

A Global Rank End Point for Clinical Trials in Acute Heart Failure

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Hospitalization for acute heart failure (AHF) is a major public health problem, with >1 million hospitalizations annually in the United States.¹ The development of new therapies for patients with AHF remains a significant challenge.² One aspect of clinical trial design in AHF that has been particularly vexing is the choice of appropriate end points, a topic that has recently been reviewed in detail.³ The lack of consensus on the best end points for AHF studies has led to a heterogeneous variety of end points in phase III studies, a disparity that limits the ability to make comparisons across studies.⁴

A notable feature of previous drug development programs in AHF has been the discrepancy between positive signals for efficacy in phase II studies and the lack of efficacy in more definitively powered phase III trials. This “disconnect” between phase II and phase III trials has now been observed with a variety of agents, including tezosentan,⁵ tolvaptan,⁶ and rolofylline.⁷ A notable paradox in these data is that these agents have failed to show substantive benefits in AHF, despite improving signs and symptoms of congestion, the major driver of HF decompensation.⁴ This raises the critical question as to why therapies that appear to effectively address an important pathophysiologic target (ie, congestion) have not shown demonstrable benefit on longer-term outcomes. Although there are multiple possible explanations for the failure to successfully develop new therapies, 1 potential unexplored hypothesis to explain these findings is that improvement in congestion is only beneficial if it can be accomplished while avoiding unintended consequences, such as myocardial injury or worsening of renal function. The continuing evolution of novel biomarkers that reflect these pathophysiologic processes suggests the possibility of testing this hypothesis in the context of AHF clinical trials.

Given the history of negative or neutral phase III studies in AHF, there is clearly an unmet need to define better “intermediate” end points—that is, end points that can predict the effect (or lack thereof) of new therapies earlier in the development process. Ideally, such an end point would capture both early clinical events and important pathophysiologic phenomena that might meaningfully reflect “downstream” events in the context of a larger trial. Such an end point should be quantitative, be reproducible, and have

sufficient power to allow for reasonable sample size in phase II studies. To date, several factors have limited the development of this type of phase II end point in AHF. First, the pathophysiology of AHF remains poorly understood, with a variety of incompletely characterized mechanisms contributing in a given patient.⁸ Second, our ability to accurately characterize pathophysiologic processes in vivo in patients has been limited, and many drug development programs in AHF have focused primarily on hemodynamic factors. Finally, statistical methods for combining multiple measures into a single end point are not well developed or widely used. With the continued development of novel biomarkers that reflect specific aspects of HF pathophysiology, we are now able to accurately and reproducibly assess physiologic markers of congestion, myocardial injury, and renal function, all processes that appear to play a central role in the pathogenesis of AHF. In theory, these developments suggest the possibility of designing specific intermediate end points around these measures for use in phase II clinical trials. Herein, we propose a novel biomarker-based end point that would reflect these phenomena and should be tested as an end point in clinical trials in AHF.

Biomarkers of Congestion

The natriuretic peptides, B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide, are now well established in the diagnosis and management of patients with HF. Elevated levels of these markers generally reflect elevated filling pressures in patients with acute decompensated HF.⁹ A recently released consensus statement stated that a patient admitted with acute breathlessness due to HF and an elevated natriuretic peptide level (generally >600 pg/mL for BNP or 6000 pg/mL for N-terminal pro-B-type natriuretic peptide) usually has a high filling pressure secondary to volume overload, and a treatment-induced decrease in pulmonary capillary wedge pressure will commonly lead to a rapid drop in natriuretic peptide levels.¹⁰ Observational data support the relation between improvement in BNP values during hospitalization and subsequent outcomes.^{11–14} Despite the theoretical appeal of this concept, the track record for markers of congestion alone as “intermediate end points” in AHF is mixed. In the REVIVE trials of levosimendan,

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treatment with levosimendan resulted in a significant drop in BNP levels compared with placebo over 5 days after randomization. This short-term drop in BNP mirrored clinical improvement in the trichotomous primary composite end point to day 5.¹⁵ However, levosimendan was associated with a greater incidence of symptomatic hypotension and trends toward worsened mortality, adverse effects that were not captured by measurement of changes in BNP. Similarly, in the SURVIVE study, a short-term improvement in BNP levels with levosimendan was not reflected in long-term survival benefits.¹⁶ One potential conclusion from these data is that changes in natriuretic peptide levels are not a valid surrogate for outcomes in AHF.¹⁷ An alternative hypothesis would be that decongestion is an important aspect of successful AHF therapy but only when it is achieved in a way that does not promote myocardial injury or worsening of renal function (either directly or through causing hypotension).

