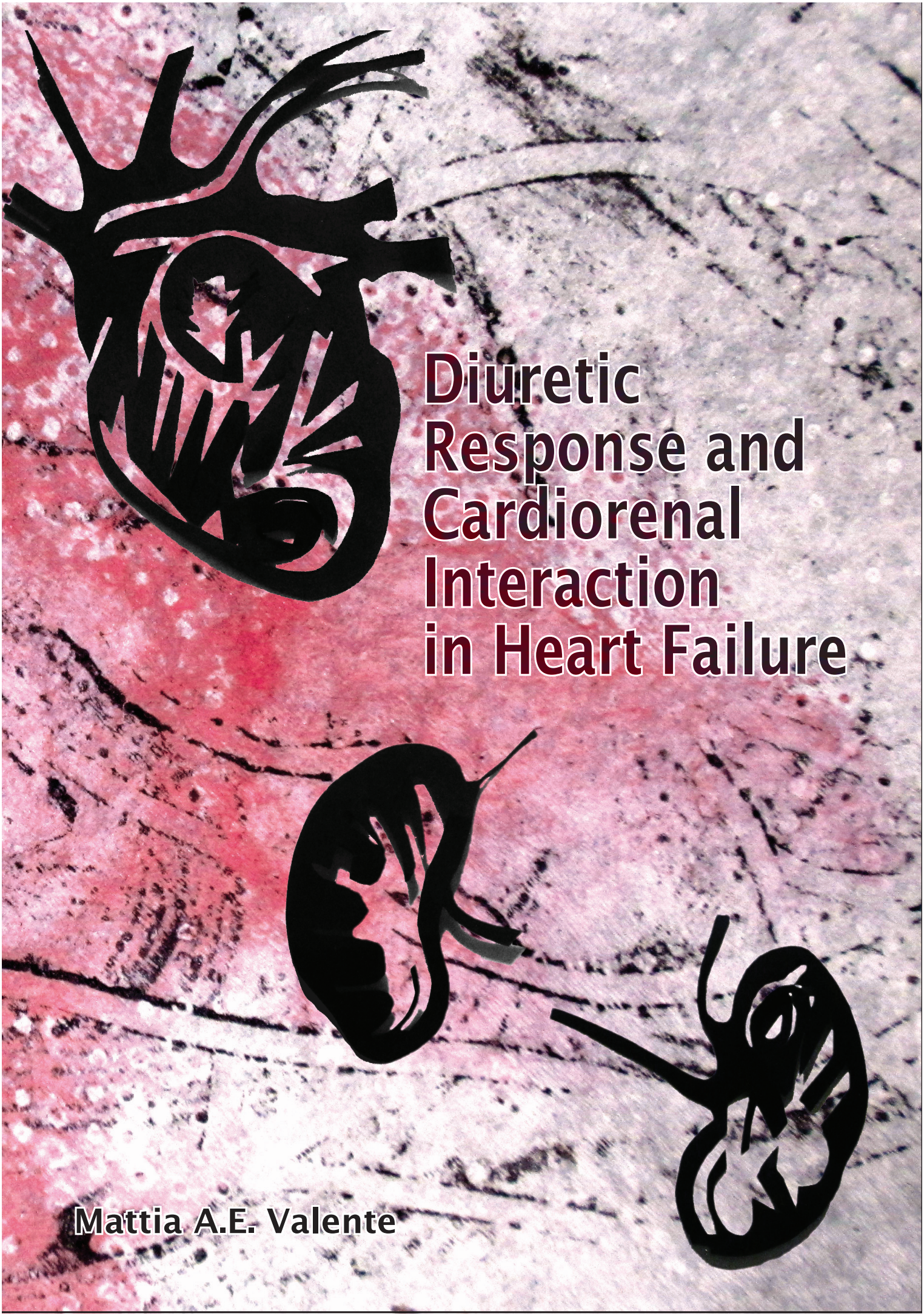

Diuretic
Response and
Cardiorenal
Interaction
in Heart Failure
Mattia A.E. Valente

# Diuretic Response and Cardiorenal Interaction in Heart failure

Mattia Adriano Egidio Valente

Valente, M.A.E.
Diuretic response and cardiorenal interaction in heart failure

ISBN 978-90-367-7630-1
ISBN (eBook) 978-90-367-7629-5



Cover & lay-out: Mattia A.E. Valente and Marilla C.L. Valente
Additional illustrations: Marilla C.L. Valente
Printed by: Grafimedia Facilitair Bedrijf RUG

university of groningen

# Diuretic Response and Cardiorenal Interaction in Heart Failure

**PhD thesis**

to obtain the degree of PhD at the
University of Groningen
on the authority of the
Rector Magnificus Prof. E. Sterken
and in accordance with
the decision by the College of Deans.

This thesis will be defended in public on

Monday 9 February 2015 at 16.15 hours

by

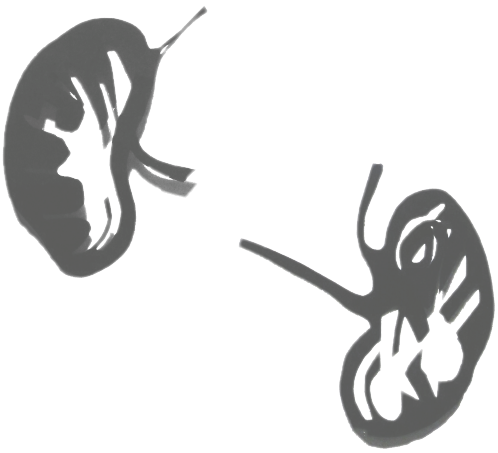
**Mattia Adriano Egidio Valente**

born on 29 March 1980
in Braine l'Alleud, Belgium

| | |
|---|---|
| Supervisors: | Prof. H.L. Hillege<br>Prof. A.A. Voors |
| Co-supervisor: | Dr. K. Damman |
| Assessment committee: | Prof. Y. Pinto<br>Prof. G.J. Navis<br>Prof. J.G.F. Cleland |

Paranypmhs: Dr. F.P.J. Brouwers
M.C.L. Valente, MSc

## Table of Contents



# Introduction

Awareness of the importance of renal dysfunction in patients with heart failure has been growing steadily over the past two decades. Preserved renal function is essential to maintaining volume and electrolyte homeostasis in the body and requires a solid hemodynamic foundation of low venous pressure and sufficient perfusion, largely provided by the heart. However, the kidney is nothing if not adaptable, capable of maintaining normal function over a wide range of blood pressures by regulating flow and filtration. It can do so thanks to various hormone systems and the sympathetic nervous system. Many of these systems are also strongly involved in cardiovascular diseases – in heart failure itself, and in causal or co-morbid conditions in heart failure patients, such as hypertension, diabetes, atrial fibrillation and coronary artery disease. Considering how closely intertwined heart and kidney are, it is unsurprising that renal impairment and worsening renal function are significant problems in heart failure, with a high prevalence and poor prognosis in both acute and chronic settings.

Heart failure is not a disease with a simple, singular cause, but a heterogeneous syndrome with diverse aetiologies in which abnormal structure or function of the heart results in an inability to provide the body with the oxygen and nutrients it requires. The specific features and degree of renal involvement vary from patient to patient. Both reduced forward flow and increased congestion – caused by the inability of the heart to manage the returning blood and/or venous pooling – cause the typical signs and symptoms of the condition: oedema, elevated venous and intracardiac pressures, rales, breathlessness and fatigue. This hemodynamic impairment is also accompanied by activation of the neurohormonal systems that play a part in regulating renal function, resulting in sodium and water retention and progressive congestion; dysfunction in either organ system can thus exacerbate failure in the other. Heart failure therapies – such as diuretics and Renin-Angiotensin-Aldosterone System (RAAS) blockers – have the potential to improve, but also further complicate matters by interfering with various aspects of renal autoregulation.

Heart failure is increasingly a disease of the elderly, and is reaching epidemic proportions as the general population ages, treatment improves and life expectancy increases. In addition to its health-economic importance as the leading cause of hospitalization in the developed world, heart failure has a major impact on patients' lives; it is associated with higher mortality rates and worse quality of life

than most forms of cancer. While treatment of co-morbid and underlying diseases in heart failure is certainly important, modern heart failure therapy is based on a broad range of effective, evidence-based medical and device interventions. The introduction of RAAS blockers, beta blockers, mineralocorticoid receptor antagonists (MRA), internal automatic cardiac defibrillators (ICD) and cardiac resynchronization therapy (CRT) have each led to significant reductions in morbidity and mortality in patients with chronic heart failure (CHF).

Unfortunately, the same cannot be said for patients with acute heart failure (AHF) – those hospitalized with worsening chronic or new-onset signs and symptoms of heart failure. Mortality and rehospitalization rates are high – approaching 40 percent during the 6 months post-admission – and therapies with a proven positive effect on outcomes are non-existent. Despite numerous recent large-scale trials with initially promising novel drugs, a convincingly effective treatment has yet to be established for this severely ill, high-risk patient population.

Treatment of AHF consists primarily of relieving symptoms of congestion, reducing volume overload and hemodynamic stabilization. Renal dysfunction is common in AHF and can contribute to reduced effectiveness of loop diuretics, which remain the cornerstone of therapy despite lacking evidence on optimal posology and administration, and no evidence for survival benefit. Further worsening of renal function is also frequently observed during hospitalisation. While generally a risk factor for poor outcome, there are indications that decline in renal function within the context of good response to (diuretic) therapy may not necessarily be harmful. However, impaired response to diuretic therapy – called diuretic resistance – is a very common and significant problem faced by clinicians who treat patients with AHF. Despite this, most definitions of diuretic resistance are qualitative and not readily applicable, and thus little is known about its true incidence, predictors or the best strategies to address it in heart failure patients. A workable definition for diuretic resistance and early identification of patients at risk for poor diuretic response may pave the road towards better-designed trials and personalized therapies for patients with this serious disease.

## Aims of the thesis

**Part I** of the thesis examines the impact, measurement and modulation of renal dysfunction in chronic and acute heart failure. Renal impairment is an established risk factor and clinical problem in both chronic and acute heart failure, and the pathophysiologic pathways involved in both organ dysfunctions are closely intertwined. There is a strong and growing interest in using renal and cardiovascular biomarkers to help elucidate these interactions and pathways, to improve risk stratification, and as potential targets for (guiding) therapy. Established heart failure therapies – particularly drugs that act on the RAAS - affect the kidney, and several novel candidate therapies for acute heart failure have renal effects or even directly target renal function.

**Chapter 1** presents the results of a systematic meta-analysis of renal impairment and worsening renal function in patients with both acute and chronic heart failure. **Chapter 2** sets out to validate the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation for estimating glomerular filtration rate (GFR) in chronic heart failure, comparing it with a gold-standard GFR measurement and several other biomarker-based GFR estimates. **Chapter 3** presents an overview of the utility of novel and established urinary biomarkers in heart failure, and **Chapter 4** examines the cardiorenal effects of various intravenous vasodilators used in the management of (acute) heart failure.

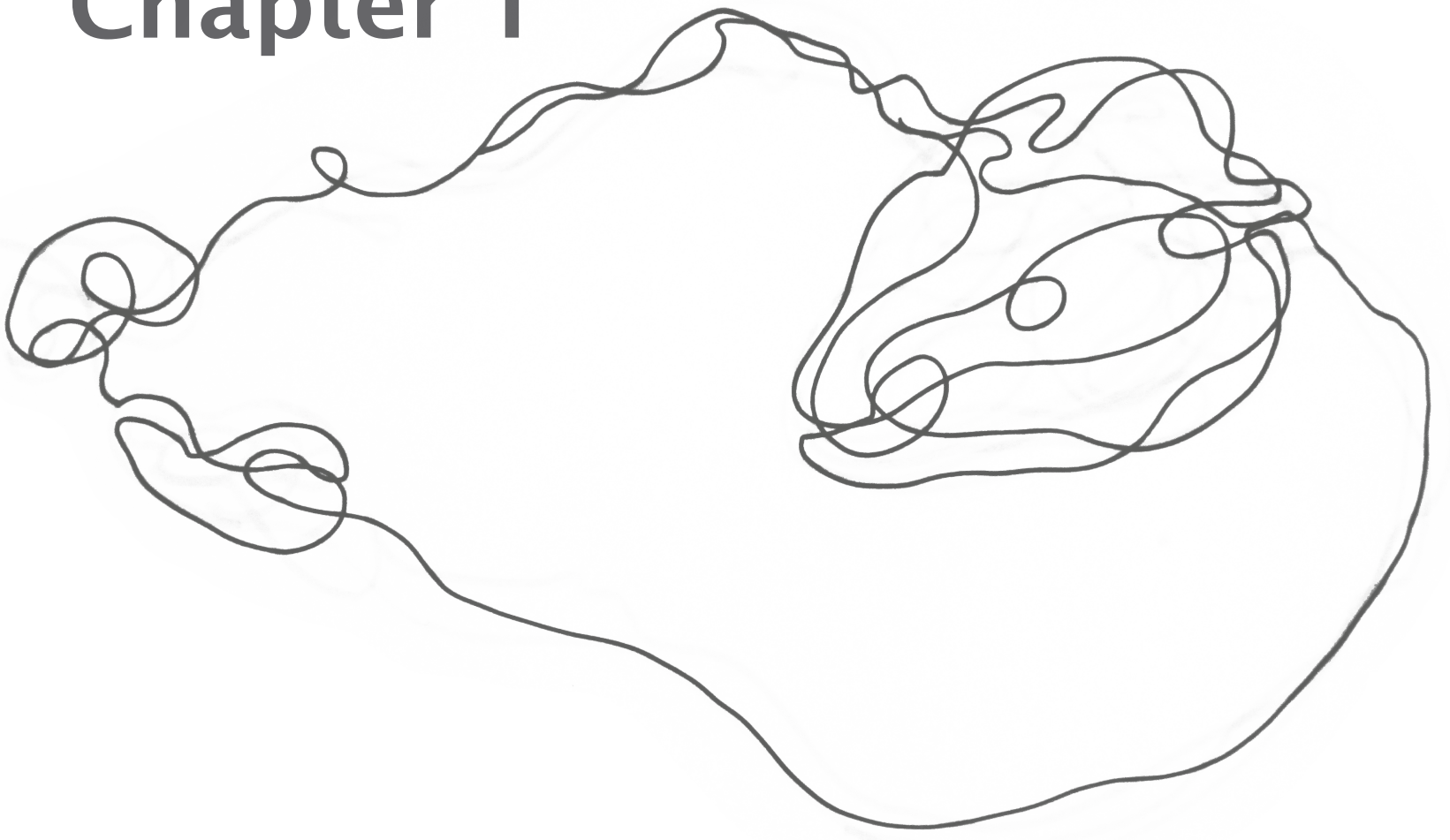
**Part II** focuses on diuretic therapy and worsening renal function in acute heart failure. Loop diuretics play a key role in the management of volume status in patients with AHF, yet strong evidence for optimal use is lacking despite decades of clinical experience. Resistance to diuretics is a common complication in AHF, and the potential mechanisms involved are legion; reduced cardiac output, congestion, renal dysfunction, azotemia, poor nutritional status and neurohormonal activation can all contribute. However, methods for quantifying response to diuretics – and thus diuretic resistance – have not been adequately defined or investigated in heart failure. **Chapters 5** and **7** are post-hoc analyses of the PROTECT trial, a randomized, controlled trial with neutral results that examined the effects of rolofylline, an adenosine A-1 antagonist, in patients with acute decompensated heart failure.

**Chapter 5** proposes a novel metric for diuretic response, defined as weight change per unit of loop diuretic, and investigates associations with clinical characteristics and outcomes. **Chapter 6** is an accompanying editorial on the importance of quantifying diuretic response in acute heart failure, written by Professor Emeritus Eugene Braunwald. **Chapter 7** describes patterns in and investigates the value of serial serum Neutrophil Gelatinase-Associated Lipocalin (NGAL, a novel tubular marker) measurements for predicting worsening renal function, and improving risk stratification in patients with AHF who develop worsening renal function. **Chapter 8** reviews the mechanisms and metrics of diuretic response and resistance, and outlines potential therapies to address the latter. Finally, the findings and relevance of this thesis and avenues for future research are discussed in the **Summary and future perspectives**.

# Part I

## Renal function in heart failure

# Chapter 1



# Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis

Kevin Damman, Mattia A.E. Valente, Adriaan A. Voors, Christopher M. O'Connor, Dirk J. van Veldhuisen and Hans L. Hillege

Published in: European Heart Journal (2014) 35, 455–469

## Abstract

**Aims** Chronic kidney disease (CKD) and worsening renal function (WRF) have been associated with poor outcome in heart failure (HF).

**Methods and results** Articles were identified by literature search of MEDLINE (from inception to 1 July 2012) and Cochrane. We included studies on HF patients and mortality risk with CKD and/or WRF. In a secondary analysis, we selected studies investigating predictors of WRF. We retrieved 57 studies (1 076 104 patients) that investigated CKD and 28 studies (49 890 patients) that investigated WRF. The prevalence of CKD was 32% and associated with all-cause mortality: odds ratio (OR) 2.34, 95% confidence interval (CI) 2.20–2.50, $P < 0.001$). Worsening renal function was present in 23% and associated with unfavourable outcome (OR 1.81, 95% CI 1.55–2.12, $P < 0.001$). In multivariate analysis, moderate renal impairment: hazard ratio (HR) 1.59, 95% CI 1.49–1.69, $P < 0.001$, severe renal impairment, HR 2.17, 95% CI 1.95–2.40, $P < 0.001$, and WRF, HR 1.95, 95% CI 1.45–2.62, $P < 0.001$ were all independent predictors of mortality. Across studies, baseline CKD, history of hypertension and diabetes, age, and diuretic use were significant predictors for the occurrence of WRF.

**Conclusion** Across all subgroups of patients with HF, CKD, and WRF are prevalent and associated with a strongly increased mortality risk, especially CKD. Specific conditions may predict the occurrence of WRF and thereby poor prognosis.

## Introduction

Despite modern heart failure (HF) therapy, the prognosis of patients with HF remains poor.[1] Risk estimation in this heterogeneous patient population has shown that HF patients frequently suffer from comorbidities. These comorbidities are not only prevalent, but also pose excess mortality risk.[2,3] As it plays a crucial role in the pathophysiology of HF, the most important comorbidity is renal impairment.[4] Defined as baseline reduction in glomerular filtration, or a worsening of renal function (WRF) over time, renal impairment has been associated with reduced survival in patients with HF over the past two decades.[5–7] In 2006, some six years after the first report on renal dysfunction and outcome in HF, a first meta-analysis showed a greatly increased mortality risk associated with renal impairment. In 2007, WRF was consistently found to increase mortality risk in HF.[8,9] However, these meta-analyses predominantly included patients recruited many years ago. Numerous new studies have since investigated the relationship between renal dysfunction and outcome, including patient populations that more closely resemble the modern HF populations. In the present analysis, we performed an updated meta-analysis of the relationship between baseline renal impairment, worsening renal function (WRF), and outcome, as well as an analysis of the clinical predictors of WRF in HF.

## Methods

### Literature search

MEDLINE was searched to identify eligible studies using search tools provided by PubMed (http://www.ncbi.nlm.nih.gov/pubmed/clinical) and via OVID (from inception to 1 July 2012). We used keywords including renal function, renal failure, chronic kidney disease, CKD, glomerular filtration rate, creatinine, cystatin C, blood urea nitrogen, GFR, heart failure, cardiac failure, CHF, AHF, ADHF, and combinations thereof. Inclusion was limited to papers published in the English language. Furthermore, we searched our own files, reviewed reference lists from eligible studies, used the 'see related articles' feature in PubMed, consulted the Cochrane Library, and searched the ISI Web of Knowledge (http://scientific.thomson.com/webofknowledge) to identify key publications. Abstracts and manuscripts were reviewed independently by two authors (K.D. and M.A.E.V.). Disagreements were solved by consensus. The corresponding author was contacted as needed to obtain data not included in the published report.

### Study selection

Our primary analyses encompassed the following studies: (i) studies investigating the relationship between baseline renal function and outcome in HF and (ii) studies investigating the relationship between WRF and outcome in HF. For both primary analyses, articles were excluded if: (i) no crude mortality data for the study groups were available even after contact with the authors, (ii) data were only published in abstract form, and (iii) no definition for HF was given. For the baseline renal

function analysis, all studies investigating chronic kidney disease (CKD) as defined by the individual studies were included. Chronic kidney disease in the individual studies had to be defined in one of the following ways: according to K/DOQI criteria [estimated glomerular filtration rate (GFR) <60 mL/min/1.73 $m^2$], other cut-offs for estimated GFR, creatinine, blood urea nitrogen or cystatin C or a combination thereof, or appropriate International Classification of Diseases (ICD) codes. For the WRF analysis, only studies that provided detailed description of the definition of WRF were included–either a decrease in estimated GFR, or an increase in serum creatinine or cystatin C over time. The primary outcome measure was defined as all-cause mortality at any time during hospitalization, shortly after hospitalization, or long-term outhospital mortality. Mean or median follow-up times from individual studies were used, and follow-up time for studies only reporting inhospital follow-up was set to 10 days.

## Study quality

The quality of the individual studies was assessed on 11 criteria: (1) sufficiently specified inclusion and exclusion criteria; (2) sufficient explanation of sample selection; (3) specification of clinical and demographic variables; (4) representativeness of the study sample for the mentioned patient population; (5) specification of outcome measures; (6) definition of renal insufficiency/WRF; (7) assessment of a 'dose–response' relationship between the extent of renal dysfunction/WRF and outcome; (8) adjustment for possible confounders in the analysis; (9) reporting of loss to follow-up rates; (10) study design; and (11) duration of follow-up. Two independent authors assessed study quality (K.D. and M.A.E.V.). The mean of both scores was used for final grading of study quality. Grading was as follows; good quality: 8–11 criteria, fair quality: 5–7 criteria, and poor quality: <5 criteria.

## Statistical analysis

Meta-analysis was performed using a random effects model to determine risk associated with the presence of either baseline CKD/WRF and all-cause mortality, as measured by combined crude mortality rates. In the secondary analysis, multivariate adjusted hazard ratios were pooled using inverse variance random effects models for either CKD or severe renal insufficiency. Severe renal insufficiency was defined as presented in the individual studies: depending on published subgroup data, lowest estimated GFR, or highest creatinine/cystatin C group/quartiles were used. Inter-study heterogeneity of risk estimates was examined using a standard $\chi^2$ test and $I^2$ statistic for heterogeneity. $I^2$ is the percentage of variance that is due to inter-study variance. Reasons for diversity in study results were explored using random effects meta-regression analysis. Variables investigated in meta-regression were: year of publication, total number of patients, acute vs. chronic HF, gender, mean age, race, mean follow-up time, left-ventricular ejection fraction (LVEF), mean baseline blood pressure, ischaemic aetiology, history of hypertension, diabetes or atrial fibrillation, renin–angiotensin system inhibitor use, diuretic use, beta-blocker use, aldosterone receptor antagonist use, baseline GFR, prevalence of CKD, base-

line creatinine, study design, and baseline haemoglobin levels, all if available. In secondary analysis, random effects meta-analysis for predictors of WRF was carried out with WRF as the outcome variable. For this analysis, baseline CKD, age, diuretic use, and a history of hypertension or diabetes were modelled separately in random effects models. A funnel plot was constructed to visually investigate possible confounding in published studies. The Metatrim command, which uses the imputation method by Duval and Tweedie[10] to account for the asymmetry of the funnel plot, was used to address significant publication bias where present. Results are presented as odds ratios (ORs) or hazard ratios (HRs) with 95% confidence intervals (CIs) and *P*-values. All reported probability values are two-tailed, and a *P*-value of <0.05 was considered statistically significant. Statistical analyses were performed using Stata 10.0, College Station, TX, USA and Revman 5.1.[11]

## Results

Our initial search identified a total of 68 studies that investigated baseline CKD or WRF and prognosis in HF. After contact with individual authors, another 17 studies with crude mortality rates were identified, resulting in 57 studies investigating baseline CKD and outcome, and 28 studies investigating WRF and outcome in HF.[5–7,12–90] In total, 55 of the 82 unique studies were of good study quality, 23 studies were of fair quality, and four studies were of poor quality. 1 076 104 patients with HF were included in the individual studies used for the CKD analyses, while a total of 49 890 HF patients were included in those for the WRF analyses. Design, number of included patients and baseline characteristics per study are presented in *Tables 1* and *2*. The QUOROM diagrams in *Figure 1* show the inclusion and exclusion of identified studies. Notably, the MAGGIC individual patient meta-analysis was excluded in the primary analysis because of a large overlap with included studies, and introduced as a replacement for these studies in secondary analysis. Furthermore, we included the study by Testani *et al*.[79] from the ESCAPE trial instead of the study by Nohria *et al*.[91], since the latter did not report crude mortality rates. For the WRF substudy of the SOLVD studies, we included the study by Khan *et al*.[88] instead of Testani *et al*.[92] for similar reasons. Mean age among all studies was 69 ± 7 years, 62% male. Among studies with published ejections fractions ($n$ = 53), mean LVEF was 34 ± 8%, while LVEF was preserved (with cut-off for preserved LVEF being different across studies) in 34% (range 8–100) of patients in 27 studies. Mean estimated GFR was 62 ± 9 mL/min/1.73 $m^2$, with a mean serum creatinine of 120 µmol/L (1.36 ± 0.20 mg/dL).

### Baseline chronic kidney disease and all-cause mortality

Of 1 076 104 patients, in total, 32% had CKD as defined in the individual studies. Excluding the registries by Kao and Herzog *et al*., which reported significantly lower figures, overall CKD prevalence was 49%, with higher prevalence in studies in acute HF (53%) vs. chronic HF (42%). After a mean follow-up of 681 ± 704 days (acute HF: 361 ± 333 days, chronic HF: 942 ± 802 days), the crude mortality rates for patients

with and without CKD at baseline were 16 and 11%, respectively. This resulted in a combined unadjusted odds ratio (OR) for mortality of 2.34, 95% CI 2.20–2.50, $P < 0.001$ (*Figure 2*). This effect was slightly greater in acute (OR = 2.39, 95% CI 2.25–2.54, $P < 0.001$) vs. chronic HF (OR = 2.26, 95% CI 2.08–2.47, $P < 0.001$). Excluding studies with only inhospital mortality data, the effect in acute HF was even more pronounced (OR = 2.50, 95% CI 2.28–2.75, $P < 0.001$). The effect of CKD in studies that used a cut-off of eGFR < 60 mL/min was similar (OR = 2.28, 95% CI 2.10–2.47, $P < 0.001$). For the overall effect, the Funnel plot showed no evidence of publication bias (*Figure 3*). A total of 44 studies assessed the multivariate adjusted mortality risk associated with moderate CKD, while 22 studies assessed adjusted mortality risk associated with severe renal impairment. Moderate CKD showed consistent association with poor outcome with an adjusted HR of 1.59, 95% CI 1.49–1.69, $P < 0.001$, while severe renal impairment was strongly associated with poor outcome in adjusted analysis: HR 2.17, 95% CI 1.95–2.40, $P < 0.001$. Significant heterogeneity was present in the main study analysis ($I^2 = 91\%$, $P < 0.001$), similar to the heterogeneity in the adjusted analyses. In meta-regression analysis, higher LVEF, diuretic use, and shorter follow-up duration were associated with the effect of CKD on outcome. The presence of CKD was of greater prognostic importance in patients

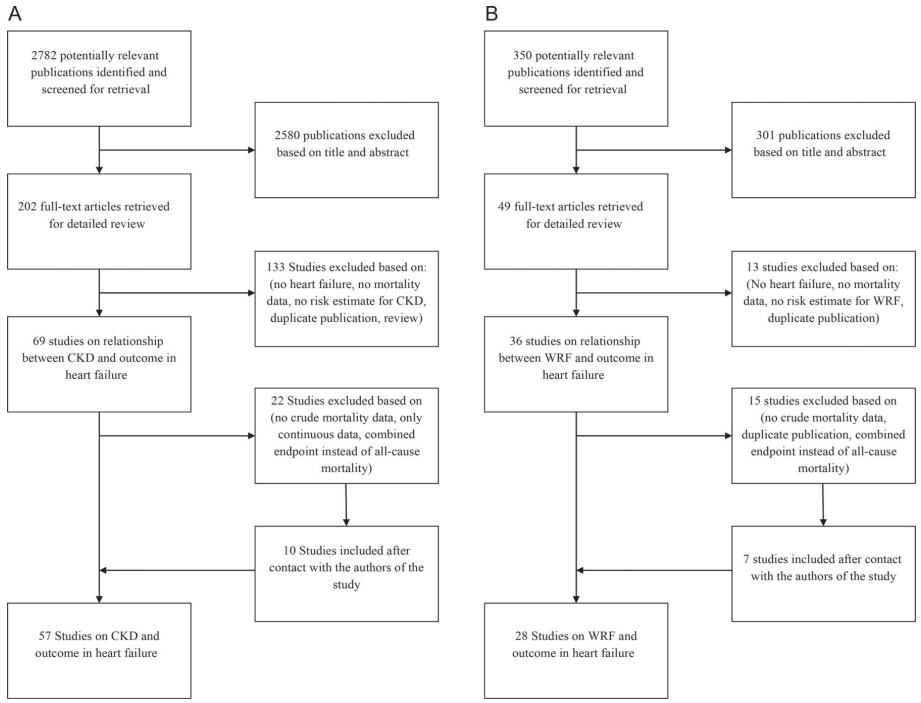



**Figure 1** (A) Quality of Reporting of Meta-Analyses (QUOROM) flow diagram for study selection for the CKD analysis. CKD, chronic kidney disease. (B) Quality of Reporting of Meta-Analyses (QUOROM) flow diagram for study selection for the WRF analysis. WRF, worsening renal function.

**Table 1** Characteristics of studies included in the chronic kidney disease analysis

| First Author (Study name), Year of publication | Study Design | N | Mean/median F/U (days | Age (yr) | Men (%) | LVEF (%) | HF-PEF (%) | DM (%) | HT (%) | IHD (%) | sCr (µmol/L) | ACEi/ARB (%) | BBL (%) | Diuretic (%) | Digoxin (%) | CKD Definition |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ACUTE HEART FAILURE | | | | | | | | | | | | | | | | |
| Madsen, 1994 [5] | Cohort | 190 | 720 | 66 | 72 | 30 | 14 | - | - | 66 | - | - | 4 | 96 | 54 | sCr > 121 µmol/L |
| Akhter (VMAC), 2004 [12] | Substudy RCT | 1 685 | 180 | 62 | 69 | - | 15 | 48 | 70 | 53 | - | 70 | 33 | 86 | 60 | sCr > 133 µmol/L |
| Aronson, 2004 [13] | Substudy RCT | 541 | 343 | 53 | 70 | - | - | 45 | - | 54 | 141 | 71 | 14 | 88 | 72 | CrCl < 60 mL/min |
| Smith (NHCP), 2005 [14] | Registry | 53 640 | 365 | 79 | 42 | - | - | 40 | 64 | 30 | 133 | - | 29 | 66 | 39 | eGFR < 60 mL/min |
| Anwaruddin (PRIDE), 2006 [15] | Substudy RCT | 599 | 60 | 62 | 51 | - | - | - | 49 | - | 98 | - | 38 | 30 | 11 | eGFR < 60 mL/min |
| Heywood(ADHERE), 2007 [16] | Registry | 118 465 | Inhospital | 72 | 48 | 38 | 46 | 44 | 73 | 57 | 156 | 61 | 56 | 89 | 32 | eGFR < 60 mL/min |
| Pimenta, 2007 [17] | AHF | 283 | 180 | 73 | 48 | - | 58 | 42 | 52 | 49 | | - | - | - | - | eGFR < 60 mL/min |
| Lassus (FINN-AKVA), 2007 [18] | Registry | 480 | 365 | 75 | 50 | 45 | 50 | 33 | 57 | 55 | 100 | 78 | 85 | 89 | 38 | Cystatin C > 1.3 mg/L |
| Petretta, 2007 [19] | Cohort | 153 | 456 | 64 | 72 | 34 | 23 | 35 | - | 79 | | 86 | 57 | - | 36 | eGFR < 60 mL/min |
| Filippatos (ACTIV in CHF), 2007 [20] | Substudy RCT | 302 | 60 | 62 | 70 | 24 | - | 47 | 72 | - | 169 | 82 | 42 | 97 | 68 | BUN > 26 mg/dL |
| Patel (GWTG-HF), 2008 [21] | Registry | 15 560 | Inhospital | 76 | 50 | 35 | 56 | 42 | 70 | 47 | 115 | - | 90 | - | - | eGFR < 60 mL/min |
| Klein (OPTIME-CHF), 2008 [22] | Registry | 937 | 60 | 66 | 66 | 24 | - | 44 | 68 | 51 | 133 | 82 | 22 | 90 | 73 | BUN > 23 mg/dL |
| Amsalem, 2008 [2] | Registry | 3 793 | 365 | 73 | 57 | - | 27 | 51 | 75 | 82 | 133 | 60 | 49 | 62 | 14 | eGFR < 60 mL/min |
| Hamaguchi (JCARE-CARD), 2009 [24] | Substudy RCT | 1 617 | 862 | 72 | 59 | 43 | - | 31 | 55 | 32 | - | 83 | 48 | 87 | 31 | eGFR < 60 mL/min |
| Martin-Pfitzenmeyer, 2009 [25] | Cohort | 104 | 365 | 87 | 39 | - | 31 | 19 | 63 | - | - | 68 | 31 | 81 | 21 | CrCl < 30 mL/min |
| Kimura, 2009 [26] | Cohort | 711 | 791 | 69 | 56 | 41 | - | 36 | 47 | 40 | 107 | - | - | - | - | eGFR < 60 mL/min |
| Takagi, 2009 [27] | Cohort | 194 | 609 | 69 | 71 | 36 | - | 31 | - | 39 | 120 | - | - | - | - | eGFR < 60 mL/min |

| First Author (Study name), Year of publication | Study Design | N | Mean/median F/U (days | Age (yr) | Men (%) | LVEF (%) | HF-PEF (%) | DM (%) | HT (%) | IHD (%) | sCr (µmol/L) | ACEi/ARB (%) | BBL (%) | Diuretic (%) | Digoxin (%) | CKD Definition |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Campbell, 2009 [28] | Cohort | 240 | 365 | 63 | 50 | 31 | 35 | 46 | 70 | 42 | 106 | - | - | - | - | Cystatin C >1.19 mg/L |
| Manzano-Fernandez, 2009 [29] | Cohort | 138 | 261 | 75 | 53 | 49 | - | 51 | 83 | 35 | - | 84 | 54 | 88 | - | eGFR < 60 mL/min |
| Harjola, 2010 [30] | Registry | 2 979 | 365 | 72 | 62 | 38 | 35 | 33 | 62 | 33 | 106 | 80 | 62 | - | - | sCr > 177 µmol/L |
| Tarantini (IS-AHF), 2010 [31] | Registry | 1 008 | 180 | 73 | 59 | 37 | 17 | 38 | 66 | 39 | 133 | 84 | 45 | 94 | 40 | eGFR < 60 mL/min |
| Velavan (EuroHeart Failure Survey I), 2010 [32] | Registry | 10 701 | 84 | 71 | 53 | - | - | 27 | 53 | - | - | 65 | 37 | 81 | 36 | ♀ sCr > 107 µmol/L<br>♂ sCr > 127 µmol/L |
| Vaz Perez, 2010 [33] | Cohort | 128 | 1 545 | 63 | 76 | 28 | - | - | - | 59 | 110 | 79 | 62 | 69 | 44 | CrCl < 60 mL/min |
| Carrasco-Sanchez, 2011 [34] | Cohort | 198 | 365 | 76 | 40 | - | 100 | 53 | 84 | 19 | 94 | 80 | 48 | 93 | - | Cystatin C > 1.45 mg/L |
| Blair (EVEREST), 2011 [35] | Substudy RCT | 2 021 | 297 | 66 | 75 | 28 | - | 38 | 71 | 66 | 125 | 84 | 70 | 97 | - | eGFR < 60 mL/min |
| Manzano-Fernandez, 2011 [36] | Cohort | 220 | 500 | 73 | 52 | 46 | - | 58 | 82 | 37 | 97 | 85 | 64 | 92 | - | eGFR < 60 mL/min |
| Kao, 2011 [37] | Registry | 596 456 | Inhospital | - | 44 | - | - | 41 | 61 | 50 | - | - | - | - | - | ICD-codes |
| CHRONIC HEART FAILURE | | | | | | | | | | | | | | | | |
| Dries (SOLVD), 2000 [6] | | | | | | | | | | | | | | | | |
| Prevention | Substudy RCT | 3 673 | 1 132 | 59 | 89 | 28 | - | 15 | 37 | 83 | 103 | 50 | - | 17 | 13 | CrCl < 60 mL/min |
| Treatment | | 2 161 | 1 278 | 61 | 82 | 25 | - | 25 | 40 | 71 | 108 | 50 | - | 84 | 69 | CrCl < 60 mL/min |
| Hillege (PRIME II), 2000 [7] | Substudy RCT | 1 866 | 277 | 65 | 80 | 26 | - | 21 | - | 59 | 120 | - | 6 | 99 | 64 | eGFR < 59 mL/min |
| Marenzi, 2001 [38] | Cohort | 3 673 | 570 | 54 | 79 | - | - | - | - | 66 | 159 | - | 0 | 98 | 72 | sCr > 133 µmol/L |
| McClellan (Medicare), 2002 [39] | Registry | 148 | 365 | 76 | 40 | 38 | 40 | 44 | 66 | 51 | 129 | - | - | - | - | ♀ sCr > 124 µmol/L<br>♂ sCr > 133 µmol/L |
| Muntwyler (IMPROVEMENT in HF), 2002 [40] | Registry | 665 | 365 | 75 | 56 | - | 18 | 18 | 20 | 39 | - | 65 | 26 | 76 | 31 | sCr > 120 µmol/L |
| Pulignano (IN-CHF), 2002 [41] | Substudy RCT | 411 | 365 | 63 | 74 | - | 26 | - | 20 | 42 | - | - | 11 | 87 | 69 | sCr > 221 µmol/L |

| First Author (Study name), Year of publication | Study Design | N | Mean/median F/U (days | Age (yr) | Men (%) | LVEF (%) | HF-PEF (%) | DM (%) | HT (%) | IHD (%) | sCr (µmol/L) | ACEi/ARB (%) | BBL (%) | Diuretic (%) | Digoxin (%) | CKD Definition |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Shlipak (DIG), 2004 [42] | Substudy RCT | 481 | 1 110 | 63 | 78 | 29 | - | 29 | 45 | 71 | 112 | - | - | 82 | 50 | eGFR ≤ 60 mL/min |
| Bibbins-Domingo (HERS), 2004 [43] | Substudy RCT | 6 800 | 2 117 | 68 | 0 | - | 40 | 33 | - | 100 | 104 | - | 40 | 65 | 28 | CrCl ≤ 60 mL/min |
| Ezekowitz (APPROACH), 2004 [44] | Substudy RCT | 722 | 365 | 69 | 65 | 37 | - | 21 | 39 | 100 | - | 58 | 56 | - | - | CrCl < 60 mL/min |
| McAllister, 2004 [45] | Cohort | 6 427 | 926 | 69 | 66 | 34 | - | 25 | 34 | 66 | - | 91 | 48 | 83 | 63 | CrCl < 60 mL/min |
| Herzog, 2004 (Medicare) [46] | Registry | 150 000 | 730 | 77 | 39 | - | - | 17 | 50 | - | - | - | - | - | - | ICD codes for CKD |
| Shlipak (CHS), 2005 [47] | Cohort | 754 | 2 373 | 77 | 78 | - | - | 44 | - | 63 | 103 | - | - | - | - | eGFR < 61.8 mL/min |
| Go (ANCHOR), 2006 [48] | Registry | 55 167 | 756 | 72 | 53 | - | 8 | 32 | 61 | 36 | 106 | 24 | 15 | 37 | - | eGFR < 60 mL/min |
| Roik, 2006 [49] | Cohort | 498 | 365 | 69 | 63 | 41 | - | 26 | 64 | 84 | 124 | - | 77 | 73 | 17 | sCr > 124 µmol/L |
| Hillege (CHARM), 2006 [50] | Substudy RCT | 2680 | 1 032 | 65 | 67 | 39 | - | 37 | - | 67 | 106 | - | 55 | 71 | 53 | eGFR < 60 mL/min |
| Bruch, 2007 [51] | Cohort | 269 | 507 | 59 | 76 | 30 | - | - | - | 50 | 127 | 97 | 89 | 86 | 55 | eGFR < 60 mL/min |
| Shalaby, 2008 [52] | Cohort | 330 | 591 | 67 | 82 | 22 | - | 41 | 63 | 64 | | 80 | 77 | - | - | sCr > 88 µmol/L |
| Cohen-Solal (SENIORS), 2009 [53] | Substudy RCT | 2 112 | 627 | 76 | 63 | 36 | 35 | 26 | 62 | 69 | 103 | 89 | 50 | 86 | 39 | eGFR < 55.5 mL/min |
| Scrutinio, 2009 [54] | Cohort | 266 | 859 | 76 | 76 | 29 | 52 | 26 | 45 | 53 | 119 | 88 | 58 | 92 | - | CrCl < 50 mL/min |
| Anand (VALHEFT), 2009 [55] | Substudy RCT | 5 010 | 810 | 62 | 80 | 27 | - | 25 | | 58 | | 143 | 34 | 85 | 67 | eGFR < 60 mL/min |
| Alehagen, 2009 [56] | Cohort | 464 | 3 650 | 73 | 52 | - | 11 | 21 | 87 | - | | 33 | 41 | 41 | 10 | Cystatin C >1.42 mg/L |
| Damman (CIBIS-II), 2010 [57] | Substudy RCT | 2 630 | 475 | 61 | 80 | 28 | - | 12 | 43 | 50 | 104 | - | 50 | 99 | 52 | eGFR < 60 mL/min |
| Hebert, 2010 [58] | | 1 301 | 2 880 | 56 | 65 | 29 | - | 33 | - | 80 | | 93 | 97 | - | 24 | eGFR < 60 mL/min |
| Wali (CAPRICORN-COPERNICUS), 2010 [59] | Substudy RCT | 4 217 | 405 | 63 | 77 | 26 | - | 24 | 45 | 21 | 123 | 99 | 50 | 72 | 40 | eGFR ≤ 60 mL/min |
| Damman (COACH), 2010 [60] | Substudy RCT | 1 049 | 550 | 71 | 62 | 34 | - | 28 | 43 | 43 | 125 | 83 | 66 | 95 | 30 | eGFR < 60 mL/min |

| First Author (Study name), Year of publication | Study Design | N | Mean/median F/U (days | Age (yr) | Men (%) | LVEF (%) | HF-PEF (%) | DM (%) | HT (%) | IHD (%) | sCr (µmol/L) | ACEi/ARB (%) | BBL (%) | Diuretic (%) | Digoxin (%) | CKD Definition |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Waldum, 2010 [61] | Registry | 1 235 | 270 | 71 | 70 | 33 | - | 19 | 30 | 59 | 111 | 89 | 78 | 88 | - | eGFR < 60 mL/min |
| Scrutinio, 2011 [62] | Cohort | 951 | 720 | 64 | 79 | - | 28 | 25 | 41 | 49 | 109 | 100 | 73 | 90 | - | eGFR < 60 mL/min |
| Filippatos (BEST), 2011 [63] | Substudy RCT | 1 260 | 750 | 60 | 78 | 23 | - | 34 | 59 | 58 | 107 | 98 | 50 | 94 | 92 | eGFR < 60 mL/min |
| Masson (GISSI-HF), 2011 [64,65] | Substudy RCT | 6 975 | 1423 | 68 | 78 | 33 | 10 | 26 | 55 | 40 | 104 | 93 | 62 | 90 | 40 | eGFR < 60 mL/min |

For serum creatinine, to convert from µmol/L to mg/dL divide by 88.4. eGFR expressed per 1.73m2 of body surface area.
ACE-i/ARB, angiotensin-converting enzyme inhibitor and/or angiotensin receptor blocker therapy; BBL, beta-blocker therapy; CKD, chronic kidney disease; DM, history of diabetes; HFPEF, heart failure with preserved ejection fraction; HT, history of hypertension; IHD, ischaemic heart disease; F/U, follow-up; LVEF, left-ventricular ejection fraction; sCr, serum creatinine.

**Table 2** Characteristics of studies included in the WRF analysis

| First Author (Study name), Year of publication | Study Design | N | Mean F/U (days) | Age (yr) | Men (%) | LVEF (%) | DM (%) | HT (%) | IHD (%) | sCr ( µmol/L) | ACEi/ ARB (%) | BBL (%) | Diuretic (%) | Digoxin (%) | WRF Definition |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ACUTE HEART FAILURE | | | | | | | | | | | | | | | |
| Krumholz (Medicare), 2000 [66] | Registry | 1 681 | 30 | 79 | 42 | - | 38 | 60 | 37 | - | - | - | 92 | - | > 26.5 µmol/L increase in sCr |
| Smith, 2003 [67] | Cohort | 412 | 180 | 72 | 51 | 39 | 47 | - | - | 159 | - | - | - | - | > 26.5 µmol/L increase in sCr |
| Akhter (VMAC), 2004 [12] | Substudy RCT | 481 | 180 | 62 | 69 | - | 48 | 70 | 53 | - | 70 | 33 | 86 | 60 | > 44.2 µmol/L increase in sCr |
| Forman, 2004 [68] | Cohort | 1 004 | Inhospital | 67 | 51 | 34 | 41 | 70 | 30 | - | 52 | 22 | 70 | 37 | > 26.5 µmol/L increase in sCr |
| Owan, 2006 [69] | Registry | 6 052 | 1 752 | 73 | 56 | - | 34 | 54 | 56 | 135 | - | - | - | - | > 26.5 µmol/L increase in sCr |
| Cowie (POSH), 2006 [70] | Substudy RCT | 299 | 180 | 68 | 74 | 28 | 33 | 47 | 51 | 140 | 137 | - | - | - | > 26.5 µmol/L increase in sCr |
| Chittineni, 2007 [71] | Cohort | 509 | Inhospital | 78 | 45 | - | 38 | 61 | - | 128 | 62 | - | 83 | - | > 44.2 µmol/L increase in sCr |
| Cioffi, 2007 [72] | Cohort | 79 | 330 | 77 | - | 42 | 38 | 43 | 43 | 114 | 85 | 53 | 100 | 60 | ≥ 25% increase in sCr and maximal value of ≥ 176 µmol/L |
| Metra, 2008 [73] | Cohort | 318 | 480 | 68 | 60 | 35 | 29 | 53 | 54 | 133 | 78 | 57 | 99 | 31 | > 26.5 µmol/L increase in sCr ánd ≥ 25% increase in sCr |
| Kociol, 2010 [74] | Registry | 20 063 | 365 | 80 | 44 | - | 39 | 72 | 48 | 134 | 61 | 63 | 83 | 29 | > 26.5 µmol/L increase in sCr |
| Lassus (FINN-AKVA), 2010 [75] | Registry | 292 | 365 | 75 | 51 | 45 | 35 | 59 | 59 | 87 | 53 | 64 | 52 | - | > 0.3 mg/L increase in Cystatin C |
| Belziti, 2010 [76] | Cohort | 200 | 416 | 78 | 57 | - | 24 | - | 38 | 139 | 72 | 71 | 98 | 20 | > 26.5 µmol/L increase in sCr ánd ≥ 25% increase in sCr |
| Herout, 2010 [77] | Registry | 827 | Inhospital | 73 | 43 | - | 46 | 84 | - | 123 | 45 | 56 | 63 | - | > 26.5 µmol/L increase in sCr |
| Hata, 2010 [78] | Cohort | 376 | Inhospital | 72 | 63 | 36 | - | - | 33 | 117 | - | - | 96 | - | ≥ 1.5 x baseline value sCr |
| Testani 2010 (ESCAPE) [104] | Substudy RCT | 401 | 180 | 56 | - | - | 41 | 80 | 42 | 159 | 79 | 69 | 74 | - | ≥ 20% decrease in eGFR |

| First Author (Study name), Year of publication | Study Design | N | Mean F/U (days) | Age (yr) | Men (%) | LVEF (%) | DM (%) | HT (%) | IHD (%) | sCr ( µmol/L) | ACEi/ ARB (%) | BBL (%) | Diuretic (%) | Digoxin (%) | WRF Definition |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Testani 2010 [80] | Cohort | 993 | 30 | 61 | 52 | 34 | 25 | 62 | 38 | - | - | 16 | 25 | 7 | ≥ 26.5 µmol/L increase in sCr |
| Verdiani, 2010 [81] | Cohort | 394 | 365 | 78 | 68 | 40 | 33 | 60 | 57 | 133 | 64 | 28 | 72 | 25 | ≥ 26.5 µmol/L increase in sCr |
| Rusinaru, 2011 [82] | Cohort | 358 | 2 555 | 76 | 53 | 62 | 26 | 74 | 28 | 115 | 51 | 26 | 82 | 20 | ≥ 25% decrease in eGFR |
| Breidthardt, 2011 [83] | Cohort | 657 | 365 | 79 | 55 | 40 | 31 | 70 | 54 | 107 | 60 | 56 | 70 | 10 | > 26.5 µmol/L increase in sCr |
| Voors (Pre-RELAX-AHF), 2011 [84] | Substudy RCT | 225 | 180 | 70 | 56 | - | 44 | 86 | 70 | 118 | 66 | 56 | - | 20 | ≥ 26.5 µmol/L increase in sCr |
| Manzano-Fernandez, 2011 [36] | Cohort | 220 | 500 | 73 | 52 | 46 | 58 | 82 | 37 | 97 | 85 | 64 | 92 | - | ≥ 26.5 µmol/L increase in sCr |
| Lanfear, 2011 [85] | Cohort | 2 465 | 767 | 70 | 51 | - | 43 | 67 | - | 116 | 78 | 50 | 95 | - | ≥ 26.5 µmol/L increase in sCr |
| Ather, 2012 [90] | Cohort | 358 | 365 | 68 | 99 | 25 | 48 | 83 | 63 | 141 | 57 | 65 | 93 | 32 | > 20% decrease in eGFR |
| CHRONIC HEART FAILURE | | | | | | | | | | | | | | | |
| De Silva, 2005 [86] | Cohort | 1 216 | 180 | 71 | 69 | 34 | 21 | 41 | 66 | 123 | 76 | 51 | 73 | - | > 26.5 µmol/L increase in sCr |
| Jose (SAVE), 2006 [87] | Substudy RCT | 1 854 | 1 104 | 59 | 83 | 31 | 21 | 42 | 35 | 105 | - | - | 34 | - | > 26.5 µmol/L increase in sCr |
| Khan (SOLVD), 2006 [88] | Substudy RCT | 6 535 | 1 026 | 60 | 86 | 27 | 19 | 39 | 79 | 103 | - | - | - | - | > 5mL/min/yr decrease in eGFR |
| Iglesias, 2008 [89] | Cohort | 682 | 60 | 80 | 47 | - | 36 | 46 | 57 | 126 | 60 | 64 | 97 | 38 | ≥ 44.2 µmol/L increase in sCr |
| Damman (COACH), 2010 [60] | Substudy RCT | 1 049 | 550 | 71 | 62 | 34 | 28 | 43 | 43 | 125 | 83 | 66 | 95 | 30 | > 26.5 µmol/L increase in sCr ánd > 25% increase in sCr |

For serum creatinine, to convert from µmol/L to mg/dL divide by 88.4. Abbreviations: ACEi/ARB: Angiotensin converting enzyme inhibitor and/or Angiotensin Receptor blocker therapy, BBL: Beta Blocker therapy, DM: History of Diabetes, HFPEF: Heart Failure with Preserved Ejection Fraction, HT: History of Hypertension, IHD: Ischemic Heart Disease, F/U: Follow Up, LVEF: Left Ventricular Ejection Fraction, sCr: serum creatinine, WRF: Worsening Renal Function.

with more preserved LVEF, more frequent diuretic use, and with shorter follow-up. *Figure 4* shows the different effect estimates of the presence of CKD, dependent on mean LVEF in the individual studies. Study quality was not associated with changes in the effect estimate. In a sensitivity analysis, excluding the study by Kao *et al.*[37] which was exceptionally large but of poor quality, the results were consistent: OR 2.34, 95% CI 2.20–2.50, $P < 0.001$. The results remained consistent in a second sensitivity analysis, excluding another four studies (NHCP, ANCHOR, ADHERE, and the study by Herzog), comprising 79% of the remaining study population: OR 2.37, 95% CI 2.21–2.54, $P < 0.001$.[14,46,48,93] Finally, including data from the MAGGIC individual patient data meta-analysis, and excluding studies examined in this meta-analysis to prevent duplicate cases,[5,32,42,50,] the results remained consistent: OR 2.35, 95% CI 2.20–2.50, $P < 0.001$.

## Worsening renal function and all-cause mortality

Of 49 890 patients, a total of 11 476 (23%) had WRF as defined in the individual studies. The definitions used for WRF are shown in *Table 2*. Prevalence of WRF was slightly lower in studies in acute HF (23%) vs. chronic HF (25%). After a mean follow-up of 448 ± 569 (range 10–2555) days (acute HF: 418 ± 594 days, chronic HF: 584 ± 476 days), the crude mortality rates for patients with and without WRF were 36 and 32%, respectively. This resulted in a combined unadjusted OR for mortality of 1.81, 95% CI 1.55–2.12, $P < 0.001$ (*Figure 5*). This effect was less pronounced in acute (OR = 1.75, 95% CI 1.47–2.08, $P < 0.001$) vs. chronic HF (OR = 1.96, 95% CI 1.48–2.61, $P < 0.001$). Excluding studies that assessed only inhospital mortality, the total effect of WRF was less pronounced (OR = 1.67, 95% CI 1.43–1.95, $P < 0.001$). The effect of WRF in studies that investigated the most generally used definition of >26.5 μmol/L (0.3 mg/dL) increase in serum creatinine was slightly lower compared to the overall effect (OR = 1.54, 95% CI 1.29–1.85, $P < 0.001$).

The Funnel plot is asymmetric for the overall effect (*Figure 6*). Larger effects are observed with greater standard errors, which suggests the possibility of publication bias. Metatrim indicated that 12 studies with positive/neutral effects of WRF were missing. Adding these studies into the random pooled analysis resulted in a significant effect of WRF on outcome: OR 1.34, 95% CI 1.14–1.56, $P < 0.001$. Significant heterogeneity was also present ($I^2 = 83\%$, $P < 0.001$). In meta-regression analysis, only study size and haemoglobin levels showed a trend towards affecting the relationship between WRF and outcome. The risk associated with the presence of WRF was smaller in larger studies and studies with lower haemoglobin levels. Study quality was not associated with changes in the effect estimate. In a sensitivity analysis, excluding Kociol *et al.*[74] which comprises 40% of the study population, the results remained consistent: OR 1.84, 95% CI 1.59–2.14, $P < 0.001$. In 10 studies assessing the multivariate adjusted association between the occurrence of WRF and mortality, WRF was associated with a significantly increased mortality risk: HR 1.95, 95% CI 1.45–2.62, $P < 0.001$. A total of 29 studies investigated the predictors of WRF in patients with HF.[12,13,35,60,66,68–71,73–77,79–88,94–99] *Table 3* shows the predictors of WRF in the individual studies.

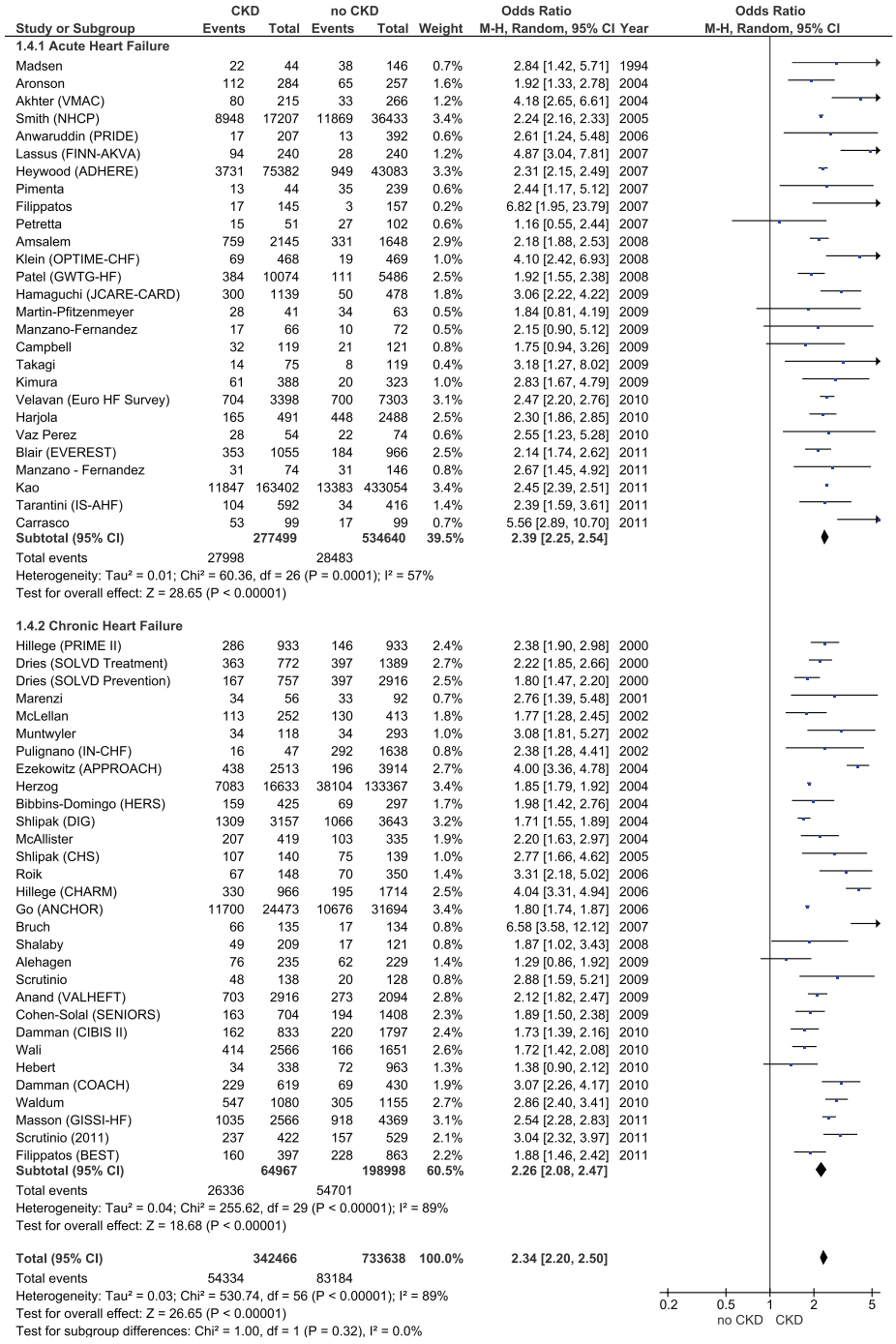



**Figure 2** Forest plot of combined all-cause mortality for CKD vs. no CKD, stratified by acute and chronic heart failure. CKD, chronic kidney disease.

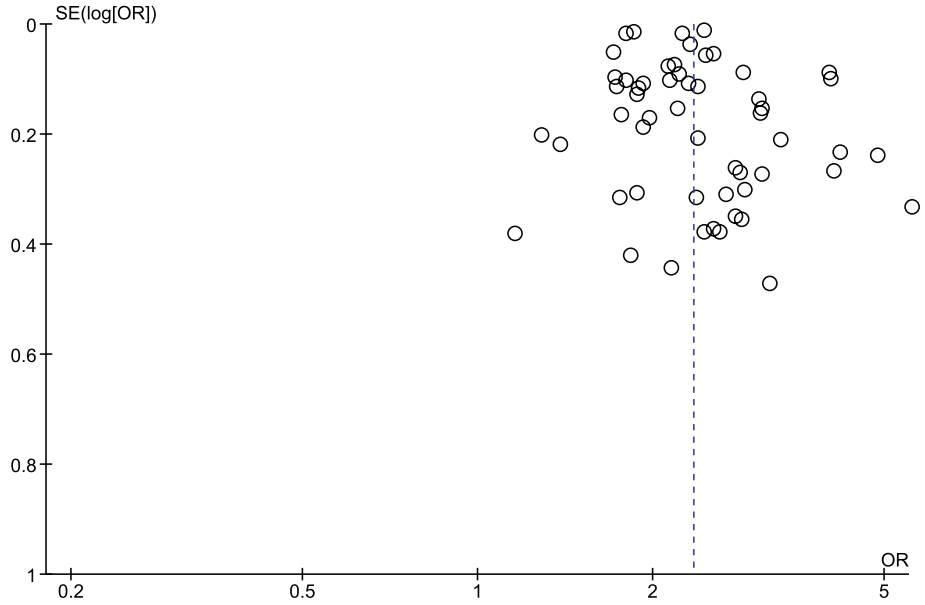



**Figure 3** Funnel plot of the main Chronic Kidney Disease (CKD) analysis.

In almost every study, lower baseline estimated GFR/higher creatinine was a significant predictor of the occurrence of WRF, while other prominent predictors were age, diabetes, hypertension, anaemia, and the use of diuretics. Pooling independent risk estimates of predictors of WRF in different studies identified baseline CKD, a history of hypertension and diabetes, age, and diuretic use as significant predictors of the occurrence of WRF in meta-analysis (*Table 4*).

## Discussion

Baseline renal impairment and WRF are common in patients with acute and chronic HF. When present, both entities are associated with strongly reduced survival rates, although the presence of CKD shows more consistent effects on mortality. Worsening renal function during or following hospitalization showed a strong relationship with long-term outcome. Across included studies, important patient characteristics were identified that may predict the occurrence of WRF.

### Baseline chronic kidney disease and mortality in heart failure

Although the importance and pathophysiologic involvement of renal failure in HF

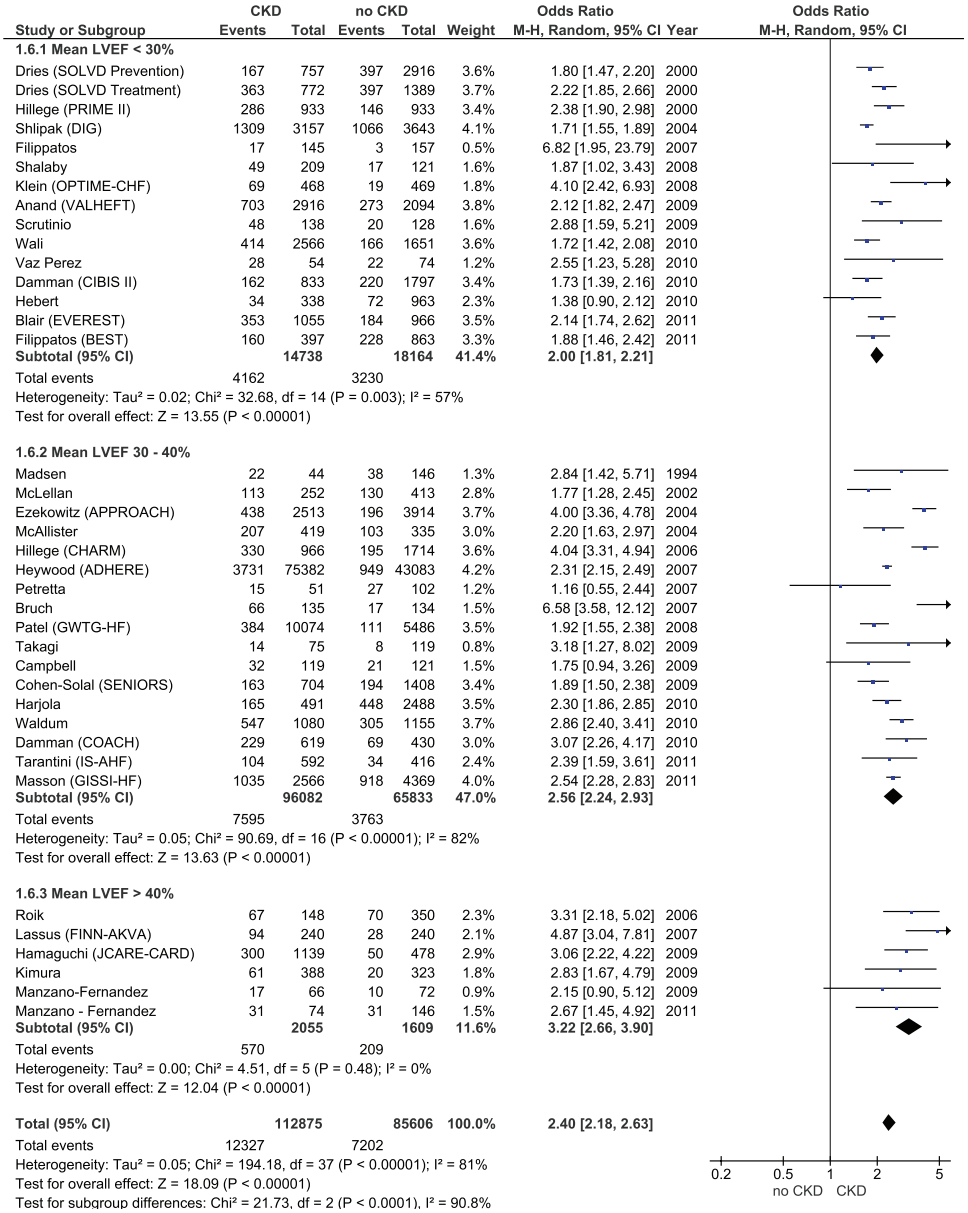



**Figure 4** Forest plot of combined all-cause mortality for CKD vs. no CKD, stratified by mean LVEF of included studies. CKD, chronic kidney disease; LVEF, left-ventricular ejection fraction.

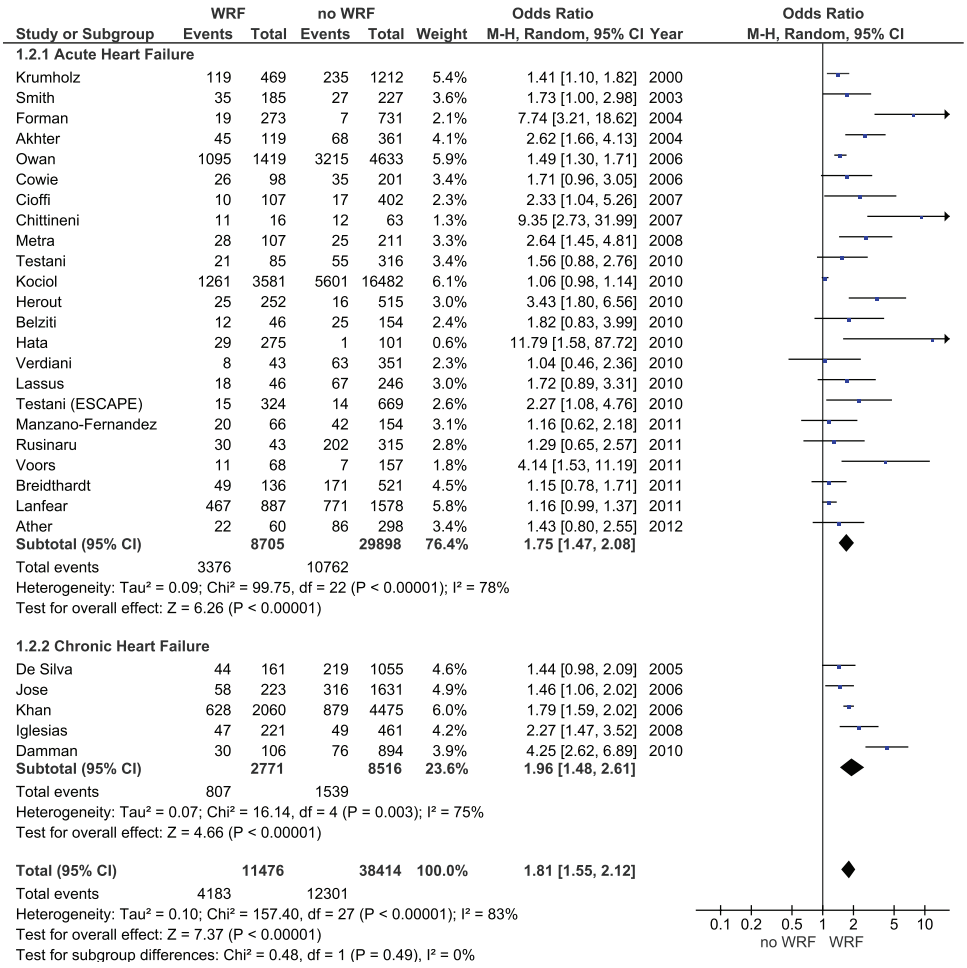



**Figure 5** Forest plot of combined all-cause mortality for WRF vs. no WRF, stratified by acute and chronic heart failure. WRF, worsening renal function.

has been recognized for over a century, the prognostic significance of a reduction in GFR has only been studied for little over a decade. In the first studies, retrospective analyses of the SOLVD studies and PRIME II study, impaired renal function was associated with strongly reduced survival rates, independently of left-ventricular function and severity of HF.[6,7] In subsequent years, 15 studies on renal impairment and outcome in HF were published, resulting in the meta-analysis by Smith *et al*. in 2006.[9] Over 80 000 HF patients were included in this meta analysis, which found that any degree of renal impairment was associated with a 56% increase in relative mortality risk. Our current meta-analysis further extends this observation. Importantly, our analysis included over 10 times the number of patients with HF, and found a strikingly similar association between any degree/moderate CKD and prognosis. Some important differences should be acknowledged, however. Our present study also included HF patients with a preserved ejection fraction (HFPEF). Although a minority across included studies, the mortality risk associated with CKD showed dependency on LVEF, suggesting CKD may be an even more powerful predictor of outcome in patients with HFPEF. This observation contrasts with findings from the MAGGIC individual patient data meta-analysis, which recently found reduced eGFR to be a stronger predictor of outcome in patients with reduced versus preserved LVEF.[100] It must be acknowledged, however, that our current meta-analysis included limited number of patients with a truly preserved ejection fraction, which–along with the differences in analytical approach, included studies and continuous

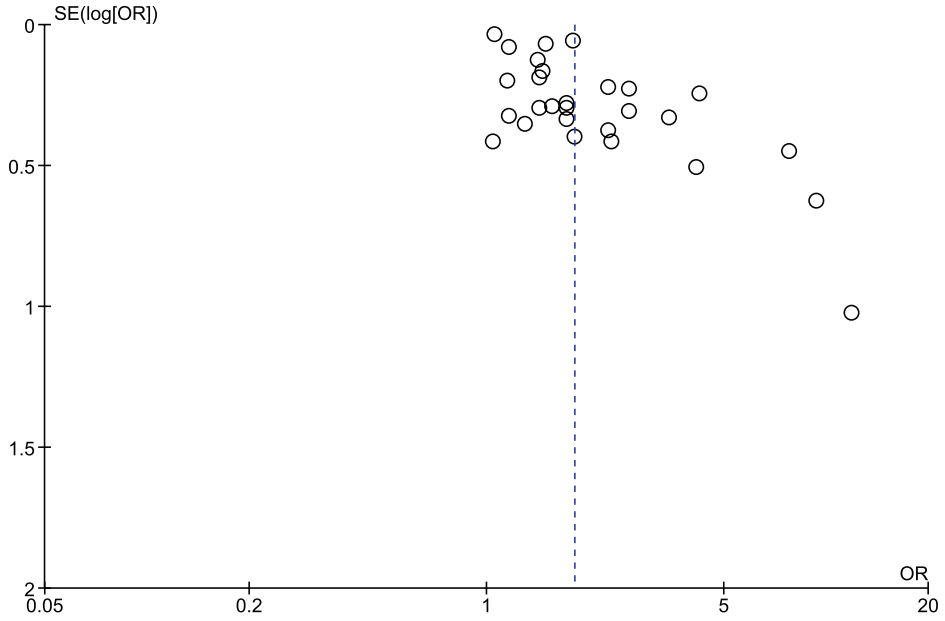



**Figure 6** Funnel plot of the main worsening renal function analysis.

**Table 3** Individual predictors of WRF

| Risk factors | Studies investigating WRF in HF | | | | | | | | | | | | | | | | | | | | | | | | | | | | | # |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Krumholz [66] | Forman [68] | De Silva [86] | Khan [88] | Owan [69] | Logeart [94] | Cowie [70] | Jose [87] | Akhter [12] | Metra [73] | Weinfeld [95] | Chittineni [71] | Damman [60] | Aronson [13] | Beliziti [76] | Breidthardt [83] | Herout [77] | Kociol [74] | Lassus [75] | Voors [96] | Voors [84] | Blair [35] | Lanfear [85] | Rusinaru [82] | Testani [97] | Testani [79] | Testani [80] | Verdiani [81] | Rossignol [98] | Maeder [99] | |
| Baseline GFR | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | | X | X | X | X | X | X | X | 28 |
| Hypertension | X | X | X | X | X | X | | | | | | | | X | | | | X | | | | X | X | X | | X | X | | X | | 13 |
| Diabetes | | X | | | X | X | X | X | | | | X | X | | | | X | X | | X | | | X | | | X | X | | | | 13 |
| Diuretic use* | | | X | | | | | X | | X | X | | | | | X | | | | | X | | X | | X | X | X | | X | X | 12 |
| Age | | | | X | | X | | X | | | X | | X | | X | | | | X | X | | | X | | | | | X | X | | 11 |
| Anemia / hemoglobin | | | X | X | X | X | | | | | | | X | | | | | X | | X | | | | | | | X | | | | 8 |
| Vascular disease/IHD | | | X | | X | X | | X | | | | | | X | | | | X | | | | | X | | | | | | | | 7 |
| Signs of congestion | X | | | | | | X | | | | | | | | | | | X | | | | | | | | X | | | | | 4 |
| LVEF | | | X | X | | | | | | X | | | | | | | | | | | | | | | | | | X | | | 4 |
| Women | X | | | X | | | | X | | | | | | | | | | | | | | | | | | | | X | | | 4 |
| Aldosterone Antagonists | | | X | | | X | | | | | | | | | | | | | | | | | | | | | | X | X | | 4 |
| NYHA class | | | | X | | | | | | X | | | | | | | | | | | X | | | | | | | | | | 3 |
| Hypotension/drop SBP | | | | | | | | | | | | | | | X | | | | | | X | X | | | | | | | | | 3 |
| Smoking | | | X | | | | | X | | | | | | | | | | | | | | | | | | | | X | | | 3 |
| Higher heart rate | X | | | | | | | | | | | | | | | | | | | | | | | | | | X | | | | 2 |
| Black ethnicity | | | | | | | | | | | | | | | | | | X | | | | | X | | | | | | | | 2 |
| Sinus rhythm | | | | | | | X | | | | | | | | | | | X | | | | | | | | | | | | | 2 |
| Atrial Fibrillation | | | | | | | | | | | X | | | | | | | | | | | | | X | | | | | | | | 2 |
| Hyponatremia | | | | | | | | | | | | X | | | | | | | | | | | | | | X | | | | | | 2 |
| Hyperkalemia | | | | | | | | | | | | | | | | | X | | | | | | | | | | | | X | | 2 |

Shaded variables are from multivariate analyses. Variables associated in one single study: Body mass index, White Ethnicity, Hypernatremia, Low sodium diet, Diastolic dysfunction, bicarbonate levels, hyperlipidemia, N-Terminal pro Brain Natriuretic Peptide, weight change, norepinephrine, statin or antiarrhytmics use. Abbreviations: GFR: Glomerular Filtration Rate, IHD: Ischemic Heart Disease, LVEF: Left Ventricular Ejection Fraction, NYHA: New York Heart Association, SBP: Systolic Blood Pressure.

versus dichotomous classification of estimated GFR–may partly explain these. Possible explanations for the observation that CKD is related to a higher mortality risk in HFPEF include underlying disease, such as hypertension and diabetes, both of which are associated with impaired eGFR and worse outcome. In general, patients with a relatively preserved ejection fraction present with a different clinical and biochemical profile, and possibly a different reason for a lower eGFR, all of which could explain the observed effect. Future research, especially in HFPEF, is needed to examine these relationships.

**Table 4** Predictors of the occurrence of worsening renal function in meta-analysis across studies

| Predictor | No. of studies | No. of patients | Adjusted HR (95% CI) | P-value |
|---|---|---|---|---|
| Baseline CKD[a] | 9 | 5,477 | 2.17 (1.79–2.63) | <0.001 |
| Hypertension | 5 | 11,611 | 1.36 (1.08–1.71) | 0.009 |
| Diabetes | 5 | 11,081 | 1.23 (1.12–1.36) | <0.001 |
| Age (per 10 years) | 5 | 9,993 | 1.38 (1.14–1.68) | 0.001 |
| Diuretic use[b] | 5 | 13,502 | 1.52 (1.07–2.15) | 0.02 |

CI, confidence interval; CKD, chronic kidney disease; H, hazard ratio.
[a]Excluding Khan ***et al***.[88] who only reported predictors of very rapid decline in glomerular filtration rate (>15 mL/min/1.73m$^2$/year).
[b]Loop diuretic therapy.

Other important differences compared with the meta-analysis by Smith *et al*. include the number of studies investigated, 35 of which were published after the meta-analysis by Smith *et al*., and the unlimited follow-up duration in our analysis. The results of these two meta-analyses and another meta-analysis by Tonelli *et al*.[101] represent robust evidence for the association between CKD and mortality in HF. This effect seems to be present irrespective of the setting; in both acute and chronic HF, baseline renal impairment was associated with poor outcome, with a greater effect in the acute setting. Baseline CKD in each setting may represent different pathophysiologic mechanisms, as CKD in the chronic setting may be the result of steadily decreasing GFR, while the increasingly congestive state in the acute setting may lead to a more pronounced decrease in GFR in a much shorter timespan. It is clear that any degree of renal impairment should be considered a strong and important risk stratifier in patients with HF.

## Worsening renal function and mortality in heart failure

Of even greater importance for treatment guidance, and possibly as a marker for treatment effect, dynamics changes in renal function are frequently observed in patients with HF. In a previous meta-analysis in over 18 000 patients with HF, we found that about 25% developed some degree of WRF during follow-up.[8] In our present study, which extended the analyses to over 45 000 patients, we found a similar prevalence of WRF, independently of the setting of HF. In agreement with

findings in CKD, the mortality risk observed for WRF in our current meta-analysis was at least as large as in our previous analysis. This association persisted after adjustment for confounders in the individual studies, although further correction for publication bias slightly weakened the association. While it is important to realize that patients with WRF are at increased risk for impaired outcome, it may be far more interesting to identify patients at risk for WRF in the first place. We found that individual studies assessing this clinically relevant question consistently identified baseline renal impairment as the most important risk factor for the development of WRF, even after adjustment for confounders. In part, this implies baseline renal failure leads to impaired survival via WRF, and that WRF is a reflection of reduced GFR. Another reason for this relationship lies in the definition of WRF. In most studies, WRF is defined as an absolute increase in serum creatinine. This indirectly implies that similar absolute changes in serum creatinine represent a smaller decline in GFR for patients with lower baseline GFR compared with patients with higher baseline GFR. It also means that the effect of this smaller decrease translated into a similar mortality risk suggesting that patients with lower baseline eGFR may be more susceptible to a WRF-induced mortality risk. However, the observed effect of WRF on mortality was not dependent on baseline GFR. Interestingly, we found that when WRF was defined as a reduction in eGFR, as was the case in two studies, higher baseline GFR was associated with more frequent WRF.[88,98] This is probably a reflection of an improper or different definition of WRF and statistical confounding, which is supported by the finding in 26 other studies that impaired baseline GFR is associated with WRF. Other important predictors of WRF include age and the presence of diabetes, hypertension, and anaemia-entities also linked to CKD and progression of CKD in various patient populations. Diuretic use and higher diuretic doses were also associated with a higher incidence of WRF, although the precise pathophysiology underlying this link is unclear. On the one hand, diuretics should reduce congestion, thereby improving renal perfusion and intrarenal pressures in some patients; on the other hand, diuretics may have direct detrimental effects on glomerular filtration.[4,102]

Multiple studies suggest the underlying reason for the occurrence of WRF may be an important mediator of the effect of WRF on outcome. In acute HF, a degree of transient WRF would appear to be tolerable, as this was not associated with poor outcome in the DOSE trial.[103] On the other hand, when WRF is associated with decreases in systolic blood pressure in acute HF, it is strongly related to poor outcome.[79,84,98,104] However, WRF or change in serum creatinine were not associated with changes in haemodynamic parameters in the ESCAPE study.[91] The clinical situation in which WRF develops may be important, as at least one study showed that WRF in the context of persistent signs and symptoms of congestion was related to poor outcome, while WRF in the presence of favourable changes in clinical signs was not.[105] In chronic HF, WRF occurring without intervention is strongly related to poor outcome, while WRF ocurring in the setting of uptitration of angiotensin-converting enzyme inhibitors is not.[88,92] Finally, various studies have shown relationships between persistent WRF, transient WRF, or even any change (increase

or decrease) in serum creatinine and poor outcome.[13,79,94] These findings suggest that clinical setting, the cause of WRF (during treatment, initiation of therapy, long-term follow-up), and associated haemodynamic changes are of major importance for evaluating the significance of WRF, further emphasizing the heterogeneity of the HF population and its response to WRF.

