Clinical Trials of Pharmacological Therapies in Acute Heart Failure Syndromes
Lessons Learned and Directions Forward

A
cute heart failure syndromes (AHFS) are characterized by a gradual or rapid onset of new or worsening signs and/or symptoms of heart failure (HF) requiring urgent therapy, usually resulting in hospitalization. The societal burden of AHFS is substantial, with >1 million hospitalizations annually in the United States and similar relative numbers in Europe. Ongoing epidemiological trends, such as the aging population, improved survival after myocardial infarction, and a decrease in sudden death due to defibrillator therapy, suggest that the prevalence of chronic HF resulting in hospitalization will continue to increase during the coming decades. The prognosis after hospitalization for AHFS remains bleak, with rates of death or recurrent hospitalization at 6 months approaching 50%, outcomes that have changed little in recent years despite improvements in the management of chronic HF. Hidden within these oft-cited statistics is a notable paradox—signs and symptoms of AHFS (dyspnea, edema, etc) are successfully treated in the majority of patients, but postdischarge outcomes remain dismal, and attempts to develop new short-term therapies for AHFS have largely been unsuccessful. Since our initial publication in 2005, large, international phase III development programs—levosimendan, tolvaptan, rololofylline—have failed to convincingly demonstrate the safety and efficacy of these agents in AHFS. Even for drugs approved for AHFS treatment (milrinone and nesiritide in the United States and levosimendan in parts of Europe), there have been persistent concerns about safety. Broadly speaking, the pharmacological armamentarium for AHFS—loop diuretics, vasodilators, and inotropes—is largely unchanged from the 1970s.

Although substantial efforts in the last decade to develop improved AHFS therapies have yielded disappointing results, we believe that as a scientific community, we are now better equipped to conduct future studies. Hospitalization for AHFS is now recognized as a critical clinical problem in both the US and European guidelines. This consensus document arose...
from the meeting organized by the International Working Group on Acute Heart Failure Syndromes, which occurred at the US Food and Drug Administration (FDA) in December 2008, which was attended by representatives from academia, industry, and regulatory authorities. Participants did not receive any compensation or honoraria, and there was no industry sponsorship. In this review, we highlight lessons learned, discuss areas in need of further development, and propose concrete ways forward to successfully develop new therapies for this major public health problem.

**Why Have We Failed to Develop New Therapies for AHFS?**

Why has there been so little progress in the development of new treatments for these disorders? Although there are many possible explanations, a general consensus around several root causes has emerged.

**Patient Heterogeneity**

The plural terminology “acute heart failure syndromes” is evidence that acute HF is not a single disease but rather a group of related disorders characterized by similar presenting signs and symptoms. Multiple definitions and varying terminology for these syndromes further highlight this heterogeneity, and there continues to be debate as to whether acute HF represents a distinct entity or is simply part of the natural progression of chronic HF. AHFS encompasses patients with diverse presentations and pathophysiology, ranging from patients presenting suddenly with severe hypertension and normal or near-normal ejection fraction (EF) to those with advanced systolic dysfunction and low output states. In between these less-common extremes of presentation lie the majority of patients who present with AHFS due to volume overload and who are equally likely to present with a preserved EF or with a low EF. It is unlikely that the same therapy would be efficacious in such varied patient populations; thus, it is not surprising that “one size fits all” approaches for developing new therapies have not met with success. Only recently has there been a more concerted effort to develop new agents that are targeted at specific subgroups. In part, this is because AHFSs have lacked a universally accepted, clinically useful classification framework for clinical subtypes under the umbrella of AHFS. By analogy, some of the progress in the development of new acute coronary syndrome therapies may be attributable to targeting selected subpopulations (eg, ST segment–elevation myocardial infarction versus non–ST segment–elevation myocardial infarction versus unstable angina), and indeed, therapies that are efficacious for 1 group (such as thrombolytic therapy for ST segment–elevation myocardial infarction) are not useful for other (such as unstable angina). Although consensus proposals for a classification framework for AHFS have been developed, they have yet to be universally accepted or integrated into the design of clinical trials. A simplified classification system focused on clinical trial design is proposed in Table 1. Whether this classification or other classification systems will identify patients who have different therapeutic responses to the same AHFS therapy remains uncertain.
Poor Understanding of Pathophysiology

