Relation of Kidney Function Decline and NT-proBNP with Risk of Mortality and Readmission in Acute Decompensated Heart Failure

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Abstract

Background—Acute declines in kidney function occur in approximately 20–30% of patients with acute decompensated heart failure, but its significance is unclear and importance of its context is not known. This study aimed to determine the prognostic value of a decline in kidney function in the context of decongestion among patients admitted with acute decompensated heart failure.

Methods—Using data from patients enrolled in the Ultrafiltration in Decompensated Heart Failure with Cardiorenal Syndrome Study (CARRESS) and Diuretic Optimization Strategies Evaluation (DOSE) trials, we used multivariable Cox regression models to evaluate the association between decline in estimated glomerular filtration rate (eGFR) and change in N-terminal pro-b-type natriuretic peptide (NT-proBNP) with the composite outcome, as well as testing for an interaction between the two.

Results—Among 435 patients, in-hospital decline in eGFR was not significantly associated with death and re-hospitalization (HR=0.89 per 30% decline, 95% CI 0.74, 1.07) while decline in NT-proBNP was associated with lower risk (HR=0.69 per halving, 95% CI 0.58, 0.83). There was a significant interaction ($p = 0.003$ unadjusted; $p = 0.03$ adjusted) between decline in eGFR and change in NT-proBNP where a decline in eGFR was associated with better outcomes when NT-proBNP declined (HR=0.78 per 30% decline in eGFR, 95% CI 0.61, 0.99), but not when NT-proBNP increased (HR=0.99, 95% CI 0.76, 1.30).

Conclusions—Decline in kidney function during therapy for acute decompensated heart failure is associated with improved outcomes as long as NT-proBNP levels are decreasing as well,

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suggesting that incorporation of congestion biomarkers may aid clinical interpretation of eGFR declines.

Introduction

Approximately 20–30% of patients admitted for acute decompensated heart failure will experience a decline in kidney function during the hospitalization.(1, 2) The pathophysiology of this decline is not well understood and its association with outcomes is controversial. While some studies suggest that decline in function is associated with adverse outcomes,(1, 3, 4) others indicate that decline can sometimes be associated with improved outcomes.(5–7) Declines in kidney function in the setting of acute decompensated heart failure can have multiple causes, and understanding the mechanism responsible for decline is likely to assist clinical decision making.

There have been many proposed mechanisms of kidney function decline in acute decompensated heart failure, including renal congestion from volume overload.(8–10) Improvements in kidney function have been observed following decongestion,(11) however, decongestion itself can sometimes lead to acute declines in estimated glomerular filtration rate (eGFR) as well.(12) Congestion and volume overload can be evaluated by biomarkers including brain natriuretic peptide (BNP) and its prohormone N-terminal prohormone of brain natriuretic peptide (NT-proBNP), which are released from cardiac myocytes in response to stretch from volume overload. A prior study did not find that the relation of eGFR decline and mortality was modified by baseline NT-proBNP level.(7) There are no data however, evaluating the relation between changes in kidney function and clinical outcomes in the context of changes in natriuretic peptide levels.

Because changes in congestion during therapy for acute decompensated heart failure may contribute to trends in renal function, we utilized patient data from the Ultrafiltration in Decompensated Heart Failure with Cardiorenal Syndrome Study (CARRESS) and the Diuretic Optimization Strategies Evaluation (DOSE) trials to evaluate whether an interaction exists between in-hospital changes in eGFR and NT-proBNP and subsequent clinical outcomes among patients being treated for acute decompensated heart failure.

Methods

Study Population and Design

The National Heart Lung and Blood Institute (NHLBI)-funded CARRESS(13) and DOSE(14) trials were two randomized controlled trials that investigated multiple decongestion strategies in patients with acute decompensated heart failure. Both studies enrolled patients hospitalized with manifestations of congestion, and had 60-day follow-up with similar intervals of biomarker measurement, allowing for pooling of the two patient cohorts to increase statistical power, as done in previous studies.(15, 16) Detailed enrollment criteria have been published previously.(14, 17) Serum creatinine thresholds for exclusion were >3.5 mg/dl in CARRESS and >3 mg/dl in DOSE. Importantly, patients enrolled in CARRESS were required to have evidence of declining kidney function at the time of enrollment (increase in serum creatinine by >0.3 mg/dl). Both trials excluded patients

requiring vasoactive medications. In CARRESS, patients were randomized to either a stepped pharmacologic diuretic strategy or to ultrafiltration. In DOSE, patients were randomized in a 2×2 factorial fashion to either bolus or continuous intravenous furosemide, and to either low or high dose regimens. Serum creatinine and NT-proBNP levels were measured at randomization, as well as 96 hours into hospitalization for CARRESS and 72 hours for DOSE and then again on Day 7 or day of discharge if discharged prior to Day 7. (17) Patients without a baseline or follow-up creatinine (n=9) were excluded from the analysis.

