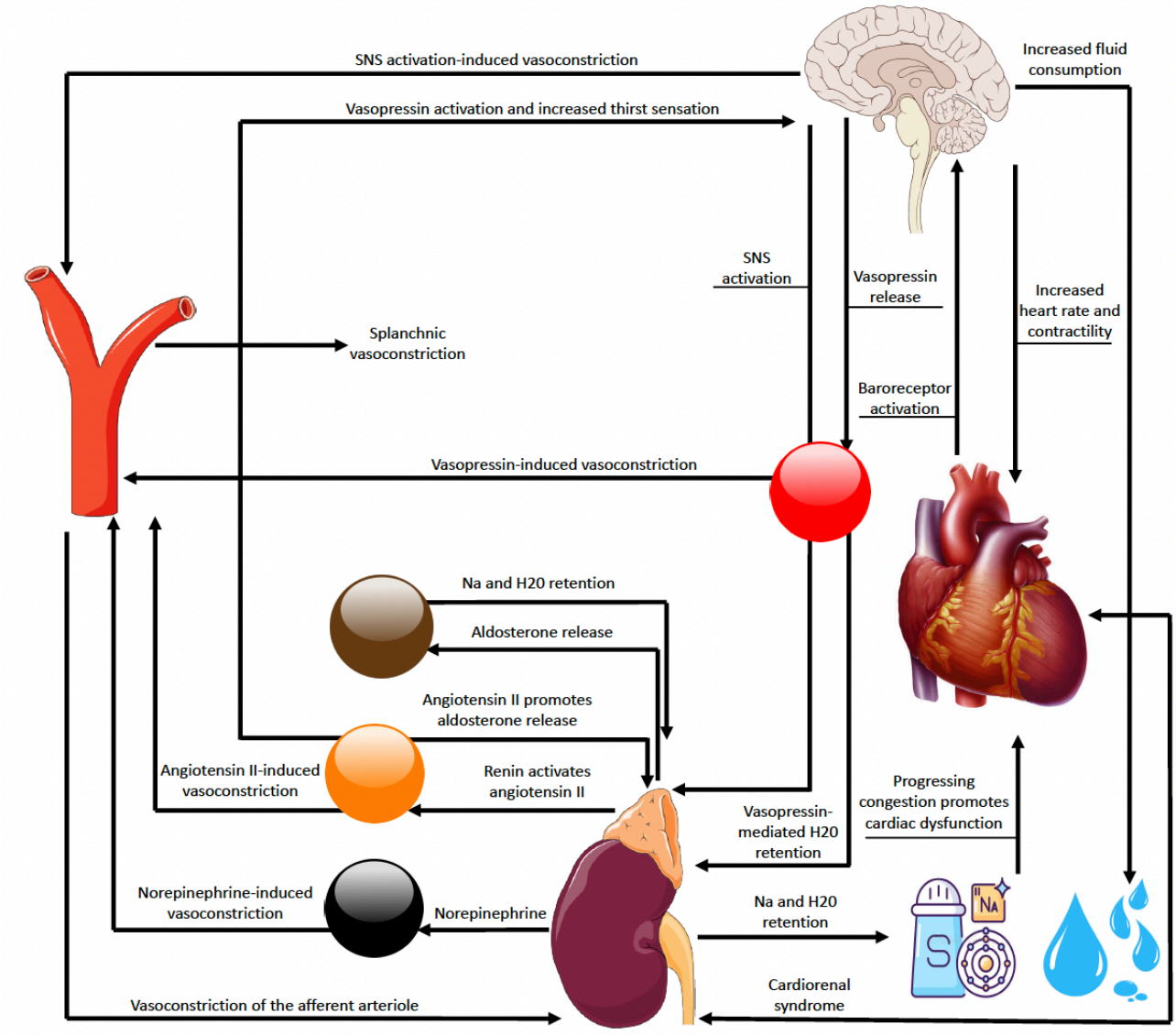
The complex mechanisms and their interactions leading to sodium and water retention in congestive heart failure are summarised in **Figure 2.**

1.4 Congestion detection and grading

Daily clinical practice of congestion management is almost exclusively based on clinical examination, meaning that congestion is detected and graded by assessing clinical signs and symptoms of fluid accumulation. However, data obtained from implantable devices of haemodynamic and intrathoracic impedance monitoring indicate that clinical congestion is a late manifestation of a long-standing process of fluid accumulation in the human body[58–60]. This means that in clinical practice we are often unable to timely initiate decongestive interventions. The CHAMPION trial proved that by targeting haemodynamic congestion the rate of HF-related hospitalization can be reduced by 37%[61]. Still, the invasive nature and the high cost limit the applicability of such measures and there remains an unmet need for other non-invasive alternatives. A marker of (residual) congestion could assist the clinicians in identifying patients suitable for discharge after an acute decompensation, in selecting an

optimal moment to switch from intravenous to oral therapy, or the timely initiation or intensification of diuretic therapy, as all of them are clinically very challenging.

Figure 2. The mechanisms and their complex interactions leading to sodium and water retention in congestive heart failure



SNS: sympathetic nervous system

Blood biomarkers might fill this knowledge gap, but there is no reliable, sensitive, and congestion-specific blood biomarker available in clinical practise yet. Blood biomarkers are objective, easily available, some even in a point-of-care setting, can be repeatedly measured, and have a known sensitivity and specificity for a certain outcome. Natriuretic peptides are often seen as such biomarkers of congestion, but the mechanisms of their release and

metabolism are complex and not only cardiac[62]. Moreover, fluid primarily accumulates in the interstitial compartment and the vasculature, whereas natriuretic peptides are released from the failing heart. A study of acute HF found that NT-proBNP could not predict the presence of congestive intrarenal venous flow – a recently recognised imaging marker of intravascular congestion[63]. The shortcomings of natriuretic peptides for congestion detection have also been noted earlier[64], and the trials of chronic HF that included loop diuretic dose adjustment based on natriuretic peptide levels failed to prove that such a regimen improve outcome[65]. The recent ESC guidelines advice on diuretic management based on signs and symptoms of fluid accumulation, without any recommendation on an implementation of a particular blood biomarker, including natriuretic peptides[1]. Therefore, the lack of evidence-based data regarding blood biomarkers and congestion prevents the set-up of interventional trials, and subsequently the implementation of blood biomarkers into daily clinical practice for assessment of congestion so far.

1.5 Emerging role of plasma bio-ADM as a marker of tissue congestion

Biologically active adrenomedullin (bio-ADM) is a small-sized peptide that is synthetised by various organs with a primary site of origin being the vasculature[66,67]. Its role in HF was first described in 1995 by Nishikimi et al., who observed a relationship between decongestion and plasma adrenomedullin levels[68]. Later studies revealed that volume overload induces bio-ADM release to stimulate vasodilation and suppress vascular permeability[69]. Indeed, an experimental study showed that the lack of adrenomedullin in the endothelial surface induces vascular leakage[70]. A recent experimental study also found that adrenomedullin decreases osmotic water permeability in the kidney via cAMP-independent pathways[71]. Such effects of bio-ADM can be seen as a compensatory response, preventing tissue oedema in a pathological state, such as congestive HF. A retrospective analysis of the PROTECT trial showed a close relationship between bio-ADM levels and clinical signs of congestion[72]. Also, bio-ADM level in patients with persistent congestion remained elevated, meanwhile BNP concentration dropped in both reduced and persistent congestion groups[72]. Another study identified bio-ADM as the strongest predictor of HF-related clinical congestion among 19 other biomarkers[73]. This was especially true for oedema[73]. In acute HF, bio-ADM was related to pulmonary congestion as assessed by chest radiography[74], whereas in advanced chronic HF bio-ADM levels were related to invasively measured biventricular filling pressures[75]. The present findings suggest that bio-ADM is of potential value in congestion management. In fact, a retrospective study of acute HF conducted in Europe suggests that bio-ADM may assist in

selecting post discharge diuretic regimen[76]. Another retrospective study of acute dyspnoea patients found that patients presenting with high plasma bio-ADM level might benefit from decongestive interventions[77]. However, these observations remain hypothesis-generating only, and a more in-depth research is needed.

1.6 Emerging role of plasma soluble CD146 as a marker of intravascular congestion

CD146 is a junctional adhesion molecule originating from vascular endothelial cells. Its main function is to ensure endothelial integrity[78]. Its soluble form (sCD146) is released into the circulation as a response to venous vascular stretch[79,80]. An extracardiac origin of sCD146 was proven by an experimental study with compression-induced venous congestion[79]. Retrospective analysis of the MEDIA-DHF trial revealed that sCD146, but not BNP correlated with echocardiographic markers of venous congestion[16]. Also, a decrease in sCD146 concentration was noted in this population, despite no change in estimated plasma volume[81], probably because of the refilling from the interstitial compartment and increased venous capacitance power as a response to treatment. Similar relationship between overhydration and elevated sCD146 concentration was observed in haemodialysis patients. Importantly, in haemodialysis population, sCD146 was able to identify overhydrated patients even if BNP concentration was low[82]. Despite its vascular origin and the relationship with congestion, sCD146 is not recommended for routine testing by the current guidelines[1], given the lack of evidence for its value in clinical practice.

1.7 Acute dyspnoea as a platform for congestion research

Dyspnoea is the most common symptom among patients with acute HF, noted in more than 90% of cases[83]. This determines high sensitivity for HF diagnosis, but the specificity remains only 17-34%[14]. Although the pathophysiological mechanisms of shortness of breath are complex and diverse[84], pulmonary venous and tissue congestion and volume overload-related increase in intracardiac filling pressures are responsible for dyspnoea in HF (see *Congestion pathophysiology* for more details). Given the diverse picture of dyspnoea causes, unselected acute dyspnoea population might serve as a perfect platform to explore blood biomarkers of congestion. Testing a potential biomarker of congestion in a selected population of HF only might miss some important information, as the properties of the study population are very similar, and an appropriate control group is missing. In contrast, acutely dyspnoeic patients might share very similar clinical pictures at presentation with a very different adjudicated diagnosis behind it. Therefore, the acute dyspnoea setting was chosen to explore the two

emerging plasma biomarkers of congestion.

1.8 Congestion management

Loop diuretics remain the cornerstone of congestion management. About 80% of HF patients receive chronic diuretic treatment to control congestion[85]. The current guidelines acknowledge that the use of loop diuretics is not supported by evidence from large randomised controlled trials, in contrast to other therapies recommended to treat HF[1]. Retrospective data indicate that chronic loop diuretic administration is related to poor outcome, especially if high doses of diuretics are administered[86–90]. Potential mechanisms related to diuretic-induced harm cover diverse derangements in homeostasis, including electrolyte imbalance, activation of the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system, volume depletion, acid-base disorders, and renal impairment among others[91]. At the same time, congestion – the target of diuretic drugs – is also a recognised marker of poor outcome in both acute and chronic settings (see *The burden of congestion* for more details). Moreover, early loop diuretic administration is related to better outcome as compared to a delayed strategy[92,93], although randomised data supporting this concept is also lacking. The concerns related to loop diuretic-related harm led to a practical recommendation to use loop diuretics in the lowest dose that keeps the patient euvolemic[1]. However, in the absence of reliable markers of euvolemia, this rule is very difficult to implement, and real-life evidence suggest that many patients remain congested, despite treatment with diuretic agents. In addition, there are no studies to determine if congestion itself or loop diuretic treatment *per se* cause poor outcome.

The present thesis addresses important questions related to these key aspects in the management of HF. **Chapter 2** covers the evidence behind loop diuretic use in HF, with a special focus on loop diuretic-related potential harm and benefit as well as some practical considerations of loop diuretic administration in light of contemporary knowledge. In **Chapter 3**, the prognostic role of a longitudinal clinical congestion pattern in chronic HF is analysed, showing that the lack of decongestion is related to poor outcome but present in a substantial number of patients despite optimising HF therapy. A simple and easily applicable 7-item clinical congestion index has been developed to achieve this aim that may be used in clinical practice and in future studies. In **Chapter 4**, the question whether chronic HF patients receive optimal decongestive interventions in Europe is challenged. **Chapter 5** analyses the important and very complex interaction between diuretic treatment intensification, the need of high dose administration, congestion, and chronic HF outcome to shed further light into the question if

diuretic therapy is simply a marker of poor outcome or a causative factor. In **Chapters 6, 7 and 8**, the role of two emerging congestion biomarkers, i.e. bio-ADM and sCD146, is investigated. The value of bio-ADM in congestion detection and grading is analysed in **Chapter 6**, with a special focus on the interaction between bio-ADM levels and neurohumoral blockade. In **Chapter 7**, congestion assessment properties of sCD146 are introduced. **Chapter 8** covers the potential of circulating sCD146 to identify tissue, intravascular and intracardiac congestion. The relationship between echocardiography-derived morphological and functional parameters of the left and the right heart is also analysed. Together, these chapters add to the understanding of congestion detection, grading and management. The findings are discussed in **Chapter 9**.

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2

CHAPTER 2

LOOP DIURETICS IN CHRONIC HEART FAILURE: HOW TO MANAGE CONGESTION?

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Abstract

Loop diuretics remain the cornerstone of congestion management in contemporary chronic heart failure care. However, their use is not supported by high quality data and there is doubt about the safety in the outpatient heart failure setting. Still, congestion is related to worse outcome and there is general consensus among experts that congestion should not be tolerated in heart failure patients. Recommendations in international guidelines regarding decongestion strategies in chronic heart failure are limited. Thus, there is an emerging need for clinical decision-making support about the best strategy for using loop diuretics and decongestion in the chronic setting. The present review provides a comprehensive overview over the evidence of chronic loop diuretic use. Strategies for the assessment of congestion in the outpatient setting and decongestion algorithm are provided to assist health care specialists in delivering high-quality heart failure care

INTRODUCTION

The majority of patients with stage C and D heart failure (HF) are treated with loop diuretics, particularly after admission for HF decompensation[1–3]. In ASCEND-HF trial, 64% of patients admitted for acute HF were already on loop diuretic therapy, which increased to 91% of patients at discharge[1]. However, there are no sufficiently large, randomized, placebo-controlled trials showing that chronic loop diuretic therapy improves outcome[4–6].

The present review outlines current evidence of loop diuretic administration in chronic HF and provides recommendations for guiding loop diuretic therapy in daily outpatient practice.

LOOP DIURETICS IN CHRONIC HEART FAILURE: THE EVIDENCE

A meta-analysis of diuretics in chronic HF published in 2012 included 14 trials (7 placebo controlled, 7 against other HF therapy) but only 525 patients[6]. Mortality data was available only in three of the placebo-controlled trials (202 participants) and the marked reduction by diuretics is therefore very questionable (odds ratio (OR) 0.24, 95% confidence interval (CI) 0.07-0.83; p = 0.02). The same holds true regarding admission for worsening HF (two trials, 169 participants, OR 0.07, p = 0.01). In four trials comparing diuretics to active control (91 participants), exercise capacity was improved. The included trials lasted from 4 to 24 weeks only and the use of diuretic drug was not standardized across the studies. Finally, the trials were published between 1977-1997 and cannot be transferred to today's HF care. Taken together, the conclusion that diuretics are beneficial not only for symptomatic relief, but also regarding hard endpoints remains unclear.

The ESC guidelines recommend diuretics to reduce the risk of HF hospitalization in patients with signs and/or symptoms of congestion (class of recommendation IIa, level of evidence B)[4]; the recommendation is solely based on the above mentioned meta-analysis[6].

The 2013 ACCF/AHA Guidelines for the Management of HF recommend diuretics in patients with HF and fluid retention, unless contraindicated, to improve symptoms (class I recommendation, level of evidence C)[5]. This recommendation was not changed in the 2017 Focused Update[7]. The question therefore arises as to whether this recommendation on a liberal use of diuretics in chronic HF is justified or not.

Diuretic use in chronic heart failure: reflection of risk or direct harm?

Several studies uniformly concluded that diuretic administration is accompanied by worse outcome[8–19] (**Table 1**). In addition, up-titration of diuretics was related to worsening renal function (WRF), increased readmission rate and mortality[8]. In severely symptomatic patients,

an independent, dose-dependent association between loop diuretic use and impaired outcome was found[9]. Similar findings were obtained in a large cohort study[10] (**Supplementary Table**).

Although a dose dependent relation between loop diuretic use and outcome is established, intensified treatment with loop diuretics is prescribed for advanced HF patients with impaired functional capacity, relevant comorbidities, older age and difficulties to establish evidence-based treatment due to low blood pressure or other adverse events[3,9,10,14,20]. All those factors indicate more advanced disease and worse prognosis. In fact, the severity of HF has been graded according to the diuretic dose[21]. It may be questionable if full statistical adjustment is possible given the significant differences among high- / low- / non-users.

In order to overcome the shortcoming of significant selection bias, the potential prognostic impact of loop diuretics was tested by propensity score matching, seemingly confirming the negative influence of loop diuretic therapy in HF[14–19] (**Table 1**). In the large DIG trial, diuretic use was associated with significantly increased risk of cardiovascular mortality and HF hospitalization, both in patients above 65 years[15] and regardless of age[16]. Similar results were found in other large cohorts[14,17,18]. The association between loop diuretics and increased mortality was also observed in subjects without HF and renal failure (hazard ratio (HR) 1.82, number needed to harm 7.2[19]).

Propensity score matching has become an increasingly popular statistical method to simulate randomization in observational studies. However, full adjustment may not always be possible as not all relevant variables may be available and factors potentially influencing outcome may be unknown. Moreover, the lower the sample size, the lower the probability is to find suitable matching[22]. Many quality issues are noted in papers that draw conclusions with the help of propensity matching[23,24] and there is serious doubt regarding the reliability of such data[25]. Therefore, the results of all above mentioned studies cannot reliably investigate the prognostic impact of loop diuretic therapy in HF.

Still, response to diuretic therapy may not be uniform in all HF patients. High diuretic doses may be deleterious in chronic euvolemic HF patients[12], whereas in hypervolemic patients, the diuretic dose may not have prognostic implications[11]. In a retrospective analysis of ASCEND-HF, initiation of loop diuretic therapy was associated with better outcome as compared with no dose change[1]. One of the reasons contributing to the positive effect of loop diuretics may be that patients not using diuretics before hospitalization had fluid overload requiring decongestion.

Table 1. The major observational studies of loop diuretics

Author/Trial	Data collected (year)	Year published	Propensity score matching	Subjects (n)	Follow-up (months)	Mean age (years)	NYHA III/IV (%)	EF (%)	Conclusion
Martens et al.[8]	2008-2015	2017	No	648	6	71-74	61	29-31	LD dose down-titration after CRT system implantation related to lower rate of HF readmissions and all-cause mortality
Eshaghian et al.[9]	1985-2004	2006	No	1,029	48	53	86	24	Independent, dose-dependent association between LD use and impaired survival was found.
Abdel-Quadir et al./EFFECT[10]	1999-2001	2010	No	4,270	60	77-79	NA	NA	Dose-dependent increase in risk of mortality and hospitalization was found among LD users
Martins et al[11]	NA	2011	No	244	48	68	8	NA*	Higher LD doses were associated strongly and independently with adverse long-term outcome in chronic HF
Dini etl al[12]	NA	2012	No	400	32	69	45	31	The study group identified furosemide dose as a major determinant of prognosis in patients with chronic HF but without ongoing signs and symptoms of congestion
Neuberg et al./ PRAISE[13]	1992-1994	2002	No	1, 153	14	64-66	100	21-22	High LD doses were independently associated with mortality, sudden death, and pump failure death
Damman et al./ CORONA[14]	2003-2005	2016	Yes	1659 pairs (50% LD users)	32.8	72-74	53-59	30-32	The use of LD (compared with no use) and higher LD doses (compared with lower doses) were associated with higher risks of CV mortality and hospitalization owing to HF
Ahmed et al./ DIG ≥65 years[15]	1991-1995	2009	Yes	651 pairs (50% LD users)	36.7	71.5	14	35	Chronic LD therapy was associated with increased mortality and hospitalization
Ahmed et al./ DIG[16]	1991-1995	2006	Yes	1391 pairs (50% LD users)	40	62.9	20	36	Chronic LD therapy was associated with increased mortality
Dini et al.[17]	NA	2013	Yes	813	44	65	34	31	The risk of death increased linearly across quartiles of furosemide daily dose
Hamaguchi et al./ JCARE-CARD registry†[18]	NA	2012	Yes	2,549 (79% LD users)	26.4	71	6	42	Before and after propensity matching, LD use was associated with all-cause death, cardiac death and all-cause death and hospitalization
Schartum-Hansen et al./ WENBIT‡[19]	199-2004	2015	Yes	109 pairs	26,4	65	9.6-11.9	66-67	LD use was associated with all-cause mortality.

** Median EF is not provided. The distribution according to EF is as follows: 24% - preserved EF; 15% - mildly depressed EF; 24% - moderately depressed EF; 37% - severely depressed EF.*

† Sufficient data how the propensity was done is not provided. Data in this table reflect the entire study population before the propensity matching.

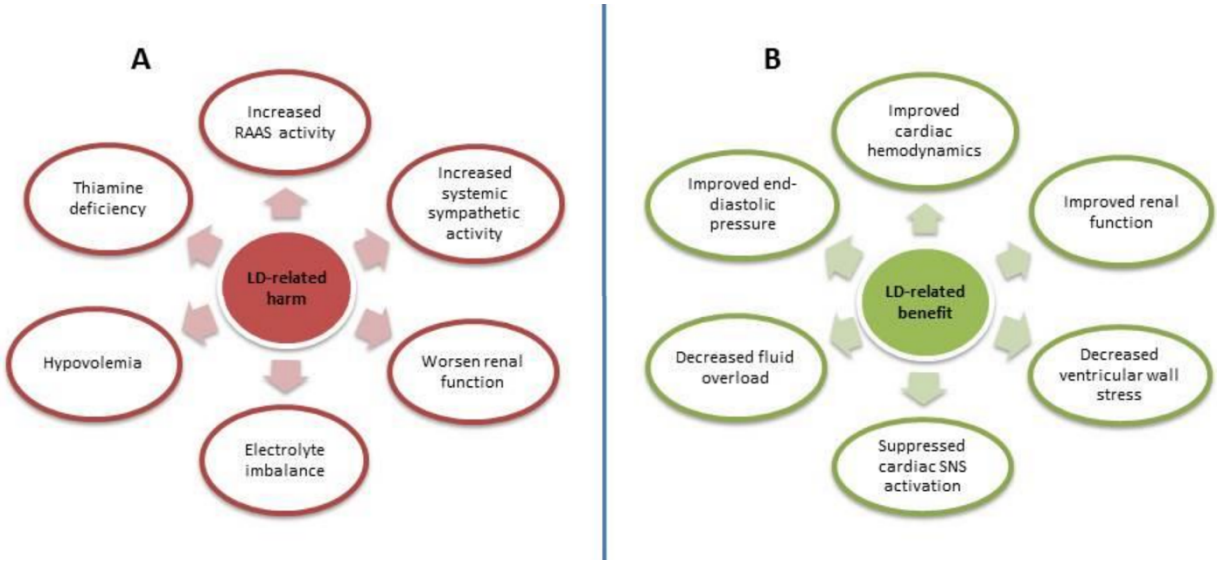
‡ Patients with systolic HF were excluded from the study

CORONA: Controlled Rosuvastatin Multinational Trial in Heart Failure; CRT: cardiac resynchronization therapy; CV: cardiovascular; DIG: digitalis investigation group; EF: ejection fraction; EFFECT: enhanced feedback for effective cardiac treatment; HF: heart failure; JCARE-CARD: Japanese Cardiac Registry of Heart Failure in Cardiology; LD: loop diuretic; NA: not available; NYHA: New York Heart Association functional class; PRAISE: prospective randomized amlodipine survival evaluation; WENBIT: Western Norway B Vitamin Intervention trial

Potential mechanisms of harm and benefits

There are several potential mechanisms of loop diuretic-related harm **(Figure 1A**). Loop diuretics can stimulate the Renin-Angiotensin-Aldosterone System (RAAS)[26–29] as well as lead to electrolyte imbalance (hypokalaemia, hyponatremia, hypomagnesaemia) in a dose dependent manner[26]. Hypokalaemia and hypomagnesaemia can lead to life threatening arrhythmias[10,30], especially in the presence of severe myocardial fibrosis and digoxin use. Volume depletion can cause hypotension (potentially resulting in falls and injuries), impair cognitive status, or worsen renal function. Also, hypovolemia can reduce cardiac output and impair blood supply to vital organs[31]. Long-term use of high doses of loop diuretics may trigger thiamine deficiency[26,32,33]. Loop diuretics (especially furosemide) may increase systemic sympathetic activity[27], potentially contributing to worse outcome.

Figure 1. Potential mechanisms of loop diuretic-related harm (A) and benefit (B)



LD: loop diuretic; RAAS: renin-angiotensin-aldosterone system; SNS: sympathetic nervous system

However, there are also effects of loop diuretics that can be beneficial in HF patients (**Figure 1B**). Loop diuretics decrease systemic, venous and pulmonary overload as well as extracellular oedema[26,27,34], leading to more favourable end-diastolic pressure, decreased ventricular wall stress and increased cardiac output[27]. Decreased volume overload results in decreased secondary mitral and tricuspid regurgitations and improved cardiac hemodynamic profile. There is some evidence that loop diuretics (especially long acting) can suppress cardiac sympathetic activity[35,36]. This is in line with vasodilation-induced cardiac sympathetic tone

reduction in patients with HF[37]. As cardiac autonomous sympathetic activation is particularly deleterious on outcome[38], its inhibition by reducing filling pressure may be beneficial. Additionally, venous congestion is the most important hemodynamic factor driving WRF[39]. Venous overload in the splanchnic venous system results in increased intra-abdominal pressure. By reducing fluid overload, diuretics reduce intra-abdominal pressure, resulting in improved renal function[40]. Thus, (high-doses of) loop diuretics may not only result in worsening, but also improvement of renal function[27,34], depending on the individual need. Moreover, cardiac status as determined by NT-proBNP seems to be more important than renal function regarding prognosis[41].

Finally, there might be some differences between loop diuretics. In a rat model of induced autoimmune myocarditis, torasemide significantly improved cardiac function and left ventricular remodelling as compared to furosemide[42]. In humans, retrospective data suggest that torasemide might be superior to furosemide in HF[43–45]. The prospective, randomized, though open label TORIC study was the largest study comparing furosemide with a newer class loop diuretic. It found that patients treated with torasemide had better outcome than those treated with furosemide[46]. The superiority of torasemide to other loop diuretics is attributed to its relatively stable and predictable oral bioavailability, longer half-life, RAAS-suppressing properties as well as torasemide-mediated cardiac sympathetic nerve deactivation and left ventricular remodelling suppression[43– 46].

Animal models of loop diuretic therapy

In a rat model of ischemic HF, both, valsartan and hydrochlorothiazide, but not furosemide improved cardiac function (left ventricular ejection fraction (LVEF) 49.5±1.8%, 49.4±2.1% and 39.9±1.9%, respectively) as compared to control animals (LVEF 40.1±2.2%). Similar differences were seen regarding interstitial cardiac fibrosis and collagen volume fraction (10.0±1.3% and 9.7±1.2% versus 14.1±0.8% and 15.9±1.1%, respectively)[47]. In a tachycardia-induced porcine model of HF, furosemide was related to significant acceleration of both contractile and metabolic features of chronic HF[48]. A rat model was used to investigate the impact of furosemide on survival in rats with ischaemia-induced HF. The survival rate in furosemide group was lower than in the placebo group (HR 3.39, 95% CI 1.14 to 10.09, p = 0.028), whereas ramipril improved survival[49]. On the other hand, another rat model of ischemic HF showed that furosemide has no effect on collagen content, LVEF and mortality rate[50]. Testing the impact of ramipril vs furosemide or a combination of both showed that all treatment regimens improved cardiac remodelling and decreased angiotensin-converting

enzyme (ACE) activity. However, mortality was only reduced in ramipril treated animals, irrespectively if they received furosemide or not[51]. The results of animal model studies of diuretic safety are, therefore, controversial and inconclusive as well. Still, the latter studies suggest that loop diuretics may have different effect if combined with ACE-inhibition (and possibly other treatment improving prognosis), which would be relevant to the clinical setting.

LOOP DIURETICS IN CHRONIC HEART FAILURE: CLINICAL PRACTICE

Diuretics must be adjusted according to the individual needs[4,5]. Still, the significance of clinical signs and symptoms, instrumental monitoring, and blood biomarkers for assessing (de)congestion has not yet been studied extensively. Right heart catheterization may be seen as gold standard for fluid status assessment[52], but due to its invasive nature, large trials in the outpatient setting are difficult to carry out. No congestion evaluation and management algorithm has been widely implemented into daily clinical practice. Therefore, identification of the individual needs remains challenging.

Outpatient fluid status assessment

Signs and symptoms

Table 2. Clinical signs and symptoms of heart failure related congestion

Signs and symptoms of left-sided congestion
• (Increasing) dyspnoea
• Orthopnoea
• Paroxysmal nocturnal dyspnoea
• Bendopnoea
• (Bilateral) pulmonary rales
• (Bilateral) pleural effusion
• Third heart sound
• Weight gain
Signs and symptoms of right-sided congestion
• Jugular venous dilation
• Bilateral peripheral oedema
• Congested hepatomegaly
• Hepatojugular reflux
• Ascites
• Symptoms of gut congestion (e.g., appetite loss)
• Weight gain

Clinical signs and symptoms of congestion (**Table 2**) lack sensitivity and specificity[52,53]. This is particularly true for elderly patients and those with advanced HF stage, significant comorbidities, impaired mental status and limited physical capacity. Therefore, additional laboratory and/or instrumental assessment in daily outpatient practice is advisable. Still, clinical signs and symptoms of congestion are key elements to guide management of HF patients[4,5].

HF patients should be encouraged to monitor symptoms of congestion, including daily measurement of their body weight. Worsening of symptoms of congestions or weight gain may indicate fluid accumulation[4,5], potentially requiring temporary increase in diuretic dose or consulting a medical professional. If physical or mental status limits self-care, this should

be ensured by the caregivers. Also, nursing professionals should play an active role in educating patients to recognize signs and symptoms of fluid overload[54]. However, congestion might trigger appetite loss and contribute to malnutrition leading to loss of lean body mass. Thus, fluid accumulation can occur without significant change in the absolute body weight. Importantly, individual patients may have their own pattern of signs and symptoms in case of fluid accumulation. Knowing such individual pattern may increase accuracy significantly.

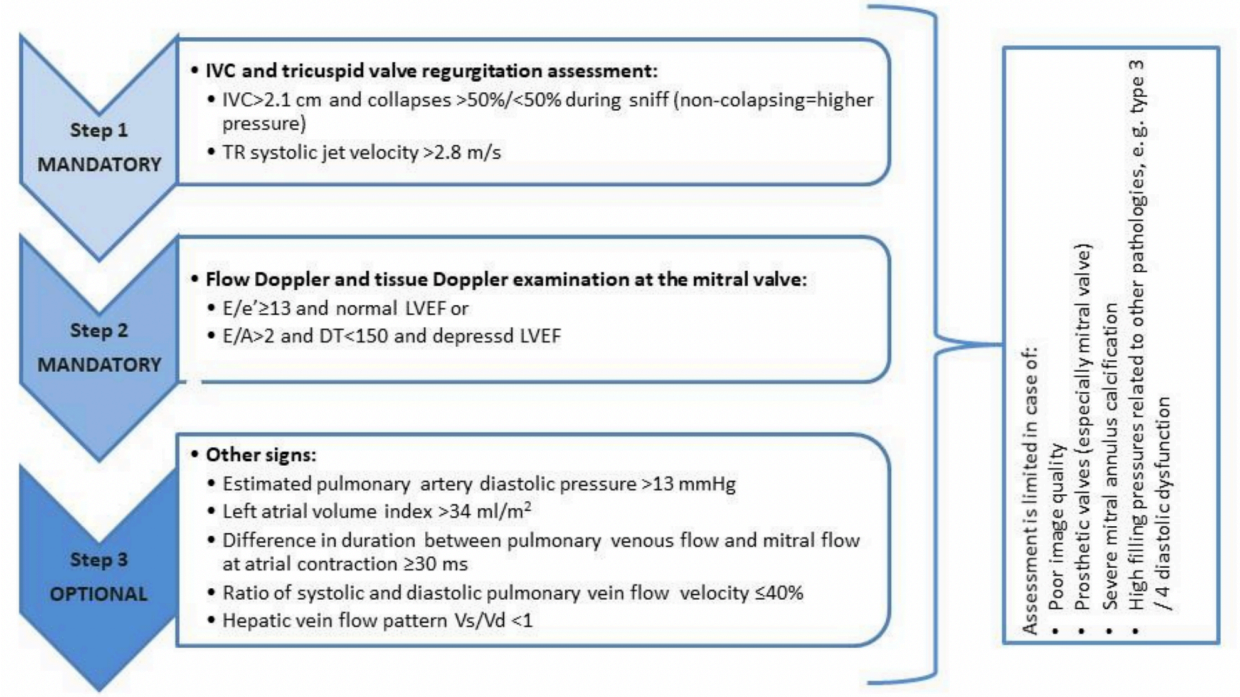
The role of telemonitoring-based symptom monitoring system in chronic HF has been investigated[55], but results are mixed and improvement of outcome is not yet clear. Several clinical congestion scores have been proposed; however, their diagnostic value is still uncertain[52]. Moreover, no studies have tested their value for diuretic dose adjustment in clinical practice.

Hypovolemia related signs and symptoms, e.g. hypotension, thirst, dry mouth and skin, are even less reliable than those caused by volume overload and clinical examination does not provide sufficient evidence in volume depletion states[56]. Thus, laboratory and/or instrumental assessment may be even more important to detect hypovolemia than hypervolemia.

Instrumental monitoring

If signs and symptoms leave uncertainties, the second step should be instrumental evaluation. Although easily accessible even for primary care physicians, chest X-ray examination is more helpful in the acute setting[4]; therefore, X-ray guided diuretic therapy is of little value in chronic HF. Doppler echocardiography requires specific training; however, it enables assessment of volume status (ventricular filling pressures) with reasonable accuracy[57,58], but limitations of echocardiographic fluid assessment must be considered. Three-step echocardiographic fluid status assessment algorithm is shown in **Figure 2**. A small study found that echocardiography-guided therapy may decrease HF morbidity[59]. A recent study compared two HF treatment approaches (echocardiography and BNP vs clinically guided): the daily dose of loop diuretics did not change in echocardiography and BNP-guided group, while it increased in 65% of patients in clinically-guided group, resulting in more deaths and worsening renal function[60]. However, additional studies are required to define the value of echocardiography-guided diuretic therapy.

Figure 2. Three-step echocardiographic fluid status assessment algorithm



Every examination should include Step 1 and Step 2; Step 3 is required if fluid status still remains uncertain. IVC: inferior vena cava; LVEF: left ventricular ejection fraction

Bioimpedance is widely used in many dialysis centres to guide fluid removal[61]. However, its routine use in HF is not advocated. A recent IMPEDANCE-HF trial suggested that lung bioimpedance-guided treatment of chronic HF might reduce hospitalizations for HF and mortality[62]. Diuretics were less often up-titrated as well as more often down-titrated in the bioimpedance guided group compared to the controls[62]. Intrathoracic bioimpedance is being investigated; however, current evidence does not support its routine use today[63,64]. A wearable bioimpedance measuring vest has been proposed; however, its value is not yet known[65]. Thus, bioimpedance might improve fluid management in HF, but a standardized method must be validated before its wide implementation.

B-lines visualized by means of lung ultrasound have been shown to reflect pulmonary fluid accumulation in the outpatient setting[66]. In the emergency department, lung ultrasound may improve accuracy of acute decompensated HF (ADHF) diagnosis[67]. However, lung ultrasound does not seem to be superior to echocardiography in chronic HF and its routine use remains to be better defined, since B-lines are a later finding of pulmonary water accumulation[68].

In a large randomized trial, wireless pulmonary artery hemodynamic monitoring (PAHM) in HF patients with New York Heart Association class III has been shown to reduce HF-related hospitalizations at 6 months by 28% and by 37% at 15 months[69]. Changes in medication, particularly diuretic dose adjustments, were more often initiated in the treatment group[69,70].

The treatment group had a significant up-titration of loop diuretic total daily dose[71]. Cost-effectiveness of PAHM is supported by economic modelling[72]. Still, PAHM is not yet a part of standard care in many countries, mainly due to its invasive nature requiring a device implantation and its costs.

Blood biomarkers

Although a single sensitive and specific biomarker of congestion does not exist, blood analysis may serve as a valuable tool for congestion management. This may include changes in haematocrit, haemoglobin, albumin and total protein over time, reflecting the shift from haemoconcentration to haemodilution and vice versa[73]. Haemoconcentration is a reasonable means to guide diuretic therapy in both acute and chronic HF[73,74], but accuracy and clinical value needs to be shown.

The rise in creatinine during diuretic administration is a red flag, since rising creatinine can reflect hypovolemia, effective decongestion, but also (remaining) congestion. Thus, a significant change in creatinine requires careful, possibly instrumental fluid status assessment and potentially indicates management modification.

Liver damage related markers should be tested once a year as persistent congestion can potentially lead to liver injury[75]. If they are elevated, careful fluid status assessment is required and effects of decongestion on liver markers should be evaluated. Elevated cholestasis markers have been associated with systemic congestion, whereas, the increase in aminotransferases is more common in hypoperfusion-related liver damage[76]. The rise in bilirubin but not in aminotransferases in HF decompensation was also associated with increased mortality[77].

Natriuretic peptides play an important role in the diagnosis of HF[4,5] and have been investigated to guide chronic HF therapy[78]. Although they are released from the myocardium in response to stretching[79], they poorly correlate with congestion[80–82]. In addition, (NT-pro)BNP guided therapy studies mainly focusing on intensifying of diuretic therapy did not improve outcome whereas intensifying of other HF drugs did. Therefore, the use of natriuretic peptides to monitor congestion is limited despite their excellent prognostic value and being biomarkers of cardiac dysfunction.

Soluble CD146, a novel congestion biomarker, is released from the peripheral vasculature in response to venous stretch[83] and has been shown to reflect congestion[80], however, its value in acute and chronic HF setting is yet uncertain. The same can be said about biologically active adrenomedullin. Further studies of their potential role in daily clinical practice are needed.

Successful outpatient decongestion approach

Step 1: Identification of congestion

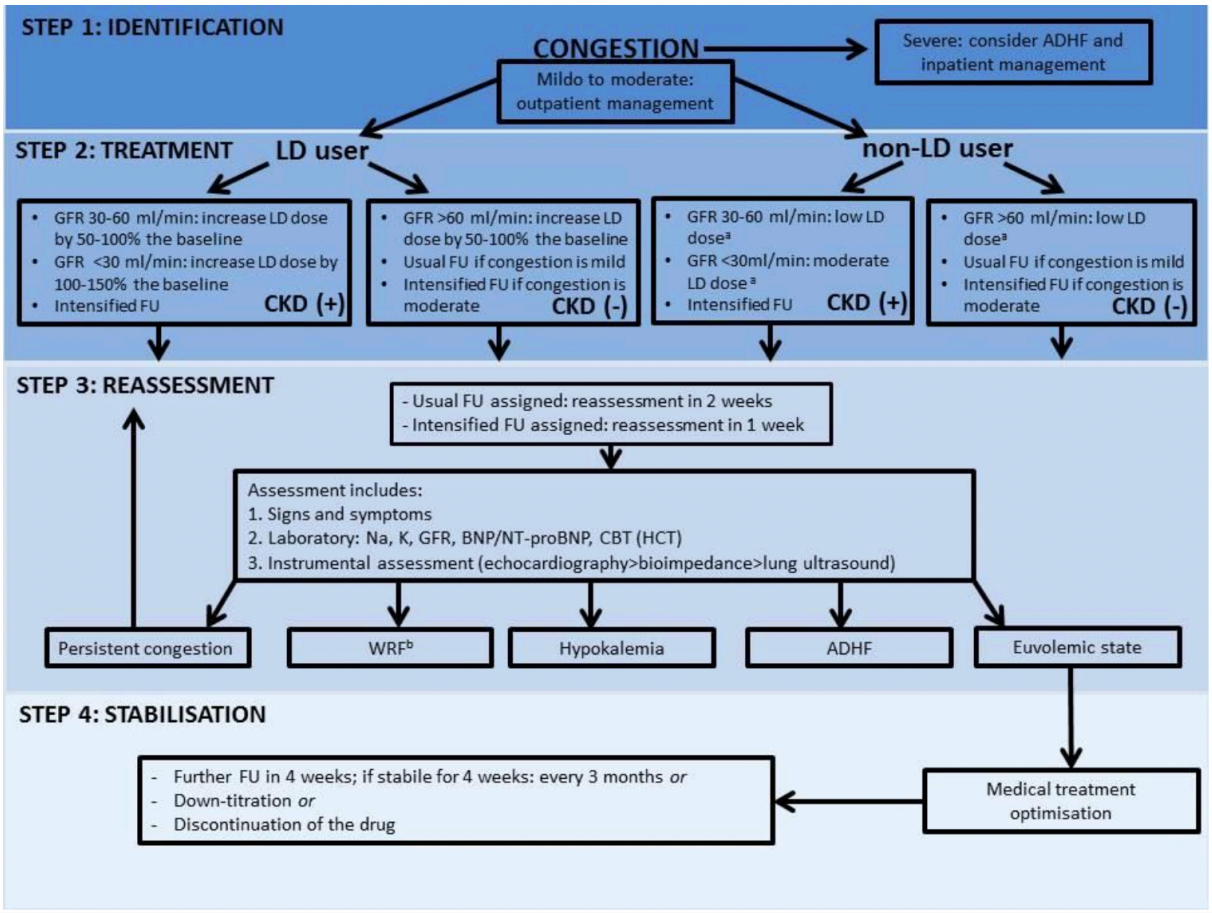
The responsibility for regular screening should be organized regionally or nationally and can be done by a trained HF nurse, general practitioner, cardiologists or a HF specialist. However, an active role of general practitioners and HF nurses is encouraged, following the recommendations of multidisciplinary care[4]. Screening of congestion should be done regularly. The intervals may vary depending on the severity of HF. More importantly, if patients develop symptoms, clinical evaluation is required and laboratory testing should be done in every patient, including at least creatinine / glomerular filtration rate (GFR), blood urea nitrogen, sodium, and potassium (if stable every 6 months). Liver function testing should be done every 12 months for all stable HF patients and if clinical congestion is present. An increase in liver enzymes by more than two times the upper normal reference level or total bilirubin concentration higher than 50 μmol/L requires – if congestion is not obvious – instrumental fluid status assessment and abdominal ultrasound if no congestion is present or values do not normalize after decongestion.

