**New Medicinal Products for Chronic Heart Failure: Advances in Clinical Trial Design and Efficacy Assessment**

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**Abstract**

Despite the availability of a number of different classes of therapeutic agents with proven efficacy in heart failure, the clinical course of heart failure patients is characterized by a reduction in life expectancy, and a progressive decline in health-related quality of life, functional status, and a high risk of hospitalization. New approaches are needed to address the unmet medical needs of this patient population. The European Medicines Agency (EMA) is undertaking a revision of its Guideline on Clinical Investigation of Medicinal Products for the Treatment of Chronic Heart Failure. The draft version of the Guideline was released for public consultation in January 2016. The Cardiovascular Round Table (CRT) of the European Society of Cardiology (ESC), in partnership with the Heart Failure Association (HFA) of the ESC, convened a dedicated two-day workshop to discuss three main topic areas of major interest in the field and addressed in this draft EMA guideline: 1) assessment of efficacy (i.e., endpoint selection and statistical analysis); 2) clinical trial design (i.e., issues pertaining to patient population, optimal medical therapy, run-in period); and 3) research approaches for testing novel therapeutic principles (i.e., cell therapy). This paper summarizes the key outputs from the workshop, reviews areas of expert consensus, and identifies gaps that require further research or discussion. Collaboration between regulators, industry, clinical trialists, cardiologists, Health Technology Assessment (HTA) bodies, payers, and patient organizations is critical to address the ongoing challenge of heart failure and to ensure the development and market access of new therapeutics in a scientifically robust, practical and safe way.

**INTRODUCTION**

Chronic heart failure is a prevalent condition affecting more than 10-12% of people over 60 years of age in developed countries.1;2 Application of evidence-based therapy prolongs survival and reduces heart failure hospitalizations in patients with reduced ejection fraction (HFrEF), but not in those with preserved ejection fraction (HFpEF). Heart failure remains a progressive condition characterized by frequent hospitalizations, functional decline, impaired quality of life, and ultimately death. Cardiovascular mortality approached 30% at 3.5 years in an optimally treated chronic heart failure population enrolled in a recent clinical trial.3 It may be higher in routine practice outside of closely monitored tertiary settings.4;5

The persistent morbidity and poor long-term survival associated with heart failure underscores the continued need for therapeutic innovations that slow or reverse progression and improve outcomes for these patients. However, concerns have been raised that investment in development of heart failure therapeutics is declining for many reasons.6;7 Regulatory requirements are perceived by some stakeholders as one major barrier to therapeutic development in heart failure because large and lengthy trials are necessary before marketing authorization to demonstrate evidence of a treatment effect on mortality and morbidity endpoints and to provide assurance of safety even when mortality and morbidity are not primary targets of therapy.7 The quest for safety has been advocated, mainly by regulators, after the withdrawal of drugs (e.g, flosequinan, ibopamine, milrinone) that were shown to be associated with unfavorable long-term prognosis.8-10 However, it must be highlighted that at the time of the original approvals, warning signs as regards safety were present in the small studies that suggested benefit. Additionally, the feasibility and relevance of clinical trials in heart failure are affected by shifts in heart failure practice that have occurred over time (e.g. trends in hospitalization patterns, location of care delivery).

In recognition of these concerns and the changing heart failure landscape, the European Medicines Agency (EMA) is undertaking a revision of its Guideline on Clinical Investigation of Medicinal Products for the Treatment of Chronic Heart Failure (EMA/CHMP/392958/2015). EMA released a draft for public consultation in January 2016.11 The Cardiovascular Round Table (CRT) of the European Society of Cardiology (ESC) is a strategic forum for high-level dialogues between ESC leadership, academia, and industry to identify and discuss key strategic issues for the future of cardiovascular health in Europe. In partnership with the Heart Failure Association (HFA) of the ESC, and with involvement of representatives from EMA and members of other national Health Authorities in the European Union, the CRT convened a dedicated two-day workshop to provide feedback on three main topic areas addressed in the EMA guidance: 1) assessment of efficacy (i.e., endpoint selection and analytic methods); 2) clinical trial design (i.e., issues pertaining to patient population, optimal medical therapy, run-in period); and 3) research approaches for novel therapeutic principles (i.e. cell therapy). Although the scope of heart failure clinical research expands beyond these three topics, these were the focus areas for the workshop and the subjects of this manuscript. This paper summarizes the key outputs from the workshop, reviews areas of expert consensus, and identifies gaps that need further research or discussion (Table 1).

