Clinical Trial Design, Endpoints and Regulatory Considerations in Heart Failure

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Abstract

After the withdrawal of flosequinan in the early 1990's, because of an increased risk of mortality and fatal arrhythmias, the bar for the approval of new drugs in heart failure has been raised and regulatory agencies have requested evidence for the efficacy of new treatments on mortality and morbidity end-points. However, more recently, regulatory agencies have become more open to include the assessment of functional capacity as an efficacy endpoint, at least in selected subgroups of patients. Therefore, a new therapy for the treatment of heart failure can be approved if it improves survival and/or reduces hospitalisations or if it safely improves functional capacity. This article reviews clinical trial design, trial endpoints and regulatory issues in Heart Failure trials.

Keywords: Heart failure; end-points; regulatory approval; clinical trial design

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Introduction

After the withdrawal of flosequinan in the early 1990's, because of an increased risk of mortality and fatal arrhythmias, the bar for the approval of new drugs in heart failure has been raised and regulatory agencies have requested evidence for the efficacy of new treatments on mortality and morbidity end-points. However, more recently, regulatory agencies have become more open to include the assessment of functional capacity as an efficacy end-point, at least in selected subgroups of patients. Therefore, a new therapy for the treatment of heart failure can be approved if it improves survival and/or reduces hospitalisations or if it safely improves functional capacity.

Therefore, in order to justify regulatory approval, the clinical development programme of new agent must demonstrate clinically relevant improvement in a meaningful clinical end point. Composite end points can be devised to improve trial efficiency and adequate assessment of efficacy of newer therapeutic agents provided that they are associated with a good safety profile.[1-3]

Furthermore, apart from heart failure with reduced ejection fraction (HFrEF) newer entities such as heart failure with a normal or relatively preserved ejection fraction (HFpEF, HFmrEF), for which no treatment is currently available, have been recognised. [4] The distinction between patients with HFrEF from those with HFpEF and HFmrHF is important because differentiating between groups with different underlying pathophysiological,

haemodynamic, and neurohormonal abnormalities may help explain differing clinical features, different outcomes and most importantly differing responses to therapy.[4]

Patients with heart failure may fluctuate between periods of stability and periods of de-compensation leading to hospitalisations [termed hospitalized heart failure (HFH)].[5-7] With the exception of early trials in ACE inhibitors and to a lesser extent angiotensin receptor blockers in the related area of post-MI heart failure, heart failure therapies approved for patients with chronic heart failure have not been tested in patients recently discharged after an episode of de-compensation. The mortality at 3 months of patients discharged after an acute episode of heart failure is approximately 10-15% and reaches 20-35% at 1 year. Clinical trials for the development of new therapeutic agents have traditionally included either patients in the acute phase who had just been hospitalized (within few days or hours) or patients that have been stable for few months. Patients who are still hospitalised but are not receiving intra-venous therapies and those who are in the immediate post-discharge phase have classically been excluded from heart failure clinical trials.

HFH is often used as a co-primary or part of a composite primary endpoint in heart failure trials. Despite its clinical relevance, its use as an endpoint in heart failure trials is controversial since the threshold for hospitalization, local standards of care and length of hospitalisation may differ across different regions. Therefore,

there is a need for a better definition of HFH in order to harmonise its adjudication. Furthermore, some patients with heart failure are repeatedly hospitalized because of repetitive episodes of decompensation and yet such repeated events are often ignored and “time to first event” analyses are used instead. Repeated event analyses may increase statistical power, leading to smaller sample sizes and better quantification of morbid events.

Another important point in clinical trial design in heart failure is the identification of surrogate end points that may predict significant clinical benefits. Indeed, despite phase II clinical trials suggesting efficacy of new compounds on surrogate end points, most agents have either failed to demonstrate efficacy or have even been proven negative on long-term outcomes. [8-9] Therefore, there is still the need to identify end points that may represent an adequate prognostic surrogate. Similarly biomarkers have not been shown to predict the clinical efficacy of drug therapies in heart failure.

Efficacy criteria for developing agents for the treatment of chronic heart failure

The primary aim of new treatments for chronic heart failure is to improve prognosis (survival and/or hospitalisations). Functional capacity is also an important end point to assess in patients with heart failure. However, the approval of new agents based on functional capacity has been made difficult by the problems encountered in the past with some treatments that were effective in improving exercise capacity, but that also had a negative effect on survival.