There is no uniform definition for severity of congestion, but severe congestion may be equivalent to ADHF. The difference between mild and moderate congestion is more difficult to establish. A NYHA class II or III patient with obvious signs and symptoms of congestion but without acute deterioration fits the picture of moderate congestion. Mild congestion might not be clinically noted and is detected by means of blood analysis and (or) instrumental investigation. Some severely congested (ADHF) patients can be managed in the outpatient setting if done by sufficiently experienced care providers[84,85], but hospital admission is often required. Importantly, rapid treatment of ADHF is recommended as it may improve outcome[4,5]. Mild to moderate congestion can usually be treated in an outpatient setting.

Step 2: Treatment of congestion

HF patients with congestion are normally treated with loop diuretics as thiazides are usually not sufficient. Two main factors are important to consider before choosing the dose. Firstly, the decision depends on if the patient is already taking loop diuretics or not and at which dose. Secondly, kidney function is important as it influences the response to loop diuretic therapy (**Figure 3**).

Figure 3. Outpatient congestion management algorithm in chronic heart failure



The 4-step congestion management algorithm should be initiated as soon as congestion is identified. ADHF: acute decompensated heart failure; BNP: B-type natriuretic peptide; CBT: complete blood count; CKD: chronic kidney disease; FU: follow-up; GFR: glomerular filtration rate; HCT: haematocrit; LD: loop diuretic; NT-proBNP: N-terminal pro B-type natriuretic peptide; WRF: worsening renal function
*a - see **Table 3**;*
b - deterioration of GFR ≥25%

In patients with chronic kidney disease (CKD), higher doses are usually needed to achieve the same diuresis as in non-CKD patients[86]. If there is no urgent clinical need, it is still reasonable to initiate a low loop diuretic dose (**Table 3**) regardless of renal function, because initial response to a loop diuretic is difficult to predict. If the patient already takes a loop diuretic, the baseline dose serves as a starting point. Loop diuretic initiation and modification strategy is shown in **Figure 3**.

Torasemide and bumetanide have a roughly consistent oral bioavailability[29], whereas furosemide represents a drug with a highly variable oral bioavailability (from 10 to 90 in percentage[29], thus precise equipotent oral doses between furosemide and other loop diuretics are difficult to establish. The authors suggest using equipotent doses of loop diuretics shown in **Table 3**. Loop diuretic with better bioavailability (bumetanide, torasemide) and longer half-

life (torasemide) is recommended as a first line loop diuretic. If a short acting loop diuretic (furosemide, bumetanide) is chosen, it should be administered twice or three times a day.

Table 3. Oral loop diuretic dosage in chronic heart failure

	Low dose	Moderate dose	High dose	Very high dose	Max dose*
Furosemide	≤40 mg/day	>40-100 mg/day	>100-200 mg/day	>200 mg/day	600 mg/day
Torasemide	≤10 mg/day	>10-25mg/day	>25-50 mg/day	>50 mg/day	200mg/day
Bumetanide	≤1 mg/day	>1-2.5 mg/day	>2.5-5 mg/day	>5 mg/day	10mg/day

* - *maximal doses of loop diuretics are not well studies; thus, higher doses might be used in different centres worldwide*

Step 3: Reassessment

Patients with mild congestion and normal renal function should be reassessed two weeks after the initial visit. However, CKD patients are vulnerable: they might not respond to the initial therapy and develop ADHF; they are susceptible for acute kidney injury (AKI)[87] that requires timely intervention; they often have more comorbidities that might worsen. Therefore, all patients with a GFR < 60 ml/min should receive an intensified follow-up strategy with a follow-up visit in 1 week. The same is true regarding patients with moderate congestion, since the risk of acute decompensation is higher in such setting. The follow-up interval needs to be adjusted to the individual need of patients, but the timing has not been investigated so far and remains at the discretion of the treating physician.

Reassessment protocol covers the same laboratory work-up as in the identification step. Instrumental assessment needs to be done if the clinical situation is not clear. In particular, remaining (mild) congestion may not be detected clinically and may be accompanied with worse outcome.

There are a few common scenarios that can be identified at the reassessment step:

1. WRF (i.e. deterioration of GFR ≥25%) is most likely related to congestion-related cardiorenal syndrome or iatrogenic hypovolemia. It is noted that WRF translates into poor outcome if it develops in the presence of persistent congestion[88], whereas in case of successful decongestion its prognostic implication is limited[73]. Therefore, further decisions depend on the results of congestion status determined by means of clinical, laboratory and if uncertain instrumental investigation. If congestion is no longer present, loop diuretic dose should be reduced by 50%, whereas persistent congestion should be treated with intensified diuretic therapy despite WRF, possibly in the clinical setting. Other drugs potentially leading to kidney injury (e. g. non-steroidal drugs, some

antibiotics) should be discontinued or re-considered. Patients with AKI (increase in serum creatinine by ≥26.5 μmol/L / ≥0.3 mg/dL or decrease in GFR ≥25% within 48 hours, or urine volume <0.5 mL/kg/hour for six hours[87]) must be admitted to hospital for adequate monitoring and treatment.

2. Persistent congestion is common, often because loop diuretic dose at Step 2 was too low to control fluid overload. Unless treated with very high loop diuretic dose, the dose should be doubled, and the patient reassessed at a usual or intensified interval. If dose is maximal or escalation is not effective, diuretic resistance or pseudoresistance may be present (**Table 4**, see chapter *Diuretic resistance* for more details). If patients deteriorate and/or present with ADHF, admission to hospital should be considered.
3. Hypokalaemia is a known and potentially life-threatening side effect of loop diuretics. Even potassium levels < 4.1 mmol/L has been associated with increased risk of death in chronic HF[89]. In case plasma potassium level drop < 4.1 mmol/l, potassium supplementation or mineralocorticoid-receptor antagonists (MRA), unless contraindicated, should be given. If a single-drug treatment approach is not effective, the combination of potassium supplementation and MRA can be considered but requires an intensified follow-up regimen.
4. If the initial treatment was effective, the patient might no longer be congested. In this case, the stabilization step should take place (see *Step 4: Stabilization*).

Step 4: Stabilization

Some euvolemic patients may benefit from loop diuretic dose reduction or even discontinuation of the drug, particularly after establishment of optimal HF therapy (drugs and devices). Such approach may be considered in patients with good functional capacity and no history of unsuccessful down-titration, after medical treatment with evidence-based drugs was established and the probability of relapse was considered as low. Careful monitoring is important, and some patients need maintaining loop diuretic dose as otherwise congestion reoccurs. This recommendation applies particularly to patients with previous relapse after loop diuretic dose down-titration or those who have experienced frequent decompensations. However, optimal regiment in individual patients has not been sufficiently studied. The CHAMPION trial suggests that optimal euvolemic fluid status with the according dose of diuretics encompasses the best outcome[69–71]. In general, the aim should be to use the lowest loop diuretic dose that is sufficient to keep the patient euvolemic, but this needs to be carefully

evaluated. Partial decongestion and some degree of residual volume overload are potentially harmful[90].

Medical treatment with evidence-based HF medication should remain unchanged during recompensation whenever possible. After recompensation, HF treatment must be revised and optimized if needed. It is important to continuously re-evaluate compliance because congestion in HF is closely related to non-compliance (medication, excess water and salt intake). Compliance problems should be managed by educational programs mainly led by HF nursing team.

Diuretic resistance

The lack of decongestion despite adequate / high (very high) dose of loop diuretic (**Table 3**) is called diuretic resistance. Although diuretic resistance is noted in up to one third of HF patients[91], there is no uniform definition[92]. It is related to increased morbidity and mortality[92,93] and can be attributed to both renal and non-renal causes[29,92–94]. There is a number of reasons that resemble diuretic resistance (e. g. noncompliant patient). These reasons must be clearly identified, because true resistance requires different management approach[92,95]. Possible causes of diuretic resistance / pseudoresistance are listed in **Table 4**. Obviously, identified causes should be treated specifically if possible.

Loop diuretic agent, dose and route of administration as well as timing play important

Table 4. Possible causes of diuretic resistance and pseudoresistance

Usage/compliance or diagnosis related causes
- Unrestricted water intake
- Not taking the drug
- Excessive sodium intake
- No monitoring of body weight
- Inadequate diuretic therapy (too low or too infrequent)
- Incorrect diagnosis (e.g., lymphatic oedema)

Renal causes
- Tubular uptake of diuretic impaired by uremic toxins
- Decreased kidney blood flow
- Decreased functional kidney mass
- Low GFR
- RAAS activation related non-responding
- Nephron adaptation
- Proteinuria

Cardiovascular causes
- Severe HF
- Arrhythmias
- Hypertension and hypotension
- Ischemia
- Valvular disease
- Endocarditis

Pharmacological causes
- NSAIDs use
- Negative inotropes
- Probenecid
- Lithium
- Some antihypertensive drugs

Acute and chronic comorbidities
- Pneumonia
- Pulmonary embolism
- COPD
- Thyroid disease
- Anaemia
- Surgery related stress
- Electrolyte imbalance
- Gut oedema impaired absorption
- Intestinal hypoperfusion
- Hypoproteinaemia
- SIADH

COPD: chronic obstructive pulmonary disease; GFR: glomerular filtration rate; HF: congestive heart failure; NSAIDs: non-steroid anti-inflammatory drugs; RAAS: renin-angiotensin-aldosterone system; SIADH: syndrome of inappropriate antidiuretic hormone secretion

roles in the diuretic efficacy. Switching furosemide to another loop diuretic with stable pharmacokinetic profile (torasemide, bumetanide) can be sufficient to increase efficacy. Also, timing should be adjusted to half-life of the drugs; thus 2 or even 3 times daily administration is usually more effective (applies particularly to furosemide and bumetanide), because a rebound effect may be seen during the loop diuretic-free period[86, 93].

Chronic administration of loop diuretics results in several functional and structural changes in the kidney leading to so-called "braking phenomenon". This adaptation contributes to the diminished effect of loop diuretics. As sodium reabsorption is blocked in the ascending loop of Henle, more sodium ions reach distal convoluted tubule. This effect induces hypertrophy and hyperplasia of distal tubular cells and increases their sodium reabsorption capacity[86]. Therefore, dual[94] or even triple[92] nephron blockage with a loop diuretic and thiazide / thiazide-like diuretic and (or) MRA may overcome diuretic resistance, as these drugs block sodium reabsorption in the distal convoluted tubule. However, such treatment should be administrated with caution because of potential side effects such as hypokalaemia, hypomagnesaemia, hypovolemia and renal dysfunction[92]. Some authors describe possible benefits of acetazolamide[93,96] or mannitol[93] in the treatment of diuretic resistance, but further research is required before this can be recommended.

If the above-mentioned means are ineffective to overcome diuretic resistance, congestion is likely to lead to ADHF. ADHF and diuretic resistance represent a challenging clinical scenario[29]. Treatment with vasopressin receptor antagonists[92], hypertonic salt solution co-administrated with diuretics[29,92,97], ultrafiltration[98,99] and inotropic support[100] are all being investigated. Recently published results of a small randomized study suggest that a novel subcutaneously administered furosemide formulation is as effective as intravenous form in decompensated HF, thus this possibility might open new cost-effective outpatient decongestion options in the nearest future[101]. ADHF is not the scope of this review, therefore the above-mentioned modalities are not further discussed.

Limitations

Most of the above-outlined recommendations and the 4-step congestion management algorithm (**Figure 3**) represent an authors' opinion-based consensus, since evidence is lacking. On the other hand, the lack of evidence-based guidelines makes this decision support tool valuable, given the uncertainties about loop diuretic dosage in chronic HF[8–18]. The aspects suggested in this document need to be prospectively studied in appropriate clinical trials.

Conclusion

High doses of loop diuretics identify HF patients at increased risk; however, it remains unclear if this is due to more advanced disease severity or a direct negative effect of loop diuretics. The importance of extensive evaluation of fluid retention has not yet been properly investigated, but indirect evidence suggests that decongestion using diuretic therapy might improve outcome. Which patients benefit from diuretics and which experience potential harm remains uncertain, but it is likely that this is not uniform across all HF patients. Large, randomized, prospective clinical trials of chronic HF patients are urgently needed testing different approaches for the clinical use of diuretics and means of fluid status assessment (**Table 5**). A small randomized double-blind trial evaluating the safety and tolerability of furosemide withdrawal in stable chronic HF patients is currently on-going[102]. Until such data is available, careful screening including instrumental monitoring for congestion and treating it whenever present with the minimum effective diuretic dose may be the best approach.

Table 5. Possible designs of diuretic management trials

1. A large, randomized, prospective, single-blind, controlled clinical trial where clinically stable chronic HF patients are randomized to one of three arms:
1.1. no deliberate attempt to minimalize the dose or discontinue the drug;
1.2. attempt to minimalize diuretic dose or discontinue the drug as soon as clinically determined euvolemia is achieved (clinically guided approach);
1.3. attempt to reduce / tailor diuretic dose or discontinue the drug according to the evidence of fluid retention determined by means of instrumental monitoring (e.g. echocardiography or bioimpedance-guided approach)
2. A large, randomized, prospective, double-blind, placebo-controlled trial where euvolemic HF patients are randomly assigned to either receive:
2.1. the same diuretic dose
2.2. dose reduction by 50% (or discontinued if the dose of loop diuretic administrated was low)

HF: heart failure

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SUPPLEMENTS

Supplementary Table

The relationship between loop diuretic dose and outcomes in a large HF cohort of 4,406 patients[1]

	Low dose	Medium dose	High dose
Dynamic furosemide dose-adjusted HRs (95% CI)*			
All mortality	Referent	1.96 (1.79-2.15)†	3.00 (2.72-3.31)†
In-hospital death	Referent	2.00 (1.78-2.24)†	3.12 (2.76-3.53)†
Out-of-hospital death	Referent	1.91 (1.65-2.20)†	2.81 (2.40-3.29)†
HF hospitalizations	Referent	1.24 (1.12-1.38)†	1.43 (1.26-1.63)†
CV hospitalizations	Referent	1.12 (1.02-1.22)‡	1.29 (1.15-1.44)†
All hospitalizations	Referent	1.06 (0.98-1.14)	1.22 (1.10-1.35)†
Renal dysfunction	Referent	1.56 (1.38-1.76)†	2.16 (1.88-2.49)†
Arrhythmias	Referent	1.15 (1.03-1.30)‡	1.45 (1.27-1.66)†

***** *Hazard ratios adjusted for age, sex ischemic heart disease, prior myocardial infarction, aortic/mitral valve disease, hypertension, diabetes, atrial fibrillation, cancer, cerebrovascular disease, chronic obstructive pulmonary disease, dementia, smoking, New York Heart Association class, left ventricular ejection fraction, hypo/normo/hypernatremia, hypo/normo/hyperkalaemia, creatinine, urea, cardiomegaly, heart rate, respiratory rate, preadmission use of furosemide, presenting and discharge systolic blood pressure, and other discharge medications.*

† *$p < 0.001$ vs low loop diuretic dose*

‡ *$p < 0.05$ vs low loop diuretic dose*

HRs: hazard ratios; CI: confidence interval; HF: heart failure; CV: cardiovascular

1- Based on: Abdel-Qadir HM, Tu JV, Yun L, Austin PC, Newton GE, Lee DS. Diuretic dose and long-term outcomes in elderly patients with heart failure after hospitalization. Am Heart J. 2010;160:264-271.e1

3

CHAPTER 3

PROGNOSTIC SIGNIFICANCE OF LONGITUDINAL CLINICAL CONGESTION PATTERN IN CHRONIC HEART FAILURE: INSIGHTS FROM TIME-CHF TRIAL

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and

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Abstract

Background: The relationship between longitudinal clinical congestion pattern and heart failure outcome is uncertain. This study was designed to assess the prevalence of congestion over time and to investigate its impact on outcome in chronic heart failure.

Methods: A total of 588 chronic heart failure patients ≥ 60 years with New York Heart Association (NYHA) functional class ≥ II from the TIME-CHF study were included. The endpoints for this study were survival and heart failure hospitalization-free survival. Orthopnoea, NYHA ≥ III, paroxysmal nocturnal dyspnoea, hepatomegaly, peripheral pitting oedema, jugular venous distension and rales were repeatedly investigated and related to outcomes. These congestion-related signs/symptoms were used to design a 7-tem Clinical Congestion Index.

Results: Sixty-one percent of patients had a Clinical Congestion Index ≥ 3 at baseline, which decrease to 18% at month 18. During the median [interquartile range] follow-up of 27.2 [14.3 – 39.8] months, 17%, 27%, and 47% of patients with baseline Clinical Congestion Index of 0, 1-2, and ≥ 3 at inclusion, respectively, died ($p<0.001$). Clinical Congestion Index was identified as an independent predictor of mortality at all visits ($p<0.05$) except month 6 and reduced heart failure hospitalization-free survival ($p<0.05$). Successful decongestion was related to better outcome as compared to persistent congestion or partial decongestion (log-rank $p<0.001$).

Conclusions: The extent of congestion as assessed by means of clinical signs and symptoms decreased over time with intensified treatment, but remained present or relapsed in a substantial number of heart failure patients, associated with poor outcome. This highlights the importance of appropriate decongestion in chronic heart failure.

Key words: Congestion; Heart failure; Loop diuretic; Prognosis; Signs; Symptoms

Introduction

Despite advances in management, heart failure remains a leading cause of disease-related hospitalizations and in-hospital deaths[1]. One-quarter of patients are re-hospitalized within 30 days after discharge[2], and 43% either die or are hospitalized within 1 year. The rate of events is even higher if congestion persists at discharge[3]. Therefore, congestion is an important target for treatment[4].

The CHAMPION trial showed that reduction in pulmonary artery pressure translates into a reduced rehospitalization rate[5]. However, wireless pulmonary artery pressure monitoring systems will become standard care in only a small proportion of heart failure patient. Other means to assess congestion are either not generally available for point-of-care testing, not sufficiently accurate or not adequately validated. Therefore, clinical assessment remains the standard to identify congestion. However, little is known how congestion develops over time. This is very important, given the ongoing discussion about the use and safety of diuretics in chronic heart failure[6]. In fact, guidelines recommend to use diuretics cautiously in the lowest dose required to achieve effective decongestion[7]. Appropriate assessment of (de)congestion is therefore crucial.

Some congestion scores have been proposed[8-14], but none of them has been evaluated repeatedly over time, and their implementation into clinical practice is limited. The present study was, therefore, designed to assess the prevalence of congestion over time and its impact on outcome in an outpatient population of chronic heart failure.

Methods

Data source and study population

This is a post-hoc analysis of the Trial of Intensified versus standard Medical therapy in Elderly patients with Congestive Heart Failure (TIME-CHF). The design[15] and main results[16] were published previously. Briefly, TIME-CHF was a randomized, controlled multicentre trial that compared an N-terminal-pro B-type natriuretic peptide (NT-proBNP)-guided vs a symptom-guided management in patients with chronic heart failure (n=622), age ≥ 60 years, symptoms corresponding to New York Heart Association (NYHA) functional class ≥ II, heart failure hospitalization within 12 months prior to inclusion, and NT-proBNP levels > 400ng/L (<75 years) or > 800ng/L (≥75 years), respectively. Patients with both reduced (*n*=499) and preserved (*n*=123) left ventricular ejection fraction (cut-off in TIME-CHF: 45%) were included between 2003 and 2006 and followed-up clinically for 18 months. The investigation conforms

with the principles of the Declaration of Helsinki, was approved by the local ethics committees, and all participants provided written informed consent.

Clinical signs and symptoms

The presence or absence of signs and symptoms of congestion (hepatomegaly, NYHA ≥ III, peripheral pitting oedema, jugular venous distension, orthopnoea, rales, third heart sound and paroxysmal nocturnal dyspnoea) was analysed independent of the severity. If data about any sign/symptom was missing at inclusion, the patient was excluded. Hence, the present analysis includes 588 patients, i.e. 95% of the TIME-CHF population. Patients were followed-up after 1, 3, 6, 12, and 18 months. Signs, symptoms, and laboratory analysis were assessed at every visit.

Outcome events

Death unless cancer related was the primary outcome event for this study, with death or heart failure hospitalization as secondary outcome. Although the study duration was 18 months, the patients underwent a systematic long-term follow-up up to 5½ years.

Statistical analysis

Results are presented as mean ± standard deviation or median [interquartile range] as appropriate for continuous variables and numbers (percentage) for categorical variables. For group comparisons, Kruskal–Wallis, Mann-Whitney U or χ^2 test was used as appropriate. Kaplan–Meier curves were used for calculation of the time-dependent occurrence of events. Survival between groups was compared using the log-rank test. Hazard ratios (HRs) with 95% confidence intervals (95% CIs) were derived from univariable and multivariable Cox regression models. Adjustment for the following covariates was performed: gender, age, coronary artery disease as the main cause of heart failure, reduced LVEF and Charlson comorbidity score at baseline; NT-proBNP, systolic blood pressure and estimated glomerular filtration rate (eGFR; CKD-EPI equation) at each time point. For cluster analysis, data was transformed to sequential data and ordered by clinical congestion index evaluation time. Hierarchical clustering with an agglomerative nesting algorithm was done using the longest common subsequence-based distance metric. When applied to categorical time series, such metric finds the largest number of elements that follow each other, preserving the symbol order between two sequences[17]. A two-sided *P*-value of 0.05 was considered as statistically significant. Calculations were performed using the SPSS statistical package version 23.0 (SPSS Inc., Chicago, IL, USA) and R statistical software version 3.5.1.

Results

Baseline characteristics

Baseline characteristics are shown in **Table 1**. Patients were elderly and ischemic aetiology was the cause of heart failure in more than half of patients. The prevalence of comorbidities was high (median Charlson score 3 [2-4]). Patients were severely symptomatic (76% in NYHA class ≥ III) and most were on loop diuretics at baseline.

Table 1. Baseline Characteristics of the Entire Study Population and Patients in the Three Clinical Congestion Index (CCI) Categories

	All patients (n = 588)	CCI = 0 (n = 36)	CCI = 1-2 (n = 194)	CCI ≥3 (n = 358)	*P*
Age (years)	77 ± 8	72 ± 8	75 ± 8	78 ± 7	<.001
Male gender	351 (60%)	29 (81%)	121 (62%)	201 (56%)	.011
HFrEF (LVEF<45%)	474 (81%)	32 (89%)	165 (85%)	277 (77%)	.040
LVEF (%)	35 ± 13	33 ± 12	34 ± 12	35 ± 14	.381
Body mass index (kg/m^2)	25.5 ± 4.3	24.2 ± 3.2	24.4 ± 3.9	26.2 ± 4.5	<.001
Ischemic cause of HF	307 (52%)	17 (47%)	96 (50%)	194 (54%)	.473
Diabetes	205 (35%)	6 (17%)	59 (30%)	140 (39%)	.008
Hypertension	434 (74%)	25 (69%)	131 (68%)	278 (78%)	.029
COPD	118 (20%)	2 (6%)	28 (14%)	88 (25%)	.001
Cancer	83 (14%)	7 (19%)	27 (14%)	49 (14%)	.636
Kidney disease	334 (57%)	17 (47%)	103 (53%)	214 (60%)	.155
Liver disease	50 (8%)	1 (3%)	12 (6%)	37 (10%)	.111
Gout	49 (8%)	2 (6%)	16 (8%)	31 (9%)	.812
Arthrosis	154 (26%)	6 (17%)	41 (21%)	107 (30%)	.034
Anemia	166 (28%)	8 (22%)	43 (22%)	115 (32%)	.033
Charlson score	3 [2-4]	2 [1-4]	2 [2-4]	3 [2-4.25]	<.001
Systolic BP (mm Hg)	122 ± 20	122 ± 21	122 ± 20	121 ± 19	.848
Heart rate (bpm)	76 ± 14	69 ± 12	74 ± 14	77 ± 14	<.001
Atrial fibrillation	196 (34%)	5 (14%)	53 (28%)	138 (39%)	.001
NYHA class ≥III	445 (76%)	0 (0%)	115 (59%)	330 (92%)	<.001
History of edema	272 (46%)	2 (6%)	40 (21%)	230 (64%)	<.001
6MWD (m)	260 [180-351]	410 [323-490]	315 [230-380]	213 [150-300]	<.001
NT-proBNP (ng/L)	3688 [1855-6760]	2487 [1252 - 3989]	2923 [1710-5028]	4607 [2125-7642]	<.001
eGFR (mL/min/1.73 m^2)	53 ± 19	58 ± 16	56 ± 20	51 ± 19	.005
Potassium (mmol/L)	4.1 ± 0.5	4.2 ± 0.4	4.2 ± 0.5	4.1 ± 0.5	.008
Hemoglobin (g/L)	131 ± 18	138 ± 15	135 ± 17	130 ± 18	.004
Sodium (mmol/L)	140 ± 7.8	139 ± 4	139 ± 3	140 ± 8	.670
Loop diuretic use	543 (92%)	34 (94%)	117 (91%)	332 (93%)	.726
Loop diuretic dose (mg of furosemide equivalent)	80 [40-80]	40 [20-80]	40 [40-80]	80 [40-120]	<.001

6MWD= 6-minute walking distance; BP = blood pressure; bpm = beats per minute; CAD = coronary artery disease; CCI = Clinical Congestion Score; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; HFrEF = heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

Congestion-related clinical signs and symptoms

The prevalence of congestion-related signs and symptoms was high at baseline and decreased during follow-up (**Table 2**). Univariate predictors of mortality are shown in **Table 3**. All clinical congestion parameters were good predictors of mortality except third heart sound. Similar results were found regarding heart failure hospitalization-free survival (**Supplementary Table 1**).

Table 2. The Prevalence of congestion-related signs and symptoms during the entire study period

Variable	Baseline	Month 1	Month 3	Month 6	Month 12	Month 18
Hepatomegaly	21%	11%	9%	4%	4%	4%
NYHA ≥III	76%	48%	37%	33%	33%	29%
Edema	41%	31%	27%	26%	26%	31%
JVD	61%	43%	39%	30%	33%	31%
Orthopnoea	31%	16%	15%	12%	11%	10%
Rales	44%	23%	22%	16%	14%	16%
S3	14%	10%	6%	5%	5%	3%
PND	34%	14%	12%	11%	10%	6%

JVD = jugular venous distention; NYHA = New York Heart Association functional class; PND = paroxysmal nocturnal dyspnea; S3 = third heart sound.

Clinical congestion index and outcome

Clinical parameters identified as univariate predictors were used to design a Clinical Congestion Index as the sum of the parameters of congestion (one point for each parameter, **Supplementary Figure 1**). Sixty-one percent of patients had ≥ 3 signs and/or symptoms of congestion at baseline, whereas only 6% of patients had none. The latter group increased to 40% at month 18. Reduction of Clinical Congestion Index was noted at each visit until month 6 and remained stable afterwards (**Figure 1**). Clinical Congestion Index did not differ between the NT-proBNP-guided and symptom-guided treatment arms during the study (data not shown; P>0.05).

Figure 1. Distribution of the Clinical Congestion Index (CCI) during the study period

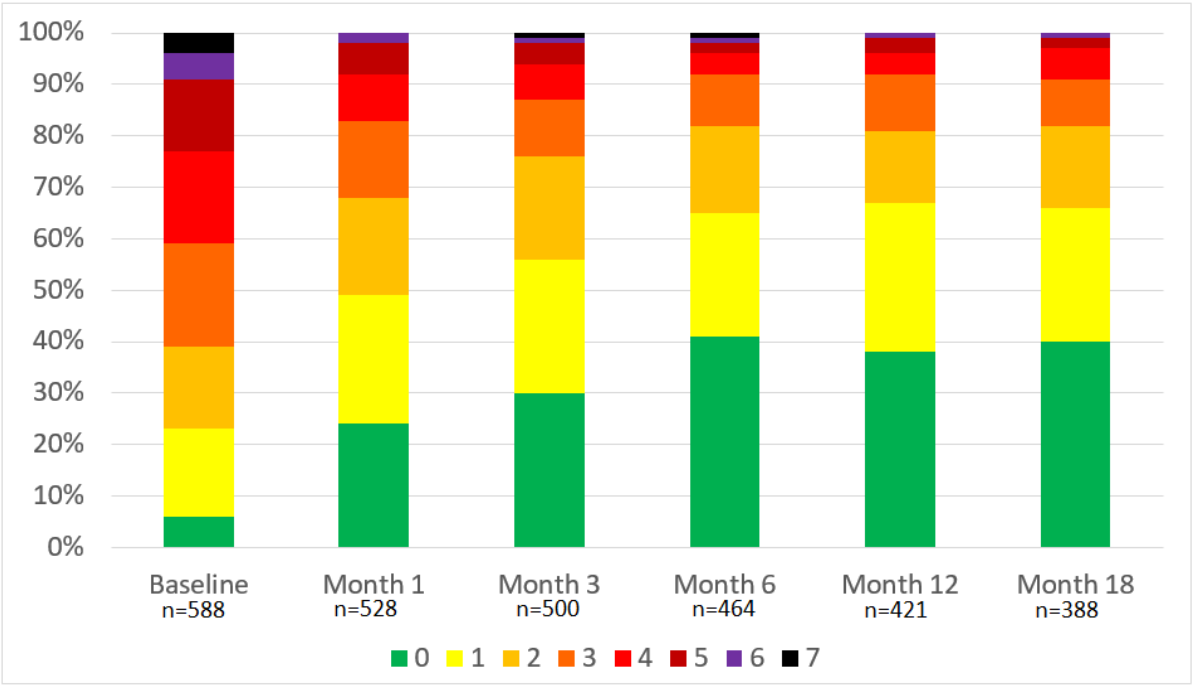


Table 3. Cox Regression Analysis for Signs and Symptoms of Congestion as Univariate Predictors of Death at Different Follow-Up Time-Points

	Baseline (n = 588)			Month 1 (n = 528)			Month 3 (n = 500)			Month 6 (n = 464)			Month 12 (n = 421)			Month 18 (n = 388)		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Hepatomegaly	1.43	1.07;1.9	.016	2.31	1.61;3.31	<.001	2.27	1.52;3.39	<.001	2.04	1.15;3.62	.015	2.64	1.33;5.25	.005	3.10	1.54;6.24	.002
NYHA ≥III	1.69	1.29;2.33	.001	1.68	1.28;2.22	<.001	1.85	1.37;2.50	<.001	1.78	1.29;2.47	.001	1.17	1.50;3.15	<.001	1.97	1.29;3.01	.002
Edema	1.42	1.10;1.82	.008	1.38	1.04;1.83	0.25	1.35	0.98;1.85	.066	1.69	1.21;2.37	.002	1.51	1.01;2.25	.042	1.61	1.04;2.50	.033
JVD	1.49	1.13;1.96	.004	1.85	1.40;2.43	<.001	1.67	1.24;2.25	.001	1.77	1.27;2.47	.001	2.03	1.39;2.97	<.001	1.67	1.08;2.57	.021
Orthopnea	1.45	1.12;1.89	.005	1.51	1.09;2.11	.014	2.51	1.78;3.53	<.001	2.02	1.33;3.07	.001	1.55	0.94;2.57	.086	1.21	0.62;2.34	.577
Rales	1.81	1.40;2.34	<.001	1.81	1.36;2.41	<.001	2.08	1.52;2.83	<.001	1.92	1.34;2.75	<.001	1.55	1.01;2.39	.045	2.62	1.66;4.12	<.001
S3	1.02	0.71;1.45	.921	1.03	0.68;1.58	.88	1.33	0.77;2.30	.312	0.82	0.34;2.02	.671	0.82	0.34;2.02	.671	0.57	0.18;1.81	.337
PND	0.99	0.76;1.30	.961	1.74	1.23;2.45	.002	1.73	1.15;2.60	.008	2.26	1.48;3.47	<.001	1.63	0.98;2.70	.060	2.53	1.30;4.92	.006

CI = confidence interval; HR = hazard ratio; JVD = jugular venous distension; NYHA = New York Heart Association functional class; PND = paroxysmal nocturnal dyspnea; S3: third heart sound.

During follow-up, 39% of patients died. In univariate analysis, Clinical Congestion Index as a continuous measure was identified as a strong predictor of death and death or heart failure hospitalization at all time-points (**Table 4**). After multivariate adjustment, Clinical Congestion Index retained largely its predictive value, except for death at month 6 (**Table 4**). We divided the patients into three groups based on the Clinical Congestion Index: no congestion (0), mild congestion (1-2) and moderate to severe congestion (≥3). Baseline characteristics of the subgroups are provided in **Table 1**. Patients with congestion were older and more often female, had higher BMI, higher ejection fraction, Charlson score, heart rate, NT-proBNP and received higher loop diuretic doses. At month 6, patients with no as compared to mild and moderate to severe congestion had better 6-month renal function (eGFR 52±18 versus 46±19 versus 45±20 ml/min/1.73 m^2), lower NT-proBNP levels (1515 [675-2658] versus 2157 [1238-4608] versus 3878 [2073-6855] ng/l), received lower loop diuretic doses (40 [20-80] versus 40 [40-120] versus 80 [40-150] mg), and presented with lower heart rate (67±11 versus 69±12 versus 72±13 bpm; all $p < 0.05$).

Table 4. Univariate and Multivariate Analysis of Clinical Congestion Index (CCI)

	Univariate analysis				Multivariate analysis*			
	Death		Death or hospitalization for HF		Death		Death or hospitalization for HF	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Baseline (n = 588)	1.23[a]	1.12;1.28	1.18[a]	1.11;1.26	1.13[b]	1.04;1.22	1.12[b]	1.05;1.20
At 1 month (n = 528)	1.30[a]	1.20;1.41	1.28[a]	1.20;1.38	1.17[b]	1.06;1.29	1.16[a]	1.07;1.26
At 3 months (n = 500)	1.38[a]	1.27;1.51	1.41[a]	1.31;1.53	1.17[b]	1.05;1.31	1.23[a]	1.12;1.35
At 6 months (n = 464)	1.37[a]	1.23;1.52	1.49[a]	1.36;1.63	1.10[d]	0.98;1.24	1.25[a]	1.13;1.39
At 12 months (n = 421)	1.33[a]	1.19;1.49	1.33[a]	1.21;1.46	1.14[c]	1.00;1.29	1.20[b]	1.08;1.34
At 18 months (n = 388)	1.33[a]	1.17;1.51	1.27[a]	1.14;1.42	1.25[b]	1.08;1.45	1.35[c]	1.03;1.77

Hazard ratios (HR) are presented per 1 point increase in CCI
CI = confidence interval; HF = heart failure
*Adjusted for gender, age, coronary artery disease the cause of HF, systolic dysfunction at baseline, Charlson score, NT-proBNP level at each time point, systolic blood pressure at each time point, and estimated glomerular filtration rate (CKD-EPI) at each time point
[a]$P < .001$
[b]$P < .01$
[c]$P < .05$
dnon significant

During follow-up, 17% of patients with no congestion at baseline, 27% with mild congestion, and 47% with moderate to severe congestion, respectively, died (p<0.001). Patients with congestion had worse survival at all time-points (p<0.001; **Figure 2**). Heart failure hospital-free survival rate was lower among patients with congestion at all time-points (**Supplementary Figure 2**).

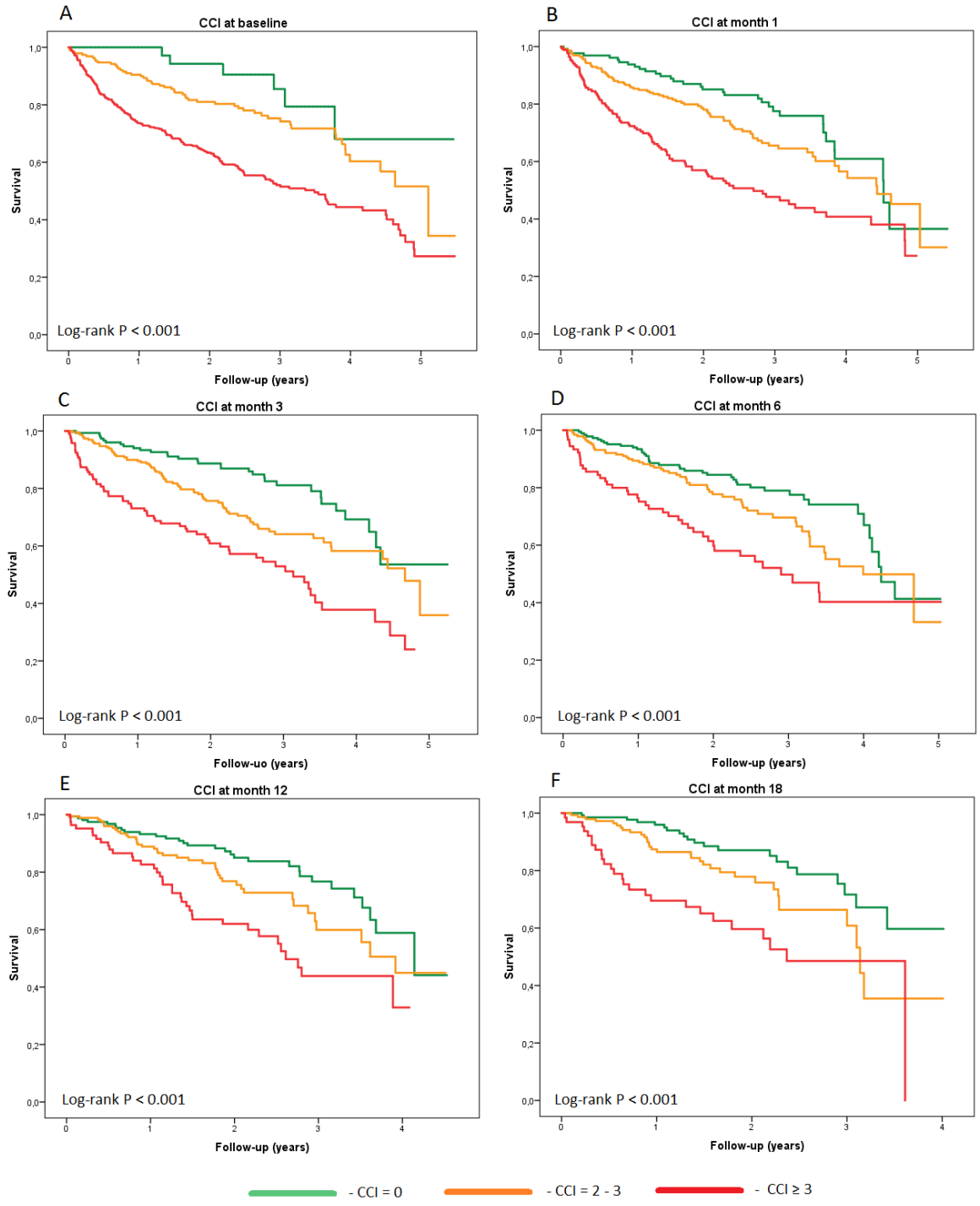
Clinical Congestion Index during follow-up

As reduction in congestion was noted during the first 6 months (**Figure 1**), we analysed whether changes in congestion during this period were of prognostic significance. An increase in Clinical Congestion Index between baseline and month 6 was noted in 12% of patients. These patients had worse outcome (**Figure 3, A and B**). Patients with no or only mild congestion both at baseline and month 6 (39% of patients) had the best outcome (**Figure 3, C and D**). Patients with successful clinical decongestion (43% of patients) did only slightly less well, whereas patients that deteriorated (5% of patients) did almost equally poor as patients that were congested at both time-points (13% of patients; **Figure 3 C and D**; p<0.001).

Longitudinal dynamics of congestion and its importance on outcome

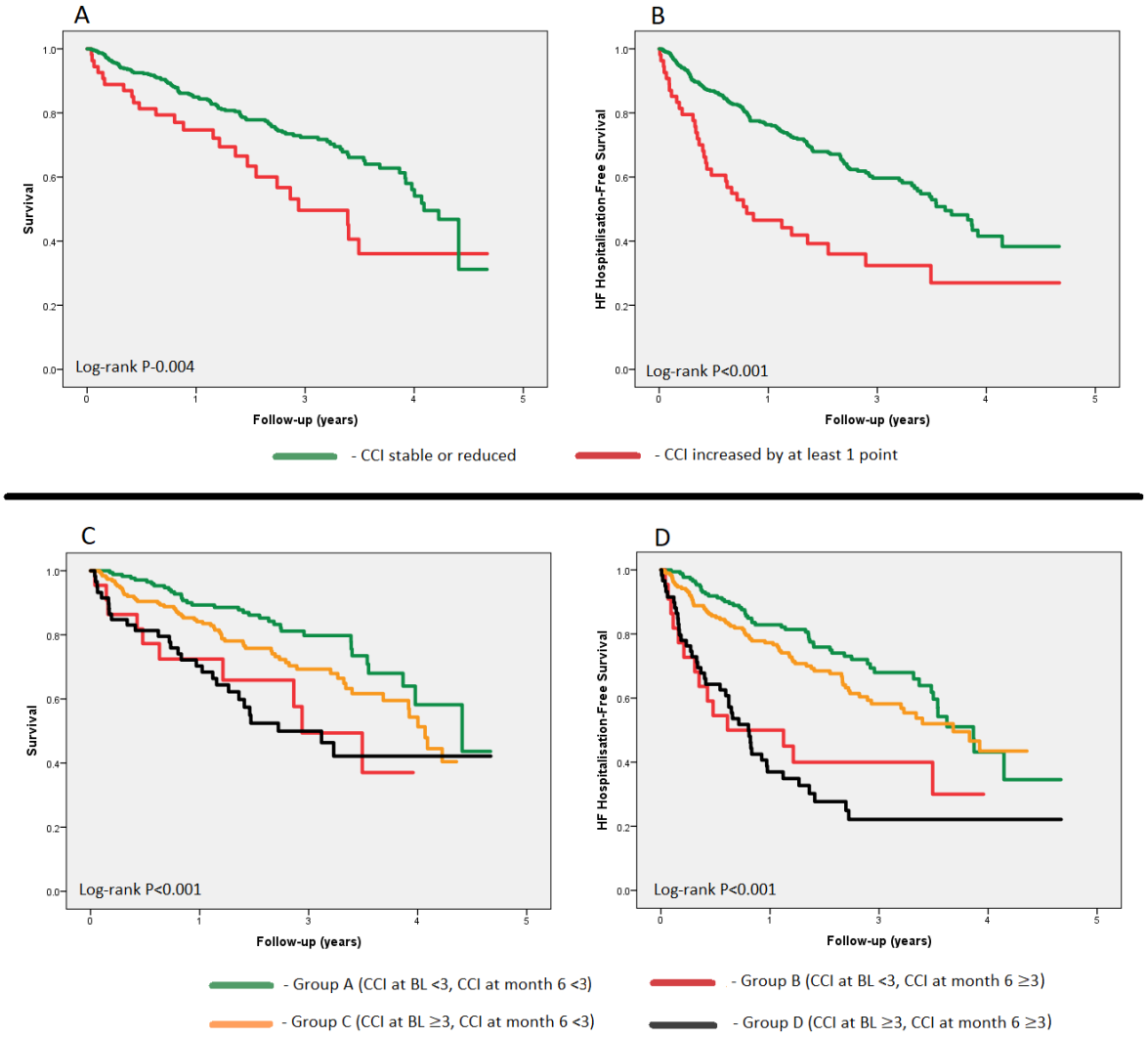
Five clusters were identified according to the longest common subsequence of Clinical Congestion Index during the follow-up (**Figure 4A**). The best outcome (**Figure 4B and 4C**) was noted among patients with early and consistent decongestion (Cluster 1). Two patterns of fluctuations were identified: the first pattern (Cluster 2) was characterized by freedom from congestion with transient minor relapses.

