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Competing Risk of Cardiac Status and Renal Function During Hospitalization for Acute Decompensated Heart Failure

Khibar Salah, MD,* Wouter E. Kok, MD, PhD,* Luc W. Eurlings, MD,† Paulo Bettencourt, MD, PhD,‡ Joana M. Pimenta, MD, PhD,‡ Marco Metra, MD, PhD,§ Valerio Verdiani, MD, PhD,‖ Jan G. Tijssen, PhD,* Yigal M. Pinto, MD, PhD*

ABSTRACT

OBJECTIVES The aim of this study was to analyze the dynamic changes in renal function in combination with dynamic changes in N-terminal pro-B-type natriuretic peptide (NT-proBNP) in patients hospitalized for acute decompensated heart failure (ADHF).

BACKGROUND Treatment of ADHF improves cardiac parameters, as reflected by lower levels of NT-proBNP. However this often comes at the cost of worsening renal parameters (e.g., serum creatinine, estimated glomerular filtration rate [eGFR], or serum urea). Both the cardiac and renal markers are validated indicators of prognosis, but it is not yet clear whether the benefits of lowering NT-proBNP are outweighed by the concomitant worsening of renal parameters.

METHODS This study was an individual patient data analysis assembled from 6 prospective cohorts consisting of 1,232 patients hospitalized for ADHF. Endpoints were all-cause mortality and the composite of all-cause mortality and/or readmission for a cardiovascular reason within 180 days after discharge.

RESULTS A significant reduction in NT-proBNP was not associated with worsening of renal function (WRF) or severe WRF (sWRF). A reduction of NT-proBNP of more than 30% during hospitalization determined prognosis (all-cause mortality hazard ratio [HR]: 1.81; 95% confidence Interval [CI]: 1.32 to 2.50; composite endpoint: HR: 1.36, 95% CI: 1.13 to 1.64), regardless of changes in renal function and other clinical variables.

CONCLUSIONS When we defined prognosis, NT-proBNP changes during hospitalization for treatment of ADHF prevailed over parameters for worsening renal function. Severe WRF is a measure of prognosis, but is of lesser value than, and independent of the prognostic changes induced by adequate NT-proBNP reduction. This suggests that in ADHF patients it may be warranted to strive for an optimal decrease in NT-proBNP, even if this induces WRF.
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From the *Heart Failure Research Center and Department of Cardiology, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands; †Department of Cardiology, University Hospital Maastricht, Maastricht, the Netherlands; ‡Department of Internal Medicine, Hospital S. João, University of Porto Medical School, Porto, Portugal; §Department of Experimental and Applied Medicine, University of Brescia, Brescia, Italy; and the ‖Department of Internal Medicine and Emergency, Careggi University Hospital, Florence, Italy. Drs. Eurling and Pinto have received research funding for their original study from the Dutch Heart Foundation, Dutch Organisation for Scientific Research (NWO), Royal Dutch Academy of Arts and Sciences-Interuniversity Cardiology Institute of the Netherlands, Pfizer, AstraZeneca, and Medtronic. Dr. Pinto has received compensation for lectures and speaker bureau membership and has received research grants from Roche Diagnostics; and holds a patent and owns stock in a university spinoff company. Dr. Kok has received a grant from Dutch Heart Foundation for an unrelated study. Dr. Bettencourt is a paid consultant with Boehringer-Ingelheim; and has received grants from FCT-Portuguese Science and Technology Foundation and payment for lectures and service on the speakers bureau of Servier. Dr. Metra is a member of the board of Corthera and Novartis; and receives payment for lectures and service on speakers bureau from Servier. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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ABBREVIATIONS AND ACRONYMS

ACE = angiotensin-converting enzyme

ADHF = acute decompensated heart failure

AF = atrial fibrillation

COPD = chronic obstructive pulmonary disease

DBP = diastolic blood pressure

eGFR = estimated glomerular filtration rate

ESC = European Society of cardiology

HF = heart failure

JVP = jugular venous pressure

LVEF = left ventricle ejection fraction

MDRD = modification of diet in renal disease

MeSH = Medical Subject Headings

NT-proBNP = N-terminal pro-B-type natriuretic peptide

NYHA = New York Heart Association

SBP = systolic blood pressure

sWRF = severe worsening renal function

Acute decompensated heart failure (ADHF) remains associated with high hospitalization rate, morbidity, and mortality, most noticeably in the first months after discharge, with high rehospitalization rates (1–4). Renal impairment is a common comorbidity in these patients (5–8). Previous studies have shown that worsening renal function (WRF) during hospitalization (9,10), decreased levels of estimated glomerular filtration rate (eGFR) (11–13), or increased levels of serum urea (14,15) are associated with poorer outcomes (9–13,16–18).

On the other hand, N-terminal pro-B-type natriuretic peptide (NT-proBNP) and brain natriuretic peptide (BNP) are also a strong predictor of HF morbidity and mortality (19). High levels of NT-proBNP and BNP predicts adverse events after discharge, while lower levels of NT-proBNP or BNP are related to better cardiac status and left ventricular (LV) function and outcome (20–23).

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Hence, this creates the paradox that proven beneficial therapies (like angiotensin-converting enzyme [ACE] inhibitors) for HF also impair renal function (10,24–26). As a result, the therapy to improve cardiac outcome also introduces a risk factor associated with a poorer outcome. Studies have shown that in chronic HF, ACE inhibitors can be given without adverse prognostic significance despite worsening of renal parameters (27,28). However, it remains unclear whether this also holds true for patients hospitalized for ADHF. Other studies have partially addressed this issue in similar patients (7,9,10,29–31), even comparing BNP changes with renal function parameters (31), but to our knowledge, none of these studies included NT-proBNP with prespecified reduction levels in their analyses, and none of these studies made head-to-head comparisons between renal parameters and NT-proBNP for analysis of prognosis.