Exposure

Estimates of GFR were determined using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula with serum creatinine.(18) Serum creatinine measurements in the original trials were analyzed at either a core or local laboratory, with labs drawn at the baseline visit measured at both facilities concomitantly. Deming regressions were used to relate local and core lab measurements separately for each trial, allowing determination of a correction factor (slope=1.06, intercept= −0.22, for CARRESS; slope=0.99, intercept= −0.06 for DOSE) which were applied to local lab results to allow for both consistency and inclusion of all local laboratory measurements. While the CKD-EPI equation has not yet been validated in the heart failure population, prior literature has shown its accuracy as compared to the Modification of Diet in Renal Disease Study equation in chronic kidney disease, the general population and heart failure.(18–20) Values of eGFR were transformed on the log scale given non-normal distribution and modeled as a continuous exposure. For comparison of baseline characteristics, patients were categorized according to whether there was a decline or increase in eGFR from baseline to hospitalization discharge values. Change was determined as the difference between the log-transformed baseline eGFR and the last in-hospital eGFR prior to discharge. Log transformation by base 10/7 enabled hazard ratios to be assessed per a 3/10 decline, synonymous to a 30% decline which has been demonstrated as a surrogate endpoint in chronic kidney disease literature.(21, 22)

As for NT-proBNP, all NT-proBNP samples were analyzed at the core laboratory facility. Baseline and follow-up values were transformed using log base 2 given the skewed distribution of the data. Change was determined as the difference between the log-transformed baseline NT-proBNP and last in-hospital NT-proBNP measurement obtained prior to discharge.

Outcomes

The primary outcome of interest was a composite endpoint of death from any cause or rehospitalization from any cause over the course of follow-up through day 60. The time at risk for the composite outcome began at the time of discharge from the initial hospitalization.

Covariates

Several covariates were selected as potential confounding variables in our regression analyses based on review of the literature and clinical relevance, including demographic

characteristics (age, sex, race, body mass index [BMI]), comorbid conditions (hypertension, diabetes), medications (angiotensin-converting enzyme inhibitors [ACEI] or angiotensin II receptor blockers [ARB], loop diuretics), trial assignment (CARRESS, DOSE) as well as randomization arm for each trial. In-hospital change in weight was also included as a covariate, as were baseline eGFR and baseline NT-proBNP.

Statistical Analysis

Differences in the baseline characteristics of patients by whether they had an increase or decrease in their eGFR were examined using χ^2 tests and the t-test for categorical and continuous variables, as appropriate. The functional relationship between change in eGFR, and change in NT-proBNP with the endpoint were evaluated using restricted cubic splines. Multivariable Cox proportional hazards regression models were used to evaluate the association between decline in eGFR on the continuous scale and the composite outcome, as well as the association between changes in NT-proBNP with the composite outcome. To evalate for effect modification, interaction testing between decline in eGFR and change in NT-proBNP was performed with the outcome. Hazards ratios of mortality were calculated based on a fixed eGFR decline of 30%, chosen on the basis of it being associated with increased risk of mortality and considered as a surrogate end point in trials of chronic kidney disease.(21, 22) As a sensitivity analysis, patients who were randomized to ultrafiltration (n=92) were excluded from the model.

Results

There were 435 patients with complete kidney function and NT-proBNP data available (Figure 1). Median (IQR) follow-up was 59 days (52, 64).

Baseline Patient Characteristics

Baseline characteristics for the pooled studies as well as separately by change in eGFR are presented in Table 1. Baseline characteristics by change in NT-proBNP are available in Supplemental Table S1. Median baseline serum creatinine was 1.67 mg/dl (IQR 1.21, 2.11), with median eGFR of 40.0 ml/min/1.73 m^2 (29.4, 59.2) and 75.4% of patients had a baseline eGFR < 60 ml/min/1.73 m^2. Baseline median NT-proBNP was 4509 pg/ml (IQR 2323, 9985). Among the pooled studies, 81.4% patients had hypertension and 58.2% had diabetes, which were similar in patients with and without in-hospital declines in eGFR. Most patients had baseline use of loop diuretics and 57.7% were taking either an ACEI or an ARB; there were no differences in baseline use of these medications amongst those with and without changes in eGFR (Table 1). There were similar distributions of both decline and increase in eGFR among all trial arms.

