



## EDITORIAL

# Clinical trial design, endpoints and regulatory considerations in heart failure

Giuseppe M.C. Rosano

Cardiovascular Clinical Academic Group, St George's University Hospital, London, United Kingdom; Department of Cardiology, San Raffaele Cassino Hospital, Cassino, Italy

## Abstract

Following the withdrawal of flosequinan in the early 1990s due to heightened mortality and fatal arrhythmia risks, regulatory agencies have demanded evidence of the efficacy of novel treatments in managing heart failure, with mortality and morbidity endpoints becoming more stringent criteria for approval. In recent times, regulatory agencies have exhibited a greater willingness to permit the evaluation of functional capacity as an efficacy endpoint, albeit limited to specific patient groupings. Consequently, a novel therapeutic intervention for heart failure may be granted approval provided that it enhances survival rates, decreases length of hospital stays, and/or safely improves functional capacity. This article reviews clinical trial design, trial endpoints and regulatory issues in heart failure trials.

**Key words** heart failure, endpoints, regulatory approval, clinical trial design.

Received: 12 February 2024; Accepted: 20 February 2024.

\*Correspondence to: Giuseppe M.C. Rosano, Department of Cardiology, San Raffaele Cassino Hospital, Via G. di Biasio 1, 03043 Cassino, Italy.  
E-mail: giuseppe.rosano@gmail.com

## 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 endpoints. 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 hospitalizations or if it safely improves functional capacity.

Therefore, in order to justify regulatory approval, the clinical development program 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.<sup>1-3</sup>

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 recognized.<sup>4</sup> The distinction between patients with HFrEF from those with HFpEF and HFmrHF is important because differentiating

between groups with different underlying pathophysiological, hemodynamic, and neurohormonal abnormalities may help explain differing clinical features, different outcomes and most importantly differing responses to therapy.<sup>4</sup>

Patients with heart failure may fluctuate between periods of stability and periods of de-compensation leading to hospitalizations [termed hospitalized heart failure (HFH)].<sup>5-7</sup> With the exception of early trials in angiotensin-converting enzyme inhibitors and to a lesser extent angiotensin receptor blockers in the related area of post-myocardial infarction 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 hospitalized 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.

Hospitalized heart failure 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 hospitalization may differ across different regions. Therefore, there is a need for a better definition of HFH in order to harmonize 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.<sup>8,9</sup> 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 hospitalizations). 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 endpoints must be clinically relevant and can be usefully classified into three groups. Group 1: all-cause mortality, cardiovascular mortality, hospitalization for heart failure and recurrent morbid events (HFH, worsening heart failure without hospitalization, hospitalization for cardiac causes, cardiovascular mortality). Group 2: functional capacity. Group 3: hemodynamic changes (*e.g.* left ventricular ejection fraction, 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, favorable effects on mortality and morbidity; but group 3 endpoints are proof of concept only, as they do not in themselves confer patient benefit.

## Primary endpoints

Primary endpoints should include all-cause mortality, hospitalization for heart failure and/or the clinical composite end point of cardiovascular mortality, hospitalization for heart failure, worsening heart failure without hospitalization, or hospitalization for cardiac causes. Pre-specified composite end points may be acceptable but must include mortality and hospitalization for heart failure and, ideally, for cardiovascular causes.

Composite endpoints including repeated hospitalizations can be used as primary composite endpoints.

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.<sup>11</sup>

Hospitalization for heart failure may be used as endpoint for efficacy. These hospitalizations should be centrally adjudicated. Hospitalization for heart failure can be defined as those hospitalizations associated with signs and symptoms of deteriorating clinical condition along with increased plasma levels of brain natriuretic peptide (BNP)/proBNP and the need for acute treatments for heart failure (*e.g.*, increase in diuretic dose, intravenous diuretics, or intravenous vasodilators/inotropes).<sup>12-14</sup>

## 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 (sometimes referred as peak oxygen uptake,) 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 multicenter studies must use standardized 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 lifelong. 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-ischemic effects, hypotension, bradycardia, renal function and electrolyte homeostasis.