Figure 2. Kaplan-Meier curves of survival comparing patients with a Clinical Congestion Index (CCI) of 0 to those with a CCI of 1-2 and ≥ 3 at different time-points during the study period



CCI: Clinical Congestion Index

Figure 3. Kaplan-Meier curves of survival (A, C) and heart failure hospitalisation-free survival (B, D) comparing patients with different dynamics of Clinical Congestion Index (CCI) between baseline and month 6. Follow-up = 0 years refers to visit at month 6.

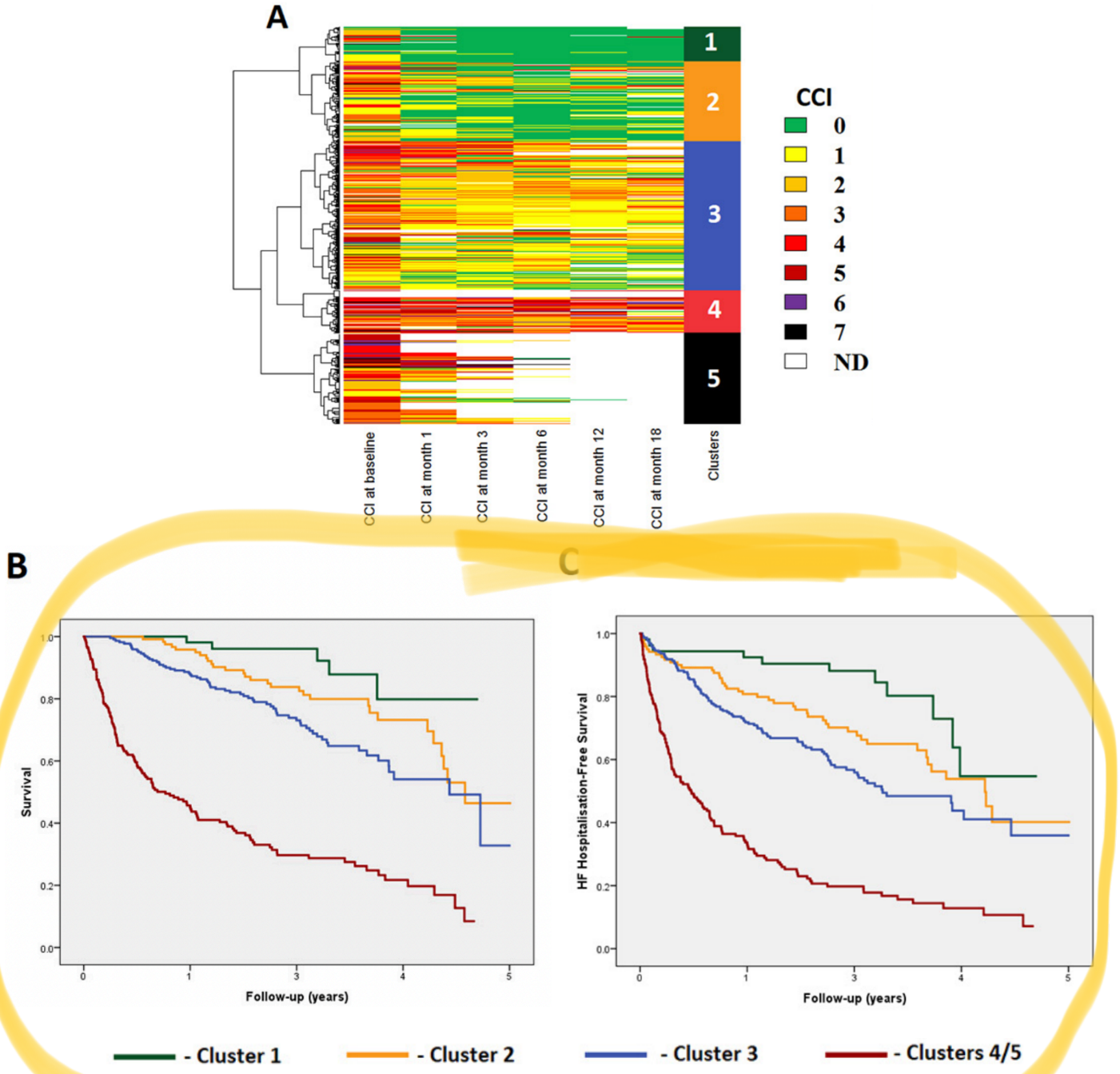


BL: baseline; CCI: Clinical Congestion Index

The second pattern (Cluster 3) was characterized by partial decongestion and more frequent/severe relapses. Patients experiencing minor relapses (Cluster 2) had a worse prognosis than those in whom complete decongestion was achieved (Cluster 1), whereas patients with partial decongestion (Cluster 3) had worse outcome than the previously described two subgroups (Clusters 1 and 2). An even worse prognosis was noted, if severe congestion persisted (Cluster 4), or if patients had a short follow-up (Cluster 5). These two groups of patients were severely congested at baseline (Clinical Congestion Index 4 [3-5] vs 2 [1-4] in other cluster ($p<0.001$)). As Cluster 5 contains many patients with early death (and some dropouts) and persistent congestion in short term, Cluster 4 and 5 are combined regarding outcome analysis (**Figure 4B and 4C**). Despite being treated with higher loop diuretic doses

than the rest of the population at baseline (80 [40 – 160] vs 40 [40 – 80], respectively, p<0.001), these patients had very poor outcome. The comparison of baseline characteristics between clusters is shown in **Supplementary Table 2**. Patients in Clusters 4 and 5 were older and more symptomatic, had more comorbidities and worse functional capacity.

Figure 4. Longitudinal congestion patterns (A) and Kaplan-Meier curves of survival (B) and heart failure hospitalization-free survival (C) comparing patients with different longitudinal congestion patterns



CCI: Clinical Congestion Index; ND: No data

Discussion

Intensification of heart failure therapy resulted in significant reduction of congestion during the initial 6 months. However, congestion persisted or relapsed in a significant proportion of patients. This resulted in worse outcome, highlighting the importance of freedom from congestion on heart failure prognosis. Moreover, severely congested patients are likely not to achieve complete decongestion and die early. Still, it remains to be determined how to best achieve decongestion and if it is possible in (almost) all patients.

Signs and symptoms of congestion are related to increased ventricular filling pressures[18]. Poor prognosis may be more dependent on congestion than low cardiac output as shown in acute decompensated heart failure[19]. About 40% of patients are still symptomatic at discharge[20]. Symptomatic patients have higher intracardiac filling pressures, that persist and determine adverse events[21]. All these points highlight the clinical importance of (persistent) congestion. The TIME-CHF trial population received an intensive treatment with evidence-based medicine and more than 90% received loop diuretics. This may explain the significant decrease in clinically overt congestion, particularly during early follow-up when therapy was intensified. It may be hypothesized that without the intensive follow-up and predefined escalation roles[15], the prevalence of clinical congestion would have been even higher. Patients in daily outpatient practice rarely receive such strict follow-up regimen and escalation of therapy. Despite overall improvement, however, a substantial number of patients remained congested and negative influence of congestion remained after intensifying chronic heart failure therapy.

Congested patients at month 6 had higher NT-proBNP level, worse renal function and received higher loop diuretic doses. All these factors are common in diuretic resistance and cardiorenal syndrome, previously related to unfavourable outcome[22]. Interestingly, renal function worsened on average also in patients with no or little congestion 6 months after inclusion as compared to baseline. Such dynamics can be related to progressing heart failure, progression of renal injury and medication-mediated kidney dysfunction. However, it is generally accepted that the prognosis is mainly dependent on cardiac function rather than worsening renal function, as the reduction of eGFR does not translate into impaired outcome if the clinical status is stable or improves[23,24].

Our findings support the importance of rapid decongestive therapies in daily chronic heart failure practice, particularly if congestion is severe or persists. However, it must be prospectively investigated if specifically targeting high-risk groups with more aggressive decongestion results in better outcome.

As Clinical Congestion Index did not differ between NT-proBNP-guided and symptom-guided treatment arms and loop diuretics were equally prescribed[16], it is possible that decongestion *per se* is not the main driver for better outcome and the other heart failure interventions are more important than diuretic therapy. In fact, improved outcome was mainly found in those (NT-pro)BNP guided trials where therapy escalation did not primarily focused on intensification of diuretic therapy but on up-titration of neurohormonal blockade[25]. However, the best approach other than diuretic therapy to treat congestion is unknown and requires future studies. In addition, the CHAMPION trial improved outcome by reducing filling pressures mainly through diuretic therapy[5].

There are four main reasons that determine the failure to overcome congestion. First, volume overload is not easy to recognize as patients may have elevated filling pressures without apparent clinical manifestation of congestion[18]. Still, our study suggests that careful clinical evaluation reveals congestion in many heart failure patients and patients without signs and symptoms of congestion have good outcome. Second, one-third of heart failure patients presents with a mismatch between right- and left-sided filling pressures[26]. Therefore, signs and symptoms of both right and left sided congestion must be part of congestion assessment, which is not always the case. Third, the use of high dose of loop diuretics has been related to worse prognosis[6]. These results created doubts regarding the rationale for using high loop diuretic doses. Thus, clinicians may be reluctant to prescribe sufficiently high doses of loop diuretics. Fourth, up to one third of patients develop diuretic resistance[27], accompanied with persistent congestion and unfavourable outcome[22], but the best approach to overcome diuretic resistance is not well defined[25].

Some previously described signs and symptoms[8,9,11,12] were not included in the Clinical Congestion Index. There was no prognostic value of the third heart sound, although it has been previously attributed to restrictive ventricular filling[28] and associated with adverse outcome[29]. However, physician performance to detect third heart sound may be variable[30] and correct identification is poor[31]. This might explain the finding in this study. The importance of weight change – another sign used in other congestion scores[8,9,11] – is stressed in recent heart failure guidelines[7]. However, data from the COMPASS trial found no correlation between changes in weight and filling pressure[32]. Also, meta-analyses show that the performance of weight gain in diagnosing acute decompensation is poor[33,34]. This can be explained by the facts that short-term redistribution of volume may result in large changes in filling pressures but not weight and that long-term congestion-related gut oedema and

consequent appetite loss may result in malnutrition. Therefore, weight change was not considered.

This study has some limitations. The most important is the lack of measurements of ventricular filling pressures to validate the accuracy of our score. Regardless of clear definitions, all congestion-related signs and symptoms share some degree of subjectivity and this might bias the findings. The TIME-CHF population was elderly. Therefore, the performance of the Clinical Congestion Index in a younger population is uncertain. This might be also true for other subgroups of patients, although sensitivity analyses in various subgroups did not influence results (data not shown). Given the retrospective nature of our analysis, it is impossible to establish a certain reference value that would indicate the need for therapeutic intervention. In particular, we did not test if interventions based on this score may result in better outcome. Finally, we did not include some other previously used measures such as biomarkers (NT-proBNP). Although biomarkers are related to clinical congestion, this relationship may be limited[35] and we aimed to investigate the prognostic significance of clinical (de)congestion. In fact, this is the first study we are aware of that extensively analysed the dynamics of clinical congestion in a large heart failure population and revealed the importance of longitudinal congestion pattern on outcome.

Conclusion

The extent of congestion as assessed by means of clinical signs and symptoms decreased over time with intensified treatment, but congestion persisted or relapsed in a substantial number of heart failure patients, associated with poor outcome. Severe congestion was accompanied with early death, whereas clinical decongestion was related to improved outcome. If treatment strategies based on clinical congestion result in better outcome, however, needs to be prospectively tested.

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SUPPLEMENTS

Supplementary Table 1. Cox regression analysis for signs and symptoms of congestion as univariate predictors of death or heart failure related hospitalization at different follow-up time-points

	Baseline (n=588)			***Month 1 (n=528)***			***Month 3 (n=500)***		
	HR	**95% CI**	**p**	**HR**	**95% CI**	**p**	**HR**	**95% CI**	**p**
Hepato-megaly	1.26	0.97;1.64	0.09	**1.76**	1.25;2.48	**0.001**	**2.11**	1.45;3.07	**<0.001**
NYHA ≥III	**1.51**	1.15;1.99	**0.003**	**1.64**	1.28;2.09	**<0.001**	**1.97**	1.51;2.58	**<0.001**
Oedema	**1.45**	1.15;1.82	**0.001**	**1.47**	1.14;1.89	**0.003**	**1.47**	1.11;1.95	**0.008**
JVD	**1.56**	1.22;1.98	**<0.001**	**2.00**	1.57;2.56	**<0.001**	**1.94**	1.50;2.53	**<0.001**
Orthopnoea	**1.51**	1.19;1.91	**0.001**	**1.80**	1.34;2.42	**<0.001**	**3.15**	2.33;4.26	**<0.001**
Rales	**1.79**	1.42;2.25	**<0.001**	**1.72**	1.33;2.23	**<0.001**	**1.88**	1.42;2.49	**<0.001**
S3	0.98	0.71;1.36	0.980	1.04	0.71;1.52	0.855	1.05	0.62;1.77	0.859
PND	1.05	0.82;1.33	0.72	**1.84**	1.35;2.50	**<0.001**	**1.82**	1.27;2.62	**0.001**
	Month 6 (n=464)			***Month 12 (n=421)***			***Month 18 (n=388)***		
	HR	**95% CI**	**p**	**HR**	**95% CI**	**p**	**HR**	**95% CI**	**p**
Hepato-megaly	**1.89**	1.05;3.40	**0.034**	**2.20**	1.19;4.07	**0.012**	**2.46**	1.24;4.89	**0.010**
NYHA ≥III	**2.10**	1.58;2.80	**<0.001**	**2.17**	1.58;2.98	**<0.001**	**1.75**	1.20;2.56	**0.004**
Oedema	**1.71**	1.26;2.33	**0.001**	**1.62**	1.15;2.28	**0.006**	**1.48**	1.01;2.18	**0.046**
JVD	**2.15**	1.61;2.88	**<0.001**	**1.94**	1.41;2.68	**<0.001**	**1.84**	1.26;2.69	**0.002**
Orthopnoea	**2.68**	1.88;3.83	**<0.001**	**2.45**	1.64;3.65	**<0.001**	1.31	0.75;2.30	0.342
Rales	**1.99**	1.44;2.74	**<0.001**	**1.74**	1.20;2.53	**0.004**	**1.89**	1.23;2.90	**0.004**
S3	0.89	0.42;1.90	0.761	0.91	0.43;1.95	0.808	0.72	0.26;1.99	0.532
PND	**2.87**	1.99;4.15	**<0.001**	**1.97**	1.28;3.05	**0.002**	**2.33**	1.28;4.24	**0.006**

CI: confidence interval; HR: hazard ratio; JVD: jugular venous distension; NYHA: New York Heart Association functional class; PND: paroxysmal nocturnal dyspnoea; S3: third heart sound

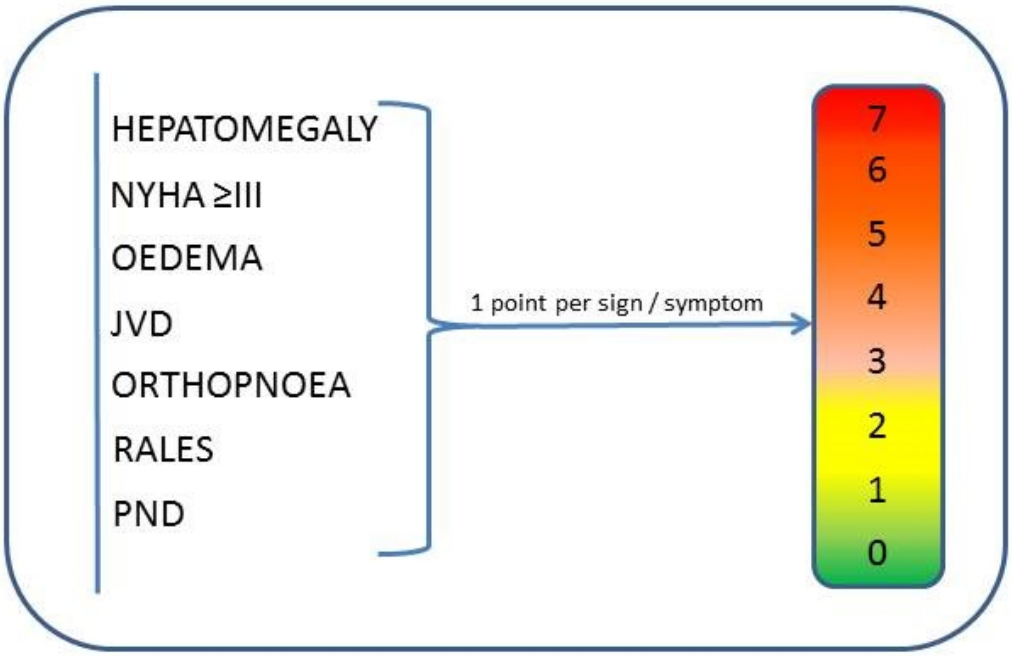
Supplementary Table 2. Comparison of baseline parameters between subjects in Clusters 4-5 and the remaining study population (Clusters 1-3)

	Clusters 1-3 (n = 393)	*Clusters 4-5 (n = 195)*	*p*		*Clusters 1-3 (n = 393)*	*Clusters 4-5 (n = 195)*	*p*
Age (years)	76 ± 8	78 ± 7	**<0.001**	*Charlson score*	3 [2-4]	3 [2-5]	**<0.001**
Male gender	238 (61%)	113 (58%)	0,592	*Systolic BP (mmHg)*	121 ± 20	122 ± 21	0.269
HFrEF (LVEF<45%)	336 (86%)	138 (71%)	**<0.001**	*Heart rate (bpm)*	75 ± 14	77 ± 14	0.153
LVEF (%)	34 ± 12	37 ± 14	**0.019**	*Atrial fibrillation*	115 (30%)	81 (42%)	**0.004**
Body mass index (kg/m^2)	25.2 ± 4.2	25.9 ± 4.6	0.154	*NYHA class ≥III*	268 (68%)	117 (91%)	**<0.001**
Ischemic cause of HF	183 (47%)	124 (64%)	**<0.001**	*6MWD (m)*	297 [209 – 379]	195 [120 – 280]	**<0.001**
Diabetes	121 (33%)	84 (42%)	**0.003**	*NT-proBNP (ng/l)*	3503 [1816 – 6429]	4708 [2338 – 8518]	**<0.001**
Hypertension	287 (73%)	147 (75%)	0.541	*eGFR (ml/min/1.73 m^2)*	55 ± 19	48 ± 18	**<0.001**
COPD	64 (16%)	54 (28%)	**0.001**	*Potassium (mmol/l)*	4.1 ± 0.5	4.1 ± 0.5	0.330
Cancer	51 (13%)	32 (16%)	0.260	*Haemoglobin (g/l)*	134 ± 17	125 ± 19	**<0.001**
Kidney disease	200 (54%)	134 (67%)	**<0.001**	*Sodium (mmol/l)*	139 ± 7	140 ± 9	0.428
Liver disease	28 (7%)	22 (11%)	0.089	*Loop diuretic use*	361 (92%)	182 (93%)	0.526
Gout	30 (8%)	19 (10%)	0.383	*Loop diuretic dose**	40 [40 – 80]	80 [40 – 160]	**<0.001**
Arthrosis	97 (25%)	57 (29%)	0238	*CCI (points)*	2 [1-4]	4 [3-5]	**<0.001**
Anaemia	89 (23%)	77 (40%)	**<0.001**				

6MWD: six-minute walking distance; BP: blood pressure; bpm: beats per minute; CAD: coronary artery disease; CCI: Clinical Congestion Index; COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration rate; HF: heart failure; HFrEF: heart failure with reduced ejection fraction; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association

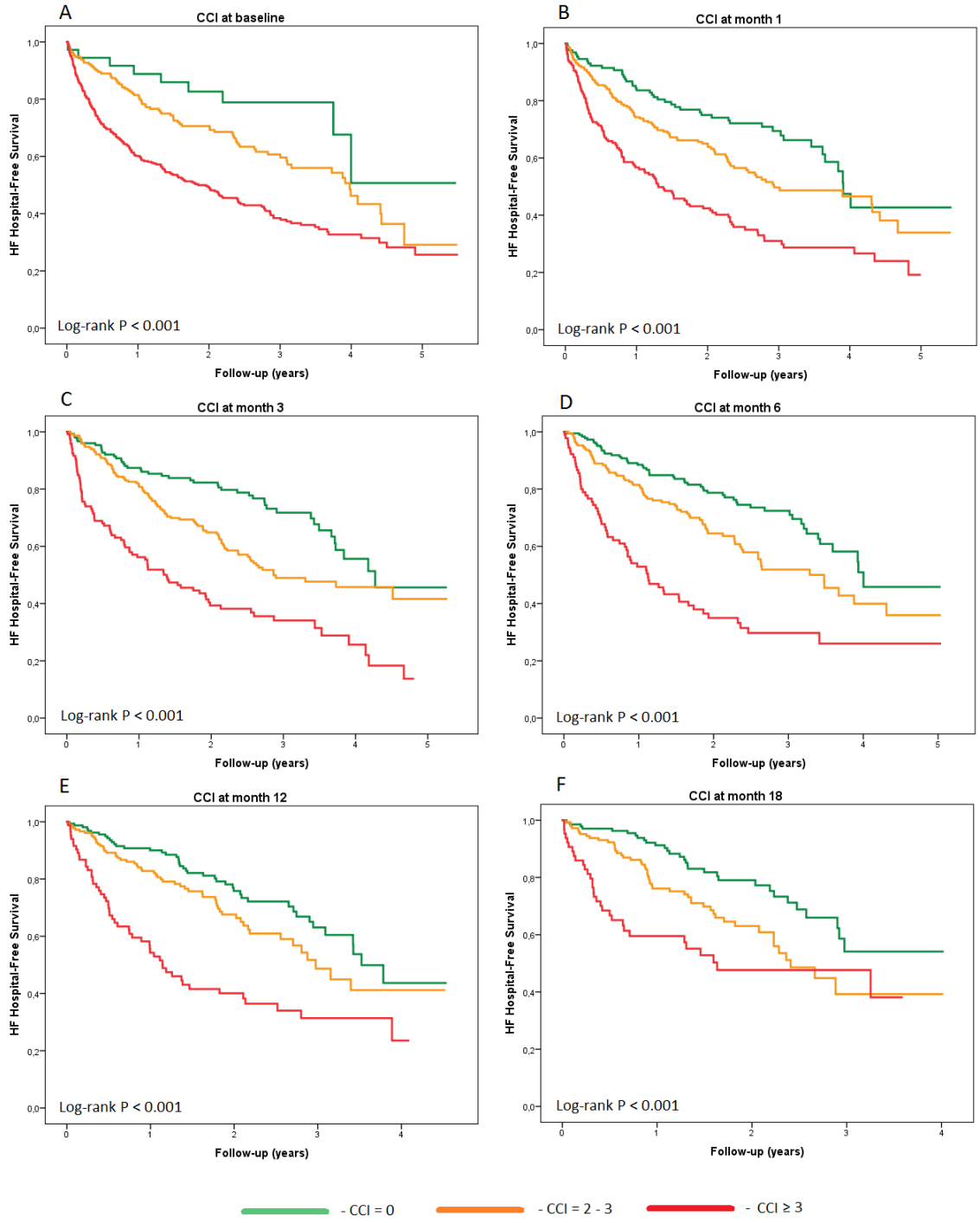
** mg of furosemide equivalent*

Supplementary Figure 1. Composition of the Clinical Congestion Index



JVD: jugular venous distension; NYHA: New York Heart Association functional class; PND: paroxysmal nocturnal dyspnoea

Supplementary Figure 2. Kaplan-Meier curves of heart failure hospitalization-free survival comparing patients with a Clinical Congestion Index (CCI) of 0 to those with a CCI of 1-2 and ≥3 at different time-points during the study period



CCI: Clinical Congestion Index

The reply to a letter by Zhou et al.

We read with great interest the letter by Zhou et al. concerning our recently published article on the importance of clinical congestion in chronic heart failure (HF)[1]. We are delighted to clarify the issues raised.

Indeed, the assumption of proportional hazards using Schoenfeld residuals may not be true at 3 time-points: baseline, months 1 and 18. However, differences in results were clinically not meaningful at the different timepoints, making an impact on the main findings unlikely. Also, the comparison of the three clinical congestion index (CCI) groups by means of Gehan‘s generalized Wilcoxon test revealed highly significant differences ($p < 0.001$), supporting the conclusions.

To analyse the importance and independence of CCI, we constructed multivariable Cox regression models for survival and HF hospitalization-free survival including CCI as an independent variable[1]. Recommendations for the number of independent variables to be included in Cox regression model varies from 5 to 20 or more[2,3], with the rule of thumb being 10 events per variable (EPV).

Given the high number of primary endpoints (229 events) during the 5½ follow-up, 11 independent variables may be included for multivariable adjustment, even when applying the conservative 20 EPV rule. The most clinically relevant predictors, including Charlson comorbidity index and NT-proBNP among others, were included after their prognostic properties were proven in univariate analysis. This enabled us to optimize the model and ensured the avoidance of over- and underfit.

We obviously agree with Zhou et al. regarding the need of validation and calibration of CCI, as acknowledged in the article[1]. Our aim was to present the potential prognostic impact of CCI in a representative HF cohort. To better illustrate the performance of our models, we supplement the time-dependent ROC curves and calibration plots for 2-, 3- and 4-years survival (**Figure 1**) and HF hospitalization-free survival (**Figure 2**) prediction. The area under the curve ranged from 73 to 81.1 for survival and 70.6 to 82.3 for HF hospitalization-free survival (**Table 1**). Calibration plots showed adequate calibration for most models with small deviations (**Figures 1, 2**).

These additional findings strongly support the conclusion of the article and underscore the importance of clinical congestion in chronic HF[1]. We plan to externally validate the CCI and to construct more precise models, taking additional biomarkers into account.

Table 1. Time-Dependent Receiver Operating Characteristic Curve Analysis

	Death						Death or Hospitalization for Heart Failure					
	2 years		3 years		4 years		2 years		3 years		4 years	
	AUC	95% CI	AUC	95% CI	AUC	95% CI	AUC	95% CI	AUC	95% CI	AUC	95% CI
Baseline	76.2	71.8;80.6	77.4	72.5;82.1	73	66.1;79.9	74.5	70.2;78.8	80.3	75.9;84.7	75.4	68.5;82.2
Month 1	76.5	71.7;81.3	77.9	72.9;82;9	77.6	71;84.2	73.7	69.1;78.3	79.2	74.2;84.1	73.7	66.3;81
Month 3	76.9	71.2;82.6	78.1	73;83.2	78.8	72.2;85.5	76.9	72.4;81.4	78.6	73.4;83.7	73.8	66.1;81.4
Month 6	79.3	73.4;85.2	80.1	74.7;85.4	81.1	74.5;87.6	79.6	74.9;84.3	80.2	74.7;85.7	70.6	60;81.2
Month 12	74.8	66.6;83	78	71.9;84	75.9	68;83.8	77.1	71.4;82.8	75.2	67.5;82.9	75.2	59.9;90.6
Month 18	74	59;89	78	70.7;85.3	77.6	69.5;85.8	77.4	70.7;84	70.7	58.8;82.6	82.3	58.3;100

AUC = area under the curve; CI = confidence interval.

Figure 1. (A) Calibration plot for 2-years survival, (B) Time-dependent ROC analysis for 2-years survival, (C) Calibration plot for 3-years survival, (D) Time-dependent ROC analysis for 3-years survival, (E) Calibration plot for 4-years survival, (F) Time-dependent ROC analysis for 4-years survival

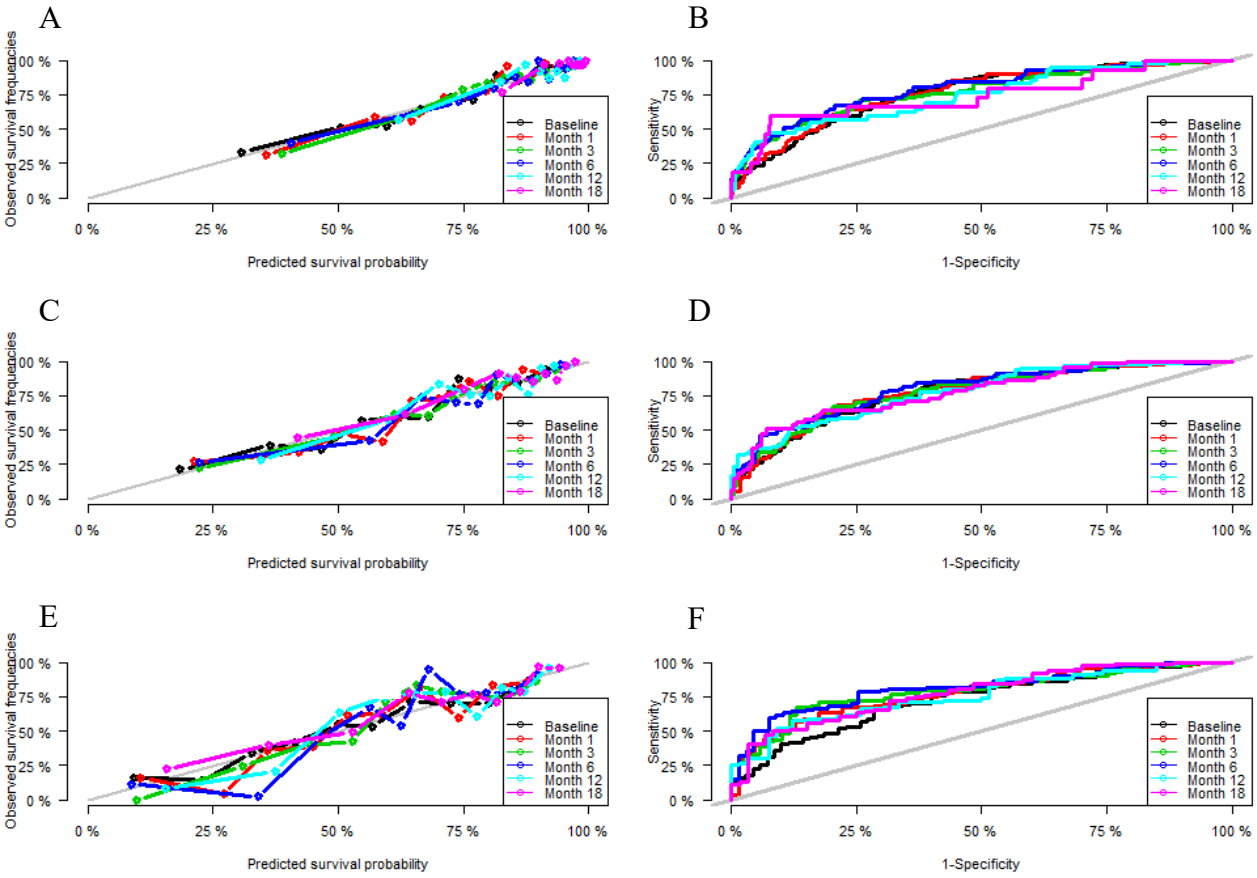
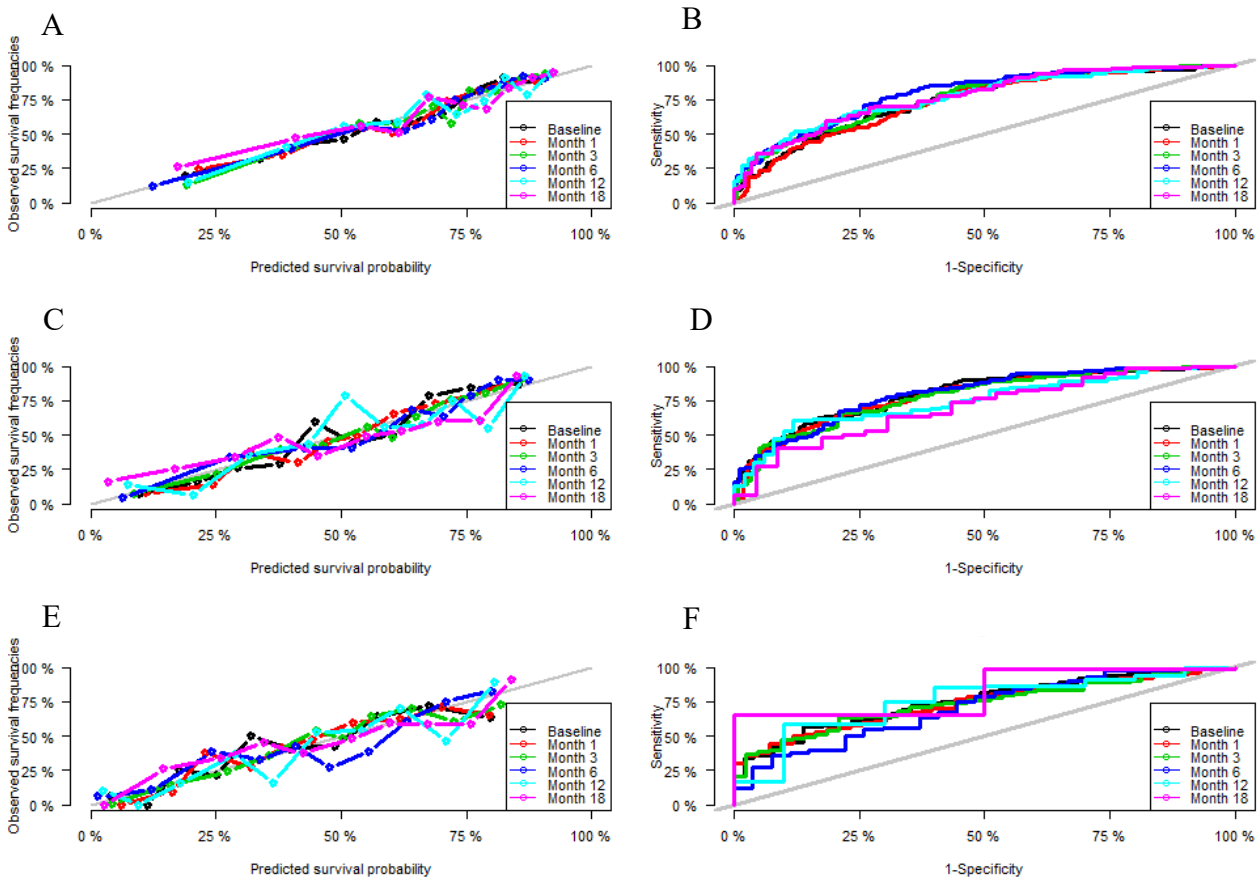


Figure 2. (A) Calibration plot for 2-years heart failure hospitalization-free survival, (B) Time-dependent ROC analysis for 2-years heart failure hospitalization-free survival, (C) Calibration plot for 3-years heart failure hospitalization-free survival, (D) Time-dependent ROC analysis for 3-years heart failure hospitalization-free survival, (E) Calibration plot for 4-years heart failure hospitalization-free survival, (F) Time-dependent ROC analysis for 4-years heart failure hospitalization-free survival



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CHAPTER 4

DO CHRONIC HEART FAILURE PATIENTS RECEIVE OPTIMAL DECONGESTIVE INTERVENTIONS IN A REAL-LIFE SETTING?

LETTER REGARDING THE ARTICLE 'ASSOCIATION BETWEEN LOOP DIURETIC DOSE CHANGES AND OUTCOMES IN CHRONIC HEART FAILURE: OBSERVATIONS FROM THE ESC-EORP HEART FAILURE LONG-TERM REGISTRY'

Simonavicius J, Brunner-La Rocca HP. Eur J Heart Fail. 2021 Feb;23(2):342

We read with interest the recent investigation by Kapelios et al., concerning the analysis of the European Society of Cardiology Heart Failure Long Term (ESC-HF-LT) registry[1]. It underscores the widespread inertia in congestion management, as only 24% of patients underwent loop diuretic (LD) dose modification in ESC-HF-LT. Also, guidelines-directed medication was better up-titrated in patients receiving LD dose adjustment, presuming that physician's discretion may be a stronger predictor of individualised therapy than patient's clinical status. The authors also found that successful decongestion is unlikely for patients with peripheral oedema[1]. Still, peripheral oedema is not the best parameter to guide decongestion, given the high prevalence of causes other than chronic heart failure (CHF). In daily practice clinical signs and symptoms remain the cornerstone of congestion assessment, but an extensive clinical investigation is crucial[2]. Given the low rate of LD adjustments, it may be speculated that clinical assessment was not sufficiently extensive, at least in some patients[1].

In contrast to down-titration, up-titration was related to worse outcome. The authors noted that extensive adjustment was done to prove the independence of up-titration as a risk factor. However, (de)congestion and CHF outcome interact by means of complex and incompletely investigated mechanisms, making full adjustment almost impossible. In addition, registries contain a limited number of variables, limiting the extent of adjustment. Theoretically, LD treatment can trigger various mechanisms of harm[3], but the adaptability of the human body is likely to counterbalance these effects[4], meaning that the effective impact of LD therapy remains unclear. Also, down-titration in patients with no clinical congestion might worsen the already existing haemodynamic congestion. The ESC-HF-LT registry revealed that de-escalation was unsuccessful in 52% of the cases although it only took place in 8.3% of all patients, questioning whether the right intervention was chosen for the right patient. Despite little support by the literature and effective down-titration in only roughly 4%, the authors suggest attempting LD de-escalation more often. We are convinced that the target should not be the reduction of LD dose *per se* but the achievement of euvolemia with full decongestion. This is supported by the findings of the CHAMPION trial, where adjustment of therapy based on invasively measured filling pressures improved outcome. Importantly, LD therapy was the most common adjustment of therapy and in the majority, it was LD up-titration[5]. Therefore, comprehensive clinical assessment is crucial, which may include additional exams, such as cardiothoracic or long ultrasound to achieve euvolemia. Unfortunately, clinical inertia is highly prevalent[1], resulting in suboptimal treatment.

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CHAPTER 5

INTENSIFICATION OF PHARMACOLOGICAL DECONGESTION BUT NOT THE ACTUAL DAILY LOOP DIURETIC DOSE PREDICTS WORSE CHRONIC HEART FAILURE OUTCOME: INSIGHTS FROM TIME-CHF

Simonavičius J, Maeder MT, Eurlings CGMJ, Aizpurua AB, Čelutkienė J, Barysienė J, Toggweiler S, Kaufmann BA, Brunner-La Rocca HP. Clin Res Cardiol. 2021 Aug;110(8):1221-1233

Abstract

Background. Both loop diuretics (LD) and congestion have been related to worse heart failure (HF) outcome. The relationship between the cause and effect is unknown. The aim of this study was to investigate the interaction between congestion, diuretic use and HF outcome.

Methods. Six-hundred-twenty-two chronic HF patients from TIME-CHF were studied. Congestion was measured by means of a clinical congestion index (CCI). Loop diuretic dose was considered at baseline and month 6. Treatment intensification was defined as the increase in LD dose over 6 months or loop diuretic and thiazide or thiazide-like diuretic co-administration. The end-points were survival and HF hospitalisation-free survival.

Results. High LD dose at baseline and month 6 (≥80 mg of furosemide per day) was not identified as an independent predictor of outcome. CCI at baseline remained independently associated with impaired survival (hazard ratio (HR) 1.34, [95% confidence interval] (95% CI) [1.20-1.50], p<0.001 and HF hospitalisation-free survival (HR 1.09, 95% CI [1.02-1.17], p=0.015). CCI at month 6 was independently associated with HF hospitalisation-free survival (HR 1.24, 95% CI [1.11-1.38], p<0.001). Treatment intensification was independently associated with survival (HR 1.75, 95% CI [1.19-1.38], p=0.004) and HF hospitalisation-free survival (HR 1.69, 95% CI [1.22-2.35], p=0.002). Patients undergoing treatment intensification resulting in decongestion had better outcome than patients with persistent (worsening) congestion despite LD dose up-titration (p<0.001).

Conclusion. Intensification of pharmacological decongestion but not the actual LD dose was related to poor outcome in chronic HF. If treatment intensification translated into clinical decongestion, outcome was better than in case of persistent or worsening congestion.

Introduction

Although never properly tested to improve prognosis of chronic heart failure (CHF)[1], loop diuretics (LD) are an important part of the complex treatment for the vast majority of CHF patients[2]. On the one hand, such an approach seems to be justified, given the high prevalence of fluid accumulation in CHF patients and the well-established relationship between congestion, symptoms, quality of life and unfavourable prognosis[3–8]. In addition, invasively monitored pressure-triggered up-titration of medication in patients with advanced heart failure (HF) has been shown to improve outcome, which was primarily based on up-titration of LD therapy[9]. On the other hand, the safety of LD is being questioned, since the use of high doses of LD has been related to worsening renal function (WRF) and worse outcome in a large number of observational trials[1]. Still, data about congestion status were not available for comprehensive adjustment of adequate diuretic therapy in most databases previously used to analyse the safety profile of LD. Hence, the assumption that high doses of LD are harmful may be biased, as patients with advanced CHF are more likely to be congested and to have worse renal function[10]. As a consequence, they receive more often and higher doses of LD, sometimes co-administered with thiazide or thiazide-like diuretics[11–15]. Thus, high-dose LD therapy may be a surrogate for advanced disease and thereby a marker of poor outcome despite attempts to adjust for confounders in previous studies. In the Trial of Intensified versus standard Medical therapy in Elderly patients with Congestive Heart Failure (TIME-CHF), extensive phenotyping and detailed information on medication are available from multiple time-points[16], which makes this trial ideally suited to study the prognostic impact of decongestion. Therefore, this post-hoc analysis was designed to investigate the interaction between diuretic use, congestion and outcome in CHF.

Methods

Data source and study population

This is a post-hoc analysis of TIME-CHF. The design[17] and main results[16] of the trial have been previously reported. Briefly, TIME-CHF was a randomized, controlled multicentre trial conducted in Switzerland and Germany that compared an NT-proBNP-guided vs a symptom-guided management in patients with CHF (n=622), age ≥60 years, symptoms corresponding to New York Heart Association (NYHA) functional class ≥ II, HF hospitalisation within 12 months prior to inclusion, and an age-adjusted elevated NT-proBNP level (>400 ng/L in those <75 years, 800 ng/L in those ≥75 years). Patients with both reduced (HFrEF) (n=499) and preserved (n=123) left ventricular ejection fraction were included between January 2003 and

December 2006 and followed-up clinically for 18 months. The investigation conforms with the principles outlined in the Declaration of Helsinki, was approved by the local ethics committees, and all participants provided their written informed consent.