There were 61 patients in whom follow-up NT-proBNP data were missing, and among these, 9 were also missing follow-up kidney function measurements. Compared to patients with complete data, those with missing data had greater tendency to be women and self-reported non-white race and had higher baseline ACEI or ARB use (Supplemental Table S2). There were no differences in follow-up length of time between those with and without missing NT-proBNP data and these patients were similarly distributed between CARRESS and DOSE.

Outcomes

Over a median follow-up of 59 days (IQR 52, 64), there were 58 (12%) deaths and 217 patients (44%) experienced the composite outcome of death or hospitalization. Outcome rates were similar in the cohort of patients with missing follow-up NT-proBNP data.

In-hospital Changes in Biomarkers

Median change in eGFR was −0.7 ml/min/1.73 m^2 (IQR −6.8, 6.1 ml/min/1.73 m^2) for the entire cohort, with 232 (53%) patients experiencing a decline in eGFR. Of those who had a decline, the median absolute decline was −6.1 ml/min/1.73m^2 (IQR −11.9, −2.6). Median change in NT-proBNP was −841.3 pg/ml (IQR −2765.0, 106.5), with 71.3% of patients experiencing a decline in NT-proBNP levels. There was no correlation between changes in eGFR with changes in NT-proBNP ($\rho = -0.07$, $p = 0.13$) (Figure 2).

In-hospital Decline in eGFR

An in-hospital decline in eGFR was not significantly associated with the composite outcome in either univariate or multivariable models (HR=0.86 per every 30% decline in eGFR; 95% CI 0.72, 1.02; p=0.09 in univariate model; HR=0.89 per every 30% decline in eGFR; 95% CI 0.74, 1.07; p=0.21 in adjusted model) (Table 2). In-hospital declines in NT-proBNP were associated with lower hazard for the composite outcome, with a HR= 0.75 per halving of the change in NT-proBNP (95% CI 0.65, 0.86; p<0.001) in univariate analysis and HR=0.70 (95% CI 0.58, 0.83; p<0.001) in multivariable adjusted model.

Interaction between Decline in eGFR and Change in NT-proBNP

There was a significant interaction between in-hospital decline in eGFR and change in NT-proBNP (p=0.002 in unadjusted model; p=0.03 in adjusted model). A decline in eGFR was associated with significantly lower hazard of the composite outcome when NT-proBNP also declined (Table 2). When NT-proBNP declined, each 30% decline in eGFR was associated with a 22% reduction in the composite outcome (HR=0.78; 95% CI 0.61, 0.99; p=0.04). In contrast, when NT-proBNP increased, each 30% decline in eGFR had no association with outcomes (HR=0.99; 95% CI 0.76, 1.29; p=0.94). Larger declines in NT-proBNP were associated with progressively decreased risks of the composite outcome for each 30% decline in eGFR (Figure 3).

When patients randomized to ultrafiltration were removed from the analysis (n=92), the interaction remained significant and direction of the relationship the same (HR=0.66 for every 30% decline in eGFR as long as NT-proBNP decreased [95% CI 0.47, 0.91]; HR=0.95 for every 30% decline in eGFR if NT-proBNP increased [95% CI 0.68, 1.33]).

Discussion

This study demonstrates that acute decline in eGFR during hospitalization for acute decompensated heart failure was not significantly associated with death and re-hospitalization in the two months following discharge. However, there was a significant interaction between decline in eGFR and change in NT-proBNP such that decline in eGFR was associated with lower risk for death or readmission as long as there was also a decline in

NT-proBNP. Progressively greater degrees of decline in NT-proBNP levels were associated with greater reductions in the risk of death and re-hospitalization associated with a 30% eGFR decline. This supports the notion that decongestion needs to be taken into account when evaluating the prognostic importance of a declining eGFR during therapy for acute decompensated heart failure.