Biomarkers of Myocardial Injury and Renal Function

The assessment of myocardial injury, as measured by circulating cardiac troponin, is central to the diagnosis and management of acute coronary syndromes. Multiple studies have now identified the presence of elevated troponins in HF populations, an observation that appears to be independent of the presence or absence of epicardial coronary artery disease.^{13,18,19} Newer, “ultrasensitive” troponin assays will increase our ability to quantify the time course and extent of myocardial injury in patients with HF.¹⁹ Many questions about the mechanisms and timing of myocardial injury in AHF remain unanswered, and a variety of mechanisms, including apoptosis, inflammatory or oxidative stress, and subendocardial ischemia, have been proposed.^{20–23} Regardless of the underlying mechanism(s), myocardial injury as reflected by elevated troponins may play a role in the progression of HF, and thus, avoiding myocardial injury may be an important goal of AHF therapy. Preliminary data from small studies suggest that the development of a new troponin elevation is a strong predictor of adverse events and HF progression in both acute²⁴ and chronic²⁵ HF. Although many uncertainties remain about how best to respond to troponin elevations in HF patients, ongoing work may help clarify a framework by which troponin measurement can be incorporated as a measure of safety in drug development.²⁶

The interaction between the heart and kidney in AHF is complex and has recently been reviewed in detail.²⁷ Worsening renal function due to intrinsic renal disease and/or hemodynamic factors may be a trigger for decompensation, or alternatively, it may develop during hospitalization in response to therapy. Regardless, worsening renal function during therapy for AHF has been clearly shown to have a poor prognosis, and the “cardiorenal syndrome” remains a major management challenge.^{28,29} A variety of renal markers, such as cystatin C and neutrophil gelatinase-associated lipocalin, are emerging that may allow better discrimination of changes in renal function due to hemodynamic perturbations versus frank renal injury.^{30,31} Although this field is rapidly evolving, these markers may allow better characterization of the impact of new AHF therapies on the kidney, potentially allowing

for more accurate targeting of renal perseveration as a goal of therapy. Taken as a whole, these data support the hypothesis that successful decongestion without myocardial injury or worsening renal function is an important intermediate goal of therapy that could be quantified by biomarker-based assessment.

Global Rank Method: Combining Biomarkers and Clinical End Points

Incorporating biomarkers into end points in clinical trials requires a framework for combining both clinical events and continuous data into a unified metric. This is in contrast to the way most end points in phase III clinical trials are framed, most typically as “time-to-event” analyses, for example, time to cardiovascular death or HF hospitalization. Given that phase II studies are, by definition, underpowered to conclusively demonstrate significant differences on clinical end points, alternative approaches are necessary. One such approach is to examine the results across multiple clinical end points while recognizing that none are likely to reach nominal statistical significance and basing decisions on the totality of observed trends across multiple clinical domains. This approach was recently used in a phase II study of relaxin, a novel vasodilator for AHF.³² An alternative approach is to use composite end points, which can incorporate both clinical events (such as rehospitalization) and other continuous measures in an effort to more completely characterize the biological effect of an intervention in a smaller study. One such framework for considering composite end points is the global rank score. Although initially proposed by O’Brien³³ in 1984 as a means for dealing with multiple end points, this technique has not been widely adopted in clinical trials. In this method, all patients participating in a clinical trial (regardless of treatment assignment) are ranked on the basis of a prespecified hierarchical ranking of outcomes. Such components could include both “events” (such as death or hospitalization) and quantitative assessments (such as biomarker measurements). The global rank score has recently been proposed for use in trials of mechanical cardiac support devices.³⁴

Because it can combine both clinical events and continuous variables into a single comprehensive measure, the global rank is well suited for combining biomarker data with other clinical measurements. In the Figure, we propose a global rank end point for AHF studies that would reflect the following clinical and pathophysiologic goals of treatment: (1) avoid early mortality; (2) successfully treat acute symptoms (primarily dyspnea); (3) avoid myocardial injury; (4) avoid worsening renal function; and (5) successfully implement “biochemical” decongestion.