Patients were clinically evaluated at baseline and after 1, 3, 6, 12 and 18 months. At each visit, history was taken and patients underwent a detailed clinical examination to determine the presence and extent of congestion by means of a clinical congestion index (CCI) as previously described[3,18]. Briefly, CCI is a composite clinical marker of congestion taking into account the presence of hepatomegaly, NYHA ≥ III, peripheral oedema, jugular venous distension, orthopnoea, rales and paroxysmal nocturnal dyspnoea. The CCI value for each patient can vary from 0 (no congestion) to 7 (severe congestion)[3].

Information on all drugs including doses and changes between the visits was collected. LD dose is expressed as furosemide equivalent, where 10 mg torasemide and 1 mg bumetanide, respectively, are converted to 40 mg furosemide. Difference in LD dose between baseline and month 6 was used for investigation of changes in LD doses over time. The only thiazide and thiazide-like drugs used in TIMECHF were hydrochlorothiazide and metolazone. Patients taking any of the two were considered thiazide users. Given the fact that in clinical practice thiazides are usually co-administered with LD for short courses, the use of thiazides of any duration was considered as treatment intensification during a certain timeframe. Intensification of pharmacological decongestion was described as an increase in LD dose during the first 6 months of follow-up or a co-administration of a thiazide or thiazide-like drug with a LD. WRF was defined as an increase in serum creatinine by ≥44.2 μmol/l (0.5 mg/dl) over 6 months[19].

Outcome events

Death except cancer-related was the primary outcome event for this study, with death or HF hospitalisation as a secondary outcome. Although the study duration was 18 months, the subjects underwent a systematic long-term follow-up up to 5½ years, based on medical records or phone calls to patients and/or their general practitioners every 6 months.

Haemodialysis or haemofiltration was not used for the purpose of mechanical fluid extraction in TIME-CHF. Overall, three patients received temporary haemodialysis and one haemofiltration due to worsening renal failure. They were included as WRF in the analysis.

Statistical analysis

Descriptive statistics are expressed as median [interquartile range] for continuous variables, as the distribution of all continues variables was not normal (Kolmogorov-Smirnov test), and as numbers (percentages) for categorical variables. The groups were compared using Mann-

Table 1 Baseline characteristics of the study population

Characteristic	Value (n = 622)
Age (years)	77 (71–82)
Male gender	369 (59%)
BMI (kg/m^2)	25.1 (22.7–28.1)
LVEF ≤ 45%	499 (80%)
Cause of HF	
CAD	330 (53%)
DCM	89 (14%)
HHD	173 (28%)
Other	30 (5%)
Diabetes	222 (36%)
COPD	124 (20%)
PAOD	124 (20%)
CKD	355 (57%)
NYHA ≥ III	473 (76%)
AF	210 (34%)
Charlson score	3 (2–4)
sBP (mmHg)	120 (110–135)
HR (bpm)	74 (65–84)
NT-proBNP (ng/L)	3836 (1916–6905)
Creatinine (μmol/L)	108 (87–140)
eGFR (mL/min/1.73 m^2)	51.5 (36.0–67.1)
Potassium (mmol/L)	4.1 (3.8–4.5)
Sodium (mmol/L)	139 (137–142)
Haemoglobin (g/L)	131 (118–143)
6MWT distance (metres)	250 (180–350)
CCI	3 (2–4)
CCI ≥ 3	358 (61%)
LVEF (%)	32 (25–42)
MLHFQ	40 (25–55)
ACEi/ARB use	480 (77%)
β-blocker use	476 (77%)
MRA use	234 (38%)
LD use	575 (93%)
Thiazide use	25 (4%)

6MWT 6-min walk test distance, *ACEi/ARB* angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker, *AF* atrial fibrillation, *BMI* body mass index, *CAD* coronary artery disease, *CCI* clinical congestion index, *CKD* chronic kidney disease, *COPD* chronic obstructive pulmonary disease, *DCM* dilated cardiomyopathy, *eGFR* estimated glomerular filtration rate (chronic kidney disease epidemiology collaboration equation), *HF* heart failure, *HHD* hypertensive heart disease, *HR* heart rate, *bpm* beats per minute, *LD* loop diuretic, *LVEF* left ventricular ejection fraction, *MLHFQ* Minnesota living with heart failure questionnaire, *MRA* mineralocorticoid receptor antagonist, *NT-proBNP* N-terminal pro B-type natriuretic peptide, *NYHA* New York heart association functional class, *PAOD* peripheral arterial occlusive disease, *sBP* systolic blood pressure

Whitney U tests for continuous variables and chi-squared test for categorical variables. To test the association between LD use (low vs high dose) and intensification of pharmacological decongestion and outcome, Cox regression was performed. Independence of these associations was tested using multivariable Cox regression analysis. When testing the prognostic significance of intensification of pharmacological decongestion, only the events taking place after the month 6 follow-up visit were considered. A stepwise forward model was used (inclusion $P \leq 0.05$, exclusion $P > 0.1$). The Kaplan-Meier method was used to construct survival curves, with the log-rank test used for comparison among groups. All analyses using both baseline and month 6 values included only patients who survived and remained in the study. For all other analyses all patients were considered. A two-sided P-value of 0.05 or less was considered to be statistically significant. Statistical analysis was performed using the IBM® SPSS® for Windows® software (version 23.0, SPSS® Inc, Chicago, IL).

Results

Baseline Characteristics

Baseline characteristics are presented in **Table 1**. The patients were elderly and severely symptomatic – three out of four were in NYHA ≥ III. The majority (n=499 (80%)) had HFrEF with HF due to ischaemic heart disease being most prevalent. Most had significant comorbidities and poor disease-related quality of life. A high percentage of patients received evidence-based HF medications already at baseline.

The prevalence of congestion

The prevalence of congestion in TIME-CHF population was extensively analysed previously[3,18]. Briefly, congestion was highly prevalent at baseline and decreased continuously during the first 6 months (CCI ≥ 3 in 53% vs 19% of patients at baseline and month 6, respectively, of those who survived and remained in the study after 6 months).

The use of diuretics

The use of LD was high during the entire follow-up with 575 of 622 (92%), 509 of 567 (90%), 469 of 521 (90%), 440 of 489 (90%), 391 of 446 (88%), 358 of 406 (88%) patients using LD at baseline, month 1, 3, 6, 12, and 18, respectively. Median daily LD dose was 80 [40-100] at baseline, 40 [40-80] at month 1, 40 [25-80] at month 3, 40 [40-80] at month 6, 40 [20-80] at month 12, and 40 [20-80] mg of furosemide equivalent at month 18.

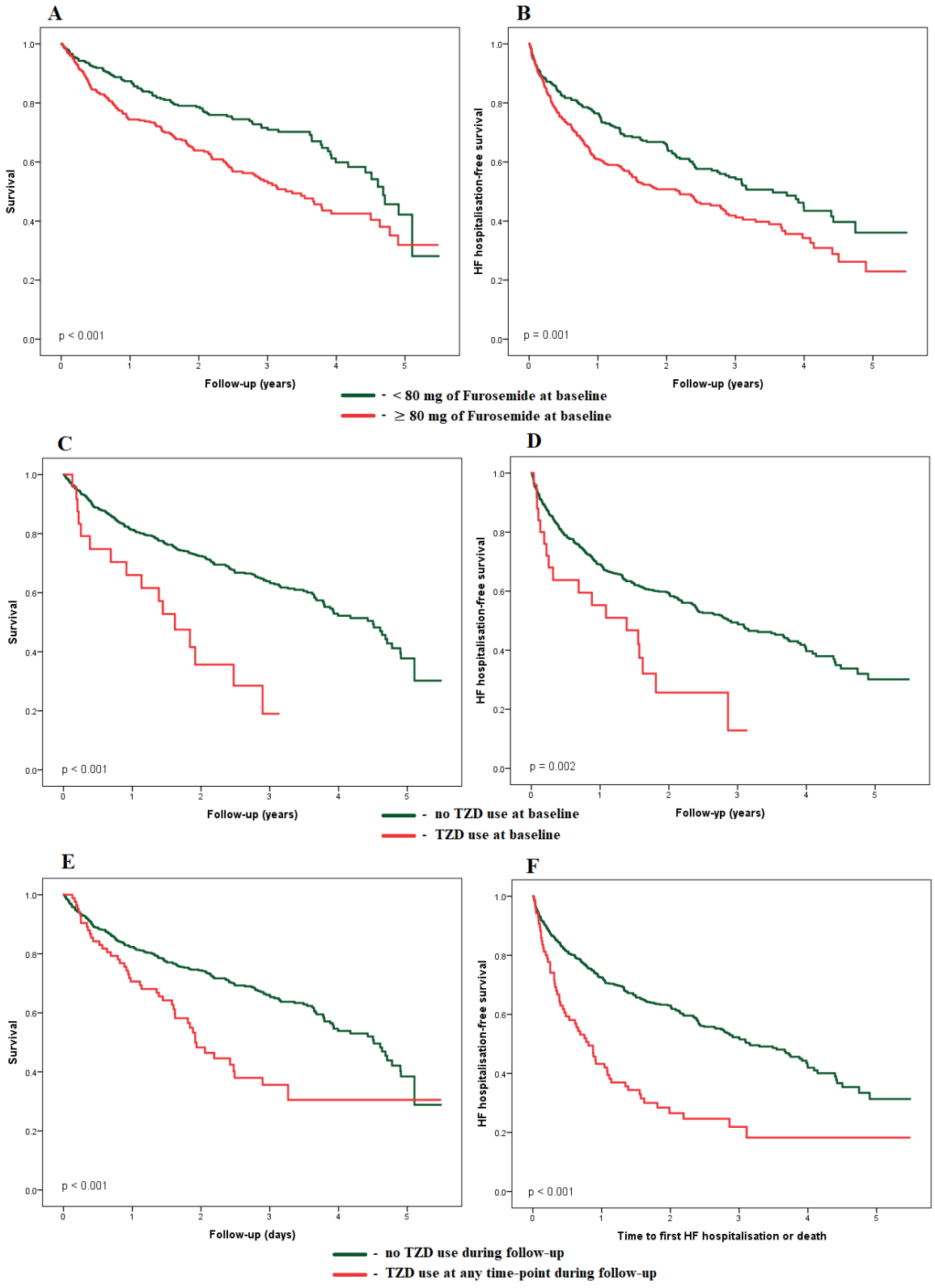
The use of thiazides was relatively low. Twenty-five (4%) patients used thiazides at baseline and 86 (14%) used them at any time-point during the follow-up. Sixty (10%) patients received thiazides during the first 6 months, whereas 56 (12%) were on thiazides after month 6. There were only 21 (4%) 6 month-survivors not on thiazides during the first 6 months, who received such treatment later during follow-up.

Prognostic relevance of diuretic therapy

During the median total follow-up of 27 [14-41] months, 241 (39%) patient died; 317 (51%) either died or were hospitalised for HF. Patients using high LD dose (≥80 mg of furosemide per day) at baseline (**Figures 1A, 1B**), as well as a thiazide diuretic at baseline (**Figures 1C, 1D**) and at any time-point during follow-up (**Figures 1E, 1F**) were at increased risk of dying or being hospitalised for worsening heart failure.

Univariable and multivariable predictors of death, and death or HF hospitalisation are shown in **Table 2**. High LD dose at baseline (≥80 mg of furosemide per day) and the use of thiazides at baseline were not identified as independent predictors of outcome, whereas congestion remained strongly and independently associated with impaired survival and HF hospitalisation-free survival.

Figure 1. Kaplan-Meier curves of survival and heart failure hospitalisation-free survival comparing high loop diuretic dose (≥ 80 mg per day) users with low loop diuretic dose (< 80 mg per day) users at baseline (A, B), thiazide diuretic users and non-users at baseline (C, D), and thiazide diuretic users and non-users at any time-point during follow-up (E, F)



HF: heart failure, TZD: thiazide or thiazide-like diuretic

Table 2. Univariable and multivariable forward stepwise COX regression analysis for survival and HF hospitalisation-free survival

	Univariable			Multivariable		
	HR	CI	*p*	HR	CI	*p*
Death after inclusion						
Age (per year)	1.05	1.03; 1.07	<0.001			
CAD	2.55	1.85; 3.48	<0.001	1.79	1.15; 2.80	0.010
Diabetes	1.53	1.18; 1.97	0.001			
PAOD	1.44	1.08; 1.92	0.013			
CKD	1.77	1.36; 2.32	<0.001			
Anaemia	1.83	1.41; 2.38	<0.001			
Angina	1.23	1.15; 1.47	<0.001			
CCI (per 1 point)	1.20	1.12; 1.28	<0.001	1.34	1.20–1.50	<0.001
sBP (per 1 mmHg)	0.99	0.98; 0.998	0.011	0.99	0.977–0.998	0.020
Haemoglobin (per 1 g/L)	0.98	0.98; 0.99	<0.001			
QRS width (lg10)	8.37	2.98; 23.49	<0.001	8.28	2.00–34.29	0.004
NT-proBNP (lg10)	3.14	2.26; 4.36	<0.001	2.38	1.46–3.88	<0.001
LD dose ≥ 80 mg	1.58	1.13; 2.20	<0.001			
eGFR (per 1 mL/min/1.73 m^2)	0.98	0.97; 0.99	<0.001			
Charlson score (per 1 point)	1.29	1.21; 1.39	<0.001	1.20	1.08–3.45	0.001
Male gender	0.73	0.56; 0.95	0.018			
6MWT distance (lg10)	0.29	0.19; 0.45	<0.001			
TZD use	2.78	1.67; 4.63	<0.001			
Death or HF hospitalisation after inclusion						
Age (per year)	1.05	1.03–1.07	0.001	1.03	1.01–1.05	<0.001
CAD	2.11	1.63; 2.73	<0.001			
Diabetes	1.63	1.30; 2.03	<0.001			
PAOD			n.s.			
CKD	1.79	1.42; 2.26	<0.001			
Anaemia	1.73	1.37; 2.18	<0.001	1.37	1.04; 1.79	0.024
Angina	1.25	1.12; 1.40	<0.001	1.16	1.02–1.33	0.029
CCI (per 1 point)	1.18	1.11–1.26	<0.001	1.09	1.02; 1.17	0.015
sBP (per 1 mmHg)			n.s.			
Haemoglobin per 1 g/l)	0.99	0.98; 0.99	<0.001			
QRS width (lg10)	5.12	2.07–12.69	<0.001	5.02	1.80–14.04	0.002
NT-proBNP (lg10)	2.18	1.64; 2.91	<0.001			
LD dose ≥ 80 mg	1.45	1.16–1.81	0.001			
eGFR (per 1 mL/min/1.73 m^2)	0.98	0.97; 0.98	<0.001	0.99	0.98; 0.995	0.001
Charlson score (per 1 point)	1.27	1.20; 1.35	<0.001	1.24	1.16–1.33	<0.001
Male gender			n.s.			
6MWT distance (lg10)	0.29	0.20; 0.43	<0.001			
TZD use	2.1	1.30–3.39	0.002			

6MWT 6-min walk test distance, *CAD* coronary artery disease, *CCI* clinical congestion index, *CI* confidence interval, *CKD* chronic kidney disease, *eGFR* estimated glomerular filtration rate (chronic kidney disease epidemiology collaboration equation), *HF* heart failure, *HR* hazard ratio, *n.s.* not significant, *NT-proBNP* N-terminal pro B-type natriuretic peptide, *PAOD* peripheral arterial occlusive disease, *sBP* systolic blood pressure, *TZD* thiazide or thiazide-like diuretic

As congestion decreased significantly among patients surviving 6 months (**Table 3**), we analysed the prognostic significance of LD use at month 6 and intensification of congestion treatment during the first 6 months of follow-up. Median daily LD dose (mg of furosemide equivalent) administered to patients surviving 6 months was as follows: 60 [40-80] at baseline, 40 [20-80] at month 1, 40 [20-80] at month 3, 40 [40-80] at month 6, 40 [20-80] at month 12, and 40 [20-80] at month 18. Of note, the difference between median daily dose of furosemide at baseline and month 6 was not statistically significant ($p>0.05$).

A total of 489 patients, i.e. 79% of TIME-CHF participants survived the first 6 months and did not drop out. Of those, 316 (65%) required LD dose down-titration or remained on a stable LD dose and received no thiazides together with a LD (*No treatment intensification group*); 173 (35%) required LD dose up-titration or a co-administration of a thiazide drug (*Treatment intensification group*). The comparison of patients receiving no intensification with patients undergoing intensification of congestion treatment is shown in **Table 3**. Patients in the intensification group were sicker: they had a higher comorbidity burden, their functional capacity was more impaired, their plasma NT-proBNP level at month 6 was higher, their haemoglobin was lower, their renal function was worse, and they were more likely to experience a WRF and to be congested.

The median follow-up of patients with survival ≥6 months was 30 [19-43] months. Univariable and multivariable predictors of death, and death or HF hospitalisation are shown in **Table 4**. LD dose administered at month 6 was not identified as an independent predictor of outcome, whilst treatment intensification remained an independent predictor of outcome. Although congestion at month 6 did not appear as an independent predictor of mortality, it remained a strong and independent predictor of HF hospitalisation-free survival after month 6.

Loop diuretic dose adjustment, congestion, and outcome

A total of 256 (55%) patients had no or only mild congestion (CCI < 3) at month 6 without treatment intensification; 118 (25%) patients had no or only mild congestion (CCI < 3) at month 6 following treatment intensification within the first 6 months; 46 (10%) patients were congested (CCI ≥ 3) at month 6 but had not received treatment intensification; and 44 (10%) patients were congested (CCI ≥ 3) at month 6 despite treatment intensification. The best prognosis was noted if congestion had been manageable without treatment intensification (**Figure 2**). If treatment intensification had been required to decongest, the prognosis was worse than without intensification. The worst prognosis was noted if obvious clinical congestion was present (CCI ≥ 3) despite treatment intensification. This was especially true for HF hospitalisation-free survival (**Figure 2B**).

Table 3. Comparison of patients undergoing diuretic treatment intensification versus those without.

Characteristic	No treatment intensification ($n=316$)	Treatment intensification ($n=173$)	p
Parameters at baseline			
Age (years)	77 (70–82)	77 [71–82]	0.302
Charlson score	3 (2–4)	3 (2–4)	0.002
QRS width (ms)	114 (96–140)	116 (94–148)	0.876
CKD	154 (49%)	107 (62%)	0.006
CCI	3 (1–4)	3 (2–4)	<0.001
sBP (mmHg)	120 (110–132)	120 (110–135)	0.519
HR (bpm)	74 (64–82)	74 (66–84)	0.684
Creatinine (µmol/L)	102 (84–133)	111 (89–143)	0.005
eGFR (mL/min/1.73 m^2)	56 (40–71)	47 (35–63)	0.001
Urea (mmol/L)	9.7 (7.3–12.8)	10.9 (8.0–13.9)	0.113
Potassium (mmol/L)	4.1 (3.8–4.4)	4.1 (3.8–4.5)	0.525
Sodium (mmol/L)	140 (138–142)	139 (137–141)	0.131
NT-proBNP (ng/L)	3161 (1785–6097)	4051 (2152–6805)	0.094
Haemoglobin (g/L)	133 (121–145)	130 (118–143)	<0.001
NYHA ≥ III	218 (69%)	135 (78%)	0.035
6MWT (m)	284 (195–375)	245 (1769–330)	<0.001
LD dose (mg furosemide equivalent)	80 (40–80)	40 (20–80)	<0.001
TZD use	0 (0%)	16 (9%)	<0.001
Parameters at month 6			
CCI	1 (0–2)	1 (0–3)	<0.001
sBP (mmHg)	122 (110–140)	120 (108–138)	0.170
HR (bpm)	68 (60–77)	70 (60–76)	0.665
Creatinine (µmol/L)	118 (91–141)	124 (99–169)	0.001
eGFR (mL/min/1.73 m^2)	49 (36–64)	42 (30–55)	<0.001
Urea (mmol/L)	10.7 (7.6–13.4)	12.6 (9.3–18.0)	<0.001
Potassium (mmol/L)	4.4 (4.1–4.7)	4.3 (4.0–4.7)	0.024
Sodium (mmol/L)	139 (137–141)	139 (136–141)	0.191
NT-proBNP (ng/L)	1762 (839–3644)	2693 (1334–5873)	<0.001
Haemoglobin (g/L)	132 (122–142)	128 (117–141)	0.054
NYHA ≥ III	87 (28%)	75 (44%)	0.001
LD dose (mg furosemide equivalent)	40 (20–80)	80 (60–200)	<0.001
WRF	39 (13%)	36 (21%)	0.018
TZD use over 6 months	0 (0%)	46 (27%)	<0.001

6MWT 6-min walk test distance, *bpm* beats per minute, *CCI* clinical congestion index, *CKD* chronic kidney disease, *eGFR* estimated glomerular filtration rate (chronic kidney disease epidemiology collaboration equation), *HR* heart rate, *LD* loop diuretic, *NT-proBNP* N-terminal pro B-type natriuretic peptide, *NYHA* New York heart association functional class, *sBP* systolic blood pressure, *TZD* thiazide or thiazide-like diuretic, *WRF* worsening renal function, defined as an increase in serum creatinine by ≥44.2 µmol/L over 6 months

Table 4. Univariable and multivariable forward stepwise COX regression analysis for survival and HF hospitalisation-free survival of patients alive at month 6

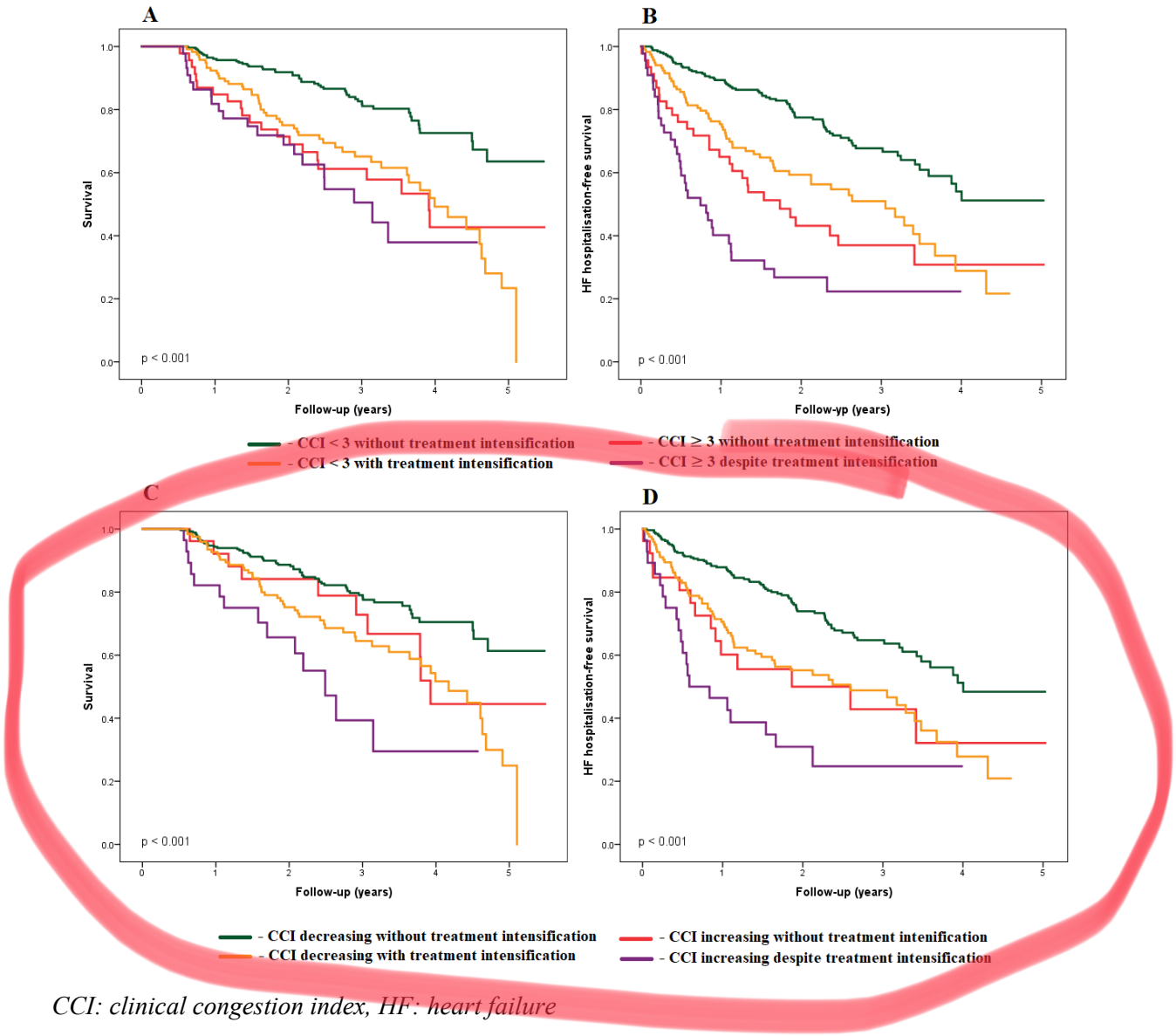
	HR	CI	p	HR	CI	p
Death after month 6						
Age (per year)	1.05	1.03–1.07	<0.001			
CAD	2.53	1.72; 3.72	<0.001			
Diabetes	1.65	1.20; 2.28	0.002			
PAOD	1.50	1.05; 2.14	0.027			
CKD	1.54	1.11; 2.14	0.010			
Anaemia at BL	1.66	1.19; 2.33	0.003			
Angina at BL	1.29	1.09; 1.52	0.003	1.29	1.05; 1.67	0.013
CCI at month 6 (per 1 point)	1.37	1.424; 1.52	<0.001			
sBP at month 6 (per 1 mmHg)	0.98	0.98; 0.99	<0.001	0.99	0.98; 0.999	0.029
Haemoglobin at month 6 (per 1 g/L)	0.98	0.97; 0.99	0.001			
QRS width at BL (lg10)	8.37	2.98; 23.49	<0.001			
NT-proBNP at month 6 (lg10)	6.55	4.43; 9.68	<0.001	5.58	3.42; 9.08	<0.001
LD dose at month 6 ≥ 80 mg	1.72	1.23; 1.40	0.002			
eGFR at month 6 (per 1 mL/min/1.73 m2)	0.98	0.97; 0.99	<0.001			
Charlson score (per 1 point)	1.28	1.17; 1.39	<0.001	1.16	1.03; 1.30	0.013
Male gender	0.66	0.47; 0.92	0.015			
6MWT distance at BL (lg10)	0.37	0.21; 0.68	0.001			
WRF	2.29	1.58; 3.32	<0.001			
Treatment intensification	1.85	1.34; 2.56	<0.001	1.75	1.19; 2.56	0.004
Death or HF hospitalisation after month 6						
Age (per year)	1.05	1.03; 1.07	<0.001	1.03	1.003; 1.050	0.029
CAD	2.08	1.54; 2.81	<0.001			
Diabetes	1.72	1.33–2.24	<0.001			
PAOD			n.s.			
CKD	1.74	1.33; 2.28	<0.001			
Anaemia at BL	1.54	1.16; 2.04	0.003			
Angina at BL	1.62	1.19; 2.20	0.002	1.19	1.002; 1.403	0.048
CCI at month 6 (per 1 point)	1.46	1.35; 1.61	<0.001	1.24	1.11; 1.38	<0.001
sBP at month 6 (per 1 mmHg)	0.99	0.98; 0.995	0.001	0.99	0.98; 0.998	0.018
Haemoglobin at month 6 (per 1 g/L)	0.98	0.98; 0.99	<0.001			
QRS width at BL (lg10)	4.54	1.55; 13.34	0.006			
NT-proBNP at month 6 (lg10)	5.12	3.67; 7.14	<0.001	2.82	1.85; 4.29	<0.001
LD dose at month 6 ≥ 80 mg	1.74	1.31; 2.31	<0.001			
eGFR at month 6 (per 1 mL/min/1.73 m2)	0.98	*0.97; 0.98*	<0.001			
Charlson score (per 1 point)	1.28	*1.19; 1.38*	<0.001	1.15	1.04; 1.28	0.006
Male gender			n.s.			
6MWT distance at BL (lg10)	0.30	0.19; 0.48	<0.001			
WRF	1.98	1.42; 2.78	<0.001			
Treatment intensification	2.09	1.59; 2.75	<0.001	1.69	1.22; 2.35	0.002

Treatment intensification is defined as the increase in loop diuretic dose over 6 months or loop diuretic and thiazide or thiazide-like diuretic co-administration

6MWT 6-min walk test distance, *BL* baseline, *CAD* coronary artery disease, *CCI* clinical congestion index, *CI* confidence interval, *CKD* chronic kidney disease, *eGFR* estimated glomerular filtration rate (chronic kidney disease epidemiology collaboration equation), *HF* heart failure, *HR* hazard ratio, *LD* loop diuretic, *LD*↑ loop diuretic dose up-titration over 6 months, *n.s.* not significant, *NT-proBNP* N-terminal pro B-type natriuretic peptide, *PAOD* peripheral arterial occlusive disease, *sBP* systolic blood pressure, *WRF* worsening renal function, defined as an increase in serum creatinine by ≥44.2 μmol/L over 6 months

Changes in CCI were observed in 442 patients (90% of 6-month-survivors). The decrease in CCI by at least 1 point without treatment intensification was noted in the majority of patients (265 (60%)). These patients had the best outcome (**Figures 2C, 2D**). One hundred and twenty-three (28%) patients underwent treatment intensification, resulting in decreasing CCI, whereas 26 (6%) patients experienced progressive congestion (an increase in CCI by at least 1 point) without treatment intensification. The latter two groups had comparable outcome (**Figures 2C, 2D**). Progressive congestion despite treatment intensification was noted in 28 (6%) patients. This subgroup demonstrated a very poor outcome (**Figures 2C, 2D**).

Figure 2. Kaplan-Meier curves of survival and heart failure hospitalisation-free survival, comparing patients receiving different strategies of diuretic administration and (A) – congestion status at month 6; (B) – congestion course over 6 months



CCI: clinical congestion index, HF: heart failure

Discussion

This study adds significantly to our understanding of the complex interaction between diuretic use, congestion and CHF outcome. 1) Intensification of pharmacological decongestion, but not the actual LD dose, was related to worse outcome in CHF. 2) The need of intensification of pharmacological decongestion is a marker of more advanced disease with worse clinical, biochemical and functional properties. 3) CHF outcome in patients with no or reduced congestion undergoing treatment intensification is at least as good as in patients with no treatment intensification but persistent congestion. These findings suggest that advanced CHF and congestion are the main drivers of poor outcome and not treatment with LD or thiazides *per se*.

The role of loop diuretics in heart failure care

Cardiac dysfunction-mediated renin-angiotensin-aldosterone system (RAAS) activation with consecutive sodium and water retention is a key component of CHF pathophysiology[10,20] and determines an unfavourable outcome[3,9,21,22]. To date, no other decongestive means have been shown to be superior to LD both in acute and chronic HF care[1,2,23,24]. The DOSE trial showed that LD are capable of reducing signs and symptoms of fluid accumulation in the setting of acute decompensation,[25]. However, their use, both acutely and long-term, has never been demonstrated to improve outcome in a well-designed prospective trial[1]. Despite that, this class of drugs is as often prescribed to CHF patients as evidence-based neurohormonal blockers[11]. Rohde et al. has recently demonstrated in a small though randomised, double-blinded clinical trial that LD withdrawal may be possible in stable CHF patients[26], but the trial was underpowered to assess hard outcome. Therefore, the clinical impact of such intervention needs to be further investigated. Still in daily clinical practice, decongestive interventions are rarely modified[27].

A post-hoc analysis of the DIG trial showed that LD users with CHF are more likely to be rehospitalised or to die than patients not taking these drugs[28]. This association between LD use and death persisted after propensity matching. Similar results were obtained from the JCARE-CARD database by Hamaguchi et al., who found an independent association between LD use after discharge and long-term adverse events[29]. Besides, high dose LD treatment has been demonstrated to limit the up-titration of ACE inhibitors[30] – the first-line drugs in HFrEF[2]. Other investigators analysed different HF populations and found similar relationship between LD use and mortality in a dose-dependent manner[12,13,31,32].

However, these studies share similar limitations. First, the authors did not include LD dose changes over time, but analysed different doses at a certain time-point only. Second, congestion status was not generally available for adjustment. Therefore, the most important parameter for the use of LD therapy and multivariable adjustment was often missing. Also, co-administration of thiazides to boost natriuresis was often not taken into consideration. The TIME-CHF database provides a unique opportunity to analyse the prognostic significance of LD use and CHF outcome taking into account these important factors. Contrary to previous findings, our data show that the actual dose of LD is not an independent predictor of adverse outcome. Instead, intensification of pharmacological decongestion – most likely a marker of clinical deterioration and persistent congestion – but not the LD dose itself independently predicted outcome. In fact, patients requiring treatment intensification were still more congested than patients without this need during the first 6 months of follow-up. In addition, they were already at a more advanced state of HF prior to adaptation of diuretic therapy. Also, if congestion was controlled with treatment intensification, the prognosis was better than in patients with obvious persistence of clinical congestion. Dini et al. have previously demonstrated that congested patients could potentially benefit from high LD doses[33]. This is in line with the CHAMPION trial where adjustments based on filling pressure mainly concerned diuretic therapy which resulted in better outcome[9]. These findings together with the results of this study highlight the importance of effective decongestion in CHF. It may be hypothesised that higher doses of LD or higher rate of thiazides' coadministration would have been effective to control congestion among patients with persistent congestion at month 6 and such interventions could have potentially translated into better outcome. The fact that many patients remained congested despite treatment intensification supports this hypothesis. Still, it needs to be tested in a prospective interventional trial to see if more aggressive decongestive therapy results in better outcome than the current, often cautious approach.

The importance of persistent congestion

Resistance to adequate LD doses is common[34]. Still, there is no general agreement regarding a universal definition of diuretic resistance, which may include the lack of diuretic response to an absolute high daily LD dose, or urinary output, weight loss, or urinary sodium excretion, as a response to a certain LD dose[35,36]. Regardless of the definition, patients with impaired LD response are known to be at increased risk of adverse events[1,34,35,37]. Still, the use of diuretic therapy differs significantly between centres[11] and reluctance to increase diuretic therapy due to potential negative effects on the kidneys is common[3]. These facts indicate that

interpretation of diuretic need in HF patients vary significantly and highlight the need for uniform recommendations on the use of decongestive therapies.

From a pharmacological point of view, increasing LD dose during chronic administration may be inevitable. If sodium reabsorption is inhibited in the distal loop of Henle, more sodium reaches the distal convoluted tubule, resulting in hypertrophy of the distal tubular cells[37]. These histological alterations lead to increased sodium reabsorption capacity of the distal part of the nephron[38]. Rao et al. have elegantly demonstrated that only approximately 35% of the LD–induced sodium delivered from the loop of Henle into the distal tubule ultimately ended up in the urine in HF patients, which is much less than in normal subjects[39]. Thus, distal nephron adaptation might be a reason for persistent congestion despite LD dose escalation. In this study, some patients were still congested at month 6, meaning that dose up-titration was not always sufficient. Co-administration of thiazides may be chosen to overcome distal tubular hypertrophy-mediated diuretic resistance. In TIME-CHF thiazide users were at a 2-fold increased risk of dying, but only 14% of patients were considered suitable for such therapy during the entire follow-up. Such adjustment was considered as treatment intensification and appeared as an independent predictor of outcome. Until interventional trials of thiazide and LD co-administration are conducted, the selection of potential candidates for such therapy relies on physician's discretion.

Does the renal function matter?

Significant WRF was present in 16% of patients over 6-months[19,40]. The decline in renal function identifies patients at high risk of rehospitalisation and mortality[10,14,19,40]. It has been shown that renal function may be an even stronger predictor of mortality than cardiac function in CHF patients[41]. On the one hand, WRF can be caused by the failing heart, because of venous and intraabdominal hypertension, and arterial blood pressure drop[20,42], called Type 2 cardiorenal syndrome[42]. On the other hand, treatment with LD can potentially lead to intravascular volume depletion and renal hypoperfusion, even in the presence of persistent interstitial fluid retention[1]. As WRF interacts with treatment, renal function and CHF prognosis, physicians are forced to modify treatment strategies. Still, there is no evidence-based consensus on how to react to WRF in CHF and how to adjust LD therapy. In the presence of acute kidney injury during acute decompensation, it was reported that LD dose down-titration or discontinuation was the most common treatment adjustment[43]. However, it is not clear whether this was justified, and in clinical practice it often remains uncertain, if renal function decline is related to hypo- or hypervolemia. It has been shown that WRF if accompanied with

successful haemoconcentration may even predict a better outcome[5], meanwhile the occurrence of WRF in patients with persistent congestion indicate a worse prognosis[44] in the setting of acute heart failure. The present study shows that remaining congestion is a clinically important problem in CHF patients, i.e. even in the chronic setting with the aim of target up-titration of medication and regular clinical controls. We previously reported that the need of chronically high doses of LD during the first months was related to poor outcome in TIME-CHF only if WRF was present[40]. Together with the findings of the present analysis, it may be hypothesised that reluctance to sufficiently decongest patients, e.g. in case of WRF, may result in poor outcome. However, the precise interaction between these three factors has not yet been prospectively studied, and our study has not the statistical power for full adjustment of all these factors including interactions. These complex interactions may be further complicated by the influence of non-haemodynamic factors on renal filtration, such as activation of RAAS, sympathetic nervous system, inflammation and endothelial dysfunction[45]. Also, clinical congestion has been recognised as a late manifestation of fluid retention in HF[4], meaning that a certain proportion of CHF patients may have no signs/symptoms of congestion, despite significant haemodynamic congestion[46].

Limitations

We acknowledge a number of potential limitations of our study. The results of the present analysis are based on an elderly CHF population, thus potentially limiting their generalizability. Also, the estimation of LD dose change took into account only the doses administered at baseline and month 6, excluding the effect of possible fluctuations and day-by-day variations. Still, considering daily medication changes as done in a previous analysis or intermediate changes between the different visits did not change the main findings of the study (data not shown)[40]. Since there is no known formula to calculate the diuretic effects of thiazides in combination with LD we did not consider the dose, although thiazide use-related potential harms might be dose-dependent. Also, information on intracardiac filling pressures was not available; therefore we had to rely on clinical congestion, which does not always reflect intravascular (haemodynamic) volume overload. However, we have previously shown that clinical congestion is a highly prevalent and powerful marker of outcome, potentially serving as a target for treatment with LD[3]. TIME-CHF participants were recruited from 2003 till 2008, i.e. before the introduction of angiotensin receptor-neprilysin inhibitor (ARNi) into CHF care. A recent secondary analysis of the PARADIGM-HF trial showed that treatment with ARNi can potentially reduce the need of LD[15]; still, the reduction in LD use 6 months after

randomisation was only 2%[15]. In addition, patients were not treated with sodium/glucose cotransporter 2 (sGLT-2) inhibitors, which very recently have been shown to improve outcome in HF patients with reduced ejection fraction[47,48]. The use of sGLT-2 inhibitors may change the role of diuretics in HF significantly, as they have a significant diuretic effect[49]. Also, TIME-CHF participants received close monitoring and strict follow-up regimen with effective escalation of evidence-based medications, making the intervention different from those usually seen in the real-world population. Besides, there was no data about the potential increase in tubular damage markers of patients with WRF. Finally, the size of the study was not sufficient for full adjustment of all relevant factors including interactions.

Conclusion

Treatment intensification but not the actual dose of LD was related to poor outcome in CHF. If treatment intensification translated into clinical decongestion, outcome was better than in case of persistent or progressing congestion. These findings suggest that HF and congestion are the main drivers of poor outcome and not the LD dose per se. There is an urgent need for prospective testing whether liberal use of LD or thiazide co-administration to completely decongest HF patients improves outcome.

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6

CHAPTER 6

BIOLOGICALLY ACTIVE ADRENOMEDULLIN (BIO-ADM) IS OF POTENTIAL VALUE IN IDENTIFYING CONGESTION AND SELECTING PATIENTS FOR NEUROHORMONAL BLOCKADE IN ACUTE DYSPNOEA

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Abstract

Purpose. This study was designed to evaluate the role of bio-ADM in congestion assessment and risk stratification in acute dyspnoea.

Methods. This is a sub-analysis of Lithuanian Echocardiography Study of Dyspnoea in Acute Settings. Congestion was assessed by means of clinical (peripheral oedema, rales) and sonographic (estimated right atrial pressure [eRAP]) parameters. Ninety-day mortality was chosen for outcome analysis.

Results. 1188 patients were included. Bio-ADM concentration was higher in patients with peripheral oedema at admission (48.2 [28.2-92.6] vs 35.4 [20.9-59.2] ng/L, $p < 0.001$). There was a stepwise increase in bio-ADM concentration with increasing prevalence of rales: 29.8 [18.8-51.1], 38.5 [27.5-67.1], and 51.1 [33.1-103.2] ng/L in patients with no rales, rales covering < ½, and ≥ ½ of the pulmonary area, respectively ($p < 0.001$). Bio-ADM concentration demonstrated gradual elevation in patients with normal, moderately, and severely increased eRAP: 25.1 [17.6-42.4] ng/L, 36.1 [23.1-50.2] and 47.1 [30.7-86.7] ng/L, respectively ($p < 0.05$). Patients with bio-ADM concentration > 35.5 ng/L were at more than two-fold increased risk of dying ($p < 0.001$). Survival in those with high bio-ADM was significantly modified by neurohormonal blockade at admission ($p < 0.05$), especially if NT-proBNP levels were lower than the median ($p = 0.002$ for interaction).

Conclusion. Bio-ADM reflects the presence and the degree of pulmonary, peripheral, and intravascular volume overload and is strongly related to 90-day mortality in acute dyspnoea. Patients with high bio-ADM levels demonstrated survival benefit from neurohormonal blockade.

Introduction

Dyspnoea accounts for 5% of total emergency department visits, two-thirds of which require hospitalisation[1]. The in-hospital mortality rate of dyspnoeic patients remains relatively high and reaches 5-6%[1,2]. Moreover, a half of acute dyspnoea patients are readmitted within 6 months, and readmission is closely related to a dramatically increased risk of death, irrespective of the initial cause of dyspnoea[3]. Conventional signs and symptoms accompanying dyspnoea are of limited value in differential diagnostics and risk stratification[4]. Moreover, the identification of patients at high risk is extremely difficult, as dyspnoeic patients with similar clinical pictures may have rather different outcome. Even more, initial treatment of acute dyspnoea patients often remains symptomatic, given the heterogeneous aetiologies and diverse pathophysiological processes behind this condition. Therefore, blood biomarkers are now being extensively investigated as decision-making support tools, not only guiding the allocation of medical care in the presence of limited resources[5], but also as measures for individualised treatment selection[6]. One of the novel biomarkers showing promising prognostic and congestion assessment properties[7-19] is biologically active adrenomedullin (bio-ADM)[20]. This study was designed to evaluate the role of circulating bio-ADM in congestion assessment and risk stratification of acute dyspnoea patients.