We addressed this question by analyzing dynamic changes in renal function as measured by creatinine and serum urea at admission and at discharge, with simultaneous sequential measurements of NT-proBNP (as an indicator of cardiac status) in patients hospitalized for ADHF. We investigated the extent to which NT-proBNP in combination with parameters of renal function predicted outcome. We did this in order to understand the balance between the improvement of cardiac status on one hand and deterioration in renal function during hospitalization on the other hand.

METHODS

SOURCE AND STUDY POPULATIONS. Details for search strategy and source gathering of relevant studies for inclusion in this collaborative analysis have been reported previously (23). Briefly, our study population was assembled from 6 cohorts consisting of 1,232 patients by selecting those patients who satisfied the following inclusion criteria: 1) admitted because of clinically validated ADHF (32); 2) discharged alive; 3) creatinine level; and 4) NT-proBNP measurements were available at admission and at discharge. All studies were approved by the ethical commission in their respected centers, and for the current study, we again received approval from the ethical commission. More detailed information on data collection and definitions can be seen in the Online Appendix.

STATISTICAL ANALYSIS. The primary endpoint of this study was time until death of any cause within 180 days. The secondary endpoint was time until death of any cause or time until first readmission for cardiovascular reason within 180 days. There were no cases lost to follow-up. The relationship between NT-proBNP and WRF was investigated using Fisher exact test. Clinical events were charted by the Kaplan-Meier method and compared with log-rank test results for all patients to investigate the relationship between WRF (absolute increase in serum creatinine level of >0.3 mg/dl in combination with >25% increase in serum creatinine level), severe WRF (sWRF) (absolute increase in serum creatinine level of >0.5 mg/dl in combination with >25% increase in serum creatinine level), eGFR (≥25% decrease), serum urea nitrogen (≥25% increase), and NT-proBNP (≤30% or >30% percentage reduction) all during hospitalization to death from all causes and to the composite endpoint. Univariate and multivariate proportional hazard regression models were made with and without adjustment for a total of 15 clinically relevant prognostic variables (≥75 years of age at admission, history of hypertension at admission, diabetes mellitus at admission, peripheral edema at admission, systolic blood pressure ≤115 mm Hg at admission, anemia [hemoglobin <8 mmol/l in men; <7.5 mmol/l in women] at admission, hyponatremia [sodium <135 mmol/l] at admission, eGFR <30 ml/min/1.73 m^2 at admission, left ventricular ejection fraction [LVEF] <25% at admission, New York Heart Association functional class III/IV at discharge, serum urea nitrogen ≥15 mmol/l at discharge,

NT-proBNP >5,000 pg/ml at discharge, diuretic therapy at discharge, ACE inhibitor therapy received at discharge, and beta-blocker received at discharge). In addition, separate baseline hazard functions were used for the different cohorts to adjust for between-study differences. Moreover, a binary logistic regression, with sWRF being the failure variable, was used to determine univariate and multivariate predictors of the occurrence of sWRF during hospitalization.

Demographic characteristics are presented as frequencies and percentages when it concerns categorical data, and the Fisher exact test was used to make a comparison. Normally distributed, continuous variables are reported as mean ± SD. Other continuous data are expressed as medians with interquartile ranges (IQRs). Multiple imputation pooling algorithms (n = 10) were performed to correct for missing values, using predictive mean matching. All patient, medical history, and treatment variables (including outcome variables) were used when creating the multiple imputation data sets. All probability values were 2-sided and considered significant if <0.05. Statistical analyses were conducted using SPSS version 21.0.0.1 software (SPSS Inc., Chicago, Illinois).

RESULTS

DEMOGRAPHIC CHARACTERISTICS. Table 1 (left panel) shows baseline characteristics of the 1,232 patients included in our study. Median age of the study population was 74 years (IQR: 64 to 81 years), with 569 patients (46%) 75 years of age or older. Of the 1,232 patients admitted for ADHF, 576 patients (49%) were known to have an ischemic cause, 813 patients (74%) had an EF of <45%, and 486 patients (43%) had atrial fibrillation (AF) at admission. NT-proBNP levels at admission were available in 98% (n = 1,209) of patients, and NT-proBNP levels at discharge in 99% of patients (n = 1,220). Median NT-proBNP value was 6,557 pg/ml (IQR: 3,163 to 12,855 pg/ml) at admission and 3,405 pg/ml (IQR: 1,453 to 7,457 pg/ml) at discharge. Serum creatinine levels at admission were available in 99% of patients (n = 1,222), and serum creatinine levels at discharge in 97% (n = 1,192). The mean serum creatinine concentration was 1.52 ± 0.87 mg/dl at admission and 1.49 ± 0.81 mg/dl at discharge. During hospitalization, the mean delta serum creatinine was −0.02 ± 0.51 mg/dl. The mean eGFR was 56 ± 33 ml/min/1.73 m^2 at admission and 57 ± 42 ml/min/1.73 m^2 at discharge. At admission, 63% of the patients had eGFR below 60 ml/min/1.73 m^2, and 16% of the patients had eGFR below 30 ml/min/1.73 m^2. During hospitalization, 18% of the patients displayed a decrease in eGFR of more than 10 ml/min/1.73 m^2. The mean serum urea nitrogen was 13 ± 7.8 mmol/l at admission and 14 ± 8.0 mmol/l at discharge. During hospitalization, 19% of the patients displayed an increase in serum urea nitrogen of more than 5 mmol/l. At discharge, 1,156 patients (95%) received diuretic therapy, 806 patients (66%) received ACE inhibitor/AT-II receptor antagonist therapy, and 685 patients (57%) received beta-blocker therapy.