Finally, our meta-analysis highlights that increases in serum creatinine and related changes in GFR are associated with increased mortality. However, this does not directly imply that survival improves if serum creatinine decreases. Only in one study in chronic HF was improvement in serum creatinine associated with improved survival.[86] Most importantly, no study to date has evaluated whether therapy targeting improvement or preservation of renal function leads to improved survival. Although the PROTECT trial aimed to improve renal function using Rolofylline therapy, the investigational drug actually significantly increased serum creatinine levels, suggesting that either the treatment failed to improve renal function, or that serum creatinine is a poor marker for renal function in the acute stages of treatment.[96] To provide an answer to this important clinical question, studies are needed that identify individual patients at risk for WRF, adequately define or calculate (changes in) renal function, and are focused on preservation or improvement of renal function over time.

## Limitations

We found possible evidence of publication bias in the analysis on WRF and outcome. This suggests that studies reporting higher mortality risk with WRF are published more often, which meaning the observed increased mortality risk with WRF in our analysis may be an overestimation of true risk. This is further strengthened by our observation that mortality risk associated with WRF was higher in smaller studies. Furthermore, although we tried to gather all information available, we could not acquire crude data for all studies, which included at least one study that showed a limited effect of WRF on mortality, and two important clinical trials in acute HF.[96,99,103] Other inherent limitations of meta-analysis include significant heterogeneity among studies, which was the reason for using a random effect model. However, this will never fully account for intrinsic differences between included studies. Importantly, we found significant heterogeneity in all analyses, suggesting that the observed risk associated with both WRF and CKD may not be applicable to all patient populations in HF. Reasons for diversity among studies include the differing inclusion criteria, selection bias, different cut-off for both WRF and CKD, and the shift in the type of HF patients from reduced to more preserved ejection fraction seen in recent years. The patient cohorts included were also relatively younger than observed in a general HF population, which may lead to some underestimation of the prevalence of both CKD and WRF. We have tried to account for some degree of heterogeneity via meta-regression, but as not all studies published important covariates, meta-regression could only be performed using a limited number of studies and variables. Furthermore, we used mean values for variables reported by included studies, which does not account for in-study variance. Individual pa-

tient-level data would be needed to confirm our results. Importantly, we could not establish whether there are specific patients or patient groups that have a different response to renal impairment or WRF. These observations highlight limitations to the generalizability of our findings. Finally, we did not include a meta-analysis of continuous data, as studies reporting such data were limited and used divergent cut-off points. Use of continuous data could potentially have shown better accuracy.

## Conclusions

Baseline renal impairment and WRF over time are frequently observed in patients with acute and chronic HF. When present, both entities relate to strongly impaired survival, with the presence of CKD showing a more consistent relationship with poor outcome. Across studies, baseline CKD, a history of hypertension and diabetes, age, and diuretic use are associated with the occurrence of WRF.

**Acknowledgements**

K.D. and M.A.E.V. accept full responsibility for the work and had access to the data. K.D. controlled the decision to publish. A.A.V., H.L.H., C.M.O'C., and D.J.v.V. made significant contributions to design, drafting, and revising the paper, and have given final approval of the version to be published. The authors wish to express their gratitude to Alan Go, MD (Division of Research, Kaiser Permanente, Northern CA, USA), Domenico Scrutinio, MD (Division of Cardiology and Cardiac Rehabilitation 'S. Maugeri' Foundation, IRCCS. Institute of Cassano Murge, Bari, Italy), Sergio Manzano-Fernandez, MD (University Hospital Virgen de la Arrixaca, Murcia, Italy), Jeffrey Testani, MD, MTR (University of Pennsylvania, PA, USA), Daniel J. Brotman, MD (Hospitalist Program, Johns Hopkins Hospital, Baltimore, USA), Vieri Lastrucci, MD (Universita degli studi di Firenze, Florence, Italy), Veli-Pekka Harjola, MD, PhD (Helsinki University Central Hospital, Helsinki), Christophe Tribouilloy, MD, PhD (Department of Cardiology, University Hospital, South Hospital Amiens, France), Bård Waldum, MD (Institute of Clinical Medicine, Faculty of Medicine, University of Oslo Department of Nephrology, Oslo University Hospital, Oslo, Norway), Amalia Vaz Pérez, MD (Sci) (Department of Cardiology, Charité University Hospital, Berlin, Germany), David Lanfear, MD (Henry Ford Health System, Detroit, USA), Doron Aronson, MD (Rambam health Care Campus, Haifa, Israel), Joana Pimenta, MD (Internal Medicine Department, University of Porto Medical School, Hospital S. João, Porto, Portugal), Charles Herzog, MD (Hennepin County Medical Center, University of Minnesota and United States Renal Data System, Minneapolis, USA), Dan Rusinaru, MD (Department of Cardiology, University Hospital Amiens, Amiens, France), Luigi Tavazzi, MD (GVM Care&Research – E.S. Health Science Foundation, Cotignola, Italy), Gianni Tognoni, MD (Consorzio Mario Negri Sud, Santa Maria Imbaro, Chieti, Italy), Biykem Bozkurt, MD, PhD (Baylor College of Medicine, Houston, TX, USA), Sameer Ather, MD, PhD (Birmingham, AL, USA), and Marco Metra, MD (Department of Cardiology, University of Brescia, Brescia, Italy) for providing additional data that was not available in the original manuscripts.

## References


1. Bueno H, Ross JS, Wang Y, Chen J, Vidan MT, Normand SL, Curtis JP, Drye EE, Lichtman JH, Keenan PS, Kosiborod M, Krumholz HM. Trends in length of stay and short-term outcomes among Medicare patients hospitalized for heart failure, 1993–2006. JAMA 2010;303:2141–2147.
2. Mogensen UM, Ersboll M, Andersen M, Andersson C, Hassager C,Torp-Pedersen C, Gustafsson F, Kober L. Clinical characteristics and major comorbidities in heart failure patients more than 85 years of age compared with younger age groups. Eur J Heart Fail 2011;13:1216–1223.
3. Postmus D, van Veldhuisen DJ, Jaarsma T, Luttik ML, Lassus J, Mebazaa A, Nieminen MS, Harjola VP, Lewsey J, Buskens E, Hillege HL. The COACH risk engine: a multistate model for predicting survival and hospitalization in patients with heart failure. Eur J Heart Fail 2012;14:168–175.
4. Damman K, Voors AA, Navis G, van Veldhuisen DJ, Hillege HL. The cardiorenal syndrome in heart failure. Prog Cardiovasc Dis 2011;54:144–153.
5. Madsen BK, Keller N, Christiansen E, Christensen NJ. Prognostic value of plasma catecholamines, plasma renin activity, and plasma atrial natriuretic peptide at rest and during exercise in congestive heart failure: comparison with clinical evaluation, ejection fraction, and exercise capacity. J Card Fail 1995;1:207–216.
6. Dries DL, Exner DV, Domanski MJ, Greenberg B, Stevenson LW. The prognostic implications of renal insufficiency in asymptomatic and symptomatic patients with left ventricular systolic dysfunction. J Am Coll Cardiol 2000;35:681–689.
7. Hillege HL, Girbes AR, de Kam PJ, Boomsma F, de Zeeuw D, Charlesworth A, Hampton JR, van Veldhuisen DJ. Renal function, neurohormonal activation, and and survival in patients with chronic heart failure. Circulation 2000;102:203–210.
8. Damman K, Navis G, Voors AA, Asselbergs FW, Smilde TD, Cleland JG, van Veldhuisen DJ, Hillege HL. Worsening renal function and prognosis in heart failure: systematic review and meta-analysis. J Card Fail 2007;13:599–608.
9. Smith GL, Lichtman JH, Bracken MB, Shlipak MG, Phillips CO, DiCapua P, Krumholz HM. Renal impairment and outcomes in heart failure: systematic review and meta-analysis. J Am Coll Cardiol 2006;47:1987–1996.
10. Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 2000;56:455–463.
11. The Cochrane Collaboration. Review Manager (RevMan) Version 5.1. 2011.
12. Akhter MW, Aronson D, Bitar F, Khan S, Singh H, Singh RP, Burger AJ, Elkayam U. Effect of elevated admission serum creatinine and its worsening on outcome in hospitalized patients with decompensated heart failure. AmJ Cardiol 2004;94:957–960.
13. Aronson D, Mittleman MA, Burger AJ. Elevated blood urea nitrogen level as a predictor of mortality in patients admitted for decompensated heart failure. Am J Med 2004;116:466–473.
14. Smith GL, Shlipak MG, Havranek EP, Masoudi FA, McClellan WM, Foody JM, Rathore SS, Krumholz HM. Race and renal impairment in heart failure: mortality in blacks versus whites. Circulation 2005;111:1270–1277.
15. Anwaruddin S, Lloyd-Jones DM, Baggish A, Chen A, Krauser D, Tung R, Chae C, Januzzi JL Jr. Renal function, congestive heart failure, and amino-terminal pro-brain natriuretic peptide measurement: results from the ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) Study. J Am Coll Cardiol 2006; 47:91–97.
16. Heywood JT, Fonarow GC, Costanzo MR, Mathur VS, Wigneswaran JR, Wynne J. High prevalence of renal dysfunction and its impact on outcome in 118,465 patients hospitalized with acute decompensated heart failure: a report from the ADHERE database. J Card Fail 2007;13:422–430.
17. Pimenta JM, Almeida R, Araujo JP, Azevedo A, Frioes F, Rocha-Goncalves F,Ferreira A, Bettencourt P. Amino terminal B-type natriuretic peptide, renal function, and prognosis in acute heart failure: a hospital cohort study. J Card Fail 2007; 13:275–280.
18. Lassus J, Harjola VP, Sund R, Siirila-Waris K, Melin J, Peuhkurinen K, Pulkki K, Nieminen MS. Prognostic value of cystatin C in acute heart failure in relation to other markers of renal function and NT-proBNP. Eur Heart J 2007;28:1841–1847.
19. Petretta M, Scopacasa F, Fontanella L, Carlomagno A, Baldissara M, de Simone A, Petretta MP, Bonaduce D. Prognostic value of reduced kidney function and anemia in patients with chronic heart failure. J Cardiovasc Med (Hagerstown) 2007;8:909–916.
20. Filippatos G, Rossi J, Lloyd-Jones DM, Stough WG,Ouyang J, Shin DD, O'connor C, Adams KF, Orlandi C, Gheorghiade M. Prognostic value of blood urea nitrogen in patients hospitalized with worsening heart failure: insights from the Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Chronic Heart Failure (ACTIV in CHF) study. J Card Fail 2007;13:360–364.
21. Patel UD,Hernandez AF, Liang L, Peterson ED,

LaBresh KA, Yancy CW, Albert NM, Ellrodt G, Fonarow GC. Quality of care and outcomes among patients with heart failure and chronic kidney disease: a Get With the Guidelines—Heart Failure Program study. Am Heart J. 2008;156:674–681.

22. Klein L, Massie BM, Leimberger JD, O'Connor CM, Pina IL, Adams KF Jr, Califf RM, Gheorghiade M. Admission or changes in renal function during hospitalization for worsening heart failure predict postdischarge survival: results from the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF). Circ Heart Fail 2008;1:25–33.
23. Amsalem Y, Garty M, Schwartz R, Sandach A, Behar S, Caspi A, Gottlieb S, Ezra D, Lewis BS, Leor J. Prevalence and significance of unrecognized renal insufficiency in patients with heart failure. Eur Heart J 2008;29:1029–1036.
24. Hamaguchi S, Tsuchihashi-Makaya M, Kinugawa S, Yokota T, Ide T, Takeshita A, Tsutsui H. Chronic kidney disease as an independent risk for long-term adverse outcomes in patients hospitalized with heart failure in Japan. Report from the Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD). Circ J 2009;73:1442–1447.
25. Martin-Pfitzenmeyer I, Gauthier S, Bailly M, Loi N, Popitean L, d'Athis P, Bouvier AM, Pfitzenmeyer P. Prognostic factors in stage D heart failure in the very elderly. Gerontology 2009;55:719–726.
26. Kimura H, Hiramitsu S, Miyagishima K, Mori K, Yoda R, Kato S, Kato Y, Morimoto S, Hishida H, Ozaki Y. Cardio-renal interaction: impact of renal function and anemia on the outcome of chronic heart failure. Heart Vessels 2010;25:306–312.
27. Takagi A, Iwama Y, Yamada A, Aihara K, Daida H. Estimated glomerular filtration rate is an independent predictor for mortality of patients with acute heart failure. J Cardiol 2010;55:317–321.
28. Campbell CY, Clarke W, Park H, Haq N, Barone BB, Brotman DJ. Usefulness of cystatin C and prognosis following admission for acute heart failure. Am J Cardiol 2009;104:389–392.
29. Manzano-Fernandez S, Boronat-Garcia M, baladejo-OtonMD,Pastor P, Garrido IP, Pastor-Perez FJ, Martinez-Hernandez P, Valdes M, Pascual-Figal DA. Complementary prognostic value of cystatin C, N-terminal pro-B-type natriuretic Peptide and cardiac troponin T in patients with acute heart failure. Am J Cardiol 2009;103:1753–1759.
30. Harjola VP, Follath F, Nieminen MS, Brutsaert D, Dickstein K, Drexler H,Hochadel M, Komajda M, Lopez-Sendon JL, Ponikowski P, Tavazzi L. Characteristics, outcomes, and predictors of mortality at 3 months and 1 year in patients hospitalized for acute heart failure. Eur J Heart Fail 2010;12:239–248.
31. Tarantini L, Cioffi G, Gonzini L, Oliva F, Lucci D, Di TG, MaggioniAP, Tavazzi L. Evolution of renal function during and after an episode of cardiac decompensation: results from the Italian survey on acute heart failure. J Cardiovasc Med (Hagerstown) 2010;11:234–243.
32. Velavan P, Khan NK, GoodeK, Rigby AS, Loh PH, Komajda M, Follath F, Swedberg K, Madeira H, Cleland JG. Predictors of short term mortality in heart failure: insights from the Euro Heart Failure survey. Int J Cardiol 2010;138:63–69.
33. Vaz Perez A, Otawa K, Zimmermann AV, Stockburger M, Muller-Werdan U, Werdan K, Schmidt HB, Ince H, Rauchhaus M. The impact of impaired renal function on mortality in patients with acutely decompensated chronic heart failure. Eur J Heart Fail 2010;12:122–128.
34. Carrasco-Sanchez FJ, Galisteo-Almeda L, Paez-Rubio I, Martinez-Marcos FJ, Camacho-Vazquez C, Ruiz-Frutos C, Pujol-De La LE. Prognostic value of cystatin C on admission in heart failure with preserved ejection fraction. J Card Fail 2011;17:31–38.
35. Blair JE, Pang PS, Schrier RW, Metra M, Traver B, Cook T, Campia U, Ambrosy A, Burnett JC Jr, Grinfeld L, Maggioni AP, Swedberg K, Udelson JE, Zannad F, Konstam MA, Gheorghiade M. Changes in renal function during hospitalization and soon after discharge in patients admitted for worsening heart failure in the placebo group of the EVEREST trial. Eur Heart J 2011;32:2563–2572.
36. Manzano-Fernandez S, Januzzi JL Jr, Boronat-Garcia M, Bonaque-Gonzalez JC, Truong QA, Pastor-Perez FJ, Munoz-Esparza C, Pastor P, baladejo-Oton MD, CasasT, Valdes M, Pascual-Figal DA. beta-trace protein and cystatinCas predictors of long-termoutcomes in patients with acute heart failure. JAmColl Cardiol 2011;57:849–858.
37. Kao DP, Kreso E, Fonarow GC, Krantz MJ. Characteristics and outcomes among heart failure patients with anemia and renal insufficiency with and without blood transfusions (public discharge data from California 2000–2006). Am J Cardiol 2011;107:69–73.
38. Marenzi G, Lauri G, Guazzi M, Assanelli E, Grazi M, Famoso G, Agostoni P. Cardiac and renal dysfunction in chronic heart failure: relation to neurohumoral activation and prognosis. Am J Med Sci 2001;321:359–366.
39. McClellan WM, Flanders WD, Langston RD, Jurkovitz C, Presley R. Anemia and renal insufficiency are independent risk factors for death among patients with congestive heart failure admitted to community hospitals: a population-based study. J Am Soc Nephrol 2002;13:1928–1936.
40. Muntwyler J, Abetel G, Gruner C, Follath F. One-year mortality among unselected

outpatients with heart failure. Eur Heart J 2002;23:1861–1866.

41. Pulignano G, Del SD, Tavazzi L, Lucci D, Gorini M, Leggio F, Porcu M, Scherillo M,Opasich C, Di LA, Senni M, Maggioni AP. Clinical features and outcomes of elderly outpatients with heart failure followed up in hospital cardiology units: data from a large nationwide cardiology database (IN-CHF Registry). Am Heart J 2002;143:45–55.
42. Shlipak MG, Smith GL, Rathore SS, Massie BM, Krumholz HM. Renal function, digoxin therapy, and heart failure outcomes: evidence from the digoxin intervention group trial. J Am Soc Nephrol 2004;15:2195–2203.
43. Bibbins-Domingo K, Lin F, Vittinghoff E, Barrett-Connor E, Grady D, Shlipak MG.Renal insufficiency as an independent predictor of mortality among women with heart failure. J Am Coll Cardiol 2004;44:1593–1600.
44. Ezekowitz J, McAlister FA, Humphries KH, Norris CM, Tonelli M, Ghali WA, Knudtson ML. The association among renal insufficiency, pharmacotherapy, and outcomes in 6,427 patients with heart failure and coronary artery disease. J Am Coll Cardiol 2004;44:1587–1592.
45. McAlister FA, Ezekowitz J, Tonelli M, ArmstrongPW. Renal insufficiency and heart failure: prognostic and therapeutic implications from a prospective cohort study. Circulation 2004;109:1004–1009.
46. Herzog CA, Muster HA, Li S, Collins AJ. Impact of congestive heart failure, chronic kidney disease, and anemia on survival in the Medicare population. J Card Fail 2004;10:467–472.
47. Shlipak MG, Katz R, Fried LF, Jenny NS, Stehman-Breen CO, Newman AB, Siscovick D, Psaty BM, Sarnak MJ. Cystatin-C and mortality in elderly persons with heart failure. J Am Coll Cardiol 2005;45:268–271.
48. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization.NEngl JMed2004;351:1296–1305.
49. Roik M, Starczewska MH, Stawicki S, Solarska-Polchlopek A, Warszawik O, Oreziak A, Kochanowski J, Kosior D, Opolski G. The prognostic value of renal dysfunction in patients with chronic heart failure: 12-month follow-up. Kardiol Pol 2006;64:704–711.
50. Hillege HL, Nitsch D, Pfeffer MA, Swedberg K, McMurray JJ, Yusuf S, Granger CB, Michelson EL, Ostergren J, Cornel JH, de Zeeuw D, Pocock S, van Veldhuisen DJ. Renal function as a predictor of outcome in a broad spectrum of patients with heart failure. Circulation 2006;113:671–678.
51. Bruch C, Rothenburger M, Gotzmann M, Wichter T, Scheld HH, Breithardt G, Gradaus R. Chronic kidney disease in patients with chronic heart failure–impact on intracardiac conduction, diastolic function and prognosis. Int J Cardiol 2007;118:375–380.
52. Shalaby A, El-Saed A, Voigt A, Albany C, Saba S. Elevated serum creatinine at baseline predicts poor outcome in patients receiving cardiac resynchronization therapy. Pacing Clin Electrophysiol 2008;31:575–579.
53. Cohen-Solal A, Kotecha D, van Veldhuisen DJ, Babalis D, Bohm M, Coats AJ, Roughton M, Poole-Wilson P, Tavazzi L, Flather M. Efficacy and safety of nebivolol in elderly heart failure patients with impaired renal function: insights from the SENIORS trial. Eur J Heart Fail 2009;11:872–880.
54. Scrutinio D, Passantino A, Santoro D, Cacciapaglia E, Farinola G. Prognostic value of formulas estimating excretory renal function in the elderly with systolic heart failure. Age Ageing 2009;38:296–301.
55. Anand IS, Bishu K, Rector TS, Ishani A, Kuskowski MA, Cohn JN. Proteinuria, chronic kidney disease, and the effect of an angiotensin receptor blocker in addition to an angiotensin-converting enzyme inhibitor in patients with moderate to severe heart failure. Circulation 2009;120:1577–1584.
56. Alehagen U, Dahlstrom U, Lindahl TL. Cystatin C and NT-proBNP, a powerful combination of biomarkers for predicting cardiovascular mortality in elderly patients with heart failure: results from a 10-year study in primary care. Eur J Heart Fail 2009;11:354–360.
57. Damman K, Voors AA, Hillege HL, Navis G, Lechat P, van Veldhuisen DJ, Dargie HJ.Congestion in chronic systolic heart failure is related to renal dysfunction and increased mortality. Eur J Heart Fail 2010;12:974–982.
58. Hebert K, Dias A, Delgado MC, Franco E, Tamariz L, Steen D, Trahan P, Major B, Arcement LM. Epidemiology and survival of the five stages of chronic kidney disease in a systolic heart failure population. Eur J Heart Fail 2010;12:861–865.
59. Wali RK, Iyengar M, Beck GJ, Chartyan DM, Chonchol M, Lukas MA, Cooper C, Himmelfarb J,Weir MR, Berl T, Henrich WL, Cheung AK. Efficacy and safety of carvedilol in treatment of heart failure with chronic kidney disease: a meta-analysis of randomized trials. Circ Heart Fail 2011;4:18–26.
60. Damman K, Jaarsma T, Voors AA, Navis G, Hillege HL, van Veldhuisen DJ. Both in and out-hospital worsening of renal function predict outcomein patients with heart failure: results from the Coordinating Study Evaluating Outcome of Advising and Counseling in Heart Failure (COACH). Eur J Heart Fail 2009;11:847–854.
61. Waldum B,Westheim AS, Sandvik L, Flonaes B, Grundtvig M, Gullestad L, Hole T, Os I. Renal function in outpatients with chronic heart failure. J Card Fail 2010;16:374–380.

62. Scrutinio D, Passantino A, Santoro D, Catanzaro R. The cardiorenal anaemia síndrome in systolic heart failure: prevalence, clinical correlates, and long-term survival. Eur J Heart Fail 2011;13:61–67.

63. Filippatos GS, Ahmed MI, Gladden JD, Mujib M, Aban IB, Love TE, Sanders PW, Pitt B, Anker SD, Ahmed A. Hyperuricaemia, chronic kidney disease, and outcomes in heart failure: potential mechanistic insights from epidemiological data. Eur Heart J 2011;32:712–720.

64. Tavazzi L, Maggioni AP, Marchioli R, Barlera S, Franzosi MG, Latini R, Lucci D, Nicolosi GL, Porcu M, Tognoni G. Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. Lancet 2008;372:1223–1230.

65. Tavazzi L, Maggioni AP, Marchioli R, Barlera S, Franzosi MG, Latini R, Lucci D, Nicolosi GL, Porcu M, Tognoni G. Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. Lancet 2008;372:1231–1239.

66. Krumholz HM, Chen YT, Vaccarino V, Wang Y, Radford MJ, Bradford WD, Horwitz RI. Correlates and impact on outcomes of worsening renal function in patients.or ¼65 years of age with heart failure.AmJ Cardiol 2000;85:1110–1113.

67. Smith GL, Vaccarino V, Kosiborod M, Lichtman JH, Cheng S, Watnick SG, Krumholz HM. Worsening renal function: what is a clinically meaningful change in creatinine during hospitalization with heart failure? J Card Fail 2003;9:13–25.

68. Forman DE, Butler J, Wang Y, Abraham WT, O'Connor CM, Gottlieb SS, Loh E,Massie BM, RichMW, Stevenson LW, Young JB, Krumholz HM. Incidence, predictors at admission, and impact of worsening renal function among patients hospitalized with heart failure. J Am Coll Cardiol 2004;43:61–67.

69. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Secular trends in renal dysfunction and outcomes in hospitalized heart failure patients.J Card Fail 2006;12:257–262.

70. Cowie MR, Komajda M, Murray-Thomas T, Underwood J, Ticho B. Prevalence and impact of worsening renal function in patients hospitalized with decompensated heart failure: results of the prospective outcomes study in heart failure (POSH).Eur Heart J 2006;27:1216–1222.

71. Chittineni H, Miyawaki N, Gulipelli S, Fishbane S. Risk for acute renal failure in patients hospitalized for decompensated congestive heart failure. Am J Nephrol 2007;27:55–62.

72. Cioffi G, Tarantini L, Pulignano G, Del SD, De FS, Opasich C, Dilenarda A, Stefenelli C, Furlanello F. Prevalence, predictors and prognostic value of acute impairment in renal function during intensive unloading therapy in acommunity population hospitalized for decompensated heart failure. J Cardiovasc Med Hagerstown) 2007;8:419–427.

73. Metra M, Nodari S, Parrinello G, Bordonali T, Bugatti S, Danesi R, Fontanella B, Lombardi C, Milani P, Verzura G, Cotter G, Dittrich H, Massie BM, Dei Cas L.Worsening renal function in patients hospitalised for acute heart failure: clinical implications and prognostic significance. Eur J Heart Fail 2008;10:188–195.

74. Kociol RD, Greiner MA, Hammill BG, Phatak H, Fonarow GC, Curtis LH, Hernandez AF. Long-term outcomes of medicare beneficiaries with worsening renal function during hospitalization for heart failure. Am J Cardiol 2010;105:1786–1793.

75. Lassus JP, Nieminen MS, Peuhkurinen K, Pulkki K, Siirila-Waris K, Sund R, Harjola VP. Markers of renal function and acute kidney injury in acute heart failure: definitions and impact on outcomes of the cardiorenal syndrome. Eur Heart J 2010;31:2791–2798.

76. Belziti CA, Bagnati R, Ledesma P, Vulcano N, Fernandez S.Worsening renal function in patients admitted with acute decompensated heart failure: incidence, risk factors and prognostic implications. Rev Esp Cardiol 2010;63:294–302.

77. Herout PM, Harshaw Q, Phatak H, Saka G, McNeill A, Wu D, Sazonov V, DeSagun R, Shirani J. Impact of worsening renal function during hospital admission on resource utilization in patients with heart failure. Am J Cardiol 2010;106:1139–1145.

78. Hata N, Yokoyama S, Shinada T, Kobayashi N, Shirakabe A, Tomita K, Kitamura M, Kurihara O, Takahashi Y. Acute kidney injury and outcomes in acute decompensated heart failure: evaluation of the RIFLE criteria in an acutely ill heart failure population.Eur J Heart Fail 2010;12:32–37.

79. Testani JM, McCauley BD, Kimmel SE, Shannon RP. Characteristics of patients with improvement or worsening in renal function during treatment of acute decompensated heart failure. Am J Cardiol 2010;106:1763–1769.

80. Testani JM, McCauley BD, Chen J, Shumski M, Shannon RP.Worsening renal function defined as an absolute increase in serum creatinine is a biased metric for the study of cardio-renal interactions. Cardiology 2010;116:206–212.

81. Verdiani V, Lastrucci V, Nozzoli C.Worsening renal function in patients hospitalized with acute heart failure: risk factors and prognostic significances. Int J Nephrol 2010;2011:785974.

82. Rusinaru D, Buiciuc O, Houpe D, Tribouilloy C. Renal function and long-term survival after hospital discharge in heart failure with preserved ejection fraction. Int J Cardiol 2011;147:278–282.

83. Breidthardt T, Socrates T, Noveanu M, Klima T, Heinisch C, Reichlin T, Potocki M, Nowak A, Tschung C, Arenja N, Bingisser R, Mueller C. Effect and clinical prediction of worsening renal function in acute decompensated heart failure.AmJ Cardiol 2011;107:730–735.

84. Voors AA, Davison BA, FelkerGM,Ponikowski P,Unemori E, Cotter G,Teerlink JR,Greenberg BH, Filippatos G, Teichman SL, Metra M. Early drop in systolic blood pressure and worsening renal function in acute heart failure: renal results of Pre-RELAX-AHF. Eur J Heart Fail 2011;13:961–967.

85. Lanfear DE, Peterson EL, Campbell J, Phatak H, Wu D, Wells K, Spertus JA,Williams LK. Relation of worsened renal function during hospitalization for heart failure to long-term outcomes and rehospitalization. Am J Cardiol 2011;107:74–78.

86. de Silva R, Nikitin NP, Witte KK, Rigby AS, Goode K, Bhandari S, Clark AL,Cleland JG. Incidence of renal dysfunction over 6 months in patients with chronic heart failure due to left ventricular systolic dysfunction: contributing factors and relationship to prognosis. Eur Heart J 2006;27:569–581.

87. Jose P, Skali H, Anavekar N, Tomson C, Krumholz HM, Rouleau JL, Moye L, Pfeffer MA, Solomon SD. Increase in creatinine and cardiovascular risk in patients with systolic dysfunction after myocardial infarction. J Am Soc Nephrol 2006;10:2886–2891.

88. Khan NA,Mal, Thompson CR,Humphries K, Salem DN, Sarnak MJ, Levin A. Kidney function and mortality among patients with left ventricular systolic dysfunction.J Am Soc Nephrol 2006;17:244–253.

89. Iglesias JI, DePalma L, Hom D, Antoniotti M, Ayoub S, Levine JS. Predictors of mortality in adult patients with congestive heart failure receiving nesiritide: retrospective analysis showing a potential adverse interaction between nesiritide and acute renal dysfunction. Nephrol Dial Transplant 2008;23:144–153.

90. Ather S, Bavishi C, McCauley MD, Dhaliwal A, Deswal A, Johnson S, Chan W, Aguilar D, Pritchett AM, Ramasubbu K, Wehrens XH, Bozkurt B. Worsening renal function is not associated with response to treatment in acute heart failure. Int J Cardiol 2013;167:1912–1917.

91. Nohria A, Hasselblad V, Stebbins A, Pauly DF, Fonarow GC, Shah M, Yancy CW, Califf RM, Stevenson LW, Hill JA. Cardiorenal interactions: insights from the ESCAPE trial. J Am Coll Cardiol 2008;51:1268–1274.

92. Testani JM, Kimmel SE, Dries DL, Coca SG. Prognostic importance of early worsening renal function after initiation of angiotensin-converting enzyme inhibitor therapy in patients with cardiac dysfunction. Circ Heart Fail 2011;4:685–691.

93. Fonarow GC, Adams KF Jr, Abraham WT, Yancy CW, Boscardin WJ. Risk stratification for in-hospital mortality in acutely decompensated heart failure: classification and regression tree analysis. JAMA 2005;293:572–580.

94. Logeart D, Tabet JY, Hittinger L, Thabut G, Jourdain P, Maison P, Tartiere JM, Solal AC. Transient worsening of renal function during hospitalization for acute heart failure alters outcome. Int J Cardiol 2008;127:228–232.

95. Weinfeld MS, Chertow GM, Stevenson LW. Aggravated renal dysfunction during intensive therapy for advanced chronic heart failure. Am Heart J 1999;138:285–290.

96. Voors AA, Dittrich HC, Massie BM, Delucca P, Mansoor GA, Metra M, Cotter G, Weatherley BD, Ponikowski P, Teerlink JR, Cleland JG, O'Connor CM, Givertz MM. Effects of the adenosine A1 receptor antagonist rolofylline on renal function in patients with acute heart failure and renal dysfunction: results from PROTECT (Placebo-Controlled Randomized Study of the Selective Adenosine A1 Receptor Antagonist Rolofylline for Patients Hospitalized with Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function). J Am Coll Cardiol 2011;57:1899–1907.

97. Testani JM, Cappola TP, McCauley BD, Chen J, Shen J, Shannon RP, Kimmel SE. Impact of worsening renal function during the treatment of decompensated heart failure on changes in renal function during subsequent hospitalization. Am Heart J 2011;161:944–949.

98. Rossignol P, Cleland JG, Bhandari S, Tala S, Gustafsson F, Fay R, Lamiral Z, Dobre D, Pitt B, Zannad F. Determinants and consequences of renal function variations with aldosterone blocker therapy in heart failure patients post myocardial infarction. Insights from the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS). Circulation 2012;125:271–279.

99. Maeder MT, Rickli H, Pfisterer ME, Muzzarelli S, Ammann P, Fehr T, Hack D, Weilenmann D, Dieterle T, Kiencke S, EstlinbaumW, Brunner-La Rocca HP. Incidence, clinical predictors, and prognostic impact of worsening renal function in elderly patients with chronic heart failure on intensive medical therapy. Am Heart J 2012;163:407–14,414.

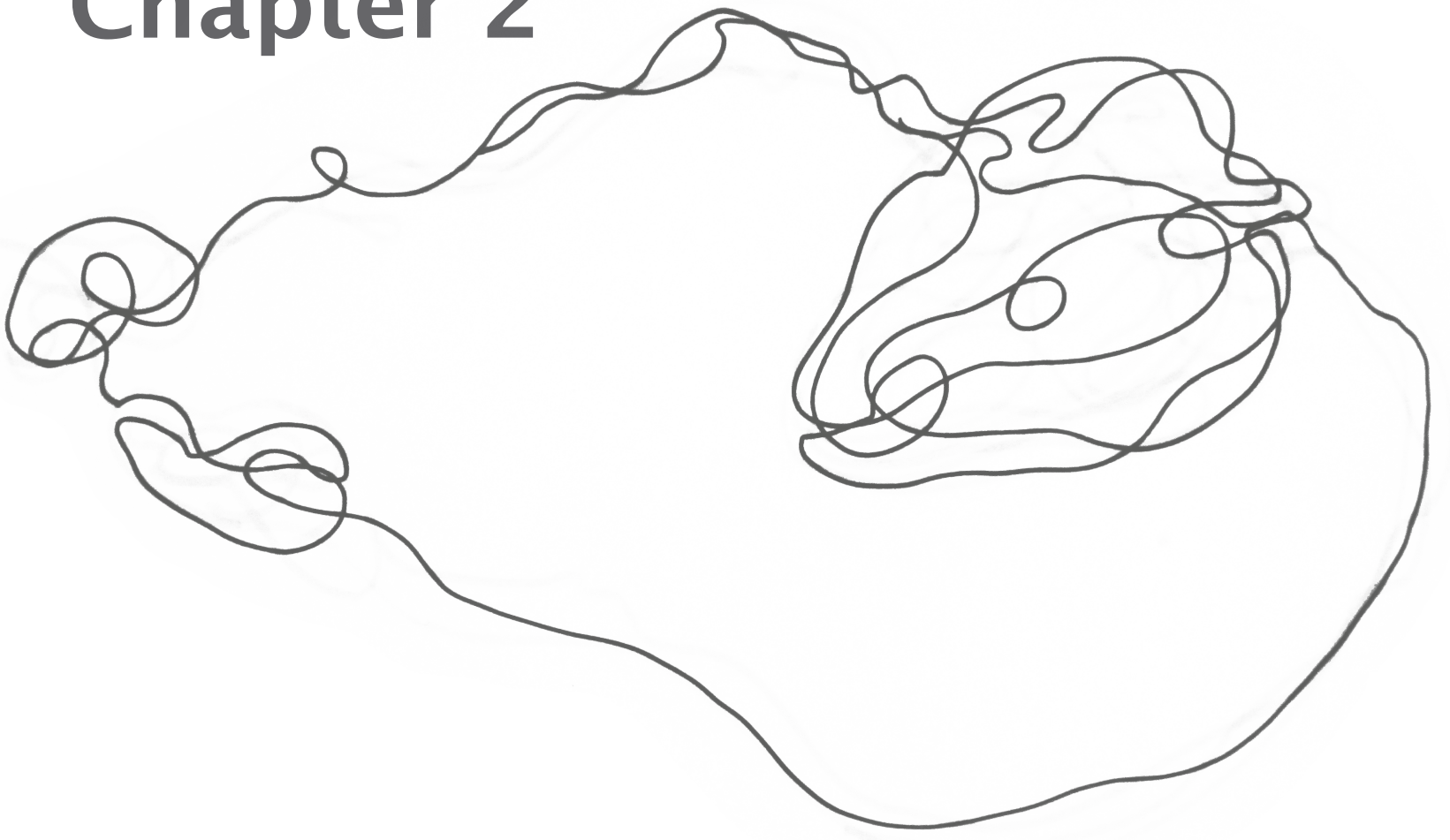
100. McAlister FA, Ezekowitz J, Tarantini L, Squire I, Komajda M, Bayes-Genis A, Gotsman I, Whalley G, Earle N, Poppe KK, Doughty RN. Renal dysfunction in patients with heart failure with preserved versus reduced ejection fraction: impact of the new chronic kidney disease-epidemiology collaboration group formula. Circ Heart Fail 2012;5:309–314.

101. Tonelli M, Wiebe N, Culleton B, House A, Rabbat C, Fok M, McAlister F, Garg AX. Chronic kidney disease and mortality risk: a systematic review. J Am Soc Nephrol

2006;17:2034–2047.

102. Damman K, Ng Kam Chuen MJ, MacFadyen RJ, Lip GY, Gaze D, Collinson PO, Hillege HL, van OeverenW, Voors AA, van Veldhuisen DJ. Volume status and diuretic therapy in systolic heart failure and the detection of early abnormalities in renal and tubular function. J Am Coll Cardiol 2011;57:2233–2241.
103. Felker GM, Lee KL, Bull DA, Redfield MM, Stevenson LW, Goldsmith SR, LeWinter MM, Deswal A, Rouleau JL, Ofili EO, Anstrom KJ, Hernandez AF, McNulty SE, Velazquez EJ, Kfoury AG, Chen HH, Givertz MM, Semigran MJ, Bart BA, Mascette AM, Braunwald E, O'Connor CM. Diuretic strategies in patients with acute decompensated heart failure. N Engl J Med 2011;364:797–805.
104. Testani JM, Coca SG, McCauley BD, Shannon RP, Kimmel SE. Impact of changes in blood pressure during the treatment of acutedecompensated heart failure on renal and clinical outcomes. Eur J Heart Fail 2011;13:877–884.
105. Metra M, Davison B, Bettari L, Sun H, Edwards C, Lazzarini V, Piovanelli B,Carubelli V, Bugatti S, Lombardi C, Cotter G, Dei CL. Is worsening renal function an ominous prognostic sign in patients with acute heart failure? The role of congestion and its interaction with renal function. Circ Heart Fail 2012;5:54–62

# Chapter 2



# The CKD-EPI equation outperforms the MDRD equation for estimating glomerular filtration rate in chronic systolic heart failure

Mattia A.E. Valente, Hans L. Hillege, Gerjan Navis,
Adriaan A. Voors, Dirk J. van Veldhuisen and Kevin Damman

Published in: European Journal of Heart Failure (2014) 16, 86–94

## Abstract

**Aims** The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula estimates glomerular filtration rate (GFR) better than the simplified Modification of Diet in Renal Disease (sMDRD) formula in numerous populations. It has not previously been validated in heart failure patients.

**Methods and results** The GFR was measured in 120 patients with chronic systolic heart failure (CHF) using [$^{125}$I]iothalamate clearance ($GFR_{IOTH}$) and estimated using the sMDRD and CKD-EPI equations. Accuracy, bias, and prognostic performance were compared. Cockcroft–Gault, CKD-EPI serum cystatin C, and CKD-EPI creatinine–serum cystatin C equations were compared in secondary analyses. Mean age was 59 ± 12 years, 80% were male. Mean LVEF was 29 ± 10%. Mean $GFR_{IOTH}$ was 74 ± 27 mL/min/1.73 m$^2$, and mean estimated GFR was 66 ± 23 mL/min/1.73 m$^2$ (CKD-EPI) and 63 ± 21 mL/min/1.73m$^2$ (sMDRD). CKD-EPI showed less bias than sMDRD (–8 ± 15 vs. –11 ± 16 mL/min/1.73 m$^2$, $P < 0.001$). Both equations underestimate at higher and overestimate at lower $GFR_{IOTH}$. Eleven patients (9%) were accurately reclassified into lower CKD classes with CKD-EPI. Cockcroft–Gault showed lower bias (–3 ± 16 mL/min/1.73 m$^2$) but worse precision and accuracy. Cystatin C-based estimation showed the lowest bias (–3 ± 14 mL/min/1.73 m$^2$) and the best precision and accuracy. Prognostic value did not differ between all GFR estimates

**Conclusion** The CKD-EPI equation more accurately estimates measured GFR than the sMDRD equation in CHF patients, with less bias and greater accuracy and precision. The prognostic power of all GFR assessments was equivalent. Based on better performance and equal risk prediction, we believe the CKI-EPI equation should be the preferred creatinine-based GFR estimation method in heart failure patients, particularly those with preserved or moderately impaired renal function.


## Abbreviations

| | |
|---|---|
| GFR | Glomerular Filtration Rate |
| $GFR_{IOTH}$ | GFR measured using Iothalamate clearance |
| $GFR_{CKD\text{-}EPI}$ | GFR estimated with CKD-EPI equation |
| $GFR_{SMDRD}$ | GFR estimated with simplified MDRD equation |
| $GFR_{CG}$ | Cockcroft-Gault creatinine clearance |
| $GFR_{CYS}$ | GFR estimated with CKD-EPI cystatin C equation |
| $GFR_{CYSCR}$ | GFR estimated with CKD-EPI cystatin C/creatinine equation |

## Introduction

Impaired renal function, defined as decreased glomerular filtration rate (GFR), is common in chronic heart failure (CHF) and has consistently been associated with strongly reduced survival.[1-4] As the gold standard measurement of GFR using inulin or iothalamate clearance is not feasible for every patient, simpler methods have been developed to estimate GFR. The most commonly used creatinine-based equation was developed in the Modification of Diet in Renal Disease (MDRD) study in patients with chronic kidney disease (CKD), and has been validated in CHF.[5, 6] However, the MDRD equation strongly underestimates GFR at levels higher than 60 mL/min/1.73 $m^2$in patients with renal disease and patients with CHF.[5, 7] A new equation—the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation—was developed that shows considerably less bias, particularly in patients with higher GFR.[7, 8] Accurate estimation of GFR in CHF patients is important for risk stratification, titration of treatment, and prognosis. Recent publications suggest that the CKD-EPI equation provides better risk stratification than the MDRD equation in patients with CHF; however, no study has validated the CKD-EPI equation in the CHF population.[9, 10] In this study, we validate the CKD-EPI equation in patients with CHF and examine its prognostic value compared with the MDRD equation, and in secondary analyses compare it with creatinine clearance using the Cockcroft–Gault equation and GFR estimates using cystatin C-based equations.

## Methods

The main study design has been published previously.[11] The present study is an extension of the main study. In brief, 120 clinically stable CHF patients with an LVEF <45%, included between 2003 and 2010, underwent renal function testing using [$^{125}$I]iothalamate clearance measurement at the University Medical Center Groningen, The Netherlands. Medication had to be stable for at least 1 month and all patients had to be on renin–angiotensin system (RAS) inhibition. All subjects gave informed consent for study participation. The study was approved by the institutional ethics board and conducted in accordance with Declaration of Helsinki guidelines.

### Renal function measurement using iothalamate clearance

The glomerular filtration rate ($GFR_{IOTH}$) was measured via constant infusion of a radiolabelled tracer, [$^{125}$I]iothalamate. This method has a day-to-day variation coefficient of 2.5% for $GFR_{IOTH}$.[12] $GFR_{IOTH}$ and $GFR_{CG}$ were normalized per 1.73 $m^2$ of body surface area (BSA), which was calculated as follows: $0.007184 \times weight^{0.425} \times height^{0.725}$.[13] A description of the protocol has been published previously.[5, 14]

### Laboratory methods

A venous blood sample was collected 2 h after the beginning of renal function measurements. Serum creatinine level was measured in all patients, using Jaffe alkaline picrate assays prior to 1 March 2006 and Roche Modular enzymatic assays

after 1 March 2006. Both methods were calibrated to the Cleveland Clinic Laboratory standard, traceable to isotope dilution mass spectrophotometry, as proposed by Coresh *et al*.[15] Details of the calibration equations used for our laboratory have been published recently.[16] Serum cystatin C levels were measured in 101 patients by nephelometry (BN-II N, Dade Behring Diagnostic) and calibrated to international reference standard ERM®-DA471/IFCC. All GFR estimates were calculated using calibrated creatinine and cystatin C values.

## Estimated glomerular filtration rate

The CKD-EPI formula expressed as a single equation is:

$$GFR_{CKD\text{-}EPI} = 141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018 \text{ [if female]} \times 1.159 \text{ [if black]}$$

where Scr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is –0.329 for females and –0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1. We compared the CKD-EPI equation with the most commonly used equation in clinical practice, the simplified MDRD, re-expressed for standardized serum creatinine values.[17]

$$GFR_{SMDRD} = 175 \times (Scr)^{-1.154} \times (age)^{-0.203} \times 0.742 \text{ [if female]} \times 1.212 \text{ [if black]}$$

Creatinine clearance using the Cockcroft–Gault formula[18] normalized for BSA expressed as a single equation is:

$$GFR_{CG} = ((140\text{-}Age) \times Weight) / (72 \times Scr) \times 0.85 \text{ [if female]} \times (1.73/BSA)$$

Estimated GFR based on serum cystatin C was calculated using the recently published CKD-EPI equations for use with standardized cystatin C and creatinine values.[19] Expressed as a single equation, the serum cystatin C-based formula is:

$$GFR_{CYS} = 133 \times \min(Scys/0.8, 1)^{-0.499} \times \max(Scys\ 0.8, 1)^{-1.328} \times 0.996^{Age} \times 0.932 \text{ [if female]}$$

where Scys is serum cystatin C.

Estimated GFR using the CKD-EPI combined creatinine–cystatin C formula expressed as a single equation is:

$$GFR_{CYSCR} = 135 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-0.601} \times \min(Scys/0.8, 1)^{-0.375} \times \max(Scys/0.8, 1)^{-0.711} \times 0.995^{Age} \times 0.969 \text{ [if female]} \times 1.08 \text{ [if black]}$$

where Scr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is –0.248 for females and –0.207 for males, min indicates the minimum of Scr/κ or 1, max indicates the maximum of Scr/κ or 1, and Scys is serum cystatin C.

## Follow-up

Follow-up data for all patients were obtained at 36 months after renal function measurement via chart review by two independent investigators. Median follow-up was 36 months (interquartile range 32–36). All patients were followed up at our cardiology outpatient clinic. There was no loss to follow-up. A combined endpoint of death due to any cause, heart transplantation, or first hospitalization for worsening heart failure was used.

## Statistical analysis

Data are presented as mean ±standard deviation when normally distributed, as median with interquartile range for skewed distribution, and as frequencies with percentages for categorical variables. Student's *t*-test was used to compare normally distributed continuous variables. The precision, accuracy, and bias of CKD-EPI, sMDRD, Cockcroft–Gault, and CKD-EPI cystatin C and creatinine–cystatin C equations in predicting $GFR_{IOTH}$ were evaluated. Precision was determined by assessing the degree of correlation between estimated and measured GFR using linear regression. $r^2$ statistics were used to provide an indication of the model's overall fit. The accuracy of each equation, or how well it reflects measured GFR, was assessed by comparing estimated GFR with the gold standard ($GFR_{IOTH}$). We used the following equation: [predicted value – measured value ($GFR_{IOTH}$)] × 100/$GFR_{IOTH}$. For each equation, the number of subjects with predicted GFR values within 15% or 30% of the $GFR_{IOTH}$ was counted.

Bias is any systematic, non-random deviation resulting in a prediction error, and was calculated as the difference between $GFR_{IOTH}$ and estimated GFR using individual equations. Logistic regression analysis was performed to determine area under the receiver operating characteristic (ROC) curve (AUC) for the relationship between various GFR estimates for different $GFR_{IOTH}$ cut-off values. These ROC curves were compared to analyse the performance of different renal function estimates. Bland–Altman analyses were performed to determine agreement between $GFR_{IOTH,}$ $GFR_{SMDRD}$, and $GFR_{CKD\text{-}EPI}$. The prognostic performances of $GFR_{IOTH}$, $GFR_{CKD\text{-}EPI}$, $GFR_{SMDRD}$, $GFR_{CG}$, $GFR_{CYS}$, and $GFR_{CYSCR}$ for the combined endpoint were evaluated using logistic regression. ROC curves were used to compare the predictive ability of the six renal function measures. All reported probability values are two-tailed, and a *P*-value <0.05 was considered statistically significant. Statistical analyses were performed using STATA (College Station, TX, USA), version 11.0.

## Results

The mean age of the study population was 59 ±12 years, and 80% were male (*Table* 1). One patient was Asian; all others were Caucasian. Most were in NYHA class II and III [56 (47%) and 35 (29%) patients, respectively]. All renal function measurements showed mild impairment of GFR, with a mean $GFR_{IOTH}$ of 74 ±27 mL/min/1.73 $m^2$. The CKD-EPI (66 ±23 mL/min/1.73 $m^2$), sMDRD (63 ±21 mL/min/1.73 $m^2$), Cockcroft–Gault (70 ±25 mL/min/1.73 $m^2$), and CKD-EPI cystatin C (72 ±26 mL/min/1.73 $m^2$) equations underestimated mean measured $GFR_{IOTH}$ (*P*-value for all comparisons <0.001). The CKD-EPI creatinine–cystatin C equation (86 ±20 mL/min/1.73 $m^2$) overestimated mean measured $GFR_{IOTH}$ (*P*-value for all comparisons <0.05).

### Glomerular filtration rate estimates relative to measurement of glomerular filtration rate determined using iothalamate clearance

*Figure* 1 shows the difference between estimated GFR using sMDRD and CKD-EPI equations and $GFR_{IOTH}$ relative to $GFR_{IOTH}$. Both equations considerably underestimated measured GFR at higher values and slightly overestimated measured GFR at lower values. *Figures S1* and *S2* in the Supplementary material show the Bland–Altman plots for CKD-EPI and sMDRD equations compared with $GFR_{IOTH}$. There was a strong correlation between $GFR_{CKD\text{-}EPI}$ and $GFR_{SMDRD}$ (*Figure* 2, $r^2 = 0.97$, $P < 0.001$).

Bias, accuracy, and precision for all five GFR estimation equations are presented in *Table* 2. Both $GFR_{CKD\text{-}EPI}$ and $GFR_{SMDRD}$ more accurately estimated measured GFR for lower GFR values (bias −8 ±15 and −11 ±16 mL/min/1.73 $m^2$, respectively), while GFR was more strongly underestimated in patients with a GFR ≥60 mL/min/1.73 $m^2$. $GFR_{CG}$ and $GFR_{CYS}$ showed negative bias (−3 ±16 and −3 ±14 mL/min/1.73 $m^2$, respectively), performing better in patients with impaired vs. more preserved renal function. $GFR_{CYSCR}$ overestimated measured GFR, showing better performance in patients with GFR ≥60 mL/min/1.73 $m^2$ and much wider variation at GFR below 60 mL/min/1.73 $m^2$. Of the creatinine-only based equations, $GFR_{CKD\text{-}EPI}$ outperformed $GFR_{SMDRD}$ and $GFR_{CG}$ with respect to precision and overall accuracy.

While $GFR_{CG}$ displayed less bias and slightly better accuracy at the 15% cut-off, though worse at the 30% cut-off, the variation was greater and precision lower than for $GFR_{CKD\text{-}EPI}$ and $GFR_{SMDRD}$. The cystatin C-based equations yielded lower bias and greater accuracy and precision (*Table* 2, all $P < 0.05$) than the creatinine-based equations.

Bias stratified by equation-related characteristics is presented in *Table* 3 for $GFR_{CKD\text{-}EPI}$ and $GFR_{SMDRD}$. $GFR_{CKD\text{-}EPI}$ showed less bias across most patient characteristics—particularly in younger and middle-aged patients, for both sexes, at all levels of creatinine, in patients with no albuminuria or microalbuminuria (all $P$ <0.05), but no difference in patients with overt macroalbuminuria. *Table S1* in the Supplementary material presents bias stratified by various patient characteristics for all GFR estimation equations. $GFR_{CG}$ showed less bias in women, younger patients, and

**Table 1** Baseline Characteristics

| Patient Characteristics | Total Population (n = 120) |
|---|---|
| Age (years) | 59 ± 12 |
| Sex (n, % male) | 96 (80) |
| Race (n, % Caucasian) | 119 (99) |
| NYHA class I / II / III / IV (n) | 19 / 56 / 35 / 10 |
| LVEF (%) | 29 ± 10 |
| Ischemic etiology (n, %) | 60 (50) |
| **Physical examination** | |
| Systolic BP (mm Hg) | 119 ± 20 |
| Diastolic BP (mm Hg) | 69 ± 12 |
| Weight (kg) | 86 ± 15 |
| BMI (kg/m$^2$) | 27 ± 4 |
| NT-proBNP (pg/mL) | 634 [267 – 1856] |
| **Renal Function** | |
| Serum creatinine (mg/dL) | 1.3 [1.0 – 1.4] |
| Serum cystatin C (mg/L) | 0.95 [.082 – 1.19] |
| $GFR_{IOTH}$ (mL/min/1.73m$^2$) | 74 ± 27 |
| $GFR_{CKD-EPI}$ (mL/min/1.73m$^2$) | 66 ± 23 |
| $GFR_{SMDRD}$ (mL/min/1.73m$^2$) | 63 ± 21 |
| $GFR_{CG}$ (mL/min/1.73m$^2$) | 70 ± 25 |
| $GFR_{CYS}$ (mL/min/1.73m$^2$) | 72 ± 26 |
| $GFR_{CYSCR}$ (mL/min/1.73m$^2$) | 86 ± 20 |
| Urinary Albumin Excretion (mg/24h) | 9 [6 – 18] |
| **Medication use (N (%))** | |
| RAS-inhibition | 120 (100) |
| Beta-blocker | 101 (84) |
| Mineralocorticoid receptor antagonist | 37 (31) |
| Diuretics | 81 (68) |

Abbreviations: BMI, body mass index; BP, blood pressure; $GFR_{CKD-EPI}$, estimated Glomerular Filtration Rate using Chronic Kidney Disease Epidemiology Collaboration equation; $GFR_{IOTH}$, Glomerular Filtration Rate using Iothalamate clearance; $GFR_{SMDRD}$, estimated Glomerular Filtration Rate using simplified modification of diet in renal disease equation; $GFR_{CG}$, Cockcroft-Gault creatinine clearance; $GFR_{CYS}$, estimated Glomerular Filtration Rate using cystatin C equation; $GFR_{CYSCR}$, estimated Glomerular Filtration Rate using Chronic Kidney Disease Epidemiology Collaboration cystatin C and creatinine equation; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; BP: blood pressure; BMI: Body Mass Index; NT-proBNP: N-type pro Brain Natriuretic Peptide; RAS, Renin Angiotensin System.

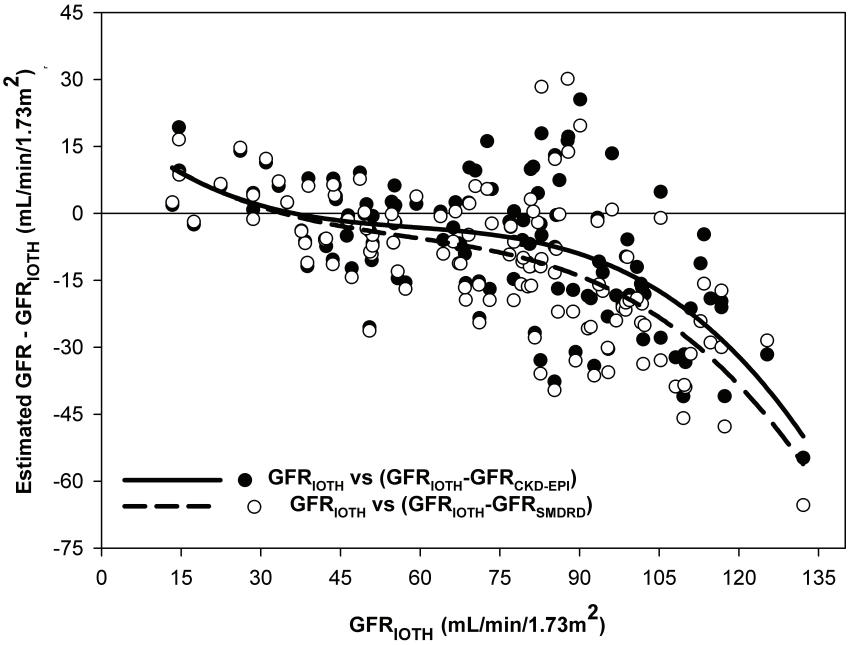



**Figure 1** Comparative performance of CKD-EPI and MDRD equations versus $GFR_{IOTH}$

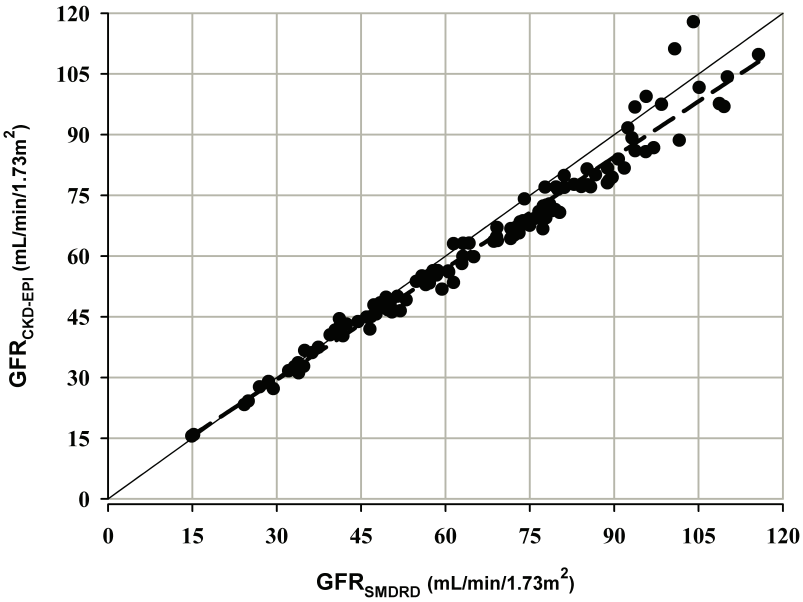



**Figure 2 Correlation between** $GFR_{CKD-EPI}$ and $GFR_{SMDRD}$

**Table 2** Bias, Precision and Accuracy of $GFR_{CKD\text{-}EPI}$ and $GFR_{SMDRD}$ versus $GFR_{IOTH}$

| Variable | All patients | | | | GFR < 60 mL/min/1.73m² | | GFR ≥ 60 mL/min/1.73m² | | Precision | Accuracy ( % [n]) | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | Median | Mean Bias | Median Bias | Mean Bias | Median Bias | Mean Bias | Median Bias | $r^2$ | 15% | 30% |
| $GFR_{IOTH}$ | 74 ± 27 | 78 [51 – 94] | - | - | - | - | - | - | - | - | - |
| $GFR_{CKD\text{-}EPI}$ | 66 ± 23 | 70 [48 – 81] | -8 ± 15 | -6 [-17 – 2] | -1 ± 9 | 1.1 [-6 – 6] | -11 ± 16 | -12 [-20 - -1] | 0.70 | 48 [58] | 86 [103] |
| $GFR_{SMDRD}$ | 62 ± 21 | 64 [47 – 77] | -11 ± 16 | -10 [-21 – 0] | -2 ± 9 | -2 [-7 – 4] | -16 ± 17 | -17 [-25 - -6] | 0.65 | 43 [51] | 80 [96] |
| $GFR_{CG}$ | 70 ± 25 | 68 [51 – 86] | -3 ± 16 | -3 [-14 – 7] | 2 ± 10 | 4 [-4 – 9] | -6 ± 18 | -9 [-19 – 4] | 0.65 | 45 [61] | 73 [94] |
| $GFR_{CYS}$ | 72 ± 26 | 75 [52 – 92] | -3 ± 14 | -3 [-12 – 6] | 0 ± 10 | -1 [-5 – 7] | -5 ± 16 | -6 [-14 – 5] | 0.73 | 54 [55] | 89 [90] |
| $GFR_{CYSCR}$ | 86 ± 20 | 88 [72 – 98] | 10 ± 14 | 11 [1 – 21] | 23 ± 8 | 24 [17 – 27] | 5 ± 12 | 3 [-2 – 15] | 0.76 | 46 [48] | 71 [72] |

All units are mL/min/1.73m² unless otherwise indicated.

patients with high body mass index, lower systolic blood pressure, and higher creatinine levels, albeit with generally larger standard deviations than the other equations. $GFR_{CYS}$ most accurately assessed measured GFR across patient characteristics, while $GFR_{CY\text{-}SCR}$ displayed greater variability.

Using $GFR_{IOTH}$ cut-offs of ≥30 and ≥60 mL/min/1.73 m², there were strong correlations and almost no significant differences between the areas under the ROC curves for $GFR_{CKD\text{-}EPI}$, $GFR_{SMDRD}$, $GFR_{CG}$, $GFR_{CYS}$, and $GFR_{CYSCR}$ (*Table* 4); at ≥90 mL/min/1.73 m², $GFR_{CG}$ showed worse performance than the other equations ($P$ = 0.03), while the other four equations were comparable [$P$ = non-significant (NS)]. In reclassification analysis, 15 (12.5%) patients were reclassified into different KDOQI (Kidney Disease Outcomes Quality Initiative) stages using the CKD-EPI vs. the sMDRD equation, all into less severe CKD classes (*Table* 5). Compared with $GFR_{IOTH}$, 11 (9%) of these patients were accurately reclassified using $GFR_{CKD\text{-}EPI}$, while the remaining 4 patients were accurately classified using $GFR_{SMDRD}$.

## Glomerular filtration rate estimates and prognosis

After 3 years, 33 patients had experienced an event: there were 7 deaths, 21 heart failure hospitalizations, and 5 heart transplantations. *Figure* 3 shows the ROC curves for logistic regression analyses of the combined endpoint vs. $GFR_{IOTH}$, $GFR_{SMDRD}$, and $GFR_{CKD\text{-}EPI}$; $GFR_{IOTH}$ showed the best predictive ability, with an AUC of 0.77, while both CKD-EPI and $GFR_{SMDRD}$ showed similar performance (AUC = 0.76, $P$ = NS). Comparing all six measures ($n$ = 101), all showed similar performance, with all AUCs between 0.76 and 0.78 ($P$ = NS). There were no statistically significant differences between predictive abilities on the combined endpoint or any of its individual components for any of the measures.

**Table 3** Bias of $GFR_{CKD-EPI}$ and $GFR_{SMDRD}$ equations stratified by equation variables and clinical characteristics

| | | $GFR_{CKD-EPI}$ | $GFR_{SMDRD}$ |
|---|---|---|---|
| | n | Mean [95% CI] | Mean [95% CI] |
| Age [years][a] | | | |
| < 56 [b] | 44 | -9 [-14 – -4] | -16 [-21 – -10] |
| 56 – 63 [b] | 36 | -7 [-12 – -3] | -10 [-15 – -5] |
| > 63 | 40 | -7 [-11 – -3] | -7 [-11 – -3] |
| Sex | | | |
| Male [b] | 96 | -8 [-11 – -6] | -12 [-15 – -9] |
| Female [b] | 24 | -4 [-10 – 3] | -9 [-16 – -2] |
| Creatinine [mg/dL] [a] | | | |
| 0.69 – 1.03 [b] | 41 | -5 [-10 – 0] | -10 [-16 – -4] |
| 1.04 – 1.32 [b] | 40 | -13 [-18 – -9] | -18 [-23 – -13] |
| 1.34 – 3.87 [b] | 39 | -4 [-9 – 1] | -5 [-9 – -1] |
| Urinary albumin excretion [mg/24h] | | | |
| None (0-29) [b] | 93 | -8 [-12 – -6] | -13 [-16 – -10] |
| Microalbuminuria (30-300) [b] | 19 | -8 [-14 – 1] | -9[-18 – -1] |
| Macroalbuminuria (>300) | 8 | 5 [-3 – 12] | 4 [-8 – 16] |
| NT-proBNP [pg/ml] [a] | | | |
| 28 – 344 [b] | 40 | -10 [-15 – -5] | -14 [-20 – -9] |
| 360 – 1230 [b] | 40 | -12 [-17 – -6] | -15 [-21 – -10] |
| 1272 – 25224 [b] | 40 | -1 [-5 – 3] | -4 [-7 – 0] |
| NYHA Class | | | |
| I-II [b] | 75 | -11 [-14 – -7] | -14 [-18 – -11] |
| III-IV [b] | 45 | -3 [-6 – 1] | -6 [-9 – -2] |
| LVEF [%][a] | | | |
| < 25 [b] | 40 | -5 [-9 – -1] | -9 [-13 – -5] |
| 25 – 33 [b] | 40 | 8 [-13 – -3] | -11 [-16 – -6] |
| > 33 [b] | 40 | -10 [-15 – -5] | -14 [-20 – -8] |
| Ischemic etiology | | | |
| No [b] | 60 | -7 [-10 – -3] | -11 [-15 – -6] |
| Yes [b] | 60 | -9 [-12 – -5] | -12 [-16 – -7] |
| Systolic BP [mm Hg] [a] | | | |
| < 111 [b] | 44 | -4 [-8 – -1] | -8 [-12 – -4] |
| 111 – 125 [b] | 37 | -9 [-14 – -4] | -14 [-19 – -9] |
| > 125 [b] | 39 | -10 [-15 – -5] | -12 [-18 – -6] |
| Diastolic BP [mm Hg] [a] | | | |
| < 64 [b] | 41 | -6 [-10 – -2] | -9 [-13 – -4] |
| 64 – 74 [b] | 40 | -6 [-10 – -2] | -10 [-15 – -5] |
| > 74 [b] | 39 | -11 [-17 – -6] | -15 [-21 – -9] |

| | | $GFR_{CKD-EPI}$ | $GFR_{SMDRD}$ |
|---|---|---|---|
| | n | Mean [95% CI] | Mean [95% CI] |
| BMI [kg/m²] [a] | | | |
| <26 [b] | 40 | -3 [-9 – 2] | -6 [-13 – -0] |
| 26 – 29 [b] | 40 | -8 [-11 – -4] | -11 [-15 – -7] |
| >29 [b] | 40 | -12 [-17 – -7] | -16 [-21 – -11] |
| Beta blocker | | | |
| No [b] | 19 | -3 [-11 – 5] | -7 [-15 – 2] |
| Yes [b] | 101 | -8 [-11 – -6] | -12 [-15 – -9] |
| MRA | | | |
| No [b] | 83 | -10 [-13 – -7] | -14 [-17 – -10] |
| Yes [b] | 37 | -2 [-7 – 3] | -6 [-10 – -1] |
| Diuretic use | | | |
| No [b] | 39 | -10 [-16 – -6] | -15 [-20 – -10] |
| Yes [b] | 81 | -6 [-9 – -3] | -9 [-13 – -6] |

[a] divided in tertiles; [b] $p \leq 0.05$; Abbreviations: NYHA: New York Heart Association classification; LVEF: Left Ventricular Ejection Fraction; BP: blood pressure; BMI: Body Mass Index; UAE: Urinary Albumin Excretion; MRA: Mineralocorticoid receptor antagonist; NT-proBNP: N-type pro Brain Natriuretic Peptide

**Table 4** ROC analysis for different GFR cut-offs

| $GFR_{IOTH}$ cut-off | Equation | AUC (95% CI) | P-value |
|---|---|---|---|
| ≥ 30 mL/min/1.73m² | $GFR_{CKD-EPI}$ | 0.98 (0.95 – 1.00) | |
| | $GFR_{SMDRD}$ | 0.98 (0.95 – 1.00) | |
| | $GFR_{CG}$ | 0.96 (0.93 – 1.00) | |
| | $GFR_{CYS}$ | 0.98 (0.95 – 1.00) | |
| | $GFR_{CYSCR}$ | 0.97 (0.94 – 1.00) | 0.55 |
| ≥ 60 mL/min/1.73m² | $GFR_{CKD-EPI}$ | 0.97 (0.95 – 1.00) | |
| | $GFR_{SMDRD}$ | 0.97 (0.95 – 1.00) | |
| | $GFR_{CG}$ | 0.97 (0.93 – 1.00) | |
| | $GFR_{CYS}$ | 0.98 (0.96 – 1.00) | |
| | $GFR_{CYSCR}$ | 0.98 (0.96 – 1.00) | 0.36 |
| ≥ 90 mL/min/1.73m² | $GFR_{CKD-EPI}$ | 0.85 (0.78 – 0.92) | |
| | $GFR_{SMDRD}$ | 0.85 (0.78 – 0.92) | |
| | $GFR_{CG}$ | 0.83 (0.75 – 0.91) | |
| | $GFR_{CYS}$ | 0.88 (0.82 – 0.95) | |
| | $GFR_{CYSCR}$ | 0.89 (0.83 – 0.95) | 0.03 |

Abbreviations: AUC: Area under the receiver-operator characteristics curve; CI: confidence interval.

## Discussion

In the present study, we found that the CKD-EPI equation more accurately estimated measured GFR compared with the sMDRD equation in patients with chronic systolic heart failure. Use of the CKD-EPI equation resulted in the accurate reclassification of 9% of patients into less severe CKD classes. In secondary analysis, confirming earlier findings,[5] the Cockcroft–Gault equations showed the worst performance among the cre-

**Table 5.** Reclassification of patients into different KDOQI classes by $GFR_{CKD-EPI}$

| | $GFR_{SMDRD}$ (mL/min/1.73m²) | | | | |
|---|---|---|---|---|---|
| $GFR_{CKD-EPI}$ (mL/min/1.73m²) | Stage IV (< 30) | Stage IIIb (30 – 44) | Stage IIIa (45 – 59) | Stage II (60 – 90) | Stage I (> 90) |
| Stage IV (< 30) | 7 | 0 | 0 | 0 | 0 |
| Stage IIIb (30 – 44) | 0 | 17 | 0 | 0 | 0 |
| Stage IIIa (45 – 59) | 0 | 2 | 23 | 0 | 0 |
| Stage II (60 – 90) | 0 | 0 | 6 | 47 | 0 |
| Stage I (> 90) | 0 | 0 | 0 | 7 | 11 |

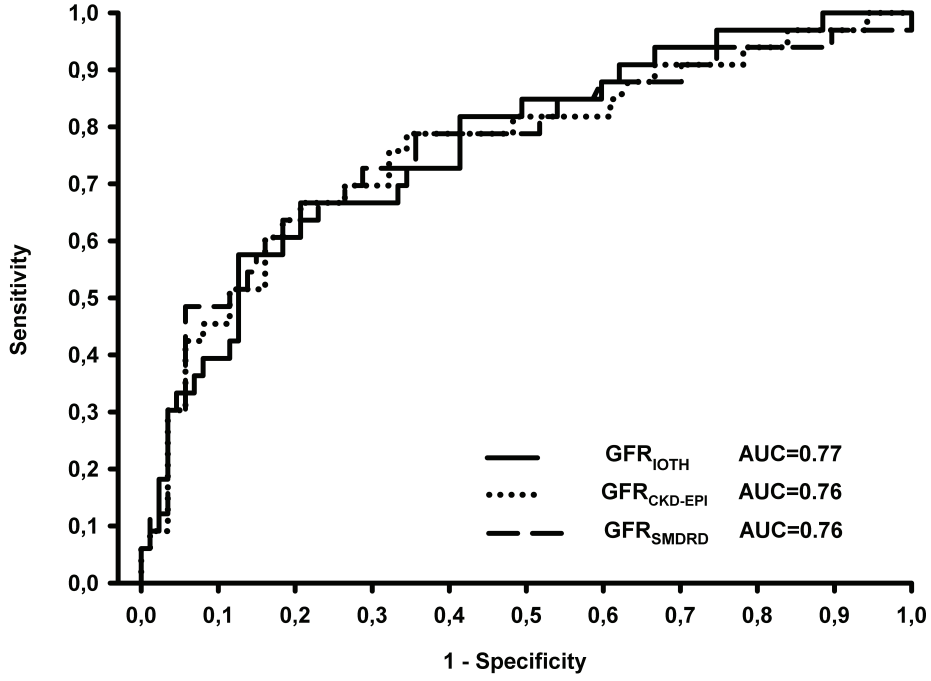



**Figure 3** Receiver operating characterisitic curves for combined endpoint at 3 years.

AUC: area under the receiver-operator characteristics curve

atinine-based GFR estimation equations. The best overall performance was found for $GFR_{CYS}$, with the lowest bias, good precision, and the greatest accuracy, while $GFR_{CYSCR}$ had the best precision but greater variability.

## Estimating the glomerular filtration rate in patients with chronic heart failure

Accurate assessment of glomerular filtration is important in all populations, including patients with CKD, hypertension, cardiovascular disease, and heart failure, as a reduced GFR is related to increased mortality and morbidity in all of these groups.[2, 20, 21] Creatinine-based equations remain the cornerstone of GFR estimation, but despite validation studies and calibration of serum creatinine, substantial biases remain.[22] For patients with heart failure, the six-variable simplified MDRD equation showed the best prognostic value but still overestimated GFR in patients with low GFR, while underestimating GFR in patients with preserved GFR.[5] Similar underestimation of GFR at higher GFR values was also observed in large nephrologic studies, which led to the development of the new CKD-EPI equation. In a population of 8254 patients, this more complex equation was able to decrease the observed mean bias to +2.5 mL/min/1.73 $m^2$, compared with +5.5 mL/min/1.73 $m^2$ for the sMDRD equation.[7] Bias was reduced most in patients with a GFR ≥60 mL/min/1.73 $m^2$, where bias was reduced from +10.6 to +3.5 mL/min/1.73 $m^2$. The reduced bias for CKD-EPI in patients with a GFR ≥60 mL/min/1.73 $m^2$ was confirmed by Stevens *et al.*[8] Although these differences between measured GFR and estimated GFR seem small, they can significantly affect risk stratification, as even 5 mL/min/1.73 $m^2$ of deterioration in renal function has been associated with strongly increased risk for mortality.[23] The CKD-EPI equation has been validated in various patient subgroups, with mixed results. In patients with type II diabetes, for example, CKD-EPI still significantly underestimated GFR and was outperformed by the sMDRD equation,[24, 25] while use of the CKD-EPI equation led to a lower prevalence of CKD in another study.[26] In the present study, we found that the CKD-EPI equation better estimated $GFR_{IOTH}$ compared with the simplified MDRD equation. Both equations underestimated GFR for higher $GFR_{IOTH}$ levels, and slightly overestimated values for lower $GFR_{IOTH}$ levels. Though our results reflect those found in other populations, the absolute bias was greater than reported in other studies.[7, 8] The reason for this greater bias is unclear. Using the CKD-EPI rather than the sMDRD equation resulted in the reclassification of 12.5% of patients into better KDOQI CKD stages in this particular cohort. In our present analysis in patients with CHF, the CKD-EPI equation provides improved accuracy, bias, and precision in almost all patients. The exception in our cohort are patients over the age of 60 years and patients with macroalbuminuria, in whom CKD-EPI and sMDRD equations showed similar bias. As heart failure is primarily a disease of the elderly, it is speculated that while use of the CKD-EPI equation may not lead to better risk stratification in HF populations, its performance is certainly no worse. Our secondary analyses showed that the Cockcroft–Gault equation demonstrated relatively minimal bias, though precision was lower and variation greater than for the CKD-EPI and sMDRD equations. Our analyses also clearly

demonstrated the superiority of cystatin C in estimating GFR, confirming previous analyses.[19,27,28] However, as routine cystatin C measurements have thus far failed to enter daily practice, and are only recommended in specific subsets of patients screened using creatinine-based equations,[29] we believe identifying and validating the best creatinine-based GFR estimation equation remains clinically relevant.

## Risk prediction using the CKD-EPI vs. the simplified MDRD equation

Estimation of GFR is not only important for the assessment of renal function, it also serves as a strong (mortality) risk indicator in patients with heart failure.[2,30] Smilde *et al.* showed that equations estimating GFR may be less powerful predictors of outcome compared with $GFR_{IOTH}$.[5] This inferiority is probably a reflection of decreased accuracy in determining GFR. The prognostic importance of CKD-EPI has been evaluated in different settings. In one study in patients with myocardial infarction, CKD-EPI was inferior to the Cockcroft–Gault equation in predicting mortality,[31] but was a powerful predictor of in-hospital events in a study of patients with acute coronary syndrome.[32] In a large population of acute myocardial infarction patients with impaired systolic function or signs of heart failure, use of the CKD-EPI equation improved risk stratification compared with sMDRD.[33] A recent study by Zamora *et al.* comparing the prognostic performance of CKD-EPI, sMDRD, and Cockcroft–Gault equations in a heart failure cohort found the latter to be the best predictor for mortality, with CKD-EPI and sMDRD equations showing similar performance.[9] In contrast, a meta-analysis by McAlister *et al.* evaluating the performance of sMDRD and CKD-EPI for mortality risk stratification in heart failure patients found that CKD-EPI outperformed sMDRD.[10] Matsushita *et al.*, in a large pooled meta-analysis of >1.1 million patients with diverse backgrounds, including general and cardiovascular disease populations, found that the CKD-EPI equation classified fewer individuals as having CKD and provided more accurate risk stratification for mortality and end-stage renal disease.[34] Our results show that the CKD-EPI and sMDRD equations have numerically similar prognostic capacity compared with the gold standard, with no indication of any improvement in risk classification for either equation, despite accurate reclassification into less severe CKD classes by CKD-EPI. We also saw no differences in our secondary analyses. However, our study population is small, with a relatively low number of events. We elected to use a composite endpoint that included hospitalization, which—along with sample size—may explain the lack of effect on outcome despite significant KDOQI CKD reclassification.

## Clinical implications

Our data show that the CKD-EPI equation more accurately reflects measured GFR in CHF patients, with more accurate classification into KDOQI classes, and no significant differences in predicting risk. Accuracy and precision were better for CKD-EPI than for sMDRD and Cockcroft–Gault estimates, while bias was lower for $GFR_{CG}$, though with greater error margins. Although cystatin C-based estimates do perform better, there is still a place for creatinine-based GFR estimates in daily clini-

cal practice. In large meta-analyses in a broad spectrum of populations, including heart failure patients, CKD-EPI has been found to improve mortality and renal outcome risk stratification.[10,34] Considering these findings, we believe that the CKD-EPI equation should be the preferred creatinine-based method for estimating the GFR in heart failure patients, particularly those with preserved or moderately impaired renal function.

### Limitations and strengths

Our study has several important limitations. First, our cohort of patients with heart failure was relatively young with only mild renal impairment. Furthermore, we only included patients with reduced EF. Our cohort also consists almost exclusively of Caucasians. While this does not invalidate the analyses, the conclusions cannot simply be applied to a general heart failure population. The sample size is also limited due to the relatively cumbersome study design. Combined with a low number of events, this limits the study's statistical power for evaluating risk stratification improvement for CKD-EPI vs. sMDRD equations. Nonetheless, this is the largest cohort of heart failure patients with iothalamate clearances available.

## Conclusion

In patients with chronic systolic heart failure, the CKD-EPI equation more accurately estimates GFR compared with the sMDRD equation, with less bias, greater accuracy, and improved precision. The Cockcroft–Gault equation, while providing lower mean bias, shows greater variance and worse precision and accuracy. Although cystatin C-based equations provided more accurate estimates of measured GFR, cystatin C has yet to establish itself in routine clinical practice. The prognostic power of all creatinine-based GFR assessments was equivalent in our population, although evidence from meta-analyses indicates that the CKD-EPI equation provides better risk stratification. Based on a better performance and equal to better risk prediction, we believe the CKI-EPI equation should be the preferred method for creatinine-based GFR estimation in heart failure patients, particularly for patients with preserved or moderately impaired renal function.

**Funding:** The Netherlands Heart Foundation. D.J.vV. and A.A.V. are clinical established investigators of the Netherlands Heart Foundation (grant D97.017 and grant 2006T037). K.D. is supported by the Netherlands Heart Foundation (grant 2006B157). The funding organization had no influence on the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

**Conflicts of interest:** mone declared.

**Authors' contributions:** M.A.E.V had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. M.A.E.V., H.L.H., G.N., A.A.V., P.H.J.M.D., D.J.vV., and K.D. contributed to analysis and interpretation of data; M.A.E.V., K.D., H.L.H., and A.A.V. contributed to data conception and design. All authors have drafted and revised the manuscript critically for important intellectual content.

