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The Vulnerable Phase of Heart Failure

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BACKGROUND

The heart failure population is ever expanding, with about 23 million people worldwide diagnosed with heart failure. In the United States, acute heart failure (AHF) accounts for over one million hospital admissions.[1–3] Despite improvements in morbidity and mortality for patients with chronic HF with reduced EF due to pharmacological and device based therapies, rates of admission, readmission and mortality remain high. Overall, in-hospital mortality is relatively low; it is the early post-discharge period, termed the “vulnerable phase” (VP), where the greatest number of adverse outcomes occurs. (Figure 1).

The VP begins with an AHF exacerbation and lasts up to 6 months post-discharge. Patients who survive this 6-month period following AHF represent a uniform cohort without significant variability amongst clinical profiles or systolic blood pressure classifications at the time of admission, thus suggesting an end point for the VP.[4] This VP period is associated with an increased risk of readmission and mortality, with rates of 30% and 10% respectively, within the first few weeks.[5] Such poor outcomes may be attributed to cardiac factors (such as myocardial infarctions, atrial fibrillation, and uncontrolled hypertension), non-cardiac comorbidities (such as diabetes, COPD, and infection), patient related factors (medication non-adherence, alcohol and substance abuse, dietary indiscretions), and system-based factors (such as poor access to discharge follow up).[6] Additionally, the VP can be further categorized into 3 overlapping subphases: early, middle and late phases. The very early VP includes the acute exacerbation and lasts into the first few days post discharge. This was evident in the European Society of Cardiology Heart Failure Long-Term (ESC-HF-LT) registry where 49% of patients admitted in cardiogenic shock died within the first 24 hours

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following presentation illustrating the importance of early identification of hypoperfusion as well as appropriate in-hospital triage of these high risk patients.[4] The early VP begins at the moment of discharge and readmissions during this time frame have been attributed to both patient and system related factors. The later VP takes into account all precipitating factors and comorbidities within 6 months of discharge.[7] (Table 1) As time progresses following a AHF, the readmission and mortality rates gradually decline, as highlighted in the Candesartan in Heart Failure: Assessment of Reduction on Mortality and Morbidity (CHARM) trial. Odds for mortality declined from six-fold during the first month post discharge to two-fold over the time of the trial.[8] The susceptibility of patients during the VP presents a potential opportunity to improve patient outcomes by altering the trajectory of an otherwise poor prognosis.[9]

AREAS OF UNCERTAINTY

PATHOPHYSIOLOGY OF THE VULNERABLE PHASE

Although there is a significant variability within the AHF population, the pathophysiology of the VP can be attributed to numerous contributing factors including the short-term worsening of hemodynamics attributed to a failure to relieve congestion during the index hospitalization, with progressively increased left ventricular (LV) filling pressures.[10, 11] This elevation of LV pressure ultimately leads to persistent hemodynamic congestion and long term persistent multi-organ injury reflected in abnormalities in markers including troponin and creatinine.

Often it is the signs and symptoms associated with congestion that ultimately lead to heart failure admissions and subsequent readmissions.[12–14] During AHF, intravenous diuretics are employed with the goal of lowering elevated filling pressures. Over the course of the hospitalization, there is a resolution of symptomatic congestion.[5] However, about 20% of patients are discharged despite persistent signs and symptoms of HF[4]. A negligible decrease or an increase in body weight suggests a possible failure to relieve clinical congestion during index hospitalization, which may potentially contribute to the high post-discharge event rate in the ESC-HF-LT registry.[4] In the Romanian Acute Heart Failure Syndrome (RO-AHF) registry, regardless of age, gender and LVEF, 83% of AHF patients reported their status to be improved at discharge.[15] However, despite symptomatic improvement, there often remains persistent hemodynamic, subclinical congestion at the time of discharge.[5]

