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Kamilė Čerlinskaitė-Bajorė

The Stratification of Prognosis in Acute Heart Failure Patients: The Effect of Rehospitalizations and Optimal Medical Treatment

DOCTORAL DISSERTATION

Medical and Health Sciences,
Medicine (M 001)

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Academic Supervisor:
Prof. Dr. Jelena Čelutkienė (Vilnius University, Medical and Health Sciences, Medicine – M 001).
Academic Consultant:
Prof. Dr. Alexandre Mebazaa (Paris Cité University, Medical and Health Sciences, Medicine – M 001)

This doctoral dissertation will be defended in a public meeting of the Dissertation Defence Panel:
Chairperson – Assoc. Prof. Dr. Karolis Ažukaitis (Vilnius University, Medical and Health Sciences, Medicine – M 001).
Members:
Prof. Dr. Maria Generosa Crespo Leiro (University of A Coruña, A Coruña, Spain, Medicine – M 001),
Assoc. Prof. Dr. Vilius Janušauskas (Vilnius University, Medical and Health Sciences, Medicine – M 001),
Prof. Dr. Jolanta Laukaitienė (Lithuanian University of Health Sciences, Medical and Health Sciences, Medicine – M 001),
Assoc. Prof. Dr. Rytis Masiliūnas (Vilnius University, Medical and Health Sciences, Medicine – M 001).

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Kamilė Čerlinskaitė-Bajorė

Ūminio širdies nepakankamumo pacientų prognozės stratifikacija: rehospitalizacijų ir optimalaus gydymo įtaka

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Mokslinė vadovė – prof. dr. Jelena Čelutkienė (Vilniaus universitas, medicinos ir sveikatos mokslai, medicina – M 001).
Mokslinis konsultantas – prof. dr. Alexandre Mebazaa (Paris Cité universitetas, medicinos ir sveikatos mokslai, medicina – M 001)

Gynimo taryba:
Pirmininkas – doc. dr. Karolis Ažukaitis (Vilniaus universitetas, medicinos ir sveikatos mokslai, medicina – M 001).
Nariai:
Prof. dr. Maria Generosa Crespo Leiro (A Coruña universitetas, A Coruña, Ispanija, medicinos ir sveikatos mokslai, medicina – M 001),
Doc. dr. Vilius Janušauskas (Vilniaus universitetas, medicinos ir sveikatos mokslai, medicina – M 001),
Prof. dr. Jolanta Laukaitienė (Lietuvos sveikatos mokslų universitetas, medicinos ir sveikatos mokslai, medicina – M 001).
Doc. dr. Rytis Masiliūnas (Vilniaus universitetas, medicinos ir sveikatos mokslai, medicina – M 001),

Disertacija ginama viešame Gynimo tarybos posėdyje 2026 m. rugsėjo 3 d. 14 val. Vilniaus universiteto Medicinos fakulteto Medicinos mokslo centre, Amfiteatro auditorijoje. Adresas: Žaliųjų ežerų g. 2, Vilnius, Lietuva.

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TABLE OF CONTENTS

ABBREVIATIONS

ACE – angiotensin-converting-enzyme;
ACEi – angiotensin-converting-enzyme inhibitor;
AHF – acute heart failure;
aHR – adjusted hazard ratio;
ANCOVA – analysis of covariance;
ANOVA – analysis of variance;
ARB – angiotensin receptor blocker;
ARNI – angiotensin receptor-neprilysin inhibitor;
b.i.d. – bis in die (twice daily);
BiPAP – Bilevel Positive Airway Pressure;
BMI – body mass index;
bpm – beats per minute;
CHF – chronic heart failure;
CI – confidence interval;
COPD – chronic obstructive pulmonary disease;
CPAP – Continuous Positive Airway Pressure;
CT – coronary tomography;
CV – cardiovascular;
eGFR – Estimated Glomerular Filtration Rate;
EQ-VAS – EuroQol Visual Analogue Scale;
ESC – European Society of Cardiology;
FEV1 – Forced Expiratory Volume in 1 Second;
GDMT – guideline-directed medical therapy;
HF – heart failure;
HFmrEF – heart failure with mildly reduced ejection fraction;
HFpEF – heart failure with preserved ejection fraction;
HFrEF – heart failure with reduced ejection fraction;
HIC – high-intensity care;
HR – hazard ratio;
hs-TnT – high-sensitivity troponin T;
ICD-10 – International Classification of Diseases;
KCCQ – Kansas City Cardiomyopathy Questionnaire;
LVEF – left ventricle ejection fraction;
MDRD – Modification of Diet in Renal Disease;
mEq/L –Milliequivalents per Liter;
MLHFQ – Minnesota Living with Heart Failure Questionnaire;
MRA – mineralocorticoid receptor antagonist;
NP – natriuretic peptide;

NT-proBNP – N-terminal pro–B-type natriuretic peptide;
NYHA – New York Heart Association;
q.d. – quaque die (once a day);
RAS – renin-angiotensin system;
RASi – renin-angiotensin system inhibitor;
SGLT2i – sodium-glucose cotransporter 2 inhibitor;
TIA – Transient Ischemic Attack;
t.i.d. – ter in die (three times a day)
UC – usual care;
VT – Ventricular Tachycardia.

LIST OF PUBLICATIONS

This doctoral thesis is based on the following publications which shall be referred to in the Roman numerals in this text:

I. **Čerlinskaitė K**, Mebazaa A, Cinotti R, Matthay M, Wussler DN, Gayat E, Juknevičius V, Kozhuharov N, Dinort J, Michou E, Gualandro DM, Palevičiūtė E, Alitoit-Marrote I, Kablučko D, Bagdonaitė L, Balčiūnas M, Vaičiulienė D, Jonauskienė I, Motiejūnaitė J, Stašaitis K, Kukulskis A, Damalakas Š, Laucevičius A, Mueller C, Kavoliūnienė A, Čelutkienė J; GREAT network. Readmission following both cardiac and non-cardiac acute dyspnoea is associated with a striking risk of death. ESC Heart Fail. 2021 Aug;8(4):2473-2484. doi: 10.1002/ehf2.13369. Epub 2021 Jun 10. PMID: 34110099; PMCID: PMC8318470.

II. **Čerlinskaitė-Bajorė K**, Lam CSP, Sliwa K, Adamo M, Ter Maaten JM, Léopold V, Mebazaa A, Davison B, Edwards C, Arrigo M, Barros M, Biegus J, Chioncel O, Cohen-Solal A, Damasceno A, Diaz R, Filippatos G, Gayat E, Kimmoun A, Metra M, Novosadova M, Pagnesi M, Pang PS, Ponikowski P, Saidu H, Takagi K, Tomasoni D, Voors AA, Cotter G, Čelutkienė J. Sex-specific analysis of the rapid up-titration of guideline-directed medical therapies after a hospitalization for acute heart failure: Insights from the STRONG-HF trial. Eur J Heart Fail. 2023 Jul;25(7):1156-1165. doi: 10.1002/ejhf.2882. Epub 2023 Jun 1. PMID: 37191154.

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1. INTRODUCTION

1.1. Background

1.1.1. Definitions and epidemiology of heart failure

According to the universal definition of heart failure (HF), it is defined as a clinical syndrome with symptoms and/or signs caused by a structural and/or functional cardiac abnormality and corroborated by elevated natriuretic peptide (NP) levels and/or objective evidence of pulmonary or systemic congestion[1]. Characterized as a global pandemic, in 2017, 64.3 million people were estimated to suffer from HF worldwide[2], which accounts to approximately 1% of the world's adult population. Reported mortality rates have differed between the studies but are substantial – more than 50% of patients die within 5 years of receiving HF diagnosis[3,4]. Heart failure is a significant challenge for patients and the healthcare system, associated with poor quality of life, high morbidity, mortality, as well as increasing economic costs[5].

Heart failure is classified to three phenotypes according to the left ventricle ejection fraction (LVEF)[6]:

- Heart failure with reduced ejection fraction (HFrEF) – when LVEF is ≤40%.
- HF with mildly reduced ejection fraction (HFmrEF) – when LVEF is between 41% and 49%.
- HF with preserved ejection fraction (HFpEF) – when LVEF is ≥50%.

The heart failure syndrome has also been classified into "chronic" and "acute", with chronic heart failure (CHF) describing patients in the outpatient setting and acute heart failure (AHF) – hospitalized patients. AHF can be further classified into acute *de novo* (new onset) HF and acutely decompensated chronic HF[6]. However, it is increasingly recognised that the natural trajectory of HF encompasses multiple changes in the clinical status and risk of adverse outcomes[7]. Furthermore, the indications for hospitalisation may vary between the countries and patients who are hospitalized for HF may have chronic progressively worsening symptoms, rather than an acute singular event[1]. Yet, for the purposes of this dissertation, the term "acute heart failure" will be used to describe patients requiring hospitalisation or urgent care due to worsening of their heart failure symptoms.

In HF patients, huge driver of poor outcomes and economic burden is frequent hospitalizations. A 2014 study of nationwide hospital discharge registry in Sweden revealed that on average HF patients are hospitalized once every

year[8]. Worldwide, acute heart failure (AHF) is the most common cause of hospitalisations of people older than 65 years old[6]. After the hospitalization for AHF, prognosis of the disease is much worse than that of the chronic patient as 1-year mortality can reach up to 25–30%[9].

1.1.2. Guideline-directed medical therapy of HF

The treatment of heart failure, mainly HFrEF, has gone through vast improvements in recent decades, which has led to a significant reduction of mortality and hospitalizations in chronic heart failure. The current pharmacological management of HFrEF consists of initiation and rapid up-titration of 4 pillars: renin-angiotensin system inhibitor (RASi, including angiotensin-converting-enzyme inhibitor [ACEi] or angiotensin receptor blocker [ARB], or angiotensin receptor-neprilysin inhibitor, [ARNI]), beta-blocker, a mineralocorticoid receptor antagonist (MRA) and sodium-glucose cotransporter 2 inhibitor (SGLT2i)[6].

Historically, heart failure has been treated with diuretics and digoxin for decades before ACE inhibitor enalapril significantly reduced mortality in severe congestive heart failure patients compared to placebo in CONSENSUS trial in 1987[10]. This landmark achievement sparked a new era in heart failure trials. In 1996, a beta-blocker carvedilol added on to a combination of diuretics, digoxin and ACEi, significantly reduced the risk of death and cardiovascular hospitalization in heart failure patients with LVEF $\leq$ 35%[11]. A third pillar was added in 1999, when RALES study showed that MRA spironolactone (on top of diuretic, ACEi and, in most of the cases, digoxin) significantly reduced the risk of all-cause mortality compared to placebo in patients with severe heart failure and LVEF $\leq$ 35%[12]. In the following years, multiple studies have solidified these three groups as a cornerstone of HFrEF treatment[13–16]. More recently, in 2014, PARADIGM-HF trial showed that an ARNI – sacubitril/valsartan – was superior to enalapril in reducing HF hospitalizations, cardiovascular and all-cause mortality in chronic heart failure patients with LVEF $\leq$ 35%[17].

A rather accidental and ground-breaking addition to HF pharmacotherapy have been SGLT inhibitors – dapagliflozin and empagliflozin. First developed as antidiabetic drugs, in DAPA-HF and EMPEROR-Reduced trials respectively, both SGLT2 inhibitors significantly reduced the risk of cardiovascular mortality or HF worsening in patients with HFrEF[18,19]. Moreover, both medications also improved outcomes in patients with LVEF $\geq$ 40%[20,21]. Consequently, they are the first, and currently only, medications, recommended in heart failure across the LVEF spectrum[22].

The combination of ARNI, beta-blocker, MRA, and SGLT2 inhibitor has been demonstrated to significantly increase the average lifespan of the patient with HFrEF and is the therapeutic standard for HFrEF[23].

However, it must be acknowledged that most of the trials were focused on stable heart failure patients, mostly with reduced ejection fraction. Thus, there are still gaps in knowledge in acute heart failure, across the LVEF spectrum.

1.1.3. Gaps in knowledge in specific aspects of AHF

The rationale for investigating prospective cohorts of patients presenting with acute dyspnoea stems from the complexity of overlapping acute cardiorespiratory syndromes, the challenges of risk stratification and prognostication in this population, and the clinical uncertainty surrounding decisions regarding hospitalization, discharge, and follow-up care[24,25]. Including not only patients with AHF but also those with other causes of acute dyspnoea provides a broader perspective on 1-year outcomes, as diagnoses established in acute care settings are often not nosologically precise. Furthermore, several recent AHF clinical trials have failed to demonstrate the efficacy of novel therapeutic interventions, including inodilators and vasodilators[26,27]. This series of neutral or negative findings has raised important questions regarding trial design in AHF. It remains unclear how short-term interventions administered during acute hospitalization might influence outcomes measured at 1, 3, or 6 months, and how mortality - whether cardiovascular or non-cardiovascular - interacts with rehospitalizations, which are themselves influenced by local healthcare practices. These uncertainties are highly relevant to understanding the natural history of AHF and other causes of acute dyspnoea, as well as to selecting appropriate endpoints for future clinical trials. Addressing these knowledge gaps motivated the research presented in **Publication I**.

Sex-specific analyses remain underrepresented in biomedical research, including the field of HF. The major HF phenotypes described above exhibit distinct demographic profiles, with HFpEF being more prevalent among women[28]. Women are frequently under-represented in clinical trials and frequently receive less GDMT than men in real-world clinical practice[29–32]. Therefore, it is important to determine whether the benefits of rapid GDMT up-titration, as demonstrated in the landmark STRONG-HF trial, are consistent across sexes. This question is addressed in **Publication II**.

Despite strong recommendations in clinical guidelines, the implementation of GDMT in routine clinical practice remains suboptimal

across real-world registries, in contrast to the high adherence rates achieved in recent clinical trials[33]. Contributing factors include therapeutic inertia among physicians and reluctance among patients to initiate or intensify medications that may lower blood pressure or increase diuresis[34]. It is unclear whether patients with poorer baseline quality of life are less tolerant of rapid GDMT up-titration and thus are less likely to achieve optimal treatment targets associated with improved outcomes. Conversely, these patients may also experience greater improvements in patient-reported outcomes if therapy is successfully implemented. Whether changes in quality of life following rapid GDMT optimization differ according to baseline health status was investigated in **Publication III**.

Finally, therapeutic inertia in acute heart failure has also been linked to disease complexity and the high burden of comorbidities, which may limit rapid GDMT optimization[34,35]. Among these comorbidities, anaemia is particularly relevant owing to its high prevalence in AHF and its associations with chronic kidney disease and the use of antithrombotic therapy[36]. The impact of both prevalent and incident anaemia during the STRONG-HF study on the reduction of the primary endpoint was therefore investigated in **Publication IV**.

1.2. The aim of the dissertation

The aim of the dissertation was to investigate the impact of rehospitalizations and optimal medical treatment on the prognosis of patients with acute heart failure.

1.3. The objectives of the dissertation

1. To investigate the relation between rehospitalizations and mortality risk in patients after the index episode of admission to the emergency department due to acute dyspnoea (caused by acute heart failure and other causes).
2. To investigate the potential differences between men and women in the feasibility and impact of rapid up-titration of guideline-directed medical therapy on their outcomes after hospitalization for acute heart failure.
3. To investigate the feasibility and impact of rapid up-titration of guideline-directed medical therapy on quality of life in patients following hospitalization for acute heart failure, and to assess the

influence of baseline quality-of-life measures on the outcomes of optimal medical treatment.

4. To investigate the effect of anaemia on rapid up-titration of guideline-directed medical therapy in patients after hospitalization for acute heart failure.

1.4. Scientific novelty of the studies presented in the doctoral thesis

This doctoral thesis examines prognostication of patients with acute heart failure in two different settings and from different important perspectives.

The rehospitalisation and mortality study (**Publication I**) of two observational cohorts of patients with acute dyspnoea – one from Lithuania, one from Switzerland – analysed immediate and delayed post-discharge period after an index episode of acute dyspnoea (including AHF and non-AHF patients) and the relationship between two most frequent endpoints in AHF trials – readmission and death. An approach to study these endpoints was developed in the Lithuanian derivation cohort and then validated in a Swiss cohort [37]. Before our study, the immediate post-discharge period, also known as a "vulnerable phase" had not been analysed in a heterogenous population of patients with acute dyspnoea including AHF and non-AHF patients.

STRONG-HF (Safety, Tolerability and Efficacy of Rapid Optimization, Helped by NT-proBNP Testing, of Heart Failure Therapies) was the first prospective, randomised study to compare an intensified protocol implemented at the end of an acute heart failure admission, in which patients were either quickly up-titrated within 2 weeks of discharge to 100% doses of guideline-directed medical therapy under strict follow-up (high-intensity care), including of clinical assessments, laboratory assessment, and measurement of N-terminal pro-B-type natriuretic peptide, or were followed up per local practice (usual care). The sex-specific analysis of the STRONG-HF clinical trial (**Publication II**) addressed an important knowledge gap in particularities, efficacy and safety of rapid guideline-directed treatment up-titration in men and women after a hospitalisation for acute heart failure[38]. Before the study, there was a lack of sex-specific analyses of treatment response to guideline-directed medical therapy in patients hospitalized with AHF.

The quality-of-life analysis in the STRONG-HF clinical trial (**Publication III**) examined characteristics, changes and treatment effect on quality-of-life – a very important patient-centred outcome – in patients after hospitalisation for acute heart failure. The study was done in a multinational setting, thus addressing geographical and racial differences. The study also

addressed treatment safety based on quality-of-life, analysed different dimensions of quality-of-life and gave insight into how not only hard outcomes but also subjective health status improves under intensive treatment regimen[39].

The anaemia analysis of the STRONG-HF clinical trial (**Publication IV**) analysed the efficacy and safety of rapid up-titration of guideline-directed medical therapy in groups based on one of the most frequent and limiting comorbidities of heart failure – anaemia. The study analysed independent predictors of baseline and incident anaemia and anaemia relationship to quality-of-life[40]. As comorbidities are one of the main reasons of inappropriate prescription of guideline-directed medical therapy, this analysis provided an important perspective on the relation of one of the main comorbidities and optimal medical treatment.

1.5. Statements to be defended in the doctoral thesis

1. Rehospitalization in 6 months after index admission to the emergency department due to acute dyspnoea significantly increases 1-year all-cause mortality risk.
2. Rapid up-titration of guideline-directed medical therapy is attainable and significantly improves the outcomes of both men and women after hospitalization for acute heart failure.
3. Rapid up-titration of guideline-directed medical therapy is attainable and improves quality-of-life and hard outcomes regardless of quality-of-life at baseline in patients after hospitalization for acute heart failure.
4. Rapid up-titration of guideline-directed medical therapy significantly improves outcomes regardless of baseline anaemia in patients after hospitalization for acute heart failure.

2. LITERATURE REVIEW

2.1. Vulnerable phase in acute heart failure

Although it has been recognised that long-term prognosis of chronic stable heart failure patients has been consistently improving with development of new treatment strategies, despite all available therapy, post-discharge outcomes for patients hospitalized for AHF remain persistently poor[41]. Despite rapid and substantial improvements in signs and symptoms of congestion that can be achieved with intravenous diuretics and vasodilators, approximately 25% of patients hospitalized with AHF are readmitted and up to 10% of patients die within 30 days of discharge[42,43]. The early post-discharge period immediately after hospitalization for AHF is known as the "vulnerable phase"[44]. This period is a major focus of HF care: early post-discharge clinic visits and monitoring during this period are encouraged and 30-day readmission rates are used as an important health care quality measure[45,46]. Despite the acknowledged meaningfully increased risk, it has been reported that only a handful of patients are closely followed-up or treated with full doses of guideline-recommended medical therapies immediately after admission for acute heart failure[47–49]. In the results of the American CHAMP-HF (Change the Management of Patients with Heart Failure) registry, HFrEF patients who had a recent hospitalization for heart failure were, surprisingly, less likely to achieve target doses of any guideline-recommended therapy or even receive it at all[47]. A retrospective analysis of patients < 65 years old before and after a worsening heart failure event revealed that use of heart failure medications decreased after a hospitalization for heart failure or outpatient intravenous diuretic use, despite recurrent hospitalizations[48]. CONNECT-HF (Care Optimization Through Patient and Hospital Engagement Clinical Trial for Heart Failure) trial was designed to examine whether HF patient care would improve by randomising 150 centres across the US to either a hospital and post discharge quality improvement intervention or usual care[50]. The intervention in this trial included partnering national HF experts with local hospitals to directly support quality improvement teams in the adoption of guideline-recommended medical therapy. However, the trials results did not demonstrate the superiority of this strategy in improving a composite quality score for HF care processes or reducing risk of first HF readmission or all-cause death[51]. A subsequent in-depth analysis of the trial revealed that even in the highest-performing centres, the adoption of guideline-recommended therapies after an acute heart failure hospitalization was low – 29.6% patients achieved 50% or more of the target

dose for RAS inhibitors at 12 months.; the proportion was 41.2% for the beta-blockers[49].

Several review papers have noted that in-hospital admission might be an ideal opportunity to initiate and up-titrate optimal medical treatment under close supervision[52–54]. Furthermore, the 2021 European Society of Cardiology (ESC) Guidelines for the diagnosis and treatment of acute and chronic heart failure recommend early (1-2 weeks post-discharge) follow-up visit and initiation/up-titration of HF medications[6]. However, before STRONG-HF trial, the level of evidence for this recommendation was low and there were no randomised controlled trials to support this strategy.

2.2. STRONG-HF impact on acute heart failure treatment

Safety, Tolerability and Efficacy of Rapid Optimization, Helped by NT-proBNP Testing, of Heart Failure Therapies (STRONG-HF) was a multinational, open-label, randomised, prospective clinical trial, designed to assess the safety and efficacy of rapid up-titration of guideline-directed medical therapy (GDMT) before discharge from an acute heart failure admission and during the following weeks compared with usual care[55,56]. The study included 1078 AHF patients from 14 different countries in different regions of the world. The main results of the study were published in 2022 and demonstrated a substantial benefit of the high-intensity care strategy of close follow-up visits and rapid up-titration of guideline-recommended medication after AHF admission. The intervention significantly reduced the risk of 180-day all-cause death or heart failure readmission compared with usual care[57]. Subsequently, further analyses revealed that the treatment strategy was beneficial independently from baseline LVEF, supporting the rapid medication up-titration across the LVEF spectrum[58]. Prespecified subgroup analysis in patients with LVEF ≤40% vs >40% revealed that rapid up-titration was achieved similarly in both groups and no significant treatment-by-LVEF interaction was reported in any of the endpoints. Post-hoc analysis performed in groups of LVEF <50% vs ≥50% showed similar results. When analysing LVEF as a continuous variable, no significant interaction between LVEF and the treatment strategy was observed with hazard ratio consistently below 1 across the whole LVEF spectrum[58]. Due to limited sample sizes, the effect of specific medications could not be studied, however the consistent effect of neurohormonal blockade support aiming for similar guideline-directed medical therapies in HFpEF and in HFrEF after a hospitalization for acute heart failure.

Based on the results of the study, 2023 Focused Update of the 2021 ESC Heart Failure Guidelines updated the recommendation and now recommend high-intensity care for initiation and rapid up-titration of guideline-recommended HF medical treatment and close follow-up in the first 6 weeks after discharge for an acute HF hospitalization to reduce HF readmission or all-cause death[22]. It should be noted that achieving up-titration in this short period of time might not be feasible in different health care systems due to organizational constraints. Yet, regulations of healthcare systems should aim to implement the results of the study by prescribing and adjusting doses of GDMT during the hospitalization and organizing timely follow-up visits for up-titration. During any ambulatory visit for heart failure, especially after recent HF hospitalization, the main goal should be achieving quadruple therapy.

2.3. The challenge of acute dyspnoea

Acute dyspnoea is one of the most common complaints in the emergency department, associated with poor short and long-term outcomes in multiple diseases and settings[59–63]. In chronic obstructive pulmonary disease (COPD), dyspnoea severity predicted 3-month readmission or death after admission for acute hypercapnic respiratory failure[59], and in-hospital mortality and early readmission during and after acute COPD exacerbation[60]. Patient-reported dyspnoea severity at admission for acute heart failure has been associated with a higher comorbidity burden, longer length-of-stay, increased mortality and HF readmission risk and higher health care costs[61]. In a prospective emergency department cohort, dyspnoea as a chief complaint was associated with the highest in-hospital mortality[62]. Even with improving diagnostic techniques, the exact cause of dyspnoea is frequently uncertain, and this clinical uncertainty has also been associated with longer length of stay and increased risk of mortality and readmission[25]. Interestingly, another common complaint in the emergency department – chest pain – has been shown to have a much lower rate of readmission[64]. Altogether, this suggests that acute dyspnoea represents a unique population, where more research is needed to improve patient prognosis. Before our study, the aforementioned “vulnerable phase” had not been analysed in a heterogenous population of patients with acute dyspnoea including AHF and non-AHF patients.

2.4. Sex-specific analyses in heart failure

There are important differences in heart failure related to biological sex that are important and frequently under-appreciated[29]. Disparities have been reported between men and women in HF risk factors, clinical characteristics and phenotypes. Regarding phenotypes, men are more likely to develop HFrEF, while women predominate in HFpEF[65,66]. In a study of four community-based cohorts, which included 28 820 individuals with a follow-up of 12 years for incident HF, men had an almost two-fold higher risk than women for HFrEF but not for HFpEF[65]. Of 42 987 patients in the Swedish HF Registry, 55% of patients with HFpEF were women, compared with 39% of in HFmrEF, and 29% in HFrEF[66]. Predominance of different phenotypes in men and women can be explained by differences in traditional HF risk factors. It has long been recognised that in women, diabetes is more related to development of incident HF than men[67]. Moreover, obesity predisposes HFpEF more strongly than HFrEF and more so in women than in men[68,69]. The higher risk of HFrEF in men has been estimated to be caused by a higher prevalence of macrovascular coronary artery disease and myocardial infarction, while women are more predisposed to coronary microvascular dysfunction, which leads to HFpEF[29].

Better long-term outcomes have been reported in women compared to men in both epidemiological and clinical studies of chronic HF[70–72]. In the analysis from Framingham Heart Study in 1993, 5-year survival rate in men was reported to be 25% in men and 38% in women[70]. In a sex-specific analysis of the CHARM (Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity) randomised controlled trial, women had significantly lower risk of most analysed outcomes, including all-cause mortality, cardiovascular mortality or HF hospitalization and this risk was independent from LVEF or heart failure aetiology[71]. In another analysis of the I-PRESERVE (The Irbesartan in Heart Failure With Preserved Ejection Fraction), in patients with LVEF ≥ 45%, relative mortality and rehospitalisation risk was, respectively, 36% and 20% lower in women compared to men[72].

Conversely from chronic HF, multiple analyses of AHF patients (both of randomised controlled trials or registries) did not report better survival in women or in men[73–75].

In a sex-specific analysis of the PROTECT (Placebo-controlled Randomized Study of the Selective A1 Adenosine Receptor Antagonist Rolofylline for Patients Hospitalized with Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and

Renal FuncTion) trial, multivariable risk-adjusted 180-day mortality was similar in both sexes[73]. In the sex-specific analysis of the THESUS-HF (The sub-Saharan Africa Survey of Heart Failure) registry data, there were no differences in any of the analysed outcomes between men and women[74]. Similarly, there were no differences in 6-month all-cause and cardiovascular mortality rates between men and women in a retrospective analysis of a multicentre registry of hospitalized AHF patients[75].

Important sex-related differences in HF probably do not concern biological characteristics. There is evidence of widespread under-representation of women in clinical trials, with proportion ranging from 20 to 30% in pivotal HFrEF trials, when real-world proportion of women in HFrEF is around 40%[29,76]. It has been speculated that this might preclude guidelines on making evidence-based recommendations in women[29], however, meta-analyses with pooled individual patient data of these trials, published more than twenty years ago, showed that trial benefit is the same in both men and women[77,78]. Still, women are less likely to achieve evidence-based therapy than men, even in HFrEF[30]. Furthermore, women are less likely to be referred to specialists and receive follow-up visits after the initial consultation[31,32]. This sex-related treatment inertia persists, even though no sex-related differences in treatment effect have been found in multiple trials of chronic HFrEF and in pooled analyses of SGLT2 inhibitors in patients with chronic HF, regardless of LVEF[11,12,17,79–82]. The bias in treatment initiation and up-titration between men and women is not fully understood but it suggests that more analyses are needed to convince doctors that optimal medical treatment is as feasible and safe in women as in men.

2.5. Quality of life in heart failure

According to multiple studies, patients with heart failure prioritize improved quality-of-life as a measure of treatment efficacy rather than improved survival[83–86]. In a survey published in 2013, 61% of patients with HF preferred better quality-of-life over longevity and 9% and 14% were willing to trade 6 and 12 months of survival, respectively, for perfect health. Patients who said they would trade survival for perfect well-being had higher severity of dyspnoea during exertion and higher NT-proBNP (N-terminal pro–B-type natriuretic peptide) concentration[83]. In another survey of over 500 HF patients, 69% prioritized quality-of-life as the most important aspect of heart failure treatment[86]. Acceptable level of quality-of-life for heart failure patients include daily life activities, adequate mobility, independence and participation in their communities, unhindered or less hindered by heart failure symptoms[87].

Moreover, patient-reported health status is an independent predictor of hard outcomes, such as hospital admissions, mortality, and higher health care costs[88]. Therefore, patient-reported outcomes are more increasingly used in clinical trials to evaluate treatment effect and in clinical practice to monitor disease progression[87].

Several questionnaires are used to assess quality-of-life in heart failure patients. Minnesota Living with Heart Failure Questionnaire (MLHFQ) and the Kansas City Cardiomyopathy Questionnaire (KCCQ) are disease-specific tools, developed to measure features specific to heart failure and frequently used in HF clinical trials[89–91]. Both tools have been shown to strongly correlate with NYHA (New York Heart Association) class and 6-minute walking distance[92–94]. However, KCCQ has a 2-week recall period, while MLHFQ has a 4-week recall period, which may limit their use immediately during or after an acute HF exacerbation.

Conversely, EQ-5D-5L is a generic questionnaire, which assesses global health status on the given day unlike other tools with higher recall periods. The EQ-5D-5L consists of two pages: the EQ-5D descriptive system and the EQ (EuroQol) visual analogue scale (EQ-VAS). One of its advantages is that, compared to disease-specific questionnaires, it is much shorter. EQ-5D consists of only five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) with 5 options each (no/slight/moderate/severe/extreme problems)[95]. The second page – EQ-VAS – records the patient's self-rated health as a single number from 0 to 100. This relative simplicity permits its use in different regions, populations, health care settings, in patients with multiple comorbidities[96]. It also facilitates comparing quality-of-life results in different diseases[87]. While HF-specific questionnaires can provide a more precise impact of heart failure symptoms on health status, a generic tool, such as EQ-5D, can assess of the impact of acute heart failure hospitalization and post-discharge management more broadly.

2.6. The importance of anaemia in heart failure

The trajectory of heart failure patients is challenging not only because of the syndrome itself but also due to multiple concomitant diseases, both cardiac and non-cardiac comorbidities[6]. Patients with multiple comorbidities have a more pronounced disease severity, worse quality-of-life and physical capacity, and are more vulnerable to destabilization leading to hospitalization and increased risk of mortality[97–101]. This has been demonstrated in observational studies of both chronic[98,99] and acute heart failure[100,101] patients. Particularly, in acute heart failure, a higher comorbidity burden has been

linked to increased complexity of clinical management, more residual congestion and less GDMT at discharge[100].

One of the most frequent non-cardiac comorbidities in heart failure is anaemia.

Different prevalence of anaemia in heart failure patients has been reported in clinical trials and observational registries[17,18,99,100]. In the PARADIGM-HF and the DAPA-HF clinical trials, prevalence of anaemia was 20% and 22%, respectively[17,18]. However, it was considerably higher in observational data: 36% in BIOSTAT-HF (The BIOlogy Study to TAilored Treatment in Chronic Heart Failure) observational cohort and up to 50% (depending on LVEF) in ESC-HF-LT (ESC-Heart Failure Long-Term) registry[99,100]. In the ASCEND-HF (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure) clinical trial, which specifically included acute heart failure patients, baseline anaemia was the most prevalent non-cardiac comorbidity reaching 60.3%[101]. These differences reveal that recognition and management anaemia is of particular importance in acute heart failure.

In the meta-analysis, published in 2008, across chronic HF studies, patients with anaemia were more likely to be older, have more pronounced chronic kidney disease and more severe heart failure[36]. In an observational study from 2005 of 260 patients admitted with decompensated heart failure, anaemia was more common in women, even after controlling for renal function and congestion[102]. Conversely, in the analysis of Swedish heart failure registry of patients with heart failure managed in primary care was more common in men, patients 75 years old or older, and in those with kidney dysfunction[103].

Anaemia has been associated with worse outcomes in heart failure patients. In the meta-analysis from 2008, presence of anaemia was associated with almost 2-fold unadjusted higher mortality risk[36]. More recently, In the ESC-HF-LT registry of a large cohort of AHF patients, anaemia was also associated with 60% higher relative risk of all-cause mortality[100]. In the Swedish heart failure registry, presence of anaemia was related to 30% adjusted higher relative risk of all-cause hospitalization and 40% adjusted higher relative risk of all-cause mortality[103].

Importantly, anaemia also greatly affects quality-of-life in heart failure. In BIOSTAT-CHF cohort of chronic HF patients, anaemia was associated with both lower KCCQ scores and lower EQ-VAS score in the overall population[99]. In AHF, analysis of the COACH study (Coordinating study evaluating Outcomes of Advising and Counselling in Heart Failure) that included 1013 patients hospitalised with AHF, revealed anaemia as an independent predictor of lower physical capabilities, worse general health and worse global well-being[104].

3. METHODS

3.1. Analysed cohorts

Three distinct populations were analysed in this dissertation. Two patient cohorts from observational studies were analysed in **Publication I**. A cohort from a randomised clinical trial was analysed in **Publications II-IV**. The overview of the publications' main characteristics is presented in Table 1.

Table 1. Summary of study designs, study populations, and outcomes for the Publications, presented in this dissertation.

	Publication I	**Publication II**	**Publication III**	**Publication IV**
Study design	Two prospective observational multicentre studies	Randomised controlled trial		
Scope	2 university centres in Lithuania and 2 university centres in Switzerland	87 centres in 14 countries		
Study population	Acute dyspnoea patients	Patients after a hospitalisation for acute heart failure		
Population size	3357 (1371 from Lithuania; 1986 from Switzerland)	1078		
Intervention	None	High-intensity care (rapid up-titration of guideline-directed medical therapy)		
Observation period	Lithuania: From 2015 to 2018 Switzerland: From 2006 to 2015	From 2018 to 2021		
Outcomes	1-year all-cause mortality	(1) 180-day heart failure readmission or all-cause mortality (2) Change in quality of life from baseline to day 90 as measured by the EQ-5D visual analogue scale (VAS); (3) 180-day all-cause mortality; (4) 90-day heart failure readmission or all-cause mortality.		
Controls	None	Usual care (follow-up per local practice)		
Statistical analysis	Multivariate Cox regression	Cox proportional hazards regression		

3.1.1. Cohorts in Publication I

3.1.1.1. LEDA cohort

Lithuanian Echocardiography Study of Dyspnoea in Acute Settings was a prospective observational multicentre study, performed in two Lithuanian university centres in collaboration with the international GREAT (Global Research on Acute Conditions Team) network[37]. Study enrolment period was from March 2015 to December 2017. The study was registered in clinicaltrials.gov under the identifier NCT03048032. Adult patients admitted to the emergency departments of Vilnius University Hospital Santaros Clinics or The Hospital of Lithuanian University of Health Sciences Kaunas Clinics with chief complaint of acute dyspnoea due to any cause were included. Patients were excluded if acute coronary syndrome was suspected during the first 4 hours of admission (mainly to exclude patients with apparent ST elevation myocardial infarction) or if they had organ transplantation during index admission or readmission. If the patients were admitted more than once, only the first episode was taken as index admission. Patient demographic data, comorbidities, baseline medication, clinical signs and laboratory parameters at admission, early in-hospital treatment, medication at discharge were recorded according to the GREAT protocol[105]. Blood samples were taken within 4 h of presentation, frozen at -80°C, and sent to a core laboratory in the Inserm UMR-942 institute in Paris for biomarker measurements. Teams of three cardiologists blinded to post-discharge outcomes adjudicated the cause of acute dyspnoea in their respective centres. According to the adjudication, patients were classified into two groups: acute heart failure (AHF) and non-acute heart failure (non-AHF). Non-AHF group included COPD/asthma exacerbation, pulmonary embolism, pulmonary/non-pulmonary infections, and cancer, among others.

A 1-year follow-up was completed in December 2018 in collaboration with Lithuanian nationwide administrative registries. Data on unplanned all-cause readmissions coded by the 10th Revision of the International Classification of Diseases (ICD-10) were provided by National Health Insurance Fund under the Ministry of Health. Data on all-cause mortality were obtained from death certificates provided by Causes of Death Registry from Institute of Hygiene. Causes of death were also coded by the ICD-10. Therefore, there were no patients lost to follow-up. For the purposes of the analysis in the **Publication I**, cardiovascular or non-cardiovascular cause of rehospitalization or mortality was assigned based on codes of the ICD-10.

LEDA study included 1455 patients. For the analysis of the **Publication I**, 1371 patients who survived their initial index admission comprised the derivation cohort.

3.1.1.2. BASEL V cohort

Basics in Acute Shortness of Breath EvaLuation Study (BASEL V) was a prospective observational study, which included adult patients with acute, non-traumatic dyspnoea presenting to the emergency departments of two university centres in Switzerland – University Hospital Basel and University Hospital Zurich from 2006 to 2014[106–108]. Patients on haemodialysis were excluded. The study was registered in clinicaltrials.gov under the identifier NCT01831115.

Patient history, physical examination and laboratory parameters were systematically obtained. Blood samples were collected and frozen at -80°C until assayed in a blinded fashion in a dedicated core laboratory.

The final diagnosis defining the main cause of dyspnoea was centrally adjudicated by two independent cardiologists-internists. Adjudication was performed using patients' medical records such as clinical history, physical examination, available laboratory findings, 12-lead electrocardiogram, echocardiography chest x-ray, coronary computed tomography angiography, microbiological findings, the response to therapy according to the most current European guidelines at the time, and autopsy data for patients who died in hospital. In situations of disagreement about the final diagnosis, a third cardiologist reviewed and adjudicated the case. Based on the adjudication, patients were classified into AHF and non-AHF groups.

Patients were followed-up by telephone at 3 and 6 months and 1 year after the index episode. In case of uncertainties, referring physicians and administrative databases were contacted regarding health status or further hospitalizations. In case of a possible relevant medical event such as HF rehospitalization or all-cause death, referring physicians and administrative databases were contacted regarding health status or further hospitalizations. Only 0.5% of the patients were lost-to-follow-up at 1 year.

BASEL V included 2105 patients. For the analysis of the **Publication I**, 1986 patients who survived their initial index admission and had data on the 1-year all-cause mortality comprised the validation cohort.

3.1.2. Cohort in Publications II-IV

Safety, Tolerability and Efficacy of Rapid Optimization, Helped by NT-proBNP Testing, of Heart Failure Therapies (STRONG-HF) was a

multinational, open-label, randomised, prospective clinical trial, designed to assess the safety and efficacy of rapid up-titration of guideline-directed medical treatment (GDMT) before discharge from an acute heart failure admission and during the following weeks compared with usual care[55,56]. Eligible patients were recruited from 87 centres in 14 countries (Argentina, Austria, Bulgaria, Columbia, France, Hungary, Israel, Mozambique, Nigeria, Russia, Serbia, Slovakia, South Africa, and Tunisia).

Patients were included if they were aged 18–85 years; had been admitted to hospital for acute heart failure within 72 hours before screening**,** defined as dyspnoea at rest and pulmonary congestion on chest x-ray, and other signs or symptoms of heart failure, but had to be haemodynamically stable. Patients were included if they had not been treated with optimal doses of oral heart failure therapies within 2 days before anticipated hospital discharge. NT-proBNP had to be >2500 ng/L at screening with a more than 10% decrease in concentration but still > 1500 ng/L between screening and before randomisation. Patients were included across the LVEF spectrum. Main exclusion criteria were a clear intolerance to high doses of beta-blockers, renin-angiotensin system inhibitor, other inclusion and exclusion criteria are detailed in the Table 2 [55,56].

Table 2. Inclusion and exclusion criteria of the STRONG-HF study.

Inclusion criteria	**Exclusion criteria**
Hospital admission within the 72 hours prior to screening for AHF with dyspnea at rest and pulmonary congestion on chest X-ray, and other signs and/or symptoms of HF.	Age < 18 or > 85 years.
All measures within 24 hours prior to randomization of systolic blood pressure ≥ 100 mmHg, and of heart rate ≥ 60 bpm.	Clearly documented intolerance to high doses of beta-blockers.
All measures within 24 hours prior to randomization of serum potassium ≤ 5.0 mEq/L (mmol/L).	Clearly documented intolerance to high doses of RAS inhibitor (both ACEi /ARB).
Biomarker criteria for persistent congestion: • At Screening, NT-proBNP > 2,500 pg/mL. • At the time of randomization (1-2 days	Mechanical ventilation (not including CPAP/BIPAP) in the 24 hours prior to Screening.
	Significant pulmonary disease contributing substantially to the patients' dyspnea such as FEV1< 1 liter or need for chronic systemic or non-systemic steroid therapy, or any kind

Inclusion criteria	Exclusion criteria
prior to discharge), NT-proBNP > 1,500 pg/mL (to ensure the persistence of congestion) that has decreased by more than 10% compared to screening (to ensure the acuity of the index episode).	of primary right HF such as primary pulmonary hypertension or recurrent pulmonary embolism.
	Myocardial infarction, unstable angina or cardiac surgery within 3 months, or cardiac resynchronization therapy device implantation within 3 months, or percutaneous transluminal coronary intervention, within 1 month prior to screening.
At 1 week prior to admission, at screening, and at visit 2 (just prior to randomization) either • ≤ ½ the recommended dose of ACEi/ARB/ARNi prescribed, no beta-blocker prescribed, and ≤½ the recommended dose of MRA prescribed or • no ACEi/ARB/ARNi prescribed, ≤½ the recommended dose of beta-blocker prescribed, and ≤ ½ the recommended dose of MRA prescribed.	Index event (admission for AHF) triggered primarily by a correctable etiology such as significant arrhythmia (e.g., sustained ventricular tachycardia, or atrial fibrillation/flutter with sustained ventricular response >130 beats per minute, or bradycardia with sustained ventricular arrhythmia <45 beats per minute), infection, severe anemia, acute coronary syndrome, pulmonary embolism, exacerbation of COPD, planned admission for device implantation or severe non-adherence leading to very significant fluid accumulation prior to admission and brisk diuresis after admission. Troponin elevations without other evidence of an acute coronary syndrome are not an exclusion.
	Uncorrected thyroid disease, active myocarditis, or known amyloid or hypertrophic obstructive cardiomyopathy.
	History of heart transplant or on a transplant list or using or planned to be implanted with a ventricular assist device.
	Sustained ventricular arrhythmia with syncopal episodes within the 3 months prior to screening that is untreated.
Written informed consent to participate in the study.	Presence at screening of any hemodynamically significant valvular stenosis or regurgitation, except mitral or tricuspid regurgitation secondary to left ventricular dilatation, or the presence of any hemodynamically significant obstructive lesion of the left ventricular outflow tract.

Inclusion criteria	Exclusion criteria
	Active infection at any time during the AHF hospitalization prior to randomization based on abnormal temperature and elevated whole blood count or need for intravenous antibiotics.
	Stroke or TIA within the 3 months prior to screening.
	Primary liver disease considered to be life threatening.
	Renal disease or eGFR < 30 mL/min/1.73m^2 (as estimated by the simplified MDRD formula) at screening or history of dialysis.
	Psychiatric or neurological disorder, cirrhosis, or active malignancy leading to a life expectancy < 6 months.
	Prior (defined as less than 30 days from screening) or current enrolment in a CHF trial or participation in an investigational drug or device study within the 30 days prior to screening.
	Discharge for the AHF hospitalization anticipated to be > 14 days from admission, or to a long-term care facility. Randomization must occur within 12 days following admission and at 1-2 days prior to anticipated discharge.
	Inability to comply with all study requirements, due to major co-morbidities, social or financial issues, or a history of noncompliance with medical regimens, that might compromise the patient's ability to understand and/or comply with the protocol instructions or follow-up procedures
	Pregnant or nursing (lactating) women.

Abbreviations: ACEi – angiotensin-converting enzyme inhibitor; AHF – acute heart failure; ARB – angiotensin receptor blocker; BiPAP – bilevel positive airway pressure; bpm – beats per minute; CHF – chronic heart failure; CPAP – continuous positive airway pressure; eGFR – estimated glomerular filtration rate; FEV1 – forced expiratory volume in 1 second; HF – heart failure; MDRD – Modification of Diet in Renal Disease; mEq/L –milliequivalents per liter; MRA – mineralocorticoid receptor antagonist; NT-proBNP – N-terminal pro–B-type natriuretic peptide; NS – not significant; RAS – renin–angiotensin system; RASi – renin–angiotensin system inhibitor; TIA – transient ischemic attack; VT – ventricular tachycardia.

The study was registered in clinicaltrial.gov under the identifier NCT03412201.

Patients were randomly assigned in 1:1 fashion to usual care or high-intensity care strategy, which consisted of intensification of treatment with beta-blocker, and ACE inhibitor (or ARB) or ARNi, and a mineralocorticoid receptor antagonist. At the time of start of the study, SGLT2 inhibitors were either not approved for the treatment of heart failure or not widely used in many countries, therefore they were not a mandatory part of the treatment protocol. Patients in the usual care arm of the study were managed and followed-up according to the discretion of the treating physician until day 90 after randomisation when they were seen by the study team. Patients in the high-intensity care strategy group were prescribed medical therapy with a beta-blocker, RAS inhibitor, and a mineralocorticoid receptor antagonist adjusted to at least half the optimal dose within two days of assumed hospital discharge. The appropriate doses of recommended medications are shown in Table 3. The up-titration to full doses was then encouraged at 2 weeks post discharge according to the safety criteria (Table 4), or if not possible, at 6 weeks at the latest. The high-intensity care group patients had scheduled outpatient visits at 1, 2, 3, and 6 weeks post-discharge. Safety and tolerability were assessed at every visit by full physical examination and laboratory assessments of NT-proBNP, sodium, potassium, glucose, kidney function, and haemoglobin measures. All patients (including usual care and high intensity care group) were seen by the study team at day 90 and contacted by telephone at day 180 for an assessment of mortality or rehospitalization, and current prescriptions of oral HF medications.