A wide variety of mechanisms and triggers have been implicated in the pathogenesis of AHFS,22 but the relative contribution of each is uncertain, and potentially important mechanisms may remain unidentified. Although increased ventricular filling pressures (and, less frequently, low cardiac output) are clearly central to the development of AHFS, these hemodynamic concepts alone fail to capture the complex set of interactions between the heart, kidney, peripheral vasculature, and a variety of circulating mediators that occur in AHFS. With AHFS presentation, injury to the myocardium or other end organs (such as the kidney) may occur, potentially accelerating the trajectory of disease progression.23,24 Although a detailed review of AHFS pathophysiology is beyond the scope of this review, greater investment in fundamental research aimed at improving our understanding of underlying mechanisms is required to improve the precision of classification, the accuracy of therapeutic targeting, the identification of organ injury, and the probability of success in developing new treatments.

Background Therapy and Natural History

Randomized controlled trials in AHFS have traditionally compared a new intervention with placebo, in addition to “standard” therapy for AHFS. However, standard therapy has rarely been explicitly defined and has differed among studies, although efforts for greater standardization of therapy in ongoing trials are under way.25 Although intravenous loop diuretics are the cornerstone of background therapy for AHFS, the dose and route of administration vary markedly among providers and institutions, and questions remain about the safety and efficacy of these drugs in AHFS.26,27 This variability is even more significant for other therapies, such as inotropes, vasodilators, and noninvasive ventilation. Finally, there is large variability in the use and dosing of oral neurohormonal antagonists (such as angiotensin-converting enzyme inhibitors, β-blockers, and aldosterone antagonists) in patients hospitalized with AHFS, which may have substantial effect on clinical outcomes.28,29 Taken together, this lack of standardization may obfuscate the efficacy and safety of new drugs. Importantly, given the clinical urgency of AHFS, background therapy is often continuously adjusted during the course of hospitalization. This complicates the evaluation of new therapies because the placebo group may receive more treatments over time, and diminish the observed treatment effect.

A related issue is whether new treatments must be developed as “add-ons” to background therapy or alternatively whether new treatments should be compared directly with existing therapies (ie, active control trials). Active control trials would potentially allow a more direct comparison of new therapies with existing ones (eg, comparing a new drug for volume management directly against to loop diuretics). Given the lack of standardization of “standard” therapy for AHFS, active controlled trials would be feasible and could potentially allow for the more rapid advancement of AHFS therapy. In addition to comparing single agents, this paradigm could be extended to include “strategy” trials, directly comparing 1 therapeutic approach in a given patient population with others. One notable example of this approach was the UNLOAD [Ultrafiltration versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure] study, which compared mechanical ultrafiltration directly with loop diuretics in patients hospitalized with AHFS and volume overload.30 This study showed greater weight loss in the ultrafiltration group but no difference in dyspnea improvement between the study groups. Although not the primary end point of the study, there were significant rehospitalizations for HF in the ultrafiltration group.

Finally, despite greater understanding of AHFS from international registries, we still lack detailed data on the “natural history” of these disorders. Comprehensive data on potential precipitants of AHFS in large cohorts have only recently been published.9 Preliminary studies demonstrate an association between the passage of time and symptom resolution; however, much more data are needed. Analysis of the placebo group from large trials such as EVEREST [Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan] may help clarify the natural history of AHFS and better define the goals of therapy and areas for further research.