**EFFICACY ASSESSMENT**

**Morbidity and Mortality Outcomes**

A composite endpoint that includes death (all-cause or cardiovascular) and hospitalization (usually due to heart failure) is an accepted standard efficacy measure for chronic heart failure trials.12 Composite endpoints have become more widely used in the past 15 years because they reflect both survival and morbidity burden (i.e., reflected by hospitalization), and standard composites are more feasible than a single endpoint since event rates are higher, which can reduce the sample size and increase power.13 For efficacy, cause-specific mortality (i.e., cardiovascular) has been included in the composite primary endpoint in preference to all-cause mortality in recent heart failure trials.3;14;15 Cardiovascular death reflects the target of treatments for heart failure, whereas non-cardiovascular deaths are unlikely to be influenced by heart failure therapies, even though other competing risks as a potential source of bias should be considered when drugs improve cardiovascular death. The Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) trial illustrates this point. The hazard ratio (HR) for candesartan versus placebo on cardiovascular mortality was 0.88 (95% confidence interval [CI] 0.79-0.97, P=0.012), whereas no statistically significant effect on non-cardiovascular mortality was observed (P=0.45).16 Candesartan’s lack of effect on non-cardiovascular mortality diminished the treatment effect of candesartan on all-cause mortality (HR 0.91, 95% CI 0.83-1.00, P=0.055).16 In contrast to all-cause mortality, cardiovascular death may often require adjudication by an *ad hoc* committee. Duration of follow-up is also an important consideration, since most deaths in a trial with relatively short follow-up will be from cardiovascular causes. In the draft EMA Guideline,11 it was proposed that overall mortality is the preferred endpoint. However, cardiovascular mortality, alone or as a composite endpoint, can also be considered as the primary mortality endpoint provided that all-cause mortality is assessed as a secondary endpoint. The majority of workshop participants suggested that cardiovascular (and thus cause-specific) mortality may be preferred to all-cause mortality for evaluating efficacy in chronic heart failure trials: any effect on all-cause mortality is likely to be driven by cardiovascular death in the heart failure population, and it is implausible that a heart failure therapy would affect all components of all-cause mortality. All-cause mortality should still be assessed (with adequate power to rule out an increase) to evaluate safety and potential off-target effects on non-cardiovascular death.

Composite endpoints in heart failure trials have been previously reviewed in detail.12;17 It is outside the scope of this manuscript to consider all the strengths and limitations of composite endpoints, except to emphasize the importance of selecting appropriate components. The draft EMA document11 stated that composite and hierarchically-ordered endpoints can be applied to chronic heart failure studies, provided that mortality (overall or cardiovascular) and hospitalization for heart failure are the first two hierarchical endpoints, respectively. The relevance of the components of a composite endpoint varies with the mortality rate of the population under study. Combining mortality with many other (less serious) time-to-event components might (but not necessarily will) result in an over-estimation of the treatment effect (see below) and decrease the clinical importance of the results if the effect is driven by the non-mortality components. Conversely, adding multiple components may effectively increase the event rate, but if those components are unresponsive to the treatment, then the treatment effect may be muted by the ‘noise’ of non-response. Thus, when used, composite endpoints should be comprised of only the most clinically relevant components.12;17

**Outpatient Management of Worsening Heart Failure as an Endpoint**

Patients with worsening heart failure are increasingly being managed in non-hospitalized settings (e.g., emergency departments, specialized clinics, observation units, hospital-at-home services), which is among other reasons, motivated by an effort to contain healthcare costs.18-20 The EMA draft Guideline11 addressed this trend by proposing that events of worsening of heart failure without hospitalization may be used as an additional endpoint. Modern heart failure clinics have developed capabilities to monitor and provide treatments in the outpatient setting that were previously available only to inpatients. As a result of these advances and regional differences in heart failure treatment practices, the location of where heart failure events are managed has become less relevant than the characteristics of the worsening heart failure event itself.

Until recently, worsening heart failure in the outpatient setting has not been considered a primary event in many trials because of concerns that these events might be less severe than those requiring hospitalization, or that patients who can be managed as outpatients differ from those who are hospitalized. Importantly, worsening heart failure that requires outpatient management portends a poor prognosis similar to that of hospitalization events.21-23 In the Prospective Comparison of ARNI (angiotensin-receptor-neprilysin inhibitor) with ACEI (angiotensin-converting enzyme inhibitor) to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial (PARADIGM-HF), the risk of all-cause mortality was similar among patients whose first event was a heart failure hospitalization (HR 6.1, 95% CI 5.4-6.8), emergency department visit for heart failure (HR 4.5, 95% CI 3.0-6.7), or intensification of heart failure therapy (HR 5.2, 95% CI 4.2-6.3).22 Similar findings were reported from the Multicenter Automatic Defibrillator Implantation with Cardiac Resynchronization Therapy (MADIT-CRT) trial, where the mortality rates per 100 patient-years were 1.5 in patients without a primary heart failure event, 15.9 in patients with an outpatient heart failure event, and 18.5 in patients with an inpatient heart failure event.21

