Association of Volume Overload With Kidney Function Outcomes Among Patients With Heart Failure With Reduced Ejection Fraction

Wendy McCallum[1], Hocine Tighiouart[2,3], Jeffrey M. Testani[4], Matthew Griffin[4], Marvin A. Konstam[5], James E. Udelson[5] and Mark J. Sarnak[1]

[1]Division of Nephrology, Tufts Medical Center, Boston, Massachusetts, USA; [2]Institute for Clinical Research and Health Policy Studies, Tufts Medical Center, Boston, Massachusetts, USA; [3]Tufts Clinical and Translational Science Institute, Tufts University, Boston, Massachusetts, USA; [4]Division of Cardiovascular Medicine, Yale School of Medicine, New Haven, Connecticut, USA; and [5]Division of Cardiology and the CardioVascular Center, Tufts Medical Center, Boston, Massachusetts, USA

Introduction: In patients with heart failure with reduced ejection fraction (HFrEF), volume overload is associated with mortality. Few studies that have examined the relation between volume and long-term kidney function outcomes in HFrEF.

Methods: Using data from the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) trial, we used multivariable Cox regression models to evaluate the association between volume overload as evaluated by B-type natriuretic peptide (BNP) and N-terminal pro B-type natriuretic peptide (NT-proBNP), and a clinical congestion score (scale of 0–12) composed of pedal edema, jugular venous distension, rales, and orthopnea with the occurrence of estimated glomerular filtration rate (eGFR) decline by >40%, and incident chronic kidney disease (CKD) stage ≥4 defined by eGFR of <30 ml/min per 1.73 m^2, over a median 10-month follow-up.

Results: Among 3718 patients (mean eGFR 59 ± 22 ml/min per 1.73 m^2), 340 (9%) reached an eGFR decline >40% and 337 (10%) developed incident CKD stage ≥4. In multivariable models, compared with those in the quartile of lowest NT-proBNP, those within the highest quartile had a significantly higher risk of eGFR decline by >40% (hazard ratio [HR] = 2.62 [95% confidence interval {CI} = 1.62, 4.23]) and incident CKD stage ≥4 (HR = 2.66 [95% CI = 1.49, 4.77]), with similar trends for BNP. Similarly in multivariable models, patients in the quartile of highest congestion score had a 48% increased risk for eGFR decline by >40% (HR = 1.48 [95% CI = 1.07, 2.06]) and a 42% increased risk for CKD stage ≥4 (HR = 1.42 [95% CI = 1.01, 1.99]), compared with the lowest quartile.

Conclusion: Volume overload, as indicated both by elevated natriuretic peptides and clinical signs and symptoms, is associated with increased risk for clinically important kidney function outcomes in HFrEF.

Reduced levels of kidney function are highly prevalent among patients with HFrEF and are associated with adverse clinical outcomes.[1–4] Acute declines in kidney function, such as during hospitalizations or after starting certain medications, may or may not be associated with worse clinical outcomes[5,6];

however, longer-term declines in kidney function are consistently associated with increased risk for mortality and cardiovascular outcomes in HFrEF.[7,8] Few studies have examined risk factors for longitudinal declines in eGFR among patients with HFrEF.

The hallmarks of HFrEF include hemodynamic derangements and volume overload. Natriuretic peptides, including BNP and NT-proBNP, are released from cardiac myocytes in response to stretch from volume overload and levels have been shown to correlate with severity of heart failure.[9–11] Higher levels of NT-proBNP in particular have been associated with greater risk for kidney function decline in non–HFrEF

related cohorts.[12–14] Evidence of volume overload by physical examination, characterized by signs and symptoms of fluid overload, are associated with greater risk of poor cardiovascular endpoints such as all-cause mortality and HF hospitalizations,[15,16] but long-term kidney endpoints have not been examined.

It has been traditionally presumed that reduced levels of kidney function among patients with HFrEF stemmed from decreased renal perfusion pressure due to low cardiac output, but more recent data suggest that congestion itself plays a role in kidney function decline.[17,18] Prior cross-sectional studies have shown that volume overload, quantified by elevated central venous pressure and elevated intra-abdominal pressure, is associated with reduced levels of eGFR,[19,20] but there are few longitudinal studies examining the relation between volume overload and longer-term kidney function.

We hypothesized that volume overload, as indicated by elevated natriuretic peptides as well as by clinical signs and symptoms of volume overload, would be associated with kidney function decline among patients with HFrEF. Using data from the EVEREST trial,[21] we evaluated whether an array of assessments of volume overload, including BNP and NT-proBNP as well as a clinical congestion score incorporating pedal edema, jugular venous distention, rales, and orthopnea, are associated with longer-term longitudinal kidney outcomes.