Study Design Issues: Inclusion Criteria

The lack of objective criteria for the diagnosis of AHFS has been a barrier to precise identification of the most relevant study populations. AHFS is a clinical diagnosis based on hospitalization for symptoms (usually dyspnea) and signs (edema, pulmonary congestion by examination or chest radiograph, increased jugular venous pressure). In general, these measures are subjective, qualitative, and highly variable among patients, providers, and institutions. In addition, these measures are not “static” but “dynamic” and vary over time and with treatment. Finally, the decision to hospitalize a patient may be influenced by a variety of social and cultural factors unrelated to disease severity. The lack of agreed and objective criteria for enrollment in AHFS clinical trials has made the identification of a homogeneous clinical trial population who clearly have the disease of interest a challenge. Inclusion of patients without AHFS in clinical trials will dilute any potential treatment effect of a new therapy, just as inclusion of patients with noncardiac chest pain in acute coronary syndrome studies would decrease the observed treatment effect in acute coronary syndrome. Similarly, enrolling ST segment—elevation myocardial infarction patients 12 hours after an event versus within 90 minutes would also significantly influence results. Thus, there is a substantial need to use more objective, quantitative criteria for the diagnosis of AHFS and for enrollment in clinical trials. As discussed in further detail in the following section, carefully defining the type or “stage” of the trial, as well as the emergence of natriuretic peptide (brain natriuretic peptide, or N-terminal pro—B-type natriuretic peptide) measurements as an inclusion criterion, has led to greater homogeneity of study populations (ie, fewer patients without AHFS) and seems to represent a major methodological improvement in the design and conduct of randomized controlled trials in AHFS.
Study Design Issues: Timing and Duration of Intervention

Timing is fundamental to the treatment of acute myocardial infarction—acute reperfusion therapies that are highly efficacious when given within a few hours of presentation show diminished benefit when used later. To date, there has been surprisingly little investigation of the effect of the timing of intervention on treatment benefits in AHFS, and whether a “therapeutic window” exists for AHFS intervention is unknown. Observational data from ADHERE [Acute Decompensated Heart Failure National Registry] suggest that earlier natriuretic peptide measurement and earlier implementation of therapy may lead to improved AHFS outcomes, but little is known about the optimal timing for applying specific therapies. A previously suggested scheme for dividing the timing of AHFS interventions into stages may provide a useful framework for considering the timing of AHFS interventions and is discussed in detail later in this article.1

In addition to timing, the optimal duration of therapy is not well understood. To date, most trials have focused on short-term (hours to days) intravenous therapy, and controversy persists as to whether short-term therapies alter the underlying pathophysiology to a sufficient degree to reap long-term benefits. Although the possibility that AHF therapies could be continued after hospital discharge has not been carefully investigated, the high short-term rehospitalization rate associated with HF suggests that continuing an effective treatment into this postdischarge “vulnerable phase” could be beneficial and should be explored in future studies. This phase might also be used to reintroduce therapy to those who display high-risk features.

Study Design: End Points

One major impediment to progress in AHFS has been the lack of consensus on appropriate end points for phase III studies in AHFS.34 A review of the large phase III randomized controlled trials conducted in AHFS during the past decade clearly indicates this lack of consensus because no 2 studies have used the same primary end point (Table 2). Some of the uncertainty about clinical end points relates to a fundamental (and as yet unanswered) question about AHFS therapies—can an acute intervention given for a brief period (hours to days) at the time of hospitalization be anticipated to improve postdischarge outcomes at 30, 60, or 180 days? Clearly, there are examples of this phenomenon in other areas of cardiology, such as acute reperfusion therapy for myocardial infarction. For a short-term therapy to improve long-term outcomes, it would need to (1) fundamentally change the pathophysiology of the acute disease process in a way that fundamentally alters the substrate, resulting in improved performance (“a better heart”) and/or leads to greater preservation of downstream organ function (either cardiac function or other end organs); (2) markedly affect in-hospital mortality; (3) enable resolution of congestion without the potentially harmful effects (such as neurohormonal activation from diuretics) of current therapies; and/or (4) facilitate the addition or intensification of lifesaving long-term therapies. The fact that no short-term therapy for AHFS has done so to date has resulted in a shift of focus (for efficacy but not for safety) toward short-term symptom relief and/or shorter-term outcomes (5 to 7 days). Controversy continues as to whether such a shift represents an unacceptable “lowering of the bar” or simply recognition of the limitations of current therapies and a rational focus on more achievable goals. Given the lack of robust evidence for most AHFS therapies currently in use, a substantial improvement in short-term symptoms combined with demonstrated safety would appear to mark an advance over the current standard of care.