One risk of adding more components to a composite endpoint is that the magnitude of effect on the overall composite may be diluted if the treatment effect is inconsistent across all components. However, an analysis of data from the PARADIGM-HF trial showed that the effect of sacubitril/valsartan on outpatient worsening was similar to its effect on cardiovascular death and heart failure hospitalizations.22 Another challenge of including outpatient heart failure events in a primary composite endpoint is that the overall treatment effect may be dominated by less severe events, but the increasing evidence supporting the prognostic importance of outpatient worsening provides a rationale for its inclusion.22

Worsening heart failure managed in the outpatient setting should be rigorously defined, well documented and adjudicated irrespective of whether it is a component of a primary composite endpoint or not.24 A variety of definitions for non-hospitalized worsening heart failure have been used in clinical trials12 and generally have required outpatient or emergency department administration of intravenous therapy (i.e., diuretics, vasodilators, or inotropes) for a specific duration (e.g., ≥4 hours) or outpatient intensification of heart failure therapy (e.g., sustained [≥1 month] increase in oral diuretic dose,22 new drug therapy for heart failure22). Inclusion of events based on admission to emergency department or urgent care center in the primary endpoint could be acceptable provided that they are strictly defined (i.e. elevated natriuretic peptides, need of intravenous diuretics and up-titration of therapy) and centrally adjudicated, and that it can convincingly be shown that the subpopulation of heart failure patients admitted to emergency department or urgent care centers is similar regarding disease severity and outcome to patients admitted to hospital, thus providing reassurance that there is no difference in the type or severity of event identified. Given the frequency of these events, their prognostic importance, the evolution in heart failure care, and the global nature of modern trials, the inclusion of outpatient treatment for worsening heart failure in composite primary endpoints may be considered, but its role needs further justification as might be supplied from its use in future clinical trials.

**Functional and Quality of Life Endpoints**

The ability of patients to undertake normal daily activities and to enjoy a reasonable quality of life has become ever more relevant as patients survive longer with heart failure. In addition to a reduction in life expectancy, chronic heart failure is characterized by repeat hospitalizations, often debilitating symptoms and impaired quality of life, and progressive functional decline. Heart failure patients’ complaints generally focus on poorly controlled symptoms and/or functional impairment, which to date has not been the primary objective for the development of new drugs in heart failure. Few studies have robustly evaluated effects of treatment on these aspects of the heart failure patient’s experience.

A composite endpoint reflecting morbidity and mortality provides the most robust assessment of efficacy and safety for a pivotal trial in chronic heart failure. Functional capacity, symptoms, or other patient reported outcome endpoints may be valid primary efficacy endpoints under certain circumstances when the approach is justified by a potential benefit to public health that outweighs the potential risk of incomplete (i.e. ongoing collection of) morbidity and mortality data. However, for most studies, these endpoints would be most accepted as secondary or supportive endpoints to reflect the patient’s and physician’s additional treatment goals. The authors agree that heart failure patients need therapies that affect all aspects of disease burden and the patient’s journey, and different treatment goals may be relevant for different stages of the syndrome.25 This is recognized in the draft EMA Guideline which states that exercise testing objectively evaluates functional capacity in patients with chronic heart failure and may be relevant to measure as a secondary endpoint under certain conditions (e.g., patients with HFpEF).11 A primary endpoint measuring treatment effect on functional capacity, symptoms, or other patient reported outcome endpoints may only be appropriate for use in a pivotal heart failure trial in selected patient populations with an unmet medical need, e.g. patients with end-stage heart failure or patients with specific aetiologies such as hypertrophic cardiomyopathies and amyloidosis, provided that appropriate blinding, with sham procedures or placebo is implemented. However, this depends on the specific type of population, and an assessment of all-cause mortality remains an important part of the safety evaluation to confirm the absence of off-target effects. Clinical trials in heart failure should be sufficiently sized and of an appropriate duration to provide evidence of no harm at the time of registration.