These current findings add to the growing body of literature supporting the concept that the mechanism underlying the acute decline in eGFR is vital to interpreting the prognostic implications of the decline. These data are consistent with those from an analysis of 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) trial, which found that among patients who had an increase in serum creatinine of 0.3 mg/dl during their hospital admission, only those that were volume-overloaded at the time of the measurement were found to have higher risk of death or readmission over 30 days.(23) An analysis of the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness trial (ESCAPE) also demonstrated that hemoconcentration, as a proxy for decongestion, was associated with acute decline in kidney function as well as with lower mortality.(24) In the current analysis, decline in eGFR was associated with decreased risk of a composite outcome of death and re-hospitalization as long as there was a concominant decline in NT-proBNP, supporting the notion that decongestion, even at the cost of a decline in eGFR, is an important priority for outcomes in patients with acute decompensated heart failure.

Understanding the relation between kidney function and biomarkers of congestion could potentially guide management of patients with acute decompensated heart failure who have acute eGFR changes. Natriuretic peptides, which are released from cardiac myocytes in response to stretch from volume overload, are routinely measured and readily available. High levels of circulating BNP and NT-proBNP have been associated with higher rates of mortality and re-hospitalization,(25) and lack of reduction in natriuretic peptides levels during decongestion therapy is associated with worse survival.(26, 27) The present findings suggest that decline in eGFR could be considered a benign event as long as the NT-proBNP levels are also decreasing, thus providing reassurance to the treating physician and helping to guide care and subsequent clinical decision making. The finding of a significant interaction between decline in eGFR and change in NT-proBNP could also explain prior conflicting results regarding the impact of decline in kidney function, as some studies had found that it was associated with poor clinical outcomes(1–4) and others with improved outcomes.(24) A separate analysis of the DOSE trial noted that an in-hospital decline in kidney function from day 1 to 3 similarly was not associated with worse outcomes. Tests for interaction in that analysis were performed between decline in eGFR and baseline NT-proBNP levels, in contrast to the current study which utilized in-hospital change in NT-proBNP levels.(7) While baseline NT-proBNP levels were not found to have a modifying effect on decline in kidney function, our study suggests that changes in in-hospital NT-proBNP levels do have a significant modifying effect on decline in eGFR.

Natriuretic peptides are established biomarkers that aid in the diagnosis of acute decompensated heart failure, with levels correlating with severity of heart failure.(29, 30) Other methods to assess for changes in congestion status are limited, and clinical assessment of physical exam findings have been shown to have poor sensitivity especially if cardiac valvular disease is present.(31, 32) In clinical practice, some patients may have invasive hemodynamic monitoring via pulmonary artery catheterization, but for the majority of patients admitted with acute decompensated heart failure, these data may not be readily available. Direct methods of measuring plasma volume are available, but challenging to obtain and not yet widely used. Daily weights are also difficult to obtain accurately, especially in patients who are critically ill and bed-bound, as can often be the case for patients with chronic heart failure. Use of hemoconcentration, such as was examined in the analysis of the ESCAPE trial data,(24) can serve as a proxy of decongestion but changes can be subtle and are influenced by a multitude of other factors that occur frequently in this population such as bleeding, iron deficiency or bone marrow suppression.

There are a number of limitations to this analysis. The composite outcome is predominantly driven by recurrent hospitalizations and is underpowered to evaluate the impact of changes in kidney function on mortality alone. Nevertheless, available data supports that re-hospitalizations are closely tied to increased mortality in patients with advanced heart failure.(33, 34) The patient populations comprising CARRESS and DOSE were slightly different given that patients from CARRESS required demonstration of decline in kidney function to meet inclusion criteria. We performed a complete case analysis without imputation for missing follow-up NT-proBNP data, which can have potential for bias; however, patients with missing follow-up data did not have differing lengths of follow-up or different event rates from those with complete follow-up data, suggesting that missingness was not conditional on other variables.