The rationale for the proposed hierarchy is based on the fact that avoiding early mortality and providing adequate relief of symptoms seem to be necessary components of any successful treatment strategy for AHF. Available data suggest that even with currently available therapies, in-hospital mortality is low (2.9% in the placebo group of EVEREST)³⁵ and that dyspnea improves substantially in most patients.^{5,36} Given that postdischarge outcomes remain poor after AHF hospitalization, it is clear that these goals of therapy are necessary but not sufficient to completely define “successful” AHF treatment. The proposed global rank end point is based

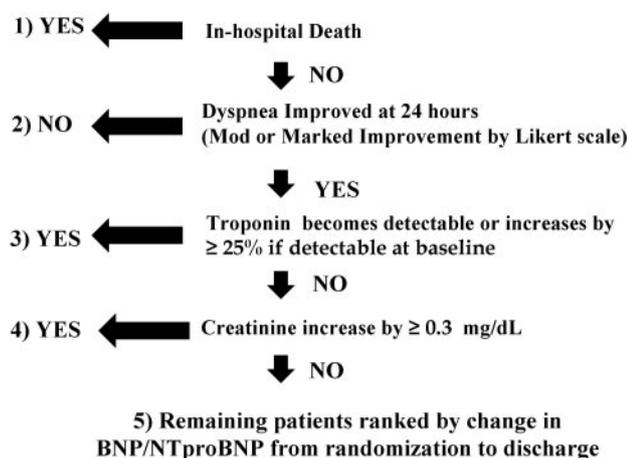


Figure. Proposed global rank end point for phase II AHF studies. All randomized patients enrolled in the study are ranked into 5 groups according to the hierarchy shown. Within groups, ties are broken by time to event (for death) or degree of quantitative change (for continuous end points). The primary comparison of interest is the comparison of ranks between patients randomized to the intervention vs the control group.

on the hypothesis that therapies most likely to be successful in larger studies will be those that achieve the maximal degree of decongestion while minimizing the occurrence of myocardial injury or worsening renal function.

In the Table, we provide a hypothetical example on how this end point might function in a small (n=200) phase II study of a novel AHF agent. This hypothetical agent shows trends toward greater improvements in dyspnea (P=0.12) and greater decreases in N-terminal pro-B-type natriuretic peptide (P=0.09), with neutral effects on other components of

Table. Application of Global Rank End Point in a Hypothetical Phase II AHF Study

	Active (n=101)	Placebo (n=99)	P Value
In-hospital mortality, %	4	4	0.98
Without at least moderate dyspnea improvement at 24 h			0.12
In overall trial, %	44	54	
Of unranked patients remaining (No.)	40	50	
Troponin becomes detectable or increases by 25% during index hospitalization			0.58
In overall trial, %	7	5	
Of unranked patients remaining (No.)	1	2	
Creatinine increase by ≥0.3 mg/dL			0.42
In overall trial, %	7	10	
Of unranked patients remaining (No.)	5	3	
Average decrease in N-terminal pro-BNP, mean±SD, pg/mL	1600±2500	1000±2500	0.09
Sum of global rank score (higher is better)	108.6	92.2	0.044

the end point. Although none of these findings individually reach statistical significance given the small sample size, the global rank suggests that the active agent is preferable to placebo (P=0.04), a result that would support studying the agent in larger trials powered to detect differences in clinical end points.