STRONG-HF included 1078 patients (542 in the high-intensity care group and 536 in usual care group). The study showed that the high-intensity care strategy of rapid up-titration of guideline-recommended medication and close follow-up visits after an acute heart failure admission reduced the risk of 180-day all-cause death or heart failure readmission compared with usual care[57]. The later substudy also demonstrated that the treatment strategy was effective independently from baseline LVEF, supporting the rapid medication up-titration in all patients after an acute heart failure hospitalization[58]. **Publications II, III and IV** presented in this dissertation report on important additional analyses of this study cohort.

Table 3. Optimal doses of heart failure oral medications, recommended in STRONG-HF trial.

Medication generic name	**Dose (half daily dose) at visit 2**	**Optimal (full) dose at visit 4**
MRA		
Eplerenone	25 mg q.d.	50 mg q.d.
Spironolactone	25 mg q.d. each 2 days	25 mg q.d.
BB		
Bisoprolol	5 mg q.d.	10 mg q.d.
Carvedilol	12.5–25 mg b.i.d.	25–50 mg b.i.d.
Metoprolol succinate extended-release tablet	100 mg q.d.	200 mg q.d.
Nebivolol	5 mg q.d.	10 mg q.d.
ACEi		
Captopril	25 mg t.i.d.	50 mg t.i.d.
Enalapril	10 mg b.i.d.	20 mg b.i.d.
Lisinopril	17.5 mg q.d.	35 mg q.d
Ramipril	2.5 mg b.i.d. or 5 mg q.d.	5 mg b.i.d. or 10 mg q.d.
Trandolapril	2 mg q.d.	4 mg q.d.
Perindopril	4 mg q.d.	8 mg q.d.
ARB		
Candesartan	16 mg q.d.	32 mg q.d.
Valsartan	80 mg b.i.d.	160 mg b.i.d.
Losartan	75 mg q.d.	150 mg q.d.
ARNi		
Sacubitril/valsartan	49/51 mg b.i.d.	97/103 b.i.d.

Abbreviations: ACEi – angiotensin-converting enzyme inhibitor; ARB – Angiotensin Receptor Blocker; ARNi – angiotensin receptor-neprilysin inhibitor; BB – beta-blockers; b.i.d. – bis in die (twice daily); MRA – mineralocorticoid receptor antagonist; q.d. – quaque die (once a day), t.i.d. – ter in die (three times a day).

Table 4. Safety criteria for delaying medication up-titration in STRONG-HF trial.

Medications	**Criteria for delaying up-titration**
ACEi/ARB/ARNi and/or MRAs	Systolic blood pressure < 95 mmHg, serum potassium > 5.0 mmol/L or eGFR < 30 mL/min/1.73 m2. *If eGFR alone was < 30 mL/min/1.73 m2, investigators were encouraged to reduce the dose of diuretics, if those were deemed high or had been recently up-titrated.

Medications	Criteria for delaying up-titration
Beta-blockers	Heart rate < 55 bpm or systolic blood pressure < 95 mmHg. *If the NT-proBNP level was > 10% higher than the pre-discharge level, physicians were encouraged to not up-titrate BBs and consider increasing diuretics.

Abbreviations: ACEi – angiotensin-converting enzyme inhibitor; ARB – Angiotensin Receptor Blocker; ARNi – angiotensin receptor-neprilysin inhibitor; eGFR – Estimated Glomerular Filtration Rate; MRA – mineralocorticoid receptor antagonist; NT-proBNP – N-terminal pro–B-type Natriuretic Peptide.

3.2. Ethical considerations

LEDA study was approved by the Lithuanian Bioethics Committee (No. L-15-01) and supported by the Lithuanian Research Council. BASEL V study was also approved by the local ethical committee in Switzerland. In STRONG-HF, the study was approved in each participating country by appropriate ethics committees. All of studies analysed in this dissertation were carried out in accordance with the Declaration of Helsinki. Participants of all studies provided written informed consent.

3.3. Study endpoints and statistical analysis

3.3.1. Publication I

3.3.1.1. Study endpoints

The primary endpoint was 1-year all-cause mortality.

3.3.1.2. Statistical analysis

Continuous variables are presented as median and inter-quartile ranges, and categorical variables are presented as counts (percentage). The differences between study groups were compared using Kruskal–Wallis test for continuous variables and chi-square test for the categorical variables.

We examined the association between the first all-cause readmission within 6 months after discharge and 1-year all-cause mortality in acute dyspnoea patients, AHF and non-AHF patients separately and the association between the first cardiovascular (CV) or non-cardiovascular (non-CV)

readmission within 6 months after discharge and 1-year all-cause mortality. An unadjusted and adjusted Cox regression analysis was performed comparing non-readmitted and readmitted patients. Multivariate Cox regression included age, sex, several co-morbidities (history of heart failure, coronary artery disease, and diabetes), systolic blood pressure, heart rate, estimated glomerular filtration rate, and sodium. The same analyses were performed that compared non-readmitted and readmitted patients at three periods: first month, second and third months, and fourth to sixth months after discharge. The analyses were repeated in the AHF and non-AHF groups and for CV or non-CV readmissions against non-readmitted patients as the reference group.

Subgroup analysis was performed by conducting unadjusted Cox regression analyses dividing patients by age, sex, history of heart failure, aetiology of acute dyspnoea, N-terminal pro-B-type natriuretic peptide, high-sensitivity troponin T, and left ventricular ejection fraction measurements. All statistical analyses were performed using R Version 3.5.3 (The R Foundation for Statistical Computing, Vienna, Austria). All tests were two sided, and a P value of <0.05 was considered significant. No imputation was used for missing data.

3.3.2. Publication II

3.3.2.1. Study endpoints

The primary endpoint was 180-day heart failure readmission or all-cause mortality.

The secondary endpoints were:

- Change in quality of life from baseline to day 90 as measured by the EQ-5D visual analogue scale (VAS);
- 180-day all-cause mortality;
- 90-day heart failure readmission or all-cause mortality.

3.3.2.2. Statistical analysis

Continuous variables are presented as mean (standard deviation) or as adjusted mean (standard error), as appropriate, and categorical variables as absolute and relative frequencies. Patients were compared with respect to continuous variables using ANOVA (analysis of variance) models, binary variables using chi-square tests, and ordered categorical variables using Cochran–Mantel–Haenszel chi-square tests.

Subgroup analyses comparing treatment effects on primary and secondary efficacy endpoints by sex at birth were performed. Potential modification of the treatment effect by sex was examined by inclusion of a treatment-by-sex interaction term in the models. Sexes were compared with respect to clinical outcomes using Cox proportional hazards regression, and with respect to EQ-VAS change using ANCOVA (analysis of covariance, including adjustment for baseline EQ-VAS, geographic region, and baseline LVEF ≤40%/>40%).

Treatment effects on changes in vital signs and in local laboratory values from baseline to day 90 were compared between sexes using ANCOVA models adjusted for baseline value.

Two-sided *p*-values of <0.05 were considered statistically significant. All analyses were done using SAS version 9.4 (SAS Institute, Cary, NC, USA).

3.3.3. Publication III

3.3.3.1. Study endpoints

The primary endpoint of the study was 180-day heart failure readmission or all-cause mortality.

The secondary endpoints of the study were:

- The change in quality-of-life from baseline to day 90 as measured by the EQ-VAS as a continuous variable and in all separate domains of EQ-5D-5L;
- 180-day all-cause mortality;
- 90-day heart failure readmission or all-cause mortality.

3.3.3.2. Statistical analysis

The EQ-5D is a standardized instrument for assessing generic health status and consists of a descriptive system and a visual analogue scale. The EQ-VAS recorded the patient's self-rated health on a 20-cm vertical visual analogue scale score from 0 (The worst health you can imagine) to 100 (The best health you can imagine). The descriptive system EQ-5D-5L addressed 5 domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Patients ranked their state of health in each domain on a 5-point ordinal scale ranging from no problems to extreme problems.

Variable presentation was the same as in **Publication II**. For analysis and comparison of baseline characteristics, patients were divided into terciles

based on their baseline EQ-VAS levels, if not missing: ≤50, 51 to 65, and >65. The association of other baseline variables with EQ-VAS tercile was tested using Jonckheere-Terpstra trend test for continuous variables, Cochran-Armitage trend test for binary variables, Cochran-Mantel-Haenszel general association for categorical variables, and Cochran-Mantel-Haenszel nonzero correlation for ordinal variables. Treatment groups were compared using ANCOVA with adjustment for baseline value, region, and LVEF (≤40/>40%). Covariates for a multivariable linear regression model predicting 90-day change in EQ-VAS were selected using backwards selection across 10 multiple imputation data sets with a criterion for staying of P<0.10.

Possible modification of the effect of high-intensity care strategy on the primary end point by EQ-VAS as a categorical variable was examined using Kaplan-Meier curves by baseline EQ-VAS tercile and testing the treatment-by-EQ-VAS interaction in a Cox regression model. A separate Cox regression model was used to test the interaction of treatment with EQ-VAS as a continuous variable, modelled as a restricted cubic spline with 3 knots. Two-sided P<0.05 was considered statistically significant. SAS version 9.4 (SAS Institute, Cary, NC) was used for analysis.

3.3.4. Publication IV

3.3.4.1. Study endpoints

The primary endpoint of the study was 180-day heart failure readmission or all-cause mortality.

The secondary endpoints of the study were:

- Change in quality-of-life from baseline to day 90 as measured by the EQ-5D-VAS.
- 180-day all-cause mortality;
- 90-day HF readmission or all-cause mortality;

3.3.4.2. Statistical analysis

Baseline characteristics, clinical and safety outcomes, and treatment effect of high-intensity care strategy vs usual care on the primary and secondary outcomes were compared in groups based on baseline anaemia, which was defined as baseline haemoglobin < 120 g/L in women and <130 g/L in men and in groups according to median haemoglobin values in women (130 g/L) and men (141 g/L). Dynamics of haemoglobin during the study follow-up and predictors of incident anaemia at 90 days were investigated.

Variable presentation and analyses comparing baseline characteristics were the same as in **publications II and III**. Separate multivariable logistic regression models were constructed to investigate potential predictors among baseline characteristics associated with the presence of anaemia at baseline and at day 90. Both univariable and multivariable results for the model assessing anaemia at day 90 were additionally adjusted for baseline haemoglobin value.

To determine the impact of anaemia on clinical outcomes, Cox proportional hazards regression analysis was applied. The impact of anaemia on changes in EQ-VAS scores from baseline to day 90 was evaluated with a linear regression model, adjusted for baseline EQ-VAS scores, and the randomization stratification factors LVEF category (≤40% or >40%), and geographic region. The effect of the treatment strategy on the primary endpoint was modeled using baseline haemoglobin levels as a continuous variable in a restricted cubic spline with three knots. The results are presented as hazard ratios (HR) with 95% confidence intervals (CI). A two-sided P value of less than 0.05 was considered statistically significant. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

4. PERSONAL CONTRIBUTION

Publications, presented in this dissertation, were either entirely wrote by me (**Publications I, II**) or together with my academic supervisor (**Publications III, IV**).

I participated in the collection of the data of the LEDA study since the study inception in 2015, which included communication with administrative databases of Lithuania to obtain follow-up data. I have also prepared the database for analysis presented in this dissertation and analyses beyond the scope of this dissertation by performing extensive data cleaning. Together with the supervisors, throughout multiple steps and discussions, we devised the plans for statistical analysis and data visualisation, which I performed in the R statistical program. After the statistical analysis was performed in the LEDA cohort, I presented our results to colleagues from Switzerland, who kindly accepted our invitation to participate in the study and provided us with the required data. I then repeated all the analyses in the BASEL V cohort.

Regarding **publications II-IV**, together with the supervisors we devised the concepts for statistical analyses, which were then performed by the statistician of the STRONG-HF study. During the process of data analysis, we revised the plans and finalised the analyses and data visualisation presented in the respective publications.

5. RESULTS

5.1. The results of the study of rehospitalisation and mortality in acute dyspnoea – Publication I

In the derivation LEDA cohort, median age of the patients was 71 [61–79] years, 599 (43.6%) were women and 731 (53.3%) had adjudicated diagnosis of AHF. During the 6 months after discharge, 666 (48.6%) patients were readmitted, 379 (56.9%) for cardiovascular and 287 (43.1%) for non-cardiovascular causes. Readmitted patients were older and had more co-morbidities, higher heart rate, higher concentrations of cardiac, renal, and inflammatory biomarkers, and lower haemoglobin. AHF patients were readmitted more frequently than non-AHF patients at 6 months (53.5% vs. 43%, respectively, $P < 0.001$). In AHF patients, cardiovascular causes of readmission dominated (68.3%), in contrast to non-AHF patients (59.3% non-cardiovascular readmissions). At 1 year, 282 patients died in the derivation LEDA cohort (1- year mortality rate 20.6%). The trajectory of acute dyspnoea patients within 12 months after index admission in the LEDA derivation cohort is depicted in Figure 1. One-year all-cause mortality was similar between AHF and non-AHF patients (20% vs. 21.2%, respectively, $P = 0.61$).

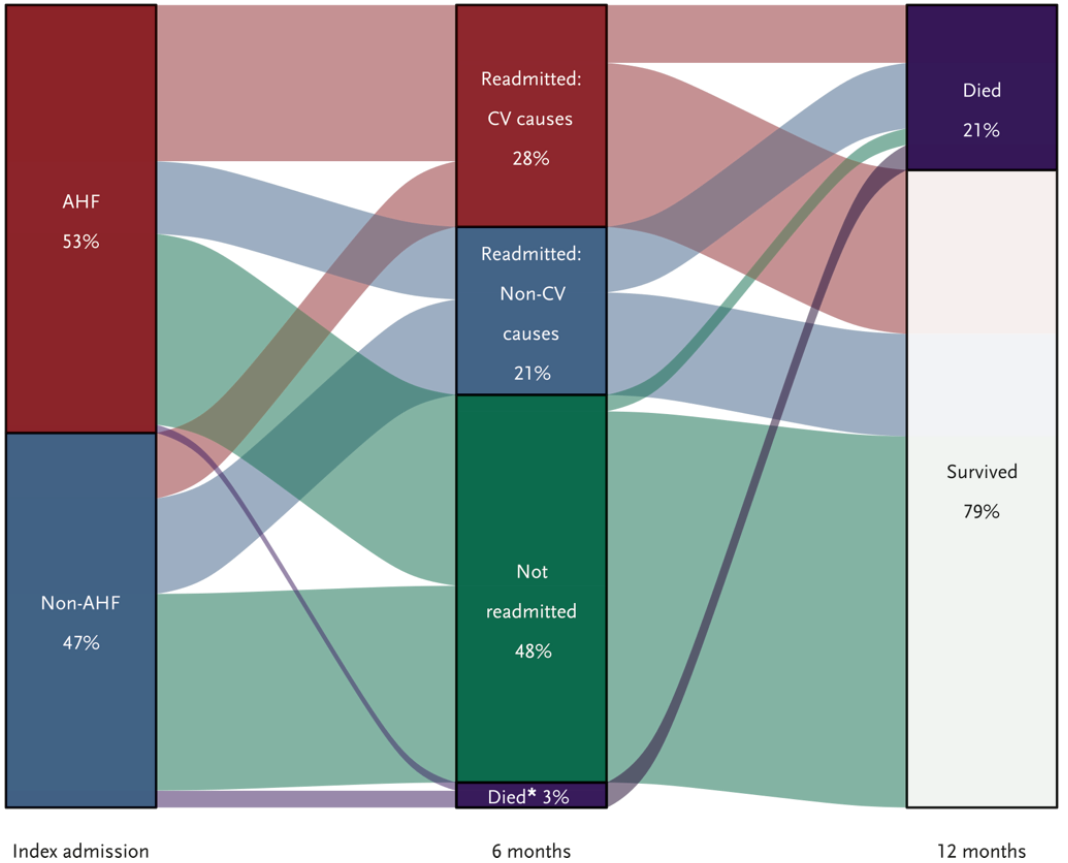

Figure 1. Trajectory of acute dyspnoea patients within 12 months after index admission in the LEDA derivation cohort. Explanations and abbreviations: Red – (re)admitted due to cardiovascular (CV) causes; blue – (re)admitted due to non-CV causes; green – survived without readmission; purple – died. AHF, acute heart failure. *Died at 6 months without readmission.

In the validation BASEL V cohort, median age was 74 [61–82] years, 888 (44.7%) patients were women, and 993 (50%) patients had AHF. At 6 months, 812 (40.9%) patients were readmitted with 348 (42.9%) readmitted for cardiovascular and 464 (57.1%) – for non-cardiovascular causes. Similarly to LEDA cohort, AHF patients were readmitted more frequently than non-AHF patients (45.9% vs. 35.9%, respectively, $P < 0.001$). In AHF patients, 62.1% readmissions were for cardiovascular causes, whereas 81.7% of readmitted non-AHF patients were readmitted for non-cardiovascular causes. At 1 year, 377 patients died (1-year mortality rate 19%).

In LEDA cohort, patients readmitted within 6 months died three times more frequently than non-readmitted patients [211 (31.7%) vs. 71 (10.1%), respectively, $P < 0.001$]. The first episode of readmission within 6 months was associated with a three-fold risk of 1 year all-cause mortality [adjusted hazard ratio (aHR) 3.0, 95% confidence interval (CI) 2.2–4.0, $P < 0.001$, Figure 2 IA]. The mortality risk was consistently high, whether the first readmission occurred in the first month, in the second and third months or in the fourth to sixth months (Figure 2 IA). Readmission within 6 months was also associated with increased risk of 1-year mortality in both AHF and non-AHF patients [aHR 3.2, 95% CI 2.1–4.9, $P < 0.001$, and aHR 2.9, 95% CI 1.9–4.5, $P < 0.001$, respectively, Figure 2 IB]. Furthermore, the association between readmission and mortality persisted, regardless of cause of readmission. Both CV and non-CV causes of readmission were associated with an increased risk of 1 year mortality [aHR 2.2, 95% CI 1.6–3.1, and aHR 4.1, 95% CI 2.9–5.7, respectively ($P < 0.001$ for both), Figure 2 IC].

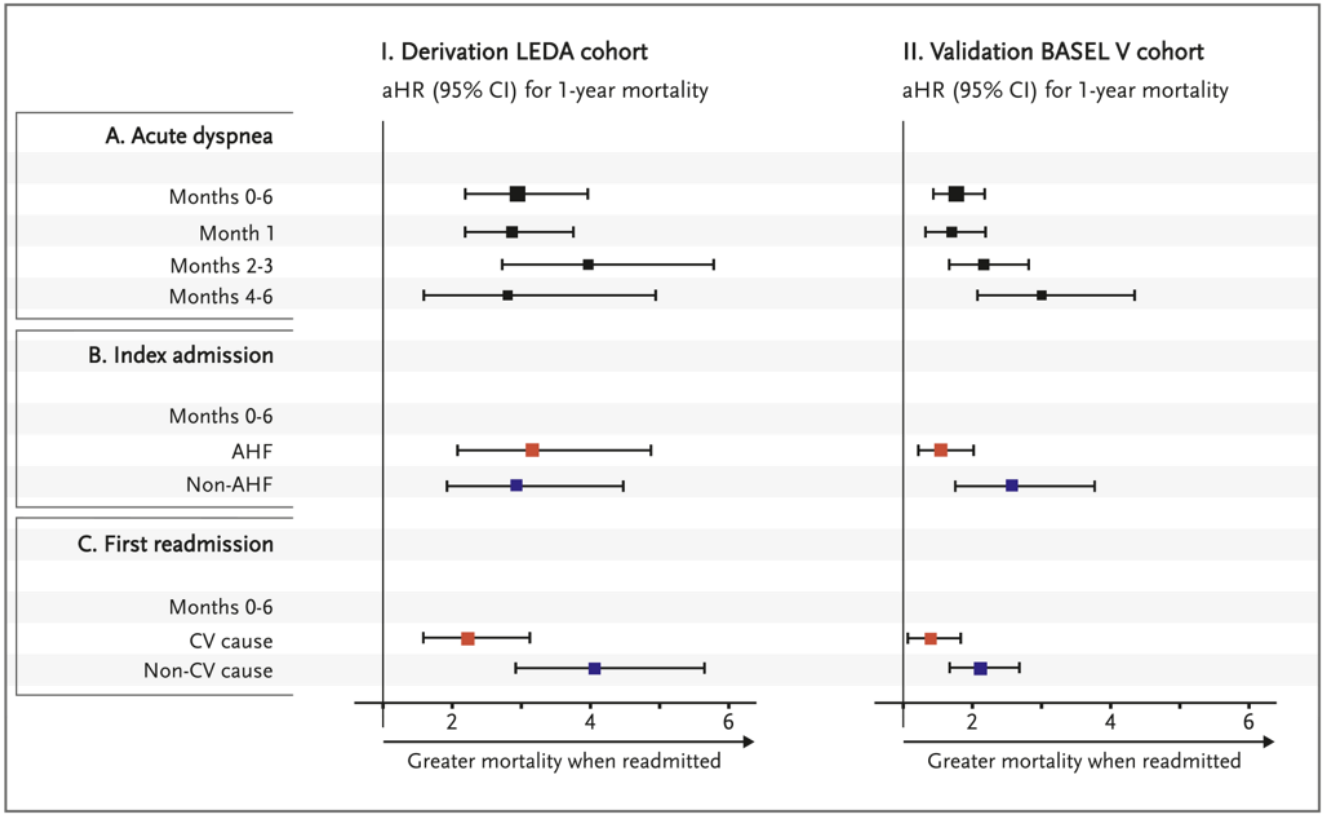

Figure 2. Primary endpoint and subgroup analysis: relationship between all-cause readmissions and 1-year all-cause mortality in (I) derivation LEDA and (II) validation BASEL V cohorts.

The figure depicts Cox hazard proportional regression results adjusted with age, gender, co-morbidities (history of chronic heart failure, coronary artery disease, and diabetes mellitus), systolic blood pressure, heart rate, creatinine, and sodium <136 mmol/L. The size of the point represents sample size of readmitted patients in a group, red colour represents either AHF or CV cause of readmission, blue colour represents either non-AHF or non-CV cause of readmission. (A) Risk of death depending on the exact time or readmission. (B) First readmission in any time in the 6 months following index admission in acute heart failure (AHF) and non-AHF groups. (C) Analysis for cardiovascular (CV) and non-CV causes of readmissions. aHR – adjusted hazard ratio; CI – confidence interval.

The association between 6-month all-cause readmission and 1-year all-cause mortality remained consistent throughout all studied subgroups (Figure 3).

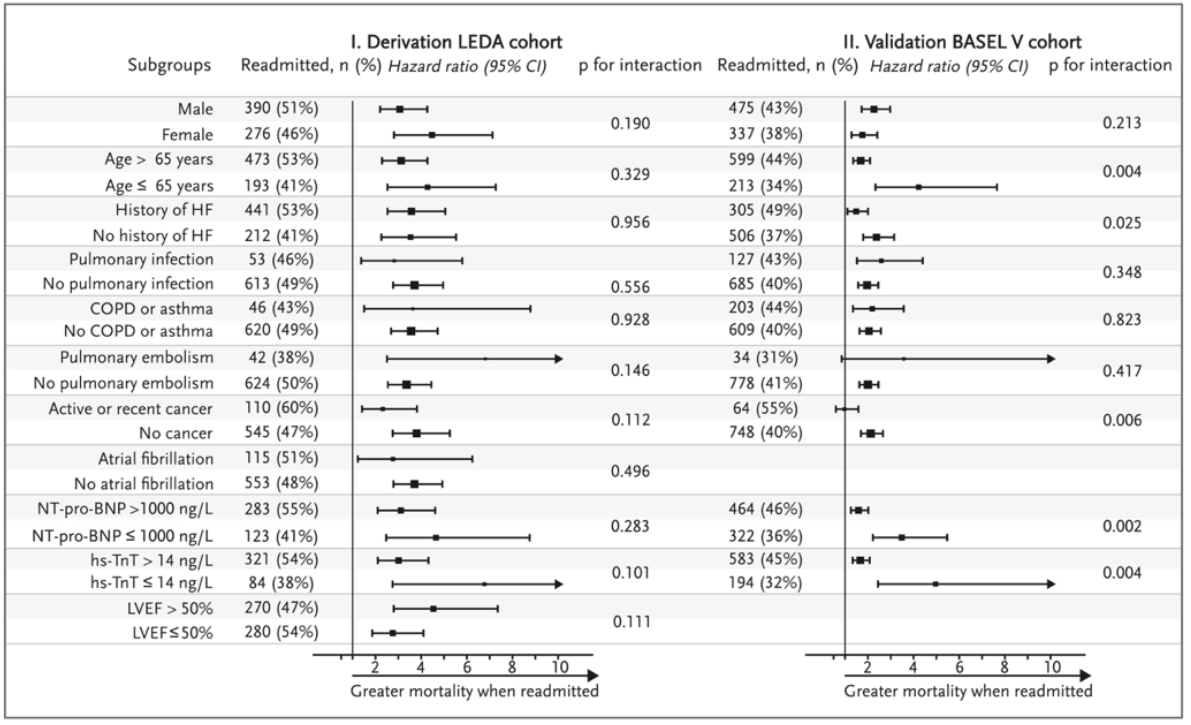

Figure 3. Subgroup analysis: the relationship between all-cause readmission and 1-year all-cause mortality in the subgroups of (I) derivation LEDA and (II) validation BASEL V cohorts.

Explanation and abbreviations: the size of the point represents the readmitted sample size in a group. CI – confidence interval; COPD – chronic obstructive pulmonary disease; HF – heart failure; hs-TnT – high-sensitivity troponin T; LVEF – left ventricular ejection fraction; NT-pro-BNP – N-terminal pro-B-type natriuretic peptide.

The results were then validated in BASEL V cohort. Patients readmitted within 6 months died significantly more often than non-readmitted patients [218 (26.8%) vs. 159 (13.5%), respectively, P < 0.001]. Six-month readmission in the validation cohort was also significantly associated with an increased risk of 1-year mortality in acute dyspnoea patients (aHR 1.8, 95% CI 1.4–2.2, P < 0.001, Figure 2 IIA). This relationship was uniform irrespective of the timing of readmission, aetiology of index admission, and aetiology of first readmission (Figures 2 IIB and IIC).

5.2. The results of the sex-specific analysis of the STRONG-HF trial – Publication II

Of 1078 randomised AHF patients, 416 (39%) were women. There were significantly more non-white and non-European women, compared to men. Men were more likely to have HF of ischaemic origin and more frequently had a history of acute coronary syndrome, prior coronary surgery or intervention. Men were also more likely to have a history of atrial fibrillation, to be in New York Heart Association (NYHA) class IV and to have a lower LVEF. Conversely, women were more likely to have worse baseline quality-of-life. There were no differences in rate of implanted devices. At baseline, men had lower blood pressure and heart rate, worse renal and liver function. NT-proBNP did not differ significantly between the sexes (3153.2 (2977.7–3339.0) ng/L in women vs 3242.9 (3084.1–3410.0) ng/L in men, P = 0.4796).

Medication up-titration in the high-intensity care strategy throughout the study period was similar between men and women. At week 2 there were no differences between the number of fully up-titrated patients (P = 0.074, 0.51, and 0.54 for RASi, beta-blockers and MRA, respectively) or loop diuretic doses (P = 0.50) between women and men in the high-intensity care group. By day 90, most patients of both sexes in the high-intensity care group had been up-titrated to full doses of each of the three oral HF medication classes compared to only a small number in the usual care group (RASi 56.6% vs. 1.6% in women, 54.0% vs. 2.5% in men, interaction P = 0.65; beta-blockers 45.4% vs. 2.2% in women, 51.8% vs. 5.1% in men, interaction P = 0.43; MRA 83.2% vs. 44.8% in women, 84.1% vs. 47.5% in men, interaction P = 0.73). The average percentage of the optimal dose across the three GDMT classes by sex in the high-intensity care group throughout the study visits is shown in Figure 4.

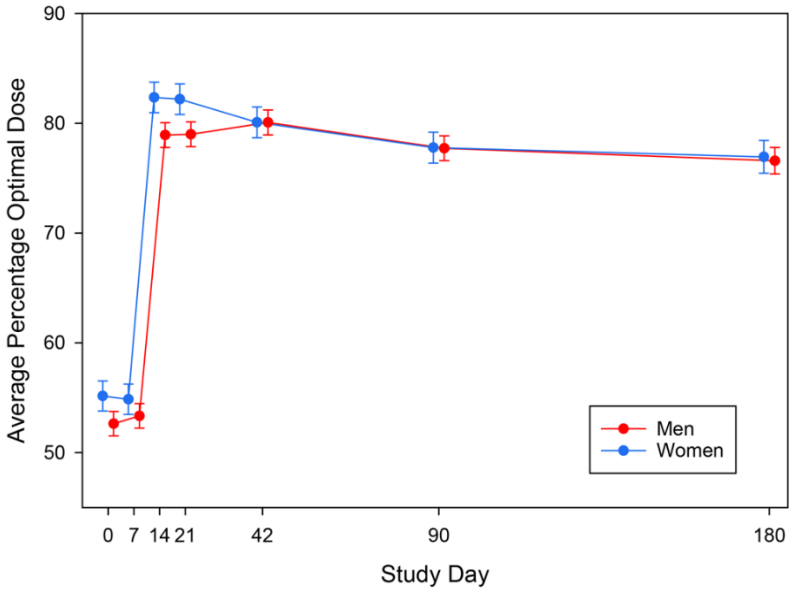

Figure 4. Average optimal dose of three oral guideline-directed medical therapies (renin–angiotensin system inhibitors, beta-blockers, mineralocorticoid receptor antagonists) by visit and sex in the high-intensity care group. (216 women; 326 men in high-intensity care group).

The primary endpoint (HF readmission or all-cause death at day 180) occurred in 73 (19.6%) women and in 110 (19.2%) men (adjusted hazard ratio [HR] 0.87, 95% confidence interval [CI] 0.62–1.21; P = 0.41). The outcomes did not differ by sex, regardless of the treatment strategy (Figure 5). The high-intensity care strategy reduced the incidence of the primary endpoint in both women (30 [15.8%] in the high-intensity care group vs. 43 [23.5%] in the usual care group; adjusted HR 0.67 [95% CI 0.40–1.13]) and men (44 [14.9%] in the high-intensity care group vs. 66 [23.5%] in the usual care group; adjusted HR 0.57 [95% CI 0.38–0.88]). Sex was not a modifier of the treatment strategy effect (adjusted interaction P = 0.65). All-cause death by day 180 occurred in 17 (9.2%) women in the high-intensity care group and in 20 (9.8%) women in the usual care group (adjusted HR 0.97 [95% CI 0.46–2.06]); and in 22 (8.2%) men in the high-intensity care group and in 28 (10.3%) men in the usual care group (adjusted HR 0.69 [95% CI 0.38–1.25], adjusted interaction P = 0.48). There was no treatment-by-sex interaction when analysing HF readmission by day 180 (adjusted interaction p = 0.90). The quality-of-life improved similarly in men and women in the high-intensity care strategy group compared to usual care group and again, sex was not found to modify the effect of the treatment strategy on quality of life (interaction P

= 0.08). Similarly in both men and women, NT-proBNP decreased more in the high-intensity care group compared to usual care (interaction P = 0.49). Rapid medication up-titration was found to be similarly safe in both men and women. There was no significant increase of adverse event risk in either of the sexes or a significant treatment-by-sex interaction (all P values > 0.05).

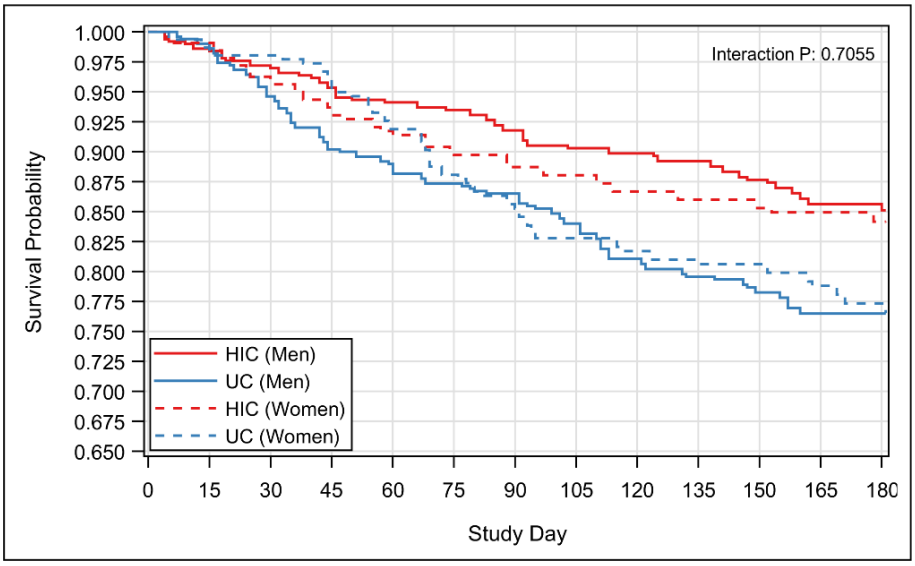

Figure 5. Unadjusted Kaplan–Meier curves for all-cause death or heart failure readmission through day 180 by sex at birth and treatment arm. Women: 216 in the high-intensity care group; 200 in the usual care group. Men: 326 in the high-intensity care group; 336 in the usual care group.

Abbreviations: HIC – high-intensity care; UC – usual care.

5.3. The results of the quality-of-life analysis of the STRONG-HF trial – Publication III

The mean baseline EQ-VAS score was 59.2 (SD 15.1) with no statistically significant difference between the treatment groups. Patients with worse baseline quality-of-life were more likely to be women, black and non-European (P<0.001). The terciles of QoL were not statistically significantly different in terms of age, baseline NT-proBNP, LVEF, NYHA class and major comorbidities. Patients with the lowest baseline quality-of-life had a longer history of heart failure and more HF hospitalizations in the previous year.

The improvement of EQ-VAS from baseline to day 90 was significantly greater in patients allocated to high-intensity care group (adjusted treatment effect 3.49 (95% CI 1.74-5.24), P < 0.0001). The benefit of high-intensity care

strategy on quality-of-life was seen across patient subgroups of different ages, with LVEF above or below 40%, NT-proBNP and systolic blood pressure above or below the median value, as well as regardless of the history of atrial fibrillation or flutter. The quality-of-life improved similarly in the high-intensity care group, regardless of baseline quality-of-life, measured as a continuous variable (interaction P value = 0.32). High-intensity care strategy improved all separate EQ-5D dimensions of health status including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression (Figure 6).

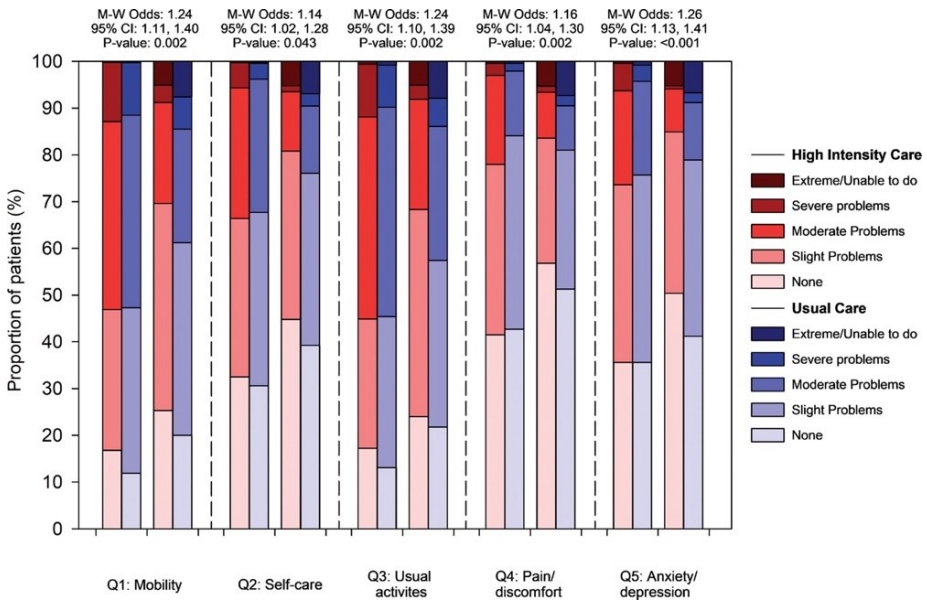

Figure 6. Effects of high-intensity care vs usual care on dimensions of the EQ-5D.

M-W odds indicate Mann-Whitney U test odds.

Medication up-titration in the high-intensity care strategy throughout the study period was similar in tertiles based on baseline EQ-VAS (Figure 7). A higher average percentage optimal dose at week 2 in the high-intensity care group was associated with a greater EQ-VAS increase (P<0.001).

The effect of high-intensity care strategy on the primary endpoint (all-cause death or HF hospitalization at day 180) was not significantly affected by baseline quality-of-life, as measured either as a categorical (interaction P value = 0.58) or as a continuous variable (interaction P value = 0.87, Figure 8).

High-intensity care strategy was safe in all groups based on baseline quality-of-life (all interaction P values > 0.05 in adverse events or serious adverse events).

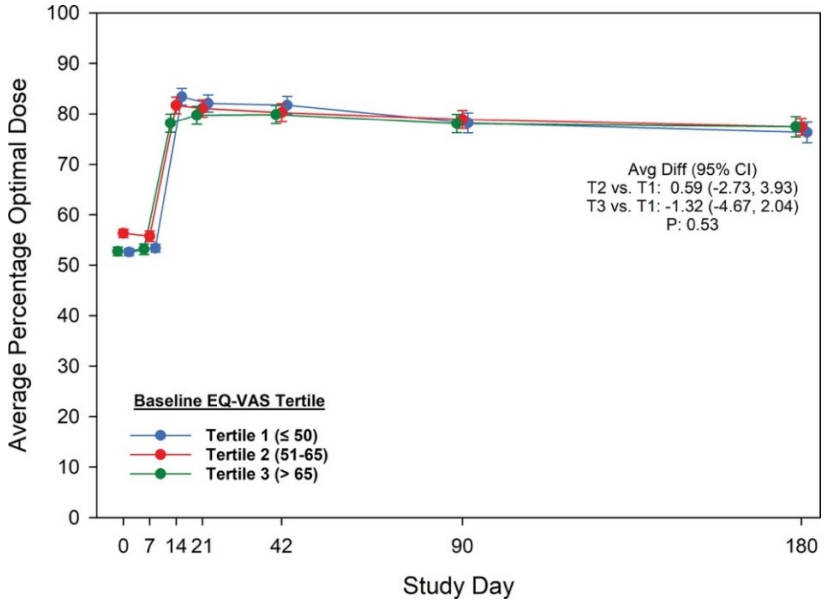

Figure 7. Average percentage optimal dose of three oral guideline-directed medical therapies (renin–angiotensin system inhibitors, beta-blockers, mineralocorticoid receptor antagonists) by baseline EQ-visual analogue scale (VAS) tertile in the high-intensity care group.

Explanation and abbreviations: Avg Diff average difference, CI – confidence interval; T1 – tertile 1; T2 – tertile 2; and T3 – tertile 3.

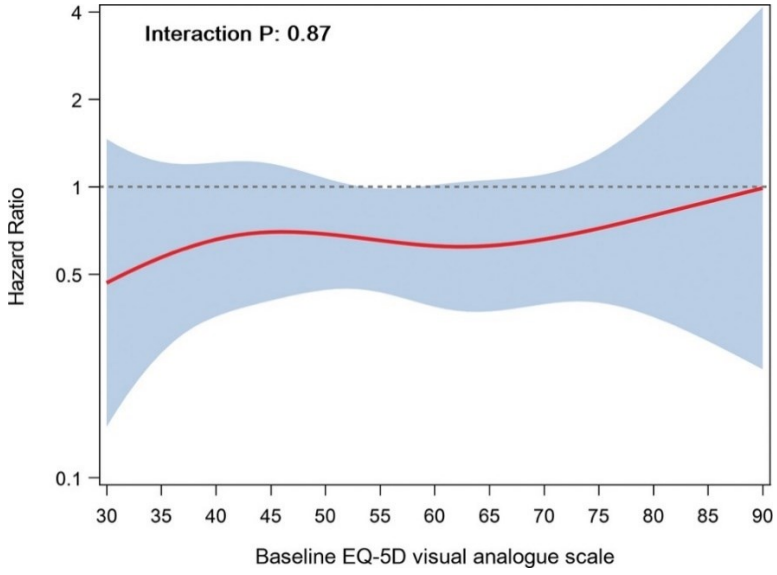

Figure 8. Treatment effect of high-intensity care vs usual care on the primary end point by baseline EQ-visual analogue scale (VAS).

5.4. The results of the anaemia analysis of the STRONG-HF trial – Publication IV

The prevalence of anaemia at enrolment was 27.2% and 32.1% at day 90. Patients with baseline anaemia were more likely to be black and non-European, had higher NT-proBNP and more signs of congestion. Independent predictors of anaemia at baseline were older age, lower BMI (body mass index), non-white race, elevated systolic blood pressure, worse renal function, reduced potassium, lower total bilirubin, decreased white blood cell count, and lower cholesterol levels. The predictors of incident anaemia at 90 days were male sex, geographical region other than Europe, ischemic aetiology of HF, higher glucose and uric acid concentration at baseline. High-intensity care strategy did not increase rate of incident anaemia at 90 days. The primary outcome (HF readmission or all-cause death at day 180) occurred similarly in patients with and without baseline anaemia (22.5% vs 18.2%, respectively, unadjusted HR 1.27; 95% CI 0.90–1.80, P > 0.05). However, patients with baseline anaemia had significantly less improvement of EQ-VAS questionnaire values from baseline to day 90 (adjusted LS-Mean difference −2.34 (−4.37, −0.31), P = 0.02).

Medication up-titration in the high-intensity care strategy throughout the study period was similar regardless of presence of baseline anaemia (Figure 9).

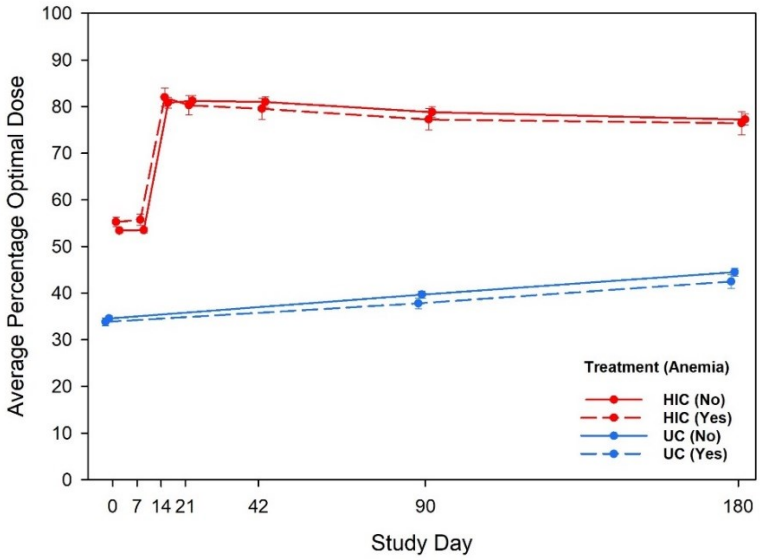

Figure 9. Average percentage optimal dose of three oral guideline-directed medical therapies (renin–angiotensin system inhibitors, beta-blockers, mineralocorticoid receptor antagonists) by treatment and baseline anaemia status.

Abbreviations: HIC – high-intensity care; UC – usual care.

The effect of high-intensity care strategy on the primary endpoint (all-cause death or HF hospitalization at day 180) was not significantly affected by either presence of anaemia (adjusted interaction P value = 0.28) or haemoglobin measured either as a continuous variable (interaction P value = 0.53, Figure 10).

The frequency of serious adverse events was higher in anaemic patients (P = 0.0058). However, high-intensity care strategy was safe in all groups based on baseline anaemia or level of haemoglobin (all interaction P values > 0.05 in adverse events or serious adverse events).

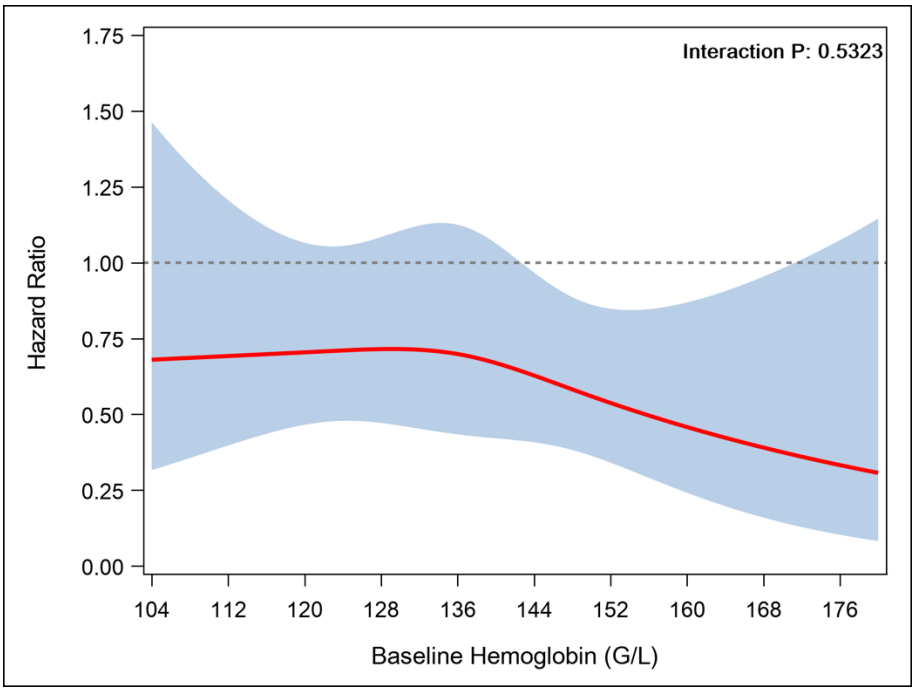

Figure 10. Treatment effect of high-intensity care vs. usual care on primary endpoint by continuous baseline haemoglobin.