Conclusions

Declines in kidney function in the setting of targeted decongestion for acute decompensated heart failure appears to be a benign event as long as decongestion is being achieved. Incorporation of objective measures of biomarkers of congestion, such as NT-proBNP, may add to clinical decisions regarding interpretation and management of acute declines in eGFR. Both serum creatinine and natriuretic peptides such as BNP and NT-proBNP are readily available and could provide guidance for patients with acute decompensated heart failure and changes in eGFR.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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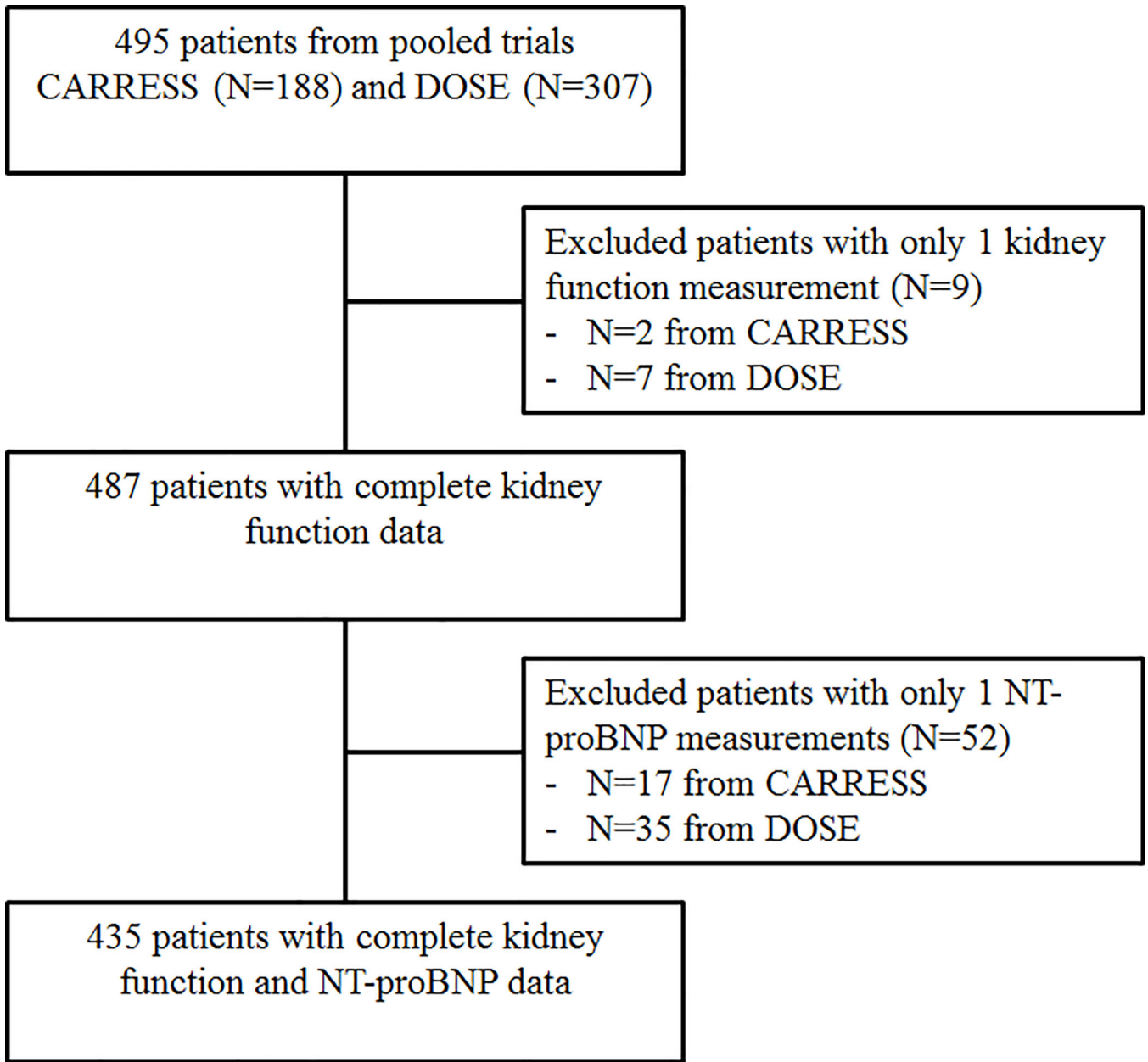
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│      495 patients from pooled trials      │
│   CARRESS (N=188) and DOSE (N=307)        │
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                    │      │ Excluded patients with only 1 kidney │
                    ├──────│ function measurement (N=9)           │
                    │      │   - N=2 from CARRESS                 │
                    │      │   - N=7 from DOSE                    │
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│   487 patients with complete kidney       │
│            function data                  │
└─────────────────────────────────────────┘
                    │
                    │      ┌──────────────────────────────────────┐
                    │      │ Excluded patients with only 1 NT-   │
                    ├──────│ proBNP measurements (N=52)           │