Given the poor hemodynamic reserve commonly seen following a heart failure exacerbation, the AHF patient population is exquisitely sensitive to changes in LV filling pressures with even the most modest increase potentially leading to worsening of symptoms, worsening multi-organ failure, and readmission.[10, 11] This cycle of admission and readmission ultimately predisposes patients to worse outcomes with poor prognosis as well as an increased risk of morbidity and mortality.[16]

AHF patients often are burdened with numerous comorbidities that contribute to early post discharge event rates and predispose this population to AHF during the VP. Addressing both cardiac and non-cardiac comorbidities is vital in preventing decompensation during the VP;

approximately 40% of deaths and readmissions within 60 days of AHF were secondary to non-cardiovascular causes.[12]

The current culture of medicine, where system based failures predisposes patients to delayed care, contributes to the worsening of outcomes during the VP. The inappropriate triage of critically ill and complex patients during the very early VP, to hospital facilities or care settings poorly equipped to manage them, leaves the patient at risk for worse outcomes compared to those who initiated their care at facilities equipped to handle high acuity patients.[4] The lack of a comprehensive discharge plan, either via difficulty arranging immediate outpatient follow up. Lack of resources to pay for medications, follow-up and transportation, or poor medical education leaves this population vulnerable for deterioration and rehospitalization.

DATA SOURCES

IDENTIFICATION OF PATIENTS AT HIGHEST RISK

Although the VP following AHF is marked by high risk for post-discharge events, there are certain subgroups of patients at higher risk than others.[17, 18] The identification of these high-risk groups with the use of emerging prognostic biomarkers as well as risk-stratifying tools may allow for targeted treatment of higher risk patients during hospitalization or immediate post-discharge period. (table 2).

Natriuretic peptides (NP) levels are amongst the most powerful post-discharge risk stratification markers in HF.[19, 20] Serial measurements of NP may help identify patients at high risk for decompensation during the VP, especially during the transition from hospitalization to early outpatient follow up.[21] Greene et al. analyzed both baseline and 30 day post discharge levels of NT-proBNP in the Aliskiren Trial in Acute Heart Failure Outcomes (ASTRONAUT) cohort and found that an increased trajectory in NT-proBNP was independently associated with cardiovascular mortality (CVM) and AHF (HR 1.14, 95% CI 1.02–1.26).[22] Similarly, when coupled with improvement in clinical congestion, a downward trend in NT-proBNP represented an overall lowering risk for HF readmission.[23] However, the Guiding Evidence Based Therapy Using Biomarker Intensified Treatment in Heart Failure (GUIDE-IT) study, which followed 894 patients with HFrEF, found that the use of NT-proBNP was not useful in predicting the time-to-first AHF or CVM in this population (HR 0.98, 95% CI 0.79–1.22; P=0.88).[24] The fact that the control arm underwent more frequent outpatient visits per year compared to what typically occurs in standard practice suggests that more frequent outpatient follow up above usual care improves outcomes. This does not imply guided biomarker therapy is better; rather, perhaps more frequent follow up of patients is needed.

During AHF, a significant number of patients have elevations in troponin secondary to myocardial injury outside of an acute coronary syndrome. The elevation in troponin levels has been associated with worsening HF exacerbation, more severe symptoms, greater needs for aggressive supportive measures, and worse overall outcomes.[25] Analysis of the ASTRONAUT cohort found that troponin elevations at the 30-day post discharge mark were associated with increased all-cause mortality (ACM) (HR 1.59, 95% CI 1.18–2.13) and

cardiovascular mortality/AHF (HR 1.28, 95% CI 1.03–1.58) at 12 months. Assessing troponin levels post-discharge identifies patients with long-term persistence of myocardial injury; such patients are at the highest risk for readmission and may serve as a complement to NP levels in risk-stratification.[26]

Activation of the RAAS in response to decreased renal blood flow leads to a compensatory mechanism aimed at augmenting the inadequate arterial pressure. Consequently there are often fluctuations in blood urea nitrogen (BUN) levels during AHF, reflecting both congestion and fluid retention.[27] Fluctuations in BUN levels during AHF have been investigated by numerous trials. Two retrospective analysis suggested BUN could serve as a marker of neurohormonal activation even in the presence of renal dysfunction.[28, 29] In 171 patients admitted with AHF, there was a rise in BUN independent of basal renal dysfunction thus pointing to the activation of RAAS as the inciting event.[29] As with the previous markers, decreases in BUN without resolution of clinical congestion were not associated with improved outcomes.