Methods

Study design

This is a sub-analysis of Lithuanian Echocardiography Study of Dyspnoea in Acute Settings (LEDA, NCT03048032). LEDA was a prospective observational multicentre study, performed in two academic centres in Lithuania between March 2015 and December 2017 in collaboration with a research protocol of international Global Research on Acute Conditions Team (GREAT) network. Consecutive adult patients admitted to an emergency department for acute dyspnoea were included, unless acute coronary syndrome was suspected within the first 4 hours of admission. Patient comorbidities, baseline medications, clinical signs and laboratory parameters at admission, early in-hospital treatment, medications at discharge or in-hospital death were recorded. Blood samples were taken within 4 hours of presentation, frozen at -80°C and sent to the INSERM UMR942 institute for centralized laboratory measurements of bio-ADM (SphingoTec GmbH, Hennigsdorf, Germany), N-terminal pro-B-type natriuretic peptide, and high-sensitive troponin T (NT-proBNP and Troponin T, Roche Diagnostics® GmbH, Mannheim, Germany). Bio-ADM was analysed using a novel immunoluminometric assay.

This immunoassay selectively detects the C-terminally amidated form of adrenomedullin as described elsewhere[20]. This study was approved by the national ethical committee and carried out according to the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants.

Diagnosis adjudication

Three cardiologists at each centre blinded to post-discharge outcomes adjudicated the cause of acute dyspnoea. All available records including medical history, symptoms and signs at admission, previous or admission natriuretic peptides, routine laboratory measurements and echocardiography were reviewed. Final diagnoses were classified as acute heart failure or non-acute heart failure. The later included chronic obstructive pulmonary disease (COPD) or asthma exacerbation, pulmonary embolism, pulmonary/non-pulmonary infections, cancer, among others.

Congestion status

Peripheral, pulmonary, and intravascular congestion status was determined by assessing the presence or absence of peripheral oedema, rales, and inferior vena cava (IVC) dilation and (or) reduction in collapsibility, respectively. IVC assessment was used to determine estimated right atrial pressure (eRAP): IVC diameter ≤ 2.1 cm and collapsing ≥ 50% - normal eRAP (3 mmHg); IVC diameter ≤ 2.1 cm and collapsing < 50% or IVC diameter > 2.1 cm and collapsing ≥ 50% - moderately elevated eRAP (8 mmHg); IVC diameter > 2.1 cm and collapsing < 50% - severely elevated eRAP (15 mmHg)[21].

Mortality follow-up

Death from any cause within 90 days after admission was chosen as an endpoint for survival analysis. The State Register of Death Cases and Their Causes provided data on mortality, therefore, there were no patients lost during follow-up.

Statistical analysis

Values are expressed as counts and frequencies for qualitative variables and as means and standard deviations or medians with interquartile range for quantitative variables, depending on the distribution. The $\chi 2$-test was used to compare categories. The means of continuous nonparametric variables were compared using the Mann-Whitney U or Kruskal-Wallis H test when appropriate. For group comparison, Dunn's pairwise tests adjusted using the Bonferroni correction was used. The Kaplan-Meier method was used to construct survival curves, with the log-rank test used for comparison among groups. Hazard ratios (HRs) with 95% confidence intervals (95% CIs) were derived from univariable and multivariable Cox regression models.

Qualitative variables were used for Cox regression only if their prevalence was ≥ 10%. For multivariable adjustment, a stepwise forward conditional model was used (inclusion $p \leq 0.05$, exclusion $p > 0.01$) with univariable predictors as potential candidates for multivariable adjustment, excluding active / recent cancer. Some univariable predictors were excluded from multivariable adjustment because of high multicollinearity risk. Univariable predictors that were considered for stepwise forward conditional model and the excluded predictors are listed in a **Supplementary Table 1**. Bio-ADM, NT-proBNP, and C-reactive protein (CRP) were log-transformed, and troponin T was categorised based on the median of 28 ng/L for Cox regression because of the distribution. HRs with the corresponding CIs were used to construct the Forest Plots. The P values for interaction in NT-proBNP <1799 ng/L and ≥ 1799 ng/L subgroups were obtained by means of a Cox proportional hazard model where the use of angiotensin converting enzyme inhibitor (ACEi) / angiotensin receptor blocker (ARB) and / or β-blocker (BB), bio-ADM subgroup, and neurohormonal blockade-by-subgroup were included as fixed-effect factors. Conditional inference tree-based survival analysis (hereinafter referred to as Survival tree) was used to analyse the prognostic value of bio-ADM. Survival tree is a non-linear machine-learning-based survival analysis. It classifies patients using machine-learning algorithms to determine prognostic importance of the input variables and their cut-off values. The method selects the variables with the strongest association to the outcome (with corresponding p values), implements a binary split based on the cut-off value and repeats these steps until groups (*nodes*) of different mortality risk (expressed by Kaplan-Meier curves) are produced. Univariate bed-side predictors of 90-day mortality were considered as the input variables for the survival tree analysis, including demographic data, comorbidities, chronic treatment, physical examination upon admission, and baseline conventional blood biomarkers. To discern the prognostic role of bio-ADM, three well-known confounding factors of outcome in acute dyspnoea were removed, namely cancer, age, and NT-proBNP level. To summarize, cancer patients were kept for the analysis of congestion, however they were removed for outcome analysis. Statistical analysis was performed with the use of the SPSS statistical package version 23.0 (SPSS Inc., Chicago, IL, USA), R version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria) with the statistical package 'party', and XLSTAT for Microsoft Excel (Addinsoft, Paris, France).

Results

Study population

Bio-ADM was available for 1188 patients (i.e., 81.6% of LEDA population). There were no differences in baseline characteristics between patients with bio-ADM available versus unavailable (**Supplementary Table 2**).

Baseline characteristics of the study population are detailed in **Table 1**. Most patients were elderly (median age 70 [62-79] years), and 57.7% of the cohort were male. Acute heart failure was confirmed for 643 (54%) patients and acute heart failure-unrelated acute dyspnoea was confirmed for 545 (46 %).

Table 1. Baseline characteristics of the study population stratified by the median bio-ADM concentration

Variables	N (%)	Total	bio-ADM <35.5 ng/L (n=594)	bio-ADM >35.5 ng/L (n=594)	p Value
Confirmed diagnosis					
AHF, n (%)	1188 (100)	643 (54.1)	263 (40.9)	380 (59.1)	**<0.001**
Non-AHF, n (%)	1188 (100)	545 (45.9)	330 (60.6)	215 (39.4)	**<0.001**
Demographics					
Age, years	1188 (100)	70 [62-79]	69 [59-78]	71 [64-79]	**0.001**
≥65 years, n (%)	1188 (100)	775 (65.2)	360 (60.8)	415 (69.9)	**0.001**
Male, n (%)	1188 (100)	685 (57.7)	337 (56.7)	348 (58.6)	0.557
Examination					
Heart rate, BPM	1167 (98.2)	88 [74-105]	84 [72-102]	90 [75-110]	**<0.001**
SBP, mmHg	1167 (98.2)	140 [123-159]	140 [127-160]	137 [120-157]	**0.001**
DBP, mmHg	1166 (98.1)	80 [71-90]	80 [74-90]	80 [70-90]	**0.004**
BMI, kg/m²	696 (58.6)	29.4 [25.4-34.5]	28.4 [24.9-32.6]	30.9 [26.1-37.0]	**<0.001**
Pulmonary rales, n (%)	1056 (88.9)	546 (51.7)	224 (43.1)	322 (60.1)	**<0.001**
Peripheral oedema, n (%)	483 (40.7)	264 (54.7)	105 (48.8)	159 (59.3)	**0.022**
Respiratory rate, breaths/minute	601 (50.6)	20 [16-22]	20 [16-22]	20 [17-23]	**0.008**
Axillary temperature, °C	567 (47.7)	36.7±0.6	36.6±0.5	36.8±0.7	**0.005**
Oxygen saturation (SpO_2), %	857 (72.1)	93 [89-96]	94 [90-96]	93 [88-96]	**0.001**
Medical history					
CHF, n (%)	1172 (98.7)	728 (62.1)	314 (53.6)	414 (70.4)	**<0.001**
Hypertension, n (%)	1172 (98.7)	927 (79.1)	450 (77.1)	477 (81.1)	0.098
CAD, n (%)	1172 (98.7)	413 (35.2)	187 (32.0)	226 (38.4)	**0.024**
Severe VHD or previous valvular surgery, n (%)	1172 (98.7)	213 (18.2)	84 (14.4)	129 (21.9)	**0.001**
Atrial fibrillation/flutter, n (%)	1172 (98.7)	513 (43.8)	197 (33.7)	316 (53.7)	**<0.001**
Pacemaker, n (%)	1172 (98.7)	148 (12.6)	69 (11.8)	79 (13.4)	0.429
Stroke, n (%)	1172 (98.7)	103 (8.8)	39 (6.7)	64 (10.9)	**0.013**
Diabetes, n (%)	1172 (98.7)	273 (23.3)	95 (16.3)	178 (30.3)	**<0.001**
Dyslipidaemia, n (%)	1172 (98.7)	322 (27.5)	155 (26.5)	167 (28.4)	0.513
Active/recent cancer, n (%)	1172 (98.7)	165 (14.1)	75 (12.8)	90 (15.3)	0.24

Table 1 (continued).

COPD/Asthma, n (%)	1172 (98.7)	235 (20.1)	129 (22.1)	106 (18.0)	0.302
Anaemia, n (%)	1172 (98.7)	258 (22.0)	91 (15.6)	167 (28.4)	**<0.001**
Medications before admission					
ACE inhibitors or ARB, n (%)	1172 (98.7)	545 (46.5)	274 (46.9)	271 (46.1)	0.815
β-blockers, n (%)	1172 (98.7)	591 (50.4)	269 (45.5)	322 (54.8)	**0.003**
Aldosterone antagonist, n (%)	1172 (98.7)	205 (17.5)	82 (14.0)	123 (17.9)	**0.002**
Loop diuretic, n (%)	1172 (98.7)	518 (44.2)	203 (34.8)	315 (53.6)	**<0.001**
Cardiac glycoside, n (%)	1172 (98.7)	70 (6.0)	22 (3.8)	48 (8.2)	**0.002**
Nitrate, n (%)	1172 (98.7)	90 (7.7)	45 (7.7)	45 (7.7)	1
Statin, n (%)	1172 (98.7)	149 (12.7)	83 (14.2)	66 (11.2)	0.136
Antiplatelets, n (%)	1172 (98.7)	280 (23.9)	141 (24.1)	139 (23.6)	0.891
Anticoagulants, n (%)	1172 (98.7)	325 (27.7)	129 (22.1)	196 (33.3)	**<0.001**
CCB, n (%)	1172 (98.7)	171 (14.6)	83 (14.2)	88 (15.0)	0.741
Inhaled steroid, n (%)	1172 (98.7)	73 (6.2)	44 (7.5)	29 (4.9)	0.07
β2 agonist, n (%)	1172 (98.7)	101 (8.6)	63 (10.8)	38 (6.5)	**0.009**
None of the above, n (%)	1172 (98.7)	249 (21.2)	138 (23.6)	111 (18.9)	0.054
Biomarkers					
bio-ADM (ng/L)	1188 (100)	35.5 [22.5-60.7]	22.5 [16.9-28.5]	60.7 [43.7-104.8]	**<0.001**
NT-proBNP (ng/L)	1187 (99.9)	1799 [451-5135]	859 [214-2833]	3238 [1229-8919]	**<0.001**
Troponin T (ng/L)	1187 (99.9)	28 [13-47]	20 [10-30]	31 [20-60]	**<0.001**
CRP (mg/L)	996 (83.8)	10.6 [3.6-33.5]	6.6 [2.3-22.7]	16.3 [5.8-48.8]	**<0.001**
Hb (g/L)	1128 (94.9)	131 [117-144]	134 [120-146]	128 [111-141]	**<0.001**
K (mmol/L)	1130 (95.1)	4.3 [4.0-4.6]	4.2 [3.9-4.5]	4.4 [4.0-4.7]	**<0.001**
Na (mmol/L)	1014 (85.4)	139 [136-141]	140 [137-141]	138 [135-141]	**<0.001**
Creatinine (µmol/L)	1107 (93.2)	94 [76-123]	84 [71-104]	109 [83-146]	**<0.001**

ACE = angiotensin-converting enzyme; ACS = acute coronary syndrome; AHF = acute heart failure; ARB = angiotensin-receptor blocker; bio-ADM = biologically active adrenomedullin; BMI = body mass index; BPM = beats per minute; CAD = coronary artery disease; CCB = calcium-channel blocker; CHF = chronic heart failure; COPD= chronic obstructive pulmonary disease; CRP = C-reactive protein; DBP = diastolic blood pressure; Hb = haemoglobin; K = potassium; MI = myocardial infarction; n = number of subjects; Na = sodium; NT-proBNP = N-terminal pro–B-type natriuretic peptide; SBP = systolic blood pressure; VHD = valvular heart disease

Plasma Bio-ADM and NT-proBNP in the study population

The median plasma bio-ADM concentration was 35.5 [22.5-60.7] ng/L. Baseline characteristics of patients stratified by the median of bio-ADM are shown in **Table 1**.

Patients with plasma bio-ADM concentration above 35.5 ng/L were older, had more frequent cardiovascular comorbidities and were more likely to exhibit clinical signs of congestion, namely rales and peripheral oedema (**Table 1**). Bio-ADM concentrations in patients with different causes of acute dyspnoea are depicted in a **Supplementary Figure 1.**

The median plasma NT-proBNP concentration in the study population was 1799 [451-5135] ng/L. NT-proBNP concentration in acute heart failure patients was higher than in non-acute

heart failure patients (3174 [1302-7611] vs 628 [167-2522] ng/L, respectively, p<0.001). NT-proBNP was also greater in patients with bio-ADM concentration above the median of 35.5 ng/L (p<0.001, **Table 1**).

Bio-ADM as a marker of congestion

Data about the presence or absence of peripheral oedema, pulmonary rales and ultrasound data on the size and collapsibility of IVC was available in 483 (40.7%), 1056 (88.9%) and 244 (20.5%) patients, respectively.

Peripheral Oedema

Plasma bio-ADM concentration was higher in patients with vs without peripheral oedema at admission (48.2 [28.2-92.6] vs 35.4 [20.9-59.2] ng/L, p<0.001, **Figure 1A**). Of note, plasma bio-ADM concentration in patients without documented oedema status was 33.0 [21.2-52.8] ng/L, which was similar to the value observed in patients with no peripheral oedema (p=0.694). NT-proBNP concentration was also higher in patients with peripheral oedema at admission 2954 [1098-7139] vs 1698 [412-4579] ng/L, p<0.001), **Figure 1B**).

Pulmonary Rales

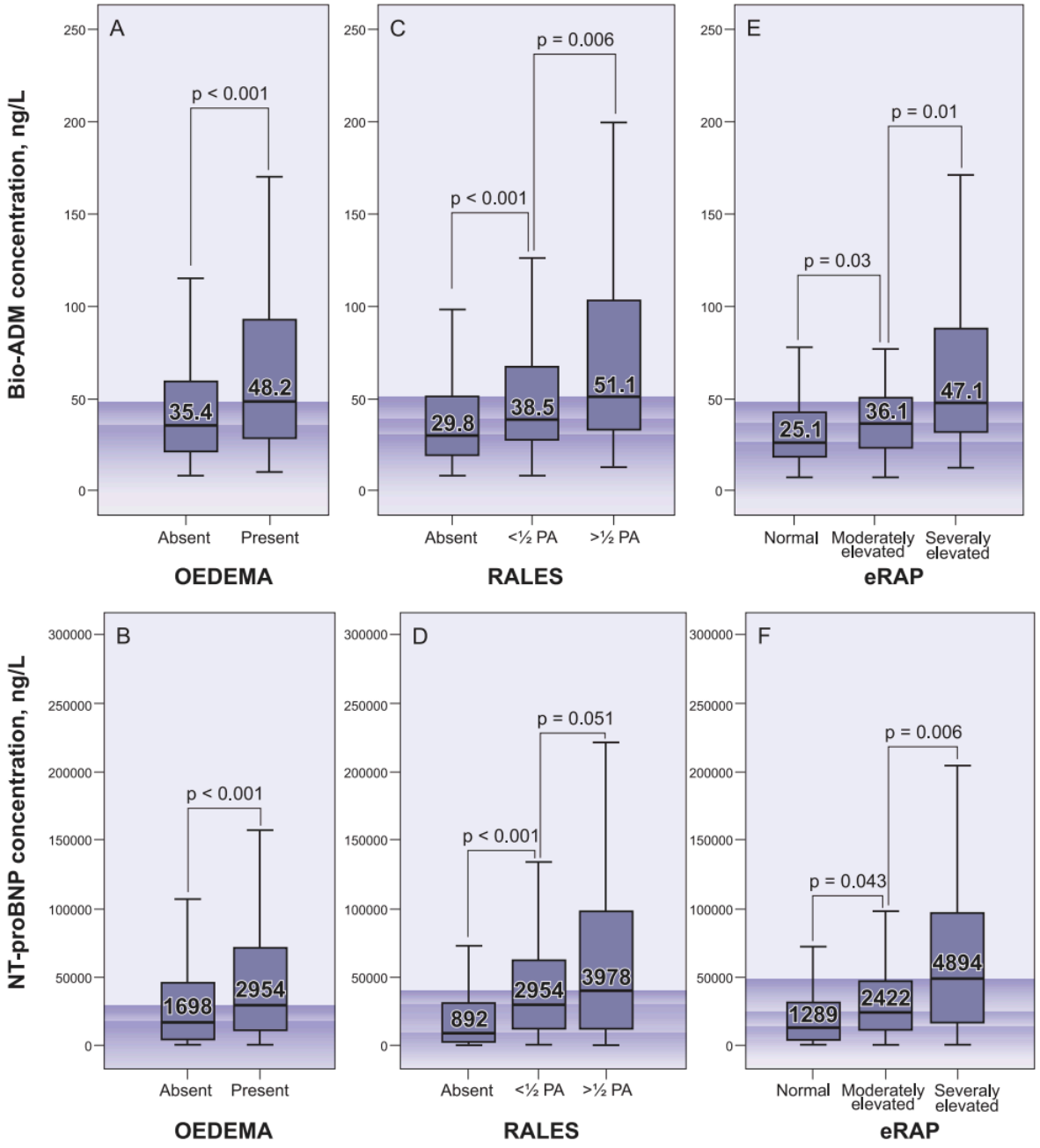
There were 510 (42.9%) patients with no rales at admission, 431 (36.3%) had rales covering less than ½ of the pulmonary area, 115 (9.7%) had rales covering more than ½ of the pulmonary area. Plasma bio-ADM concentrations in these three groups were 29.8 [18.8-51.1], 38.5 [27.5-67.1], and 51.1 [33.1-103.2] ng/L, respectively (p<0.001). In summary, the greater the extension of pulmonary rales, the greater the values of plasma bio-ADM (**Figure 1C**).

NT-proBNP concentration in patients without rales at admission was 892 [243-3082] ng/L. It was lower than in patients with rales covering less than ½ of the pulmonary area (2954 [1221-6231] ng/L, p<0.001, **Figure 1D**). However, no difference in NT-proBNP values was seen in patients with rales lower or greater than ½ of the pulmonary area (p=0.051).

Estimated right atrial pressure

The median bio-ADM concentration in patients undergoing IVC study was 37.5 [23.6-65.4] ng/L. A positive relationship between the level of eRAP and plasma bio-ADM concentration is depicted in **Figure 1E**. The lowest bio-ADM concentration was detected in patients with normal eRAP (25.1 [17.6-42.4] ng/L), while patients with moderately increased eRAP had high bio-ADM concentration (36.1 [23.1-50.2] ng/L, p=0.03). Patients with severely elevated eRAP had the highest median bio-ADM concentration (47.1 [30.7-86.7] ng/L, p<0.05 for both comparisons, **Figure 1E**).

Figure 1. Median concentrations of bio-ADM (A, C, E) and NT-proBNP (B, D, F) in patients with different signs and degree of congestion



Bio-ADM = circulating biologically active adrenomedullin; eRAP: estimated right atrial pressure; NT-proBNP = N-terminal pro–B-type natriuretic peptide; PA = pulmonary area

Figure 1F also shows incremental values of NT-proBNP with greater eRAP. Indeed, NT-proBNP concentration in patients with normal eRAP was 1289 [410-3142] ng/L which was lower than the concentration detected in patients with moderately elevated eRAP (2422 [1137-4703] ng/L, p=0.043. The highest NT-proBNP concentration was detected in patients with severely elevated eRAP (4894 [1669-9667] ng/L, p<0.05 for both comparisons, **Figure 1F**).

Bio-ADM and short-term prognosis

There were 176 deaths within 90 days (survival rate 85.2%). Baseline characteristics of patients alive or dead at day 90 are presented in a **Supplementary Table 3**.

Non-survivors were older (74 [65-82] vs 70 [61-78] years, p<0.001), their systolic and diastolic blood pressure as well as blood oxygen saturation at admission were lower (p<0.001). Non-survivors were also more likely to have a history of cancer (36.1 vs 10.4 %, p<0.001) and previous pulmonary embolism (10.7 vs 5.8 %, p=0.027).

Patients with bio-ADM concentration above the median (35.5 ng/L) were more likely to die or be rehospitalised within 90 days (**Supplementary Figure 2**).

Bio-ADM as a marker of survival

Log-transformed bio-ADM (bio-ADM [log10]) was identified as a univariable predictor of 90-day mortality: HR 4.52, 95% CI [3.21-6.35]. All univariable predictors of 90-day mortality are listed in a **Supplementary Table 1**. In a multivariable analysis bio-ADM (log10) remained a strong and independent predictor of 90-day survival: HR 3.52, 95% CI [2.16-5.74], p<0.001 (**Table 2**). Although more frequent in patients with high bio-ADM, atrial fibrillation did not appear as an independent predictor of mortality (**Table 2**). The area under the ROC curve for 90-day mortality was 0.65 [0.58-0.71], whereas the performance of NT-proBNP was worse (0.53 [0.46-0.61], **Supplementary Table 4**).

Bio-ADM and benefits of neurohormonal blockade

To further investigate the predictive value of bio-ADM among other confounding variables, we constructed a 90-day survival tree. The tree produced five distinct groups with significantly different death rates, as illustrated by Kaplan-Meier curves (**Figure 2**).

Table 2. Multivariable forward stepwise Cox regression analysis for 90-day survival

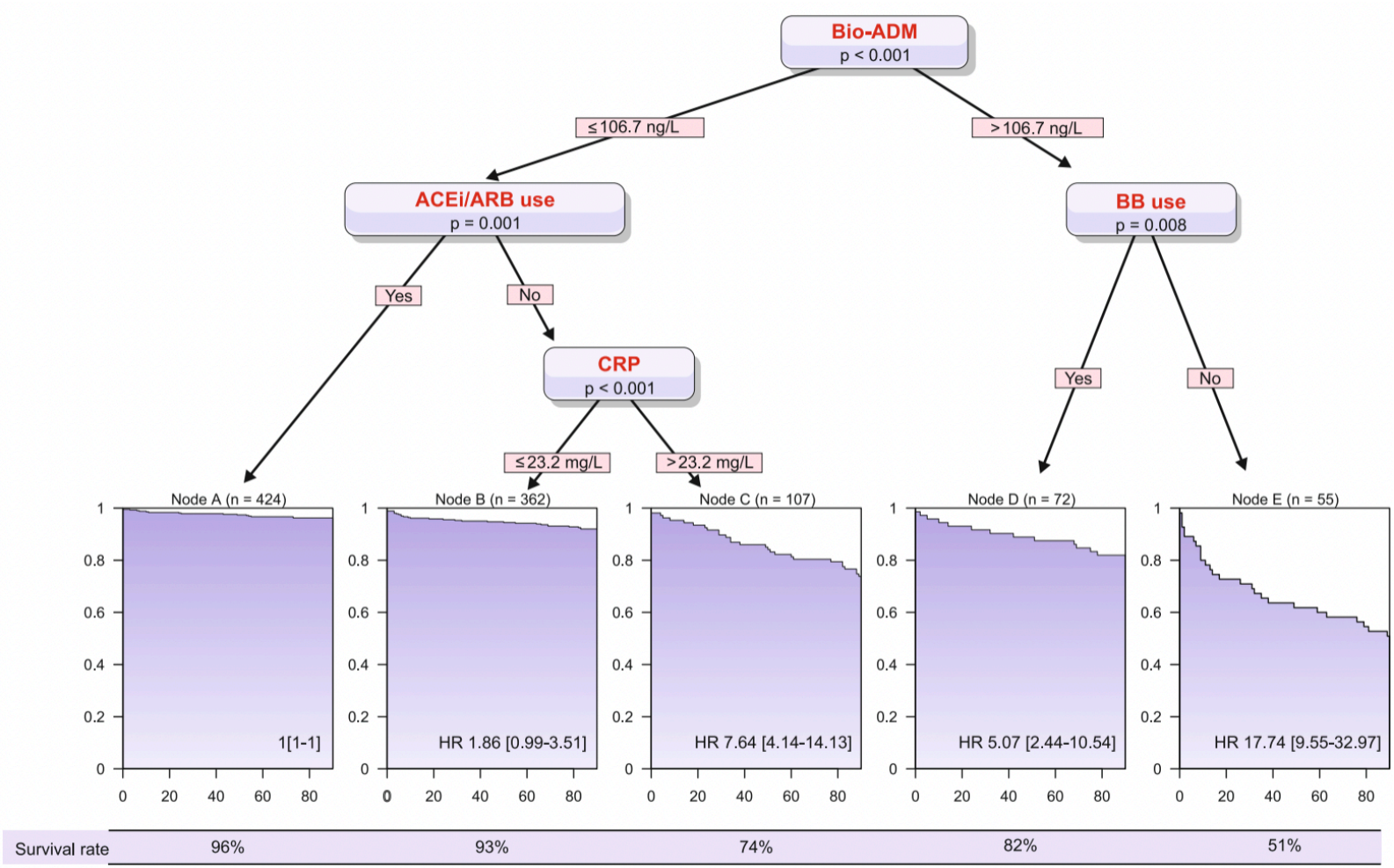
Variable	Wald	HR	95 % CI	p
Age, years	4.56	1.02	1.00-1.04	0.033
ACEi / ARB and / or BB use	7.36	0.56	0.37-0.85	0.007
Pacemaker history	5.51	0.33	0.13-0.83	0.019
Bio-ADM (log10)	17.64	2.98	1.79-4.95	<0.001
CRP (log10)	28.56	2.54	1.81-3.58	<0.001
Troponin (> median)	7.36	2.07	1.23-3.49	0.007

ACEi / ARB = ACE = angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker; BB = β-blocker; Bio-ADM = circulating biologically active adrenomedullin; CI = confidence interval; CRP = C-reactive protein; HR = hazard ratio; NT-proBNP = N-terminal pro–B-type natriuretic peptide

Bio-ADM, CRP, and the use of ACEi or ARB and BB on admission were selected by an unsupervised tree algorithm as important prognostic predictors. Bio-ADM was found to be the most potent predictor for mortality, with a cut-off value of 106.7 ng/L, distinguishing dyspnoeic patients with a low survival rate (**Figure 2**). Importantly, in patients with a bio-ADM level >106.7 ng/L, the use of BB on admission was associated with better outcome (**Figure 2**, Node D, HR 5.07, 95% CI [2.44-10.54]), meanwhile the survival of patients with bio-ADM level >106.7 ng/L and not on BB was extremely poor (**Figure 2**, Node E, HR 17.74, 95% CI [9.55-32.97]). In patients with bio-ADM level <106.7 ng/L, the use of ACEi/ARB on admission further improved survival (**Figure 2**, Node A, used as a reference group with the lowest risk of death within 90 days for comparison of HRs). In patients with bio-ADM <106.7 ng/L and no ACEi/ARB use on admission, the prognosis was additionally affected by the level of CRP: HR 7.64 (95% CI [4.14-14.3]) for Node C (CRP >23.2 mg/L) vs HR 1.86 (95% CI [0.99-3.51], for Node B (CRP ≤23.2 mg/L), **Figure 2**).

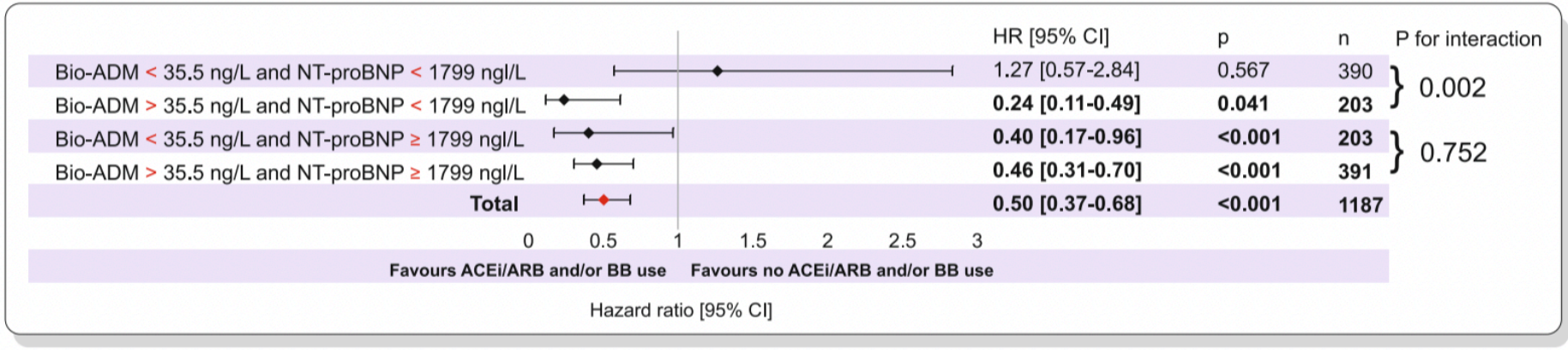
Based on the results of the survival tree analysis we further analysed the association between neurohormonal blockade on admission, the level of biomarkers and 90-day outcome. **Figure 3** shows that ACEi/ARB and/or BB users on admission had a 50% lower relative risk of dying within 90 days, as compared to patients not receiving those medications (HR 0.50, 95% CI [0.37-0.68], p<0.001, **Figure 3**). We found that the beneficial effect of neurohormonal blockade on admission was significantly associated with the biomarker profile. In particular, patients with both NT-proBNP and bio-ADM below the median value of 1799 ng/L and 35.5 ng/L, respectively, had no benefit from neurohormonal blockade, meanwhile patients with any of the two biomarkers above the median benefited from ACEi / ARB and / or BB use (**Figure 3**). The beneficial effect of neurohormonal blockade was prominent in acute heart failure patients (HR 0.37, 95% CI [0.24-0.59], p < 0.001), while in non-acute heart failure patients this beneficial association did not reach statistical significance (HR 0.72, 95% CI [0.48-1.08], p = 0.111, **Supplementary Figure 3**). Likewise, this effect was prominent in patients with low left ventricular ejection fraction, but not in patients with preserved left ventricular ejection fraction (**Supplementary Table 5**). Still, **Figure 3** further shows that the interaction between bio-ADM levels and the benefit of neurohormonal blockade was significant in patients with low NT-proBNP level at admission (p = 0.002).

Figure 2. Ninety-day survival tree of acute dyspnoea patients



ACEi / ARB = ACE = angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker; Bio-ADM = circulating biologically active adrenomedullin; CRP = C-reactive protein; HR = hazard ratio. HR comparison: Node A was selected as a reference node with the best survival rate. P = 0.054 for Node A vs Node B, p < 0.001 for Node A vs Node C, D, E

Figure 3. Forest Plots of 90-day all-cause mortality assessing the effect of neurohormonal blockade in patient subgroups divided by the median values of plasma bio-ADM and NT-proBNP



ACEi / ARB = ACE = angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker; BB = β-blocker; Bio-ADM = circulating biologically active adrenomedullin; CI = confidence interval; HR = hazard ratio; N = number; NT-proBNP = N-terminal pro–B-type natriuretic peptide

Discussion

The present study reveals a clear association between bio-ADM, congestion and prognosis in a large prospectively enrolled population of acute dyspnoea. Our results indicate that 1) plasma bio-ADM concentration reflects the presence and the degree of congestion as assessed by means of clinical and sonographic markers; 2) bio-ADM is a strong predictor of 90-day mortality in acute dyspnoea; and 3) high bio-ADM levels identify patients with a pronounced benefit of neurohormonal blockade.

Adrenomedullin was discovered in 1993[22]. Since then its inactive form - mid-regional pro-adrenomedullin (MR-proADM) - has been investigated in various medical conditions, including chronic and acute heart failure[23,24], community acquired pneumonia[25], respiratory tract infection[26], sepsis[27], COPD[28], pulmonary embolism[29], unselected patients admitted to an emergency department with any complaint[30-32], as well as patients with suspected infection[33], or acute dyspnoea[34-41]. All these studies uniformly related increased MR-proADM concentration with worse outcome. Only recently a new double monoclonal sandwich immunoassay has been developed to measure not the surrogate of ADM (MR-proADM), but its biologically active form (bio-ADM)[17,20]. It seems reasonable to assess not the precursor, but a biologically active form which can bind to its receptors and initiate biochemical reactions. Also, bio-ADM may be more time-dependent, meaning that it may better reflect fast-changing intracardiac/vascular haemodynamic derangements[42]. It has been previously reported that MR-proADM explains merely 30% of the variance in bio-ADM levels and the correlation between MR-proADM and bio-ADM is only moderate[18,43]. Also, bio-ADM correlates less strongly with age, NT-proBNP, and serum creatinine as compared to MR-proADM[18], therefore, the two biomarkers likely have different ability to reflect pathophysiological processes.

The pathophysiology of bio-ADM

Bio-ADM is secreted by various organs, but its main site of production is the vasculature[44]. Bio-ADM acts in the extravascular and intravascular spaces, inducing vasodilation and preserving endothelial integrity[43]. To some extent, bio-ADM is a compensatory protein, released in response to increased vascular permeability or dilation, including septic damage and volume overload[17]. The exact mechanism of bio-ADM release in not yet fully understood, but mechanical and humoral stimuli are believed to play their role in its secretion[45]. Its function

is to increase vascular capacitance and reduce vascular permeability, in turn leading to the prevention of vascular leakage and tissue oedema[17,45].

Bio-ADM and congestion

The relationship between volume overload and bio-ADM secretion makes it a potential marker of congestion. The present study reveals that plasma bio-ADM concentration is significantly higher in patients with peripheral (oedema), pulmonary (rales) and intravascular (IVC) congestion. Our findings are in line with the results of previous research, finding an association between clinical congestion and plasma bio-ADM concentration[15,16,46,47]. In a retrospective analysis of the PROTECT trial, bio-ADM was identified as a marker of residual clinical congestion at discharge after acute heart failure[47]. A sub-analysis of Aldo-DHF trial related plasma adrenomedullin levels with increasing E/e' and decreasing peak VO2 levels – two indirect markers of congestion - in heart failure with preserved ejection fraction (HFpEF)[48]. Our results extend these findings, demonstrating the relationship between the dilation and impaired collapsibility of IVC and high bio-ADM concentration.

In heart failure patients, bio-ADM and NT-proBNP are both elevated since NT-proBNP is released by the failing heart, which often leads to congestion. Our study delineates the properties of endothelial bio-ADM that are more related to vascular stretch and integrity, while NT-proBNP is related to cardiac wall stress. A recent research revealed that acute heart failure patients with high plasma bio-ADM level exhibit a much higher all-cause mortality if they are not on diuretics at discharge, whereas no interaction between plasma NT-proBNP level and diuretics at discharge was observed[18]. Our study showed that a significant number of acute dyspnoea patients have high bio-ADM, despite the fact that their plasma concentration of NT-proBNP is below 1799 ng/L. This indicates that bio-ADM and NT-proBNP are complementary in disclosing the mechanisms of fluid accumulation in a human body. Still, despite a well-established relationship between congestion and hard outcome[49], many patients do not receive optimal decongestive interventions[50].

Bio-ADM and treatment guidance

The relationship between plasma bio-ADM concentration and hard outcome in acute dyspnoea has recently been described[51]. Still, there are some major differences between the present analysis and the previously published data. In particular, LEDA participants were sicker, as reflected by the higher median values of prognostic biomarkers, including bio-ADM and NT-

proBNP. Also, systematic adjudication of the causes of acute dyspnoea is not reported, and echocardiographic data is also missing. Our results add to the already existing findings by demonstrating for the first time a clinically meaningful association between bio-ADM levels, neurohormonal blockade and survival. In particular, dyspnoeic patients with high bio-ADM benefited from neurohormonal blockade (ACEi/ARB and/or BB) on admission, even if their NT-proBNP concentration was low. Moreover, we revealed a significant interaction between plasma bio-ADM concentration, neurohormonal blockade and survival in dyspnoeic patients with low NT-proBNP concentration. These findings underscore the potential role of neurohormonal activation in acute dyspnoea, which is accompanied by endothelial dysfunction, resulting in worse outcome. Given the fact that neurohormonal blockers demonstrated a different effect on outcome depending on an individual biomarker profile, bio-ADM is of potential value in identifying acute dyspnoea patients suitable for neurohormonal suppression, which has been shown to improve outcome of patients with heart failure with reduced ejection fraction (HFrEF)[52]. Moreover, a recent sub-analysis of Aldo-DHF trial showed that treatment with spironolactone results in increasing adrenomedullin levels in HFpEF patients, again underscoring the role of bio-ADM in neurohumoral processes[48]. Even more, a recent research revealed a significant interaction between high bio-ADM level, diuretic treatment, and heart failure outcome[18]. This interaction was the strongest in patients with HFrEF, i.e. in patients with prevailing neurohumoral activation[18]. There exists a close relationship between neurohumoral activation and congestion pathophysiology[53], therefore, our results extend the current evidence of bio-ADM as a potential guide of personalised treatment.

Limitations

Given the observational nature of this analysis we were unable to test, whether interventions based on bio-ADM-derived risk stratification improve outcome. Also, the potential benefit of ACEi/ARB and/or BB in patients with high bio-ADM concentration is only hypothesis-generating and needs to be tested in a prospective interventional trial. In addition, we used the median bio-ADM concentration for exploratory purposes, but the optimal values of bio-ADM for future interventional trials need to be validated in other cohorts. While the present results were derived from a population enrolled in two academic centres in Europe, their applicability in other continents is not clear, given the previously reported differences in dyspnoeic populations between North America and Europe[54]. When analysing the relationship between

bio-ADM and congestion we had to rely on clinical and sonographic markers of congestion, as we were unable to stratify the patients based on actual intracardiac filling pressures. Still, the relationship between bio-ADM and systolic pulmonary artery pressure[7], and more recently mean right atrial, pulmonary artery and pulmonary capillary wedge pressures[42] has already been established. Also, we could not make any insights about the impact of bio-ADM-based decongestive approaches on congestion and hard outcome. Another limitation might be the absence of reclassification analysis to assess incremental value of bio-ADM on top of NT-proBNP. However, bio-ADM but not NT-proBNP showed its independent association with outcome, limiting the role of reclassification analysis in the present setting.

Future directions

The present research creates a background for various future clinical trials. In particular, parallel changes of bio-ADM and clinical signs of congestion might be evaluated before and after administration of diuretic treatment. Also, future prospective randomized interventional trials might confirm that decongestion based on the reduction in bio-ADM is associated with improved outcome. Furthermore, the benefit of combining measures of bio-ADM and NT-proBNP in light of congestion assessment, grading and treatment adjustment should be confirmed. The role of bio-ADM in a multimarker congestion management approach should also be prospectively evaluated, given the already recognized advantages of integration of biomarkers and imaging[55]. In another hand, ongoing trials are assessing the survival benefits of modulating bio-ADM pathway using non-neutralizing antibodies in sepsis[56]. Future research needs to assess whether modulation of bio-ADM pathway might also improve outcome in acute dyspnoea. Innovative machine learning-based strategies are being investigated and applied in emergency medicine[57]. These approaches look attractive, given the understaffing issue and the overcrowded emergency settings worldwide. Powerful blood biomarkers, including a combination of bio-ADM and NT-proBNP, can serve as a substrate for future machine learning-based algorithms. Bio-ADM could also be used in future clinical trials of acute dyspnoea as an inclusion criterion as well as an exploratory outcome, given its close relationship with hard outcome. Finally, the value of neurohumoral blockade in acute dyspnoea should be prospectively evaluated since this interaction is clinically meaningful and has a potential of personalized medicine.

Conclusions

Bio-ADM seems to be a reliable circulating biomarker of congestion, reflecting pulmonary, peripheral and intravascular volume overload. Bio-ADM is a strong predictor of 90-day mortality in acute dyspnoea patients. High bio-ADM concentration identified those acute dyspnoea patients who benefited the most from the use of neurohormonal blockers.