## References


1. Damman K, Navis G, Voors AA, Asselbergs FW, Smilde TD, Cleland JG, van Veldhuisen DJ, Hillege HL. Worsening renal function and prognosis in heart failure: systematic review and meta-analysis. J Card Fail 2007;13:599–608.
2. Hillege HL, Girbes AR, de Kam PJ, Boomsma F, de Zeeuw D, Charlesworth A, Hampton JR, van Veldhuisen DJ. Renal function, neurohormonal activation, and survival in patients with chronic heart failure. Circulation 2000;102:203–210.
3. Scrutinio D, Passantino A, Santoro D, Catanzaro R. The cardiorenal anaemia síndrome in systolic heart failure: prevalence, clinical correlates, and long-term survival. Eur J Heart Fail 2011;13:61–67.
4. Testani JM, Coca SG, Shannon RP, Kimmel SE, Cappola TP. Influence of renal dysfunction phenotype on mortality in the setting of cardiac dysfunction: analysis of three randomized controlled trials. Eur J Heart Fail 2011;13:1224–1230.
5. Smilde TD, van Veldhuisen DJ, Navis G, Voors AA, Hillege HL. Drawbacks and prognostic value of formulas estimating renal function in patients with chronic heart failure and systolic dysfunction. Circulation 2006;114:1572–1580.
6. O'Meara E, Chong KS, Gardner RS, Jardine AG, Neilly JB, McDonagh TA. The Modification of Diet in Renal Disease (MDRD) equations provide valid estimations of glomerular filtration rates in patients with advanced heart failure. Eur J Heart Fail 2006;8:63–67.
7. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J, CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604–612.
8. Stevens LA, Schmid CH, Greene T, Zhang YL, Beck GJ, Froissart M, Hamm LL, Lewis JB, Mauer M, Navis GJ, SteffesMW, EggersPW, Coresh J, Levey AS. Comparative performance of theCKDEpidemiology Collaboration (CKD-EPI) and the Modification of Diet in Renal Disease (MDRD) Study equations for estimating GFR levels above 60 mL/min/1.73 m2. Am J Kidney Dis 2010;56:486–495.
9. Zamora E, Lupon J, Vila J, Urrutia A, de Antonio M, Sanz H, Grau M, Ara J, Bayes-Genis A. Estimated glomerular filtration rate and prognosis in heart failure: value of the Modification of Diet in Renal Disease Study-4, chronic kidney disease epidemiology collaboration, and cockroft-gault formulas. J Am Coll Cardiol 2012; 59:1709–1715.
10. McAlister FA, Ezekowitz J, Tarantini L, Squire I, Komajda M, Bayes-Genis A, Gotsman I, Whalley G, Earle N, Poppe KK, Doughty RN, Meta-analysis Global Group in Chronic Heart Failure (MAGGIC) Investigators. Renal dysfunction in patients with heart failure with preserved versus reduced ejection fraction: impact of the new chronic kidney disease-epidemiology collaboration group formula. Circ Heart Fail 2012;5:309–314.
11. Smilde TD, Damman K, van der Harst P, Navis G, Westenbrink BD, Voors AA, Boomsma F, van Veldhuisen DJ, Hillege HL. Differential associations between renal function and 'modifiable' risk factors in patients with chronic heart failure. Clin Res Cardiol 2009;98:121–129.
12. Apperloo AJ, de Zeeuw D, Donker AJ, de Jong PE. Precision of glomerular filtration rate determinations for long-term slope calculations is improved by simultaneous infusion of 125I-iothalamate and 131I-hippuran. J Am Soc Nephrol 1996;7:567–572.
13. Du Bois D, Du Bois EF. A formula to estimate the approximate surface area if height and weight be known. 1916. Nutrition 1989;5:303–311; discussion 312–313.
14. DonkerAJ, van derHemGK, Sluiter WJ, Beekhuis H.Aradioisotope method for simultaneous determination of the glomerular filtration rate and the effective renal plasma flow. Neth J Med 1977;20:97–103.
15. Coresh J, Eknoyan G, Levey AS. Estimating the prevalence of low glomerular filtration rate requires attention to the creatinine assay calibration. JAmSoc Nephrol 2002;13:2811–2812; author reply 2812–2816.
16. Tent H, Waanders F, Krikken JA, Heerspink HJ, Stevens LA, Laverman GD, Navis G. Performance of MDRD study and CKD-EPI equations for long-term follow-up of nondiabetic patients with chronic kidney disease. Nephrol Dial Transplant 2012;27 Suppl 3:iii89–iii95.
17. Levey AS, Coresh J, Greene T, Marsh J, Stevens LA, Kusek JW, Van Lente F, Chronic Kidney Disease Epidemiology Collaboration. Expressing the Modification of Diet in Renal Disease Study equation for estimating glomerular filtration rate with standardized serum creatinine values. Clin Chem 2007;53:766–772.
18. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31–41.
19. Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, Kusek JW, Manzi J, VanLente F, Zhang YL, Coresh J, Levey AS,CKD-EPI Investigators. Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med 2012;367:20–29.
20. Rifkin DE, Katz R, Chonchol M, Fried LF, Cao J,

de Boer IH, Siscovick DS, Shlipak MG, Sarnak MJ. Albuminuria, impaired kidney function cardiovascular outcomes or mortality in the elderly. Nephrol Dial Transplant 2010;25:1560–1567.

21. Shlipak MG, Heidenreich PA, Noguchi H, Chertow GM, Browner WS, McClellan MB. Association of renal insufficiency with treatment and outcomes after myocardial infarction in elderly patients. Ann Intern Med 2002;137:555–562.
22. Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, Kusek JW, Van Lente F, Chronic Kidney Disease Epidemiology Collaboration. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med 2006;145:247–254.
23. Khan NA, Ma I, Thompson CR, Humphries K, Salem DN, Sarnak MJ, Levin A. Kidney function and mortality among patients with left ventricular systolic dysfunction. J Am Soc Nephrol 2006;17:244–253.
24. Rognant N, Lemoine S, Laville M, Hadj-Aissa A, Dubourg L. Performance of the chronic kidney disease epidemiology collaboration equation to estimate glomerular filtration rate in diabetic patients. Diabetes Care 2011;34:1320–1322.
25. Silveiro SP, Araujo GN, Ferreira MN, Souza FD, Yamaguchi HM, Camargo EG. Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation pronouncedly underestimates glomerular filtration rate in type 2 diabetes. Diabetes Care 2011;34:2353–2355.
26. McFarlane SI, McCullough PA, Sowers JR, Soe K, Chen SC, Li S, Vassalotti JA, Stevens LA, Salifu MO, Kurella Tamura M, Bomback AS, Norris KC, Collins AJ, Bakris GL, Whaley-Connell AT, KEEP Steering Committee. Comparison of the CKD Epidemiology Collaboration (CKD-EPI) and Modification of Diet in Renal Disease (MDRD) study equations: prevalence of and risk factors for diabetes mellitus in CKD in the Kidney Early Evaluation Program (KEEP). Am J Kidney Dis 2011;57:S24–S31.
27. Damman K, van der Harst P, Smilde TD, Voors AA, Navis G, van Veldhuisen DJ, Hillege HL. Use of cystatin C levels in estimating renal function and prognosis in patients with chronic systolic heart failure. Heart 2012;98:319–324.
28. Dharnidharka VR,KwonC, Stevens G. Serum cystatinCis superior to serum creatinine as a marker of kidney function: a meta-analysis. AmJ Kidney Dis 2002;40:221–226.
29. Stevens PE, Levin A, Kidney Disease: Improving Global Outcomes Chronic Kidney Disease Guideline Development Work Group Members. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. Ann Intern Med 2013; 158:825–830.
30. Hillege HL, Nitsch D, Pfeffer MA, Swedberg K, McMurray JJ, Yusuf S, Granger CB, Michelson EL, Ostergren J, Cornel JH, de Zeeuw D, Pocock S, van Veldhuisen DJ, Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) Investigators. Renal function as a predictor of outcome in a broad spectrum of patients with heart failure. Circulation 2006;113:671–678.
31. Tomaszuk-Kazberuk A, Kozuch M, Malyszko J, Bachorzewska-Gajewska H, Dobrzycki S, Musial WJ. Which method of GFR estimation has the best prognostic value in patients treated with primary PCI: Cockcroft–Gault formula, MDRD, or CKD-EPI equation?—A 6-year follow-up. Ren Fail 2011;33:983–989.
32. AlFaleh HF, Alsuwaida AO, Ullah A, Hersi A, AlHabib KF, AlShahrani A, AlNemer K, AlSaif S, Taraben A, Ahmed WH, Balghith MA, Kashour T. Glomerular filtration rate estimated by the CKD-EPI formula is a powerful predictor of in-hospital adverse clinical outcomes after an acute coronary syndrome. Angiology 2012;63:119–126.
33. Skali H, Uno H, Levey AS, Inker LA, Pfeffer MA, Solomon SD. Prognostic assessment of estimated glomerular filtration rate by the new Chronic Kidney Disease Epidemiology Collaboration equation in comparison with the Modification of Diet in Renal Disease Study equation. Am Heart J 2011;162:548–554.
34. Matsushita K, Mahmoodi BK, Woodward M, Emberson JR, Jafar TH, Jee SH, Polkinghorne KR, Shankar A, Smith DH, Tonelli M, Warnock DG, Wen CP, Coresh J, Gansevoort RT, Hemmelgarn BR, Levey AS, Chronic Kidney Disease Prognosis Consortium. Comparison of risk prediction using the CKD-EPI equation and the MDRD study equation for estimated glomerular filtration rate. JAMA 2012;307:1941–1951.

## Supplemental material

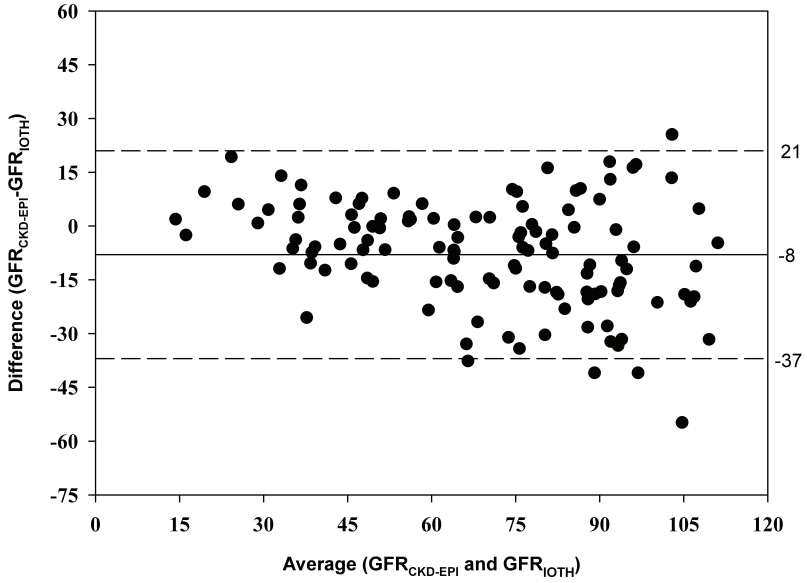



**Figure S1** Bland-Altman analysis for $GFR_{CKD-EPI}$ versus $GFR_{IOTH}$

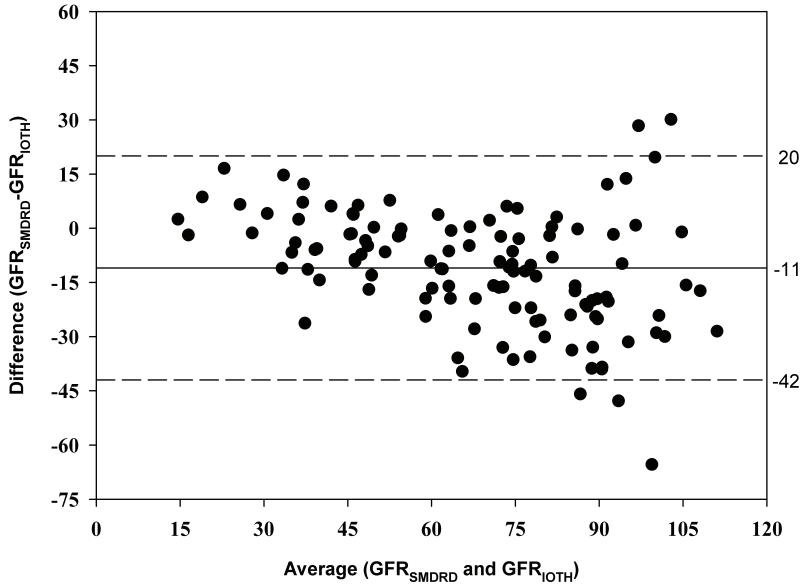


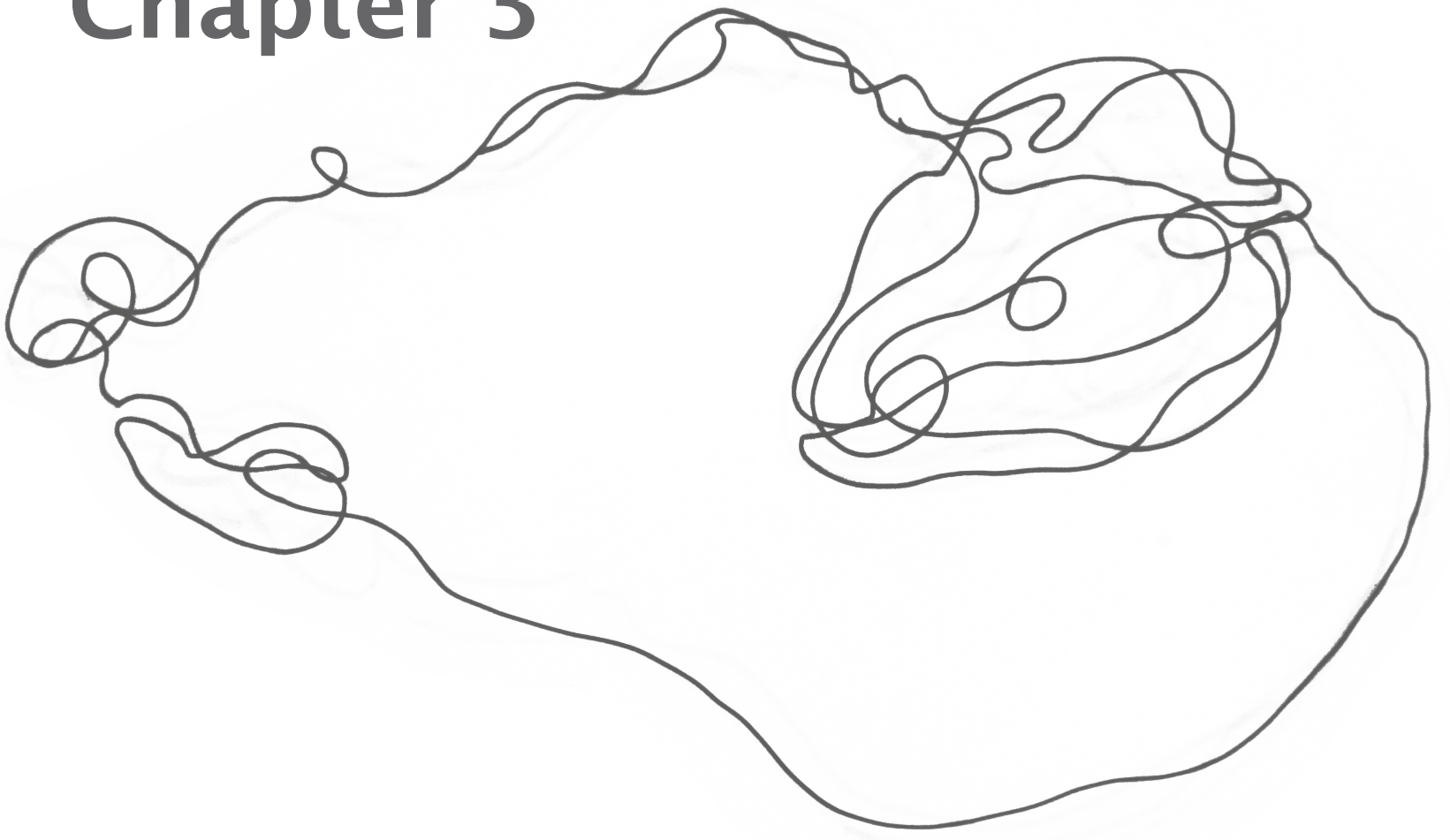

**Figure S2** Bland-Altman analysis for $GFR_{SMDRD}$ versus $GFR_{IOTH}$

**Table S1** Bias of eGFR stratified by equation variables and clinical characteristics

| | | $GFR_{CKD-EPI}$ | $GFR_{SMDRD}$ | $GFR_{CG}$ | | $GFR_{CYS}$ | $GFR_{CYSCR}$ |
|---|---|---|---|---|---|---|---|
| | n | Mean ± SD | Mean ± SD | Mean ± SD | n | Mean ± SD | Mean ± SD |
| Age [years][a] | | | | | | | |
| < 56 | *44* | -9 ± 18 | -16 ± 18 | 1 ± 21 | *38* | -5 ± 16 | 11 ± 14 |
| 56 – 63 | *36* | -7 ± 14 | -10 ± 16 | -3 ± 13 | *33* | -2 ± 14 | 9 ± 13 |
| > 63 | *40* | -7 ± 13 | -7 ± 13 | -8 ± 13 | *30* | -2 ± 12 | 12 ± 14 |
| Sex | | | | | | | |
| Male | *96* | -8 ± 15 | -12 ± 16 | -5 ± 16 | *77* | -3 ± 14 | 9 ± 13 |
| Female | *24* | -4 ± 16 | -9 ± 17 | 2 ± 16 | *24* | -5 ± 15 | 17 ± 13 |
| Body Mass Index [kg/m²] [a] | | | | | | | |
| <26 | *40* | -3 ± 16 | -6 ± 19 | -5 ± 17 | *33* | 1 ± 16 | 15 ± 14 |
| 26 – 29 | *40* | -8 ± 12 | -11 ± 12 | -4 ± 13 | *35* | -4 ± 12 | 10 ± 13 |
| >29 | *40* | -12 ± 15 | -16 ± 15 | -1 ± 19 | *33* | -7 ± 14 | 7 ± 13 |
| Systolic BP [mm Hg] [a] | | | | | | | |
| < 111 | *44* | -4 ± 12 | -8 ± 14 | 1 ± 12 | *34* | -2 ± 11 | 16 ± 11 |
| 111 – 125 | *37* | -9 ± 16 | -14 ± 16 | -5 ± 18 | *35* | -2 ± 15 | 8 ± 14 |
| > 125 | *39* | -10 ± 17 | -12 ± 18 | -8 ± 19 | *32* | -4 ± 17 | 8 ± 14 |
| Diastolic BP [mm Hg] [a] | | | | | | | |
| < 64 | *41* | -6 ± 13 | -9 ± 14 | -2 ± 13 | *39* | -4 ± 12 | 15 ± 13 |
| 64 – 74 | *40* | -6 ± 14 | -10 ± 15 | -3 ± 15 | *36* | -1 ± 14 | 10 ± 14 |
| > 74 | *39* | -11 ± 17 | -15 ± 19 | -6 ± 21 | *34* | -5 ± 17 | 7 ± 14 |
| NYHA Class | | | | | | | |
| I-II | *75* | -11 ± 16 | -14 ± 17 | -7 ± 17 | *61* | -5 ± 16 | 6 ± 12 |
| III-IV | *45* | -3 ± 12 | -6 ± 13 | -3 ± 13 | *40* | -1 ± 12 | 18 ± 13 |
| LVEF [%][a] | | | | | | | |
| < 25 | *40* | -5 ± 12 | -9 ± 12 | 1 ± 14 | *36* | -1 ± 13 | 15 ± 11 |
| 25 – 33 | *40* | 8 ± 16 | -11 ± 16 | -5 ± 17 | *36* | -2 ± 15 | 10 ± 15 |
| > 33 | *40* | -10 ± 16 | -14 ± 19 | -6 ± 17 | *29* | -7 ± 16 | 6 ± 14 |
| Ischemic etiology | | | | | | | |
| No | *60* | -7 ± 15 | -11 ± 16 | -2 ± 18 | *54* | -2 ± 15 | 12 ± 14 |
| Yes | *60* | -9 ± 14 | -12 ± 16 | -5 ± 15 | *47* | -5 ± 14 | 9 ± 14 |
| Creatinine [mg/dL] [a] | | | | | | | |
| 0.69 – 1.03 | *40* | -5 ± 16 | -10 ± 18 | -2 ± 20 | *36* | 3 ± 15 | 8 ± 13 |
| 1.04 – 1.32 | *42* | -13 ± 15 | -18 ± 15 | -7 ± 16 | *36* | -9 ± 13 | 6 ± 13 |
| 1.33 – 3.87 | *38* | -4 ± 11 | -5 ± 12 | -1 ± 11 | *29* | -4 ± 12 | 19 ± 12 |
| UAE [mg/24h] | | | | | | | |
| None (0-29) | *93* | -8 ± 15 | -13 ± 15 | -5 ± 16 | *79* | -4 ± 15 | 10 ± 13 |
| Microalbuminuria (30-300) | *19* | -8 ± 15 | -10 ± 17 | 1 ± 18 | *17* | -5 ± 14 | 12 ± 15 |
| Macroalbuminuria (>300) | *8* | 5 ± 9 | 4 ± 14 | 11 ± 10 | *4* | 4 ± 13 | 21 ± 8 |
| Beta blocker | | | | | | | |
| No | *19* | -3 ± 17 | -7 ± 17 | 0 ± 19 | *16* | 0 ± 15 | 12 ± 12 |
| Yes | *101* | -8 ± 15 | -12 ± 16 | -4 ± 16 | *85* | -4 ± 14 | 11 ± 14 |
| MRA | | | | | | | |
| No | *83* | -10 ± 15 | -14 ± 17 | -6 ± 17 | *64* | -5 ± 15 | 7 ± 12 |
| Yes | *37* | -2 ± 13 | -6 ± 13 | 3 ± 14 | *37* | 0 ± 13 | 18 ± 13 |
| Diuretic use | | | | | | | |
| No | *39* | -10 ± 15 | -15 ± 16 | -9 ± 17 | *31* | -4 ± 14 | 5 ± 12 |
| Yes | *81* | -6 ± 15 | -9 ± 16 | -1 ± 16 | *70* | -3 ± 15 | 13 ± 14 |
| KDOQI CKD class [GFR] | | | | | | | |
| Stage I (> 90) | *36* | -19 ± 15 | -24 ± 15 | -13 ± 18 | *33* | -9 ± 16 | 0 ± 12 |
| Stage II (60 – 90) | *44* | -5 ± 14 | -9 ± 14 | 0 ± 16 | *37* | -1 ± 15 | 10 ± 10 |
| Stage IIIa (45 – 59) | *19* | -4 ± 9 | -6 ± 8 | -1 ± 12 | *15* | -2 ± 11 | 19 ± 7 |
| Stage IIIb (30 – 44) | *13* | 0 ± 8 | 0 ± 8 | 1 ± 7 | *8* | 0 ± 8 | 22 ± 6 |
| Stage IV (< 30) | *8* | 7 ± 7 | 6 ± 7 | 11 ± 7 | *8* | 6 ± 8 | 32 ± 8 |

[a] divided in tertiles. abbreviations: see table 3

# Chapter 3



# Urinary proteins in heart failure

Mattia A.E. Valente, Kevin Damman, Peter H.J.M. Dunselman,
Hans L. Hillege and Adriaan A. Voors

Published in: Progress in Cardiovascular Diseases 55 (2012) 44–55

## Summary

Renal insufficiency is common in patients with heart failure (HF), with both acute kidney injury and worsening renal function being associated with poor prognosis. The interplay between cardiac and renal failure has been termed the cardiorenal syndrome and is currently the subject of intense investigation. Urinary biochemistry has several advantages over blood or serum analyses, including lower costs, better patient comfort, and higher sensitivity to renal injury. However, urinalysis is currently not part of routine daily practice in cardiology. Recent advances in proteomics have allowed identification of numerous novel urinary biomarkers, many of which show promise in HF populations. In this review, we aim to provide an overview of both traditional and novel urinary biomarkers, examining evidence for diagnostic and prognostic value in HF as well as potential clinical utility.

### Abbreviations

| | |
|---|---|
| AHF | Acute Heart Failure |
| AKI | Acute kidney injury |
| ARB | Angiotensin Receptor Blocker |
| BNP | Brain natriuretic peptide |
| CHF | Chronic Heart Failure |
| CKD | Chronic kidney disease |
| ET-1 | Endothelin 1 |
| FABP | Fatty acid-binding protein |
| FENa | Fractional excretion of sodium |
| FEU | Fractional extraction of urea |
| GFR | Glomerular filtration rate |
| HF | Heart failure |
| IL-18 | Interleukin 18 |
| KIM-1 | Kidney injury molecule 1 |
| NAG | N-acetyl-beta-D-glucosaminidase |
| NGAL | Neutrophil Gelatinase Associated Lipocalin |
| NTproBNP | N-terminal pro-brain natriuretic peptide |
| NYHA | New York Heart Association |
| UACR | Urinary albumin-to-creatinine ratio |
| WRF | Worsening renal function |

## Introduction

Renal insufficiency is common in patients with heart failure (HF), with both worsening renal function (WRF) and acute kidney injury (AKI) being associated with poor prognosis.[1-6] This mutual association has been called the cardiorenal syndrome. Five subtypes are identified,[7] although the mechanisms underlying these interactions are complex and not yet fully elucidated; systemic and intrarenal hemodynamic changes, neurohormonal changes, inflammatory processes, disruption of tubular and glomerular feedback mechanisms, and the congestive state all contribute to the functional decline of both organ systems. The proposed syndrome, with specific subtypes of cardiorenal and renocardiac interaction, does not take into account dynamic interplay between the heart and the kidney, where acute and chronic changes in both renal and cardiac function usually coexist. Differentiating between specific subtypes in daily practice is, therefore, unfeasible and currently has little clinical value. In cardiologic daily practice, evaluation of renal function is generally limited to assessing urine production to evaluate diuretic response and monitoring glomerular filtration rate (GFR) using serum creatinine–based equations. At the present time, urinalysis does not hold a prominent place in clinical practice. Recent technological advances in proteomics have allowed a wide-scope analysis of protein patterns in bodily fluids, allowing the identification of numerous promising protein markers in various conditions. Urine is an ideal biological fluid for proteomic analysis; it is easily collected in large amounts in a noninvasive manner.[8] In addition to "traditional" proteinuria, focusing primarily on albumin excretion, a number of candidate biomarker proteins have been identified using proteomics methods. Research to determine prognostic and diagnostic value as well as clinical utility in various disease states is ongoing. In this review, we will provide an overview of both traditional and novel urinary biomarkers in patients with HF. Underlying postulated mechanisms, diagnostic and prognostic value and clinical utility will be examined.

Urinary markers may be categorized in a number of ways; from a basic physiologic perspective, all substances that are filtered through the glomerular membrane and appear in urine may be used as markers. Because of this dependency on filtration, they may reflect GFR to some degree. However, active secretion, reabsorption, and tubular degradation all impact urine concentrations of different markers. An understanding of filtration and reabsorption characteristics as well as marker origins is therefore important. Markers may also be classified based on biological function—neurohormonal modulators and inflammatory markers—or by the structural injury they represent, such as glomerular membrane injury or tubulointerstitial damage. In this review, we first examine traditional markers familiar to clinicians and subsequently review promising novel urinary biomarkers.

## Traditional markers

### Creatinine

Creatinine is a breakdown product of creatine phosphate, which appears in the blood at a constant rate based on skeletal muscle turnover. Creatinine is freely filtered through the glomerulus and enters the urine at a steady rate, dependent on glomerular filtration. In clinical practice, serum creatinine is used as an accurate marker for GFR as an absolute parameter or as part of serum creatinine–based estimations of GFR. Because of active tubular secretion, serum creatinine usually overestimates GFR, especially when GFR is impaired.[9]

In urine, creatinine can be used in 2 ways. First, urinary creatinine can be used to adjust urinary protein concentrations for urine dilution/concentration, allowing a degree of standardization. Second, the balance between the delivery of serum creatinine to the glomerulus and the amount of creatinine in the urine has been used as an easy measure of renal function for decades. This creatinine clearance (a reflection of glomerular filtration) is most commonly used in the nephrologic community, but it can also be used in the acute setting, where serum creatinine alone is notoriously biased and inaccurate in estimating renal function. 24-hour urine collection should be performed for adequate and accurate determination of creatinine clearance, a test with well-known reliability issues, particularly due to voiding errors. Two consecutive 24-hour collections may be used to overcome this bias.[10] Where accurate creatinine clearance values can be obtained, they show moderate correlation with the gold standard for renal function measurement (iothalamate clearance) in chronic HF (CHF).[11] Serum creatinine–based formulas also outperform urine creatinine clearance as prognostic markers.[11] Therefore, only in selected clinical situations where adequate urine sampling can be achieved and serum creatinine–based formulas are deemed inaccurate can and should creatinine clearance be used to assess renal function.

### Proteinuria

Proteinuria—the presence of (serum) proteins in urine—is a well-established risk factor for cardiovascular morbidity and mortality.[12-15] Usually, proteinuria is thought synonymous with albuminuria, the amount of albumin in urine. Endothelial dysfunction, neurohormonal activation, increased glomerular pressure, and atherosclerosis, leading to increased glomerular permeability, are considered key etiologic mechanisms.[16] Excess serum protein levels and tubular reabsorption dysfunction may contribute but are less common. There are also indications that albuminuria in HF may be related to reduced renal perfusion and increased venous congestion, 2 important pathophysiologic mechanisms that also drive reduced GFR in HF.[17-21]

Routine testing for albuminuria involves determination of the albumin-to-creatinine ratio in spot urine or 24-hour urine as a surrogate marker for daily albumin excretion. The full spectrum of albuminuria, ranging from elevated urinary albumin-to-creatinine ratio (UACR) to overt microalbuminuria (30-299 mg/g creatinine)

and macroalbuminuria (≥300 mg/g creatinine), is an important prognostic marker in numerous populations, including patients with CHF.[12,13,22-24] Microalbuminuria (30%) and macroalbuminuria (10%) were both strongly prevalent in GISSI-HF (Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca–Heart Failure) and CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and morbidity) studies (Fig 1).[12,13] In both diabetic patients and the general population, increased UACR has been associated with higher levels of incident HF.[25-27] Data from the Aliskiren Observation of Heart Failure Treatment (ALOFT) study showed independent associations between increased UACR and hemoglobin A1c and Nterminal pro–brain natriuretic peptide (NTproBNP) levels in patients with both diabetic and non-diabetic HF.[28] Other studies have found associations between inflammatory markers and elevated UACR, indicating glomerular damage alone may not be the only mechanism responsible for albumin leakage.[29] In general population studies, overt albuminuria is strongly associated with traditional cardiovascular risk factors including hypertension and diabetes and, as such, may merely reflect damage caused by these comorbid conditions.[30] However, it is also an independent predictor of incident CHF in diabetic patients[31] and the community[32-34]; the question remains whether albuminuria should be seen as an early or late sign of renal injury, and whether mechanisms besides glomerular leakage are also in play.

Qualitative dipstick testing is a less accurate measure of proteinuria, but positive tests also correlate strongly with negative outcome,[35,36] making it a potentially useful population screening tool due to ease of use and cost. Although albuminuria is an established therapy target in patients with chronic kidney disease (CKD), evidence for efficacy is lacking. Reduction of urinary albumin excretion using an angiotensin receptor blocker or statin therapy has shown survival benefit in hypertensive[37] and diabetic[38,39] populations. In HF cohorts, both CHARM and GISSI-HF studies failed to show significant reduction in albuminuria with angiotensin receptor blocker and statin therapy, respectively, although both found a strong correlation between albuminuria and negative outcome.[12,13]

The advantages of proteinuria as a marker—including low cost—are evident, despite the lack of specificity due to a broad spectrum of potential and incompletely understood underlying mechanisms. This, along with the fact that correlations between albuminuria and mortality in HF populations were only recently described for the first time,[14] may explain why proteinuria/albuminuria currently does not hold a prominent place in HF guidelines. It may serve as a prognostic marker in patients with HF and as a predictor of HF in patients with preserved cardiac function independently of GFR, but the clinical applicability for monitoring or guidance of treatment in HF is still limited. A possible reason for the lack of clinical use of albuminuria may be the lack of evidence that lowering proteinuria in patients with HF improves prognosis.

## Fractional excretion of sodium and urea

Sodium is the most important electrolyte in extracellular volume homeostasis. Under normal circumstances, sodium is freely filtered in the glomerulus. In the loop of Henle, active and passive water and sodium transport result in either dilution or concentration of preurine, depending on volume status. Further reabsorption of sodium may follow in the final part of the nephron, regulated by various neurohor-

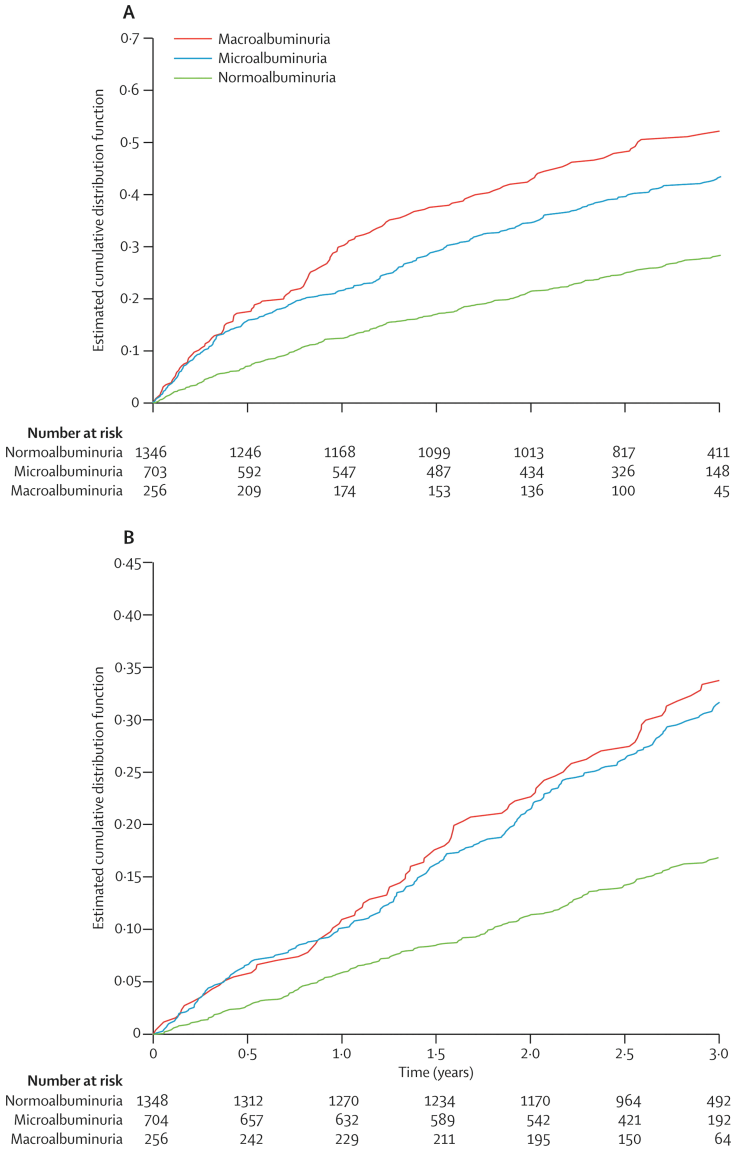



**Figure 1** Albuminuria and outcome in CHARM study population

Reprinted with permission from Elsevier[12]

monal mechanisms. However, in HF, extracellular volume is increased and effective circulating volume is decreased, resulting in a strong increase in sodium reabsorption. This imbalance means that despite a congestive state, increasing amounts of sodium are reabsorbed, resulting in even greater water retention, leading to further congestion. Sodium retention and the counteraction of diuretic therapy are therefore a key aspect of the pathophysiology of congestion in HF.

Urinary fractional excretion of sodium (FENa), expressed as a percentage of serum values, reflects sodium and water extraction from the glomerular filtrate. It may be used to differentiate between prerenal and renal causes of AKI and acute tubular necrosis, although it may be unreliable in a number of conditions including chronic low-flow status such as HF, renal artery stenosis, acute glomerulonephritis, acute interstitial nephritis, and a number of etiologies of tubular necrosis where sodium reabsorption is increased.[40] Evidence-based therapy in HF, such as renin angiotensin system blockers, mineral corticoid inhibitors (spironolactone, eplerenone), and β-blockers, all impact sodium reabsorption at different places in the nephron. Most importantly, loop diuretics and thiazides strongly influence FENa because they inhibit tubular sodium reabsorption. Absolute sodium excretion is therefore increased in patients on diuretic therapy. This strongly limits the applicability of sodium excretion as clinical decision-making tool in HF, although low fractional sodium excretion in the presence of diuretic therapy could still be of some value for the differential diagnosis of the cause of renal failure in selected patients.

Unlike FENa, fractional excretion of urea is not affected by diuretic use.[40] Urea is normally reabsorbed in the proximal convoluted tubules and the medullary collecting ducts. Because urea handling is thought to be independent of diuretic therapy, fractional excretion of urea (FEU) may be an alternative to FENa in distinguishing between prerenal and intrinsic AKI. A prospective study in patients diagnosed with AKI found no significant correlation between FENa and FEU and prognosis, while demonstrating strong correlations with neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule 1 (KIM-1), and interleukin 18 (IL-18),[41] suggesting a relationship between FEU and tubular damage in these patients. A prospective study in patients admitted with acute HF (AHF), however, found a strong correlation between elevated FENa after a dose of diuretics and a complicated clinical course with a higher incidence of renal insufficiency.[42] Further data in chronic and acute HF are limited, and additional investigations are warranted to determine the clinical utility of FENa and FEU in routine practice.

## Novel markers

### Tubular markers: NAG

N-acetyl-β-D-glucosaminidase is a lysosomal enzyme found in cells of the proximal tubule and is involved in the degradation of mucopolysaccharides and glycoproteins. Elevated urinary concentrations are thought to be a marker for proximal tubular damage and have been studied extensively in a number of patient popu-

lations, including patients with CKD, patients with diabetic nephropathy, and patients undergoing cardiopulmonary bypass.[43-45] Nacetyl-β-D-glucosaminidase is an early marker for AKI and WRF in a number of populations.[46,47] As a general marker for tubular injury, NAG levels are not specific to HF, are high in a number of other conditions such as urinary tract infections,[48] and are also elevated in CKD in the absence of HF. In HF, reduced renal blood flow shows a strong relationship with elevated urinary NAG, suggesting a link with reduced renal perfusion and renal hypoxia as a result of lower cardiac output.[47]

N-acetyl-β-D-glucosaminidase levels in CHF are elevated compared with age- and sex-matched controls and correlate with worse clinical outcome independently of GFR.[47,49] In the GISSI-HF trial, urinary NAG levels were strongly increased in patients with CHF.[13] Independently of GFR and albuminuria, NAG levels were strongly related to impaired outcome, including mortality and HF hospitalizations (Fig 2).[50] In a much smaller proof-of-concept study, NAG levels varied with the initiation and withdrawal of diuretic therapy, suggesting that NAG may be used to monitor response to diuretic treatment in CHF.[51] In summary, NAG levels correlate with renal hypoperfusion, are related to poor clinical outcome, and are susceptible to diuretic-induced alterations in volume status. Usefulness for monitoring acute changes in renal function and guiding therapy has yet to be determined.

## Tubular markers: KIM-1

Kidney injury molecule 1 is a transmembrane protein that is undetectable in healthy kidney tissue or urine under normal circumstances. It is an immunoglobulin cell surface protein that is highly up-regulated after hypoxic tubular injury, which leads to expression of high levels of KIM-1 in proximal tubule epithelium, primarily in areas exhibiting signs of early fibrosis.[52,53] Kidney injury molecule 1 is thought to be involved in postinjury apoptosis and phagocytic repair processes.[54] Urinary levels have been found to accurately reflect KIM-1 renal tissue expression in animal studies, making KIM-1 a candidate for monitoring response to renal damage.[55]

In a pediatric cardiosurgical population, KIM-1 was found to be superior to NAG in predicting AKI. Both KIM-1 and NAG were detectable almost 24 hours before a rise in serum creatinine.[56] Furthermore, in patients with hypertension, reduction in blood pressure was associated with a reduction of KIM-1 levels and proteinuria.[57] Elevated KIM-1 levels are also present in CKD[52] and are associated with graft loss in patients with renal transplant.[58] Elevated levels of KIM-1 have also been found in nondiabetic proteinuretic patients with CKD, with urinary levels decreasing in response to treatment targeting proteinuria.[57] In one animal study, KIM-1 correlated better with renal tubular histopathology than serum creatinine, blood urea nitrogen, or NAG levels.[59] Thus, both KIM-1 and NAG may be involved in both chronic and acute tubulointerstitial damage and could potentially be used to identify at-risk patients.

Urinary KIM-1 levels are strongly elevated in HF.[47,49,50] Possible mechanisms include ischemic damage due to reduced renal perfusion, hypertensive renal damage, or

direct tubular toxicity of elevated urinary albumin levels also commonly seen in patients with HF, as discussed earlier. In a small study of 100 patients with CHF and moderate renal impairment, urinary KIM-1 levels were elevated compared with age- and sex-matched controls.[47] Importantly, KIM-1 levels were strong predictors for outcome independently of GFR. Jungbauer et al[49] also found strong correlations between KIM-1 levels, reduced left ventricular function, and New York Heart Association (NYHA) class in patients with CHF, and found KIM-1 and NAG to be predictors for both allcause mortality and the combined endpoint of mortality and HF hospitalization. Urinary KIM-1 levels were also susceptible to diuretic-induced volume changes, similar to the effect seen with NAG.[51] Finally, in the GISSI-HF study population, KIM-1 showed only a moderate relationship with outcome and did not independently relate to outcome.[50] The clinical applicability of KIM-1 in HF has yet to be determined.

## Tubular markers: neutrophil gelatinase–associated lipocalin

Neutrophil gelatinase–associated lipocalin (NGAL) is a small protein normally found in serum and secreted by a number of organs.[60] It is thought to possess bacteriostatic properties, thanks to its iron-scavenging properties.[61] Serum NGAL levels are elevated in sepsis, inflammation, and malignant disease.[60] Importantly, urinary levels of NGAL seem to be unaffected by a rise in serum levels; normally, plasma NGAL is freely filtered by the glomerulus, but completely reabsorbed by the tubules. In AKI, however, NGAL is produced and secreted from within the kidney.[60,61] Most NGAL production is located in the distal nephron (loop of Henle and collecting ducts), although elevated levels have also been seen in proximal tubular injury.[60-62] The rise in urinary NGAL levels after AKI is rapid and extreme, with up to 1000-fold increases compared with baseline values.[60-62] Importantly, serum NGAL levels are affected by strongly elevated urinary/renal concentrations, resulting in a parallel increase in serum concentrations. The massive potential of NGAL foridentifying patients at risk for the development of AKI has been investigated in numerous studies and a variety of populations. Mishra and colleagues[62] found that both urinary and serum NGAL levels were strongly elevated in children who underwent cardiopulmonary bypass grafting and developed AKI, 2 days before any rise in serum creatinine. Parikh et al[63] found associations between urinary NGAL levels and poor outcome in pediatric post–cardiac surgery populations, and between both urinary and plasma NGAL and poor outcome in adult post–cardiac surgery populations. In a recent meta-analysis,[65] urinary NGAL levels were strongly associated with the occurrence of AKI, an effect that was more pronounced in patients with reduced baseline kidney function.

In CHF, urinary NGAL levels were found to be significantly elevated compared with matched controls, although unlike NAG and KIM-1, there was no correlation with mortality, left ventricular function, or severity of HF.[47,49] In addition, neither urinary nor serum NGAL levels were susceptible to diuretic-induced volume changes in a small study of patients with CHF.[51] In the GISSI-HF study, urinary NGAL levels were elevated compared with normal values and had independent prognostic value in

addition to estimated GFR, urinary albumin excretion, and established risk factors.[50] Interestingly, NGAL levels predicted mortality but not HF hospitalizations. This suggests that NGAL is a strong marker of disease severity and outcome in CHF but is not a suitable predictor of worsening HF requiring hospitalization and intervention. To date, no study has assessed the ability of urinary NGAL levels to predict WRF or AKI. Studies of plasma NGAL have found associations between increased NGAL levels, WRF, and early mortality,[66] although the largest analysis from the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) study suggested no additive prognostic value in patients with ischemic HF.[67] Several studies are currently underway to assess the prognostic and predictive value of urinary and plasma NGAL levels in clinical practice in AHF and CHF.

## Interleukin 18

Interleukin 18 is a proinflammatory cytokine found in macrophages as well as other cell lines and involved in the activation of cell-mediated immunity in response to infection.[68] It plays a role in numerous inflammatory disorders.[69-74] It is also released by epithelial cells in the proximal tubule in response to AKI. Interleukin 18 levels rise before serum creatinine, albeit later than NGAL. Like other cytokines, IL-18 is also elevated in a variety of other inflammatory conditions and, as such, has low specificity.

In pediatric populations undergoing cardiac surgery, a rise in urinary IL-18 levels was a good predictor of AKI.[63] Several studies have identified IL-18 as an early marker of post–cardiac surgery AKI in adults.[75-77] In a large, prospective study in post–cardiac surgery adults, in addition to predicting AKI, IL-18 levels correlated with risk of death, renal replacement therapy, and prolonged intensive care unit (ICU) and hospital admission.[64] In another study in adult post–cardiac surgery patients, urinary IL-18 levels at the time of first diagnosis of early AKI were found to strongly predict AKI severity.[78] Other studies in patients admitted with AKI found a strong correlation between IL-18 levels and worse clinical outcome.[41] In a population of patients undergoing elective coronary angiography, higher urinary IL-18 levels were not only associated with the occurrence of contrastinduced nephropathy, but also predictors of cardiac events during follow-up.[79]

In HF, IL-18 concentrations were found to be elevated in myocardial tissue and plasma, which could suggest a possible direct pathophysiologic role in HF. Plasma levels also predict outcome in ischemic heart disease and, consequently, incident HF.[80] Studies investigating the role of urinary IL-18 in CHF or AHF are currently lacking, and further research to elucidate various pathophysiologic roles and utility in management of cardiorenal syndrome is required.

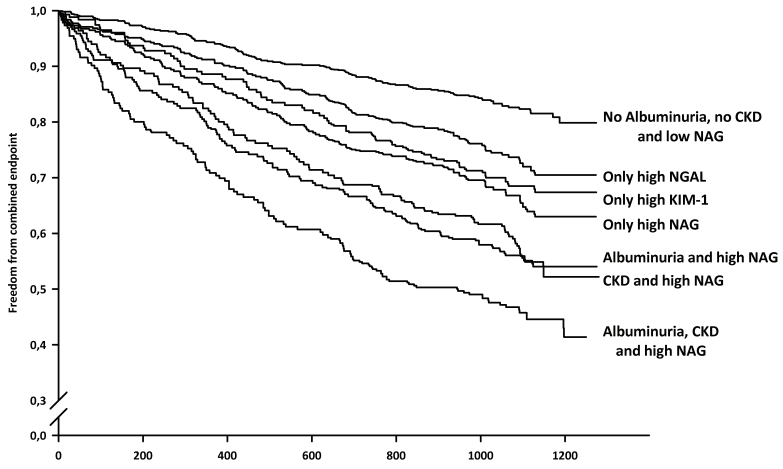
## Fatty acid–binding proteins

Fatty acid–binding proteins (FABPs) are a class of proteins that bind selectively with free fatty acids and are found in a variety of organs including the heart (FABP-1) and liver (FABP-3).[81] Several of these proteins are thought to play a role in energy metab-

olism in renal tubules: FABP-1 (liver FABP) in the proximal and FABP-3 (heart FABP) in the distal tubules.[82] Both have been associated with impaired renal function.[83]

In (chronic) HF, renal perfusion is strongly reduced, which is an important pathophysiologic mechanism for the occurrence of hypoxic tubular injury. Elevated levels of FABPs are shed into urine in response to ischemic tubular injury and are sensitive and specific early markers for AKI. There are indications that FABP-1 may outperform both NGAL and KIM-1 as an early predictor for AKI.[84]

Urinary FABP-1 levels decrease in response to additive renin angiotensin system inhibition in patients with CKD, an effect associated with a reduction in proteinuria.[85] The combination of urinary NAG and FABP-1 outperforms either single measurement for predicting AKI after cardiac surgery,[86] although at least one study suggests a single measurement of FABP-1 could also be of clinical use.[87] Furthermore, elevated urinary FABP-1 levels are associated with impaired peritubular capillary blood flow, which further underlines an association between increased urinary FABP concentrations and decreased renal perfusion, as present in HF.[82] Data on urinary levels of FABPs in HF are currently scarce. Serum FABP-3 levels have been correlated with worse outcome in CHF.[88] However, no study has shown correlations between urinary FABP-1 or FABP-3 levels and outcome in HF populations, nor has its value in predicting AKI/WRF been assessed.




Subjects at risk

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| No albuminuria, no CKD, low NAG | 731 | 710 | 684 | 660 | 603 | 475 | 52 |
| Only high NGAL | 354 | 326 | 301 | 277 | 238 | 171 | 25 |
| Only high KIM-1 | 466 | 443 | 419 | 395 | 341 | 252 | 25 |
| Only high NAG | 215 | 202 | 189 | 177 | 152 | 117 | 26 |
| Albuminuria and high NAG | 208 | 186 | 166 | 149 | 128 | 103 | 10 |
| CKD and high NAG | 254 | 218 | 192 | 176 | 147 | 110 | 14 |
| Albuminuria, CKD and high NAG | 208 | 167 | 144 | 126 | 94 | 74 | 13 |

**Figure 2** Relationship of urinary markers of tubular damage, albuminuria, chronic kidney disease with outcome in the GISSI-HF study

Reprinted with permission from Oxford University Press[50]
Abbreviations: CKD: Chronic Kidney Disease, KIM-1: Kidney Injury Molecule 1, NAG: N-acetyl-beta-D-glucosaminidase, NGAL: Neutrophil Gelatinase Associated Lipocalin

## Cystatin C

Cystatin C is a proteinase inhibitor produced by all nucleated cells, and serum concentration has swiftly established itself as a solid marker for GFR.[89] Data on reliability of serum concentrations are mixed, with some studies indicating inflammatory status may affect concentrations, but others finding no bias.[90-92] Cystatin C has been shown to outperform creatinine-based estimates of GFR and better predict outcome in a variety of populations including diabetic patients, patients with coronary artery disease, and the elderly.[24,90,93] Data on the value of cystatin C serum levels in HF populations are scarce but promising, with 2 studies in CHF and 1 in AHF showing correlations with outcome.[93-96]

Under normal circumstances, cystatin C is freely filtered by the glomerulus and fully metabolized in the proximal tubules.[97] Elevated urinary levels are therefore reliable markers of tubular dysfunction and, thus, may be of value for patients with HF with or at risk for cardiorenal syndrome. Studies in patients with cardiopulmonary bypass found serum[98-101] and urinary[102] cystatin C levels to be good predictors of AKI. In an unselected ICU population, urinary cystatin C levels correlated with AKI, sepsis, and increased mortality at 30 days.[103] Although studies assessing the value of urinary cystatin C levels in HF populations are currently lacking, low assay costs and solid pathophysiologic foundations could stimulate future research into clinical applicability.

## Urinary natriuretic peptides

Plasma levels of brain natriuretic peptide and NTproBNP hold a prominent position in the serologic diagnosis of HF and may aid in assessing prognosis in patients with AHF and CHF.[104-107] Both peptides are highly sensitive markers for ventricular dysfunction and/or hypertrophy. These small natriuretic peptides, released by the myocardium in response to ventricular wall stress, hypertrophy, or volume overload, are part of the complex neurohormonal processes activated in HF, counteracting various vasoconstrictors and antinatriuretic peptides.[104-107]

In 2004, Ng et al[108] were the first to show a correlation between elevated urinary natriuretic peptide levels and HF. Urinary NTproBNP levels showed similar diagnostic accuracy compared with plasma NTproBNP in a small study of patients with AHF.[108] Other studies have shown similar[109,110] or contradictory results.[111] In subsequent studies, urinary NTproBNP correlated reasonably well with plasma levels, severity of CHF, and predicted cardiac events in patients with stable CHF.[112-114] Because of itsparticularly small size, NTproBNP is thought to be completely filtered by the glomerulus. This means that with more severe HF, exponentially large amounts are filtered through the glomerular membrane because of very high plasma levels in very severe HF. Although this is partly counteracted by a reduction in GFR and, thus, reduction in glomerular filtration of the molecule, the strong relative increase in NTproBNP should result in large amounts of the protein appearing in urine. However, Linssen and colleagues[114] found lower amounts of NTproBNP in 24-hour urine of patients with HF compared with age-and sex-matched controls. Although this

**Table 1** Overview of urinary marker characteristics

| Marker | Acute Heart Failure | Chronic Heart Failure | Worsening Renal Function / Acute Kidney Injury |
|---|---|---|---|
| **Creatinine** | CrCl associated with outcome<br>Urinary Creatinine as marker of urine concentration | CrCl associated with outcome<br>Urinary Creatinine as marker of urine concentration | Serum values are established as definition of WRF/AKI |
| **Cystatin C** | Serum values relate to mortality<br>No data on urinary values | Serum values relate to mortality<br>No data on urinary values | No data |
| **NAG** | No data on urinary values | Elevated levels compared to controls<br>Association with renal perfusion | Susceptible to diuretic induced volume changes<br>Predicts AKI in ICU<br>No data in heart failure |
| **KIM-1** | No data on urinary values | Elevated levels compared to controls<br>Association with severity of heart failure<br>Contradictory findings with respect to prognosis | Susceptible to diuretic induced volume changes<br>Predicts AKI in various populations<br>No data in heart failure |
| **NGAL** | Plasma NGAL increased in AHF and relate to prognosis | Elevated levels compared to controls<br>Association with renal function and severity of heart failure<br>Strong relationship with mortality, not HF hospitalization | Not susceptible to diuretic induced volume changes<br>Plasma NGAL predicts AKI/WRF in chronic HF<br>Urinary NGAL predicts AKI in ICU patients, incl HF |
| **IL-18** | No data on urinary values | No data on urinary values | IL-18 predicts AKI in ICU patients, incl HF |
| **FABP-1** | No data on urinary values | Plasma levels increased<br>No data on urinary values | Strong predictor of AKI in non-HF population |
| **Endothelin-1** | No data on urinary values | No data on urinary values | Associated with disease severity in CKD |
| **Albuminuria** | No data in AHF | Prevalent in CHF<br>Micro and macroalbuminuria associated with outcome | No relationship established |
| **Urinary Sodium** | Increased sodium excretion during therapy | Fractional sodium excretion associated with renin angiotensin system activity | No data in heart failure |
| **Urinary Natriuretic peptides** | No data in AHF | Contradictory results<br>Some studies show diagnostic as well as prognostic role of urinary (NTpro)BNP, others found no evidence | No data in heart failure |

finding is incompletely understood, it may indicate either degradation of NTproBNP in the tubules or active reabsorption into the circulation, which would, in part, explain elevated serum concentrations in HF. More recent studies demonstrated similar excretion of BNP and NTproBNP independently of GFR.[113,115] To date, only small observational studies have investigated the diagnostic and prognostic capabilities of urinary NTproBNP in HF. Larger, prospective studies are needed to establish the clinical utility of urinary NTproBNP in patients with (suspected) HF.

### Endothelin 1

Endothelin 1 (ET-1) is an endothelial peptide that plays a key role in vascular homeostasis, with strong vasopressive and vasoconstrictive properties. Elevated plasma levels have been found in patients with HF[116] and correlate with mortality and hemodynamic status. In addition, treatment with endothelin pathway inhibitors has been shown to improve survival in animal models for HF,[117] although results from human trials have thus far been disappointing. Renal formation of ET-1 results in elevated urinary levels and appears to be unaffected by circulating ET-1 concentrations.[118-120] In patients with renovascular hypertension, elevated urinary, not plasma concentrations of ET-1, were found and decreased after renal artery angioplasty.[121]

In a prospective cohort study, ET-1 was found to correlate with NYHA class in patients with HF, with increased ET-1 values already present in patients with NYHA II HF.[122] Endothelin 1 was also a strong predictor for increased FENa in patients not receiving diuretics.[122] This indicates that urinary ET-1 rises earlier than plasma levels in patients with HF and may be a target for therapy, although further research is needed to confirm and expand on these findings.

## Conclusions

Urinalysis is an easy, noninvasive, and therefore patient-friendly way to identify and characterize patients at risk for WRF, AKI, and impaired clinical outcome. Traditional markers including proteinuria and albuminuria are particularly interesting tools for risk stratification in chronic populations, and as screening tools for identifying individuals at risk for developing HF. Novel markers such as KIM-1, NGAL, NAG, cystatin C, and IL-18 are of particular interest in AHF populations and may contribute to the early identification of patients at risk for AKI and poor prognosis (Table 1). Currently, there is an evidence gap to support the implementation of any novel urinary biomarker in daily clinical cardiologic practice. Further observational and subsequent interventional studies in various cardiologic populations are required—and are currently underway—to determine the diagnostic and prognostic utility of a multitude of urinary markers. Given the rapid response many of these markers exhibit, some are interesting candidates for monitoring intervention effect, whereas others may be treatment targets themselves, both areas that merit further research.

**Conflicts of Interest**: M.A.E. Valente, K. Damman, P.H.J.M. Dunselman, and J.L. Hillege have no conflicts of interest to declare. A.A. Voors is supported by educational grants from Alere.

## References


1. Damman K, Jaarsma T, Voors AA, et al: Both in- and out-hospital worsening of renal function predict outcome in patients with heart failure: results from the Coordinating Study Evaluating Outcome of Advising and Counseling in Heart Failure (COACH). Eur J Heart Fail 2009;11:847-854.
2. Hillege HL, Girbes AR, de Kam PJ, et al: Renal function, neurohormonal activation, and survival in patients with chronic heart failure. Circulation 2000;102:203-210.
3. Vaz Perez A, Otawa K, Zimmermann AV, et al: The impact of impaired renal function on mortality in patients with acutely decompensated chronic heart failure. Eur J Heart Fail 2010;12:122-128.
4. Damman K, Navis G, Voors AA, et al: Worsening renal function and prognosis in heart failure: systematic review and meta-analysis.J Card Fail 2007;13:599-608.
5. Metra M, Nodari S, Parrinello G, et al: Worsening renal function in patients hospitalised for acute heart failure: clinical implications and prognostic significance. Eur J Heart Fail 2008;10:188-195.
6. Hata N, Yokoyama S, Shinada T, et al: Acute kidney injury and outcomes in acute decompensated heart failure: evaluation of the RIFLE criteria in an acutely ill heart failure population. Eur J Heart Fail 2010;12:32-37.
7. Ronco C, McCullough PA, Anker SD, et al: Cardiorenal syndromes: an executive summary from the consensus conference of the Acute Dialysis Quality Initiative (ADQI). Contrib Nephrol 2010;165:54-67.
8. Albalat A, Mischak H, Mullen W: Clinical application of urinary proteomics/peptidomics. Expert Rev Proteomics 2011;8:615-629.
9. Levey AS, Coresh J, Greene T, et al: Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med 2006;145:247-254.
10. Ix JH, Wassel CL, Stevens LA, et al: Equations to estimate creatinine excretion rate: the CKD epidemiology collaboration. Clin J Am Soc Nephrol 2011;6:184-191.
11. Smilde TD, van Veldhuisen DJ, Navis G, et al: Drawbacks and prognostic value of formulas estimating renal function in patients with chronic heart failure and systolic dysfunction. Circulation 2006;114:1572-1580.
12. Jackson CE, Solomon SD, Gerstein HC, et al: Albuminuria in chronic heart failure: prevalence and prognostic importance. Lancet 2009;374:543-550.
13. Masson S, Latini R, Milani V, et al: Prevalence and prognostic value of elevated urinary albumin excretion in patients with chronic heart failure: data from the GISSI-Heart Failure trial. Circ Heart Fail 2010;3:65-72.
14. van de Wal RM, Asselbergs FW, Plokker HW, et al: High prevalence of microalbuminuria in chronic heart failure patients. J Card Fail 2005;11:602-606.
15. Peeroo K, Clark A: The prevalence of proteinuria in patients presenting with fluid retention due to heart failure. J R Coll Physicians Edinb 2010;40:301-303.
16. Comper WD, Hilliard LM, Nikolic-Paterson DJ, et al: Diseasedependent mechanisms of albuminuria. Am J Physiol Renal Physiol 2008;295:F1589-F1600.
17. Smilde TD, Damman K, van der Harst P, et al: Differential associations between renal function and "modifiable" risk factors in patientswith chronic heart failure.Clin Res Cardiol 2009;98:121-129.
18. Damman K, Navis G, Smilde TD, et al: Decreased cardiac output, venous congestion and the association with renal impairment in patients with cardiac dysfunction. Eur J Heart Fail 2007;9:872-878.
19. Damman K, van Deursen VM, Navis G, et al: Increased central venous pressure is associated with impaired renal function and mortality in a broad spectrum of patients with cardiovascular disease. J Am Coll Cardiol 2009;53:582-588.
20. Damman K, Voors AA, Hillege HL, et al: Congestion in chronic systolic heart failure is related to renal dysfunction and increased mortality. Eur J Heart Fail 2010;12:974-982.
21. Wegria R, Capeci NE, Blumenthal MR, et al: The pathogenesis of proteinuria in the acutely congested kidney. J Clin Invest 1955;34:737-743.
22. Klausen KP, Scharling H, Jensen JS: Very low level of microalbuminuria is associated with increased risk of death in subjects with cardiovascular or cerebrovascular diseases. J Intern Med 2006;260:231-237.
23. Villacorta H, Ferradaes Pde V, Mesquita ET, et al: Microalbuminuria is an independent prognostic marker in patients with chronic heart failure. Arq Bras Cardiol 2012;98:62-69.
24. de Boer IH, Katz R, Cao JJ, et al: Cystatin C, albuminuria, and mortality among older adults with diabetes. Diabetes Care 2009;32:1833-1838.
25. de Simone G, Devereux RB, Roman MJ, et al: Does cardiovascular phenotype explain the association between diabetes and incident heart failure? The Strong Heart Study. Nutr Metab Cardiovasc Dis 2011 [Epub ahead of print].
26. Blecker S, Matsushita K, Kottgen A, et al: High-normal albuminuria and risk of heart failure in the community. Am J Kidney Dis

2011;58:47-55.

27. Velagaleti RS, Gona P, Larson MG, et al: Multimarker approach for the prediction of heart failure incidence in the community. Circulation 2010;122:1700-1706.
28. Jackson CE, MacDonald MR, Petrie MC, et al: Associations of albuminuria in patients with chronic heart failure: findings in the ALiskiren Observation of heart Failure Treatment study. Eur J Heart Fail 2011;13:746-754.
29. Zambrano-Galvan G, Rodriguez-Moran M, Simental-Mendia LE, et al: C-reactive protein is directly associated with urinary albumin-to-creatinine ratio. Arch Med Res 2011;42:451-456.
30. Hillege HL, Fidler V, Diercks GF, et al: Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in general population. Circulation 2002;106:1777-1782.
31. Vaur L, Gueret P, Lievre M, et al: DIABHYCAR Study Group (type 2 DIABetes, Hypertension, CARdiovascular Events and Ramipril) study. Development of congestive heart failure in type 2 diabetic patients with microalbuminuria or proteinuria: observations from the DIABHYCAR (type 2 DIABetes, Hypertension, Cardiovascular Events and Ramipril) study. Diabetes Care 2003;26:855-860.
32. Kistorp C, Raymond I, Pedersen F, et al: N-terminal pro–brain natriuretic peptide, C-reactive protein, and urinary albumin levels as predictors of mortality and cardiovascular events in older adults.JAMA 2005;293:1609-1616.
33. Ingelsson E, Sundstrom J, Lind L, et al: Low-grade albuminuria and the incidence of heart failure in a community-based cohort of elderly men. Eur Heart J 2007;28:1739-1745.
34. Bello AK, Hemmelgarn B, Lloyd A, et al: Associations among estimated glomerular filtration rate, proteinuria, and adverse cardiovascular outcomes. Clin J Am Soc Nephrol 2011;6:1418-1426.
35. Anand IS, Bishu K, Rector TS, et al: Proteinuria, chronic kidney disease, and the effect of an angiotensin receptor blocker in addition to an angiotensin-converting enzyme inhibitor in patients with moderate to severe heart failure. Circulation 2009;120:1577-1584.
36. Miura M, Shiba N, Nochioka K, et al: Urinary albumin excretion in heart failure with preserved ejection fraction: an interim analysis of the CHART 2 study. Eur J Heart Fail 2012;14:367-376.
37. Ibsen H, Olsen MH, Wachtell K, et al: Reduction in albuminuria translates to reduction in cardiovascular events in hypertensive patients with left ventricular hypertrophy and diabetes. J Nephrol 2008;21:566-569.
38. Holtkamp FA, de Zeeuw D, de Graeff PA, et al: Albuminuria and blood pressure, independent targets for cardioprotective therapy in patients with diabetes and nephropathy: a post hoc analysis of the combined RENAAL and IDNT trials. Eur Heart J 2011;32:1493-1499.
39. Eijkelkamp WB, Zhang Z, Brenner BM, et al: Renal function and risk for cardiovascular events in type 2 diabetic patients with hypertension: the RENAAL and LIFE studies. J Hypertens 2007;25:871-876.
40. Gotfried J, Wiesen J, Raina R, et al: Finding the cause of acute kidney injury: which index of fractional excretion is better? Cleve Clin J Med 2012;79:121-126.
41. Hall IE, Coca SG, Perazella MA, et al: Risk of poor outcomes with novel and traditional biomarkers at clinical AKI diagnosis. Clin J Am Soc Nephrol 2011;6:2740-2749.
42. Alattar FT, Imran N, Debari VA, et al: Fractional excretion of sodium predicts worsening renal function in acute decompensated heart failure. Exp Clin Cardiol 2010;15:e65-e69.
43. Bazzi C, Petrini C, Rizza V, et al: Urinary N-acetyl-betaglucosaminidase excretion is a marker of tubular cell dysfunction and a predictor of outcome in primary glomerulonephritis. Nephrol Dial Transplant 2002;17:1890-1896.
44. Liangos O, Perianayagam MC, Vaidya VS, et al: Urinary N-acetylbeta-(D)-glucosaminidase activity and kidney injury molecule-1 level are associated with adverse outcomes in acute renal failure. J Am Soc Nephrol 2007;18:904-912.
45. Wellwood JM, Ellis BG, Price RG, et al: Urinary N-acetyl-beta-Dglucosaminidase activities in patients with renal disease. Br Med J 1975;3:408-411.
46. Westhuyzen J, Endre ZH, Reece G, et al: Measurement of tubular enzymuria facilitates early detection of acute renal impairment in the intensive care unit. Nephrol Dial Transplant 2003;18:543-551.
47. Damman K, Van Veldhuisen DJ, Navis G, et al: Tubular damage in chronic systolic heart failure is associated with reduced survival independent of glomerular filtration rate. Heart 2010;96:1297-1302.
48. Mohkam M, Karimi A, Habibian S, et al: Urinary N-acetyl-beta-Dglucosaminidase as a diagnostic marker of acute pyelonephritis in children. Iran J Kidney Dis 2008;2:24-28.
49. Jungbauer CG, Birner C, Jung B, et al: Kidney injury molecule-1 and N-acetyl-beta-D-glucosaminidase in chronic heart failure: possible biomarkers of cardiorenal syndrome. Eur J Heart Fail 2011;13:1104-1110.
50. Damman K, Masson S, Hillege HL, et al: Clinical outcome of renal tubular damage in chronic heart failure. Eur Heart J 2011;32:2705-2712.
51. Damman K, Ng Kam Chuen MJ, MacFadyen RJ, et al: Volume status and diuretic therapy in systolic heart failure and the detection of early abnormalities in renal and tubular function. J

Am Coll Cardiol 2011;57:2233-2241.

52. van Timmeren MM, van den Heuvel MC, Bailly V, et al: Tubular kidney injury molecule-1 (KIM-1) in human renal disease. J Pathol 2007;212:209-217.
53. Han WK, Bailly V, Abichandani R, et al: Kidney injury molecule-1 (KIM-1): a novel biomarker for human renal proximal tubule injury. Kidney Int 2002;62:237-244.
54. Ichimura T, Asseldonk EJ, Humphreys BD, et al: Kidney injury molecule-1 is a phosphatidylserine receptor that confers a phagocytic phenotype on epithelial cells. J Clin Invest 2008;118:1657-1668.
55. Kramer AB, van Timmeren MM, Schuurs TA, et al: Reduction of proteinuria in adriamycin-induced nephropathy is associated with reduction of renal kidney injury molecule (Kim-1) over time. Am J Physiol Renal Physiol 2009;296:F1136-F1145.
56. Han WK, Waikar SS, Johnson A, et al: Urinary biomarkers in the early diagnosis of acute kidney injury. Kidney Int 2008;73:863-869.
57. Waanders F, Vaidya VS, van Goor H, et al: Effect of reninangiotensin-aldosterone system inhibition, dietary sodium restriction, and/or diuretics on urinary kidney injury molecule 1 excretion in nondiabetic proteinuric kidney disease: a post hoc analysis of a randomized controlled trial. Am J Kidney Dis 2009; 53:16-25.
58. van Timmeren MM, Vaidya VS, van Ree RM, et al: High urinary excretion of kidney injury molecule-1 is an independent predictor of graft loss in renal transplant recipients. Transplantation 2007;84: 1625-1630.
59. Vaidya VS, Ozer JS, Dieterle F, et al: Kidney injury molecule-1 outperforms traditional biomarkers of kidney injury in preclinical biomarker qualification studies. Nat Biotechnol 2010;28:478-485.
60. Schmidt-Ott KM, Mori K, Li JY, et al: Dual action of neutrophil gelatinase–associated lipocalin. J Am Soc Nephrol 2007;18:407-413.
61. Mori K, Lee HT, Rapoport D, et al: Endocytic delivery of lipocalinsiderophore-iron complex rescues the kidney from ischemiareperfusion injury. J Clin Invest 2005;115:610-621.
62. Mishra J, Dent C, Tarabishi R, et al: Neutrophil gelatinase–associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery. Lancet 2005;365:1231-1238.
63. Parikh CR, Devarajan P, Zappitelli M, et al: Postoperative biomarkers predict acute kidney injury and poor outcomes after pediatric cardiac surgery. J Am Soc Nephrol 2011;22:1737-1747.
64. Parikh CR, Coca SG, Thiessen-Philbrook H, et al: Postoperative biomarkers predict acute kidney injury and poor outcomes after adult cardiac surgery. J Am Soc Nephrol 2011;22:1748-1757.
65. Haase M, Devarajan P, Haase-Fielitz A, et al: The outcome of neutrophil gelatinase–associated lipocalin-positive subclinical acute kidney injury: a multicenter pooled analysis of prospective studies. J Am Coll Cardiol 2011;57:1752-1761.
66. Bolignano D, Basile G, Parisi P, et al: Increased plasma neutrophil gelatinase–associated lipocalin levels predict mortality in elderly patients with chronic heart failure. Rejuvenation Res 2009;12:7-14.
67. Nymo SH, Ueland T, Askevold ET, et al: The association between neutrophil gelatinase–associated lipocalin and clinical outcome in chronic heart failure: results from CORONA*. J Intern Med 2011;271:436-443.
68. Biet F, Locht C, Kremer L: Immunoregulatory functions of interleukin 18 and its role in defense against bacterial pathogens. J Mol Med (Berl) 2002;80:147-162.
69. Mason DR, Beck PL, Muruve DA: Nucleotide-binding oligomerization domain-like receptors and inflammasomes in the pathogenesis of non-microbial inflammation and diseases. J Innate Immun 2012;4:16-30.
70. Zhang Y, Moffatt MF, Cookson WO: Genetic and genomic approaches to asthma: new insights for the origins. Curr Opin Pulm Med 2012;18:6-13.
71. Lamkanfi M, Walle LV, Kanneganti TD: Deregulated inflammasome signaling in disease. Immunol Rev 2011;243:163-173.
72. Mikita N, Ikeda T, Ishiguro M, et al: Recent advances in cytokines in cutaneous and systemic lupus erythematosus. J Dermatol 2011;38:839-849.
73. Volin MV, Koch AE: Interleukin-18: a mediator of inflammation and angiogenesis in rheumatoid arthritis. J Interferon Cytokine Res 2011;31:745-751.
74. Liu Z, Wang H, Xiao W, et al: Thyrocyte interleukin-18 expression is up-regulated by interferon-gamma and may contribute to thyroid destruction in Hashimoto's thyroiditis. Int J Exp Pathol 2010;91:420-425.
75. Xin C, Yulong X, Yu C, et al: Urine neutrophil gelatinase–associated lipocalin and interleukin-18 predict acute kidney injury after cardiac surgery. Ren Fail 2008;30:904-913.
76. Parikh CR, Mishra J, Thiessen-Philbrook H, et al: Urinary IL-18 is an early predictive biomarker of acute kidney injury after cardiac surgery. Kidney Int 2006;70:199-203.
77. Che M, Xie B, Xue S, et al: Clinical usefulness of novel biomarkers for the detection of acute kidney injury following elective cardiac surgery. Nephron Clin Pract 2010;115:c66-c72.
78. Che M, Xie B, Xue S, et al: Biomarkers predict progression of acute kidney injury after cardiac surgery. J Am Soc Nephrol 2012.

79. Ling W, Zhaohui N, Ben H, et al: Urinary IL-18 and NGAL as early predictive biomarkers in contrast-induced nephropathy after coronary angiography. Nephron Clin Pract 2008;108:c176-c181.
80. Hartford M, Wiklund O, Hulten LM, et al: Interleukin-18 as a predictor of future events in patients with acute coronary syndromes. Arterioscler Thromb Vasc Biol 2010;30:2039-2046.
81. Veerkamp JH, Paulussen RJ, Peeters RA, et al: Detection, tissue distribution and (sub) cellular localization of fatty acid-binding protein types. Mol Cell Biochem 1990;98:11-18.
82. Noiri E, Doi K, Negishi K, et al: Urinary fatty acid-binding protein 1: an early predictive biomarker of kidney injury. Am J Physiol Renal Physiol 2009;296:F669-F679.
83. Maatman RG, Van Kuppevelt TH, Veerkamp JH: Two types of fatty acid-binding protein in human kidney. Isolation, characterization and localization. Biochem J 1991;273:759-766.
84. Ferguson MA, Vaidya VS, Waikar SS, et al: Urinary liver-type fatty acid-binding protein predicts adverse outcomes in acute kidney injury. Kidney Int 2010;77:708-714.
85. Nakamura T, Sato E, Amaha M, et al: Addition of aliskiren to olmesartan ameliorates tubular injury in chronic kidney disease patients partly by reducing proteinuria. J Renin Angiotensin Aldosterone Syst 2012;13:122-127.
86. Katagiri D, Doi K, Honda K, et al: Combination of two urinary biomarkers predicts acute kidney injury after adult cardiac surgery. Ann Thorac Surg 2012;93:577-583.
87. Matsui K, Kamijo-Ikemori A, Sugaya T, et al: Usefulness of urinary biomarkers in early detection of acute kidney injury after cardiac surgery in adults. Circ J 2012;76:213-220.
88. Niizeki T, Takeishi Y, Arimoto T, et al: Persistently increased serum concentration of heart-type fatty acid-binding protein predicts adverse clinical outcomes in patients with chronic heart failure. Circ J 2008;72:109-114.
89. Dharnidharka VR, Kwon C, Stevens G: Serum cystatin C is superior to serum creatinine as a marker of kidney function: a metaanalysis. Am J Kidney Dis 2002;40:221-226.
90. Shlipak MG, Sarnak MJ, Katz R, et al: Cystatin C and the risk of death and cardiovascular events among elderly persons. N Engl J Med 2005;352:2049-2060.
91. Singh D, Whooley MA, Ix JH, et al: Association of cystatin C and estimated GFR with inflammatory biomarkers: the Heart and Soul Study. Nephrol Dial Transplant 2007;22:1087-1092.
92. Okura T, Jotoku M, Irita J, et al: Association between cystatin C and inflammation in patients with essential hypertension. Clin Exp Nephrol 2010;14:584-588.
93. Shlipak MG, Katz R, Fried LF, et al: Cystatin-C and mortality in elderly persons with heart failure. J Am Coll Cardiol 2005;45:268-271.
94. Arimoto T, Takeishi Y, Niizeki T, et al: Cystatin C, a novel measure of renal function, is an independent predictor of cardiac events in patients with heart failure. J Card Fail 2005;11:595-601.
95. Damman K, van der Harst P, Smilde TD, et al: Use of cystatin C levels in estimating renal function and prognosis in patients with chronic systolic heart failure. Heart 2012;98:319-324.
96. Lassus J, Harjola VP, Sund R, et al: Prognostic value of cystatin C in acute heart failure in relation to other markers of renal function and NT-proBNP. Eur Heart J 2007;28:1841-1847.
97. Tenstad O, Roald AB, Grubb A, et al: Renal handling of radiolabelled human cystatin C in the rat. Scand J Clin Lab Invest 1996;56:409-414.
98. Krawczeski CD, Vandevoorde RG, Kathman T, et al: Serum cystatin C is an early predictive biomarker of acute kidney injury after pediatric cardiopulmonary bypass. Clin J Am Soc Nephrol 2010;5:1552-1557.
99. Wald R, Liangos O, Perianayagam MC, et al: Plasma cystatin C and acute kidney injury after cardiopulmonary bypass. Clin J Am Soc Nephrol 2010;5:1373-1379.100.
100. Felicio ML, Andrade RR, Castiglia YM, et al: Cystatin C and glomerular filtration rate in the cardiac surgery with cardiopulmonary bypass. Rev Bras Cir Cardiovasc 2009;24:305-311.
101. Abu-Omar Y, Mussa S, Naik MJ, et al: Evaluation of cystatin C as a marker of renal injury following on-pump and off-pump coronary surgery. Eur J Cardiothorac Surg 2005;27:893-898.
102. Koyner JL, Bennett MR, Worcester EM, et al: Urinary cystatin C as an early biomarker of acute kidney injury following adult cardiothoracic surgery. Kidney Int 2008;74:1059-1069.
103. Nejat M, Pickering JW, Walker RJ, et al: Urinary cystatin C is diagnostic of acute kidney injury and sepsis, and predicts mortality in the intensive care unit. Crit Care 2010;14:R85.
104. de Lemos JA, McGuire DK, Drazner MH: B-type natriuretic peptide in cardiovascular disease. Lancet 2003;362:316-322.
105. Koglin J, Pehlivanli S, Schwaiblmair M, et al: Role of brain natriuretic peptide in risk stratification of patients with congestive heart failure. J Am Coll Cardiol 2001;38:1934-1941.
106. Mair J, Hammerer-Lercher A, Puschendorf B: The impact of cardiac natriuretic peptide determination on the diagnosis and management of heart failure. Clin Chem Lab Med 2001;39:571-588.

107. Clerico A, Iervasi G, Mariani G: Pathophysiologic relevance of measuring the plasma levels of cardiac natriuretic peptide hormones in humans. Horm Metab Res 1999;31:487-498.

108. Ng LL, Geeranavar S, Jennings SC, et al: Diagnosis of heart failure using urinary natriuretic peptides. Clin Sci (Lond) 2004;106:129-133.

109. Cortes R, Portoles M, Salvador A, et al: Diagnostic and prognostic value of urine NT-proBNP levels in heart failure patients. Eur J Heart Fail 2006;8:621-627.

110. Cortes R, Rivera M, Salvador A, et al: Urinary B-type natriuretic peptide levels in the diagnosis and prognosis of heart failure. J Card Fail 2007;13:549-555.54

111. Michielsen EC, Bakker JA, Kimmenade RR, et al: The diagnostic value of serum and urinary NT-proBNP for heart failure. Ann Clin Biochem 2008;45:389-394.

112. Song J, Li P, Li H, et al: The clinical significance of a urinary B type natriuretic peptide assay for the diagnosis of heart failure. Clin Chim Acta 2011;412:1632-1636.

113. Cortes R, Portoles M, Rosello-Lleti E, et al: Impact of glomerular filtration rate on urinary BNP and NT-proBNP levels in heart failure. Peptides 2012;33:354-358.

