Development of Therapeutics for Heart Failure

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 rololysline.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,
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 the presence of mechanical cardiac support devices.34

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 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.

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Phase II AHF Study
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In this 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 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 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.

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**References**


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