METHODS

Study Population and Design

The EVEREST trial was a multicenter randomized controlled trial that investigated the use of the vasopressin V_2 receptor blocker tolvaptan in patients with HFrEF.[21] Conducted from 2003 to 2006, it enrolled patients with reduced left ventricular ejection fraction ($\leq 40\%$) who were admitted for acute heart failure with evidence of congestion based on ≥ 2 clinical signs or symptoms, and were <48 hours into the hospitalization. Patients were randomized to receiving either 30 mg of tolvaptan or placebo for a minimum of 60 days, in addition to their standard medical therapy, and were followed for a maximum 2.5 years. Major findings included no difference in the primary outcome of all-cause mortality or cardiovascular events but did show short-term improvement in HF-related symptoms over placebo. Key exclusion criteria included a serum creatinine >3.5 mg/dl and any comorbid condition with an expected survival of <6 months. Participants in EVEREST provided informed consent at the time of enrollment; the present study was deemed exempt from review by the Tufts Health Sciences Institutional Review Board.

Exposure

Volume overload was examined in 2 ways. The first was by biomarker, which comprised levels of BNP and NT-proBNP at the time of randomization into the trial (within 48 hours of index hospital admission). For administrative reasons, some centers measured BNP whereas others measured NT-proBNP, both of which were assayed in a central laboratory. The second was by clinical signs and symptoms, which were evaluated by physician-investigators at the time of randomization into the trial. These included a standardized 4-point graded scale for pedal edema (absent/trace, slight, moderate, marked), jugular venous distention (≤ 6, 6–9, 10–15, >15 cm), rales (none, bases, up to $<50\%$, to $>50\%$), and orthopnea (none, seldom, frequent, continuous), which were then incorporated into a single congestion score with range from 0 to 12. Although there is yet to be a validated and widely accepted standardized score for grading volume overload based on physical examination, this is a modification of a previously published congestion score based on data from the EVEREST trial[15] and comprise the findings believed to be most specific to volume overload.[22]

Outcomes

The primary kidney function outcomes of interest included (i) decline of eGFR of $>40\%$ because it is accepted as a surrogate endpoint in trials of CKD[23–25]; and (ii) incident CKD stage ≥ 4 as defined by eGFR of <30 ml/min per 1.73 m^2, given the high risk for adverse outcomes and propensity for development of complications from the loss of renal clearance.[26–28] The secondary kidney function endpoints included (i) increase in serum creatinine of ≥ 0.3 mg/dl as this has been used in prior studies of patients with HFrEF to define acute kidney injury[29–31] and in studies in the general population is associated with adverse outcomes[32] and (ii) decline of eGFR of $>30\%$ from baseline as this also can be used as a surrogate endpoint in CKD trials.[23–25]

Kidney function was estimated by using serum creatinine and the CKD-EPI formula.[33] Serum creatinine was measured at the time of randomization, at day 3, day 7, and day of discharge from the initial hospitalization and then every 4–8 weeks thereafter during follow-up. Measurements of kidney function obtained outside of these prespecified protocol visits were excluded, as indication for testing was unclear. Given the known variability in kidney function during in-hospital treatment for acute HF and the fact that the relation of short-term declines in kidney function with outcomes is controversial,[5,6,34] only kidney endpoints occurring after discharge from the initial hospitalization were included in the primary analysis. In order to

avoid short-term perturbation in hemodynamics that resulted in reaching the kidney outcomes, reaching the kidney endpoint required 2 consecutive measures of eGFR. The exception was if the kidney outcome was based on the last measure of kidney function available, in which case a confirmatory measure was not required to meet the definition of reaching the outcome.

Covariates

Several baseline covariates were selected for analysis as potential confounding variables based on review of the literature and clinical relevance, including demographic characteristics (age, sex, race, body mass index), severity of cardiac disease including ejection fraction, New York Heart Association functional class, systolic blood pressure, baseline medication (angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, mineralocorticoid receptor antagonists), as well as randomization arm (tolvaptan or placebo). Baseline eGFR was included as an adjustment variable.

Statistical Analysis

Values are presented as mean $\pm$ SD or median (interquartile range) for non-normal distributions. Baseline characteristics were compared by quartiles of baseline biomarker and baseline congestion score using analysis of variance and Kruskal-Wallis tests, as well as by χ^2 and Fisher exact tests for categorical and continuous variables, as appropriate. Correlations were examined between baseline BNP, NT-proBNP, and congestion score by baseline eGFR using Spearman correlations.

