JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
© 2017 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER

VOL. 69, NO. 11, 2017
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2017.01.018

EDITORIAL COMMENT

Acute Heart Failure

Searching for a New Evident Truth*

Clyde W. Yancy, MD, MSc

"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.

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**).

SEE PAGE 1409

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 adenyl 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:

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

From the Northwestern University Feinberg School of Medicine, Chicago, Illinois. Dr. Yancy has reported that he has no relationships relevant to the contents of this paper to disclose.

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 Serelaxin 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

Safety of Ularitide for the Treatment of Acute Decompensated Heart Failure) trial intervened at the earliest window studied and again failed to realize a positive result (15).

CAN ANY ACUTE INTERVENTION CHANGE NATURAL HISTORY?

The greater consequence of an episode of AHF is perhaps not the interventions occurring in the first 96 h, but those that occur over the next 361 days. The contrarian notion we propose that AHF is a milepost on an inexorable journey changes our view. Although it lacks appeal, exploring the etiology of decompensation, optimizing guideline-directed, evidence-based therapies, and entering patients at increased risk in disease management programs while recognizing the need for palliative care programs in others might be the new evident truths.

WHAT SHOULD HAPPEN NOW?

The battle against AHF is far from over. At each step, we deepen our understanding of this event and recognize that hospitalization may represent a dramatic moment in the continuum of a chronic illness. We should not lose focus on prevention, and when faced with hospitalization, make wise decisions regarding medical and device therapy, and institute disease management. The potential benefit of an implantable pulmonary artery monitor as a disruptive technology to enable early detection and disease management is a promising direction worthy of further definitive study (16). Ongoing investigation in highly selected subgroups, (e.g., seralaxin in those with dyspnea, pulmonary congestion, systolic blood pressure >125 mm Hg, and estimated glomerular filtration rate >30 ml/min but <75 ml/min) may find traction (17). In addition, intriguing morbidity data early after initiation of the angiotensin II receptor blocker/neprilysin inhibitor compound versus angiotensin-converting enzyme inhibitor therapy also merit prospective study (18).

So indeed, this is not the beginning of the end, but the end of a beginning that has informed us clearly on the magnitude of AHF, its natural history, and what has not worked. A pivot may be in order. If we can only heed past lessons and treat AHF as an event along a continuum, we may add treatment of AHF to our list of HF successes.

ADDRESS FOR CORRESPONDENCE: Dr. Clyde W. Yancy, Northwestern University Feinberg School of Medicine, 676 North St. Clair, Suite 600, Chicago, Illinois 60611. E-mail: cyancy@nm.org.

REFERENCES

1. Brainyquote. Winston Churchill quotations. Available at: https://www.brainyquote.com/quotes/quotes/w/winstonchu163144.html. Accessed January 30, 2017.

2. Yancy CW, Jessup M, Bozkurt B, et al. 2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. J Am Coll Cardiol 2016;68:1476–88.

3. Wilcox JE, Yancy CW. Heart Failure-A New Phenotype Emerges. JAMA Cardiol 2016;1:507–9.

4. SPRINT Research Group, Wright JT Jr., Williamson JD, Whelton PK, et al. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. N Engl J Med 2015;373:2103–16.

5. Ledwidge M, Gallagher J, Conlon C, Tallon E, et al. Natriuretic peptide-based screening and collaborative care for heart failure: the STOP-HF randomized trial. JAMA 2013;310:66–74.

6. Konstam MA, Kiernan M, Chandler A, et al. Short-term effects of tolvaptan in patients with acute heart failure and volume overload. J Am Coll Cardiol 2017;69:1409–19.

7. Wasilewski MA, Myers VD, Recchia FA, Feldman AM, Tilley DG. Arginine vasopressin receptor signaling and functional outcomes in heart failure. Cell Signal 2016;28:224–33.

