

Measurement of End Points in Heart Failure Trials:

Jousting at Windmills?

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Abstract

Advances in the treatment of congestive heart failure, a condition of increasing incidence and prevalence, have been made possible by knowledge gained from randomized clinical trials. The selection of end points in these trials has become a pivotal step in the drug and device approval process. In part because of the success of earlier trials, the number of study subjects required in order to realize an important improvement in survival has increased. This has led to the development of alternative combined and composite end points, often including surrogates for mortality. The limitations of these end points, the specific challenges associated with studies of patients with decompensated and diastolic heart failure, and other issues encountered during and after completion of heart failure trials, are discussed.

Key Words: Heart failure, end points, clinical trials.

“Fortune disposes our affairs better than we ourselves could have desired: look yonder, friend Sancho Panza, where thou mayest discover somewhat more than thirty monstrous giants, whom I intend to encounter and slay, and with their spoils we will begin to enrich ourselves....”

Don Quixote, in *The Adventures of Don Quixote*, Chapter VIII (1)

CONGESTIVE HEART FAILURE (HF) is a condition of increasing incidence and prevalence, with a pronounced impact on patients, providers and payers (2–5). According to statistics from the American Heart Association, there are 550,000 new cases in the United States each year, and males and females aged 40 who do not have a diagnosis of HF have a one-in-five lifetime chance of developing the disease (2). Epidemiologic

data from Framingham and Olmstead County, and from other evaluations suggest that HF is a condition characterized by considerable morbidity and mortality (6–8). The situation places enormous pressure on physicians to devise strategies that can decrease mortality and improve quality of life for patients with the disease.

For over twenty years, advances in therapeutic options for HF have been driven by knowledge gained from numerous phase II and phase III clinical trials, many with acronyms that say little about the drug or device under study but nonetheless reflect optimism about the process and/or ultimate outcome of the drug discovery and development effort (PRECISE, BEST, MERIT, PROVED, SOLVD and IMPRESS, to name a few (9–14). Randomized, placebo-controlled double-blinded clinical trials (RCTs) are more than just experimental studies: they are pivotal for therapy approval and labeling; help to confirm and generate hypotheses about and/or provide insight into disease pathophysiology; and facilitate a therapy’s acceptance into clinical practice now heavily influenced by evidence-based decision-making. The selection of appropriate end points for these trials is therefore a crucial component of clinical trial design, and by extension, drug and device approval.

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Presented in part at a Cardiology Grand Rounds presentation to the Department of Medicine, Mount Sinai School of Medicine, New York, NY, on February 4, 2002, and updated as of June 2004.

Standard End Points

Traditionally, the standard so-called “hard” end point in trials that measure drug or device efficacy has been all-cause mortality. Cardiovascular mortality, all-cause hospitalization and heart failure hospitalization are often used as secondary stand-alone end points. Although clearly a binary outcome (the study subject is either dead or alive), mortality can be subject to uncertainty. Evaluation of the mode of death can be limited by lack of detail, in large part because many deaths occur out of hospital. Formal, unbiased adjudication processes reduce the degree of ambiguity, but categorization of mode of death is best viewed as an artificial construct. First proposed by Hinkle and Thaler (15), the classic description of mode of death as sudden arrhythmic versus circulatory failure has been criticized (16–18) because of significant overlap and difficulties in recreating the events leading up to death. Some investigators have proposed a variety of alternative classification schemes (19–21) to assist in clarifying mode of death. This has relevance, because a drug or intervention that simply causes a redistribution among the various terminal events will not be considered a significant advance.

Combined and Composite End Points: Is There a Role for a Substitute for Mortality?

With multiple randomized clinical trials demonstrating mortality benefits, mostly additive, from the use of angiotensin-converting enzyme inhibitors (of between 20–25%), beta-adrenergic antagonists (of at least 30–35%, depending on the drug) and the aldosterone antagonist aldactone (31%) (22–24), the proverbial bar for achieving statistical significance has been raised. The power calculations in clinical trials now must reflect the fact that appropriately treated patients are living longer with heart failure. In lieu of designing trials that require 5000 or more patients to show a survival benefit, alternative combined or composite end points have been proposed (Table). One commonly used end point is the combination of all-cause mortality and heart failure hospitalization, since it joins together death from any cause with a disease-specific event. Alternatively, the combination of death, hospitalization, and either emergency department visit or unscheduled office visit has been combined to form an “event” end point.

Packer has proposed a composite of heart failure hospitalization plus change in quality of

TABLE
Types of End Points

Combined	All-cause mortality and heart failure hospitalizations
Composite	Composite heart failure hospitalization plus change in quality-of-life score plus change in left-ventricular end-diastolic dimension
Surrogate	Neurohormonal panel Ejection fraction Hemodynamics

life score plus change in end-diastolic dimension (25). One of the challenges with this and other composites that incorporate multiple possible outcomes is that it is difficult if not impossible to devise a scoring system that, on a sound scientific basis, weighs the relative importance of the different parameters. This can be best highlighted in the A-HeFT trial, in which points are assigned according to the outcome achieved (26). For example, a significant change in quality of life as measured by the Minnesota Living with Heart Failure Questionnaire at six months will be assigned 2 points, whereas death will be 3 points (27).