6. DISCUSSION

This doctoral thesis examines prognostication of patients with acute dyspnoea and more specifically, with acute heart failure, in two observational cohorts and one cohort from a major randomised clinical trial.

The study presented in the **Publication I** demonstrates a long-lasting detrimental relationship between readmission and risk of death in AHF and non-AHF patients. Almost half of the patients presenting with acute dyspnoea to the emergency department in both Lithuania and Switzerland were readmitted in the following 6 months, and this readmission was associated with a substantial risk of 1-year death[37]. The two-fold to three-fold increase in the risk of 1-year death was found in both cohorts from two different regions of Europe with different income and healthcare systems and different time frames of patient inclusion.

Acute dyspnoea is a complex symptom, associated with multiple causes, enormous diagnostic challenges and poor prognosis[25]. Patients in our study were frequently readmitted at 6 months for similar causes to their initial presentation, suggesting that the index admission and readmission form a continuum of an unresolved disease, which leads to significantly increased risk of death. Patients who present to the emergency department with acute dyspnoea require multiple strategies to establish a primary cause, clear risk stratification to identify the most vulnerable patients, a close individualized follow-up and, in case of acute heart failure, timely implementation of GDMT.

The positive effect of rapid initiation and up-titration of guideline-recommended treatment in patients after a hospitalization for acute heart failure on 180-day all-cause death or heart failure readmission risk has been determined in the STRONG-HF randomised controlled trial[57]. The cohort from the trial was the basis of the **Publications II-IV**, presented in this PhD thesis. The analyses in these publications further expanded the results of the study.

In the study, presented in **Publication II**, a rapid up-titration of optimal medical treatment implemented immediately after hospitalization for acute heart failure reduced all-cause 180-day death or heart failure readmission risk in both men and women with no significant treatment-by-sex interaction. The high-intensity treatment strategy also improved quality-of-life in both men and women. The treatment strategy was safe in men and women.

Better outcomes in women than men have been reported in both epidemiological and clinical studies of chronic HF[80,109–111]. In one epidemiological analysis of AHF patients from different regions of the world,

women had lower risk of 1-year mortality than men[30]. However, multiple AHF trials have reported that the outcomes are not different for women and men with AHF[73–75]. Accordingly, in our analysis the rates of 180-day HF readmission and/or all-cause death were similar between women and men with AHF, regardless of the treatment strategy.

It has been reported that women are less often prescribed with evidence-based therapy than men, even in HFrEF[30], although no sex-related treatment attenuation has been reported in subgroup analyses of pivotal randomised controlled trials in chronic HFrEF[11,12,17,79,112]. The reasons of this gender bias are not entirely clear. One of the reasons might be an unsupported belief that treatment with higher doses is not as attainable or as safe in women. Observational studies have suggested that women benefit from lower medication doses than men but no safety concerns with higher doses have been documented[113]. Retrospective analyses and reviews have shown that women are less likely to be referred to cardiologists, less likely to be referred to HF specialists, and less likely to receive follow-up visits after the initial consultation, which may also affect medication prescription and treatment intensification in women[31,32].

In our analysis, the achieved doses of medications and proportion of AHF patients up-titrated to full optimal doses of optimal medical treatment were very similar in men and women in the high-intensity care group. Moreover, the safety profile was comparable between men and women. Most importantly, mortality and readmission risk was reduced and quality-of-life was improved with high-intensity treatment strategy in both sexes. Altogether, these results strongly underline the importance of close follow-up and rapid up-titration of the heart failure medication in women and in men.

For most patients with heart failure, good quality of life and preserved functional capabilities are just as essential as prolonging survival[114]. Patients with heart failure experience a range of symptoms, both physical and psychological, that reduce their capacity for usual activity[115,116]. The main endpoints of large randomised controlled trials in heart failure and evidence for treatment efficacy are hospitalizations and mortality. In recent years, quality-of-life assessment, reflecting patients' priorities has been gaining more awareness and is increasingly more researched[117]. Quality-of-life changes in a large randomised controlled trial of acute heart patients were evaluated in the **Publication III** of this thesis.

In the study, a rapid up-titration of optimal medical treatment after hospitalization for acute heart failure improved quality-of-life at 90 days. High-intensity care strategy improved quality-of-life measured by EQ-VAS,

and all five EQ-5D health domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression).

The analysis showed that rapid up-titration of guideline-recommended medical therapy after hospitalization for acute heart failure reduced the composite primary outcome of STRONG-HF study consistently across the entire spectrum of baseline quality-of-life scores. Furthermore, target doses of medications were reached independently from baseline level of quality-of-life in the high-intensity treatment arm. These findings highlight that close follow-up and rapid medication up-titration after acute heart failure hospitalization prolong survival and significantly improve patient well-being.

Importantly, this study revealed that patients with the worst quality-of-life at baseline were more likely to be women, self-reported Black, and non-European. This is in parallel with multiple observational studies and randomised trials in HF, which have shown similar health-related sex and racial/ethnic disparities in quality-of-life analyses[118–123].

Women, suffering from HF, are usually older, report less caregiver support and more mental and physical limitations[124]. As mentioned before, they are also less likely to receive guideline-directed therapies[30,124]. All this potentially contributes to poor health-related well-being. Regarding Black and non-European individuals with HF, research on the exact causes of lower quality-of-life is lacking but the consistent findings from multiple trials reflect the possible importance of socioeconomic determinants of health, structural racism, income inequality, and lack of access to health care[125,126]. The findings of our analysis highlight the importance of studies in diverse clinical environments and the need to address patient-preferred outcomes in underprivileged communities.

One of the main hindrances to better well-being in heart failure is anaemia. It is one of the most frequent non-cardiac comorbidities in patients with heart failure, related to increased risk of mortality, repeated hospitalizations and poor quality of life[36,102,127]. In our study, presented in **Publication IV**, anaemia was associated with more severe congestion, worse kidney function and older age. Furthermore, in parallel with other studies, patients with baseline anaemia had significantly less improvement in quality-of-life at 90 days. These findings support treatment of anaemia and concurrent iron deficiency (although testing for iron deficiency was not performed in STRONG-HF) during the hospitalization or in early post-discharge period.

In heart failure, particularly in acute settings, a higher comorbidity burden can lead to suboptimal prescription of GDMT as patients might be perceived to be at higher risk of adverse reactions[34,128,129]. Yet, our analysis showed that, regardless of baseline anaemia, a rapid up-titration of optimal

medical treatment was feasible, safe and effective in patients after a hospitalization for acute heart failure. We showed that high-intensity treatment improved all clinical outcomes throughout the whole haemoglobin spectrum. Although anaemic patients were more prone to adverse events in the whole population, high-intensity treatment strategy did not increase the risk of them. Another analysis of the STRONG-HF cohort expanded these findings to multiple other non-cardiac comorbidities[129]. These results refute many concerns arising when treating a highly comorbid heart failure patient and reiterate the feasibility and benefit of rapid up-titration of guideline-recommend medical treatment in a heterogenous acute heart failure population.

7. LIMITATIONS

Publications, presented in this doctoral thesis have certain limitations.

The **Publication I** analysed two European cohorts. Therefore, the results may not be generalizable to other continents and health care systems. Furthermore, there are some missing data in both cohorts, for which multiple imputation was not used. AHF patients in the observational LEDA cohort received fewer diuretics and less neurohormonal blockade compared to specialized heart failure registry data. Considering the observational nature of the cohort and knowing that a wide spectrum of cardiologists, internists and emergency doctors treat patients in Lithuanian hospitals, the treatment strategies might have differed from dedicated heart failure specialists participating in the registries. The discrepancy in the admission and adjudicated diagnoses may also explain this finding since final diagnoses were determined by the adjudication committee long after the initial admission. Nonetheless, our study results demonstrate that regardless of some possible discrepancies in initial diagnoses, the increased risk of mortality related to readmission remained consistent in the two cohorts of acute dyspnoea, acute and non-acute heart failure patients and throughout all analysed subgroups.

STRONG-HF randomised clinical trial, which was the basis for **Publications II-IV** had several limitations. First, the study protocol was amended to change the primary endpoint from 90-day to 180-day death or heart failure readmission and to increase target enrolment, based on a low event rate[56]. However, when the cohort enrolled before the amendment was removed from the sensitivity analysis, the study result was unchanged. Second, the study was stopped early by the data safety monitoring boards, because it was no longer ethical to continue including patients in the usual care group due to the large treatment effect and significance of the results. Third, due to the nature of the study, the treatment allocation could not be blinded. However, the main separation in the rate of the primary endpoint occurred between day 90 and day 180, a period when patients were no longer seen by the study team in either group. Fourth, the causes of readmissions were not adjudicated. However, in the post-hoc analysis, the effect size on 180-day all-cause death or all-cause readmission was comparable to that on 180-day all-cause death or heart failure readmission. Finally, SGLT2 inhibitors were not approved in heart failure or available in the participating countries for most of the study, so they were not prescribed to most patients.

Separately, the limitation in **Publication II** was a low percentage of included women patients (39%). Because of that, we could not properly

evaluate the benefit of lower doses of GDMT in women with AHF, although no safety concerns were noted in women up-titrated to full doses. The open-label treatment allocation in the study might have affected quality-of-life results in **Publication III**, since patients might be biased to report greater improvements when they know they are allocated to an interventional group. The documented racial and regional disparities of the baseline quality-of-life might have been affected by the cultural and language barriers. In **Publication IV**, we could not examine the causes and types of anaemia in greater detail, since haematocrit values, markers of iron metabolism and data on treatment of iron deficiency were not collected in the study.

8. CONCLUSIONS

1. Unplanned rehospitalization during the first 6 months after discharge is associated with significantly increased 1-year all-cause mortality risk in acute heart failure and non-acute heart failure patients admitted to the emergency department with acute dyspnoea.
2. Rapid up-titration of guideline-directed medical therapy after hospitalization for acute heart failure is feasible, safe and reduces 180-day all-cause death or heart failure readmission risk and improves quality-of-life in both men and women.
3. Rapid up-titration of guideline-directed medical therapy after hospitalization for acute heart failure is associated with improved quality-of-life, including all five dimensions, and clinical outcomes across different baseline quality-of-life categories.
4. Rapid up-titration of guideline-directed medical therapy after hospitalization for acute heart failure is feasible, safe and reduces 180-day all-cause death or heart failure readmission risk and improves quality-of-life, regardless of baseline anaemia.

9. PRACTICAL RECOMMENDATIONS

1. A patient presenting to the emergency department with acute dyspnoea due to both cardiac and non-cardiac causes should be considered a ‘vulnerable patient’ for a long period after discharge, warranting a close follow-up and treatment optimization, addressing main cause of dyspnoea and comorbidities.
2. Optimal medical treatment for heart failure should be prescribed and rapidly up-titrated at the same rate in both men and women after a hospitalization for acute heart failure.
3. Optimal medical treatment for heart failure should be rapidly up-titrated after a hospitalization for acute heart failure to improve not only prognosis but also quality of life.
4. Optimal medical treatment for heart failure should be rapidly up-titrated after a hospitalization for acute heart failure regardless of baseline anaemia and baseline quality-of-life.

10. SANTRAUKA LIETUVIŲ KALBA

Ši daktaro disertacija parengta mokslinių publikacijų, tolesniame tekste žymimų romėniškais skaitmenimis, rinkinio pagrindu:

I. **Čerlinskaitė K**, Mebazaa A, Cinotti R, Matthay M, Wussler DN, Gayat E, Juknevičius V, Kozhuharov N, Dinort J, Michou E, Gualandro DM, Palevičiūtė E, Alitoit-Marrote I, Kablučko D, Bagdonaitė L, Balčiūnas M, Vaičiulienė D, Jonauskienė I, Motiejūnaitė J, Stašaitis K, Kukulskis A, Damalakas Š, Laucevičius A, Mueller C, Kavoliūnienė A, Čelutkienė J; GREAT network. Readmission following both cardiac and non-cardiac acute dyspnoea is associated with a striking risk of death. ESC Heart Fail. 2021 Aug;8(4):2473-2484. doi: 10.1002/ehf2.13369. Epub 2021 Jun 10. PMID: 34110099; PMCID: PMC8318470.

II. **Čerlinskaitė-Bajorė K**, Lam CSP, Sliwa K, Adamo M, Ter Maaten JM, Léopold V, Mebazaa A, Davison B, Edwards C, Arrigo M, Barros M, Biegus J, Chioncel O, Cohen-Solal A, Damasceno A, Diaz R, Filippatos G, Gayat E, Kimmoun A, Metra M, Novosadova M, Pagnesi M, Pang PS, Ponikowski P, Saidu H, Takagi K, Tomasoni D, Voors AA, Cotter G, Čelutkienė J. Sex-specific analysis of the rapid up-titration of guideline-directed medical therapies after a hospitalization for acute heart failure: Insights from the STRONG-HF trial. Eur J Heart Fail. 2023 Jul;25(7):1156-1165. doi: 10.1002/ejhf.2882. Epub 2023 Jun 1. PMID: 37191154.

III. Čelutkienė J, **Čerlinskaitė-Bajorė K**, Cotter G, Edwards C, Adamo M, Arrigo M, Barros M, Biegus J, Chioncel O, Cohen-Solal A, Damasceno A, Diaz R, Filippatos G, Gayat E, Kimmoun A, Léopold V, Metra M, Novosadova M, Pagnesi M, Pang PS, Ponikowski P, Saidu H, Sliwa K, Takagi K, Ter Maaten JM, Tomasoni D, Lam CSP, Voors AA, Mebazaa A, Davison B. Impact of Rapid Up-Titration of Guideline-Directed Medical Therapies on Quality of Life: Insights From the STRONG-HF Trial. Circ Heart Fail. 2024 Apr;17(4):e011221. doi: 10.1161/CIRCHEARTFAILURE.123.011221. Epub 2024 Mar 6. PMID: 38445950.

IV. Čelutkienė J, **Čerlinskaitė-Bajorė K**, Cotter G, Edwards C, Adamo M, Arrigo M, Barros M, Biegus J, Chioncel O, Cohen-Solal A, Damasceno A, Diaz R, Filippatos G, Gayat E, Kimmoun A, Léopold

V, Deniau B, Metra M, Novosadova M, Pagnesi M, Pang PS, Ponikowski P, Saidu H, Sliwa K, Takagi K, Ter Maaten JM, Tomasoni D, Lam CSP, Voors AA, Mebazaa A, Davison B. Insights on prevalence and incidence of anemia and rapid up-titration of oral heart failure treatment from the STRONG-HF study. Clin Res Cardiol. 2024 Nov;113(11):1589-1603. doi: 10.1007/s00392-024-02518-y. Epub 2024 Sep 11. PMID: 39259364.

SANTRUMPOS

aGFG – apskaičiuotas glomerulų filtracijos greitis;
AKF – angiotenziną konvertuojantis fermentas;
AKFI – angiotenziną konvertuojančio fermento inhibitorius;
ANCOVA – kovariacinė analizė;
ANOVA – dispersinė analizė;
ARB – angiotenzino II receptorių blokatorius;
ARNI – angiotenzino receptorių ir neprilizino inhibitorius;
b.i.d. – *bis in die* (du kartus per parą);
BiPAP – dviejų lygių teigiamo slėgio kvėpavimo takų ventiliacija;
CPAP – nuolatinio teigiamo slėgio kvėpavimo takuose ventiliacija;
EKD – Europos kardiologų draugija;
EQ-VAS – EuroQol vaizdinė analoginė skalė;
FEV1 – forsuoto iškvėpimo tūris per pirmąją sekundę;
iIFŠN – širdies nepakankamumas, kai yra išlikusi išstūmio frakcija;
k./min. – širdies susitraukimų dažnis (kartai per minutę);
KMI – kūno masės indeksas;
KSIF – kairiojo skilvelio išstūmio frakcija;
KT – kompiuterinė tomografija;
LOPL – lėtinė obstrukcinė plaučių liga;
MDRD – Dietos modifikavimo sergant inkstų ligomis formulė;
mEq/L – miliekvivalentai litre;
MRA – mineralokortikoidų receptorių antagonistas;
NP – natriuretinis peptidas;
NT-proBNP – N-galinis pro-B tipo natriuretinis peptidas;

NYHA – Niujorko širdies asociacija;
PI – pasikliautinasis intervalas;
PRS – pakoreguotas rizikos santykis;
PSIP – praeinantis smegenų išemijos priepuolis;
q.d. – *quaque die* (vieną kartą per parą);
RAS – renino–angiotenzino sistema;
RASI – renino–angiotenzino sistemos inhibitorius;
RS – rizikos santykis;
SGLT2i – natrio ir gliukozės kotransporterio 2 inhibitorius;
sIFŠN – širdies nepakankamumas, kai yra sumažėjusi išstūmio frakcija;
ST – skilvelinė tachikardija;
ŠN – širdies nepakankamumas;
t.i.d. – *ter in die* (tris kartus per parą);
TLK-10 – Tarptautinės statistinės ligų ir sveikatos sutrikimų klasifikacijos dešimtasis leidimas;
vsIFŠN – širdies nepakankamumas, kai yra vidutiniškai sutrikusi išstūmio frakcija

ĮVADAS

Disertacijos aktualumas

Pagal universalų apibrėžimą, širdies nepakankamumas (ŠN) yra klinikinis sindromas, kurio tipiniai simptomai ir (arba) požymiai, sukeliami struktūrinių ir (arba) funkcinių širdies pakitimų, o jo buvimą patvirtina padidėjusi natriuretinių peptidų (NP) koncentracija ir (arba) objektyvūs plaučių ar sisteminės stazės požymiai[1]. ŠN laikomas globalia pandemija, jo paplitimas sudaro maždaug 1% pasaulio suaugusiųjų populiacijos (64,3 milijono žmonių)[2]. Per penkis metus nuo ŠN diagnozės miršta daugiau negu 50% pacientų[3,4]. Šis sindromas sukelia daug iššūkių pacientams, sveikatos apsaugos sistemoms, nes yra susijęs su bloga pacientų gyvenimo kokybe, dideliu sergamumu ir mirštamumu, taip pat vis didėjančiomis sveikatos sistemos išlaidomis[5].

Širdies nepakankamumas skirstomas į tris fenotipus, atsižvelgiant į kairiojo skilvelio išstūmio frakciją (KSIF)[6]:

- Širdies nepakankamumas, kai yra sumažėjusi išstūmio frakcija (sIFŠN) – KSIF esant ≤40%.
- Širdies nepakankamumas, kai yra vidutiniškai sutrikusi išstūmio frakcija (vsIFŠN) – KSIF esant tarp 41 ir 49%.

- Širdies nepakankamumas, kai yra išlikusi išstūmio frakcija (iIFŠN) – KSIF esant ≥50%.

Vienas svarbiausių veiksnių, lemiančių blogas pacientų, sergančių ŠN, išeitis ir didelę šio sindromo ekonominę naštą, yra dažnos hospitalizacijos. 2014 metais atliktas Švedijos nacionalinio ligoninių registro tyrimas parodė, kad ŠN sergantys pacientai vidutiniškai hospitalizuojami bent kartą per metus[8]. Ūminis širdies nepakankamumas visame pasaulyje yra dažniausia vyresnių nei 65 metų žmonių hospitalizacijos priežastis[6]. Po hospitalizacijos dėl ūminio ŠN, ligos prognozė yra daug blogesnė nei lėtinės ligos, o mirtingumas per metus po hospitalizacijos gali siekti ir 25-30%[9].

Pastaraisiais dešimtmečiais, širdies nepakankamumo (ypač sIFŠN) gydymas ženkliai patobulėjo, todėl reikšmingai sumažėjo pacientų, sergančių lėtiniu ŠN, mirštamumas ir hospitalizacijų skaičius. Dabartinį medikamentinį sIFŠN gydymą sudaro vadinamosios 4 „kolonos“: renino-angiotenzino sistemos inhibitorius (RASi, įskaitant angiotenziną konvertuojančio fermento inhibitorių [AKFI] arba angiotenzino receptorių blokatorių [ARB], arba angiotenzino receptorių-neprilizino inhibitorių [ARNI]), beta blokatorius, mineralkortikoidų receptorių antagonistas (MRA) ir natrio-gliukozės kotransporterio 2 inhibitorius (SGLT2i)[6]. Istoriškai širdies nepakankamumas dešimtmečius buvo gydomas diuretikų ir digoksino deriniu iki 1987 metų, kai pasirodė CONSENSUS klinikinis tyrimas, įrodęs AKF inhibitoriaus enalaprilio efektyvumą, gydant sunkų širdies nepakankamumą[10]. Šis tyrimas buvo tikras lūžio taškas ŠN gydymo istorijoje, o po jo sekė kiti svarbūs tyrimai, įrodę beta blokatorių ir MRA efektyvumą[11–16]. 2014 metais PARADIGM-HF tyrimas parodė, kad ARNI grupės atstovas – sakubitrilas/valsartanas – buvo pranašesnis už enalaprilį, mažinant hospitalizacijas dėl ŠN bei mirtis dėl širdinių ir dėl visų priežasčių, lėtiniu ŠN sergantiems pacientams, kurių KSIF buvo ≤ 35%[17]. Gana atsitiktinai prie ŠN medikamentinio gydymo buvo pridėti SGLT2 inhibitoriai – dapagliflozinas ir empagliflozinas. Pirmiausiai vystyti kaip vaistai gydyti cukriniam diabetui, abu paminėti SGLT2 inhibitoriai klinikiniuose tyrimuose buvo efektyvūs, gydant ŠN per visą KSIF spektrą[18–21] ir tapo pirmaisiais vaistais, rekomenduojamais ŠN gydymui, nepaisant kairiojo skilvelio išstūmio frakcijos[22].

Keturguba – ARNI, beta blokatoriaus, MRA ir SGLT2 inhibitoriaus – kombinacija reikšmingai prailgina sIFŠN sergančio paciento išgyvenamumą ir yra laikoma sIFŠN gydymo standartu[23]. Visgi, reikia paminėti, kad dauguma paminėtų tyrimų buvo atlikti pacientų, sergančių lėtiniu širdies nepakankamumu, daugiausiai esant sumažėjusiai kairiojo skilvelio išstūmio

frakcijai. Taigi, reikalingi tyrimai ūminio širdies nepakankamumo srityje per visa KSIF spektrą.

Ūminis dusulys apima sudėtingus, tarpusavyje persidengiančius širdies ir kvėpavimo ligų sindromus, tai nulemia diagnostikos, rizikos stratifikacijos ir pacientų prognozės nuspėjimo iššūkius bei didelį klinikinį neapibrėžtumą šioje populiacijoje[24,25]. Ūmiu laikotarpiu priėmimo skyriuje nustatytos diagnozės nebūtinai gali būti tikslios, todėl svarbu tirti ūminio dusulio populiacijas, įtraukiant ne tik pacientus, sergančius ūminiu širdies nepakankamumu, bet ir kitomis dusulio priežastimis, tam kad būtų galima susidaryti platesnę perspektyvą apie pacientų prognozę. Taip pat, po neseniai atliktų klinikinių tyrimų ūminio ŠN srityje, kurių rezultatai buvo neutralūs arba neigiami[26,27], išlieka daug neaiškumų, kaip trumpalaikės intervencijos ūmios hospitalizacijos metu paveikia atokius rezultatus ir kaip klinikinės baigtys – pakartotinė hospitalizacija ir mirštamumas – sąveikauja tarpusavyje. Šie aspektai labai svarbūs, norint geriau suprasti ūminio ŠN ir kitų ūminio dusulio priežasčių natūralią eigą, taip pat norint tinkamai pasirinkti ateities klinikinių tyrimų tiriamąsias baigtis. Tyrimas, publikuotas **I publikacijoje** buvo paskatintas šių žinių trūkumo.

Biomedicininiuose tyrimuose, įskaitant ir ŠN klinikinius tyrimus, vis dar nepakankamai skiriama dėmesio specifinėms vyrų ir moterų analizėms. Aukščiau aprašyti ŠN fenotipai yra skirtingai paplitę tarp lyčių[28]. Atsižvelgiant į realią klinikinę praktiką, moterys nėra pakankamai įtraukiamos į klinikinius tyrimus[29]. Taip pat, moterims dažniau skiriamas nepakankamas medikamentinis gydymas arba nepakankamos optimalaus medikamentinio gydymo dozės negu vyrams[29–32]. Dėl šių priežasčių svarbu ištirti, ar greito optimalaus medikamentinio gydymo titravimo nauda po hospitalizacijos dėl ūminio širdies nepakankamumo yra tokia pati vyrams ir moterims. Ši analizė publikuota **II publikacijoje**.

Nors klinikinėse gairėse pateikiamos griežtos širdies nepakankamumo optimalaus medikamentinio gydymo rekomendacijos, šio gydymo įdiegimas klinikinėje praktikoje yra nepakankamas dėl vadinamojo gydytojų ir pacientų terapinės inercijos fenomeno[33,34]. Nėra aišku, ar pacientai, kurių gyvenimo kokybė prieš skiriant gydymą yra prastesnė, blogiau toleruoja optimalų medikamentinį gydymą ir jo greitą titravimą ir todėl jiems pasiekiamos mažesnės medikamentinio gydymo dozės ir dėl to pacientų prognozė galimai yra blogesnė. Tai tirta **III publikacijoje**. Terapinė inercija, esant ūminiam širdies nepakankamumui, taip pat gali būti susijusi su sindromo sudėtingumu ir didele gretutinių ligų našta, kas gali riboti greitą optimalaus medikamentinio gydymo skyrimą[34,35]. Iš gretutinių ligų anemija yra ypač svarbi dėl didelio jos paplitimo tarp ūminio širdies nepakankamumo pacientų ir ryšio su bloga

gyvenimo kokybe ir blogesne pacientų prognoze[36]. Todėl **IV publikacijoje** buvo tirta anemijos įtaka greito optimalaus medikamentinio gydymo titravimo efektyvumui.

Disertacijos tikslas

Disertacijos tikslas buvo ištirti pakartotinių hospitalizacijų ir optimalaus medikamentinio gydymo įtaką pacientų, sergančių ūminiu širdies nepakankamumu pacientų, prognozei.

Disertacijos uždaviniai

1. Ištirti pakartotinių hospitalizacijų ryšį su mirštamumo rizika pacientams, besikreipusiems į priėmimo skyrių dėl ūminio dusulio (tiek dėl širdies nepakankamumo, tiek dėl kitų dusulio priežasčių).
2. Ištirti greito gairių rekomenduojamo optimalaus medikamentinio gydymo titravimo ypatumus ir galimus skirtumus tarp vyrų ir moterų ir optimalaus medikamentinio gydymo poveikį vyrų ir moterų baigtims po hospitalizacijos dėl ūminio širdies nepakankamumo.
3. Ištirti greito gairių rekomenduojamo optimalaus medikamentinio gydymo titravimo poveikį gyvenimo kokybei ir gyvenimo kokybės įtaką optimalaus medikamentinio gydymo rezultatams pacientams po hospitalizacijos dėl ūminio širdies nepakankamumo.
4. Ištirti anemijos įtaką greito gairių rekomenduojamo optimalaus medikamentinio gydymo rezultatams pacientams po hospitalizacijos dėl ūminio širdies nepakankamumo.

Disertacijos mokslinis naujumas

Disertacijoje nagrinėjamas pacientų, sergančių ūminiu širdies nepakankamumu, baigčių prognozavimas skirtinguose klinikiniuose tyrimuose – stebėsenos ir kontroliuojamame atsitiktinių imčių tyrime – ir iš svarbių skirtingų perspektyvų.

Dviejų pacientų kohortų –iš Lietuvos ir iš Šveicarijos – sudarytų iš stebėsenos tyrimų, į kuriuos įtraukti pacientai, sergantys ūminiu dusuliu pakartotinės hospitalizacijos ir mirtingumo tyrime (**I publikacija**) analizuotas ankstyvas ir vėlyvas išrašymo iš ligoninės laikotarpis po pirmojo ūminio dusulio epizodo (įtraukiant pacientus, sergančius ūminiu širdies nepakankamumu ir kitomis dusulio priežastimis), ir ryšys tarp dviejų dažniausių ūminio širdies nepakankamumo tyrimuose vertinamųjų klinikinių baigčių – pakartotinės hospitalizacijos ir mirties. Iki mūsų tyrimo ankstyvas

išrašymo iš ligoninės laikotarpis, dar vadinamas „pažeidžiamąja faze“, nebuvo analizuotas sudėtinėje pacientų, sergančių ūminiu dusuliu, populiacijoje, įtraukusioje ūminiu ŠN ir kitomis dusulio priežastimis sirgusius pacientus[37].

STRONG-HF (*Safety, Tolerability and Efficacy of Rapid Optimization, Helped by NT-proBNP testinG, of Heart Failure Therapies*) buvo pirmasis prospektyvinis kontroliuojamas atsitiktinių imčių tyrimas, kuriame intensyvus gydymo protokolas, įdiegtas po hospitalizacijos dėl ūminio širdies nepakankamumo, kuriuo remiantis pacientams paskirti optimalaus medikamentinio gydymo vaistai ir greitai didinamos jų dozės iki maksimalios per 2 savaites, griežtai stebint įvairius rodiklius, įskaitant klinikinius rodiklius, laboratorinius tyrimus ir N-galinio pro-B tipo natriuretinio peptido (NT-proBNP) koncentraciją (intensyvi priežiūra) buvo lygintas su įprasta priežiūra. Disertacijoje pateikiama STRONG-HF klinikinio tyrimo moterų ir vyrų analizė (**II publikacija**) buvo atlikta atliepti reikšmingą žinių trūkumą apie greito optimalaus medikamentinio gydymo titravimo ypatumus, veiksmingumą ir saugumą vyrams ir moterims po hospitalizacijos dėl ūminio širdies nepakankamumo[38].

STRONG-HF klinikinio tyrimo gyvenimo kokybės analizėje (**III publikacija**) buvo nagrinėjamas greito optimalaus medikamentinio gydymo titravimo poveikis gyvenimo kokybei – labai svarbiai į pacientą orientuotai klinikinio tyrimo baigčiai. Taip pat nagrinėtas gydymo saugumas ir gyvenimo kokybės įtaka kitoms klinikinio tyrimo baigtims. Kadangi tyrimas buvo tarptautinis, įtraukęs pacientus 14 šalių įvairiuose pasaulio regionuose, jame buvo atsižvelgta į geografinius ir rasinius skirtumus[39].

STRONG-HF klinikinio tyrimo anemijos analizėje (**IV publikacija**) buvo analizuojamas greito optimalaus medikamentinio gydymo titravimo veiksmingumas ir saugumas grupėse, suskirstytose pagal pradinės anemijos buvimą. Tyrime taip pat buvo analizuojami nepriklausomi pradinės ir tyrimo metu atsiradusios anemijos prognozavimo veiksniai bei anemijos ryšys su gyvenimo kokybe[40]. Ši analizė suteikė svarbią perspektyvą apie vienos iš pagrindinių gretutinių ligų ir optimalaus medikamentinio gydymo ryšį tarp pacientų, sergančių širdies nepakankamumu.

Disertacijos ginamieji teiginiai

1. Pakartotinės hospitalizacijos per 6 mėnesius po kreipimosi dėl ūminio dusulio į priėmimo skyrių reikšmingai didina 1 metų mirties dėl visų priežasčių riziką.
2. Greitas gairių rekomenduojamo optimalaus medikamentinio gydymo titravimas vienodai pasiekiamas ir reikšmingai gerina

baigtis tiek vyrams, tiek moterims po hospitalizacijos dėl ūminio širdies nepakankamumo.

3. Greitas gairių rekomenduojamo optimalaus medikamentinio gydymo titravimas pasiekiamas ir reikšmingai gerina gyvenimo kokybę ir baigtis, nepriklausomai nuo pradinės gyvenimo kokybės pacientams po hospitalizacijos dėl ūminio širdies nepakankamumo.
4. Greitas gairių rekomenduojamo optimalaus medikamentinio gydymo titravimas reikšmingai gerina baigtis, nepriklausomai nuo pradinės anemijos buvimo pacientams po hospitalizacijos dėl ūminio širdies nepakankamumo.

METODIKA

Analizuotos kohortos

Šioje disertacijoje analizuotos trys skirtingos populiacijos. Dvi pacientų kohortos iš stebėsenos studijų buvo analizuotos **I publikacijoje**. Kontroliuojamo atsitiktinių imčių tyrimo kohorta buvo analizuota **II-IV publikacijose**. Disertacijos tyrimų apžvalga pateikta 1 lentelėje.

1 lentelė. Disertacijoje pateikiamų tyrimų dizainų, populiacijų ir baigčių apžvalga.

	Publikacija I	**Publikacija II**	**Publikacija III**	**Publikacija IV**
Tyrimo dizainas	Du perspektyvūs stebėsenos daugiacentriniai tyrimai	Kontroliuojamas atsitiktinių imčių tyrimas		
Apimtis	2 universitetinės ligoninės Lietuvoje ir 2 universitetinės ligoninės Šveicarijoje	87 centrai 14 šalių		
Tyrimo populiacija	Pacientai, besiskundžiantys ūminiu dusuliu	Pacientai po hospitalizacijos dėl ūminio širdies nepakankamumo		
Imties dydis	3357 (1371 iš Lietuvos; 1986 iš Šveicarijos)	1078		
Intervencija	Nėra	Intensyvi priežiūra (greitas gairėmis rekomenduojamo medikamentinio gydymo titravimas)		

	Publikacija I	**Publikacija II**	**Publikacija III**	**Publikacija IV**
Stebėjimo laikotarpis	Lietuva: 2015-2018 m. Šveicarija: 2006-2015 m.	2018–2021 m.		
Baigtys	1 metų mirštamumas dėl visų priežasčių	(1) 180 dienų pakartotinė hospitalizacija dėl širdies nepakankamumo arba mirštamumas dėl visų priežasčių; (2) Gyvenimo kokybės pokytis nuo pradinio lygio iki 90 dienos, matuojamas pagal EQ-5D vizualinę analoginę skalę (VAS); (3) 180 dienų mirštamumumas dėl visų priežasčių; (4) 90 dienų pakartotinė hospitalizacija dėl širdies nepakankamumo arba mirštamumas dėl visų priežasčių.		
Kontrolė	Nėra	Įprastinė priežiūra (stebėjimas pagal vietinę praktiką)		
Statistinė analizė	Daugiamatė Cox regresija	Cox proporcinių rizikų regresija		

I publikacijos kohortos

LEDA kohorta

LEDA (*Lithuanian Echocardiography Study of Dyspnoea in Acute Settings*) buvo prospektyvinė stebėsenos daugiacentrė studija, atlikta dviejose Lietuvos universitetinėse ligoninėse, bendradarbiaujant su tarptautiniu GREAT (*Global Research on Acute Conditions Team*) tyrimų tinklu. Studijos įtraukimo laikotarpis buvo nuo 2015 kovo iki 2017 gruodžio, studija buvo užregistruota klinikinių tyrimų registre *clinicaltrials.gov*, jai priskirtas identifikatorius NCT03048032. Į studiją buvo įtraukti vyresni negu 18 metų pacientai, kurie įtraukimo laikotarpiu kreipėsi į Vilniaus universiteto ligoninės Santaros klinikų arba Lietuvos sveikatos mokslų universiteto ligoninės Kauno klinikų priėmimo skyrius dėl ūminio dusulio dėl bet kokios priežasties. Pacientai nebuvo įtraukti į tyrimą, jei jiems per pirmąsias 4 valandas priėmimo skyriuje buvo įtartas ūminis koronarinis sindromas (daugiausia siekiant atmesti pacientus, kuriems buvo akivaizdus ST segmento pakilimo miokardo

infarktas) arba jei jiems buvo atlikta organų transplantacija pirmojo epizodo ar pakartotinės hospitalizacijos metu. Jei pacientai dėl dusulio į priėmimo skyrių kreipėsi daugiau nei vieną kartą, tik pirmasis epizodas buvo įtrauktas į tyrimą. Tyrime rinkti pacientų demografiniai duomenys, gretutinės ligos, pradiniai vaistai, klinikiniai požymiai ir laboratoriniai parametrai priėmimo metu, ankstyvas gydymas ligoninėje, vaistai išrašymo metu buvo registruojami pagal GREAT protokolą[105]. Pacientų kraujo plazmos mėginiai buvo paimami per pirmas 4 valandas priėmimo skyriuje, užšaldyti -80°C temperatūroje ir išsiųsti į pagrindinę laboratoriją Inserm UMR-942 institute Paryžiuje, Prancūzijoje biožymenų matavimams. Pagal patvirtintą ūminio dusulio priežastį pacientai suskirstyti į ūminio širdies nepakankamumo ir ne ūminio širdies nepakankamumo (kitų dusulio priežasčių) grupes. Pacientų sekimo laikotarpis buvo 1 metai po išrašymo iš priėmimo skyriaus arba ligoninės, jeigu jie buvo hospitalizuoti. Pacientų sekimas buvo atliktas, bendradarbiaujant su Lietuvos valstybiniais administraciniais registrais – Valstybine ligonių kasa ir Higienos institutu, todėl buvo surinktos visų pacientų pakartotinės hospitalizacijos ir mirtys per vienerių metų laikotarpį po išrašymo. Atliekant analizę, publikuotą **I publikacijoje**, kardiovaskulinės ir nekardiovaskulinės pakartotinių hospitalizacijų ir mirčių priežastys buvo suskirstytos, atsižvelgiant į Tarptautinės statistinės ligų ir sveikatos sutrikimų klasifikacijos dešimtojo leidimo (TLK-10) kodavimą.

LEDA studija iš viso įtraukė 1455 pacientus. Į kohortą, analizuotą I publikacijoje, neįtraukti pacientai, mirę priėmimo skyriuje arba pirmos hospitalizacijos metu, taigi iš viso įtrauktas 1371 pacientas.

BASEL V kohorta

BASEL V (*Basics in Acute Shortness of Breath EvaLuation Study*) buvo prospektyvinė stebėsenos studija, kuri įtraukė suaugusius pacientus, kurie kreipėsi į dviejų Šveicarijos universitetinių ligoninių – Bazelio ir Ciuricho universitetų ligoninių – priėmimo skyrius dėl ūminio, ne traumos sukelto dusulio nuo 2006 iki 2014 metų[106–108]. Pacientai, kuriems buvo atliekama hemodializė, buvo neįtraukti į studiją. Studija buvo užregistruota klinikinių tyrimų registre *clinicaltrials.gov*, jai priskirtas identifikatorius NCT01831115. Buvo surinkti pacientų demografiniai duomenys, klinikiniai ir laboratoriniai rodikliai. Pagal patvirtintą ūminio dusulio priežastį, pacientai buvo suskirstyti į ūminio širdies nepakankamumo ir ne ūminio širdies nepakankamumo (kitų dusulio priežasčių) grupes. Su pacientais buvo susisiekiama telefonu, praėjus 3, 6 mėnesiams ir 1 metams po įtraukimo į studiją. Kilus neaiškumų, buvo susisiekiama su jų gydytojais arba

administracinių duomenų bazių atstovais. Pakartotinės hospitalizacijos ar mirtys taip pat buvo patikslintos susisiekus su gydytojais arba administracinėse duomenų bazėse. Šios baigtys nebuvo prieinamos tik 0,5% visų įtrauktų pacientų.

Į BASEL V studiją buvo įtraukti 2105 pacientai, iš kurių 1986 buvo įtraukti į **I publikacijos** analizę.

II-IV publikacijų kohorta

STRONG-HF tyrimo kohorta

STRONG-HF (*Safety, Tolerability and Efficacy of Rapid Optimization, Helped by NT-proBNP Testing, of Heart Failure Therapies*) buvo tarptautinis daugiacentrinis, atviro dizaino, prospektyvinis kontroliuojamas atsitiktinių imčių tyrimas, skirtas įvertinti greito gairių rekomenduojamo medikamentinio gydymo saugumą ir veiksmingumą po hospitalizacijos dėl ūminio širdies nepakankamumo, palyginti su įprasta priežiūra[55,56]. Pacientai buvo įtraukti 87 centruose 14 šalių.

Į tyrimą įtraukti 18-85 metų pacientai, kurie per 72 valandas iki atrankos buvo hospitalizuoti dėl ūminio širdies nepakankamumo ir kuriems 2 dienos iki numatomo išrašymo iš ligoninės nebuvo skirtos optimalios širdies nepakankamumo medikamentinio gydymo dozės. Atrankos į tyrimą metu pacientų NT-proBNP turėjo būti > 2500 ng/L, o tarp atrankos ir prieš randomizavimą koncentracija sumažėti daugiau nei 10%, bet likti > 1500 ng/L. Taip pat, pacientai įtraukti, nepaisant KSIF. Pagrindinis neįtraukimo į tyrimą kriterijus buvo akivaizdus didelių beta blokatorių ar renino ir angiotenzino sistemos inhibitorių dozių netoleravimas.

Tyrimas buvo užregistruotas klinikinių tyrimų registre *clinicaltrial.gov*, jam suteiktas identifikatorius NCT03412201.

Pacientai buvo atsitiktine tvarka suskirstyti santykiu 1:1 į įprastos arba intensyvios priežiūros grupes. Intensyvią priežiūrą sudarė greitas beta adrenoblokatorių, RAS inhibitorių (ARNI arba AKF inhibitoriaus, arba ARB) ir mineralokortikoidų receptorių antagonistų dozės didinimas iki maksimalios per 2-6 savaites po hospitalizacijos dėl ūminio širdies nepakankamumo. Tyrimo pradžioje SGLT2 inhibitoriai nebuvo patvirtinti širdies nepakankamumui gydyti arba daugelyje šalių nebuvo plačiai naudojami, todėl jie nebuvo privaloma gydymo protokolo dalis.

Pacientai įprastos priežiūros grupėje buvo gydomi ir stebimi gydančio gydytojo nuožiūra pagal atitinkamos šalies vietinės praktikos rekomendacijas iki 90 tyrimo dienos, kai visus pacientus apžiūrėdavo tyrėjų komanda. Į

intensyvios priežiūros grupę įtrauktiems pacientams buvo paskirtas medikamentinis gydymas beta blokatoriais, RAS inhibitoriumi ir mineralokortikoidų receptorių antagonistu, bent puse optimalios dozės dvi dienas iki numatomo išrašymo iš ligoninės. Optimalios širdies nepakankamumo medikamentinio gydymo vaistų dozės pateiktos 2 lentelėje. Atsižvelgiant į saugumo kriterijus (3 lentelė) praėjus 2 savaitėms po išrašymo, buvo rekomenduojama didinti dozę iki visos dozės arba, jei tai buvo neįmanoma, tai rekomenduota padaryti ne vėliau kaip po 6 savaičių. Intensyvios priežiūros grupės pacientams buvo atliekami suplanuoti ambulatoriniai vizitai 1, 2, 3 ir 6 savaitę po išrašymo, kurių metu buvo vertinimas gydymo režimo saugumas ir toleravimas, atliekant išsamią fizinę apžiūrą ir laboratorinius NT-proBNP, natrio, kalio, gliukozės, inkstų funkcijos ir hemoglobino matavimus. Visus pacientus (įskaitant įprastos priežiūros ir didelio intensyvumo priežiūros grupes) tyrimo komanda apžiūrėjo 90 dieną ir susisiekė telefonu 180 dieną, kad būtų surinkti duomenys apie tuo metu vartojamus geriamuosius širdies nepakankamumo vaistus klinikines baigtis (pakartotines hospitalizacijas ir mirtis).

Į STRONG-HF tyrimą įtraukti 1078 pacientai (542 į intensyvios priežiūros ir 536 į įprastos priežiūros grupę). Tyrimo pagrindiniai rezultatai parodė, kad intensyvi priežiūra sumažino 180 dienų mirštamumo dėl visų priežasčių arba pakartotinės hospitalizacijos dėl širdies nepakankamumo riziką, palyginti su įprasta priežiūra[57]. Vėlesnė papildoma analizė taip pat parodė, kad intensyvios priežiūros strategija buvo veiksminga, nepriklausomai nuo pradinės kairiojo skilvelio išstūmio frakcijos[58]. Šioje disertacijoje pateiktose **II, III ir IV publikacijose** pateikiamos svarbios papildomos šio tyrimo kohortos analizės.

2 lentelė. Optimalios širdies nepakankamumo medikamentinio gydymo vaistų dozės, rekomenduotos STRONG-HF tyrime.

Vaisto bendrinis pavadinimas	**Pusė paros tikslinės dozes 2-ojo vizito metu**	**Optimali (pilna) dozė 4-ojo vizito metu**
Mineralokortikoidų receptorių antagonistai		
Eplerenonas	25 mg 1 k./d.	50 mg 1 k./d.
Spironolaktonas	25 mg kas antrą dieną	25 mg 1 k./d.
Beta blokatoriai		
Bizoprololis	5 mg 1 k./d.	10 mg 1 k./d.
Karvedilolis	12,5–25 mg 2 k./d.	25–50 mg 2 k./d.

