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

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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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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,