Efficacy end-points must be clinically relevant, and can be usefully classified into three groups. Group 1: all cause mortality, cardiovascular mortality, hospitalisation for heart failure and recurrent morbid events (HFH, worsening heart failure without hospitalisation, hospitalisation for cardiac causes, cardiovascular mortality). Group 2: functional capacity. Group 3: haemodynamic changes (eg LVEF, left ventricular remodeling), biomarkers, symptoms, quality of life

Group 1 endpoints are by and large approvable; group 2 potentially so, but given the negative experiences of the past, positive effects on functional capacity must be supported by neutral or, preferably, favourable effects on mortality and morbidity; but group 3 end-points are proof of concept only, as they do not in themselves confer patient benefit.

Primary end points

Primary end points should include all cause mortality, hospitalisation for heart failure and/or the clinical composite end point of cardiovascular mortality, hospitalisation for heart failure, worsening heart failure without hospitalisation, or hospitalisation for cardiac causes. Pre-specified composite end points may be acceptable but must include mortality and hospitalisation for heart failure and, ideally, for cardiovascular causes. Composite end-points including repeated hospitalizations can be used as primary composite end-points.

The effect of a new pharmacological agent for the treatment of heart failure on mortality can only be assessed with a randomized placebo or active treatment-controlled trial. Survival studies using positive control drug(s) may be acceptable but the comparator

agent should be limited to drugs that have consistently shown efficacy on survival.

Although overall mortality should be the preferred mortality end point in chronic heart failure studies, both total death and cause-specific death must be assessed and reported. Cardiovascular death may represent an adequate end point provided that the therapeutic effect on overall mortality is at least neutral. An excess in non-cardiovascular mortality could be acceptable, if the overall mortality is reduced or unchanged. It is important to define the mode of cardiac death and a central adjudication of the causes of death may be warranted.[11]

Hospitalisation for heart failure may be used as endpoint for efficacy. These hospitalisations should be centrally adjudicated. Hospitalisation for heart failure can be defined as those hospitalisations associated with signs and symptoms of deteriorating clinical condition along with increased plasma levels of BNP/proBNP and the need for acute treatments for heart failure (e.g., increase in diuretic dose, intravenous diuretics, or intravenous vasodilators/inotropes).

Functional capacity

Exercise capacity is a marker of clinical status and it is a more reliable end point than subjective assessment with patient related outcomes. Both maximal oxygen consumption test (MVO₂, sometimes referred as peak oxygen uptake, peakVO₂) and supervised 6 minute walking test (6MWT) are reliable methods for the assessment of functional capacity. Exercise testing should be performed using appropriate protocols specifically designed for the functional assessment of patients with cardiac failure.

Sub-maximal protocols should specify a priori the reasons for termination of the tests. Naïve patients to exercise protocols (bicycle, treadmill, measurement oxygen consumption) should first be made familiar with the technique before they are included in the trial. Repeated baseline and repeated follow up testing may reduce variability of the results and increase statistical power. Because of the variability in the execution and settings of the 6MWT multicentre studies must use standardised criteria and settings. The test should be supervised by a physical therapist, patients should be asked to walk on their own, and no phrases of encouragement should be offered. Patients may be allowed to stop walking if signs or symptoms of significant distress occur during the test and they should be instructed to resume walking as soon as possible.

Safety

Therapies for chronic heart failure are life-long. Therefore, the effect of new therapies on the occurrence of adverse effects and drug-to-drug interactions should always be investigated. Attention should be focused towards effects on cardiac rhythm, pro-ischaemic effects, hypotension, bradycardia, renal function and electrolyte homeostasis.

Conclusions

Newer regulatory and reimbursement practices require innovative study designs.[15] New agents for the treatment of heart failure should show a sound clinical benefit and an adequate safety profile. For these reasons all intervention studies conducted in heart failure should be reported and published.[16]

Declarations of interest

The authors declare no conflict of interest.

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The authors state that they abide by the authors' responsibilities and ethical publishing guidelines of the International Cardiovascular Forum Journal.[17]

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