Vaisto bendrinis pavadinimas	Pusė paros tikslinės dozes 2-ojo vizito metu	Optimali (pilna) dozė 4-ojo vizito metu
Metoprololio sukcinatas (pailginto atpalaidavimo tabletės)	100 mg 1 k./d.	200 mg 1 k./d.
Nebivololis	5 mg 1 k./d.	10 mg 1 k./d.
Angiotenziną konvertuojančio fermento inhibitoriai		
Kaptoprilis	25 mg 3 k./d.	50 mg 3 k./d.
Enalaprilis	10 mg 2 k./d.	20 mg 2 k./d.
Lizinoprilis	17,5 mg 1 k./d.	35 mg 1 k./d.
Ramiprilis	2,5 mg 2 k./d. arba 5 mg 1 k./d.	5 mg 2 k./d. arba 10 mg 1 k./d.
Trandolaprilis	2 mg 1 k./d.	4 mg 1 k./d.
Perindoprilis	4 mg 1 k./d.	8 mg 1 k./d.
Angiotenzino II receptorių blokatoriai		
Kandesartanas	16 mg 1 k./d.	32 mg 1 k./d.
Valsartanas	80 mg 2 k./d.	160 mg 2 k./d.
Losartanas	75 mg 1 k./d.	150 mg 1 k./d.
Angiotenzino receptorių ir neprilizino inhibitorius		
Sakubitrilas/valsartanas	49/51 mg 2 k./d.	97/103 mg 2 k./d.

Paaiškinimai: k./d. – kartai per dieną.

3 lentelė. Saugumo kriterijai, kuriais remtasi atidedant greitą medikamentinio gydymo titravimą STRONG-HF tyrime.

Vaistai	Kriterijai, kada atidėti dozės didinimą
AKFI / ARB / ARNI ir (arba) MRA	Sistolinis arterinis kraujospūdis < 95 mmHg, kalio koncentracija serume > 5,0 mmol/l arba GFG < 30 ml/min/1,73 m². Jei vienintelis kriterijus buvo GFG < 30 ml/min/1,73 m², tyrėjams buvo rekomenduojama sumažinti diuretikų dozę, jei ji buvo laikoma didele arba neseniai buvo padidinta.
Betablokatoriai	Širdies susitraukimų dažnis < 55 k./min. arba sistolinis arterinis kraujospūdis < 95 mmHg. Jei NT-proBNP koncentracija buvo > 10 % didesnė nei prieš išrašymą iš ligoninės, gydytojams buvo rekomenduojama nedidinti betablokatorių dozės ir apsvarstyti diuretikų dozės didinimą.

Santrumpos: AKFI – angiotenziną konvertuojančio fermento inhibitorius; ARB – angiotenzino II receptorių blokatoriai; ARNI – angiotenzino receptorių ir neprilizino inhibitorius; BB – betablokatorius; GFG – glomerulų filtracijos greitis; MRA – mineralokortikoidų receptorių antagonistas; NT-proBNP – N-galinis pro-B tipo natriuretinis peptidas.

Etiniai aspektai

LEDA tyrimui leidimą suteikė Lietuvos bioetikos komitetas (Nr. L-15-01) ir parėmė Lietuvos mokslo taryba. BASEL V tyrimui leidimą suteikė vietos etikos komitetas Šveicarijoje. STRONG-HF tyrimui bioetikos leidimus kiekvienoje dalyvaujančioje šalyje suteikė atitinkami etikos komitetai. Visi tyrimai buvo atlikti remiantis Helsinkio deklaracijos principais. Visų tyrimų dalyviai pateikė raštišką informuotą sutikimą dalyvauti tyrime.

Tyrimų vertinamosios baigtys

I publikacijos pirminė vertinamoji baigtis buvo 1 metų mirštamumas dėl visų priežasčių.

II-IV publikacijų pirminė vertinamoji baigtis buvo 180 dienų pakartotinė hospitalizacija dėl širdies nepakankamumo arba mirtis dėl visų priežasčių.

Antrinės **II-IV publikacijų** vertinamosios baigtys:

- Gyvenimo kokybės pokytis nuo pradinio lygio iki 90 dienos, matuojamas EQ-5D vizualinės analogijos skale (VAS) (**III publikacijoje** papildomai analizuoti visų 5 EQ-5D-5L klausimyno dimensijų pokyčiai atskirai);
- 180 dienų mirštamumas dėl visų priežasčių;
- 90 dienų pakartotinė hospitalizacija dėl širdies nepakankamumo arba mirštamumas dėl visų priežasčių.

Statistinė analizė

I publikacija

Kiekybiniai tolydieji kintamieji pateikiami kaip mediana ir tarpkvartilinis plotis, o kokybiniai kintamieji – kaip absoliutus skaičius (procentai). Skirtumai tarp tyrimo grupių buvo analizuojami, naudojant Kruskal-Wallis testą tolydiesiems kintamiesiems ir Chi kvadrato testą kokybiniams kintamiesiems.

Tyrime analizuotas ryšys tarp pirmosios pakartotinės hospitalizacijos dėl visų priežasčių per 6 mėnesius po išrašymo iš priėmimo skyriaus arba ligoninės ir 1 metų mirštamumo dėl visų priežasčių pacientams, besikreipusiems dėl ūminio dusulio, taip pat grupėse pagal patikslintą dusulio priežastį – ūminio širdies nepakankamumo ir ne ūminio širdies

nepakankamumo grupėse atskirai. Taip pat atskirai buvo tirtas ryšys tarp hospitalizacijų ir mirštamumo, pakartotines hospitalizacijas suskirsčius pagal jų priežastį – kardiovaskulines ir nekardiovaskulines.

Pirmiausiai buvo atlikta nekoreguota ir koreguota Cox regresinė analizė, lyginant pakartotinai hospitalizuotus per 6 mėnesius ir nehospitalizuotus pacientus, kaip baigtį naudojant 1 metų mirštamumą dėl visų priežasčių. Koreguota daugiamatė Cox regresija įtraukė tokias kovariantes: esamus lėtinį širdies nepakankamumą, vainikinių arterijų ligą, cukrinį diabetą, sistolinį arterinį kraujospūdį, širdies susitraukimų dažnį, glomerulų filtracijos greitį, natrio koncentraciją. Cox analizės pakartotos, lyginant nehospitalizuotus ir pacientus, pakartotinai hospitalizuotus per tris laikotarpius: pirmą mėnesį, antrą ir trečią mėnesį bei ketvirtą–šeštą mėnesį po išrašymo iš priėmimo skyriaus arba ligoninės. Taip pat analizės pakartotos ūminio ŠN ir ne ūminio ŠN grupėse, taip pat suskirsčius pakartotines hospitalizacijas pagal jų priežastį į kardiovaskulines ir nekardiovaskulines (abiem atvejais nehospitalizuotų pacientų mirštamumas buvo naudojamas kaip atskaitos taškas).

Taip pat buvo atliktą pogrupių analizė, atliekant nekoreguotą Cox regresinę analizę pacientų pogrupiuose, atsižvelgiant į amžių, lytį, esamą lėtinį širdies nepakankamumą, patikslintą ūminio dusulio priežastį, NT-proBNP koncentraciją, didelio jautrumo troponino T koncentraciją, kairiojo skilvelio išstūmio frakcijos matavimus. Statistinė analizė atlikta naudojant R statistinę programą, 3.5.3 versiją (*The R Foundation for Statistical Computing*, Viena, Austrija). Visi atlikti testai buvo dvipusiai, o P reikšmė < 0,05 buvo laikoma reikšminga.

II publikacija

Kiekybiniai tolydieji kintamieji pateikiami kaip vidurkis (standartinis nuokrypis) arba pakoreguotas vidurkis (standartinė paklaida), o kokybiniai kintamieji – kaip absoliutūs skaičiai ir santykiniai dažniai. Tolydieji kintamieji buvo lyginami naudojant ANOVA (dispersinės analizės) modelius, binariniai kintamieji – naudojant Chi kvadrato testą, o ranginiai kokybiniai kintamieji – naudojant Cochran-Mantel-Haenszel Chi kvadrato testus.

Buvo atliktos pogrupių analizės, kuriose lygintas intensyvios priežiūros strategijos poveikis pirminės ir antrinėms tyrimo baigtims, suskirsčius į pogrupius pagal lytį. Taip pat į modelius buvo įtraukta ir analizuota galima gydymo efektyvumo ir lyties sąveika. Vyrų ir moterų klinikinės baigtys (pakartotinės hospitalizacijos ir mirtys) buvo lygintos atliekant Cox proporcinę regresiją, o gyvenimo kokybės pokytis pagal EQ-VAS – atliekant

ANCOVA (kovariacijos analizė, įskaitant koregavimą pagal pradinį EQ-VAS, geografinį regioną ir pradinę KSIF ≤40%/>40%).

Gydymo poveikis klinikinių rodiklių ir laboratorinių tyrimų reikšmių pokyčiams nuo pradinio lygio iki 90 dienos tarp lyčių (gydymo saugumo analizė) buvo lyginamas, naudojant ANCOVA modelius, pakoreguotus pagal pradinę atitinkamų rodiklių reikšmę.

Visi atlikti testai buvo dvipusiai, o P reikšmės <0,05 buvo laikomos statistiškai reikšmingomis. Statistinė analizė atlikta, naudojant SAS 9.4 versiją (SAS institutas, Keris, Šiaurės Karolina, JAV).

III publikacija

Šioje publikacijoje publikuotame tyrime pacientai vertino savo gyvenimo kokybę, sveikatos būklę EQ-5D įrankių. EQ-5D yra standartizuota priemonė įvertinti bendrai sveikatos būklei, kurią sudaro 5 klausimai, turintys po 5 variantus (aprašomoji dalis, toliau – EQ-5D-5L) ir vizualinė analoginė skalė (toliau – EQ-VAS). EQ-VAS fiksuoja paciento savo paties sveikatos vertinimą būtent tą pačią vertinimo dieną 20 cm vertikalioje vizualinėje analoginėje skalėje nuo 0 (blogiausia sveikatos būklė, kokią galite įsivaizduoti) iki 100 (geriausia sveikatos būklė, kokią galite įsivaizduoti). EQ-5D-5L vertina 5 sritis: judrumą, savirūpą, įprastą veiklą, skausmą/diskomfortą ir nerimą/depresiją. Pacientai savo sveikatos būklę kiekvienoje iš šių sričių vertina nuo 1 iki 5 balų rangine skale, svyruojančia nuo jokių sunkumų iki itin išreikštų sunkumų.

Kintamųjų pateikimas buvo toks pats, kaip ir **II publikacijoje**. Pradinių charakteristikų ir kitų kintamųjų, gydymo saugumo kriterijų analizei ir palyginimui pacientai buvo suskirstyti į terciles pagal pradinį EQ-VAS lygį (≤50; 50-65, >65). Kintamųjų ryšys su EQ-VAS tercile buvo tiriamas naudojant Jonckheere-Terpstra tendencijos testą tolydiesiems kintamiesiems, Cochran-Armitage tendencijos testą binariniams kategoriniams kintamiesiems, Cochran-Mantel-Haenszel bendrąją asociaciją kategoriniams kintamiesiems ir Cochran-Mantel-Haenszel nenulinę koreliaciją ranginiams kintamiesiems. Skirtingos gydymo (intensyvios ir įprastos priežiūros) grupės buvo lyginamos naudojant ANCOVA, koreguojant pagal pradinę kintamojo vertę, geografinį regioną ir KSIF (≤40%/>40%). Daugiafaktorinio tiesinės regresijos modelio, prognozuojančio 90 dienų EQ-VAS pokytį, kovariantės buvo atrinktos naudojant atgalinę atranką iš 10 daugialypių duomenų praleistų reikšmių įrašymo rinkinių, taikant P reikšmės < 0,10 atrankos kriterijų.

Galimas intensyvios priežiūros strategijos poveikio vertinamajai baigčiai modifikavimas, priklausomas nuo EQ-VAS kaip kategorinio kintamojo buvo tiriamas naudojant Kaplan-Meier kreives pagal pradinę EQ-VAS tercilę ir testuojant gydymo strategijos ir EQ-VAS sąveiką Cox regresijos modelyje. Atskiras Cox regresijos modelis buvo sukurtas gydymo strategijos sąveikai su EQ-VAS kaip tolydžiu kintamuoju, modeliuotu apribotoje kubinėje diagramoje su trimis mazgais, patikrinti. Visi atlikti testai buvo dvipusiai, P reikšmė < 0,05 buvo laikoma statistiškai reikšminga. Analizei buvo naudojama SAS 9.4 versija (SAS institutas, Keris, Šiaurės Karolina, JAV).

IV publikacija

Pradinės charakteristikos, klinikiniai ir saugumo rezultatai bei intensyvios priežiūros ir įprastos priežiūros poveikis pirminei ir antrinėms baigtims buvo palyginti grupėse, suskirsčius pacientus pagal pradinės anemijos buvimą (hemoglobino kiekis < 120 g/l moterims ir < 130 g/l vyrams) ir pagal hemoglobino medianą (130 g/l moterims ir 141 g/l vyrams). Taip pat buvo tirta hemoglobino dinamika tyrimo stebėjimo laikotarpiu ir veiksniai, prognozuojantys naujos anemijos atsiradimą po 90 dienų.

Kintamųjų pateikimas ir analizė, lyginanti pradines charakteristikas, buvo tokia pati kaip ir **II ir III publikacijose**. Buvo sukurti atskiri daugianarės logistinės regresijos modeliai, siekiant ištirti galimus prognozuojančius veiksnius, susijusius su pradinės anemijos buvimu ir naujos anemijos atsiradimu iki 90 tyrimo dienos. Visi modeliai, vertinantys anemijos atsiradimo prognozavimą per 90 dienų, buvo papildomai pakoreguoti pagal pradinę hemoglobino vertę.

Siekiant nustatyti anemijos poveikį klinikinėms baigtims, buvo taikoma Cox proporcinės rizikos regresijos analizė. Anemijos įtaka EQ-VAS balų pokyčiams nuo pradinio lygio iki 90 dienos buvo įvertinta naudojant tiesinės regresijos modelį, pakoreguotą pagal pradinius EQ-VAS balus, KSIF (≤40 % arba >40 %) ir geografinį regioną. Gydymo strategijos poveikis pirminei vertinamajai baigčiai buvo modeliuojamas naudojant pradinį hemoglobino lygį kaip tolydųjį kintamąjį, modeliuotą apribotoje kubinėje diagramoje su trimis mazgais. Visi atlikti testai buvo dvipusiai. P reikšmė < 0,05, buvo laikoma statistiškai reikšminga. Visos analizės buvo atliktos naudojant SAS 9.4 versiją (SAS institutas, Keris, Šiaurės Karolina, JAV).

REZULTATAI

Pakartotinių hospitalizacijų ir mirštamumo ūminio dusulio populiacijoje studija – I publikacija

LEDA kohortoje pacientų amžiaus mediana buvo 71 [61–79] metai, 599 (43,6 %) buvo moterys, o 731 (53,3 %) buvo diagnozuotas ūminis ŠN. Per 6 mėnesius po išrašymo iš priėmimo skyriaus arba ligoninės 666 (48,6 %) pacientai buvo pakartotinai hospitalizuoti: 379 (56,9 %) dėl kardiovaskulinių, o 287 (43,1 %) – dėl ne kardiovaskulinių priežasčių. Pakartotinai hospitalizuoti pacientai buvo vyresnio amžiaus, turėjo daugiau gretutinių ligų, didesnį širdies susitraukimų dažnį, didesnę širdies, inkstų nepakankamumo ir uždegimo biožymenų koncentraciją ir mažesnį hemoglobino kiekį. Pacientai, kuriems nustatytas ūminis ŠN, po 6 mėnesių buvo pakartotinai hospitalizuoti dažniau nei ne ūminio ŠN pacientai (atitinkamai 53,5% ir 43%, $P < 0,001$). Ūminiu ŠN sergančių pacientų pakartotinės hospitalizacijos atvejais vyravo kardiovaskulinės priežastys (68,3%), priešingai nei pacientų, kuriems nustatytos kitos dusulio priežastys, atveju (59,3% pakartotinių hospitalizacijų dėl ne kardiovaskulinių priežasčių). Po 1 metų išvestinės LEDA kohortoje mirė 282 pacientai (1 metų mirtingumas – 20,6%). Vienerių metų mirštamumas dėl visų priežasčių buvo panašus tarp pacientų, sirgusių ūminiu ŠN, ir pacientų, nesirgusių ŪŠN (atitinkamai 20% ir 21,2%, $P = 0,61$).

BASEL V kohortoje vidutinis amžius buvo 74 [61–82] metai, 888 (44,7%) pacientų buvo moterys, o 993 (50%) pacientams buvo nustatytas ūminis ŠN. Po 6 mėnesių 812 (40,9%) pacientų buvo pakartotinai hospitalizuoti: 348 (42,9 %) dėl kardiovaskulinių priežasčių, o 464 (57,1%) – dėl ne kardiovaskulinių priežasčių. Panašiai kaip ir LEDA kohortoje, ūminiu ŠN sergantys pacientai buvo pakartotinai hospitalizuoti dažniau nei pacientai be ūminio ŠN (atitinkamai 45,9% ir 35,9%, $P < 0,001$). Pacientai, kuriems nustatytas ūminis ŠN, 62,1% pakartotinai hospitalizuoti dėl kardiovaskulinių priežasčių, iš pacientų, kuriems nustatytos kitos dusulio priežastys – 81,7% pakartotinai hospitalizuoti dėl ne kardiovaskulinių priežasčių. Po 1 metų mirė 377 pacientai (1 metų mirštamumas 19%).

LEDA kohortoje pacientai, pakartotinai hospitalizuoti per 6 mėnesius, mirė tris kartus dažniau nei pacientai, kurie nebuvo pakartotinai hospitalizuoti (atitinkamai 211 (31,7%) ir 71 (10,1%), $P < 0,001$). Pirmasis pakartotinės hospitalizacijos epizodas per 6 mėnesius buvo susijęs su tris kartus didesne 1 metų mirštamumo dėl visų priežasčių rizika (koreguotas rizikos santykis (RS) 3,0, 95% pasikliautinasis intervalas (PI) 2,2–4,0, $P < 0,001$]. Mirštamumo rizika išliko padidėjusi, nepriklausomai nuo to, ar pirmoji pakartotinė

hospitalizacija įvyko pirmą mėnesį, antrą ir trečią mėnesius, ar ketvirtą–šeštą mėnesį. Pakartotinė hospitalizacija per 6 mėnesius taip pat buvo susijusi su padidėjusia 1 metų mirštamumo dėl visų priežasčių rizika tiek pacientams, sirgusiems ūminiu ŠN, tiek pacientams, kuriems nebuvo ūminio ŠN (atitinkamai koreguotas RS 3,2, [95% PI 2,1–4,9], P < 0,001, ir koreguotas RS 2,9, [95% PI 1,9–4,5], P < 0,001). Be to, ryšys tarp pakartotinės hospitalizacijos ir mirštamumo išliko, nepriklausomai nuo pakartotinės hospitalizacijos priežasties. Tiek kardiovaskulinės, tiek ne kardiovaskulinės pakartotinės hospitalizacijos buvo susijusios su padidėjusia 1 metų mirštamumo rizika (atitinkamai koreguotas RS 2,2 [95% PI 1,6–3,1], P < 0,001 ir koreguotas RS 4,1 [95 % PI 2,9–5,7], P < 0,001). Ryšys tarp 6 mėnesių pakartotinės hospitalizacijos dėl visų priežasčių ir 1 metų mirštamumo dėl visų priežasčių taip pat išliko pastovus visuose tirtuose pogrupiuose.

Šie rezultatai buvo patvirtinti BASEL V kohortoje. Pacientai, pakartotinai hospitalizuoti per 6 mėnesius, mirė reikšmingai dažniau nei pacientai, kurie nebuvo pakartotinai hospitalizuoti [atitinkamai 218 (26,8%) ir 159 (13,5%), P < 0,001]. Pakartotinė hospitalizacija po 6 mėnesių buvo reikšmingai susijusi su padidėjusia 1 metų mirštamumo dėl visų priežasčių rizika visiems pacientams, besikreipusiems dėl ūminio dusulio į priėmimo skyrių (koreguotas RS 1,8, [95% PI 1,4–2,2], P < 0,001). Šis ryšys buvo pastovus, nepriklausomai nuo pakartotinės hospitalizacijos laiko, dusulio priežasties ir pakartotinės hospitalizacijos priežasties.

Lyčiai specifiškos STRONG-HF analizės rezultatai – II publikacija

Iš 1078 į STRONG-HF tyrimą įtrauktų pacientų po hospitalizacijos dėl ūminio ŠN, 416 (39%) buvo moterys. Palyginti su vyrais, ne baltaodžių ir ne europiečių moterų buvo reikšmingai daugiau. Vyrams buvo didesnė tikimybė sirgti išeminės kilmės ŠN, jie dažniau buvo sirgę ūminiu vainikinių arterijų sindromu, jiems dažniau buvo atlikta aortos ir vainikinių arterijų jungčių operacija arba vainikinių kraujagyslių perkutaninė intervencija. Vyrai taip pat dažniau sirgo prieširdžių virpėjimu, jiems dažniau buvo priskirta IV funkcinė Niujorko širdies asociacijos (NYHA) klasė, taip pat vyrų vidutinė KSIF buvo mažesnė. Nepaisant to, moterų pradinis gyvenimo kokybės lygis buvo žemesnis. Tarp vyrų ir moterų implantuotų prietaisų dažnis reikšmingai nesiskyrė. Tyrimo pradžioje vyrų kraujospūdis ir širdies susitraukimų dažnis buvo žemesni, inkstų ir kepenų funkcija buvo blogesnė. Pradinis NT-proBNP tarp lyčių reikšmingai nesiskyrė (3153,2 (2977,7–3339,0) ng/l moterims ir 3242,9 (3084,1–3410,0) ng/l vyrams, P = 0,4796).

Pasiektos vaistų dozės intensyvios priežiūros grupėje viso tyrimo laikotarpiu buvo panašios tiek vyrams, tiek moterims. 2 tyrimo savaitę intensyvios priežiūros gydymo grupėje nebuvo skirtumų tarp pacientų, pasiekusių maksimalias vaistų dozes, proporcijos tarp vyrų ir moterų (P = 0,074, 0,51 ir 0,54 atitinkamai RASi, beta blokatorių ir MRA atvejais) ir pacientams skirtų kilpinių diuretikų dozių (P = 0,50). Iki 90 tyrimo dienos daugumai abiejų lyčių pacientų intensyvios priežiūros grupėje visų trijų geriamųjų ŠN vaistų klasių dozės buvo padidintos iki pilnos, palyginti su nedideliu skaičiumi įprastos priežiūros grupėje (RASi 56,6% ir 1,6% moterų, 54,0% ir 2,5% vyrų, sąveikos P = 0,65; beta blokatoriai 45,4% ir 2,2% moterų, 51,8% ir 5,1% vyrų, sąveikos P = 0,43; MRA 83,2% ir 44,8% moterų, 84,1% ir 47,5% vyrų, sąveikos P = 0,73).

Pirminė vertinamoji baigtis (180 dienų pakartotinė hospitalizacija dėl ūminio ŠN arba mirtis dėl visų priežasčių) pasireiškė 73 (19,6%) moterims ir 110 (19,2%) vyrams (koreguotas rizikos santykis [RS] 0,87, 95% pasikliautinasis intervalas [PI] 0,62–1,21; P = 0,41). Rezultatai nesiskyrė pagal lytį, nepriklausomai nuo gydymo grupės. Intensyvios priežiūros strategija sumažino pirminės vertinamosios baigties dažnį tiek moterims (30 [15,8%] intensyvios priežiūros grupėje, palyginti su 43 [23,5%] įprastos priežiūros grupėje; pakoreguotas RS 0,67 [95% PI 0,40–1,13]), tiek vyrams (44 [14,9%] intensyvios priežiūros grupėje, palyginti su 66 [23,5%] įprastos priežiūros grupėje; pakoreguotas RS 0,57 [95% PI 0,38–0,88]). Lytis nebuvo intensyvios priežiūros efektyvumo modifikatorius (koreguota sąveika, P = 0,65).

Intensyvios priežiūros grupės vyrų ir moterų gyvenimo kokybė pagerėjo panašiai, palyginti su įprastos priežiūros grupe, ir vėlgi, nenustatyta, kad lytis pakeistų gydymo strategijos efektyvumą (sąveika P = 0,08). Tiek vyrams, tiek moterims NT-proBNP sumažėjo labiau intensyvios priežiūros grupėje, palyginti su įprastine priežiūra (sąveika P = 0,49). Taip pat nustatyta, kad greitas vaistų titravimas buvo vienodai saugus tiek vyrams, tiek moterims: nebuvo reikšmingo nepageidaujamų reiškinių rizikos padidėjimo nė vienai iš lyčių ir reikšmingos gydymo ir lyties sąveikos (visos P vertės $> 0,05$).

Gyvenimo kokybės analizė STRONG-HF kohortoje – III publikacija

Vidutinis pradinis EQ-VAS balas buvo 59,2 (standartinis nuokrypis 15,1), statistiškai reikšmingo skirtumo tarp gydymo grupių tyrimo pradžioje nenustatyta. Pacientai, kurių pradinė gyvenimo kokybė buvo blogesnė, dažniau buvo moterys, juodaodžiai ir ne europiečiai ($P < 0,001$). Nenustatyta statistiškai reikšmingų skirtumų gyvenimo kokybės tercilėse, lyginant pagal

amžių, pradinę NT-proBNP koncentraciją, kairiojo skilvelio išstūmimo frakciją, NYHA funkcinę klasę ir pagrindines gretutines ligas. Pacientai, kurių pradinė gyvenimo kokybė buvo blogiausia, turėjo ilgesnę širdies nepakankamumo istoriją ir daugiau hospitalizacijų dėl širdies nepakankamumo per paskutinius metus.

EQ-VAS pagerėjimas nuo pradinio lygio iki 90 dienos buvo reikšmingai geresnis intensyvios priežiūros grupės pacientams (koreguotas gydymo efektas 3,49 (95% PI 1,74–5,24), P < 0,0001). Intensyvios priežiūros nauda gyvenimo kokybei buvo pastebėta pacientų pogrupiuose, suskirstytuose pagal amžių, KSIF (>40%/≤40%), NT-proBNP (pagal medianą) ir sistolinį kraujospūdį (pagal medianą) ir prieširdžių virpėjimą ar plazdėjimą. Gyvenimo kokybė panašiai pagerėjo intensyvios priežiūros grupėje, nepriklausomai nuo pradinės gyvenimo kokybės, matuojamos kaip tolydaus kintamojo (sąveikos P reikšmė = 0,32). Intensyvios priežiūros strategija taip pat pagerino visus atskirus EQ-5D sveikatos būklės matmenis, įskaitant judrumą, savirūpą, įprastą veiklą, skausmą/diskomfortą ir nerimą/depresiją.

Pasiektos vidutinės visų trijų vaistų dozės intensyvios priežiūros grupėje buvo panašios gyvenimo kokybės tercilėse per visą tyrimo laikotarpį. Didesnė pasiekta vidutinė optimali dozė 2 savaitę intensyvios priežiūros grupėje buvo reikšmingai susijusi su didesniu EQ-VAS pagerėjimu (P < 0,001).

Intensyvios priežiūros efektyvumas, vertinant pirminę vertinamąją baigtį nebuvo reikšmingai paveiktas pradinės gyvenimo kokybės, vertinant EQ-VAS kaip ranginį kintamąjį (sąveikos P reikšmė = 0,58) ar kaip tolydųjį kintamąjį (sąveikos P reikšmė = 0,87).

Intensyvios priežiūros strategija buvo saugi visose tercilėse (visos sąveikos P reikšmės > 0,05 nepageidaujamų reiškinių arba sunkių nepageidaujamų reiškinių atveju).

Anemijos analizė STRONG-HF kohortoje – IV publikacija

Anemijos paplitimas buvo 27,2% tyrimo pradžioje ir 32,1% 90 tyrimo dieną. Pacientai, kuriems buvo nustatyta pradinė anemija, dažniau buvo juodaodžiai ir ne europiečiai, turėjo didesnę NT-proBNP koncentraciją ir daugiau stazės požymių. Nepriklausomi pradinės anemijos prognostiniai veiksniai buvo: vyresnis amžius, mažesnis kūno masės indeksas, buvimas ne baltaodžiu, padidėjęs sistolinis kraujospūdis, blogesnė inkstų funkcija, mažesnė kalio ir bendro bilirubino, cholesterolio koncentracija ir sumažėjęs leukocitų skaičius. Nepriklausomi veiksniai, prognozavę anemijos atsiradimą po 90 dienų buvo vyriškoji lytis, bet kuris kitas geografinis regionas nei Europa, išeminė ŠN

kilmė, didesnė gliukozės ir šlapimo rūgšties koncentracija pradinėje stadijoje. Intensyvios priežiūros strategija reikšmingai nepadidino anemijos atsiradimo dažnio po 90 dienų.

Pagrindinis rezultatas (pakartotinė hospitalizacija dėl ŠN arba mirtis dėl visų priežasčių 180 dieną) buvo panašus tarp pacientų, kuriems buvo ir nebuvo pradinės anemijos (atitinkamai 22,5% ir 18,2%, nekoreguotas RS 1,27; 95% PI 0,90–1,80, P > 0,05). Vis dėlto, pacientams, kuriems buvo pradinė anemija, EQ-VAS klausimyno verčių pagerėjimas nuo pradinio lygio iki 90 dienos buvo reikšmingai mažesnis (koreguotas vidurkio skirtumas −2,34 (−4,37, −0,31), P = 0,02). Pasiektos dozės intensyvios priežiūros grupėje buvo panašios, nepriklausomai nuo pradinės anemijos buvimo.

Intensyvios priežiūros strategijos poveikis pirminei vertinamajai baigčiai neturėjo reikšmingos sąveikos nei su pradinės anemijos buvimu (koreguota sąveikos P = 0,28), nei hemoglobino koncentracijos, kaip tolydaus kintamojo (sąveikos P vertė = 0,53).

Sunkių nepageidaujamų reiškinių dažnis buvo didesnis anemija sergantiems pacientams (P = 0,0058). Visgi, intensyvios priežiūros strategija buvo saugi visose grupėse, nepriklausomai nuo pradinės anemijos buvimo ar hemoglobino koncentracijos atsižvelgiant į pradinę anemiją arba hemoglobino koncentraciją (visos sąveikos P vertės > 0,05).

IŠVADOS

1. Pakartotinė hospitalizacija per pirmuosius 6 mėnesius po kreipimosi dėl ūminio dusulio į priėmimo skyrių yra susijusi su ženkliai padidėjusia 1 metų mirties dėl visų priežasčių rizika pacientams, sirgusiems ūminiu širdies nepakankamumu ir kitomis ligomis, sukėlusiomis ūminį dusulį.
2. Greitas gairių rekomenduojamo optimalaus medikamentinio gydymo titravimas po hospitalizacijos dėl ūminio širdies nepakankamumo yra pasiekiamas, saugus ir sumažina 180 dienų mirties dėl visų priežasčių ar pakartotinės hospitalizacijos dėl širdies nepakankamumo riziką bei pagerina gyvenimo kokybę tiek vyrams, tiek moterims.
3. Greitas gairių rekomenduojamo optimalaus medikamentinio gydymo titravimas po hospitalizacijos dėl ūminio širdies nepakankamumo pagerina gyvenimo kokybę ir visas penkias gyvenimo kokybės klausimyno dalis ir sumažina 180 dienų mirties dėl visų priežasčių ar pakartotinės hospitalizacijos dėl širdies nepakankamumo riziką, nepaisant pradinės gyvenimo kokybės.

4. Greitas gairių rekomenduojamo optimalaus medikamentinio gydymo titravimas po hospitalizacijos dėl ūminio širdies nepakankamumo yra pasiekiamas, saugus ir sumažina 180 dienų mirties dėl visų priežasčių ar pakartotinės hospitalizacijos dėl širdies nepakankamumo riziką bei pagerina gyvenimo kokybę, nepriklausomai nuo pradinės anemijos buvimo.

PRAKTINĖS REKOMENDACIJOS

1. Pacientas, besikreipiantis į skubios pagalbos skyrių dėl ūminio dusulio, kurį sukėlė tiek širdinės, tiek ne širdinės priežastys, ilgą laiką po išrašymo turėtų būti laikomas „pažeidžiamu pacientu“, todėl jį reikia atidžiai sekti ir optimizuoti gydymą, atsižvelgiant į pagrindinę dusulio priežastį ir gretutines ligas.
2. Optimalus širdies nepakankamumo gydymas turėtų būti skiriamas ir titruojamas tokiu pačiu greičiu tiek vyrams, tiek moterims po hospitalizacijos dėl ūminio širdies nepakankamumo.
3. Optimalus širdies nepakankamumo gydymas turėtų būti greitai titruojamas po hospitalizacijos dėl ūminio širdies nepakankamumo, siekiant pagerinti ne tik pacientų prognozę, bet ir gyvenimo kokybę.
4. Optimalus širdies nepakankamumo gydymas turėtų būti greitai titruojamas po hospitalizacijos dėl ūminio širdies nepakankamumo, neatsižvelgiant į pradinę anemiją ir pradinę gyvenimo kokybę.

PADĖKA

Disertacijos rašymas būtų buvęs neįmanomas be mano vadovų, kolegų, draugų ir šeimos padrąsinimo ir palaikymo, kuriems labai norėčiau padėkoti.

Pirmiausia norėčiau nuoširdžiai padėkoti darbo mokslinei vadovei profesorei Jelenai Čelutkienei. Nuo pat 2013 metų, kai pradėjome dirbti kartu, jūsų disciplina ir visada aukšti lūkesčiai skatino mane eiti į priekį ir padėjo rasti savo mokslinį kelią. Taip pat nuoširdžiai dėkoju darbo moksliniam konsultantui profesoriui Alexandre Mebazaa. Jūs esate toks mentorius, apie kokį svajoja kiekvienas jaunas tyrėjas. Nuo mūsų susitikimo 2017 metais, jūsų palaikymas, pozityvumas ir nuolatinis skatinimas įkvėpė mane tikėti, kad galiu pasiekti visko, ko užsibrėžiu.

Labai dėkoju savo šeimai – tėvams Irutei ir Rolandui, sesei Saulei ir broliui Rokui, seneliams Irenai, Zigmui ir Bronei, jau išėjusiam seneliui Antanui, tetoms ir dėdėms, pusbroliams ir pusseserėms. Jūsų įskiepytos

vertybės – ryžtas, atsakomybė, atkaklumas, teisingumas ir sąžiningumas – padėjo man įveikti visus iššūkius.

Taip pat norėčiau padėkoti visiems draugams, kuriuos sutikau per savo gyvenimą ir kurie mane palaikė skirtingais gyvenimo etapais. Juste ir Dovile – ačiū už daugybę kavos puodelių, vakarienių, kelionių ir nesibaigiančių pokalbių, per kuriuos galėjau išlieti visus nusivylimus ir švęsti pasiekimus. Emilija ir Egle – ačiū, kad jau beveik du dešimtmečius esate šalia, suprantate mano trūkumus ir padedate nepamiršti mano stiprybių. Pauliau, Egle, Tadai ir Urte – ačiū, kad esate visų svarbiausių gyvenimo įvykių dalis. Kristijonai ir Mindaugai – ačiū už alternatyvų ir humoristinį požiūrį į kasdienį gyvenimą.

Dėkoju kolegoms iš Vilniaus universiteto ligoninės Santaros klinikų Ambulatorinės kardiologijos ir Širdies ir kraujagyslių vaizdinių tyrimų skyrių, kurie buvo ir yra didžiulė mano klinikinio ir mokslinio darbo dalis. Ypatinga padėka skirta nuostabiai slaugytojai Linai Stambrauskienei, su kuria dirbu jau penkerius metus ir be kurios savo darbo neįsivaizduoju.

Savo disertacijos recenzentams – profesorei Sigitai Glaveckaitei, docentui Karoliui Ažukaičiui ir docentui Ryčiui Masiliūnui – nuoširdžiai dėkoju už skirtą laiką ir vertingas įžvalgas, kurios neabejotinai pagerino mano disertaciją.

Taip pat turiu padėkoti visiems tyrėjams, dirbusiems prie LEDA, BASEL V ir STRONG-HF tyrimų, ir publikacijų bendraautoriams. Taip pat visiems pacientams, kurie sutiko dalyvauti šiuose tyrimuose, ir visiems pacientams, kurie dalyvauja moksliniuose tyrimuose – jūsų indėlis į mokslo pažangą yra neįkainojamas.

Galiausiai norėčiau padėkoti savo vyrui Vilhelmui. Nežinau, ar kada galėsiu tinkamai atsidėkoti už visus drąsinimus, pagalbą įveikiant visus sunkumus ir kaskart sklaidant visas mano abejones. Visi mano pasiekimai buvo galimi tik dėl besąlyginės meilės ir palaikymo, kuriuos gavau iš tavęs kiekvieną mūsų 15 metų kartu dieną. Pažadu savo visokeriopą paramą tau ir labai laukiu ateinančio mūsų šeimos etapo.

APIE AUTORĘ

Kamilė Čerlinskaitė-Bajorė 2017 metais su pagyrimu (Magna Cum Laude) baigė medicinos studijas Vilniaus universitete ir įgijo medicinos gydytojo kvalifikaciją. 2021 metais baigusi ketverių metų rezidentūros studijas, ji tapo gydytoja kardiologe. Autorė specializuojasi širdies nepakankamumo ir echokardiografijos srityse.

2021 metais ji atliko klinikinę stažuotę širdies vaizdinių tyrimų srityje Rigshospitalet ligoninėje, Kopenhagoje, Danijoje, taip pat baigė specializuotą

širdies nepakankamumo specializacijos kursą Vilniaus universitete. 2024 metais autorė baigė dvejų metų trukmės podiplominius širdies nepakankamumo kursus Londone, organizuotus Zurich Heart House. Nuo 2021 metų, Kamilė dirba gydytoja kardiologe, besispecializuojančia širdies nepakankamumo srityje, Vilniaus universiteto ligoninės Santaros klinikų Ambulatorinės kardiologijos skyriuje, kur teikia specializuotas širdies nepakankamumo priežiūros paslaugas.

2017–2018 metais ji vykdė mokslinių tyrimų stažuotę Lariboisière ligoninėje ir INSERM UMR-S 942 mokslinių tyrimų institute, vadovaujama profesoriaus Alexandre Mebazaa. Nuo 2021 metų dirba jaunesniąja mokslo darbuotoja ir dėstytoja Vilniaus universiteto Medicinos fakultete. 2022 metais Vilniaus universitete pradėjo doktorantūros studijas. Kaip mokslininkė, ji yra daugelio mokslinių publikacijų autorė ir bendraautorė, dalyvavo klinikiniuose tyrimuose bei tarptautiniuose projektuose, taip pat skaitė pranešimus nacionalinėse ir tarptautinėse mokslinėse konferencijose.

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12. ANNEXES

LIST OF PRESENTATIONS

List of presentations of the dissertation results at the international events:

1. Impact Of Rapid Up-Titration of Guideline-Directed Medical Therapies On Quality of Life: Insights From The STRONG-HF Trial. Kamilė Čerlinskaitė-Bajorė. Oral presentation, presented in Late-Breaking Clinical Science session. Conference "THT 2024: Technology and Heart Failure Therapeutics", 4-6th March 2024, Boston, USA.
2. Machine Learning-Based Phenotypes of Acute Dyspnea Patients Have Strikingly Different Prognosis. Kamilė Čerlinskaitė-Bajorė. Moderated poster presentation. Congress of the American College of Cardiology „ACC.23 together with WCC", 4-6th March, 2023, New Orleans, USA.
3. „Utilizing multiple biomarkers in characterization and risk-stratification of patients presenting with acute dyspnea". Kamilė Čerlinskaitė-Bajorė. Oral presentation. Remote conference "The 4th Biomarkers of the Future Conference", 15-16th November 2022. 3rd place in the Young scientists category.
4. Unplanned readmissions after discharge increases risk of death in acute dyspnoea patients: non-cardiac is as severe as cardiac causes. Kamilė Čerlinskaitė. Poster presentation. Congress of the European Society of Cardiology (ESC Congress 2019). 31st August – 3rd September 2019. Paris, France.

Other presentations on the topic of the dissertation:

1. New and emerging therapies for HFpEF. Session: *Is left ventricular ejection fraction still relevant for guideline-directed medical therapy implementation?* Heart Failure Congress of the European Society of Cardiology, 17-20th May 2025 Belgrade, Serbia.
2. Decompensated heart failure: case presentation. Session: *Guidelines in Practice: implementing the 2023 Focused Update on Heart Failure - target, treat, and titrate.* Congress of the European Society of Cardiology (ESC Congress 2024), 30th August – 2nd September 2024. London, United Kingdom.
3. Diabetes and heart failure. 14th Asia Pacific Congenital and Structural Heart Intervention Symposium (APCASH 2024). 7-8th December 2024, Hong Kong.

ABOUT THE AUTHOR

Kamilė Čerlinskaitė-Bajorė received a Master's degree in Medicine with Magna Cum Laude from Vilnius University in 2017 and obtained a Medical Doctor qualification.

In 2021, after four years of residency, she became a cardiologist, specialising in heart failure and echocardiography. In 2021, she did a clinical fellowship in cardiac imaging in Rigshospitalet, Copenhagen, Denmark. Also in 2021, she finished a heart failure specialisation course in Vilnius University. In 2024, she graduated from a two-year Postgraduate Course in Heart Failure Management in London, organised by the Zurich Heart House. She has been working as a heart failure cardiologist in the outpatient department of Vilnius University Hospital Santaros Klinikos since 2021, providing specialised heart failure services.

In 2017-2018 she did a research fellowship under supervision of Professor Alexandre Mebazaa in Lariboisière hospital and INSERM UMR-S 942 research institute in Paris, France. She has been working as a junior researcher and a lecturer in Vilnius University, Faculty of Medicine, since 2021. She started the Vilnius University doctoral study programme in 2022. As a researcher, Kamilė authored multiple publications, participated in clinical trials and international projects and presented in local and international conferences.

COPIES OF PUBLICATIONS INCLUDED IN THE THESIS

Publication I

Čerlinskaitė K, Mebazaa A, Cinotti R, Matthay M, Wussler DN, Gayat E, Juknevičius V, Kozhuharov N, Dinort J, Michou E, Gualandro DM, Palevičiūtė E, Alitoit-Marrote I, Kablučko D, Bagdonaitė L, Balčiūnas M, Vaičiulienė D, Jonauskienė I, Motiejūnaitė J, Stašaitis K, Kukulskis A, Damalakas Š, Laucevičius A, Mueller C, Kavoliūnienė A, Čelutkienė J; GREAT network. Readmission following both cardiac and non-cardiac acute dyspnoea is associated with a striking risk of death.

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ORIGINAL RESEARCH ARTICLE

Readmission following both cardiac and non-cardiac acute dyspnoea is associated with a striking risk of death

Kamilė Čerlinskaitė[1,2,3], Alexandre Mebazaa[2,3,4]*, Raphaël Cinotti[5], Michael Matthay[6,7], Desiree N. Wussler[8], Etienne Gayat[2,3,4], Vytautas Juknevičius[1,9], Nikola Kozhuharov[8], Julia Dinort[8], Eleni Michou[8], Danielle M. Gualandro[8], Eglė Palevičiūtė[1,9], Irina Alitoit-Marrote[9], Denis Kablučko[9], Loreta Bagdonaitė[10,11], Mindaugas Balčiūnas[1,9], Dovilė Vaičiulienė[12], Ieva Jonauskienė[12], Justina Motiejūnaitė[12], Kęstutis Stašaitis[12], Audrys Kukulskis[12], Šarūnas Damalakas[12], Aleksandras Laucevičius[1], Christian Mueller[8], Aušra Kavoliūnienė[12], Jelena Čelutkienė[1,9] and GREAT network

[1]*Clinic of Cardiac and Vascular Diseases, Institute of Clinical Medicine, Faculty of Medicine, Vilnius University, Vilnius, Lithuania;* [2]*Inserm UMR-S 942, Cardiovascular Markers in Stress Conditions (MASCOT), Paris, France;* [3]*Department of Anesthesiology and Critical Care, Hôpitaux Universitaires Saint Louis-Lariboisière, Assistance Publique des Hopitaux de Paris, 2 Rue Ambroise Paré, Paris, 75010, France;* [4]*Université de Paris, Paris, France;* [5]*Department of Anesthesia and Critical Care, Hôpital Laennec, University Hospital of Nantes, Saint-Herblain, France;* [6]*Department of Medicine and Anesthesia, University of California, San Francisco, CA, USA;* [7]*Cardiovascular Research Institute, University of California, San Francisco, CA, USA;* [8]*Cardiology Department and Cardiovascular Research Institute Basel (CRIB), University Hospital Basel, University of Basel, Basel, Switzerland;* [9]*Centre of Cardiology and Angiology, Vilnius University Hospital Santaros Klinikos, Vilnius, Lithuania;* [10]*Institute of Biomedical Science, Faculty of Medicine, Vilnius University, Vilnius, Lithuania;* [11]*Centre of Laboratory Medicine, Vilnius University Hospital Santaros Klinikos, Vilnius, Lithuania; and* [12]*Lithuanian University of Health Sciences, Kaunas, Lithuania*

Abstract

Aims Readmission and mortality are the most common and often combined endpoints in acute heart failure (AHF) trials, but an association between these two outcomes is poorly investigated. The aim of this study was to determine whether unplanned readmission is associated with a greater subsequent risk of death in patients with acute dyspnoea due to cardiac and non-cardiac causes.

Methods and results Derivation cohort (1371 patients from the LEDA study) and validation cohort (1986 patients from the BASEL V study) included acute dyspnoea patients admitted to the emergency department. Cox regression analysis was used to determine the association of 6 month readmission and the risk of 1 year all-cause mortality in AHF and non-AHF patients and those readmitted due to cardiovascular and non-cardiovascular causes. In the derivation cohort, 666 (49%) of patients were readmitted at 6 months and 282 (21%) died within 1 year. Six month readmission was associated with an increased 1 year mortality risk in both the derivation cohort [adjusted hazard ratio (aHR) 3.0 (95% confidence interval, CI 2.2–4.0), $P < 0.001$] and the validation cohort (aHR 1.8, 95% CI 1.4–2.2, $P < 0.001$). The significant association was similarly observed in AHF (aHR 3.2, 95% CI 2.1–4.9, $P < 0.001$) and other causes of acute dyspnoea (aHR 2.9, 95% CI 1.9–4.5, $P < 0.001$), and it did not depend on the aetiology [aHR 2.2, 95% CI 1.6–3.1 for cardiovascular readmissions; aHR 4.1, 95% CI 2.9–5.7 for non-cardiovascular readmissions ($P < 0.001$ for both)] or timing of readmission.

