

EDITORIAL COMMENT

Acute Heart Failure

Searching for a New Evident Truth*

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“This is not the beginning of the end but the end of the beginning...”

—Winston Churchill, 1942 (1)

The field of heart failure (HF) has benefitted recently from remarkable advances in the pharmacological treatment of reduced ejection fraction HF with a proven treatment armamentarium that now represents at least 7 highly evidence-based, guideline-directed medical interventions, 3 separate device therapies, and multiple disease management schemes (2). Never before have we had such an array of interventions available to modulate this disease’s natural history. Moreover, we recently discovered that not all reduced ejection fraction HF will necessarily remain as such. Improved function, either promoted by early intervention with neurohormonal antagonism or via novel biological pathways, currently under intense investigation, is not a rare occurrence (3). As research continues, we anticipate a time when further modulation of the natural history of reduced ejection fraction HF may be possible. In addition, as a point of special emphasis, we now understand that HF prevention is a reality; focusing on target blood pressure reduction in those at the highest risk of cardiovascular disease reduces the incidence of HF (4), which may be further enhanced with biomarker screening in American College of Cardiology/American Heart Association stage B HF (5). What has previously been described as an epidemic that devours resources and threatens the quality of life for millions may now be at the dawn of a new horizon.

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Yet these favorable trajectories have not been shared equitably across the HF spectrum; certain dimensions of HF continue to cause great consternation, specifically, acute HF (AHF). Many therapies have been explored that will either reduce volume status (diuretics and renal replacement strategies), promote vasodilation (nitrates, natriuretic peptides, ularitide, and relaxin), or augment contractility (catecholamines, levosimendan, and phosphodiesterase isoenzyme 3 inhibitors). None have been noted to change the natural history of AHF, whereas some therapies have been associated with harm (Table 1).

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In this issue of the *Journal*, Konstam et al. (6) report the results of the SECRET of CHF (Study to Evaluate Challenging Responses to Therapy in Congestive Heart Failure) trial. This well-intentioned study explored the potential benefit of the selective V2 arginine vasopressin antagonist, tolvaptan, in patients with AHF who were most likely to respond to therapy. Targeting the arginine vasopressin receptor is consistent with known neurohormonal perturbations in HF. Arginine vasopressin interfaces with a family of receptors: V1 (a,b) and V2. The V1a receptor modulates vascular tone and vasoconstriction, whereas the V2 receptor, expressed in the distal convoluted tubule and collecting ducts, modulates blood volume and maintains water homeostasis. Stimulation of the V2 receptor activates adenylyl cyclase and protein kinase A, which leads to fusion of aquaporin 2 in the apical membrane, thus inducing increased permeability to water (7). Therefore, targeting arginine vasopressin via the V2 receptor should have yielded positive results, but after >10 years of study, this has not been the case.

The investigators completed the current study with the background of the 2 previous EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure:

TABLE 1 Results of Acute Heart Failure Therapy Trials

Therapy	Trial (Ref. #)	Target	Morbidity	Mortality
Diuretics	DOSE-AHF (19)	High and low dose; Continuous infusion	Modest	NA
AVP antagonists	EVEREST (8,9) SECRET of CHF (6) TACTICS (10)	AVP receptor type II & free water excretion	No benefit on dyspnea	No mortality benefit
Ultra-filtration?	UNLOAD (20) CARRESS (21)	Volume removal	Relief of dyspnea	No benefit; worsened renal function
Seralaxin	RELAX-AHF (17)	Vasodilation Adequate BP Mild CRI	Modest dyspnea relief	No proven benefit; awaiting RELAX II
Nesiritide	ASCEND- HF (22)	Vasodilation Adequate BP	Modest symptom relief	No harm but also no benefit
Levosimendan	SURVIVE (23) REVIVE II (24)	Ca ⁺⁺ sensitization	Modest symptom relief	Possible harm

ASCEND-HF = Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure; AVP = arginine vasopressin; BP = blood pressure; CARRESS = Effectiveness of Ultrafiltration in Treating People With Acute Decompensated Heart Failure and Cardiorenal Syndrome; CRI = chronic renal insufficiency; DOSE-AHF = Determining Optimal Dose and Duration of Diuretic Treatment in People With Acute Heart Failure; EVEREST = Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan; RELAX-AHF-EU = Effect of Seralaxin Versus Standard of Care in Acute Heart Failure (AHF) Patients; REVIVE-HF = Randomized Evaluation of Intravenous Levosimendan Efficacy; SECRET of CHF = Study to Evaluate Challenging Responses to Therapy in Congestive Heart Failure; SURVIVE = The Survival of Patients With Acute Heart Failure in Need of Intravenous Inotropic Support; TACTICS-HF = Targeting Acute Congestion with Tolvaptan in Congestive Heart Failure; UNLOAD = UNload the Left Ventricle in Patients With ADVanced Heart Failure.

Outcome Study with Tolvaptan trial) trials (8,9) and the concurrently executed TACTICS-HF (Targeting Acute Congestion with Tolvaptan in Congestive Heart Failure) trial (10). The design of the SECRET of CHF trial was informed by the previous studies; a cognitive Bayesian approach was used to select patients with a pre-intervention likelihood of a favorable response. Specifically, there was reasonable expectation that the target population, which consisted of those with hyponatremia, diuretic resistance, and/or pre-existing renal insufficiency, might represent the sweet spot for drug response. Despite a diligent effort, this study, like its predecessors, returned a neutral effect on the primary outcome. These data in aggregate prompt an important discussion regarding the future of tolvaptan therapy for HF, but that is not the subject of this commentary.

More compelling is the recurring theme of neutral results from this and many previous studies in AHF. If we now change our direction, what are the current evident truths?

AHF: A DISEASE OR AN EVENT?

AHF imparts a worrisome prognosis as an inflection point in the natural history of HF. Thirty-day readmission rates remain at 20% despite the intense regulatory pressure placed on this phenomenon; 6-month event rates for readmission approach 50%; and mortality at 1 year remains stubbornly at nearly 25% (11). These metrics worsen for multiple admissions, for those with multiple comorbidities, and for those who are older (12). AHF is characterized by markers of exaggerated neurohormonal response,

increased ventricular wall stress, and frank injury (13,14). Thus, this is an appropriate query to address: is AHF an illness, per se, with a unique pathophysiology, or a pivotal milestone on a journey of worsening HF characterized by insurmountable biological perturbations that overwhelm any singular intervention?

HOSPITALIZED HF: GOALS OF CARE

The goals of AHF therapy have long been focused on the relief of dyspnea and the absence of harm. As the SECRET of CHF investigators and others have identified, measuring dyspnea, a highly variable interindividual sensation, is complicated, perhaps hopelessly so. We have used Likert scales, visual analog scales, and, in the current study, a “self-assessed 5-point absolute dyspnea score.” The yield has been unrewarding. Moreover, it is unclear if we understand what causes dyspnea and when dyspnea is best measured. Early vasodilator trials measured dyspnea relief within 4 h of therapy, others have measured it at day 1, and the current study took measurements made at hours 8 and 16 within the first day. Yet a new signal emerged on day 3. Why the dissonant observation? Play of chance or previously unrealized treatment response? It is evident that we either need to find alternative strategies to measure dyspnea or supplant the subjective assessment of dyspnea with more objective measures of congestion. We have also come up empty exploring the notion that early intervention (i.e., “door to diuretic” time) in the emergency department would change the natural history. The recent TRUE-AHF (Efficacy and

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