114. Linssen GC, Damman K, Hillege HL, et al: Urinary N-terminal prohormone brain natriuretic peptide excretion in patients with chronic heart failure. Circulation 2009;120:35-41.

115. Manzano-Fernandez S, Januzzi JL, Boronat-Garcia M, et al: Impact of kidney dysfunction on plasma and urinary N-terminal pro–B type natriuretic peptide in patients with acute heart failure. Congest Heart Fail 2010;16:214-220.

116. Wei CM, Lerman A, Rodeheffer RJ, et al: Endothelin in human congestive heart failure. Circulation 1994;89:1580-1586.

117. Sakai S, Miyauchi T, Kobayashi M, et al: Inhibition of myocardial endothelin pathway improves long-term survival in heart failure. Nature 1996;384:353-355.

118. Modesti PA, Cecioni I,Migliorini A, et al: Increased renal endothelin formation is associatedwith sodiumretention and increased free water clearance. Am J Physiol 1998;275:H1070-H1077.

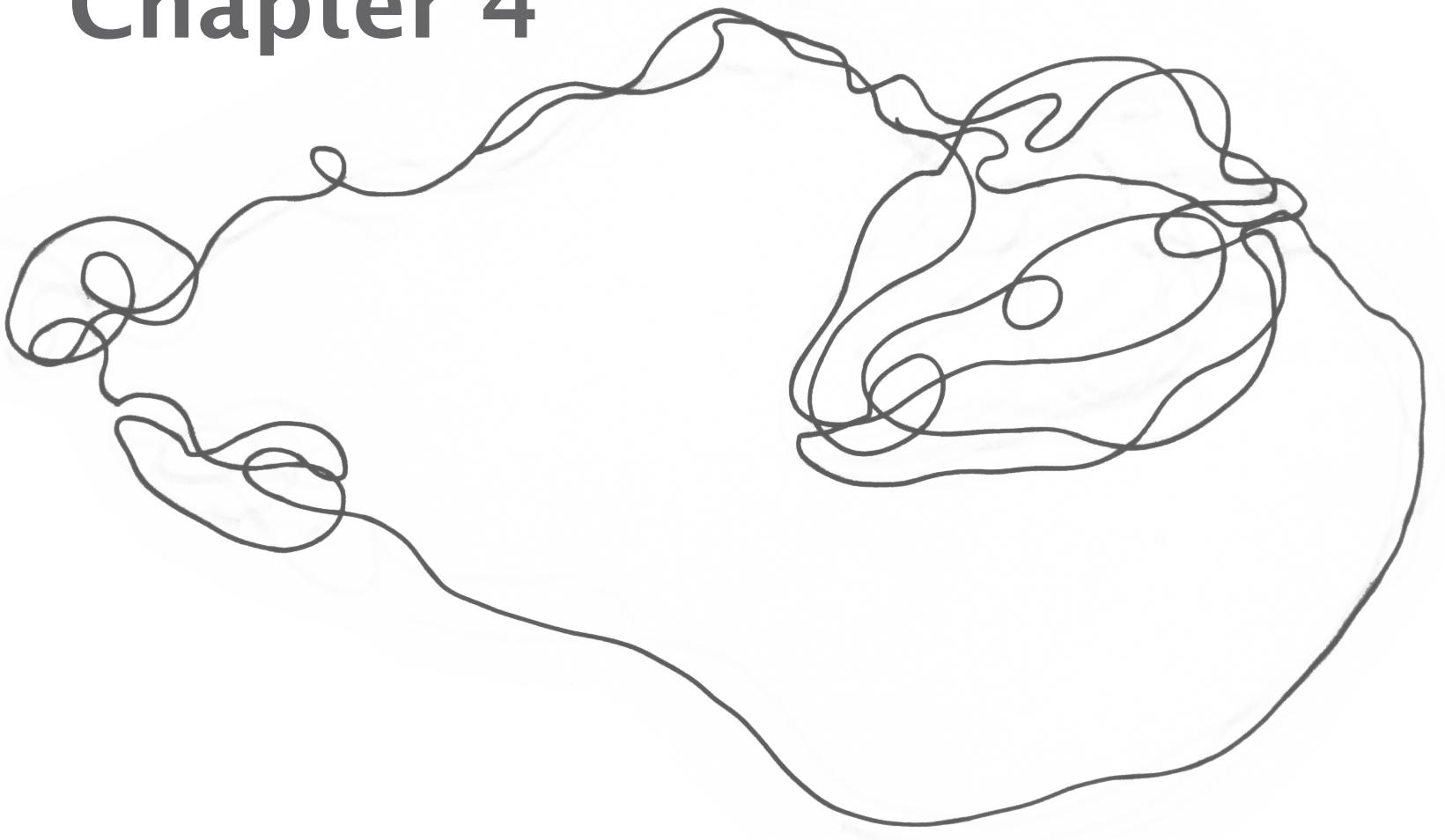
119. Serneri GG, Modesti PA, Cecioni I, et al: Plasma endothelin and renal endothelin are two distinct systems involved in volume homeostasis. Am J Physiol 1995;268:H1829-H1837.

120. Neri Serneri GG, Cecioni I, Migliorini A, et al: Both plasma and renal endothelin-1 participate in the acute cardiovascular response to exercise. Eur J Clin Invest 1997;27:761-766.

121. Cecioni I, Modesti PA, Poggesi L, et al: Endothelin-1 urinary excretion, but not endothelin-1 plasma concentration, is increased in renovascular hypertension. J Lab Clin Med 1999;134:386-391.

122. Modesti PA, Cecioni I, Costoli A, et al: Renal endothelin in heart failure and its relation to sodium excretion. Am Heart J 2000;140: 617-622

# Chapter 4



# Renal effects of vasodilators in acute heart failure

Mattia A.E. Valente and Adriaan A. Voors

Published in: World Journal of Cardiovascular Diseases, 2013, 3, 8-17

## Summary

Vasodilator therapy is common in acute heart failure (AHF) patients, although evidence for morbidity and mortality benefits is limited for many of these drugs. AHF is frequently accompanied by renal dysfunction, which is a strong, independent predictor for poor prognosis. Several hemodynamic and neurohormonal effects of vasodilators – including preload and afterload reduction, activation or inhibition of neurohormonal and inflammatory cascades – have the potential to modulate cardiorenal interaction and impact renal function. However, the effect of vasodilators on renal function in acute heart failure is often poorly described. In this review, we provide an overview of the known cardiorenal effects of traditional and novel vasodilators in patients with acute heart failure.

## Introduction

Acute heart failure (AHF) is a heterogeneous collection of syndromes with variable aetiologies and clinical profiles. Despite this, initial management is relatively uniform – albeit with regional variation – and focused on hemodynamic stabilization and symptom control. Diuretics for decongestion, supportive therapy with oxygen, and treatment with opiates, vasodilators and inotropics in selected patients are the foundation of AHF management - a paradigm that has not changed significantly in decades. The evidence for survival benefits of many vasodilators in acute heart failure is limited. According to the 2012 European Society of Cardiology heart failure guidelines, vasodilators 'may' or 'should' be considered in AHF patients presenting with normal or elevated blood pressure in the absence of valvular disease (class IIa and IIb recommendations, level of evidence B or C).[1]

Chronic kidney disease is common in AHF, with reported rates of up to 30% in registry studies[2] and 37% in randomised trials.[3] Renal function is a strong, independent predictor for outcome in AHF, including increased risk of death and higher rehospitalization rates.[4] In addition to renal impairment caused by AHF directly, therapies such as diuretics and vasodilators may affect renal function. The effects of vasodilators on renal function are important, but unfortunately often remain unexamined. This review will focus on what is known about the renal effects of vasodilator treatment in AHF.

## Defining renal function

Creatinine has a long history as a marker for renal function. Serum creatinine and glomerular filtration rate (GFR) estimated using creatinine-based formulas – Cockroft-Gault, Modification of Diet in Renal Disease (MDRD) and more recently, Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formulas – are the measures most commonly used in both research and clinical settings to monitor renal function, and are strongly correlated with each other and with clinical outcome.[5,6] In recent years, interest in and evidence for the prognostic value of other markers for renal function has grown– including cystatin C, Blood Urea Nitrogen (BUN) and a host of novel serum and urinary markers.[7-10] Although a number of these novel markers outperform creatinine-based equations for risk stratification and provide insight into aspects of renal function other than GFR – particularly tubular function – the majority of the literature is based on creatinine-derived measures for renal function.[7,11,12]

## Cardiorenal interaction and vasodilators

Cardiorenal interaction in acute heart failure – collectively referred to as type 1 cardiorenal syndrome – is common, occurring in over 30% of hospitalized patients.[13,14] Although poor renal function is consistently associated with poor prognosis, the data on worsening renal function during hospitalization for AHF is

mixed.[4,15-17] There are indications that transient worsening of renal function may even be beneficial.[16] Such transient changes may reflect good treatment response rather than lasting injury.

The mechanisms responsible for the high prevalence of renal dysfunction in heart failure populations are complex.[18] Chronic comorbid conditions endemic in heart failure populations, such as hypertension, diabetes mellitus and atherosclerosis, result in chronic kidney disease. The direct hemodynamic consequences of AHF play key roles in acute injury, and can ultimately lead to lasting renal damage: forward failure and backward failure. A reduction in cardiac output (forward failure) triggers renal vasoconstriction and a drop in renal blood flow. Compensatory angiotensin II release and efferent arteriolar vasoconstriction increase the filtration fraction (GFR to renal blood flow ratio), preserving GFR for a relatively long time.[19,20] In patients on renin-angiotensin-aldosterone system (RAAS) blockers – guideline therapy for heart failure - the kidney's ability to increase the filtration fraction is blunted, making the kidney critically dependent on renal blood flow to maintain GFR.[21] The rise in venous pressures in AHF (backward failure) reduces venous compliance, while congestion and rising intra-abdominal pressures contribute to a further drop in renal blood flow.[20,22]

Beyond the response to hemodynamic changes, the complex network of pathophysiological processes present in heart failure – including myocardial injury, inflammation, response to fluid retention, arrhythmias, RAAS and sympathetic nervous system activation – can exacerbate renal impairment (Figure 1).[13] Regional vasoconstriction can limit renal blood flow independently of blood pressure, leading to impaired renal function even if cardiac output is preserved.[21] Various other neurohormonal processes, including endothelial activation and adenosine release can cause tubular injury and nephron loss. Persistent low flow states, neurohormonal activation and inflammation can ultimately lead to nephrosclerosis and fibrosis, with permanent renal injury and dysfunction as a result.[23] Diuretic treatment also leads to decreased renal blood flow and glomerular filtration via tubuloglomerular feedback. This mechanism is regulated by adenosine-mediated vasoconstriction and results in compensatory tubular sodium retention.[24]

## Renal effects of vasodilators in AHF

Given the key role vascular tone plays in preserving renal function, vasodilating therapies that improve or protect renal perfusion may be of value in AHF. Vasodilators are a double-edged sword where renal function is concerned – while counteracting regional vasoconstriction may improve renal perfusion, the potential drop in blood pressure may have negative effects. The balance between these effects will depend on the individual patient's hemodynamic profile, congestive state and the specific pharmacological properties of individual vasodilators. Careful selection and (hemodynamic) monitoring of patients is required in order to achieve the positive effects - preload and afterload reduction - without the negative - decreased perfusion due to a drop in blood pressure, shock and rebound neurohormonal activation.

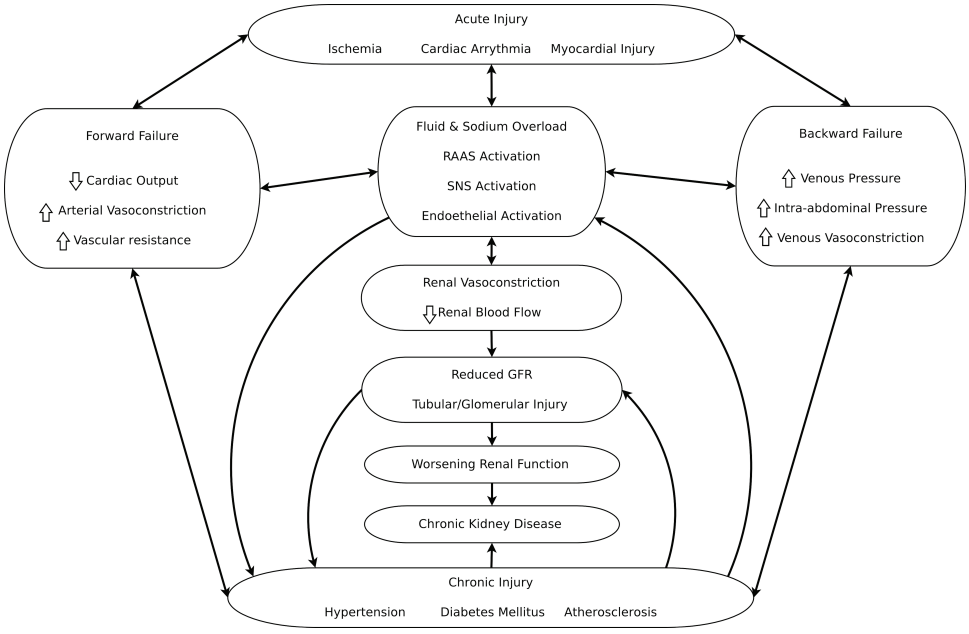



**Figure 1** Mechanisms of renal dysfunction in heart failure.

## Renal effects of specific vasodilators

### Nitrates

Nitrates – nitroprusside and nitroglycerine – have a long history in the management of AHF. Nitroglycerine is a potent venodilator with mild arterial vasodilating effects. Its primary effects are achieved by decreasing venous preload, alleviating filling pressures, wall stress and thus myocardial oxygen consumption, as well as reducing systemic vascular resistance. Cardiac output generally remains stable or rises.[25] Small studies have shown some effects on symptom relief and short-term outcome, but solid evidence for survival benefit is lacking.[26,27] Effects on renal function have not been studied.

Nitroprusside is a balanced venous and arterial vasodilator that acts on smooth muscle cells, reducing preload and afterload. One small, observational study found an association between nitroprusside therapy and improved renal and hemodynamic outcomes, despite worse hemodynamic profiles at baseline.[28] Both nitroglycerine and nitroprusside therapy have been associated with rebound neurohormonal activation, which may negate some of the potentially beneficial effects of vasodilation on renal blood flow.

## Milrinone

Milrinone is a selective phosphodiesterase-3 inhibitor which improves cardiac contractility by preventing degradation of cyclic AMP in cardiomyocytes. Though often used for its positive inotropic effects, it also has peripheral vasodilating properties that contribute to afterload reduction. Although short-term hemodynamic improvement has been described for milrinone, long-term oral use has been associated with increased mortality.[29,30] Common side-effects include – as with all vasodilators – hypotension. It should be used with caution in patients with pre-existing renal dysfunction, as it is cleared primarily via the glomerulus.[31]

Results from the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) trial showed slight improvement in renal function with Milrinone treatment, without any mortality impact.[32] However, renal function was not a predefined outcome parameter. Based on its mechanism of action, Milrinone has to potential to help preserve renal function as long as adequate renal blood flow is maintained.

## Endothelin antagonists

Endothelin-1 (ET-1) is a powerful vasoconstrictor with a variety of pro-inflammatory, mitogenic and pro-fibrotic properties, and is a potential treatment target in AHF. Elevated levels have been observed in AHF patients, and are associated with increased morbidity and mortality, which led to the development and study of various endothelin antagonists, including Tezosentan, Darusentan, Sitaxsentan and Bosentan.[33,34] Tezosentan has been studied most extensively in AHF. Treatment results in lower pulmonary wedge pressure and higher cardiac index. Despite a safe clinical profile in high-risk AHF patients, multiple large-scale studies with Tezosentan failed to show clinical benefit, with some terminated early due to lack of effect.[3,35-37]

ET-1 plays a key role in the kidney, modulating renal blood flow, GFR, sodium exchange and acid-base balance. Receptors are present throughout various kidney compartments. In addition to regulating blood pressure via vasoconstriction, ET-1 both directly and indirectly regulates sodium and water retention, with elevated levels triggering natriuresis and diuresis in the healthy kidney.[34] In kidney disease, ET-1 has been associated with increased inflammatory and fibrotic response, playing a key role in proteinuria-mediated injury and in nephron loss.[38] Blockade of ET-1 receptors in the kidney may counteract vasoconstriction and inhibit inflammation and remodeling cascades. In heart failure, renal ET-1 levels rise before plasma levels correlate with worse New York Heart Association (NYHA) functional class and outcome.[34] Although there is evidence from animal models that ET-1 blockade can prevent renal injury and the theoretical pathophysiological framework for use of ET-1 antagonists to preserve renal function appears sound, evidence from human trials in AHF is extremely limited and inconclusive.

## Guanylate Cyclase System Activators - Natriuretic peptides

Recombinant natriuretic peptides have been investigated for the treatment of acute heart failure, with early studies showing favourable hemodynamic effects.[39-42] These substances, released in response to myocardial stretch (B-type), atrial stretch (A-type) and by the vascular endothelium (C-type), activiate the particulate guanylate cyclase system and initiate a cascade resulting in increased diuresis, vasodilation and lower blood pressure.[43]

Nesiritide is a recombinant form of B-type Natriuretic Peptide with vasodilator and natriuretic properties, authorized for AHF treatment in the USA but not Europe. Although there is evidence for effective symptom relief, some studies also indicated higher re-admission and mortality rates as well as more renal damage.[39,40,44-46] The prospective Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) trial, however, found no survival benefit for nesiritide treatment in a population of over 7000 patients with severe acute heart failure, nor was a higher incidence of worsening renal function observed.[47] Although nesiritide treatment appears to be safe, benefits in terms of outcome and renal function are not apparent.

Other novel investigational natriuretic peptides include ularitide and CD-NP. Ularitide is a recombinant form of A-type natriuretic peptide that acts on the renal tubule and plays a role in sodium and water excretion, with early hemodynamic studies reporting improved symptoms, hemodynamics and diuresis.[41,48] One small study in AHF patients found ularitide preserves short-term renal function, possibly by maintaining cardiac output and preserving the pressure gradient between mean arterial and renal arterial pressures.[49] Data on long-term renal outcomes are not available.

CD-NP is a fusion product of C-type and D-type natriuretic peptides, with natriuretic promoting, GFR-enhancing, renin-inhibiting and decongestive effects, with a lower risk of hypotension and greater preservation of GFR compared with B-type peptides.[42,50,51] Current data is limited to animal studies, with human trials still underway.[52]

Natriuretic peptides are released by various tissues in response to volume overload, and their natriuretic and vasodilator effects may improve renal perfusion and increase water and salt excretion. The current evidence in AHF does not suggest any specific benefit, though data on ularitide and CD-NP appear promising.

## Guanylate Cyclase System Activators - BAY 58-2667 / Cinaciguat

Natriuretic peptides exert their effect by activating particulate guanylate cyclase in various tissues. An analogous enzyme, soluble guanylate cyclase (sGC), is present in the vascular endothelium and activated by nitric oxide (NO). The endothelial dysfunction common in heart failure can result in impaired NO formation and responsiveness,[53] which led to the development of novel methods for sGC system activation.

BAY 58-2667, or Cinaciguat, is a potent, NO-independent sGC activator.[54] Administration to HF patients in a dose-finding study and a phase IIb study showed significant reduction of filling pressures, blood pressure and both systemic and pulmonary vascular resistance, accompanied by elevated heart rate, cardiac output and improvement in dyspnea.[55,56]

Infusion increases norepinephrin and plasma renin activity, and symptomatic hypotension is common.[56] Results from a series of phase IIb studies in AHF patients showed similar results, but the studies were terminated early due to excess hypotension in the cinaciguat arms.[57] The early termination of these studies makes it unlikely this drug has a future in the treatment of AHF, and though its renal effects are unknown, the potential for harm due to hypoperfusion and RAAS activation would seem to outweigh the theoretical unloading benefits for the kidney.

## Vasopressin antagonists

Arginine vasopressin is a hormone released by the pituitary gland with antidiuretic and vasoconstrictor effects. Low blood pressure present in HF trigger release, and stimulation of V1 and V2 receptors causes, among other effects, vasoconstriction and changes in the renal collecting tubules, leading to reduced diuresis and hyponatermia. Antagonism of vasopressin receptors in AHF aims to increase water clearance while retaining sodium and preventing RAAS activation.[58]

Tolvaptan is a selective oral V2 receptor antagonist that showed promise in phase II trials in HF patients, improving hyponatremia, increasing weight loss and reducing oedema without significant adverse effects.[59-61] The Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) trial confirmed some of these positive results, showing improved dyspnea relief without negative effects on long-term mortality or HF morbidity.[62, 63] Available data does not show any negative effects on renal function.

Conivaptan is an intravenous non-selective vasopressin antagonist. Despite non-selective vasodilating properties, early results suggest its safety and efficacy is similar to that of tolvaptan.[64,65] There are indications that conivaptan may have a more beneficial cardiorenal profile, with data from animal studies showing a reduction in afterload, compared with an increase for tolvaptan.[66] One small-scale study in chronic heart failure patients found a significant improvement in diuresis and natriuresis following conivaptan administration, without negative effects on glomerular filtration rate, renal blood flow or neurohormonal activation.[67] Overall, there is no suggestion that vasopressin antagonists negatively affect renal function, and there are indications of positive effects.

## Adenosine A-1 receptor antagonists

Elevated adenosine levels, commonly present in patients with AHF, can cause afferent arterial vasoconstriction result in decreased renal blood flow and, ultimately, renal damage. Adenosine A-1 receptor antagonists prevent reduction of renal

blood flow and GFR, caused by adenosine release triggered by tubuloglomerular response to sodium overload in the distal tubule.[24]

Rolofylline, an intravenous selective A-1 receptor antagonist, has been studied in heart failure patients. Early results showed that administration of rolofylline significantly increases renal blood flow and glomerular filtration.[68,69] However, the prospective PROTECT Placebo-Controlled Randomized Study of the Selective A-1 Adenosine Receptor Antagonist Rolofylline for Patients Hospitalized with Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function) study found no significant impact of rolofylline administration on outcome, renal function or dyspnea relief.[16,70] Tonapofylline, an oral and intravenous A-1 receptor antagonist, showed similar promise in early trials, showing positive effects on diuresis while preserving GFR.[71,72] However, the results of the unpublished and prematurely terminated Treatment with intravenous BG9928 for Patients with Acutely Decompensated Heart Failure and Renal Insufficiency (TRIDENT-1) trial showed results consistent with those of PROTECT – no impact on outcome, weight loss or renal function.

## Levosimendan

Levosimendan is a phosphodiesterase inhibitor that improves cardiomyocyte contractility by increasing calcium sensitivity, improving both systolic and diastolic function.[73-75] It also has vasodilator effects achieved by binding to adenosine triphosphate-sensitive potassium channels in vascular smooth muscle.[76,77] These mechanisms result in improved cardiac output with both preload and afterload reduction.

The REVIVE trials showed symptom relief with levosimendan, but incidence of arrhythmias, hypotension and early mortality was also higher.[78] The SURVIVE study failed to reach the primary endpoint of all-cause mortality reduction or any of the secondary endpoints other than reduction of BNP levels.[79] The RUSLAN and LIDO trials, though underpowered for mortality, did show survival benefit for levosimendan treatment.[80,81]

A number of studies have reported positive effects of Levosimendan treatment on renal function.[81-84] The explanation likely lies with levosimendan's vasodilator activity, with stronger venous compared to arterial vasodilation along with its positive inotropic effects.[85] As elevated central venous pressures and congestion are associated strongly with reduced GFR,[21] Levosimendan treatment will benefit highly congested patients with AHF, as long as cardiac output and blood pressure provide adequate renal perfusion. The balance for patients with low blood pressure may remain neutral or even turn negative.

## Serelaxin

Relaxin is an endogenous hormone that regulates maternal adaptations to pregnancy, with numerous potentially interesting effects for the treatment of heart failure.[86] Serelaxin is a recombinant form of this hormone. Activation of relaxin recep-

tors in the heart, kidney and cardiovascular system leads to increased endothelial activity and increased nitric oxide synthase activity, resulting in greater arterial compliance, increased cardiac output, and higher renal blood flow.[87,88] In AHF, the Pre-RELAX-AHF and RELAX-AHF trials showed improvement in dyspnea relief and reduced 180 day mortality, but no effects on readmission rates. Hypotension was equally common in both treatment groups.[89] In terms of renal effects, patients receiving serelaxin showed a lower incidence of events related to renal impairment. Subsequent biomarker analysis showed indications that short-term serelaxin administration in AHF patients may improve organ protection – including renal protection – resulting in better 6 month mortality outcomes.[90]

## Discussion

Data on the effects of vasodilators on renal function in AHF is limited. While trials investigating novel drugs increasingly include renal outcomes as primary endpoints, the effects of the most commonly used vasodilators – nitrates – on the kidney are largely unknown. Theoretically, the variable local and systemic effects of vasodilators will determine their impact on renal function - both preload and afterload reduction may be beneficial, provided compensatory neurohormonal activation and blood pressure drops are kept in check. Maintaining hemodynamic stability while improving local blood flow is key, so careful patient selection, monitoring and treatment titration remains essential.

While numerous vasodilators have been studied in AHF, most have failed to deliver on the promise suggested by preclinical and pilot studies. Nitrates are still in common use, and while effective for symptom relief and acute reduction of filling pressures, data on their renal effects is practically non-existent. This evidence gap is most glaring for vasodilators introduced over 10 years ago; identification of renal function as a key prognostic indicator in HF is relatively recent, and understanding of its importance has grown steadily over time. This understanding is exemplified by rolofylline – and the PROTECT hypothesis that improving renal blood flow and function could improve outcome in AHF – despite the neutral results of the PROTECT study.[16] Levosimendan has demonstrated renoprotective effects, albeit with inconclusive survival effects, further supporting the hypothesis that vasodilators can benefit renal function in AHF.[84,91]

Serelaxin is, without a doubt, the most interesting novel vasodilator in terms of renal function. In addition to reducing renal events, serelaxin also improved mortality outcomes. This unexpected finding makes it the first therapy for acute heart failure to show survival benefit. Furthermore, it underlines the importance of renal function in AHF. Studies investigating existing or novel treatments for AHF should continue to focus on renal outcomes in addition to the more traditional mortality and hospitalization endpoints. There is also a strong case to be made for considering renal function measures that go beyond traditional creatinine-based assessments, and encompass tubular function as well as glomerular filtration. Novel urine and serum biomarkers may have an important role to play.

## References


1. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The task force for the diagnosis and treatment of acute and chronic heart failure 2012 of the european society of cardiology. developed in collaboration with the heart failure association (HFA) of the ESC. Eur J Heart Fail. 2012 Aug;14(8):803-69.
2. Adams KF,Jr, Fonarow GC, Emerman CL, LeJemtel TH, Costanzo MR, Abraham WT, et al. Characteristics and outcomes of patients hospitalized for heart failure in the united states: Rationale, design, and preliminary observations from the first 100,000 cases in the acute decompensated heart failure national registry (ADHERE). Am Heart J. 2005 Feb;149(2):209-16.
3. McMurray JJ, Teerlink JR, Cotter G, Bourge RC, Cleland JG, Jondeau G, et al. Effects of tezosentan on symptoms and clinical outcomes in patients with acute heart failure: The VERITAS randomized controlled trials. JAMA. 2007 Nov 7;298(17):2009-19.
4. Damman K, Jaarsma T, Voors AA, Navis G, Hillege HL, van Veldhuisen DJ, et al. Both in- and out-hospital worsening of renal function predict outcome in patients with heart failure: Results from the coordinating study evaluating outcome of advising and counseling in heart failure (COACH). Eur J Heart Fail. 2009 Sep;11(9):847-54.
5. Smilde TD, van Veldhuisen DJ, Navis G, Voors AA, Hillege HL. Drawbacks and prognostic value of formulas estimating renal function in patients with chronic heart failure and systolic dysfunction. Circulation. 2006 Oct 10;114(15):1572-80.
6. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF,3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009 May 5;150(9):604-12.
7. Lassus J, Harjola VP, Sund R, Siirila-Waris K, Melin J, Peuhkurinen K, et al. Prognostic value of cystatin C in acute heart failure in relation to other markers of renal function and NT-proBNP. Eur Heart J. 2007 Aug;28(15):1841-7.
8. Shenkman HJ, Zareba W, Bisognano JD. Comparison of prognostic significance of amino-terminal pro-brain natriuretic peptide versus blood urea nitrogen for predicting events in patients hospitalized for heart failure. Am J Cardiol. 2007 Apr 15;99(8):1143-5.
9. Filippatos G, Rossi J, Lloyd-Jones DM, Stough WG, Ouyang J, Shin DD, et al. Prognostic value of blood urea nitrogen in patients hospitalized with worsening heart failure: Insights from the acute and chronic therapeutic impact of a vasopressin antagonist in chronic heart failure (ACTIV in CHF) study. J Card Fail. 2007 Jun;13(5):360-4.
10. Valente MA, Damman K, Dunselman PH, Hillege HL, Voors AA. Urinary proteins in heart failure. Prog Cardiovasc Dis. 2012 Jul-Aug;55(1):44-55.
11. Campbell CY, Clarke W, Park H, Haq N, Barone BB, Brotman DJ. Usefulness of cystatin C and prognosis following admission for acute heart failure. Am J Cardiol. 2009 Aug 1;104(3):389-92.
12. Damman K, Van Veldhuisen DJ, Navis G, Vaidya VS, Smilde TD, Westenbrink BD, et al. Tubular damage in chronic systolic heart failure is associated with reduced survival independent of glomerular filtration rate. Heart. 2010 Aug;96(16):1297-302.
13. Ronco C, Cicoira M, McCullough PA. Cardiorenal syndrome type 1: Pathophysiological crosstalk leading to combined heart and kidney dysfunction in the setting of acutely decompensated heart failure. J Am Coll Cardiol. 2012 Sep 18;60(12):1031-42.
14. Damman K, Navis G, Voors AA, Asselbergs FW, Smilde TD, Cleland JG, et al. Worsening renal function and prognosis in heart failure: Systematic review and meta-analysis. J Card Fail. 2007 Oct;13(8):599-608.
15. Felker GM, Mentz RJ. Diuretics and ultrafiltration in acute decompensated heart failure. J Am Coll Cardiol. 2012 Jun 12;59(24):2145-53.
16. Voors AA, Dittrich HC, Massie BM, DeLucca P, Mansoor GA, Metra M, et al. Effects of the adenosine A1 receptor antagonist rolofylline on renal function in patients with acute heart failure and renal dysfunction: Results from PROTECT (placebo-controlled randomized study of the selective adenosine A1 receptor antagonist rolofylline for patients hospitalized with acute decompensated heart failure and volume overload to assess treatment effect on congestion and renal function). J Am Coll Cardiol. 2011 May 10;57(19):1899-907.
17. Metra M, Nodari S, Parrinello G, Bordonali T, Bugatti S, Danesi R, et al. Worsening renal function in patients hospitalised for acute heart failure: Clinical implications and prognostic significance. Eur J Heart Fail. 2008 Feb;10(2):188-95.
18. Ronco C, McCullough PA, Anker SD, Anand I, Aspromonte N, Bagshaw SM, et al. Cardiorenal syndromes: An executive summary from the consensus conference of the acute dialysis quality initiative (ADQI). Contrib Nephrol. 2010;165:54-67.
19. Damman K, Voors AA, Hillege HL, Navis G, Lechat P, van Veldhuisen DJ, et al. Congestion in chronic systolic heart failure is related to renal dysfunction and increased mortality.

Eur J Heart Fail. 2010 Sep;12(9):974-82.

20. Damman K, van Deursen VM, Navis G, Voors AA, van Veldhuisen DJ, Hillege HL. Increased central venous pressure is associated with impaired renal function and mortality in a broad spectrum of patients with cardiovascular disease. J Am Coll Cardiol. 2009 Feb 17;53(7):582-8.
21. Damman K, Navis G, Smilde TD, Voors AA, van der Bij W, van Veldhuisen DJ, et al. Decreased cardiac output, venous congestion and the association with renal impairment in patients with cardiac dysfunction. Eur J Heart Fail. 2007 Sep;9(9):872-8.
22. Mullens W, Abrahams Z, Skouri HN, Francis GS, Taylor DO, Starling RC, et al. Elevated intra-abdominal pressure in acute decompensated heart failure: A potential contributor to worsening renal function? J Am Coll Cardiol. 2008 Jan 22;51(3):300-6.
23. Damman K, Voors AA, Navis G, van Veldhuisen DJ, Hillege HL. The cardiorenal syndrome in heart failure. Prog Cardiovasc Dis. 2011 Sep-Oct;54(2):144-53.
24. Weatherley BD, Cotter G, Dittrich HC, DeLucca P, Mansoor GA, Bloomfield DM, et al. Design and rationale of the PROTECT study: A 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. J Card Fail. 2010 Jan;16(1):25-35.
25. Elkayam U, Bitar F, Akhter MW, Khan S, Patrus S, Derakhshani M. Intravenous nitroglycerin in the treatment of decompensated heart failure: Potential benefits and limitations. J Cardiovasc Pharmacol Ther. 2004 Dec;9(4):227-41.
26. Cotter G, Metzkor E, Kaluski E, Faigenberg Z, Miller R, Simovitz A, et al. Randomised trial of high-dose isosorbide dinitrate plus low-dose furosemide versus high-dose furosemide plus low-dose isosorbide dinitrate in severe pulmonary oedema. Lancet. 1998 Feb 7;351(9100):389-93.
27. Sharon A, Shpirer I, Kaluski E, Moshkovitz Y, Milovanov O, Polak R, et al. High-dose intravenous isosorbide-dinitrate is safer and better than bi-PAP ventilation combined with conventional treatment for severe pulmonary edema. J Am Coll Cardiol. 2000 Sep;36(3):832-7.
28. Mullens W, Abrahams Z, Francis GS, Skouri HN, Starling RC, Young JB, et al. Sodium nitroprusside for advanced low-output heart failure. J Am Coll Cardiol. 2008 Jul 15;52(3):200-7.
29. Bayram M, De Luca L, Massie MB, Gheorghiade M. Reassessment of dobutamine, dopamine, and milrinone in the management of acute heart failure syndromes. Am J Cardiol. 2005 Sep 19;96(6A):47G-58G.
30. Packer M, Carver JR, Rodeheffer RJ, Ivanhoe RJ, DiBianco R, Zeldis SM, et al. Effect of oral milrinone on mortality in severe chronic heart failure. the PROMISE study research group. N Engl J Med. 1991 Nov 21;325(21):1468-75.
31. Stroshane RM, Koss RF, Biddlecome CE, Luczkowec C, Edelson J. Oral and intravenous pharmacokinetics of milrinone in human volunteers. J Pharm Sci. 1984 Oct;73(10):1438-41.
32. Klein L, Massie BM, Leimberger JD, O'Connor CM, Pina IL, Adams KF,Jr, et al. Admission or changes in renal function during hospitalization for worsening heart failure predict postdischarge survival: Results from the outcomes of a prospective trial of intravenous milrinone for exacerbations of chronic heart failure (OPTIME-CHF). Circ Heart Fail. 2008 May;1(1):25-33.
33. Wei CM, Lerman A, Rodeheffer RJ, McGregor CG, Brandt RR, Wright S, et al. Endothelin in human congestive heart failure. Circulation. 1994 Apr;89(4):1580-6.
34. Modesti PA, Cecioni I, Costoli A, Poggesi L, Galanti G, Serneri GG. Renal endothelin in heart failure and its relation to sodium excretion. Am Heart J. 2000 Oct;140(4):617-22.
35. Kaluski E, Kobrin I, Zimlichman R, Marmor A, Krakov O, Milo O, et al. RITZ-5: Randomized intravenous TeZosentan (an endothelin-A/B antagonist) for the treatment of pulmonary edema: A prospective, multicenter, double-blind, placebo-controlled study. J Am Coll Cardiol. 2003 Jan 15;41(2):204-10.
36. Torre-Amione G, Young JB, Colucci WS, Lewis BS, Pratt C, Cotter G, et al. Hemodynamic and clinical effects of tezosentan, an intravenous dual endothelin receptor antagonist, in patients hospitalized for acute decompensated heart failure. J Am Coll Cardiol. 2003 Jul 2;42(1):140-7.
37. Teerlink JR, McMurray JJ, Bourge RC, Cleland JG, Cotter G, Jondeau G, et al. Tezosentan in patients with acute heart failure: Design of the value of endothelin receptor inhibition with tezosentan in acute heart failure study (VERITAS). Am Heart J. 2005 Jul;150(1):46-53.
38. Neuhofer W, Pittrow D. Role of endothelin and endothelin receptor antagonists in renal disease. Eur J Clin Invest. 2006 Sep;36 Suppl 3:78-88.
39. Colucci WS, Elkayam U, Horton DP, Abraham WT, Bourge RC, Johnson AD, et al. Intravenous nesiritide, a natriuretic peptide, in the treatment of decompensated congestive heart failure. nesiritide study group. N Engl J Med. 2000 Jul 27;343(4):246-53.
40. Mills RM, LeJemtel TH, Horton DP, Liang C, Lang R, Silver MA, et al. Sustained hemodynamic effects of an infusion of nesiritide (human b-type natriuretic peptide) in heart failure: A randomized, double-blind, placebo-controlled clinical trial. natrecor

study group. J Am Coll Cardiol. 1999 Jul;34(1):155-62.

41. Mitrovic V, Seferovic PM, Simeunovic D, Ristic AD, Miric M, Moiseyev VS, et al. Haemodynamic and clinical effects of ularitide in decompensated heart failure. Eur Heart J. 2006 Dec;27(23):2823-32.
42. McKie PM, Sangaralingham SJ, Burnett JC,Jr. CD-NP: An innovative designer natriuretic peptide activator of particulate guanylyl cyclase receptors for cardiorenal disease. Curr Heart Fail Rep. 2010 Sep;7(3):93-9.
43. Mitrovic V, Hernandez AF, Meyer M, Gheorghiade M. Role of guanylate cyclase modulators in decompensated heart failure. Heart Fail Rev. 2009 Dec;14(4):309-19.
44. Sackner-Bernstein JD, Skopicki HA, Aaronson KD. Risk of worsening renal function with nesiritide in patients with acutely decompensated heart failure. Circulation. 2005 Mar 29;111(12):1487-91.
45. Sackner-Bernstein JD, Kowalski M, Fox M, Aaronson K. Short-term risk of death after treatment with nesiritide for decompensated heart failure: A pooled analysis of randomized controlled trials. JAMA. 2005 Apr 20;293(15):1900-5.
46. Arora RR, Venkatesh PK, Molnar J. Short and long-term mortality with nesiritide. Am Heart J. 2006 Dec;152(6):1084-90.
47. O'Connor CM, Starling RC, Hernandez AF, Armstrong PW, Dickstein K, Hasselblad V, et al. Effect of nesiritide in patients with acute decompensated heart failure. N Engl J Med. 2011 Jul 7;365(1):32-43.
48. Mitrovic V, Luss H, Nitsche K, Forssmann K, Maronde E, Fricke K, et al. Effects of the renal natriuretic peptide urodilatin (ularitide) in patients with decompensated chronic heart failure: A double-blind, placebo-controlled, ascending-dose trial. Am Heart J. 2005 Dec;150(6):1239.
49. Luss H, Mitrovic V, Seferovic PM, Simeunovic D, Ristic AD, Moiseyev VS, et al. Renal effects of ularitide in patients with decompensated heart failure. Am Heart J. 2008 Jun;155(6):1012.e1,1012.e8.
50. Martin FL, Sangaralingham SJ, Huntley BK, McKie PM, Ichiki T, Chen HH, et al. CD-NP: A novel engineered dual guanylyl cyclase activator with anti-fibrotic actions in the heart. PLoS One. 2012;7(12):e52422.
51. Rose RA. CD-NP, a chimeric natriuretic peptide for the treatment of heart failure. Curr Opin Investig Drugs. 2010 Mar;11(3):349-56.
52. Lee CY, Chen HH, Lisy O, Swan S, Cannon C, Lieu HD, et al. Pharmacodynamics of a novel designer natriuretic peptide, CD-NP, in a first-in-human clinical trial in healthy subjects. J Clin Pharmacol. 2009 Jun;49(6):668-73.
53. Fischer D, Rossa S, Landmesser U, Spiekermann S, Engberding N, Hornig B, et al. Endothelial dysfunction in patients with chronic heart failure is independently associated with increased incidence of hospitalization, cardiac transplantation, or death. Eur Heart J. 2005 Jan;26(1):65-9.
54. Surmeli NB, Marletta MA. Insight into the rescue of oxidized soluble guanylate cyclase by the activator cinaciguat. Chembiochem. 2012 May 7;13(7):977-81.
55. Erdmann E, Semigran MJ, Nieminen MS, Gheorghiade M, Agrawal R, Mitrovic V, et al. Cinaciguat, a soluble guanylate cyclase activator, unloads the heart but also causes hypotension in acute decompensated heart failure. Eur Heart J. 2013 Jan;34(1):57-67.
56. Lapp H, Mitrovic V, Franz N, Heuer H, Buerke M, Wolfertz J, et al. Cinaciguat (BAY 58-2667) improves cardiopulmonary hemodynamics in patients with acute decompensated heart failure. Circulation. 2009 Jun 2;119(21):2781-8.
57. Gheorghiade M, Greene SJ, Filippatos G, Erdmann E, Ferrari R, Levy PD, et al. Cinaciguat, a soluble guanylate cyclase activator: Results from the randomized, controlled, phase IIb COMPOSE programme in acute heart failure syndromes. Eur J Heart Fail. 2012 Sep;14(9):1056-66.
58. Oghlakian G, Klapholz M. Vasopressin and vasopressin receptor antagonists in heart failure. Cardiol Rev. 2009 Jan-Feb;17(1):10-5.
59. Gheorghiade M, Gattis WA, O'Connor CM, Adams KF,Jr, Elkayam U, Barbagelata A, et al. Effects of tolvaptan, a vasopressin antagonist, in patients hospitalized with worsening heart failure: A randomized controlled trial. JAMA. 2004 Apr 28;291(16):1963-71.
60. Gheorghiade M, Gattis WA, Barbagelata A, Adams KF,Jr, Elkayam U, Orlandi C, et al. Rationale and study design for a multicenter, randomized, double-blind, placebo-controlled study of the effects of tolvaptan on the acute and chronic outcomes of patients hospitalized with worsening congestive heart failure. Am Heart J. 2003 Feb;145(2 Suppl):S51-4.
61. Gheorghiade M, Niazi I, Ouyang J, Czerwiec F, Kambayashi J, Zampino M, et al. Vasopressin V2-receptor blockade with tolvaptan in patients with chronic heart failure: Results from a double-blind, randomized trial. Circulation. 2003 Jun 3;107(21):2690-6.
62. Konstam MA, Gheorghiade M, Burnett JC,Jr, Grinfeld L, Maggioni AP, Swedberg K, et al. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: The EVEREST outcome trial. JAMA. 2007 Mar 28;297(12):1319-31.
63. Gheorghiade M, Konstam MA, Burnett JC,Jr, Grinfeld L, Maggioni AP, Swedberg K, et al. Short-term clinical effects of tolvaptan, an oral vasopressin antagonist, in patients hospitalized for heart failure: The EVEREST clinical status trials. JAMA. 2007 Mar 28;297(12):1332-43.

64. Udelson JE, Smith WB, Hendrix GH, Painchaud CA, Ghazzi M, Thomas I, et al. Acute hemodynamic effects of conivaptan, a dual V(1A) and V(2) vasopressin receptor antagonist, in patients with advanced heart failure. Circulation. 2001 Nov 13;104(20):2417-23.

65. Burnier M, Fricker AF, Hayoz D, Nussberger J, Brunner HR. Pharmacokinetic and pharmacodynamic effects of YM087, a combined V1/V2 vasopressin receptor antagonist in normal subjects. Eur J Clin Pharmacol. 1999 Nov;55(9):633-7.

66. Mondritzki T, Kolkhof P, Sabbah HN, Gheorghiade M, Furstner C, Schmeck C, et al. Differentiation of arginine vasopressin antagonistic effects by selective V2 versus dual V2/V1a receptor blockade in a preclinical heart failure model. Am J Ther. 2011 Jan;18(1):31-7.

67. Goldsmith SR. Hyponatremia and outcomes in patients with heart failure. Heart. 2012 Dec;98(24):1761-2.

68. Givertz MM, Massie BM, Fields TK, Pearson LL, Dittrich HC, CKI-201 and CKI-202 Investigators. The effects of KW-3902, an adenosine A1-receptor antagonist,on diuresis and renal function in patients with acute decompensated heart failure and renal impairment or diuretic resistance. J Am Coll Cardiol. 2007 Oct 16;50(16):1551-60.

69. Gottlieb SS, Brater DC, Thomas I, Havranek E, Bourge R, Goldman S, et al. BG9719 (CVT-124), an A1 adenosine receptor antagonist, protects against the decline in renal function observed with diuretic therapy. Circulation. 2002 Mar 19;105(11):1348-53.

70. Massie BM, O'Connor CM, Metra M, Ponikowski P, Teerlink JR, Cotter G, et al. Rolofylline, an adenosine A1-receptor antagonist, in acute heart failure. N Engl J Med. 2010 Oct 7;363(15):1419-28.

71. Gottlieb SS, Ticho B, Deykin A, Abraham WT, Denofrio D, Russell SD, et al. Effects of BG9928, an adenosine A(1) receptor antagonist, in patients with congestive heart failure. J Clin Pharmacol. 2011 Jun;51(6):899-907.

72. Greenberg B, Thomas I, Banish D, Goldman S, Havranek E, Massie BM, et al. Effects of multiple oral doses of an A1 adenosine antagonist, BG9928, in patients with heart failure: Results of a placebo-controlled, dose-escalation study. J Am Coll Cardiol. 2007 Aug 14;50(7):600-6.

73. Sorsa T, Heikkinen S, Abbott MB, Abusamhadneh E, Laakso T, Tilgmann C, et al. Binding of levosimendan, a calcium sensitizer, to cardiac troponin C. J Biol Chem. 2001 Mar 23;276(12):9337-43.

74. Janssen PM, Datz N, Zeitz O, Hasenfuss G. Levosimendan improves diastolic and systolic function in failing human myocardium. Eur J Pharmacol. 2000 Sep 15;404(1-2):191-9.

75. Hasenfuss G, Pieske B, Castell M, Kretschmann B, Maier LS, Just H. Influence of the novel inotropic agent levosimendan on isometric tension and calcium cycling in failing human myocardium. Circulation. 1998 Nov 17;98(20):2141-7.

76. Krassoi I, Pataricza J, Kun A, Papp JG. Calcium-dependent vasorelaxant capacity of levosimendan in porcine and human epicardial coronary artery preparations. Cardiovasc Drugs Ther. 2000 Dec;14(6):691-3.

77. Pataricza J, Hohn J, Petri A, Balogh A, Papp JG. Comparison of the vasorelaxing effect of cromakalim and the new inodilator, levosimendan, in human isolated portal vein. J Pharm Pharmacol. 2000 Feb;52(2):213-7.

78. Packer M. REVIVE-II: Multicenter placebo-controlled trial of levosimendan on clinical status in acutely decompensated heart failure Circulation. 2005 2005;112:3362-3364;112:3362.

79. Mebazaa A, Nieminen MS, Packer M, Cohen-Solal A, Kleber FX, Pocock SJ, et al. Levosimendan vs dobutamine for patients with acute decompensated heart failure: The SURVIVE randomized trial. JAMA. 2007 May 2;297(17):1883-91.

80. Moiseyev VS, Poder P, Andrejevs N, Ruda MY, Golikov AP, Lazebnik LB, et al. Safety and efficacy of a novel calcium sensitizer, levosimendan, in patients with left ventricular failure due to an acute myocardial infarction. A randomized, placebo-controlled, double-blind study (RUSSLAN). Eur Heart J. 2002 Sep;23(18):1422-32.

81. Follath F, Cleland JG, Just H, Papp JG, Scholz H, Peuhkurinen K, et al. Efficacy and safety of intravenous levosimendan compared with dobutamine in severe low-output heart failure (the LIDO study): A randomised double-blind trial. Lancet. 2002 Jul 20;360(9328):196-202.

82. Yilmaz MB, Yalta K, Yontar C, Karadas F, Erdem A, Turgut OO, et al. Levosimendan improves renal function in patients with acute decompensated heart failure: Comparison with dobutamine. Cardiovasc Drugs Ther. 2007 Dec;21(6):431-5.

83. Zemljic G, Bunc M, Yazdanbakhsh AP, Vrtovec B. Levosimendan improves renal function in patients with advanced chronic heart failure awaiting cardiac transplantation. J Card Fail. 2007 Aug;13(6):417-21.

84. Hou ZQ, Sun ZX, Su CY, Tan H, Zhong X, Hu B, et al. Effect of levosimendan on estimated glomerular filtration rate in hospitalized patients with decompensated heart failure and renal dysfunction. Cardiovasc Ther. 2012 Jul 30.

85. Parissis JT, Farmakis D, Nieminen M. Classical inotropes and new cardiac enhancers. Heart Fail Rev. 2007 Jun;12(2):149-56.

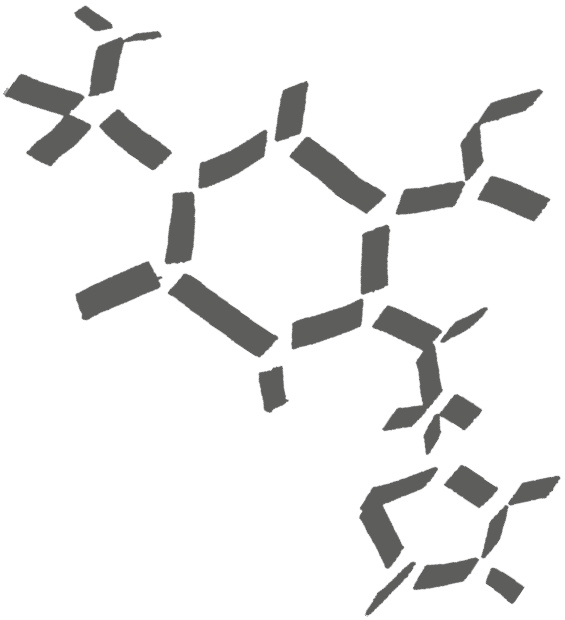
86. Teichman SL, Unemori E, Dschietzig T,

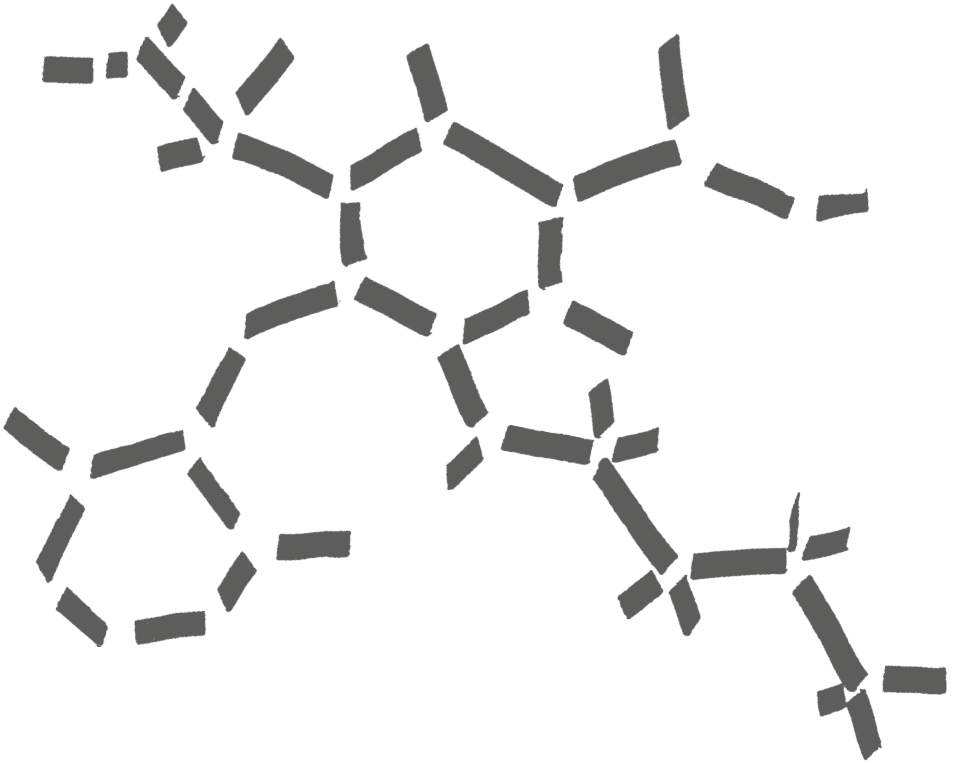
Conrad K, Voors AA, Teerlink JR, et al. Relaxin, a pleiotropic vasodilator for the treatment of heart failure. Heart Fail Rev. 2009 Dec;14(4):321-9.

87. Dschietzig T, Teichman S, Unemori E, Wood S, Boehmer J, Richter C, et al. Intravenous recombinant human relaxin in compensated heart failure: A safety, tolerability, and pharmacodynamic trial. J Card Fail. 2009 Apr;15(3):182-90.
88. Teichman SL, Unemori E, Teerlink JR, Cotter G, Metra M. Relaxin: Review of biology and potential role in treating heart failure. Curr Heart Fail Rep. 2010 Jun;7(2):75-82.
89. Teerlink JR, Cotter G, Davison BA, Felker GM, Filippatos G, Greenberg BH, et al. Serelaxin, recombinant human relaxin-2, for treatment of acute heart failure (RELAX-AHF): A randomised, placebo-controlled trial. Lancet. 2013 Jan 5;381(9860):29-39.
90. Metra M, Cotter G, Davison BA, Felker GM, Filippatos G, Greenberg BH, et al. Effect of serelaxin on cardiac, renal, and hepatic biomarkers in the relaxin in acute heart failure (RELAX-AHF) development program: Correlation with outcomes. J Am Coll Cardiol. 2013 Jan 15;61(2):196-206.
91. Damman K, Voors AA. Levosimendan improves renal function in acute decompensated heart failure: Cause and clinical application. editorial to: "levosimendan improves renal function in patients with acute decompensated heart failure: Comparison with dobutamine by yilmaz et al.". Cardiovasc Drugs Ther. 2007 Dec;21(6):403-4.

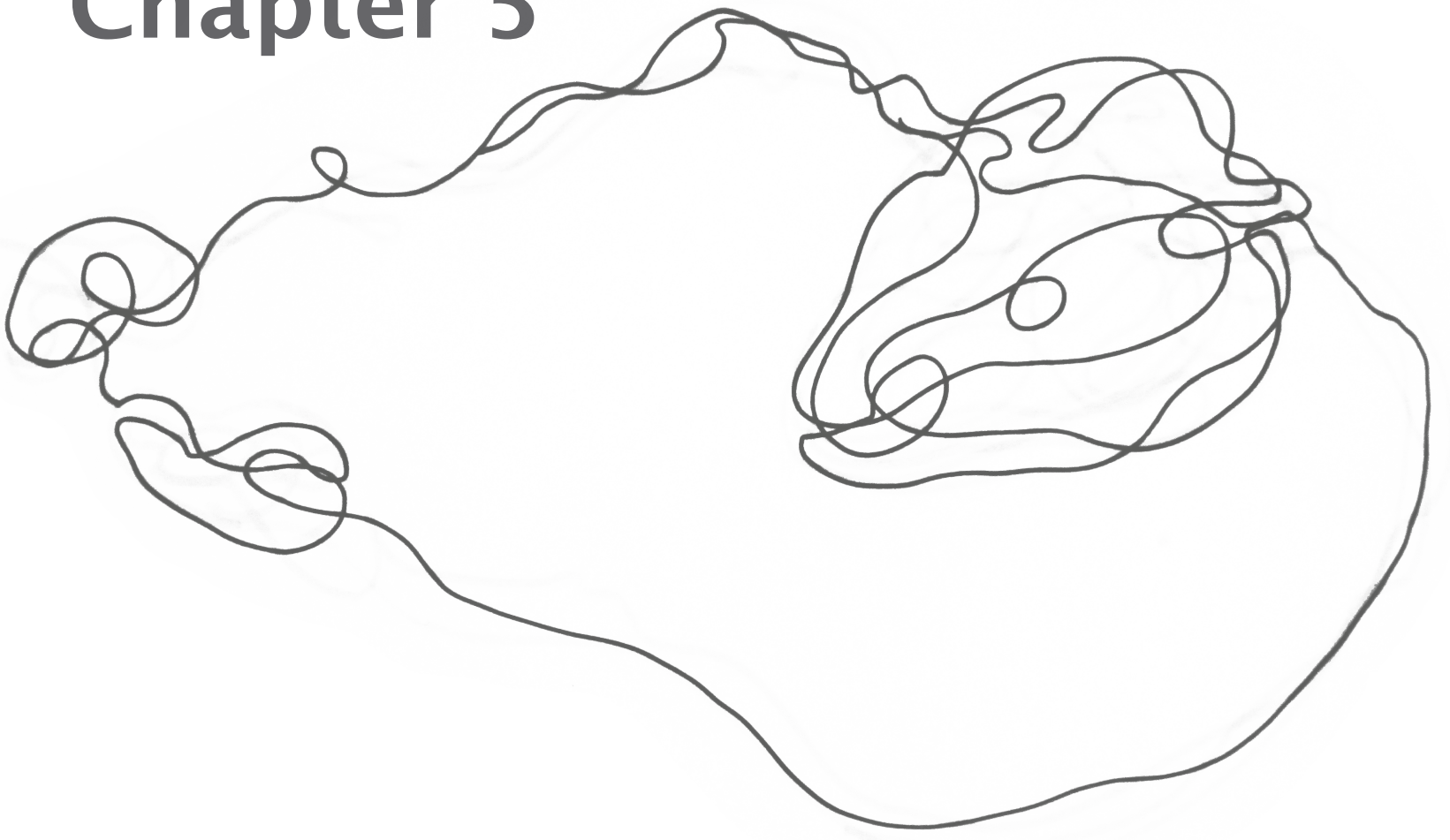
# Part II

## Diuretic response and worsening renal function in acute heart failure



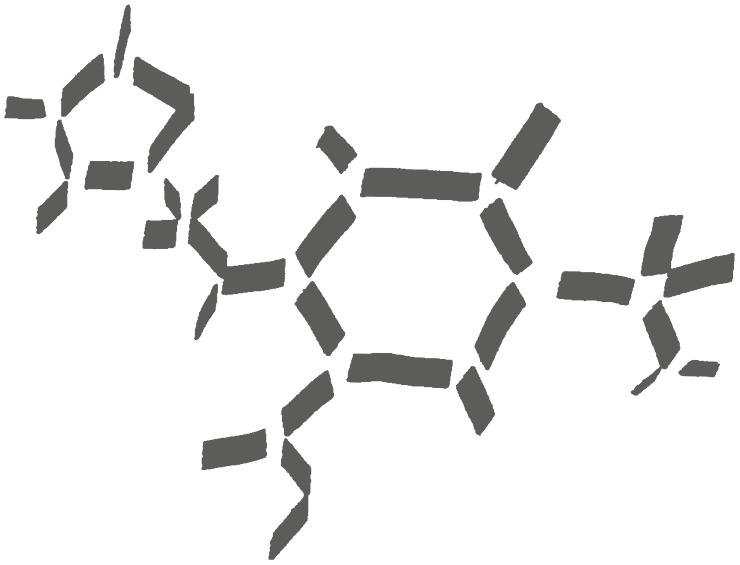


# Chapter 5



# Diuretic response in acute heart failure: clinical characteristics and prognostic significance

Mattia A.E. Valente, Adriaan A. Voors, Kevin Damman, Dirk J. Van Veldhuisen, Barrie M. Massie, Christopher M. O'Connor, Marco Metra, Piotr Ponikowski, John R.Teerlink, Gad Cotter, Beth Davison, John G.F. Cleland, Michael M. Givertz, Daniel M. Bloomfield, Mona Fiuzat, Howard C. Dittrich, and Hans L. Hillege



Published in: European Heart Journal (2014) 35, 1284–1293

## Abstract

**Aim** Diminished diuretic response is common in patients with acute heart failure, although a clinically useful definition is lacking. Our aim was to investigate a practical, workable metric for diuretic response, examine associated patient characteristics and relationships with outcome.

**Methods and results** We examined diuretic response (defined as Δ weight kg/40 mg furosemide) in 1745 hospitalized acute heart failure patients from the PROTECT trial. Day 4 response was used to allow maximum differentiation in responsiveness and tailoring of diuretic doses to clinical response, following sensitivity analyses. We investigated predictors of diuretic response and relationships with outcome. The median diuretic response was -0.38 (-0.80 to -0.13) kg/40 mg furosemide. Poor diuretic response was independently associated with low systolic blood pressure, high blood urea nitrogen, diabetes, and atherosclerotic disease (all $P < 0.05$). Worse diuretic response independently predicted 180-day mortality (HR: 1.42; 95% CI: 1.11–1.81, $P = 0.005$), 60-day death or renal or cardiovascular rehospitalization (HR: 1.34; 95% CI: 1.14–1.59, $P < 0.001$) and 60-day HF rehospitalization (HR: 1.57; 95% CI: 1.24–2.01, $P < 0.001$) in multivariable models. The proposed metric—weight loss indexed to diuretic dose—better captures a dose–response relationship. Model diagnostics showed diuretic response provided essentially the same or slightly better prognostic information compared with its individual components (weight loss and diuretic dose) in this population, while providing a less biased, more easily interpreted signal.

**Conclusions** Worse diuretic response was associated with more advanced heart failure, renal impairment, diabetes, atherosclerotic disease and in-hospital worsening heart failure, and predicts mortality and heart failure rehospitalization in this post hoc, hypothesis-generating study.

## Introduction

Heart failure (HF) is a growing public health problem and the leading cause of hospitalization in Europe and the USA.[1,2] Loop diuretics are a cornerstone of acute heart failure (AHF) therapy—administered to up to 90% of hospitalized patients[1,3,4]—and while some observational data suggest higher doses are associated with worse outcomes,[5–7] others found no difference after case matching.[8] The question of whether diuretics cause poor outcome or merely reflect disease severity remains unanswered;[9,10] data on optimal posology and administration are conflicting at best,[11–14] although the prospective Diuretic Optimization Strategies Evaluation (DOSE) trial suggests that safety concerns associated with high-dose diuretics may be unfounded.[15]

A frequently mentioned complication of diuretic therapy in AHF is diuretic resistance, which is associated with worsening renal function (WRF) and cardiorenal syndromes.[16] Existing definitions of resistance—which include congestion refractory to 'standard' diuretic therapy, reduced diuresis and natriuresis upon repeated dosing, and persistent congestion despite increasing (≥80 mg oral furosemide) daily diuretic doses[17,18]—are of limited use. Despite the clinical importance of the issue, few studies have explicitly examined the importance of effective decongestion using diuretics within the setting of AHF.

Heart failure guidelines recommend using weight loss to monitor volume status,[11] and correlations between weight loss and outcomes have been reported. However, post-discharge changes in body weight only predicted rehospitalization and were unrelated to mortality in one study,[19] highlighting the limitations of examining body weight alone, while others found diuretic dose did not predict weight loss.[5,20] This is perhaps unsurprising, considering both the non-linear dose–response relationship and the diuretic resistance commonly seen in HF.[21] A simple, continuous, quantitative measure for diuretic response—combining decongestive effect and diuretic dose—may help better unravel diuretic 'resistance' and open new avenues towards individualized, tailored treatment. The aim of this study was to define a clinically applicable measure for diuretic response, characterize the unresponsive patient, and determine the prognostic significance of diuretic response.

## Methods

### Study design and procedures

A total of 2033 adult patients with a history of HF were enrolled in the Placebo-controlled Randomized Study of the Selective A1 Adenosine Receptor Antagonist Rolofylline for Patients Hospitalized with acute heart failure and Volume Overload to Assess Treatment Effect on Congestion and Renal FuncTion (PROTECT) trial, a multicentre, randomized, double-blind, placebo-controlled trial with neutral results. Study design and main results have been published previously.[22,23] The trial was conducted in accordance with the Declaration of Helsinki and approved by all local Ethics Committees. All the patients provided written informed consent.

Heart failure signs and symptoms, serum creatinine, and blood urea nitrogen (BUN) were assessed daily until discharge or Day 6, and on Days 7 and 14. Other laboratory values were measured at least at baseline and Days 2, 7, and 14. Body weight was recorded from baseline through Day 4. Estimated glomerular filtration rate (eGFR) was calculated using the simplified modification of diet in renal disease equation.[24] Total diuretic dose was defined as the i.v. plus 0.5 × oral dose from randomization through Day 3, to correct for biological availability.[25]

## Study population

Of the 2033 included patients, subjects with missing data for diuretic response (n = 278), >20 kg weight loss (n = 3), or who underwent dialysis through Day 4 (n = 7) were excluded from analysis, resulting in a primary study population of 1745 patients.

## Measuring diuretic response

We propose a quantitative measure for diuretic response: weight change on Day 4 per 40 mg of furosemide administered on Days 1–3 (equivalent doses: bumetanide: 1 mg; torsemide: 20 mg). As diuretic resistance develops over time, weight change on Day 4 and loop diuretics administered on Days 1–3 were selected to allow time for greater differentiation in responsiveness and for tailoring of diuretic doses to clinical response. Our proposed measure for diuretic response—in effect an indexed weight change variable—was chosen in part based on available data. Sensitivity analyses were performed, examining alternative combinations of weight loss (a surrogate for decongestion in the absence of data on diuresis) and diuretic dose and administration routes—comparing response on Days 2, 3, and 4, changes in responsiveness over time, and definitions using only i.v. diuretics, within the full population and the placebo group. As reduced diuretic responsiveness in AHF is primarily a concern in patients with manifest volume overload, we performed sensitivity analyses in a subset of patients with objective signs of congestion—any oedema and any rales at baseline (n = 1368)—and in the congested subset excluding patients receiving inotropes or vasodilators on Days 1–4 (n = 1192).

## Endpoints

The primary endpoint was a trichotomous outcome of treatment success (marked or moderate dyspnoea improvement at 24 and 48 h), no change, or treatment failure.[23] Secondary endpoints were 180-day mortality, 60-day HF rehospitalization, and 60-day death or renal or cardiovascular rehospitalization.

## Statistical analysis

Considering the design of PROTECT, analyses were performed in the intention-to-treat population, correcting for study treatment. Continuous variables are summarized as means ± SD or median (inter-quartile range) as appropriate. Student's t-test or ANOVA (normal distribution) and Wilcoxon or Kruskall–Wallis

(skewed distribution) tests were used for group comparisons. Linear trends across categories were tested using general linear models for continuous covariates with polynomial contrasts, and non-parametric tests for trend for categorical variables. No imputations were performed.

Multivariable regression models were constructed via backward elimination and validated using bootstrap re-sampling (Supplementary material, Methods). Kaplan–Meier survival estimates and Cox proportional hazards models were used to examine associations with endpoints. Harrell's C-index (higher is better), Akaike's Information Criterion (AIC, lower is better), and continuous net reclassification improvement (NRI) were used to evaluate differences between models including diuretic response vs. individual components (Supplementary material, Methods). Tests were two-tailed, and an unadjusted P-value of <0.05 was considered statistically significant. All analyses were performed using R: A Language and Environment for Statistical Computing, version 3.0.1 (R Foundation for Statistical Computing, Vienna, Austria).

## Results

### Baseline characteristics and identifiers of diuretic response

Baseline characteristics of the entire study population are presented in Supplementary material, Table S1. Patients excluded from analysis had lower blood pressures and worse NYHA class, renal function, and outcomes (Supplementary material, Tables S1-2). Baseline characteristics per quintile of diuretic response are presented in Table 1.

The mean weight change on Day 4 was −2.8 ± 3.0 kg. The median diuretic dose through Day 3 was 240 mg (140–400) and 1702 (97%) patients received furosemide. The median diuretic response was −0.38 (−0.80 to −0.13) kg/40 mg furosemide. Poor responders showed strong differences in baseline characteristics, including more frequent renal impairment, diabetes, and ischaemic heart disease, but less hypertension and atrial fibrillation (all P < 0.05). Trends were similar in the placebo group and the congested subgroups (Supplementary material, Tables S3-5).

Predictors of diuretic response are presented in Table 2. Low systolic blood pressure, low serum potassium, high BUN, diabetes, and atherosclerotic disease were associated with poor diuretic response. Rolofylline treatment independently predicted good diuretic response (all P < 0.05). Patients on rolofylline showed a better diuretic response than those on placebo [−0.39 (−0.82–0.14) vs. −0.38 (−0.75–0.133) kg/40 mg furosemide, P = 0.018], despite excellent baseline matching (Supplementary material, Table S6). This effect was driven by greater weight loss for rolofylline vs. placebo (3.0 ± 2.8 vs. 2.6 ± 2.9 kg, P = 0.019) as diuretic doses through Day 3 were similar [240 (140–380) vs. 240 (140–412) mg, P = n.s.] There were no interactions between any of the predictors, patient characteristics, study treatment or renal function parameters (BUN, eGFR, or serum creatinine).

**Table 1** Baseline characteristics per quintile of diuretic response

| Diuretic Response (kg/40mg furosemide) | -1.33 [-1.95 to 0.07] *(n=349)* | -0.70 [-0.80 to -0.60] *(n=349)* | -0.38 [-0.44 to -0.33] *(n=351)* | -0.18 [-0.24 to -0.13] *(n=347)* | 0.00 [-0.04 to 0.18] *(n=349)* | P trend |
|---|---|---|---|---|---|---|
| **Demographics** | | | | | | |
| Sex (% Male) | 66.2 (231) | 67.9 (237) | 63.5 (223) | 71.8 (249) | 66.2 (231) | 0.631 |
| Age (years) | 70.1±11.6 | 69.5±11.8 | 70.6±10.6 | 69.8±11 | 69.8±12.2 | 0.837 |
| BMI (kg/m2) | 29.1±6.4 | 28.6±6.3 | 28.9±5.7 | 28.7±5.8 | 28.4±6 | 0.168 |
| LVEF (%) | 33.7±11.7 | 33.1±13 | 32.5±12.5 | 29.6±13 | 32.3±13.7 | 0.049 |
| Systolic BP (mmHg) | 128.6±16.3 | 126.1±17.3 | 125.6±17.2 | 121.6±17.9 | 120.9±18 | <0.001 |
| Diastolic BP (mmHg) | 77.4±11.8 | 75±11.7 | 74.8±10.9 | 72.1±11.3 | 71.4±11.9 | <0.001 |
| Heart Rate (beats/min) | 83.5±17.1 | 80.1±15.2 | 80.2±15.2 | 79.5±15.3 | 79.3±15.2 | 0.001 |
| Rolofylline (%(n)) | 74.8 (261) | 63.3 (221) | 65.8 (231) | 66.3 (230) | 63.9 (223) | 0.018 |
| **Clinical Profile** | | | | | | |
| Orthopnea ≥+2 (%(n)) | 95.9 (329) | 97.7 (337) | 95.4 (332) | 97.1 (336) | 96 (332) | 0.873 |
| Rales >1/3 lung fields (%(n)) | 61.9 (216) | 61.4 (213) | 61.3 (215) | 64.6 (224) | 59.2 (206) | 0.787 |
| Edema ≥+2 (%(n)) | 71.6 (250) | 72.8 (254) | 69.5 (244) | 69.2 (240) | 62.8 (219) | 0.006 |
| JVP ≥10 cm (%(n)) | 44.9 (137) | 42.1 (127) | 38.4 (124) | 40.3 (129) | 41.9 (135) | 0.392 |
| **Medical History** | | | | | | |
| Hypertension (%(n)) | 83.1 (290) | 81.4 (284) | 81.5 (286) | 78.1 (271) | 77.1 (269) | 0.023 |
| Diabetes Mellitus (%(n)) | 32.1 (112) | 41 (143) | 48.7 (171) | 54.2 (188) | 50.9 (177) | <0.001 |
| Hypercholesterolemia (%(n)) | 39.5 (138) | 46.1 (161) | 48.3 (169) | 58.8 (204) | 58.7 (205) | <0.001 |
| Smoking (%(n)) | 16.7 (58) | 15.5 (54) | 19.2 (67) | 22.2 (77) | 23.5 (82) | 0.002 |
| IHD (%(n)) | 66.2 (231) | 68.1 (237) | 69.4 (243) | 74.9 (259) | 73.4 (256) | 0.006 |
| Myocardial Infarction (%(n)) | 50.7 (177) | 43.2 (150) | 44.9 (157) | 56.9 (197) | 54.2 (189) | 0.015 |
| PCI (%(n)) | 13.7 (47) | 21.2 (73) | 22.2 (77) | 35.1 (121) | 31.6 (110) | <0.001 |
| CABG (%(n)) | 10.5 (36) | 16.9 (58) | 22.4 (78) | 26.4 (91) | 28.9 (101) | <0.001 |
| PVD (%(n)) | 10.3 (36) | 9.2 (32) | 10.6 (37) | 12.4 (43) | 11.8 (41) | 0.248 |

| Diuretic Response (kg/40mg furosemide) | | -1.33 [-1.95 to 0.07] (n=349) | -0.70 [-0.80 to -0.60] (n=349) | -0.38 [-0.44 to -0.33] (n=351) | -0.18 [-0.24 to -0.13] (n=347) | 0.00 [-0.04 to 0.18] (n=349) | P trend |
|---|---|---|---|---|---|---|---|
| Atrial Fibrillation (%(n)) | | 60.2 (209) | 57.5 (199) | 51.1 (179) | 53.5 (185) | 52.3 (181) | 0.019 |
| NYHA Class (%(n)) | | | | | | | 0.002 |
| | I-II | 13.5 (47) | 17.5 (61) | 17.7 (62) | 17.9 (62) | 16 (56) | |
| | III | 46.1 (161) | 43.6 (152) | 44.4 (156) | 52.4 (182) | 51 (178) | |
| | IV | 34.4 (120) | 36.1 (126) | 33.9 (119) | 25.6 (89) | 25.8 (90) | |
| ICD therapy (%(n)) | | 7.7 (27) | 12.9 (45) | 14.9 (52) | 18.4 (64) | 24.1 (84) | <0.001 |
| CRT therapy (%(n)) | | 4.3 (15) | 8 (28) | 9.2 (32) | 13.3 (46) | 13.2 (46) | <0.001 |
| Stroke (%(n)) | | 8.6 (30) | 8.9 (31) | 9.1 (32) | 9.2 (32) | 10 (35) | 0.512 |
| COPD (%(n)) | | 17.5 (61) | 17.5 (61) | 19.2 (67) | 20.8 (72) | 22.3 (78) | 0.052 |
| **Prior medication use** | | | | | | | |
| ACEi or ARB (%(n)) | | 75.1 (262) | 79.1 (276) | 76.6 (269) | 73.8 (256) | 74.2 (259) | 0.333 |
| Beta blockers (%(n)) | | 66.8 (233) | 71.1 (248) | 77.2 (271) | 83 (288) | 84 (293) | <0.001 |
| MRAs (%(n)) | | 49.6 (173) | 40.1 (140) | 46.2 (162) | 43.8 (152) | 46.4 (162) | 0.757 |
| **Laboratory Values** | | | | | | | |
| Creatinine (mg/dL) | | 1.3 [1.1-1.5] | 1.3 [1.1-1.7] | 1.4 [1.1-1.7] | 1.5 [1.2-1.9] | 1.5 [1.2-1.9] | <0.001 |
| eGFR (ml/min/1.73m2) | | 54 [42-67] | 53 [39-68] | 49 [38-65] | 46 [34-58] | 45 [34-60] | <0.001 |
| Blood Urea Nitrogen (mg/dL) | | 26 [20-33] | 28 [21-38] | 28 [21-41] | 35 [26-47] | 33 [24-45] | <0.001 |
| Sodium (mmol/L) | | 141 [138-143] | 140 [137-143] | 140 [137.2-143] | 139 [137-142] | 139 [135-141] | <0.001 |
| Potassium (mmol/L) | | 4.3 [3.9-4.7] | 4.3 [3.9-4.7] | 4.3 [3.9-4.6] | 4.2 [3.9-4.6] | 4.1 [3.8-4.5] | <0.001 |
| Haemoglobin (g/dL) | | 13.1±2 | 12.8±2 | 12.8±1.9 | 12.5±2.1 | 12.5±1.9 | <0.001 |
| Cholesterol (mmol/L) | | 151.1±41.4 | 149.2±45.3 | 149.6±48.1 | 143.9±43.1 | 144.1±44.6 | 0.011 |
| BNP (mg/dL) | | 1239 [835-2423] | 1045.5 [769-1450] | 1290 [805-2276] | 1270 [773-2180] | 1346 [891-2405] | 0.250 |

Abbreviations: BMI: Body Mass Index; LVEF: Left Ventricular Ejection Fraction; BP: blood pressure; JVP: Jugular Venous Pressure; IHD: Ischemic Heart Disease; PCI: Percutaneous Coronary Intervention; CABG: Coronary Artery Bypass Graft; PVD: Peripheral vascular disease; NYHA: New York Heart Association; ICD: Internal Cardiac Defibrillator; ACEi: Angiotensin Converting Enzyme inhibitor; ARB: Aldosterone Receptor Blocker; MRA: Mineralocorticoid Receptor Antagonist; eGFR: estimated Glomerular Filtration Rate; BNP: Brain Natriuretic Peptide.

**Table 2** Multivariable linear regression model, predictors of diuretic response

| | β Coefficient | 95% CI | T value | P |
|---|---|---|---|---|
| Weight day 1 (per SD) | -0.119 | (-0.16--0.08) | -6.059 | <0.001 |
| Systolic BP (per SD) | -0.081 | (-0.12--0.04) | -4.178 | <0.001 |
| Diabetes Mellitus | 0.193 | (0.12-0.27) | 4.858 | <0.001 |
| Hypercholesterolemia | 0.087 | (0.01-0.16) | 2.192 | 0.029 |
| PCI | 0.102 | (0.01-0.19) | 2.267 | 0.024 |
| Past beta blocker use | 0.118 | (0.03-0.21) | 2.603 | 0.009 |
| Log BUN (per SD) | 0.106 | (0.07-0.15) | 5.259 | <0.001 |
| Serum Potassium (per SD) | -0.104 | (-0.14--0.07) | -5.421 | <0.001 |
| Rolofylline treatment | -0.122 | (-0.2--0.04) | -3.091 | 0.002 |
| Spironolactone use | -0.125 | (-0.2--0.05) | -3.183 | 0.001 |
| Metozalone use | 0.212 | (0.04-0.38) | 2.464 | 0.014 |

Abbreviations: SD: standard deviation, BP: Blood Pressure, PCI: Percutaneous Coronary Intervention; BUN: Blood Urea Nitrogen.

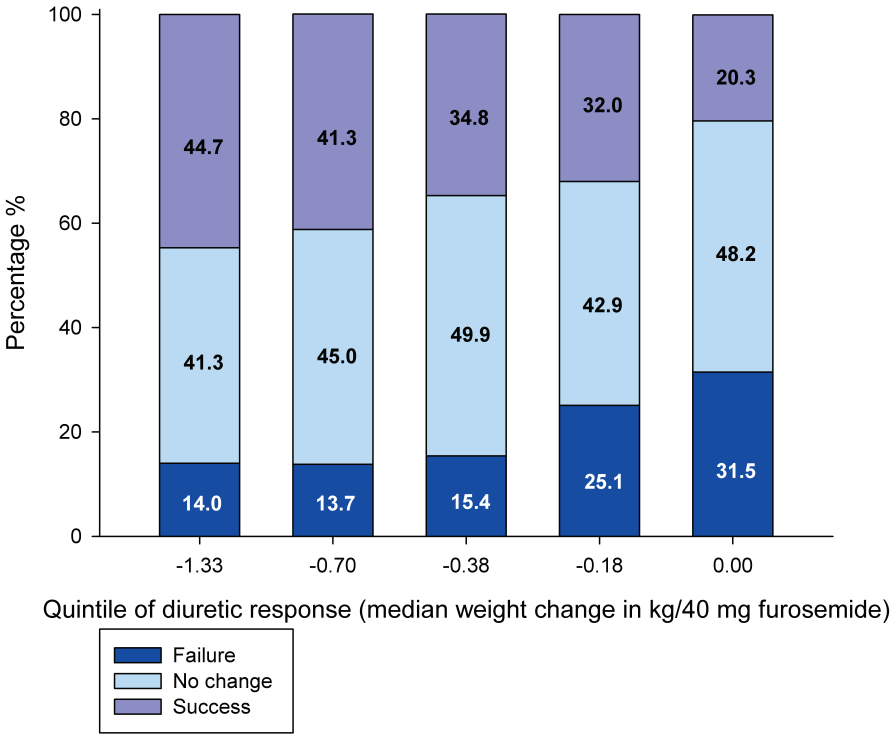



**Figure 1** Distribution of the Primary Composite Endpoint per quintile of diuretic response

P for trend = <0.001. Medians are presented per quintile, see table 1 for interquartile range per quintile.