Regulatory Issues

The lack of consensus from the scientific community in defining a clinically meaningful benefit has led to a lack of regulatory consensus. Differences in regulatory requirements between the FDA in the United States and European Medicines Agency in Europe have led to substantial variability in the design and conduct of large international clinical trials, including the use of coprimary end points for some trials to satisfy the requirements of both agencies.35 This has resulted in agents such as nesiritide being approved in the United States but not in Europe, whereas other drugs, such as levosimendan, are approved in some parts of Europe but not in the United States. This lack of harmony between regulatory agencies can be seen as both contributing to a lack of progress (commercial sponsors are reluctant to invest resources in areas where the requirements for approval are not clear) and reflecting a more general lack of consensus about the most appropriate metrics to measure efficacy and safety in AHFS.

Directions Forward: Roadmap for Phase III Studies in AHFS

The historical lack of success in developing safe and effective new therapies and the barriers described earlier have led to a diminished enthusiasm for pursuing novel compounds and clinical trials in this area. However, in light of the substantial and growing effect of AHFS on public health, it is imperative to continue to develop potential new treatments for AHFS. In the following sections, we summarize concepts that we believe will help provide a framework for moving forward with the development of new therapies for AHFS.

Defining and Targeting Appropriate Study Populations

As noted earlier, a major limitation of previous clinical trials in AHFS has been the heterogeneity of the enrolled patient population. Increasingly, several trends seem to be improving the ability to identify and target specific patient populations.

Timing: Applying the Right Therapy at the Right Time to the Right Patient Population

A staging system for considering the distinct phases of the AHFS presentation has been proposed.1 The right therapy given at the wrong time may lead to an incorrect conclusion regarding efficacy. Defining the target, based on a comprehensive mechanistic understanding of the drug, will allow for proper staging of the trial.

Stage A trials target patients during their initial presentation.36 For stage A, the main goals are hemodynamic stabilization; rapid, meaningful, and sustained improvement in
breathlessness; preservation of hemodynamic reserve; and prevention of downstream harm (ie, organ protection/organ preservation). Studies targeting patients in stage A should enroll patients early, although patients are still symptomatic (eg, emergency department). Repeated assessments of symptoms (eg, dyspnea) should occur at multiple time points during the first 24 hours and then daily to assess the speed and sustainability of improvement.

Stage B trials include therapies for patients who remain symptomatic or deteriorate despite initial therapy during hospitalization (therapies started 24 hours or more after initial presentation). These patients can be recognized early by the
presence of adverse prognostic markers (low blood pressure, increased natriuretic peptide levels, increased troponin, and/or renal dysfunction), failure to respond to diuretic therapy, or deterioration (hypotension or worsening renal function) with initial treatment. Such interventions could be designed to improve cardiac function directly, manage congestion in a safer and/or more effective way, or improve or preserve renal function.

Stage C trials include interventions targeted at improving long-term outcomes through improved implementation of evidence-based therapies or use of long-term pharmacological or device therapy. To be successful, interventions for stage C trials would either have to be continued after discharge or have a sustained pharmacological or biological effect.

Stage D trials target patients during the “vulnerable” phase or early postdischarge phase. For those patients who are identified during close follow-up to be at higher risk, intervention at this time might mitigate the natural tendency for patients to worsen to the point of acute decompensation.

Clearly, various interventions may be used at different times in the AHFS course with differing therapeutic aims. In addition, although outlined in distinct stages, there is definite overlap. Creation of a “matrix,” with clinical subgroups and various interventions, may serve as a useful framework for more focused clinical trials.