Kaplan-Meier estimates of the proportion of patients who remained outcome-free were performed separately for each exposure for the primary and secondary kidney outcomes of interest. Multivariable Cox proportional hazards regression models were used to evaluate the association between baseline BNP, NT-proBNP, congestion score, and the kidney outcomes of interest. Log transformation was performed for BNP and NT-proBNP given the skewed distribution. Analyses were performed with baseline natriuretic peptide levels and congestion scores treated as a continuous variable as well as divided into quartiles. The 4 components of the congestion score (pedal edema, jugular venous distention, rales, orthopnea) were also examined separately with each outcome. Time at risk for each of these outcomes began at the time of randomization. Patients were censored at the date of their last kidney function measurement. They were not censored at the time of rehospitalizations during follow-up; however, kidney function measures obtained during rehospitalizations were not included in the analyses. For the outcome of

CKD stage ≥ 4, patients who had a baseline eGFR <30 ml/min per 1.73 m^2 were excluded. Interaction testing between randomized group (tolvaptan vs. placebo) and each exposure with kidney outcomes was also performed.

Several sensitivity analyses were performed. First, analyses were repeated by including any kidney function endpoints that occurred during the course of follow-up, including during the initial hospitalization. Second, the definition of meeting each respective kidney endpoint was modified to exclude outcomes that were based only on the last measure of kidney function. Third, we assessed whether the relation between volume overload and kidney outcomes differed in the early postdischarge period versus later in follow-up by including an interaction with time split at <30 days and ≥ 30 days. And fourth, analyses were repeated with death treated as a competing event.

All analyses were performed using SAS Enterprise Guide (version 7.12; SAS, Cary, NC) and R language (version 3.3.1; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

There were 3718 patients with both baseline and at least 1 additional kidney function data point available and were included into the analysis. Median follow-up was 10.4 months (interquartile range: 5.7–16.5), and up to a maximum of 30 months, given the rolling study enrollment.

Baseline Patient Characteristics

Baseline characteristics by quartiles of baseline BNP are presented in Table 1, and then presented by quartiles of baseline NT-proBNP and congestion score in the Supplementary Material (Supplementary Tables S1 and S2, respectively). Overall, 71% had hypertension, 38% had diabetes, and median baseline eGFR was 57 ml/min per 1.73 m^2 (interquartile range: 41–74). Those with the highest levels of BNP and NT-proBNP and highest congestion scores were more likely to have lower levels of eGFR (Table 1; Supplementary Tables S1 and S2). BNP and NT-proBNP scores were weakly negatively correlated with baseline eGFR (Spearman correlation $r = -0.22$ [95% CI $= -0.26$, -0.19] for BNP, $r = -0.35$ [95% CI $= -0.40$, -0.30] for NT-proBNP), whereas the congestion score was minimally correlated ($r = -0.06$ [95% CI $= -0.09$, -0.03]).

BNP and Kidney Endpoints
Primary Outcomes

Event rates of eGFR decline by $>40\%$ and incident CKD stage ≥ 4 and their association with baseline BNP are shown in Table 2. In continuous models, BNP was