## Clinical, mortality, and rehospitalization outcomes

Across quintiles, patients with a poor diuretic response had worse outcomes on all endpoints (Figure 1 and Table 3). Patterns for the placebo group alone and in patients with manifest signs of congestion (with and without inotrope use) were similar (Supplementary material, Tables S7-S9).

In Cox proportional hazards models, worse diuretic response was associated with poor outcome (all $P < 0.001$), and remained independently associated with a poor outcome even after multivariable adjustment (Tables 4 and 5, all $P < 0.05$). There were no interactions between diuretic response and renal function (BUN, eGFR, and serum creatinine), study treatment, left ventricular ejection fraction, or other patient characteristics. Similar patterns were seen in the placebo and congested subsets (Supplementary material, Table S10).

Figure 2 shows the adjusted Cox hazard function for diuretic response for the 180-day mortality endpoint, fitted using a penalized spline function. Unadjusted Kaplan–Meier survival estimates across quintiles showed consistent survival benefit for a better diuretic response (log-rank $P < 0.001$) (Figure 3).

## Sensitivity analyses

Associations between responsiveness on Days 2 and 3 and measures using i.v. doses only were examined; all showed consistent, similar patterns in baseline characteristics and outcomes, with the chosen definition presenting the largest effect size and smallest P-value in models (data not shown). Trends across quintiles of diuretic response were examined separately in patients receiving low vs. high dose furosemide (above and below the median dose of 240 mg on Days 1–3, i.e. an average of 80 mg furosemide per day), which showed improved diuretic response was consistently associated with similar differences in baseline characteristics (including low systolic blood pressure, worse renal function, diabetes, and atherosclerotic disease, all $P < 0.05$). The incidence of 180-day mortality, 60-day heart failure rehospitalization and 60-day death or cardiovascular or renal rehospitalization was also consistently higher across quintiles in both groups (all P for trend $< 0.05$). Patients on high vs. low diuretic doses did have worse 180-day and 60-day outcomes (unadjusted log-rank $P < 0.001$), though these differences did not persist after multivariable correction (covariates form Tables 4–5) in survival models (all P = n.s.).

Next, we examined the effect of changes in diuretic response over time. Patients were divided into three groups, based on whether they remained in the same quintile of diuretic response or were reclassified between Day 2 and Day 4. In univariable Cox models, corrected for baseline (Day 2) diuretic response, patients with stable vs. improving diuretic response did not show any statistically significant differences in 180-day mortality or the 60-day endpoints. Patients with worsening diuretic response, however, were more likely to meet all endpoints (all $P < 0.05$). After multivariable correction, this only held for the 60-day outcomes [corrected for covariates in Tables 4 and 5; 60-day HF rehospitalization: hazard ratio (HR) 1.48,

95% confidence interval (CI) 1.13–1.93, P = 0.004; 60-day death or renal or cardiovascular rehospitalization: HR: 1.49, 95% CI: 1.22–1.81, P < 0.001].

## Diuretic response vs. weight change and diuretic dose

Analyses were performed to evaluate the added value of introducing diuretic response compared with its individual components (weight change and diuretic dose) as covariates in Cox proportional hazards models. In univariable models, diuretic response showed a greater effect size per SD than weight change and diuretic dose alone (Tables 4–5).

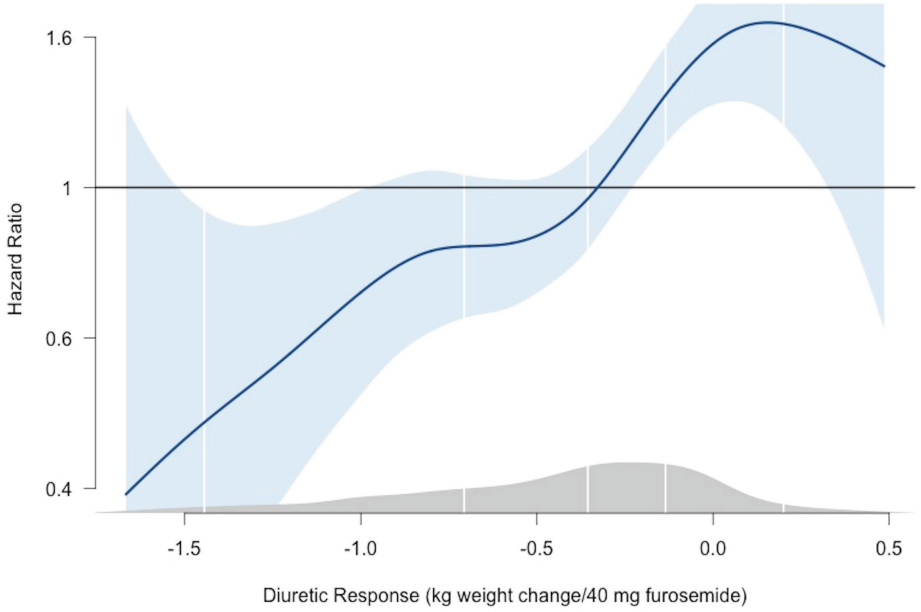



**Figure 2** Adjusted hazard ratio for 180-day mortality for diuretic response

Adjusted for model 3 covariates (table 4). Legend: dark blue: hazard function, fitted using a penalized spline, light blue: 95% CI; grey: density plot.

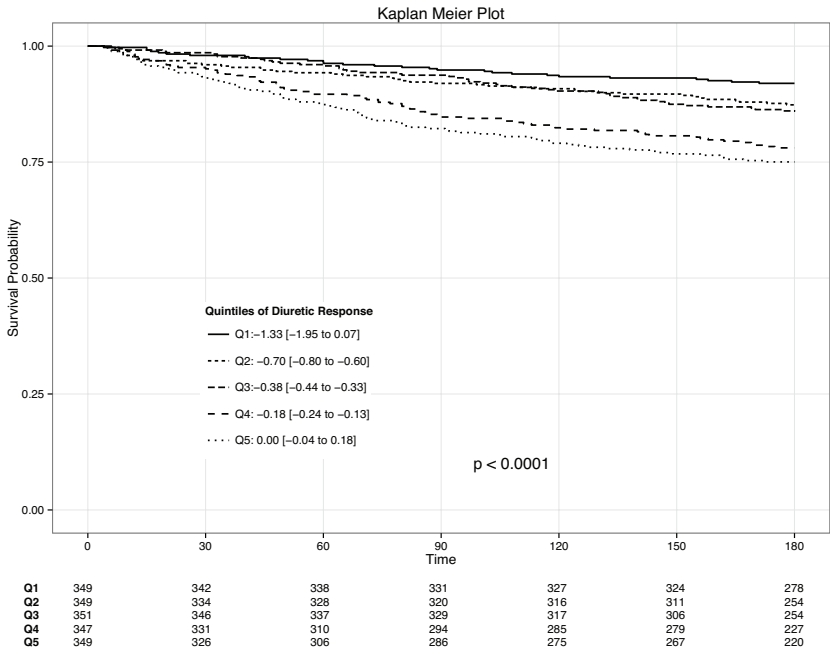



**Figure 3** Survival per quintile of diuretic response - unadjusted Kaplan-Meier curves

In multivariable 180-day mortality models, inclusion of diuretic response vs. its components showed similar performance, with a trend favouring diuretic response; in the full-study population, Harrell's C-index (higher is better) and AIC (lower is better)—measures for model performance and fit—were similar for both models (0.720 and 3409, respectively, for both), while the continuous NRI—a measure for reclassification improvement—slightly favoured diuretic response (0.01, 95% CI: −0.26–0.18). In patients with manifest congestion, diuretic response showed a slightly stronger trend towards an improved performance for Harrell's C-index (0.717 vs. 0.712), AIC (2464 vs. 2468), and continuous NRI (0.08, 95% CI: −0.16–0.31). Similar patterns for diuretic response vs. the components were observed for 60-day death or renal or cardiovascular rehospitalization in the full population (Harrell's C-index 0.650 vs. 0.647, AIC 6425 vs. 6432, continuous NRI 0.16, 95% CI: −0.06–0.28) and the congested subgroup (Harrell's C-index 0.651 vs. 0.646, AIC 4643 vs. 4650 continuous NRI 0.23, 95% CI: −0.11–0.37).

Diuretic response showed a better performance than its components in 60-day heart failure rehospitalization models. In the full population, the diuretic response model outperformed diuretic dose and weight change individually (C-index 0.692 vs. 0.686; AIC 3537 vs. 3550; continuous NRI 0.29, 95% CI: 0.04–0.47). These effects were also present in patients with manifest congestion (C-index 0.681 vs. 0.672; AIC 2538 vs. 2554; continuous NRI 0.35, 95% CI: 0.01–0.47).

**Table 3** Clinical, rehospitalization and mortality outcomes per quintile of diuretic response

| Diuretic Response (kg/40mg furosemide) | -1.33 [-1.95 to 0.07] | -0.70 [-0.80 to -0.60] | -0.38 [-0.44 to -0.33] | -0.18 [-0.24 to -0.13] | 0.00 [-0.04 to 0.18] | P-trend |
|---|---|---|---|---|---|---|
| | *(n=349)* | *(n=349)* | *(n=351)* | *(n=347)* | *(n=349)* | |
| Weight change day 1 - 4 (kg) | -5.7±3 | -3.9±2 | -2.8±1.8 | -2.1±1.6 | 0.5±2.1 | <0.001 |
| Total diuretic dose, day 1-3 (mg) | 130 [100-180] | 200 [140-280] | 240 [160-400] | 380 [240-607.5] | 330 [200-640] | <0.001 |
| Thiazide diuretics during admission | 15.2 (53) | 18.3 (64) | 16.8 (59) | 23.6 (82) | 21.2 (74) | 0.009 |
| Inotropes during admission (%(n)) | 2 (7) | 1.4 (5) | 4 (14) | 8.6 (30) | 14.6 (51) | <0.001 |
| Inotropes or vasodilators during admission (%(n)) | 13.8 (48) | 12 (42) | 14.8 (52) | 19 (66) | 21.8 (76) | <0.001 |
| WRF, day 7 (%(n)) | 21.9 (75) | 16 (54) | 18.2 (62) | 26.8 (90) | 25.1 (84) | 0.016 |
| WRF, day 14 (%(n)) | 21.9 (75) | 18.6 (63) | 22 (75) | 25 (84) | 29.6 (99) | 0.003 |
| Treatment failure due to Death (%(n)) | 0.3 (1) | 0.9 (3) | 0.3 (1) | 0.9 (3) | 1.1 (4) | 0.218 |
| Treatment failure due to Worsening HF (%(n)) | 3.4 (12) | 4.9 (17) | 5.7 (20) | 14.1 (49) | 18.3 (64) | <0.001 |
| Treatment failure due to WRF (%(n)) | 11.4 (39) | 8.9 (30) | 10 (34) | 14.1 (47) | 16 (53) | 0.011 |
| Treatment Failure due to HF rehospitalisation (%(n)) | 0.3 (1) | 0 (0) | 0.3 (1) | 0.3 (1) | 0.3 (1) | 0.722 |
| Hemoconcentration on day 4 (%(n)) | 65.8 (156) | 66.4 (176) | 61.6 (165) | 55.7 (151) | 47.1 (123) | <0.001 |
| 180-day mortality (%(n)) | 8 (28) | 12.6 (44) | 14 (49) | 21.9 (76) | 24.9 (87) | <0.001 |
| 60-day Heart Failure Rehospitalization (%(n)) | 7.4 (26) | 8.9 (31) | 15.7 (55) | 19 (66) | 23.2 (81) | <0.001 |
| 60-day Death or Renal or CV Rehospitalization (%(n)) | 15.8 (55) | 19.2 (67) | 27.9 (98) | 35.2 (122) | 38.4 (134) | <0.001 |

Unadjusted incidence rates are reported
Abbreviations: WRF: Worsening Renal Function; HF: Heart Failure; CV: Cardiovascular
WRF=0.3 mg/dL creatinine increase from baseline

**Table 4** 180-day mortality regression analyses for diuretic response

| | Univariable HR | 95% CI | p |
|---|---|---|---|
| Weight change (per SD) | 1.26 | 1.13-1.43 | <0.001 |
| Diuretic dose (per SD) | 1.22 | 1. 13-1.31 | <0.001 |
| Diuretic response (per SD) | 1.52 | 1.29-1.78 | <0.001 |

| Multivariable | Model 1 | | | Model 2 | | | Model 3 | | |
|---|---|---|---|---|---|---|---|---|---|
| | HR | 95% CI | p | HR | 95% CI | p | HR | 95% CI | p |
| Diuretic response | 1.73 | 1.40-2.12 | <0.001 | 1.42 | 1.11-1.81 | 0.005 | 1.40 | 1.12-1.74 | 0.003 |
| Age | 1.02 | 1.01-1.03 | <0.001 | 1.03 | 1.02-1.04 | <0.001 | 1.03 | 1.01-1.04 | <0.001 |
| Male Sex | 1.40 | 1.07-1.83 | 0.014 | - | - | - | 1.01 | 0.76-1.35 | 0.942 |
| Rolofylline | 1.12 | 0.88-1.44 | 0.360 | 0.99 | 0.76-1.31 | 0.972 | 1.13 | 0.87-1.46 | 0.371 |
| Systolic BP | | | | 0.99 | 0.98-0.99 | <0.001 | 0.99 | 0.98-0.99 | 0.001 |
| eGFR | | | | - | - | - | 1.00 | 0.99-1.02 | 0.367 |
| Log(BUN) | | | | 2.78 | 1.83-4.21 | <0.001 | 2.83 | 1.92-4.16 | <0.001 |
| Log(Creatinine) | | | | 0.70 | 0.40-1.22 | 0.213 | | | |

Adjustment: Univariable models are adjusted for baseline weight and study treatment.
Model 1: Age, sex, baseline weight, study treatment.
Model 2: study treatment, baseline weight, age, log(Creatinine), log(BUN), systolic BP, albumin, sodium, bicarbonate, glucose, rales, NYHA class, previous hospitalization (see supplementary methods).
Model 3: backward elimination model: study treatment, age, sex, baseline weight, systolic blood pressure, previous calcium antagonist use, log BUN, sodium, triglycerides, eGFR.
Abbreviations: BP: blood pressure; eGFR: estimated Glomerular Filtration Rate; BUN: Blood Urea Nitrogen.

**Table 5** 60-day heart failure rehospitalization and 60-day death or renal or cardiovascular rehospitalization regression analyses for diuretic response

| 60-day outcomes | HF rehospitalization | | | Death, renal, CV rehospitalization | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | p | HR | 95% CI | p |
| **Univariable** | | | | | | |
| Weight change (per SD) | 1.27 | 1.12-1.44 | <0.001 | 1.23 | 1.12-1.35 | <0.001 |
| Diuretic dose (per SD) | 1.21 | 1.12-1.30 | <0.001 | 1.17 | 1.10-1.25 | <0.001 |
| Diuretic response (per SD) | 1.69 | 1.43-2.00 | <0.001 | 1.40 | 1.25-1.56 | <0.001 |
| **Multivariable** | | | | | | |
| Diuretic response | 1.58 | 1.24-2.01 | <0.001 | 1.34 | 1.13-1.58 | <0.001 |
| Age | 1.01 | 0.98-1.01 | 0.412 | 1.00 | 0.99-1.01 | 0.618 |
| Male Sex | 0.93 | 0.69-1.24 | 0.608 | 0.90 | 0.73-1.12 | 0.351 |
| Rolofylline | 1.21 | 0.92-1.59 | 0.170 | 1.11 | 0.91-1.35 | 0.314 |
| Systolic BP | - | - | - | 0.99 | 0.98-0.99 | 0.018 |
| eGFR | 1.00 | 0.99-1.01 | 0.728 | 1.00 | 0.99-1.01 | 0.522 |
| Log(BUN) | 1.93 | 1.31-2.85 | <0.001 | 1.82 | 1.35-2.44 | <0.001 |

Adjustment: Univariable models are adjusted for baseline weight and study treatment.
Multivariable 60-day HF rehospitalization model adjusted for: Age, sex, study treatment, edema >2+, eGFR, log BUN, serum sodium, and a history of PCI, cardiac resynchronization therapy and hypercholesterolemia. Multivariable 60-day death, renal, CV rehospitalization model adjusted for: Age, sex, study treatment, edema >2+, eGFR, log BUN, serum sodium, systolic and diastolic blood pressure, history of percutaneous coronary intervention (PCI) and hypercholesterolemia

## Discussion

We showed that poor diuretic response is associated with more advanced HF, renal impairment, diabetes, atherosclerotic disease, and in-hospital worsening HF, and independently predicts HF rehospitalization and mortality.

Current definitions of diuretic resistance are all similar—failure to diurese (or decongest) in response to escalating doses of diuretics.[18,26] Diuretic absorption and efficacy is reduced in HF patients, and response is blunted further in AHF.[27–29] This is the result of numerous pathophysiological processes present in HF, including reduced renal perfusion due to haemodynamic impairment, increased congestion, and neurohormonal activation, which contribute to renal impairment, WRF and cardiorenal syndromes, all highly prevalent in AHF.[16,30,31] Yet despite a solid pathophysiological understanding of the underlying mechanisms, data examining both diuretic dose and effects in HF populations are scarce. Most studies have focused on diuretic dosage and outcomes,[5,7,8,15] while the prognostic significance of effects on body weight or urinary output—as proxies for volume status—has not been examined prospectively in HF. Post hoc analyses from the DOSE trial indicate weight loss is associated with a better outcome,[20] though Hasselblad et al.[5] found no association between diuretic dose and weight loss in a post hoc analysis of the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheter Effectiveness (ESCAPE) trial. Van der Meer et al.[32] have shown that haemoconcentration—a marker for intravascular decongestion—correlates with weight loss, lower diuretic doses, and lower mortality.[33] In a recent study, Testani et al.[34] retrospectively investigated what they termed diuretic efficiency in two AHF populations—net fluid output indexed to diuretic dose, and dichotomized into high and low efficiency. Similarly to our analyses, they found an independent prognostic effect on survival.

The proposed diuretic response metric—weight loss indexed to diuretic dose—reflects a 'dose–response' effect that can be understood intuitively. On a conceptual level, it can limit the bias intrinsic to each individual component; weight loss, for example, is not merely a marker for diuretic responsiveness, which may in part explain the inconsistent associations between weight loss and outcomes in past studies—better in DOSE and PROTECT, no differences in ESCAPE. A sicker patient may have accumulated more weight, and thus have the potential to loose more weight, but correction for diuretic dose should allow for 'correct' classification. Similarly, diuretic dose reflects a variety of patient and physician-related factors, so examining dose without its effect can lead to bias. While diuretic response does not capture an individual patient's (non-linear) dose–response curve, it does allow identification of patients with blunted response. This is supported by the observations that haemoconcentration was more common in good responders, that thiazides—often used to address loop diuretic resistance—were prescribed more often to less responsive patients, and that metozalone use independently predicted a poor diuretic response.

The value on Day 4 was chosen to reflect the fact resistance to diuretics is a dynamic process, not a static one, as outlined below. Sensitivity analyses showed consistent patterns in baseline characteristics and outcomes irrespective of high vs. low diuretic dose. We did note that patients who developed worsening diuretic response over time had a greater risk of rehospitalization outcomes in particular; while the initial diuretic response after 1 day of treatment is already predictive of outcome, responsiveness at a later time provides more accurate prognostic information. From a clinical perspective, examination of diuretic response is best suited for patients with manifest volume overload rather than those with redistribution HF alone. The findings in the congested group bear this out, with higher HRs and lower P-values on all endpoints in multivariable models and a slightly better model fit. Based on various measures for model performance (Harrell's C-index, AIC, and continuous NRI), diuretic response essentially provided the same prognostic information as the component variables in our population, even outperforming them for the prediction of HF rehospitalization. We believe this equivalence may be accepted, considering diuretic response provides a 'cleaner' signal for the matter under investigation. Further research will be necessary to confirm this.

## Determinants of diuretic response

In our study, patients with a poor diuretic response showed signs of more advanced HF and worse renal function. Comorbid conditions underlying both HF and renal impairment—including diabetes, atherosclerosis, and low haemoglobin levels—were also more common. The complex underlying physiology is reflected in the strong overlap with these and other clinical characteristics (Table 1). Most were not independently predictive, suggesting strong colinearity with many of these variables; diuretic response may therefore merely reflect the confluence of these factors. The recent study by Testani et al.[34] examining a fluid output-based diuretic efficiency metric showed some similarities to our results; diabetes, elevated BUN levels and a reduced eGFR were more common in poor responders.[34] However, these analyses were limited in part by incomplete data on diuretic doses, examination of a dichotomized rather than continuous metric, and a lack of analyses examining independent predictors of efficiency, making meaningful comparisons difficult.

Diuretics exert their effects via the kidney, relying on secretion and to a minor degree on glomerular filtration to achieve therapeutic concentrations in the tubule. Diabetes and atherosclerosis can both cause glomerular damage and glomerulosclerosis, affecting GFR, while the Renin-Angiotensin system activation and inflammation common to both conditions likely also contributes to a reduced response.[35–37] Haemodynamic impairment in HF causes congestion and reduced renal perfusion, while feedback mechanisms designed to preserve renal blood flow, GFR, and sodium levels lead to WRF and further congestion.[35] In untreated HF, short-term decongestion with diuretics can acutely lower certain neurohormone levels.[38] However, chronic diuretic use may cause structural changes in the tubular epithelium, resulting in sodium retention, worsening congestion, and neurohormonal activation, necessitating higher diuretic doses, with the potential for more renal

damage.[17]As a result of these effects, patients with AHF display a steeper dose–response curve than healthy controls or HF patients in a compensated state.[21]

An intriguing finding in our study was the relatively small difference in renal function between good and poor responders—a difference of only 9 mL/min/1.73 $m^2$ in estimated GFR, 0.2 mg/dL in creatinine, and 7 mg/dL in BUN between bottom and top quintiles of diuretic response. Except BUN, none of these renal function parameters independently predicted diuretic response outright, and there were no interactions with diuretic response in survival models. This is in contrast with the traditional view of diuretic resistance, in which renal function is the primary determinant. The explanation may lie in the limitations of creatinine (and creatinine-based GFR estimates) as a marker for renal function, as it provides no direct information about tubular function or injury. Novel tubular or combined (urinary) markers, such as cystatin C, NGAL, NAG, or KIM-1, may provide better insights into diuretic resistance phenomena.[39] Another interesting finding was the relatively high incidence of WRF in the best quintile of diuretic response, despite better long-term outcomes. This is consistent with findings by Metra et al.[40] indicating that effective decongestion is more important than (transient) WRF.

Interestingly, rolofylline independently predicted diuretic response. As this effect was driven by weight loss, not diuretic dose, it suggests either a direct diuretic effect, or potentiation of diuretics via improved haemodynamics, consistent with findings from earlier trials.[23,41–43] Metra et al.[44] previously noted an association between improvement in dyspnoea and rolofylline, though it should be noted that overall, rolofylline's effects on clinical outcomes were neutral, which, combined with safety concerns,[42] resulted in discontinuation of the development programme. In PROTECT, patients received diuretics based on clinical assessment, and those with a poor diuretic response received higher doses and had worse outcomes. Although rolofylline did not prevent WRF,[43] there is still a strong need for adjuvant therapies that improve diuresis without compromising renal function.

## Clinical perspectives

Loop diuretic therapy remains the cornerstone of decongestive treatment in AHF, despite a lack of convincing evidence or consensus on optimal dosage,[45] and mixed evidence on survival impact.[5–8,46,47] Alternative decongestive treatments, such as ultrafiltration, may be effective, but remain unproven.[26,48,49]

We feel the simple measure of weight change per unit of diuretic provides better insight into patient response to therapy than examining weight loss or diuretic dose independently; diuretic dose provides insufficient information, as higher doses with adequate weight loss will be misclassified, while weight loss alone does not reflect the degree of resistance. Once validated and investigated further, diuretic response could be used in clinical research settings to help identify patients who might benefit from alternative or adjuvant decongestive therapies.

### Limitations

This study is a post hoc analysis of a randomized clinical trial, with all attendant limitations. The excluded subpopulation differed significantly from the analysed group, with higher incidences of multiple co-morbidities and worse outcomes. Multivariable modelling alone may not be sufficient to account for the differences, and our findings should be considered hypothesis-generating. Furthermore, available data did not allow extensive investigation of differences in diuretic responsiveness in HF with reduced vs. preserved ejection fraction. The true degree of volume overload in the congested subgroup also cannot be ascertained with certainty, as both oedema and rales may have other causes or be due to redistribution. Additionally, diuretic response as defined in this study is a linear relationship, while the dose–response relationship in vivo is S-shaped, and dependent on individual patient characteristics,[21] making it difficult to model accurately post hoc.

Given the focus on diuretic response, data on urinary output and fractional sodium excretion would be preferred, although body weight is easily measured and recommended for monitoring volume status.[11] The results from Testani et al.[34] indicate indexed net fluid output contains similar prognostic information, and validation and comparison of both metrics in the same populations would be valuable. The study protocol did not specify how to assess weight, which could affect data quality. Serial measurements of these variables should be considered for all future AHF trials.

## Conclusion

In this retrospective study, we present a novel measure for diuretic response in acute HF—weight loss indexed to diuretic use. This metric yielded at least equivalent prognostic information compared with its component parts, while providing a more easily interpreted signal for patient response to diuretics. Further research will be needed to confirm our findings. In this study, patients with a poor diuretic response had more advanced HF, worse renal function and were more likely to have a history of atherosclerosis and diabetes. Poor diuretic response was strongly and independently associated with less dyspnoea relief and an increased incidence of in-hospital worsening HF, as well as post-discharge mortality and rehospitalization for HF. Early identification of subjects with impaired diuretic response may open doors towards patient-tailored treatment strategies.

**Conflicts of interest:**

M.A.E.V, K.D., M.F., and H.L.H. have nothing to disclose. A.A.V. has received speaker and consultancy fees from Merck and NovaCardia. D.J.V.V. has received Board Membership fees from Amgen, BG Medicine, Biocontrol, Johnson and Johnson, Novartis, Sorbent, and Vifor. B.M.M. has received consulting fees from NovaCardia, sponsors of the study, and from Merck, that purchased the rights to rolofylline after the completion of the PROTECT pilot study. C.M.O.C. is a consultant to Merck. M.M. has received honoraria and reimbursements from NovaCardia, sponsors of the study, and from Merck, that purchased the rights to rolofylline after completion of the PROTECT pilot study. P.P. has received honoraria from Merck. J.R.T. has received research funds and consulting fees from Merck, the producer of rolofylline for the conduct of this study and has also received research funds and consulting fees from Abbott, Amgen, Biogen Idec, Corthera, Cytokinetics, Johnson and Johnson/ Scios, Novartis, Relypsa, and Solvay for research in related areas. G.C. and B.A.W. are employees of Momentum Research, Inc., which was contracted to perform work on the project by Merck & Co., Inc., J.G.F.C. was on the Steering Committee for the study, served on the Advisory Board for MSD, and received payments for both. M.M.G. has received institutional research support and served on a scientific Advisory Board for Merck. D.A.B. is an employee of Merck. H.C.D was an employee of NovaCardia and a consultant to Merck.

## References


1. Adams KF,Jr, Fonarow GC, Emerman CL, LeJemtel TH, Costanzo MR, Abraham WT, Berkowitz RL, Galvao M, Horton DP, ADHERE Scientific Advisory Committee and Investigators. Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). Am Heart J 2005;149:209-216.
2. Hall MJ, Levant S, Defrances CJ. Hospitalization for congestive heart failure: United States, 2000-2010. NCHS Data Brief 2012;(108):1-8.
3. Cleland JG, Swedberg K, Follath F, Komajda M, Cohen-Solal A, Aguilar JC, Dietz R, Gavazzi A, Hobbs R, Korewicki J, Madeira HC, Moiseyev VS, Preda I, van Gilst WH, Widimsky J, Freemantle N, Eastaugh J, Mason J, Study Group on Diagnosis of the Working Group on Heart Failure of the European Society of Cardiology. The EuroHeart Failure survey programme-- a survey on the quality of care among patients with heart failure in Europe. Part 1: patient characteristics and diagnosis. Eur Heart J 2003;24:442-463.
4. Sato N, Kajimoto K, Asai K, Mizuno M, Minami Y, Nagashima M, Murai K, Muanakata R, Yumino D, Meguro T, Kawana M, Nejima J, Satoh T, Mizuno K, Tanaka K, Kasanuki H, Takano T, ATTEND Investigators. Acute decompensated heart failure syndromes (ATTEND) registry. A prospective observational multicenter cohort study: rationale, design, and preliminary data. Am Heart J 2010;159:949-955.e1.
5. Hasselblad V, Gattis Stough W, Shah MR, Lokhnygina Y, O'Connor CM, Califf RM, Adams KF,Jr. Relation between dose of loop diuretics and outcomes in a heart failure population: results of the ESCAPE trial. Eur J Heart Fail 2007;9:1064-1069.
6. Butler J, Forman DE, Abraham WT, Gottlieb SS, Loh E, Massie BM, O'Connor CM, Rich MW, Stevenson LW, Wang Y, Young JB, Krumholz HM. Relationship between heart failure treatment and development of worsening renal function among hospitalized patients. Am Heart J 2004;147:331-338.
7. Ahmed A, Husain A, Love TE, Gambassi G, Dell'Italia LJ, Francis GS, Gheorghiade M, Allman RM, Meleth S, Bourge RC. Heart failure, chronic diuretic use, and increase in mortality and hospitalization: an observational study using propensity score methods. Eur Heart J 2006;27:1431-1439.
8. Yilmaz MB, Gayat E, Salem R, Lassus J, Nikolaou M, Laribi S, Parissis J, Follath F, Peacock WF, Mebazaa A. Impact of diuretic dosing on mortality in acute heart failure using a propensity-matched analysis. Eur J Heart Fail 2011;13:1244-1252.
9. Neuberg GW, Miller AB, O'Connor CM, Belkin RN, Carson PE, Cropp AB, Frid DJ, Nye RG, Pressler ML, Wertheimer JH, Packer M, PRAISE Investigators. Prospective Randomized Amlodipine Survival Evaluation. Diuretic resistance predicts mortality in patients with advanced heart failure. Am Heart J 2002;144:31-38.
10. Mielniczuk LM, Tsang SW, Desai AS, Nohria A, Lewis EF, Fang JC, Baughman KL, Stevenson LW, Givertz MM. The association between high-dose diuretics and clinical stability in ambulatory chronic heart failure patients. J Card Fail 2008;14:388-393.
11. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Kober L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Ronnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A, Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology, Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S, McDonagh T, Sechtem U, Bonet LA, Avraamides P, Ben Lamin HA, Brignole M, Coca A, Cowburn P, Dargie H, Elliott P, Flachskampf FA, Guida GF, Hardman S, Iung B, Merkely B, Mueller C, Nanas JN, Nielsen OW, Orn S, Parissis JT, Ponikowski P, ESC Committee for Practice Guidelines. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2012;14:803-869.
12. Aaser E, Gullestad L, Tollofsrud S, Lundberg J, Hall C, Djoseland O, Kjekshus J, Forfang K. Effect of bolus injection versus continuous infusion of furosemide on diuresis and neurohormonal activation in patients with severe congestive heart failure. Scand J Clin Lab Invest 1997;57:361-367.
13. Dormans TP, van Meyel JJ, Gerlag PG, Tan Y, Russel FG, Smits P. Diuretic efficacy of high dose furosemide in severe heart failure: bolus injection versus continuous infusion. J Am Coll Cardiol 1996;28:376-382.
14. Kramer WG, Smith WB, Ferguson J, Serpas T, Grant AG,3rd, Black PK, Brater DC. Pharmacodynamics of torsemide administered as an intravenous injection and as a continuous infusion to patients with congestive heart failure. J Clin Pharmacol 1996;36:265-270.
15. Felker GM, Lee KL, Bull DA, Redfield MM,

Stevenson LW, Goldsmith SR, LeWinter MM, Deswal A, Rouleau JL, Ofili EO, Anstrom KJ, Hernandez AF, McNulty SE, Velazquez EJ, Kfoury AG, Chen HH, Givertz MM, Semigran MJ, Bart BA, Mascette AM, Braunwald E, O'Connor CM, NHLBI Heart Failure Clinical Research Network. Diuretic strategies in patients with acute decompensated heart failure. N Engl J Med 2011;364:797-805.

16. Ronco C, Cicoira M, McCullough PA. Cardiorenal syndrome type 1: pathophysiological crosstalk leading to combined heart and kidney dysfunction in the setting of acutely decompensated heart failure. J Am Coll Cardiol 2012;60:1031-1042.
17. Ellison DH. Diuretic therapy and resistance in congestive heart failure. Cardiology 2001;96:132-143.
18. Leto L, Aspromonte N, Feola M. Efficacy and safety of loop diuretic therapy in acute decompensated heart failure: a clinical review. Heart Fail Rev 2012;
19. Blair JE, Khan S, Konstam MA, Swedberg K, Zannad F, Burnett JC,Jr, Grinfeld L, Maggioni AP, Udelson JE, Zimmer CA, Ouyang J, Chen CF, Gheorghiade M, EVEREST Investigators. Weight changes after hospitalization for worsening heart failure and subsequent re-hospitalization and mortality in the EVEREST trial. Eur Heart J 2009;30:1666-1673.
20. Kociol RD, McNulty SE, Hernandez AF, Lee KL, Redfield MM, Tracy RP, Braunwald E, O'Connor CM, Felker GM, NHLBI Heart Failure Network Steering Committee and Investigators. Markers of decongestion, dyspnea relief, and clinical outcomes among patients hospitalized with acute heart failure. Circ Heart Fail 2013;6:240-245.
21. von Lueder TG, Atar D, Krum H. Diuretic use in heart failure and outcomes. Clin Pharmacol Ther 2013;94:490-498.
22. Weatherley BD, Cotter G, Dittrich HC, DeLucca P, Mansoor GA, Bloomfield DM, Ponikowski P, O'Connor CM, Metra M, Massie BM, PROTECT Steering Committee, Investigators, and Coordinators. Design and rationale of the PROTECT study: a 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. J Card Fail 2010;16:25-35.
23. Massie BM, O'Connor CM, Metra M, Ponikowski P, Teerlink JR, Cotter G, Weatherley BD, Cleland JG, Givertz MM, Voors A, DeLucca P, Mansoor GA, Salerno CM, Bloomfield DM, Dittrich HC, PROTECT Investigators and Committees. Rolofylline, an adenosine A1-receptor antagonist, in acute heart failure. N Engl J Med 2010;363:1419-1428.
24. Smilde TD, van Veldhuisen DJ, Navis G, Voors AA, Hillege HL. Drawbacks and prognostic value of formulas estimating renal function in patients with chronic heart failure and systolic dysfunction. Circulation 2006;114:1572-1580.
25. Hammarlund MM, Paalzow LK, Odlind B. Pharmacokinetics of furosemide in man after intravenous and oral administration. Application of moment analysis. Eur J Clin Pharmacol 1984;26:197-207.
26. Costanzo MR, Saltzberg M, O'Sullivan J, Sobotka P. Early ultrafiltration in patients with decompensated heart failure and diuretic resistance. J Am Coll Cardiol 2005;46:2047-2051.
27. Brater DC. Diuretic therapy in congestive heart failure. Congest Heart Fail 2000;6:197-201.
28. Vasko MR, Cartwright DB, Knochel JP, Nixon JV, Brater DC. Furosemide absorption altered in decompensated congestive heart failure. Ann Intern Med 1985;102:314-318.
29. Vargo DL, Kramer WG, Black PK, Smith WB, Serpas T, Brater DC. Bioavailability, pharmacokinetics, and pharmacodynamics of torsemide and furosemide in patients with congestive heart failure. Clin Pharmacol Ther 1995;57:601-609.
30. Damman K, Voors AA, Navis G, van Veldhuisen DJ, Hillege HL. The cardiorenal syndrome in heart failure. Prog Cardiovasc Dis 2011;54:144-153.
31. Damman K, Valente MA, Voors AA, O'Connor CM, van Veldhuisen DJ, Hillege HL. Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis. Eur Heart J 2013;
32. van der Meer P, Postmus D, Ponikowski P, Cleland JG, O'Connor CM, Cotter G, Metra M, Davison BA, Givertz MM, Mansoor GA, Teerlink JR, Massie BM, Hillege HL, Voors AA. The predictive value of short-term changes in hemoglobin concentration in patients presenting with acute decompensated heart failure. J Am Coll Cardiol 2013;61:1973-1981.
33. Testani JM, Chen J, McCauley BD, Kimmel SE, Shannon RP. Potential effects of aggressive decongestion during the treatment of decompensated heart failure on renal function and survival. Circulation 2010;122:265-272.
34. Testani JM, Brisco MA, Turner JM, Spatz ES, Bellumkonda L, Parikh CR, Tang WH. Loop Diuretic Efficiency: A Metric of Diuretic Responsiveness with Prognostic Importance in Acute Decompensated Heart Failure. Circ Heart Fail 2013;
35. Damman K, Kalra PR, Hillege H. Pathophysiological mechanisms contributing to renal dysfunction in chronic heart failure. J Ren Care 2010;36 Suppl 1:18-26.
36. Libby P. Inflammation in atherosclerosis. Nature 2002;420:868-874.
37. Romeo GR, Lee J, Shoelson SE. Metabolic syndrome, insulin resistance, and roles of

inflammation--mechanisms and therapeutic targets. Arterioscler Thromb Vasc Biol 2012;32:1771-1776.

38. Bayliss J, Norell M, Canepa-Anson R, Sutton G, Poole-Wilson P. Untreated heart failure: clinical and neuroendocrine effects of introducing diuretics. Br Heart J 1987;57:17-22.
39. Valente MA, Damman K, Dunselman PH, Hillege HL, Voors AA. Urinary proteins in heart failure. Prog Cardiovasc Dis 2012;55:44-55.
40. Metra M, Davison B, Bettari L, Sun H, Edwards C, Lazzarini V, Piovanelli B, Carubelli V, Bugatti S, Lombardi C, Cotter G, Dei Cas L. Is worsening renal function an ominous prognostic sign in patients with acute heart failure? The role of congestion and its interaction with renal function. Circ Heart Fail 2012;5:54-62.
41. Ponikowski P, Mitrovic V, O'Connor CM, Dittrich H, Cotter G, Massie BM, Givertz MM, Chen E, Murray M, Weatherley BD, Fujita KP, Metra M. Haemodynamic effects of rolofylline in the treatment of patients with heart failure and impaired renal function. Eur J Heart Fail 2010;12:1238-1246.
42. Teerlink JR, Iragui VJ, Mohr JP, Carson PE, Hauptman PJ, Lovett DH, Miller AB, Pina IL, Thomson S, Varosy PD, Zile MR, Cleland JG, Givertz MM, Metra M, Ponikowski P, Voors AA, Davison BA, Cotter G, Wolko D, Delucca P, Salerno CM, Mansoor GA, Dittrich H, O'Connor CM, Massie BM. The safety of an adenosine A(1)-receptor antagonist, rolofylline, in patients with acute heart failure and renal impairment: findings from PROTECT. Drug Saf 2012;35:233-244.
43. Voors AA, Dittrich HC, Massie BM, DeLucca P, Mansoor GA, Metra M, Cotter G, Weatherley BD, Ponikowski P, Teerlink JR, Cleland JG, O'Connor CM, Givertz MM. Effects of the adenosine A1 receptor antagonist rolofylline on renal function in patients with acute heart failure and renal dysfunction: results from PROTECT (Placebo-Controlled Randomized Study of the Selective Adenosine A1 Receptor Antagonist Rolofylline for Patients Hospitalized with Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function). J Am Coll Cardiol 2011;57:1899-1907.
44. Metra M, O'Connor CM, Davison BA, Cleland JG, Ponikowski P, Teerlink JR, Voors AA, Givertz MM, Mansoor GA, Bloomfield DM, Jia G, DeLucca P, Massie B, Dittrich H, Cotter G. Early dyspnoea relief in acute heart failure: prevalence, association with mortality, and effect of rolofylline in the PROTECT Study. Eur Heart J 2011;32:1519-1534.
45. Campbell PT, Ryan J. Diuretic dosing in acute decompensated heart failure: lessons from DOSE. Curr Heart Fail Rep 2012;9:260-265.
46. Felker GM, Mentz RJ. Diuretics and ultrafiltration in acute decompensated heart failure. J Am Coll Cardiol 2012;59:2145-2153.
47. Cooper HA, Dries DL, Davis CE, Shen YL, Domanski MJ. Diuretics and risk of arrhythmic death in patients with left ventricular dysfunction. Circulation 1999;100:1311-1315.
48. Costanzo MR, Guglin ME, Saltzberg MT, Jessup ML, Bart BA, Teerlink JR, Jaski BE, Fang JC, Feller ED, Haas GJ, Anderson AS, Schollmeyer MP, Sobotka PA, UNLOAD Trial Investigators. Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. J Am Coll Cardiol 2007;49:675-683.
49. Bart BA, Goldsmith SR, Lee KL, Givertz MM, O'Connor CM, Bull DA, Redfield MM, Deswal A, Rouleau JL, Lewinter MM, Ofili EO, Stevenson LW, Semigran MJ, Felker GM, Chen HH, Hernandez AF, Anstrom KJ, McNulty SE, Velazquez EJ, Ibarra JC, Mascette AM, Braunwald E, the Heart Failure Clinical Research Network. Ultrafiltration in Decompensated Heart Failure with Cardiorenal Syndrome. N Engl J Med 2012;

# Supplemental material

## Supplementary methods

Covariates for multivariable regression models were selected through backward elimination. First, fractional polynomial transformations were applied to continuous variables in linear, logistic and Cox proportional hazards regression to test for non-linearity. Next, a multivariable model containing all variables with a univariable association at a significance level of $p \leq 0.1$ and any variables considered likely to contribute was created, corrected for study treatment, age, sex and baseline weight. A parsimonious model was obtained via backward hierarchical elimination of covariates based on P-value (alpha 0.05), starting with higher order interaction terms. Age, sex, study treatment and GFR were forced into all models. Separate models were constructed to test individual interactions with patient characteristics, renal function parameters – creatinine, BUN and GFR – and study treatment. The components of diuretic response (weight change and diuretic dose) were examined in separate models, and compared to models with diuretic response as a covariate using Harrell's C-index (higher is better), continuous net reclassification improvement (NRI) and the Akaike information criterion (AIC, lower is better). Adjusted Harrell's C-indices were obtained via internal bootstrap resampling; no confidence intervals are reported as these are unreliable without an external dataset for validation. Continuous NRI confidence intervals were obtained via internal bootstrap validation (1,000 iterations). AIC was used as an overall measure for model fit for each model pair.

The internal validity of the regression models was evaluated using the bootstrap re-sampling technique. A resampling analysis with 1,000 iterations was performed to identify variables that entered into 50% of regression models based on best fit using the AIC. A second series of 1,000 iterations was performed using only the variables retained in the first iterations in order to assess the robustness of the adjusted hazard ratios and confidence intervals in the presented multivariable analyses.

The 180-day mortality outcome was corrected for a model developed in the PROTECT study population[1] and cross-validated using models constructed using the backward elimination and bootstrap resampling method described above. This 180-day mortality model (table 3, model 2) was developed in 25 datasets created using multiple imputation of missing values. Logarithmic and linear spline transformations were applied to candidate continuous variables in one imputed data set to check for significant non-linearity. Groups of continuous predictors with strong multi-colinearity were identified. One representative variable was chosen from each group based on best predictive power. The multivariable Cox proportional hazards model was selected through backwards elimination in each imputed dataset, and variables retained in at least 20 datasets were kept. The model was validated via forward selection and bootstrap re-sampling. Finally, a simplified model using the eight best predictor variables readily available during routine patient care was selected.

The covariates for 180-day mortality models are presented in Table 4. The multivariable model for 60-day death or renal or cardiovascular rehospitalization constructed via backward elimination and bootstrap validation is adjusted for: age, sex, study treatment, edema >2+, GFR, log BUN, serum sodium, systolic and diastolic blood pressure history of percutaneous coronary intervention (PCI) and hypercholesterolemia; the 60-day heart failure rehospitalization model is adjusted for age, sex, study treatment, edema >2+, log BUN, serum sodium, and a history of PCI, cardiac resynchronization therapy and hypercholesterolemia.

## References

1. Cleland JG, Chiswell K, Teerlink JR, Stevens S, Fiuzat M, Givertz MM, Davison BA, Mansoor GA, Ponikowski P, Voors AA, Cotter G, Metra M, Massie BM, O'Connor CM. Predictors of Post-Discharge Outcomes from Information Acquired Shortly After Admission for Acute Heart Failure: A Report from the PROTECT Study. Circ Heart Fail 2013;

**Table S1** Baseline characteristics of analysed and excluded patients

| | Analyzed *(n=1745)* | Excluded *(n=288)* | P value |
|---|---|---|---|
| **Demographics** | | | |
| Sex (% Male) | 67.1 (1171) | 67 (193) | 0.971 |
| Age (years) | 70±11.4 | 71.3±12.2 | 0.089 |
| BMI (kg/m2) | 28.7±6 | 29.5±6.8 | 0.084 |
| LVEF (%) | 32.3±12.9 | 32.8±14.5 | 0.652 |
| Systolic BP (mmHg) | 124.6±17.6 | 122.6±17.8 | 0.082 |
| Diastolic BP (mmHg) | 74.1±11.7 | 71.1±12.3 | <0.001 |
| Heart Rate (beats/min) | 80.5±15.7 | 77.5±13.9 | <0.001 |
| Rolofylline (%(n)) | 66.8 (1166) | 66 (190) | 0.83 |
| **Clinical Profile** | | | |
| Orthopnea ≥ +2 (%(n)) | 96.4 (1666) | 93.4 (254) | 0.028 |
| Rales >1/3 lung fields (%(n)) | 61.7 (1074) | 56.4 (158) | 0.11 |
| Edema ≥ +2 (%(n)) | 69.2 (1207) | 60 (168) | 0.003 |
| JVP ≥ 10 cm (%(n)) | 41.5 (652) | 35.3 (90) | 0.073 |
| **Medical History** | | | |
| Hypertension (%(n)) | 80.2 (1400) | 74.7 (215) | 0.037 |
| Diabetes Mellitus (%(n)) | 45.4 (791) | 45.5 (131) | 0.982 |
| Hypercholesterolemia (%(n)) | 50.3 (877) | 61.8 (178) | <0.001 |
| Smoking (%(n)) | 19.4 (338) | 28.1 (81) | <0.001 |
| IHD (%(n)) | 70.4 (1226) | 66.3 (191) | 0.187 |
| Myocardial Infarction (%(n)) | 50 (870) | 45.6 (131) | 0.195 |
| PCI (%(n)) | 24.8 (428) | 33 (94) | 0.004 |
| CABG (%(n)) | 21.1 (364) | 25 (72) | 0.153 |
| Peripheral Vascular Disease (%(n)) | 10.9 (189) | 10.8 (31) | 0.94 |
| Atrial Fibrillation (%(n)) | 54.9 (953) | 52.8 (150) | 0.55 |
| Heart Failure (%(n)) | 95.3 (1663) | 91.7 (264) | 0.015 |
| NYHA Class | | | <0.001 |
| I-II | 16.5 (288) | 19.4 (56) | |
| III | 47.5 (829) | 53.1 (153) | |
| IV | 31.2 (544) | 19.1 (55) | |
| ICD therapy (%(n)) | 15.6 (272) | 18.4 (53) | 0.264 |
| CRT therapy (%(n)) | 9.6 (167) | 14.2 (41) | 0.021 |
| Stroke (%(n)) | 9.2 (160) | 8 (23) | 0.59 |
| COPD (%(n)) | 19.5 (339) | 21.9 (63) | 0.385 |
| **Prior Medication Use** | | | |
| ACEi or ARB (%(n)) | 75.8 (1322) | 74.9 (212) | 0.815 |
| Beta blockers (%(n)) | 76.4 (1333) | 75.3 (213) | 0.736 |
| MRAs (%(n)) | 45.2 (789) | 35.1 (99) | 0.002 |
| **Laboratory Values** | | | |
| Creatinine (mg/dL) | 1.4 [1.1-1.8] | 1.4 [1.2-1.9] | 0.042 |
| eGFR (ml/min/1.73m2) | 49 [37-64] | 47 [35-62] | 0.056 |
| Blood Urea Nitrogen (mg/dL) | 29 [22-40] | 31 [23-46] | 0.005 |
| Sodium (mmol/L) | 140 [137-142] | 139 [136-141] | 0.002 |
| Potassium (mmol/L) | 4.3 [3.9-4.7] | 4.1 [3.8-4.5] | 0.001 |
| Haemoglobin (g/dL) | 12.7±2 | 12.3±1.9 | <0.001 |
| Cholesterol (mmol/L) | 147.6±44.6 | 144.4±41.6 | 0.249 |
| BNP (mg/dL) | 1237 [818-2211] | 1456 [826-2599] | 0.149 |

Abbreviations: BMI: Body Mass Index; LVEF: Left Ventricular Ejection Fraction; BP: blood pressure; JVP: Jugular Venous Pressure; IHD: Ischemic Heart Disease; PCI: Percutaneous Coronary Intervention; CABG: Coronary Artery Bypass Graft; PVD: Peripheral vascular disease; NYHA: New York Heart Association; ICD: Internal Cardiac Defibrillator; ACEi: Angiotensin Converting Enzyme inhibitor; ARB: Aldosterone Receptor Blocker; MRA: Mineralocorticoid Receptor Antagonist; eGFR: estimated Glomerular Filtration Rate; BNP: Brain Natriuretic Peptide. Categorical variables are presented as: % (N).

**Table S2** Clinical and out-hospital outcomes of analysed and excluded patients

| | Analyzed *(n=1746)* | Excluded *(n=288)* | P-value |
|---|---|---|---|
| Weight change day 1 - 4 (kg) | -2.8±3 | -2.5±1.1 | 0.66 |
| Total diuretic dose, day 1 - 3 (mg) | 240 [140-400] | 260 [160-460] | 0.061 |
| Thiazide diuretics during admission | 19 (332) | 12.5 (36) | 0.008 |
| Inotropes during admission (%) | 6.1 (107) | 12.5 (36) | <0.001 |
| Inotropes or vasodilators during admission (%) | 16.3 (284) | 17.7 (51) | 0.544 |
| WRF, day 7 (%(n)) | 21.6 (365) | 27.6 (67) | 0.044 |
| WRF, day 14 (%(n)) | 23.4 (396) | 24.6 (60) | 0.74 |
| Primary Endpoint (%(n)) | | | 0.003 |
| Failure | 19.9 (348) | 28.5 (82) | |
| No Change | 45.4 (793) | 37.8 (109) | |
| Success | 34.6 (604) | 33.7 (97) | |
| Treatment failure due to Death (%(n)) | 0.7 (12) | 8.7 (25) | <0.001 |
| Treatment failure due to Worsening Heart Failure (%(n)) | 9.3 (162) | 10.6 (27) | 0.582 |
| Treatment failure due to WRF (%(n)) | 12 (203) | 18.6 (44) | 0.006 |
| Treatment Failure due to HF rehospitalisation (%(n)) | 0.2 (4) | 1.7 (5) | 0.002 |
| Hemoconcentration on day 4 (%(n)) | 59.2 (771) | 58.3 (35) | 0.999 |
| 180-day mortality (%(n)) | 16.3 | 25.7 | <0.001 |
| 60-day Heart Failure Rehospitalization (%(n)) | 14.8 | 16 | 0.683 |
| 60-day Death or Renal or Cardiovascular Rehospitalization (%(n)) | 27.3 | 36.5 | 0.002 |

Unadjusted incidence rates are reported
Abbreviations: WRF: Worsening Renal Function; HF: Heart Failure
Worsening renal function = 0.3 mg/dL rise in creatinine compared to baseline

**Table S3** Baseline characteristics per quintile of diuretic response – Placebo group

| Diuretic Response (kg/40mg furosemide) | -1.33 [-1.95 to 0.07] *(n=116)* | -0.70 [-0.80 to -0.60] *(n=116)* | -0.38 [-0.44 to -0.33] *(n=115)* | -0.18 [-0.24 to -0.13] *(n=116)* | 0.00 [-0.04 to 0.18] *(n=116)* | P-trend |
|---|---|---|---|---|---|---|
| **Demographics** | | | | | | |
| Sex (% Male) | 68.1 (79) | 67.2 (78) | 64.3 (74) | 73.3 (85) | 65.5 (76) | 0.950 |
| Age (years) | 70.1±12.1 | 68.7±11.5 | 72.4±10.5 | 69.7±11.3 | 69.6±11 | 0.988 |
| BMI (kg/m2) | 28.8±6.7 | 28.4±5.8 | 28.9±6.3 | 28.6±5.6 | 28.5±6.1 | 0.812 |
| LVEF (%) | 33.8±13 | 32±12.8 | 32.6±11.8 | 31.5±14.8 | 32.8±13.2 | 0.668 |
| Systolic BP (mmHg) | 127.8±14.8 | 126.4±18.6 | 124.4±16.4 | 122.5±18.3 | 123.4±18.8 | 0.013 |
| Diastolic BP (mmHg) | 76.9±10.5 | 74.9±11.3 | 74.7±10.9 | 74.1±12.3 | 72.6±13.2 | 0.006 |
| Heart Rate (beats/min) | 84.1±18.3 | 81.7±15.1 | 80.8±15.4 | 78.3±14.9 | 80±15.8 | 0.013 |
| **Clinical Profile** | | | | | | |
| Orthopnea ≥+2 (%(n)) | 95.7 (110) | 97.4 (111) | 96.5 (110) | 98.3 (114) | 98.2 (112) | 0.210 |
| Rales >1/3 lung fields (%(n)) | 66.4 (77) | 48.2 (55) | 59.1 (68) | 60.3 (70) | 63.8 (74) | 0.640 |
| Edema ≥+2 (%(n)) | 75.9 (88) | 69.8 (81) | 70.4 (81) | 68.1 (79) | 59.5 (69) | 0.011 |
| JVP ≥10 cm (%(n)) | 44.6 (45) | 42.6 (43) | 36.4 (39) | 38.2 (39) | 44.8 (47) | 0.814 |
| **Medical History** | | | | | | |
| Hypertension (%(n)) | 82.8 (96) | 81 (94) | 78.3 (90) | 76.7 (89) | 76.7 (89) | 0.170 |
| Diabetes Mellitus (%(n)) | 33.6 (39) | 44 (51) | 45.2 (52) | 53.4 (62) | 50 (58) | 0.004 |
| Hypercholesterolemia (%(n)) | 42.2 (49) | 44 (51) | 48.2 (55) | 62.1 (72) | 60.3 (70) | <0.001 |
| Smoking (%(n)) | 16.5 (19) | 12.9 (15) | 19.1 (22) | 19 (22) | 19 (22) | 0.325 |
| IHD (%(n)) | 62.1 (72) | 62.6 (72) | 71.3 (82) | 69 (80) | 75.9 (88) | 0.013 |
| Myocardial Infarction (%(n)) | 40.5 (47) | 40 (46) | 47.8 (55) | 50.9 (59) | 56 (65) | 0.004 |
| PCI (%(n)) | 14 (16) | 18.6 (21) | 22.1 (25) | 33.6 (39) | 32.8 (38) | <0.001 |
| CABG (%(n)) | 9.7 (11) | 15.8 (18) | 19.5 (22) | 25.9 (30) | 31.9 (37) | <0.001 |
| PVD (%(n)) | 8.6 (10) | 7.8 (9) | 9.6 (11) | 10.3 (12) | 7.8 (9) | 0.903 |
| Atrial Fibrillation (%(n)) | 59.1 (68) | 54.4 (62) | 57.9 (66) | 64 (73) | 55.2 (64) | 0.913 |
| NYHA Class (%(n)) | | | | | | 0.837 |
| I-II | 19 (22) | 20.7 (24) | 17.4 (20) | 18.1 (21) | 17.2 (20) | |
| III | 44.8 (52) | 47.4 (55) | 42.6 (49) | 55.2 (64) | 43.1 (50) | |
| IV | 31.9 (37) | 27.6 (32) | 35.7 (41) | 24.1 (28) | 31 (36) | |
| ICD therapy (%(n)) | 6 (7) | 12.9 (15) | 11.4 (13) | 23.3 (27) | 22.4 (26) | <0.001 |
| CRT therapy (%(n)) | 3.4 (4) | 5.2 (6) | 12.4 (14) | 16.4 (19) | 10.3 (12) | 0.004 |
| Stroke (%(n)) | 7.8 (9) | 7.8 (9) | 12.2 (14) | 7.8 (9) | 9.5 (11) | 0.681 |
| COPD (%(n)) | 19.8 (23) | 13.8 (16) | 15.9 (18) | 22.4 (26) | 24.1 (28) | 0.136 |

| Diuretic Response (kg/40mg furosemide) | -1.33 [-1.95 to 0.07] *(n=116)* | -0.70 [-0.80 to -0.60] *(n=116)* | -0.38 [-0.44 to -0.33] *(n=115)* | -0.18 [-0.24 to -0.13] *(n=116)* | 0.00 [-0.04 to 0.18] *(n=116)* | P-trend |
|---|---|---|---|---|---|---|
| **Prior medication use** | | | | | | |
| ACEi or ARB (%(n)) | 72.4 (84) | 79.3 (92) | 73.9 (85) | 71.6 (83) | 75.9 (88) | 0.946 |
| Beta blockers (%(n)) | 63.8 (74) | 65.5 (76) | 81.7 (94) | 85.3 (99) | 84.5 (98) | <0.001 |
| MRAs (%(n)) | 42.2 (49) | 44.8 (52) | 38.3 (44) | 47.4 (55) | 40.5 (47) | 0.953 |
| **Laboratory Values** | | | | | | |
| Creatinine (mg/dL) | 1.3 [1.1-1.6] | 1.2 [1-1.6] | 1.4 [1.1-1.7] | 1.4 [1.2-1.9] | 1.4 [1.2-1.8] | 0.001 |
| eGFR (ml/min/1.73m2) | 46.3 [44.3-69.5] | 55.5 [45.3-65.6] | 63.8 [60.4-67.3] | 45.9 [35.2-61.3] | 33.2 [22.7-53.8] | <0.001 |
| Blood Urea Nitrogen (mg/dL) | 25 [20-33] | 25 [20-37.5] | 29 [22-41.2] | 35 [26-46] | 31.5 [22.8-44] | <0.001 |
| Sodium (mmol/L) | 140.5 [138-143] | 140 [138-143] | 140 [137-143] | 139 [136-142] | 138.5 [135-141] | <0.001 |
| Potassium (mmol/L) | 4.4 [4.1-4.7] | 4.2 [3.9-4.6] | 4.2 [3.8-4.6] | 4.2 [3.9-4.6] | 4.2 [3.8-4.6] | 0.042 |
| Haemoglobin (g/dL) | 12.9±1.7 | 12.8±2.1 | 12.6±1.8 | 12.6±1.9 | 12.7±1.9 | 0.276 |
| Cholesterol (mmol/L) | 149.5±39.9 | 153.8±47.7 | 146±48.6 | 143.8±43 | 152.4±42.6 | 0.749 |
| BNP (mg/dL) | 1051 [733-2541] | 1249 [978-2087] | 1596 [1007-2280] | 1064 [819-2147] | 1157 [772-1925] | 0.789 |

Abbreviations: see Table S1

**Table S4** Baseline characteristics per quintile of diuretic response – congested patients*

| Diuretic Response (kg/40mg furosemide) | -1.33 [-1.95 to 0.07] *(n=274)* | -0.70 [-0.80 to -0.60] *(n=273)* | -0.38 [-0.44 to -0.33] *(n=275)* | -0.18 [-0.24 to -0.13] *(n=273)* | 0.00 [-0.04 to 0.18] *(n=273)* | P-trend |
|---|---|---|---|---|---|---|
| **Demographics** | | | | | | |
| Sex (% Male) | 67.5 (185) | 64.8 (177) | 59.3 (163) | 72.2 (197) | 65.6 (179) | 0.707 |
| Age (years) | 70.9±11.3 | 69.8±11.5 | 71.2±10.7 | 70±11.2 | 69.8±12 | 0.356 |
| BMI (kg/m2) | 29.3±6.3 | 29±6 | 29.1±5.8 | 29±5.8 | 28.8±5.9 | 0.451 |
| LVEF (%) | 34.3±12.3 | 33.1±13 | 33.7±13 | 28.5±12.9 | 32.9±14.4 | 0.045 |
| Systolic BP (mmHg) | 128.9±15.9 | 127.7±17 | 125.5±16.5 | 122.4±18.4 | 122.5±18.4 | <0.001 |
| Diastolic BP (mmHg) | 77.8±11.5 | 75.6±11.8 | 74.3±10.6 | 73±11.1 | 72.1±12.1 | <0.001 |
| Heart Rate (beats/min) | 83.9±17.4 | 79.9±15.3 | 80.5±15.5 | 80.5±15.6 | 79.9±15.7 | 0.016 |
| Rolofylline (%(n)) | 74.1 (203) | 63.7 (174) | 65.8 (181) | 66.7 (182) | 64.8 (177) | 0.083 |
| **Clinical Profile** | | | | | | |
| Orthopnea ≥ +2 (%(n)) | 97 (261) | 98.5 (265) | 96.7 (263) | 96.7 (264) | 95.9 (260) | 0.227 |
| Rales >1/3 lung fields (%(n)) | 66.8 (183) | 64.5 (176) | 61.1 (168) | 70.3 (192) | 63 (172) | 0.850 |
| Edema ≥ +2 (%(n)) | 79.2 (217) | 81.3 (222) | 77.8 (214) | 82.1 (224) | 74.4 (203) | 0.252 |
| JVP ≥ 10 cm (%(n)) | 46.6 (111) | 41.2 (98) | 37.1 (93) | 43 (108) | 41.9 (106) | 0.461 |
| **Medical History** | | | | | | |
| Hypertension (%(n)) | 82.5 (226) | 83.2 (227) | 80.4 (221) | 79.5 (217) | 78.4 (214) | 0.116 |
| Diabetes Mellitus (%(n)) | 34.3 (94) | 41 (112) | 48.4 (133) | 56.8 (155) | 53.7 (146) | <0.001 |
| Hypercholesterolemia (%(n)) | 38.7 (106) | 45.1 (123) | 47.4 (130) | 54.9 (150) | 57.1 (156) | <0.001 |
| Smoking (%(n)) | 14.2 (39) | 16.2 (44) | 18.5 (51) | 23.2 (63) | 24.2 (66) | <0.001 |
| IHD (%(n)) | 66.8 (183) | 71 (193) | 70.1 (192) | 73.5 (200) | 73.3 (200) | 0.074 |
| Myocardial Infarction (%(n)) | 51.1 (140) | 42.8 (116) | 44.5 (122) | 53.7 (146) | 52.4 (143) | 0.162 |
| PCI (%(n)) | 13 (35) | 20.4 (55) | 20.6 (56) | 32.6 (88) | 30.5 (83) | <0.001 |
| CABG (%(n)) | 10 (27) | 15.9 (43) | 21.6 (59) | 24.1 (65) | 27.1 (74) | <0.001 |
| Peripheral Vascular Disease (%(n)) | 9.5 (26) | 9.5 (26) | 9.8 (27) | 13.2 (36) | 13.2 (36) | 0.064 |
| Atrial Fibrillation (%(n)) | 62.3 (170) | 57.4 (155) | 54.7 (150) | 52.6 (143) | 56.1 (152) | 0.070 |
| NYHA Class | | | | | | 0.004 |
| I-II | 13.5 (37) | 16.5 (45) | 17.1 (47) | 17.9 (49) | 16.5 (45) | |
| III | 45.3 (124) | 41.8 (114) | 42.5 (117) | 51.3 (140) | 50.2 (137) | |
| IV | 36.1 (99) | 38.5 (105) | 36.4 (100) | 26.4 (72) | 26.4 (72) | |
| ICD therapy (%(n)) | 7.7 (21) | 9.9 (27) | 13.9 (38) | 17.6 (48) | 22.7 (62) | <0.001 |
| CRT therapy (%(n)) | 4.4 (12) | 7.7 (21) | 8.8 (24) | 13.2 (36) | 11.4 (31) | <0.001 |
| Stroke (%(n)) | 9.5 (26) | 8.8 (24) | 9.1 (25) | 9.5 (26) | 9.2 (25) | 0.990 |
| COPD (%(n)) | 16.8 (46) | 18.8 (51) | 20.5 (56) | 21.7 (59) | 22 (60) | 0.081 |

| Diuretic Response (kg/40mg furosemide) | -1.33 [-1.95 to 0.07] *(n=274)* | -0.70 [-0.80 to -0.60] *(n=273)* | -0.38 [-0.44 to -0.33] *(n=275)* | -0.18 [-0.24 to -0.13] *(n=273)* | 0.00 [-0.04 to 0.18] *(n=273)* | P-trend |
|---|---|---|---|---|---|---|
| **Prior Medication Use** | | | | | | |
| ACEi or ARB (%(n)) | 74.1 (203) | 79.1 (216) | 76.4 (210) | 73.6 (201) | 73.3 (200) | 0.387 |
| Beta blockers (%(n)) | 66.1 (181) | 70.3 (192) | 77.1 (212) | 81.7 (223) | 83.2 (227) | <0.001 |
| MRAs (%(n)) | 48.5 (133) | 40.3 (110) | 47.3 (130) | 44 (120) | 45.1 (123) | 0.726 |
| **Laboratory Values** | | | | | | |
| Creatinine (mg/dL) | 1.3 [1.1-1.5] | 1.3 [1.1-1.7] | 1.3 [1.1-1.7] | 1.5 [1.2-1.9] | 1.5 [1.2-1.9] | <0.001 |
| eGFR (ml/min/1.73m2) | 54.5 [41.9-67] | 53.4 [38.6-66.9] | 48.2 [37.7-66.3] | 47.4 [34.6-58.6] | 44.1 [32.8-59.8] | <0.001 |
| Blood Urea Nitrogen (mg/dL) | 26 [20-33] | 28 [21-37] | 27 [21-39.2] | 35 [26-47] | 33 [24-46] | <0.001 |
| Sodium (mmol/L) | 141 [138-143] | 140 [137-143] | 141 [138-143] | 139 [136-142] | 139 [136-141] | <0.001 |
| Potassium (mmol/L) | 4.3 [3.9-4.7] | 4.3 [4-4.8] | 4.3 [3.8-4.7] | 4.3 [3.9-4.6] | 4.1 [3.8-4.5] | 0.001 |
| Haemoglobin (g/dL) | 13.1±2 | 12.7±2 | 12.8±1.9 | 12.5±2 | 12.5±1.9 | <0.001 |
| Cholesterol (mmol/L) | 150.9±40.9 | 149.2±45.9 | 152.3±48.4 | 143.3±43.3 | 141.3±43.4 | 0.004 |
| BNP (mg/dL) | 1483 [830-2801] | 1009 [659-1413] | 1130 [735-2287] | 1297 [761-2231] | 1340 [859-2208] | 0.623 |

* Patients with rales and oedema at baseline, and who did not receive Inotropes during admission on days 1-4
Abbreviations: see Table S1

**Table S5** Baseline characteristics per quintile of diuretic response–congested patients not on inotropes or vasodilators*

| Diuretic Response (kg/40mg furosemide) | -1.33 [-1.95 to 0.07] *(n=239)* | -0.70 [-0.80 to -0.60] *(n=238)* | -0.38 [-0.44 to -0.33] *(n=238)* | -0.18 [-0.24 to -0.13] *(n=238)* | 0.00 [-0.04 to 0.18] *(n=239)* | P-trend |
|---|---|---|---|---|---|---|
| **Demographics** | | | | | | |
| Sex (% Male) | 68.2 (163) | 65.5 (156) | 57.1 (136) | 74.4 (177) | 67.4 (161) | 0.461 |
| Age (years) | 70.9±11.5 | 69.5±11.8 | 71.5±10.6 | 69.7±11.4 | 69.7±12.3 | 0.350 |
| BMI (kg/m2) | 29±6.3 | 29.2±6.3 | 29.1±5.9 | 29.3±5.8 | 28.9±6 | 0.935 |
| LVEF (%) | 34.1±12.5 | 33.1±13.1 | 34.5±13 | 28±12.8 | 32.6±14.7 | 0.035 |
| Systolic BP (mmHg) | 127.9±15.2 | 126.8±17.2 | 125.5±16.4 | 122.3±18.5 | 122.3±18.2 | <0.001 |
| Diastolic BP (mmHg) | 77.8±11.1 | 75.5±11.9 | 74±10.8 | 72.9±10.9 | 72.1±11.6 | <0.001 |
| Heart Rate (beats/min) | 84±17.6 | 80±15.1 | 79.5±14.5 | 79.3±14.8 | 79.2±15.2 | 0.001 |
| Rolofylline (%(n)) | 72.8 (174) | 63 (150) | 66.8 (159) | 66.8 (159) | 64 (153) | 0.152 |
| **Clinical Profile** | | | | | | |
| Orthopnea ≥ +2 (%(n)) | 96.6 (226) | 98.3 (230) | 97.4 (229) | 96.6 (230) | 95.8 (227) | 0.357 |
| Rales >1/3 lung fields (%(n)) | 68.2 (163) | 63.9 (152) | 61.3 (146) | 68.9 (164) | 62.3 (149) | 0.493 |
| Edema ≥ +2 (%(n)) | 77.8 (186) | 81.5 (194) | 78.2 (186) | 81.9 (195) | 73.2 (175) | 0.295 |
| JVP ≥ 10 cm (%(n)) | 48.5 (100) | 41.5 (85) | 34.9 (76) | 43.6 (96) | 40.9 (90) | 0.236 |
| **Medical History** | | | | | | |
| Hypertension (%(n)) | 81.2 (194) | 81.9 (195) | 79 (188) | 79 (188) | 77.4 (185) | 0.203 |
| Diabetes Mellitus (%(n)) | 33.5 (80) | 39.5 (94) | 47.5 (113) | 57.6 (137) | 52.5 (125) | <0.001 |
| Hypercholesterolemia (%(n)) | 38.9 (93) | 46.6 (111) | 46.4 (110) | 55.9 (133) | 58.6 (140) | <0.001 |
| Smoking (%(n)) | 13 (31) | 17.7 (42) | 18.5 (44) | 22.8 (54) | 25.5 (61) | <0.001 |
| IHD (%(n)) | 66.5 (159) | 71 (169) | 70.9 (168) | 72.2 (171) | 72 (172) | 0.198 |
| Myocardial Infarction (%(n)) | 51.5 (123) | 43 (102) | 42.2 (100) | 51.5 (122) | 51 (122) | 0.461 |
| PCI (%(n)) | 13.1 (31) | 21.1 (50) | 21.3 (50) | 33.6 (79) | 31.9 (76) | <0.001 |
| CABG (%(n)) | 9.3 (22) | 16.9 (40) | 22.5 (53) | 25.5 (60) | 26.8 (64) | <0.001 |
| Peripheral Vascular Disease (%(n)) | 10.1 (24) | 9.2 (22) | 9.7 (23) | 13.1 (31) | 12.6 (30) | 0.165 |
| Atrial Fibrillation (%(n)) | 61.8 (147) | 57.9 (136) | 57 (135) | 51.5 (122) | 55.3 (131) | 0.057 |
| NYHA Class | | | | | | 0.002 |
| I-II | 13.8 (33) | 14.3 (34) | 17.2 (41) | 19.3 (46) | 16.7 (40) | |
| III | 46.9 (112) | 45 (107) | 43.7 (104) | 51.7 (123) | 52.7 (126) | |
| IV | 34.3 (82) | 38.2 (91) | 35.7 (85) | 23.9 (57) | 24.7 (59) | |
| ICD therapy (%(n)) | 7.5 (18) | 10.5 (25) | 14.3 (34) | 16.4 (39) | 24.3 (58) | <0.001 |
| CRT therapy (%(n)) | 4.6 (11) | 7.6 (18) | 8.9 (21) | 13 (31) | 13 (31) | <0.001 |
| Stroke (%(n)) | 9.6 (23) | 8.4 (20) | 8.8 (21) | 9.2 (22) | 8.8 (21) | 0.886 |
| COPD (%(n)) | 15.1 (36) | 17.7 (42) | 20.7 (49) | 20.3 (48) | 21.8 (52) | 0.048 |

| Diuretic Response (kg/40mg furosemide) | -1.33 [-1.95 to 0.07] *(n=239)* | -0.70 [-0.80 to -0.60] *(n=238)* | -0.38 [-0.44 to -0.33] *(n=238)* | -0.18 [-0.24 to -0.13] *(n=238)* | 0.00 [-0.04 to 0.18] *(n=239)* | P-trend |
|---|---|---|---|---|---|---|
| **Prior Medication Use** | | | | | | |
| ACEi or ARB (%(n)) | 75.3 (180) | 79.8 (190) | 76.9 (183) | 74.4 (177) | 73.2 (175) | 0.271 |
| Beta blockers (%(n)) | 65.7 (157) | 71 (169) | 78.6 (187) | 83.2 (198) | 84.1 (201) | <0.001 |
| MRAs (%(n)) | 49 (117) | 42 (100) | 47.1 (112) | 45.4 (108) | 43.5 (104) | 0.459 |
| **Laboratory Values** | | | | | | |
| Creatinine (mg/dL) | 1.3 [1.1-1.6] | 1.3 [1.1-1.7] | 1.4 [1.1-1.7] | 1.5 [1.2-1.9] | 1.5 [1.2-1.9] | <0.001 |
| eGFR (ml/min/1.73m2) | 54.8 [41.9-67.1] | 53 [38.2-67.4] | 47.1 [36.4-65.6] | 47.2 [34.7-58] | 44.8 [32.2-59.9] | <0.001 |
| Blood Urea Nitrogen (mg/dL) | 26 [20-33] | 28 [21-37.2] | 28 [22-40] | 35 [26-46] | 34 [24-46] | <0.001 |
| Sodium (mmol/L) | 140 [138-143] | 140 [137-142.2] | 141 [137.5-143] | 139 [136-142] | 139 [136-142] | <0.001 |
| Potassium (mmol/L) | 4.4 [4-4.7] | 4.3 [4-4.8] | 4.3 [3.9-4.7] | 4.2 [3.9-4.6] | 4.1 [3.8-4.5] | <0.001 |
| Haemoglobin (g/dL) | 13.1±2 | 12.7±2 | 12.8±1.9 | 12.5±1.9 | 12.6±1.8 | 0.002 |
| Cholesterol (mmol/L) | 149.9±41.9 | 148.9±46.2 | 151.5±47.2 | 142.2±42.6 | 141±42.2 | 0.008 |
| BNP (mg/dL) | 1444 [821-2580] | 1001 [673-1328] | 1145 [793-2372.5] | 1319 [825-2212] | 1296 [850-2056] | 0.409 |

* Patients with rales and oedema at baseline, and who did not receive Inotropes or vasodilators on days 1-4
Abbreviations: see Table S1

**Table S6** Baseline characteristics in placebo and rolofylline groups

| Study treatment | | Placebo *(n=579)* | Rolofylline *(n=1166)* | P-value |
|---|---|---|---|---|
| **Demographics** | | | | |
| Sex (% Male) | | 67.7 (392) | 66.8 (779) | 0.749 |
| Age (years) | | 70.1±11.3 | 69.9±11.5 | 0.763 |
| BMI (kg/m2) | | 28.6±6.1 | 28.8±6 | 0.654 |
| LVEF (%) | | 32.5±13.1 | 32.1±12.8 | 0.715 |
| Systolic BP (mmHg) | | 124.9±17.5 | 124.4±17.6 | 0.574 |
| Diastolic BP (mmHg) | | 74.6±11.7 | 73.9±11.7 | 0.206 |
| Heart Rate (beats/min) | | 81±16 | 80.3±15.5 | 0.401 |
| **Clinical Profile** | | | | |
| Orthopnea ≥+2 (%(n)) | | 97.2 (557) | 96 (1109) | 0.265 |
| Rales >1/3 lung fields (%(n)) | | 59.6 (344) | 62.7 (730) | 0.239 |
| Edema ≥+2 (%(n)) | | 68.7 (398) | 69.4 (809) | 0.827 |
| JVP ≥10 cm (%(n)) | | 41.3 (213) | 41.6 (439) | 0.955 |
| **Medical History** | | | | |
| Hypertension (%(n)) | | 79.1 (458) | 80.8 (942) | 0.442 |
| Diabetes Mellitus (%(n)) | | 45.3 (262) | 45.4 (529) | 0.991 |
| Hypercholesterolemia (%(n)) | | 51.4 (297) | 49.7 (580) | 0.552 |
| Smoking (%(n)) | | 17.3 (100) | 20.5 (238) | 0.132 |
| IHD (%(n)) | | 68.2 (394) | 71.5 (832) | 0.171 |
| Myocardial Infarction (%(n)) | | 47.1 (272) | 51.4 (598) | 0.096 |
| PCI (%(n)) | | 24.3 (139) | 25 (289) | 0.797 |
| CABG (%(n)) | | 20.6 (118) | 21.3 (246) | 0.81 |
| PVD (%(n)) | | 8.8 (51) | 11.9 (138) | 0.068 |
| Atrial Fibrillation (%(n)) | | 58.1 (333) | 53.4 (620) | 0.068 |
| NYHA Class (%(n)) | | | | 0.281 |
| | I-II | 18.5 (107) | 15.5 (181) | |
| | III | 46.6 (270) | 47.9 (559) | |
| | IV | 30.1 (174) | 31.7 (370) | |
| ICD therapy (%(n)) | | 15.2 (88) | 15.8 (184) | 0.817 |
| CRT therapy (%(n)) | | 9.5 (55) | 9.6 (112) | 0.97 |
| Stroke (%(n)) | | 9 (52) | 9.3 (108) | 0.917 |
| COPD (%(n)) | | 19.2 (111) | 19.6 (228) | 0.913 |
| **Prior medication use** | | | | |
| ACEi or ARB (%(n)) | | 74.6 (432) | 76.3 (890) | 0.466 |
| Beta blockers (%(n)) | | 76.2 (441) | 76.5 (892) | 0.924 |
| MRAs (%(n)) | | 42.7 (247) | 46.5 (542) | 0.144 |
| **Laboratory Values** | | | | |
| Creatinine (mg/dL) | | 1.3 [1.1-1.7] | 1.4 [1.1-1.8] | 0.268 |
| eGFR (ml/min/1.73m2) | | 46.1 [36.2-70.4] | 55.5 [36.5-65.5] | 0.619 |
| Blood Urea Nitrogen (mg/dL) | | 28 [21-40] | 29 [22-41] | 0.321 |
| Sodium (mmol/L) | | 140 [137-142] | 140 [137-142] | 0.393 |
| Potassium (mmol/L) | | 4.3 [3.9-4.6] | 4.3 [3.9-4.7] | 0.814 |
| Haemoglobin (g/dL) | | 12.7±1.9 | 12.8±2 | 0.519 |
| Cholesterol (mmol/L) | | 149.1±44.5 | 146.9±44.7 | 0.335 |
| BNP (mg/dL) | | 1190 [837-2203] | 1248 [816-2217] | 0.836 |