**Biomarkers and Patient Selection**

The use of more objective inclusion criteria, such as brain natriuretic peptide or N-terminal pro–B-type natriuretic peptide, in AHFS clinical trials has led to a study population with a higher event rate, increasing the statistical power of clinical trials. Recent phase II clinical trials that have required increases in natriuretic peptide levels for inclusion have suggested a lesser effect of standard therapy on the resolution of signs and symptoms. Although it has been suggested that further improvements in signs and symptoms are difficult targets given their rapid improvement with standard therapy, these more recent observations suggest that a substantial degree of dyspnea persists in higher-risk patients who could serve as a potential target for therapy. In addition to natriuretic peptides, analyses of both clinical trials and observational data have consistently identified a number of other important markers of risk in AHFS, including decreased renal function, hyponatremia, lower systolic blood pressure, and troponin release.

**Targeting Selected Subgroups**

Rather than using a “one size fits all approach,” clinical trials of new therapies should target specific subgroups that seem most likely to respond, based on the mechanism of action of the proposed agent. Combined with the importance of timing and use of objective measures for patient inclusion, other readily available clinical characteristics can be used to rapidly distinguish various patient subgroups to determine therapy and selection of patients for trials. At the time of initial presentation to the emergency department (stage A), severity of signs and symptoms, systolic blood pressure, degree of hypoxia, troponin release, and renal function allow for risk stratification of patients in terms of both disease severity as well as the need for specific therapies and appropriateness for specific clinical trials. After initial stabilization, additional variables such as EF, the presence of coronary artery disease, the degree of systemic congestion, and any specific triggers identified (such as atrial fibrillation) provide added discrimination of relevant subgroups (stage B trials). For variables such as EF, which may be less central to early management but play a critical role in subsequent care, stratification of enrollment or prespecified subgroup analysis by EF may be considered.

Systolic blood pressure has emerged as a critical prognostic factor in AHFS. Data from large registries have demonstrated that the majority of patients with AHFS present with normal or increased systolic blood pressure, often with preserved systolic function. Clinical observation of these patients suggests the possibility that they have a unique pathophysiology, because many such patients have acute pulmonary edema in the setting of relatively little change in weight or other measures of volume status. This fact has suggested the hypothesis that vasoconstriction and contractility-afterload mismatch may play a critical role in these patients, a mechanism that would be amenable to vasodilator therapy. However, only recently have trials of novel vasodilators focused specifically on this patient population.

Another underrecognized covariate in defining appropriate patient populations for study may be the presence or absence of coronary artery disease. Data from the OPTIME-CHF study have suggested that the balance of safety and efficacy of milrinone may differ on the basis of the underlying substrate, with potentially beneficial effects in nonischemic patients and clear evidence of harm in those with underlying coronary artery disease. Hibernating/ischemic myocardium may be particularly vulnerable to therapies that may increase oxygen demand and/or lead to myocardial injury. This finding underscores the need to target therapy based on pathophysiology, and this paradigm may be operative with other therapies as well. Recent focus on the effects of AHFS therapies on coronary perfusion has led to the hypothesis that this may be another critical “mechanism of harm” in patients with obstructive coronary artery disease.

Patients with renal dysfunction may represent another specific substrate for treatment. These patients are a heterogeneous group and include patients with a history of chronic kidney disease due to diabetes, hypertension, and arteriosclerosis and/or patients with renal dysfunction secondary to the AHF-related hemodynamic, neurohormonal, or intrinsic renal abnormalities (“vasomotor nephropathy”). Worsening renal dysfunction caused by intrinsic renal disease and/or vasomotor nephropathy may be a trigger for decompensation or may develop during hospitalization. All of these patient subgroups have a poor prognosis, and specific therapies targeted at renal preservation are currently under investigation. Although pilot data on using the renal-protective agent rolofylline were suggestive of benefit, the results from the larger phase III PROTECT [Placebo-controlled Randomized Study of the Selective A1 Adenosine Receptor Antagonist Rolofylline for Patients Hospitalized with Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on
Congestion and Renal Function did not demonstrate benefits on either renal function or downstream clinical outcomes. Renal protection may still represent a novel target of treatment for patients with AHFS, although the most appropriate patient population and the best intervention remain uncertain.