                    │      │   - N=17 from CARRESS                │
                    │      │   - N=35 from DOSE                   │
                    │      └──────────────────────────────────────┘
                    │
┌─────────────────────────────────────────┐
│   435 patients with complete kidney       │
│      function and NT-proBNP data          │
└─────────────────────────────────────────┘
```

Figure 1.

Study patient population

Our analysis included 435 patients with complete data, including baseline and follow-up measurements of both NT-proBNP and of kidney function. CARRESS: Cardiorenal Rescue Study in Acute Decompensated Heart Failure; DOSE: Diuretic Optimization Strategies in Acute Heart Failure.
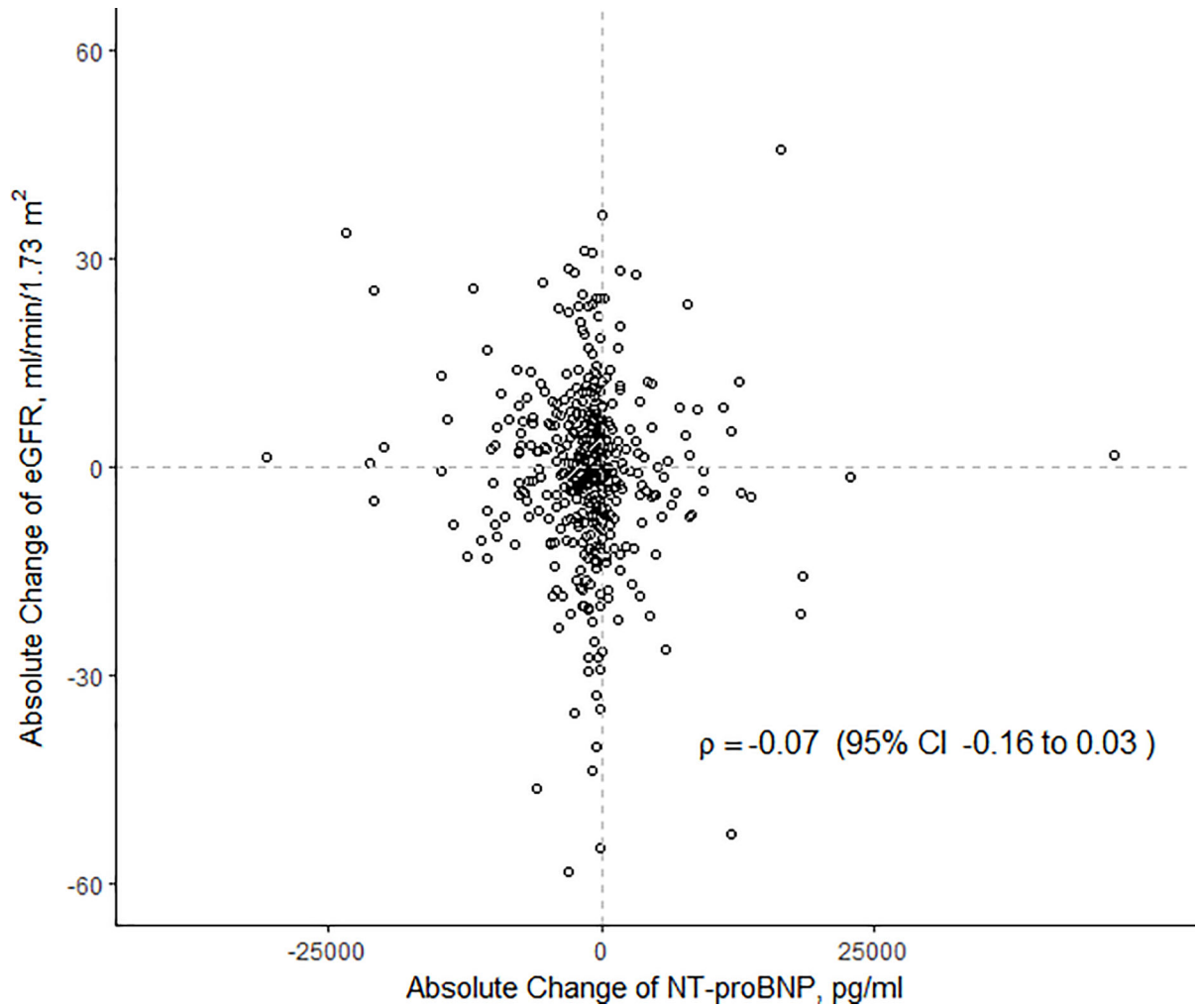
Figure 2.
Scatterplot for in-hospital changes in eGFR and NT-proBNP. Changes were calculated on the absolute scale from baseline to last measurement prior to discharge. Correlation coefficient $\rho=-0.07$, $p=0.13$. NT-proBNP: N-terminal prohormone of brain natriuretic peptide; eGFR: estimated glomerular filtration rate.
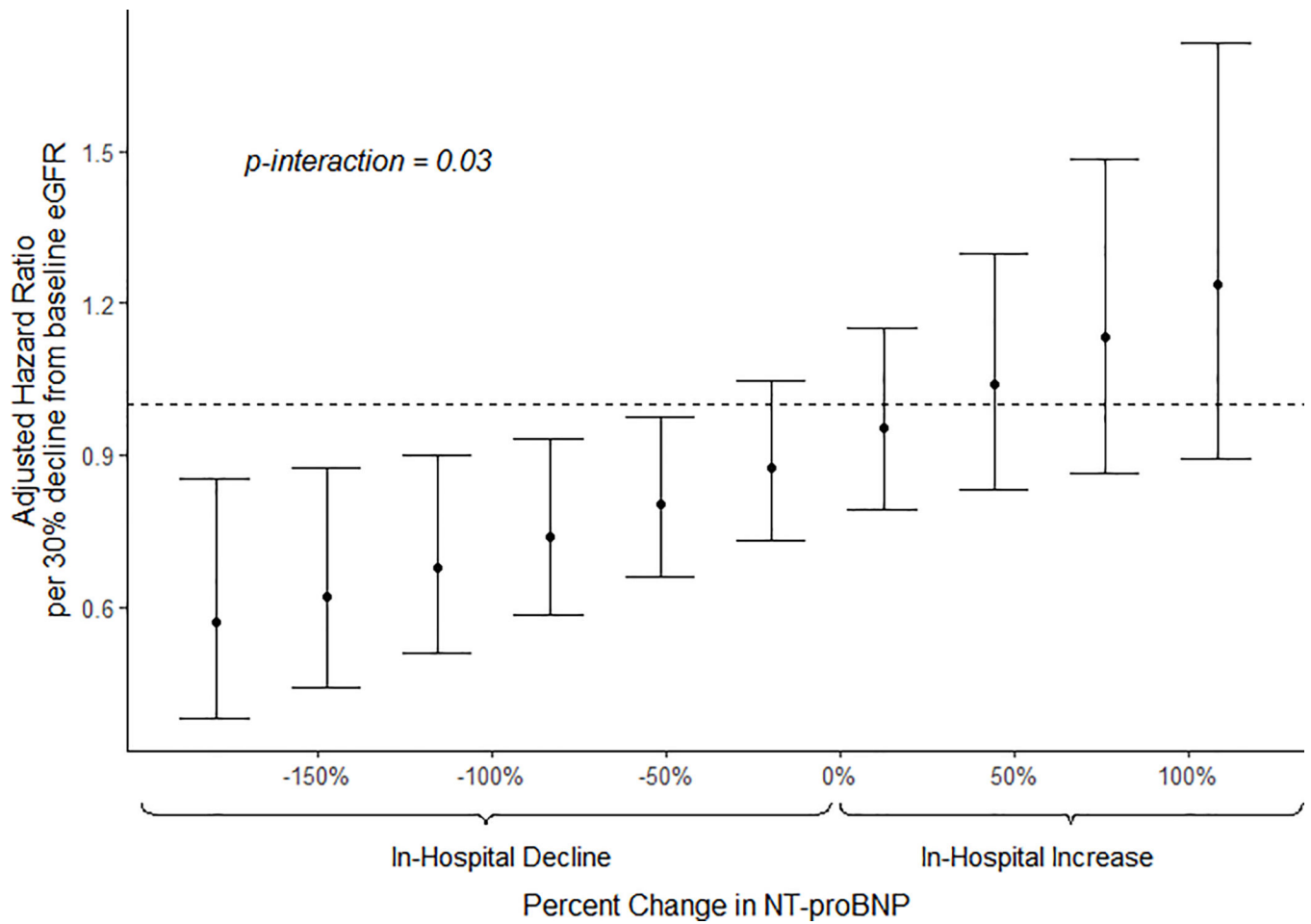
Figure 3.
Adjusted hazard ratios for composite outcome of death or re-hospitalization for each 30%
decline in eGFR by varying levels of change in NT-ProBNP.

Multivariable adjusted Cox regression model including the interaction (*p*=0.03) between
decline in eGFR and change in NT-proBNP. Both eGFR and NT-proBNP were log-
transformed; eGFR by base 10/7 enabling hazard ratios to be assessed for a 3/10 decline,
synonymous to a 30% decline. HR: hazard ratio; eGFR: estimated glomerular filtration rate;