Abbreviations: see Table S1

**Table S7** Clinical and out-hospital outcomes per quintile of diuretic response – Placebo group

| Diuretic Response (kg/40mg furosemide) | -1.33 [-1.95 to 0.07] *(n=116)* | -0.70 [-0.80 to -0.60] *(n=116)* | -0.38 [-0.44 to -0.33] *(n=115)* | -0.18 [-0.24 to -0.13] *(n=116)* | 0.00 [-0.04 to 0.18] *(n=116)* | P-trend |
|---|---|---|---|---|---|---|
| Weight change day 1 - 4 (kg) | -5.1±2.7 | -3.6±1.9 | -3±1.9 | -2±1.3 | 0.8±2 | <0.001 |
| Total diuretic dose, day 1-3 (mg) | 140 [100-200] | 200 [140-280] | 280 [180-447] | 428 [260-615] | 315 [180-540] | <0.001 |
| Thiazide diuretics during admission | 14.7 (17) | 16.4 (19) | 17.4 (20) | 23.3 (27) | 25 (29) | 0.017 |
| Inotropes during admission (%) | 0 (0) | 0.9 (1) | 5.2 (6) | 10.3 (12) | 12.1 (14) | <0.001 |
| Inotropes or vasodilators during admission (%) | 11.2 (13) | 9.5 (11) | 18.3 (21) | 19.8 (23) | 19 (22) | 0.015 |
| WRF, day 7 (%(n)) | 17.9 (20) | 14.4 (16) | 17 (19) | 23 (26) | 25 (28) | 0.053 |
| WRF, day 14 (%(n)) | 18.8 (21) | 23.4 (26) | 19.6 (22) | 23.9 (27) | 25.9 (29) | 0.236 |
| Primary Endpoint (%(n)) | | | | | | 0.007 |
| Failure | 11.2 (13) | 16.4 (19) | 11.3 (13) | 26.7 (31) | 25 (29) | |
| No Change | 48.3 (56) | 44 (51) | 51.3 (59) | 40.5 (47) | 44.8 (52) | |
| Success | 40.5 (47) | 39.7 (46) | 37.4 (43) | 32.8 (38) | 30.2 (35) | |
| Treatment failure due to Death (%(n)) | 0 (0) | 0.9 (1) | 0 (0) | 0.9 (1) | 0.9 (1) | 0.413 |
| Treatment failure due to Worsening Heart Failure (%(n)) | 1.7 (2) | 5.2 (6) | 7.8 (9) | 15.5 (18) | 16.4 (19) | <0.001 |
| Treatment failure due to WRF (%(n)) | 10.7 (12) | 10.8 (12) | 6.2 (7) | 15 (17) | 12.6 (14) | 0.391 |
| Treatment Failure due to HF rehospitalisation (%(n)) | 0 (0) | 0 (0) | 0.9 (1) | 0.9 (1) | 0 (0) | 0.617 |
| Hemoconcentration on day 4 (%(n)) | 65 (52) | 61.4 (54) | 62.1 (54) | 60 (57) | 46.1 (41) | 0.019 |
| 180-day mortality (%(n)) | 6 (7) | 12.1 (14) | 12.2 (14) | 19.8 (23) | 27.6 (32) | <0.001 |
| 60-day Heart Failure Rehospitalization (%(n)) | 5.2 (6) | 7.8 (9) | 16.5 (19) | 17.2 (20) | 22.4 (26) | <0.001 |
| 60-day Death, Renal or CV Rehospitalization (%(n)) | 12.9 (15) | 19 (22) | 30.4 (35) | 33.6 (39) | 39.7 (46) | <0.001 |

Unadjusted incidence rates are reported. Abbreviations: see Table S3

**Table S8** Clinical and out-hospital outcomes per quintile of diuretic response – congested patients*

| Diuretic Response (kg/40mg furosemide) | -1.33 [-1.95 to 0.07] *(n=274)* | -0.70 [-0.80 to -0.60] *(n=273)* | -0.38 [-0.44 to -0.33] *(n=275)* | -0.18 [-0.24 to -0.13] *(n=273)* | 0.00 [-0.04 to 0.18] *(n=273)* | P-trend** |
|---|---|---|---|---|---|---|
| Weight change day 1 - 4 (kg) | -5.7±2.9 | -3.9±1.9 | -2.8±1.7 | -2.2±1.6 | 0.4±2.1 | <0.001 |
| Total diuretic dose, day 1 - 3 (mg) | 138.1 [100-180] | 200 [140-280] | 240 [160-360] | 360 [240-580] | 348 [190-642] | <0.001 |
| Thiazide diuretics during admission | 17.2 (47) | 20.1 (55) | 15.3 (42) | 23.1 (63) | 22.3 (61) | 0.08 |
| Inotropes during admission (%) | 2.2 (6) | 1.8 (5) | 4.4 (12) | 8.4 (23) | 15.4 (42) | <0.001 |
| Inotropes or vasodilators during admission (%) | 14.2 (39) | 13.2 (36) | 14.9 (41) | 18.3 (50) | 23.1 (63) | 0.001 |
| WRF, day 7 (%) | 22.7 (61) | 16.3 (43) | 17.2 (46) | 22.8 (60) | 24.7 (65) | 0.185 |
| WRF, day 14 (%) | 20.8 (56) | 20.1 (53) | 22.4 (60) | 24.2 (64) | 28.9 (76) | 0.013 |
| Trichotomous Endpoint (%) | | | | | | <0.001 |
| Failure | 13.5 (37) | 13.6 (37) | 14.5 (40) | 23.8 (65) | 33.3 (91) | |
| No Change | 36.5 (100) | 42.9 (117) | 47.3 (130) | 41.4 (113) | 40.3 (110) | |
| Success | 50 (137) | 43.6 (119) | 38.2 (105) | 34.8 (95) | 26.4 (72) | |
| Treatment failure due to Death (%) | 0.4 (1) | 1.1 (3) | 0.4 (1) | 1.1 (3) | 1.5 (4) | 0.217 |
| Treatment failure due to Worsening Heart Failure (%) | 3.3 (9) | 4.4 (12) | 4.7 (13) | 13.6 (37) | 20.9 (57) | <0.001 |
| Treatment failure due to WRF (%) | 11.2 (30) | 9.1 (24) | 9.7 (26) | 13.4 (35) | 15 (39) | 0.059 |
| Treatment Failure due to HF rehospitalisation (%) | 0.4 (1) | 0 (0) | 0.4 (1) | 0 (0) | 0.4 (1) | 0.999 |
| Hemoconcentration on day 4 (%) | 65.2 (118) | 65.2 (133) | 61.4 (132) | 50 (104) | 48.5 (96) | <0.001 |
| 180-day mortality (%) | 6.9 (19) | 11.7 (32) | 14.5 (40) | 20.1 (55) | 23.4 (64) | <0.001 |
| 60-day Heart Failure Rehospitalization (%) | 7.7 (21) | 7 (19) | 14.5 (40) | 17.9 (49) | 23.1 (63) | <0.001 |
| 60-day Death or Heart Failure Rehospitalization (%) | 9.9 (27) | 12.1 (33) | 18.2 (50) | 24.9 (68) | 30 (82) | <0.001 |
| 60-day Death or Renal or Cardiovascular Rehospitalization (%) | 15.3 (42) | 17.2 (47) | 26.5 (73) | 33 (90) | 37.7 (103) | <0.001 |

Unadjusted incidence rates are reported
* Patients with rales and oedema at baseline
** P for trend across quintiles (linear regression)
Abbreviations: see Table S3

**Table S9** Clinical and out-hospital outcomes per quintile of diuretic response – congested patients not on Inotropes or vasodilators*

| Diuretic Response (kg/40mg furosemide) | -1.33 [-1.95 to 0.07] *(n=239)* | -0.70 [-0.80 to -0.60] *(n=238)* | -0.38 [-0.44 to -0.33] *(n=238)* | -0.18 [-0.24 to -0.13] *(n=238)* | 0.00 [-0.04 to 0.18] *(n=239)* | P-trend** |
|---|---|---|---|---|---|---|
| Weight change day 1 - 4 (kg) | -5.6±2.9 | -4±2 | -2.8±1.7 | -2.2±1.7 | 0.3±1.9 | <0.001 |
| Total diuretic dose, day 1 - 3 (mg) | 130 [100-180] | 200 [140-280] | 240 [150-360] | 344 [220-579] | 350 [190-725] | <0.001 |
| Thiazide diuretics during admission | 17.2 (41) | 21.4 (51) | 15.5 (37) | 23.5 (56) | 23.4 (56) | 0.075 |
| Inotropes during admission (%) | 1.7 (4) | 1.3 (3) | 2.1 (5) | 4.2 (10) | 9.6 (23) | <0.001 |
| Inotropes or vasodilators during admission (%) | 2.9 (7) | 1.7 (4) | 2.1 (5) | 5 (12) | 10.5 (25) | <0.001 |
| WRF, day 7 (%) | 23.4 (55) | 15.2 (35) | 15.2 (35) | 24.6 (56) | 23.8 (55) | 0.236 |
| WRF, day 14 (%) | 21.3 (50) | 21.7 (50) | 22.6 (52) | 26.2 (60) | 28.6 (66) | 0.032 |
| Trichotomous Endpoint (%) | | | | | | <0.001 |
| Failure | 13.4 (32) | 13 (31) | 13.4 (32) | 23.1 (55) | 32.6 (78) | |
| No Change | 37.7 (90) | 45.4 (108) | 48.3 (115) | 39.9 (95) | 38.1 (91) | |
| Success | 49 (117) | 41.6 (99) | 38.2 (91) | 37 (88) | 29.3 (70) | |
| Treatment failure due to Death (%) | 0.4 (1) | 0.8 (2) | 0.4 (1) | 1.3 (3) | 1.3 (3) | 0.262 |
| Treatment failure due to Worsening Heart Failure (%) | 2.5 (6) | 4.2 (10) | 3.8 (9) | 11.3 (27) | 20.5 (49) | <0.001 |
| Treatment failure due to WRF (%) | 12 (28) | 9.2 (21) | 9.6 (22) | 15 (34) | 14.3 (33) | 0.120 |
| Treatment Failure due to HF rehospitalisation (%) | 0.4 (1) | 0 (0) | 0.4 (1) | 0 (0) | 0.4 (1) | 1.000 |
| Hemoconcentration on day 4 (%) | 65 (104) | 62.8 (113) | 65.3 (124) | 49.7 (89) | 49.7 (88) | <0.001 |
| 180-day mortality (%) | 7.1 (17) | 11.3 (27) | 16.4 (39) | 19.7 (47) | 21.8 (52) | <0.001 |
| 60-day Heart Failure Rehospitalization (%) | 8.4 (20) | 6.7 (16) | 15.5 (37) | 17.6 (42) | 24.7 (59) | <0.001 |
| 60-day Death or Renal or Cardiovascular Rehospitalization (%) | 16.3 (39) | 16 (38) | 27.7 (66) | 34.5 (82) | 38.5 (92) | <0.001 |
| Frequency of Rehospitalization | 0 [0-0] | 0 [0-0] | 0 [0-1] | 0 [0-1] | 0 [0-1] | <0.001 |

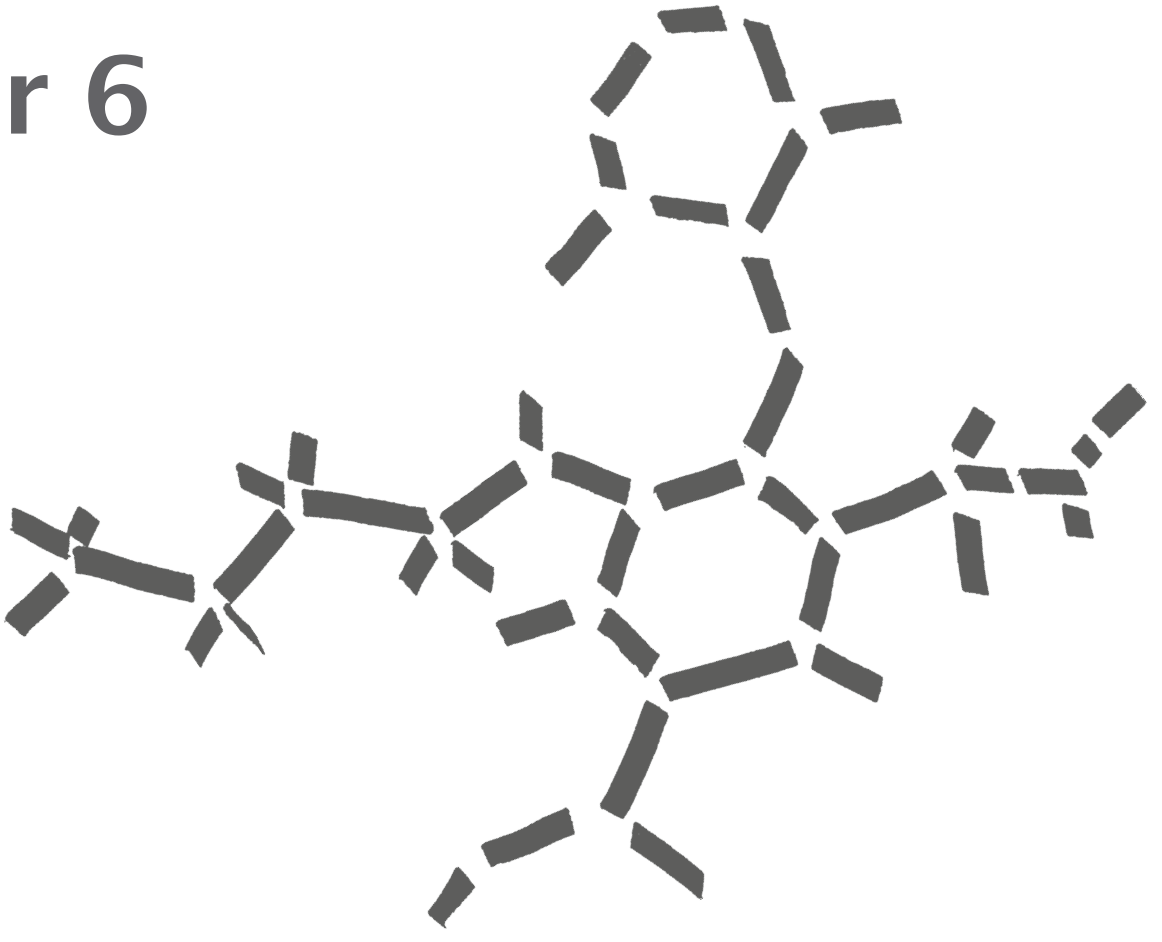
Unadjusted incidence rates are reported
* Patients with rales and oedema at baseline, and who did not receive Inotropes or vasodilators on days 1-4
** P for trend across quintiles (linear regression)
Abbreviations: see Table S3

**Table S10** Hazard ratios per SD on mortality and rehospitalization endpoints in subpopulations

| | 180-day Mortality** | | | 60-day HF rehospitalization** | | | 60-day death, renal, CV rehospitalization** | | |
|---|---|---|---|---|---|---|---|---|---|
| | HR | 95% CI | p | HR | 95% CI | p | HR | 95% CI | p |
| Univariable HR, Diuretic Response* | | | | | | | | | |
| Placebo group (n=579) | 2.30 | 1.48–3.56 | <0.001 | 2.18 | 1.37–3.49 | 0.001 | 1.65 | 1.21–2.26 | 0.002 |
| Congested group (n=1368) | 1.93 | 1.51–2.48 | <0.001 | 2.22 | 1.71–2.90 | <0.001 | 1.70 | 1.41–2.05 | <0.001 |
| Congested group, no inotropes (n=1192) | 1.88 | 1.42–2.47 | <0.001 | 2.30 | 1.71–3.09 | <0.001 | 1.71 | 1.34–2.10 | <0.001 |
| Multivariable HR, Diuretic Response | | | | | | | | | |
| Placebo group (n=579) | 1.71 | 1.07–2.73 | 0.025 | 1.67 | 1.01–2.78 | 0.047 | 1.31 | 0.94–1.81 | 0.11 |
| Congested group (n=1368) | 1.63 | 1.24–2.13 | <0.001 | 1.80 | 1.35–2.40 | <0.001 | 1.41 | 1.16–1.72 | <0.001 |
| Congested group, no inotropes (n=1192) | 1.55 | 1.16–2.08 | 0.003 | 1.85 | 1.36–2.58 | <0.001 | 1.43 | 1.15–1.76 | 0.001 |

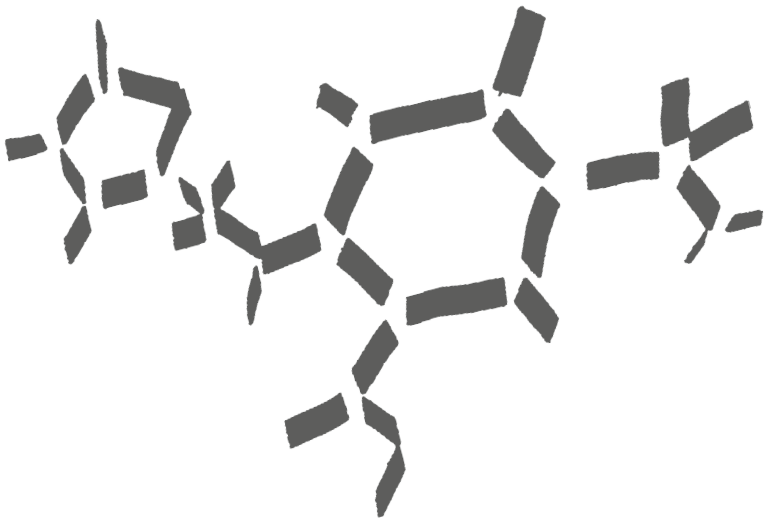
* Adjusted for baseline weight (and study treatment for congested groups)
** Adjusted for covariates from backward elimination models

# Chapter 6



# Responsiveness to loop diuretics in heart failure

Eugene Braunwald



Published in: European Heart Journal (2014) 35, 1235–1237.

*This editorial refers to to Chapter 5, 'Diuretic response in acute heart failure: clinical characteristics and prognostic significance', by M.A.E. Valente et al.*

Loop diuretics are the most commonly used drugs in the management of pulmonary and systemic congestion in patients with acute decompensated heart failure (ADHF), as well as chronic congestive HF. The diuresis results from blockade of the Na-K-Cl cotransporter in the ascending limb of the loop of Henle. The pharmacodynamics of loop diuretics are illustrated in *Figure 1*, and are best described as an S-shaped curve.[1] The first few i.v. administrations to patients with HF and congestion cause a brisk diuresis with accompanying weight loss. Although loop diuretics may be life saving in patients with ADHF and pulmonary oedema, they have not been shown definitively to extend survival in patients with chronic HF, although they do play a critically important role in the reduction of oedema and dyspnoea.

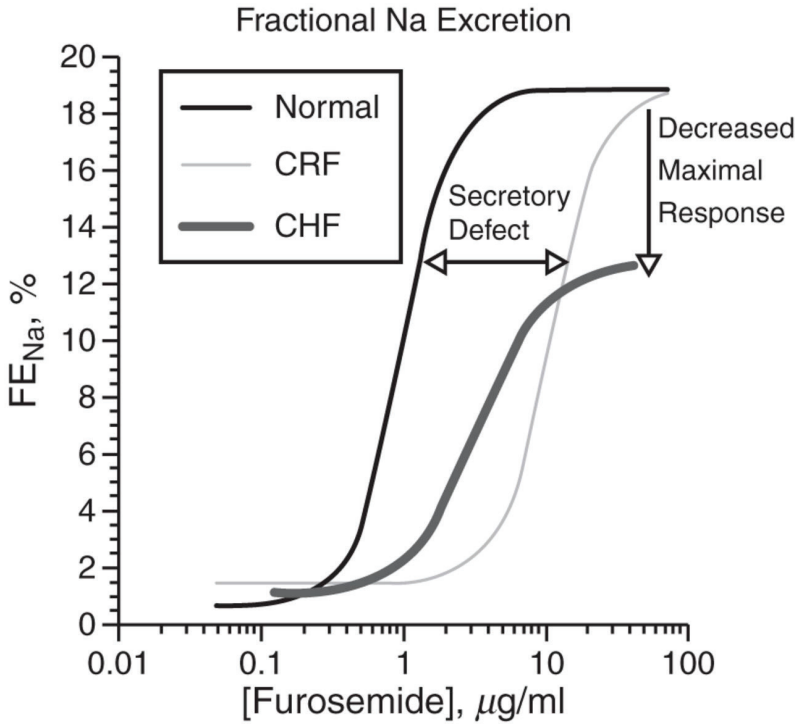



**Figure 1** Dose-response curves for loop diuretics.

Patients with chronic kidney disease (CKD) exhibit a rightward shift consequent to a reduction in the secretion of the diuretic. Patients with heart failure (HF) who have received multiple doses of a loop diuretic exhibit both a rightward shift and depression of the peak (maximal response reduced). Not shown is the elevation of the natriuretic threshold which further limits the response to orally administered diuretics. Reprinted with permission from Ellison DH. Diuretic therapy and resistance in congestive heart failure. Cardiology 2001;96:132-143. S. Karger AG.

Unfortunately, drug resistance develops frequently with repeated administration of loop diuretics[2,3] and, as a consequence, fluid retention and congestion recur. Loop diuretic resistance is likely to be due to the operation of several counter-regulatory processes, which cause fluid retention. These include: (i) activation of the renin–angiotensin–aldosterone system (RAAS); (ii) activation of the sympathetic nervous system (SNS), which reduces renal blood flow and the quantities of $Na^+$ and of the diuretic reaching the loop of Henle; and (iiii) hypertrophy of the epithelial cells in the distal nephron, causing increased $Na^+$ reabsorption.[1] As a consequence, the diuretic concentration–$Na^+$ excretion curve is displaced downward and to the right (*Figure 1*), the threshold concentration of drug required to achieve any diuretic effect rises, and the maximal diuresis that can be achieved declines. In addition, the presence of chronic kidney disease (CKD) contributes to the pathogenesis of diuretic resistance (*Figure 1*). In a meta-analysis including > 1 million patients with HF enrolled into 57 trials, Damman *et al.* found that one-third exhibited CKD during hospitalization, and one-fourth exhibited worsening renal function (WRF).[4] Both CKD and WRF were independent predictors of mortality.[4] Other investigators have also reported that WRF is an independent predictor of mortality, but only in patients with persistent congestion.[5]

It is not clear whether the progression of HF and the accompanying activation of the RAAS and SNS combined with the reduction of renal blood flow is responsible for diuretic resistance and/or whether diuretic resistance plays a role in the poor outcome of patients with advanced HF. Most probably there is a vicious circle, in which impaired cardiac function, as well as excessive activation of both the RAAS and the SNS, augment $Na^+$ retention. The reduction of renal perfusion, sometimes superimposed on CKD, leads to diuretic resistance. The latter, in turn, is responsible for the need for progressively escalating doses of loop diuretic, which cause further activation of the neurohormonal axes and of renal dysfunction culminating, in some patients, in the development of the cardiorenal syndrome,[6] as well as in an increasing risk of adverse clinical outcomes. The latter include prolonged hospitalization, and/or rehospitalization for failure to relieve congestion, and shortened survival. In this vicious circle it is not clear whether diuretic resistance is only a risk marker for future adverse clinical outcomes, or whether it plays a causal role. I think that it is likely that diuretic resistance is both a marker and a 'player'. Whatever the pathophysiological mechanisms involved, it has been well established that the development of loop diuretic resistance is an ominous prognostic sign in patients with HF.

Increased efforts are underway to measure loop diuretic responsiveness and determine whether it predicts clinical outcome. Hasselblad *et al.* have reported a close correlation between the maximum in-hospital daily dose of loop diuretic and subsequent mortality in patients with HF[7] (*Figure 2*). Two recent studies in patients hospitalized with HF have measured loop diuretic responsiveness and have related it to subsequent clinical outcomes. Testani *et al.* calculated what they termed 'loop diuretic efficiency' as the fluid output in ml per 40 mg of furosemide equivalents administered. They found, in a post-hoc analysis, that patients whose loop diuretic

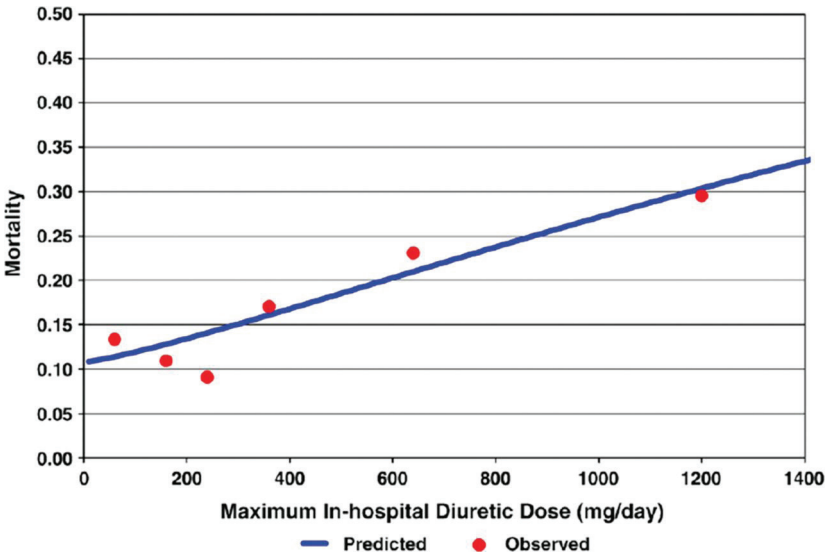



**Figure 2** Relationship between maximum daily dose of loop diuretic, expressed in furosemide equivalents, and mortality at 180 days in 395 patients admitted to the hospital with decompensated heart failure.

P = 0.003. Reprinted with permission from Hasselblad V, Stough WG, Shah MR, Lokhnygina Y, O'Connor CM, Califf RM, Adams KF Jr. Relation between dose of loop diuretics and outcomes in a heart failure population: results of the ESCAPE trial. Eur J Heart Fail 2007;9:1064–1069

efficiency was below the median had a significantly higher mortality than those in whom it was above the median. Importantly, they then validated this approach in a second population.[8]

Valente *et al.*, in a post-hoc analysis of HF patients in the PROTECT trial, have now quantified the diuretic response defined as 'Δ weight kg/40 mg furosemide'.[9] Like Testani *et al.*, they reported that a low diuretic response was an independent predictor of mortality and that it was an independent predictor of HF rehospitalization as well. A reduced diuretic response also correlated significantly with low systolic pressure, high blood urea nitrogen (BUN), diabetes, and arteriosclerosis, but surprisingly not with serum creatinine or estimated glomerular filtration rate. In addition, they found that age, BUN, and systolic pressure (all simpler to measure than diuretic responsiveness) were also independent predictors of mortality. Another recent analysis of the PROTECT trial, by some of the same authors, showed that the risk of mortality and hospital readmission could be predicted by renal function, as assessed by both creatinine and BUN 7 days after entry, as well as by the trajectory of plasma creatinine concentration during the first 7 days after hospital admission.[10]

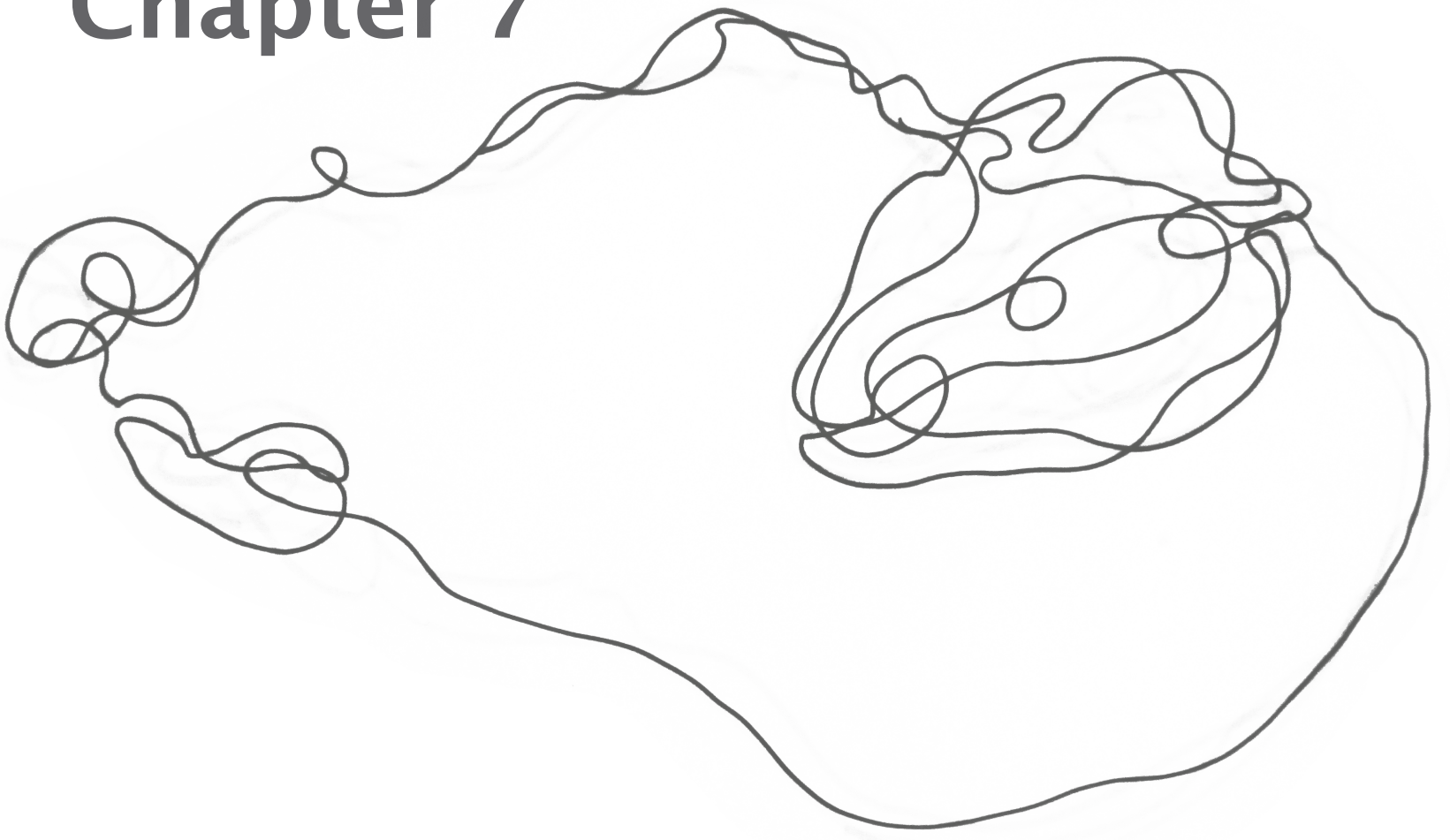
The aforementioned efforts to quantify the diuretic response and to relate it to clinical outcome are highly commendable, since they may ultimately aid in the development of more individualized treatment plans for patients with HF, as more therapeutic options, such as device therapy, become available. However, there are significant limitations to both metrics, some of which have been recognized by the authors:[8,9] (i) Both urine output and weight changes, while obviously simple markers of diuretic responsiveness, are notoriously difficult to measure precisely in hospitalized patients unless very special care is taken by a trained and motivated staff. (ii) Sodium intake is an important determinant of diuretic responsiveness, and is often difficult to control, even in hospitalized patients. (iii) The co-administration of other diuretics such as thiazides and/or mineralocorticoid receptor antagonists that are often administered to patients with loop diuretic resistance, as well as drugs which affect cardiac performance, such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and beta-adrenergic blockers, were not controlled. All of these could affect the diuretic response. (iv) The dose–response curve to loop diuretics is far from linear, and normally reaches an asymptote with increased dosing (*Figure 1*). This makes changes in weight or urine volume per 40 mg of furosemide equivalents difficult to interpret. (v) Finally, in the two studies mentioned above,[8,9] the loop diuretics were administered both intravenously and orally. The conversion factor among these routes may differ between patients with HF whose intestinal absorption of orally administered drugs may differ. This conversion factor may also change in any given patient as the severity of HF waxes and wanes.

Given the aforementioned issues, the interpretation of these metrics is challenging and they may not yet be of value in the assessment of individual patients. It would be interesting to ascertain their reproducibility in the same subjects and under similar conditions. However, they may be quite useful in comparing groups of patients in assessing the effect of interventions on such groups. For example, the analysis by Valente *et al.*, which was carried out in 1745 patients who were randomized to rolofylline, an adenosine A1 antagonist, or to placebo, showed a statistically significantly better diuretic response in the rolofylline group.[9] Despite the current limitations, the efforts of these investigators represent the first serious attempts to put a number on an important variable in patients with HF—loop diuretic responsiveness, a variable that clinicians have previously described only qualitatively. This work is the forerunner of future approaches which will provide precise measurement of loop diuretic responsiveness and will thereby permit optimal dosing of these important drugs.

## References


1. Ellison DH. Diuretic therapy and resistance in congestive heart failure. Cardiology 2001;96:132–143.
2. Neuberg GW, Miller AB, O'Connor CM, Belkin RN, Carson PE, Cropp AB, Frid DJ, Nye RG, Pressler ML, Wertheimer JH, Packer M. Diuretic resistance predicts mortality in patients with advanced heart failure. Am Heart J 2002;144:31–38.
3. Von Lueder TG, Atar D, Krum H. Diuretic use in heart failure and outcomes. Clin Pharm Ther 2013;94:490–498.
4. Damman K, Valente MAE, Voors AA, O'Connor CM, van Veldhuisen DJ, Hillege HL. Renal impairment, worsening renal function and outcome in patients with heart failure: an updated meta-analysis. Eur Heart J 2014;35:455–469.
5. Metra M, Davison B, Bettari L, Sun H, Edwards C, LazzariniV, Piovanelli B, Carubelli V,Bugatti S, Lombardi C, Cotter G, Dei Cas L. Is worsening renal function an ominous prognostic sign in patients with acute heart failure? The role of congestion and its interaction with renal function. Circ Heart Fail 2012;5:54–62.
6. Ronco C, Cicoira M, McCullough PA. Cardiorenal syndrome type 1. Pathophysiological crosstalk leading to combined heart and kidney dysfunction in the setting of acutely decompensated heart failure. J Am Coll Cardiol 2012;60:1031–1042.
7. Hasselblad V Jr., Stough WG, Shah MR, Lokhnygina Y, O'Connor CM, Califf RM, Adams KF Jr. Relation between dose of loop diuretics and outcomes in a heart failure population: results of the ESCAPE trial. Eur J Heart Fail 2007;9:1064–1069.
8. Testani JM, Brisco MA, Turner JM, Spatz ES, Bellumkonda L, Parikh CR, TangWHW. Loop diuretic efficiency: a metric of diuretic responsiveness with prognostic importance in acute decompensated heart failure. Circ Heart Fail 2014;in press.
9. Valente MAE, Voors AA,Damman K, Van Veldhuisen DJ, Massie BM, O'Connor CM, Metra M, Ponikowski P, Teerlink JR, Cotter G, Davison B, Cleland JGF, Givertz MM, Bloomfield DM, Fiuzat M, Dittrich HC, Hillege HL. Diuretic response in acute heart failure: clinical characteristics and prognostic significance. Eur Heart J 2014;35:1284–1293.
10. Givertz MM, Postmus D, Hillege HL, Mansoor GA, Massie BM, Davison BA, Ponikowski P, Metra M, Teerlink JR, Cleland JGF, Dittrich HC, O'Connor CM, Cotter G, Voors AA. Renal function trajectories and clinical outcomes in acute heart failure. Circ Heart Fail 2014;7:59–6

# Chapter 7



# Predicting clinically relevant worsening renal function in acute heart failure with Neutrophil Gelatinase-Associated Lipocalin

Mattia A.E. Valente, Adriaan A. Voors, Dirk J. van Veldhuisen, Christopher M. O'Connor, Marco Metra, Piotr Ponikowski, Gad Cotter, Beth Davison, John G.F. Cleland, Michael M. Givertz, Daniel M. Bloomfield, Hans L. Hillege, Kevin Damman

Ready for submission

## Abstract

**Objectives** To examine the value of serum Neutrophil Gelatinise-Associated Lipocalin (NGAL) for predicting clinically relevant worsening renal function (WRF) in patients with acute heart failure (AHF).

**Background** WRF is associated with a poorer outcome in patients with AHF. NGAL may predict the development of WRF and its subsequent prognosis.

**Methods and results** We investigated baseline and short-term changes in serum NGAL and creatinine in patients hospitalized for AHF and enrolled in the PROTECT study. Analysis was confined to 1447 patients with available data with serial measurements for ≥4 days. WRF was defined as an increase in serum creatinine of ≥0.3 mg/dL through day 4. WRF developed in 325 patients (22%). Serum NGAL did not rise earlier than creatinine in patients who developed WRF. After multivariable adjustment, baseline serum NGAL, but not creatinine, predicted WRF. Overall, WRF was associated with a poor clinical outcome. Interactions between baseline NGAL and WRF were observed. Patients with WRF and a high baseline serum NGAL had a greater risk of death, renal or cardiovascular rehospitalisation by 60 days than patients with a low baseline serum NGAL ($p = 0.024$). A rise in serum NGAL after baseline was associated with worse outcome in patients with WRF but not in patients without ($p=0.003$).

**Conclusions** In patients with AHF, serum NGAL is not an earlier marker for WRF than changes in serum creatinine and is only a modest predictor of WRF and overall prognosis. However, serum NGAL helps identify those patients with in-hospital WRF who subsequently have a poor prognosis.

## Introduction

Worsening renal function (WRF) during hospitalization for acute heart failure (AHF) is associated with poorer outcome. However, some studies suggest that a transient decline in renal function during treatment for AHF may not be harmful, and may even reflect a better therapeutic response.[1-4] We recently showed that patients with AHF and a good diuretic response had a higher incidence of WRF but better outcomes.[5] The reasons for WRF appear important. Early identification of patients at risk of WRF, a robust definition and better understanding of its cause and consequences may improve risk stratification. Novel biomarkers may play a role in achieving this goal.

Neutrophil Gelatinase Associated Lipocalin (NGAL), a 25 kDa member of the Lipocalin family expressed by the renal tubular epithelium, is released into both urine and blood in response to tubular injury. Studies in various settings have suggested both blood and urinary NGAL levels to be good early markers for acute kidney injury, with levels increasing hours to days before serum creatinine or cystatin-c.[6] Several small studies, the largest including only 207 patients, have examined the value of serum NGAL for predicting WRF in AHF, with mixed results; some found NGAL to be superior to traditional renal markers, while others found no difference or even inferior predictive performance.[7-13] There are also few reports on the value of short-term changes in serum NGAL in AHF and they are similarly conflicting.[8,9] Higher serum NGAL has also been associated with poorer clinical outcomes in AHF,[10,14,15] and a large-scale, prospective, observational study examining associations with mortality outcomes is ongoing (AKINESIS, ClinicalTrials.gov ID no. NCT01291836). In order to address these issues, we investigated baseline and short-term changes in serum NGAL and creatinine during hospitalization for AHF in patients enrolled in the PROTECT study.

## Methods

### Study design and population

This is a post-hoc analysis of the Placebo-controlled Randomized Study of the Selective A1 Adenosine Receptor Antagonist Rolofylline for Patients Hospitalized with acute heart failure and Volume Overload to Assess Treatment Effect on Congestion and Renal FuncTion (PROTECT) trial, a randomized, double-blind, placebo-controlled, multi-center study that enrolled 2033 patients admitted for acute decompensated heart failure, randomized 2:1 to rolofylline, with neutral overall results. Study design, inclusion and exclusion criteria and main results have been published previously.[16,17] The trial was approved by all local Ethics Committees and conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent. Of the patients who remained hospitalized for at least 4 days (n=1681), those with available NGAL and creatinine values at baseline (n=1470) and at least one follow-up measurement for each marker during the first 4 days were included in the analysis, resulting in a study population of 1447 patients. To examine

the effects of biomarker levels and changes on day 2, the patients who had already developed WRF by day 2 (n=101) were excluded from analyses.

## Procedures and definitions

Heart failure signs and symptoms, serum creatinine and other hematologic and biochemical markers were assessed daily from baseline (day 1) until discharge or day 6 and on day 7.[16] Serum NGAL levels were measured in frozen serum samples collected on the same days and stored at -80°C. Measurements were performed by Alere Inc. (San Diego, USA) using sandwich enzyme-linked immunosorbent assays (ELISA) on a microtiter plate. Estimated glomerular filtration rate (GFR) was calculated using the simplified modification of diet in renal disease (MDRD) study equation.

## Endpoints

The focus of this study was WRF occurring during the first 4 days of hospitalization, defined as a creatinine increase of ≥0.3 mg/dL occurring any time between day 1 (baseline) and day 4. Initiation of hemofiltration or dialysis within the first 4 days was considered WRF irrespective of creatinine measurements. Considering the literature describes NGAL as an early marker for WRF, later decline in renal function was not considered for these analyses.

Sensitivity analyses were performed with other definitions of WRF occurring during the first four days, including: absolute creatinine change as a continuous variable; a relative creatinine increase of ≥25%; and a combined creatinine increase of ≥0.3 mg/dL and ≥25%. Additionally, the value of NGAL was also assessed for several cut-offs: serum creatinine increases of ≥0.6 mg/dL, ≥1.2 mg/dL, ≥50% and ≥100%.

The prognostic relevance of (changes in) NGAL within the context of WRF / changes in creatinine was examined using two endpoints: 180-day mortality and a composite of 60-day death or renal or cardiovascular rehospitalization. Both endpoints were adjudicated. To examine NGAL patterns in patients with WRF with good and poor outcome, patients were classified into groups based on whether they developed WRF and whether they experienced a clinical endpoint.

## Statistical methods

Continuous data are presented as mean ± standard deviation if normally distributed or median [interquartile range] if not. Group comparisons were performed using Student's T-test, ANOVA, Wilcoxon or Kruskall-Wallis tests, as appropriate. Differences between relative changes in biomarkers were assessed using paired Wilxocon rank sum tests. Correlations between biomarkers were evaluated using Spearman's rank correlation. Trends across categories were assessed using non-parametric trend tests for categorical variables, and univariable generalized linear models with polynomial contrasts for continuous variables. Missing data were assumed to be missing at random, and no imputations were performed.

Random slope, random intercept linear mixed-effects models were used to examine changes in serial NGAL and creatinine levels over time, adjusting for study treatment. A mixed-effects model is a hierarchical regression model including fixed and random (subject-specific) effects, allowing for within-subject correlation between repeated measurements. Both NGAL and Creatinine were log-transformed for modelling. Model selection was based on combined assessment of likelihood ratio tests of nested models for selection of random effects, and of Bayesian and Akaike's information criteria (measures for model fit, lower is better) for selection of fixed effects. Best fit was obtained using a second order polynomial (quadratic) time transformation for creatinine and third order polynomial (cubic) time transformation for NGAL for both fixed and random effects.

Receiver Operator Characteristic (ROC) curve analyses and multivariable logistic regression were performed evaluate predictors of WRF, and added value was assessed using likelihood ratio tests of nested models. Multivariable models were constructed via backward elimination of candidate covariates with a univariable association at $p<0.1$, with a P for retention of 0.05.

Kaplan Meier survival analyses were performed to examine group associations with the mortality and composite endpoints. Outcomes between groups were compared with log-rank tests. Cox proportional hazards regression was performed to evaluate univariable and multivariable associations with 180-day mortality and the 60-day composite, adjusting for covariates from a previously published prognostic model – age, creatinine, BUN, systolic blood pressure, edema, previous hospitalization for heart failure, serum albumin and serum sodium.[18] Multiple fractional polynomials were used to check for non-linearity in survival analyses. Interactions were investigated graphically. Proportionality of hazards assumptions were evaluated graphically and tested statistically. A two-tailed p-value of 0.05 was considered statistically significant. All analyses were performed using R: A Language and Environment for Statistical Computing, version 3.1.0 (R Foundation for Statistical Computing, Vienna, Austria) and Stata, version 11.2 (College Station, TX, USA).

## Results

Baseline data for patients with an without WRF and by vital status are presented in Table 1; patients who developed WRF during the first four days (n = 325; 22%) had a higher left ventricular ejection fraction (LVEF), higher systolic blood pressure, less edema, worse baseline renal function, higher NGAL levels, lower haemoglobin and more anaemia (all $p<0.05$). Profiles for survivors at 180 days versus patients who died were similar in patients with and without WRF; patients who died had a lower ejection fraction, lower blood pressure, worse renal function, reflected by higher BUN and serum concentrations of creatinine and NGAL and lower serum cholesterol and triglyceride (all $p<0.05$). Patients without WRF who died had a lower BMI, were older, and more likely to be treated with CRT than those without WRF who survived (all $p<0.05$), but this was not the case for patients who developed WRF.

**Table 1** Baseline characteristics for patients with and without worsening renal function and by vital status at day 180

| | No WRF, alive (n=936) | No WRF, dead (n=186) | P | No WRF, total (n=1122) | WRF, alive (n=247) | WRF, dead (n=78) | P | WRF, total (n=325) | P |
|---|---|---|---|---|---|---|---|---|---|
| **Demographics** | | | | | | | | | |
| Sex (% Male) | 64 (599) | 68.3 (127) | *0.302* | 64.7 (726) | 69.6 (172) | 71.8 (56) | *0.825* | 70.2 (228) | *0.079* |
| Age (years) | 69.6±11.6 | 72.4±10.7 | *0.001* | 70±11.5 | 71.1±10.3 | 71.9±10.7 | *0.578* | 71.3±10.4 | *0.058* |
| BMI (kg/m2) | 28.8±6 | 27.8±5.7 | *0.032* | 28.6±6 | 29.1±5.8 | 28.3±6 | *0.311* | 28.9±5.9 | *0.516* |
| LVEF (% (n)) | 32.7±12.8 | 28.6±11 | *0.001* | 31.9±12.5 | 36.5±13.9 | 30.5±13.4 | *0.021* | 34.9±14 | *0.020* |
| Systolic Blood Pressure (mmHg) | 125.7±17.3 | 117.8±17.2 | *<0.001* | 124.4±17.6 | 129.2±16.6 | 120.1±16.4 | *<0.001* | 127±17 | *0.015* |
| Diastolic Blood Pressure (mmHg) | 74.8±11.5 | 71±10.7 | *<0.001* | 74.1±11.5 | 76.9±12.1 | 71.2±10.8 | *<0.001* | 75.5±12 | *0.060* |
| Heart Rate (beats/min) | 81.6±16.4 | 80.3±15.1 | *0.286* | 81.4±16.2 | 80.3±14.9 | 78.8±14.8 | *0.452* | 79.9±14.9 | *0.124* |
| Rolofylline administration (% (n)) | 65.2 (610) | 69.4 (129) | *0.310* | 65.9 (739) | 72.5 (179) | 65.4 (51) | *0.291* | 70.8 (230) | *0.112* |
| **Clinical Profile** | | | | | | | | | |
| Orthopnea (% (n)) | 96.6 (896) | 94.6 (175) | *0.287* | 96.2 (1071) | 95.1 (233) | 100 (78) | *0.099* | 96.3 (311) | *1.000* |
| Rales (% (n)) | 63.5 (594) | 61.3 (114) | *0.621* | 63.2 (708) | 64.8 (160) | 65.4 (51) | *1.000* | 64.9 (211) | *0.605* |
| Edema (% (n)) | 71.2 (666) | 71 (132) | *1.000* | 71.1 (798) | 63.6 (157) | 60.3 (47) | *0.695* | 62.8 (204) | *0.005* |
| Jugular venous pressure (% (n)) | 41.2 (344) | 49.4 (81) | *0.064* | 42.5 (425) | 40.3 (87) | 43.7 (31) | *0.716* | 41.1 (118) | *0.716* |
| **Medical History** | | | | | | | | | |
| Hypertension (% (n)) | 80.1 (750) | 79 (147) | *0.810* | 79.9 (897) | 79.8 (197) | 74.4 (58) | *0.394* | 78.5 (255) | *0.612* |
| Diabetes Mellitus (% (n)) | 44.9 (420) | 45.7 (85) | *0.899* | 45 (505) | 44.5 (110) | 41.6 (32) | *0.743* | 43.8 (142) | *0.754* |
| Hypercholesterolemia (% (n)) | 45.7 (427) | 42.5 (79) | *0.472* | 45.1 (506) | 51.4 (127) | 48.7 (38) | *0.775* | 50.8 (165) | *0.084* |
| Smoking (% (n)) | 18.6 (174) | 19.5 (36) | *0.867* | 18.8 (210) | 14.2 (35) | 20.5 (16) | *0.250* | 15.7 (51) | *0.247* |
| Ischemic Heart Disease (% (n)) | 69.3 (648) | 74.6 (138) | *0.177* | 70.2 (786) | 69.2 (171) | 73.1 (57) | *0.613* | 70.2 (228) | *1.000* |
| Myocardial Infarction (% (n)) | 49 (458) | 54.3 (100) | *0.216* | 49.9 (558) | 48.2 (119) | 52.6 (41) | *0.585* | 49.2 (160) | *0.879* |
| PCI (% (n)) | 21.9 (203) | 26.8 (49) | *0.182* | 22.7 (252) | 22.3 (55) | 23.4 (18) | *0.962* | 22.5 (73) | *1.000* |
| CABG (% (n)) | 18.6 (172) | 21.9 (40) | *0.349* | 19.1 (212) | 21.9 (54) | 25.6 (20) | *0.590* | 22.8 (74) | *0.168* |
| Peripheral Vascular Disease (% (n)) | 10.2 (95) | 15.1 (28) | *0.069* | 11 (123) | 11 (27) | 14.3 (11) | *0.559* | 11.8 (38) | *0.769* |
| Atrial Fibrillation (% (n)) | 55.6 (518) | 57 (106) | *0.797* | 55.9 (624) | 55.1 (136) | 50 (39) | *0.515* | 53.8 (175) | *0.561* |
| NYHA Class | | | *0.426* | | | | *0.059* | | *0.578* |
| I-II | 16.6 (155) | 13.4 (25) | | 16 (180) | 19.8 (49) | 10.3 (8) | | 17.5 (57) | |
| III | 44.9 (420) | 49.5 (92) | | 45.6 (512) | 45.7 (113) | 59 (46) | | 48.9 (159) | |
| IV | 32.8 (307) | 31.7 (59) | | 32.6 (366) | 31.6 (78) | 26.9 (21) | | 30.5 (99) | |

| | No WRF, alive (n=936) | No WRF, dead (n=186) | P | No WRF, total (n=1122) | WRF, alive (n=247) | WRF, dead (n=78) | P | WRF, total (n=325) | P |
|---|---|---|---|---|---|---|---|---|---|
| ICD therapy (% (n)) | 12.6 (118) | 17.2 (32) | *0.119* | 13.4 (150) | 12.6 (31) | 19.2 (15) | *0.197* | 14.2 (46) | *0.790* |
| CRT therapy (% (n)) | 7.2 (67) | 14 (26) | *0.003* | 8.3 (93) | 11.3 (28) | 9 (7) | *0.706* | 10.8 (35) | *0.205* |
| Stroke (% (n)) | 8.3 (78) | 9.1 (17) | *0.828* | 8.5 (95) | 12.6 (31) | 19.2 (15) | *0.197* | 14.2 (46) | *0.003* |
| COPD (% (n)) | 19.4 (181) | 21.6 (40) | *0.545* | 19.7 (221) | 18.6 (46) | 21.8 (17) | *0.650* | 19.4 (63) | *0.953* |
| **Prior Medication Use** | | | | | | | | | |
| ACE inhibitors or ARB (% (n)) | 76.4 (715) | 69.9 (130) | *0.074* | 75.3 (845) | 76.5 (189) | 71.8 (56) | *0.488* | 75.4 (245) | *1.000* |
| Beta blockers (% (n)) | 74.7 (699) | 75.3 (140) | *0.939* | 74.8 (839) | 74.5 (184) | 67.9 (53) | *0.323* | 72.9 (237) | *0.547* |
| MRAs (% (n)) | 45.8 (429) | 48.4 (90) | *0.577* | 46.3 (519) | 47.4 (117) | 59 (46) | *0.097* | 50.2 (163) | *0.239* |
| Calcium Antagonists (% (n)) | 12.7 (119) | 8.6 (16) | *0.147* | 12 (135) | 21.9 (54) | 7.7 (6) | *0.008* | 18.5 (60) | *0.004* |
| Nitrates (% (n)) | 26.9 (252) | 26.9 (50) | *1.000* | 26.9 (302) | 27.5 (68) | 29.5 (23) | *0.849* | 28 (91) | *0.752* |
| Digoxin (% (n)) | 31 (290) | 31.2 (58) | *1.000* | 31 (348) | 32.4 (80) | 20.5 (16) | *0.063* | 29.5 (96) | *0.660* |
| **Laboratory Values** | | | | | | | | | |
| Creatinine (mg/dL) | 1.3 [1.1-1.7] | 1.5 [1.2-2.1] | *<0.001* | 1.3 [1.1-1.7] | 1.4 [1.2-1.8] | 1.7 [1.3-2] | *0.002* | 1.5 [1.2-1.8] | *<0.001* |
| eGFR (ml/min/1.72m2) | 52 [39-66] | 45 [33-60] | *<0.001* | 51 [38-65] | 48 [38-62] | 40 [32-51] | *<0.001* | 46 [37-59] | *<0.001* |
| NGAL (ng/mL) | 78 [50-123] | 96 [58-137] | *0.008* | 81 [52-127] | 90 [56-142] | 131 [72-187] | *0.002* | 93 [58-151] | *<0.001* |
| Blood Urea Nitrogen (mg/dL) | 28 [21-38] | 37 [26-51] | *<0.001* | 29 [22-40] | 28 [22.5-38] | 41 [30-55] | *<0.001* | 31 [24-43] | *0.029* |
| Sodium (mmol/L) | 140 [137-143] | 138 [135-141] | *<0.001* | 140 [137-142] | 141 [138-143] | 139 [136-142] | *0.010* | 140 [138-143] | *0.063* |
| Potassium (mmol/L) | 4.2 [3.9-4.6] | 4.3 [3.9-4.8] | *0.175* | 4.2 [3.9-4.6] | 4.3 [4-4.7] | 4.3 [3.9-4.7] | *0.815* | 4.3 [3.9-4.7] | *0.090* |
| Haemoglobin (g/dL) | 12.9±2 | 12.7±1.9 | *0.216* | 12.8±2 | 12.5±1.9 | 12.3±1.8 | *0.399* | 12.5±1.9 | *0.007* |
| Anaemia (% (n)) | 38.3 (314) | 44.4 (75) | *0.169* | 39.4 (389) | 46.6 (102) | 49.3 (34) | *0.800* | 47 (136) | *0.021* |
| Total Cholesterol (mmol/L) | 149±43 | 134±40 | *<0.001* | 146±43 | 160±51 | 142±39 | *0.001* | 155±49 | *0.002* |
| Triglycerides (mmol/L) | 101±54 | 91±45 | *0.009* | 99±53 | 108±66 | 96±49 | *0.078* | 105±63 | *0.087* |
| BNP (mg/dL) | 1195 [815-2228] | 1895 [1172-3300] | *<0.001* | 1351 [852-2433] | 1073 [718-1616] | 1749 [1153-2829] | *0.006* | 1190 [779-2078] | *0.227* |

Abbreviations: BMI: Body Mass Index; LVEF: Left Ventricular Ejection Fraction; PCI: Percutaneous Coronary Intervention; CABG: Coronary Artery Bypass Graft NYHA: New York Heart Association; ICD: Internal Cardiac Defibrillator; CRT: Cardiac Resynchronization Therapy; COPD: chronic obstructive pulmonary disease; ACE: Angiotensin Converting Enzyme ; ARB: Aldosterone Receptor Blocker; MRA: Mineralocorticoid Receptor Antagonist; eGFR: estimated Glomerular Filtration Rate; BNP: Brain Natriuretic Peptide. Categorical variables are presented as: % (N)

Supplementary tables S1 and S2 present baseline characteristics by tertile of baseline serum creatinine and NGAL. Higher biomarker levels were associated with more advanced age and more co-morbidity. Serum concentrations of NGAL correlated reasonably well with serum creatinine (Spearman's rho 0.58 at baseline and 0.60 at day 4, both p<0.001), estimated GFR (Spearman's rho -0.60 at baseline and -0.62 at day 4, both p<0.001) and BUN (Spearman's rho 0.52 at baseline and 0.54 at day 4, both p<0.001), and a modestly but significantly with CRP (Spearman's rho 0.12 at day 1, 0.13 at day 4, both p<0.001).

## NGAL and WRF

Figure 1 displays changes in serum creatinine and NGAL during the first week after admission in patients with and without WRF, adjusted for study treatment. Trajectories for alternative WRF definitions are presented as supplementary figures S1 and S2 and display similar patterns. The interactions of time and WRF, indicating different biomarker trajectories for the two groups, were highly significant in all models (all p<0.001), and there were no significant effects of or interactions with rolofylline treatment. Figure 2 shows the relative change in creatinine and NGAL levels over the first 7 days in patients with and without WRF. In patients who developed WRF, NGAL levels did not rise significantly sooner than creatinine levels; both markers increased in parallel over the first 2 days (P for difference n.s.), with NGAL rising further than creatinine over the course of 7 days while displaying greater variability (median relative change in NGAL vs. Creatinine: day 3: 23% [-7% to 79%] vs. 21.8% [10% to 33.3%], P=0.015; day 4: 33% [-4% to 99%] vs. 25% [17% to 42%], P<0.001; day 7: 38% [-8% to 93%] vs. 20% [0% to 36%], P<0.001). Patterns were similar for alternative definitions of WRF (Supplementary Figures S3 and S4).

In ROC curve analyses, baseline NGAL and creatinine values similarly and modestly predicted WRF; a non-diagnostic change in creatinine on day 2 was a much stronger predictor of WRF than change in NGAL on day 2 (Table 2). The added value of NGAL on top of creatinine was modest, but statistically significant for almost all cut-offs (Supplementary Table S4). Serum NGAL was independently associated with WRF in a multivariable model (Table 3), while serum creatinine was not, and contributed significantly to improving model discrimination (AUC 0.648 vs. 0.635 for model with vs. without NGAL, P=0.002). Multivariable models for other cut-offs selected via backward elimination consistently included NGAL, which consistently improved model discrimination (all P<0.05), but not creatinine.

## NGAL and clinically relevant WRF

To investigate the value of NGAL for distinguishing between WRF with good and poor outcome, we first examined NGAL and creatinine trajectories in patients who experienced WRF (or not) who had died (or not) by 180 days (Figure 3). Baseline serum NGAL was higher and rose further in patients who died compared to survivors and was higher in patients with WRF irrespective of outcome. The pattern was similar for patients who did or did not reach the 60-day endpoint. WRF with a poor outcome was better

predicted by a non-diagnostic increase in creatinine on day 2 than change in NGAL (P<0.05, Supplementary Table S5). NGAL did show significant added value when added to creatinine, with consistently higher Goodness of Fit in mutually adjusted models (Table 4).

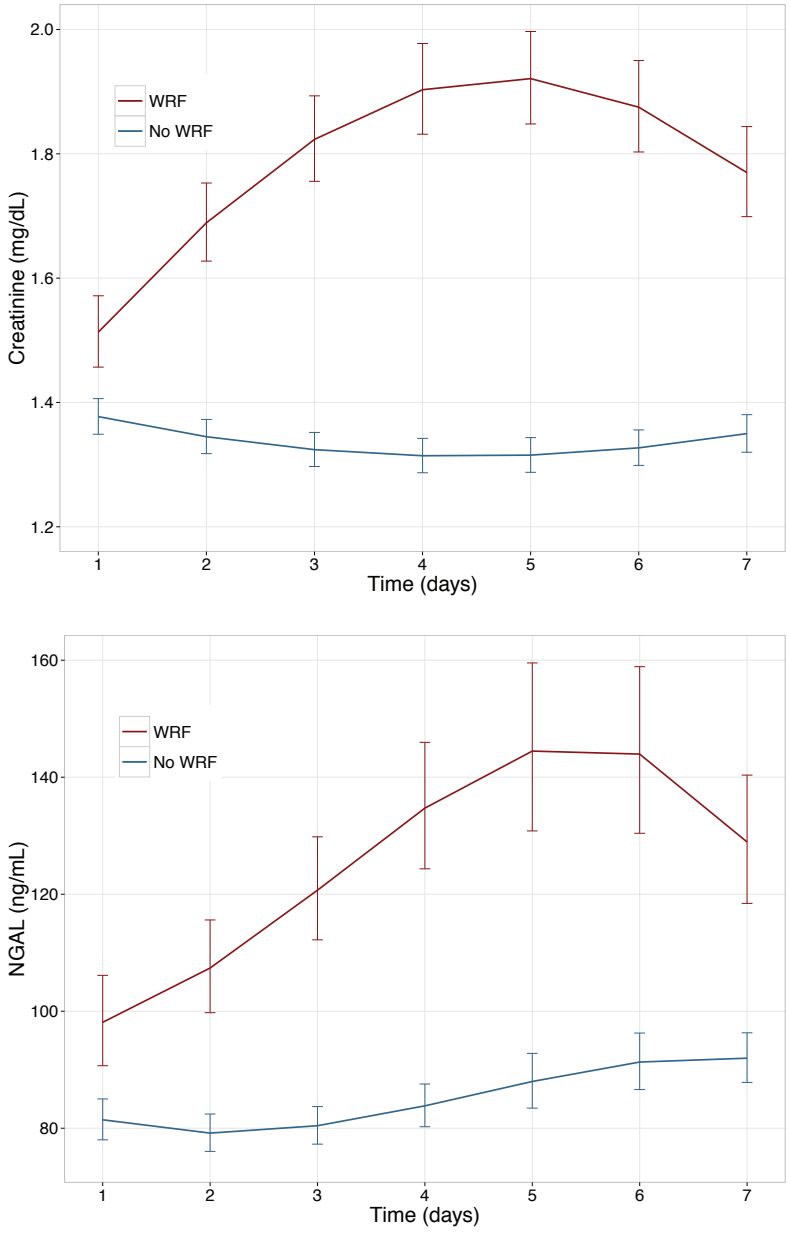



**Figure 1** Changes in serum Creatinine and NGAL in patients with and without WF

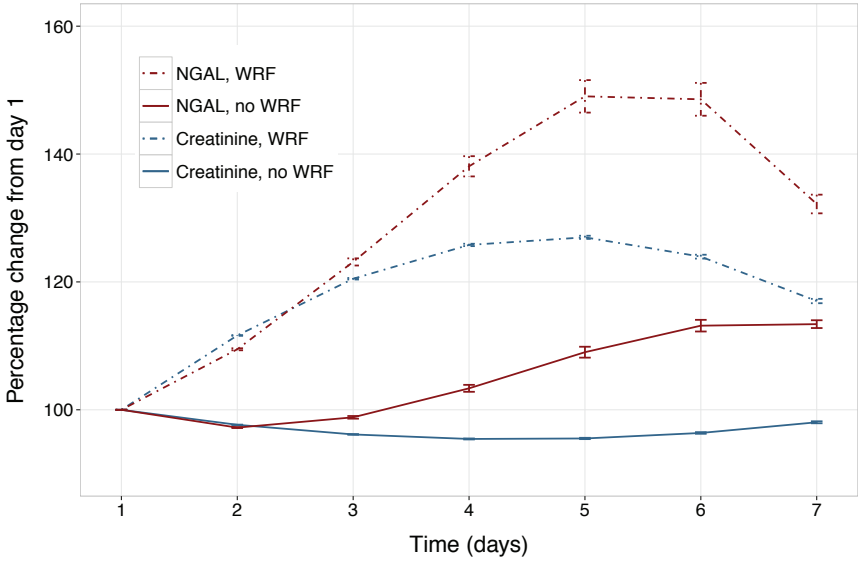



**Figure 2** Relative changes in serum Creatinine and NGAL

## NGAL, WRF and clinical outcome

In Cox models, baseline serum creatinine and NGAL were both associated, in univariable analysis, with 180-day mortality (HR per SD: 1.27, 95% CI 1.15-1.41 vs. 1.16, 95% CI 1.07-1.27, respectively, both p<0.001) and the 60-day composite of death or rehospitalization for renal or cardiovascular causes (HR per SD: 1.24, 95% CI 1.15-1.35 vs. 1.16, 95% CI 1.08-1.25, respectively, both p<0.001). After correction for either serum creatinine or eGFR, NGAL was no longer associated with either endpoint. WRF was independently associated with both endpoints (multivariable HR for 180-day mortality: 1.45, 95% CI 1.12-1.88, p=0.004; multivariable HR for the 60-day composite: 1.27, 95% CI 1.01-1.59, p=0.04); sensitivity analyses with absolute change in creatinine and other definitions for WRF showed similar results (data not shown).

Figure 4 displays the multivariable hazard ratios for the 60-day composite endpoint for the continuous interaction between absolute change in creatinine and baseline values of creatinine and NGAL, illustrating an incrementally greater relative risk of any given absolute creatinine increase in patients with higher NGAL levels (P=0.024), but not higher creatinine levels (P=0.464) There were no significant interactions between changes in creatinine and baseline levels of NGAL or creatinine for 180-day mortality, although patterns were similar. Study treatment had no effect on outcomes or interactions with WRF or other covariates in any of the models.

**Table 2** Predictive value of NGAL and Creatinine for WRF

| | Baseline Values | | |
|---|---|---|---|
| **WRF definition** | **Creatinine AUC** | **NGAL AUC** | **P** |
| ≥ 0.3 mg/dL increase | 0.571 | 0.569 | 0.930 |
| ≥ 0.6 mg/dL increase | 0.637 | 0.656 | 0.429 |
| ≥ 1.2 mg/dL increase | 0.678 | 0.689 | 0.753 |
| ≥ 25% increase | 0.575 | 0.512 | 0.077 |
| ≥ 50% increase | 0.515 | 0.564 | 0.395 |
| ≥ 100% increase | 0.524 | 0.590 | 0.083 |
| ≥ 0.3 mg/dL & ≥ 25% increase | 0.532 | 0.545 | 0.710 |
| | **Day 2 values** | | |
| **WRF definition** | **Creatinine AUC** | **NGAL AUC** | **P** |
| ≥ 0.3 mg/dL increase | 0.617 | 0.570 | 0.097 |
| ≥ 0.6 mg/dL increase | 0.701 | 0.637 | 0.142 |
| ≥ 1.2 mg/dL increase | 0.758 | 0.672 | 0.202 |
| ≥ 25% increase | 0.517 | 0.512 | 0.870 |
| ≥ 50% increase | 0.583 | 0.564 | 0.818 |
| ≥ 100% increase | 0.659 | 0.590 | 0.509 |
| ≥ 0.3 mg/dL & ≥ 25% increase | 0.517 | 0.520 | 0.939 |
| | **Change on day 2** | | |
| **WRF definition** | **Creatinine AUC** | **NGAL AUC** | **P** |
| ≥ 0.3 mg/dL increase | 0.718 | 0.491 | <0.001 |
| ≥ 0.6 mg/dL increase | 0.768 | 0.493 | <0.001 |
| ≥ 1.2 mg/dL increase | 0.818 | 0.486 | <0.001 |
| ≥ 25% increase | 0.737 | 0.514 | <0.001 |
| ≥ 50% increase | 0.790 | 0.514 | <0.001 |
| ≥ 100% increase | 0.759 | 0.574 | 0.001 |
| ≥ 0.3 mg/dL & ≥ 25% increase | 0.722 | 0.506 | <0.001 |

Abbreviations: WRF: worsening renal function, defined as diagnostic increase through day 4; AUC: area under the receiver-operator characteristics (ROC) curve.

**Table 3** Multivariable logistic regression for prediction of worsening renal function

| | **OR (95% CI)** | $\chi^2$ | **P** |
|---|---|---|---|
| Cholesterol (per SD) | 1.33 (1.16-1.52) | 16.26 | <0.001 |
| Haemoglobin (per SD) | 0.77 (0.67-0.90) | 11.45 | 0.001 |
| NGAL (per SD) | 1.23 (1.08-1.40) | 9.79 | 0.002 |
| History of Stroke | 1.89 (1.25-2.83) | 9.52 | 0.002 |
| Male Sex | 1.48 (1.10-2.01) | 6.55 | 0.010 |
| Albumin (per SD) | 1.19 (1.03-1.38) | 5.77 | 0.016 |
| Rolofylline treatment | 1.39 (1.04-1.87) | 4.78 | 0.029 |

Abbreviations: SD: standard deviation

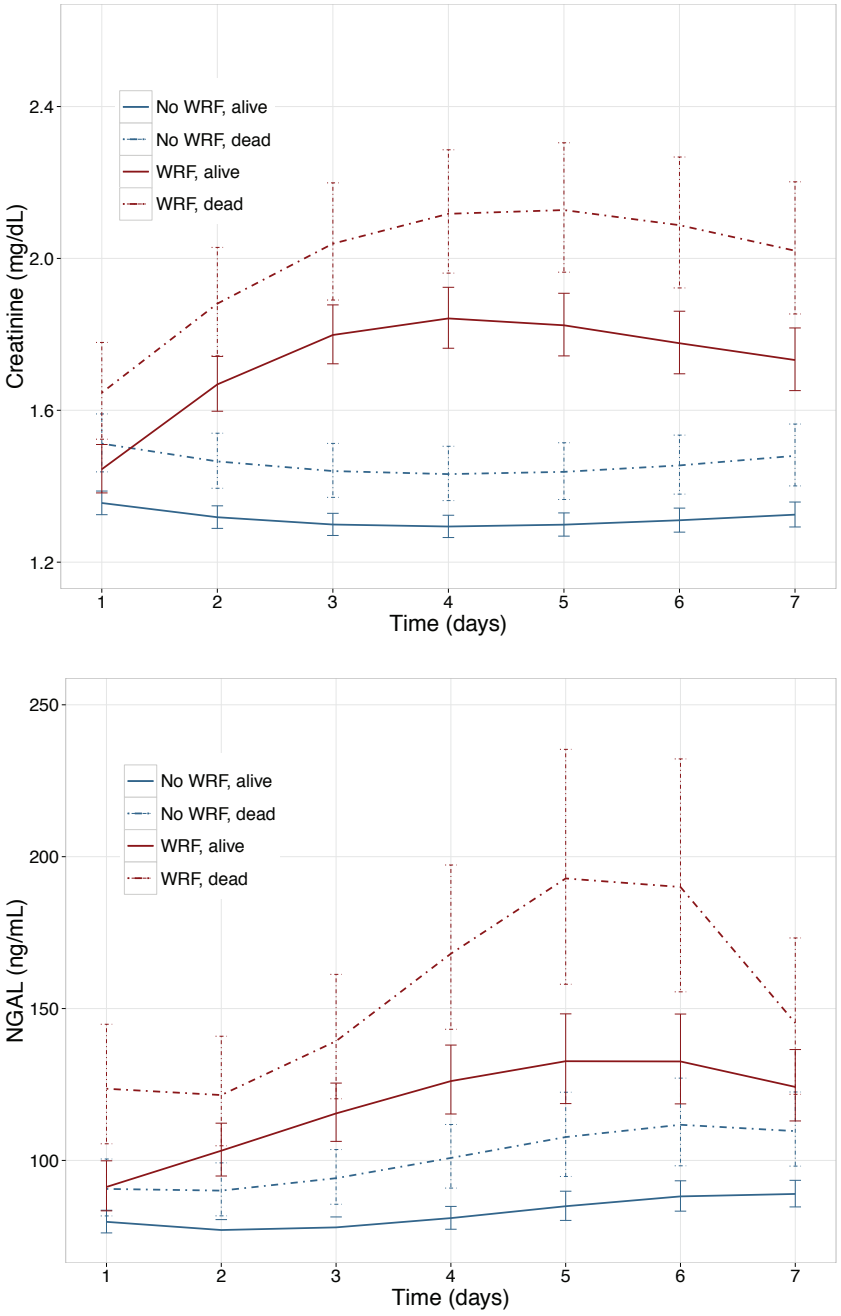



**Figure 3** Changes in serum Creatinine and NGAL in patients with and without worsening renal function by vital status at 180 days

Change in NGAL on day 2 was not multivariably associated with either outcome. The clinical value of changes in NGAL within the context of WRF was examined by comparing clinical outcomes between patients with and without WRF, and with a similar rise in NGAL on day 2. This was defined as an increase of ≥1 SD (≥ 88 ng/mL), as the SD for change in creatinine by day 4 was about 0.3 mg/dL, resembling the definition of WRF. The Kaplan-Meier curve is displayed as Figure 5, showing a significantly increased risk of mortality if both markers increased significantly (P-value for WRF with NGAL increase ≥ 88 ng/mL versus the other three groups = 0.007). After multivariable adjustment, compared to patients with no WRF and <1 SD NGAL increase, only patients with WRF had an increased risk of mortality, irrespective of NGAL levels (HR for WRF with <1 SD NGAL increase: 1.64, 95% CI 1.22-2.20, p<0.001; HR for WRF with ≥1 SD NGAL increase: 1.97, 95% CI 1.13-3.44, p=0.016). Only WRF and ≥1 SD NGAL increase was multivariably predictive of the 60-day composite endpoint (HR 1.67, 95% CI 1.03-2.72, P=0.037). Considered continuously, there was no significant multivariable interaction for change in creatinine and change in NGAL on either endpoint.

**Table 4** Added value of NGAL over Creatinine for predicting clinically relevant WRF

| | MV Model* | | | | |
|---|---|---|---|---|---|
| **WRF definition** | **OR (95% CI)** | **$\chi^2$** | **P** | **AUC** | **P**** |
| **WRF and 180-day mortality ***** | | | | | |
| **≥ 0.3 mg/dL Increase** | | | | | |
| Creatinine | 1.26 (1.02-1.55) | 4.81 | 0.028 | 0.670 | 0.021 |
| NGAL | 1.25 (1.04-1.48) | 6.52 | 0.011 | | |
| **≥ 25% & ≥ 0.3mg/dL Increase** | | | | | |
| Creatinine | 1.03 (0.78-1.33) | 0.04 | 0.833 | 0.637 | 0.017 |
| NGAL | 1.31 (1.06-1.56) | 7.53 | 0.006 | | |
| **WRF and 60-day endpoint ***** | | | | | |
| **≥ 0.3 mg/dL Increase** | | | | | |
| Creatinine | 1.25 (1.03-1.5) | 5.36 | 0.021 | 0.656 | 0.001 |
| NGAL | 1.32 (1.12-1.55) | 11.69 | 0.001 | | |
| **≥ 25% & ≥ 0.3mg/dL Increase** | | | | | |
| Creatinine | 1.03 (0.81-1.29) | 0.05 | 0.821 | 0.633 | 0.005 |
| NGAL | 1.31 (1.09-1.55) | 9.57 | 0.002 | | |

* Multivariable logistic model including both creatinine and NGAL, OR presented per standard deviation
** Likelihood ratio test for added value of adding NGAL to a model with creatinine alone
*** Prediction of WRF with poor clinical outcome compared to all other patients
Abbreviations: WRF: worsening renal function, defined as diagnostic increase through day 4; AUC: area under the receiver-operator characteristics (ROC) curve. OR: Odds Ratio.

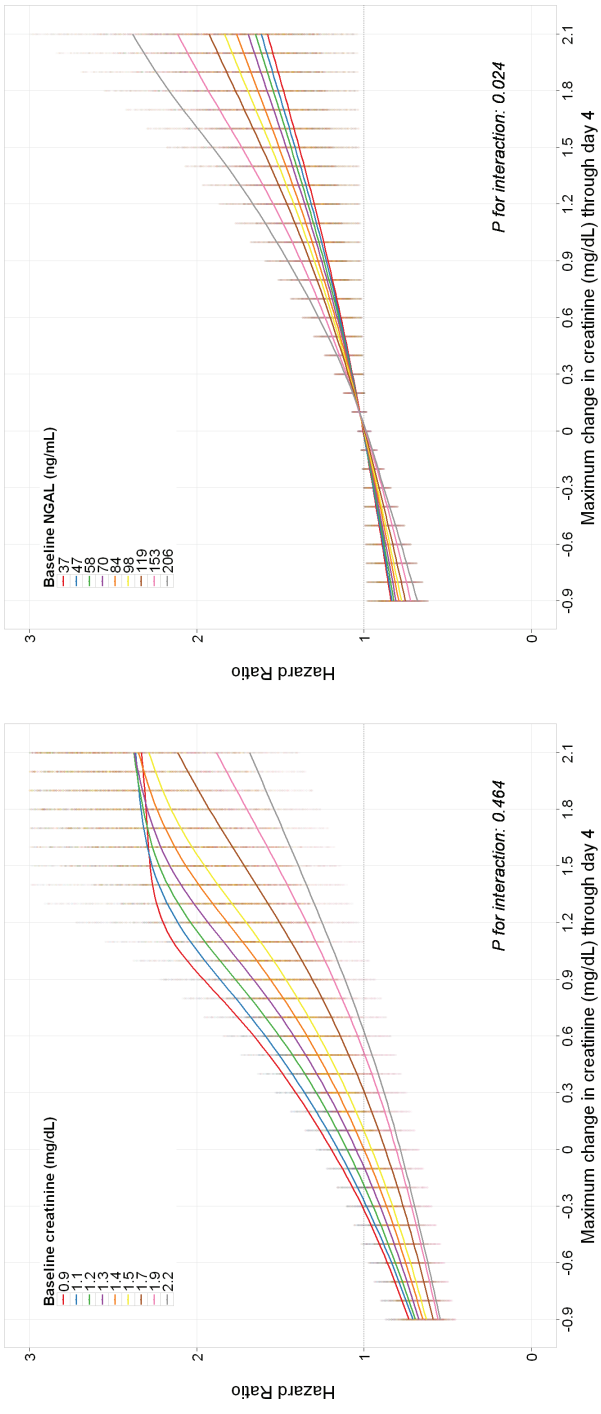



**Figure 4** Relationships of baseline NGAL, creatinine and absolute change in creatinine with the 60-day composite endpoint

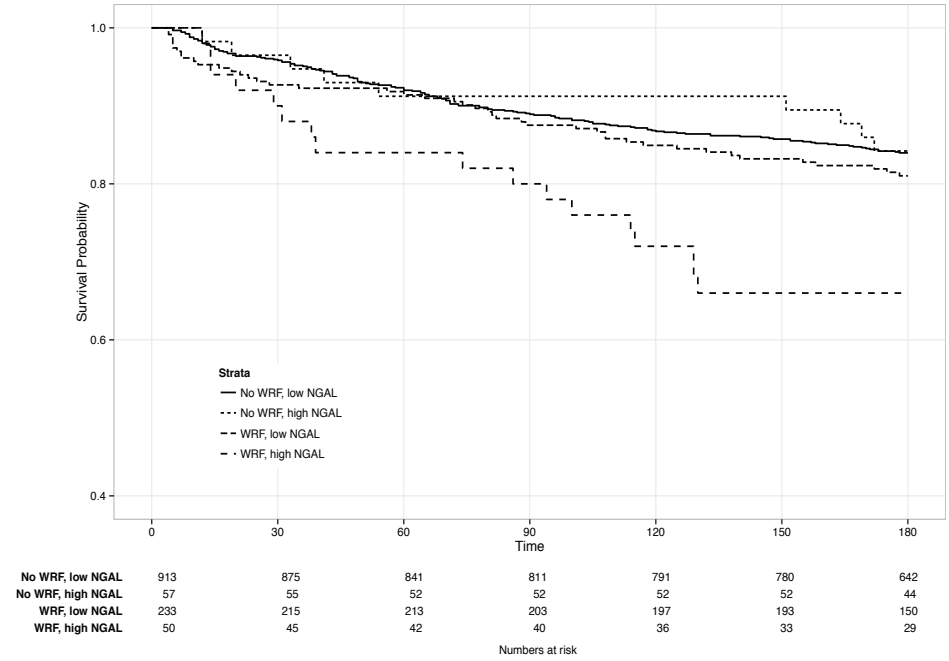



**Figure 5** 180-day survival in patients with vs. without WRF, high vs. low change in NGAL

## Discussion

We examined the value of NGAL for predicting clinically relevant WRF and outcomes in 1447 patients admitted with acute heart failure, to our knowledge the largest cohort of AHF patients with available serial serum NGAL measurements. WRF was common, occurring in 22% of patients during the first four days of admission. Patients who developed WRF were more likely to have poor renal function at baseline, although only NGAL - but not creatinine - was independently associated with its development after multivariable correction. Contrary to many previous reports in heart failure and other populations, we found no indication that serum NGAL rises earlier than creatinine in patients who develop WRF; both markers rose in tandem over the first two days of admission. The ability of both NGAL and creatinine to predict WRF was modest at best, with AUCs – individual or combined – below 0.60. NGAL showed statistically significant but very modest incremental value when added to creatinine for predicting WRF, for all definitions and cut-offs examined. Furthermore, while high levels of both NGAL and creatinine at baseline were associated with poor outcome, neither was independently predictive after adjustment for clinical covariates. However, change in creatinine was a strong, independent predictor of outcome (as shown previously in by Givertz et al.,[19]) both as a continuous variable and dichotomized as WRF, and carried significantly greater prognostic significance for short-term outcome in patients with higher NGAL levels.

## Prediction of WRF

NGAL has been identified as a powerful early predictor of WRF in a number of different clinical settings,[6,20-27] although the data in acute heart failure are conflicting.[8-14,28] Similarly to Breidthardt et al.,[8] we found only very modest predictive ability for serum NGAL, which provided only slight improvement on top of creatinine for predicting WRF. The clinical value of these minimal increases in discrimination is debatable at best.

One potential issue is the self-fulfilling nature of predicting a rise in creatinine using creatinine; this is reflected clearly by the much higher AUCs for delta creatinine compared to delta NGAL on day 2. Interestingly, however, we found that baseline NGAL values – but not baseline creatinine values – predicted WRF in multivariable models; other explanatory covariates included male sex, low haemoglobin levels and rolofylline treatment itself. Regardless, the hypothesis that NGAL rises earlier than creatinine does not hold true in this AHF cohort, as illustrated by the estimated trajectories corrected for study treatment.

