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Post-discharge hemodilution, congestion, and clinical outcomes among patients hospitalized for heart failure with reduced ejection fraction: from the EVEREST trial

Running title: Hemodilution Following Hospitalization for Heart Failure

Ankeet S. Bhatt MD MBA¹, Muthiah Vaduganathan MD MPH¹, Ravi B. Patel MD², Gregg C. Fonarow MD³, Haris P. Subacius MA⁴, Marvin A. Konstam MD⁵, Faiez Zannad MD PhD⁶, Javed Butler MD MPH MBA⁷, Stephen J. Greene MD^{8,9}

¹ Brigham and Women's Hospital Heart & Vascular Center and Harvard Medical School, Boston, MA, USA

² Division of Cardiology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

³ Ahmanson-UCLA Cardiomyopathy Center, University of California Los Angeles, Los Angeles, CA, USA

⁴ Center for Cardiovascular Innovation, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

⁵ The CardioVascular Center, Tufts Medical Center, Boston, MA, USA

⁶ Université de Lorraine, Inserm, Centre d'Investigations Cliniques - 1433, and Inserm U1116, CHRU Nancy, F-CRIN INI-CRCT, Nancy, France

⁷ Department of Medicine, University of Mississippi Medical Center, Jackson, MS, USA

⁸ Division of Cardiology, Duke University Medical Center, Durham, NC, USA

⁹ Duke Clinical Research Institute, Durham, NC, USA

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Address for Correspondence: Stephen J Greene, MD, Duke Clinical Research Institute, 200 Morris Street, Durham, NC 27701; telephone: 919-684-8111; fax: 919-668-7078; email: stephen.greene@duke.edu; Twitter: @SJGreene_md, @DCRINews

Previous studies have found hemoconcentration during hospitalization for heart failure (HF) to correlate with superior decongestion and improved post-discharge outcomes, despite increased risk of in-hospital worsening renal function (WRF).¹⁻³ These data suggest that hemoconcentration may represent an objective and evidence-based measure of the adequacy of in-hospital decongestion.^{1,2,4} However, assessment of congestion remains challenging after the in-hospital period.⁵ This post-discharge “vulnerable phase” represents a high-risk period for death, rehospitalization, and worsening hemodynamics, and despite strong guideline recommendations for early post-discharge follow-up, there are little data to guide titration and assessment of decongestive therapy at these outpatient visits.⁶ As such, it is possible that post-discharge hemodilution could signal re-accumulation of intravascular fluid and be an early subclinical marker of worsening HF. The EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan) trial offers a novel opportunity to (1) study the relationship between early post-discharge hemodilution, WRF, and markers of congestion among patients recently hospitalized for HF, and (2) to determine the association between post-discharge hemodilution and subsequent long-term clinical outcomes.

The study design and primary results of the EVEREST trial have been previously reported.^{7,8} In brief, EVEREST was a prospective, global, randomized clinical trial that studied the effect of tolvaptan versus placebo on clinical outcomes among patients hospitalized for worsening chronic HF with reduced ejection fraction (HFrEF) (ejection fraction [EF] $\leq 40\%$). Median trial follow-up was 9.9 months. Complete blood counts (including hematocrit), basic chemistries, and body weight were collected at randomization, discharge (or day 7 if occurred first), and 1-month post discharge. Since tolvaptan has been shown to increase renal excretion of free water, the present *post-hoc* analysis included only trial participants assigned to placebo. Other inclusion criteria for the present study were complete data for hematocrit at discharge (or day 7) and 1-month post-discharge. The variable of interest in the present study was post-

discharge hematocrit absolute change, defined as the difference between discharge and 1-month post-discharge hematocrit. Patients were divided in quartiles by degree of post-discharge hematocrit change, with negative values (i.e., decreasing hematocrit) reflecting hemodilution. Quartile 1 represented patients with the greatest hemodilution in the 1-month post-discharge period and quartile 4 represented patients with the least hemodilution (i.e. most hemoconcentration).

Primary endpoints were 1) all-cause mortality and 2) the composite of cardiovascular mortality or HF hospitalization. Endpoint events were landmarked at 1 month post-discharge, so that only events occurring after the hemodilution assessment interval were counted. All endpoints were assessed as time-to-first event. We also assessed the association between post-discharge hematocrit change and changes in renal function, body weight, and B-type natriuretic peptide (BNP) from discharge to 1 month. Worsening serum creatinine was defined as an increase in the serum creatinine level ≥ 0.3 mg/dL. Worsening estimated glomerular filtration rate (eGFR) and blood urea nitrogen (BUN) were defined as $\geq 25\%$ increase in respective laboratory values.