NT-proBNP AND WORSENING RENAL FUNCTION. WRF occurred in 140 patients (58 women and 82 men [12%]). sWRF occurred in 82 patients (33 women and 49 men [6.9%]). The relationship between response of NT-proBNP and renal function to treatment during hospitalization is shown in Table 2. WRF or sWRF was not related to the presence or absence of a drop in NT-proBNP. Of 457 patients in whom NT-proBNP failed to drop more than 30%, in 45 patients (10%) renal function worsened during hospitalization. Similarly, of the 700 patients in whom NT-proBNP dropped more than 30%, in 89 patients (13%; p = 0.136) renal function worsened. This nondiscriminatory pattern of the effect of the change in NT-proBNP on renal function also applied to the occurrence of a more severe worsening of renal function. Where NT-proBNP failed to drop more than 30%, 32 patients (7%) had sWRF. Likewise, of the 700 patients in whom NT-proBNP dropped more than 30%, 49 patients (7%; p = 0.999) had sWRF. Similarly, this nondiscriminatory pattern in occurrence of sWRF was seen when discerning the 344 patients with an NT-proBNP drop of 30% to 60% (6.3%) from the 378 patients with an NT-proBNP drop of ≥60% (7.6%; p = 0.796).

CLINICAL EVENTS. Of the study patients, 189 (83 women and 106 men) died of any cause within 180 days (primary endpoint), which was equal to an all-cause mortality of 15%. Furthermore, 536 study patients (219 women and 317 men) reached the composite endpoint (all-cause mortality/cardiovascular readmissions at 180 days), which produced an event rate of 44%.

RENAL FUNCTION AND OUTCOME. Figures 1A and 1B show Kaplan-Meier curves that display the relationship between WRF or sWRF and clinical events. There were no differences in 180-day cumulative mortality between patients with WRF and those without WRF (16% vs. 16%, respectively; p = 0.81). However, mortality was significantly higher in patients with sWRF than in those without sWRF (24% vs. 15%, respectively; p = 0.02). For the composite endpoint (Figure 1B), there were no differences between patients with WRF and those without WRF (49% vs. 44%, respectively; p = 0.23). There was a nonsignificant difference for composite endpoint between

TABLE 1 Baseline Characteristics Study Population

	Total Cohort (N = 1,232)	sWRF (n = 82)	No sWRF (n = 1,102)	p Value	NT-proBNP Reduction ≤30% (n = 475)	NT-proBNP Reduction >30% (n = 722)	p Value
Age, yrs	74 (64-81)	77 (70-81)	73 (64-80)	0.019	74 (67-81)	73 (63-80)	0.131
Age ≥75 yrs	569 (46)	47 (57)	501 (46)	0.039	231 (49)	324 (45)	0.193
Males	734 (60)	49 (60)	656 (60)	1.000	297 (63)	421 (58)	0.148
History of DM	391 (32)	31 (38)	347 (32)	0.271	165 (35)	212 (30)	0.056
History of COPD	176 (16)	9 (12)	159 (16)	0.506	66 (16)	104 (16)	0.932
History of hypertension	613 (50)	48 (60)	541 (49)	0.136	224 (48)	367 (51)	0.214
Ischemic cause	576 (49)	37 (47)	521 (50)	0.815	192 (43)	365 (53)	0.001
LVEF				0.038			0.667
Preserved (≥45%)	283 (26)	27 (37)	246 (25)		103 (25)	168 (26)	
Mild to moderate (25%-44%)	491 (45)	32 (44)	437 (45)		180 (44)	296 (46)	
Severe (<25%)	322 (29)	14 (19)	297 (30)		129 (31)	187 (29)	
JVP distended at admission	594 (63)	44 (67)	534 (63)	0.691	220 (63)	361 (64)	0.621
Pulmonary rales at admission	764 (76)	54 (76)	677 (76)	1.000	266 (72)	475 (79)	0.013
Peripheral edema at admission	634 (63)	46 (65)	563 (63)	0.799	253 (68)	364 (60)	0.020
SBP at admission, mm Hg	133 ± 31.6	139 ± 34.2	132 ± 31.1	0.058	127 ± 28.9	137 ± 32.4	<0.001
DBP at admission, mm Hg	80 ± 20.4	81 ± 19.0	81 ± 20.5	0.969	78 ± 19.6	83 ± 20.4	<0.001
Heart rate at admission, beats/min	93 ± 24.6	91 ± 23.3	93 ± 24.8	0.405	89 ± 21.6	96 ± 26.1	<0.001
Atrial fibrillation at admission	486 (43)	38 (51)	428 (42)	0.144	191 (44)	284 (43)	0.709
NYHA functional class at discharge				0.289			0.180
III	212 (18)	14 (18)	190 (18)		79 (18)	128 (19)	
IV	4 (0.3)	1 (1)	2 (0.2)		3 (0.7)	1 (0.1)	
Laboratory findings							
Hemoglobin at admission, mmol/l	7.8 ± 1.3	7.5 ± 1.1	7.9 ± 1.3	0.017	7.6 ± 1.2	8.0 ± 1.3	<0.001
Serum urea at admission, mmol/l	12.6 ± 7.8	13.5 ± 7.9	12.6 ± 7.8	0.336	13.8 ± 8.6	11.8 ± 7.2	<0.001
Serum urea at discharge, mmol/l	13.7 ± 8.0	20.9 ± 10.4	13.2 ± 7.5	<0.001	14.7 ± 8.8	13.0 ± 7.5	0.001
Serum sodium at admission, mmol/l	138.7 ± 4.8	138.4 ± 4.8	138.6 ± 4.8	0.707	138.5 ± 4.8	138.8 ± 4.8	0.298
Serum sodium at discharge, mmol/l	138.9 ± 4.0	137.6 ± 3.7	139.0 ± 4.0	0.002	138.8 ± 4.2	138.9 ± 3.9	0.837
Serum creatinine at admission, mg/dl	1.52 ± 0.9	1.62 ± 0.9	1.51 ± 0.9	0.297	1.62 ± 1.0	1.46 ± 0.9	0.003
Serum creatinine at discharge, mg/dl	1.49 ± 0.8	2.49 ± 1.2	1.42 ± 0.7	<0.001	1.61 ± 0.9	1.42 ± 0.7	<0.001
eGFR at admission, ml/min/1.73 m^2*	56.3 ± 33.2	50.7 ± 25.9	57.0 ± 34.0	0.098	54.4 ± 29.2	57.5 ± 35.9	0.106
eGFR at discharge, ml/min/1.73 m^2	56.9 ± 42.0	28.3 ± 10.7	58.8 ± 42.8	<0.001	53.7 ± 27.7	58.9 ± 49.6	0.42
NT-proBNP at admission, pg/ml	6,557 (3,163-12,855)	7,468 (2,911-12,362)	6,542 (3,204-12,907)	0.832	5,380 (2,579-11,254)	7,095 (3,536-1,336)	<0.001
NT-proBNP at discharge, pg/ml	3,405 (1,453-7,457)	4,230 (1,411-7,952)	3,319 (1,455-7,525)	0.679	6,470 (2,734-13,364)	2,358 (1,113-4,899)	<0.001
Duration at admission	9 (6-14)	10 (7-15)	9 (6-14)	0.995	9 (6-15)	9 (6-14)	0.150
Discharge medication							
Diuretics	1,156 (95)	79 (96)	1,033 (95)	0.792	437 (93)	685 (96)	0.041
ACE inhibitor	806 (66)	43 (52)	351 (68)	0.007	303 (65)	485 (68)	0.312
Beta-blocker	685 (57)	45 (55)	611 (56)	0.818	245 (53)	425 (60)	0.016