Another potential surrogate marker for assessing the underlying risk of AHF patients is serum osmolality. In a post-hoc analysis of the EVEREST trial, lower discharge serum osmolality was predictive of higher ACM (HR 1.61, 95%CI 1.19–1.75) and those patients at the lower spectrum of osmolality demonstrated many features of advanced HF. This marker may represent a marker of residual congestion beyond currently available parameters, including serum sodium and natriuretic peptides.[30]

In addition to markers of risk, numerous risk stratification tools have been developed to aid in the identification of patients at highest risk based on their position on the VP timeline. During the earlier portion of the VP, both the Acute Decompensated Heart Failure National Registry (ADHERE) risk tree and the Improving Heart Failure Risk Stratification in the ED (STRATIFY) tool may be used to stratify risk.[13, 31] Once patients progress to the early VP, the Pro-BNP Outpatient Tailored Chronic Heart Failure Therapy (PROTECT) risk score and the Center for Outcome Research and Evaluation (CORE) online readmission risk calculator for heart failure can help identify patients at risk for poor outcomes within 7 days of discharge and the 30 day all cause readmission rates, respectively. The Get With the Guidelines–Heart Failure (GWTG-HF) risk score aids in stratifying patients during the late subphase of VP and predicts ACM for future AHF.

Potential Solutions

OPTIMIZING MANAGEMENT

Despite being able to identify markers predictive of worse outcomes, the greatest threat to AHF patients is the risk of readmission secondary to persistent congestion.[3, 33, 34] The primary focus during an AHF hospitalization must be the achievement of both clinical and subclinical decongestion. This can only be accomplished by identifying those patients with persistent congestion despite clinical improvement. Thus, the assessment and grading of congestion prior to hospital discharge remains a crucial opportunity to treat patients who have yet to reach optimal euvolemia.[34]

PHARMACOLOGIC THERAPIES

Once optimal decongestion has been achieved…

Despite the challenge associated with the management of heart failure with preserved ejection fraction due to the lack of life saving therapies, a wide spectrum of medications has been shown to reduce mortality in those patients with heart failure and a reduced ejection fraction (HFrEF). These medications include beta-blockers, angiotensin converting enzyme (ACE) inhibitors, aldosterone receptor blockers (ARBs), aldosterone antagonists, and angiotensin receptor-neprilysin inhibitors (ARNIs). Yet despite their proven clinical efficacy, the initiation and uptitration of these medications remains suboptimal. Analysis of the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) registry revealed that fewer than 10% of the patients were at target beta-blocker doses upon discharge with the average beta-blocker dose being less than 50% of the target dose.[35, 36] Further compounding the problem was the failure to up-titrate medications within 90 days post-discharge. Numerous studies, including the Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION), Systolic Heart failure treatment with the If inhibitor ivabradine Trial (SHIFT), and Cardiac Insufficiency Bisoprolol Study in Elderly (CIBIS-ELD) trials, have demonstrated the overall suboptimal dosing of beta-blockers upon discharge.[37–39] With regards to ACE inhibitors and ARBs, hyperkalemia and renal dysfunction remain the major concerns leading to underutilization, with nearly 20% of the eligible HFrEF patients not receiving ACE inhibitors or ARBs.[40] The utilization of mineralocorticoid receptor antagonists is equally poor, with less than a third of eligible patients receiving prescriptions at discharge.[41, 42] Similarly, in the subset of African American population with heart failure intolerant of ACE inhibitors, the usage rate of hydralazine with isosorbide dintirate remains below 25% despite evidence showing a mortality benefit in this population.[43, 44]