Patient characteristics at discharge were compared across quartiles of hematocrit change using χ^2 tests, analysis of variance (ANOVA), and Kruskal-Wallis tests, as appropriate. Continuous variables were reported as mean \pm standard deviation or median (interquartile range [IQR]) based on distribution. Multivariable Cox proportional hazards models were used to assess the association between continuous post-discharge change in hematocrit (per 5% absolute decrease in hematocrit) and both all-cause mortality and the composite endpoint (CV mortality or HF hospitalization). Models were adjusted for 24 pre-specified covariates measured at discharge, including age, sex, geographic region, ischemic HF etiology, NYHA class, systolic blood pressure, serum sodium, BUN, eGFR, BNP, QRS duration, EF, past medical history (diabetes mellitus, hypertension, chronic kidney disease, coronary artery disease, chronic

obstructive pulmonary disease, atrial fibrillation/ flutter, prior HF hospitalization) and concurrent medications (angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, β -blockers, mineralocorticoid receptor antagonists, digoxin, and intravenous inotropes).

Among 2,061 EVEREST patients assigned to placebo, 463 (22%) did not have complete hematocrit data at discharge and/or 1 month. The remaining 1598 (78%) patients alive with available discharge and 1-month post-discharge hematocrit data were included. Mean hematocrit change from discharge to 1 month was $-1.5\% \pm 4.0\%$ (range: -21.0% to $+14.0\%$). Overall, 452 (26%) patients had $\geq 4\%$ absolute decrease in hematocrit and were considered “hemodilutors” (quartile 1). Patient characteristics were generally well-balanced by quartile of hematocrit change (**Table**). Discharge hematocrit was highest among hemodilutors (quartile 1), and decreased progressively across quartiles of post-discharge hematocrit change ($p < 0.01$). Patients with the greatest degree of post discharge hemodilution had lower BNP level and weight at discharge (all $p \leq 0.02$).

Patients with post-discharge hemodilution had the lowest rates of worsening renal function as defined by eGFR and BUN (all $p < 0.01$) (**Figure**). Rates of worsening renal function increased in stepwise fashion from quartile 1 to quartile 4. Hemodilutors experienced the greatest post-discharge increases in body weight and BNP, with lesser increases in quartiles 2 and 3, and decreases in these measures in quartile 4. After adjustment for patient characteristics, every 5% decrease in change in hematocrit from discharge to 1 month was significantly associated with an increased risk of all-cause mortality (hazard ratio [HR] 1.03, 95% confidence interval [CI], 1.00-1.06, $p = 0.045$), but not the composite of cardiovascular mortality or HF hospitalization (HR 1.01, 95% CI 0.99-1.03, $p = 0.39$).

To our knowledge, we present the first study evaluating the clinical significance of early post-discharge hemodilution after HF hospitalization. Hemodilution at 1-month post-discharge correlated with lower risk of worsening renal function, but worsening measures of congestion,

during this interval. After adjustment for clinical factors, early post-discharge hemodilution was significantly associated with subsequent higher risk of mortality over long-term post-discharge follow-up.

Although early post-discharge follow-up is recommended following HF hospitalization, such transitional care strategies have not conclusively improved clinical outcomes.^{6,9} These inconsistent results may stem from the difficulty and variability in the interpretation of patient congestion by clinicians.⁵ Hematocrit represents a widely available and inexpensive laboratory test that can be easily ordered in the outpatient clinic. The current data suggest that post-discharge hemodilution may provide a simple and objective marker of the degree of congestion, beyond physical exam and natriuretic peptides that is independently associated with subsequent mortality. In the context of no guideline-recommended standardized approaches for grading congestion at these early follow-up visits, measurement of early post-discharge hematocrit and comparison with the discharge value may hold promise as an evidence-based marker of congestive status that reflects clinical risk.

Multiple studies have examined the role of discharge hemoconcentration as a surrogate for adequate in-hospital decongestion.¹⁻³ These analyses have generally found greater degrees of in-hospital hemoconcentration to be associated with improved post-discharge clinical outcomes, but higher rates of WRF.^{1,3} Our findings build on prior work, and suggest that the concept of hemodilution/ hemoconcentration extends beyond the HF hospitalization to the early post-discharge period, where hemodilution is associated with worsening markers of congestion and higher risk of clinical events, despite a lower risk of WRF. Moreover, the current study provides further support for the relative importance of congestive status in interpreting the clinical significance of WRF, and further highlights the assessment of congestion as a critical piece of the early post-discharge clinic visit.

Limitations of this study should be noted. First, this *post-hoc* observational analysis cannot definitively prove causal relationships. Moreover, data for other surrogates of plasma

volume including albumin and uric acid were not available for internal validation of the hemodilution findings based on hematocrit changes. Likewise, these data should be recognized as hypothesis-generating and further confirmatory data from other cohorts are needed to confirm the relationships seen here. Finally, although simultaneous changes in weight and BNP suggest that decreases in hematocrit were mediated by intravascular volume expansion, alternative reasons for interval changes in hematocrit (e.g., bleeding, anemia of chronic disease, regression to the mean) cannot be excluded.