Value are median (interquartile range), n (%), or mean ± SD. *eGFR was calculated as [186.3 × (creatinine mg/dl)$^{-1.154}$ × (age)$^{-0.203}$ × (0.742 if female) × (1.210 if black)].

ACE = angiotensin-converting enzyme; COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus; DPB = diastolic blood pressure; eGFR = estimated glomerular filtration rate; JVP = jugular venous pressure; LVEF = left ventricle ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; SBP = systolic blood pressure.

patients with sWRF and without sWRF (53% vs. 44%, respectively; p = 0.10). Furthermore, there were no significant differences between mortality rates (17% vs. 16%, respectively; p = .732) or composite endpoints (46% vs. 44%, respectively; p = 0.838) in patients with and without a decrease of ≥25% in eGFR during hospitalization. Similarly, there were no differences between patients with and those without an increase in serum urea of ≥25% for both mortality rates (13% vs. 16%, respectively; p = 0.996) and composite endpoints (39% vs. 44%, respectively; p = 0.460).

NT-proBNP AND OUTCOME. Figure 2 shows the relationship between NT-proBNP percentage of reduction during hospitalization and clinical events. The 180-day cumulative mortality was more than twice as high (25% vs. 10%, respectively) in patients in whom NT-proBNP failed to drop at least 30% in comparison to patients with an NT-proBNP reduction of >30% (p < 0.001). For the composite endpoint, this

TABLE 2 Relationship Between NT-proBNP Reduction and WRF During Hospitalization

Renal Function	NT-proBNP Reduction ≤30 (%)	NT-proBNP Reduction >30 (%)	p Value
Occurrence of WRF*	10 (45)	13 (89)	0.136
No WRF	90 (412)	87 (611)	
Occurrence of sWRF†	7 (32)	7 (49)	0.999
No sWRF	93 (425)	93 (651)	

Values are n (N). *Worsening renal function was defined as an absolute increase in serum creatinine levels of >0.3 mg/dl in combination with >25% increase during hospitalization. †Severe worsening renal function was defined as an absolute increase in serum creatinine levels of >0.5 mg/dl in combination with >25% increase during hospitalization.

Abbreviations as in Table 1.

difference was similar, with cumulative event rates of 55% and 38%, respectively ($p < 0.001$).

OUTCOME FOR NT-proBNP COMBINED WITH WORSENING RENAL FUNCTION. Figure 3 shows mortality and composite endpoints stratified by NT-proBNP percentage of reduction combined with the presence or absence of sWRF during hospitalization. The Figure shows that among patients with NT-proBNP reduction of ≤30%, there is a nonsignificant, but clinically relevant difference between patients with and without sWRF for mortality (33% vs. 24%, respectively; $p = 0.180$) as well as for the composite endpoint (64% vs. 55%, respectively; $p = 0.241$) at 180 days. Among patients with NT-proBNP reduction of >30%, there was a significant and clinically relevant difference between patients with and without sWRF for mortality (19% vs. 9%, respectively; $p = 0.024$). For the composite endpoint, a nonsignificant but clinically relevant difference was found between patients with and without sWRF (47% vs. 37%, respectively; $p = 0.151$).

PREDICTORS OF SEVERE WORSENING RENAL FUNCTION. Table 3 shows univariate and multivariate analyses for the predictors of sWRF. In our study, anemia (hemoglobin <129 g/l [8 mmol/l] in men, <121 g/l [7.5mmol/l] in women) at admission was the only independent significant predictor (HR: 1.92; 95% CI: 1.16 to 3.17) of the occurrence of sWRF, whereas other predictors like age, diabetes, hypertension, systolic blood pressure, and eGFR admission were not.