8. Gheorghiade M, Konstam MA, Burnett JC Jr., et al. Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) Investigators. Short-term clinical effects of tolvaptan, an oral vasopressin antagonist, in patients hospitalized for heart failure: the EVEREST Clinical Status Trials. JAMA 2007;297:1332–43.

9. Konstam MA, Gheorghiade M, Burnett JC Jr., et al. Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) Investigators. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. JAMA 2007;297:1319–31.

10. Felker GM, Mentz RJ, Cole RT, et al. Efficacy and safety of tolvaptan in patients hospitalized with acute heart failure. J Am Coll Cardiol 2017;69:1399–406.

11. Teerlink JR, Alburikan K, Metra M, Rodgers JE. Acute decompensated heart failure update. Curr Cardiol Rev 2015;11:53–62.

12. Setoguchi S, Stevenson LW, Schneeweiss S. Repeated hospitalizations predict mortality in the community population with heart failure. Am Heart J 2007;154:260–6.

13. Peacock WFIV, De Marco T, Fonarow GC, et al. Cardiac troponin and outcome in acute heart failure. N Engl J Med 2008;358:2117–26.

14. Pandey A, Golwala H, Sheng S, et al. Factors Associated With and Prognostic Implications of Cardiac Troponin Elevation in Decompensated Heart Failure With Preserved Ejection Fraction: Findings From the American Heart Association Get With The Guidelines-Heart Failure Program. JAMA Cardiol 2016 Dec 28 [E-pub ahead of print].

15. Packer M, Holcomb R, Abraham WT, et al., TRUE-AHF Investigators and Committees. Rationale for and design of the TRUE-AHF trial: the effects of ularitide on the short-term clinical course and long-term mortality of patients with acute heart failure. Eur J Heart Fail 2016 Nov 13 [E-pub ahead of print].

16. Abraham WT, Stevenson LW, Bourge RC, et al., CHAMPION Trial Study Group. Sustained efficacy of pulmonary artery pressure to guide adjustment of chronic heart failure therapy: complete follow-up results from the CHAMPION randomised trial. Lancet 2016;387:453–61.

17. Teerlink JR, Cotter G, Davison BA, et al., RELAX in Acute Heart Failure (RELAX-AHF) Investigators. Serelaxin, recombinant human relaxin-2, for treatment of acute heart failure (RELAX-AHF): a randomised, placebo-controlled trial. Lancet 2013;381:29–39.

18. Packer M, McMurray JJ, Desai AS, et al., PARADIGM-HF Investigators and Coordinators.

Angiotensin receptor neprilysin inhibition compared with enalapril on the risk of clinical progression in surviving patients with heart failure. Circulation 2015;131:54–61.

19. Felker GM, Lee KL, Bull DA, et al. Diuretic strategies in patients with acute decompensated heart failure. N Engl J Med 2011;364:797–805.

20. Costanzo MR, Saltzberg MT, Jessup M, et al. Ultrafiltration is associated with fewer rehospitalizations than continuous diuretic infusion in patients with decompensated heart failure: results from UNLOAD. J Card Fail 2010;16:277–84.

21. Bart BA, Goldsmith SR, Lee KL, et al. Ultrafiltration in decompensated heart failure with cardiorenal syndrome. N Engl J Med 2012;367:2296–304.

22. O'Connor CM, Starling RC, Hernandez AF, et al. Effect of nesiritide in patients with acute decompensated heart failure. N Engl J Med 2011;365:32–43.

23. Mebazaa A, Nieminen MS, Packer M, et al. Levosimendan vs dobutamine for patients with acute decompensated heart failure: the SURVIVE Randomized Trial. JAMA 2007;297:1883–91.

24. Packer M, Colucci W, Fisher L, et al. Effect of levosimendan on the short-term clinical course of patients with acutely decompensated heart failure. J Am Coll Cardiol HF 2013;1:103–11.

KEY WORDS acute heart failure, arginine vasopressin antagonists, dyspnea, hospitalization