Targeting Appropriate Level of Risk
In addition to targeting subgroups with specific agents aimed at specific mechanisms, it is critical to direct interventions to patients with appropriate levels of risk. A small number of variables, including blood pressure, renal function, and natriuretic peptide levels, have been shown to provide robust risk stratification in patients with AHFS. Clinical trials have often excluded patients with high-risk features, complicating the extrapolation of results to broader patient populations. From a clinical perspective, it is important to identify patients at both extremes of the risk spectrum. For patients at very low risk of events, additional interventions are unlikely to improve outcomes further. For patients with high risk for future events (either because of the severity of HF or to the degree of comorbidities), traditional AHFS interventions may be unlikely to change the natural history of the disease. Although such patients make up a small portion of the AHFS population, they contribute substantially to the burden of in-hospital mortality. Clinical profiles defined for the INTERMACS [Interagency Registry for Mechanically Assisted Circulatory Support] registry provide guidance for when such patients should be considered for mechanical support. Appropriate identification and triage of such patients at the time of hospitalization to either mechanical support (or alternatively to end-of-life care) is an important goal of AHFS management and has been emphasized in recent guidelines.

Study Design: Methodological Issues in AHFS Clinical Trials
Essential to the conduct of clinical trials is the use of established, validated, and reproducible measures to assess efficacy and safety. Surprisingly, many efficacy measures for clinical trials in AHFS remain highly subjective and have not been validated. As an example, recent large clinical trials that have included assessments of symptoms (often as the primary end point or a component of the primary end point) have used widely variable methodology (Likert versus visual analog scale) and time points, none of which have been carefully validated in AHFS. Such variability has introduced “random error” that has resulted in decreased statistical power to detect real differences in symptomatic benefit and has also precluded comparison across studies. Recently, several efforts have been made to evaluate the evolution of symptoms in AHFS, the relative change in various instruments compared with each other, and the association of such changes with other outcomes. A recent proposal for standardized dyspnea assessment is an important first step toward better application of patient reported outcomes in clinical trials in AHFS.

As with breathlessness, the evaluation of congestion is dependent on relatively qualitative measures (jugular venous pressure, peripheral edema, rales, congestion on chest radiograph) that may not be highly correlated with more objective measures. Although resolution of congestion is clinically important, current tools for assessing it are too qualitative and subject to intraobserver variability to be used as a primary end point in clinical trials.

Moving Beyond Congestion: Preventing Injury as a Target of Therapy
Given that signs and symptoms of congestion are the major drivers of hospitalization for AFHS, it is not surprising that much of drug development in AHFS has viewed congestion as a major target of therapy. Despite significant clinical improvement, patients continue to have persistent elevation in pulmonary capillary wedge pressure, severely abnormal hemodynamics, and neurohormonal abnormalities that likely continue into the postdischarge period. Although relief of congestion remains an important goal, it is clear that effectively addressing congestion only during the initial hospitalization does not necessarily correlate with improving post-discharge outcomes. There is a major need to identify alternative or additional targets. Targeting the prevention of end-organ damage in the myocardium and kidney is a potential therapeutic goal. Reverse cardiac remodeling may also be an important end point.

Multiple datasets have demonstrated that detectable levels of troponin are present in patients with both chronic HF and AHFS and are associated with adverse long-term outcomes. The underlying mechanisms of troponin release in patients with HF remain unclear. It occurs in patients both with and without coronary artery disease. Whether prevention of troponin release is a useful surrogate of organ damage during AHFS that improves outcome is unknown but has been tested in pilot studies. As described previously, a large body of recent evidence supports the concept that worsening renal function is associated with adverse outcomes, both during the index hospitalization and after discharge. The failure of the adenosine A1 blocker rololofylline to improve outcomes in the pivotal PROTECT trial has called into question whether worsening renal function is a mediator of worse outcome or simply a marker of poor prognosis. Newer plasma and urinary markers (such as cystatin C and neutrophil gelatinase-associated lipocalin [NGAL]) may provide more sensitive or specific measures of renal injury that could provide mechanistic evidence of a link between organ damage and outcome and potentially allow better targeting of renoprotective strategies.