At present, the proposed end point is hypothetical and would clearly need to be validated in multiple datasets before it could be prospectively incorporated into clinical trials. If validated, such an end point has several theoretical advantages for drug development in AHF. It could be assessed at the end of index hospitalization (or alternatively, at a given time interval after randomization, such as 5 days) in all patients. Because the global rank method “counts” all patients enrolled in the trial, it is relatively insensitive to event rates in terms of statistical power. Because it incorporates changes in pathophysiologic axes known to be important mechanisms of benefit and of harm in AHF, we suggest that it may provide important insights into dose selection as well as efficacy and safety earlier in the development process than do more traditional phase II end points focused on hemodynamics. In addition, the specific components of the global rank end point could be flexible, adjusted for treatments with different mechanisms or those applied at different times in the disease course. Although end points evaluating the effect of therapies on major morbidity and mortality will remain the ultimate test of new therapies for regulatory approval, continued improvement in the methodology of AHF clinical trials across all phases of the development process may help in developing new therapies for this major public health problem.

Disclosures

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References

1. Fang J, Mensah GA, Croft JB, Keenan NL. Heart failure-related hospitalization in the U.S., 1979 to 2004. *J Am Coll Cardiol.* 2008;52:428–434.
2. Felker GM, Pang PS, Adams KF, Cleland JGF, Cotter G, Dickstein K, Filippatos GS, Fonarow GC, Greenberg BH, Hernandez AF, Khan S, Komajda M, Konstam MA, Liu PP, Maggioni AP, Massie BM, McMurray JJ, Mehra M, Metra M, O’Connell J, O’Connor CM, Pina IL, Ponikowski P, Sabbah HN, Teerlink JR, Udelson JE, Yancy CW, Zannad F, Gheorghide M, on behalf of the International AHFS Working Group. Clinical trials of pharmacological therapies in acute heart failure syndromes: lessons learned and directions forward. *Circ Heart Fail.* 2010;3:314–325.
3. Allen LA, Hernandez AF, O’Connor CM, Felker GM. End points for clinical trials in acute heart failure syndromes. *J Am Coll Cardiol.* 2009;53:2248–2258.
4. Gheorghide M, Pang PS. Acute heart failure syndromes. *J Am Coll Cardiol.* 2009;53:557–573.
5. McMurray JJ, Teerlink JR, Cotter G, Bourge RC, Cleland JG, Jondeau G, Krum H, Metra M, O’Connor CM, Parker JD, Torre-Amione G, van Veldhuisen DJ, Lewsey J, Frey A, Rainisio M, Kobrin I. Effects of tezosentan on symptoms and clinical outcomes in patients with acute heart failure: the VERITAS randomized controlled trials. *J Am Med Assoc.* 2007;298:2009–2019.
6. Konstam MA, Gheorghide M, Burnett JC Jr, Grinfeld L, Maggioni AP, Swedberg K, Udelson JE, Zannad F, Cook T, Ouyang J, Zimmer C, Orlandi C, for the Efficacy of Vasopressin Antagonism in Heart Failure