There are several potential explanations for the lack of prognostic accuracy for WRF seen in our and other studies in AHF. First, there are likely multiple mechanisms for WRF at play in AHF patients. For example, true acute kidney injury resulting in tubular damage, with substantial and rapid loss of function and decreased urine output is probably not comparable to the kind of WRF studied extensively AHF. In the clinical context of AHF, changes in renal function may be driven more by hemodynamic and neurohormonal (mal)adaptation and drug effects than by the (hypoxic) kidney injury common in intensive care or post-surgical settings; Dupont et al. showed that despite a relatively high incidence of AKI defined based on creatinine increases, tubular injury was relatively uncommon in a small, prospective study of 141 AHF patients.[28] Second, in contrast with studies in post-surgical or post-intervention patients,[20-22,26,27,29] the timing of renal injury is often unclear in AHF, and its preclinical course may vary significantly and could include preclinical WRF. Pre-admission worsening congestion and intensification of diuretic therapy may have already triggered progressive renal impairment in the patients in our study – all of whom had at least a brief history of heart failure. Thus, the lack of an early rise in NGAL may simply reflect the fact damage had already occurred prior to admission. Third, there is some debate on the best measure for renal function and injury; definition of WRF based on a more 'pure' marker, such as cystatin C or measured GFR, may have yielded different results. Fourth, serum NGAL is more than merely a tubular marker, and strongly related to glomerular filtration rate - as reflected by its correlation with GFR and creatinine - and also involved in iron scavenging and immune response, as indicated by the correlation with markers such as CRP and markers of anaemia.[30,31] Shrestha et al noted strong correlations between urinary NGAL and measures for natriuresis and response to diuretics, while serum NGAL only correlated well with GFR, though both were predictive of WRF.(12) Importantly, our additional analysis of clinically relevant WRF (that is, WRF associated with poor clinical outcome), showed patients with WRF and an adverse outcome had much

higher NGAL levels overall. Additionally, NGAL showed a greater independent predictive value for WRF than creatinine, as shown in Table 3.

## NGAL, creatinine and outcome

Impaired and worsening renal function are established risk markers in heart failure.[32] Data on the prognostic value of NGAL is mixed, with many[10,14,15,33-36] – but not all[37] - studies in both chronic and acute heart failure reporting prognostic value, though the degree of correction for potential confounders varies greatly. Givertz et al. previously reported on the prognostic value of various renal markers in PROTECT during the first seven days of admission, concluding that change in creatinine and baseline BUN were strong predictors of outcome.[19] Overall, we found no independent predictive value of NGAL for either outcome. However, our analyses show that NGAL modulates the risk of outcome when examined together with worsening renal function, conferring a greater relative risk to patients with higher NGAL levels with a creatinine increase, but not in patients without. This effect is independent of baseline creatinine. Thus, while serum NGAL levels appear to largely reflect GFR (and thus creatinine) and are not independently prognostic, they do have some incremental value for assessing the risk associated with WRF, and can help discriminate between higher and lower risk WRF.

## Clinical perspectives

Identifying patients at high risk of developing cardiorenal syndromes and poor outcomes remains a challenge in AHF. Coupled with a lack of effective therapeutic options, this poses a problem for both clinicians and the development of targeted therapies. Biomarkers such as NGAL can be used as diagnostic or prognostic tools, though their application requires careful and thorough evaluation. Despite the extensive, but conflicting literature on (serum) NGAL, our analyses in this very large group of well-characterized AHF patients indicate poor to modest accuracy for predicting WRF. While our results indicate patients with high baseline levels of NGAL and WRF have a statistically significant greater risk of poor outcome compared to patients with similarly elevated levels of baseline creatinine and WRF, the clinical relevance of these findings – given the lack of independent prognostic value for NGAL – remains to be established. Ultimately, the results of large, prospective, adequately powered trials will hopefully help resolve the uncertainties surrounding the clinical utility of NGAL.

## Limitations

Due to the retrospective nature of this study, our results should be considered hypothesis-generating and interpreted cautiously. Nevertheless, this is currently the largest cohort of acute heart failure patients with available serial NGAL and creatinine measurements. Furthermore, NGAL was measured in frozen samples, which may have affected data quality. No urine was collected, so the performance of urinary NGAL could not be compared that of serum NGAL, and may have shown very different patterns and results.

## Conclusion

In this study in 1447 acute heart failure patients, we showed that NGAL levels did not rise earlier than creatinine in patients who developed WRF. Additionally, both NGAL and creatinine were similarly poor to modest predictors of WRF during the first four days of hospitalization. NGAL had limited incremental discriminative value when added to creatinine, but only NGAL – not creatinine – remained independently predictive of WRF after multivariable adjustment. Baseline NGAL levels provided some incremental risk information for predicting 60-day death or renal or cardiovascular rehospitalization in patients who developed worsening renal function, though it was not itself independently predictive of outcome. Our results suggest that serial serum NGAL levels provide some additional information for the prediction of clinically significant WRF in patients with AHF.

## References


1. Felker GM, Lee KL, Bull DA, Redfield MM, Stevenson LW, Goldsmith SR, LeWinter MM, Deswal A, Rouleau JL, Ofili EO, Anstrom KJ, Hernandez AF, McNulty SE, Velazquez EJ, Kfoury AG, Chen HH, Givertz MM, Semigran MJ, Bart BA, Mascette AM, Braunwald E, O'Connor CM, NHLBI Heart Failure Clinical Research Network. Diuretic strategies in patients with acute decompensated heart failure. *N Engl J Med* 2011;364:797-805.
2. Testani JM, Chen J, McCauley BD, Kimmel SE, Shannon RP. Potential effects of aggressive decongestion during the treatment of decompensated heart failure on renal function and survival. *Circulation* 2010;122:265-272.
3. Metra M, Davison B, Bettari L, Sun H, Edwards C, Lazzarini V, Piovanelli B, Carubelli V, Bugatti S, Lombardi C, Cotter G, Dei Cas L. Is worsening renal function an ominous prognostic sign in patients with acute heart failure? The role of congestion and its interaction with renal function. *Circ Heart Fail* 2012;5:54-62.
4. Testani JM, Kimmel SE, Dries DL, Coca SG. Prognostic importance of early worsening renal function after initiation of angiotensin-converting enzyme inhibitor therapy in patients with cardiac dysfunction. *Circ Heart Fail* 2011;4:685-691.
5. Valente MA, Voors AA, Damman K, Van Veldhuisen DJ, Massie BM, O'Connor CM, Metra M, Ponikowski P, Teerlink JR, Cotter G, Davison B, Cleland JG, Givertz MM, Bloomfield DM, Fiuzat M, Dittrich HC, Hillege HL. Diuretic response in acute heart failure: clinical characteristics and prognostic significance. *Eur Heart J* 2014;35:1284-1293.
6. Haase M, Devarajan P, Haase-Fielitz A, Bellomo R, Cruz DN, Wagener G, Krawczeski CD, Koyner JL, Murray P, Zappitelli M, Goldstein SL, Makris K, Ronco C, Martensson J, Martling CR, Venge P, Siew E, Ware LB, Ikizler TA, Mertens PR. The outcome of neutrophil gelatinase-associated lipocalin-positive subclinical acute kidney injury: a multicenter pooled analysis of prospective studies. *J Am Coll Cardiol* 2011;57:1752-1761.
7. Aghel A, Shrestha K, Mullens W, Borowski A, Tang WH. Serum neutrophil gelatinase-associated lipocalin (NGAL) in predicting worsening renal function in acute decompensated heart failure. *J Card Fail* 2010;16:49-54.
8. Breidthardt T, Socrates T, Drexler B, Noveanu M, Heinisch C, Arenja N, Klima T, Zusli C, Reichlin T, Potocki M, Twerenbold R, Steiger J, Mueller C. Plasma neutrophil gelatinase-associated lipocalin for the prediction of acute kidney injury in acute heart failure. *Crit Care* 2012;16:R2.
9. Mortara A, Bonadies M, Mazzetti S, Fracchioni I, Delfino P, Chioffi M, Bersano C, Specchia G. Neutrophil gelatinase-associated lipocalin predicts worsening of renal function in acute heart failure: methodological and clinical issues. *J Cardiovasc Med (Hagerstown)* 2013;14:629-634.
10. Palazzuoli A, Ruocco G, Beltrami M, Franci B, Pellegrini M, Lucani B, Nuti R, Ronco C. Admission plasma neutrophil gelatinase associated lipocalin (NGAL) predicts worsening renal function during hospitalization and post discharge outcome in patients with acute heart failure. *Acute Card Care* 2014;
11. Alvelos M, Pimentel R, Pinho E, Gomes A, Lourenco P, Teles MJ, Almeida P, Guimaraes JT, Bettencourt P. Neutrophil gelatinase-associated lipocalin in the diagnosis of type 1 cardio-renal syndrome in the general ward. *Clin J Am Soc Nephrol* 2011;6:476-481.
12. Shrestha K, Shao Z, Singh D, Dupont M, Tang WH. Relation of systemic and urinary neutrophil gelatinase-associated lipocalin levels to different aspects of impaired renal function in patients with acute decompensated heart failure. *Am J Cardiol* 2012;110:1329-1335.
13. Macdonald S, Arendts G, Nagree Y, Xu XF. Neutrophil Gelatinase-Associated Lipocalin (NGAL) predicts renal injury in acute decompensated cardiac failure: a prospective observational study. *BMC Cardiovasc Disord* 2012;12:8-2261-12-8.
14. Alvelos M, Lourenco P, Dias C, Amorim M, Rema J, Leite AB, Guimaraes JT, Almeida P, Bettencourt P. Prognostic value of neutrophil gelatinase-associated lipocalin in acute heart failure. *Int J Cardiol* 2013;165:51-55.
15. Maisel AS, Mueller C, Fitzgerald R, Brikhan R, Hiestand BC, Iqbal N, Clopton P, van Veldhuisen DJ. Prognostic utility of plasma neutrophil gelatinase-associated lipocalin in patients with acute heart failure: the NGAL EvaLuation Along with B-type NaTriuretic Peptide in acutely decompensated heart failure (GALLANT) trial. *Eur J Heart Fail* 2011;13:846-851.
16. Weatherley BD, Cotter G, Dittrich HC, DeLucca P, Mansoor GA, Bloomfield DM, Ponikowski P, O'Connor CM, Metra M, Massie BM, PROTECT Steering Committee, Investigators, and Coordinators. Design and rationale of the PROTECT study: a 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. *J Card Fail* 2010;16:25-35.
17. Massie BM, O'Connor CM, Metra M, Ponikowski P, Teerlink JR, Cotter G, Weatherley BD, Cleland JG, Givertz MM, Voors A, DeLucca P, Mansoor GA, Salerno CM, Bloomfield DM,

Dittrich HC, PROTECT Investigators and Committees. Rolofylline, an adenosine A1-receptor antagonist, in acute heart failure. *N Engl J Med* 2010;363:1419-1428.

18. Cleland JG, Chiswell K, Teerlink JR, Stevens S, Fiuzat M, Givertz MM, Davison BA, Mansoor GA, Ponikowski P, Voors AA, Cotter G, Metra M, Massie BM, O'Connor CM. Predictors of postdischarge outcomes from information acquired shortly after admission for acute heart failure: a report from the 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 (PROTECT) Study. *Circ Heart Fail* 2014;7:76-87.
19. Givertz MM, Postmus D, Hillege HL, Mansoor GA, Massie BM, Davison BA, Ponikowski P, Metra M, Teerlink JR, Cleland JG, Dittrich HC, O'Connor CM, Cotter G, Voors AA. Renal function trajectories and clinical outcomes in acute heart failure. *Circ Heart Fail* 2014;7:59-67.
20. Mishra J, Dent C, Tarabishi R, Mitsnefes MM, Ma Q, Kelly C, Ruff SM, Zahedi K, Shao M, Bean J, Mori K, Barasch J, Devarajan P. Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery. *Lancet* 2005;365:1231-1238.
21. Xin C, Yulong X, Yu C, Changchun C, Feng Z, Xinwei M. Urine neutrophil gelatinase-associated lipocalin and interleukin-18 predict acute kidney injury after cardiac surgery. *Ren Fail* 2008;30:904-913.
22. Ling W, Zhaohui N, Ben H, Leyi G, Jianping L, Huili D, Jiaqi Q. Urinary IL-18 and NGAL as early predictive biomarkers in contrast-induced nephropathy after coronary angiography. *Nephron Clin Pract* 2008;108:c176-81.
23. Che M, Xie B, Xue S, Dai H, Qian J, Ni Z, Axelsson J, Yan Y. Clinical usefulness of novel biomarkers for the detection of acute kidney injury following elective cardiac surgery. *Nephron Clin Pract* 2010;115:c66-72.
24. Koyner JL, Garg AX, Coca SG, Sint K, Thiessen-Philbrook H, Patel UD, Shlipak MG, Parikh CR, for the TRIBE-AKI Consortium. Biomarkers Predict Progression of Acute Kidney Injury after Cardiac Surgery. *J Am Soc Nephrol* 2012;
25. Torregrosa I, Montoliu C, Urios A, Elmlili N, Puchades MJ, Solis MA, Sanjuan R, Blasco ML, Ramos C, Tomas P, Ribes J, Carratala A, Juan I, Miguel A. Early biomarkers of acute kidney failure after heart angiography or heart surgery in patients with acute coronary syndrome or acute heart failure. *Nefrologia* 2012;32:44-52.
26. Parikh CR, Coca SG, Thiessen-Philbrook H, Shlipak MG, Koyner JL, Wang Z, Edelstein CL, Devarajan P, Patel UD, Zappitelli M, Krawczeski CD, Passik CS, Swaminathan M, Garg AX, TRIBE-AKI Consortium. Postoperative biomarkers predict acute kidney injury and poor outcomes after adult cardiac surgery. *J Am Soc Nephrol* 2011;22:1748-1757.
27. Parikh CR, Devarajan P, Zappitelli M, Sint K, Thiessen-Philbrook H, Li S, Kim RW, Koyner JL, Coca SG, Edelstein CL, Shlipak MG, Garg AX, Krawczeski CD, TRIBE-AKI Consortium. Postoperative biomarkers predict acute kidney injury and poor outcomes after pediatric cardiac surgery. *J Am Soc Nephrol* 2011;22:1737-1747.
28. Dupont M, Shrestha K, Singh D, Awad A, Kovach C, Scarcipino M, Maroo AP, Tang WH. Lack of significant renal tubular injury despite acute kidney injury in acute decompensated heart failure. *Eur J Heart Fail* 2012;14:597-604.
29. Parikh CR, Jani A, Mishra J, Ma Q, Kelly C, Barasch J, Edelstein CL, Devarajan P. Urine NGAL and IL-18 are predictive biomarkers for delayed graft function following kidney transplantation. *Am J Transplant* 2006;6:1639-1645.
30. Schmidt-Ott KM, Mori K, Li JY, Kalandadze A, Cohen DJ, Devarajan P, Barasch J. Dual action of neutrophil gelatinase-associated lipocalin. *J Am Soc Nephrol* 2007;18:407-413.
31. Shrestha K, Borowski AG, Troughton RW, Klein AL, Tang WH. Association between systemic neutrophil gelatinase-associated lipocalin and anemia, relative hypochromia, and inflammation in chronic systolic heart failure. *Congest Heart Fail* 2012;18:239-244.
32. Damman K, Valente MA, Voors AA, O'Connor CM, van Veldhuisen DJ, Hillege HL. Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis. *Eur Heart J* 2014;35:455-469.
33. Bolignano D, Basile G, Parisi P, Coppolino G, Nicocia G, Buemi M. Increased plasma neutrophil gelatinase-associated lipocalin levels predict mortality in elderly patients with chronic heart failure. *Rejuvenation Res* 2009;12:7-14.
34. Damman K, Van Veldhuisen DJ, Navis G, Vaidya VS, Smilde TD, Westenbrink BD, Bonventre JV, Voors AA, Hillege HL. Tubular damage in chronic systolic heart failure is associated with reduced survival independent of glomerular filtration rate. *Heart* 2010;96:1297-1302.
35. Damman K, Masson S, Hillege HL, Maggioni AP, Voors AA, Opasich C, van Veldhuisen DJ, Montagna L, Cosmi F, Tognoni G, Tavazzi L, Latini R. Clinical outcome of renal tubular damage in chronic heart failure. *Eur Heart J* 2011;32:2705-2712.
36. van Deursen VM, Damman K, Voors AA, van der Wal MH, Jaarsma T, van Veldhuisen DJ, Hillege HL. Prognostic value of plasma neutrophil gelatinase-associated lipocalin for mortality in patients with heart failure. *Circ Heart Fail* 2014;7:35-42.

37. Nymo SH, Ueland T, Askevold ET, Flo TH, Kjekshus J, Hulthe J, Wikstrand J, McMurray J, Van Veldhuisen DJ, Gullestad L, Aukrust P, Yndestad A. The association between neutrophil gelatinase-associated lipocalin and clinical outcome in chronic heart failure: results from CORONA*. *J Intern Med* 2011;

# Supplementary materials – NGAL and WRF

**Table S1** Baseline characteristics across creatinine tertiles

| Creatinine tertiles | 1 [0.9-1.2] *(n=559)* | 1.4 [1.3-1.5] *(n=445)* | 2 [1.8-2.4] *(n=443)* | P-lin |
|---|---|---|---|---|
| **Demographics** | | | | |
| Sex (% Male) | 53.7 (300) | 67.2 (299) | 80.1 (355) | <0.001 |
| Age (years) | 69.2±12 | 70.9±11 | 71.1±10.3 | 0.008 |
| BMI (kg/m2) | 28.2±6.5 | 28.9±5.8 | 29.1±5.3 | 0.019 |
| LVEF (% (n)) | 33.7±13.1 | 32.9±13.5 | 30.9±12 | 0.021 |
| Systolic Blood Pressure (mmHg) | 125.5±17.1 | 125.2±17.4 | 124.1±18 | 0.187 |
| Diastolic Blood Pressure (mmHg) | 75.2±11.4 | 75.1±11.7 | 72.8±11.6 | 0.001 |
| Heart Rate (beats/min) | 83±16.1 | 81.3±15.9 | 78.4±15.3 | <0.001 |
| Rolofylline administration (% (n)) | 63.7 (356) | 68.5 (305) | 69.5 (308) | 0.045 |
| **Clinical Profile** | | | | |
| Orthopnea (% (n)) | 96.2 (532) | 96.8 (428) | 95.7 (422) | 0.711 |
| Rales (% (n)) | 66 (369) | 64.7 (288) | 59.3 (262) | 0.031 |
| Edema (% (n)) | 68 (380) | 71 (316) | 69.1 (306) | 0.663 |
| Jugular venous pressure (% (n)) | 39.7 (200) | 43.6 (170) | 44.1 (173) | 0.168 |
| **Medical History** | | | | |
| Hypertension (% (n)) | 78.4 (438) | 81.1 (361) | 79.7 (353) | 0.563 |
| Diabetes Mellitus (% (n)) | 38.6 (216) | 43.8 (195) | 53.4 (236) | <0.001 |
| Hypercholesterolemia (% (n)) | 36.7 (205) | 50.2 (223) | 54.9 (243) | <0.001 |
| Smoking (% (n)) | 15.9 (89) | 18.5 (82) | 20.4 (90) | 0.070 |
| Ischemic Heart Disease (% (n)) | 67.9 (378) | 67.6 (301) | 75.6 (335) | 0.010 |
| Myocardial Infarction (% (n)) | 46 (256) | 46.6 (207) | 57.6 (255) | <0.001 |
| PCI (% (n)) | 19.7 (109) | 20.8 (92) | 28.4 (124) | 0.002 |
| CABG (% (n)) | 11.9 (66) | 20.8 (92) | 29.2 (128) | <0.001 |
| Peripheral Vascular Disease (% (n)) | 8.6 (48) | 11.7 (52) | 13.8 (61) | 0.009 |
| Atrial Fibrillation (% (n)) | 53.9 (300) | 59.3 (262) | 53.5 (237) | 0.992 |
| NYHA Class | | | | <0.001 |
| I-II | 15.7 (88) | 16.2 (72) | 17.4 (77) | |
| III | 42 (235) | 47.6 (212) | 50.6 (224) | |
| IV | 37.6 (210) | 30.3 (135) | 27.1 (120) | |
| ICD therapy (% (n)) | 7.5 (42) | 14.6 (65) | 20.1 (89) | <0.001 |
| CRT therapy (% (n)) | 4.8 (27) | 10.6 (47) | 12.2 (54) | <0.001 |
| Stroke (% (n)) | 7.2 (40) | 11.2 (50) | 11.5 (51) | 0.017 |
| COPD (% (n)) | 19 (106) | 17.8 (79) | 22.4 (99) | 0.201 |
| **Prior Medication Use** | | | | |
| ACE inhibitors or ARB (% (n)) | 76.2 (426) | 77.5 (345) | 72 (319) | 0.149 |
| Beta blockers (% (n)) | 69.8 (390) | 76.2 (339) | 78.3 (347) | 0.002 |
| MRAs (% (n)) | 47.8 (267) | 48.3 (215) | 45.1 (200) | 0.433 |
| Calcium Antagonists (% (n)) | 11.3 (63) | 13.3 (59) | 16.5 (73) | 0.017 |
| Nitrates (% (n)) | 23.3 (130) | 26.5 (118) | 32.7 (145) | 0.001 |
| Digoxin (% (n)) | 36.5 (204) | 30.8 (137) | 23.3 (103) | <0.001 |
| **Laboratory Values** | | | | |
| eGFR (mL/min/1.73m2) | 68 [61-78] | 48.6 [42-55] | 32 [27-39] | <0.001 |
| NGAL (ng/ml) | 57 [41-84] | 81 [58-127] | 137 [95-204] | <0.001 |
| Blood Urea Nitrogen (mg/dL) | 22 [18-26] | 30 [25-38] | 45 [36-59] | <0.001 |
| Sodium (mmol/L) | 140 [138-143] | 140 [137-143] | 140 [137-142] | <0.001 |
| Potassium (mmol/L) | 4.2 [3.9-4.6] | 4.3 [3.9-4.6] | 4.4 [3.9-4.8] | <0.001 |
| Hemoglobin (g/dL) | 13.1±1.9 | 12.8±1.9 | 12.3±2 | <0.001 |
| Anemia (% (n)) | 28.1 (139) | 40.6 (162) | 58.5 (224) | <0.001 |
| Total Cholesterol (mmol/L) | 155±42 | 146±46 | 143±45 | <0.001 |
| Triglycerides (mmol/L) | 99±52 | 98±53 | 104±60 | 0.105 |
| BNP (mg/dL) | 1172 [775-2232] | 1302 [916-2152] | 1362 [811-2773] | 0.180 |

Abbreviations: see Chapter 7, table 1

**Table S2** Baseline characteristics across NGAL tertiles

| NGAL Tertiles | 44 [35-53] *(n=478)* | 83 [72-94] *(n=477)* | 166 [132-223] *(n=492)* | P-lin |
|---|---|---|---|---|
| **Demographics** | | | | |
| Sex (% Male) | 64.6 (309) | 66.9 (319) | 66.3 (326) | 0.599 |
| Age (years) | 67.5±12 | 70.7±11.1 | 72.7±9.9 | <0.001 |
| BMI (kg/m2) | 28.5±6.6 | 28.6±5.8 | 29±5.5 | 0.238 |
| LVEF (% (n)) | 31.9±12.3 | 31.7±12.9 | 33.9±13.4 | 0.101 |
| Systolic Blood Pressure (mmHg) | 124.9±17 | 124.4±17.5 | 125.6±17.8 | 0.521 |
| Diastolic Blood Pressure (mmHg) | 75.8±11.3 | 74.6±11.7 | 73±11.7 | <0.001 |
| Heart Rate (beats/min) | 83.8±16.4 | 80.8±16.1 | 78.7±14.9 | <0.001 |
| Rolofylline administration (% (n)) | 68 (325) | 65.4 (312) | 67.5 (332) | 0.871 |
| **Clinical Profile** | | | | |
| Orthopnea (% (n)) | 96.2 (456) | 96 (453) | 96.5 (473) | 0.786 |
| Rales (% (n)) | 67.2 (321) | 60.7 (289) | 62.8 (309) | 0.163 |
| Edema (% (n)) | 69 (330) | 70 (334) | 68.7 (338) | 0.906 |
| Jugular venous pressure (% (n)) | 43.6 (185) | 39.6 (168) | 43.4 (190) | 0.950 |
| **Medical History** | | | | |
| Hypertension (% (n)) | 77.4 (370) | 78.6 (375) | 82.7 (407) | 0.039 |
| Diabetes Mellitus (% (n)) | 35.8 (171) | 45.7 (218) | 52.5 (258) | <0.001 |
| Hypercholesterolemia (% (n)) | 41.2 (197) | 45.4 (216) | 52.4 (258) | <0.001 |
| Smoking (% (n)) | 18.4 (88) | 15.8 (75) | 20 (98) | 0.533 |
| Ischemic Heart Disease (% (n)) | 67.3 (321) | 69.8 (333) | 73.3 (360) | 0.040 |
| Myocardial Infarction (% (n)) | 47.9 (228) | 48.7 (232) | 52.5 (258) | 0.147 |
| PCI (% (n)) | 19 (90) | 23.8 (113) | 25.2 (122) | 0.024 |
| CABG (% (n)) | 14.2 (67) | 20.1 (95) | 25.4 (124) | <0.001 |
| Peripheral Vascular Disease (% (n)) | 9.2 (44) | 10.5 (50) | 13.7 (67) | 0.027 |
| Atrial Fibrillation (% (n)) | 54.1 (256) | 55.6 (265) | 56.5 (278) | 0.457 |
| NYHA Class | | | | 0.081 |
| I-II | 15.3 (73) | 15.5 (74) | 18.3 (90) | |
| III | 43.5 (208) | 46.8 (223) | 48.8 (240) | |
| IV | 36.2 (173) | 33.5 (160) | 26.8 (132) | |
| ICD therapy (% (n)) | 10.9 (52) | 14 (67) | 15.7 (77) | 0.031 |
| CRT therapy (% (n)) | 8.6 (41) | 9.2 (44) | 8.8 (43) | 0.931 |
| Stroke (% (n)) | 9.6 (46) | 7.5 (36) | 12 (59) | 0.208 |
| COPD (% (n)) | 18.4 (88) | 20.5 (98) | 20 (98) | 0.558 |
| **Prior Medication Use** | | | | |
| ACE inhibitors or ARB (% (n)) | 77.4 (370) | 75.9 (362) | 72.8 (358) | 0.093 |
| Beta blockers (% (n)) | 72.8 (348) | 74.4 (355) | 75.8 (373) | 0.283 |
| MRAs (% (n)) | 50.2 (240) | 47.4 (226) | 43.9 (216) | 0.049 |
| Calcium Antagonists (% (n)) | 9 (43) | 11.9 (57) | 19.3 (95) | <0.001 |
| Nitrates (% (n)) | 23.8 (114) | 26.8 (128) | 30.7 (151) | 0.017 |
| Digoxin (% (n)) | 35.1 (168) | 31.2 (149) | 25.8 (127) | 0.002 |
| **Laboratory Values** | | | | |
| Creatinine (mg/dL) | 1.1 [0.9-1.3] | 1.4 [1.1-1.7] | 1.8 [1.4-2.3] | <0.001 |
| eGFR (mL/min/1.73m2) | 64 [52-75] | 50 [40-63] | 37 [29-46] | <0.001 |
| Blood Urea Nitrogen (mg/dL) | 23 [18-30] | 29 [22-38] | 40 [30-54] | <0.001 |
| Sodium (mmol/L) | 140 [137-143] | 140 [137-143] | 140 [137-142] | 0.043 |
| Potassium (mmol/L) | 4.2 [3.8-4.5] | 4.2 [3.9-4.6] | 4.4 [4-4.8] | <0.001 |
| Hemoglobin (g/dL) | 13.4±1.9 | 12.7±1.9 | 12.2±1.9 | <0.001 |
| Anemia (% (n)) | 30.5 (129) | 41.3 (173) | 51.4 (223) | <0.001 |
| Total Cholesterol (mmol/L) | 153±43 | 146±47 | 146±44 | 0.015 |
| Triglycerides (mmol/L) | 97±51 | 99±56 | 105±57 | 0.015 |
| BNP (mg/dL) | 1265 [794-2276] | 1216 [868-2238] | 1340 [864-2336] | 0.605 |

Abbreviations: see Chapter 7, table 1

**Table S3** Added value of NGAL on top of Creatinine for predicting WRF

| WRF definition | MV Model* OR (95% CI) | $\chi^2$ | P | AUC | P** |
|---|---|---|---|---|---|
| **≥ 0.3 mg/dl increase** | | | | | |
| Creatinine | 1.12 (0.98-1.29) | 2.87 | 0.090 | 0.580 | 0.013 |
| NGAL | 1.18 (1.04-1.35) | 6.21 | 0.013 | | |
| **≥ 0.6 mg/dl increase** | | | | | |
| Creatinine | 1.33 (1.11-1.59) | 9.67 | 0.002 | 0.663 | 0.005 |
| NGAL | 1.27 (1.08-1.48) | 8.86 | 0.003 | | |
| **≥ 1.2 mg/dl increase** | | | | | |
| Creatinine | 1.49 (1.15-1.92) | 9.65 | 0.002 | 0.705 | 0.022 |
| NGAL | 1.31 (1.05-1.59) | 7.16 | 0.007 | | |
| **≥ 25% increase** | | | | | |
| Creatinine | 0.69 (0.58-0.82) | 16.47 | 0.000 | 0.595 | 0.009 |
| NGAL | 1.21 (1.05-1.4) | 7.03 | 0.008 | | |
| **≥ 50% increase** | | | | | |
| Creatinine | 0.84 (0.65-1.07) | 1.83 | 0.176 | 0.603 | 0.013 |
| NGAL | 1.27 (1.06-1.51) | 7.51 | 0.006 | | |
| **≥ 100% increase** | | | | | |
| Creatinine | 1.01 (0.67-1.44) | 0.00 | 0.953 | 0.603 | 0.058 |
| NGAL | 1.31 (0.99-1.61) | 5.34 | 0.021 | | |
| **≥ 0.3 mg/dL & ≥ 25% increase** | | | | | |
| Creatinine | 0.8 (0.67-0.94) | 6.66 | 0.010 | 0.576 | 0.007 |
| NGAL | 1.22 (1.06-1.42) | 7.69 | 0.006 | | |

* Mutually adjusted
** P value for likelihood ratio test versus creatinine alone, indicating the added value of NGAL on top of creatinine

**Table S4** Prediction of clinically relevant WRF

| WRF and 180-day mortality | Creatinine AUC | NGAL AUC | P-value |
|---|---|---|---|
| **WRF definition** | **Baseline Values** | | |
| ≥ 0.3 mg/dL increase | 0.647 | 0.649 | 0.954 |
| ≥ 25% increase | 0.539 | 0.623 | 0.012 |
| ≥ 0.3 mg/dL and ≥ 25% increase | 0.573 | 0.647 | 0.034 |
| | **Day 2 values** | | |
| ≥ 0.3 mg/dL increase | 0.715 | 0.653 | 0.184 |
| ≥ 25% increase | 0.595 | 0.593 | 0.979 |
| ≥ 0.3 mg/dL and ≥ 25% increase | 0.637 | 0.671 | 0.524 |
| | **Change on day 2** | | |
| ≥ 0.3 mg/dL increase | 0.625 | 0.487 | 0.007 |
| ≥ 25% increase | 0.640 | 0.503 | 0.015 |
| ≥ 0.3 mg/dL and ≥ 25% increase | 0.624 | 0.589 | 0.603 |
| **WRF and 60-day death, renal or CV rehospitalization** | **Creatinine AUC** | **NGAL AUC** | **P-value** |
| **WRF definition** | **Baseline Values** | | |
| ≥ 0.3 mg/dL increase | 0.635 | 0.639 | 0.901 |
| ≥ 25% increase | 0.539 | 0.610 | 0.020 |
| ≥ 0.3 mg/dL and ≥ 25% increase | 0.565 | 0.633 | 0.035 |
| | **Day 2 values** | | |
| ≥ 0.3 mg/dL increase | 0.680 | 0.633 | 0.330 |
| ≥ 25% increase | 0.603 | 0.576 | 0.646 |
| ≥ 0.3 mg/dL and ≥ 25% increase | 0.624 | 0.633 | 0.871 |
| | **Change on day 2** | | |
| ≥ 0.3 mg/dL increase | 0.712 | 0.469 | 0.000 |
| ≥ 25% increase | 0.711 | 0.481 | 0.000 |
| ≥ 0.3 mg/dL and ≥ 25% increase | 0.708 | 0.551 | 0.004 |

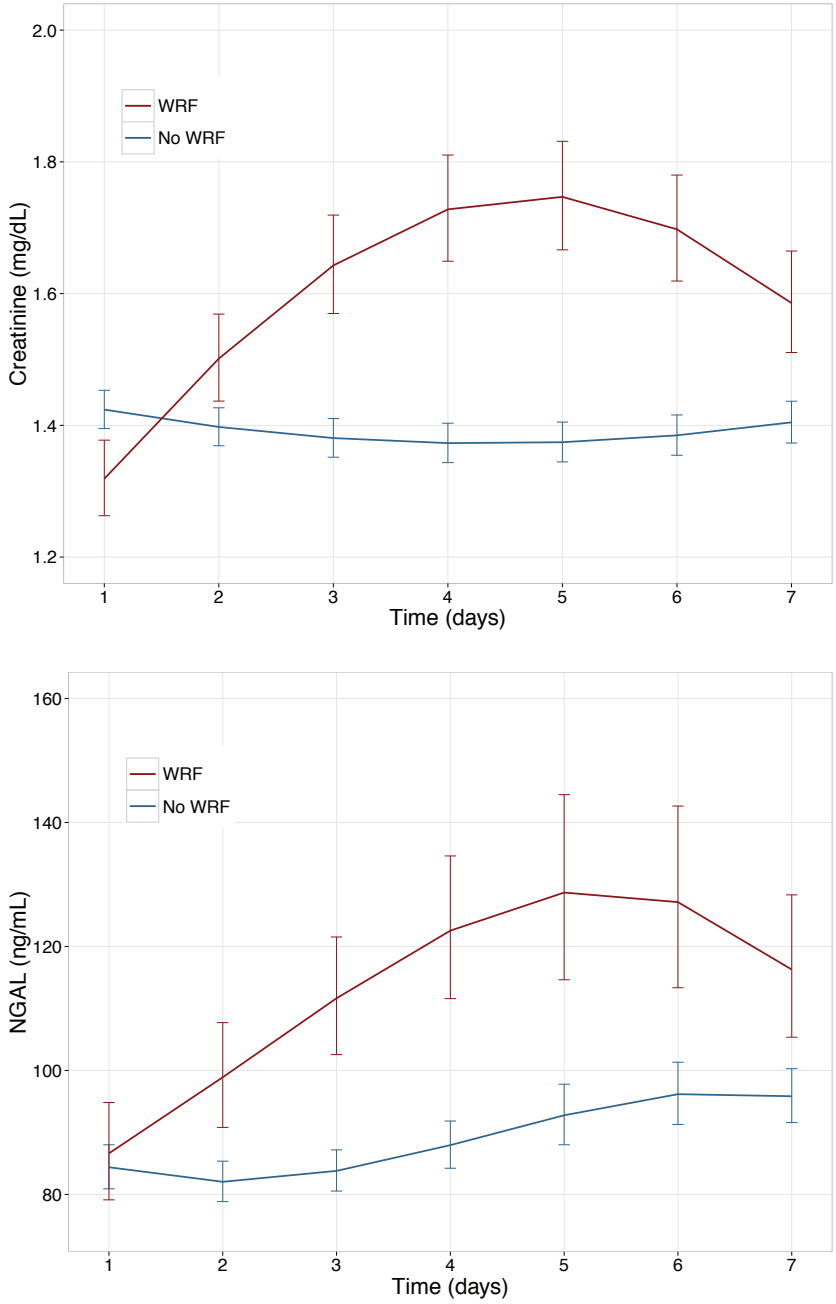



**Figure S1** Changes in serum Creatinine and NGAL in patients with and without WRF, defined as a creatinine increase of ≥ 25%.
Least square means with 95% confidence intervals. WRF: worsening renal function, defined as creatinine rise ≥ 25% by day 4

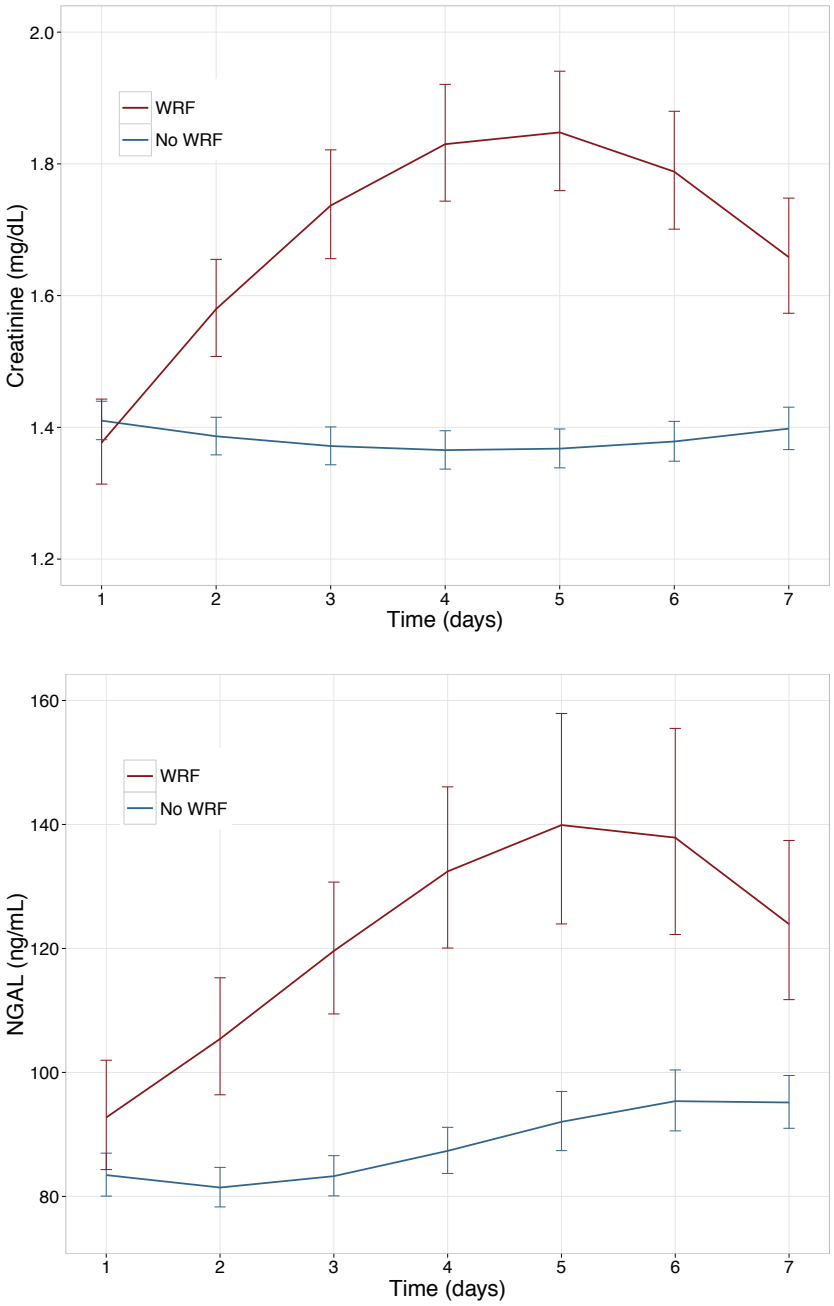



**Figure S2** Changes in serum Creatinine and NGAL in patients with and without WRF, defined as a combined creatinine increase of ≥0.3 mg/dL and ≥ 25%
Least square means with 95% confidence intervals over time, WRF: worsening renal function, defined as combined creatinine increase of ≥ 0.3 mg/dL and ≥25% by day 4

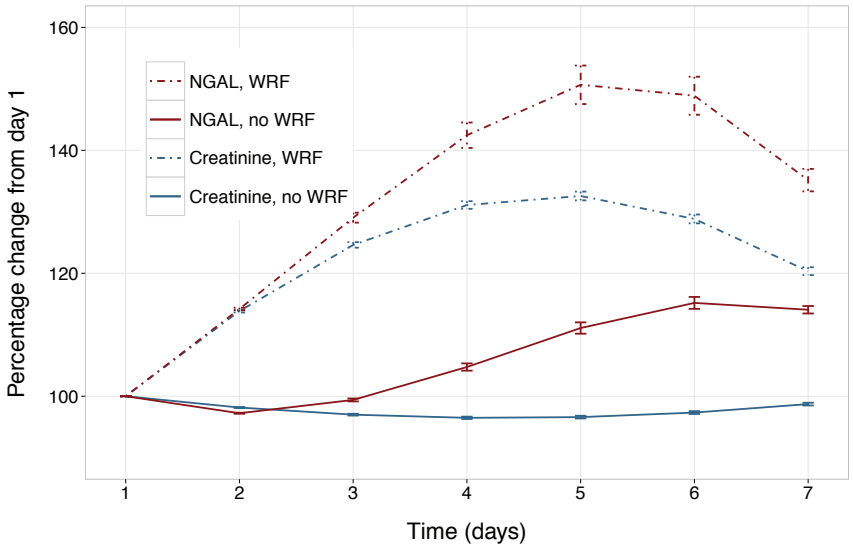



**Figure S3** Relative changes in serum Creatinine and NGAL in patients with WRF, defined as a creatinine increase of ≥ 25%

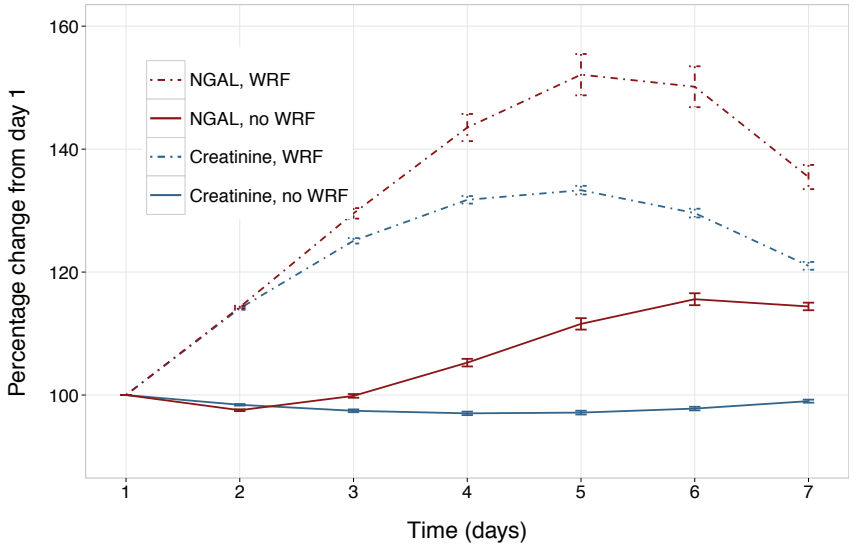
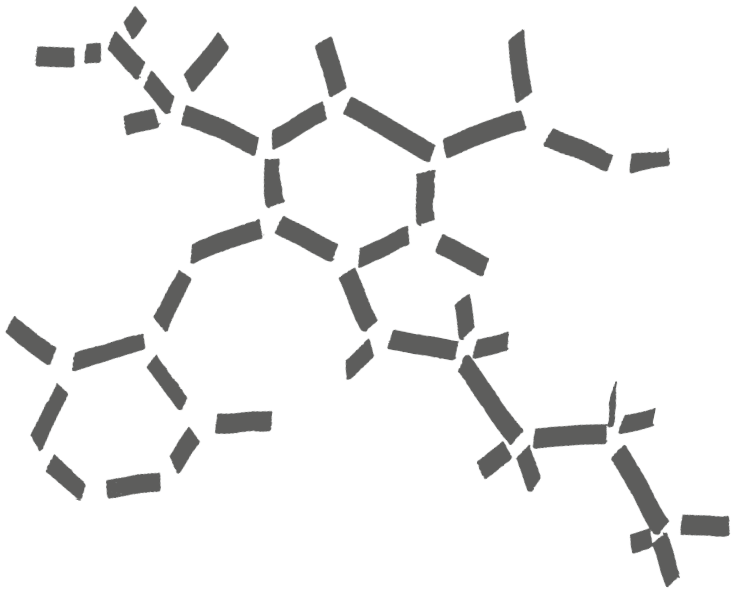



**Figure S3** Relative changes in serum Creatinine and NGAL in patients with WRF, defined as a combined creatinine increase of ≥0.3 mg/dL and ≥ 25%

# Chapter 8

# Diuretic response and resistance in acute heart failure: pathophysiology, evaluation and therapy

Jozine M. ter Maaten, Mattia A.E. Valente, Kevin Damman, Hans L. Hillege, Gerjan Navis and Adriaan A. Voors



Accepted for publication, Nature Reviews Cardiology

## Summary

Administration of loop diuretics to achieve decongestion is the cornerstone of acute heart failure therapy. Unfortunately, impaired response to diuretics is common and associated with adverse outcomes. Diuretic resistance is thought to result from a complex interplay between cardiac and renal dysfunction and specific renal adaptation and escape mechanisms. However, our understanding of diuretic response in acute heart failure is still limited and a uniform definition is lacking. Several strategies have been proposed to overcome diuretic resistance, including combination therapy and ultrafiltration, but prospective studies in truly unresponsive patients are lacking. A better understanding of diuretic response should ultimately lead to a better, individualized approach to treating patients with acute heart failure.

## Abbreviations

| | |
|---|---|
| ADH | Anti-Diuretic Hormone, arginine vasopressin |
| AHF | Acute Heart Failure |
| BUN | Blood Urea Nitrogen |
| ECV | Extracellular Volume |
| GFR | Glomerular Filtration Rate |
| MRA | Mineralocorticoid Receptor Antagonist |
| OAT | Organic Anion Transporter |
| RAAS | Renin-Angiotensin-Aldosterone System |

## Introduction

Acute heart failure (AHF) is one of the leading causes of hospital admission worldwide, and is associated with high morbidity, mortality and high rehospitalization rates.[1, 2] Most of the symptoms associated with acute heart failure are the result of excessive fluid retention, and loop diuretics are the treatment of choice to combat them. Loop diuretics are administered in up to 90% of patients hospitalized for acute heart failure, despite the lack of evidence for outcome benefit.[2, 3] Poor response to diuretics - persistent signs and symptoms despite adequate diuretic therapy, called diuretic resistance – frequently occurs during hospitalization for acute heart failure. In two recent studies, a poor response to diuretics was more frequently found in patients with diabetes, lower glomerular filtration rate (GFR), higher blood urea nitrogen (BUN) levels and a lower systolic blood pressure. Importantly, a poor diuretic response was independently associated with less symptom relief and a higher risk of in-hospital worsening heart failure, and increased post-discharge mortality and three times higher rehospitalization rates.[4, 5] In an accompanying editorial, Braunwald stressed the importance of diuretic resistance and called upon better definition and quantification of diuretic response to loop diuretics.[6] However, the pathophysiology behind diuretic resistance is not completely understood, but is thought to result from the complex interplay between cardiac and renal dysfunction and specific renal adaptation and escape mechanisms. This review will address the pathophysiologic background of diuretic resistance, the evaluation and definition of diuretic response, and current and future strategies aimed at improving diuretic response.

## Pathophysiology

### Cardiorenal interplay

Heart and kidney act in concert, regulating circulatory homeostasis through several mechanisms and feedback loops. In healthy individuals, glomerular filtration remains stable despite changes in volume and blood pressure. When triggered by sodium and volume overload, a rise in atrial pressure and release of natriuretic peptides facilitates renal sodium excretion via direct tubular effects and an increase in glomerular filtration rate.[7-9] Concomitant suppression of the renin-angiotensin-aldosterone system (RAAS) contributes to stable blood pressure via systemic vasodilation and renal sodium excretion by inhibiting the tubular effects of angiotensin II and aldosterone.[10] In contrast, in a volume depleted state, increased RAAS activity contributes to maintenance of blood pressure and renal sodium retention. Furthermore, angiotensin II induces renal efferent vasoconstriction, helping maintain renal filtration pressure and filtration rate despite decreasing arterial pressure. Sympathetic nervous system activation mirrors that of the RAAS. Moreover, the cardiorenal interaction affects osmoregulation via effects on water diuresis. Under physiological conditions, the release of arginine vasopressin (antidiuretic hormone, ADH) is stimulated by a high plasma osmolarity.[11] The ensuing renal water reten-

tion restores normal osmolarity. However, during pronounced volume disturbances, responses to volume depletion or overload can overrule the osmotic triggers, contributing to restoration of volume status at the expense of osmoregulation.

In acute heart failure, a decrease in cardiac function causes reduced cardiac output and arterial underfilling, leading to decreased activation of arterial stretch receptors, resulting in compensatory systemic and intrarenal vasoconstriction.[12] Decreased stretch of the glomerular afferent arteriole stimulates renin release, which leads to angiotensin II production. Angiotensin II causes afferent and efferent vasoconstriction, stimulates sodium retention in the proximal tubule and aldosterone release.[13] In turn, aldosterone increases sodium reabsorption in the collecting duct, resulting in extracellular fluid expansion and systemic congestion.[14] Normal, healthy subjects display an aldosterone escape mechanism, with sodium delivery to distal renal tubules caused by increased vascular volume overcoming the sodium retaining effect of aldosterone; this mechanism is impaired in heart failure patients, where reduced renal blood flow forces continued sodium retention in response to aldosterone.[12, 15]

Heart failure also causes baroreceptor-mediated sympathetic nervous system activation that promotes vasoconstriction and contributes to further RAAS activation and renal sodium and water retention.[16] ADH release exacerbates these effects.[17] Additionally, the protective effect of natriuretic peptides is diminished in AHF due to renal vasoconstriction, reduced sodium delivery, less active forms of natriuretic peptides and down-regulation of their receptors.[18, 19] The combination of the pathways described above creates a vicious circle that causes congestion and worsening heart failure.

A major symptom of heart failure is decreased organ perfusion. The kidney can compensate for a drop in renal blood flow by increasing the filtration fraction via the abovementioned angiotensin II-mediated efferent vasoconstriction, thus preserving GFR.[20] The combination of pump failure, neurohormonal activation and heart failure therapies – particularly angiotensin-converting enzyme inhibitors and angiotensin receptor blockers – can eventually overcome the kidney's ability to compensate for reduced perfusion.[21, 22] Additionally, increased venous filling and abdominal pressures caused by ascites can increase renal afterload and intrarenal pressure, reducing the transrenal perfusion gradient (and thus renal perfusion pressure), increasing renal interstitial pressure (directly opposing filtration pressure) and contributing further to renal insufficiency.[23-25]

## Mechanisms of diuretic resistance

Diuretics are the first-line therapy for volume overload resulting from these mechanisms, and aim to establish a negative sodium and thus fluid balance. Poor response to diuretics is an important clinical problem in patients with acute heart failure and its underlying pathophysiologic mechanisms are diverse.[2, 26]

Regulation of renal sodium excretion involves several sequential transport mechanisms in the renal tubule. Diuretics act on specific transport mechanisms, and are classified based on their tubular site of action (Figure 1). Acetazolamide and mannitol act on the proximal tubule, where up to two-thirds of the sodium load is filtered under physiologic conditions. Acetazolamide produces alkaline diuresis via bicarbonate excretion with sodium and potassium by inhibiting carbonic anhydrase in the proximal tubule.[27] Mannitol is an osmotic diuretic that acts primarily on the loop of Henle and the proximal tubule by increasing the osmotic pressure of glomerular filtrate, thus inhibiting tubular reabsorption.[28] Loop diuretics inhibit the Na+/2Cl-/K+ co-transporter in the thick ascending limb of the loop of Henle, causing decreased sodium and chloride reabsorption from the urine.[29] Thiazide diuretics act on the distal convoluted tubule by blocking the sodium chloride transporter in the distal tubule. Metolazone is a thiazide-like diuretic that exhibits its effect in the distal tubule by inhibiting the reabsorption of sodium and chloride ions.[30] Aldosterone antagonists (mineralocorticoid receptor antagonists) act on the collecting duct by competitively antagonizing the aldosterone receptor, thereby reducing sodium reabsorption.

Delivery of diuretics to the site of action relies on several mechanisms (Figure 2). First, orally administered diuretics first have to be absorbed in the gut to enter the bloodstream. In the presence of gastro-intestinal edema or gut hypoperfusion, absorption of orally administered diuretics is impaired, and may differ significantly between diuretics.[31] For example, bumetanide absorption is likely better than that of furosemide under these circumstances. Intravenous administration can overcome impaired absorption of orally administered diuretics. In patients with renal insufficiency and heart failure, a higher diuretic dose is required to achieve the same effects, and increasing diuretic doses will be less effective.[26]

Second, most loop diuretics (though interestingly not bumetanide), thiazide diuretics, metolazone and acetazolamide are bound to plasma albumin and act on their molecular target from the luminal side, meaning that they must be filtered by the glomerulus and actively secreted into the tubular lumen by the proximal tubule's organic anion transporter (OAT) in order to function.[32, 33] Hypoalbuminaemia, common in heart failure patients, impairs uptake and secretion of active furosemide and enhances conversion to its inactive form.[34, 35] Additionally, albumin lost into the tubule may bind furosemide and prevent it from acting on the Na+/2Cl-/K+ co-transporter.[36, 37] Co-administration of albumin and furosemide improves diuretic response in patients with cirrhosis, nephrotic syndrome or chronic kidney disease, but no data are available in heart failure.[38-40]

Third, patients with heart failure and chronic renal dysfunction have elevated levels of circulating organic acids, like BUN, which competitively inhibit the OAT and further reduce diuretic availability at the site of action.[41, 42] RAAS and sympathetic nervous system activation cause flow-dependent passive resorption of urea in the distal tubule; a concentration gradient created by increased sodium and water resorption in the proximal tubule results in diminished distal flow and increased

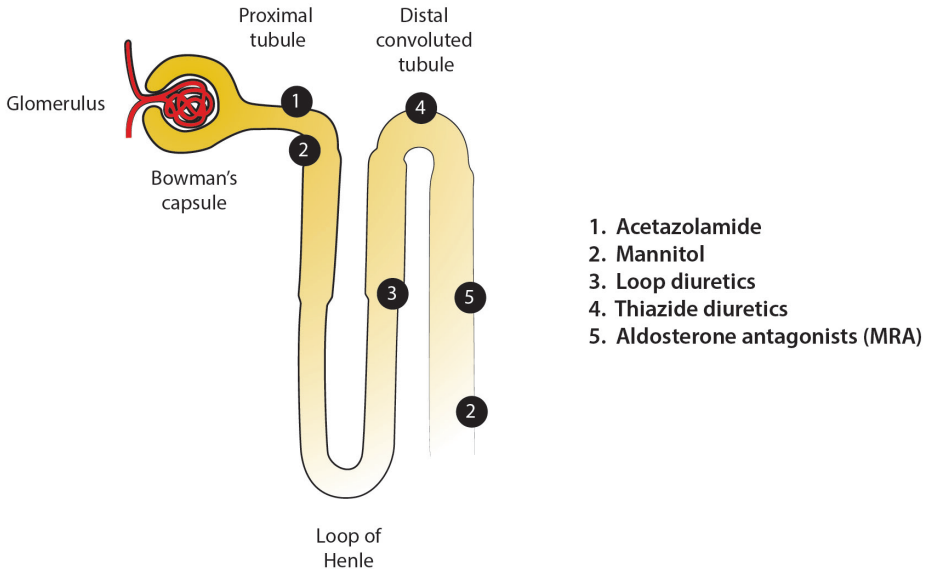



**Figure 1** Sites of action for diuretic and alternative therapies

reabsorption.[43, 44] High circulating BUN levels therefore not only contribute directly to diuretic resistance, but also reflect a kidney actively working to retain sodium and water. Thus, in patients with heart failure, impaired absorption, decreased renal blood flow, azotemia, hypoalbuminemia and proteinuria – resulting in reduced levels of active diuretics in the tubular lumen - may affect diuretic effectiveness.

At the onset of diuretic treatment, the natriuretic effect results in the intended negative sodium balance. The resulting decrease in extracellular volume (ECV) triggers a homeostatic response, mediated by activation of the RAAS and the sympathetic nervous system, leading to increased sodium retention at tubular sites not targeted by the specific diuretic.[45, 46] After several days, this homeostatic response counterbalances the diuretic effect of the drug, balancing sodium excretion and intake, and creating a new steady state with a lower ECV. This "braking phenomenon" is an appropriate homeostatic response that prevents excessive volume depletion during continued diuretic therapy. However, in conditions with pre-existent secondary hyperaldosteronism, such as heart failure, this phenomenon can be very pronounced and contribute to diuretic resistance.[47] Furthermore, persistent delivery of sodium or diuretics to the distal tubule causes hypertrophy of the distal tubular cells.[48] This bypasses the proximal effect of the loop diuretic and leads to enhanced sodium retention. Other non-cardiac mechanisms causing a diminished response to diuretics, including reduced renal blood flow caused by renal artery stenosis or drug-drug interactions, should also be considered.[29]

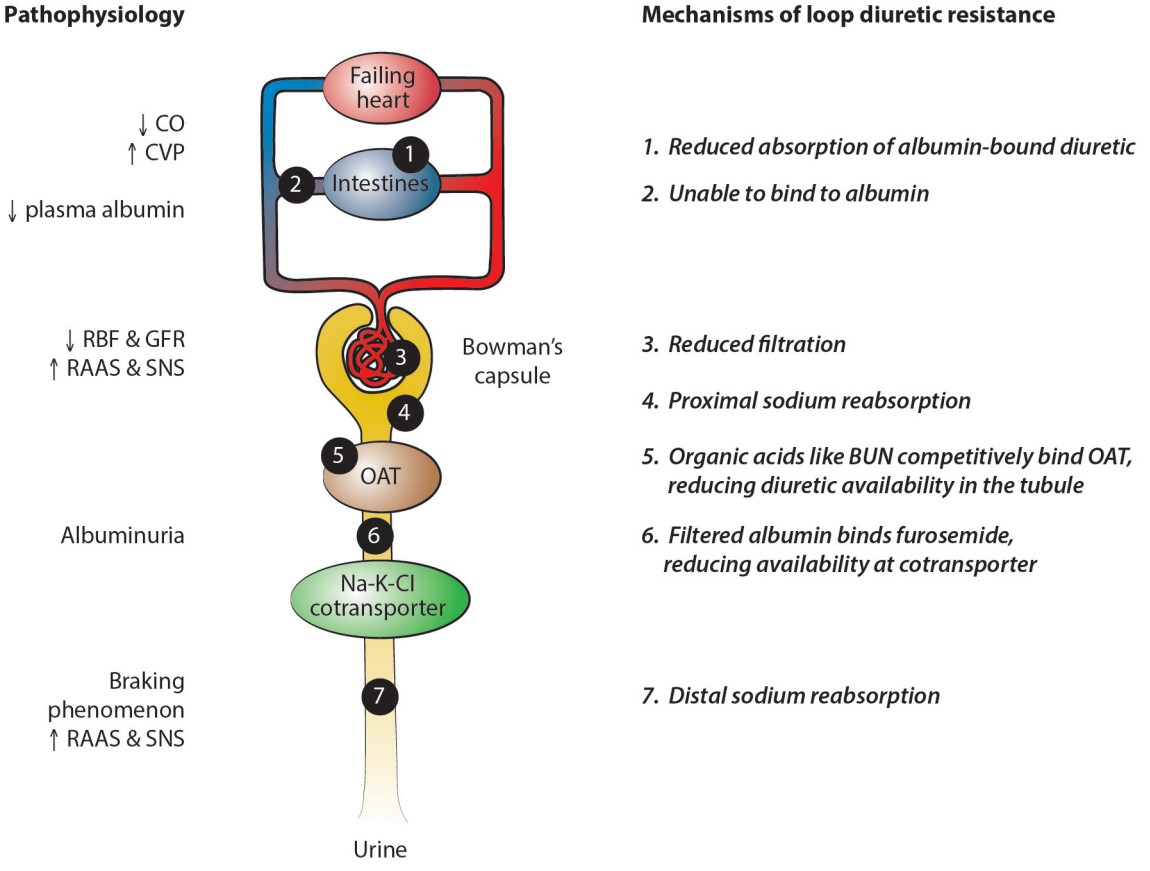



**Figure 2** Pathophysiology and mechanisms of loop diuretic resistance

## How to evaluate diuretic response and resistance?

There is no single accepted definition of diuretic resistance. Several have been proposed, the most frequently mentioned being "failure to decongest despite adequate and escalating doses of diuretics." Less clinically applicable definitions have also been suggested (Table 1). In clinical practice, unresponsiveness to diuretics leading to persistent signs and symptoms of congestion is usually considered diuretic resistance. Three objective methods to evaluate diuretic response have recently been introduced (Table 2). These measures suggest diuretic response should be determined based on the effect of diuretic dose administered.

**Table 1** Definitions of diuretic resistance

| | |
|---|---|
| Persistent congestion despite adequate and escalating doses of diuretic (>80 mg furosemide/day) | Neuberg et al.[89] |
| Fractional sodium excretion (amount of sodium excreted as a percentage of filtered load) of <0.2% | Knauf et al.[90] |
| Failure to excrete at least 90 mmol of sodium within 72 hours of a 160 mg oral furosemide dose given twice daily | Epstein et al.[91] |

Valente et al. investigated a quantitative measure of diuretic response, combining decongestive effect and diuretic dose.[4] Diuretic response was defined as weight loss per 40 mg furosemide (or equivalent). A poor diuretic response independently predicted heart failure rehospitalization and mortality. This metric was recently investigated in RELAX-AHF, confirming these findings.[49] Using weight change per unit of furosemide may provide an applicable metric to confirm the clinician's impression that a patient is resistant to diuretics. Testani et al. used similar metric to define diuretic response, termed diuretic efficiency, defined as net fluid loss per mg of loop diuretic (40 mg of furosemide or equivalent) during hospitalization for acute heart failure, dichotomizing above and below the median.[5] Consistently with results by Valente et al, low diuretic efficiency was associated with worse long-term outcomes. In both studies, poor diuretic response or efficiency was associated with renal impairment and higher BUN levels. However, diuretic response is not only a reflection of renal impairment; poor diuretic response was also associated with more advanced heart failure, diabetes and atherosclerotic disease.

More recently, Singh et al examined a ratio of urinary sodium to urinary furosemide, measured in spot urine samples. A poor response (< 2 mmol/mg) was associated with impaired clinical outcome, independently of renal function.[50] Hemoconcentration has also been suggested as a practical and readily applicable strategy to assess diuretic response.[51] Ultimately, following more extensive validation and investigation, use of such diuretic response metrics could be used to help identify patients who might benefit from alternative decongestive therapies and guide treatment selection.

**Table 2** metrics of diuretic response

| | |
|---|---|
| Weight loss on day 4 divided by administered unit of 40 mg furosemide (or equivalent) on days 1-3 | Valente et al.[4] Voors et al [49] |
| Net fluid loss per mg of loop diuretic (40 mg of furosemide or equivalent) during hospitalization | Testani et al.[5] |
| Natriuretic response to furosemide as the ratio of urinary sodium to urinary furosemide | Singh et al.[50] |

## Treatment of diuretic resistant patients

Several strategies have been proposed to overcome diuretic resistance (Figure 3). First, non-compliance should be ruled out by verifying mediation intake and sodium restriction.[26] Second, non-steroidal inflammatory drugs (NSAIDs) should be discontinued, because they potentially cause diuretic resistance by inhibiting cyclo-oxygenase and thus interfering with prostaglandin synthesis, which antagonizes the natriuretic response to loop diuretics.[52] Third, switching loop diuretics may be useful. Bumetanide and torsamide, for example, have higher biological absorption compared to furosemide in CHF patients.[31, 47] In the TOrasemide In Congestive heart failure (TORIC) study in outpatients with CHF, torasemide treatment was associated with a lower mortality and a significant improvement in NYHA class compared to furosemide or other diuretics.[53] A recent small meta-analysis confirmed these findings, suggesting a trend toward improvement in NYHA class and mortality with torsamide treatment.[54] Fourth, efficacy of diuretic therapy can be improved by switching from oral to intravenous administration to circumvent impaired enteral drug uptake in congested patients. Several smaller studies have suggested that continuous infusion improves diuresis, renal function and leads to fewer adverse events compared to bolus injections.[55-57] However, the Diuretic Optimization Strategies Evaluation (DOSE) trial found no differences in either treatment response or outcome in patients randomized to bolus versus continuous infusion, although diuretic doses and the incidence of worsening renal function were higher in the bolus group.[58]

### Combined diuretic therapy

If escalating (intravenous) doses of loop diuretics are insufficient, combination therapy with two classes of diuretic drugs may improve diuretic efficacy. The addition of a thiazide diuretic enhances sodium excretion via several mechanisms, including inhibition of distal sodium reabsorption.[59] As thiazides have a longer half-life, they prevent post-diuretic sodium retention after cessation of loop diuretic activity.[29] Potential dangers of combination therapy include hypokalaemia, hyponatraemia, dehydration, worsening renal function and metabolic acidosis; therefore,

careful monitoring is required.[60] Addition of metozalone to a loop diuretic results in marked diuresis and is especially useful in patients with renal failure, since metozalone is able to produce diuresis despite a low GFR.[61, 62]

Since a large amount of sodium is reabsorbed in the proximal tubule, adding a proximally acting diuretic may be beneficial. In healthy volunteers, addition of acetazolamide to furosemide showed a minor additive effect.[63] Khan et al reported an additional effect of acetazolamide in terms of correcting metabolic acidosis and increased diuresis when used intermittently in combination with furosemide and spironolactone therapy in congestive heart failure.[64] As acetazolamide is cleared renally, caution is recommended in patients with advanced renal failure due to the risk of concentration-dependent side-effects. Another option is mannitol; Turagam et al reported effective diuresis in 80.3% of acute heart failure patients treated with furosemide-mannitol infusion, though the study had no control group.[65] To date, studies evaluating combination therapy in (diuretic resistant) heart failure patients are scarce and evidence remains inconclusive. Two trials (DIURESIS-CHF, clinicaltirals.gov no. NCT01973335 and CLOROTIC, clinicaltrials.gov no. NTCT01647932) investigating combination therapy are respectively ongoing and planned. Neither study explicitly defines diuretic resistance as a inclusion criterion. Adding a natriuretic dose of mineralocorticoid receptor antagonist (MRA) to diuretics may also help overcome diuretic resistance by blocking the aldosterone receptor and thus preventing excess sodium reabsorption in the collecting duct caused by secondary hyperaldosteronism.[66] MRAs at low doses are guideline-recommended therapy in heart failure and significantly improve survival.[1, 67, 68] The randomized aldactone evaluation study (RALES) dose-finding study revealed that higher doses of spironolactone (50-75 mg daily) had natriuretic effects.[69] In two relatively small, single centre studies, addition of high dose spironolactone was associated with increased diuresis or earlier resolution of symptoms and signs of congestion.[70, 71] A common side-effect of high dose MRAs is hyperkalaemia; new MRAs with a lower potential for causing electrolyte disturbances are currently being investigated.[72, 73]

## Dopamine

Addition of low dose dopamine to diuretic therapy has been suggested as a way to improve renal blood flow and thus preserve renal function and improve diuresis.[74] The Renal Optimization Strategies Evaluation (ROSE) trial tested two independent hypotheses – that addition of low dose dopamine or low dose nesiritide, compared with placebo, to diuretic therapy will enhance decongestion and preserve renal function in patients with acute heart failure and renal dysfunction.[75] However, neither dopamine nor nesiritide had a significant effect on urine volume or change in Cystatin C, suggesting no added benefit to diuretic therapy. More recently, the prematurely discontinued, small-scale Dopamine in Acute Decompensated Heart Failure II (DAD-HF II) trial confirmed these findings, despite promising results in DAD-HF I.[76, 77] The results of these studies suggest dopamine does not improve diuretic response in acute heart failure.

## Ultrafiltration

Ultrafiltration is an effective method for fluid removal that filters plasma water directly across a semipermeable membrane using a pressure gradient.[78] This yields an ultrafiltrate that is iso-osmotic compared to plasma. Several studies comparing the efficacy and safety of ultrafiltration to diuretics in heart failure have been conducted in recent years. Two randomized controlled trials comparing diuretic therapy to ultrafiltration, the Relief for Acutely Decompensated Congestive Heart Failure (RAPID-CHF) and the Ultrafiltration versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure (UNLOAD) found greater fluid removal in the ultrafiltration group, though weight loss after 24 hours did not differ in the former and dyspnea scores were similar in the latter.[79, 80] Interestingly, ultrafiltration was associated with significant reductions in heart failure rehospitalization and fewer unscheduled visits. The Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF) examined the use of ultrafiltration in AHF patients with cardiorenal syndrome.[81] Patients were randomized to stepped diuretic therapy or fixed-rate ultrafiltration. Ultrafiltration was inferior to pharmacological therapy, primarily due to an increase in the creatinine level in the ultrafiltration group, along with more adverse events. It must be noted that not all patients in the ultrafiltration group received ultrafiltration therapy, and that the rate of fluid removal in the ultrafiltration arm has been questioned. So far, ultrafiltration has not been studied specifically in diuretic resistant patients. Multiple studies on ultrafiltration in heart failure are ongoing, while a recent phase III outcome trial (AVOID-HF, clinicaltrials.gov NCT01474200) was terminated due to recruitment problems. Unfortunately, none of the ongoing studies explicitly address diuretic resistance.

## Alternative therapies

Various intravenous agents have been investigated in acute heart failure, and although none have shown convincing survival benefits to date, several have mechanisms of action that may be helpful in overcoming diuretic resistance. Tolvaptan (a vasopressin $V_2$ receptor blocker) is effective in increasing sodium concentrations in patients with hyponatremia, increases urine output in patients with symptomatic heart failure and may therefore have additive value in diuretic resistant patients.[82, 83]

Several synthetic natriuretic peptides have been developed and investigated in heart failure. Nesiritide, a synthetic B-type natriuretic peptide approved for symptom relief by the FDA, but not by European regulators due to lack of efficacy, did not increase urine output in patients with acute heart failure, and is therefore unlikely to have additive value in patients with diuretic resistance.[84] Ularitide is a synthetic form of urodilatin, a human endogenous natriuretic peptide that is expressed in the kidney and induces natriuresis and diuresis by binding to specific natriuretic peptide receptors.[85] It may have therapeutic advantages in acute heart failure and specifically in diuretic resistant patients. The Efficacy and Safety of Ularitide for the Treatment of Acute Decompensated

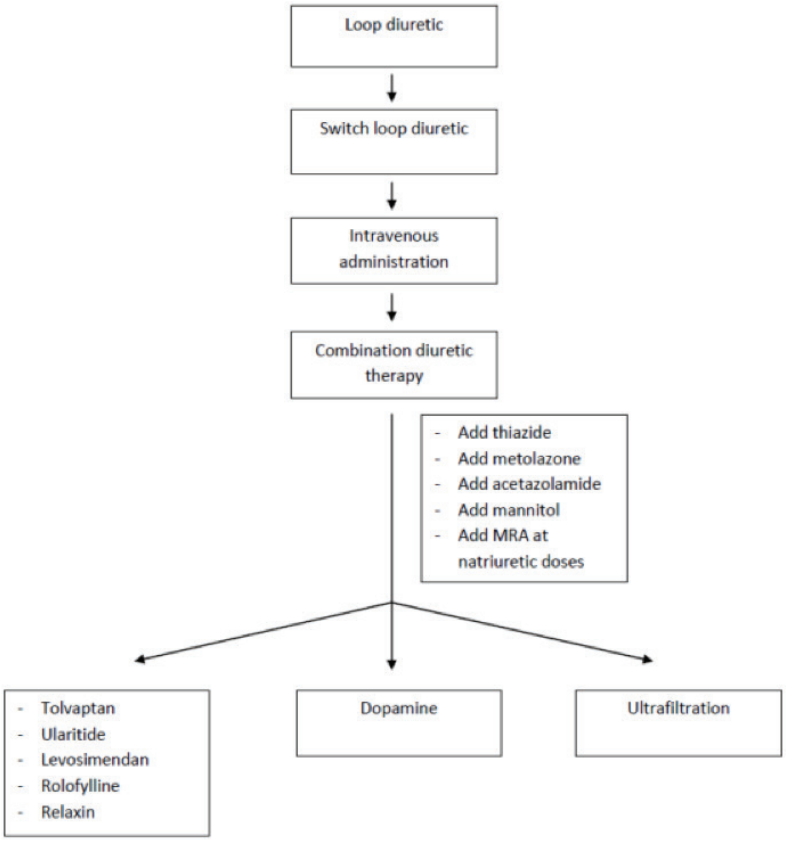



**Figure 3** Strategies for overcoming diuretic resistance

Heart Failure trial (TRUE-AFH; clinicaltrials.gov no. NCT01661634) is ongoing. Levosimendan is a phosphodiesterase inhibitor with vasodilator and positive inotropic properties that provides rapid and durable symptom relief and has positive effects on renal function, and could therefore help treat symptoms in diuretic resistant patients.[86]

A small study suggests that addition of prednisone in patients with diuretic resistance results in marked diuresis and improved renal function.[87] Further studies are needed to confirm these findings.

As shown by Valente et al, treatment with the adenosine A-1 antagonist rolofylline was a significant predictor of diuretic response due to greater weight loss, possibly due to improved renal perfusion or direct diuretic effects.[4] In a specific subset of patients, adenosine A-1 inhibition may help overcome diuretic resistance, although

the side-effect profile of rolofylline, in addition to lack of efficacy, led to discontinuation of its development. Serelaxin is a human recombinant of the vasodilator relaxin-2, with systemic and renal effects. Though no significant effect of serelaxin on diuretic response was observed, it may be that its beneficial effects are related to prevention of organ damage.[49, 88]

## Conclusions and future perspectives

Impaired diuretic response is a common problem in patients with acute heart failure and strongly associated with poor in-hospital and post-discharge clinical outcomes. Recently, quantitative measures for diuretic response were proposed but need to be validated in other acute heart failure populations. In addition to establishing the value of diuretic response metrics as prognostic markers, early identification of patients at risk of a poor response may allow initiation of therapies aimed at modifying response. Prospective studies using a validated diuretic response metric to identify diuretic resistant patients are a necessary first step towards identifying the best strategies for overcoming diuretic resistance, and determining whether this leads to improved outcomes. This could ultimately result in a better, individualized approach to treating the acutely decompensated heart failure patient, for whom no evidence based therapies exist.

## References


1. McMurray, J. J. *et al*. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur. Heart J.* 33, 1787-1847 (2012).
2. Adams, K. F.,Jr *et al*. Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). *Am. Heart J.* 149, 209-216 (2005).
3. Sato, N. *et al*. Acute decompensated heart failure syndromes (ATTEND) registry. A prospective observational multicenter cohort study: rationale, design, and preliminary data. *Am. Heart J.* 159, 949-955.e1 (2010).
4. Valente, M. A. *et al*. Diuretic response in acute heart failure: clinical characteristics and prognostic significance. *Eur. Heart J.* (2014).
5. Testani, J. M. *et al*. Loop Diuretic Efficiency: A Metric of Diuretic Responsiveness with Prognostic Importance in Acute Decompensated Heart Failure. *Circ. Heart Fail.* (2013).
6. Braunwald, E. Responsiveness to loop diuretics in heart failure. *Eur. Heart J.* 35, 1235-1237 (2014).
7. Cadnapaphornchai, M. A., Gurevich, A. K., Weinberger, H. D. & Schrier, R. W. Pathophysiology of sodium and water retention in heart failure. *Cardiology* 96, 122-131 (2001).
8. Levin, E. R., Gardner, D. G. & Samson, W. K. Natriuretic peptides. *N. Engl. J. Med.* 339, 321-328 (1998).
9. Harris, P. J., Thomas, D. & Morgan, T. O. Atrial natriuretic peptide inhibits angiotensin-stimulated proximal tubular sodium and water reabsorption. *Nature* 326, 697-698 (1987).
10. Guyton, A. & Hall, J. in *Medical physiology* (Elsevier Saunders, 2006).
11. Baylis, P. H. Osmoregulation and control of vasopressin secretion in healthy humans. *Am. J. Physiol.* 253, R671-8 (1987).
12. Schrier, R. W. & Abraham, W. T. Hormones and hemodynamics in heart failure. *N. Engl. J. Med.* 341, 577-585 (1999).
13. Unger, T. & Li, J. The role of the renin-angiotensin-aldosterone system in heart failure. *J. Renin Angiotensin Aldosterone Syst.* 5 Suppl 1, S7-10 (2004).
14. Weber, K. T. Aldosterone in congestive heart failure. *N. Engl. J. Med.* 345, 1689-1697 (2001).
15. Schrier, R. W. Aldosterone 'escape' vs 'breakthrough'. *Nat. Rev. Nephrol.* 6, 61 (2010).
16. Levine, T. B., Francis, G. S., Goldsmith, S. R., Simon, A. B. & Cohn, J. N. Activity of the sympathetic nervous system and renin-angiotensin system assessed by plasma hormone levels and their relation to hemodynamic abnormalities in congestive heart failure. *Am. J. Cardiol.* 49, 1659-1666 (1982).
17. Schrier, R. W., Berl, T. & Anderson, R. J. Osmotic and nonosmotic control of vasopressin release. *Am. J. Physiol.* 236, F321-32 (1979).
18. Charloux, A., Piquard, F., Doutreleau, S., Brandenberger, G. & Geny, B. Mechanisms of renal hyporesponsiveness to ANP in heart failure. *Eur. J. Clin. Invest.* 33, 769-778 (2003).
19. Liang, F. *et al*. Evidence for functional heterogeneity of circulating B-type natriuretic peptide. *J. Am. Coll. Cardiol.* 49, 1071-1078 (2007).
20. Damman, K., Voors, A. A., Navis, G., van Veldhuisen, D. J. & Hillege, H. L. The cardiorenal syndrome in heart failure. *Prog. Cardiovasc. Dis.* 54, 144-153 (2011).
21. Smilde, T. D. *et al*. Differential associations between renal function and "modifiable" risk factors in patients with chronic heart failure. *Clin. Res. Cardiol.* 98, 121-129 (2009).
22. Hillege, H. L. *et al*. Renal function, neurohormonal activation, and survival in patients with chronic heart failure. *Circulation* 102, 203-210 (2000).
23. Damman, K. *et al*. Decreased cardiac output, venous congestion and the association with renal impairment in patients with cardiac dysfunction. *Eur. J. Heart Fail.* 9, 872-878 (2007).
24. Damman, K. *et al*. Congestion in chronic systolic heart failure is related to renal dysfunction and increased mortality. *Eur. J. Heart Fail.* 12, 974-982 (2010).
25. Mullens, W. *et al*. Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. *J. Am. Coll. Cardiol.* 53, 589-596 (2009).
26. Ellison, D. H. Diuretic therapy and resistance in congestive heart failure. *Cardiology* 96, 132-143 (2001).
27. Maren, T. H. Use of inhibitors in physiological studies of carbonic anhydrase. *Am. J. Physiol.* 232, F291-7 (1977).
28. Warren, S. E. & Blantz, R. C. Mannitol. *Arch. Intern. Med.* 141, 493-497 (1981).
29. Ellison, D. H. The physiologic basis of diuretic synergism: its role in treating diuretic resistance. *Ann. Intern. Med.* 114, 886-894 (1991).

30. Steinmuller, S. T. & Puschett, J. B. Effects of metolazone in man: comparison with chlorothiazide. *Kidney Int.* 1, 169-181 (1972).

31. Vargo, D. L. *et al.* Bioavailability, pharmacokinetics, and pharmacodynamics of torsemide and furosemide in patients with congestive heart failure. *Clin. Pharmacol. Ther.* 57, 601-609 (1995).

32. Uwai, Y., Saito, H., Hashimoto, Y. & Inui, K. I. Interaction and transport of thiazide diuretics, loop diuretics, and acetazolamide via rat renal organic anion transporter rOAT1. *J. Pharmacol. Exp. Ther.* 295, 261-265 (2000).

33. Kim, E. J. & Lee, M. G. Pharmacokinetics and pharmacodynamics of intravenous bumetanide in mutant Nagase analbuminemic rats: importance of globulin binding for the pharmacodynamic effects. *Biopharm. Drug Dispos.* 22, 147-156 (2001).

34. Jackson, C. E. *et al.* Albuminuria in chronic heart failure: prevalence and prognostic importance. *Lancet* 374, 543-550 (2009).