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SUPPLEMENTS

Supplementary Table 1. Univariable predictors of 90-day mortality

	n	HR	95% CI	p
Univariate predictors considered for the stepwise forward conditional model				
Age, years	1188	1.02	1.01-1.04	<0.001
ACEi / ARB and / or BB use	1172	0.50	0.37-0.68	<0.001
Statin use	1172	0.24	0.11-0.54	0.001
Obesity	1172	0.62	0.43-0.90	0.011
Pacemaker history	1172	0.46	0.25-0.85	0.013
Rales	1056	1.65	1.19-2.30	0.003
SBP (mmHg)	1167	0.98	0.97-0.99	<0.001
Oxygen saturation (%)	857	0.96	0.95-0.98	<0.001
Bio-ADM (log10)	1188	4.52	3.21-6.35	<0.001
NT-proBNP (log10)	1188	1.92	1.55-2.39	<0.001
Troponin T (> median)	1188	3.08	2.20-4.31	<0.001
C-reactive protein (log10)	996	3.35	2.63-4.28	<0.001
Sodium (mmol/l)	1014	0.93	0.91-0.96	<0.001
Creatinine (log10)	1107	3.33	1.70-6.54	<0.001
Haemoglobin (mmol/l)	1128	0.87	0.81-0.92	<0.001
Univariate predictors excluded from the stepwise forward conditional model				
Beta blocker use	1172	0.50	0.37-0.69	<0.001
ACEi / ARB use	1172	0.50	0.36-0.69	<0.001
Hypertension	1172	0.48	0.35-0.66	<0.001
Dyslipidaemia	1172	0.46	0.30-0.69	<0.001
Active / recent cancer	1172	4.08	2.98-5.59	<0.001
Anaemia	1172	1.57	1.13-2.18	0.007
Peripheral oedema	483	0.63	0.41-0.96	0.034
DBP (mmHg)	1166	0.97	0.96-0.98	<0.001
Respiratory rate (BPM)	601	1.06	1.02-1.10	0.001
Urea (mmol/l)	709	1.05	1.03-1.07	<0.001

ACEi / ARB = ACE = angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker; BB = β-blocker; Bio-ADM = circulating biologically active adrenomedullin; BPM: breaths per minute; CI = confidence interval; CRP = C-reactive protein; DBP: diastolic blood pressure; HR = hazard ratio; N = number; NT-proBNP = N-terminal pro–B-type natriuretic peptide, SBP = systolic blood pressure

Supplementary Table 2. Comparison of baseline characteristics between patients included in the present sub-analysis and the entire LEDA population

Variables	LEDA population n=1455 (%)	Bio-ADM population n=1188 (%)	p
Confirmed diagnosis			
AHF, n (%)	761 (52.3)	643 (54.1)	0.209
Non-AHF, n (%)	694 (47.7)	545 (45.9)	0.209
Demographics			
Age, years	71 [62-79]	70 [62-79]	0.838
≥65 years, n (%)	955 (65.6)	775 (65.2)	0.772
Male, n (%)	824 (56.6)	685 (57.7)	0.475
Examination			
Heart rate, BPM	88 [73-104]	88 [74-105]	0.905
SBP, mmHg	140 [123-160]	140 [123-159]	0.837
DBP, mmHg	80 [71-90]	80 [71-90]	1.000
BMI, kg/m²	29.4 [23.4-34.4]	29.4 [25.4-34.5]	0.966
Pulmonary rales, n (%)	651 (50.3)	546 (51.7)	0.351
Peripheral oedema, n (%)	299 (52.5)	264 (54.7)	0.351
Respiratory rate, breaths/minute	20 [16-22]	20 [16-22]	0.332
Axillary temperature, °C	36.7±0.6	36.7±0.6	0.847
Oxygen saturation (SpO_2), %	94 [89-96]	93 [89-96]	0.355
Medical history			
CHF, n (%)	877 (61.4)	728 (62.1)	0.601
Hypertension, n (%)	1120 (78.4)	927 (79.1)	0.55
CAD, n (%)	495 (34.6)	413 (35.2)	0.666
Severe VHD or previous valvular surgery, n (%)	277 (19.4)	213 (18.2)	0.295
Atrial fibrillation/flutter, n (%)	618 (43.2)	513 (43.8)	0.717
Pacemaker, n (%)	169 (11.8)	148 (12.6)	0.395
Stroke, n (%)	128 (9.0)	103 (8.8)	0.84
Diabetes, n (%)	324 (22.7)	273 (23.3)	0.612
Dyslipidaemia, n (%)	390 (27.3)	322 (27.5)	0.888
Active/recent cancer, n (%)	204 (14.3)	165 (14.1)	0.847
Asthma/COPD, n (%)	275 (19.2)	235 (20.1)	0.483
Anaemia, n (%)	331 (22.7)	258 (22.0)	0.833
Medication before admission			
ACE inhibitors or ARB, n (%)	650 (45.5)	545 (46.5)	0.499
β-blocker, n (%)	713 (49.9)	591 (50.4)	0.734
Aldosterone antagonist, n (%)	243 (17.0)	205 (17.5)	0.665
Loop diuretic, n (%)	615 (43.1)	518 (44.2)	0.434

Supplementary Table 2 (continued)

Cardiac glycoside, n (%)	74 (5.1)	70 (6.0)	0.222
Nitrate, n (%)	106 (7.3)	90 (7.7)	0.738
Statin, n (%)	184 (12.9)	149 (12.7)	0.861
Antiplatelet, n (%)	335 (23.5)	280 (23.9)	0.727
Anticoagulant, n (%)	390 (27.3)	325 (27.7)	0.747
CCB, n (%)	212 (14.8)	171 (14.6)	0.806
Inhaled steroid, n (%)	80 (5.6)	73 (6.2)	0.351
β2 agonist, n (%)	115 (8.1)	101 (8.6)	0.478
None of the above, n (%)	313 (21.9)	249 (21.2)	0.578
Biomarkers			
bio-ADM (ng/L)	35.5 [22.5-60.7]	35.5 [22.5-60.7]	1.000
NT-proBNP (ng/L)	1828 [453-5305]	1799 [451-5143]	0.934
Troponin T (ng/L)	27 [13-48]	28 [13-47]	0.946
CRP (mg/L)	10.3 [3.5-33.8]	10.6 [3.6-33.5]	0.892
Hb (g/L)	131 [116-144]	131 [117-144]	0.912
K (mmol/L)	4.3 [4.0-4.7]	4.3 [4.0-4.6]	0.655
Na (mmol/L)	139 [136-141]	139 [136-141]	0.905
Creatinine (µmol/L)	94 [75-122]	94 [76-123]	0.830

ACE = angiotensin-converting enzyme; ACS = acute coronary syndrome; AHF = acute heart failure; ARB = angiotensin-receptor blocker; bio-ADM = biologically active adrenomedullin; BMI = body mass index; BPM = beats per minute; CAD = coronary artery disease; CCB = calcium-channel blocker; CHF = chronic heart failure; COPD= chronic obstructive pulmonary disease; CRP = C-reactive protein; DBP = diastolic blood pressure; Hb = haemoglobin; K = potassium; MI = myocardial infarction; n = number of subjects with available data; Na = sodium; NT-proBNP = N-terminal pro–B-type natriuretic peptide; SBP = systolic blood pressure; VHD = valvular heart disease

Supplementary Table 3. Baseline characteristics of the 90-days survivors and non-survivors

Variables	N (%)	Dead (n = 176)	Alive (n=1012)	p Value
Confirmed diagnosis				
AHF, n (%)	643 (54.1)	74 (42.0)	569 (56.2)	<0.001
Non-AHF, n (%)	545 (45.9)	102 (58)	443 (43.8)	<0.001
Demographics				
≥65 years, n (%)	1188 (100)	136 (77.3)	677 (66.9)	0.006
Male, n (%)	1188 (100)	113 (64.2)	572 (56.5)	0.058
Examination				
Heart rate, BPM	1167 (98.2)	93 [80-106]	87 [73-105]	0.018
SBP, mmHg	1167 (98.2)	130 [110-144]	140 [125-160]	<0.001
DBP, mmHg	1166 (98.1)	77 [65-85]	80 [73-90]	<0.001
BMI, kg/m²	696 (58.6)	29.6 [25.6-34.6]	29.0 [23.7-33.2]	0.106
Pulmonary rales, n (%)	1056 (88.9)	94 (62.7)	452 (49.9)	0.005
Peripheral oedema, n (%)	483 (40.7)	37 (44.6)	227 (56.8)	0.052
Respiratory rate, breaths/minute	601 (50.6)	20 [18-24]	20 [16-22]	<0.001
Axillary temperature, °C	567 (47.7)	36.8±0.7	36.7±0.6	0.342
Oxygen saturation (SpO_2), %	857 (72.1)	91 [87-94]	94 [90-96]	<0.001
Medical history				
CHF, n (%)	1172 (98.7)	102 (60.4)	626 (62.4)	0.608
Hypertension, n (%)	1172 (98.7)	112 (66.3)	815 (81.3)	<0.001
CAD, n (%)	1172 (98.7)	52 (30.8)	361 (36.0)	0.193
Severe VHD or previous valvular surgery, n (%)	1172 (98.7)	34 (20.1)	179 (17.8)	0.518
Atrial fibrillation/flutter, n (%)	1172 (98.7)	69 (40.8)	444 (44.3)	0.451
Pacemaker, n (%)	1172 (98.7)	11 (6.5)	137 (13.7)	0.008
Stroke, n (%)	1172 (98.7)	21 (12.4)	82 (8.2)	0.078
Diabetes, n (%)	1172 (98.7)	35 (20.7)	238 (23.7)	0.432
Dyslipidaemia, n (%)	1172 (98.7)	26 (15.4)	296 (29.5)	<0.001
Active/recent cancer, n (%)	1172 (98.7)	61 (36.1)	104 (10.4)	<0.001
COPD/Asthma, n (%)	1172 (98.7)	33 (20.7)	200 (20.0)	0.423
Anaemia, n (%)	1172 (98.7)	86 (50.9)	337 (33.6)	<0.001
Medication before admission				
ACE inhibitors or ARB, n (%)	1172 (98.7)	53 (31.4)	492 (49.1)	<0.001
Beta blockers, n (%)	1172 (98.7)	59 (34.9)	532 (53.0)	<0.001
Aldosterone antagonist, n (%)	1172 (98.7)	24 (14.2)	181 (18.0)	0.273
Loop diuretic, n (%)	1172 (98.7)	65 (38.5)	453 (45.2)	0.112
Cardiac glycoside, n (%)	1172 (98.7)	12 (7.1)	58 (5.8)	0.484
Nitrate, n (%)	1172 (98.7)	9 (5.3)	81 (8.1)	0.274
Statin, n (%)	1172 (98.7)	6 (3.6)	143 (14.3)	<0.001

Supplementary Table 3 (continued)

Antiplatelets, n (%)	1172 (98.7)	30 (17.8)	250 (24.9)	0.051
Anticoagulants, n (%)	1172 (98.7)	38 (22.5)	287 (28.6)	0.114
CCB, n (%)	1172 (98.7)	17 (10.1)	154 (15.4)	0.077
Inhaled steroid, n (%)	1172 (98.7)	8 (4.7)	65 (6.5)	0.491
Beta2 agonist, n (%)	1172 (98.7)	13 (7.7)	88 (8.8)	0.767
None of the above, n (%)	1172 (98.7)	50 (29.6)	199 (19.8)	0.006
Biomarkers				
bio-ADM (ng/L)	1188 (100)	58.2 [31.7-121.7]	33.0 [21.7-54.6]	<0.001
NT-proBNP (ng/L)	1187 (99.9)	3547 [1036-10846]	1654 [419-4660]	<0.001
Troponin T (ng/L)	1187 (99.9)	42 [21-80]	22 [10-40]	<0.001
CRP (mg/L)	996 (83.8)	34.7 [14.5-86.2)	8.7 [3.1-27.0]	<0.001
Hb (g/L)	1128 (94.9)	122 [107-140]	132 [118-145]	<0.001
K (mmol/L)	1130 (95.1)	4.2 [3.9-4.7]	4.3 [4.0-4.6]	0.318
Na (mmol/L)	1014 (85.4)	137 [133-140]	139 [136-141]	<0.001
Creatinine (µmol/L)	1107 (93.2)	105 [77-145]	93 [75-120]	0.008

ACE = angiotensin-converting enzyme; ACS = acute coronary syndrome; AHF = acute heart failure; ARB = angiotensin-receptor blocker; bio-ADM = biologically active adrenomedullin; BMI = body mass index; BPM = beats per minute; CAD = coronary artery disease; CCB = calcium-channel blocker; CHF = chronic heart failure; COPD= chronic obstructive pulmonary disease; CRP = C-reactive protein; CRT =cardiac resynchronization therapy; DBP = diastolic blood pressure; Hb = haemoglobin; K = potassium; MI = myocardial infarction; n = number of subjects with available data; Na = sodium; NT-proBNP = N-terminal pro–B-type natriuretic peptide; PAD = peripheral artery disease; SBP = systolic blood pressure; VHD = valvular heart disease

Supplementary Table 4. The performance of bio-ADM and NT-proBNP in 90-day mortality prediction as assessed by the Area under the curve (AUC) of Receive characteristic operator (ROC) analysis

Ninety-day mortality prediction										
Biomarker	**Value**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**LR +**	**LR -**	**AUC**	**You-den index**	**Diagnos-tic odds ratio**
Bio-ADM	42,2	0.65 [0.58-0.71]	0.65 [0.62-0.68]	0,24	0,91	1,83	0,55	0.68 [0.63-0.72]	0,29	3,35
NT-proBNP	3206	0.53 [0.46-0.61]	0.67 [0.64-0.70]	0,22	0,89	1,61	0,70	0.64 [0.59-0.68]	0,20	2,310

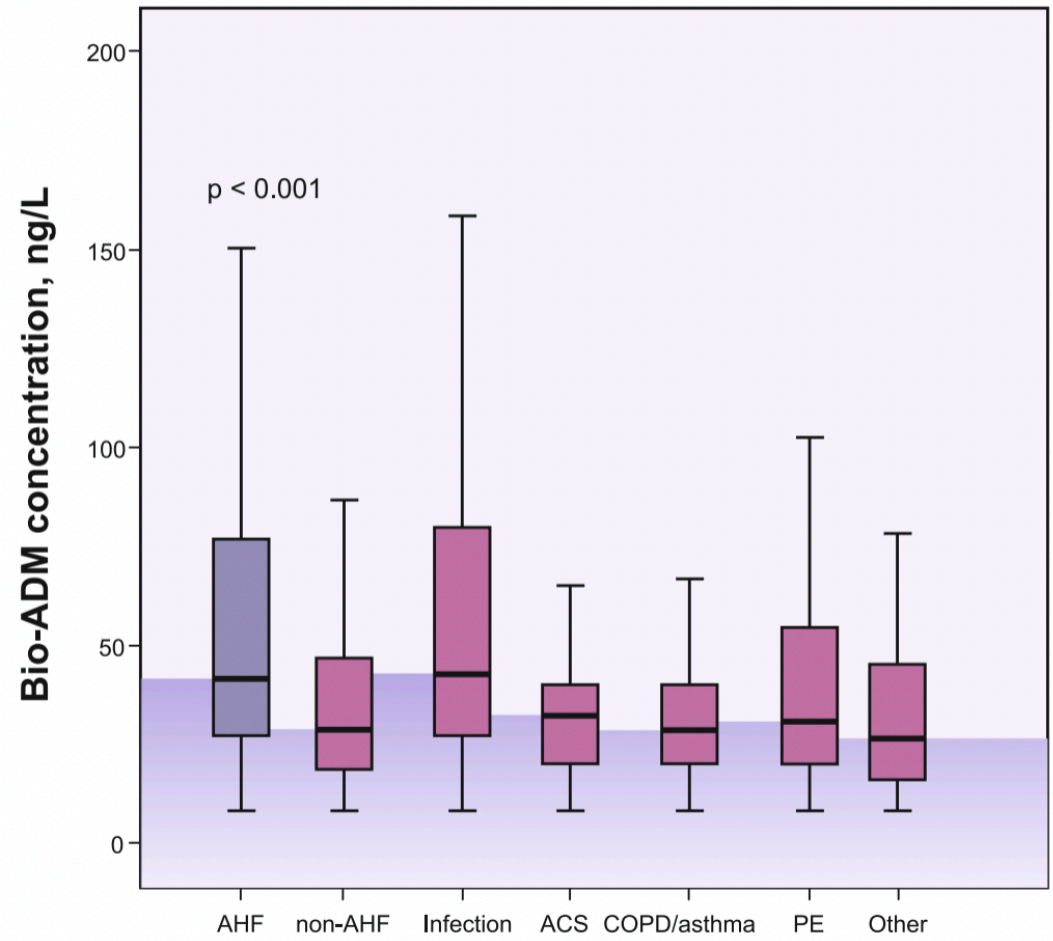
AUC = area under the curve; Bio-ADM = circulating biologically active adrenomedullin; LR- = negative likelihood ratio; LR+ = positive likelihood ratio; NPV = negative predictive value; NT-proBNP = N-terminal pro–B-type natriuretic peptide; PPV = positive predictive value

Supplementary Table 5. The effect of neurohormonal blockade on 90-day all-cause mortality in patients with different biomarker profiles, based on left ventricular ejection fraction category

LVEF ≥ 50 %				
Biomarker profile	HR [CI]	p	n	Total number of events
Bio-ADM < median, NT-proBNP < median	0.307 [0.079-1.188]	0,087	206	11 (5.3 %)
Bio-ADM > median, NT-proBNP < median	0.719 [0.216-2.387]	0,59	99	12 (2.1 %)
Bio-ADM < median, NT-proBNP ≥ median	0.528 [0.118-2.361]	0,404	77	7 (9%)
Bio-ADM > median, NT-proBNP ≥ median	0.446 [0.198-1.005]	0,052	108	24 (22.2 %)
Total	0.589 [0.343-1.012]	0,055	490	54 (11.0 %)
LVEF < 50 %				
Biomarker profile	HR [CI]	p	n	Total number of events
Bio ADM < median, NT-proBNP < median	1.251 [0.151-10.393]	0,836	81	7 (8.6 %)
Bio ADM > median, NT-proBNP < median	**0.074 [0.008-0.665]**	**0,02**	**55**	**5 (9.1 %)**
Bio ADM < median, NT-proBNP ≥ median	0.381 [0.116-1.248]	0,11	99	11 (11.1 %)
Bio ADM > median, NT-proBNP ≥ median	**0.505 [0.285-0.895]**	**0,019**	**222**	**47 (21.2 %)**
Total	**0.413 [0.259-0.660]**	**<0.001**	**457**	**70 (15.3 %)**

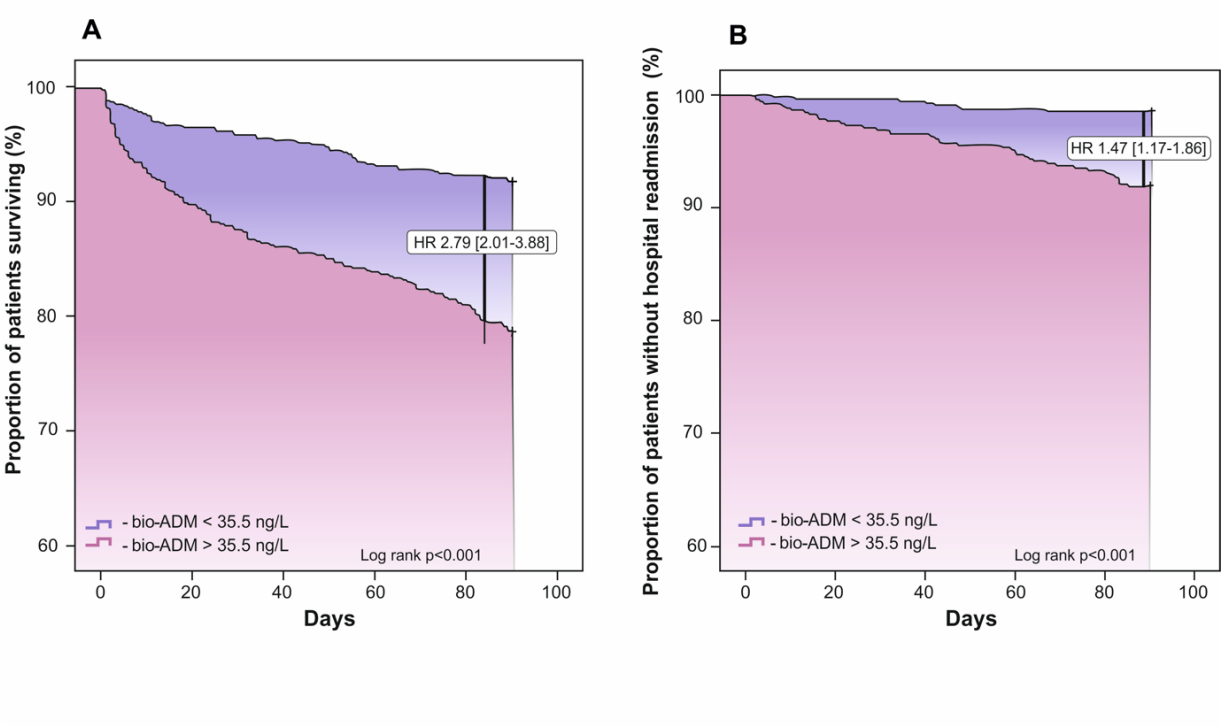
Bio-ADM = circulating biologically active adrenomedullin; CI = confidence interval; HR = hazard ratio; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro–B-type natriuretic peptide

Supplementary Figure 1. The comparison of median bio-ADM concentration among patients with different causes of acute dyspnoea



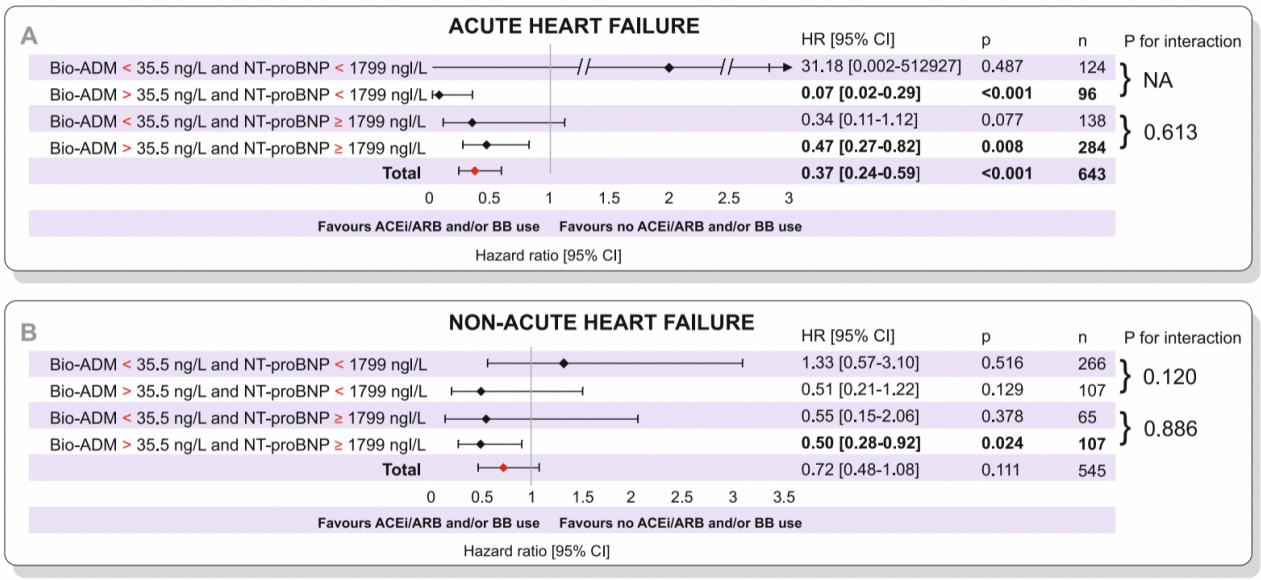
The median plasma bio-ADM concentration in AHF patients was 41.8 [18.8-46.8] ng/L and in non-AHF patients 28.6 [18.8-46.8] ng/L. In the non-AHF group, the median plasma bio-ADM concentrations based on adjudicated diagnosis were: 41.2 [24.8-84.6] ng/L in infection, 28.7 [19.5-39.8] ng/L in acute coronary syndrome, 27.7 [18.8-38.7] ng/L in chronic obstructive pulmonary disease/asthma, 26.3 [18.8-44.7] ng/L in pulmonary embolism, 25.0 [16.3-43.5] ng/L in other causes. ACS = acute coronary syndrome; AHF = acute heart failure; bio-ADM = biologically active adrenomedullin; COPD = chronic obstructive pulmonary disease; PE = pulmonary embolism

Supplementary Figure 2. Kaplan Meier curves of survival (A) and freedom from rehospitalization (B) comparing acute dyspnoea patients with plasma bio-ADM level above vs below the median level of 35.5 ng/L



Supplementary Figure 3. Forest Plots of 90-day all-cause mortality comparing the effect of treatment with ACEi/ARB and (or) β-blocker in patients with different plasma NT-proBNP and bio-ADM profiles

A) Acute heart failure population; B) Non-acute heart failure population



ACEi / ARB = ACE = angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker; BB = β-blocker; *Bio-ADM = circulating biologically active adrenomedullin;* CI = confidence interval; *HR = hazard ratio;* N = number; NA = not available; *NT-proBNP = N-terminal pro–B-type natriuretic peptide*

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CHAPTER 7

SOLUBLE CD146 – AN UNDERREPORTED NOVEL BIOMARKER OF CONGESTION: A COMMENT ON A REVIEW CONCERNING CONGESTION ASSESSMENT AND EVALUATION IN ACUTE HEART FAILURE

Simonavičius J, Mikalauskas A, Brunner-La Rocca HP. Heart Fail Rev. 2021 May;26(3):731-732

Abstract

In spite of high prevalence, congestion remains a poorly understood phenomenon in heart failure pathophysiology. Its negative impact on outcome has been widely recognised. Still, data from various registries reveal the failure of the contemporary treatment strategies to overcome congestion. This shortcoming is closely related to the fact that there are no universe means for congestion assessment and grading, making it a difficult process to recognise. CD146 is a novel blood biomarker of congestion, that has been shown to reflect intravascular fluid accumulation in a number of experimental and clinical studies. This observation deserves special attention, given the huge gap of knowledge about decongestive strategies in acute and chronic heart failure. Randomised clinical trials testing the effect of CD146-guided management intervention are urgently needed to estimate its value in heart failure care.

We read with great interest the review article entitled ‘Congestion occurrence and evaluation in acute heart failure scenario: time to reconsider different pathways of volume overload’ by Palazzuoli et al. in Heart Failure Reviews[1]. Although the authors extensively review the complex phenomenon of fluid accumulation in acute heart failure, the section concerning novel applications of congestion assessment and grading lacks comprehensiveness. In particular, soluble cluster of differentiation (sCD146) – an emerging blood biomarker for congestion assessment – is not reviewed.

CD146 is found across the whole vasculature and its soluble form (sCD146) containing the extracellular part of the protein is released to the blood stream in response to congestion-mediated venous stretching[2,3]. In an elegant experimental study Arrigo et al. clearly demonstrated that the application of passive stress by means of a pressure cuff around the dominant arm induced a rapid and pronounced increase in circulating concentration of sCD146 in the congested arm[3]. In another study involving a few acute heart failure cohorts and an animal model, sCD146 was related to clinical and echocardiographic signs of congestion and lung weight[4]. The association between sCD146 and haemodynamic congestion was also demonstrated in another acutely decompensated heart failure cohort[5]. In addition, sCD146 was able to differentiate overhydrated haemodialysis patients with low B-type natriuretic peptide (BNP) values[6]. The superiority of sCD146 over BNP in pulmonary congestion assessment and grading was also shown in a large population of acute coronary syndrome patients[7].

Therefore, we strongly believe that sCD146 is an important and promising biomarker of congestion, that should be mentioned at the same level as the other two potential blood biomarkers, i.e. adrenomedullin and tumour marker antigen carbohydrate 125 to make the review comprehensive[1]. In addition, a clear link between congestion and its treatment is important as done in a comprehensive review article ‘Loop diuretics in chronic heart failure: how to manage congestion’, which was recently published in Heart Failure Reviews[8], to complete our understanding of this clinically highly relevant problem.

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CHAPTER 8

CD146 REFLECTS INTRAVASCULAR AND TISSUE CONGESTION IN ACUTE DYSPNOEA: INSIGHTS FROM LEDA STUDY

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Abstract

Background: Endothelial soluble cluster of differentiation 146 (sCD146) is a cell adhesion molecule that is suggested as a diagnostic biomarker for peripheral congestion.

Objectives: This study was designed to evaluate the potential of sCD146 in the detection and grading of congestion in patients with acute dyspnoea.

Methods: This is a subanalysis of the prospective observational Lithuanian Echocardiography Study of Dyspnoea in Acute Settings. Congestion was assessed using clinical and sonographic parameters. All patients underwent sCD146 and NT-proBNP testing.

Results: The median value of sCD146 concentration in the study cohort (n=437) was 405 [315;509] ng/mL. sCD146 was higher in patients with peripheral oedema as compared to those without (472 [373;535] vs 400 [304;501] ng/mL, p=0.009) and with pulmonary rales than in those without (439 [335;528] vs 394 [296;484] ng/mL, p=0.001). We found a parallel increase of eRAP and sCD146 concentration: sCD146 was 337 [300;425], 404 [290;489] and 477 [363;572] ng/mL in patients with normal, moderately elevated and high eRAP, respectively (p=0.001). In patients with low NT-proBNP, high sCD146 distinguished a subgroup with a higher prevalence of oedema as compared to patients with low levels of both biomarkers (76.0% vs 41.0%, p=0.010). Moreover, high sCD146 indicated a higher prevalence of elevated eRAP, irrespective of NT-proBNP concentration ($p<0.05$).

Conclusion: sCD146 concentration reflects the degree of intravascular and tissue congestion assessed by clinical and echocardiographic indices, with this association maintained in patients with low NT-proBNP. Our data support the notion that NT-proBNP might represent heart stretch while sCD146 rather represents peripheral venous congestion.

Introduction

Assessment of clinical congestion is challenging, particularly in an acute setting as it can be present in the vascular system (intravascular congestion) or the interstitium (tissue congestion), although the majority of patients will have a mix of both[1]. Endothelial soluble cluster of differentiation 146 (sCD146) is a cell adhesion molecule that is secreted in the intercellular junction of endothelial cells mediating interaction with other cells or extracellular matrix[2]. Soluble CD146 is involved in the control of vessel integrity, while its release is potentially dependent on endothelial cell stretch[3]. This makes sCD146 a potential marker for congestion[4].

This study was designed to examine the levels of sCD146 in a cohort of patients with acute dyspnoea due to multiple causes and its relationship with clinical signs and sonographic markers of congestion as well as cardiac morphology and function.

Methods

Study design

This is a subanalysis of the Lithuanian Echocardiography Study of Dyspnoea in Acute Settings, LEDA, NCT03048032. LEDA was a prospective observational multicentre study performed in two Lithuanian university centres in collaboration with a research protocol of the international GREAT network (Global Research on Acute Conditions Team). The enrolment period, inclusion/exclusion criteria, data collection, and diagnosis adjudication have been previously described[5]. Briefly, adult acute dyspnoea patients admitted to the Emergency Department at two Lithuanian university centres were enrolled; patients with acute coronary syndrome occurring during the first 4 hours of admission were excluded. Demographic data, baseline medication, comorbidities, clinical signs and laboratory parameters at admission were recorded. Clinical signs of congestion included peripheral oedema and pulmonary rales.

The main cause of acute dyspnoea was adjudicated by three cardiologists in their respective centres. Final diagnoses were classified as acute heart failure (AHF) or non-AHF; the latter included chronic obstructive pulmonary disease (COPD)/asthma exacerbation, pulmonary embolism, pulmonary/non-pulmonary infections, cancer, acute coronary syndrome (ACS), and others. The study was approved by the Lithuanian Bioethics Committee (No. L-15-01) and conducted in accordance with the Declaration of Helsinki. All participants provided their written informed consents.

This analysis includes a subgroup of patients who had their sCD146 levels measured at admission and cardiac ultrasound performed within 48 hours of admission.

Ultrasound examination

Echocardiographic measurements of cardiac chambers, ventricular systolic and diastolic function and inferior vena cava (IVC) diameters were obtained by experienced operators using System Vivid 4 (GE Healthcare, Israel), System Vivid 7 and 9 machines (GE Healthcare, Norway) and Philips EPIQ 7 (Koninklijke Philips N.V., the Netherlands) according to the guidelines for cardiac chamber quantification[6]. Right atrial pressure (RAP) was estimated based on the IVC size and collapsibility: normal – IVC diameter <2.1 cm and collapsing ≥50%, moderately elevated – IVC diameter ≥ 2.1 cm and collapsing ≥50% or IVC diameter <2.1 cm and collapsing <50%, high – IVC diameter ≥2.1 cm and collapsing <50%.

Focused right-sided parameters, including right ventricular (RV) basal diameter, tricuspid annular plane systolic excursion (TAPSE), RV fractional area change (RV FAC), and peak systolic velocity of tricuspid annulus (TA S') were obtained when feasible. Furthermore, images for the right ventricular deformation assessment were obtained from apical 4-chamber view as described by Rudski et al.[7]. Offline speckle tracking analysis was performed by the 2D strain software in the EchoPac (version 110.1.2 GE Healthcare, Norway) and QLAB (version 9.0, Koninklijke Philips N.V., the Netherlands). Both the entire RV strain (including basal, mid, and apical segments of the RV free wall and interventricular septum) and RV free wall strain (excluding septal segments) were calculated.

Lung ultrasound was performed with a phased array transducer scanning in four chest sites bilaterally[8]. The total number of B-lines was recorded as the final result.

Biomarkers

Blood samples were taken within 4 hours of presentation, frozen at -80°C and sent to the INSERM UMR942 institute (Paris, France) for centralised measurements of sCD146 (BioCytex, Marseille, France), N-terminal pro-B-type natriuretic peptide and high-sensitive troponin-T (NT-proBNP and hs-TnT, Roche Diagnostics® GmbH, Mannheim, Germany).

Statistical analysis

Values were expressed as counts and frequencies for qualitative variables and as means and standard deviations (SD) or medians with interquartile range (IQR) for quantitative variables, depending on the distribution.

All study parameters were compared between two groups based on the median value of plasma sCD146 for a more detailed description of the biomarker in the acute dyspnoea cohort. To assess the relationship between sCD146 and cardiac morphology and function, sCD146 concentration was compared between the groups based on terciles of echocardiographic parameters.

The possible value of combining sCD146 and NT-proBNP in assessing congestion was examined by dividing the patients into 4 subgroups on the basis of the median values of the biomarkers: (1) both biomarkers below the median, (2) only NT-proBNP above the median, (3) only sCD-146 above the median, and (4) both biomarkers above the median. Congestion parameters (presence of peripheral oedema and estimated RAP (eRAP)) were compared between the groups.

The $\chi 2$-test was used to compare categories. We used adjusted residuals with the Bonferroni correction for post hoc tests following the $\chi 2$-test. The means of continuous nonparametric variables were compared using the Mann-Whitney U or Kruskal-Wallis H test when appropriate. For group comparison, Dunn's tests with the Bonferroni correction were performed.

The performance of sCD146 and NT-proBNP in the prediction of IVC dilation and reduced collapsibility, B-lines and cardiac abnormalities were assessed conducting a Receiver Operating Characteristics (ROC) analysis using the Area Under the ROC Curve (AUC). The difference between two AUCs was tested as described by DeLong et al.[9].

The analysis was carried out using IBM SPSS Statistics for Windows, version 23.0 (IBM Corp) and MedCalc for Windows, version 14.8 (MedCalc software). All tests were 2-sided and a p-value of <0.05 was considered significant.

Results

Study population

Soluble CD146 measurements were available for 437 out of 1455 LEDA participants (30%). There were some differences in the baseline characteristics between patients included in the present subanalysis and the entire LEDA population (**Supplementary Table 1).** The included patients were more likely to be dyspnoeic because of AHF and ACS, had higher plasma NT-proBNP and hs-TnT concentration and were more often on diuretics.

The baseline characteristics of the study population are shown in **Table 1**. The patients were elderly (median age 70 [61;78] years) and 270 (68.1%) were male. AHF was the dominant cause of acute dyspnoea. The frequency of cardiovascular and non-cardiovascular comorbidities was high.

Soluble CD146 in the study population

The median value of sCD146 concentration in the study cohort was 405 [315;509] ng/mL. The comparison of patients with plasma sCD146 concentration above and below the median is

shown in **Table 1**. Patients with sCD146 levels above the median were older and more frequently diagnosed with CHF, atrial fibrillation, valvular heart disease (VHD) and anaemia before admission. Pulmonary rales at admission and chronic diuretic treatment were more common in patients with elevated sCD146: 58.9% vs 48.2% (p=0.036) and 53.0% vs 43.1% (p=0.044), respectively. Likewise, patients with sCD146 levels above the median had a higher plasma concentration of NT-proBNP, hs-TnT and creatinine (p<0.001 for all, see **Table 1**). Regarding the cause of acute dyspnoea, the highest median value of sCD146 was found in patients with AHF: 441 [344;541]) ng/mL, while the lowest was measured in patients diagnosed with COPD/asthma: 271 [220;363] ng/mL (**Supplementary Table 2)**.

Soluble CD146 and clinical signs of congestion

Soluble CD146 concentration was higher in patients with oedema, as compared to those without oedema (472 [373;535] vs 400 [304;501] ng/mL, p=0.009), see **Figure 1A (**documented data about the presence or absence of peripheral oedema was available for 161 (37%) patients). Of note, the median sCD146 concentration in patients without a documented oedema status (394 [306;498]) was similar to the concentration measured in patients with no oedema on admission (p=0.93).

Figure 1. sCD146 concentration in patients categorized according to the presence or absence of peripheral oedema (**A**) and rales (**B**)

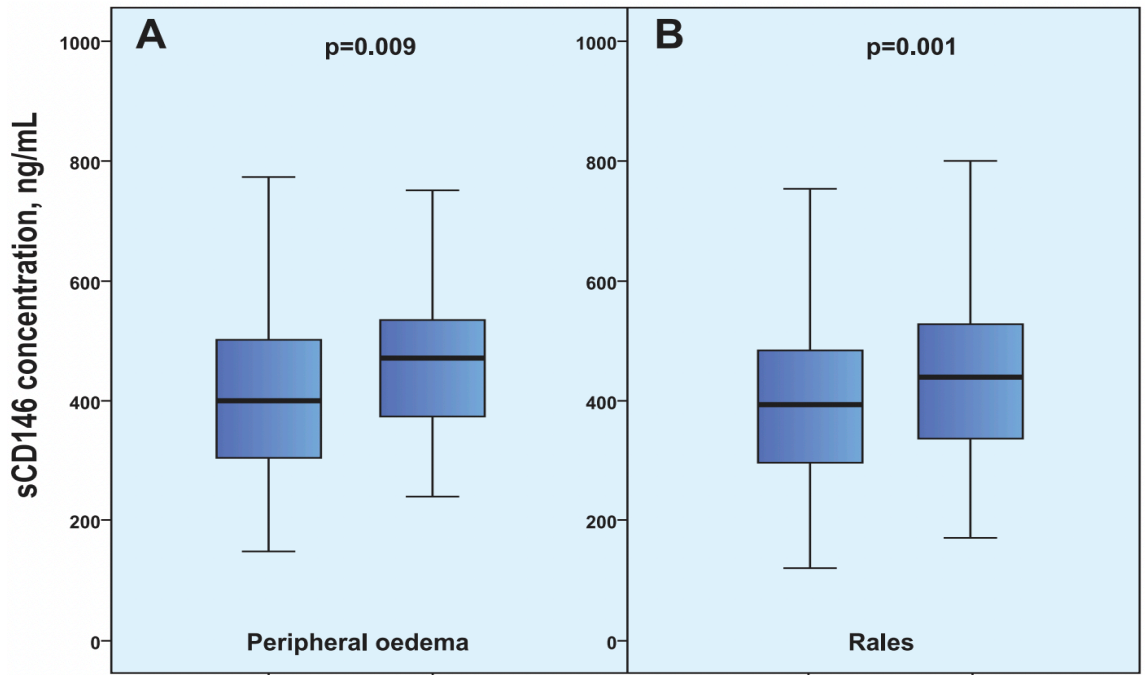


Table 1. Baseline characteristics of the study population stratified by the median concentration of sCD146

Variables	Total, n=437	sCD146 below the median, n=218	sCD146 above the median, n=219	p-value
Demographics				
Age, years	70 [61; 78]	68 [60; 77]	72 [62; 79]	**0.037**
≥65 years	281 (64.3)	129 (59.2)	152 (69.4)	**0.028**
Male	270 (61.8)	135 (61.9)	135 (61.6)	1
Adjudicated diagnosis				
AHF	281 (64.3)	112 (51.4)	169 (77.2)	**<0.001**
COPD/asthma	18 (4.1)	15 (6.9)	3 (1.4)	**0.004**
Pulmonary embolism	37 (8.5)	27 (12.4)	10 (4.6)	**0.003**
Infection	18 (4.1)	12 (5.5)	6 (2.7)	0.158
ACS	42 (9.6)	26 (11.9)	16 (7.3)	0.107
Other	25 (5.7)	18 (8.3)	7 (3.2)	**0.024**
Examination				
Heart rate, BPM	88 [74; 102]	86 [74; 101]	90 [72; 103]	0.675
SBP, mmHg	135 [120; 152]	137 [120; 152]	135 [116; 152]	0.256
DBP, mmHg	80 [70; 90]	80 [70; 90]	80 [70; 90]	0.503
BMI, kg/m^2	29.4 [25.7; 34.2]	29.4 [25.8; 34.5]	29.5 [25.7; 43.1]	0.887
Pulmonary rales	217 (58.4)	95 (48.2)	122 (58.9)	**0.036**
Peripheral oedema	94 (53.7)	37 (51.4)	57 (64.0)	0.111
Respiratory rate, breaths/minute	20 [17; 24]	20 [17; 24]	20 [17; 24]	0.372
Axillary temperature, °C	36.7±0.5	36.7±0.5	36.8±0.5	**0.015**
Oxygen saturation (SpO$_2$), %	93 [90; 96]	94 [89; 96]	93 [90; 96]	0.686
Examination				
CHF	301 (69.2)	131 (60.6)	170 (77.6)	**<0.001**
Hypertension	340 (78.2)	170 (78.7)	170 (77.6)	0.817
CAD	183 (42.1)	84 (38.9)	99 (45.2)	0.207
Severe VHD /previous valvular surgery	94 (21.6)	33 (15.3)	61 (27.9)	**0.002**
Atrial fibrillation/flutter	200 (46.0)	76 (35.2)	124 (56.6)	**<0.001**
Pacemaker	48 (11.0)	21 (9.7)	27 (12.3)	0.445
Stroke	36 (8.3)	16 (7.4)	20 (9.1)	0.603
Diabetes	98 (22.5)	44 (20.4)	54 (24.7)	0.303
Dyslipidaemia	128 (29.4)	70 (32.4)	58 (26.5)	0.207
Active/recent cancer	48 (11.0)	29 (13.4)	19 (8.7)	0.127
Asthma/COPD	72 (16.6)	39 (18.1)	33 (15.1)	0.377
Anaemia	120 (27.5)	50 (23.1)	70 (32.0)	**0.042**
Medication before admission				
Beta blocker	216 (49.7)	100 (46.3)	116 (53.0)	0.18
Aldosterone antagonist	83 (19.1)	37 (17.1)	46 (21.0)	0.33
Loop diuretic	209 (47.8)	93 (43.1)	116 (53.0)	**0.044**
Statin	54 (12.4)	31 (14.4)	23 (10.5)	0.246
Antiplatelet	109 (24.9)	55 (25.5)	54 (24.7)	0.912
Anticoagulant	116 (26.7)	38 (17.6)	78 (35.6)	**<0.001**
CCB	70 (16.1)	42 (19.4)	28 (12.8)	0.068
None of the above	89 (20.5)	53 (24.5)	36 (16.4)	**0.043**
Biomarkers				
NT-proBNP (ng/L)	2547 [737-6669]	1361 [381-3898]	4558 [1596-9817]	**<0.001**
Troponin T (ng/L)	30 [20-60]	24 [13-40]	40 [20-70]	**<0.001**
CRP (mg/L)	9.1 [3.5-27.7]	9.2 [3.5-30.0]	9.0 [3.5-23.8]	0.975
Hb (g/L)	132 [117-144]	134 [118-146]	130 [116-144]	0.122
K (mmol/L)	4.3 [4.0-4.7]	4.3 [3.9-4.6]	4.4 [4.0-4.8]	**0.013**
Na (mmol/L)	139 [136-141]	139 [136-141]	139 [137-142]	0.248
Creatinine (µmol/L)	95 [77-127]	87 [72-116]	103 [83-135]	**<0.001**

The abbreviations are explained in the next page.