Conclusions Our study demonstrated a long-lasting detrimental association between readmission and death in AHF and non-AHF patients with acute dyspnoea. These patients should be considered 'vulnerable patients' that require personalized follow-up for an extended period.

Keywords Acute dyspnoea; Emergency department; Vulnerable phase; Acute heart failure; Mortality; Readmission

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**Correspondence to: Alexandre Mebazaa, Department of Anesthesiology and Critical Care, Hôpitaux Universitaires Saint Louis-Lariboisière, Assistance Publique des Hopitaux de Paris, 2 Rue Ambroise Paré, 75010 Paris, France. Tel: +33 1 49958085; Fax: +33 1 49958073. Email: alexandre.mebazaa@aphp.fr*
Kamilė Čerlinskaitė, Alexandre Mebazaa and Jelena Čelutkienė contributed equally to this manuscript.

Introduction

Acute dyspnoea, due to cardiac or non-cardiac causes, is one of the chief complaints in the emergency department (ED) and cardiac intensive care unit and is associated with poor short-term and long-term outcomes.[1–8] In acute heart failure (AHF), the immediate post-discharge period is described as the 'vulnerable phase' that corresponds to high readmission and death rates within a few months after discharge.[9] Thus, reduction in readmission and/or death are the most frequent efficacy endpoint in AHF trials.[10,11] However, though often combined in recent trials, whether unscheduled readmission and subsequent death are associated remains poorly investigated.[12–14] Also, the vulnerable phase has not been described in large population of patients with acute dyspnoea including AHF and non-AHF groups.

We aimed to evaluate the relationship between readmission and the risk of death in acute dyspnoea patients after discharge and to compare this association between AHF and other causes of dyspnoea using large cohorts from two European countries.

Methods

Study design

We analysed two independent acute dyspnoea cohorts for derivation and validation purposes.

Derivation cohort

Derivation cohort was derived from LEDA (Lithuanian Echocardiography Study of Dyspnoea in Acute Settings, ClinicalTrials.gov: NCT03048032) prospective observational multicentre study, performed in two Lithuanian university centres in collaboration with a research protocol of international GREAT (Global Research on Acute Conditions Team) network. The study enrolled patients from March 2015 to December 2017. A 1 year follow-up was completed in December 2018. 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 written informed consent.

Inclusion criteria Consecutive adult patients admitted to the ED with chief complaint of acute dyspnoea due to any cause were included.

Exclusion criteria Patients with acute coronary syndrome suspected during the first 4 h of admission were excluded. If the patients were admitted more than once, only the first episode was taken as index admission. Further exclusion criteria were in-hospital mortality or organ transplantation during index admission or readmission.

Data collection Patient demographic data, co-morbidities, baseline medication, clinical signs and laboratory parameters at admission, early in-hospital treatment, medication at discharge, and in-hospital death were recorded.[15] Patient sex was self-reported. The severity of dyspnoea at admission was assessed using subjective Borg scale.[16] Blood samples were taken within 4 h of presentation, frozen at −80°C, and sent to the Inserm UMR-942 institute for measurements of N-terminal pro-B-type natriuretic peptide and high-sensitivity troponin T (Roche Diagnostics® GmbH, Mannheim, Germany).

Validation cohort

Validation cohort was derived from BASEL V (Basics in Acute Shortness of Breath EvaLuation Study, ClinicalTrials.gov: NCT01831115) prospective multicentre observational study. Enrolment period and inclusion/exclusion criteria have been reported elsewhere.[17] Briefly, adult patients with acute, non-traumatic dyspnoea presenting to the ED were enrolled into the study from 2006 to 2014 in two university centres in Switzerland. Patients on haemodialysis were excluded. The study was approved by the local ethical committee and carried out according to the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants.

Diagnosis adjudication

In the derivation cohort, teams of three cardiologists blinded to post-discharge outcomes adjudicated the cause of acute dyspnoea. All available patient 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 AHF or non-AHF; the latter included chronic obstructive pulmonary disease (COPD)/asthma exacerbation, pulmonary embolism, pulmonary/non-pulmonary infections, and cancer, among others. Central adjudication of the diagnosis in the validation cohort has been previously described.[17]

Readmission and mortality

Derivation cohort

All patients were followed up for 1 year after discharge. Lithuanian administrative databases provided data on mortality and unplanned all-cause readmissions coded by the 10th Revision of the International Classification of Diseases. Lithuania's national administrative databases capture all of the events because there are no private hospitals that admit

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acute patients and are not covered by healthcare insurance. Therefore, there were no patients lost to follow-up.

Validation cohort

Patients were contacted by telephone at 3 and 6 months and 1 year after the index episode.[17] In case of uncertainties, referring physicians and administrative databases were approached.

Study endpoints

The primary endpoint was the association between the first all-cause readmission within 6 months after discharge and 1 year all-cause mortality in patients with AHF and non-AHF causes of dyspnoea.

Secondary endpoints were as follows:

i the association between the first readmissions due to cardiovascular (CV) vs. non-cardiovascular (non-CV) causes within 6 month and 1 year mortality;

ii the association between the first readmissions within 6 month and 1 year mortality in different subgroups, based on age, sex, co-morbidities, causes of dyspnoea, and biomarker levels.

Statistical analysis

Continuous variables are presented as median and inter-quartile ranges, and categorical variables are presented as counts (percentage). The differences between study groups were compared using Kruskal–Wallis test for continuous variables and χ^2 test for the categorical variables.

To investigate the impact of 6 month readmission on 1 year mortality, an unadjusted and adjusted Cox regression analysis was performed comparing non-readmitted and readmitted patients. To investigate if the precise timing of the first readmission influenced 1 year mortality, the same analyses were performed that compared non-readmitted and readmitted patients at three periods (first month, second and third months, and fourth to sixth months after discharge). First, the analysis was performed in all patients, comparing survival between patients readmitted and not readmitted during the first month. Then, data were censored by removing patients who either died or were readmitted during the first month. The same analysis was then repeated in patients readmitted and not readmitted during second and third months and, finally, in the same manner in patients readmitted and not readmitted between the fourth and sixth months. Multivariate Cox regression included criteria known to affect prognosis: age, sex, co-morbidities (history of heart failure, coronary artery disease, and diabetes), systolic blood pressure, heart rate, estimated glomerular filtration rate <60 mL/min/1.73 m^2, and sodium <136 mmol/L.[15] The analysis described earlier was repeated in the AHF and non-AHF groups and for CV or non-CV readmissions against non-readmitted patients as the reference group.

Subgroup analysis was performed by conducting unadjusted Cox regression analyses dividing patients by age (>65 and ≤ 65 years old), sex, history of heart failure, aetiology of acute dyspnoea, N-terminal pro-B-type natriuretic peptide (>1000 and ≤ 1000 ng/L),[18] high-sensitivity troponin T (>14 and ≤ 14 ng/L), and left ventricular ejection fraction ($>50\%$ and $\leq 50\%$) measurements.

Sensitivity analysis was performed by conducting unadjusted and adjusted Cox regression omitting patients who died prior to the analysed readmission follow-up point; for example, when analysing association of 6 month readmission with 1 year mortality, only patients who survived the first 6 months after discharge were analysed.

All statistical analyses were performed using R Version 3.5.3 (The R Foundation for Statistical Computing, Vienna, Austria) with the statistical packages 'survival' for survival analyses and 'icd' to decode causes of death and readmission.[19,20] All tests were two sided, and a P value of <0.05 was considered significant. No imputation was used for missing data.

Results

Derivation cohort

Demographic and clinical data

The LEDA study enrolled 1566 patients (Supporting Information, *Figure S1*). After excluding duplicate, transplanted patients and those who died in the hospital during the index admission, 1371 (87.5%) patients were included in the analysis (median age 71 [61–79] years and 599 (43.6%) female). Baseline characteristics are described in *Table 1*.

During the 6 months after discharge, 666 (48.6%) patients were readmitted, 379 (56.9%) for CV and 287 (43.1%) for non-CV causes (*Figure 1A*). Readmitted patients were older and had more co-morbidities, higher heart rate, higher concentrations of cardiac, renal, and inflammatory biomarkers, and lower haemoglobin (*Table 1*).

The characteristics of the 731 (53.3%) AHF and 640 (46.7%) non-AHF patients are described in Supporting Information, *Tables S1* and *S2*. In the first months after discharge (*Figure 1B* and *1C*), readmission rate in AHF and non-AHF groups was similarly high, whereas at 6 months, AHF patients were readmitted more frequently (53.5% vs. 43%, respectively, $P < 0.001$). In AHF patients, CV causes of readmission dominated (68.3%), in contrast to non-AHF patients (59.3% non-CV readmissions). Furthermore, the aetiology of readmission (CV or not) was often the same as the causes of index admission (*Figure 2*).

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Table 1 Baseline characteristics, treatment at discharge, and outcomes of the derivation LEDA cohort

	Total (N = 1371)	Readmitted at 6 months (N = 666)	Non-readmitted at 6 months (N = 705)	P value	n
Age, median [IQR]	71 [61–79]	72 [64–79]	69 [59–78]	0.001	1371
Female sex, n (%)	599 (43.7%)	276 (41.4%)	323 (45.8%)	0.115	1371
AHF, n (%)	731 (53.3%)	391 (58.7%)	340 (48.2%)	<0.001	1371
Co-morbidities, n (%)					
History of chronic heart failure	829 (61.5%)	441 (67.5%)	388 (55.7%)	<0.001	1349
Hypertension	1068 (79.2%)	530 (81.2%)	538 (77.3%)	0.093	1349
Diabetes mellitus	310 (23%)	169 (25.9%)	141 (20.3%)	0.017	1349
Coronary artery disease	467 (34.6%)	246 (37.7%)	221 (31.8%)	0.026	1349
COPD	179 (13.3%)	93 (14.2%)	86 (12.4%)	0.347	1349
Asthma	82 (6.1%)	38 (5.8%)	44 (6.3%)	0.786	1349
Active or recent cancer	175 (13%)	105 (16.1%)	70 (10.1%)	0.001	1349
Anaemia	481 (35.7%)	251 (38.4%)	230 (33.0%)	0.044	1349
Medications at admission, n (%)					
ACEi/ARB	625 (46.4%)	312 (47.9%)	313 (45%)	0.315	1348
Beta-blockers	686 (50.9%)	346 (53.1%)	340 (48.9%)	0.135	1348
Diuretics[a]	585 (43.4%)	311 (47.7%)	274 (39.4%)	0.002	1348
Aldosterone antagonists	226 (16.8%)	126 (19.3%)	100 (14.4%)	0.018	1348
Inhaled steroids	76 (5.6%)	34 (5.2%)	42 (6%)	0.593	1348
β_2 mimetics	110 (8.2%)	54 (8.3%)	56 (8%)	0.953	1348
Anti-diabetics	172 (12.8%)	97 (14.9%)	75 (10.8%)	0.03	1348
Clinical parameters at admission, median [IQR]					
BMI (kg/m^2)	29.5 [25.6–34.5]	29.7 [25.5–34.6]	29.4 [25.6–34.4]	0.656	779
Borg scale of dyspnoea severity	7 [5–8]	7 [5–8]	7 [5–8]	0.039	1139
Duration of dyspnoea (days)	6 [1–14]	7 [1–14]	5 [1–14]	0.236	1085
Systolic blood pressure (mmHg)	140 [125–160]	139 [124–159]	140 [125–160]	0.093	1345
Heart rate (b.p.m.)	88 [74–104]	90 [75–107]	85 [72–101]	0.025	1073
Respiratory rate	20 [16–22]	20 [16–22]	20 [16–22]	0.275	665
SpO_2 (%)	94 [90–96]	93 [89–96]	94 [90–96]	0.164	1002
Laboratory parameters, median [IQR]					
NT-proBNP (ng/L)	1957 [438–5289]	2604 [691–6542]	1410 [322–3980]	<0.001	813
hs-TnT (ng/L)	30 [10–50]	30 [20–50]	20 [10–40]	<0.001	812
BNP (ng/L)	387 [139.5–1103]	513 [178.5–1284.5]	321 [109–1019]	0.001	683
Creatinine (μmol/L)	93 [75–121]	98 [77–134]	89 [74–112]	<0.001	1270
eGFR (mL/min/1.73 m^2)	62 [45–79]	58 [41–75]	64 [48–80]	<0.001	1270
eGFR < 60 mL/min/1.73 m^2, n (%)	605 (47.6%)	326 (52.9%)	279 (42.7%)	<0.001	1270
CRP (mg/L)	9.4 [3.4–31.2]	10.6 [4.0–34.1]	8.6 [2.8–26.7]	0.003	1131
HGB (g/dL)	13.1 [11.7–14.4]	13.0 [11.5–14.3]	13.3 [11.9–14.5]	0.015	1293

(*Continues*)

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Table 1 (continued)

	Total (N = 1371)	Readmitted at 6 months (N = 666)	Non-readmitted at 6 months (N = 705)	P value	n
Blood glycaemia (mmol/L)	6.2 [5.5–7.4]	6.4 [5.5–7.65]	6.1 [5.4–7.3]	0.018	1000
Treatment at discharge, *n* (%)					
ACEi/ARB	724 (54.2%)	359 (55.5%)	365 (52.9%)	0.371	1337
Beta-blockers	804 (60.1%)	395 (61.1%)	409 (59.3%)	0.544	1337
Diuretics[a]	773 (57.8%)	402 (62.1%)	371 (53.8%)	0.002	1337
Aldosterone antagonists	365 (27.3%)	196 (30.3%)	169 (24.5%)	0.02	1337
Inhaled steroids	91 (6.8%)	43 (6.6%)	48 (7%)	0.907	1337
β_2 mimetics	125 (9.3%)	62 (9.6%)	63 (9.1%)	0.849	1337
Anti-diabetics	201 (15%)	109 (16.8%)	92 (13.3%)	0.085	1337
Outcomes					
Hospitalized, *n* (%)	808 (58.9%)	420 (63.1%)	388 (55%)	0.003	1371
LOS, median [IQR]	9 [7–13]	9 [7–13]	9 [7–13]	0.994	808[b]
Death at 12 months, *n* (%)	282 (20.6%)	211 (31.7%)	71 (10.1%)	<0.001	1371

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; AHF, acute heart failure; BMI, body mass index; BNP, B-type natriuretic peptide; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HGB, haemoglobin; hs-TnT, high-sensitivity troponin T; IQR, inter-quartile range; LOS, length of stay; NT-pro-BNP, N-terminal pro-B-type natriuretic peptide.

Baseline characteristics, treatment at discharge, and outcomes in acute dyspnoea overall population and patients readmitted and not readmitted at 6 months. Data are presented as medians [IQR] or counts (%).

[a]Any diuretic.

[b]Only hospitalized patients.

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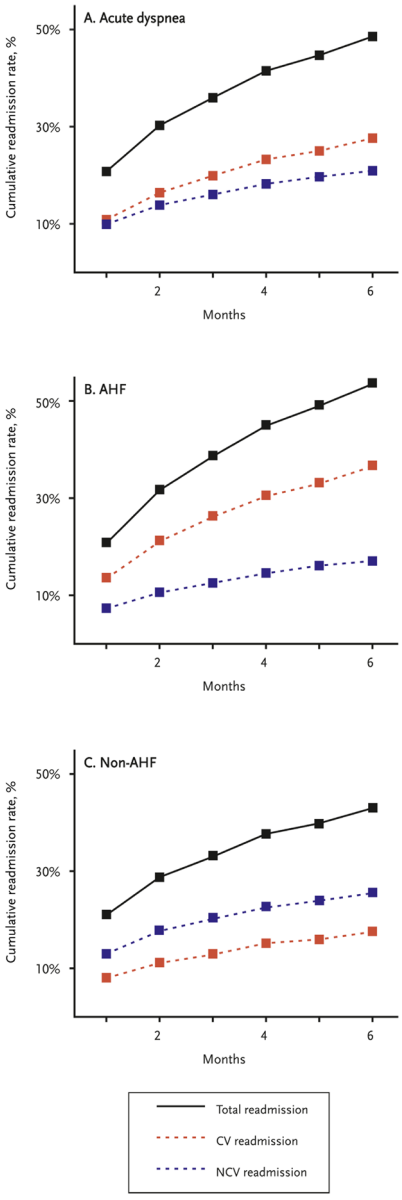
Figure 1 Rates of unplanned all-cause first hospital readmission in the first 6 months in (A) acute dyspnoea (n = 1371), (B) acute heart failure (AHF) (n = 731), and (C) non-AHF (n = 640) patients of the derivation LEDA cohort. CV, cardiovascular; NCV, non-cardiovascular.



Primary endpoint

The 1 year mortality was 20.6% (282 patients). Patients readmitted within 6 months died three times more frequently than non-readmitted patients [211 (31.7%) vs. 71 (10.1%), respectively, $P < 0.001$]. The first episode of readmission within 6 months was associated with a three-fold risk of 1 year all-cause mortality [adjusted hazard ratio (aHR) 3.0, 95% confidence interval (CI) 2.2–4.0, $P < 0.001$] [*Figure 3* (IA)]. Furthermore, the mortality risk was consistently high, whether the first readmission occurred in the first month (aHR 2.9, 95% CI 2.2–3.8, $P < 0.001$) or later: in the second and third months (aHR 4.0, 95% CI 2.7–5.8, $P < 0.001$) or in the fourth to sixth months (aHR 2.8, 95% CI 1.6–4.9, $P < 0.001$).

One year all-cause mortality was equally high in patients with AHF or non-AHF (20% vs. 21.2%, respectively, P = 0.61). Readmitted patients died much more frequently than non-readmitted patients in both the AHF [117 (29.9%) vs. 29 (8.5%), $P < 0.001$] and the non-AHF [94 (34.2%) vs. 42 (11.5%), $P < 0.001$] groups. Readmission within 6 months was associated with similarly increased risk of 1 year mortality in both AHF and non-AHF groups [aHR 3.2, 95% CI 2.1–4.9, $P < 0.001$, and aHR 2.9, 95% CI 1.9–4.5, $P < 0.001$, respectively, *Figure 3* (IB)]. The detrimental association between readmission and death was persistently high at Month 1, Months 2 and 3, and Months 4–6 in both AHF and non-AHF groups (P for interaction >0.05 for all periods) [Supporting Information, *Figure S2* (IA)].

Secondary endpoints

Figure 3 (C) shows that CV or non-CV causes of readmission were both associated with an increased risk of 1 year mortality [aHR 2.2, 95% CI 1.6–3.1, and aHR 4.1, 95% CI 2.9–5.7, respectively ($P < 0.001$ for both)], also at any time of readmission within the first 6 months after discharge [Supporting Information, *Figure S2* (IB)].

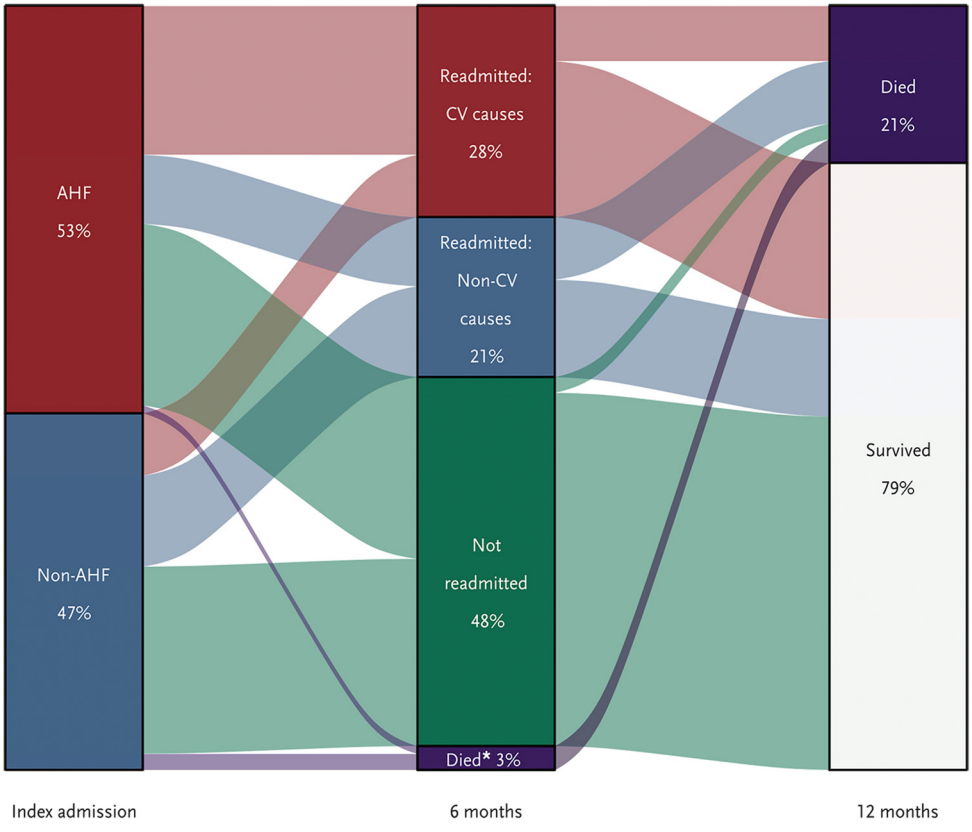
Subgroup and sensitivity analysis

The association between the first 6 month readmission and higher risk of 1 year mortality remained consistent throughout all studied subgroups [*Figure 4* (I)]. Furthermore, the relationship between readmission and mortality remained significant in all time periods in the sensitivity analysis, performed in the subgroup of patients who survived first 6 months after discharge (Supporting Information, *Table S3*).

Validation cohort

The validation cohort included 1986 patients of the BASEL V study discharged alive with 1 year follow-up (median age 74 [61–82] years, 888 [44.7%] female, and 50% AHF) (Supporting Information, *Figure S3*). There were 812 (40.9%) patients readmitted at 6 months with 348 (42.9%) readmitted for CV and 464 (57.1%)—for non-CV causes. Characteristics of the

Figure 2 Trajectory of acute dyspnoea patients within 12 months after index admission in the LEDA derivation cohort. Almost half of the patients were readmitted at 6 months. A small percentage of patients died without being readmitted at 6 months (in purple). Patients who were readmitted died strikingly more frequently at 1 year than patients who were not readmitted at 6 months (32% vs. 10%, respectively, $P < 0.001$). Red = (re)admitted due to cardiovascular (CV) causes; blue = (re)admitted due to non-CV causes; green = survived without readmission; purple = died. AHF, acute heart failure. *Died at 6 months without readmission.



cohort are described in Supporting Information, *Table S4*. AHF patients were readmitted more frequently than non-AHF patients (45.9% vs. 35.9%, respectively, $P < 0.001$). In AHF patients, 62.1% readmissions were for CV causes, whereas 81.7% of readmitted non-AHF patients were readmitted for non-CV causes.

The total 1 year mortality was 19% (377 patients). Patients readmitted within 6 months died significantly more often than non-readmitted patients [218 (26.8%) vs. 159 (13.5%), respectively, $P < 0.001$]. *Figure 3* (IIA) shows that 6 month readmission in the validation cohort was also significantly associated with an increased risk of 1 year mortality in acute dyspnoea patients (aHR 1.8, 95% CI 1.4–2.2, $P < 0.001$). This relationship was uniform irrespective of the timing of readmission, aetiology of index admission, and first readmission, except for the first month readmission in AHF patients and CV readmission [*Figure 3* (IIA and IIB) and Supporting Information, *Figure S2* (IIA and IIB)]. Subgroup analysis of the validation cohort is shown in *Figure 4* (II), and sensitivity analysis is presented in Supporting Information, *Table S5*.

Discussion

Our study clearly demonstrates long-lasting detrimental relationship between readmission and risk of death in AHF, as well as in non-AHF patients. Half of the patients presenting

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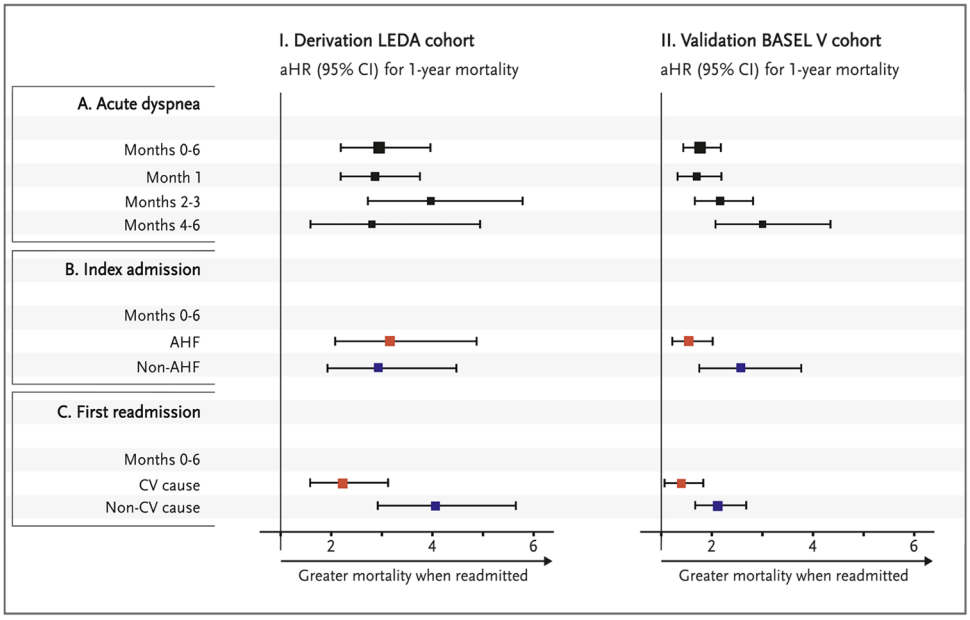
Figure 3 Primary and secondary endpoints: relationship between all-cause readmissions and 1 year all-cause mortality in (I) derivation LEDA and (II) validation BASEL V cohorts. The figure depicts Cox hazard proportional regression results adjusted with age, gender, co-morbidities (history of chronic heart failure, coronary artery disease, and diabetes mellitus), systolic blood pressure, heart rate, creatinine, and sodium <136 mmol/L. The size of the point represents sample size of readmitted patients in a group. (A) Risk of death depending on the exact time or readmission. (B) First readmission in any time in the 6 months following index admission in acute heart failure (AHF) and non-AHF groups. (C) Analysis for cardiovascular (CV) and non-CV causes of readmissions. aHR, adjusted hazard ratio; CI, confidence interval.



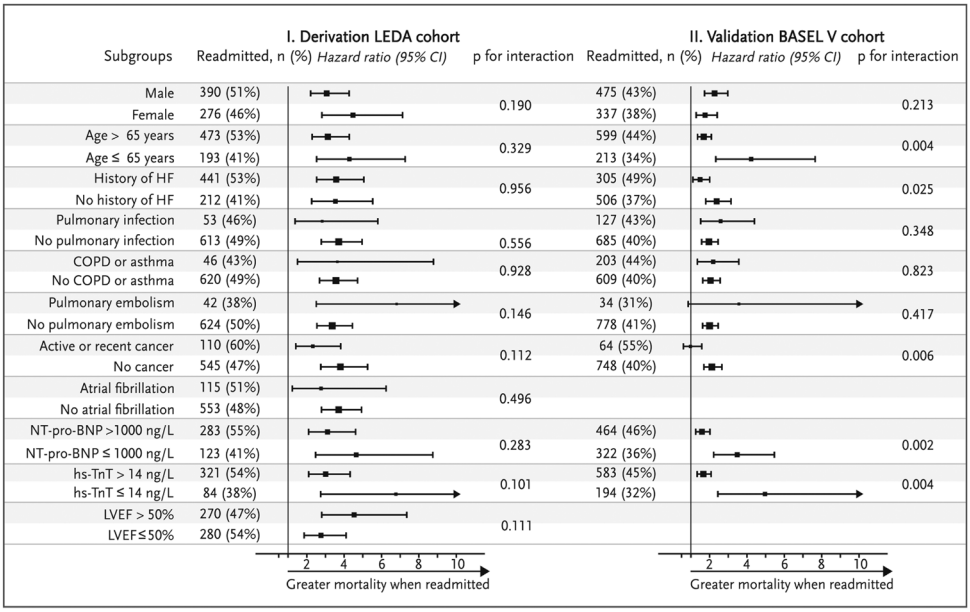
with acute dyspnoea were readmitted in the following months for similar causes as index admissions, and every readmission was associated with a striking risk of death.

Our study examined the link between readmission and mortality in the two largest contemporary cohorts of consecutive patients admitted with acute dyspnoea, with long-term follow-up, namely, LEDA and BASEL V. There were almost no patients lost to follow-up in both cohorts. Distribution of diagnoses, rates of readmission, and mortality were similar in both cohorts and comparable with those reported previously.[4,21,22] Despite some discrepancy, the two-fold to three-fold increase in the risk of 1 year mortality in patients readmitted after an acute dyspnoea event was found in both cohorts in two different regions of Europe with different income and healthcare systems and at different time frames.

Even with emerging diagnostic strategies, such as natriuretic peptides testing and fast imaging techniques, acute dyspnoea remains a tremendous clinical challenge to treating physicians. It has been suggested that uncertainty in diagnosis and aetiology of acute dyspnoea may be associated with longer length of stay and increased risk of mortality and readmission.[23] Our study demonstrated that, regardless of the underlying cardiac or non-cardiac cause, a strikingly high number of patients who had an ED visit for acute dyspnoea returned to the hospital: one-fifth in 1 month and one-half at 6 months. Such high rate of readmission in a short time frame is unique in medicine. For example, chest pain, another common ED complaint, is associated with a much lower rate of readmission.[24] Altogether, our results suggest that readmission may be linked to the persistent underlying disease despite seemingly resolved symptoms.[25] There is an urgent need of randomized trials investigating if diagnostic work-up and short and long-term personalized management of patients with acute dyspnoea including biomarkers and/or lung ultrasound could improve prognosis of this heterogeneous patient group. Our data also urge, in case of heart failure, the rapid implementation of guideline-recommended therapies.[26,27]

A growing interest in readmission has been observed in recent years due to US healthcare policies designed to reduce 30 day readmission rates of some acute CV and pulmonary

Figure 4 Secondary endpoint: the relationship between all-cause readmission and 1 year all-cause mortality in the subgroups of (I) derivation LEDA and (II) validation BASEL V cohorts. The size of the point represents the readmitted sample size in a group. CI, confidence interval; COPD, chronic obstructive pulmonary disease; HF, heart failure; hs-TnT, high-sensitivity troponin T; LVEF, left ventricular ejection fraction; NT-pro-BNP, N-terminal pro-B-type natriuretic peptide.



diseases by using financial incentives.[28–30] Indeed, a low rate of 30 day readmission has been acknowledged as a key quality indicator of patient management during index hospitalization. A small number of studies showed that 30 day readmission was associated with greater mortality in AHF, COPD, or elderly patients.[12–14,31] Our study confirmed and extended the detrimental relationship between readmission and the risk of death in patients with acute dyspnoea to at least 6 months. The relationship between readmission and mortality was found not only in AHF but also in other causes of acute dyspnoea. Indeed, our data showed that, despite several differences including age and co-morbidities, acute respiratory failure associated with AHF, pulmonary infection, or decompensated COPD carried an equally high risk of death after readmission. Accordingly, this finding strongly suggests that index admission and subsequent readmissions are a continuum in patients for whom the underlying cardiac and/or pulmonary dysfunction(s) have not been resolved. In our study, impaired oxygenation and high C-reactive protein were common findings in both heart failure and non-heart failure patients and might be potential drivers of unfavourable prognosis.

A 'vulnerable' phase has been described in AHF patients as an early and transient post-discharge period with high rates of readmission and mortality.[9] Yet our results do not support the concept of a transient vulnerable phase neither in AHF nor in non-AHF patients. Alternatively, this study indicates that a patient who visits the ED with acute respiratory distress should instead be considered a 'vulnerable patient' even if dyspnoea is relieved, likely for a long period after discharge and possibly forever.

The present study has a few limitations. The study analysed two European cohorts; therefore, the results may not be applicable in other continents. Furthermore, because the LEDA protocol was designed to collect the clinical data at admission, data on patients' status and biology at discharge or during follow-up were not recorded. In addition, due to observational nature of the cohorts, there are some missing data. It has been noted that in a significant proportion of AHF patients, the main complaint may not be acute dyspnoea but a predominant peripheral congestion, which also has a poor prognosis,[32] so these patients might not have been included in our study. Also, a larger proportion of AHF patients did not receive diuretic on admission and/or discharge in LEDA

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cohort compared with specialized heart failure registry data (a difference of more than 10%).[33] The patients were undertreated in terms of neurohormonal blockers on admission and/or discharge as well. This might reflect that a wide spectrum of cardiologists and internists treated patients in our study and there could have been different congestion evaluation and treatment strategies between them and dedicated heart failure specialists who participate in registries. Our study also emphasizes the need of the adjudication committee because differences in the diagnosis between adjudication committee and treating physician could also explain this discrepancy. Nonetheless, our study results demonstrate that regardless if there were some discrepancies in initial diagnoses, the result remained similar independently from adjudicated cause of acute dyspnoea, cause of readmission, and throughout all analysed subgroups, and it applies to any acute dyspnoea patient.

In summary, our study demonstrated the long-lasting detrimental association between readmission and death in AHF and non-AHF patients admitted to the ED with acute breathlessness. Although breathlessness is usually relieved at discharge, patients should be considered 'vulnerable patients' that require personalized follow-up, including the rapid implementation of guideline-recommended therapies in AHF patients.

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Conflict of interest

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf. K.Č., A.M., V.J., E. P., I.M., D.K., L.B., M.B., D.V., I.J., J.M., K.S., Audrys K., Š.D., A.L., Aušra K., and J.Č. declare that they received financial support from Research Council of Lithuania for the submitted work. A.M. received speaker's honoraria from Orion, Otsuka, Philips, Roche, and Servier. A.M. received fee as a member of advisory board and/or steering committee and/or research grant from Adrenomed, Epygon, Neurotronik, Roche, Sanofi, and Sphyngotec. A.M. owns shares in S-Form Pharma. M.M. reports grants from NIH/NHLBI, Department of Defence, NIH/FDA, Bayer Pharmaceuticals, and GlaxoSmithKline and personal fees from CS Berhling, Boerhinger Ingelheim, Cerus Therapeutics, Roche Genentec, Quark Pharmaceuticals, and Thesan Pharamceuticals, outside the submitted work. E.G. received research grants from Sphingotec, Deltex Medical, and Retia Medical and consultancy fees from Magnisense, Roche Diagnostics, and Adrenomed. C.M. has received research support from the Swiss National Science Foundation, the Swiss Heart Foundation, the Kommission für Technologie und Innovation, the Stiftung für kardiovaskuläre Forschung Basel, Abbott, Alere, Amgen, AstraZeneca, Beckman Coulter, Biomerieux, Brahms, Roche, Siemens, Singulex, Sphingotec, the University of Basel, and the University Hospital Basel, as well as speaker honoraria/consulting honoraria from Abbott, Alere, AstraZeneca, Biomerieux, Boehringer Ingelheim, BMS, Brahms, Cardiorentis, Novartis, Roche, Siemens, Sanofi, and Singulex. Aušra K. received speaker honoraria from Servier, Bayer, Berlin-Chemie Menarini, Pfizer, and KRKA. Audrys K. received fee as member of Steering Committee Cardiorentis, Novartis, and Servier. J.Č. received investigator and speaker fees from Sanofi, Amgen, Novartis, Roche Diagnostics, Servier, and AstraZeneca. Other authors declared no conflicts of interest.

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data collection, analysis and interpretation, writing the paper, and the decision to submit the paper for publication.

Supporting information

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

Table S1. Baseline characteristics of the derivation LEDA cohort.
Table S2. Early treatment in the emergency department, treatment at discharge and outcomes of the LEDA derivation cohort.
Table S3. Sensitivity analysis of the derivation LEDA cohort.
Table S4. Baseline characteristics and outcomes of the validation BASEL V cohort.
Table S5. Sensitivity analysis of the validation BASEL V cohort.
Figure S1. Patient flowchart of the derivation LEDA cohort.
Figure S2. Secondary endpoints: relationship between all-cause readmission and one-year all-cause mortality in the derivation LEDA and validation BASEL V cohorts.
Figure S3. Patient flowchart of the validation BASEL V cohort.

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Publication II

Sex-specific analysis of the rapid up-titration of guideline-directed medical therapies after a hospitalization for acute heart failure: Insights from the STRONG-HF trial.

Čerlinskaitė-Bajorė K, Lam CSP, Sliwa K, Adamo M, Ter Maaten JM, Léopold V, Mebazaa A, Davison B, Edwards C, Arrigo M, Barros M, Biegus J, Chioncel O, Cohen-Solal A, Damasceno A, Diaz R, Filippatos G, Gayat E, Kimmoun A, Metra M, Novosadova M, Pagnesi M, Pang PS, Ponikowski P, Saidu H, Takagi K, Tomasoni D, Voors AA, Cotter G, Čelutkienė J.

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RESEARCH ARTICLE

Sex-specific analysis of the rapid up-titration of guideline-directed medical therapies after a hospitalization for acute heart failure: Insights from the STRONG-HF trial

Kamilė Čerlinskaitė-Bajorė[1], Carolyn S.P. Lam[2], Karen Sliwa[3], Marianna Adamo[4], Jozine M. Ter Maaten[5], Valentine Léopold[6,7], Alexandre Mebazaa[6,7], Beth Davison[6,8], Christopher Edwards[9], Mattia Arrigo[10], Marianela Barros[9], Jan Biegus[11], Ovidiu Chioncel[12], Alain Cohen-Solal[6,13], Albertino Damasceno[14], Rafael Diaz[15], Gerasimos Filippatos[16], Etienne Gayat[6,7], Antoine Kimmoun[17], Marco Metra[4], Maria Novosadova[8], Matteo Pagnesi[4], Peter S. Pang[18], Piotr Ponikowski[11], Hadiza Saidu[19], Koji Takagi[9], Daniela Tomasoni[4], Adriaan A. Voors[5], Gad Cotter[6,8], and Jelena Čelutkienė[1]*

[1]Clinic of Cardiac and Vascular Diseases, Institute of Clinical Medicine, Faculty of Medicine, Vilnius University, Vilnius, Lithuania; [2]National Heart Centre Singapore and Duke-National, University of Singapore, Singapore; [3]Cape Heart Institute, Division of Cardiology, Department of Medicine, Groote Schuur Hospital and University of Cape Town, Cape Town, South Africa; [4]Cardiology, Cardiology, ASST Spedali Civili and Department of Medical and Surgical Specialties, Radiological Sciences, and Public Health, University of Brescia, Brescia, Italy; [5]Department of Cardiology, Medical Centre Groningen, Groningen, Netherlands; [6]Université Paris Cité, INSERM UMR-S 942 (MASCOT), Paris, France; [7]Department of Anesthesiology and Critical Care and Burn Unit, Saint-Louis and Lariboisière Hospitals, FHU PROMICE, DMU Parabol, APHP Nord, Paris, France; [8]Heart Initiative, Durham, NC, USA; [9]Momentum Research, Inc., Durham, NC, USA; [10]Department of Internal Medicine, Stadtspital Zurich, Zurich, Switzerland; [11]Institute of Heart Diseases, Wroclaw Medical University, Wrocław, Poland; [12]Emergency Institute for Cardiovascular Diseases 'Prof. C.C. Iliescu', University of Medicine "Carol Davila", Bucharest, Romania; [13]Department of Cardiology, APHP Nord, Lariboisière University Hospital, Paris, France; [14]Faculty of Medicine, Eduardo Mondlane University, Maputo, Mozambique; [15]Estudios Clínicos Latinoamérica, Instituto Cardiovascular de Rosario, Rosario, Argentina; [16]National and Kapodistrian University of Athens, School of Medicine, Attikon University Hospital, Athens, Greece; [17]Université de Lorraine, Nancy ; INSERM, Défaillance Circulatoire Aigue et Chronique, Service de Médecine Intensive et Réanimation Brabois, CHRU de Nancy, Vandœuvre-lès-Nancy, France; [18]Department of Emergency Medicine, Department of Medicine, Indiana University School of Medicine, Indianapolis, IN, USA; and [19]Murtala Muhammed Specialist Hospital, Bayero University Kano, Kano, Nigeria

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Aims The aim of this study was to evaluate efficacy and safety of rapid up-titration of guideline-directed medical therapies (GDMT) in men and women hospitalized for acute heart failure (AHF).

Methods and results In STRONG-HF, AHF patients were randomized just prior to discharge to either usual care (UC) or a high-intensity care (HIC) strategy of GDMT up-titration. In these analyses, we compared the implementation, efficacy, and safety of the HIC strategy between men and women. In the randomized AHF population, 416/1078 (39%) were women. By day 90, a higher proportion of both sexes in the HIC group had been up-titrated to full doses of GDMT compared to UC. Overall, there were no differences in the primary endpoint between the sexes. The primary endpoint, 180-day heart failure readmission or death, occurred in 15.8% HIC women versus 23.5% women in the UC group (adjusted hazard ratio [HR] 0.67, 95% confidence interval [CI] 0.40–1.13) and in 14.9% HIC men versus 23.5% UC men

*Corresponding author. Clinic of Cardiac and Vascular Diseases, Institute of Clinical Medicine, Faculty of Medicine, Vilnius University, Santariškių g. 2, 08661 Vilnius, Lithuania. Tel: +370 616 00180, Email: jelena.celutkiene@santa.lt

(adjusted HR 0.57, 95% CI 0.38–0.88) (adjusted interaction $p = 0.65$). There was no significant treatment-by-sex interaction in quality-of-life improvement or in adverse events, including serious or fatal adverse events.

Conclusion The results of the current analyses suggest that a rapid up-titration of GDMT immediately after an AHF hospitalization can and should be implemented similarly in men and women, as it results in reduction of 180-day all-cause death or heart failure readmission, quality-of-life improvement in both men and women with a similar safety profile.

Keywords Acute heart failure • Medical therapy • Up-titration • Vulnerable phase • Readmission • High-intensity care

Introduction

The association of biological sex with multiple aspects of heart failure (HF) risk factors, phenotype and response to treatment has been the subject of many studies.[1] There are important differences between chronic and acute HF (AHF) with regard to sex-specific aspects. While long-term outcomes have been reported to be better in women than men with chronic HF,[2–4] in AHF outcomes have been reported to be similar in men and women.[5–7]

Although some treatment response differences to guideline-directed medical therapies (GDMT) have been noted in men and women with chronic HF with preserved ejection fraction (HFpEF),[8,9] no sex-related differences in treatment effect have been found in chronic HF with reduced ejection fraction (HFrEF) patients[10–13] and, more recently, pooled analyses of sodium–glucose cotransporter 2 (SGLT2) inhibitors found no sex-related treatment effect attenuation across the left ventricular ejection fraction (LVEF) spectrum in patients with chronic HF.[14,15] Data of the interaction between treatment effects and sex in AHF are lacking. Discrepancy in GDMT use between men and women with HF has been reported,[16] however there is a lack of sex-specific analyses of treatment response to GDMT in patients hospitalized with AHF.

The Safety, Tolerability and Efficacy of Rapid Optimization, Helped by NT-proBNP Testing, of Heart Failure Therapies (STRONG-HF) study was a multinational, open-label, randomized, prospective clinical trial, designed to assess the safety and efficacy of rapid up-titration of treatments before discharge from an AHF admission and during the following weeks compared with usual care (UC). Pre-specified analyses of STRONG-HF showed no difference between the sexes regarding the high-intensity care (HIC) effect on the primary endpoint of 180-day readmission for HF or all-cause death. To address the knowledge gap of sex-specific treatment response among AHF patients, we further compared the implementation, efficacy, and safety of the HIC strategy between men and women hospitalized for AHF.

Methods

The study design, randomization process and procedures of STRONG-HF have been previously described in detail.[17–19] Briefly, STRONG-HF was a multinational, multicentre, open-label, randomized, parallel-group study designed to assess the safety and efficacy of up-titration of guideline-recommended HF medical therapy on morbidity and mortality when initiated during and up-titrated early after hospitalization for AHF. Patients aged 18–85 years admitted to hospital within 72 h of screening and not treated with optimal doses of oral HF therapies were included. Exclusion criterion was clear intolerance to high doses of GDMT. Patients across the LVEF spectrum were included. Included patients were randomized within 2 days prior to anticipated discharge in a 1:1 fashion to either HIC or UC group. Randomization was stratified by LVEF and country. Due to the nature of the study, treatment allocation could not be blinded. Patients assigned to HIC were up-titrated at randomization to half optimal doses, and at 2 weeks to full doses, of medications in three classes: renin–angiotensin system inhibitor (RASI, including angiotensin-converting enzyme inhibitor [ACEI], angiotensin receptor blocker [ARB], or angiotensin receptor–neprilysin inhibitor [ARNI]), beta-blocker, and mineralocorticoid receptor antagonist (MRA). HIC patients had scheduled outpatient visits at 1, 2, 3, and 6 weeks post-discharge. Both HIC and UC patients were seen at day 90 and contacted by telephone at day 180 for an assessment of vital status and occurrence of any rehospitalization, and current prescriptions of oral HFmedications. The primary cause of death and primary reason for readmission were defined by investigator report and were not adjudicated.

Protocol amendments have also been detailed elsewhere[17,19]; first, a patient contact was added at 180 days for safety and, second, the primary endpoint was changed from 90- to 180- day HF readmission or death and target enrolment increased from 900 to 1800 to increase study power. The study was approved by appropriate competent authorities and ethics committees prior to enrolment. All patients provided written informed consent. An independent data and safety monitoring board was responsible for the safety of trial participants. This study is registered at ClinicalTrials.gov, NCT03412201.

Outcomes

The primary endpoint of the trial was 180-day HF readmission or all-cause death. Secondary endpoints were change in quality of life from baseline to day 90 as measured by the EQ-5D visual analogue scale (VAS),[20] 180-day all-cause death, and 90-day HF readmission or all-cause death. Safety was evaluated by the incidence of treatment-emergent adverse events, and changes in vital signs (systolic and diastolic blood pressure, heart rate, and body weight) and local laboratory results up to 90 days.