- Outcome Study With Tolvaptan I. Effects of Oral Tolvaptan in Patients Hospitalized for Worsening Heart Failure: the EVEREST Outcome Trial. *J Am Med Assoc.* 2007;297:1319–1331.
7. Metra M. Effects of rolofylline in patients with acute heart failure syndromes and renal impairment: results of the PROTECT Study: late-breaking clinical trials. Barcelona, Spain: European Society of Cardiology; 2009.
 8. Cotter G, Felker GM, Adams KF, Milo-Cotter O, O'Connor CM. The pathophysiology of acute heart failure—is it all about fluid accumulation? *Am Heart J.* 2008;155:9–18.
 9. Kazanegra R, Cheng V, Garcia A, Krishnaswamy P, Gardetto N, Clopton P, Maisel A. A rapid test for B-type natriuretic peptide correlates with falling wedge pressures in patients treated for decompensated heart failure: a pilot study. *J Card Fail.* 2001;7:21–29.
 10. Maisel A, Mueller C, Adams K Jr, Anker SD, Aspromonte N, Cleland JG, Cohen-Solal A, Dahlstrom U, DeMaria A, Di Somma S, Filippatos GS, Fonarow GC, Jourdain P, Komajda M, Liu PP, McDonagh T, McDonald K, Mebazaa A, Nieminen MS, Peacock WF, Tubaro M, Valle R, Vandeheyden M, Yancy CW, Zannad F, Braunwald E. State of the art: using natriuretic peptide levels in clinical practice. *Eur J Heart Fail.* 2008;10:824–839.
 11. Bettencourt P, Azevedo A, Pimenta J, Frieos F, Ferreira S, Ferreira A. N-terminal-pro-brain natriuretic peptide predicts outcome after hospital discharge in heart failure patients. *Circulation.* 2004;110:2168–2174.
 12. Logeart D, Thabut G, Jourdain P, Chavelas C, Beyne P, Beauvais F, Bouvier E, Solal AC. Pre-discharge B-type natriuretic peptide assay for identifying patients at high risk of re-admission after decompensated heart failure. *J Am Coll Cardiol.* 2004;43:635–641.
 13. Metra M, Nodari S, Parrinello G, Specchia C, Brentana L, Rocca P, Fracassi F, Bordonali T, Milani P, Danesi R, Verzura G, Chiari E, Dei CL. The role of plasma biomarkers in acute heart failure: serial changes and independent prognostic value of NT-proBNP and cardiac troponin-T. *Eur J Heart Fail.* 2007;9:776–786.
 14. Dunlay SM, Gheorghiade M, Reid KJ, Allen LA, Chan PS, Hauptman PJ, Zannad F, Maggioni AP, Swedberg K, Konstam MA, Spertus JA. Critical elements of clinical follow-up after hospital discharge for heart failure: insights from the EVEREST trial. *Eur J Heart Fail.* 2010;12:367–374.
 15. Cleland JG, Freemantle N, Coletta AP, Clark AL. Clinical trials update from the American Heart Association: REPAIR-AMI, ASTAMI, JELIS, MEGA, REVIVE-II, SURVIVE, and PROACTIVE. *Eur J Heart Fail.* 2006;8:105–110.
 16. Cohen-Solal A, Logeart D, Huang B, Cai D, Nieminen MS, Mebazaa A. Lowered B-type natriuretic peptide in response to levosimendan or dobutamine treatment is associated with improved survival in patients with severe acutely decompensated heart failure. *J Am Coll Cardiol.* 2009;53:2343–2348.
 17. Gheorghiade M, Pang PS. Are BNP changes during hospitalization for heart failure a reliable surrogate for predicting the effects of therapies on post-discharge mortality? *J Am Coll Cardiol.* 2009;53:2349–2352.
 18. Peacock WF, De Marco T, Fonarow GC, Diercks D, Wynne J, Apple FS, Wu AHB. Cardiac troponin and outcome in acute heart failure. *N Engl J Med.* 2008;358:2117–2126.
 19. Latini R, Masson S, Anand IS, Missov E, Carlson M, Vago T, Angelici L, Barlera S, Parrinello G, Maggioni AP, Tognoni G, Cohn JN. Prognostic value of very low plasma concentrations of troponin T in patients with stable chronic heart failure. *Circulation.* 2007;116:1242–1249.
 20. Logeart D, Beyne P, Cusson C, Tokmakova M, Leban M, Guiti C, Bourgoin P, Solal AC. Evidence of cardiac myolysis in severe nonischemic heart failure and the potential role of increased wall strain. *Am Heart J.* 2001;141:247–253.