Digoxin is another underutilized medical therapy that may improve outcomes. While there is no mortality benefit associated with its use, digoxin decreases HF hospitalization by 28%.[45] Furthermore, in high-risk patients, defined as New York Heart Association class III-IV symptoms, left ventricular ejection fraction <25% or cardiothoracic ratio >55%, digoxin has also been showed to reduce the composite of all-cause mortality or hospitalization, while withdrawing digoxin therapy leads to an increased risk of heart failure.[46, 47] Use of digoxin remains controversial however.

The index hospitalization provides an opportune time for both the initiation and appropriate uptitration of guideline directed medical therapy (GDMT) in a monitored setting. Studies have indicated that initiation and aggressive uptitration of medications prior to discharge were associated with a significant reduction in the adjusted risk of death and re-hospitalization. This was seen in the analysis of beta-blocker usage in eligible patients within the OPTIMIZE-HF trial cohort.[48] Additionally, an analysis of the metabolic exercise test data combined with cardiac and kidney indexes (MECKI) score database suggests higher dose beta-blockers were associated with an overall better prognosis compared to those on medium and low doses.[49] The GWTG-HF registry revealed that patients who were continued or newly started on medication prior to discharge had a significantly improved

thirty-day mortality in comparison to those not started on therapy with one-year mortality was 28.2% for patients continued and 29.7% for patients started on ACEi/ARB compared to 41.6% for patients discontinued and 41.7% for patients not started on therapy.[50]

DEVICE THERAPIES

Patients with severe heart failure must be evaluated for implantable cardiac defibrillators (ICDs) or cardiac resynchronization therapy (CRT) prior to discharge. While the Danish Study to Assess the Efficiency of ICDs in Patients With Non-ischemic Systolic Heart Failure on Mortality (DANISH) study raises some questions regarding the use of ICDs in all HFrEF patients, ICD therapy remains an integral component in the care of HFrEF patients.[51, 52] CRT provides the added benefit of reverse remodeling, which in turn leads to reductions in cardiac volumes, improvements in ejection fractions, and subsequently a reduction in heart failure events and mortality.[53, 54]

NON-PHARMACOLOGIC SYSTEM STRATEGIES

Patient education, home based monitoring (either via the patient or by a visiting nurse service [VNS]), and close follow up in multidisciplinary heart failure clinics are all additional strategies that serve to address system based factors that potentiate readmissions following AHF. Close post-discharge follow up within 1 week of discharge led to fewer readmissions at 30 days (risk-adjusted HR 0.85, 95% CI, 0.78–093).[55] Additionally, a meta-analysis of transitional care services such as follow up with home-visiting programs, multidisciplinary heart failure clinics and structured telephone support, revealed that these interventions result in a reduction in all-cause readmission and mortality at 3–6 months post discharge.[56] Home visiting programs resulted in a significant reduction in both mortality and readmissions (HR of 0.77 and 0.75, respectively), while multidisciplinary heart failure clinics had even higher reductions in mortality and readmissions at the 6-month mark (HR 0.56 and 0.70, respectively). However, there are some conflicting data in regards to ideal or best transitional care management. Visiting nurse programs and increased surveillance via telemonitoring failed to demonstrate any significant improvement in outcomes.[57–60] Observational data failed to consistently support an outcomes benefit associated with dietary modifications towards a salt restricted diet. In fact, in the setting of high diuretic doses, a normal sodium diet was shown to reduce rates of renal dysfunction and readmission when compared to a low sodium diet.[61–63] There are inconsistent impacts on outcomes for other interventions such as regular post-discharge telephone calls and the practice of alerting outpatient physicians to patient discharge.[64]