End Points in AHFS Studies
No single end point can capture all elements of the clinical course of AHFS, and therefore, no single end point will be appropriate for all interventions or patient populations. We suggest that each of the 4 domains detailed next be assessed and reported in all phase III AHFS studies, recognizing that various weights will be given to each domain depending on the mechanism of action of specific therapies. This would allow interventions to be compared and contrasted and is similar to the “consumer reports” approach that has been previously described for acute myocardial infarction studies.
Signs and Symptoms

- Symptom relief (visual analog scale, Likert, provocative dyspnea assessment, other)
- Measures of congestion relief (edema, rales, jugular venous pressure, weight)

The primary symptom of AHFS is breathlessness, and the development and validation of accurate and reproducible metrics for measuring symptom relief would be a major step forward in AHFS research. Controversy remains about both the rapidity and the degree of resolution of signs and symptoms in patients with AHFS. Some studies have suggested that breathlessness improves quickly in the majority of patients, whereas other studies (using stricter inclusion criteria) have suggested that a clinically important burden of breathlessness may be unaddressed in AHFS. Consistent with the goals of making patients “feel better or live longer,” breathlessness is an important target for phase III studies in AHFS. However, given that symptoms of breathlessness are relatively short-lived (ie, hours to days) in many patients with standard therapy, dyspnea should be assessed early in the clinical course. Improvement in dyspnea could be combined with other measures in a clinical composite primary end point. For improvement in breathlessness to be considered clinically important, it should be rapid, substantial, and sustained beyond a few hours. To quantify this effect, measurement at multiple time points is required. In addition to timing, the conditions under which dyspnea is measured should be standardized. Signs of congestion, such as jugular venous pressure, peripheral edema, rales, and body weight, are supportive evidence of clinical effect but are probably not suitable for inclusion in primary end points of phase III studies.

Index Hospitalization

- In-hospital mortality
- Length of stay
- Worsening HF in hospital

In-hospital events occupy a middle ground between immediate symptom relief (which may be of questionable long-term benefit) and postdischarge events (which may be difficult to improve with short-term therapies). In-hospital mortality is obviously important but infrequent (≈4%), unless a subset of sick patients is chosen. Although length of stay is theoretically attractive, it is influenced by a variety of factors (financial, social, and cultural) that are not directly related to clinical status and is subject to geographic variation in international clinical trials.

Worsening HF has gained increasing acceptance as an important clinical measure in AHFS and has been a component of the primary end point of several recent phase III studies. Worsening HF is usually defined as either failure to improve (persistent signs and symptoms of HF despite therapy) or worsening signs and symptoms of HF despite therapy. Worsening HF could be considered somewhat analogous to “recurrent ischemia” in studies of acute coronary syndromes. One frequent component of the worsening HF definition is the requirement for “rescue therapy”—ie, the need to initiate or intensify intravenous therapy (such as inotropes or intravenous vasoactive agents) or implement mechanical cardiac or ventilatory support. Although the need for such rescue therapy makes intuitive sense, guidance from European Medicines Agency suggests that they do not consider this an appropriate component of an efficacy end point.

Prevention of End-Organ Damage

- Renal dysfunction or injury (blood urea nitrogen, creatinine, cystatin C, other markers)
- Myocardial injury (troponin)

As noted earlier, markers of renal dysfunction or myocardial injury are powerful predictors of outcome in AHFS. Although these markers have previously been considered primarily as markers of safety, we suggest the hypothesis that resolution of congestion while avoiding myocardial injury or worsening of renal function could be considered the major short-term goal of AHFS therapy. To evaluate this concept, we propose that serial measures of both renal function (including novel markers of renal injury, if possible) and circulating troponin be considered a standard component of the evaluation of new therapies in AHFS.