In conclusion, among patients recently hospitalized for worsening HFrEF, early post-discharge hemodilution was associated with interval worsening of congestion and increased risk of all-cause mortality, despite a lower risk of WRF. Hemodilution may represent a simple, objective, and evidence-based approach for assessing the level of congestion and clinical risk during early post-discharge follow-up. Further prospective studies are needed to determine whether assessment of post-discharge congestion by hemodilution can inform changes in decongestive therapy and improve clinical outcomes for patients recently hospitalized for HF.

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CONFLICT OF INTEREST

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Table. Characteristics at Discharge by 1-month Post-discharge Hematocrit Change

	Quartile (n=452) <i>Most hemodilution</i>	1 Quartile (n=329)	2 Quartile (n=471)	3 Quartile (n=346) <i>Least hemodilution</i>	4 P-value
Hematocrit Levels					
Absolute Δ Hct, range (%)	-21%, -4%	-3%, -2%	-1%, 2%	2%, 14%	
Hct (%), mean \pm SD	46 \pm 6	43 \pm 5	42 \pm 5	40 \pm 6	<0.01
Patient Characteristics					
Age (yrs), mean \pm SD	65 \pm 12	65 \pm 12	65 \pm 12	66 \pm 12	0.23
Men, n (%)	349 (77)	251 (76)	347 (74)	273 (79)	0.35
SBP (mmHg), mean \pm SD	114 \pm 16	116 \pm 16	116 \pm 17	115 \pm 18	0.37
HR (bpm), mean \pm SD	75 \pm 12	73 \pm 11	74 \pm 13	75 \pm 12	0.31
Weight (kg), mean \pm SD	78 \pm 17	81 \pm 18	81 \pm 18	82 \pm 19	0.02
LVEF (%), mean \pm SD	27 \pm 8	28 \pm 8	28 \pm 8	28 \pm 8	0.58
BNP (pg/mL), median (25 th , 75 th)	372 (131-809)	429 (177-979)	404 (176-980)	632 (271-1193)	<0.01
Creatinine (mg/dL), median (25 th , 75 th)	1.2 (1.0-1.5)	1.2 (1.0-1.5)	1.2 (1.0-1.6)	1.3 (1.0-1.7)	0.51
BUN (mg/dL), median (25 th , 75 th)	27 (21-38)	27 (21-37)	27 (20-38)	27 (21-41)	0.66
Diabetes mellitus, n (%)	137 (30)	122 (37)	175 (37)	138 (40)	0.03
Chronic kidney disease, n (%)	85 (19)	69 (21)	126 (27)	104 (30)	<0.01
Hospitalization for HF, n (%)	348 (77)	260 (80)	377 (81)	263 (76)	0.34
Coronary Artery Disease, n (%)	305 (68)	221 (67)	349 (74)	250 (72)	0.07
Hypertension, n (%)	296 (66)	228 (69)	354 (75)	250 (72)	0.01

Hyperlipidemia, n (%)	205 (45)	135 (41)	223 (48)	173 (50)	0.10
Signs/Symptoms of HF, n (%)					
Peripheral edema	87 (24)	88 (34)	133 (37)	136 (51)	<0.01
Rales	60 (17)	43 (17)	74 (21)	60 (23)	0.20
Dyspnea	59 (17)	37 (14)	53 (15)	54 (20)	0.24
JVP >10cm	19 (5)	9 (4)	14 (4)	16 (6)	0.46
Medical Therapy, n (%)					
ACEI/ARB	386 (86)	297 (90)	403 (86)	283 (82)	0.02
Beta Blocker	327 (73)	257 (78)	349 (74)	259 (75)	0.44
MRA	310 (69)	211 (64)	314 (67)	208 (60)	0.05
Diuretic	431 (96)	313 (95)	443 (94)	331 (96)	0.39
Event Rates, n (%)					
All-cause mortality	104 (23)	60 (18)	93 (20)	78 (23)	0.31
CVM or HF hospitalization	174 (39)	116 (35)	177 (38)	141 (41)	0.52
CVM	85 (19)	42 (13)	77 (16)	58 (17)	0.16
HF hospitalization	123 (27)	83 (25)	140 (30)	108 (31)	0.30

Abbreviations: ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin II receptor blockers; BNP = B-type natriuretic peptide; BUN = blood urea nitrogen; CVM= cardiovascular mortality; Hct= hematocrit; HF= heart failure; HR= heart rate; JVP = jugular venous pulsation; LVEF = Left ventricular ejection fraction; MRA = mineralocorticoid Receptor Antagonist; SBP = systolic blood pressure

FIGURE LEGEND

Figure. Changes in Post-Discharge Renal Function and Congestion by Post-Discharge Hematocrit Change. Patients with the most hemodilution (quartile 1) had lower rates of worsening renal function (left panel), but experienced the greatest increases in weight (middle panel) and BNP. BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; GRF, glomerular filtration rate; SCr, serum creatinine