COMORBIDITY OPTIMIZATION

The AHF population frequently has significant cardiac (e.g. atrial fibrillation, ischemia, valvular heart disease) and non-cardiac (e.g. diabetes mellitus, sleep disordered breathing, chronic lung disease, anemia, depression, chronic kidney disease) comorbidities that contribute substantially to early post-discharge event rates. These comorbid conditions and their management can directly and indirectly contribute to poor outcomes resulting in rehospitalization. Addressing these comorbidities is crucial to improving post-discharge

outcomes, especially given that 40% of all deaths and re-hospitalizations within 60 days following a HF hospitalization are due to non-cardiovascular causes.[12]

POTENTIAL FUTURE OPTIONS: MOVING TO THE LEFT

Rather than waiting one to three months per inclusion criteria of SHIFT, EMPHASIS and PARADIGM-HF trials, earlier initiation of novel therapies during the index hospitalization could potentially medically optimize patients and prevent future AHF. In addition, there are other novel therapies currently under investigation that might further reduce post-discharge risk among heart failure patients. These include ongoing clinical trials with novel agents including a sodium glucose co-transporter 2 inhibitor canagliflozin, a subcutaneous natriuretic peptide omecamtiv mecarbil (GALACTIC-HF, NCT02929329) and a sub-cutaneous guanylate cyclase stimulator vericiguat (VICTORIA, NCT02861534).[65–67] The Canagliflozin Cardiovascular Assessment Study (CANVAS) found that in patients with type-2 diabetes mellitus (T2DM) at high risk for cardiovascular events, treatment with canagliflozin lead to an overall reduction in cardiovascular events (HR 0.86, 95%CI 0.75–0.97) and AHF (HR 0.67, 95%CI 0.52–0.87).[68] The findings of the CANVAS trial can potentially lead to canagliflozin being included as an adjunct treatment for the large portion of the HF population with T2DM, however these findings are yet to be incorporated into the ACC/AHA/HFSA guidelines for the management of heart failure.[69] Recently, the Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure (COSMIC-HF) trial demonstrated omecamtiv's ability to improve cardiac output while simultaneously reducing ventricular diameter in patients with chronic HF.[66] These novel therapies may ultimately prove to be useful tools to help reduce readmissions and mortality in heart failure patients during this VP. Appropriate allocation of resources focused on close follow up and preventative measures for those at the highest risk of readmission and mortality may also provide a unique, patient centered opportunity to escort the AHF population through the vulnerable period and into a stable chronic heart failure status.[17, 18, 70, 71]

CONCLUSION

The VP following AHF is a critical period lasting 6 months post-discharge during which there is heightened risk for adverse outcomes. The risk for readmission begins and continues throughout hospitalization: Failure to adequately decongest patients and maximize proven GDMT prior to discharge or soon after discharge increases risk for adverse events. The identification of patients at risk of poor post-discharge outcomes, and the resolution of both clinical and subclinical congestion remains the most imperative of goal prior to discharge following AHF. Once at decongestive state, proper implementation of heart failure therapies and close outpatient follow up will bridge patients through the VP and into a stable, chronic heart failure status.