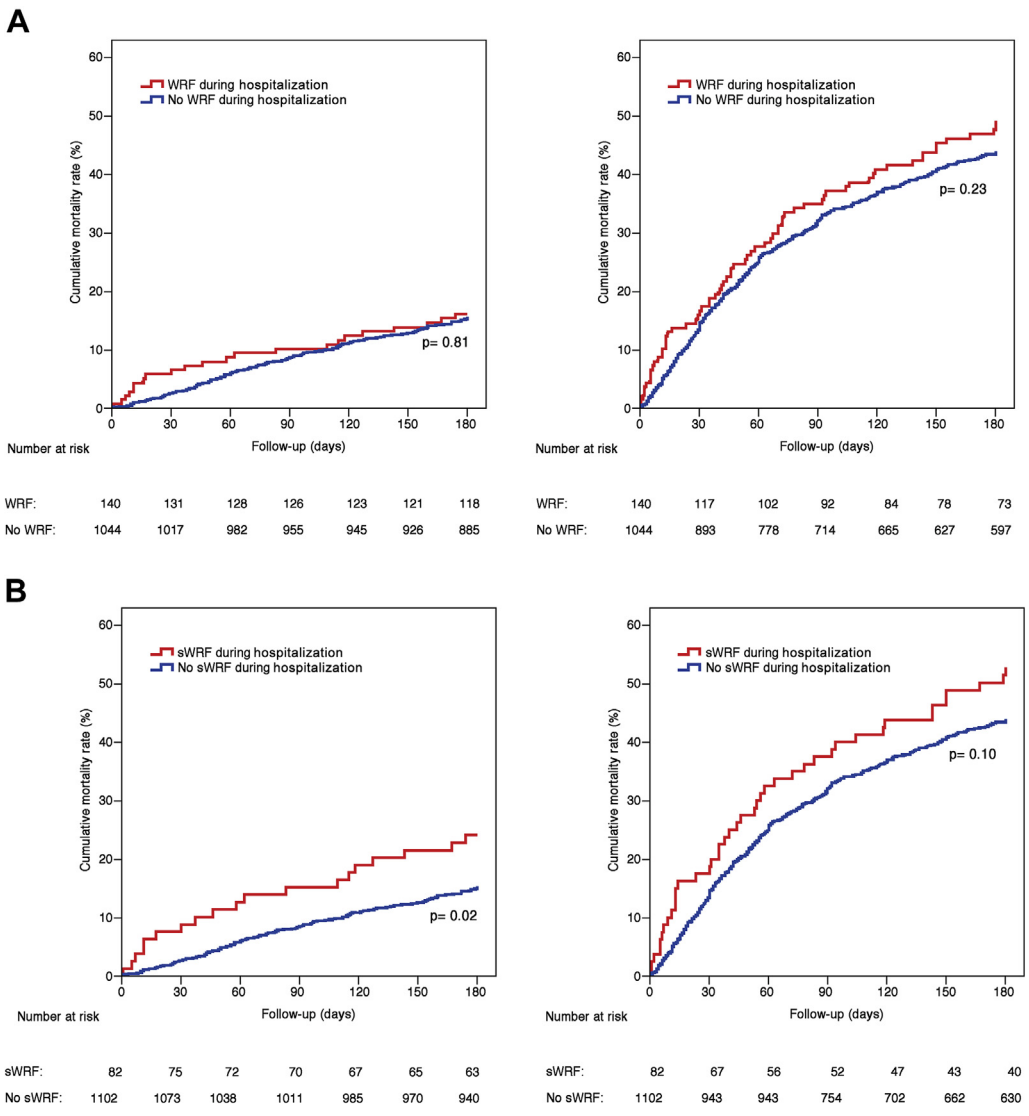
UNIVARIATE AND MULTIVARIATE ANALYSES. Table 4 shows the univariate and multivariate proportional hazard regression models. Consistent with the Kaplan-Meier curves, our univariate model (Table 4, left column) revealed that NT-proBNP reduction of ≤30% is a predictor of all-cause mortality (HR: 2.85; 95% CI: 2.11 to 3.85) as well as of the composite endpoint (HR: 1.73; 95% CI: 1.45 to 2.06), whereas sWRF during hospitalization is a predictor of mortality only (HR: 1.87; 95% CI: 1.14 to 3.72). In our bivariate model for NT-proBNP reduction of ≤30% and sWRF (Table 4, second column), both of the hazard ratios sustained for all-cause mortality (HR: 2.84; 95% CI: 2.10 to 3.85 and HR: 1.86; 95% CI: 1.13 to 3.06, respectively), whereas for the composite endpoint, sWRF was not contributive.

The third panel of Table 4 shows our adjusted multivariate model for clinically relevant variables (≥75 years of age at admission, history of hypertension at admission, diabetes mellitus at admission, peripheral edema at admission, systolic blood pressure ≤115 mm Hg at admission, anemia [hemoglobin <8 mmol/l in men; <7.5 mmol/l in women] at admission, hyponatremia [sodium <135 mmol/l] at admission, eGFR <30 ml/min/1.73 m^2 at admission, LVEF <25% at admission, New York Heart Association functional class III/IV at discharge, serum urea nitrogen ≥15 mmol/l at discharge, NT-proBNP >5,000 pg/ml at discharge, diuretic therapy at discharge, ACE inhibitor therapy received at discharge, and beta-blocker therapy received at discharge), which revealed that NT-proBNP reduction of >30% during hospitalization was the only predictor for both death (HR: 1.81; 95% CI: 1.32 to 2.50) and for the composite endpoint (HR: 1.36; 95% CI: 1.13 to 1.64) within 180 days.