Explanation of abbreviations in Table 1: *ACE: angiotensin-converting enzyme; ACS: acute coronary syndrome; AHF: acute heart failure; ARB: angiotensin-receptor blocker; BMI: body mass index; BPM: beats per minute; CAD: coronary artery disease; CCB: calcium-channel blocker; CD146: cluster of differentiation 146; CHF: chronic heart failure; COPD: chronic obstructive pulmonary disease; CRP: C-reactive protein; DBP: diastolic blood pressure; Hb: haemoglobin; K: potassium; n: number of subjects with available data; Na: sodium; NT-proBNP: N-terminal pro–B-type natriuretic peptide; SBP: systolic blood pressure; VHD: valvular heart disease*

Likewise, sCD146 concentration was higher in patients with pulmonary rales than in those without rales (439 [335;528] and 394 [296;484] ng/mL, p=0.001), see **Figure 1B** (data about the presence or absence of rales was available for 404 (92%) patients). Again, the median sCD146 concentration in patients without a documented rales status (384 [273;480]) was similar to the concentration detected in patients with no rales (p=0.79).

Soluble CD146 and echocardiographic parameters

Echocardiographic parameters of the study population and the subgroups with different sCD146 levels (higher or lower than the median) are presented in a **Supplementary Table 3**. We revealed a significant association between plasma sCD146 concentration and several functional and structural ultrasound markers, including signs of intravascular and intracardiac congestion.

First of all, the association with a dilated IVC and respiratory variations in IVC was observed (complete data on the size and collapsibility of IVC was available for 276 (63%) patients).

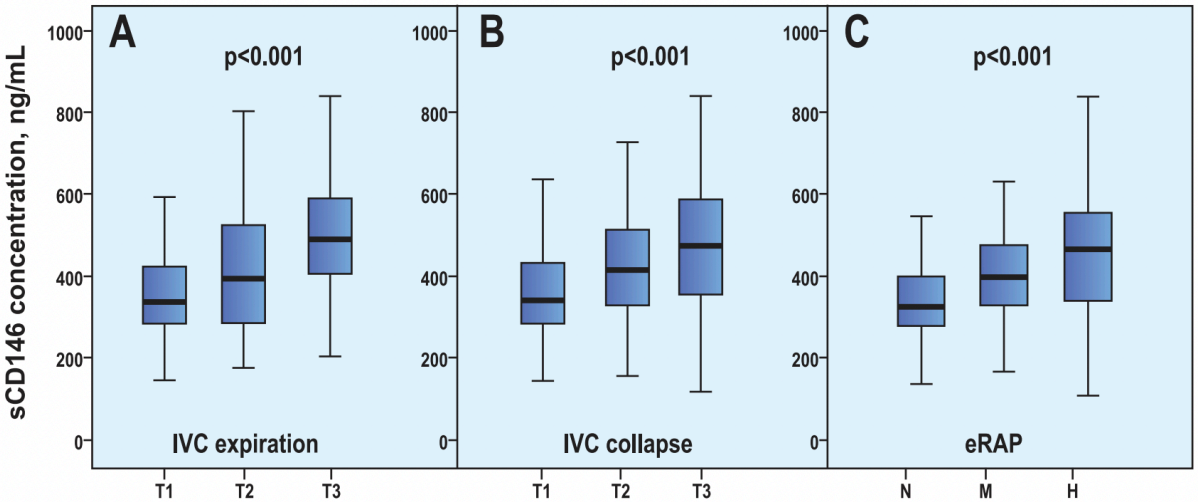
Inferior vena cava analysis revealed a relationship between sCD146 levels and IVC pattern. In particular, the more IVC was dilated and the less collapsible, the higher was the concentration of sCD146 (see **Figure 2A, 2B, Table 3).** We also found a parallel increase in eRAP and plasma sCD146 concentration: sCD146 was 337 [300;45], 404 [290;489] and 477 [363;572] ng/mL in patients with normal, moderately elevated and high eRAP, respectively (p=0.001, **Figure 2C).**

Furthermore, sCD146 level was significantly related to the average E/e' ratio - a marker of left ventricular diastolic filling (n=202 (46%)), see **Figure 3A and Table 3.** A parallel rise, though non-significant, was observed in sCD146 concentration with the increasing number of B-lines (n=77 (18%)) (**Figure 3B, Supplementary Table 4**), (p=0.06). Soluble CD146 concentration proportionally increased with increasing LAVI (**Figure 3C**) and LVDD (**Figure 3D**) (p<0.001 for both).

In addition, sCD146 concentration corresponded to the markers of left and right ventricular function. **Figures 4A and 4B** show an incremental increase of sCD146 levels in terciles of left ventricular ejection fraction (LVEF) and TAPSE. Similarly, the sCD146 concentration

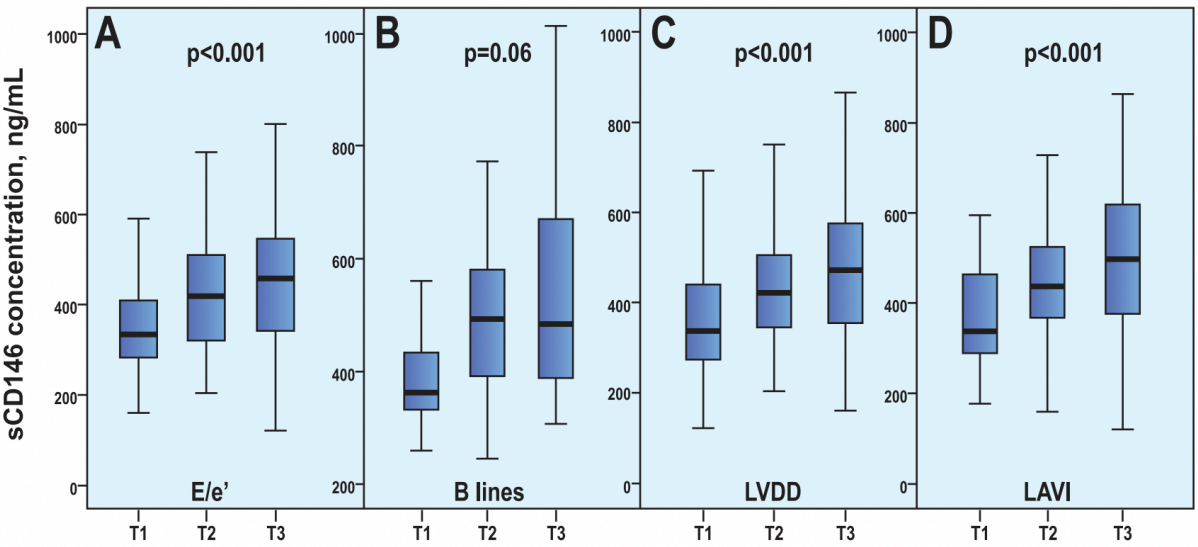
paralleled the decrease in the right ventricular strain, both the free wall and the entire right ventricle **(Figures 4C, 4D**).

Figure 2. sCD146 concentration in terciles of IVC diameter at expiration (**A**), IVC collapse (**B**), and estimated RA pressure subgroups (**C**)



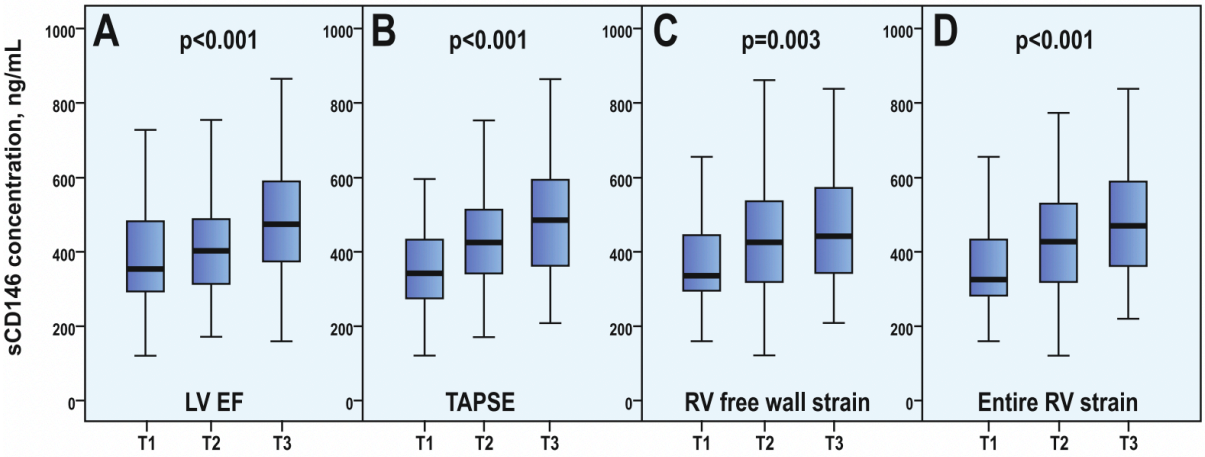
eRAP: estimated right atrial pressure, H: high; IVC: inferior vena cava, M: moderately elevated, N: normal, T: tercile

Figure 3. sCD146 concentration in terciles of ultrasound parameters: average E/e' ratio (**A**), B-lines (**B**), **l**eft ventricular end diastolic diameter (LVDD, **C**), and left atrial volume index (LAVI, **D**)



LAVI: left atrial volume index, LVDD: left ventricular end diastolic diameter, T: tercile

Figure 4. sCD146 concentration in patients categorized according to echocardiographic parameters of biventricular function in terciles: LV EF (**A**), TAPSE (**B**), RV free wall strain (**C**), Entire RV strain (**D**)



LV RF: left ventricular ejection fraction, RV: right ventricular, T: tercile, TAPSE: tricuspid anulus plane systolic excursion

Soluble CD146 and NT-proBNP

In patients with high NT-proBNP, oedema was equally present in both high and low sCD146 subgroups (p=0.99). However, in patients with low NT-proBNP, high sCD146 distinguished a subgroup of patients with a significantly higher prevalence of oedema, as compared to patients with low levels of both biomarkers (76% vs 41%, p=0.010) (**Figure 5A**). Furthermore, high sCD146 indicated a higher prevalence of elevated eRAP, irrespective of NT-proBNP concentration (p<0.05, **Figure 5B**).

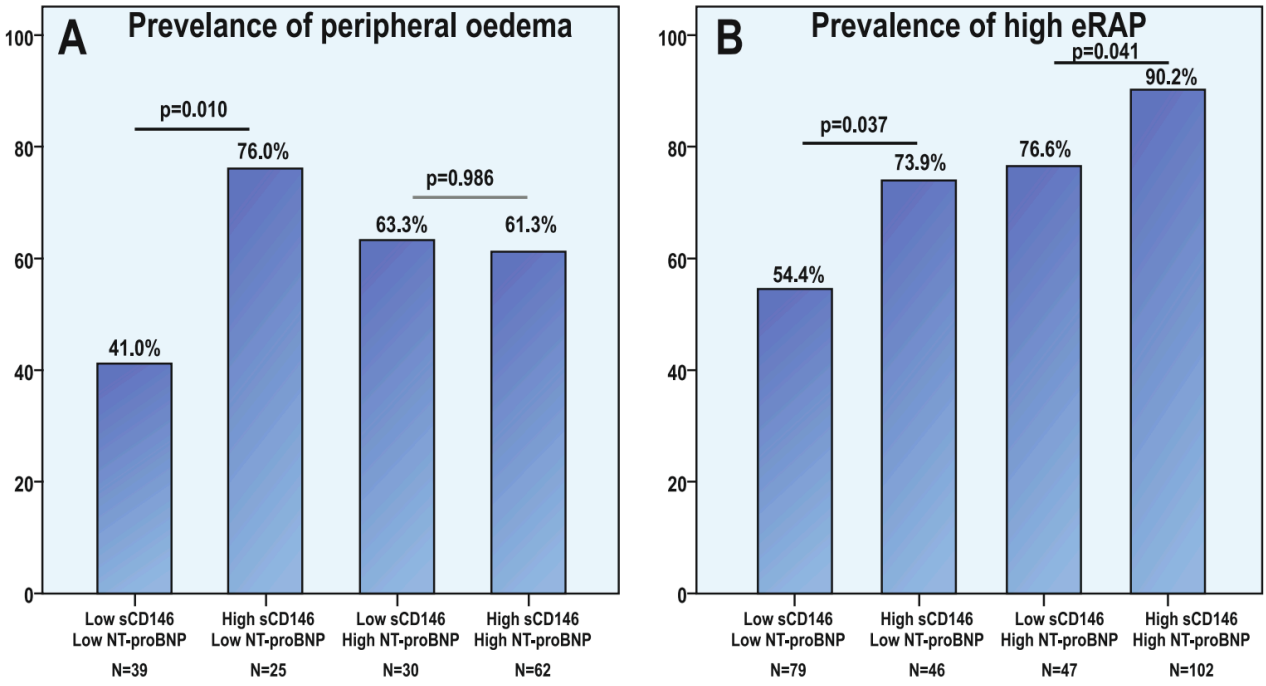
We also compared the value of sCD146 and NT-proBNP in predicting the presence of congestion and cardiac dysfunction. AUCs for sCD146 and NT-proBNP were similar for IVC diameter, IVC collapse and the number of B-lines (p>0.05, **Supplementary Figure 1**). However, sCD146 better predicted the presence of peripheral oedema than NT-proBNP (AUC 0.63 [0.51;0.70] vs 0.51 [0.43;0.59, p=0.009), whereas NT-proBNP was a better predictor of LVEF and rales than sCD146 (AUC 0.76 [0.71;0.80] vs 0.63 [0.58;0.68], p<0.001 and AUC 0.66 [0.61;0.70 vs 0.60 [0.55;0.64], p=0.049, respectively).

The ROC curves are shown in **Supplementary Figure 1** and the AUC values for echocardiographic parameters are detailed in **Supplementary Table 5.**

Discussion

The present study reveals an important relationship between circulating sCD146 and clinical and echocardiographic markers of tissue, intravascular and intracardiac congestion, which is maintained in patients even with lower NT-proBNP.

Figure 5. **A** Frequency of peripheral oedema in patients stratified according to the median values of sCD146 and NT-proBNP. **B** The prevalence of elevated estimated RA pressure in patients stratified according to the median values sCD146 and NT-proBNP.



eRAP: estimated right atrial pressure

Clinical congestion is a result of a complex pathophysiological process which in the case of heart failure starts with a gradual increase in filling pressures and culminates with extravascular fluid accumulation[10]. Yet, congestion is the main reason for hospitalisation in an AHF setting, as the majority of patients show up with signs and symptoms of volume overload[10]. It is however difficult to assess the level of congestion, and accurate detection and grading are therefore crucial for optimal medical care.

Along with a significant reduction in the length of acute heart failure-related inpatient stays, the readmission rate remained unchanged during the past four decades[11], meaning that a large proportion of AHF patients are readmitted for acute decompensation within a year[12]. The deleterious effect of congestion on outcome has been identified in other clinical scenarios, including end-stage renal disease[13], COPD[14], and COVID-19 infection[15]. Lung ultrasound is being increasingly recognised as a useful tool to assess pulmonary congestion and pleural effusion in acute dyspnoea[15–18], but may be not accessible in all facilities. Despite obvious harm, congestion management often remains suboptimal. This means that many patients remain wet and possibly experience overhydration-related events.

This difficulty is prevalent in the setting of acute dyspnoea, given often similar clinical presentations despite a diverse spectrum of aetiologies[19–21]. Delayed identification leads to delays in initiation of decongestive therapies, although early diuretic administration has been related to a better outcome in acute heart failure[22].

Recently, sCD146 - a promising blood biomarker for congestion - has been introduced. Initially, sCD146 was identified as a marker for tumour progression and metastasis formation in human melanoma[23]. Later discoveries revealed that sCD146 is involved in the control of vessel integrity and angiogenesis[2,24–27], especially in the pathogenesis of various malignant states, including paediatric leukaemia[28], breast cancer[29–31], melanoma[32] and other types of cancer[33,34]. Later observations uncovered that sCD146 concentration correlates well with weight gain and the size of IVC in acute heart failure patients[35]. The relationship between venous stretch and sCD146 was demonstrated in an elegant experimental study by Arrigo et al.[3]. The authors measured the level of sCD146 in HF patients at baseline and after 90 minutes of unilateral forearm venous congestion, and documented a rapid release of sCD146 in response to congestion-mediated venous stretch that may reflect systemic congestion in chronic HF. Another study revealed the relationship between sCD146 and pulmonary congestion in the early phase of ACS, which was independent from the severity of myocardial cell necrosis[36].

The present study extends the accumulated data by revealing a close association between the levels of sCD146 and clinical and echocardiographic evidence of congestion as well as cardiac morphology and function in an unselected population of acute dyspnoea.

Regarding the left heart and pulmonary congestion, we were able to confirm a definite link between sCD146 concentration and the presence of pulmonary rales as well as impairment of diastolic filling, as reflected by elevated E/e'. We also showed that the greater the level of sCD146, the larger the left atrium and left ventricle, and the lower the LVEF. There was a parallel rise, though non-significant, in sCD146 with the increasing number of B-lines that requires further testing in a larger population.

Concerning the right ventricle and systemic congestion, the present results demonstrate a strong relationship between sCD146 concentration and clinical (peripheral oedema) as well as sonographic signs of right-sided congestion. A stepwise increase in sCD146 concentration is demonstrated along with rising eRAP, consistent with intravascular volume overload. In addition, elevated sCD146 concentration was related to impaired right ventricular function, as evidenced by the reduction in right ventricular strain and TAPSE. The present findings indicate that sCD146 concentration proportionally increases not only with increasing congestion but also in parallel with decreasing biventricular function and progressing cardiac enlargement.

Cardiac dysfunction is a likely cause of water retention in the majority of cases, and sCD146 can reflect them both, i.e., the cause and the consequence.

We have previously shown in dialysis patients that sCD146 rapidly follows patient hydration independently of the levels of natriuretic peptides. Most haemodialysis subjects with low BNP but high sCD146 have been shown to be overhydrated[37]. The present study further confirms the significant additional value of sCD146 in detecting congestion in acutely dyspnoeic patients with relatively low NT-proBNP. For instance, subjects with high sCD146 and low NT-proBNP frequently had elevated eRAP. By contrast, sCD146 had a minor additional value in patients with high NT-proBNP that likely carry both prominent intracardiac and peripheral congestion. However, in patients with relatively low NT-proBNP, sCD146 was able to discern a subgroup of patients with a high prevalence of peripheral oedema. Altogether, these data support the notion that natriuretic peptides are more likely to represent cardiac stretch in the context of heart failure, while sCD146 reflects hypervolaemia and peripheral venous stretch in acute dyspnoea.

Clinical significance

The present study indicates that NT-proBNP – an established diagnostic biomarker - may not accurately reflect systemic congestion in some scenarios. This observation is in line with some previous findings showing that BNP-guided congestion management is not superior to a conventional clinical approach[38]. On the other hand, sCD146 presents a potential to be used as a congestion biomarker, and we hypothesise that its role in decongestion guidance might be superior to NT-proBNP, given the venous origin of its release[3]. This may be particularly helpful in patients with acute dyspnoea not related to heart failure who may have hypervolaemia and may need diuretics despite low values of natriuretic peptides. The present data further suggest that the goal of diuretic treatment might be to reduce both NT-proBNP and sCD146. Our study was held in two academic facilities with immediate access to a cardiologist experienced in echocardiography, but we assume that in other settings many patients do not have or have delayed access to cardiac ultrasound. This means that sCD146 may assist emergency physicians, internists and intensivists in prompt congestion detection, leading to faster medical care. Also, this reliable congestion biomarker has a potential to fill the current gap of knowledge regarding congestion detection and grading, especially in emergency and primary care where modalities such as advanced echocardiography and lung ultrasound are often unavailable.

Limitations

This study has several limitations. First of all, the sample size is limited as it was not always possible to perform a high-quality echocardiography study on admission. Also, some patients were excluded from different parts of the analysis due to missing values in the patient history, which is often the case in a real-life emergency setting. When assessing the association between blood biomarkers and congestion, we relied on clinical and echo-derived markers of volume overload instead of invasively measured intracardiac filling pressures. Still, we do not believe that such a trial of invasive nature would have ever been carried out in an acute dyspnoea setting. We were also unable to test how fast the sCD146 level decreases after diuretic administration and, more importantly, if sCD146-guided decongestion would improve outcome.

Conclusion

Soluble CD146 concentration reflects the degree of intravascular and tissue congestion as assessed by clinical and echocardiographic indices. This association remains present in patients with low NT-proBNP. Soluble CD146 better represents peripheral venous congestion, while NT-proBNP might better represent cardiac stretch.

References

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SUPPLEMENTS

Supplementary Table 1. Comparison of patients included in the present sub-analysis and the entire LEDA cohort

Variables	LEDA population n=1455	sCD146 population n=437	p-value
Demographics			
Age, years	71 [62-79]	70 [61-78]	0,447
≥65 years	955 (65.6)	281 (64.3)	0,577
Male	824 (56.6)	270 (61.8)	**0,030**
Adjudicated diagnosis			
AHF	761 (52.3)	281 (64.3)	**<0.001**
Non-AHF	694 (47.7)	156 (35.7)	**<0.001**
COPD/asthma	98 (6.7)	18 (4.1)	**0,029**
Pulmonary embolism	96 (6.6)	37 (8.5)	0,116
Infection	121 (8.3)	18 (4.1)	**0,001**
ACS	88 (6.0)	42 (9.6)	**0,002**
Other	291 (19.9)	41 (9.4)	**<0.001**
Examination			
Heart rate, BPM	88 [73; 104]	88 [74; 102]	0,520
SBP, mmHg	140 [123; 160]	135 [120;152]	**0,016**
DBP, mmHg	80 [71; 90]	80 [70; 90]	0.611
BMI, kg/m^2	29.4 [23.4; 34.4]	29.4 [25.7; 34.2]	0,860
Rales	651 (50.3)	217 (53.7)	0,166
Peripheral oedema	299 (52.5)	94 (58.4)	0,138
Respiratory rate, breaths/minute	20 [16; 22]	20 [17; 24]	0,072
Axillary temperature, °C	36.7±0.6	36.7±0.5	0,074
Oxygen saturation (SpO_2), %	94 [89; 96]	93 [90; 96]	0,354
Medical history			
CHF	877 (61.4)	301 (69.2)	**0,001**
Hypertension	1120 (78.4)	340 (78.2)	0,901
CAD	495 (34.6)	183 (41.9)	**0,001**
Severe VHD or previous valvular surgery	277 (19.4)	94 (21.6)	0,240
Atrial fibrillation/flutter	618 (43.2)	200 (46.0)	0,250
Pacemaker	169 (11.8)	48 (11.0)	0,609
PAD	90 (6.3)	32 (7.4)	0,369
Stroke	128 (9.0)	36 (8.3)	0,619
Pulmonary embolism	95 (6.6)	26 (6.0)	0,574
Diabetes	324 (22.7)	98 (22.5)	0,943
Dyslipidaemia	390 (27.3)	128 (29.4)	0,318
Active/recent cancer	204 (14.3)	48 (11.0)	0,053
Asthma/COPD	275 (19.2)	72 (16.6)	0,154
Anaemia	331 (22.7)	120 (27.6)	**0,029**
Chronic inflammatory disease	102 (7.0)	102 (7.6)	0,716
Medication before admission			
ACE inhibitors or ARB	650 (45.5)	191 (43.90	0,500
Beta blocker	713 (49.9)	216 (49.7)	0,909

Supplementary Table 1 (continued)

Aldosterone antagonist	243 (17.0)	83 (19.1)	0,252
Diuretic	615 (43.1)	209 (48.0)	**0,036**
Cardiac glycoside	74 (5.1)	22 (5.1)	0,907
Nitrate	106 (7.3)	34 (7.8)	0,754
Statin	184 (12.9)	54 (12.4)	0,769
Antiplatelet	335 (23.5)	109 (25.1)	0,432
Anticoagulant	390 (27.3)	116 (26.7)	0,763
CCB	212 (14.8)	70 (16.1)	0,465
Inhaled steroid	80 (5.6)	20 (4.6)	0,362
Beta2 agonist	115 (8.1)	20 (4.6)	**0,008**
Insulin	68 (4.7)	22 (5.1)	0,772
Antidiabetic (other than insulin)	180 (12.6)	60 (13.8)	0,455
None of the above	313 (21.9)	89 (20.5)	0,462
Biomarkers			
NT-proBNP (ng/L)	1828 [453; 5305]	2547 [737; 6669]	**0,001**
Troponin T (ng/L)	27 [13; 48]	30 [20; 60]	**<0.001**
CRP (mg/L)	10.3 [3.5; 33.8]	9.1 [3.5; 27.7]	0,098
Hb (g/L)	131 [116; 144]	132 [117; 144]	0,684
K (mmol/L)	4.3 [4.0; 4.7]	4.3 [4.0; 4.7]	0,562
Na (mmol/L)	139 [136; 141]	139 [136; 141]	0,194
Creatinine (µmol/L)	94 [75; 122]	95 [77; 127]	0,844

ACE: angiotensin-converting enzyme; ACS: acute coronary syndrome; AHF: acute heart failure; ARB: angiotensin-receptor blocker; BMI: body mass index; BPM: beats per minute; CAD: coronary artery disease; CCB: calcium-channel blocker; CD146: cluster of differentiation 146; CHF: chronic heart failure; COPD: chronic obstructive pulmonary disease; CRP: C-reactive protein; DBP: diastolic blood pressure; Hb: haemoglobin; K: potassium; LEDA = Lithuanian Echocardiography Study of Dyspnea in Acute Settings; n: number of subjects with available data; Na: sodium; NT-proBNP: N-terminal pro–B-type natriuretic peptide; PAD: peripheral artery disease; SBP: systolic blood pressure; VHD: valvular heart disease.

Supplementary Table 2. The median plasma sCD146 concentration in patients with different aetiologies of acute dyspnoea

Variables	Total (n=437)	sCD146 concentration, ng/L		
		Present	Absent	p-value
AHF	281 (64.3%)	440.9 [344.1; 540.6]	336.7 [281.5; 434.6]	**<0.001**
ACS	42 (9.6%)	356.5 [304.7; 467.7]	411.0 [317.4; 514.6]	**0.043**
Pulmonary embolism	37 (8.5%)	330.0 [290.2; 427.5]	415.3 [322.3; 517.4]	**0.002**
Infection	18 (4.1%)	352.1 [246.7; 469.0]	407.7 [246.7; 469.4]	0.118
COPD/asthma	18 (4.1%)	271.1 [220.3; 362.8]	411.0 [320.9; 514.6]	**<0.001**
Other	41 (9.4%)	351.4 [282.6; 439.4]	410.3 [318.9; 514.6]	0.056

ACS: acute coronary syndrome; AHF: acute heart failure; CD146: cluster of differentiation 146; COPD: chronic obstructive pulmonary disease; n: number of subjects with available data

Supplementary Table 3. Echocardiographic parameters stratified by the median plasma concentration of sCD146

Variables	n	Total	Below the median, n=218	Above the median, n=219	p-value
Intravascular Congestion parameters					
IVC_{exp} (cm)	281	2.3 [1.8; 2.7]	2.0 [1.6; 2.4]	2.4 [2.0; 2.8]	**<0.001**
IVC_{insp} (cm)	276	1.3 [0.8; 1.9]	1.0 [0.6; 1.6]	1.6 [1.2; 2.3]	**<0.001**
IVC collapsibility (%)	276	39.6 [22.3; 57.7]	46.7 [31.2; 63.4]	31.6 [14.8; 50.0]	**<0.001**
Right heart parameters					
RV basal diameter (cm)	276	4.3 [3.8; 5.0]	4.1 [3.6; 4.7]	4.5 [3.9; 5.2]	**0.001**
RA area (cm^2)	254	23.7 [18.5; 29.5]	21.6 [18.0; 26.1]	27.0 [20.0; 32.0]	**<0.001**
TAPSE (cm)	318	1.6 [1.3; 2.0]	1.8 [1.4; 2.2]	1.5 [1.2; 1.8]	**<0.001**
TA S '(cm/s)	304	10 [8;13]	11.0 [9.0; 13.0]	9.0 [7.0; 11.0]	**<0.001**
FAC (%)	222	35.3 [27.8; 48.1]	39.0 [30.2; 49.3]	31.9 [23.4; 40.5]	**<0.001**
RV free wall strain, %	189	-16.9 [-22.2; -11.6]	-18.8 [-24.0; -13.3]	-15.8 [-19.0;-11.2]	**0.003**
Entire RV strain, %	189	-13.1 [-17.4; -9.5]	-15.8 [-18.2; -10.7]	-12.0 [-14.9; -9.1]	**0.001**
Estimated SPAP (mmHg)	317	45 [36; 55]	42.0 [33.5; 50.0]	48.3 [38.0; 58.0]	**<0.001**
Left heart parameters					
LVDD (cm)	397	5.4 [4.8; 6.2]	5.1 [4.6; 5.8]	5.7 [5.0; 6.5]	**<0.001**
LVMI (g/m^2)	346	115.4 [93.7; 142.0]	106.9 [84.5; 134.0]	123.0 [100.0; 147.0]	**<0.001**
RWT	395	0.39 [0.31; 0.46]	0.40 [0.34; 0.47]	0.36 [0.30; 0.45]	**0.003**
LAVI (cm^3/m^2)	217	57.0 [42.9; 72.7]	50.0 [39.7; 66.4]	60.0 [50.8; 77.1]	**<0.001**
MV regurgitation	322	1.5 [1.0; 2.0]	1.0 [1.0; 2.0]	1.5 [1.0; 2.0]	**<0.001**
LVEF	404	45.0 [30.0; 55.0]	50.0 [35.0; 55.0]	38.0 [25.0; 55.0]	**<0.001**
LV EF ≥ 50%, yes	404	117 (43.8 %)	107 (54.0 %)	70 (34.0 %)	**<0.001**
E	310	0.8 [0.6; 1.0]	0.7 [0.5; 0.9]	0.9 [0.7; 1.1]	**<0.001**
E/A	220	1.1 [0.7; 1.9]	0.8 [0.7; 1.4]	1.6 [0.8; 2.2]	**<0.001**
Septal e'	210	5.0 [3.0; 6.7]	5.0 [4.0; 7.0]	4.0 [3.0; 6.0]	**0.001**
Septal E/e'	204	15.9 [10.4; 25.0]	12.2 [8.3; 19.5]	20.0 [13.4; 27.2]	**<0.001**
Lateral E/e'	209	10.25 [7.2; 16.1]	8.6 [6.1; 13.7]	11.4 [8.4; 17.3]	**0.003**
Average E/e'	202	12.6 [8.5; 18.3]	10.2 [7.5; 15.5]	14.7 [10.2; 20.1]	**<0.001**
Estimated PCWP	202	16.9 [11.8; 23.8]	13.8 [10.5; 20.4]	19.4 [13.9; 26.1]	**<0.001**

IVC: inferior vena cava; IVC_{exp}: inferior vena cava at expiration; IVC_{insp}: inferior vena cava at inspiration; FAC: *Fractional Area Change; LAVI: left atrial volume index; LVDD: l*eft ventricular *internal* diameter *at end-diastole; LVEF: left ventricular ejection fraction; LVMI: left ventricular mass index; MV: mitral valve; PCWP: estimated pulmonary capillary wedge pressure [PCWP = 1.24 * (E/e') + 1.9; e' = (e'lateral + e'septal) / 2RA: right atrial]; RV: right ventricular; RWT: relative wall thickness; SPAP: systolic pulmonary artery pressure; TA S': peak systolic velocity of tricuspid annulus ; TAPSE: tricuspid annular plane systolic excursion.*

Supplementary Table 4. sCD146 concentration in terciles of echocardiographic parameters

Variables	**Terciles**	**Cut-off points**	**sCD146 concentration, ng/L**
IVC expiration, cm	T1	0.5; 1.91	343.4 [298.5;434.8]
	T2	1.92; 2.48	411.0 [293.9;529.2]
	T3	2.5; 4.2	490.2 [406.3;590.0]
IVC collapse, %	T1	100; 51	348.8 [298.5;437.1]
	T2	50; 29	424.1 [327.7;525.4]
	T3	28; 0	478.6 [377.4;593.8]
B-lines	T1	0; 2	363.3 [332.4;433.7]
	T2	3; 7	439.8 [392.0;582.1]
	T3	8; 31	485.1 [388.5;671.8]
TAPSE, cm	T1	4.0; 1.9	343.4 [273.8;433.2]
	T2	1.8; 1.4	425.6 [342.1;514.1]
	T3	1.36; 0.4	484.1 [360.9;593.8]
RV free wall strain, %	T1	-34.0; -24.1	363.3 [332.4;433.7]
	T2	-19.7; -14.0	439.8 [392.0;582.1]
	T3	-13.9; -2.0	485.1 [388.5;671.8]
Entire RV strain, %	T1	-25.2; -16.4	324.8 [282.0;433.2]
	T2	-16.3; -11.0	426.8 [318.6;530.5]
	T3	-10.8; -1.2	469.4 [360.9;588.9]
E/e'	T1	3.6; 9.4	334.3 [282.1;409.7]
	T2	9.5; 15.6	421.0 [321.0;510.4]
	T3	15.7; 56.7	458.6 [340.0;546.0]
LVDD, cm	T1	3.6; 4.9	336.4 [272.3;440.5]
	T2	5.0; 5.8	421.0 [343.8;506.7]
	T3	5.9; 8.4	471.7 [352.7;575.1]
LAVI, cm^3/m^2	T1	19.7; 48.4	337.5 [287.5;464.9]
	T2	48.5; 66.4	439.4 [366.5;533.7]
	T3	66.6; 202.0	498.0 [377.4;618.6]
LV EF, %	T1	73; 55	352.8 [292.9;481.5]
	T2	54; 35	402.2 [312.1;489.8]
	T3	34; 3	473.9 [373.1;590.0]
eRAP	**Categories**		
	Normal		337.5 [299.6;424.8]
	Moderately elevated		404.4 [290.2;488.9]
	High		477.1 [363.3;572.0]

*eRAP: estimated right atrial pressure; IVC: inferior vena cava; LAVI: left atrial volume index; LVDD: l*eft ventricular *internal* diameter *at end-diastole; LV EF: left ventricular ejection fraction; RV: right ventricular; TAPSE: tricuspid annular plane systolic excursion.*

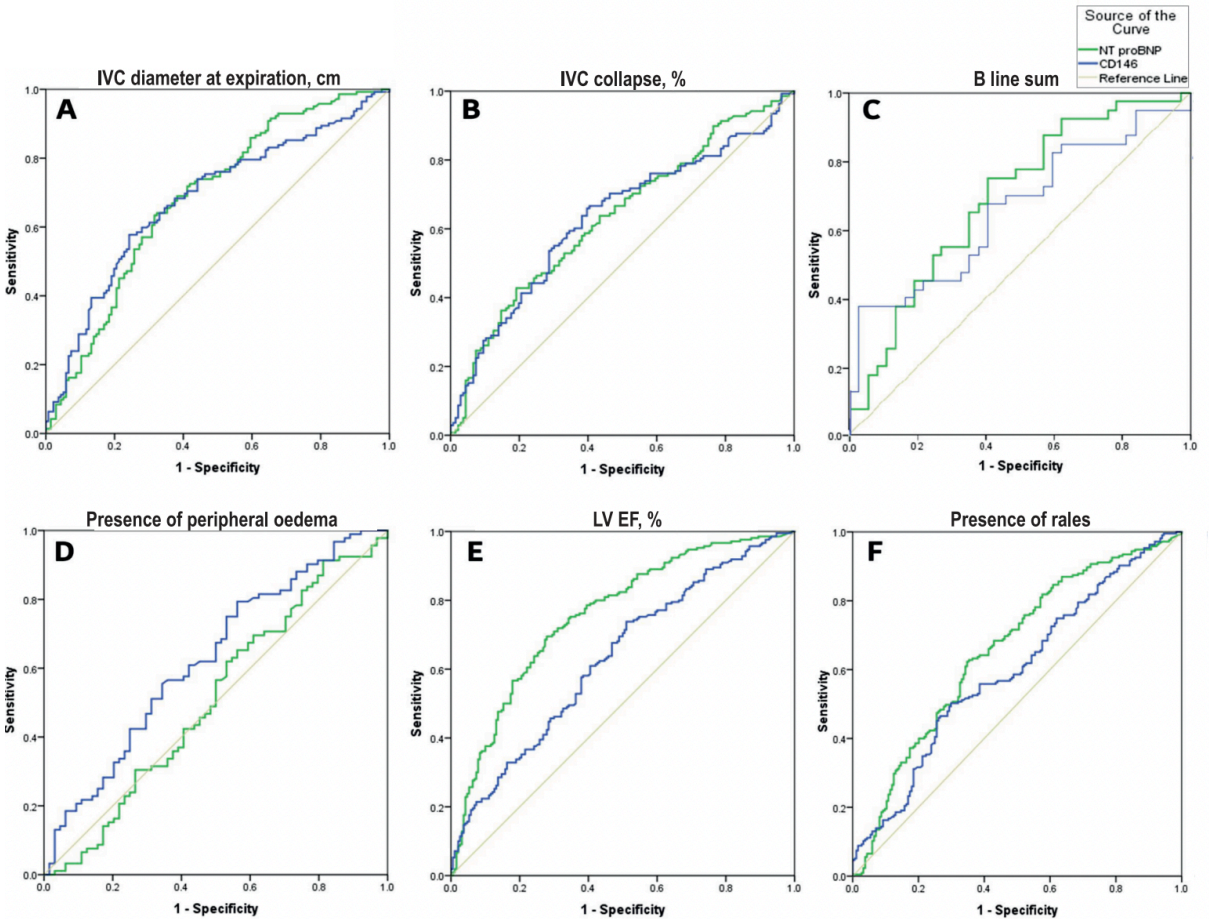
Supplementary Table 5. The comparison of AUCs between sCD146 and NT-proBNP for prediction of sonographic and clinical parameters

Variables	n	sCD146		NT proBNP		p-value #
		AUC	p-value	AUC	p-value	
Peripheral oedema, yes	156 (35.7 %)	0.626 [0.545; 0.702]	**0.029**	0.510 [0.429; 0.591]	0.837	**0.009**
Rales, yes	399 (91.3 %)	0.596 [0.546; 0.645]	**<0.001**	0.658 [0.609; 0.704]	**<0.001**	**0.049**
B-lines **	77 (17.6 %)	0.659 [0.543-0.764]	**0.011**	0.693 [0.575; 0.812]	**0.002**	0.628
IVC_{exp}, cm **	278 (63.6 %)	0.680 [0.622; 0.734]	**<0.001**	0.685 [0.627; 0.739]	**<0.001**	0.890
IVC collapse, % *	274 (62.7 %)	0.633 [0.570; 0.688]	**<0.001**	0.633 [0.573; 0.690]	**<0.001**	0.942
RV basal diameter **	275 (62.9 %)	0.600 [0.539; 0.658]	**0.004**	0.679 [0.620; 0.734]	**<0.001**	**0.032**
RA end-systolic area**	253 (57.9 %)	0.694 [0.633; 0.750]	**<0.001**	0.680 [0.619; 0.737]	**<0.001**	0.731
TAPSE*	315 (72.1 %)	0.687 [0.632; 0.737]	**<0.001**	0.702 [0.648; 0.752]	**<0.001**	0. 643
RV free wall strain, %*	189 (43.2 %)	0.632 [0.559; 0.701]	**<0.001**	0.701 [0.630; 0.765]	**<0.001**	0.095
Entire RV strain, %*	189 (43.2 %)	0.651 [0.578; 0.719]	**<0.001**	0.750 [0.682; 0.810]	**<0.001**	**0.014**
Tricuspid regurgitation velocity, m/s **	314 (71.9 %)	0.581 [0.525; 0.637]	**<0.001**	0.579 [0.516; 0.642]	**<0.001**	0.954
High eRAP, yes	274 (62.7 %)	0.674 [0.615; 0.729]	**<0.001**	0.702 [0.644; 0.756]	**<0.001**	0.506
LVDD, cm **	393 (89.9 %)	0.649 [0.600; 0.696]	**<0.001**	0.684 [0.632; 0.737]	**<0.001**	0.240
LVMI, g/m^2 **	344 (78.7 %)	0.643 [0.589; 0.693]	**<0.001**	0.749 [0.698; 0.801]	**<0.001**	**<0.001**
LAVI, mL/m^2 **	217 (40.3 %)	0.617 [0.549; 0.682]	**0.002**	0.720 [0.653; 0.787]	**<0.001**	**0.012**
LV EF, % *	400 (91.5 %)	0.632 [0.583; 0.679]	**<0.001**	0.757 [0.712; 0.798]	**<0.001**	**<0.001**
E wave *	307 (70.3 %)	0.632 [0.576; 0.686]	**<0.001**	0.665 [0.609; 0.717]	**<0.001**	0.350
E/e` ratio (average) **	201 (46.0 %)	0.632 [0.561; 0.699]	**<0.001**	0.743 [0.677; 0.802]	**<0.001**	**0.012**

** Value lower than the median, ** value greater than the median, # P for comparison between sCD146 and NT-proBNP*

Values are expressed as n, median (interquartile range) or n (%), unless otherwise stated. Significant p-values (<0.05) are presented in bold. eRAP: estimated right atrial pressure; IVC: inferior vena cava; IVC_{exp}: inferior vena cava at expiration; LAVI: left atrial volume index; LVDD: left ventricular *internal* diameter *in end-diastole; LV EF: left ventricular ejection fraction; LVMI: left ventricular mass index; RA: right atrial; RV: right ventricular; TAPSE: tricuspid annular plane systolic excursion.*

Supplementary Figure. The comparison of sCD146 and NT-proBNP in predicting the presence of congestion and cardiac dysfunction



IVC: inferior vena cava, LV EF: left ventricular ejection fraction

9

CHAPTER 9

DISCUSSION

9.1. The presence of clinical congestion in chronic heart failure

Clinical signs and symptoms of congestion remain the key indicators guiding decongestive interventions in daily clinical practice. This approach is advised by the current European Society of Cardiology (ESC) guidelines[1], although a randomised controlled trial has shown that a clinical judgement is inferior to an invasively measured pulmonary artery pressure, at least in some heart failure (HF) patients[2,3]. Still, the present research reveals the high prevalence of clinical congestion in a chronic HF setting. As extensively outlined in Chapter 3, two out of three chronic HF patients were obviously congested at baseline, as reflected by the clinical congestion index ≥ 3. This finding probably represents a contemporary real-world clinical setting given the fact that patients were considered to be clinically stable and clinical examination at baseline was done prior to an intensive treatment escalation and close follow-up[4]. Our analysis showed that treatment intensification and close follow-up may result in partial or full clinical decongestion. In fact, 40% of patients had no clinical signs and symptoms of congestion 1.5 years after inclusion, whereas there were only 6% of such patients before treatment intensification was applied. Still, a significant part of patients did not respond sufficiently to decongestive interventions and remained congested. As depicted in Chapter 3, these patients were already severely congested at baseline, meaning that current management interventions are ineffective in a significant part of chronic HF patients, especially if severe clinical congestion is present. In fact, congested TIME-CHF participants were already treated with higher loop diuretic doses as compared to less congested patients, but this treatment did not necessarily translate into successful decongestion, again underscoring an unmet need for optimised congestion management interventions in a contemporary chronic HF care.