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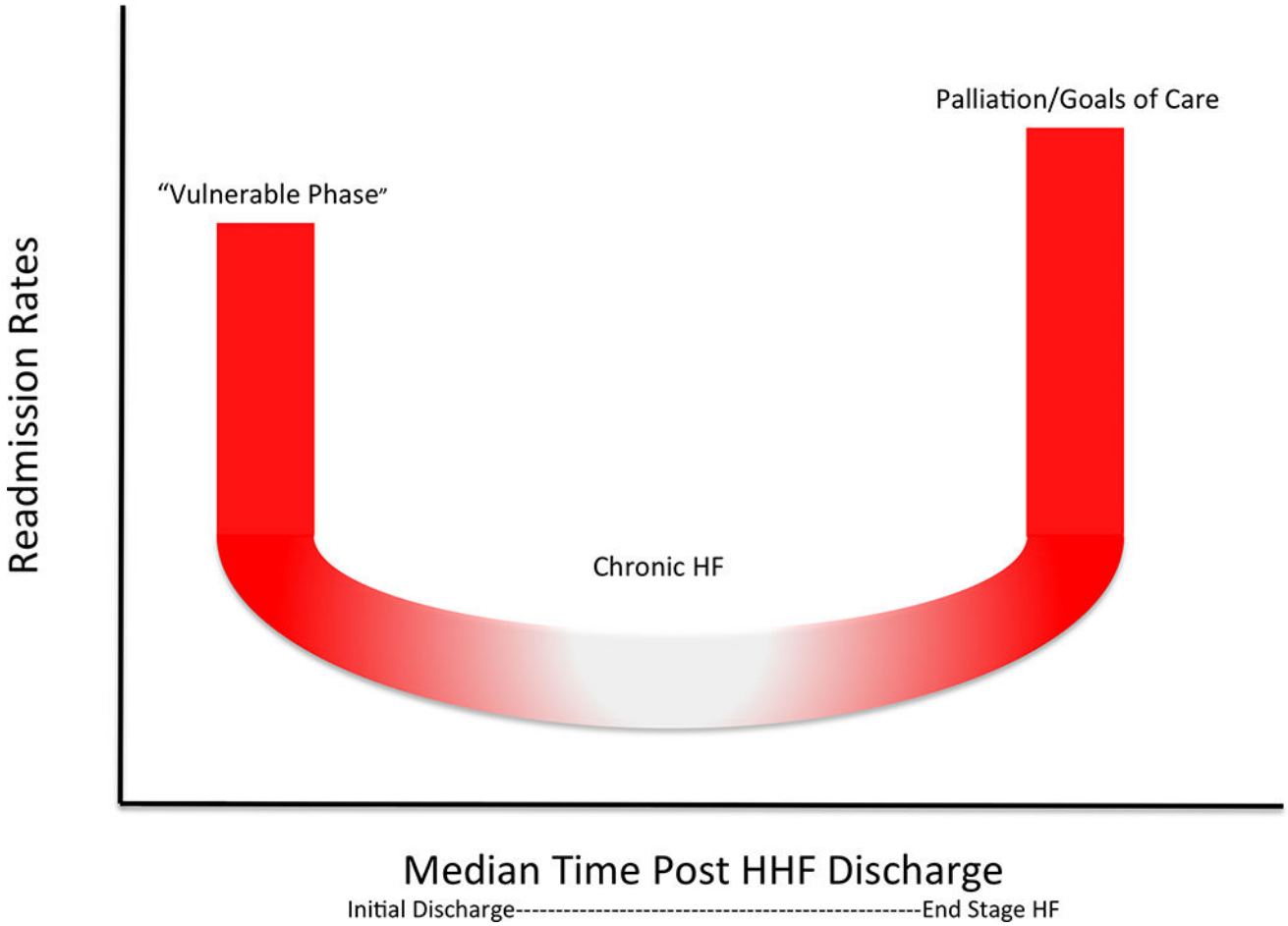

Figure 1. U-shaped distribution of readmission associated with heart failure management

Rehospitalization risk among patients hospitalized for heart failure. Among patients who have repeat hospitalization for heart failure or other cardiovascular-related disease, a three-phase lifetime readmission risk exists. Red indicates period of highest risk for readmission immediately after discharge and just before death. White indicates the lower-risk chronic phase where the rate of readmission levels off prior to end of life.