Postdischarge Events

- Death + rehospitalization at 60 days
- Days hospitalized or dead within 60 days
- Mortality (all-cause or cardiovascular) at 180 days

Poor postdischarge outcomes (ie, high rates of HF rehospitalization and death) are the major unmet medical need in AHFS and, together with the rapid relief of symptoms, are the most important targets for therapy. Because rates of noncardiovascular events are high in AHFS because of the age of the population and the presence of other comorbid conditions, formal adjudication of end points is important so that disease-specific end points can be evaluated. “Days hospitalized or dead”-type end points are attractive because they integrate both the index hospitalization and postdischarge events; however, early death may have a disproportionate influence on this end point. In addition, this end point is susceptible to the same cultural variability as length of stay, although these factors may balance out in the context of a randomized controlled trial. Longer-term mortality (eg, 180 days) seems unlikely to be affected by short-term interventions (stage A or B) alone but should be captured as a safety measure in all AHFS studies.

Safety in AHFS Studies

Drug safety has become a major focus of drug development in general and for AHFS therapies in particular. The 2 drugs approved for AHFS by the FDA in recent decades (milrinone in 1988 and nesiritide in 2001) have come under substantial scrutiny because of concerns about the balance of safety and efficacy. There remains a great deal of uncertainty about how to quantify the confidence with which a new
AHFS therapy can be declared “safe.” Phase III studies should include formal assessment of the upper boundary of risk (either relative or absolute) that can be excluded by the planned sample size. This statistical exercise quickly leads to the recognition that even large studies (eg, >5000 patients) cannot exclude an increase in rare events with a high degree of confidence. The evaluation of drug safety should consider the totality of data (using the approach suggested earlier), and the type and degree of observed benefit may have important implications for acceptable safety boundaries (eg, drugs that substantially affect worsening HF or length of stay may require less-stringent evidence of safety than do drugs that address symptoms alone). In addition, we suggest that a reduction of end-organ damage supports long-term safety, and conversely, an increase in markers of end-organ damage should heighten the need for robust evidence of safety.

Formal regulatory guidance on long-term safety assessments for AHFS therapies is currently unavailable, but recent FDA guidance on cardiovascular safety for antidiabetic therapies may provide a useful model.

Composite End Points

Given that none of the domains discussed in this article can individually capture the potential benefits of a new therapy for AHFS, there is a need to define clinical composite end points that combine these measures. Although the details of individual composites may differ, we believe composite end points that capture each of these domains (symptoms, end-organ dysfunction or injury, in-hospital events, and postdischarge events) are the best option for the primary end point in future AHFS studies. The inclusion of measures of organ function (such as creatinine) or injury (such as troponin) as a component of the primary end point is controversial. Theoretically, we suggest that such measures could provide supportive evidence of efficacy as part of a primary end point, so long as they were combined with evidence of benefit on more traditional clinical outcomes (symptoms, events). The various components of the composite and their relative weighting may differ, depending on the nature of the therapy, the pathophysiological target, the patient subgroup being targeted, and the timing of intervention. Regardless of the composite used, any evaluation of new therapies must also include a careful evaluation of longer-term safety to exclude the risk of significant harm. A variety of composite approaches have been used in previous studies, including the use of coprimary end points (eg, symptoms and postdischarge outcomes with dividing of the acceptable type I error12) or creating trichotomous composites (better/same/worse) that capture various domains within their definition. Another similar but alternative approach is the use of a “global rank” method, in which patients participating in a clinical trial are ranked on the basis of a prespecified hierarchy of events (eg, deaths are given the worst rank, rehospitalizations next worst, etc). Although these end points may be complex to interpret, 1 advantage of the global rank approach is that it “weighs” the components of the clinical experience in a way that might be congruent with clinical judgment, assuming that a consensus can be reached.

Conclusions and Next Steps

Innovation in trial design for AHFS remains a high priority. Greater consensus within the scientific community about the current challenges and the best ways forward is a critical step in this process, and we believe that many aspects of this consensus are now in place. In this document, we have identified current barriers and potential solutions for moving forward. Greater standardization and validation across the field of AHFS research—in clinical classification, inclusion-exclusion criteria, metrics for gauging clinical response to treatment, end points, and regulatory requirements—are critical for moving the field forward. Such standardization will require greater degrees of cooperation and consensus among the scientific community, industry, and regulatory agencies to achieve demonstrable progress.

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Disclosures

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References


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