The use of composite end points, increasingly common in phase II and as secondary end points in phase III trials, has encouraged an ongoing debate about the role of surrogate, non-mortality end points (28, 29). A fundamental requirement for a surrogate end point is that the relationship between the surrogate and mortality is established; that is, there is a strong correlation, preferably with an underlying pathophysiologic basis, between the two measures of drug efficacy. Further, the patient cannot have direct knowledge of the surrogate itself; hence echocardiographic parameters qualify as surrogates whereas distance on a six-mile corridor walk test and quality of life scores do not.

Recent results have suggested that the use of nonmortality endpoints including surrogates is fraught with risk. We learned more than a decade ago that suppression of premature ventricular contractions by anti-arrhythmic drugs (30), once thought of as a useful surrogate, could be associated with higher mortality (31). In the heart failure area, a multitude of drugs that provided favorable changes in hemodynamics during short-term administration were associated with higher mortality with chronic use (32–35). Data from the U.S. carvedilol

studies demonstrated that exercise distance does not correlate with survival benefit (9). These misconceptions should occur less frequently with increasing knowledge about the factors underlying the evolution of left ventricular remodeling and the mechanism of action of the drug under study. However, the favorable impact of a drug on one part of disease progression or expression does not automatically translate into a benefit for the patient, and therein one finds a challenge for clinical trialists.

Nevertheless, despite potential drawbacks, several surrogates offer promise, especially measurements of left ventricular size (36, 37) and neurohormonal levels. For example, changes in ventricular dimensions and volumes or ejection fraction (measured by echocardiography, magnetic resonance imaging or nuclear imaging) have been associated with outcomes and may provide a true window on long-term prognosis (36). Indeed, the remarkable array of factors in univariate and multivariable analyses associated with outcomes in heart failure suggests that the list of potential surrogates is much larger.

One particularly problematic end point is health-related quality of life (HRQoL), an important consideration in any chronic cardiovascular disease (38, 39). Several studies have demonstrated the problems associated with measurement of HRQoL in heart failure trials, including the participation of a select minority of subjects to whom HRQoL instruments are administered (40, 41). In many studies, the number of participating patients is not detailed and the frequency of measurements is limited. Furthermore, the instrument selected is pivotal, especially since changes in total or domain scores within each instrument may not be highly correlated with changes in another instrument (42). Indeed, the performance of quality-of-life measurements relative to a functional test (exercise time) has been disappointing (43).

Various so-called "fast tracks" to quality of life have been proposed, specifically patient global clinical assessment ratings and specific symptom ratings (such as dyspnea) on simplified 3-point, 5-point or visual analog scales (14, 44). However, the simplicity of these measures also represents a drawback. For example, while health perception on a visual analog scale was associated with New York Heart Association Class in one trial, there was significant overlap on the individual patient level (14). The predictive value for downstream adverse clinical events was reasonable, but the timing and frequency of such measurements remain uncertain. Further, as Recator asked: "Are simple symptom assessments ad-

equated measures of therapeutic efficacy? One doesn't know what is actually being measured when patients say they feel better" (45).

Similarly difficult has been the interpretation of acute hemodynamic responses to drug therapy. Important placebo effects can be demonstrated (46). More important, reliance on acute changes in hemodynamics and cardiac output, previously the basis for dose selection in a series of phase III trials, failed to translate into a survival benefit for active drug treatment. Therefore, a lowering of pulmonary capillary wedge pressure can no longer be viewed as a replacement for survival.

Other potential end points attempt to address clinical events that mark a worsening clinical status and include: rates of discontinuation of study medication due to worsening heart failure; need for intravenous inotropic therapy; need for intravenous diuretic therapy; and days alive outside hospital.

End Point Determination in Decompensated Heart Failure

The high event rate for patients with decompensated or New York Heart Association Class IV symptoms suggests that this should be a simpler population to study than cohorts consisting of patients with lesser severity of disease, at least in terms of the number of subjects required to reach specific clinical end points. However, recruitment can be more difficult, and a placebo-controlled trial is subject to frequent investigator-driven crossover into active therapy. The need for rescue therapy has been considered part of a composite end point that suggests worsening of the clinical status of the patient and by extension, prognosis. In all likelihood, the decision to use additional or alternative therapies is a legitimate measure of patient deterioration or at the very least the physician assessment of such deterioration and, as an end point, represents a step forward in gauging efficacy relative to the simple dyspnea scale that was previously in use (47).

End Point Determination in Diastolic Heart Failure

Given a low rate of death due to isolated diastolic heart failure relative to advanced systolic heart failure, a trial that demonstrates a survival advantage must be appropriately powered. The recently published CHARM protocol demonstrates this point (48). Therefore, the use of surrogate and other end points is once again an issue, but the selection of candidates appears

to be more limited. Exercise distance, performance on a cardiopulmonary exercise test or quality of life may be appropriate, but the correlations between these parameters and mortality in diastolic failure are not well established.