Table 1. Baseline characteristics according to quartile of BNP

Characteristic	Quartile 1 (5–280 pg/ml) (n = 665)	Quartile 2 (281–659 pg/ml) (n = 666)	Quartile 3 (660–1419 pg/ml) (n = 665)	Quartile 4 (1420–72,000 pg/ml) (n = 665)
Age, yr	63.7 ± 10.9	65.7 ± 11.1	65.2 ± 11.4	67.4 ± 12.2
Female sex	198 (29.8)	179 (26.9)	150 (22.6)	160 (24.1)
Black race	36 (5.4)	41 (6.2)	49 (7.4)	50 (7.5)
Hypertension	511 (76.8)	471 (70.7)	454 (68.3)	458 (68.9)
Diabetes	248 (37.3)	265 (39.8)	252 (37.9)	229 (34.4)
BMI	30.8 ± 5.7	29.3 ± 5.3	28.0 ± 5.3	26.5 ± 4.8
Ejection fraction	31.1 ± 6.9	29.0 ± 7.6	26.6 ± 7.9	25.6 ± 7.9
Ischemic etiology of LV dysfunction	447 (67.8)	433 (65.7)	425 (65.1)	442 (67.2)
Systolic blood pressure, mmHg	126.5 ± 19.2	122.0 ± 19.0	120.8 ± 19.8	117.3 ± 19.0
Congestion score	4.6 ± 1.9	4.9 ± 2.1	5.2 ± 2.0	5.6 ± 2.0
Pedal edema				
Absent/trace	129 (19.4)	138 (20.7)	143 (21.5)	113 (17.0)
Slight	182 (27.4)	160 (24.0)	150 (22.6)	105 (15.8)
Moderate	256 (38.5)	240 (36.0)	219 (33.0)	243 (36.5)
Marked	98 (14.7)	128 (19.2)	152 (22.9)	204 (30.7)
JVD				
≤6 cm	209 (31.7)	195 (29.5)	157 (23.8)	128 (19.4)
6–9 cm	325 (49.3)	329 (49.7)	296 (44.8)	306 (46.3)
10–15 cm	105 (15.9)	111 (16.8)	178 (26.9)	195 (29.5)
>15 cm	20 (3.0)	27 (4.1)	30 (4.5)	32 (4.8)
Rales				
None	138 (20.8)	109 (16.4)	111 (16.7)	137 (20.6)
Bases	404 (60.8)	402 (60.5)	401 (60.3)	368 (55.3)
To <50%	109 (16.4)	132 (19.9)	141 (21.2)	136 (20.5)
To >50%	14 (2.1)	21 (3.2)	12 (1.8)	24 (3.6)
Orthopnea				
None	201 (30.4)	194 (29.2)	156 (23.6)	138 (20.9)
Seldom	182 (27.5)	149 (22.4)	140 (21.2)	130 (19.7)
Frequent	215 (32.5)	227 (34.1)	261 (39.4)	283 (42.9)
Continuous	64 (9.7)	95 (14.3)	105 (15.9)	109 (16.5)
NYHA functional class				
Class 1 or 2	1 (0.2)	6 (0.9)	3 (0.4)	2 (0.3)
Class 3	475 (71.5)	432 (64.9)	375 (56.4)	330 (49.7)
Class 4	188 (28.3)	228 (34.2)	287 (43.2)	332 (50.0)
Current smoking	94 (14.1)	68 (10.2)	86 (13.0)	77 (11.6)
Medications				
ACEI or ARB	602 (90.5)	582 (87.4)	566 (85.1)	533 (80.2)
MRA	407 (61.2)	382 (57.4)	372 (55.9)	371 (55.8)
Diuretic	546 (82.1)	571 (85.7)	564 (84.8)	549 (82.6)
Baseline laboratory tests				
eGFR, ml/min per 1.73 m²	65.1 (49.0–81.0)	59.0 (45.1–74.0)	54.5 (40.7–72.6)	50.4 (36.9–65.7)
BNP, pg/ml	151 (80–213)	441 (364–541)	964 (805–1163)	2274 (1754–3120)
NT-proBNP, pg/ml	1259 (668–2217)	3151 (1960–4886)	5733 (4099–8437)	11475 (6185–19760)
Randomization group				
Tolvaptan	349 (52.5)	335 (50.3)	311 (46.8)	323 (48.6)

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; JVD, jugular venous distention; LV, left ventricular; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association.
Values presented as either n (%), mean ± SD, or median (25th, 75th interquartile range).

associated with both decline in eGFR by >40% in unadjusted and adjusted models (Table 2). For incident CKD stage ≥4, BNP was associated with higher risk in unadjusted models (HR = 1.21 per doubling, 95% CI = 1.12, 1.31) which was attenuated after adjustment, including for baseline eGFR, and did not meet statistical significance in the adjusted model (HR = 1.07,

95% CI = 0.98, 1.16). In reference to the lowest quartile, higher quartiles of BNP were associated with increased risk of eGFR decline of 40% and incident CKD stage ≥4 in both unadjusted and adjusted models (Table 2 and Figure 1). There was no significant interaction by randomized group (P = 0.8 and 0.6 for >40% eGFR decline and CKD stage ≥4, respectively).