Statistical analysis

All analyses included all patients validly randomized to the treatment group assigned at randomization. Continuous variables are presented

as mean (standard deviation) or as adjusted mean (standard error), as appropriate, and categorical variables as absolute and relative frequencies. N-terminal pro-B-type natriuretic peptide (NT-proBNP) values were log-transformed for analysis. Patients were classified by their reported sex at birth as either man or woman and compared with respect to continuous variables using ANOVA models, binary variables using chi-square tests, and ordered categorical variables using Cochran–Mantel–Haenszel chi-square tests.

To explore the time course of up-titration of oral HF medications, the percentage dose of each medication in each of three classes (RASI, beta-blocker, and MRA) relative to the drug optimal dose (see online supplementary *Table S3* in the original publication[19]) was calculated and then averaged across the three medication classes. The difference in average diuretic dose between sex at birth for those subjects in the HIC group was compared using a mixed method repeated measures model including terms for visit, sex, and visit by sex interaction.

As previously described,[14] because the primary endpoint was changed from 90- to 180-day HF readmission or death, analyses of 180-day outcomes down-weight, proportional to half its sample size, results of the initial cohort randomized before the change and include only patients enrolled at sites where the protocol change was approved. Subgroup analyses comparing treatment effects on primary and secondary efficacy endpoints by sex at birth were pre-specified. Sexes were compared with respect to clinical outcomes using Cox proportional hazards regression, and with respect to EQ-VAS change using ANCOVA (including adjustment for baseline EQ-VAS, geographic region, and baseline LVEF ≤40%/>40%). Covariates for further adjustment were selected from variables shown to be prognostic of each outcome in previous studies[5,6] using backwards selection in the UC group. Potential modification of the treatment effect by sex was examined by inclusion of a treatment-by-sex interaction term in the models. Results for the EQ-VAS are based on observed data, excluding data where no linguistically validated translation was available. To explore the impact of COVID-19 on all-cause mortality, we conducted sensitivity analyses where deaths due to COVID-19 were censored rather than counted as an event.

Treatment effects on changes in vital signs and in local laboratory values from baseline to day 90 were compared between sexes using ANCOVA models adjusted for baseline value.

Two-sided *p*-values of <0.05 were considered to be statistically significant. We did all analyses using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Of a total of 1078 randomized AHF patients, 416 (39%) were women. The baseline characteristics of all patients and comparisons between sexes are presented in *Table 1*. There were significantly more non-white and non-European women, compared to men. Men were more likely to have HF of ischaemic origin and more frequently had a history of acute coronary syndrome, prior coronary artery bypass surgery and percutaneous coronary intervention, compared to women. Men were also more likely than women to have a history of atrial fibrillation, to be in New York Heart Association (NYHA) class IV and to have a lower LVEF. Women were more likely than men to have a history of HF and malignancies, and to have worse baseline EQ-VAS score. There were no differences in rate of implanted devices. Compared to men, women had higher mean systolic blood pressure and heart rate, lower creatinine and liver enzyme levels, higher total cholesterol and lower potassium and sodium concentrations at screening. NT-proBNP did not differ significantly between the sexes. Other baseline signs and symptoms and laboratory findings are presented in online supplementary *Table S1*.

Medication up-titration by sex

Prior to admission, women were prescribed MRA at full optimal dose significantly more frequently than men and were chronically treated with higher loop diuretic doses (*Table 1* and online supplementary *Table S2*). Almost no men and women were prescribed full optimal doses of RASI (one woman and two men) and beta-blockers (no women and two men) prior to admission. At screening during admission, men were treated with higher loop diuretic doses. At week 2 there were no differences between the number of fully up-titrated patients ($p = 0.074$, 0.51, and 0.54 for RASI, beta-blockers and MRA, respectively) or loop diuretic doses ($p = 0.50$) between women and men in the HIC group. By day 90, most patients of both sexes in the HIC group had been up-titrated to full doses of each of the three oral HF medication classes compared to only a small number in the UC group (RASI 56.6% vs. 1.6% in women, 54.0% vs. 2.5% in men, interaction $p = 0.65$; beta-blockers 45.4% vs. 2.2% in women, 51.8% vs. 5.1% in men, interaction $p = 0.43$; MRA 83.2% vs. 44.8% in women, 84.1% vs. 47.5% in men, interaction $p = 0.73$). Dose of loop diuretics was lower in both women and men of the HIC group (total furosemide equivalence dose 54 mg furosemide equivalents in the HIC group vs. 62 mg in the UC group in women; 52 mg furosemide equivalents in the HIC group vs. 58 mg in the UC group in men, interaction $p = 0.75$). The average percentage of the optimal dose across the three GDMT classes by sex in the HIC group throughout the study visits is shown in *Figure 1*. Of note, throughout most time points men patients received less diuretics than women (online supplementary *Table S2*). However, the average difference was not significant (−3.65 [−10.95 to 3.65], $p = 0.33$).

Outcomes by sex

Day 180 results were included for 394 (95%) women and 614 (93%) men. Overall, the outcomes did not differ between the sexes, regardless of the treatment strategy (online supplementary *Table S3*). The primary endpoint (HF readmission or all-cause death at day 180) occurred in 73 (19.6% down-weighted adjusted Kaplan–Meier estimate) women and in 110 (19.2%) men (adjusted hazard ratio [HR] 0.87, 95% confidence interval [CI] 0.62–1.21; $p = 0.41$, *Figure 2*). HF readmission by day 180 occurred in 45 (12.8%) women and in 76 (13.6%) men (adjusted HR 1.06 [95% CI 0.69–1.64], $p = 0.77$). All-cause death at day 180 occurred in 37 (9.5%) women and in 50 (9.0%) men (adjusted HR 0.99 [95% CI 0.61–1.62], $p = 0.97$) (online supplementary *Figure S1*). All-cause death or HF readmission excluding COVID-related deaths occurred in 69 (18.5%) women and 108 (18.8%) men (adjusted HR 1.01 [95% CI 0.72–1.42], $p = 0.97$). All-cause death by day 180 excluding COVID-related deaths occurred in 33 (8.3%) women and 47 (8.6%) men (adjusted HR 1.11 [95% CI 0.66–1.87], $p = 0.69$).

Table 1 Demographic and clinical characteristics of the study population by sex at birth

Parameter	Women ($n = 416$)	Men ($n = 662$)	p-value
Age, years	62.4 (16.73)	63.3 (11.16)	0.2767
Self-reported race			<0.0001
Black	148 (35.6%)	82 (12.4%)	
Caucasian	263 (63.2%)	569 (86.2%)	
Native American	1 (0.2%)	0	
Other[a]	3 (0.7%)	9 (1.4%)	
Pacific Islander	1 (0.2%)	0	
Geographical region			<0.0001
Europe	252 (60.6%)	545 (82.3%)	
Non-Europe	164 (39.4%)	117 (17.7%)	
NT-proBNP at screening, ng/L[b]	5936.7 (5636.2–6253.3)	6065.5 (5797.1–6346.2)	0.5494
NT-proBNP at baseline, ng/L[b]	3153.2 (2977.7–3339.0)	3242.9 (3084.1–3410.0)	0.4796
History of AF/flutter or present at screening	158 (38.0%)	325 (49.1%)	0.0004
Baseline EQ-VAS	55.9 (13.57)	60.7 (15.52)	<0.0001
Medical history			
Stroke or transient ischaemic attack	42 (10.1%)	57 (8.6%)	0.4011
Severe liver disease	2 (0.6%)	4 (0.7%)	0.8023
Psychiatric or neurological disorder	9 (2.2%)	11 (1.7%)	0.5495
Malignancies	17 (4.1%)	12 (1.8%)	0.0248
Diabetes	121 (29.1%)	192 (29.2%)	0.9740
Diabetes control method			
Insulin	30 (7.2%)	52 (7.9%)	0.6778
Diet only	79 (19.0%)	123 (18.7%)	0.9033
Oral antidiabetic agents	93 (22.4%)	141 (21.4%)	0.7103
Pulmonary embolism	4 (1.0%)	15 (2.3%)	0.1124
Acute coronary syndrome	99 (23.8%)	212 (32.1%)	0.0035
Coronary artery bypass surgery	12 (2.9%)	47 (7.1%)	0.0031
Percutaneous coronary intervention	36 (8.7%)	116 (17.5%)	<0.0001
Angina CCS class ≥2	53 (12.8%)	72 (10.9%)	0.3419
Moderate or severe COPD or asthma	8 (1.9%)	19 (2.9%)	0.3309
Sustained ventricular arrhythmia (with syncopal episodes in past 3 months)	0	1 (0.2%)	0.4274
Cardiac resynchronization therapy	2 (0.5%)	4 (0.6%)	0.7895
Automatic internal cardiac defibrillator	2 (0.5%)	7 (1.1%)	0.3101
HF history			
History of HF	365 (87.7%)	551 (83.4%)	0.0496
NYHA class 1 month before hospital admission			0.0173
I	24 (6.1%)	39 (6.4%)	
II	138 (34.9%)	169 (27.9%)	
III	166 (42.0%)	249 (41.2%)	
IV	67 (17.0%)	148 (24.5%)	
Ischaemic aetiology	158 (38.1%)	356 (53.9%)	<0.0001
LVEF, %[c]	39.1 (13.40)	34.6 (11.63)	<0.0001
LVEF category			<0.0001
≤40%	250 (60.1%)	481 (72.7%)	
>40%	166 (39.9%)	181 (27.3%)	
Hospitalized for HF in the past year?	110 (26.4%)	163 (24.7%)	0.5126
No. of HF hospitalizations in the past year	0.4 (1.60)	0.3 (0.65)	0.2592
History of AF/flutter	167 (40.1%)	329 (49.8%)	0.0020
Type of AF/flutter			0.4997
Paroxysmal	43 (26.5%)	74 (22.6%)	
Permanent	91 (56.2%)	202 (61.6%)	
Persistent	28 (17.3%)	52 (15.9%)	

Table 1 (Continued)

Parameter	Women ($n = 416$)	Men ($n = 662$)	p-value
Oral HF medications taken at visit 2, pre-randomization			
ACEI/ARB/ARNI	274 (66.0%)	415 (63.0%)	0.3102
Beta-blockers	135 (32.5%)	248 (37.6%)	0.0891
MRA	395 (95.2%)	623 (94.5%)	0.6441
Loop diuretic	394 (94.9%)	635 (96.4%)	0.2586

Data are expressed as mean (standard deviation), *n* (%), or geometric mean (95% CI).
ACE, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; CCS, Canadian Cardiovascular Society; COPD, chronic obstructive pulmonary disease; EQ-VAS, EQ-5D visual analogue scale; HF, heart failure; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.
[a]Other reported races were African ($n = 2$), Europiod ($n = 2$), Latin American ($n = 1$), Berber ($n = 1$), Gipsy ($n = 1$), and not specified ($n = 5$).
[b]Values reported as >9000 ng/L were set to 9000 ng/L.
[c]Most recent value within 6 months before screening, including during the index hospitalization. Values <10% were set to 10% for analysis.

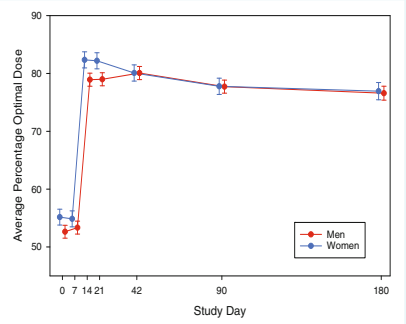

Figure 1 Average optimal dose of three oral guideline-directed medical therapies (renin–angiotensin system inhibitors, beta-blockers, mineralocorticoid receptor antagonists) by visit and sex in the high-intensity care group.

EQ-VAS change from baseline to day 90 was 9.43 (0.70) points in women and 8.40 (0.58) points in men (adjusted least square [LS] mean difference −1.35 [95% CI −3.25 to 0.55], $p = 0.1649$). These data are presented in online supplementary *Table S3*.

Effect of high-intensity care strategy by sex

The HIC strategy reduced the incidence of the primary endpoint in both women (30 [15.8%] in the HIC group vs. 43 [23.5%] in the UC group; adjusted HR 0.67 [95% CI 0.40–1.13]) and men (44 [14.9%] in the HIC group vs. 66 [23.5%] in the UC group; adjusted HR 0.57 [95% CI 0.38–0.88]) (*Table 2*). Sex was not a modifier of the treatment strategy effect (adjusted interaction $p = 0.65$). Kaplan–Meier curves with down-weighting of cohort 1 for the primary endpoint are shown in *Figure 3*. Additionally, we found no treatment attenuation by LVEF in both men and women when analysing the primary endpoint (online supplementary *Table S4*).

Furthermore, there was no significant effect modification by sex when analysing mortality separately: all-cause death by day 180 occurred in 17 (9.2%) women in the HIC group and in 20 (9.8%) women in the UC group (adjusted HR 0.97 [95% CI 0.46–2.06]); and in 22 (8.2%) men in the HIC group and in 28 (10.3%) men in the UC group (adjusted HR 0.69 [95% CI 0.38–1.25]) (adjusted interaction $p = 0.48$) (for Kaplan–Meier curves, see online supplementary *Figure S2*). The primary endpoint after excluding COVID-related deaths, occurred in 26 (13.6%) women in the HIC group and 43 (23.5%) women in the UC group (adjusted HR 0.56 [95% CI 0.32–0.97]); and in 43 (14.5%) men in the HIC group and in 65 (23.1%) men in the UC group (adjusted HR 0.57 [95% CI 0.37–0.87]); with no treatment modification by sex (interaction $p = 0.96$). After excluding COVID-related deaths, all-cause death by day 180 occurred in 13 (6.8%) women in the HIC group and in 20 (9.8%) women in the UC group (adjusted HR 0.69 [95% CI 0.30–1.57]); and in 20 (7.1%) men in the HIC group and in 27 (9.9%) men in the UC group (adjusted HR 0.64 [95% CI 0.34–1.20]) with no treatment modification by sex (interaction $p = 0.89$). There was no treatment-by-sex interaction when analysing HF readmission by day 180 (adjusted interaction $p = 0.90$; *Table 2*).

EQ-VAS was completed in 341/416 (82%) of women and 574/662 (87%) of men at baseline and day 90. Among women who completed the EQ-VAS at baseline and at day 90, there was a 11.50-point improvement in the HIC group versus 5.98 in the UC group (adjusted LS mean difference 5.48 [95% CI 2.71–8.25]). In men, there was a 10.28-point improvement in the HIC group versus 7.98 in the UC group (adjusted LS mean difference 2.68 [95% CI 0.54–4.81]). Again, sex was not found to modify the effect of the treatment strategy on quality of life (*Table 2*, *Figure 4*).

Safety of the treatment strategy

The incidence of treatment-emergent adverse events in men and women is summarized in online supplementary *Tables S5* and *S6*. Select adverse events and serious adverse events are reported in *Table 3*. Adverse events were reported through day 90 in 93 (43.1%) women in the HIC group versus 58 (29.0%) in the UC

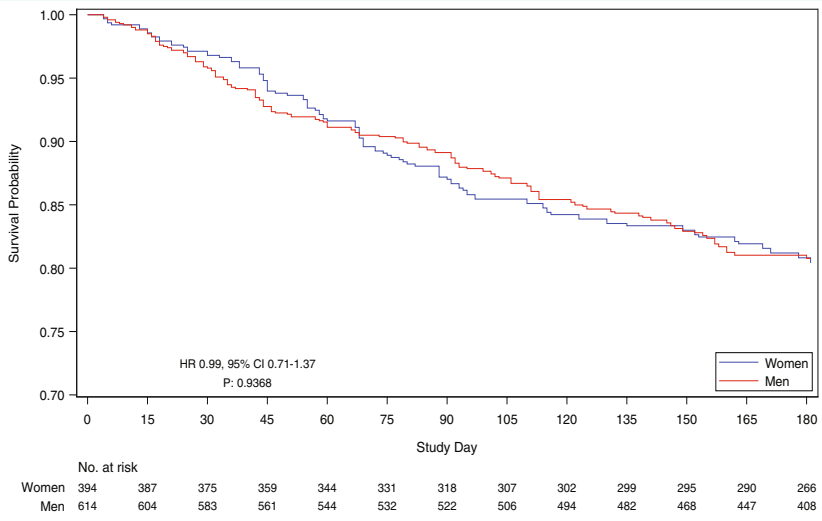

Figure 2 Unadjusted Kaplan–Meier curves for all-cause death or heart failure readmission through day 180 by sex at birth. Results in the initial cohort have been down-weighted. CI, confidence interval; HR, hazard ratio.

group. In men, 130 (39.9%) in the HIC group reported any adverse event versus 100 (29.8%) in the UC group (interaction $p = 0.52$). The most common adverse events were cardiac failure (36 [16.7%] women in the HIC group vs. 31 [15.5%] women in the UC group; 43 [13.2%] men in the HIC group vs. 42 [12.5%] men in the UC group); hypotension (9 [4.2%] vs. 1 [0.5%] in women; 18 [5.5%] vs. 1 [0.3%] in men); hyperkalaemia (3 [1.4%] vs. 0 in women; 15 [4.6%] vs. 0 in men), and renal impairment (6 [2.8%] vs. 0 in women; 8 [2.5%] vs. 1 [0.3%] in men). Any serious adverse event was reported in 37 (17.1%) HIC women versus 34 (17.0%) UC women; and in 51 (15.6%) HIC men versus 58 (17.3%) UC men (interaction $p = 0.70$). Serious adverse events included cardiac failure (14 [6.5%] vs. 21 [10.5%] in women; 24 [7.4%] vs. 26 [7.7%] in men), sudden death (3 [1.4%] vs. 5 [2.5%] in women; 2 [0.6%] vs. 5 [1.5%] in men) and viral pneumonia (4 [1.9%] vs. 0 in women; 3 [0.9%] vs. 3 [0.9%] in men). There was no significant increase of adverse event risk in either of the sexes or a significant treatment-by-sex interaction (all $p > 0.05$).

NT-proBNP decreased more in the HIC group compared to UC, similarly between the sexes (ratio of geometric mean ratios 0.73 [95% CI 0.58–0.91] in women, 0.80 [95% CI 0.67–0.96] in men, interaction $p = 0.49$). Systolic blood pressure and heart rate also decreased similarly in both sexes in the HIC group. Body weight decrease was more pronounced in women in the HIC group, although sex was not found to be a modifier of the treatment effect (interaction $p = 0.17$). Overall, there was no signal of treatment-by-sex interaction, regarding the change in vital signs from baseline to day 90 (online supplementary *Table S7*).

Discussion

In this analysis of STRONG-HF, both women and men with AHF derived benefits from a rapid up-titration of GDMT implemented immediately after an AHF hospitalization. All-cause 180-day death or HF readmission risk was reduced in both men and women in the HIC group with no significant treatment-by-sex interaction. The same was true for quality-of-life improvement. The safety of the high-intensity strategy after an AHF admission was similar in men and women. There was no evidence of relevant treatment-by-sex interaction in any outcomes or safety events.

Certain baseline sex differences of this analysis were consistent with previous HF epidemiological studies or clinical trials.[7,8,21,22] Women were more likely to have preserved LVEF, while men were more likely to have ischaemic HF aetiology, prior acute coronary syndrome, coronary artery bypass grafting or percutaneous coronary intervention, atrial fibrillation, and higher NYHA class. However, age did not differ between women and men with AHF, and baseline NT-proBNP was also similar in both sexes. Notably, the STRONG-HF population was more diverse, including more non-white and non-European female AHF patients, which could explain at least some of the deviations from prior studies, since a comparable epidemiological profile was reported in the sub-Saharan Africa Survey of Heart Failure (THESUS-HF).[6]

Underutilization of GDMT prior to admission was similar in men and women in STRONG-HF. However, there were more women on full optimal dose of MRAs – whether this is related to the higher proportion of women with HFpEF in whom secondary TOPCAT

Table 2 Primary and secondary endpoints by sex at birth and treatment group

Endpoint	Women ($n = 416$)				Men ($n = 662$)				*p*-value (treatment-by-sex interaction)	
	High intensity care	Usual care	Unadjusted treatment effect	Adjusted treatment effect	High intensity care	Usual care	Unadjusted treatment effect	Adjusted treatment effect	Unadjusted	Adjusted
Day 90 analyses	216	200			326	336				
Day 180 analyses	203	191			303	311				
All-cause death or HF readmission by day 180[a]	30 (15.8%)	43 (23.5%)	0.67 (0.40–1.13)	0.67 (0.40–1.13)	44 (14.9%)	66 (23.5%)	0.59 (0.40–1.13)	0.57 (0.38–0.88)	0.7055	0.6474
All-cause death by day 180[b]	17 (9.2%)	20 (9.8%)	0.96 (0.49–2.02)	0.97 (0.46–2.06)	22 (8.2%)	28 (10.3%)	0.76 (0.42–1.37)	0.69 (0.38–1.25)	0.6227	0.4794
HF readmission by day 180[c]	18 (9.2%)	27 (16.5%)	0.54 (0.27–1.07)	0.52 (0.27–1.04)	29 (9.6%)	47 (17.7%)	0.51 (0.31–0.86)	0.50 (0.30–0.84)	0.9069	0.8952
All-cause death or HF readmission by day 180 (excluding COVID-related deaths)[a]	26 (13.6%)	43 (23.5%)	0.56 (0.32–0.97)	0.56 (0.32–0.97)	43 (14.5%)	65 (23.1%)	0.58 (0.38–0.89)	0.57 (0.37–0.87)	0.9093	0.9626
All-cause death (excluding COVID-related deaths) by day 180[b]	13 (6.8%)	20 (9.8%)	0.69 (0.30–1.54)	0.69 (0.30–1.57)	20 (7.1%)	27 (9.9%)	0.70 (0.38–1.31)	0.64 (0.34–1.20)	0.9594	0.8855
EQ-VAS change from baseline to visit 7[d]	11.50 (1.17)	5.98 (1.05)	5.52 (2.66–8.39)	5.48 (2.71–8.25)	10.28 (1.05)	7.98 (1.05)	2.30 (0.09–4.50)	2.68 (0.54–4.81)	0.0804	0.1167

Data presented as *n* (%) or least squares mean (standard error). Unadjusted treatment effects are the least squares mean difference between treatment groups (for change in EQ-5D) and hazard ratio (95% confidence interval) for the other endpoints. Results for patients in cohort 1 were down-weighted for day 180 analyses.

EQ-VAS, EQ-5D visual analogue scale; HF heart failure; LS, least square; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

[a]Adjusted for baseline diastolic blood pressure, ischaemic heart disease, oedema severity, and NT-proBNP.

[b]Adjusted for baseline creatinine, haemoglobin, urea, and NT-proBNP.

[c]Adjusted for body mass index, baseline diastolic blood pressure, baseline cholesterol, baseline potassium, baseline NT-proBNP, baseline LVEF (≤40%/>40%), and oedema.

[d]LS mean change and LS mean difference from an ANCOVA model with baseline EQ-VAS, treatment, baseline LVEF (≤40%/>40%), region and sex at birth. Subjects from Mozambique were excluded from these analyses because of the unavailability of a linguistically validated translation of the EQ-VAS in that country (i.e. analysis includes $n = 461$ [284 men and 177 women] from the high-intensity care group and $n = 454$ [290 men and 164 women] the from the usual care group). Additional adjustment for age, haemoglobin, creatinine, cholesterol, NT-proBNP, hospitalization for HF in the previous year, oedema severity, and NYHA class.

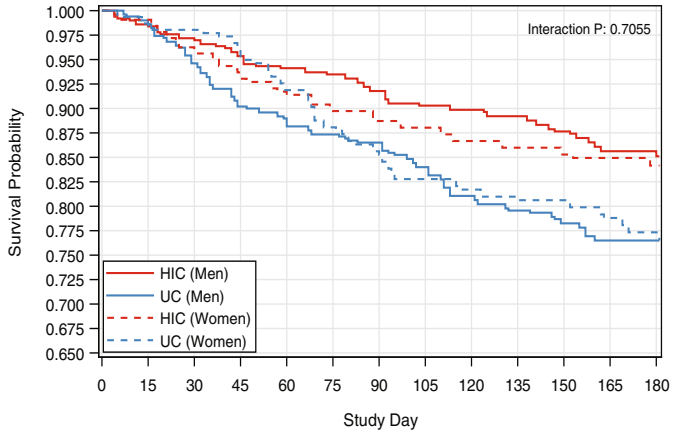

Figure 3 Unadjusted Kaplan–Meier curves for all-cause death or heart failure readmission through day 180 by sex at birth and treatment arm. Results in the initial cohort have been down-weighted. CI, confidence interval; HIC, high-intensity care; HR, hazard ratio; UC, usual care.

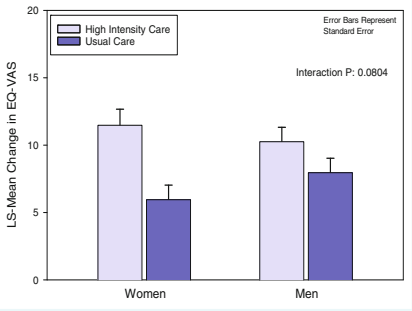

Figure 4 Change in EQ-5D visual analogue scale (EQ-VAS) from baseline to day 90 by sex at birth and treatment arm. Change at day 90 adjusted for baseline EQ-VAS, baseline LVEF (≤40%/>40%) and region. LS, least square.

analysis suggest significant benefit of MRA is unclear.[10] Interestingly, despite having a lower NYHA class, women on average received higher doses of loop diuretics at screening. This finding contradicts prior studies.[5]

Better outcomes in women have been reported in both epidemiological and clinical studies of chronic HF.[2–4,14,23] In an analysis of AHF registries, women had lower risk of 1-year mortality, even though they less often received optimal medical therapy at discharge.[16] However, there are several trials demonstrating that although women with chronic HF have better reported survival, this is not the case for AHF patients.[5–7] In a sex-specific analysis of the PROTECT trial,[5] risk-adjusted 180-day mortality was similar in men and women hospitalized for AHF. In a retrospective analysis of a multicentre registry of hospitalized AHF patients, 6-month all-cause and cardiovascular mortality rates were almost identical in men and women.[7] In the THESUS-HF, there were no differences in any of the analysed outcomes between the sexes.[6] Similarly, in our analysis the rates of 180-day HF readmission and/or all-cause death were similar between women and men with AHF, regardless of the treatment strategy.

Although significant benefit of ARNI and spironolactone has been reported in women and not men with stable HFpEF in secondary analyses,[8,9] there is substantial evidence from subgroup analyses of the pivotal randomized clinical trials indicating no sex-related treatment attenuation in HFrEF.[10–13,24,25] Sacubitril/valsartan reduced the primary outcome of death from cardiovascular causes or a first hospitalization for HF similarly in men and women in the Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial.[10] Spironolactone significantly reduced all-cause mortality in both men and women with HFrEF in the Randomized Aldactone Evaluation Study (RALES).[12] Similar results were seen with another drug of MRA class, eplerenone, which reduced hospitalization for HF or death from cardiovascular causes in both sexes in the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF).[25] Relative risk of all-cause mortality was equally reduced in women when treated with carvedilol.[13] In the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) study, carvedilol reduced combined risk of death or hospitalization for a cardiovascular reason or for HF in men and women with severe chronic HFrEF.[24] Furthermore, biological sex was not a treatment-effect modifier across the LVEF spectrum in pooled analyses of SGLT2 inhibitors.[14,15] While all these studies were

Table 3 Selected adverse events and serious adverse events by sex at birth and treatment

System organ class preferred term	Women		Men		Treatment-by-sex interaction p-value
	High intensity care (n = 216)	Usual care (n = 200)	High intensity care (n = 326)	Usual care (n = 336)	
Any adverse event	93 (43.1%)	58 (29.0%)	130 (39.9%)	100 (29.8%)	0.5267
Metabolism and nutrition disorders	6 (2.8%)	1 (0.5%)	19 (5.8%)	2 (0.6%)	0.6498
Hyperkalaemia	3 (1.4%)	0	15 (4.6%)	0	0.4368
Renal and urinary disorders	9 (4.2%)	0	11 (3.4%)	2 (0.6%)	0.9346
Renal impairment	6 (2.8%)	0	8 (2.5%)	1 (0.3%)	0.6719
Vascular disorders	13 (6.0%)	5 (2.5%)	22 (6.7%)	4 (1.2%)	0.2528
Hypotension	9 (4.2%)	1 (0.5%)	18 (5.5%)	1 (0.3%)	0.5805
Any serious adverse event	37 (17.1%)	34 (17.0%)	51 (15.6%)	58 (17.3%)	0.7047

Including events with onset date equal to or greater than date of randomization through 90 days post-randomization.

performed in patients with chronic HF, there is also evidence that treatment response does not differ between men and women hospitalized for AHF. In the Comparison of Sacubitril–Valsartan versus Enalapril on Effect on NT-proBNP in Patients Stabilized from an Acute Heart Failure Episode (PIONEER-HF) trial, ARNI reduced NT-proBNP similarly in men and women with HFrEF hospitalized for AHF.[11] Empagliflozin equally improved the primary composite outcome in men and women and found no significant treatment interaction between the sexes regardless of LVEF in the Study to Test the Effect of Empagliflozin in Patients Who Are in Hospital for Acute Heart Failure (EMPULSE).[26] In our study, rapid up-titration of GDMT after hospitalization for AHF resulted in risk reduction of 180-day all-cause death or HF readmission and improvement of quality of life in both men and women with no significant effect modification by sex. We also found no treatment attenuation related to LVEF in neither men nor women with AHF. Our findings support rapid up-titration of GDMT and HIC strategy after AHF hospitalization to improve outcomes in both sexes regardless of their LVEF.

It has recently been suggested in a post-hoc analysis of two observational HF studies that women might benefit from lower doses of ACEI or ARBs and beta-blockers than men, with maximal effects of treatment reached with 40–50% of beta-blocker and 60% of ACEI/ARB target doses.[8] However, no detrimental effects were reported with higher doses. In our cohort, the proportion of AHF patients up-titrated to full optimal doses of GDMT was very similar in men and women in the HIC arm. A higher incidence of adverse events (mostly hypotension, hyperkalaemia, and renal impairment) in the HIC group and a similar incidence of serious adverse events between the UC and HIC groups has been previously described.[19] In this sex-specific analysis, the safety profile was comparable between men and women, and we found no significant differences or treatment-by-sex interaction when analysing any, or serious adverse events.

Limitations

In addition to previously reported limitations,[19] only 39% of the included patients were women. Due to limited sample sizes, we could not properly address whether lower doses could have resulted in the same benefit in women with AHF. However, no excessive safety concerns were detected in women up-titrated to full optimal doses of GDMT.

Conclusions

An intensive treatment strategy implemented immediately after a hospitalization for AHF resulted in a reduction of 180-day all-cause death or HF readmission risk and quality-of-life improvement in both men and women. The safety of rapid up-titration of GDMT after an AHF admission was similar in men and women.

Supplementary Information

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

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S-form Pharma, FIRE-1, Implicity, 4TEEN4, and Adrenomed; and is coinventor of a patent on combination therapy for patients having acute or persistent dyspnoea. B.D., C.E., M.B., M.N., K.T., and G.C. are employees of Momentum Research, which has received grants for research from Abbott Laboratories, Amgen, Celyad, Cirius Therapeutics, Corteria Pharmaceuticals, Heart Initiative, Sanofi, Windtree Therapeutics, and XyloCor Therapeutics. B.D. and G.C. are directors of Heart Initiative, a non-profit organization. M.Ad. has received speaker fees from Abbott Vascular and Medtronic. O.C. received grants from Servier. A.C.S. has received honoraria for lectures or consultancy from AstraZeneca, Novartis, Vifor, Bayer, Merck, Sanofi, Abbott, and Boehringer Ingelheim. A.D. works for the Faculty of Medicine, Eduardo Mondlane University (Maputo, Mozambique), which received research grants from the Heart Initiative for their participation in this study. R.D. has received supporting fees for coordination of STRONG-HF trial activities. G.F. has received lecture fees or was a committee member for trials and registries sponsored by Bayer, Vifor, Boehringer Ingelheim, Medtronic, Servier and Amgen. M.P. has received personal fees from Abbott Laboratories, AstraZeneca, Boehringer Ingelheim and Vifor Pharma. P.S.P. has received grants or research contracts from American Heart Association, Roche, Siemens, Ortho Diagnostics, Abbott, Beckman Coulter, and Siemens; consulting fees from Roche; honoraria from WebMD; and he has financial interest in The Heart Course. K.S. has received grants from Medtronic, Servier, and Amylam and honoraria from MSD, Novartis, and Sanofi. A.A.V. has received consultancy fees or research support from AstraZeneca, Bayer, BMS, Boehringer Ingelheim, Cytokinetics, Myocardia, Merck, Novartis, Novo Nordisk, and Roche Diagnostics. J.C. has received personal fees from Novartis, AstraZeneca, Boehringer Ingelheim, Roche Diagnostics, and Pfizer. All other authors have nothing to disclose.

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Publication III

Impact of Rapid Up-Titration of Guideline-Directed Medical Therapies on Quality of Life: Insights From the STRONG-HF Trial.

Čelutkienė J, **Čerlinskaitė-Bajorė K**, Cotter G, Edwards C, Adamo M, Arrigo M, Barros M, Biegus J, Chioncel O, Cohen-Solal A, Damasceno A, Diaz R, Filippatos G, Gayat E, Kimmoun A, Léopold V, Metra M, Novosadova M, Pagnesi M, Pang PS, Ponikowski P, Saidu H, Sliwa K, Takagi K, Ter Maaten JM, Tomasoni D, Lam CSP, Voors AA, Mebazaa A, Davison B.

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ORIGINAL ARTICLE

Impact of Rapid Up-Titration of Guideline-Directed Medical Therapies on Quality of Life: Insights From the STRONG-HF Trial

Jelena Čelutkienė, MD, PhD; Kamilė Čerlinskaitė-Bajorė, MD; Gad Cotter, MD; Christopher Edwards, BSc; Marianna Adamo, MD; Mattia Arrigo, MD; Marianela Barros, MD; Jan Biegus, MD; Ovidiu Chioncel, MD; Alain Cohen-Solal, MD, PhD; Albertino Damasceno, MD, PhD; Rafael Diaz, MD; Gerasimos Filippatos, MD; Etienne Gayat, MD, PhD; Antoine Kimmoun, MD, PhD; Valentine Léopold, MD; Marco Metra, MD; Maria Novosadova, MD; Matteo Pagnesi, MD; Peter S. Pang, MD; Piotr Ponikowski, MD; Hadiza Saidu, MBBS; Karen Sliwa, MD; Koji Takagi, MD; Jozine M. Ter Maaten, MD, PhD; Daniela Tomasoni, MD; Carolyn S.P. Lam, MD, PhD; Adriaan A. Voors, MD; Alexandre Mebazaa, MD, PhD; Beth Davison, PhD

BACKGROUND: This analysis provides details on baseline and changes in quality of life (QoL) and its components as measured by EQ-5D-5L questionnaire, as well as association with objective outcomes, applying high-intensity heart failure (HF) care in patients with acute HF.

METHODS: In STRONG-HF trial (Safety, Tolerability, and Efficacy of Rapid Optimization, Helped by NT-proBNP Testing, of Heart Failure Therapies) patients with acute HF were randomized just before discharge to either usual care or a high-intensity care strategy of guideline-directed medical therapy up-titration. Patients ranked their state of health on the EQ-5D visual analog scale score ranging from 0 (the worst imaginable health) to 100 (the best imaginable health) at baseline and at 90 days follow-up.

RESULTS: In 1072 patients with acute HF with available assessment of QoL (539/533 patients assigned high-intensity care/usual care) the mean baseline EQ-visual analog scale score was 59.2 (SD, 15.1) with no difference between the treatment groups. Patients with lower baseline EQ-visual analog scale (meaning worse QoL) were more likely to be women, self-reported Black and non-European (P<0.001). The strongest independent predictors of a greater improvement in QoL were younger age (P<0.001), no HF hospitalization in the previous year (P<0.001), lower NYHA class before hospital admission (P<0.001) and high-intensity care treatment (mean difference, 4.2 [95% CI, 2.5–5.8]; P<0.001). No statistically significant heterogeneity in the benefits of high-intensity care was seen across patient subgroups of different ages, with left ventricular ejection fraction above or below 40%, NT-proBNP (N-terminal pro-B-type natriuretic peptide) and systolic blood pressure above or below the median value. The treatment effect on the primary end point did not vary significantly across baseline EQ-visual analog scale ($P_{interaction}$=0.87).

CONCLUSIONS: Early up-titration of guideline-directed medical therapy significantly improves all dimensions of QoL in patients with HF and improves prognosis regardless of baseline self-assessed health status. The likelihood of achieving optimal doses of HF medications does not depend on baseline QoL.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT03412201.

Key Words: atrial fibrillation ■ blood pressure ■ depression ■ heart failure ■ quality of life

See Editorial by Reza

Correspondence to: Jelena Čelutkienė, MD, PhD, Clinic of Cardiac and Vascular Diseases, Institute of Clinical Medicine, Faculty of Medicine, Vilnius University, Santariškių g. 2, 08661 Vilnius, Lithuania. Email JElena.celutkiene@santa.lt

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WHAT IS NEW?

- In a multinational study, quality of life (QoL) during the episode of admission due to acute heart failure was worse in women, Black patients, and non-European regions. At 90 days of follow-up, patient-reported health status improved significantly, especially in younger patients, in those who had not been hospitalized due to heart failure in the past year and in those with a lower NYHA class. The high-intensity strategy of rapid up-titration of guideline-directed medical therapy resulted in significantly greater improvement in QoL compared with usual care.

WHAT ARE THE CLINICAL IMPLICATIONS?

- The high-intensity strategy of rapid up-titration of guideline-directed medical therapy provides an opportunity not only to reduce the risk of adverse events, but also to effectively improve subjective health status in the postdischarge period. This restoration of QoL involves all dimensions assessed including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Baseline QoL index did not interfere with the likelihood of achieving optimal doses of heart failure medications. Compared with usual care the rapid up-titration of guideline-directed medical therapy did not increase the rate of adverse events across the spectrum of baseline QoL.

Nonstandard Abbreviations and Acronyms

AHF	acute heart failure
ARB	angiotensin receptor blocker
ARNI	angiotensin receptor neprilysin inhibitor
COPD	chronic obstructive pulmonary disease
GDMT	guideline-directed medical therapy
HF	heart failure
HIC	high-intensity care
KCCQ	Kansas City Cardiomyopathy Questionnaire
LVEF	left ventricular ejection fraction
MRA	mineralocorticoid receptor antagonist
NT-proBNP	N-terminal pro-B-type natriuretic peptide
NYHA	New York heart association
QoL	quality of life
RASI	renin-angiotensin-system inhibitor
SBP	systolic blood pressure
UC	usual care
VAS	visual analogue scale

The patients with heart failure (HF) prioritize better quality of life (QoL) as a treatment goal, frequently even over longevity, according to the recently performed surveys.[1–5] Maintaining satisfactory QoL includes the continuation of usual life activities, adequate mobility, autonomy, and participation in society.[6] The STRONG-HF study (Safety, Tolerability, and Efficacy of Rapid Optimization, Helped by NT-proBNP Testing, of Heart Failure Therapies) proved that early (2–6 weeks after discharge) up-titration of guideline-directed medical therapy (GDMT) has beneficial effects not only on patient prognosis, but also on QoL.[7] This analysis is intended to provide more details about baseline and changes in total and various components of QoL measured by the EQ-5D-5L questionnaire and the association of objective and subjective outcomes with high-intensity HF care.

METHODS

The data that support the findings of this study are available from the study's principal investigator (alexandre.mebazaa@aphp.fr) upon reasonable request. STRONG-HF was a multinational, open-label, randomized, parallel-group trial designed to assess the efficacy and safety of up-titration of guideline-recommended HF medical therapy on morbidity and mortality when initiated during and up-titrated early after hospitalization for acute HF (AHF). The study design has been previously published.[8,9]

Briefly, eligible patients with AHF aged 18 to 85 years across the left ventricular ejection fraction (LVEF) spectrum not treated with optimal doses of oral HF therapies were included. Patients were randomized within 2 days before anticipated discharge in a 1:1 fashion to either high-intensity care (HIC) or usual care (UC). Patients assigned to HIC were up titrated at randomization to half optimal doses, and at 2 weeks to full doses of medications in 3 classes: RASI (renin-angiotensin-system inhibitor; including angiotensin-converting enzyme inhibitor, ARB [angiotensin receptor blocker], or ARNI [angiotensin receptor neprilysin inhibitor]), β-blocker, and MRA (mineralocorticoid receptor antagonist). Patients with HIC were seen 1, 2, 3, and 6 weeks postdischarge. Due to the nature of the study, treatment allocation could not be blinded. Both patients with HIC and UC were seen at day 90 and contacted by telephone at day 180. The primary cause of death and primary reason for readmission were defined by investigator report and were not adjudicated.

The study was approved by appropriate competent authorities and ethics committees before enrollment. All patients provided written informed consent. An independent data and safety monitoring board was responsible for the safety of trial participants. This study is registered at https://www.clinicaltrials.gov; Unique identifier: NCT03412201.

Study Outcomes

The primary end point of the study was HF readmission or all-cause death at 180 days. Secondary end points were change in

QoL from baseline to day 90 as measured by the EQ-5D visual analog scale (VAS), all-cause death at 180 days, and all-cause mortality or HF readmission at 90 days. Safety was evaluated by the incidence of treatment-emergent adverse events, and changes in vital signs (systolic and diastolic blood pressure, heart rate, and body weight) and local laboratory results up to 90 days.

EQ-5D Questionnaire

The EQ-5D is a standardized instrument for assessing generic health status, easily self-completed, and consists of a descriptive system and a visual analog scale.[10] The descriptive system addresses 5 domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. With the EQ-5D-5L, which was used in this study, patients ranked their state of health in each domain on a 5-point ordinal scale ranging from no problems to extreme problems.[11] The unique combination of responses to these 5 domains represents a health state that can be converted to a utility score reflecting individuals' preferences within a population for different health outcomes by using valuations obtained from the general population; we computed a utility index for each patient based on the UK value set. For utilities, a score of 0 represents death and a score of 1.0 represents perfect health; negative scores are possible and indicate a state perceived to be worse than death. The EQ-VAS records the patient's self-rated health on a 20-mm vertical visual analog scale score from 0 (The worst health you can imagine) to 100 (The best health you can imagine). The EQ-5D asks respondents to rate their health "today" unlike other generic and commonly used HF-specific QoL instruments, which have longer recall periods. Thus, the baseline EQ-5D measure should reflect the predischarge status and not the recent acute episode.[12] Excellent psychometric properties of the EQ-5D-5L have been demonstrated across a range of populations, settings, and conditions (including cardiovascular diseases),[13] with more limited information specifically in HF.[14] The minimally important difference for the EQ-5D-5L utility index score has been estimated across 8 countries using a EuroQol valuation protocol, and was uniformly 1/20 of the range of the value set;[15] we have thus estimated the minimally important difference in the UK value set to be 0.07975. Some data support that a 3-point difference in EQ-VAS can be considered clinically meaningful in outpatients with HF.[16]

Statistical Analysis

Means and SDs are presented for continuous variables, or median (interquartile range) for right skewed continuous variables. The number and percent in each category are presented for categorical variables.

The main analysis of the 90-day change in EQ-VAS, previously published, was based on available data and excluded 59 patients from Mozambique because the EQ-5D-5L translation used in that country was not formally linguistically validated. Because, as previously noted, results did not differ substantially with their inclusion, the main analyses presented here include data for the 59 patients enrolled in Mozambique. For analysis, patients were divided into terciles based on their baseline EQ-VAS levels, if not missing: ≤50, 51 to 65, and >65. The association of other baseline variables with EQ-VAS tercile was tested using Jonckheere-Terpstra trend test for continuous variables, Cochran-Armitage trend test for binary variables, Cochran-Mantel-Haenszel general association for categorical variables, and Cochran-Mantel-Haenszel nonzero correlation for ordinal variables. For analyses of changes in QoL from baseline, 63 values were missing due to death and 6 and 44 other values were missing at baseline and follow-up, respectively. Sensitivity analyses were performed to evaluate the influence of missing data on estimation of the effect of HIC versus UC on change in QoL. Analyses were conducted using only observed data, multiply imputed data, multiply imputing, and then replacing values after death to the worst possible value (or 0 for utility index), and replacing missing values due to death with the worst possible value (or with 0 for the utility index) and then multiply imputing. Missing values were imputed over 10 multiple imputation datasets. Multivariate imputation by fully conditional specification methods (regression for continuous variables, logistic for dichotomous variables and discriminant function for other classification variables) was used. The imputation model included treatment group, randomization stratification factors (geographic region and LVEF, ≤/>40%), baseline and follow-up values of the EQ-5D VAS, and other baseline characteristics (sex, age, systolic blood pressure, respiratory rate, heart rate, pulse, creatinine, hemoglobin, sodium, HF cause, history of acute coronary syndrome, atrial fibrillation, diabetes, chronic obstructive pulmonary disease [COPD], prior HF hospitalization, and NYHA class). Treatment groups were compared using ANCOVA with adjustment for baseline value, region, and LVEF (≤40/40%). Covariates for a multivariable linear regression model predicting 90-day change in EQ-VAS were selected using backwards selection across 10 multiple imputation data sets with a criterion for staying of $P<0.10$.

To examine the doses of GDMT, the percentage of the optimal dose per protocol of each medication in each of the 3 classes was calculated; the average across the 3 medication classes was then taken. The mean percentage of optimal doses over the study period was compared between EQ-VAS terciles using a mixed model for repeated measures.

As prespecified, analyses of 180-day outcomes included patients enrolled at sites where ethics committees approved a protocol amendment to follow patients to day 180, and results for patients enrolled before changing the primary end point from 90 to 180 days were given half their weight proportional to sample size. Possible modification of the effect of HIC on the primary end point by EQ-VAS as a categorical variable was examined using Kaplan-Meier curves by baseline EQ-VAS tercile and testing the treatment-by-EQ-VAS interaction in a Cox regression model. A separate Cox regression model was used to test the interaction of treatment with EQ-VAS as a continuous variable, modelled as a restricted cubic spline with 3 knots. Two-sided $P<0.05$ was considered statistically significant, except where otherwise noted. SAS version 9.4 (SAS Institute, Cary, NC) was used for analysis.