NT-proBNP: N-terminal prohormone of brain natriuretic peptide.

Table 1.

Baseline characteristics (total) and by change in estimated glomerular filtration rate (eGFR).

	Overall N=435	In-Hospital eGFR Decline N=232	In-Hospital eGFR Increase N=203
Age, years	67.0 ± 13.2	66.6 ± 12.7	67.4 ± 13.9
Female	108 (24.8)	66 (28.4)	42 (20.7)
Black	104 (23.9)	53 (22.8)	51 (25.1)
BMI, kg/m²	33.9 ± 9.5	35.2 ± 10.2	32.4 ± 8.4
Ejection Fraction, %	35.2 ± 17.6	38.0 ± 17.7	34.2 ± 17.4
Ischemic etiology	259 (59.5)	138 (59.5)	121 (59.6)
NYHA Functional Class			
2	10 (2.5)	6 (2.8)	4 (2.2)
3	248 (61.8)	131 (60.9)	117 (62.9)
4	143 (35.7)	78 (36.3)	65 (34.9)
Hypertension	354 (81.4)	193 (83.2)	161 (79.3)
Diabetes	253 (58.2)	149 (64.2)	104 (51.2)
Baseline Laboratory Results			
NT-proBNP, pg/ml	4509 [2323, 9985]	4080 [2125, 7885]	5178 [2511, 12905]
Creatinine, mg/dl	1.67 [1.21, 2.11]	1.52 [1.14, 2.04]	1.75 [1.37, 2.22]
eGFR, ml/min/1.73 m²	40.0 [29.4, 59.2]	41.7 [31.4, 65.1]	37.3 [28.4, 53.9]
Hemoglobin, g/dl	11.4 ± 1.9	11.4 ± 1.9	11.5 ± 2.0
Medications			
ACEI or ARB	251 (57.7)	131 (56.5)	120 (59.1)
Aldosterone antagonist	108 (24.8)	66 (28.4)	42 (20.7)
Loop diuretic	423 (97.2)	226 (97.4)	197 (97.0)
CARRESS Trial			
Ultrafiltration Arm	83 (19.1)	42 (18.5)	41 (20.2)
Medical Therapy Arm	86 (19.8)	43 (18.5)	43 (21.2)
DOSE Trial			
Bolus, low dose	67 (15.4)	42 (18.1)	41 (20.2)
Bolus, high dose	69 (15.9)	42 (18.1)	27 (13.3)
Continuous, low dose	64 (14.7)	28 (12.1)	36 (17.7)
Continuous, high dose	66 (15.2)	35 (15.1)	31 (15.3)

Values are represented by mean ± standard deviation, or median [25th and 75th interquartile range], or n (%).