Table 1

Summary of Biomarkers and Ability to Risk Stratify

Biomarkers Predictive of Risk					
Marker	**Group**	**Study Design**	**Population**	**Endpoint**	**Conclusion**
BNP/NT-proBNP	Greene et al.	Post-Hoc Analysis of ASTRONAUT cohort	1351 HHF patients w/EF≤40%, BNP≥ 400pg/mL, or NT-proBNP ≥ 1600 pg/mL	ACM and CVM/HHF at 12 months	Worse CVM/HHF outcomes with two fold increase in NT-proBNP trajectory (HR 1.14, 95% CI 1.02–1.26). No association with ACM (HR 0.95, 95% CI 0.81–1.11)
	Ambrosy et al.	Post-Hoc Analysis of EVEREST cohort	2061 HHF patients w/EF≤40% and ≥2 signs/symptoms of fluid overload/CCS	ACM, HHF, and ACM + HHF at 30 days post discharge and overall	Worsening ACM and ACM+HHF outcomes with clinical congestion at 30 days (ACM HR 1.43, 95% CI 1.14–1.58; ACM+HHF HR 1.11, 95% CI 1.06–1.17). No association with HHF (HR 1.06, 95% CI 1.14–1.58)
Troponin	Greene et al.	Post-Hoc Analysis of ASTRONAUT cohort	1469 HHF patients w/EF≤40% and troponin measured prior to discharge and at 30 day follow up	ACM and CVM/HHF at 12 months	1 month troponin elevation predictive of increased ACM (HR 1.59, 95% CI 1.18–2.13) and CVM/HHF (HR 1.28, 95% CI 1.03–1.58)
BUN	Bruocco et al.	Prospective study	107 patients admitted for AHF and systolic dysfunction	BUN on admission and at discharge	BUN increase of >20% at discharge associated with poorer outcome independent of congestion (univariate HR 2.72, 95% CI 1.03–7.28, multivariate HR 3.00, 95% CI 1.12–8.06)
Serum Osmolality	Vaduganathan et al.	Post-Hoc Analysis of EVEREST cohort	3744 patients with EF≤40% and ≥2 signs/symptoms of fluid overload/CCS	ACM after 9.9 months	Lower discharge serum osmolality was predictive of worse post-discharge outcomes (HR 1.61, 95%CI 1.19–1.75
Hematocrit	Greene et al.	Post-Hoc Analysis of EVEREST cohort	1684 HHF patients w/EF≤40% and hematocrit measured on admission and discharge/hospital day 7	ACM and CVM/HHF at 100 days post discharge	Every 5% increase of in-hospital hematocrit associated with decreased ACM (HR 0.81, 95% CI 0.70–0.95) and CVM/HHF at ≤100 days (HR 0.73, 95% CI 0.71–0.76)

Abbreviations: ACM, all cause mortality; ASTRONAUT, Aliskiren Trial in Acute Heart Failure Outcomes; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; CCS, composite congestion score; CI, confidence interval; CVM, cardiovascular mortality; EF, ejection fraction; EVEREST, Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan; HHF, hospitalization for heart failure; HR, hazard ratio; NT-proBNP, N-terminal pro-BNP

Table 2

Summary of available methods used in the assessment of overall volume status

Methods of Assessing Volume Status					
Volume Assessment	**Method**	**Study**	**Population**	**End point**	**Conclusion**
PAC	Invasive	ESCAPE Trial	433 patients w/EF <30% admitted for NYHA class IV symptoms	Number of days hospitalized or die during 6 month period	PAC did not improve primary outcomes (HR 1.00 95%CI 0.82–1.21) and was associated with more in-hospital adverse events
CardioMEMS	Invasive	CHAMPION Trial	550 patients with moderate heart failure symptoms (NYHA class III)	Heart-failure-related hospitalizations up to 6 months post implantation	Reduction in HHF during 6 moth period (HR 0.72, 95%CI 0.60–0.85)
Ultrasound	Non-invasive	Gargani et al.	100 patients admitted for acute heart failure	B-lines present on admission and discharge	>15 B-lines present upon discharge were associated with higher risk for HHF within 6 months (HR 24.12 CI 3.15 – 184.55 P=0.002).

Abbreviations: CHAMPION, CadioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in New York Heart Association Class III Heart Failure Patients; CI, confidence interval; ESCAPE, Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness; EF, ejection fraction; HHF, hospitalization for heart failure; HR, hazard ratio; NYHA, New York Heart Association; PAC, pulmonary artery catheterization