RESULTS

Baseline QoL

In 1072 patients with AHF with available assessment of QoL at baseline (539/533 patients assigned HIC/UC) the mean baseline EQ-VAS score was 59.2 (SD, 15.1) with no statistically significant difference between

the treatment groups. However, patients with lower baseline EQ-VAS (meaning worse QoL) were more likely to be women, self-reported Black, and non-European (P<0.001). Women constituted 46.4% of the lowest QoL tercile (score, <50) versus only 27.7% in the tercile with the highest QoL (score, >65; Table 1). The percentage of Black race was the largest in the lowest QoL tercile – 31.5% versus just 10.1% of the highest QoL tercile, with the opposite gradient seen for White race (Table 1). A similar trend was found for geographic region with significantly more frequent non-European patients present in the lowest versus the highest QoL tercile (35.9% versus 17.9%).

The terciles of QoL were not statistically significantly different in terms of age, baseline NT-proBNP (N-terminal pro-B-type natriuretic peptide), LVEF, NYHA class and major comorbidities, but did differ with respect to history and number of HF hospitalizations in the past year (Table 1). Regarding prerandomization treatment, patients in the tercile with the best QoL were less often prescribed MRAs and had a lower mean loop diuretic furosemide equivalence dose. The main areas of health status affected in study patients according to EQ-5D-5L at baseline were mobility and usual activities (Figure 1).

Changes in QoL at 90 Days

As reported previously, the EQ-VAS increased in both treatment groups (mean change, 8.8 [SD, 16.8] points in 461/454 patients assigned HIC/UC), but improvement was significantly greater in patients allocated to HIC.[7] The adjusted mean difference was 3.5 (95% CI, 1.7–5.2; P<0.001) points higher in favor of the HIC group, for observed values excluding Mozambique (the main analysis), and similar results were observed in a prespecified sensitivity analysis in which deaths were assigned the worst possible value (0) and then remaining missing values multiply imputed (adjusted mean difference, 4.0 [95% CI, 1.5–6.5; P=0.002]). The change in EQ-VAS was >3 points (the minimally important difference) in 364 (67.2%) patients in HIC and 306 (57.1%) in UC (P<0.001). No statistically significant heterogeneity in the benefits of HIC was seen across patient subgroups of different ages, with LVEF above or below 40%, NT-proBNP and systolic blood pressure above or below the median value, as well as regardless of the history of atrial fibrillation or flutter (Figure 2). The effect of HIC on the EQ-VAS change did not differ by baseline EQ-VAS ($P_{interaction}$=0.32; Figure S1).

A significant positive effect of HIC versus UC was shown for all separate EQ-5D dimensions of health status including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression (Figure 1). Following imputation where deaths were assigned an index value of 0 and remaining missing values multiply imputed, the 90-day change of the EQ-5D-5L profile utility index was also significantly larger in the HIC compared with UC group, with an adjusted mean difference between the groups 0.05 (95% CI, 0.03–0.08; P<0.001). The change in utility index score was >0.080 (the approximate minimally important difference) in 259 (47.8%) patients in HIC and 203 (37.9%) in UC (P<0.001). Results were similar for all sensitivity analyses evaluating the influence of nonvalidated questionnaire translations and missing data on estimation of the effect of HIC versus UC on change in QoL (Table S1).

In the total study population, independent predictors of the improvement in the EQ-VAS score were randomization to HIC, younger age, absence of HF hospitalization in the past year, absence of COPD/asthma, lower NYHA class, lower count of lymphocytes, and lower jugular venous pressure (Table 2). HIC was associated with a mean difference of 4.2 (95% CI, 2.5–5.8) after adjusting for all other variables in the model.

Relation of QoL to Doses of GDMT

The percentage of optimal doses of medications in the HIC group did not depend on the baseline QoL (Figure 3), neither for the triple combination nor for RASI, β-blockers, and MRA separately (Figure S2). A higher average percentage optimal dose at week 2 in the HIC group was associated with a greater EQ-VAS increase (P<0.001; Figure S3).

Association of Primary Study End Point With QoL

The effect of HIC on all-cause death or HF hospitalization was not significantly different by EQ-VAS tercile ($P_{interaction}$=0.58; Figure S4). The treatment effect on the primary end point did not vary significantly across baseline EQ-VAS as a continuous variable ($P_{interaction}$ =0.87; Figure 4).

QoL and Treatment-Emergent Adverse Events

All study patients with lower QoL according to baseline EQ-VAS terciles had significantly more frequent adverse events or serious adverse events, cardiac failure events, and sudden deaths (Tables S2 and S3).

However, no significant interaction of QoL across baseline EQ-VAS terciles and treatment group with respect to adverse events or serious adverse events was found (Tables S4 and S5).

DISCUSSION

The present analysis of STRONG-HF showed that, in hospitalized patients with HF, HIC improved QoL at 90 days, independent of other factors associated with QoL

Table 1. Baseline Characteristics by Baseline EQ-VAS Terciles

Parameter	Tercile 1, ≤50 (n=384)	Tercile 2, 51–65 (n=341)	Tercile 3, >65 (n=347)	Trend, *P* value
Age, y	62 (15)	64 (13)	63 (12)	0.97
Female sex	178 (46.4%)	139 (40.8%)	96 (27.7%)	<0.001
Self-reported race				<0.001
Black	121 (31.5%)	74 (21.7%)	35 (10.1%)	
White	256 (66.7%)	265 (77.7%)	307 (88.7%)	
Native American	0	0	1 (0.3%)	
Other	6 (1.6%)	2 (0.6%)	3 (0.9%)	
Pacific Islander	1 (0.3%)	0	0	
Enrollment in Europe	246 (64.1%)	261 (76.5%)	285 (82.1%)	<0.001
Medical history				
Stroke or transient ischemic attack	35 (9.1%)	36 (10.6%)	28 (8.1%)	0.64
Severe liver disease	1 (0.3%)	3 (1.1%)	2 (0.7%)	0.60
Psychiatric or neurological disorder	11 (2.9%)	3 (0.9%)	6 (1.7%)	0.23
Malignancies	9 (2.3%)	10 (2.9%)	10 (2.9%)	0.65
Diabetes	108 (28.1%)	106 (31.1%)	98 (28.5%)	0.89
Diabetes control method				
Insulin	40 (10.4%)	14 (4.1%)	28 (8.1%)	0.24
Diet only	74 (19.3%)	72 (21.1%)	56 (16.3%)	0.32
Oral antidiabetic agents	77 (20.1%)	91 (26.7%)	65 (18.8%)	0.75
Pulmonary embolism	5 (1.3%)	7 (2.1%)	7 (2.0%)	0.49
Acute coronary syndrome	94 (24.5%)	107 (31.4%)	109 (31.4%)	0.036
Coronary artery bypass surgery	24 (6.3%)	17 (5.0%)	18 (5.2%)	0.51
Percutaneous transluminal coronary intervention	43 (11.2%)	46 (13.5%)	62 (17.9%)	0.010
Angina Canadian Cardiovascular Society class 2 or higher	56 (14.6%)	26 (7.6%)	43 (12.5%)	0.33
Moderate or severe chronic obstructive pulmonary disease or asthma	10 (2.6%)	9 (2.6%)	7 (2.0%)	0.63
Cardiac resynchronization therapy	3 (0.8%)	3 (0.9%)	0	0.22
Automatic internal cardiac defibrillator	4 (1.0%)	4 (1.2%)	1 (0.3%)	0.32
Heart failure history				
History of heart failure	342 (89.1%)	308 (90.3%)	263 (75.8%)	<0.001
NYHA class 1-month before hospital admission				0.84
1	20 (5.4%)	13 (3.9%)	29 (9.8%)	
2	129 (35.0%)	81 (24.5%)	95 (32.0%)	
3	162 (43.9%)	141 (42.7%)	111 (37.4%)	
4	58 (15.7%)	95 (28.8%)	62 (20.9%)	
Ischemic cause	184 (48.0%)	167 (49.0%)	161 (46.4%)	0.67
Left ventricular ejection fraction, %	36.9 (12.2)	36.5 (12.4)	35.3 (13.0)	0.11
Left ventricular ejection fraction, ≤40%	262 (68.2%)	227 (66.6%)	242 (69.7%)	0.68
Hospitalized for heart failure in the past year?	115 (29.9%)	98 (28.7%)	60 (17.3%)	<0.001
No. of heart failure hospitalizations in the past year	0.5 (1.7)	0.4 (0.7)	0.2 (0.5)	<0.001
History of atrial fibrillation or atrial flutter	153 (39.8%)	155 (45.5%)	186 (53.6%)	<0.001
History of atrial fibrillation or atrial flutter or present at screening	150 (39.1%)	155 (45.5%)	175 (50.4%)	0.002
Type of atrial fibrillation or atrial flutter				0.002
Paroxysmal	27 (18.0%)	41 (26.5%)	49 (26.8%)	
Permanent	109 (72.7%)	87 (56.1%)	95 (51.9%)	
Persistent	14 (9.3%)	27 (17.4%)	39 (21.3%)	
Baseline vital signs				
Systolic blood pressure at baseline, mm Hg	122 (13)	125 (13)	122 (12)	0.49

(*Continued*)

Table 1. Continued

Parameter	Tercile 1, ≤50 (n=384)	Tercile 2, 51–65 (n=341)	Tercile 3, >65 (n=347)	Trend, *P* value
Pulse, beats/min	80 (12)	78 (11)	78 (12)	0.08
Respiratory Rate, breaths/min	18.3 (2.9)	17.9 (1.9)	18.4 (7.3)	0.002
Local laboratory				
Hemoglobin, g/L	134 (19)	135 (19)	141 (21)	<0.001
Lymphocytes, %	26.4 (9.8)	28.6 (10.4)	26.8 (9.0)	0.60
White blood cells, 10^9/L	7.0 (2.1)	6.8 (2.0)	7.2 (1.8)	0.11
Glucose, mmol/L	5.5 (4.8, 6.7)	5.4 (4.9, 6.7)	5.6 (5.0, 6.9)	0.048
Creatinine, umol/L	106 (32)	106 (26)	107 (29)	0.66
Potassium, mmol/L	4.2 (0.5)	4.2 (0.4)	4.3 (0.4)	0.006
Sodium, mmol/L	139.8 (4.2)	140.3 (3.9)	140.6 (4.4)	0.003
Urea, mmol/L	8.0 (3.9)	8.0 (3.2)	8.2 (3.3)	0.07
ALT, U/l	20.0 (14.0, 30.0)	21.0 (15.3, 29.0)	24.0 (16.7, 36.1)	<0.001
Total bilirubin, µmol/L	13.2 (10.0, 20.8)	13.0 (10.0, 18.6)	14.5 (11.0, 23.3)	0.018
Total cholesterol, mmol/L	4.2 (1.1)	4.3 (1.2)	4.2 (1.1)	0.81
NT-proBNP, ng/L	2847 (1940–5212)	3086 (1955–5028)	2731 (1874–4592)	0.10
NT-proBNP at screening, ng/L	6972 (3884–9000)	6192 (3842–9000)	5919 (3829–9000)	0.07
EQ-5D				
EQ-5D Question 1: Mobility, any problems?	368 (95.8%)	315 (92.4%)	236 (68.0%)	<0.001
EQ-5D Question 2: Self-care, any problems?	329 (85.9%)	251 (73.6%)	155 (44.7%)	<0.001
EQ-5D Question 3: Usual activities, any problems?	365 (95.1%)	317 (93.0%)	227 (65.4%)	<0.001
EQ-5D Question 4: Pain or discomfort, any problems?	280 (72.9%)	199 (58.4%)	143 (41.2%)	<0.001
EQ-5D Question 5: Anxiety or depression, any problems?	312 (81.3%)	237 (69.5%)	142 (40.9%)	<0.001
EQ-5D profile utility index	0.5 (0.2)	0.6 (0.1)	0.8 (0.2)	<0.001
Oral heart failure medications taken at Visit 2: pre-randomization				
ACE inhibitors/ARBs/ARN inhibitors	224 (58.3%)	251 (73.6%)	212 (61.3%)	0.34
ß Blockers	150 (39.1%)	93 (27.3%)	139 (40.2%)	0.84
Mineralocorticoid receptor antagonists	369 (96.1%)	331 (97.1%)	318 (91.9%)	0.011
Loop diuretic	368 (95.8%)	329 (96.5%)	330 (95.4%)	0.77
Loop diuretic furosemide equivalence dose, mg	69.8 (48.8)	59.9 (45.2)	57.7 (43.9)	<0.001

Values collected at randomization unless otherwise noted. ACE indicates angiotensin-converting enzyme; ALT, alanine transaminase; ARB, angiotensin II receptor blocker; ARN, angiotensin II receptor neprilysin; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; and VAS, visual analog scale.

change. Other independent predictors of improvement in QoL were younger age, absence of HF hospitalization in the past year, absence of COPD/asthma, lower NYHA class, lower count of lymphocytes, and lower jugular venous pressure. The difference in changes of QoL between the treatment groups was significant in the analyses of QoL as a separate end point measured by EQ-VAS, EQ-5D utility index and the 5 EQ-5D health domains. The benefit in QoL change in favor of the HIC strategy was homogeneous in the subgroups by age, LVEF, NT-proBNP, systolic blood pressure, and history of atrial fibrillation. The beneficial impact of GDMT has also been shown in several previous pharmacotherapy trials and a recent meta-analysis.[17]

The QoL assessment provides a unique characterization of the experience of HF patients living with their own illness. The EQ-5D questionnaire has been widely used in cardiovascular research due to established reliability and validity.[5,6,18] Unlike more HF-specific tools such as the Minnesota Living with Heart Failure Questionnaire and the Kansas City Cardiomyopathy Questionnaire (KCCQ), the EQ-5D is a generic assessment of health status and provides a measure of utility that multiplied by survival yields quality-adjusted life years.[19] Although a HF-specific tool would have assessed the burden of HF on QoL, the EQ-5D does discriminate between NYHA classes III and IV and also reflects activities of daily living and self-care which are relevant to patients with HF.[14] The long recall periods inherent in HF-specific instruments currently in use may limit their applicability in patients immediately following an acute HF exacerbation.

At baseline patients in our study mostly suffered from limitations in mobility and usual activities. This is in line

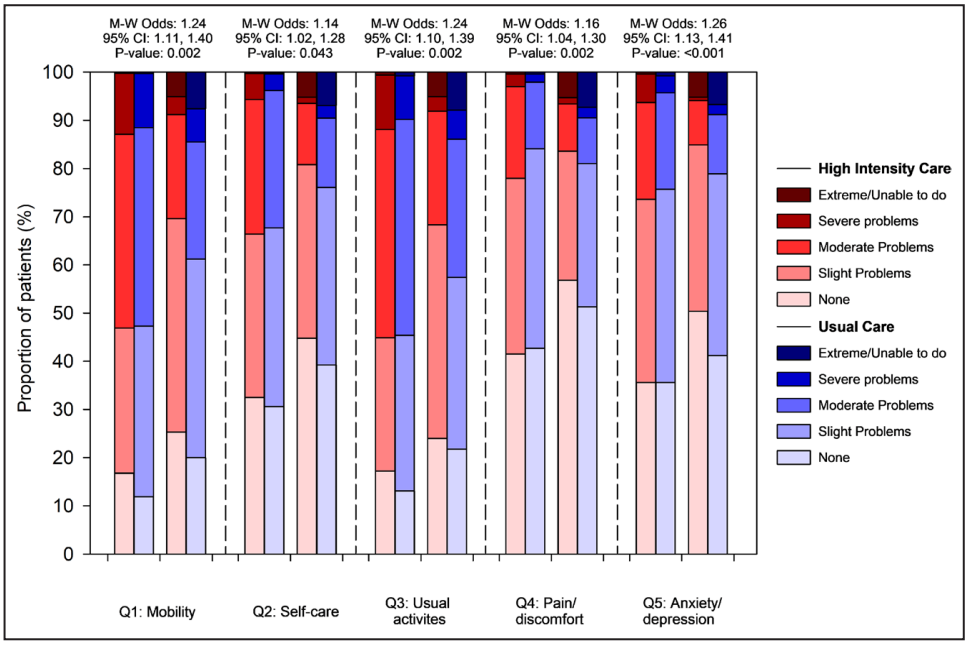

Figure 1. Effects of high-intensity care vs usual care on dimensions of the EQ-5D.
Missing values due to death were set to the worst possible score and remaining missing values multiply imputed. Mann-Whitney *U* test odds ratios are adjusted for baseline response and stratified by region and left ventricular ejection fraction (LVEF) ≤40/>40%. M-W odds indicates Mann-Whitney *U* test odds.

with the finding that ≈75% of patients with HF report difficulties in activities of daily living,[20] which makes them dependent on caregivers and leads to psychosocial distress. At 90 days of follow-up, the positive changes spanned all 5 dimensions of QoL (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), and in each dimension HIC was associated with a significantly greater improvement of QoL compared with UC.

Patients in the STRONG-HF trial with poorer QoL were more likely to be women, of Black race and from non-European sites. The sex-specific analysis of STRONG-HF[21] and present findings confirm previously published observations on sex differences in QoL in patients with HF. Worse QoL in women than in men was found in a few randomized and observational studies,[22–26] using EQ-5D-5L, Minnesota Living with Heart Failure Questionnaire, and KCCQ tools. Of note, the same sex disparity exists in other chronic diseases: after coronary artery bypass surgery[27] and in diabetes,[28] suggesting more general differences between men and women in this multidimensional construct of physical, psychological and social functioning.

Consistent with earlier HF studies we showed the association of QoL with race and geographic region, probably reflecting differences in income level, health care resources and psychosocial distress in study sites. Investigators of PARAGON-HF trial (Prospective Comparison of ARNI With ARB Global Outcomes in HF With Preserved Ejection Fraction) also reported that region is a robust determinant of KCCQ-score.[22] The GUIDE-IT (The Guiding Evidence Based Therapy Using Biomarker Intensified Treatment in Heart Failure),[29] PROVE-HF (Prospective Study of Biomarkers, Symptom Improvement, and Ventricular Remodeling During Sacubitril/Valsartan Therapy for Heart Failure),[30] CHAMP-HF (Change the Management of Patients With Heart Failure)[24] studies found lower scores and lower improvement of QoL at follow-up in Hispanic and Black patients.

Some prior studies, performed during hospitalization and in out-patient settings, demonstrated that QoL measured by EQ-5D-5L or Minnesota Living with Heart Failure Questionnaire depends on the LVEF category and worsens with lower LVEF.[31,32] Conversely, in the PARAGON-HF study mean KCCQ score was found to be lower (meaning worse QoL) than in patients of the PARADIGM-HF study.[22] After adjustment for clinical variables the difference of measured QoL between patients of these 2 large studies was no longer significant. The STRONG-HF

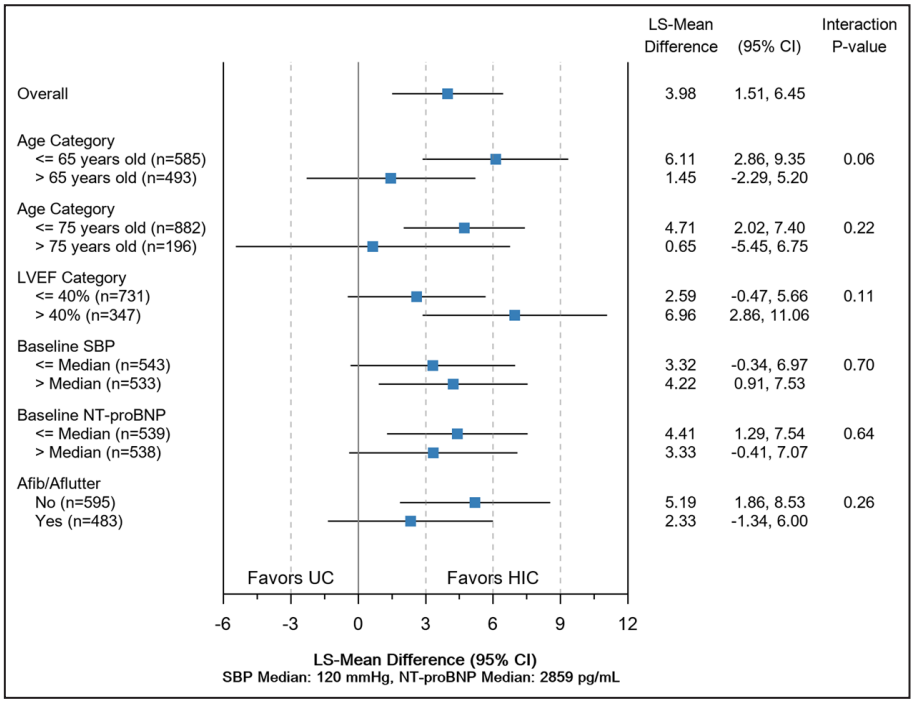

Figure 2. Effect of high-intensity care vs usual care on change in EQ-visual analog scale (VAS) from baseline to day 90 by subgroups.

Missing values due to death were set to the worst possible score and remaining missing values multiply imputed. Tests of treatment-by-subgroup interactions from ANCOVA adjusted for baseline EQ-VAS, region, and baseline left ventricular ejection fraction (LVEF; ≤40/>40%). Afib indicates atrial fibrillation; Aflutter, atrial flutter; HIC, high-intensity care; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SBP, systolic blood pressure; and UC, usual care.

trial enrolled patients regardless of LVEF, and when analyzing patients according to QoL terciles we could not find differences in their LVEF category (there were 30% to 33% of patients with LVEF >40% across QoL terciles). In addition, according to regression analysis LVEF was not predictive of improved QoL at follow-up.

Using multivariable analysis, we demonstrated that the likelihood of improved QoL was significantly greater in the HIC group, in younger patients with no previous HF hospitalizations and comorbidities, with less clinical congestion and a better functional class. Similarly, analysis of sacubitril/valsartan studies found that functional class, signs of congestion and such comorbidities as COPD correlate with subjective health status.[22] A recent study of QoL trajectories in patients with HF after discharge, consistent with our findings, showed that advanced age and HF rehospitalizations are associated with unfavorable patterns of KCCQ dynamics.[33]

In previous investigations, the association of QoL with other clinical outcomes such as mortality and hospitalizations for HF has been shown. For example, in BIOSTAT-HF (The Biology Study to Tailored Treatment in Chronic Heart Failure) observational cohort in patients with HF with reduced ejection fraction, baseline QoL measured by both EQ-5D and KCCQ was independently associated with mortality and a composite outcome at 21-month median follow-up.[23] In the QoL substudy of the EPHESUS trial (Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study) changes of KCCQ scores in HF outpatients were associated with all-cause, cardiovascular mortality, and hospitalizations.[34] In contrast, in the GALACTIC study (Global Approach to Lowering Adverse Cardiac Outcomes Through Improving Contractility in Heart Failure) of vasodilation in acute HF, admission KCCQ scores did not predict 180-day mortality.[35] Our analysis shows that the benefit of HIC for reducing the composite primary outcome of STRONG-HF study is consistent across the entire spectrum of QoL scores, though it seems that most of the responders,

Table 2. Univariable and Multivariable Model for Change in EQ-VAS

Parameter	Estimate for unit change of:	Univariable results		Multivariable results (all subjects)	
		Mean difference (95% CI)	*P* value	Mean difference (95% CI)	*P* value
Age, y	5	−1.3 (−1.6 to −0.9)	<0.001	−0.7 (−1.1 to −0.4)	<0.001
Geographic region	Europe vs not Europe	−6.9 (−8.9 to −4.9)	<0.001		
Male sex	Yes vs no	−1.2 (−3.0 to 0.6)	0.20		
White race	Yes vs no	−4.9 (−6.7 to −3.0)	<0.001		
BMI, kg/m^2	Median vs Q1	−1.1 (−1.8 to −0.4)	0.007		
	Q3 vs Median	−0.6 (−1.2 to −0.0)			
Baseline pulse, bpm	2	0.5 (0.4 to 0.7)	<0.001	0.3 (0.1 to 0.4)	0.002
Baseline systolic BP, mm Hg	Median vs Q1	−0.2 (−0.9 to 0.5)	0.045		
	Q3 vs Median	0.4 (−0.2 to 1.0)			
Left ventricular ejection fraction, %	Median vs Q1	−0.9 (−1.7 to 0.0)	0.09		
	Q3 vs Median	−1.5 (−2.7 to −0.3)			
History of HF?	Yes vs No	−4.3 (−6.8 to −1.9)	0.001		
Hospitalized for HF in prior year?	Yes vs No	−4.5 (−6.5 to −2.5)	<0.001	−4.0 (−5.9 to −2.0)	<0.001
Hx of diabetes	Yes vs No	−3.3 (−5.2 to −1.3)	0.001		
Moderate or severe COPD or asthma	Yes vs No	−9.5 (−15.7 to −3.4)	0.002	−7.4 (−13.9 to −0.9)	0.027
Hemoglobin (Prerand), g/L	5	0.3 (0.1 to 0.5)	0.007	0.2 (−0.0 to 0.4)	0.06
Baseline urea, mmol/L	1	−0.7 (−0.9 to −0.4)	<0.001		
Creatinine (Prerand), µmol/L	Median vs Q1	−0.6 (−1.4 to 0.2)	0.57		
	Q3 vs Median	−0.7 (−1.3 to −0.1)			
White blood cells, 10^9/L	5	−2.5 (−4.7 to −0.2)	0.030		
Lymphocytes, %	5	1.1 (0.6 to 1.5)	<0.001	0.1 (0.0 to 0.2)	0.026
Glucose, mmol/L	5	−1.8 (−3.8 to 0.2)	0.08		
Sodium, mmol/L	5	−0.2 (−1.3 to 0.9)	0.70		
Potassium, mmol/L	Median vs Q1	−0.9 (−1.9 to 0.1)	0.71		
	Q3 vs Median	−0.8 (−1.7 to 0.0)			
ALT (log2), U/l	Doubling	1.2 (0.2 to 2.1)	0.019		
Total bilirubin, µmol/L	5	−0.0 (−0.4 to 0.4)	0.89		
Cholesterol, mmol/L	Median vs Q1	1.3 (0.5 to 2.1)	0.004		
	Q3 vs Median	0.8 (0.1 to 1.4)			
NT-proBNP (log2), pg/mL	1	−1.6 (−2.6 to −0.6)	0.001		
JVP (Prerand)	≥6 cm vs <6 cm	−3.7 (−6.2 to −1.2)	0.004	−2.7 (−5.0 to −0.4)	0.023
Rales (Prerand)	Present vs no rales	0.5 (−2.0 to 2.9)	0.72		
Edema (Prerand)	1+/2+/3+ vs 0	−1.3 (−3.2 to 0.5)	0.15		
NYHA class (Prerand)	III/IV vs I/II	−6.3 (−8.1 to −4.4)	<0.001	−4.4 (−6.3 to −2.6)	<0.001
Treatment	HIC vs UC	3.4 (1.7 to 5.1)	<0.001	4.2 (2.5 to 5.8)	<0.001
Adjusted R^2				0.42	

Missing values due to death were set to the worst possible score and remaining missing values multiply imputed. Univariable and multivariable models are adjusted for baseline EQ-VAS. In the multivariable model, treatment group was further forced into the model. ALT indicates alanine transaminase; BMI, body mass index; BP, blood pressure; COPD, chronic obstructive pulmonary disease; HF, heart failure; HIC, high-intensity care; JVP, jugular venous pressure; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-B-type natriuretic peptide; UC, usual care; and VAS, visual analog scale.

who demonstrated the largest and earliest effect of HIC strategy, belong to the middle QoL tercile, in which patients have a moderate deterioration of their health status. Importantly, the chance to achieve target doses of GDMT did not depend on the baseline level of QoL in the high-intensity treatment arm.

Patients with lower QoL scores had significantly more frequent serious and nonserious treatment-emergent adverse events, including cardiac failure events and sudden deaths. This can be explained by the characteristics of the QoL terciles: patients with the lowest EQ-5D scores were more likely to have previous and more frequent HF hospitalizations, history of atrial fibrillation, lower levels of hemoglobin, and electrolytes, to be women, non-White/White and enrolled in non-European sites. This highlights the association of longer duration of

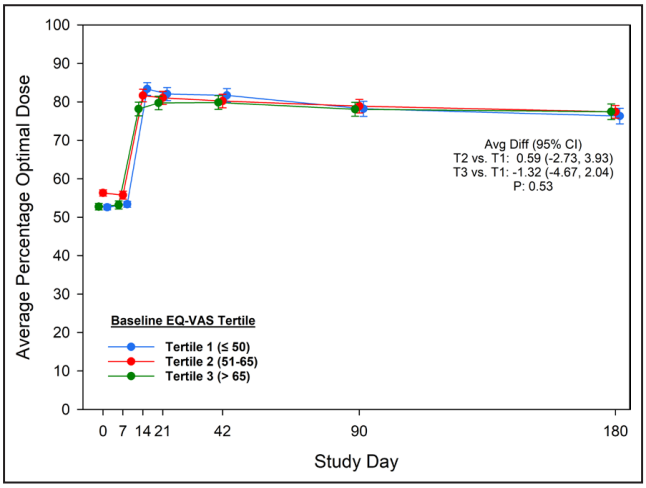

Figure 3. Average percentage optimal dose of triple combination of ACE (angiotensin-converting enzyme) inhibitors/ARBs (angiotensin II receptor blocker)/angiotensin II receptor neprilysin inhibitors (ARNi), β-blockers, and mineralocorticoid receptor antagonists by baseline EQ-visual analog scale (VAS) tertile. High-Intensity Care group only. Avg Diff indicates average difference; T1, tertile 1; T2, tertile 2; and T3, tertile 3.

the disease, unfavorable sociodemographic factors, and therefore, worse prognosis with poor QoL. No significant interaction between treatment arm, adverse events, and QoL terciles was found.

Finally, the improvement of QoL in the STRONG-HF study included improvements in anxiety/depression, self-care, and pain/discomfort. Although detailed exploration for the causes of these improvements were not made in the STRONG-HF study, it is notable[7] that patients assigned to the HIC arm had more decongestion and weight loss. This improvement in symptoms is likely to translate into reduced discomfort and better ability to self-care. Depression and anxiety are known to occur commonly in patients with HF[36] and their severity follows the severity of HF and its symptoms, therefore again it is possible that improvement in the symptoms of HF may improve patients' anxiety and depression symptoms.

Limitations

The results of this analysis should be interpreted with caution because the study was open label and so patients might have been biased to report greater improvements if they knew they were in the HIC group or because the study team was aware of the treatment assigned.

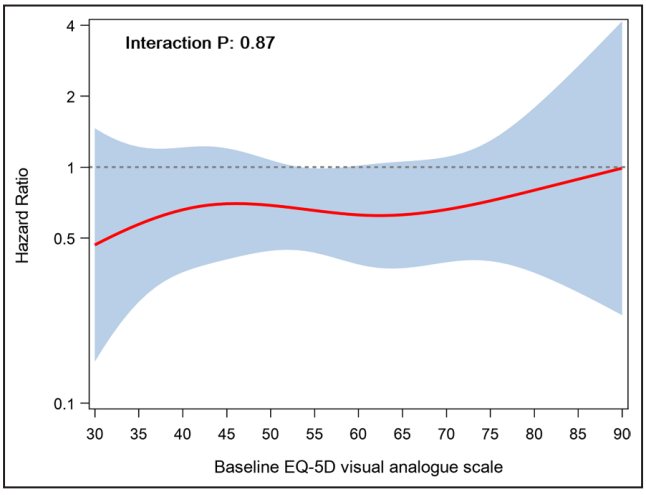

Figure 4. Treatment effect of high-intensity care vs usual care on the primary end point by baseline EQ-visual analog scale (VAS).

Caution should be taken in interpreting results of statistically significant results due to the multiple statistical tests. Besides, it can be assumed that some cultural and language barriers confounded the racial and regional disparity in the results of EQ-5D questionnaire.

Conclusions

We found sex, racial, and geographic region disparities in the QoL of patients hospitalized due to acute heart failure. Early up-titration of GDMT significantly improves all dimensions of QoL in patients with HF and improves prognosis regardless of baseline health status. The likelihood to achieve optimal doses of HF medications does not depend on baseline QoL.

ARTICLE INFORMATION

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Affiliations

Clinic of Cardiac and Vascular Diseases, Institute of Clinical Medicine, Faculty of Medicine, Vilnius University, Lithuania (J.Č., K.Č-B.). Université Paris Cité, INSERM UMR-S 942 (MASCOT), France (G.C., A.C.-S., E.G., V.L., A.M., B.D.). Heart Initiative, Durham, NC (G.C., B.D.). Momentum Research, Inc, Durham, NC. (G.C., C.E., M.B., M.N., K.T., B.D.). Cardiology, ASST Spedali Civili and Department of Medical and Surgical Specialties, Radiological Sciences, and Public Health, University of Brescia, Italy (M. Adamo, M.M., M.P., D.T.). Department of Internal Medicine, Stadtspital Zurich, Switzerland (M. Arrigo). Institute of Heart Diseases, Wroclaw Medical University, Poland (J.B., P.P.). Emergency Institute for Cardiovascular Diseases "Prof. C.C.Iliescu," University of Medicine "Carol Davila," Bucharest, Romania (O.C.). Department of Cardiology, APHP Nord, Laribosière University Hospital, Paris, France (A.C.-S.). Faculty of Medicine, Eduardo Mondlane University, Maputo, Mozambique (A.D.). Estudios Clínicos Latinoamérica, Instituto Cardiovascular de Rosario, Argentina (R.D.). National and Kapodistrian University of Athens, School of Medicine, Attikon University Hospital, Greece (G.F.). Department of Anesthesiology and Critical Care and Burn Unit, Saint-Louis and Lariboisière Hospitals, FHU PROMICE, DMU Parabol, APHP Nord, Paris, France (E.G., V.L., A.M.). Université de Lorraine, Nancy; INSERM, Défaillance Circulatoire Aigue et Chronique; Service de Médecine Intensive et Réanimation Brabois, CHRU de Nancy, France (A.K.). Departments of Emergency Medicine and Medicine, Indiana University School of Medicine, Indianapolis (P.S.P.). Murtala Muhammed Specialist Hospital/Bayero University Kano, Nigeria (H.S.). Cape Heart Institute, Division of Cardiology, Department of Medicine, Groote Schuur Hospital and University of Cape Town, South Africa (K.S.). Department of Cardiology, Medical Centre Groningen, the Netherlands (J.M.T.M., A.A.V.). National Heart Centre Singapore and Duke-National University of Singapore, Singapore (C.S.P.L.). Baim Institute for Clinical Research, Boston, MA (C.S.P.L.). University Medical Centre Groningen, the Netherlands (C.S.P.L.).

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Supplemental Material

Tables S1–S5
Figures S1–S4

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Publication IV

Insights on prevalence and incidence of anemia and rapid up-titration of oral heart failure treatment from the STRONG-HF study.

Čelutkienė J, **Čerlinskaitė-Bajorė K**, Cotter G, Edwards C, Adamo M, Arrigo M, Barros M, Biegus J, Chioncel O, Cohen-Solal A, Damasceno A, Diaz R, Filippatos G, Gayat E, Kimmoun A, Léopold V, Deniau B, Metra M, Novosadova M, Pagnesi M, Pang PS, Ponikowski P, Saidu H, Sliwa K, Takagi K, Ter Maaten JM, Tomasoni D, Lam CSP, Voors AA, Mebazaa A, Davison B.

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ORIGINAL PAPER

Insights on prevalence and incidence of anemia and rapid up-titration of oral heart failure treatment from the STRONG-HF study

Jelena Čelutkienė[1] · Kamilė Čerlinskaitė-Bajorė[1] · Gad Cotter[2,3,4] · Christopher Edwards[4] · Marianna Adamo[5] · Mattia Arrigo[6] · Marianela Barros[4] · Jan Biegus[7] · Ovidiu Chioncel[8] · Alain Cohen-Solal[2,9] · Albertino Damasceno[10] · Rafael Diaz[11] · Gerasimos Filippatos[12] · Etienne Gayat[2,13] · Antoine Kimmoun[14] · Valentine Léopold[2,13] · Benjamin Deniau[2,13] · Marco Metra[5] · Maria Novosadova[4] · Matteo Pagnesi[5] · Peter S. Pang[15] · Piotr Ponikowski[7] · Hadiza Saidu[16] · Karen Sliwa[17] · Koji Takagi[4] · Jozine M. Ter Maaten[18] · Daniela Tomasoni[5] · Carolyn S. P. Lam[19,20,21] · Adriaan A. Voors[18] · Alexandre Mebazaa[2,13] · Beth Davison[2,3,4]

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Abstract

Background Anemia is one of the most frequent comorbidities in patients with heart failure (HF), which potentially can interfere with the effect of guideline-recommended HF medical therapy and can be associated with the use of neurohormonal blockers.

Aim The aim of this analysis was to determine the prevalence and changes of anemia status in the STRONG-HF study, its association with clinical endpoints, and possible interaction of the presence of anemia with the efficacy and safety of high-intensity HF treatment.

✉ Jelena Čelutkienė
jelena.celutkiene@santa.lt

[1] Clinic of Cardiac and Vascular Diseases, Institute of Clinical Medicine, Faculty of Medicine, Vilnius University, Vilnius, Lithuania

[2] Université Paris Cité, INSERM UMR-S 942 (MASCOT), Paris, France

[3] Heart Initiative, Durham, NC, USA

[4] Momentum Research Inc, Durham, NC, USA

[5] Cardiology, Cardiology, ASST Spedali Civili and Department of Medical and Surgical Specialties, Radiological Sciences, and Public Health, University of Brescia, Brescia, Italy

[6] Department of Internal Medicine, Stadtspital Zurich, Zurich, Switzerland

[7] Institute of Heart Diseases, Wroclaw Medical University, Wrocław, Poland

[8] Emergency Institute for Cardiovascular Diseases "Prof. C.C.Iliescu", University of Medicine "Carol Davila", Bucharest, Romania

[9] Department of Cardiology, APHP Nord, Lariboisière University Hospital, Paris, France

[10] Faculty of Medicine, Eduardo Mondlane University, Maputo, Mozambique

[11] Estudios Clínicos Latinoamérica, Instituto Cardiovascular de Rosario, Rosario, Argentina

[12] National and Kapodistrian University of Athens, School of Medicine, Attikon University Hospital, Athens, Greece

[13] Department of Anesthesiology and Critical Care and Burn Unit, Saint-Louis and Lariboisière Hospitals, FHU PROMICE, DMU Parabol, APHP.Nord, Paris, France

[14] Université de Lorraine, Nancy; INSERM, Défaillance Circulatoire Aigue Et Chronique; Service de Médecine Intensive Et Réanimation Brabois, CHRU de Nancy, 54511 Vandœuvre-Lès-Nancy, France

[15] Department of Emergency Medicine, Department of Medicine, Indiana University School of Medicine, Indianapolis, IN, USA

[16] Murtala Muhammed Specialist Hospital / Bayero University Kano, Kano, Nigeria

[17] Cape Heart Institute, Division of Cardiology, Department of Medicine, Groote Schuur Hospital and University of Cape Town, Cape Town, South Africa

[18] Department of Cardiology, Medical Centre Groningen, Groningen, Netherlands

[19] National Heart Centre Singapore and Duke-National University of Singapore, Singapore, Singapore

[20] Baim Institute for Clinical Research, Boston, MA, USA

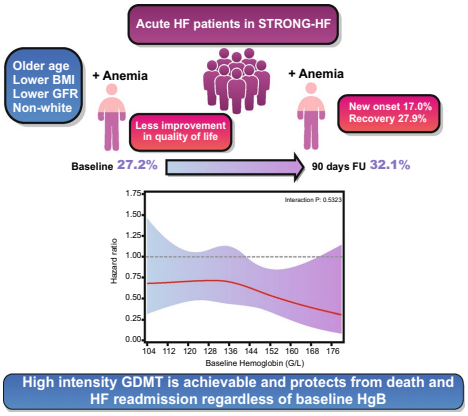
[21] University Medical Centre Groningen, Groningen, The Netherlands

Methods The design and main results of the study have been previously described. Patients were randomized within 2 days prior to anticipated hospital discharge after HF worsening in a 1:1 fashion to either high-intensity care (HIC) or usual care (UC). Baseline characteristics, clinical and safety outcomes, and treatment effect of HIC vs. UC on the primary and secondary outcomes were compared in groups based on baseline anemia. In addition, dynamics of hemoglobin during the study follow-up and predictors of incident anemia at 90 days were investigated.

Results The proportion of anemia in 1077 STRONG-HF patients at enrollment was 27.2%, while at 90 days, it changed to 32.1%. The primary composite outcome occurred in 18.2% of patients without baseline anemia, and 22.5% of patients with baseline anemia (unadjusted HR 1.27; 95% CI 0.90–1.80), a difference that did not reach statistical significance. However, patients with baseline anemia had significantly less improvement of EQ-VAS questionnaire values from baseline to day 90 (adjusted LS-Mean difference −2.34 (−4.37, −0.31), $P=0.02$). During the study, anemia developed in 19.4 and 14.6% in HIC and UC groups, respectively. The opposite phenomenon—recovery of anemia—occurred in 27.6 and 28.8% in HIC and UC groups ($P=0.1379$). The predictors of incident anemia at 90 days were male sex, geographical region other than Europe, ischemic etiology, higher glucose, and elevated uric acid at baseline. The percentages of optimal doses of renin–angiotensin system inhibitors, beta-blockers, and mineralocorticoid receptor antagonists were not different between anemic and non-anemic patients. High-intensity care strategy did not increase rate of incident anemia at 90 days and reduced the rate of primary and secondary endpoints regardless of baseline hemoglobin.

Conclusion Hemoglobin level and status of anemia have a dynamic nature in the acute HF patients in the post-discharge period dependent on multiple factors. High-intensity HF treatment is safe and beneficial regardless of baseline hemoglobin level and presence of anemia. The improvement of quality of life is significantly lower in anemic HF patients implying specific attention to correction of this condition.

Graphical abstract



Keywords Heart failure · Anemia · Guideline-directed medical therapy

Background

Currently, after the success of rapid and careful up-titration of heart failure (HF) medications was proved by a randomized trial [1], the phase of implementing suggested quick treatment algorithm follows. Clinical inertia is an important barrier to reach target doses of HF treatment and achieve them in 2–6 weeks after discharge. Reluctance of practitioners to fully adopt recent recommendations on HF medications [2, 3] is partly associated with multiple comorbidities of HF patients. Anemia is one of the most frequent leading conditions in HF patients [4], which may affect mortality, morbidity, and quality of life [5]. Besides, neurohormonal blockers are reported to affect the hemoglobin level in previous chronic HF trials [6–8].

Aim

By current analysis, we sought to determine the prevalence and changes of anemia status in the STRONG-HF study, its association with clinical endpoints, and possible interaction of the presence of anemia with the efficacy and safety of high-intensity HF treatment.

Methods

The design and main results of the study have been previously described [1]. Briefly, STRONG-HF was an international, multicenter, open-label, randomized, parallel-group trial designed to assess the efficacy and safety of early up-titration of guideline-recommended HF medical therapy (renin–angiotensin system inhibitor [RASi, including angiotensin-converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB), or angiotensin receptor neprilysin inhibitor (ARNI), beta-blocker (BB), and mineralocorticoid receptor antagonist (MRA)] in hospitalized acute heart failure (AHF) patients. AHF patients aged 18–85 years admitted for AHF with any LVEF and a high NT-proBNP value at screening (>2500 ng/L) and randomization (>1500 ng/L) not treated with optimal doses of oral HF therapies were included. Patients were randomized within 2 days prior to anticipated discharge in a 1:1 fashion to either high-intensity care (HIC) or usual care (UC). Patients assigned to HIC were up-titrated at randomization to half optimal doses, and at 2 weeks to full doses of RASi, BB, and MRA. HIC patients had follow-up visits with comprehensive evaluation at 1, 2, 3, and 6 weeks post-discharge. If there was a need to delay the up-titration, a safety visit was required 1 week after any up-titration. Both HIC and UC patients were seen at day 90 and contacted by telephone at day 180. Due to the nature of the study, treatment allocation could not be blinded. The primary cause of death and primary reason for readmission were defined by investigator report and were not adjudicated.

The study was approved by appropriate competent authorities and ethics committees prior to enrollment. All patients provided written informed consent. An independent data and safety monitoring board was responsible for the safety of trial participants. This study is registered at ClinicalTrials.gov, NCT03412201.

Study endpoints

The primary endpoint of the study was 180-day heart failure readmission or all-cause death. Secondary endpoints were 180-day all-cause death, 90-day all-cause mortality or HF readmission and change in EQ-5D visual analog scale (VAS) score from baseline to day 90.

Anemia

Baseline characteristics, clinical and safety outcomes, and treatment effect of HIC vs. UC on the primary and secondary outcomes were compared in groups based on baseline anemia. Anemia was defined as baseline Hgb < 120 g/L in women and <130 g/L in men. We also assessed characteristics of patients dividing them according to median hemoglobin in men (141 g/L) and women (130 g/L). In addition, dynamics of hemoglobin during the study follow-up and predictors of incident anemia at 90 days were investigated.

Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD), geometric mean (95% CI) for log-transformed variables, or as adjusted mean ± standard error (SE), as appropriate, and categorical variables as number (*N*) and percentage (%). NT-proBNP values were log-transformed for analysis. Baseline characteristics, categorized by anemia presence and median hemoglobin levels, were compared using ANOVA for continuous variables, Chi-square tests for nominal categorical variables, and the Cochran–Mantel–Haenszel test for general association in ordered categorical variables.

Separate multivariable logistic regression models were constructed to investigate potential predictors among baseline characteristics associated with the presence of anemia at baseline and at day 90. To mitigate potential confounding by treatment group, the multivariable model for anemia at day 90 was exclusively developed using patients in the usual care arm. Both univariable and multivariable results for the model assessing day 90 anemia were additionally adjusted for baseline hemoglobin value.