Abbreviations: BMI, body mass index; NYHA, New York Heart Association; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; eGFR, estimated glomerular filtration rate; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker

Table 2.

Hazard ratio for composite outcome of death and re-hospitalization according to in-hospital changes in eGFR and changes in NT-proBNP

	N	N of Events	Unadjusted HR (95% CI)	p-value	Adjusted HR‡ (95% CI)	p-value
IN-HOSPITAL DECLINE						
Decline eGFR (per 30% decrease)	435	197	0.86 (0.72, 1.02)	0.09	0.89 (0.74, 1.07)	0.21
Decline NT-proBNP (per halving)	435	197	0.75 (0.65, 0.86)	<0.001	0.70 (0.58, 0.83)	<0.001
Decline eGFR x Decline NT-proBNP	435	197	-	0.002	-	0.03
eGFR DECLINE (per 30%)						
Concomitant Decline NT-proBNP	435	197	0.71 (0.57, 0.90)	0.004	0.78 (0.61, 0.99)	0.04
Concomitant Increase NT-proBNP	435	197	1.07 (0.84, 1.36)	0.59	0.99 (0.76, 1.29)	0.94

Cox proportional hazards models used to evaluate association between decline in biomarkers (eGFR and NT-proBNP) with composite outcome of death and re-hospitalization. Model was also fitted with an interaction term between decline in eGFR and decline in NT-proBNP (*p*=0.03 for interaction in adjusted models). Log transformation of eGFR by base 10/7 enabled hazard ratios to be assessed per a 3/10 decline, synonymous to a 30%.

‡
adjusted for age, race, sex, BMI, trial, randomization arm, baseline NT-proBNP, use of ACEI or ARBs, and baseline eGFR.

Abbreviations: BMI, body mass index; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; eGFR, estimated glomerular filtration rate;