Table 2. Hazard ratios for primary kidney outcomes of eGFR decline by >40% and incident CKD stage ≥4

Marker of Volume Overload	eGFR Decline >40%					Incident CKD Stage ≥4				
	N	No. of Events	Event Rate per 1000-pm	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	N	No. of Events	Event Rate per 1000-pm	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
BNP										
Continuous (per doubling)	2661	210	9.7 (8.5, 11.1)	1.18 (1.09, 1.28)	1.19 (1.09, 1.30)	2417	221	11.3 (9.9, 12.9)	1.21 (1.12, 1.31)	1.07 (0.98, 1.16)
Quartile 1	665	33	5.6 (4.0, 7.9)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	630	36	6.5 (4.7, 9.1)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Quartile 2	666	57	9.9 (7.7, 12.9)	1.74 (1.13, 2.67)	1.80 (1.17, 2.79)	614	56	10.6 (8.2, 13.8)	1.60 (1.05, 2.44)	1.58 (1.03, 2.44)
Quartile 3	665	58	10.8 (8.4, 14.0)	1.89 (1.23, 2.89)	2.07 (1.32, 3.25)	598	62	13.1 (10.2, 16.8)	1.96 (1.30, 2.96)	1.55 (1.00, 2.39)
Quartile 4	665	62	13.4 (10.4, 17.1)	2.43 (1.59, 3.71)	2.61 (1.65, 4.13)	575	67	16.4 (12.9, 20.8)	2.51 (1.67, 3.76)	1.46 (0.94, 2.25)
NT-proBNP										
Continuous (per doubling)	1313	176	9.8 (8.5, 11.4)	1.26 (1.14, 1.39)	1.33 (1.19, 1.50)	1166	149	9.2 (7.8, 10.8)	1.39 (1.24, 1.55)	1.22 (1.08, 1.38)
Quartile 1	328	39	7.3 (5.3, 10.0)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	317	19	3.6 (2.3, 5.7)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Quartile 2	328	37	7.6 (5.5, 10.4)	1.04 (0.66, 1.63)	1.05 (0.66, 1.66)	309	41	9.1 (6.7, 12.4)	2.51 (1.46, 4.33)	1.69 (0.97, 2.94)
Quartile 3	329	49	11.5 (8.7, 15.2)	1.66 (1.09, 2.53)	1.71 (1.09, 2.69)	289	42	11.3 (8.3, 15.3)	3.16 (1.84, 5.45)	2.11 (1.20, 3.73)
Quartile 4	328	51	14.7 (11.2, 19.3)	2.20 (1.44, 3.34)	2.62 (1.62, 4.23)	251	47	17.0 (12.8, 22.7)	4.71 (2.76, 8.05)	2.66 (1.49, 4.77)
Congestion score										
Continuous (per 1 point higher)	3669	337	9.6 (8.6, 10.7)	1.09 (1.03, 1.15)	1.06 (1.01, 1.13)	3323	331	10.4 (9.3, 11.6)	1.07 (1.02, 1.13)	1.06 (1.00, 1.12)
Quartile 1	861	68	7.8 (6.1, 9.9)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	799	69	8.6 (6.8, 10.9)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Quartile 2	1303	112	9.0 (7.4, 10.8)	1.15 (0.85, 1.55)	1.10 (0.81, 1.49)	1171	110	9.7 (8.1, 11.7)	1.12 (0.83, 1.52)	1.18 (0.87, 1.60)
Quartile 3	584	48	8.7 (6.5, 11.5)	1.08 (0.75, 1.57)	0.98 (0.67, 1.43)	532	53	10.4 (8.0, 13.7)	1.19 (0.83, 1.71)	1.16 (0.81, 1.68)
Quartile 4	921	109	13.1 (10.9, 15.8)	1.67 (1.23, 2.26)	1.48 (1.07, 2.06)	821	99	13.4 (11.0, 16.3)	1.52 (1.12, 2.07)	1.42 (1.01, 1.99)

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; BNP, B-type natriuretic peptide; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro B-type natriuretic peptide.
Cox proportional hazards regression modeling for baseline BNP, NT-proBNP, and clinical congestion score, both as a continuous variable as well as by quartiles (with quartile 1 being lowest and quartile 4 being highest). BNP and NT-proBNP are transformed on the log scale, enabling HRs to be interpreted per every doubling of baseline BNP and NT-proBNP. HRs for congestion score (range 0–12, with higher scores indicative of greater congestion) are per every 1 point higher in baseline score. Adjusted: adjusted for age, sex, race, randomization group (tolvaptan vs. placebo), BMI, medication use (ACEI or ARB, MRA), ejection fraction, New York Heart Association functional class, systolic blood pressure, baseline eGFR and baseline BNP. Event rates are calculated per 1000 patient-month (1000-pm).