## Conclusions

Newer regulatory and reimbursement practices require innovative study designs.<sup>15</sup> 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.<sup>16</sup>

## Conflict of interest

The authors declare no potential conflict of interest.

## Funding

None.

## References

- Schüssler-Lenz M, Beuneu C, Menezes-Ferreira M, et al. Cell-based therapies for cardiac repair: a meeting report on scientific observations and European regulatory viewpoints. *Eur J Heart Fail* 2016;18:133-41.
- Anker SD, Schroeder S, Atar D, et al. Traditional and new composite endpoints in heart failure clinical trials: facilitating comprehensive efficacy assessments and improving trial efficiency. *Eur J Heart Fail* 2016;18:482-9.
- Pani L, Pecorelli S, Rosano G, et al. Steps forward in regulatory pathways for acute and chronic heart failure. *Eur J Heart Fail* 2015;17:3-8.
- ESC Committee for Practice Guidelines. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2016: the task force for the diagnosis and treatment of acute and chronic heart failure 2016 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2016;18:891-975.
- Greene SJ, Shah AN, Butler J, et al. Designing effective drug and device development programs for hospitalized heart failure: a proposal for pretrial registries. *Am Heart J* 2014;168:142-9.
- Gheorghide M, Shah AN, Vaduganathan M, et al. Recognizing hospitalized heart failure as an entity and developing new therapies to improve outcomes: academics', clinicians', industry's, regulators', and payers' perspectives. *Heart Fail Clin* 2013;9:285-90.
- Butler J, Fonarow GC, Zile MR, et al. Developing therapies for heart failure with preserved ejection fraction: current state and future directions. *JACC Heart Fail* 2014;2:97-112.
- Vaduganathan M, Greene SJ, Ambrosy AP, Gheorghide M, Butler J. The disconnect between phase II and phase III trials of drugs for heart failure. *Nat Rev Cardiol* 2013;10:85-97.
- Zannad F, Garcia AA, Anker SD, et al. Clinical outcome endpoints in heart failure trials: a European Society of Cardiology Heart Failure Association consensus document. *Eur J Heart Fail* 2013;15:1082-94.
- Fishbein DP, Hellkamp AS, Mark DB, et al. Use of the 6-min walk distance to identify variations in treatment benefits from implantable cardioverterdefibrillator and amiodarone: results from the SCD-HeFT (Sudden Cardiac Death in Heart Failure trial). *J Am Coll Cardiol* 2014;63:2560-8.
- Seltzer JH, Turner JR, Geiger MJ, et al. Centralized adjudication of cardiovascular endpoints in cardiovascular and noncardiovascular pharmacologic trials: a report from the Cardiac Safety Research Consortium. *Am Heart J* 2015;169:197-204.
- Collins SP, Pang PS, Fonarow GC, Yancy CW, Bonow RO, Gheorghide M. Is hospital admission for heart failure really necessary?: the role of the emergency department and observation unit in preventing hospitalization and rehospitalisation. *J Am Coll Cardiol* 2013;61:121-6.
- Harinstein ME, Butler J, Greene SJ, et al. Site selection for heart failure clinical trials in the USA. *Heart Fail Rev* 2015;20:375-83.
- Rosano GM, Anker SD, Marrocco W, Coats AJ. Adaptive licensing. A way forward in the approval process of new therapeutic agents in Europe. *Int J Cardiol* 2015;184:568-9.
- Pelliccia F, Rosano GM. Back to the future: the crucial role of clinical registries in the era of randomized controlled trials for identifying the optimal medical therapy of heart failure. *Eur Heart J Cardiovasc Pharmacother* 2015;1:37-8.
- Capuano A, Coats AJ, Scavone C, Rossi F, Rosano GM. Disclosure of negative trial results. A call for action. *Int J Cardiol* 2015;198:47-8.