 21. Feng J, Schaus BJ, Fallavollita JA, Lee TC, Canty JM Jr. Preload induces troponin I degradation independently of myocardial ischemia. *Circulation.* 2001;103:2035–2037.
 22. Olivetti G, Abbi R, Quaini F, Kajstura J, Cheng W, Nitahara JA, Quaini E, Di Loreto C, Beltrami CA, Krajewski S, Reed JC, Anversa P. Apoptosis in the failing human heart. *N Engl J Med.* 1997;336:1131–1141.
 23. Missov E, Calzolari C, Pau B. Circulating cardiac troponin I in severe congestive heart failure. *Circulation.* 1997;96:2953–2958.
 24. Del Carlo CH, Pereira-Barretto AC, Cassaro-Strunz C, Latorre MR, Ramires JA. Serial measure of cardiac troponin T levels for prediction of clinical events in decompensated heart failure. *J Card Fail.* 2004;10:43–48.
 25. Miller WL, Hartman KA, Burritt MF, Grill DE, Rodeheffer RJ, Burnett JC Jr, Jaffe AS. Serial biomarker measurements in ambulatory patients with chronic heart failure: the importance of change over time. *Circulation.* 2007;116:249–257.
 26. Berridge BR, Pettit S, Walker DB, Jaffe AS, Schultze AE, Herman E, Reagan WJ, Lipshultz SE, Apple FS, York MJ. A translational approach to detecting drug-induced cardiac injury with cardiac troponins: consensus and recommendations from the Cardiac Troponins Biomarker Working Group of the Health and Environmental Sciences Institute. *Am Heart J.* 2009;158:21–29.
 27. Ronco C, Haapio M, House AA, Anavekar N, Bellomo R. Cardiorenal syndrome. *J Am Coll Cardiol.* 2008;52:1527–1539.
 28. Forman DE, Butler J, Wang Y, Abraham WT, O'Connor CM, Gottlieb SS, Loh E, Massie BM, Rich MW, Stevenson LW. Incidence, predictors at admission, and impact of worsening renal function among patients hospitalized with heart failure. *J Am Coll Cardiol.* 2004;43:61–67.
 29. Butler J, Forman DE, Abraham WT, Gottlieb SS, Loh E, Massie BM, O'Connor CM, Rich MW, Stevenson LW, Wang Y. Relationship between heart failure treatment and development of worsening renal function among hospitalized patients. *Am Heart J.* 2004;147:331–338.
 30. Lassus J, Harjola V-P, Sund R, Siirila-Waris K, Melin J, Peuhkurinen K, Pulkki K, Nieminen MS, for the FINN-AKVA Study group. Prognostic value of cystatin C in acute heart failure in relation to other markers of renal function and NT-proBNP. *Eur Heart J.* 2007;28:1841–1847.
 31. Damman K, van Veldhuisen DJ, Navis G, Voors AA, Hillege HL. Urinary neutrophil gelatinase associated lipocalin (NGAL), a marker of tubular damage, is increased in patients with chronic heart failure. *Eur J Heart Fail.* 2008;10:997–1000.
 32. Teerlink JR, Metra M, Felker GM, Ponikowski P, Voors AA, Weatherley BD, Marmor A, Katz A, Grzybowski J, Unemori E, Teichman SL, Cotter G. Relaxin for the treatment of patients with acute heart failure (PRELAX-AHF): a multicentre, randomised, placebo-controlled, parallel-group, dose-finding phase IIb study. *Lancet.* 2009;373:1429–1439.
 33. O'Brien PC. Procedures for comparing samples with multiple endpoints. *Biometrics.* 1984;40:1079–1087.
 34. Felker GM, Anstrom KJ, Rogers JG. A global ranking approach to end points in trials of mechanical circulatory support devices. *J Card Fail.* 2008;14:368–372.
 35. Gheorghiade M, Konstam MA, Burnett JC Jr, Grinfeld L, Maggioni AP, Swedberg K, Udelson JE, Zannad F, Cook T, Ouyang J, Zimmer C, Orlandi C, for the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan I. Short-term clinical effects of tolvaptan, an oral vasopressin antagonist, in patients hospitalized for heart failure: the EVEREST clinical status trials. *J Am Med Assoc.* 2007;297:1332–1343.
 36. Pang PS, Konstam MA, Krasa HB, Swedberg K, Zannad F, Blair JE, Zimmer C, Teerlink JR, Maggioni AP, Burnett JC Jr, Grinfeld L, Ouyang J, Udelson JE, Gheorghiade M. Effects of tolvaptan on dyspnoea relief from the EVEREST trials. *Eur Heart J.* 2009;30:2233–2240.

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