DISCUSSION

Our analysis demonstrates that an acute but moderate WRF does not portend a poor prognosis in patients hospitalized for ADHF. However, when renal function declines more severely (sWRF: increase in creatinine of >0.5 mg/dl in combination with >25% increase in serum creatinine level between admission and discharge), 180-day mortality is significantly increased with 10%. As shown in previous studies, a decrease of more than 30% in NT-proBNP was associated with a 15% absolute lower mortality (20,22,23). If the decrease in NT-proBNP of >30% occurred concomitantly with severe WRF, then absolute mortality increased again by 10% compared to that where this desired decrease in NT-proBNP was unaccompanied by sWRF. However, absolute mortality increased with 10% in patients with sWRF, regardless of the desired decrease in NT-proBNP. The occurrence of sWRF did not differ between patients with a low and those with a high percentage drop in NT-proBNP, suggesting that severe WRF is not related to the amount of decrease of NT-proBNP. Taken together, this suggests that in patients hospitalized for ADHF,

FIGURE 1 Kaplan-Meier Curves for Renal Function During Hospitalization



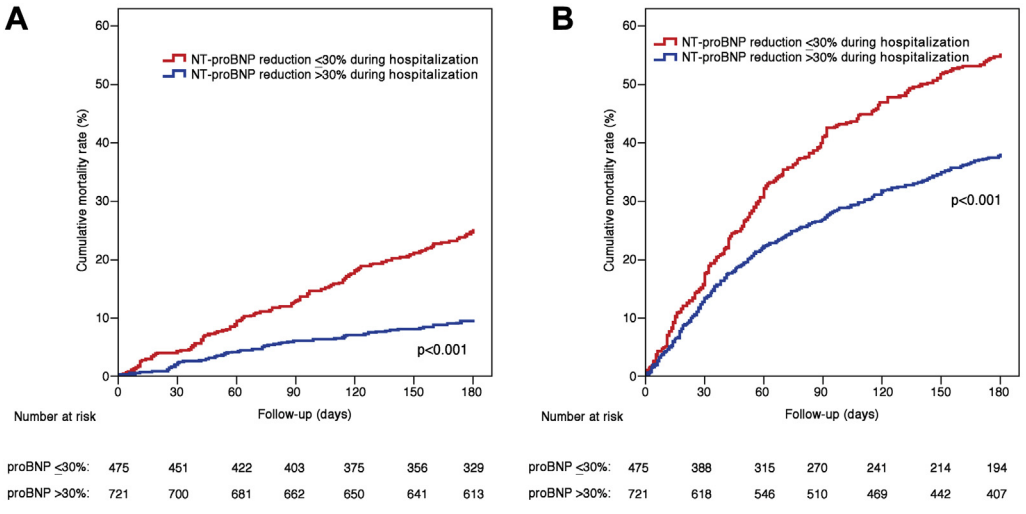
(A) Kaplan-Meier curves for all-cause mortality at 180 days according to the renal function during hospitalization. **(B)** Kaplan-Meier curves for composite endpoint at 180 days according to the renal function during hospitalization. sWRF = severe worsening renal function; WRF = worsening renal function.

the ability to decrease NT-proBNP more than 30% is the main parameter that predicts outcome, as it has the ability to improve prognosis with a 15% lower mortality, even if accompanied by mild or severe worsening of renal function.

WORSENING RENAL FUNCTION. We observed that WRF and other indicators of worsening renal function, such as an increase of ≥25% in serum urea and/or a decrease of ≥25% in eGFR during hospitalization, were not associated with adverse events. However, in our analyses we found that a more severe WRF (increase of >0.5 mg/dl and >25% increase in serum creatinine level between admission and discharge) was a predictor of mortality.

There is still debate about whether WRF alters prognosis in patients with ADHF, and there are significant reports to argue both sides. There are several studies (9,10,16,33) reporting a significant association between WRF during hospitalization and adverse events after discharge, but there are also studies showing that, although WRF occurred frequently,

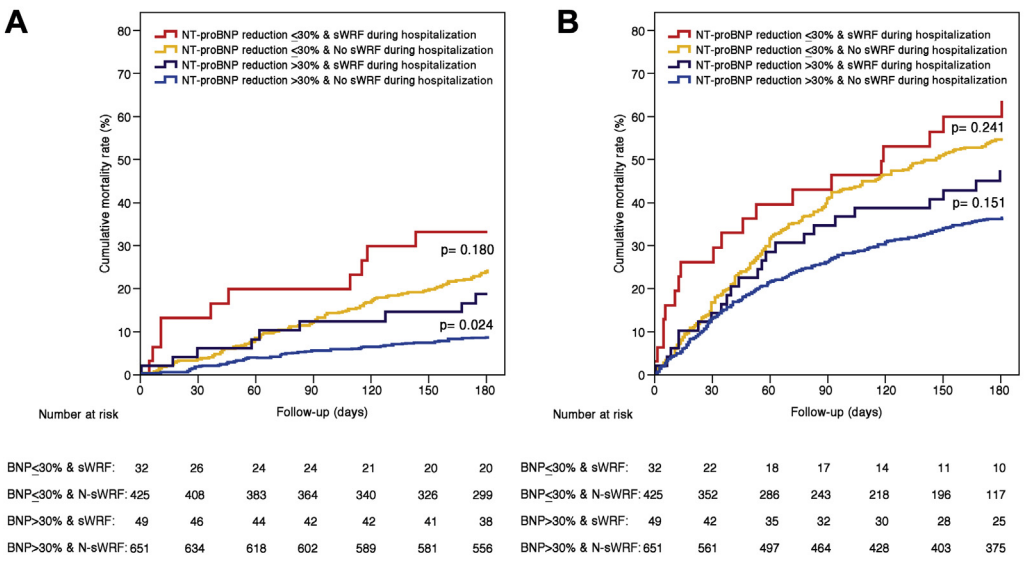
FIGURE 2 Kaplan-Meier Curves for NT-proBNP During Hospitalization



Kaplan-Meier curves for all-cause mortality **(A)** and composite endpoint **(B)** at 180 days according to NT-proBNP during hospitalization. NT-proBNP = N-terminal pro-B-type natriuretic peptide.

there was no evidence of worse clinical outcomes (29,34,35). The DOSE-AHF (Diuretic Optimal Strategy Evaluation in Acute Heart Failure) trial, comparing high- versus low-dose furosemide and infusion versus bolus administration, showed that, although WRF occurred more frequently with the high-dose strategy in the short term, there was no evidence of worse clinical outcomes in the long term (34). This would suggest that a degree of at least transient WRF would appear to be tolerable (34). Previous studies

FIGURE 3 Kaplan-Meier Curves for NT-proBNP and Renal Function During Hospitalization



Kaplan-Meier curves for all-cause mortality **(A)** and composite endpoint **(B)** at 180 days by NT-proBNP reduction and sWRS during hospitalization. Abbreviations as in Figures 1 and 2.