Secondary Outcomes

In continuous models, baseline BNP was significantly associated with both increase in serum creatinine by ≥0.3 mg/dl and decline in eGFR by >30% in unadjusted and adjusted models (Supplementary Table S3). In reference to the lowest quartile, higher quartiles of BNP were associated with secondary kidney function outcomes in both unadjusted and adjusted models (Supplementary Table S3 and Supplementary Figure S1). There was no significant interaction by randomized group (P = 0.7 and 0.8 for ≥0.3 mg/dl creatinine increase and >30% eGFR decline respectively).

NT-proBNP and Kidney Endpoints
Primary Outcomes

Event rates of eGFR decline by >40% and incident CKD stage ≥4 and their association with baseline NT-proBNP are shown in Table 2. In continuous models, baseline NT-proBNP was associated with higher risk of reaching both primary kidney endpoints in both unadjusted and adjusted models (Table 2). There was some attenuation in magnitude of risk, especially after adjustment for baseline eGFR in models examining incident CKD stage ≥4 (Table 2). This association was

also consistent in the quartile analysis, with a graded relation between quartiles of NT-proBNP and risk for both eGFR decline by >40% and incident CKD stage ≥4. In reference to the lowest quartile, the highest quartile of NT-proBNP was associated with highest risk for eGFR decline by >40% in both unadjusted (HR = 2.20, 95% CI = 1.44, 3.34) and adjusted models (HR = 2.62, 95% CI = 1.62, 4.23). Risk was similarly increased for incident CKD stage ≥4 in unadjusted (HR = 4.71, 95% CI = 2.76, 8.05) and adjusted models (HR = 2.66, 95% CI = 1.49, 4.77) (Table 2 and Figure 1). There was no significant interaction by randomized group (P = 0.8 and 0.9 for >40% eGFR decline and CKD stage ≥4 respectively).

Secondary Outcomes

In continuous models, baseline NT-proBNP was associated with higher risk of reaching both kidney endpoints in both unadjusted and adjusted models (Supplementary Table S3). This association was also consistent in the quartile analysis in both unadjusted and adjusted analyses (Supplementary Table S3 and Supplementary Figure S1). There was no significant interaction by randomized group (P = 0.8 and 0.8 for ≥0.3 mg/dl creatinine increase and >30% eGFR decline, respectively).
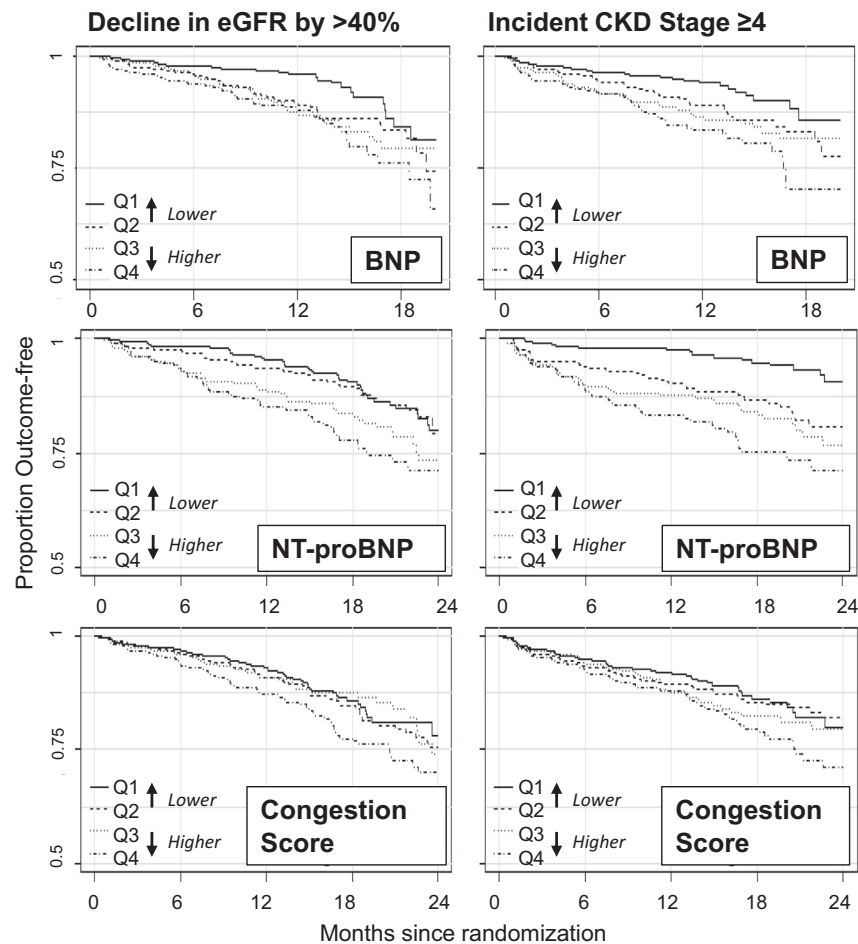
Figure 1. Kaplan-Meier plots of proportion of patients free from reaching an estimated glomerular filtration rate (eGFR) decline by >40% and chronic kidney disease (CKD) stage ≥4 based on baseline natriuretic peptide levels and baseline congestion score. Higher levels of baseline B-type natriuretic peptide (BNP) and N-terminal pro B-type natriuretic peptide (NT-proBNP); quartile 4, represented as Q4) had higher incidence of both endpoints, and similarly those with higher congestion score (quartile 4, represented as Q4). The number at risk can be found at the bottom of each plot.

