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Heart failure clinical trials: how do we define success?

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Abstract

The selection of end points for clinical trials of heart failure is challenging, with important implications for patients, the medical community, and regulatory agencies. The standards used in clinical research on patients with heart failure influence the effectiveness and value of future clinical trials, and the extent to which they can be translated into clinical practice.

Whether in sports, economics, or medicine, boundaries must be set for demarcating success from failure. Despite advances in therapies for the prevention and treatment of heart failure (HF), this syndrome continues to result in substantial morbidity, mortality (>50% at 5 years), and health-care expenditure.¹ New therapies, particularly for acute HF and HF with preserved ejection fraction, are urgently needed. The Heart Failure Association of the ESC (HFAESC) convened a 2-day summit involving experts in HF, regulators, and industry representatives to evaluate the challenges in determining clinical outcome end points in trials of HF. The resulting consensus statement was published in the *European Journal of Heart Failure* in June 2013.² The document serves as a framework for HF trialists, study sponsors, and regulators worldwide in assessing potential end points for clinical trials of HF, and identifies areas worthy of future exploration.²

With the increasing availability and use of evidenced-based, guideline-recommended therapies, event rates for the traditional ‘hard’ end points of mortality and morbidity have fallen. In the UK-Heart study,³ all-cause mortality decreased from 12.5% to 7.8% at 1 year, with an increase in the proportion of noncardiovascular mortality from 14% to 29% over a 10-year period among patients with HF. As event rates for traditional end points fall, the inclusion of alternative end points relevant to patient outcomes has become increasingly common. The benefits and limitations of a multitude of end point reporting strategies for HF clinical trials are extensively discussed in the HFA-ESC consensus statement.²

Currently, no ‘one size fits all’ standard for end points exists in randomized controlled trials of patients with HF. As studies involve the investigation of populations at various stages of acute and chronic HF, event rates vary considerably for each potential outcome. The HFA-

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ESC consensus document² stratifies classes of end points from most-scientificall y rigorous to those with increasing degrees of limitation for methodology or ease of interpretation (Figure 1). The HFA-ESC writing group identifies all-cause mortality as the most-scientificall y objective end point in assessing the benefit and safety of a given intervention, as well as for limiting potential bias. Nevertheless, if all phase III studies were powered to detect differences in all-cause mortality alone, they would require increasingly large study populations and extended periods of observation at tremendous cost. Cardiovascular or cause-specific mortality are more-selective end points, which reflect more-direct treatment effects than all-cause mortality. The authors of the HFA-ESC document specifically draw attention to challenges in accurate adjudication of cause-specific death or hospitalization. Studies suggest that adjudication can accurately classify events and correct for under-reporting.⁴ However, limitations in event classification have been well documented, even with highly experienced clinical event committees.⁵ Furthermore, concerns exist regarding the potential for introduced bias. Trials such as CHAMPION, TRITON, RECORD, and PLATO have been criticized for discrepant adjudication that might have favoured the treatment arm.⁶ The lack of routine reporting of the degree of adjudication and access to primary patient level data limits investigator and physician understanding of how events are reclassified.

Focusing on death alone ignores the substantial burden of morbidity among patients with HF. The authors of the HFA-ESC document² emphasize the importance of the rate of hospitalization for HF, which is meaningful to both health-care providers and patients. The difficulty remains in classifying a hospital admission for acute HF when evidence suggests that around two-thirds of patients with HF are readmitted for reasons other than exacerbation of HF.⁷ The authors of the HFA-ESC statement also acknowledge the importance of both HF symptoms and patient-reported health outcomes. However, the document highlights the difficulty in objectively measuring HF symptoms, and the challenges of obtaining uniformity with patient-reported quality-of-life indices.² Various instruments, such as the Minnesota Living With Heart Failure Questionnaire or the Kansas City Cardiomyopathy Questionnaire, are responsive to changes in HF symptoms and correlate with levels of biomarkers such as pro-B type natri uretic peptide.⁸ The HFA-ESC writing group acknowledges that no reliable surrogate markers for HF outcomes exist. Although biomarkers or indicators of ventricular remodelling might be useful in early phases of therapy development to provide preliminary evidence of efficacy or safety, demonstrate dose responsiveness, and identify patients most likely to benefit, they are not appropriate clinical outcome end points for phase III clinical trials.²

Owing to the statistical complexity of accounting for composite end points and recurrent events in clinical trials, results are commonly reported as time to first event. Composite end points are sometimes criticized for overstating potential therapeutic benefits by combining rare events, such as death, with less-severe and more-frequent end points, such as nonfatal myocardial infarction, hospitalization, or revascularization. In a study by Lim and colleagues, 304 published trials in which composite end points were used revealed little correlation between the primary composite end point and death.⁹ Many cardiovascular trials utilize composite end points under the term ‘major adverse cardiac events’ (MACE). However, a uniform definition for MACE has not been established, and the specific end

points included within the composite vary widely between studies.¹⁰ Interestingly, the authors of the HFA-ESC consensus document highlight an innovative methodology using “win ratios”² to organize patient treatment–placebo pairs and rank the severity of adverse events to report overall benefits of a treatment. Although the method better accounts for severity of composites and recurrent events than conventional methods, validating the model and translating the results to providers and patients will be challenging.

Selecting primary end points for clinical trials is critical, not only for the success or failure of the trial in terms of determining efficacy and achieving approval of the therapy by regulatory agencies, but has important implications for effectiveness, economic value, and translation into clinical practice. Although an outcome might be quantifiable, it could lack relevance to patients and not translate easily into the clinical environment. Efforts to run clinically relevant trials must prioritize patient values to facilitate shared decision-making. The growing field of outcomes research will continue to refine current methodologies. The Affordable Care Act, which was passed by the US government in March 2010, led to the funding and formation of the Patient Centered Outcomes Research Institute. Research conducted at this institution emphasizes methodologies and outcomes relevant to patients, to improve value-based decisions on treatment options. Future consensus standards for clinical trial end points would be enhanced if they were formally to integrate the views of patients, caregivers, and other relevant stakeholders.

As the burden of HF continues to grow, substantial collaborative efforts are needed to advance HF research and refine clinical trial design and end-point selection. This work is essential to identify safe and effective therapies that improve patient-centred outcomes, provide value, and can be rapidly translated into clinical practice.

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Figure 1.

Potential end points for phase III pivotal clinical trials. Top: Chronic heart failure. Bottom: Acute heart failure. The hierarchy (or order ranking) of the end-point options to measure efficacy is not definitive. Alternative hierarchies might be appropriate depending on the relevance of the end point to a specific patient population, the ability to measure the end point objectively in a given study, and the possibility of standardizing the end-point measurement through accurate and reliable instruments. Abbreviations: HF, heart failure; HRQOL, health-related quality of life. Modified from Zannad, F. *et al.* Clinical outcome endpoints in heart failure trials: a European Society of Cardiology Heart Failure Association consensus document.