To determine the impact of anemia on clinical outcomes, Cox proportional hazards regression analysis was applied. Analysis of the primary and secondary endpoints up to 180 days was limited to participants from sites where the ethics committee had approved the amended protocol, permitting patient follow-up through day 180. For the cohort of patients enrolled before the primary endpoint was extended from 90 to 180 days, the results were adjusted by weighting this subgroup at half the sample size. The impact of anemia on changes in EQ-VAS scores from baseline to day 90 was evaluated with a linear regression model, adjusted for baseline EQ-VAS scores, and the randomization stratification factors LVEF category (≤40% or >40%), and geographic region. Additional covariates for adjustment were chosen based on their demonstrated prognostic variables for each

outcome in prior studies, utilizing a backward selection process within the UC group. To address missing covariates in the analyses, we employed multiple imputation, creating ten imputed datasets. We integrated estimates from these imputed datasets using Rubin's rules. Results for the EQ-VAS are based on observed data and exclude data for which linguistically validated translations were not available. To assess the impact of COVID-19 on all-cause mortality, sensitivity analyses were performed where COVID-19-related deaths were censored instead of being included as events.

We calculated the average dose of three medication classes (ACEi/ARB/ARNi, β-blocker, and MRA) for each patient, relative to their optimal doses. The trajectory of this average percentage of the optimal dose over time was presented for patients categorized based on treatment and the presence of anemia at baseline. We modeled the effect of HIC vs. UC on the primary endpoint, using baseline hemoglobin levels as a continuous variable in a restricted cubic spline with three knots. The results are presented as hazard ratios (HR) with 95% confidence intervals (CI).

Safety profiles were analyzed in relation to anemia and baseline hemoglobin levels. We compared the incidence of adverse events (AEs) and serious adverse events (SAEs) across groups using Chi-square tests, categorized by anemia status and baseline hemoglobin. In addition, logistic regression assessed how the presence of anemia or baseline hemoglobin levels, along with treatment, influenced the frequency of these events.

A two-sided *P* value of less than 0.05 was considered statistically significant. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Anemia and baseline characteristics

The prevalence of anemia in 1077 STRONG-HF patients at enrollment was 27.2%, while at 90 days, it changed to 32.1%. Number of patients with hemoglobin level <100 g/L and <90 g/L was about 3 and 1%, respectively, at both time points. The frequency of anemia did not differ between the groups with LVEF above or below 40%. Patients with anemia at baseline were more likely to be black and non-European (Table 1). They also were significantly more congested compared to patients without anemia: more frequent orthopnea, edema, rales, jugular veins distention, higher NT-proBNP and respiratory rate at screening; similar differences in congestion status were seen at 90 days (Suppl Tables 1, 2), while count of lymphocytes, white blood cells, and level of sodium, potassium, bilirubin, and cholesterol were lower compared to non-anemic participants.

We also assessed characteristics of patients dividing them according to median hemoglobin of 130 g/L in women and 141 g/L in men (Table 2). In addition to differences between anemic and non-anemic patients, participants with lower than median hemoglobin had higher LV ejection fraction, higher heart rate and blood pressure, less frequent atrial fibrillation, and lower ALT.

The findings from both univariable and multivariable models assessing predictors of baseline anemia are detailed in Table 3. Following adjustments, several factors emerged as independent predictors of anemia at baseline, including older age, lower BMI, non-white race, elevated systolic blood pressure, extremes in eGFR and creatinine levels, reduced potassium, lower total bilirubin, decreased white blood cell count, and lower cholesterol levels.

Baseline anemia and clinical outcomes

The primary composite outcome occurred in 18.2% of patients without baseline anemia, and 22.5% of patients with baseline anemia (unadjusted HR 1.27; 95% CI 0.90–1.80), a difference that did not reach statistical significance. Presence of anemia at baseline also did not significantly influence the risk of all-cause death or HF readmissions by day 180 (Table 4). One sensitivity analysis showed the significant association of baseline anemia with all-cause deaths when COVID deaths were excluded [unadjusted HR 1.69 (95% CI 1.02, 2.79), $P=0.04$]; however, the statistical significance was lost after adjustment for baseline creatinine, urea, and NT-proBNP ($P=0.14$). Patients with baseline anemia had significantly less improvement of EQ-VAS questionnaire values from baseline to day 90 (adjusted LS-Mean difference −2.34 (−4.37, −0.31), $P=0.02$).

Dynamics of hemoglobin during follow-up

Among 969 (90%) patients with hemoglobin value available at both time points, hemoglobin decreased within 90 days in 58.8%. Figure 1 shows the transitions of anemia status in HIC and UC groups over time. Patients who demonstrated decrease of hemoglobin had higher baseline hemoglobin level [144.5 (18.2) vs. 125.5 (17.4) g/L], higher bilirubin, lower LVEF and were less likely to have diabetes.

During the study, anemia developed in 19.4 and 14.6% in HIC and UC groups, respectively. The opposite phenomenon—recovery of anemia—occurred in 27.6 and 28.8% in HIC and UC groups ($P=0.1379$). The predictors of incident anemia at 90 days were male sex, geographical region other than Europe, ischemic etiology, higher glucose, and elevated uric acid at baseline (Suppl. Table 3). High-intensity care strategy did not increase rate of incident anemia at 90 days.

Overall, average hemoglobin decreased in both HIC and UC groups. When analyzing subgroups based on baseline anemia

Table 1 Baseline characteristics by presence of anemia at baseline

Parameter	Statistic	Anemia*		*P* value
		No (*N* = 784)	Yes (*N* = 293)	
Age, years	Mean (SD)	62.5 (13.41)	64.2 (13.99)	0.0696
Sex				
Female	*n* (%)	308 (39.3%)	108 (36.9%)	0.4669
Male	*n* (%)	476 (60.7%)	185 (63.1%)	
Self-reported race				
Black	*n* (%)	141 (18.0%)	89 (30.4%)	<0.0001
Caucasian/White	*n* (%)	634 (81.0%)	198 (67.6%)	
Native American	*n* (%)	1 (0.1%)	0	
Other	*n* (%)	6 (0.8%)	6 (2.0%)	
Pacific Islander	*n* (%)	1 (0.1%)	0	
Geographical region				
Europe	*n* (%)	609 (77.7%)	187 (63.8%)	<0.0001
Non-Europe	*n* (%)	175 (22.3%)	106 (36.2%)	
NT-proBNP at screening, ng/L	Geom. Mean (95% CI)	5878.2 (5645.3, 6120.8)	6398.5 (6002.0, 6821.1)	0.0304
History of atrial fibrillation or atrial flutter or present at screening	*n* (%)	359 (45.8%)	123 (42.0%)	0.2630
Medical history				
Stroke or transient ischemic attack	*n* (%)	68 (8.7%)	31 (10.6%)	0.3299
Severe liver disease	*n* (%)	4 (0.6%)	2 (0.8%)	0.7551
Psychiatric or neurological disorder	*n* (%)	14 (1.8%)	6 (2.1%)	0.7754
Malignancies	*n* (%)	19 (2.4%)	10 (3.4%)	0.3624
Diabetes	*n* (%)	231 (29.5%)	82 (28.1%)	0.6400
Diabetes control method				
Insulin	*n* (%)	57 (7.3%)	25 (8.6%)	0.4847
Diet only	*n* (%)	150 (19.2%)	52 (17.8%)	0.6083
Oral antidiabetic agents	*n* (%)	169 (21.6%)	65 (22.2%)	0.8393
Pulmonary embolism	*n* (%)	12 (1.5%)	7 (2.4%)	0.3409
Acute coronary syndrome	*n* (%)	233 (29.7%)	78 (26.6%)	0.3181
Coronary artery bypass surgery	*n* (%)	41 (5.2%)	18 (6.2%)	0.5492
Percutaneous transluminal coronary intervention	*n* (%)	111 (14.2%)	41 (14.0%)	0.9388
Angina Canadian Cardiovascular Society class 2 or higher	*n* (%)	99 (12.7%)	26 (8.9%)	0.0846
Moderate or severe chronic obstructive pulmonary disease or asthma	*n* (%)	18 (2.3%)	9 (3.1%)	0.4686
Sustained ventricular arrhythmia (with syncopal episodes in past 3 months)	*n* (%)	1 (0.1%)	0	0.5408
Cardiac resynchronization therapy	*n* (%)	5 (0.6%)	1 (0.3%)	0.5608
Automatic internal cardiac defibrillator	*n* (%)	8 (1.0%)	1 (0.3%)	0.2759
Heart failure history				
History of heart failure	*n* (%)	675 (86.1%)	241 (82.3%)	0.1154
NYHA class 1-month before hospital admission				
1	*n* (%)	36 (4.9%)	27 (9.9%)	0.0019
2	*n* (%)	213 (29.3%)	94 (34.6%)	
3	*n* (%)	308 (42.3%)	107 (39.3%)	
4	*n* (%)	171 (23.5%)	44 (16.2%)	
Ischemic etiology	*n* (%)	376 (48.1%)	138 (47.1%)	0.7739
Left ventricular ejection fraction, %	Mean (SD)	36.1 (12.58)	36.8 (12.37)	0.4563
Left ventricular ejection fraction category				
LVEF ≤ 40%	*n* (%)	535 (68.2%)	196 (66.9%)	0.6739

Table 1 (continued)

Parameter	Statistic	Anemia*		*P* value
		No (*N* = 784)	Yes (*N* = 293)	
LVEF > 40%	*n* (%)	249 (31.8%)	97 (33.1%)	
Hospitalized for heart failure in the past year?	*n* (%)	194 (24.7%)	79 (27.0%)	0.4566
Number of heart failure hospitalizations in the past year	Mean (SD)	0.3 (0.63)	0.5 (1.86)	0.0558
History of atrial fibrillation or atrial flutter	*n* (%)	375 (47.8%)	121 (41.3%)	0.0555
Type of atrial fibrillation or atrial flutter				
Paroxysmal	*n* (%)	88 (23.7%)	29 (24.4%)	0.2931
Permanent	*n* (%)	217 (58.5%)	76 (63.9%)	
Persistent	*n* (%)	66 (17.8%)	14 (11.8%)	
Baseline vital signs				
Systolic blood pressure at baseline, mmHg	Mean (SD)	122.5 (12.36)	123.9 (14.36)	0.1130
Pulse, beats/min	Mean (SD)	78.5 (11.42)	79.1 (12.73)	0.4444
Respiratory rate, breaths/min	Mean (SD)	18.0 (4.34)	18.8 (5.35)	0.0104
Local laboratory				
Hemoglobin, g/L	Mean (SD)	145.3 (14.64)	112.8 (11.11)	<0.0001
Lymphocytes, %	Mean (SD)	27.6 (9.53)	26.2 (10.43)	0.0295
White blood cells, 10^9/L	Mean (SD)	7.1 (2.05)	6.8 (1.93)	0.0204
Glucose, mmol/L	Mean (SD)	6.3 (2.39)	6.1 (2.12)	0.2845
Creatinine, umol/L	Mean (SD)	105.6 (26.25)	107.8 (34.99)	0.2842
Potassium, mmol/L	Mean (SD)	4.3 (0.45)	4.2 (0.45)	0.0026
Sodium, mmol/L	Mean (SD)	140.5 (4.18)	139.5 (4.06)	0.0006
Urea, mmol/L	Mean (SD)	8.0 (3.39)	8.2 (3.77)	0.2718
ALT, U/I	Mean (SD)	30.0 (36.65)	29.3 (58.67)	0.8212
Total bilirubin, umol/L	Mean (SD)	18.2 (11.72)	14.8 (9.68)	<0.0001
Total cholesterol, mmol/L	Mean (SD)	4.3 (1.05)	3.9 (1.19)	<0.0001
NT-proBNP, ng/L	Geom. Mean (95% CI)	3071.3 (2938.8, 3209.8)	3607.5 (3355.8, 3878.0)	0.0002
eGFR, mL/min/1.73m^2	Mean (SD)	62.0 (20.37)	64.0 (23.12)	0.1595
Oral heart failure medications taken at Visit 2:pre-randomization				
ACE inhibitors/ARBs/ARN inhibitors	*n* (%)	489 (62.5%)	200 (68.5%)	0.0699
ß-blockers	*n* (%)	295 (37.7%)	88 (30.1%)	0.0209
Mineralocorticoid receptor antagonists	*n* (%)	744 (95.1%)	274 (93.8%)	0.3920
Loop diuretic	*n* (%)	748 (95.7%)	281 (96.2%)	0.6726

*Anemia defined as baseline Hgb < 120 g/L in women and <130 g/L in men

status, it was revealed that average hemoglobin increased from baseline to day 90 by 7.80 (14.83) g/L in patients with baseline anemia and decreased by 6.29 (14.72) g/L in patients without baseline anemia (both paired *t* test $P < 0.0001$). These patterns were observed regardless of the treatment strategy. We additionally investigated the subgroup of patients with baseline hemoglobin level above 160 g/L ($n = 118$, 12%); they demonstrated a prominent reduction of hemoglobin at 90 days by 20.20 (17.11) g/L.

Baseline anemia and effect of high-intensity treatment

The percentages of optimal doses of GDMT in combination and separate drug classes of RASi, BBs, MRAs were not different between anemic and non-anemic patients (Figs. 2, 3, 4, 5). No significant interaction between the effect of rapid up-titration of GDMT and baseline anemia was found. This was true for the primary composite endpoint of all-cause

Table 2 Baseline characteristics by baseline hemoglobin

Parameter	Statistic	≤Median (*N* = 539)	>Median (*N* = 538)	*P* value
Age, years	Mean (SD)	63.3 (14.25)	62.6 (12.89)	0.3510
Sex				
Female	*n* (%)	209 (38.8%)	207 (38.5%)	0.9196
Male	*n* (%)	330 (61.2%)	331 (61.5%)	
Self-reported Race				
Black	*n* (%)	161 (29.9%)	69 (12.8%)	<0.0001
Caucasian/White	*n* (%)	367 (68.2%)	465 (86.4%)	
Native American	*n* (%)	0	1 (0.2%)	
Other	*n* (%)	9 (1.7%)	3 (0.6%)	
Pacific Islander	*n* (%)	1 (0.2%)	0	
Geographical region				
Europe	*n* (%)	350 (64.9%)	446 (82.9%)	<0.0001
Non-Europe	*n* (%)	189 (35.1%)	92 (17.1%)	
NT-proBNP at screening, ng/L	Geom. Mean (95% CI)	6043.2 (5766.7, 6333.0)	5987.7 (5695.4, 6295.0)	0.7913
History of atrial fibrillation or atrial flutter or present at screening	*n* (%)	220 (40.8%)	262 (48.7%)	0.0093
Medical history				
Stroke or transient ischemic attack	*n* (%)	57 (10.6%)	42 (7.8%)	0.1114
Severe liver disease	*n* (%)	2 (0.4%)	4 (0.9%)	0.3796
Psychiatric or neurological disorder	*n* (%)	10 (1.9%)	10 (1.9%)	1.0000
Malignancies	*n* (%)	14 (2.6%)	15 (2.8%)	0.8547
Diabetes	*n* (%)	160 (29.7%)	153 (28.5%)	0.6665
Diabetes control method				
Insulin	*n* (%)	36 (6.7%)	46 (8.6%)	0.2434
Diet only	*n* (%)	100 (18.6%)	102 (19.0%)	0.8528
Oral antidiabetic agents	*n* (%)	128 (23.7%)	106 (19.8%)	0.1146
Pulmonary embolism	*n* (%)	12 (2.2%)	7 (1.3%)	0.2488
Acute coronary syndrome	*n* (%)	143 (26.5%)	168 (31.2%)	0.0891
Coronary artery bypass surgery	*n* (%)	36 (6.7%)	23 (4.3%)	0.0817
Percutaneous transluminal coronary intervention	*n* (%)	73 (13.5%)	79 (14.7%)	0.5824
Angina Canadian Cardiovascular Society class 2 or higher	*n* (%)	57 (10.6%)	68 (12.7%)	0.2802
Moderate or severe chronic obstructive pulmonary disease or asthma	*n* (%)	17 (3.2%)	10 (1.9%)	0.1740
Sustained ventricular arrhythmia (with syncopal episodes in past 3 months)	*n* (%)	1 (0.2%)	0	0.3175
Cardiac resynchronization therapy	*n* (%)	5 (0.9%)	1 (0.2%)	0.1020
Automatic internal cardiac defibrillator	*n* (%)	7 (1.3%)	2 (0.4%)	0.0947
Heart failure history				
History of heart failure	*n* (%)	466 (86.5%)	450 (83.6%)	0.1954
NYHA class 1-month before hospital admission				
1	*n* (%)	38 (7.5%)	25 (5.1%)	0.0009
2	*n* (%)	172 (33.9%)	135 (27.4%)	
3	*n* (%)	213 (41.9%)	202 (41.1%)	
4	*n* (%)	85 (16.7%)	130 (26.4%)	
Ischemic etiology	*n* (%)	252 (46.8%)	262 (48.9%)	0.4851
Left ventricular ejection fraction, %	Mean (SD)	37.1 (12.46)	35.5 (12.54)	0.0356
Left ventricular ejection fraction category				
LVEF ≤ 40%	*n* (%)	356 (66.0%)	375 (69.7%)	0.1991
LVEF > 40%	*n* (%)	183 (34.0%)	163 (30.3%)	

Table 2 (continued)

Parameter	Statistic	≤Median ($N=539$)	>Median ($N=538$)	P value
Hospitalized for heart failure in the past year?	*n* (%)	146 (27.1%)	127 (23.6%)	0.1891
Number of heart failure hospitalizations in the past year	Mean (SD)	0.4 (1.44)	0.3 (0.62)	0.1131
History of atrial fibrillation or atrial flutter	*n* (%)	222 (41.2%)	274 (50.9%)	0.0013
Type of atrial fibrillation or atrial flutter				
Paroxysmal	*n* (%)	54 (24.7%)	63 (23.2%)	0.8795
Permanent	*n* (%)	131 (59.8%)	162 (59.8%)	
Persistent	*n* (%)	34 (15.5%)	46 (17.0%)	
Baseline vital signs				
Systolic blood pressure at baseline, mmHg	Mean (SD)	123.7 (14.10)	122.0 (11.62)	0.0246
Pulse, beats/min	Mean (SD)	79.6 (12.42)	77.7 (11.06)	0.0109
Respiratory rate, breaths/min	Mean (SD)	18.4 (5.50)	18.0 (3.59)	0.1324
Local Laboratory				
Hemoglobin, g/L	Mean (SD)	121.2 (13.04)	151.7 (12.81)	<0.0001
Lymphocytes, %	Mean (SD)	26.8 (10.07)	27.7 (9.52)	0.1144
White blood cells, 10^9/L	Mean (SD)	6.7 (1.94)	7.2 (2.07)	<0.0001
Glucose, mmol/L	Mean (SD)	6.1 (1.99)	6.4 (2.60)	0.0153
Creatinine, umol/L	Mean (SD)	106.9 (32.22)	105.5 (25.12)	0.4282
Potassium, mmol/L	Mean (SD)	4.2 (0.46)	4.3 (0.44)	0.0004
Sodium, mmol/L	Mean (SD)	139.6 (3.86)	140.8 (4.38)	<0.0001
Urea, mmol/L	Mean (SD)	8.1 (3.67)	8.0 (3.32)	0.7280
ALT, U/I	Mean (SD)	26.9 (46.78)	32.7 (40.25)	0.0294
Total bilirubin, umol/L	Mean (SD)	16.0 (11.24)	18.6 (11.24)	0.0002
Total cholesterol, mmol/L	Mean (SD)	4.1 (1.12)	4.4 (1.06)	<0.0001
NT-proBNP, ng/L	Geom. Mean (95% CI)	3358.4 (3186.9, 3539.2)	3065.5 (2903.0, 3237.1)	0.0179
eGFR, mL/min/1.73m^2	Mean (SD)	61.1 (19.15)	62.5 (21.16)	0.0311
Oral heart failure medications taken at Visit 2:Pre- Randomization				
ACE inhibitors/ARBs/ARN inhibitors	*n* (%)	363 (67.6%)	326 (60.7%)	0.0186
ß blockers	*n* (%)	173 (32.2%)	210 (39.1%)	0.0184
Mineralocorticoid receptor antagonists	*n* (%)	509 (94.8%)	509 (94.8%)	1.0000
Loop diuretic	*n* (%)	519 (96.6%)	510 (95.0%)	0.1705

Median baseline hemoglobin: female: 130 g/L, male: 141 g/L

death or HF readmission, for the secondary endpoints of all-cause death and change of EQ-VAS score, and exploratory endpoint of HF readmission. Sensitivity analyses of the primary endpoint and all-cause death excluding COVID deaths showed the same results. Analysis of the rate of the primary endpoint depending on baseline hemoglobin as a continuous variable showed that high-intensity therapy was beneficial regardless of baseline hemoglobin (Fig. 6).

Baseline anemia and frequency of adverse events

The frequency of serious adverse events was higher in anemic patients ($P=0.0058$), mostly driven by cardiac disorders, namely cardiac failure events (Suppl. Table 4). Also, patients with lower than median hemoglobin experienced more frequent serious adverse events, including cardiac failure and renal disorders ($P=0.0349$, Suppl. Table 5). Risk of any adverse events was not statistically different in these subgroups (Suppl. Tables 6 and 7). There was no significant subgroup-by-treatment interaction with the presence of baseline anemia or the level of hemoglobin, when analyzing any adverse or serious adverse events (all P values > 0.05, Suppl. Tables 8, 9, 10, 11).

Discussion

The present analysis of the STRONG-HF study showed a substantial prevalence of anemia in acute HF patients, which was associated with more severe congestion, poor kidney function, and older age at baseline. We demonstrated labile hemoglobin level during decongestion and 90 days

Table 3 Multivariable logistic regression model for associations of baseline characteristics with baseline anemia

Predictor	Estimate or unit change of:	Univariable results		Multivariable results	
		OR (95% CI)	*P* value	OR (95% CI)	*P* value
Male sex	Yes vs. No	1.11 (0.84, 1.46)	0.4671		
Age, years	2	1.02 (1.00, 1.04)	0.0703	1.05 (1.03, 1.08)	0.0001
BMI, kg/m^2	1	0.96 (0.94, 0.99)	0.0018	0.98 (0.95, 1.00)	0.0712
Geographical region	Europe vs. Rest	0.51 (0.38, 0.68)	<0.0001		
White race	Yes vs. No	0.57 (0.43, 0.75)	<0.0001	0.69 (0.48, 1.01)	0.0559
History of Afib	Yes vs. No	0.77 (0.58, 1.01)	0.0561		
History of Afib or aflutter present at screening	Yes vs. No	0.86 (0.65, 1.12)	0.2634		
Stroke or TIA	Yes vs. No	1.25 (0.80, 1.96)	0.3201		
Malignancies	Yes vs. No	1.47 (0.68, 3.18)	0.3340		
Hx diabetes	Yes vs. No	0.94 (0.69, 1.26)	0.6614		
Hx coronary artery bypass surgery	Yes vs. No	1.20 (0.68, 2.12)	0.5390		
Hx PCI	Yes vs. No	0.98 (0.67, 1.45)	0.9264		
Angina CCSC Class 2 or higher	Yes vs. No	0.67 (0.42, 1.05)	0.0813		
Hx COPD	Yes vs. No	1.35 (0.60, 3.04)	0.4703		
Ischemic etiology	Yes vs. No	0.96 (0.73, 1.26)	0.7638		
History of HF	Yes vs. No	0.75 (0.52, 1.07)	0.1165		
Hospitalized for HF in past year?	Yes vs. No	1.12 (0.83, 1.52)	0.4569		
Systolic BP, mmHg	5	1.04 (0.99, 1.10)	0.1137	1.05 (0.99, 1.11)	0.0952
Pulse, bpm	2	1.01 (0.99, 1.03)	0.4454		
Respiratory rate, breaths/min	1	1.04 (1.00, 1.07)	0.0329		
LVEF, %	2	1.01 (0.99, 1.03)	0.4459		
eGFR, mL/min/1.73m^2	59.21 vs. 47.81	1.00 (0.90, 1.11)	0.1719	1.38 (1.09, 1.76)	0.0188
	73.82 vs. 59.21	1.04 (0.94, 1.15)		1.45 (1.12, 1.88)	
NT-proBNP (log2)	Doubling	1.31 (1.14, 1.52)	0.0002	1.27 (1.08, 1.50)	0.0043
ALT (log2)	Doubling	0.78 (0.66, 0.92)	0.0024		
Creatinine, umol/L	102.34 vs. 87.00	0.95 (0.86, 1.05)	0.1256	1.25 (1.01, 1.54)	0.0092
	120.00 vs. 102.34	0.99 (0.90, 1.08)		1.30 (1.05, 1.61)	
Glucose, mmol/L	1	0.97 (0.91, 1.03)	0.2801		
Potassium, mmol/L	1	0.63 (0.47, 0.85)	0.0028	0.69 (0.50, 0.97)	0.0321
Sodium, mmol/L	1	0.95 (0.92, 0.98)	0.0007		
Total bilirubin, umol/L	1	0.97 (0.95, 0.98)	<0.0001	0.96 (0.94, 0.98)	<0.0001
Urea, mmol/L	1	1.02 (0.98, 1.06)	0.3071		
White blood cells, 10^9/L	1	0.92 (0.86, 0.99)	0.0210	0.93 (0.86, 1.00)	0.0507
Cholesterol, mmol/L	4.10 vs. 3.43	0.72 (0.63, 0.81)	<0.0001	0.67 (0.59, 0.77)	<0.0001
	4.89 vs. 4.10	0.89 (0.75, 1.07)		0.80 (0.67, 0.97)	
Uric acid, umol/L	5	1.00 (0.99, 1.00)	0.6753		
JVP Pre-rand	≥6 cm vs. <6 cm	1.60 (1.13, 2.25)	0.0079		
Rales Pre-rand	1/2/3 vs. No Rales	1.86 (1.31, 2.64)	0.0006		
Edema Pre-rand	1+/2+/3+vs. 0	1.06 (0.81, 1.39)	0.6733		
NYHA Class Pre-rand	III/IV vs. I/II	1.03 (0.78, 1.36)	0.8476		
On ACE/ARB/ARNI V2:Pre-rand	Yes vs. No	1.30 (0.98, 1.73)	0.0735		
On beta-blockers V2:Pre-rand	Yes vs. No	0.71 (0.53, 0.95)	0.0216		
On MRA V2:Pre-rand	Yes vs. No	0.78 (0.44, 1.39)	0.3993		
On loop diuretics V2:Pre-rand	Yes vs. No	1.15 (0.58, 2.31)	0.6877		

*Anemia defined as baseline Hgb < 120 g/L in women and < 130 g/L in men.

Table 4 Study endpoints stratified by the presence of anemia in the total study population

Outcome	Anemia at baseline		Un-adjusted		Adjusted	
	No	Yes	effect (95% CI)	*P* value	effect (95% CI)	*P* value
Primary endpoint						
All-cause death or heart failure readmission by day 180[a]	126/737 (18.2%)	57/270 (22.5%)	1.27 (0.90, 1.80)	0.1737	1.22 (0.86, 1.72)	0.2757
Secondary endpoints						
All-cause death by day 180[b]	56/737 (8.2%)	31/270 (12.4%)	1.53 (0.94, 2.48)	0.0858	1.24 (0.76, 2.03)	0.3882
EQ-VAS Change from Baseline to Visit 7[d]	10.19 (0.83)	6.47 (1.05)	−3.73 (05.73, −1.72)	0.0003	−2.34 (−4.37, −0.31)	0.0240
Exploratory endpoints						
HF readmission by day 180[c]	84/737 (12.6%)	37/270 (15.2%)	1.24 (0.81, 1.90)	0.3295	1.10 (0.71, 1.71)	0.6684
Sensitivity analyses						
All-cause death or heart failure readmission by day 180 (excluding COVID deaths)[a]	121/737 (17.5%)	56/270 (22.1%)	1.31 (0.92, 1.86)	0.1331	1.26 (0.88, 1.79)	0.2057
All-cause death (excluding COVID deaths) by day 180[b]	50/737 (7.2%)	30/270 (11.9%)	1.69 (1.02, 2.79)	0.0409	1.40 (0.84, 2.33)	0.1986

Data presented as *n* (Kaplan–Meier %) or LS-Mean change (SE). Effects are the LS-Mean difference between groups (for change in EQ-5D) and hazard ratio for the other endpoints. Results for patients in cohort 1 were down-weighted for day 180 analyses

[a]Adjusted for baseline diastolic blood pressure, ischemic heart disease, edema severity, and NT-proBNP

[b]Adjusted for baseline creatinine, urea, and NT-proBNP

[c]Adjusted for BMI, baseline diastolic blood pressure, baseline cholesterol, baseline potassium, baseline NT-proBNP, baseline LVEF, and edema

[d]LS-Mean change and LS-Mean difference from an ANCOVA model with baseline EQ-VAS, LVEF (≤40/>40%), region, and anemia status. Subjects from Mozambique were excluded from these analyses because of the unavailability of a linguistically validated tra nslation of the EQ-5D VAS in that country. Additional adjustment for age, creatinine, cholesterol, NT-proBNP, hospitalization for heart failure in the previous year, edema severity, and NYHA class

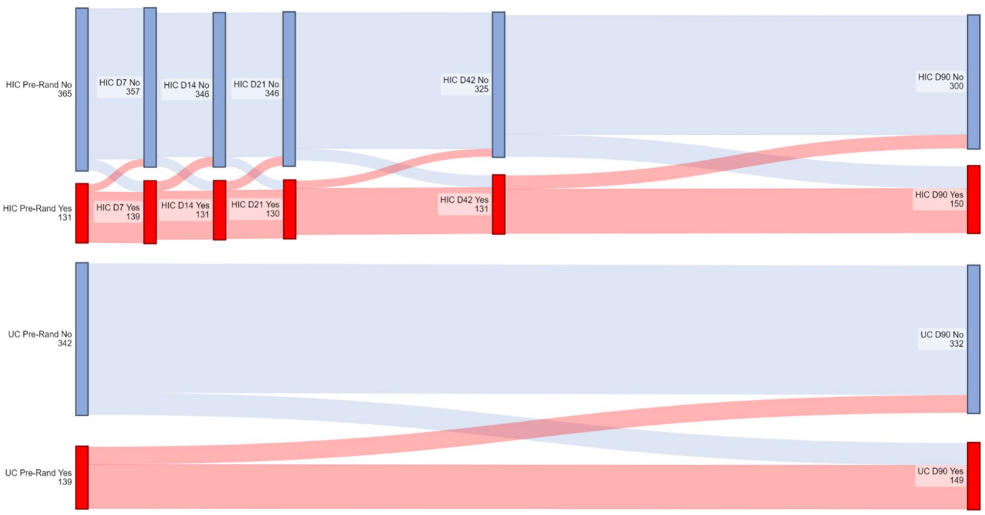


Fig. 1 Sankey plot of anemia by treatment and visit. Figure represents the progression of anemia status in high-intensity care (HIC) and usual care (UC) groups from pre-randomization to day 90. 'Yes' indicates the presence of anemia, while 'No' represents its absence

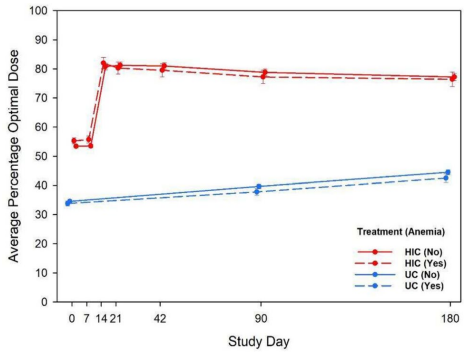


Fig. 2 Average percentage optimal dose by treatment and baseline anemia status

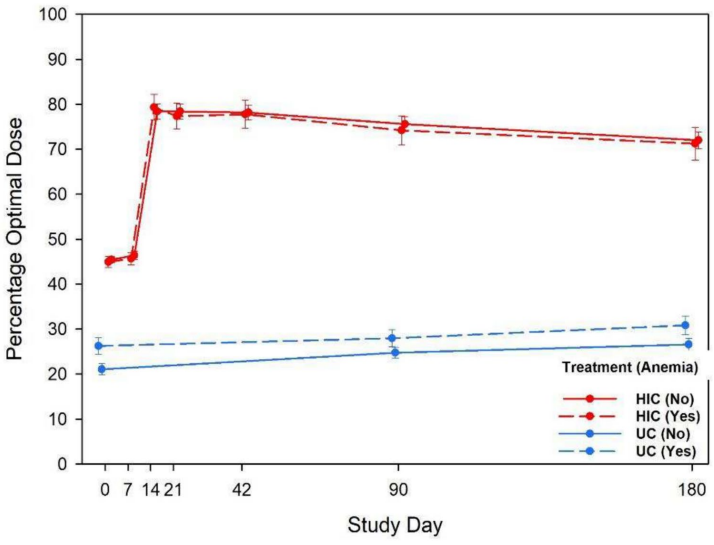
follow-up; some patients newly developed anemia during the study, while in about one quarter of study, patients' anemia recovered. The rate of all-cause death or HF readmission at 180 days was not different in anemic patients; however, their chance to improve quality of life at 90 days was significantly less compared to non-anemic participants. We showed that high-intensity treatment improved all clinical outcomes regardless of the presence of anemia and baseline hemoglobin level. Though anemic patients were more prone to serious adverse events, no interaction with the randomization group was found.

The prevalence of anemia of 27% in the STRONG-HF study exceeds the rate found in contemporary chronic randomized HF trials: 20% in the PARADIGM-HF [9] and 22% in the DAPA-HF [10] but is less than in the previous meta-analysis [5] (37%), recent observational BIOSTAT-HF cohort (36%) [11], and ESC-HF-LT registry [12]. Though performed in multiple geographical regions, the STRONG-HF study found that baseline anemia was significantly associated with non-European region and black race. Our data are consistent with previously accumulated knowledge on determinants of anemia [5]: the prevalence correlates with age, progression of kidney disease, and increasing severity of heart failure. It is notable that no sex differences are found in our analysis for baseline anemia, in contrast to prior observational data [13]. Interestingly, men were more affected by incident anemia at 90 days.

Previous research reported a significant interaction of anemia with LVEF, both as a continuous and categorical variable [11]. The prevalence of anemia in STRONG-HF was not different between subgroups of LVEF above or below 40%, similarly to ESC-HF-LT registry [12]. However, though not fulfilling criteria for anemia definition, patients with baseline hemoglobin level lower than the median had higher LVEF. In contrast, those patients who showed decrease of hemoglobin during 90 study days had lower LVEF than those who had stable or increasing hemoglobin level.

Anemia, being one of the most frequent comorbidities in HF patients, has a multifactorial etiology related to decreased renal blood flow, inflammatory cytokine inhibition

Fig. 3 Percentage optimal dose of RAASi by treatment and baseline anemia status



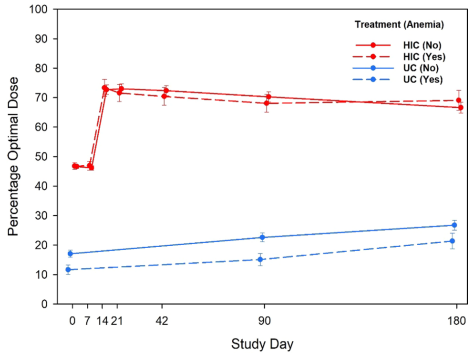


Fig. 4 Percentage optimal dose of beta-blockers by treatment and baseline anemia status

of erythropoiesis, iron deficiency, impaired erythropoietin production, as well as hemodilution.

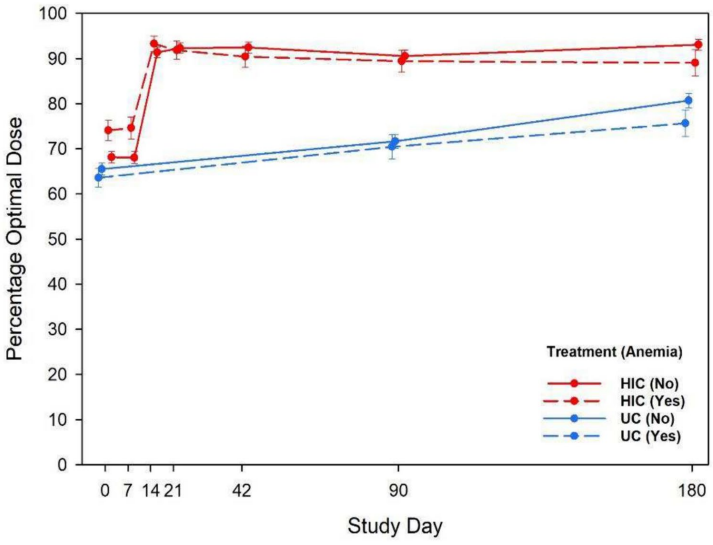
In the meta-analysis of 34 chronic HF studies (including cohort studies and secondary analyses of randomized trials), patients with HF and anemia had an unadjusted higher mortality risk compared to those without anemia: OR 1.96 [95% confidence interval (CI): 1.74 to 2.21, $P < 0.001$] [5]. Recently, in the large cohort of AHF patients with any EF, anemia was associated with higher risk of all-cause mortality [HR 1.6; 95% CI: 1.4–1.8, $P < 0.001$] [12]. Besides, observational data link anemia to repeated hospitalizations [13]. This relationship was not detected in our study, except one signal for all-cause mortality in the unadjusted sensitivity analysis which excluded COVID-related deaths. However, after adjustment to markers of kidney function and NT-proBNP, anemia was no longer related to all-cause mortality. Potential explanations for our contrasting results are: first, our acute HF trial was relatively limited in sample size and had follow-up too short to elicit the effect of the chronic comorbidity; second, anemia in HF presumably is associated with mortality most frequently indirectly, as a marker of declining renal function. Such explanation is consistent with the previously reported inverse relationship between creatinine level and effect of anemia on mortality [5, 14].

Baseline anemia did not impact the effect and safety of the HIC strategy in the STRONG-HF population. Throughout the whole hemoglobin spectrum, HIC was beneficial in improving primary, secondary, and exploratory endpoints. Allocation of anemic patients to the HIC group did not increase the risk of adverse or serious adverse events.

Like other comorbidities, such as diabetes, COPD, CKD, anemia was shown to worsen patients' quality of life [15]. This was confirmed in our analysis: anemia was a significant barrier to improvement of quality of life at 90 days assessed by EQ-5D in the total study population. This finding warrants specific attention to treatment of anemia and frequently concomitant iron deficiency in the pre-discharge and early post-discharge period.

Given that the precise cut-off of anemia in HF patients has not been rigorously validated [16], we analyzed our data according to the median sex-specific hemoglobin

Fig. 5 Percentage optimal dose of MRA by treatment and baseline anemia status



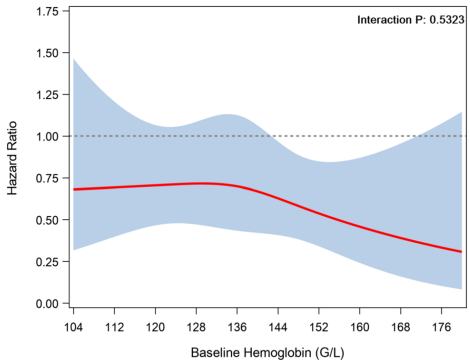


Fig. 6 Treatment effect of high-intensity care vs. usual care on primary endpoint by continuous baseline hemoglobin

level and found differences in hemodynamic and clinical profiles additional to variability based on categorization by the WHO definition of anemia. Hemoglobin level has changed during follow-up: it decreased in non-anemic patients and increased in anemic, similarly in both study groups. Decrease of hemoglobin occurred despite substantial decongestion achieved during the study.Reasons may be multiple—progression of the disease, recurrent congestion in some patients and HF drug effects. ACEis were shown to increase the risk of anemia [6]. ACE inhibitors might suppress erythropoiesis because they increase levels of hematopoiesis inhibitor N-acetyl- seryl-aspartyl-lysyl-proline [7, 17]. Valsartan also has been shown to decrease hemoglobin in patients with HFrEF [18]. In Val-HeFT study, a large decrease of hemoglobin (from 14.2 to 12.6 g/dL) was associated with increased risk of adverse events in longer follow-up, while in the subgroup of increasing hemoglobin, mortality was significantly lower. In COMET trial carvedilol, although reducing mortality in a larger extent than metoprolol, it increased the incidence of anemia [8].

Though incidence of new anemia cases at 90 days was numerically slightly higher in the HIC group (19.4 vs. 14.6%), the difference did not reach statistical significance. In the chronic HF trials SOLVD, COMET, Val-HeFT, 1-year incidence of anemia reached 9.6, 14.2, and 16.9%, respectively [6, 8, 18]. In our study, male sex, non-European location, and marker of inflammation (elevated uric acid) predicted incidence of anemia at 90 days. Men in the STRONG-HF had more frequent history of coronary artery disease, percutaneous interventions, and atrial fibrillation, therefore had to use more antithrombotic agents, which potentially could be associated with loss of hemoglobin. Besides, it has been shown previously that among elderly people, anemia was more common in men than in women, including patients with HF [19, 20]. It is also known that anemia is about three times more prevalent in African Americans than in non-Hispanic Caucasians [19].

In one quarter of patients, anemia has recovered, which can have several explanations. First, at hypervolemic status of acute HF, some cases of dilutional anemia are supposed to be at baseline. Second, GDMT potentially facilitates greater systemic iron absorption and use in a non-specific way.

Bilirubin is generated from the catalytic degradation of the heme in hemoglobin; thus, levels of these two blood parameters correlate and are diminished in anemic patients. Previously lower sodium levels were reported in anemic patients [21], relating electrolyte imbalance to the increased red-cell membrane-bound sodium–potassium adenosine triphosphatase (Na^+/K^+ ATPase) pump activity [22]. Reduced count of lymphocytes and white blood cells in anemic patients may reflect reduced stem cell production, low hematopoietic growth factor production, and altered sensitivity to hematopoietic cytokines in HF patients [23].

Limitations

The causes and types of anemia were not assessed. Also, markers of iron metabolism were not evaluated and data on iron deficiency or anemia correction during follow-up were not collected in our study. Additional predictors of anemia could be the use of antiplatelets and anticoagulants, but these data are not available. The hematocrit value would be useful in interpreting the relationship of hemoglobin level to the degree of congestion; however, it is not documented. Finally, it should be recognized that the data presented were not randomized according to hemoglobin level.

Conclusion

Hemoglobin level and status of anemia have a dynamic nature in the acute HF patients in the post-discharge period dependent on multiple factors. Anemia is most strongly associated with age, renal function, inflammatory status, and severity of congestion. High-intensity HF treatment is safe and beneficial regardless of baseline hemoglobin level and presence of anemia. The improvement of quality of life is significantly lower in anemic HF patients implying specific attention may be warranted to correction of this condition.

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Data availability The data underlying this article will be shared on reasonable request to the corresponding author.

Declarations

Conflict of interest JC has received personal fees from Novartis, AstraZeneca, Boehringer Ingelheim, Roche Diagnostics, and Pfizer. KČB has received personal fees from AstraZeneca, Boehringer Ingelheim and Bayer. GC, CE, MB, MN, KT, BD are employees of Momentum Research, which has received grants for research from Abbott Laboratories, Amgen, Celyad, Cirius Therapeutics, Corteria Pharmaceuticals, Heart Initiative, Sanofi, Windtree Therapeutics, and XyloCor Therapeutics. GC and BD are directors of Heart Initiative, a non-profit organization. MAd has received speaker fees from Abbott Vascular and Medtronic. AC-S has received honoraria for lectures or consultancy from AstraZeneca, Novartis, Vifor, Bayer, Merck, Sanofi, Abbott, and Boehringer Ingelheim. OC received grants from Servier. AD works for the Faculty of Medicine, Eduardo Mondlane University (Maputo, Mozambique), which received research grants from the Heart Initiative for their participation in this study. RD has received supporting fees for coordination of STRONG-HF trial activities. GF has received lecture fees or was a committee member for trials and registries sponsored by Bayer, Vifor, Boehringer Ingelheim, Medtronic, Servier and Amgen. MP has received personal fees from Abbott Laboratories, AstraZeneca, Boehringer Ingelheim and Vifor Pharma. PSP has received grants or research contracts from American Heart Association, Roche, Siemens, Ortho Diagnostics, Abbott, Beckman Coulter, and Siemens; consulting fees from Roche; honoraria from WebMD; and he has financial interest in The Heart Course. KS has received grants from Medtronic, Servier, and Amylam and honoraria from MSD, Novartis, and Sanofi. CSPL is supported by a Clinician Scientist Award from the National Medical Research Council of Singapore; has received research support from Novo Nordisk and Roche Diagnostics; has served as consultant or on the Advisory Board/Steering Committee/Executive Committee for Alleviant Medical, Allysta Pharma, AnaCardio AB, Applied Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Bristol.
Myers Squibb, CardioRenal, CPC Clinical Research, Eli Lilly, Impulse Dynamics, Intellia Therapeutics, Ionis Pharmaceutical, Janssen Research & Development LLC, Medscape/WebMD Global LLC, Merck, Novartis, Novo Nordisk, Prosciento Inc, Quidel Corporation, Radcliffe Group Ltd, Recardio Inc, ReCor Medical, Roche Diagnostics, Sanofi, Siemens Healthcare Diagnostics, and Us2.ai; and serves as cofounder and nonexecutive director of Us2.ai. AAV has received consultancy fees or research support from AstraZeneca, Bayer, BMS, Boehringer Ingelheim, Cytokinetics, Myocardia, Merck, Novartis, Novo Nordisk, and Roche Diagnostics. AM has received grants from Roche Diagnostics, Abbott Laboratories, 4TEEN4, and Windtree Therapeutics; honoraria for lectures from Roche Diagnostics, Bayer, and MSD; is a consultant for Corteria Pharmaceuticals, S-form Pharma, FIRE-1, Implicity, 4TEEN4, and Adrenomed; and is coinventor of a patent on combination therapy for patients having acute or persistent dyspnea. All other authors declare no competing interests.

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