The EMA’s pilot adaptive pathway programme (i.e., gradual expansion of the target population, starting from a population with high medical need, or progressive reduction of uncertainty after initial authorization based on surrogate endpoints) was launched as a to potentially accelerate patients’ access to medicines. It applied primarily to treatments in areas of high medical need where it is difficult to collect data via traditional routes and where large clinical trials would unnecessarily expose patients who are unlikely to benefit from the medicine.26 The newly launched PRIority Medicines (PRIME) scheme27 focuses on medicines with early clinical data that suggest a major therapeutic advantage for patients with conditions where there is an unmet medical need, i.e. for which no satisfactory method of diagnosis, prevention or treatment exists, or, even if such a method exists, the medicinal product concerned will be of major therapeutic advantage to those affected, but these programs only apply to select circumstances. With regard to excluding an increased risk of mortality, it is impractical to specify a single safety margin that would be considered reassuring for all trials, since the margin might conceivably differ according to the patient population. Consistency across all endpoints (i.e., outcome, functional, patient reported outcomes) should be observed to provide supportive evidence of overall improvement. Whether an adaptive pathway approach can be applied to address treatment of a specific heart failure population will require early consultation with EMA for scientific advice.

When used as an endpoint (i.e., primary, secondary, or supportive), functional status may be assessed by a variety of measures (e.g., peak oxygen consumption [VO2], 6-minute walk distance, exercise treadmill or bicycle using heart failure suitable protocols), and each has its strengths and limitations. Validation of the clinical relevance of the endpoint in the target population, as has been done in other disease states,28 is a key factor determining the acceptability of a functional endpoint in a pivotal chronic heart failure trial. The predictive value of these tests is valid only in patients whose exercise capacity is limited by heart failure. In patients with other comorbidities, which are frequent in patients with heart failure, factors such as peripheral muscular deconditioning, arthritis, or low motivation can prematurely terminate the test. Widespread consensus has not been achieved on the minimal relevant treatment effect that would need to be demonstrated for endpoints such as 6-minute walk distance or exercise testing. Conceivably, this treatment effect might also vary according to the specific study population. Notably, improvement in 6-minute walk distance led to the approval of drugs for the treatment of primary pulmonary hypertension,29;30 followed by outcome data after approval. Whether this model could be translated to specific heart failure subsets is uncertain, but the outcome of validation studies in the target population will be a key determinant.

Functional endpoints should be limited to assessments with high reproducibility and reliability, and have protocol-specified processes implemented to maximize reliability of measurements (e.g., repeated baseline and follow-up testing to reduce variability).31 Procedures to minimize drop-outs, losses to follow-up, and missing data; analytic methods to account for death and handle missing data; and designs that reduce bias (i.e. double blinding) are especially critical when these endpoints are chosen for a heart failure trial.

In conclusion, combining traditional mortality/morbidity composite endpoints and functional or patient-reported endpoints in a single composite is of limited value for most studies, but this approach might be useful as a means to increase power and reduce sample size requirements, in situations where traditionally-designed outcome studies are not feasible due to technological or epidemiological limitations. Symptoms would usually overwhelm the entire composite, yielding data that are difficult to interpret, and should generally not be used as a primary endpoint for pivotal chronic heart failure trials of traditional therapies.

**Analytic Methods**

Heart failure is a progressive syndrome characterized by repeat hospital admissions, but traditional time-to-first event analysis only considers the first event. Thus, all events that occur after the first event (i.e., repeat hospitalizations or death if it occurred after the first hospitalization) are ignored in the primary analysis,32 disregarding information that might be clinically meaningful to physicians and patients in establishing the treatment effect. Inclusion of such events may also increase a study’s power if the treatment effect is consistent among first and repeat events.32

Substantial work has been done in recent years applying methods to analyze recurrent events to completed chronic heart failure trial databases.33;34 These post-hoc analyses showed that a substantial number of important clinical events were not included in the primary analysis when only considering the first event; in the CHARM-Preserved trial, the time-to-event analysis only used 53% of all heart failure hospitalizations and 57% of all cardiovascular deaths.33 A similar proportion of events were not included in the time-to-event analysis of the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) trial.34 However, methodological issues need to be addressed, and recurrent event analyses must account for the competing risk of mortality and the lack of independence of repeat events within a given patient.32 Several different analytical methods are available to address these issues, and each has its strengths and limitations, although general agreement among the methods (negative binomial, Andersen-Gill, and joint-frailty model) has been noted.33;34 As suggested by Rogers et al, the choice of the primary analysis method depends on the desired balance between interpretability and robustness of the analysis; population characteristics (e.g., low or high death rates) also plays a role.33 The Efficacy and Safety of LCZ696 Compared to Valsartan on Morbidity and Mortality in Heart Failure Patients with Preserved Ejection Fraction (PARAGON-HF) trial was designed with the primary endpoint of cumulative number of primary composite events of cardiovascular death and total (first and recurrent) heart failure hospitalizations (http://clinicaltrials.gov, NCT01920711).35 The Calcium Upregulation by Percutaneous Administration of Gene Therapy in Patients with Cardiac Disease (CUPID 2) recently used this approach with a joint frailty analysis to assess time-to-recurrent heart hospitalizations accounting for correlated recurrent events within patients and the correlation between recurrent and terminal events.36 Consensus has not been achieved on best practice for presenting recurrent events data, and these decisions may need to be considered on a trial-by-trial basis. At a minimum, regulatory advice on proposed approaches is strongly recommended prior to initiating a heart failure trial which is intended to support product registration and labeling, and sensitivity analyses should be planned to evaluate the robustness of the findings.