TABLE 3 Univariate and Multivariate Binary Logistic Regression for sWRF During Hospitalization

Variable	Univariate Model		Multivariate Model	
	OR (95% CI)	p Value	OR (95% CI)	p Value
Age (per 10-yr increase) at admission	1.24 (1.01–1.53)	0.044	1.21 (0.95–1.54)	0.119
History of DM at admission	1.30 (0.81–2.07)	0.273		
History of hypertension at admission	1.34 (0.86–2.15)	0.255		
LVEF <25% at admission	1.65 (0.93–2.93)	0.088	1.48 (0.77–1.54)	0.237
SBP (per 10-mm Hg decrease) at admission	1.08 (1.06–1.16)	0.033	1.07 (0.98–1.16)	0.123
Anemia at admission*	1.73 (1.10–2.72)	0.018	1.92 (1.16–3.17)	0.011
Hyponatremia at admission†	1.14 (0.62–2.11)	0.677		
eGFR (per 10 ml/min/1.73 m^2 decrease) at admission‡	1.00 (0.86–1.04)	0.238	1.00 (0.90–1.10)	0.907
Serum urea (per 2 mmol/l increase) at admission	1.00 (0.91–1.11)	0.919		
NT-proBNP (per 1,000 pg/ml increase) at admission	1.00 (0.97–1.04)	0.978		
NT-proBNP (per 10% reduction) during hospitalization	1.00 (0.95–1.05)	0.916		

*Anemia was defined as hemoglobin concentration <129 g/l (8 mmol/l) in men and <121 g/l (7.5 mmol/l) in women. †Hyponatremia was defined as sodium concentration of <135 mmol/l. ‡eGFR was calculated as [186.3 × (creatinine mg/dl)$^{-1.154}$ × (age)$^{-0.203}$ × (0.742 if female) × (1.210 if black)].

Abbreviations as in Table 1.

have shown that worsening renal function during hospitalization occurs during arterial underfilling as a result of decongestion therapy (29,36). However, there are also reports of effective decongestion therapy being of more importance for prognosis than WRF as a possible result of decongestion therapy (31,35,37). Our results are in line with the latter studies suggesting that persistent decongestion, a decrease of less than 30% in NT-proBNP, is a worse prognostic indicator than the incidence of WRF. A recent study has used the comparison between BNP changes and eGFR changes in 358 patients during ADHF hospitalization (31). Results similar to ours were found, in that changes in BNP were independent of changes in eGFR. To our knowledge, none of the above-mentioned studies considered dynamic changes in NT-proBNP with predefined reduction percentage during hospitalization in their analyses or considered to weigh the competing risks of WRF with that offered by BNP and NT-proBNP measurements.

We still do not know enough. The investigators of a recently published meta-analysis concluded that although increases in serum creatinine and related changes are associated with increased mortality, this does not directly imply that preservation or improvement of renal function would improve survival

TABLE 4 Univariate and Multivariate Cox Regression Analysis for All-Cause Mortality and Composite Endpoint at 180 Days

	Univariate Model		Bivariate Model		Adjusted Multivariable Model*	
	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
Variables for mortality						
WRF during hospitalization†	1.12 (0.71–1.77)	0.632				
sWRF during hospitalization‡	1.87 (1.14–3.72)	0.014	1.86 (1.13–3.06)	0.014	1.58 (0.94–2.64)	0.083
eGFR decrease ≥25% during hospitalization§	1.01 (0.70–1.73)	0.690				
Serum urea increase ≥25% during hospitalization	1.22 (0.83–1.78)	0.317				
NT-proBNP decrease ≤30% during hospitalization	2.85 (2.11–3.85)	<0.001	2.84 (2.10–3.85)	<0.001	1.81 (1.32–2.50)	<0.001
Variables for composite endpoint						
WRF during hospitalization	1.10 (0.85–1.43)	0.456				
sWRF during hospitalization	1.22 (0.88–1.67)	0.230	1.23 (0.89–1.69)	0.208	1.09 (0.78–1.53)	0.598
eGFR decrease ≥25% during hospitalization	1.02 (0.78–1.33)	0.894				
Serum urea increase ≥25% during hospitalization	1.04 (0.80–1.30)	.886				
NT-proBNP reduction ≤30% during hospitalization	1.73 (1.45–2.06)	<0.001	1.73 (1.46–2.06)	<0.001	1.36 (1.13–1.64)	0.001

*Adjusted for ≥75 years of age at admission, history of hypertension at admission, diabetes mellitus at admission, peripheral edema at admission, systolic blood pressure ≤115 mm Hg at admission, anemia (hemoglobin <8 mmol/l in men; <7.5 mmol/l in women) at admission, hyponatremia (sodium <135 mmol/l) at admission, eGFR <30 ml/min/1.73 m^2 at admission, left ventricle ejection fraction <25% at admission, New York Heart Association functional class III/IV at discharge, serum urea nitrogen ≥15 mmol/l at discharge, NT-proBNP >5,000 pg/ml at discharge, diuretic therapy at discharge, angiotensin-converting enzyme inhibitor received at discharge, and beta-blocker received at discharge. †Worsening renal function was defined as an absolute increase in serum creatinine levels >0.3 mg/dl in combination with >25% increase during hospitalization. ‡Severe worsening renal function was defined as an absolute increase in serum creatinine levels >0.5 mg/dl in combination with >25% increase during hospitalization. §Estimated glomerular filtration rate was calculated as [186.3 × (creatinine mg/dl)$^{-1.154}$ × (age)$^{-0.203}$ × (0.742 if female) × (1.210 if black)].