End Point Determination in Device or Surgical Therapy

Trials of devices and operative approaches to the treatment of heart failure have been performed but present unique methodological problems. The definition of a placebo group is difficult at best, since sham surgery is generally not permissible and blinding can be challenging (49). Comparison of outcomes relative to historical controls is usually an unsatisfactory option. There are often technical issues during the evaluation process of a new technology; these can affect power calculations and exacerbate center-specific effects. Furthermore, the costs related to the performance of device and surgical trials are also significantly higher than for drug studies, at least on a per subject basis.

End Points for the Future

With an appreciation for the various factors that influence or characterize remodeling comes an opportunity to consider the use of surrogate candidates that represent changes in molecular, cellular, morphologic or functional expression. These include the evaluation of individual cardiomyocyte size or function (50, 51) and measurement of beta-receptor subtype (52). However, availability of endomyocardial biopsy specimens with which to perform many of these assays will almost certainly be limited. Another possible candidate is a composite neurohormonal panel consisting of factors such as brain natriuretic peptide, norepinephrine, endothelin and angiotensin II. However, as with any of the composite end points, the selection and relative importance of the different neurohormones (and the magnitude of change in levels) are not known. Furthermore, any new end point should meet the same standard as that of end points in general: each must be valid, reliable and responsive to change.

Other Issues in End Point Measurement

Heterogeneity of Outcomes and Subgroup Analysis

Large multi-center trials, by definition, have the advantage of a significant number of study

subjects and sites. As a result, there is also the potential for an array of heterogeneous outcomes, which can be analyzed by baseline factors such as patient age, gender or race; study site; region or country; dose of drug; etiology of heart failure; and other factors. Examples have included the comparison of African Americans vs. Caucasians (10, 53, 54), Europe vs. the United States (55), dosing regimens (56) and etiology (57). Although beyond the scope of this paper, the legitimacy of subgroup analysis can be called into question as the number of subgroups analyzed increases, especially if it is performed on the basis of *post-hoc* identification of efficacy trends between groups that were not defined at the start of the trial. A difference detected between subgroups in a surrogate outcome is particularly burdened with potential misinterpretations.

Long-Term Trends

Given the possible length of the approval and dissemination process for new treatments for heart failure, the results of any given trial, especially those that require an extended follow-up period, are at risk of appearing to be obsolete. New therapies are always seen in the context of standard therapy at the time of approval, not the time of randomization. The importance and influence of long-term trends has been demonstrated in both the device and drug fields (58, 59) and is, in effect, a risk that may not be avoidable.

Efficacy of Related Drugs

Chemical, pharmacokinetic, pharmacodynamic and clinical trial data suggest that drugs within “a class” are not all alike (60). Nevertheless, once efficacy is determined for a particular drug, the replication of the findings with a different drug within the same class is of dubious scientific merit unless the comparator group is the proven drug, not a placebo. An argument has been made that differences in background therapy can justify the performance of a placebo-controlled trial (59), and there may be some reasonableness behind the argument. Unfortunately, pivotal, so-called “head-to-head” clinical trials are rarely performed (61). Rather, trials are generally designed to define a new niche for the drug under development, or not designed at all, in which case a “carry over” effect from a different indication can occur based on pricing and other strategies. For example, angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers approved for treatment of hy-

pertension have been used in heart failure, even in the absence of supporting data.

After the Trial

Approval vs. Use

As noted, despite restrictive language in labeling, once a drug is approved, physicians may find avenues for use outside the original intent. A useful demonstration of this phenomenon in the heart failure field involves milrinone, approved for “the short-term intravenous treatment of acute CHF. There is no experience in controlled trials with infusions for periods exceeding 48 hours” (62). Nevertheless, much of the use of the drug is outside the 48-hour window, despite the fact that the official position of the American College of Cardiology/American Heart Association classifies chronic continuous infusions as a class IIb indication and intermittent infusions as a class III indication (63).

Efficacy vs. Effectiveness

The overall effectiveness of a drug shown to be efficacious within the confines of a clinical trial is often difficult to measure. As Heiat et al. have demonstrated, there has been, in general, an under-representation of women, minority groups and the elderly in heart failure trials (64). Whether a drug can be shown to be effective in all groups of patients, indeed whether an RCT can predict clinical outcomes, is often not established. This idea is well represented by Messerli et al., who stated: “Trials examine primarily medical interventions; randomization permits comparisons of interventions not confounded by the individuality of patients. Here is the paradox of the trial: it is the best way to assess whether an intervention works but is arguably the worst way to evaluate who will benefit from it...” (65). The problem may also be exacerbated by polypharmacy, both in terms of drug-drug interactions and cost.

Conclusion

We find ourselves in an era of “evidence-based medicine,” and our practice in heart failure is dictated in large part by the outcomes of randomized clinical trials, which have supplanted pathophysiology as the primary driver of the selection of therapeutic options. Despite the challenges brought about by our own successes in the treatment of heart failure, useful clinical trials can still be performed. Recogni-

tion of the importance of end point selection, study population and doses is crucial. Careful interpretation of the data is also important, as is a willingness to accept the limitations of the data. Unlike Don Quixote, who saw everything in the context of his own preconceptions, we need to recognize that the p value is not a windmill to be vanquished.

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