Congestion Score and Kidney Endpoints
Primary Outcomes
Event rates of eGFR decline by >40% and incident CKD stage ≥4 and their association with baseline congestion score are shown in Table 2. In continuous models, higher congestion score was associated with greater risk of eGFR decline by >40% and incident CKD stage ≥4 in both unadjusted and adjusted models (Table 2). This association was also consistent in the quartile analysis, with a graded relation between quartiles of congestion score and risk for both eGFR decline by >40% and incident CKD stage ≥4. In reference to the lowest quartile, the quartile with the highest congestion score was associated with greater risk for eGFR decline by >40% in both unadjusted (HR = 1.67, 95% CI = 1.23, 2.26) and adjusted analyses (HR = 1.48, 95% CI = 1.07, 2.06). Risk was similarly increased for incident CKD stage ≥4 in unadjusted (HR = 1.52, 95% CI = 1.12, 2.07) and adjusted models (HR = 1.42, 95% CI = 1.01, 1.99) (Table 2 and

Figure 1). There was no significant interaction by randomized group ($P = 0.57$ and 0.25 for >40% eGFR decline and CKD stage ≥4 respectively). Associations followed a consistent pattern within each individual component of the congestion score (Supplementary Table S4).

Secondary Outcomes
In continuous models, congestion score was associated with higher risk of creatinine increase by ≥0.3 mg/dl as well as eGFR decline by >30% in both unadjusted and adjusted models (Supplementary Table S3). In reference to the lowest quartile, the quartile with the highest congestion score was statistically associated with higher risk of both secondary outcomes (Supplementary Table S3 and Supplementary Figure S1). There was no significant interaction by randomized group ($P = 0.2$ and 0.9 for ≥0.3 mg/dl creatinine increase and >30% eGFR decline, respectively). Associations followed a consistent pattern

within each individual component of the congestion score (Supplementary Table S5).

Sensitivity Analyses

When analyses were repeated with inclusion of kidney endpoints that occurred during the initial hospitalization, associations were slightly weaker but for the most part similar to the primary analysis (Supplementary Table S6). Similarly, when changing the outcome definition to 2 consecutive endpoints only, the associations were also slightly weaker, but overall similar to the primary analysis (Supplementary Table S6). When examining for a difference in risk of reaching kidney endpoints in the early postdischarge period (<30 days) versus late postdischarge period (≥30 days), there was no significant interaction with time—with the exception of serum creatinine increase by ≥0.3 mg/dl, where risk was greater in the early postdischarge period compared to the late postdischarge period (Supplementary Table S7). When death was treated as a competing event, results remained consistent (Supplementary Table S8).

DISCUSSION

This study demonstrates a high incidence of clinically important kidney function endpoints among patients with HFrEF. Volume overload, as assessed in 2 different domains, by both biomarkers and clinical signs and symptoms, was associated with elevated risk for clinically important kidney function outcomes over a median 10-month follow-up. To our knowledge, this is the first analysis to explore volume overload as a risk factor for longer term clinically important kidney outcomes among patients with HFrEF.