The presence of congestion not only distinguishes hypervolemic from euvolemic/hypovolemic patients. We were able to show that congested patients have a higher comorbidity burden including more renal impairment. This is clinically very important, because renal dysfunction is often seen as a trigger to down-titrate diuretics in clinical practice[5], whereas venous congestion is probably the key driver of decreasing renal function in HF[6]. This cardiorenal interaction is often misunderstood and potentially leads to wrong clinical decisions, translating into progressing volume overload, subsequent renal damage including the development of tubular dysfunction[7]. It has been previously shown that worsening renal function is a marker of poor outcome primarily in case of persistent congestion[8]. Therefore, congestion should be seen as a primary target for treatment, even in case of renal impairment.

9.2. The impact of clinical congestion on chronic heart failure outcome

The present research indicates that the clinical congestion index may assist in congestion detection and grading. Even more, this clinical biomarker was found to be a strong and independent predictor of HF outcome. The presence and the degree of congestion was closely related to worse survival and HF hospitalisation-free survival. This is in line with previous observations relating clinical congestion with poor HF prognosis[9,10]. However, previously developed clinical congestion scoring tools are very complex and their implementation in a busy real world clinical practice is limited. In contrast, the clinical congestion index encompasses easily detectable bed-side clinical parameters without subjective grading of their severity. Despite its simplicity, the clinical congestion index was able to discriminate patients with poor outcome in a severity-dependant manner.

TIME-CHF provided a platform to check the performance of clinical congestion at different time-points during 1.5 years of active follow-up. This analysis revealed a close relationship between (the severity of) congestion and poor HF outcome, regardless of the time of evaluation. We showed that congestion is highly prognostic before, during, and after treatment intensification. Even more, the design of the trial allowed to extensively analyse different longitudinal clinical congestion patterns in a sufficiently large population of chronic HF. Previous research mostly concentrated on the presence of congestion at a single timepoint. Therefore, the present analysis adds significantly to the understanding of (de)congestion in a contemporary HF context. The clustering of congestion dynamics allowed to identify the patterns of (de)congestion over time and subsequently demonstrate that: i) rapid decongestion is related to the best outcome; ii) patients experiencing relapses of congestion are at increased risk of death, as compared to patients with consistent decongestion; iii) persistent congestion carries the worst outcome for both survival and HF hospitalisation-free survival. We showed that careful and structured clinical judgement taking into consideration right and left-sided signs and symptoms of congestion may be useful in identifying high risk groups of patients, meaning that clinical evaluation should remain the mainstay in a real-world clinical practice until other means guiding decongestion are investigated and introduced. In particular, clinical judgement taking into consideration the components of the clinical congestion index should be a part of standard clinical evaluation. Once identified, clinical congestion should be treated as patients achieving clinical decongestion have better outcome as compared to patients with relapses / persistent congestion. Still, treatment can only be initiated if congestion is detected, therefore, congestion screening remains a central component in clinical assessment of HF patients.

9.3. Diuretics in heart failure: does the dosing strategy matter?

Loop diuretics remain the cornerstone of congestion management since no other alternatives have been proven to be superior in terms of efficacy and safety. These drugs act by competing with chloride to bind to the Na-K-2Cl co-transporter in the thick ascending limb of the loop of Henle. This process diminishes electrochemical gradient across the cell, in turn leading to a decrease in sodium reabsorption from the tubular lumen[11]. Loop diuretic-induced reduction in interstitial sodium leads to a reduction in water reabsorption. Up to 25% of total tubular sodium is reabsorbed in the thick ascending loop of Henle[12–14]. This makes loop diuretics the most powerful diuretics in the contemporary medicine. The current guidelines advice diuretic therapy to all patients with signs and symptoms of congestion[1], but diuretic drugs have never been tested in a large randomized condoled trial, as extensively overviewed in Chapter 2. Therefore, guidelines mostly rely on expert opinion-based consensus, rather than evidence. Nine out of ten TIME-CHF participants were on a loop diuretic during the active follow-up period, meaning that the vast majority of chronic HF patients receive drugs without a proven benefit from such therapy.

A Canadian pharmacare database was retrospectively analysed to investigate the relationship between chronic loop diuretic use and heart failure outcome in the elderly. The authors included 4406 loop diuretic users and related increasing loop diuretic dose to worse morbidity and mortality prognosis even after extensive multivariate adjustment[15]. The Japanese Cardiac Registry of Heart Failure in Cardiology was used to analyse the relationship between the use of loop diuretics after discharge for HF decompensation and HF outcome. The authors included 2015 patients and found that loop diuretic use after discharge was associated with worse survival and HF hospitalization-free survival, even after propensity score matching was performed[16]. The Digitalis Investigation Group trial dataset was employed to include 1391 diuretic users with 1391 propensity matched non-users in order to test the effect of chronic diuretic use on HF outcome. The investigators again related chronic loop diuretic use to increased morbidity and mortality[17]. Since both congestion (see *The impact of clinical congestion on chronic heart failure outcome*) and its treatment with (high dose) loop diuretic agents were independently related to worse survival, some very important questions about the safety of current loop diuretic use remain open. The present doubts are justified, given the potential side effects of loop diuretics (see *Chapter 2*). On the other hand, reluctance to prescribe loop diuretics (especially in sufficient/high doses) may lead to persistent congestion in daily clinical practice. The fact that most TIME-CHF patients were congested at baseline

supports this hypothesis. Also, in a real-world setting diuretic dose adjustment is rarely done, as overviewed in Chapter 4. Therefore, decongestive interventions are likely suboptimal.

Thiazide and thiazide-like diuretics are much less effective in controlling volume overload when prescribed alone. Their diuretic effect is related to their site of action in the proximal segment of the distal convoluted tubule. Thiazide diuretics induce their diuretic effect by blocking the Na/Cl reabsorption in the distal convoluted tubule, which is responsible for up to 3-5% of total tubular sodium reuptake from the tubular fluid to the interstitium[14]. This makes thiazides insufficient to control volume overload in oedematous states such as HF, especially if administered in monotherapy. However, in long-term loop diuretic users chronic blockade of sodium reabsorption leads to high quantities of sodium continuously reaching the distal convoluted tubule. This chronic sodium exposure induces morphological changes in the distal part of the nephron. In particular, distal tubular cells undergo compensatory hypertrophy[18], and their sodium reabsorption potential increases significantly[19]. This makes a combination therapy with loop and thiazide diuretics an option if high dose loop diuretic treatment becomes insufficient. It has been previously shown that such combination therapy results in increased diuresis[20,21], even in patients with advanced renal failure[22]. Still, such double (sequential) nephron blockade can cause significant side effects[20], and its implementation usually means the development of diuretic resistance[21]. Diuretic resistance is very multifactorial, but its development was previously identified as an independent predictor of outcome[23].

Still, the present research showed that both high loop diuretic dose administration as well as the use of thiazides did not independently predict survival and HF hospitalisation-free survival. In contrast, persistent clinical congestion remained a strong and independent predictor of hard outcome. This finding deserves further studying, as it supports the hypothesis that persistent congestion drives poor outcome, but not the potentially harmful effects of decongestive therapies.

To better understand the prognostic role of intensification of diuretic therapy in light of clinical congestion we analysed the outcomes of patients receiving different strategies of decongestive interventions (intensification vs no intensification), taking into account the effect of the intervention (decongestion / persistent congestion / progressing congestion). As discussed in Chapter 5, one-third of patients underwent intensification of diuretic management (an increase in loop diuretic dose or a concomitant use of a thiazide) over 6 months. The worst survival and HF hospitalisation-free survival was documented in patients with persistent/progressing congestion in spite of diuretic treatment intensification. It is obvious that diuretic treatment escalation was ineffective in these patients, and this interaction led to poor outcome. Given the

fact that neither the use of high loop diuretic dose, nor the addition of a thiazide diuretic was independently associated with poor outcome, one may speculate that persistent congestion was the main driver of impaired prognosis. It is possible that a more aggressive decongestive approach (higher doses / higher frequency of administration / more combination therapy) would have translated into better outcome. This hypothesis is supported by the fact that patients achieving clinical decongestion as a result of treatment intensification were less likely to be rehospitalised or die. Thus, the negative effects of high dose diuretic therapy found in the above mentioned studies[15–17] may be related to more advanced HF rather than the use of diuretic therapy. Most likely, it is impossible to fully adjust for HF severity and congestion even with propensity score matching to replace a prospective randomised controlled trial. A beneficial effect of diuretic therapy for sufficient decongestion is also supported by the results of the CHAMPION trial, where adjustment of therapy based on intracardiac filling pressures resulted in better outcome[3]. Importantly, the most common adjustment in this study was diuretic therapy. Therefore, diuretic dose escalation should be initiated in all patients with persistent / relapsing congestion. Still, some very important knowledge gaps remain: i) when is the optimal time-point to initiate sequential nephron blockade with a loop diuretic and a thiazide diuretic instead of increasing a loop diuretic dose; ii) are there any alternatives for patients that are resistant to the intensification of diuretic treatment; iii) is clinical judgement the best trigger for diuretic dose escalation in daily clinical practice? iv) A randomised controlled trial is urgently needed to test the hypothesis that aggressive decongestion approach is superior to the conservative approach in improving hard outcome.

9.4. Bio-ADM as a marker of congestion

Bio-ADM is an endogenous peptide released from the vasculature in response to increasing vascular permeability and/or volume overload[24]. Its function is to maintain vascular integrity and prevent tissue oedema[25–28]. This makes bio-ADM a potential blood biomarker of congestion. Indeed, by using an acute dyspnoea setting as a model of congestion we were able to demonstrate its close relationship with the presence and the degree of intravascular and tissue congestion, as extensively outlined in Chapter 6. Patients with peripheral oedema at admission had a significantly higher plasma bio-ADM level, as compared to patients without oedema. The present analysis revealed that plasma bio-ADM concentration is increasing in parallel with increasing severity of rales. The relationship between plasma bio-ADM level and estimated right atrial pressure was also demonstrated in a severity-dependent manner. These findings support the hypothesis that plasma bio-ADM may serve as a marker of congestion.

As discussed in Chapter 6, a significant number of patients presented with high bio-ADM value despite an NT-proBNP concentration being below the median. This again underscores a complementary role of plasma bio-ADM in revealing the presence of congestion. The present observation is supported by a recent finding that acute HF patients with high plasma bio-ADM level exhibit a higher all-cause mortality if they are not on diuretics at discharge, whereas the same could not be said about an NT-proBNP level[29].

We were able to demonstrate that bio-ADM is not only capable to reflect congestion but is also a good predictor of outcome. Similar to the clinical congestion index, bio-ADM was identified as a strong and independent predictor of survival (90-day survival endpoint was chosen for this analysis). This finding again illustrates the relationship between congestion and worse outcome. Still, it needs to be prospectively tested if bio-ADM is helpful in guiding decongestion therapy, both in acute and chronic HF, in a prospective randomised controlled trial with sufficient power to demonstrate the effects on hard outcomes.

Moreover, an artificial intelligence-based survival tree analysis revealed a close relationship between bio-ADM level, treatment with neurohumoral blockers and 90-day survival, as depicted in Chapter 6. This finding is very important from a pathophysiological and management point of view since it opens a window for future therapeutic implications. In particular, the present research indicates that patients with both bio-ADM and NT-proBNP levels below the median had no benefit from treatment with angiotensin-converting enzyme inhibitor (ACEi)/angiotensin receptor blocker (ARB)/beta blocker (BB) (treatment with any of the three is hereinafter referred to as neurohumoral blockade). However, an elevation in any of the two biomarkers above the median indicated better survival, if neurohumoral blockade was prescribed. Moreover, a significant interaction between plasma bio-ADM concentration, neurohormonal blockade and survival in dyspnoeic patients with low NT-proBNP concentration was demonstrated. Given the well-established relationship between neurohumoral activation and the development of congestion in HF (see *Congestion pathophysiology*), this finding deserves further prospective testing.

9.5. Soluble CD146 as a marker of congestion

As overviewed in Chapter 7, soluble cluster of differentiation 146 (sCD146) has recently emerged as a promising blood biomarker of congestion, given its vascular origin and the mechanisms of its releases into systemic circulation. Arrigo et al. have demonstrated that a peripheral venous stretch-induced congestion triggers a rapid and pronounced increase in plasma sCD146 concentration[30]. This study also proved that the origin of sCD146 is

predominantly vascular, but not cardiac[30]. Since cardiac biomarkers are primarily the indicators of cardiac damage, a vascular biomarker becomes a particularly interesting object for congestion research. By using an acute dyspnoea model we demonstrated that in a real-world patient population, sCD146 concentration is significantly higher if clinical signs of congestion are present. In particular, acute dyspnoea patients presenting with rales and peripheral oedema had a significantly higher plasma sCD146 concentration as compared to patients without these clinical findings. Even more, sCD146 concentration was increasing in paralel with increasing estimated right atrial pressure, again proving its relationship with vascular stretching. An important question is if testing a biomarker of vascular stretching adds to the measurements of natriuretic peptides – a widely available biomarker of cardiac stretch. We were able to demonstrate that in patients with low plasma NT-proBNP concentration increased sCD146 was able to disect a significant number of patients with prevelent clinical (peripheral oedema) and intravascular (estimated right atrial pressure) congestion. Even more, plasma sCD146 concentration was rising with increasing E/e' ratio – a previously described ultrasound marker of congestion, reflecting diastolic left ventricular filling[31]. Taken together, sCD146 reflects intravascular, cardiac and tissue congestion and deserves further testing in a randomised interventional trials to estimate its clinical value.

9.6. The relationship between cardiac damage and congestion

Extensive echocardiographic analysis of acute dyspnoea patients with sCD146 measurements enabled to look at the relationship between congestion and cardiac damage. As discussed in Chapter 8, patients with plasma sCD146 concentration above the median had a significantly worse left and right ventricular systolic function, as well as more pronounced changes in cardiac morphology. In particular, patients with increased sCD146 values had a significantly decreased left ventricular ejection fraction as well as lower values of tricuspid anulus systolic excursion and right ventricular strain. This finding is very important from a pathophysiological point of view since it illustrates the relationship between a vascular marker with proven non-cardiac origin and cardiac damage. Although such an analysis does not reveal causality, it is possible that patients with more morphological damage and worse functional capacity are more likely to develop congestion, and in the other way round, intravascular congestion is likely to lead to cardiac chamber dilation and impaired biventricular function.

9.7. Lessons learned

The field of (de)congestion remains challenging, given the complex interactions between fluid accumulation in the human body, gaps in knowledge about diuretic management, high prevalence of serious comorbidities in heart failure patients (particularly renal failure), and the effects of each of these factors on outcome. Even more, the potential interaction of all these factors is obvious, but remains difficult to estimate. The presence/persistence of congestion indicates poor outcome in chronic HF and this association is severity dependent. At the same time, (de)congestion remains insufficiently investigated in a contemporary era of evidence-based medicine, meaning that in a daily clinical practice we do not really know if HF patients do receive optimised interventions. In the light of that, congestion remains present in many chronic HF patients. Successful treatment starts from accurate diagnostics. Therefore, in daily clinical examination congestion detection should encompass right and left-sided clinical signs and symptoms of fluid accumulation. The clinical congestion index may serve as a handy tool in clinical practice assisting in congestion detection and grading. Still, clinical congestion is already a late manifestation of a continuous process of sodium and water retention. Therefore, the goal should be to target fluid accumulation as early as possible, i.e., before clinical signs and symptoms become apparent. Blood biomarkers reflecting congestion may assist in that regard. In particular, both bio-ADM and sCD146 are capable to reflect the presence and the degree of congestion, as assessed by means of clinical and sonographic markers. Still, their role has never been tested in an interventional trial, limiting their applicability in daily clinical practice. Until such trials are carried out, a multimarker approach should be implemented in daily clinical practice, integrating extensive clinical evaluation (e. g. a clinical congestion index), imaging markers of fluid accumulation (echocardiography, pulmonary - pleural, renal / hepatic / portal / inferior vane cava sonography) and blood biomarkers. Although not supported by evidence from randomised clinical trials, such an approach is current best practice and indirect evidence suggest that it is justified as discussed above. Following this concept, we have suggested an algorithm for congestion detection in collaboration with the Biomarkers and Imaging Study Groups of the Heart Failure Association of the European Society of Cardiology[32]. Future trials will show if such emerging biomarkers of congestion as bio-ADM and sCD146 will be added to this multimarker concept.

Loop diuretic treatment and its combination with thiazide/thiazide-like diuretics remain the key elements of medical treatment for patients with congestion. Although there are some doubts about the safety of diuretic drugs in HF, congestion itself seems to be more predictive of outcome than diuretic treatment. A close follow-up and predefined escalation roles may result

in clinical decongestion for most patients, but a significant number of HF patients remain congested despite diuretic treatment intensification. This group of patients carries the worst prognosis and high loop diuretic dose / thiazide co-administration did not appear as independent predictors of outcome. Taken altogether, complete decongestion should remain the goal of treatment in heart failure, but its implementation in clinical practice is still incomplete.

9.8. Future challenges

There are several remaining challenges which should be addressed in future prospective research:

1. Does a decongestive strategy based on a clinical congestion index improve outcome?
2. Does a more aggressive treatment with diuretics in order to completely decongest improve outcome?
3. When should a thiazide co-administration be used? How long should sequential nephron blockade be used? Which thiazide drugs should be preferred?
4. Does a thiazide co-administration to completely decongest improve outcome?
5. What levels of bio-ADM and sCD146 indicate the absence of congestion in chronic heart failure? Are there even better (bio)markers to detect congestion reliably?
6. Do decongestive interventions based on bio-ADM and/or sCD146 improve outcome?
7. Does the administration of neurohumoral blockers improve outcome in acute dyspnoea patients with high bio-ADM levels on admission?

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CHAPTER 10

SUMMARY

Introduction

The burden of heart failure is continuously rising worldwide. More than 60 million people suffer from it globally, and this number is estimated to increase dramatically, given the advances in treatment of myocardial infarction in an acute setting and increasing proportion of elderly patients in the modern societies. Despite some major innovations in medical and instrumental management, the prognosis of heart failure patients remains poor. There is little improvement in rehospitalization and mortality within a year after treatment for decompensation, which is primarily caused by congestion. Congestion is a recognised contributor to heart failure events, but its treatment with loop diuretics has never been prospectively evaluated in a sufficiently powered randomised clinical trial and remains poorly understood. Even more, some observational trials have uniformly related treatment with (high doses) loop diuretic agents to increased morbidity and mortality burden, but this observation may be biased and worse outcome may be in fact driven by congestion itself. Indeed, the presence and degree of congestion was not taken into account in these studies. This is in part because congestion is difficult to detect and data about its presence is often missing. There is an unmet need to find some novel tools for congestion detection and grading, in order to optimise congestion management interventions, potentially leading to an improvement in heart failure care. An in-depth observational analysis of the Trial of Intensified versus standard Medical therapy in Elderly patients with Congestive Heart Failure (TIME-CHF) and Lithuanian Echocardiography Study of Dyspnoea in Acute Settings (LEDA) was carried out to investigate the complex relationships between congestion, its treatment with loop diuretics and outcome as well as to look for novel biomarkers assisting in congestion detection and grading.

Results

The evidence behind loop diuretic treatment is extensively analysed in Chapter 2. This descriptive analysis showed that congestion management is primarily empirical in a contemporary clinical practice, given the absence of data from modern randomized controlled clinical trials. Even more, a detailed analysis of observational trials revealed that there exists a dose-dependent relationship between loop diuretic treatment and adverse events with no good quality data on causality. Potential mechanism of harm and benefit are also reviewed in Chapter 2. Recommendations for improvement of current clinical practice are outlined, underscoring the importance of fluid status assessment with clinical, instrumental, and circulating biomarkers. Some difficult scenarios of decongestion, including worsening renal function,

electrolyte imbalance, and diuretic resistance are discussed in more detail with a special focus on practical recommendations.

Longitudinal clinical congestion patterns are analysed in Chapter 3. This analysis resulted in the development of a 7-item clinical congestion index (CCI), that showed its excellent prognostic properties. Sixty-one percent of TIME-CHF participants had a CCI ≥ 3 at baseline, which decrease to 18% at month 18. During the median [interquartile range] follow-up of 27.2 [14.3 – 39.8] months, 17%, 27%, and 47% of patients with baseline CCI of 0, 1-2, and ≥3 at inclusion, respectively, died ($p<0.001$). CCI was identified as an independent predictor of mortality and heart failure hospitalization-free survival. Successful decongestion was related to better outcome as compared to persistent congestion or partial decongestion (log-rank $p<0.001$).

The findings from the European Society of Cardiology Heart Failure Long Term (ESC-HF-LT) registry are challenged in Chapter 4. In particular, the ESC-HF-LT registry revealed that only 1 out of 4 patients undergoes loop diuretic dose adjustment in daily clinical practice, which is not likely to meet the recommendations of the current guidelines advising on the adaptation of treatment to the individual needs. Even more, loop diuretic de-escalation was unsuccessful in 52% of the cases although it only took place in only 8.3% of all patients. Despite that, the ESC-HF-LT investigation group advised on attempting loop diuretic dose de-escalation more often. Therefore, constructive criticism regarding this recommendation was shared in Chapter 4, drawing the attention from de-escalation to more accurate fluid status assessment.

The relationship between diuretic management and heart failure outcome considering the effect of this treatment on congestion is analysed in Chapter 5. Both treatment with high loop diuretic dose (≥80 mg of furosemide per day) and thiazide co-administration were not identified as independent predictors of outcome, whereas congestion remained strongly and independently related to worse survival and heart failure hospitalization-free survival. Treatment intensification (the need to increase loop diuretic dose or add a thiazide drug) was independently associated with survival (HR 1.75, 95% CI [1.19-1.38], $p=0.004$) and heart failure hospitalisation-free survival (HR 1.69, 95% CI [1.22-2.35], $p=0.002$). Still, the analysis showed that patients undergoing treatment intensification resulting in decongestion had better outcome than patients with persistent (worsening) congestion despite LD dose up-titration ($p<0.001$). This suggests that congestion but not diuretic therapy is the main driver of poor outcome in heart failure patients.

The role of biologically active adrenomedullin (bio-ADM) in an acute dyspnoea model of congestion is described in Chapter 6. Bio-ADM concentration was higher in patients with

peripheral oedema at admission (48.2 [28.2-92.6] vs 35.4 [20.9-59.2] ng/L, p<0.001). A stepwise increase in bio-ADM concentration was demonstrated with increasing prevalence of rales: 29.8 [18.8-51.1], 38.5 [27.5-67.1], and 51.1 [33.1-103.2] ng/L in patients with no rales, rales covering < ½, and ≥ ½ of the pulmonary area, respectively (p<0.001). Bio-ADM concentration showed a gradual elevation in patients with normal, moderately, and severely increased estimated right atrial pressure (eRAP): 25.1 [17.6-42.4] ng/L, 36.1 [23.1-50.2] and 47.1 [30.7-86.7] ng/L, respectively (p<0.05). Survival tree analysis revealed that bio-ADM is a potent prognostic marker in acute dyspnoea. Survival in patients with high bio-ADM was significantly modified by neurohormonal blockade at admission (p<0.05), especially if NT-proBNP levels were lower than the median (p = 0.002 for interaction).

The potential role of soluble cluster of differentiation (sCD146) in congestion detection and grading is reviewed in Chapter 7, underscoring the mechanisms of its release and the already existing experimental and observational data showing its congestion assessment potential. In an acute dyspnoea model of congestion (Chapter 8), sCD146 concentration was significantly higher in patients presenting with peripheral oedema (472 [373-535] vs 400 [304-501] ng/mL, p=0.009) and rales (439 [335-528] vs 394 [296-484] ng/mL, p=0.001) at admission. Also, a parallel increase in eRAP and sCD146 concentration was demonstrated: 337 [300;425], 404 [290;489] and 477 [363;572] ng/mL in patients with normal, moderately elevated, and severely elevated eRAP, respectively (p=0.001). The additive value of sCD146 in disclosing interstitial and intravascular congestion was also observed in patients with low NT-proBNP values. Soluble CD146 – a peripheral biomarker – was able to reflect the presence and the severity of morphological and functional changes in the heart, including chamber dilation and biventricular function.

Discussion

Congestion is highly prevalent in a chronic heart failure setting. The present research demonstrates that an extensive clinical evaluation by means of a CCI enables to discriminate congested patients who are at risk of heart failure hospitalisation and death. The use of high doses loop diuretics as well as a combination therapy with thiazides both indicate worse outcome, but this relationship is mostly dependent on the severity of heart failure, rather than a direct negative effect of diuretics on outcome. This finding is supported by the fact that neither the use of high loop diuretic dose, nor the addition of a thiazide appeared as independent predictors of outcome in an extensive multivariate model. Even more, the worst prognosis was noted in case of diuretic treatment intensification, not resulting in clinical decongestion,

whereas treatment intensification leading to complete or partial clinical decongestion was related to better outcome. Taken together, these findings underscore the importance of freedom from congestion. In clinical practice, intensive diuretic management should not be avoided in patients with persistent clinical signs / symptoms of congestion. The present research demonstrates that tolerating congestion is deleterious. Still, the effect of such strategy on outcome should be prospectively tested in a randomised controlled trial.

Bio-ADM and sCD146 both showed their ability to reflect congestion as assessed by means of clinical evaluation and ultrasound markers. Even more, an interaction between bio-ADM and neurohumoral blockade in acute dyspnoea was detected, but this observation needs further prospective testing. Soluble CD146 also showed its ability to reflect morphological and functional changes of the heart, despite being excreted from the vasculature. This finding is very important from a pathophysiological point of view since it illustrates a relationship between vascular congestion and cardiac damage. Whether congestion management interventions based on bio-ADM and sCD146 improve hard outcome should be tested in appropriate interventional clinical trials.

SAMENVATTING

De prevalentie van hartfalen neemt wereldwijd voortdurend toe. Wereldwijd lijden meer dan 60 miljoen mensen aan hartfalen en dit aantal zal naar schatting nog sterk toenemen, mede gezien de vooruitgang in de behandeling van myocardinfarcten in een acute setting en het toenemende aantal oudere patiënten in de moderne samenleving. Ondanks enkele belangrijke innovaties in de medische en instrumentele behandeling blijft de prognose van hartfalenpatiënten slecht. Er is weinig verbetering in heropnamecijfers en sterfte binnen een jaar na behandeling voor decompensatie, die voornamelijk wordt veroorzaakt door congestie. Congestie is een erkend gevolg van hartfalen, maar de behandeling ervan met lisdiuretica is nooit prospectief geëvalueerd in een voldoende grote, gerandomiseerde klinische studie en wordt nog steeds slecht begrepen. Sterker nog, sommige observationele studies hebben een verband gelegd tussen behandeling met (hoge doses) lisdiuretica en een verhoogde morbiditeit en mortaliteit, maar deze observatie kan een vertekend beeld zijn en de slechte uitkomst kan gedreven zijn door de aanwezigheid van congestie zelf; hetgeen niet in beschouwing werd genomen in deze studies. Dit komt deels doordat congestie moeilijk te detecteren is en gegevens over de aanwezigheid ervan vaak ontbreken. Er is dan ook een onvervulde behoefte voor congestiedetectie en -classificatie, om de interventies voor congestiebeheer te optimaliseren, wat mogelijk leidt tot een verbetering van de zorg voor hartfalen. Een diepgaande observationele analyse van de Trial of Intensified versus standard Medical therapy in Elderly patients with Congestive Heart Failure (TIME-CHF) en Lithuanian Echocardiography Study of Dyspnoea in Acute Settings (LEDA) werd uitgevoerd om de complexe verbanden tussen congestie, de behandeling ervan met lisdiuretica en het resultaat te onderzoeken, alsook om te zoeken naar nieuwe biomarkers die helpen bij de detectie en gradering van congestie.

Resultaten

Het bewijs achter de behandeling met lisdiuretica is uitgebreid geanalyseerd in hoofdstuk 2. Deze beschrijvende analyse toonde aan dat de behandeling van congestie in de hedendaagse klinische praktijk voornamelijk empirisch is, gezien de afwezigheid van gegevens uit gerandomiseerde gecontroleerde klinische trials. Bovendien bleek uit een gedetailleerde analyse van observationele trials dat er een dosis-afhankelijk verband bestaat tussen de behandeling met loop-diuretica en bijwerkingen, zonder gegevens van goede kwaliteit over de causaliteit. Potentiële mechanismen van voor- en nadelen van diuretica worden besproken in hoofdstuk 2. Aanbevelingen voor verbetering van de huidige klinische praktijk worden geschetst, waarbij het belang van vochtstatusbepaling met klinische, instrumentele, en

biomarkers wordt onderstreept. Enkele moeilijke scenario's van decongestie, waaronder verslechterende nierfunctie, elektrolyten onbalans, en diuretische resistentie worden in meer detail besproken met een speciale focus op praktische aanbevelingen.

Longitudinale klinische congestiepatronen worden geanalyseerd in hoofdstuk 3. Deze analyse resulteerde in de ontwikkeling van een klinische congestie index (CCI) gebaseerd op 7 items, die uitstekende prognostische eigenschappen liet zien. Eenenzestig procent van de TIME-CHF deelnemers had een CCI ≥ 3 op baseline, wat afnam tot 18% op maand 18. Tijdens de mediane [interkwartielafstand] follow-up van 27,2 [14,3 - 39,8] maanden overleed respectievelijk 17%, 27% en 47% van de patiënten met een CCI van 0, 1-2, en ≥3 bij inclusie (p<0,001). CCI werd geïdentificeerd als een onafhankelijke voorspeller van mortaliteit en hartfalen ziekenhuisopname-vrije overleving. Succesvolle decongestie was gerelateerd aan een betere uitkomst in vergelijking met persisterende congestie of gedeeltelijke decongestie (log-rank p<0,001).

De bevindingen van de European Society of Cardiology Heart Failure Long Term (ESC-HF-LT) registry worden in hoofdstuk 4 in twijfel getrokken. Met name bleek uit het ESC-HF-LT register dat bij slechts 1 op de 4 patiënten in de dagelijkse klinische praktijk de dosis van lisdiuretica wordt aangepast, wat waarschijnlijk niet in overeenstemming is met de aanbevelingen van de huidige richtlijnen die adviseren de behandeling aan te passen aan de individuele behoeften. Bovendien was de reductie van lisdiuretica in 52% van de gevallen niet succesvol, hoewel dit slechts bij 8,3% van alle patiënten gebeurde. Desondanks adviseerde de ESC-HF-LT onderzoeksgroep om vaker vermindering van de dosis lisdiuretica te proberen. Daarom werd constructieve kritiek op deze aanbeveling gedeeld in Hoofdstuk 4, waarbij de aandacht werd verlegd van de-escalatie naar een meer accurate beoordeling van de vochtstatus.

De relatie tussen diureticumbehandeling en de uitkomst van hartfalen, rekening houdend met het effect van deze behandeling op congestie, wordt geanalyseerd in hoofdstuk 5. Zowel behandeling met een hoge dosis lisdiuretica (≥80 mg furosemide per dag) als thiazide gelijktijdige toediening werden niet geïdentificeerd als onafhankelijke voorspellers van de uitkomst, terwijl congestie sterk en onafhankelijk gerelateerd bleef aan slechtere overleving en hartfalen ziekenhuisopname-vrije overleving. Intensivering van de behandeling (de noodzaak om de dosis lisdiuretica te verhogen of een thiazidemedicijn toe te voegen) was onafhankelijk geassocieerd met overleving (HR 1,75, 95% CI [1,19-1,38], p=0,004) en hartfalen ziekenhuisopname-vrije overleving (HR 1,69, 95% CI [1,22-2,35], p=0,002). Echter toonde deze analyse aan dat patiënten die intensivering van de behandeling ondergingen resulterend in decongestie, een betere uitkomst hadden dan patiënten met aanhoudende (verergerende)

congestie ondanks verhoging van de LD-dosis (p<0,001). De analyse suggereert dat congestie, maar niet de diuretische behandeling de prognose van hartfalenpatiënten verslechterd.

De rol van biologisch actief adrenomedulline (bio-ADM) in een acuut dyspnoea model van congestie wordt beschreven in hoofdstuk 6. De bio-ADM concentratie was hoger bij patiënten met perifeer oedeem bij opname (48,2 [28,2-92,6] vs 35,4 [20,9-59,2] ng/L, p<0,001). Een stapsgewijze toename van de bio-ADM concentratie werd aangetoond met toenemende prevalentie van creptitaties: 29,8 [18,8-51,1], 38,5 [27,5-67,1], en 51,1 [33,1-103,2] ng/L bij patiënten met respectievelijk geen creptitaties, creptitaties die < ½, en ≥ ½ van het pulmonale gebied bevatten (p<0,001). De bio-ADM-concentratie vertoonde een geleidelijke stijging bij patiënten met normale, matig en ernstig verhoogde rechter atriumdruk (eRAP): 25,1 [17,6-42,4] ng/L, 36,1 [23,1-50,2] en 47,1 [30,7-86,7] ng/L, respectievelijk (p<0,05). Overlevingsboomanalyse toonde aan dat bio-ADM een krachtige prognostische marker is bij acute dyspneu. De overleving bij patiënten met een hoog bio-ADM werd significant beïnvloed door neurohormonale blokkade bij opname (p<0,05), vooral als de NT-proBNP niveaus lager waren dan de mediaan (p = 0,002 voor interactie).

De potentiële rol van sCD146 in de detectie en classificatie van congestie wordt besproken in hoofdstuk 7, waarbij de mechanismen van het vrijkomen ervan en de reeds bestaande experimentele en observationele gegevens die het potentieel ervan voor de beoordeling van congestie aantonen, worden onderstreept. In een acuut dyspneu model van congestie (Hoofdstuk 8), was de sCD146 concentratie significant hoger bij patiënten die zich presenteerden met perifeer oedeem (472 [373-535] vs 400 [304-501] ng/mL, p=0.009) en crepitaties (439 [335-528] vs 394 [296-484] ng/mL, p=0.001) bij opname. Ook werd een parallelle toename van de eRAP en sCD146 concentratie aangetoond: 337 [300;425], 404 [290;489] en 477 [363;572] ng/mL bij patiënten met respectievelijk normale, matig verhoogde, en ernstig verhoogde eRAP (p=0,001). De toegevoegde waarde van sCD146 bij het aantonen van interstitiële en intravasculaire congestie werd ook gezien bij patiënten met lage NT-proBNP-waarden. sCD146 - een perifere biomarker - was in staat om de aanwezigheid en de ernst van morfologische en functionele veranderingen in het hart weer te geven, met name met betrekking tot kamerverwijding en biventriculaire functie.

Discussie

Congestie komt veel voor bij chronisch hartfalen. Het huidige onderzoek toont aan dat een uitgebreide klinische evaluatie met behulp van een CCI het mogelijk maakt om patiënten met congestie te discrimineren die risico lopen op ziekenhuisopname en overlijden als gevolg van

hartfalen. Het gebruik van hoge doses lisdiuretica en een combinatietherapie met thiaziden wijzen beide op een slechtere uitkomst, maar deze relatie is vooral afhankelijk van de ernst van hartfalen, en niet zozeer van een direct negatief effect van diuretica op de uitkomst. Deze bevinding wordt ondersteund door het feit dat noch het gebruik van een hoge dosis lisdiuretica, noch de toevoeging van een thiazide als onafhankelijke voorspellers van prognose naar voren kwamen in een uitgebreid multivariaat model. Bovendien was de prognose het slechtst in geval van intensivering van de diuretische behandeling, die niet leidde tot klinische decongestie, terwijl intensivering van de behandeling die leidde tot volledige of gedeeltelijke klinische decongestie, gerelateerd was aan een betere uitkomst. Al met al onderstrepen deze bevindingen het belang van het voorkomen van congestie. In de klinische praktijk moet intensieve diuretische behandeling niet worden vermeden bij patiënten met aanhoudende klinische tekenen / symptomen van congestie. Het huidige onderzoek toont aan dat het tolereren van congestie schadelijk is. Toch moet het effect van een dergelijke strategie op het resultaat prospectief worden getest in een gerandomiseerde gecontroleerde studie.

Bio-ADM en sCD146 toonden beide hun vermogen aan om congestie te weerspiegelen zoals beoordeeld door middel van klinische evaluatie en echografische markers. Er werd zelfs een interactie tussen bio-ADM en neurohumorale blokkade bij acute dyspnoe vastgesteld, maar deze observatie moet verder prospectief worden getest. sCD146 toonde ook zijn vermogen om morfologische en functionele veranderingen van het hart te weerspiegelen, ondanks het feit dat het uit de vasculatuur wordt uitgescheiden. Deze bevinding is zeer belangrijk vanuit pathofysiologisch oogpunt omdat zij een verband aantoont tussen vasculaire congestie en cardiale schade. Of interventies ter congestiebeheersing op basis van bio-ADM en sCD146 de harde uitkomsten verbeteren, moet worden getest in geschikte klinische studies.

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CHAPTER 11

VALORISATION

During the past four years I focused my clinical and research interest on the excellence of diagnostics and management of acute and chronic heart failure. In particular, I analysed in depth the interactions between congestion, its management with diuretics, and the effects of (de)congestion on heart failure outcome. My research interest was driven by the current gaps in knowledge about an optimal decongestive approach and the absence of a reliable biomarker assisting in congestion detection and grading. I tried to fill some of these gaps by analysing the interactions between congestion, its treatment, and heart failure outcome as well as by searching for novel tools for congestion detection and grading. My research resulted in several key findings, that altogether make a relevant background for optimised clinical practice and future research.

Firstly, my research revealed that in daily clinical practice clinicians should not rely on a single clinical parameter when screening patients for the presence of congestion. In fact, I was able to demonstrate that heart failure patients may present with different phenotypes of congestion. This finding underscores the importance of systematic clinical evaluation, which is rarely done in daily clinical practice. In order to facilitate congestion detection and grading I came up with an easily applicable clinical congestion index, consisting of 7 clinical markers of water retention in the human body. My research reveals that this novel clinical toll is highly predictive of morbidity and mortality. Clinical congestion index does not require neither expensive laboratory testing, nor any highly specific knowledge / skills. This makes it a simple tool for daily clinical evaluation.

Secondly, the more congested the patients were, the worse was the survival and heart failure hospitalisation-free survival. This finding underscores the importance of screening heart failure patients for congestion, which is not always the case. I believe that the publication of these results increased the awareness of congestion detection, even in apparently stable chronic heart failure patients.

Thirdly, the uncertainties about the safety of (high dose) loop diuretic treatment often result in suboptimal treatment and persistent congestion. To some extent, there exists some level of congestion tolerance in a real-world setting, as reflected by the findings from heart failure registries as well as by the high prevalence of congestion in TIME-CHF patients at baseline. However, my research does not justify this approach by revealing that high dose loop diuretic management / thiazide co-administration does not independently predict worse outcome. In fact, treatment intensification that does not result in clinical decongestion leads to the worst outcome. This finding is very important from a practical point of view. In particular, the present findings shift the contemporary congestion management paradigm from ‘lower dose is better’

to ‘effective dose is the best’. This means that in daily practice clinicians should try to decongest heart failure patients, even if high dose of a loop diuretic or a co-administration of a thiazide is needed.

Fourthly, clinical congestion is already a late manifestation of fluid accumulation in a human body. Therefore, the future aim should be to detect congestion non-invasively before clinical signs and symptoms become apparent. I was able to demonstrate that bio-ADM and sCD146 are both capable to reflect congestion as assessed by means of clinical evaluation and sonographic assessment. This finding creates a relevant background for future interventional trials, assessing the role of bio-ADM and/or sCD146 in decongestion guidance.

To sum up, my research adds significantly to the understanding of the complex interactions between congestion, its treatment with diuretics, and heart failure outcome. I was able to come up with three novel biomarkers of congestion detection and grading, i.e. clinical congestion index, bio-ADM, and sCD146. They all showed to reflect the presence and the degree of congestion, which should not be tolerated in clinical practice.

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CHAPTER 12

ACKNOWLEDGEMENT

Acknowledgement

I would like to express my sincere gratitude to my parents Rasa and Saulius for their continuous encouragement to devote myself to medical studies, research, and science. I would also like to acknowledge my supervisor Professor Hans-Peter Brunner-La Rocca for his scientific support and constructive advice, that let me come up with this dissertation. Through the writing of this thesis, I received a great deal of support from my close friends Aurimas and Sigutė and Goda for whom I will always be thankful. I would also like to thank my tutors Professor Jolanta Justina Vaškelytė who encouraged me to choose cardiology as my future specialty and Professor Jelena Čelutkienė, who accepted me as a team member and supported with her valuable ideas. I also express my sincere gratitude to my great colleagues at the intensive care unit of Respublikinė Panevėžio ligoninė, who continuously supported me along my professional and personal development.

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CHAPTER 13

ABOUT THE AUTHOR

CURRICULUM VITAE

Justas Simonavičius was born on the 2nd of July 1989 in Kėdainiai, Lithuania. He started his medical training at the Lithuanian University of Health Sciences in 2008, which he successfully finished in 2014, obtaining a master's degree in medicine. The same year he started his cardiology residency training at the Lithuanian University of Health Sciences, which he continued at Vilnius university from 2015. During his residency training he completed a 6-month internal medicine internship at Semmelweis University in Budapest (Hungary) and a 6-month cardiology internship at Maastricht University Medical Centre (the Netherlands), where he developed his interest in the challenging field of congestion and heart failure as a whole. He graduated from Vilnius university in 2018, obtaining a cardiologist title. He has been working in an outpatient setting and in an intensive cardiovascular care unit, focusing his clinical practice on acute and chronic heart failure. Starting from 2017 he continued his scientific research on congestion under the supervision of Professor Hans-Peter Brunner-La Rocca. The key findings of his research are detailed in this PhD thesis. Justas Simonavičius is a co-author of ten peer-reviewed research articles, most of which focus on the contemporary knowledge of congestion detection, grading, and management. He gave many lectures on congestion management in various national and international conferences.