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

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Previous studies have found haemoconcentration 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 haemoconcentration may represent an objective and evidence-based measure of the adequacy of in-hospital decongestion.[1,2,4] However, assessment of congestion remains

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challenging after the in-hospital period.[5] This post-discharge 'vulnerable phase' represents a high-risk period for death, rehospitalization, and worsening haemodynamics, 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 haemodilution 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 (i) to study the relationship between early post-discharge haemodilution, WRF, and markers of congestion among patients recently hospitalized for HF, and (ii) to determine the association between post-discharge haemodilution 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 vs. placebo on clinical outcomes among patients hospitalized for worsening chronic HF with reduced ejection fraction (HFrEF) [ejection fraction (EF) ≤40%]. Median trial follow-up was 9.9 months. Complete blood counts (including haematocrit), 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 haematocrit at discharge (or day 7) and 1-month post-discharge. The variable of interest in the present study was post-discharge haematocrit absolute change, defined as the difference between discharge and 1-month post-discharge haematocrit. Patients were divided into quartiles by degree of post-discharge haematocrit change, with negative values (i.e. decreasing haematocrit) reflecting haemodilution. Quartile 1 represented patients with the greatest haemodilution in the 1-month post-discharge period and quartile 4 represented patients with the least haemodilution (i.e. most haemoconcentration).

Primary endpoints were (i) all-cause mortality and (ii) the composite of cardiovascular mortality (CVM) or HF hospitalization. Endpoint events were landmarked at 1 month post-discharge, so that only events occurring after the haemodilution assessment interval were counted. All endpoints were assessed as time-to-first event. We also assessed the association between post-discharge haematocrit 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 ≥25%decrease and increase, respectively, in the 2 measures.

Patient characteristics at discharge were compared across quartiles of haematocrit change using χ^2 tests, analysis of variance (ANOVA), and Kruskal–Wallis tests, as appropriate. Continuous variables were reported as mean ± standard deviation or median (interquartile range) based on distribution. Multivariable Cox proportional hazards models were used to assess the association between continuous post-discharge change in haematocrit (per 5% absolute decrease in haematocrit) and both all-cause mortality and the composite endpoint (CVM or HF hospitalization). Models were adjusted for 24 pre-specified covariates

measured at discharge, including age, sex, geographic region, ischaemic HF aetiology, New York Heart Association 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, beta-blockers, mineralocorticoid receptor antagonists, digoxin, and intravenous inotropes).

Among 2061 EVEREST patients assigned to placebo, 463 (22%) did not have complete haematocrit data at discharge and/or 1 month. The remaining 1598 (78%) patients alive with available discharge and 1-month post-discharge haematocrit data were included. Mean absolute haematocrit change from discharge to 1 month was −1.5 ± 4.0% (range: −21.0% to +14.0%). Overall, 452 (26%) patients had ≥4% absolute decrease in haematocrit and were considered ‘haemodilutors’ (quartile 1). Patient characteristics were generally well-balanced by quartile of haematocrit change (Table 1). Discharge haematocrit was highest among haemodilutors (quartile 1), and decreased progressively across quartiles of post-discharge haematocrit change ($P < 0.01$). Patients with the greatest degree of post-discharge haemodilution had lower BNP level and weight at discharge (all $P \leq 0.02$).

Patients with post-discharge haemodilution had the lowest rates of WRF as defined by eGFR and BUN (all $P < 0.01$) (Figure 1). Rates of WRF increased in stepwise fashion from quartile 1 to quartile 4. Haemodilutors 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 haematocrit 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 CVM 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 haemodilution after HF hospitalization. Haemodilution at 1-month post-discharge correlated with lower risk of WRF, but worsening measures of congestion, during this interval. After adjustment for clinical factors, early post-discharge haemodilution 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 assessment of congestion by clinicians.[5] Haematocrit represents a widely available and inexpensive laboratory test that can be easily ordered in the outpatient clinic. The current data suggest that post-discharge haemodilution 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 haematocrit 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 haemoconcentration as a surrogate for adequate in-hospital decongestion.[1–3] These analyses have generally found greater degrees of in-hospital haemoconcentration to be associated with improved post-discharge clinical outcomes, despite higher rates of WRF.[1,3] Our findings build on prior work, and suggest that the concept of haemodilution/haemoconcentration extends beyond the HF hospitalization to the early post-discharge period, where haemodilution 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 haemodilution findings based on haematocrit changes. Likewise, these data should be recognized as hypothesis-generating and further data from other cohorts are needed to confirm the relationships seen here. Finally, although simultaneous changes in weight and BNP suggest that decreases in haematocrit were mediated by intravascular volume expansion, alternative reasons for interval changes in haematocrit (e.g. bleeding, anaemia of chronic disease, regression to the mean) cannot be excluded.

In conclusion, among patients recently hospitalized for worsening HFrEF, early post-discharge haemodilution was associated with interval worsening of congestion and increased risk of all-cause mortality, despite a lower risk of WRF. Haemodilution 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 haemodilution can inform changes in decongestive therapy and improve clinical outcomes for patients recently hospitalized for HF.