Reduced level of kidney function has consistently been shown to be a powerful risk factor for mortality and cardiovascular events among patients with HFrEF.[1–4] Additionally, long-term declines in kidney function have been associated with worse clinical outcomes as well.[7,25] However, despite decline in kidney function being such an important prognostic factor, the reasons for kidney function decline in HFrEF remain poorly understood. The "classic" paradigm of low cardiac output being the primary cause of decline in kidney function in HFrEF has recently been disputed.[2,35] Congestion is known to be a strong risk factor for poor clinical outcomes in patients with HFrEF,[11,36] but whether it is associated with longer-term kidney function decline is unclear. It has been shown in prior ultrasonographic studies that volume overload among patients with HFrEF transmits changes in the renal vein flow patterns,[37] which has been hypothesized as a potential mechanism for venous congestion putting the kidney at risk for future decline. This proposed

mechanism may be why studies in HF have shown increased intra-abdominal pressure to be associated with declines in kidney function,[38,39] as well as evidence of tubular injury in an animal model of renal congestion.[40] However, most of the prior literature examining congestion in terms of kidney function among patients with HFrEF has largely been cross-sectional in nature or only included acute fluctuations in kidney function over the span of a few days,[2,19,20] making it challenging to draw any longitudinal interpretations regarding the relation between volume overload and clinically important long-term changes in kidney function.

It is also important to note that the prior HFrEF literature examining volume overload and kidney outcomes has primarily used an endpoint of serum creatinine increase by ≥0.3 mg/dl. One analysis of 125 outpatients with HFrEF noted that higher NT-proBNP levels were associated with an increased odds of having an increase in serum creatinine by ≥0.3 mg/dl over a period of 18 months.[41] Other studies that have examined signs of volume overload, either by peripheral edema or elevated jugular venous distention or central venous pressure, have similarly focused on this same endpoint of serum creatinine increase by ≥0.3 mg/dl, occurring over the duration of the acute hospitalization.[19,20] Although this is an accepted definition for acute kidney injury in many settings,[32] the prognostic importance of these acute in-hospital declines among patients with HFrEF has been controversial. Declines in eGFR of more than 30% to 40% have been widely accepted as surrogate endpoints in the chronic kidney disease literature,[23,24] but whether they are observed in relation to volume overload among patients with HFrEF has not been explored. The current study significantly adds to this literature and shows that clinical markers of volume overload, including elevated NT-proBNP, and to some extent elevated BNP, are risk factors for increases in serum creatinine by at least 0.3 mg/dl but also for perhaps more important clinical outcomes including longer-term decline in eGFR by 30% to 40% and incidence of CKD stage ≥4. The results of this study are also consistent with a literature among non-HF patients (general population cohorts as well as those with coronary artery disease), which have shown that elevated natriuretic peptides levels, even among those without a clinical diagnosis of reduced ejection fraction, were risk factors for faster rates of eGFR decline and incident CKD.[12,13] However, it is important to acknowledge that the pathophysiology of cardiorenal interactions in HFrEF remain poorly understood, and that worse congestion in this specific population also potentially reflects more severe cardiac disease, and thus identify patients at higher risk for kidney function decline.

There are a number of limitations to this analysis. Patients with a serum creatinine of >3.5 mg/dl were not included in EVEREST, but as this is the highest cutoff for any trial of patients with acute HF, our analyses may in fact be more generalizable to patients with CKD and HF. There were no available measures of proteinuria. Although adjusting for measures of severity of cardiac disease, such as ejection fraction and New York Heart Association function class, did not significantly alter associations, we cannot rule out the possibility of residual confounding given the observational nature of the analysis. Even though our criteria for meeting each kidney outcome required a consecutive confirmatory measurement, we cannot rule out the possibility that the outcomes may also reflect eGFR fluctuations known to occur in HFrEF, rather than progressive decline in kidney function.

CONCLUSIONS

The incidence of clinically significant kidney function decline among patients with HFrEF is considerable. Volume overload, as indicated by elevated BNP and NT-proBNP and signs and symptoms of congestion, is a risk factor for clinically relevant kidney function outcomes. These results need to be reproduced in other cohorts, and additional studies are needed to better understand the mechanisms underlying the associations.

DISCLOSURE

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)
Table S1. Baseline characteristics according to quartile of NT-proBNP.

Table S2. Baseline characteristics according to quartile of congestion score.
Table S3. Hazard ratios for secondary kidney outcomes.
Table S4. Hazard ratios for primary kidney outcomes for components of congestion score.
Table S5. Hazard ratios of secondary kidney outcomes for components of congestions score.
Table S6. Primary and secondary outcomes using different event definitions.
Table S7. Association between volume overload and kidney function outcomes, split into the early postdischarge period (<30 days) and late follow-up (≥30 days).
Table S8. Hazard ratios for kidney outcomes with death treated as a competing risk.
Figure S1. Kaplan-Meier plots of percentage free from reaching secondary outcomes of a creatinine increase by >0.3 mg/dl and eGFR decline by >30% based on baseline natriuretic peptide and congestion score.

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