35. Hesse, B., Parving, H. H., Lund-Jacobsen, H. & Noer, I. Transcapillary escape rate of albumin and right atrial pressure in chronic congestive heart failure before and after treatment. *Circ. Res.* 39, 358-362 (1976).

36. Bowman, R. H. Renal secretion of [35-S] furosemide and depression by albumin binding. *Am. J. Physiol.* 229, 93-98 (1975).

37. Pichette, V., Geadah, D. & du Souich, P. The influence of moderate hypoalbuminaemia on the renal metabolism and dynamics of furosemide in the rabbit. *Br. J. Pharmacol.* 119, 885-890 (1996).

38. Gentilini, P. *et al.* Albumin improves the response to diuretics in patients with cirrhosis and ascites: results of a randomized, controlled trial. *J. Hepatol.* 30, 639-645 (1999).

39. Ghafari, A. *et al.* Co-administration of albumin-furosemide in patients with the nephrotic syndrome. *Saudi J. Kidney Dis. Transpl.* 22, 471-475 (2011).

40. Phakdeekitcharoen, B. & Boonyawat, K. The added-up albumin enhances the diuretic effect of furosemide in patients with hypoalbuminemic chronic kidney disease: a randomized controlled study. *BMC Nephrol.* 13, 92-2369-13-92 (2012).

41. Sweet, D. H., Bush, K. T. & Nigam, S. K. The organic anion transporter family: from physiology to ontogeny and the clinic. *Am. J. Physiol. Renal Physiol.* 281, F197-205 (2001).

42. Krick, W., Wolff, N. A. & Burckhardt, G. Voltage-driven p-aminohippurate, chloride, and urate transport in porcine renal brush-border membrane vesicles. *Pflugers Arch.* 441, 125-132 (2000).

43. Kazory, A. Emergence of blood urea nitrogen as a biomarker of neurohormonal activation in heart failure. *Am. J. Cardiol.* 106, 694-700 (2010).

44. Schrier, R. W. Blood urea nitrogen and serum creatinine: not married in heart failure. *Circ. Heart Fail.* 1, 2-5 (2008).

45. Wilcox, C. S. *et al.* Response of the kidney to furosemide. I. Effects of salt intake and renal compensation. *J. Lab. Clin. Med.* 102, 450-458 (1983).

46. Loon, N. R., Wilcox, C. S. & Unwin, R. J. Mechanism of impaired natriuretic response to furosemide during prolonged therapy. *Kidney Int.* 36, 682-689 (1989).

47. Brater, D. C. Diuretic therapy. *N. Engl. J. Med.* 339, 387-395 (1998).

48. Kaissling, B., Bachmann, S. & Kriz, W. Structural adaptation of the distal convoluted tubule to prolonged furosemide treatment. *Am. J. Physiol.* 248, F374-81 (1985).

49. Voors, A. A. *et al.* Diuretic response in patients with actue decompensated heart failure: characteristics and clinical outcome - an analysis from RELAX-AHF. *European journal of heart failure* (Article in press).

50. Singh, D. *et al.* Insufficient natriuretic response to continuous intravenous furosemide is associated with poor long-term outcomes in acute decompensated heart failure. *J. Card. Fail.* 20, 392-399 (2014).

51. Vaduganathan, M. *et al.* Hemoconcentration-Guided Diuresis in Heart Failure. *Am. J. Med.* (2014).

52. Johnston, G. D. *et al.* Factors modifying the early nondiuretic vascular effects of furosemide in man. The possible role of renal prostaglandins. *Circ. Res.* 53, 630-635 (1983).

53. Cosin, J., Diez, J. & TORIC investigators. Torasemide in chronic heart failure: results of the TORIC study. *Eur. J. Heart Fail.* 4, 507-513 (2002).

54. Bikdeli, B. *et al.* Dominance of furosemide for loop diuretic therapy in heart failure: time to revisit the alternatives? *J. Am. Coll. Cardiol.* 61, 1549-1550 (2013).

55. Dormans, T. P. *et al.* Diuretic efficacy of high dose furosemide in severe heart failure: bolus injection versus continuous infusion. *J. Am. Coll. Cardiol.* 28, 376-382 (1996).

56. Thomson, M. R. *et al.* Continuous versus intermittent infusion of furosemide in acute decompensated heart failure. *J. Card. Fail.* 16, 188-193 (2010).

57. van Meyel, J. J. *et al.* Continuous infusion of furosemide in the treatment of patients with congestive heart failure and diuretic resistance. *J. Intern. Med.* 235, 329-334 (1994).

58. Felker, G. M. *et al.* Diuretic strategies in patients with acute decompensated heart failure. *N. Engl. J. Med.* 364, 797-805 (2011).

59. Kunau, R. T.,Jr, Weller, D. R. & Webb, H. L. Clarification of the site of action of chlorothiazide in the rat nephron. *J. Clin.*

*Invest.* 56, 401-407 (1975).

60. Channer, K. S., McLean, K. A., Lawson-Matthew, P. & Richardson, M. Combination diuretic treatment in severe heart failure: a randomised controlled trial. *Br. Heart J.* 71, 146-150 (1994).
61. Ng, T. M. *et al.* Comparison of bumetanide- and metolazone-based diuretic regimens to furosemide in acute heart failure. *J. Cardiovasc. Pharmacol. Ther.* 18, 345-353 (2013).
62. Tilstone, W. J., Dargie, H., Dargie, E. N., Morgan, H. G. & Kennedy, A. C. Pharmacokinetics of metolazone in normal subjects and in patients with cardiac or renal failure. *Clin. Pharmacol. Ther.* 16, 322-329 (1974).
63. Brater, D. C., Kaojarern, S. & Chennavasin, P. Pharmacodynamics of the diuretic effects of aminophylline and acetazolamide alone and combined with furosemide in normal subjects. *J. Pharmacol. Exp. Ther.* 227, 92-97 (1983).
64. Khan, M. I. Treatment of refractory congestive heart failure and normokalemic hypochloremic alkalosis with acetazolamide and spironolactone. *Can. Med. Assoc. J.* 123, 883-887 (1980).
65. Turagam, M. K. *et al.* Outcomes of furosemide-mannitol infusion in hospitalized patients with heart failure: an observational single-center cohort study of 122 patients. *Int. J. Cardiol.* 151, 232-234 (2011).
66. Hensen, J., Abraham, W. T., Durr, J. A. & Schrier, R. W. Aldosterone in congestive heart failure: analysis of determinants and role in sodium retention. *Am. J. Nephrol.* 11, 441-446 (1991).
67. Pitt, B. *et al.* The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N. Engl. J. Med.* 341, 709-717 (1999).
68. Zannad, F. *et al.* Eplerenone in patients with systolic heart failure and mild symptoms. *N. Engl. J. Med.* 364, 11-21 (2011).
69. Effectiveness of spironolactone added to an angiotensin-converting enzyme inhibitor and a loop diuretic for severe chronic congestive heart failure (the Randomized Aldactone Evaluation Study [RALES]). *Am. J. Cardiol.* 78, 902-907 (1996).
70. van Vliet, A. A., Donker, A. J., Nauta, J. J. & Verheugt, F. W. Spironolactone in congestive heart failure refractory to high-dose loop diuretic and low-dose angiotensin-converting enzyme inhibitor. *Am. J. Cardiol.* 71, 21A-28A (1993).
71. Ferreira, J. P. *et al.* Mineralocorticoid receptor antagonism in acutely decompensated chronic heart failure. *Eur. J. Intern. Med.* 25, 67-72 (2014).
72. Kolkhof, P. *et al.* Finerenone, a novel selective non-steroidal mineralocorticoid receptor antagonist protects from rat cardiorenal injury. *J. Cardiovasc. Pharmacol.* (2014).
73. Pitt, B. *et al.* Safety and tolerability of the novel non-steroidal mineralocorticoid receptor antagonist BAY 94-8862 in patients with chronic heart failure and mild or moderate chronic kidney disease: a randomized, double-blind trial. *Eur. Heart J.* 34, 2453-2463 (2013).
74. Elkayam, U., Ng, T. M., Hatamizadeh, P., Janmohamed, M. & Mehra, A. Renal Vasodilatory Action of Dopamine in Patients With Heart Failure: Magnitude of Effect and Site of Action. *Circulation* 117, 200-205 (2008).
75. Chen, H. H. *et al.* Low-dose dopamine or low-dose nesiritide in acute heart failure with renal dysfunction: the ROSE acute heart failure randomized trial. *JAMA* 310, 2533-2543 (2013).
76. Triposkiadis, F. K. *et al.* Efficacy and safety of high dose versus low dose furosemide with or without dopamine infusion: the Dopamine in Acute Decompensated Heart Failure II (DAD-HF II) trial. *Int. J. Cardiol.* 172, 115-121 (2014).
77. Giamouzis, G. *et al.* Impact of dopamine infusion on renal function in hospitalized heart failure patients: results of the Dopamine in Acute Decompensated Heart Failure (DAD-HF) Trial. *J. Card. Fail.* 16, 922-930 (2010).
78. Ronco, C., Ricci, Z., Bellomo, R. & Bedogni, F. Extracorporeal ultrafiltration for the treatment of overhydration and congestive heart failure. *Cardiology* 96, 155-168 (2001).
79. Bart, B. A. *et al.* Ultrafiltration versus usual care for hospitalized patients with heart failure: the Relief for Acutely Fluid-Overloaded Patients With Decompensated Congestive Heart Failure (RAPID-CHF) trial. *J. Am. Coll. Cardiol.* 46, 2043-2046 (2005).
80. Costanzo, M. R. *et al.* Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. *J. Am. Coll. Cardiol.* 49, 675-683 (2007).
81. Bart, B. A. *et al.* Ultrafiltration in decompensated heart failure with cardiorenal syndrome. *N. Engl. J. Med.* 367, 2296-2304 (2012).
82. Udelson, J. E. *et al.* Acute hemodynamic effects of tolvaptan, a vasopressin V2 receptor blocker, in patients with symptomatic heart failure and systolic dysfunction: an international, multicenter, randomized, placebo-controlled trial. *J. Am. Coll. Cardiol.* 52, 1540-1545 (2008).
83. Schrier, R. W. *et al.* Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for hyponatremia. *N. Engl. J. Med.* 355, 2099-2112 (2006).
84. Gottlieb, S. S. *et al.* Effects of nesiritide and predictors of urine output in acute

decompensated heart failure: results from ASCEND-HF (acute study of clinical effectiveness of nesiritide and decompensated heart failure). *J. Am. Coll. Cardiol.* 62, 1177-1183 (2013).

85. Valentin, J. P., Sechi, L. A., Qui, C., Schambelan, M. & Humphreys, M. H. Urodilatin binds to and activates renal receptors for atrial natriuretic peptide. *Hypertension* 21, 432-438 (1993).
86. Packer, M. *et al.* Effect of levosimendan on the short-term clinical course of patients with acutely decompensated heart failure. *JACC Heart Fail.* 1, 103-111 (2013).
87. Liu, C. *et al.* Potent diuretic effects of prednisone in heart failure patients with refractory diuretic resistance. *Can. J. Cardiol.* 23, 865-868 (2007).
88. Metra, M. *et al.* Effect of serelaxin on cardiac, renal, and hepatic biomarkers in the Relaxin in Acute Heart Failure (RELAX-AHF) development program: correlation with outcomes. *J. Am. Coll. Cardiol.* 61, 196-206 (2013).
89. Neuberg, G. W. *et al.* Diuretic resistance predicts mortality in patients with advanced heart failure. *Am. Heart J.* 144, 31-38 (2002).
90. Knauf, H. & Mutschler, E. Sequential nephron blockade breaks resistance to diuretics in edematous states. *J. Cardiovasc. Pharmacol.* 29, 367-372 (1997).
91. Epstein, M., Lepp, B., Hoffman, S. & Levinson, R. Potentation of furosemide by metolazone in refractory edema. *Current Therapeutic Research* 21, 656-667 (1977).

# Summary and future perspectives

In recent years, cardiologists have developed a renewed appreciation for the pathophysiologic involvement of the kidney in heart failure, and an understanding that the two organs cannot be viewed in isolation. Renal function is not merely a strong, independent prognostic marker in heart failure; the organ plays a central role in volume homeostasis and is involved in pathways targeted by multiple evidence-based therapies for the syndrome, including RAAS inhibitors and diuretics of all types. Biomarkers for renal function – both measured directly in bodily fluids and derived estimates and metrics – have the potential to increase our understanding of these interactions, improve risk stratification, and aid the development of tailored therapies for patients with heart failure, either as treatment targets or for monitoring therapy.

## Aims of the thesis

The primary aims of this thesis are:

- **To examine the prognostic importance of renal impairment and worsening renal function in patients with acute and chronic heart failure.**
- **To assess the value of biomarkers for risk stratification and provide insight into the cardiorenal pathways involved in heart failure.**
- **To develop and investigate a quantitative measure for diuretic response to better understand the phenomenon of diuretic resistance in acute heart failure.**

The first part of the thesis focuses on the impact, measurement and modulation of renal function in both chronic and acute heart failure, while the second examines the evaluation of diuretic response and worsening renal function in acute heart failure. The principal findings are outlined per chapter below, and the thesis concludes with an overview of potential avenues for future investigation.

## Part I: Renal function in heart failure

### Impact of renal function

An understanding of the true importance of renal function is relatively recent development in cardiology. Following the publication of key papers around the turn

of the century, which showed renal function to be strong predictor of outcome in heart failure, the number of studies examining associations between renal function and prognosis in heart failure populations grew exponentially (Figure 1).

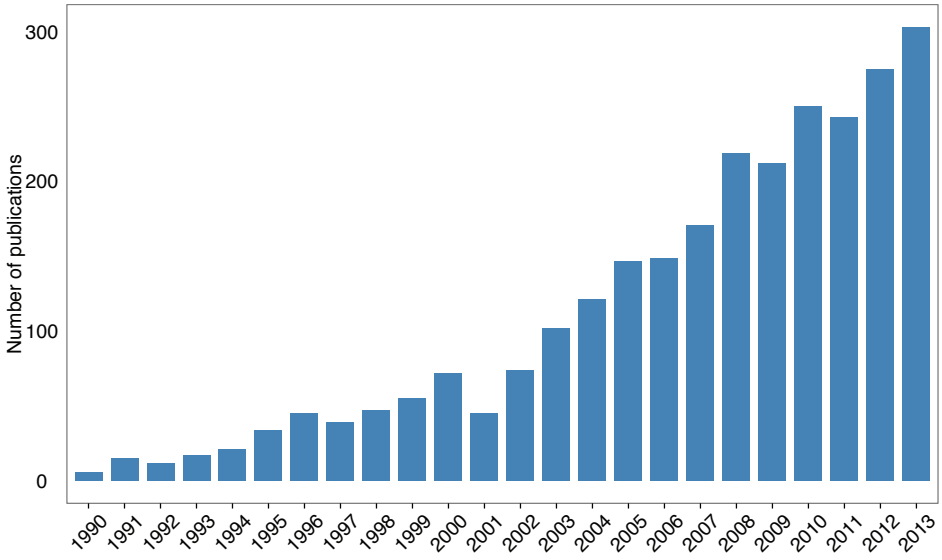



**Figure 1** Number of PubMed results for search: heart failure AND renal function AND prognosis. Adjusted R2 for quadratic fit = 0.88, P<0.0001. P for quadratic vs. linear fit = 0.0002

**Chapter 1** presents the results of our meta-analysis of studies including over one million heart failure patients, underlining the crucial importance of renal dysfunction for outcome in both chronic and acute heart failure. Using a systematic search strategy, we identified 57 studies with data on prevalent chronic kidney disease (CKD) and 28 studies with information on worsening renal function (WRF). CKD was highly prevalent in both acute and chronic heart failure, affecting about one-third of patients, and was independently associated with poor outcomes even after adjustment for potential confounders. Worsening renal function was also common, presenting in about one-quarter of the heart failure patients studied, and also independently associated with increased mortality.

In a secondary analysis, we examined predictors of worsening renal function, concluding that baseline renal impairment (CKD), age, and a history of hypertension, diabetes and diuretic use were all predictors of the development of worsening renal function. Though the results concerning the mortality risks of both CKD and WRF were convincing and consistent, there were indications of publication bias in studies reporting on the deleterious impact of WRF. Additionally, the definition of WRF remains contentious, with little consensus on which measure is best. Furthermore, numerous studies suggest that the cause of WRF may significantly affect its prognostic importance, and that WRF in the presence of good response to therapy and hemodynamic stability may be acceptable. The predictors of WRF - older age,

more co-morbidity and worse baseline renal function – suggest that it may be, to a degree, a surrogate marker of vulnerability due to frailty or renal reserve.

In conclusion, while both CKD and WRF are independently associated with increased mortality in a wide range of heart failure populations, CKD shows a more consistent relationship with poor outcome. Further investigation of the definition, causes and context for WRF in various heart failure settings will be necessary to better understand the significance of the phenomenon.

## Measurement of renal function

Renal function is traditionally assessed using creatinine-based estimates, including Cockcroft-Gault's creatinine clearance and the more recent Modification of Diet in Renal Disease (MDRD) study equation, which has been validated in numerous populations including heart failure. Despite the fact other, better markers exist for estimating renal function – such as cystatin-C – serum creatinine remains in widespread use due to low cost, physician familiarity with the marker and at least adequate performance in most settings. Though existing formulae are generally adequate, they still tend to provide unreliable estimates in both upper and lower ranges of GFR, making new equations a welcome addition, and may not perform equally well for all purposes or in all populations.

In **Chapter 2**, we examined the value of more recent creatinine-based and cystatin-C-based equations for estimating glomerular filtration rate (GFR) developed by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI). These new equations improve estimation of GFR in chronic kidney disease patients and many other populations, but had yet to be validated against a gold standard measured GFR in chronic heart failure patients.

We measured GFR in 120 chronic heart failure patients using [$^{125}$I]iothalamate clearance – the gold standard method – and compared the performance of the simplified MDRD (sMDRD) and CKD-EPI creatinine equations in terms of accuracy, bias and prognostic performance. Three additional estimation equations – Cockcroft-Gault creatinine clearance and CKD-EPI equations based on cystatin-C alone and cystatin-C combined with creatinine – were also examined in secondary analyses. We found that the CKD-EPI equation was the best of the creatinine-based equations where estimation of GFR was concerned, predicting accurate classification better than sMDRD and Cockroft-Gault equations, with equivalent prognostic performance. The cystatin-C equations did show better performance than those relying on creatinine alone, but given current clinical realities, there is still a place for equations based on creatinine alone.

In addition to serum markers, urine markers have great potential for assessing renal function. Urine – the production of which is the kidney's most visible function – is an easily collected, readily available biofluid. It provides a wealth of information that may help elucidate other aspects of renal pathopysiology – such tubular injury – complementing or even improving on serum markers. In **Chapter 3**, we present

an extensive overview of both traditional – creatinine clearance, urinary sodium and albumin excretion – and novel markers that have potential value in heart failure. The traditional markers are relatively well-established and some are recommended for risk stratification, while the value of novel markers currently lies in improving understanding of pathphysiologic processes rather than immediate clinical utility. Promising markers that may help elucidate pathways involved in heart failure include inflammatory markers (Inteleukin-18), vascular markers (Endothelin-1) and markers of myocardial stretch (urinary natriuretic peptides). Of particular interest are markers of tubular injury – including Kidney-Injury Molecule 1 (KIM-1), Neutrophil Gelatinase-Associated Lipocalin (NGAL), N-acetyl-β-D-glucosaminidase (NAG) and Fatty Acid-Binding Proteins (FABP). Tubular injury is a potential pathway towards renal function decline, a key risk factor in heart failure as shown in **Chapter 1**, and early detection may allow targeted prevention to be developed. As these markers are shed directly by the tubules, urine is the ideal biofluid in which to examine these processes. Tubular markers are the most promising candidates for clinical implementation, as they may be able to help guide heart failure therapies – such as diuretics - and improve early renal risk stratification following further validation. The diagnostic and prognostic utility of novel markers will require extensive further study before effective use in routine patient care is possible.

## Modulation of renal function

Vasodilators are guideline-recommended therapy for patients with acute heart failure and high blood pressure, despite lacking evidence for survival benefit. Various agents with vasodilating properties have been studied in acute heart failure, almost all designed to improve hemodynamics via afterload reduction. Considering the key role hemodynamic regulation plays in preserving renal function, it should be no surprise that many of these agents have effects on the kidney. For example, the investigational drug rolofylline – an adenosine A-1 antagonist – was expected to improve outcomes in acute heart failure via effects on kidney perfusion and preservation of renal function rather than via direct cardiac effects. Sadly, this drug failed to live up to this promise.

In **Chapter 4**, we present an overview of the renal effects of established and investigational therapies for acute heart failure with vasodilating properties. Renal vasoconstriction – triggered by a variety of pathways activated in the setting of acute heart failure, is an important mechanism that may contribute to renal damage and, ultimately, lasting impairment. Several established and novel vasodilators used and investigated in heart failure not only lead to general vasodilation, but have specific effects on renal afferent and/or efferent arteries, and some modulate neurohormonal pathways that play a role in renal regulation.

As mentioned, the evidence for efficacy of these agents in AHF is limited at best, and the data available on renal effects is even more limited. A few agents show promising effects on the kidney and may be useful in specific settings – such as milrinone, levosimendan and the vasopressin antagonists, and of particular inter-

est serelaxin, a recombinant form of human relaxin, which has positive hemodynamic effects and appears to improve multiple organ functions, including renal function. Strikingly, no data are available on renal effects of the most commonly used vasodilator in clinical practice, nitroglycerine. In summary, while the pharmacological effects and sites of action for many of these vasodilators may protect or improve renal function – so long as adequate perfusion is maintained – their use requires close monitoring, careful patient selection and more extensive research before routine clinical implementation can be recommended without reservations.

## Part II: Diuretic response and worsening renal function in acute heart failure

The effects of loop diuretics – the cornerstone of fluid management and symptom control in acute heart failure – are incompletely understood despite decades of clinical experience. Though their use is supported by strong guideline recommendations on the grounds of clinical experience and common sense, the evidence for optimal posology, administration and effects on outcome is limited and conflicting.

One clinical problem faced daily by doctors treating patients with acute heart failure is diuretic resistance - refractory signs or symptoms of congestion despite increasing doses of diuretics - a critical feature of so-called cardiorenal syndromes that is associated with high rates of death and rehospitalization. Its causes are manifold: reduced perfusion, congestion, renal dysfunction, neurohormonal activation, azotemia and poor nutritional status are all potential contributors. And yet, a quantitative measure to evaluate patient response to diuretics is lacking, with existing definitions of resistance generally concerning themselves solely with diuretic dosage within the context of persistent congestion, or even merely considering dose alone.

We attempted to address this urgent unmet need in **Chapter 5** by proposing a new, quantitative metric for diuretic response – weight change per unit of loop diuretic (40mg of furosemide or equivalent). The rationale was to provide a relatively easy to calculate 'dose-response' metric, bringing together both the drug dose and its clinical effect – weight loss. Unfortunately, data on urine output – the direct effect of a diuretic – were not available for validation. Weight does have several advantages, including ease of measurement, and is a guideline-recommended tool for monitoring volume status. Our metric was evaluated in 1745 patients from the PROTECT trial, a randomized controlled trail of the investigational adenosine A-1 antagonist rolofylline conducted in patients with acute decompensated heart failure, with neutral overall results. We found poor diuretic response was associated with an atherosclerotic, sicker patient profile – poor responders were older, had lower blood pressure, more vascular comorbidities, were more likely to have undergone coronary revascularisation, had more diabetes, anaemia and worse renal function, including higher blood urea nitrogen levels. There were also indications they had more advanced heart failure, such as more frequent device therapy. Good responders had lower rates of death and higher rates of

success on the primary endpoint – improvement in dyspnea after 24 and 48 hours.

Interestingly, use of rolofylline was an independent predictor of good diuretic response, possibly due to direct diuretic effects of the drug or potentiation of diuretic efficacy via increased renal perfusion. Furthermore, baseline renal function was remarkably similar between poor and good responders, indicating diuretic response is not merely a proxy for GFR. However, worsening renal function (WRF) – generally a bad thing, as we showed in **Chapter 1** – was relatively common in the best responders, despite the fact they had the best outcomes. This observation supports the theory that the context for WRF is more important than its occurrence per se. In multivariable analyses, poor diuretic response independently predicted mortality and rehospitalisation, and extensive sensitivity analyses in the placebo group alone and in a subset of highly congested patients confirmed the consistency of these findings. The strong association with rehospitalisation is striking, considering how notoriously difficult this endpoint is to predict.

**Chapter 6** is an editorial by Professor Emeritus Eugene Braunwald that accompanied publication of Chapter 5 in the European Heart Journal, underlining the importance of the development of measures for evaluating response to diuretics. The editorial also discusses recent work by Testani et al., who proposed a similar metric based on net fluid output and showed findings similar to ours. Professor Braunwald correctly identifies a number of the weaknesses and potential confounders of these simple measures – such as the complexities of accurate weight or fluid balance measurement, the lack of information on sodium intake, the effects of co-administration of other diuretics, and the fact these metrics fail to truly capture the complexity of diuretic pharmacodynamics. However, the editorial concludes that despite these limitations, the development and validation of quantitative metrics for responsiveness to diuretics is an important step towards a better understanding of diuretic resistance and optimisation of diuretic treatment in heart failure patients.

In **Chapter 7**, we described changes in serum Neutrophil Gelatinase-Associated Lipocalin (NGAL) levels during hospitalization and the value of NGAL for predicting worsening renal function (WRF) and improving risk stratification in a sub-analysis of the PROTECT trial. NGAL – a tubular marker – has been suggested as an early, sensitive indicator for the development of WRF, and is reported to have good prognostic value. We performed our analyses in 1447 patients hospitalized with acute heart failure, representing a significantly larger population than all previous studies reporting on serum NGAL in acute heart failure combined.

Contrary to a number of smaller reports, we showed NGAL rise did not precede creatinine increases in patients who developed WRF early during hospitalization for heart failure. Although NGAL – but not creatinine – was an independent predictor of WRF, neither marker had particularly good prognostic performance. Disappointingly, NGAL was also not independently predictive of either mortality or a 60-day composite endpoint of mortality and rehospitalisation. However, in patients with WRF – measured continuously as an increase in serum creatinine - the risk of death or rehospitalisation for cardiovascular or renal causes by day 60 associated with a

given creatinine increase was greater for higher NGAL levels, even after correction for baseline creatinine. Thus, NGAL provides some incremental risk information, but only in patients with a rise in creatinine.

Why our analysis failed to confirm past findings is not entirely clear; previous smaller positive studies may indicate some publication bias – which does appear to exist where reports on WRF are concerned, as shown in our meta-analysis - or may be due to differences in the studied populations. Our cohort is large and well-characterized, but PROTECT did only include patients with at least mild renal dysfunction, which may have influenced the results. However, the incidence of WRF in our study was similar to what we observed in for general heart failure populations in **Chapter 1**.

The explanation may lie with the nature of WRF in AHF; past studies in acutely ill, non-heart failure populations showed strong predictive value for NGAL. In AHF, WRF is more likely to be driven by smaller hemodynamic changes, neurohormonal changes and drug effects, in sharp contrast with hypoxic or septic injury resulting in acute kidney injury (AKI), more commonly seen in post-surgical or intensive care settings. Additionally, the exact timing of renal injury or WRF is often unclear in AHF, with the potential for undocumented pre-admission renal damage; the early NGAL rise seen by others may have already occurred and gone undetected in at least some of our patients.

In summary, based on these retrospective data, the clinical value of serum NGAL in acute heart failure seems limited. Given the other potential causes of elevated serum NGAL – including inflammation and infection – urinary levels may yet prove valuable due to their reported greater renal specificity. Hopefully the upcoming AKINESIS trial examining sequential urine and plasma levels will provide definitive answers.

The final chapter of this thesis, **Chapter 8**, is a review of the pathophysiology of diuretic resistance in acute heart failure, and examines recently proposed metrics for the evaluation of diuretic response. Most publications on the topic of diuretic resistance have been based on older, less workable definitions, and none have provided a comprehensive evaluation of the potential causes of diuretic resistance in heart failure. The recent publication of several potential metrics for evaluating response to diuretic therapy – including our own metric of weight change per unit of diuretics, a similar metric based on urine output proposed by Testani et al., and a ratio of urinary sodium to urinary furosemide – makes this a valuable and timely addition to the existing literature.

In the review, we describe several pathophysiologic mechanisms that may be involved in diuretic resistance in acute heart failure – reduced absorption, impaired transportation through the bloodstream and across the glomerular barrier into the tubule, and lack of availability at the site of action. Gut congestion and poor nutritional status resulting in low albumin (which furosemide and many other diuretics must be bound to in order to be transported) can affect the first two. Reduced car-

diac output and neurohormonal modulation can affect filtration in the kidney, and elevated BUN levels can competitively block transportation into the tubule. Once in the tubule, albumin may once again bind to the loop diuretic and render it inactive. Additionally, the direct effects of diuretics themselves – such as post-diuretic sodium retention following repeated dosing, resulting in renin-angiotensin-aldosterone system (RAAS) activation – can also contribute to reduced efficacy.

We also show there is some evidence a stepped approach combining different classes of diuretics may be effective in overcoming resistance, and ultrafiltration or vasodilator therapies (as outlined in **Chapter 4**) may be appropriate in selected populations. However, it is abundantly clear is that the lack of usable measures for diuretic response means no past or current studies have been able to prospectively and explicitly examine regimens for overcoming resistance. With new metrics in hand, we will hopefully be able to design better trials to optimise diuretic strategies in acute heart failure patients with diuretic resistance.

## Future perspectives

Cardiorenal research in heart failure is long past its infancy and well into its teens; gestated in the late 90's, born at the turn of the 20$^{th}$ century, its childhood years were full of exciting new discoveries: renal function as an essential risk factor, the 'cardiorenal syndromes', countless novel biomarkers and even drugs trials directly targeting the kidney in heart failure patients – heady times indeed. The sheer number of patients available for the updated meta-analysis (**Chapter 1**), with most data published within the past 10 years, speaks volumes.

Yet despite the field's growing maturity, there is still a strong need for further exploration, invention, and discovery.

### Acute heart failure treatments

Where treatment is concerned, it is telling that most proven, effective chronic heart failure therapies have direct renal effects – true for RAAS blockers of every stripe. In contrast, evidence for optimum use and value of one of the oldest and most prescribed heart failure drugs – the lowly loop diuretic – is frighteningly thin. The same holds true for all recommended treatments for managing that deadly and increasingly common cause of hospitalization – Acute Heart Failure (AHF).

Despite numerous flings and flirtations with sexy new AHF drugs, few have lasted long, and none have made a permanent mark. Until serelaxin – the latest crush, one we are eager to get to know a little better before we commit – none managed to improve mortality, and only a few helped patients breath a little easier. Many of these vasodilators and (novel) inotropes are used incidentally in clinical practice, often in the sickest patients and in the absence of proven alternatives.

And so, we turn back to the drugs we believe we understand; drugs that alleviate the patient's swelling, resolve breathlessness, and jumble up electrolytes and re-

nal markers in all kinds of ways – diuretics. They have a number of advantages – they are cheap, easily administered, and have known side-effects. When patients respond well, we do not worry. When patients do not, there is little evidence to guide our next step. Increase the dose? Add another diuretic? Add an inotrope or vasodilator? Add steroids? Ultrafiltrate? And what about patients who respond well, but develop worsening renal function? Or who (fail to) hemoconcentrate? How important is resolving congestion? And which of these factors is the most important?

Complicating matters further, acute heart failure patients are a diverse lot. Ischemic or non-ischemic, reduced or preserved ejection fraction, warm and wet vs. cold and dry, in every imaginable permutation and combination. And with every possible electrolyte imbalance and degree of renal impairment. This may explain why many novel AHF therapies have failed to show significant positive effects. The net result of a one-size-fits-all approach to treating a heterogenous population may be neutral, but identification of potential responders to therapy within these populations may present opportunities. In short, are the therapies we have developed failures, or have we simply been treating the wrong patients?

A better understanding of the significance of and interactions between admission values of multiple biomarkers and dynamic in-hospital changes in response to therapy – including diuretic response, blood pressure, hemoconcentration, (renal) biomarkers, congestion – requires careful, methodical analysis. Small proof-of-concept trials, using patients selected based on diuretic response and treated using a variety of protocol-driven diuretic regimens, mechanical fluid removal or treatments aimed at improving diuretic response are needed to truly understand diuretic resistance, and could pave the road towards larger, prospective trials. Ultimately, the results of such studies may help clinicians better comprehend the relative importance of phenomena such as diuretic resistance and worsening renal function, and with the aid of biomarkers or risk scores, perhaps distinguish 'benign' forms from the malignant ones. In addition to guiding in-hospital treatment, post-discharge rehospitalization and mortality risk scores may allow follow-up treatment to be tailored to suit an individual patient's needs.

## Unravelling the information

But it's not just about treatments.

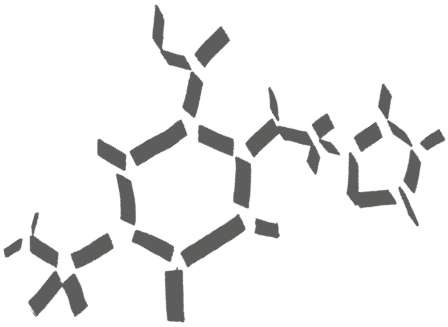
The development of better therapies for heart failure is crucially important for clinicians and patients alike, yet greater understanding of the processes and pathways involved in the intertwined failure of both heart and kidney is equally essential. Careful evaluation of novel biomarkers may not only yield improved diagnostic or prognostic information, but perhaps more interestingly, can provide insight into disease pathways and thus yield novel targets for therapy or tools for monitoring treatment response. The failure of multiple, large-scale drug trials to provide clinical benefit following promising early results highlights the need for pre-selection of potential responders – personalizing treatment at the trial level - instead of performing large-scale trials in 'unselected' patients. Analyses in smaller, well-charac-

terized populations are a crucial stepping stone along this path. Although pharmacogenetic profiling is becoming increasingly common, patient profiling based on multimarker risk or response scores is not (yet). Multimarker models to ascertain clinical risk and assess drug response may allow the identification of patient profiles likely to benefit from a specific intervention, maximizing the yield of clinical trials.

Modern computing has given us the ability to tackle these challenges, using tools undreamed of a generation ago. Genomics is improving our understanding of the stuff we are made of, proteomics yields novel markers, and advanced statistical computing provides the means to make sense of these huge quantities of data and complex networks. 'Big Data' is a hot-button social issue, and becoming a reality in medicine and research; proponents correctly point to the tremendous potential value, while privacy advocates voice their concerns. However, most health care systems are still insufficiently equipped to collect information efficiently - with patient care and ease of billing both prioritised over data collection – although national systems such as those found in Scandinavian countries provide a glimpse of what is possible, and are treasure troves for epidemiologic research. Biobanks, well-designed and maintained health care registries and observational studies may be expensive undertakings, but have enormous potential for increasing our understanding of health and disease.

Traditional statistical analyses will certainly remain a mainstay of medical science for the foreseeable future, but more complex approaches such as systems biology, structural equation modelling and pathway and network analysis can all help unravel the mysteries hidden in the numbers. In the face of ever-increasing amounts of data, the old paradigm of 'bench to bedside' is fading, replaced by a continuous cycle of bedside-to-bench-to-bedside and back; epidemiologic, clinical and biomarker studies generate hypotheses which are explored and tested statistically, and can be taken back into the lab to develop a better understanding of the mechanisms involved and generate new hypotheses to test in patients. Ultimately these insights can lead to new, better-designed studies or even novel interventions and treatments.

This burgeoning enterprise requires close cooperation between clinicans, basic science researchers, clinical trialists, epidemiologists and biostatisticians. The complexity of modern science demands sophisticated analyses, and the challenge lies in translating this complexity into a clinically meaningful, understandable form. The era of the single biomarker is ending, making way for more accurate but analytically challenging multimarker approaches, which require transformation into validated risk scores before they can be clinically applicable. In this growing web of numbers, the medical doctor with a firm grasp of both methodology and statistics has a crucial role to play. By providing the clinical perspectives required for appropriate and meaningful analysis, a bridge may be built between clinicians and statisticians, which will benefit medical knowledge and, ultimately, the people we all work so hard to help – patients.



# Dutch Summary

Cardiologen hebben in de afgelopen jaren hernieuwd respect verkregen voor de pathofysiologische rol van de nier bij hartfalen, en begrijpen steeds vaker dat de twee organen niet afzonderlijk kunnen worden gezien. Nierfunctie is niet alleen een sterke, onafhankelijke prognostische marker bij hartfalen; het orgaan speelt ook een sleutelrol bij volume homeostase en is betrokken bij processen die het aangrijpingspunt vormen voor multipele evidence-based behandelingen voor het syndroom, waaronder Renine-Angiotensine-Aldosteron Systeem (RAAS) blokkers en allerlei diuretica. Biomarkers voor nierfunctie – zowel direct gemeten in lichaamsmateriaal als afgeleide maten – hebben de potentie om ons begrip van deze interacties te vergroten en risicostratificatie te verbeteren. Ook zouden ze als therapeutische targets of markers voor effectiviteit kunnen bijdragen aan de ontwikkeling van gepersonaliseerde therapieën voor hartfalen.

## Doelen van het proefschrift

De voornaamste doelen van dit proefschrift zijn:

- **Het bestuderen van de prognostische waarde van verminderde nierfunctie en verslechtering van nierfunctie bij patiënten met acuut en chronisch hartfalen.**
- **Het evalueren van de waarde van biomarkers voor risicostratificatie en het verschaffen van inzichten in de bij hartfalen betrokken cardiorenale pathofysiologische processen.**
- **Het ontwikkelen en evalueren van een kwantitatieve maat voor diuretische respons om zo het fenomeen van diuretica resistentie in acuut hartfalen beter te doorgronden.**

Het eerste deel van dit proefschrift richt zich op belang van nierfunctie en manieren om deze te meten en beïnvloeden bij zowel chronisch als acuut hartfalen. In het tweede deel wordt de evaluatie van diuretische response en verslechtering van nierfunctie in acuut hartfalen onderzocht. The primaire uitkomsten worden hieronder per hoofdstuk belicht, gevolgd door een overzicht van potentiële richtingen voor toekomstig onderzoek.

# Deel I: Nierfunctie bij hartfalen

## Het belang van nierfunctie

In de moderne cardiologie is bewustwording van het belang van nierfunctie een relatief recente ontwikkeling. Na het verschijnen van sleutelpublicaties rond de eeuwwisseling, waarbij nierfunctie werd geïdentificeerd als sterke voorspeller van uitkomsten bij hartfalen, is het aantal studies naar associaties tussen nierfunctie en prognose bij hartfalen exponentieel gegroeid (Figuur 1, Summary and Future perspectives, pagina 189).

In **Hoofdstuk 1** worden de resultaten van een meta-analyse bij meer dan 1 miljoen patiënten gepresenteerd, waarbij het cruciale belang van nierfunctiestoornissen voor het voorspellen van uitkomst bij zowel chronisch als acuut hartfalen wordt benadrukt. Door middel van een systematische zoekstrategie werden 57 studies over chronisch nierlijden (Chronic Kidney Disease, CKD) en 28 studies over verslechtering van nierfunctie (Worsening Renal Function, WRF) geïdentificeerd. CKD kwam vaak voor bij zowel acuut als chronisch hartfalen, namelijk bij ongeveer een derde van alle patiënten, en was geassocieerd met slechte uitkomsten, zelfs na correctie voor potentiële confounders. Ook verslechtering van nierfunctie (WRF) kwam vaak voor, bij ongeveer 25% van alle hartfalen patiënten in de studie, en was ook geassocieerd met een verhoogde mortaliteit.

In een secundaire analyse hebben wij de voorspellers van WRF onderzocht, waaruit bleek dat chronische nierfunctiestoornissen (CKD) op baseline, leeftijd, hypertensie, diabetes en het gebruik van diuretica allemaal het ontwikkelen van WRF voorspellen. Hoewel zowel CKD als WRF overtuigend en consistent geassocieerd waren met een verhoogde mortaliteit, waren er wel aanwijzingen voor mogelijke publicatiebias bij studies over het prognostisch belang van WRF. Daarnaast blijft de definitie van WRF een punt van discussie, waarbij consensus nog steeds ontbreekt. Meerdere studies suggereren ook dat de oorzaak van WRF in belangrijke mate de prognostische betekenis daarvan beïnvloedt, en dat WRF bij goede respons op therapie en hemodynamische stabiliteit mogelijk geaccepteerd kan worden. De voorspellers van WRF – hogere leeftijd, meer co-morbiditeit en slechtere nierfunctie op baseline – suggereren dat WRF een surrogaat marker zou kunnen zijn voor kwetsbaarheid of renale reserve.

Concluderend kan worden gesteld dat, hoewel zowel CKD als WRF onafhankelijk geassocieerd zijn met mortaliteit in heterogene hartfalen populaties, CKD meer consistent is geassocieerd met slechte uitkomsten. Meer onderzoek naar de definitie, oorzaken en context van WRF in verschillende hartfalen settings zal nodig zijn om het belang ervan beter te begrijpen.

## Meten van nierfunctie

Nierfunctie wordt van oudsher geschat door middel van formules op basis van creatinine, waaronder creatinineklaring volgens Cockcroft-Gault, en de recentere Mod-

ification of Diet in Renal Disease (MDRD) formule, welke bij verschillende patiëntenpopulaties (waaronder hartfalen) zijn gevalideerd. Ondanks het feit dat er andere, wellicht betere biomarkers bestaan voor het schatten van nierfunctie – zoals cystatine-C – wordt serum creatinine nog steeds op grote schaal gebruikt dankzij de lage kosten, bekendheid bij artsen en tenminste redelijke prestaties onder de meeste omstandigheden. Hoewel bestaande formules grotendeels adequaat zijn, geven deze vooral bij hoge en lage glomerulaire filtratie (Glomerular Filtration Rate, GFR) waardes onbetrouwbare schattingen van de nierfunctie, waardoor nieuwe formules een waardevolle aanvulling kunnen zijn. Tevens is het mogelijk dat bepaalde formules niet voor alle populaties of doeleinden even geschikt zijn.

In **Hoofdstuk 2** hebben wij de waarde van recenter ontwikkelde creatinine en cystatine-C formules voor het schatten van glomerulaire filtratie snelheid (Glomerular Filtration Rate, GFR) geëvalueerd. Deze formules zijn ontwikkeld door de Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) en verbeteren de schatting van GFR bij patiënten met CKD en vele andere patiëntenpopulaties. Een validatie ten opzichte van volgens de gouden standaard gemeten GFR bij patiënten met chronisch hartfalen ontbrak echter.

Wij hebben bij 120 patiënten met chronisch hartfalen de GFR gemeten middels [$^{125}$I] iothalamaat klaring – de gouden standaard – en de prestaties van de geschatte simplified MDRD (sMDRD) en CKD-EPI creatinine formules vergeleken voor wat betreft accuracy (nauwkeurigheid), bias en prognostische waarde. Drie andere formules voor het schatten van GFR – creatinineklaring volgens Cockcroft-Gault, en cystatine-C en gecombineerde cystatine-C / creatinine formules ontwikkeld door CKD-EPI – zijn ook geëvalueerd in een secundaire analyse. Van de creatinine formules was de CKD-EPI formule de best presterende, en voorspelde beter classificatie in CKD klassen dan sMDRD en Cockcroft-Gault formules, met equivalente prognostische waarde. Beide Cystatine-C formules presteerden beter dan die gebaseerd op creatinine, maar gezien de huidige klinische praktijk is er nog steeds ruimte voor formules die enkel creatinine gebruiken.

Naast bloedmarkers kunnen urinemarkers van onschatbare waarde zijn voor het beoordelen van nierfunctie. Urine – het meest zichtbare product van de nier – is makkelijk te verzamelen. Er schuilt in urine een grote hoeveelheid aan informatie die andere aspecten van renale pathofysiologie – waaronder tubulaire schade – zou kunnen helpen ontrafelen en bloedwaardes zou kunnen aanvullen. In **Hoofdstuk 3** geven wij een overzicht van zowel traditionele – creatinineklaring, urine natrium en albumine excretie – als nieuwe markers die potentieel van waarde kunnen zijn bij hartfalen. De traditionele markers zijn relatief bekend en enkele worden reeds aangeraden voor risicostratificatie, terwijl de waarde van nieuwe markers vooral ligt in het beter begrijpen van pathofysiologische processen, en niet zozeer in directe klinische bruikbaarheid. Veelbelovende markers die zouden kunnen bijdragen aan betere begrip van pathofysiologische processen bij hartfalen zijn onder andere inflammatoire markers (Interleukine-18), vasculaire markers (Endotheline-1) en markers voor myocardiale rek (urine natriuretische peptides). Van groot belang

zijn ook markers van tubulaire schade – waaronder Kidney-Injury Molecule 1 (KIM-1), Neutrophil Gelatinase-Associated Lipocalin (NGAL), N-acetyl-β-D-glucosaminidase (NAG) en Fatty Acid-Binding Proteins (FABP). Tubulaire schade is een potentieel mechanisme voor verslechtering van nierfunctie - een cruciale risicofactor bij hartfalen, zie **Hoofdstuk 1** - waarbij vroege detectie mogelijk gerichte preventie mogelijk zal maken. Aangezien deze markers direct door de tubuli in de urine worden uitgescheiden, is urine de ideale vloeistof om deze processen in kaart te brengen. Tubulaire markers lijken de meest veelbelovende kandidaten voor klinisch gebruik, daar ze mogelijk gebruikt kunnen worden om hartfalentherapieën te monitoren – bijvoorbeeld diuretica – en om vroege risicostratificatie mogelijk te maken. De diagnostische en prognostische waarde van nieuwe markers zal echter uitgebreid moeten worden bestudeerd voordat routinematig en effectief gebruik in de patiëntenzorg mogelijk is.

## Moduleren van nierfunctie

Verschillende richtlijnen bevelen het gebruik van vaatverwijders bij patiënten met acuut hartfalen en adequate bloeddruk aan, ondanks gebrek aan bewijs voor een betere overleving. Verschillende vaatverwijdende stoffen zijn bestudeerd bij patiënten met hartfalen. Bijna al deze middelen hebben als doel om de hemodynamiek te verbeteren middels reductie van de afterload. Gezien de centrale rol van hemodynamische regulatie bij het behoud van nierfunctie, is het niet verassend dat veel van deze middelen effecten hebben op de nier. Met het experimentele middel rolofylline – een adenosine A-1 antagonist – was bijvoorbeeld de gedachte dat verbetering van uitkomsten bij acuut hartfalen via verbetering van nierperfusie en behoud van nierfunctie, en niet via directe cardiale effecten zou kunnen worden bewerkstelligd. Helaas is dit voor rolofylline niet het geval gebleken.

In **Hoofdstuk 4** geven wij een overzicht van de renale effecten van bestaande en experimentele vaatverwijdende therapieën voor acuut hartfalen. Renale vasoconstrictie – wat aangezet wordt door activatie van verschillende pathofysiologische processen bij acuut hartfalen – is een belangrijk mechanisme dat kan bijdragen aan nierschade en uiteindelijk blijvende nierinsufficiëntie. Meerdere bekende en nieuwe vaatverwijders die worden gebruikt en bestudeerd in hartfalen hebben niet alleen algemeen/systemisch vaatverwijdende effecten, maar ook specifieke effecten in de afferente en/of efferente niervaten, en enkele middelen grijpen aan op neurohormonale assen die een rol spelen bij nierfunctieregulatie.

Zoals hierboven vermeld is het bewijs voor de effectiviteit van deze middelen bij acuut hartfalen (AHF) beperkt, en gegevens over effecten op nierfunctie nog schaarser. Enkele middelen hebben potentieel interessante effecten op de nier en zijn mogelijk zinvol in bepaalde situaties – waaronder milrinone, levosimendan en vasopressine-antagonisten, maar vooral ook serelaxine, een recombinante vorm van humaan relaxine. Serelaxine heeft positieve hemodynamische effecten en lijkt bij te dragen aan verbetering van meerdere orgaanfuncties, waaronder nierfunctie. Opvallend genoeg zijn er geen data beschikbaar over de renale effecten van

de meest gebruikte vaatverwijdende stof in de klinische praktijk, nitroglycerine. Samengevat hebben meerdere vaatverwijders potentieel beschermende effecten op de nierfunctie – bij handhaving van adequate persfusie – maar is naast nauwkeurige selectie en continue bewaking van patiënten nog veel verder onderzoek vereist voordat routinematig gebruik kan worden aanbevolen.

## Deel II: Diuretische respons en verslechtering van nierfunctie in acuut hartfalen

De effecten van lisdiuretica – de hoeksteen van vochtregulatie en symptoombestrijding bij acuut hartfalen – worden onvolledig begrepen ondanks decennia van klinische ervaring. Hoewel het gebruik van deze middelen wordt ondersteund door sterke aanbevelingen in de behandelrichtlijnen op basis van klinische ervaring en gezond verstand, is het bewijs voor optimaal gebruik, en voor positieve effecten op uitkomsten, beperkt en soms zelfs tegenstrijdig.

Een van de problemen waar cardiologen bij de behandeling van patiënten met acuut hartfalen dagelijks mee te maken krijgen is diuretica resistentie – refractaire symptomen of tekenen van congestie ondanks verhoging van diureticadoseringen. Dit fenomeen is een essentieel onderdeel van zogeheten 'cardiorenale syndromen', en is geassocieerd met hoge mortaliteit en frequente ziekenhuisopname. Diuretica resistentie heeft velerlei oorzaken: verminderde persfusie, congestie, nierfunctiestoornissen, neurohormonale activatie, azotemie en een slechte voedingsstatus zijn allemaal potentieel bijdragend. Desondanks zijn er geen geschikte manieren om respons op diuretische therapie te meten, waarbij bestaande definities voor resistentie vooral gericht zijn op diuretica dosering bij persisterende congestie, of enkel naar dosering kijken.

In **Hoofdstuk 5** presenteren wij een mogelijke oplossing voor dit probleem in de vorm van een nieuwe, kwantitatieve maat voor diuretische respons – gewichtsverandering per eenheid lisdiureticum (40 mg furosemide of equivalente dosering). De achterliggende gedachte was om een relatief simpele maat te ontwikkelen die een 'dosis-respons' verhouding tussen het medicijn en het klinisch effect kon weergeven. Helaas waren data over urineproductie – het directe effect van diuretica - niet voorhanden ter validatie. Gewicht heeft echter wel enkele voordelen, waaronder gemak, en wordt in de richtlijn aanbevolen voor het controleren van volumestatus bij hartfalen.

Wij hebben deze nieuwe maat onderzocht bij 1745 patiënten uit de PROTECT studie, een gerandomiseerde, placebogecontroleerde trial met de experimentele adenosine A-1 antagonist rolofylline bij patiënten met gedecompenseerd acuut hartfalen met neutrale resultaten. Slechte respons op diuretica was geassocieerd hogere leeftijd, lagere bloeddrukken, meer vaatlijden, vaker coronaire revascularisatie, meer diabetes, anemie en slechtere nierfunctie, waaronder verhoogd ureum. In deze groep waren ook vaker aanwijzingen voor vergevorderd hartfalen, waaronder frequentere devicetherapie. Patiënten met een goede respons hadden

een lagere mortaliteit en behaalden vaker het primaire eindpunt van de studie – verbetering van dyspnoe na 24 en 48 uur.

Opvallend genoeg was rolofyllinegebruik een onafhankelijke voorspeller van goede diuretische respons, mogelijk door directe diuretische effecten van het medicijn of versterking van diuretische effectiviteit via verbeterde nierperfusie. Ook was de nierfunctie van patiënten met goede en slechte diuretische respons niet enorm verschillend, wat impliceert dat diuretische respons niet alleen een weerspiegeling is van GFR. Verslechtering van nierfunctie (WRF) – in het algemeen een slecht teken, zoals te lezen is in **Hoofdstuk 1** – kwam echter relatief vaak voor bij patiënten met een goede respons, ondanks de relatief beste uitkomsten voor deze groep. Dit ondersteunt de theorie dat de context voor WRF belangrijker is dan puur het ontstaan daarvan. In multivariate analyses was slechte diuretische respons onafhankelijk geassocieerd met mortaliteit en rehospitalisatie. Uitgebreide sensitiviteitsanalyses bevestigen de consistentie van deze bevindingen. Vooral de sterke associatie met rehospitalisatie is interessant, aangezien dit een moeilijk te voorspellen eindpunt blijft.

**Hoofdstuk 6** is een editorial door Professor Emeritus Eugene Braunwald, samen met Hoofdstuk 5 gepubliceerd in het European Heart Journal, waarin het belang van nieuwe maten voor respons op diuretica wordt onderstreept. Het editorial bespreekt ook een recente studie gepubliceerd door Testani et al., waarin een soortgelijke maat gebaseerd op netto vochtbalans werd geïntroduceerd, met vergelijkbare resultaten als gepresenteerd in hoofdstuk 5. Professor Braunwald benoemt terecht enkele potentiële nadelen van deze simpele maten – waaronder de complexiteit van accuraat meten van gewicht of vochtbalans, het gebrek aan informatie over zoutintake, de effecten van gecombineerde behandeling met andere diuretica, en het feit dat deze maten de farmacodynamische complexiteit van diuretische behandeling niet accuraat kunnen weergeven. Zijn conclusie is echter dat ondanks deze beperkingen, het ontwikkelen en valideren van kwantitatieve maten voor respons op diuretica een cruciale stap is richting beter begrip van diuretica resistentie en optimalisatie van diuretische therapie bij hartfalen patiënten.

In **Hoofdstuk 7** worden veranderingen in serum Neutrophil Gelatinase-Associated Lipocalin (NGAL) tijdens hospitalisatie beschreven, alsmede de waarde van NGAL voor het voorspellen van verslechtering van nierfunctie (WRF) en verbeteren van risicostratificatie in een subanalyse van de PROTECT studie. NGAL – een tubulaire marker – zou mogelijk een vroege, gevoelige marker zijn voor het ontwikkelen van WRF, en er zijn aanwijzingen dat het een goede prognostische waarde zou hebben. Onze studie is verricht in 1447 patiënten opgenomen met acuut hartfalen, een significant grotere populatie dan alle voorgaande studies over serum NGAL bij acuut hartfalen bij elkaar opgeteld.

In tegenstelling tot meerdere kleinere studies zagen wij dat NGAL niet eerder dan creatinine stijgt bij patiënten die WRF ontwikkelen in de eerste dagen na ziekenhuisopname voor hartfalen. Hoewel NGAL wel en creatinine geen onafhankelijke

voorspeller was van WRF, had geen van beide markers bijzonder goede voorspellende waarde. NGAL was ook niet voorspellend voor mortaliteit of een samengesteld eindpunt van 60-dagen mortaliteit en/of rehospitalisatie. Echter, in patiënten met WRF – uitgedrukt als stijging in creatinine tijdens de eerste vier dagen – was het risico op dood of rehospitalisatie bij eenzelfde creatininestijging groter voor hogere NGAL waardes dan voor lagere NGAL waardes, ook na correctie voor baseline creatinine. NGAL heeft derhalve enige additionele waarde, maar enkel bij patiënten die een stijging van creatinine laten zien.

Waarom onze studie eerdere resultaten lijkt tegen te spreken is niet helemaal duidelijk; de positieve resultaten van kleine voorgaande studies zijn mogelijk een uiting van publicatiebias – onze meta-analyse heeft aangetoond dat dit mogelijk voorkomt bij studies over WRF – maar wordt mogelijk ook veroorzaakt door verschillen in de bestudeerde populaties. Ons cohort is groot en goed beschreven, maar PROTECT heeft enkel patiënten met tenminste milde nierfunctiestoornissen geïncludeerd, wat mogelijk de resultaten kan hebben beïnvloed. Er moet wel worden opgemerkt dat de incidentie van WRF in onze studie ongeveer overeenkomt met de getallen voor algemene hartfalenpopulaties die we in **Hoofdstuk 1** hebben gezien.

Een mogelijke verklaring ligt bij de aard van WRF bij AHF; eerdere studies in acuut zieke niet-hartfalen populaties hebben een sterke voorspellende waarde laten zien voor NGAL. In AHF wordt WRF vaker gedreven door kleine hemodynamische veranderingen, neurohormonale verandering en medicatie effecten, in tegenstelling tot de hypoxische of septische schade leidend tot acute nierschade (AKI) die vaker bij post-chirurgische of intensive care patiënten wordt gezien. Verder is de timing van nierschade of WRF bij AHF vaak onduidelijk, waarbij er mogelijk reeds voor opname ongedocumenteerde schade is ontstaan; de vroege NGAL piek die door anderen wordt gezien kan bij een aantal van onze patiënten dus onopgemerkt zijn gebleven.

Op basis van deze retrospectieve data lijkt de klinisch waarde van serum NGAL in acuut hartfalen beperkt. Mede gezien de andere potentiële oorzaken van verhoogd serum NGAL – waaronder inflammatie en infectie – zijn urinewaardes mogelijk betrouwbaarder dankzij de verhoogde renale specificiteit. Hopelijk zal de AKINESIS trial naar urine en bloed NGAL in hartfalen die binnenkort wordt afgerond definitief antwoord geven op deze vragen.

Het laatste hoofdstuk van dit proefschrift, **Hoofdstuk 8**, beschrijft de pathofysiologie van diuretica resistentie in acuut hartfalen, en neemt recent voorgestelde maten voor diuretische respons onder de loep. De meeste artikelen over diuretica resistentie zijn gebaseerd op oudere, minder werkbare definities, en geen enkel artikel heeft een grondig overzicht van de potentiële oorzaken voor diuretica resistentie bij hartfalen gegeven. De recente publicatie van meerdere mogelijke manieren om respons op diuretische therapie te evalueren – waaronder onze eigen maat van gewichtsverandering per eenheid diureticum, een soortgelijke maat op basis van urine output en de verhouding tussen natrium en furosemide in de urine – maken

deze review tot een waardevolle toevoeging aan de bestaande literatuur.

In het artikel worden meerdere pathofysiologische mechanismes beschreven die potentieel betrokken zijn bij diuretica resistentie in acuut hartfalen – verminderde opname, verstoord transport in de bloedbaan en door de glomerulus naar de tubulus, en een gebrek aan beschikbaarheid op de transporter. Intestinaal oedeem en slechte voedingstoestand resulterend in hypoalbuminemie (nodig voor transport van furosemide en vele andere diuretica) kunnen de eerste twee factoren beïnvloeden. Verlaagde cardiac output en neurohormonale modulatie kunnen nierfiltratie beïnvloeden, en een verhoogd ureum kan competitief het transport naar de tubulus blokkeren. Eenmaal aangekomen in de tubulus kan albumine zich wederom binden aan het lisdiureticum en het zo inactiveren. Ook kunnen de directe effecten van diuretica zelf – waaronder post-diuretische natrium retentie na herhaalde dosering met als gevolg RAAS activatie – bijdragen aan verminderde diuretische effectiviteit.

Wij laten ook zien dat er enig bewijs is voor een stapsgewijze aanpak met verschillende types diuretica om resistentie te overwinnen, en dat ultrafiltratie of vaatverwijdende therapie (zoals beschreven in **Hoofdstuk 4**) mogelijk geschikt kunnen zijn bij specifieke patiënten. Wat vooral duidelijk wordt, is dat het gebrek aan bruikbare maten voor diuretische respons betekent dat er geen studies – in het heden of verleden – expliciet prospectief deze mogelijkheden om diuretica resistentie te overwinnen hebben getest. Deze nieuwe maten zullen in de toekomst hopelijk leiden tot nieuwe trials om diuretische strategieën bij resistente patiënten met acuut hartfalen te optimaliseren.

## Toekomstperspectief

Cardiorenaal onderzoek bij hartfalen is al lang de kinderschoenen ontgroeid; verwekt eind jaren negentig en geboren rond de eeuwwisseling, waren de kinderjaren vol spannende ontdekkingen: nierfunctie als essentiële risicofactor, de 'cardiorenale syndromen', ontelbaar veel nieuwe biomarkers en zelfs experimentele medicijnen die primair de nier behandelden bij patiënten met hartfalen. Het enorme aantal patiënten die voor de geüpdate meta-analyse (**Hoofdstuk 1**) beschikbaar waren zegt al genoeg, waarbij de meeste data in de afgelopen 10 jaar zijn gepubliceerd.

Echter, ondanks de volwassenheid van het veld blijft verkenning, innovatie en ontdekking van cruciaal belang.

### Behandelingen voor acuut hartfalen

Als we spreken over therapie, is het opvallend dat de meeste bewezen effectieve behandelingen voor chronisch hartfalen direct effect hebben op de nier – waaronder alle vormen van RAAS blokkade. Echter het bewijs voor optimaal gebruik en de waarde van een van de oudste en meest voorgeschreven hartfalen medicijnen – het simpele lisdiureticum – is schrikbarend mager. Dit is helaas ook het geval voor alle behandelingen gericht op een dodelijke en steeds vaker optredende oorzaak

voor ziekenhuisopname – acuut hartfalen.

Ondanks verschillende affaires met nieuwe, spannende AHF medicijnen hebben maar weinig het lang volgehouden, en geen enkele heeft een blijvende indruk achtergelaten. Tot serelaxine – de nieuwste vlam die we beter willen leren kennen voordat we ons binden – slaagde geen enkele therapie in het verbeteren van overleving, en slechts een enkele gaf patiënten iets meer lucht. Veel van deze vaatverwijders en (nieuwe) inotropica worden in de klinische praktijk nog incidenteel gebruik, vaak bij de ziekste patiënten bij gebrek aan bewezen alternatieven.

En dus keren we terug naar de medicijnen die wij denken te begrijpen; medicijnen die zwelling en kortademigheid verminderen en elektrolyten en niermarkers overhoop gooien – diuretica. Ze hebben genoeg voordelen – goedkoop, makkelijk in gebruik, met bekende bijwerkingen. Als patiënten goed reageren is er niets aan de hand. Zo niet, dan is het bewijs voor wat we dan moeten doen flinterdun. Dosis verhogen? Een ander (type) diureticum gebruiken? Vaatverwijders of inotropica geven? Steroïden? Ultrafilteren? En hoe zit het met patiënten die wel goed reageren, maar bij wie de nierfunctie achteruit gaat? Of die (niet) hemoconcentreren? Hoe belangrijk is het om overvulling volledig te herstellen? En welke van deze factoren is nou het meest belangrijke?

Om de zaken nog complexer te maken zijn patiënten met acuut hartfalen een divers gezelschap. Ischemisch of non-ischemisch, met verminderde of behouden ejectiefractie, 'warm en nat' of 'koud en droog', en alle mogelijke combinaties van dien. Met elke denkbare elektrolytstoornis en nierfunctie. Dit verklaart mogelijk waarom veel nieuwe AHF therapieën geen overtuigend positief effect hebben getoond. Het netto resultaat van een 'one-size-fits-all' behandeling voor een heterogeen ziektebeeld kan neutraal zijn – maar het identificeren van potentiële responders biedt mogelijkheden. De vraag blijft of de therapieën die wij hebben echt hebben gefaald, of dat we simpelweg de verkeerde patiënten hebben behandeld.

Beter inzicht in het belang van en in de interacties tussen biomarkers bij opname en dynamische verandering in respons op therapie tijdens opname – waaronder diuretische respons, bloeddruk, hemoconcentratie, (renale) biomarkers, congestie – vergt gedetailleerde analyse. Kleine proof-of-concept studies in patiënten geselecteerd op basis van diuretische respons en behandeld volgens verschillende, protocol-gedreven diuretica schema's, mechanische vochtverwijdering of behandelingen met als doel diuretica respons te vergroten zijn essentieel om diuretische resistentie te doorgronden, en kunnen de weg vrijmaken voor grotere, prospectieve trials.

Uiteindelijk kunnen zulke studies clinici helpen om het belang van fenomenen zoals diuretica resistentie en verslechtering van nierfunctie te doorgronden, en om met behulp van biomarkers of risicoscores de 'benigne' van de 'maligne' varianten te onderscheiden. Naast het sturen van behandeling tijdens opname, zouden risicoscores voor heropname en mortaliteit een gepersonaliseerde follow-up voor de individuele patiënt mogelijk kunnen maken.

## De data ontrafelen

Het onderzoek naar behandelingen is echter slechts een deel van het verhaal.

De ontwikkeling van betere hartfalentherapieën is van cruciaal belang voor zowel clinici als patiënten, maar beter begrip van de processen en mechanismen die betrokken zijn bij het gecombineerd falen van hart en nier zijn dat evenzeer. Naast het verschaffen van betere diagnostische en prognostische informatie, kan gedegen evaluatie van nieuwe biomarkers ook leiden tot fascinerende inzichten in ziekteprocessen en dus tot nieuwe targets voor therapie of mogelijkheden om het effect van therapie te monitoren. Het falen van meerdere grootschalige geneesmiddelenstudies na veelbelovende vroege resultaten onderstreept het belang van preselectie van potentiële responders – gepersonaliseerde behandeling op trial niveau. Analyses in kleinere, goed beschreven populaties zijn een cruciale stap op deze weg. Hoewel farmacogenetische selectie steeds vaker gebeurt, is selectie op basis van multimarker risico- of responsmodellen (nog) geen gemeengoed. Multimarker modellen om klinisch risico te beoordelen en respons op therapie te evalueren kunnen mogelijk leiden tot selectie van patiënten die een hoge kans hebben om goed te reageren op een interventie, en dus tot betere trials.

Moderne computertechnologie geeft ons de mogelijkheden om deze uitdagingen aan te gaan. Genomics vergroot onze kennis over de bouwstenen van de mens, proteomics geeft ons nieuwe markers, en geavanceerde statistische pakketten maken het mogelijk om deze massale hoeveelheden data en complexe netwerken te verwerken. 'Big Data' is een heikele maatschappelijke kwestie geworden, en wordt steeds meer realiteit in de geneeskunde en het onderzoek; voorstanders wijzen terecht op de enorme potentiële voordelen, terwijl privacy waakhonden hun zorgen uiten. De meeste zorgsystemen zijn momenteel onvoldoende ingericht om efficiënt informatie te verzamelen, zowel patiëntenzorg en factureringsgemak hebben prioriteit boven dataverzameling. Echter, nationale systemen naar Scandinavisch model laten zien wat er mogelijk is, het zijn ware schatkamers voor epidemiologisch onderzoek. Biobanken, goed opgezette zorg databases en observationele studies vergen veel geld en inspanning, maar zijn van onschatbare waarden om ons begrip van ziekte en gezondheid te vergroten.

Traditionele statistische analyses zullen ongetwijfeld een centrale rol blijven vervullen in de geneeskunde, maar complexere technieken waaronder systems biology, structural equation modelling, en pathway en netwerk analyses kunnen allen bijdragen aan het ontrafelen van de geheim die in de getallen verborgen liggen. De alsmaar groter wordende hoeveelheden data breken het oude 'bench-to-bedside' paradigma open, en maken plaats voor een continue cyclus van 'bedside-to-bench-to-bedside' en weer terug; epidemiologische, klinische en biomarker studies genereren hypotheses die statistisch worden onderzocht en getoetst, en dan in het lab kunnen leiden tot nieuwe inzichten in de betrokken mechanismes, om vervolgens nieuwe hypotheses te genereren die dan bij patiënten kunnen worden getest. Uiteindelijk leiden deze inzichten tot nieuwe, betere studies of zelfs innovatieve interventies of behandelingen.

Deze grote veranderingen vergen nauwe samenwerking tussen clinici, basale wetenschappers, klinisch onderzoekers, epidemiologen en biostatistici. De complexiteit van de moderne wetenschap vergt geraffineerde analyses, en de uitdaging ligt in het vertalen hiervan naar een klinisch relevante en begrijpelijke vorm. Het tijdperk van de enkele biomarker komt tot een einde. De nauwkeurigere maar analytisch uitdagendere multimarker benaderingen beginnen op te komen, maar moeten getransformeerd worden naar gevalideerde risicomodellen voordat ze klinisch bruikbaar worden. In dit groeiende web van getallen is er een belangrijke rol weggelegd voor de arts met een gedegen begrip van zowel methodologie en statistiek. Door de klinische blik die essentieel is voor relevante en adequate analyses kan een brug geslagen worden tussen clinici en statistici, om zo medische kennis te vergroten en uiteindelijk diegene te helpen waar het uiteindelijk om draait – de patiënt.

# Acknowledgements

The path I followed to end up where I am today was not as direct as I intended. What it did provide was a rich, exciting and varied set of experiences - my time as a PhD candidate remains one I will remember fondly, thanks to the people who contributed to my personal, intellectual and professional development here in Groningen.

Als eerste wil ik mijn promotores bedanken – Prof. dr. Hans Hillege en Prof. dr. Adriaan Voors. Beste Hans, vanaf het begin heb je ervoor gezorgd dat ik mij thuis voelde in Groningen. Hoe druk je ook was en bent, je deur stond – en staat nog steeds – altijd open. Toen wij voor het eerst kennis maakten begreep ik weinig van al die niermarkers, en nog minder van statistiek. Met jouw aanmoediging, steun en kritische blik heb ik mijn analytische en wetenschappelijke vleugels kunnen spreiden. Maar nog meer dan de wetenschapper bewonder ik de persoon – het luisterend oor, de gesprekken tijdens impromptu etentjes. Je bent een ware vriend en mentor voor mij.

Beste Adriaan, jij hebt mij de kans geboden om naar Groningen te komen en op de rijdende onderzoekstrein te springen. Jouw scherpzinnige, kritische vragen en focus op de klinische relevantie van onze onderzoekresultaten hebben mij altijd geholpen om terug te keren naar de kern van het verhaal als ik strandde in een wolk van getallen. Bij jou had ik de vrijheid om zelf mijn ideeën te toetsen en kreeg ik alle ruimte om mijzelf als wetenschapper te ontwikkelen en te ontplooien. Maar je hield ook nauwlettend de voortgang en resultaten in de gaten, en gaf waar nodig een kleine koerscorrectie. Met name de laatste maanden van 'kruisbestuiving' binnen de onderzoeksgroep waren inspirerend, en ik hoop nog lang bij te kunnen dragen.

Dan mijn co-promotor, dr. Kevin Damman – Kevin, je bent altijd verfrissend direct, enorm kundig en altijd bereid om jouw tijd, kennis en onderzoek te delen. Vooral in het begin heb jij inhoudelijk veel steun kunnen geven tot ik zelfstandig op mijn benen kon staan. Ik ben snel zowel je intellect als de persoon die je bent erg gaan waarderen, en hoop nog lange tijd met je samen te kunnen werken.

I wish to thank the members of the assessment committee – Professor John Cleland, Professor Ygal Pinto and Professor Gerjan Navis for taking the time to review my thesis.

Beste Gerjan, ik wil je ook bedanken voor de gesprekken over diuretica resistentie en de uitleg over de technische kanten van GFR schattingen, die mijn cardiologische blik hebben verruimd met enkele nefrologische inzichten.

Alle collega promovendi in het Triade – en sommigen verscholen bij de experimentele – het was een waar genoegen om met jullie onderzoek te doen, bier te drinken, te feesten, te fietsen, tot laat in de nacht de hangen in het Feithuis, de Pint of de Uurwerker, om maar een kleine greep uit de mooie ervaringen te noemen. Cola rondjes, taart, espressootje uit de DeLonghi, en bovenal veel gelach en gezelligheid naast het harde werk hebben mijn promotietijd bijzonder gemaakt. De hartfalen boys – Frank, Nico, IJsbrand, Vinnie, Arjen en natuurlijk mijn gekke Duitse kamergenoot Sven – Wine en Cheese, of Spareribs, of gewoon een pint bij de Pint; het was een genot en een verrijking. Met de rest van de triade hartfalenclub – Licette, Jozine en Eline, en natuurlijk Biniyam – was het minstens even gezellig, met Athene en Schier als hoogtepunten van het extracurriculaire gebeuren. Uiteraard ook de experimentele HF Gang, Rogier, Wouter M. en Harmen, en alle anderen huidige en voormalige bewoners van het Triade die het tot een bijzondere tijd hebben gemaakt – Bart, Wouter W., Rob, Chris, Marlies, Gijs, Renee, Ymkje, You Lan, Lennaert, Karim, Imke, Ernaldo, Anne, Roseanne, Marjolein, en Marieke.

Best Alma, alle dank voor de steun, de vrolijke lach en behulpzaamheid – ze zeiden altijd 'Alma weet alles', en dat blijkt keer op keer waar te zijn. Ook Audrey, Carla en Roelian wil ik bedanken voor hun bijdrage aan het organiseren en coördineren van de soms chaotisch-ogende universitaire wereld. De dames en heren van de Cardio Research wil ik ook bedanken voor hun hulp en de prettige samenwerking op mijn 'studiedag' – Vooral Geert en Peter, maar zeker ook Trienke, Margriet, Karin, Greetje, Carolien, Carlien, Anke, Anja, Bernard en Sandra. Meedraaien in de clinical trial molen heeft mij veel geleerd. Van de afdeling Epidemiologie wil ik dr. Douwe Postmus nog bedanken voor zijn statistische kennis en geduld met mijn incoherente vragen, die hopelijk in de loop der jaren wat minder onnozel zijn geworden.

Tibor, ook jou wil ik bedanken – sinds het tweede jaar geneeskunde zijn we beste vrienden, ben jij een soort 'brother I never had'. Dat jij hier in Groningen was toen ik begon maakte de overgang naar het onbekende noorden heel wat makkelijker. Onze reizen samen zal ik nooit vergeten, en ik weet dat ik altijd iemand heb waar ik op kan bouwen, en ik hoop dat je beseft dat het wederzijds is.

Petra, ik leerde je hier pas echt kennen, maar inmiddels is het een bijzondere vriendschap geworden. Er is veel gebeurd in drie jaar tijd: jij gepromoveerd, nieuwe relatie met Matthijs, prachtige dochter; ik een nieuwe liefde, binnenkort mijn verdediging en een opleidingsplek. Maar vooral ook gezelligheid, lekker eten en goeie gesprekken met een glas wijn erbij (het mag weer). Binnenkort ook maar weer dat hardlopen oppakken.

Graag wil ik Prof. Dr. Dirk-Jan van Veldhuisen, Prof. Dr. Maarten van den Berg en dr. Peter Paul van Geel bedanken voor de kans die zij mij hebben geboden om in het

UMCG opgeleid te worden als cardioloog. Ook de andere stafleden en de collega's en vrienden van de 'eerste rij' wil ik bedanken voor een leuke hernieuwde kennismaking met de kliniek na de korte onderzoeksonderbreking.

Beste Dr. Dunsleman, caro Peter. Ik wil jouw bedanken voor de kans die je me hebt gegeven om in Breda mezelf te vinden. De wortels van mijn nieuwe start liggen eigenlijk in het Amphia, en dat heb jij voor mij mogelijk gemaakt. Ook jouw collega cardiologen – in het bijzonder dr. Marco Alings - wil ik bedanken.

Mijn paranimfen wil ik bedanken – dr. Frank Brouwers en Marilla Valente.

Marilla, you're the best (little) sister a guy could hope for - fun, intelligent, and always there when you're needed. I'm not always the best at communicating it, but I'm thrilled to have some of your creativity liven up my thesis, and that you will be standing next to me when I defend. I love you.

Frank, de afgelopen drie jaar heb ik er een hele goeie vriend bij gekregen. Har(d/t) lopend een estafette naar Munchen, elkaar motiveren in de sportschool of de klimmuur, foute dansclubs in binnen of buitenland, een liquid dinner in 't Feith of de ambulanceservice (met Marko emmer), er valt met jouw altijd wel wat interessants te beleven. Moge dat nog jaren zo blijven!

I want to thank my loving parents for helping me become who I am, and for always being there for me – you've always believed in me. You gave me a unique opportunity to experience different parts of the world growing up, which has shaped who I am today. I could not have asked for more loving parents or better role models. No matter the geographic distance between us, you are always close to my heart. Mamma, Papa, vi amo.

Als laatste, en belangrijkste, lieve Leonie. Jij was mijn missende puzzelstukje. Ik was op papier eigenlijk niet wat je zocht – lastig, zo'n dokter, en gitaristen was je al op afgeknapt – maar toch heb je mij de kans gegeven, en zijn wij hard voor elkaar gevallen. Jij hebt mijn leven verrijkt, en ik kijk er naar uit om samen iets geweldigs op te bouwen en nog meer verre oorden te ontdekken. Ik hâld fan dy, popke.

## Curriculum Vitae

Mattia Adriano Egidio Valente was born on March 29th, 1980 in Braine L'Alleud, near Brussels. After a few dimly recalled years in Belgium and Canada, he moved to Germany where he attended elementary and middle school at the Frankfurt International School (1985-1992). At the age of 12, his family relocated to Paris, where he graduated from the American School of Paris with a Bilingual (French/English) International Baccalaureate diploma in 1998.

He moved to The Netherlands at the age of 18 to attend university in Maastricht, hoping to study medicine, an ambition which was postponed by a year due to the vagaries of the lottery system. While he waited, he obtained his propadeutic diploma in Health Sciences from Maastricht University. In 1999, he moved to Amsterdam to study medicine at the VU University. After his first year, he was invited to participate in the Master Class in Medicine pilot programme, his first real - albeit brief - contact with medical research. At the end of his pre-clinical training, after his 4-month research internship in Cape Town, South Africa, where he studied the innervation of the internal vertebral venous plexus in an animal model, he interrupted his studies for a time before starting his clinical rotations. During this period he worked as a freelance (medical) translator, travelled and interned at the interventional cardiology department of the AMC Amsterdam under Professor R.J. de Winter. After graduating from university and obtaining his MD degree in 2008, he worked as a cardiology resident at the Medical Center Alkmaar, the VU University Medical Centre and, finally, the Amphia Hospital in Breda. There he became involved with the BIOSTAT-CHF study, and first met Professor Adriaan Voors.

A few months and two trips to Groningen later, he began his PhD training under the supervision of Professors Hans Hillege and Adriaan Voors, and the support of Dr Kevin Damman on January 1st, 2012. In Groningen, he was given the opportunity to develop his scientific and analytical skills in a stimulating academic environment. He plans to defend his thesis in early 2015 and begin his cardiology training in July 2015.

## Bibliography


1. Valente M, Zwaan E, Wit M, Kimman GP, Umans V. Effects of a digital clinical pathway for elective electrocardioversion for atrial fibrillation on quality of care. Crit Pathw Cardiol. 2010 Dec;9(4):207-11.
2. Valente MA, Damman K, Dunselman PH, Hillege HL, Voors AA. Urinary proteins in heart failure. Prog Cardiovasc Dis. 2012 Jul-Aug;55(1):44-55.
3. Valente, M. and Voors, A. Renal effects of vasodilators in acute heart failure. World Journal of Cardiovascular Diseases, 3, 8-17
4. Mattia A.E. Valente, MD, Hans L. Hillege, MD, PhD, Gerjan Navis, MD, PhD, Adriaan A. Voors, MD, PhD, Peter H.J.M. Dunselman, MD, PhD, Dirk J. van Veldhuisen, MD, PhD, Kevin Damman, MD, PhD. The Chronic Kidney Disease Epidemiology Collaboration equation outperforms the Modification of Diet in Renal Disease equation for estimating glomerular filtration rate in chronic systolic heart failure. Eur J Heart Failure 2014 Jan;16(1):86-94. Epub 2013 Dec 3.
5. K. Damman, M.A.E. Valente, A.A. Voors, C.M. O'Connor, D.J. van Veldhuisen, J.L. Hillege. Renal impairment, worsening renal function and outcome in patients with heart failure – an updated meta analysis Eur Heart J. 2014 Feb;35(7):455-69. Epub 2013 Oct 27
6. Liu LC, Voors AA, Valente, M.A., van der Meer, P. A novel approach to drug development in heart failure: towards personalized medicine. Can J Cardiol. 2014 Mar;30(3):288-95. Epub 2013 Dec 17.
7. Valente MA, Voors AA, Damman K, Van Veldhuisen DJ, Massie BM, O'Connor CM, Metra M, Ponikowski P, Teerlink JR, Cotter G, Davison B, Cleland JG, Givertz MM, Bloomfield DM, Fiuzat M, Dittrich HC, Hillege HL. Diuretic response in acute heart failure: clinical characteristics and prognostic significance. Eur Heart J. 2014 May 14;35(19):1284-93. Epub 2014 Feb 28.
8. Demissei BG, Postmus D, Valente MA, van der Harst P, van Gilst WH, Van den Heuvel ER, Hillege HL. Should non-cardiovascular mortality be considered in the SCORE model? Findings from the Prevention of Renal and Vascular End-stage Disease (PREVEND) cohort. Eur J Epidemiol. 2014 Nov 7. [Epub ahead of print]