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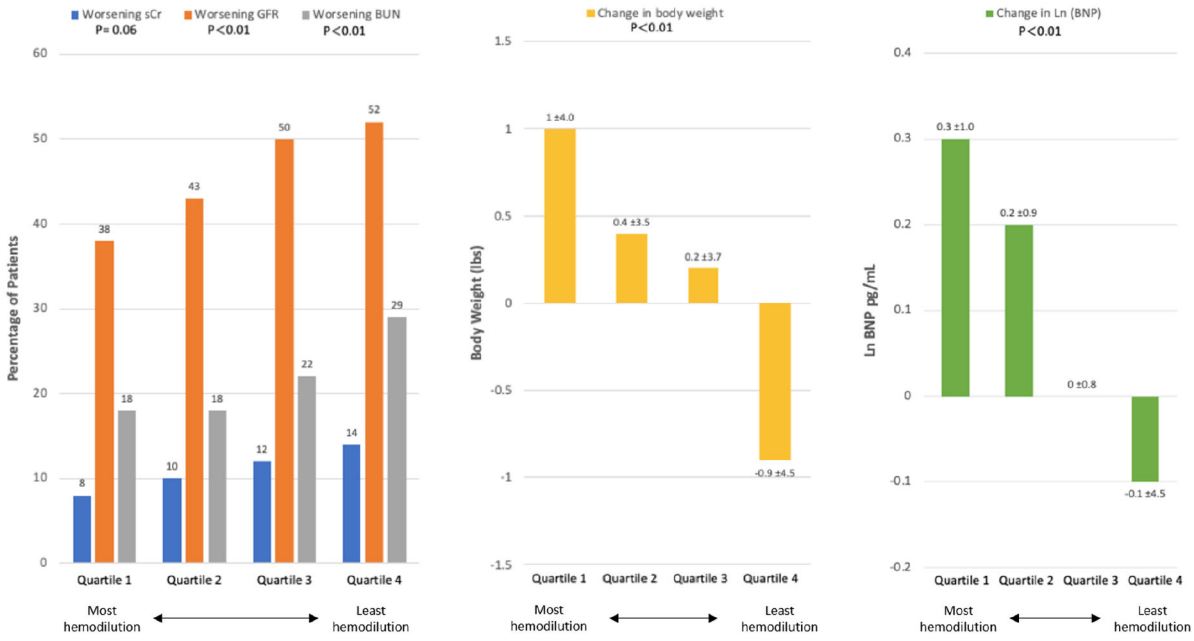

Figure 1.

Changes in post-discharge renal function and congestion by post-discharge haematocrit change. Patients with the most haemodilution (quartile 1) had lower rates of worsening renal function (left panel), but experienced the greatest increases in weight (middle panel) and B-type natriuretic peptide (BNP). BUN, blood urea nitrogen; GRF, glomerular filtration rate; sCr, serum creatinine.

Table 1

Characteristics at discharge by 1-month post-discharge haematocrit change

	Quartile 1 (*n* = 452) Most haemodilution	**Quartile 2 (*n* = 329)**	**Quartile 3 (*n* = 171)**	**Quartile 4 (*n* = 346) Least haemodilution**	***P*-value**
Hct levels					
Absolute ΔHct, range (%)	−21, −4	−3, −2	−1,2	2, 14	
Hct (%), mean ± SD	46 ± 6	43 ± 5	42 ± 5	40 ± 6	<0.01
Patient characteristics					
Age (years), mean ± SD	65 ± 12	65 ± 12	65 ± 12	66 ± 12	0.23
Male sex, *n* (%)	349 (77)	251 (76)	347 (7.4)	273 (79)	0.35
SBP (mmHg), mean ± SD	114 ± 16	116 ± 16	116 ± 17	115 ± 18	0.37
HR (bpm), mean ± SD	75 ± 12	73 ± 11	74 ± 13	75 ± 12	0.31
Weight (kg), mean ± SD	78 ± 17	81 ± 18	81 ± 18	82 ± 19	0.02
LVEF (%), mean ± SD	27 ± 8	28 ± 8	28 ± 8	28 ± 8	0.58
BNP (pg/mL), median (25th-75th)	372 (131–809)	429 (177–979)	404 (176–980)	632 (271–1193)	<0.01
Creatinine (mg/dL), median (25th-75th)	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 (25th-75th)	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
Prior HF Hospitalization, *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
Hyperlipidaemia, *n* (%)	205 (45)	135 (41)	223 (4.8)	173 (50)	0.10
Signs/symptoms of HF, *n* (%)					
Peripheral oedema	87 (24)	88 (34)	133 (37)	136 (51)	<0.01
Rales	60 (17)	43 (17)	74 (21)	60 (23)	0.20
Dyspnoea	59 (17)	37(14)	53 (15)	54 (20)	0.24
JVP >10 cm	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 (7.4)	259 (75)	0.44
MRA	310 (69)	211 (64)	314 (67)	208 (60)	0.05

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	Quartile 1 (*n* = 452) Most haemodilution	Quartile 2 (*n* = 329)	Quartile 3 (*n* = 171)	Quartile 4 (*n* = 346) Least haemodilution	*P*-value
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

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; CVM, cardiovascular mortality; Hct, haematocrit; HF, heart failure; HR, heart rate; JVP, jugular venous pressure; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; SBP, systolic blood pressure; SD, standard deviation.