Abbreviations as in Table 1.

(17). In our study we observed that up to 16% fewer patients received ACE inhibitor or angiotensin receptor blocker therapy in the group with sWRF compared to the group without sWRF. Whether this translated into survival benefit or not could not be determined due to small numbers.

NT-proBNP RESPONSE AND WRF. In our current analysis, counter to what we expected, we did not see more WRF or sWRF among patients who achieved a larger NT-proBNP reductions. We demonstrated that even in patients with a NT-proBNP reduction of more than 60% during hospitalization, there was no increase in the incidence of WRF or sWRF compared to those with less NT-proBNP reduction. Moreover, neither NT-proBNP levels at admission nor NT-proBNP percentage reduction during hospitalization was a predictor of sWRF. The possible assumption that more NT-proBNP reduction indicates more volume depletion and must lead to WRF or even sWRF is therefore not right. Conversely, a WRF and sWRF are often viewed as the sole results of underfilling due to aggressive diuretic therapies, while this is probably not the only factor as a lower baseline eGFR is consistently identified as a strong predictor of WRF and sWRF (17,38). In our study, eGFR at admission was not a predictor of sWRF, and still other factors may be involved. In our analysis anemia at admission was the only predictor of sWRF, which is consistent with previous studies (6,9,12,18,33) and could be linked to progression of renal dysfunction (39).

We could not demonstrate an interaction between NT-proBNP and sWRF for mortality risk, suggesting that these are independent risk factors. It seems that during hospitalization for ADHF, although severe WRF is a measure of prognosis, severe WRF is quite unpredictable and evenly distributed among patients with low, intermediate, and high percentages of NT-proBNP reductions without NT-proBNP being a predictor of sWRF. Worsening of renal function therefore does not need to be an important limitation when trying to reach the lowest NT-proBNP possible.

STUDY LIMITATIONS. Several limitations of our analyses should be acknowledged. First, the current study was an individual patient data meta-analysis; hence, the study was conceived after publication of the original studies. However, we think that this retrospective aspect of the study does not compromise the validity of our analysis, because each of the original studies was a prospective cohort study with dedicated pre-designed data collection. However, variation in treatment and inclusion criteria in the different centers should be considered. We did not have all the data regarding the changes in medication during hospitalization, with the use of better understanding if patients experiencing sWRF actually had their HF medication stopped, or had too many or too high doses of medication. In addition, it should be mentioned that we did not adjust for multiple testing, because inclusion of variables in a multivariate modeling is guided by p values without adjustment. Also, missing data should be considered as a limitation in our study. However, we did correct for the bias from data missing at random by using multiple imputation pooling algorithms and it should be noted that for our most important variables, NT-proBNP and creatinine, both static and dynamic values were almost completely available. A limitation is that only measurements of admission and discharge were considered, of which, by being time-varying measurements, the actual direction of changes may not always have been in the direction of the change that was indicated when compared to that of baseline. The definitions of WRF used in this study, although commonly accepted, are arbitrary. Furthermore, although 1,232 patients were included in the overall analysis, only 82 patients had sWRF and when this category is divided to compare those with adequate NT-proBNP reduction, this number is reduced to only 49. The eGFR formula used is only a surrogate marker of real GFR, but has been shown to be accurate in heart failure (40).

CONCLUSIONS

An NT-proBNP reduction of >30% is the leading indicator of survival in patients after hospitalization for ADHF rather than mild worsening renal function. Severe WRF is a measure of prognosis but occurs in an unpredictable way during therapy and does not seem to influence the response of NT-proBNP or seem to be influenced by the response of NT-proBNP. Because decongestion therapy and measures to reduce the activity of the renin-angiotensin-aldosterone system is associated with reductions in NT-proBNP, a more aggressive therapy in the face of insufficient reduction in NT-proBNP may be acceptable even in the presence of worsening of renal function, because the lower the NT-proBNP, the better the prognosis without intrinsic negative influence on renal function.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Yigal M. Pinto, Heart Failure Research Center, Academic Medical Center, Meibergdreef 15, K2-119, 1105 AZ Amsterdam, the Netherlands. E-mail: y.pinto@amc.uva.nl.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: This study examines an important conundrum that frequently arises when caring for patients with ADHF, and prior data has been inconclusive. Our study suggests that during hospitalization for ADHF kidney function should not limit efforts to try reaching the lowest NT-proBNP possible. It seems that even given the finding of increased mortality with sWRF, one should strive for lower NT-proBNP levels, because the latter has no intrinsic negative influence on renal function, while the lower the NT-proBNP, the better the prognosis. The principal strength of this analysis is that changes from admission to discharge in both NT-proBNP and renal function were examined with adequate follow up.

TRANSLATIONAL OUTLOOK: Additional larger clinical studies are needed to validate the prognostic value of NT-proBNP outweighing the prognostic value of renal makers and therapeutic implications of these findings whether a more aggressive decongestion therapy may be acceptable even in the presence of worsening of renal function.

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KEY WORDS heart failure, prognosis, renal function, NT-proBNP, WRF

APPENDIX For supplemental data collection and definitions, please see the online version of this article.