**CLINICAL TRIAL DESIGN**

**Patient Population**

The target population enrolled in a pivotal trial should be easily identifiable and generally representative of the intended population post-approval. Enrichment criteria are often employed in modern clinical trials either to 1) define the population and ensure enrollment of patients with the condition (e.g., B-type natriuretic peptide [BNP] or N-terminal-proBNP [NT-proBNP] criteria to confirm the diagnosis of heart failure); 2) ensure enrollment of a sufficiently at-risk population to meet event rate and sample size assumptions; 3) homogenize risk among enrolled patients; or 4) select patients where a positive benefit/risk relationship is most likely based on the documented presence of the target mechanism of action. An enrichment strategy designed to increase the event rate also identifies the patients with the greatest medical need.

If an enrichment approach is applied in a clinical study intended to support product registration, justification that the extrapolation to use in lower risk patients is likely to be required by regulators when a broader indication is claimed. Approved labelling may need to reflect some of the eligibility criteria used in a clinical trial to identify patients with the condition who have the highest likelihood of therapeutic response. This will also depend on the risks. Conversely, the label should not reflect enrollment criteria used solely for the purpose of enriching or homogenizing the risk of the population (e.g., BNP or NT-proBNP above a threshold level, prior heart failure hospitalization), unless the criteria excluded a large proportion of potential patients. If a treatment effect is shown in an enriched population and the results are applied to a lower risk population, the absolute benefit of treatment may be less in the lower risk population, which may also have implications for health technology assessments and payer decisions. Broader regulatory indications allow local authorities and downstream stakeholders to determine how the results most appropriately apply to their populations.

Patients admitted to hospital with acute heart failure should not be enrolled in chronic heart failure trials in the early phase of that admission while the patient is unstable. Many interventions may take place during a hospitalization for acute heart failure (e.g., administration of intravenous diuretic and vasoactive therapies, uptitration of evidence based therapies, implantation of cardiac devices), and these treatment measures may mask the treatment effects of the investigational therapy. It may be valuable, though, to enroll patients hospitalized for heart failure in the hospital setting who are stabilized and not receiving parenteral therapy to evaluate the effect of chronic therapies that are started during the hospitalization, at discharge or in the early post-discharge period (e.g., 30-days post-discharge).

Patients enrolled in ‘chronic’ heart failure trials should generally be clinically stable, although the definition of clinical “stability” should not be confused with the “stability” of concomitant standard care, i.e. routine dynamic adjustment of background medication and other disease management approaches should be permitted in heart failure trials. One pragmatic approach may be to avoid recruiting patients who remain on parenteral therapies or who are in the early phase of hospital admission before decongestion has been achieved.

**Optimal Medical Therapy**

Clinical trials should be conducted against a background of optimal evidence-based care in accordance with treatment practice guidelines.1 However, clinical trials should also reflect real-world practice. Global trials are a necessity to achieve the large patient numbers needed in modern randomized outcome trials, to allow for worldwide regulatory approval, and to assess the generalizability of treatments. Some variation in standard of care across geographic regions is expected, particularly with cardiac devices, because of differences in product availability, reimbursement policies, local standards of care, or other factors that affect patient access.37 Patients enrolled within a region should be representative of local standards of care, and randomization should minimize the impact of any differences in standard of care between groups. Efforts should be made to minimize imbalances in use of standard of care between groups, and lower than expected use of evidence-based therapies will need to be justified to Health Authorities. Given the usually lengthy timeframe required for recruitment and follow-up of randomized trials, changes in standard of care may occur and should be allowed, but also should be documented and justified.

Geographical differences in event rates, as well as treatment responses, have often been observed in heart failure and other cardiovascular clinical trials.38-42 Pre-specified analyses to evaluate the consistency of treatment effect by geographic region are often performed. However, it is important to recognize the limitations of subgroup analyses,43-47 and consider the likelihood that observed differences between subgroups could be due to chance because of multiple testing and the small number of patients, especially when considering regional or individual country differences.

**Run-In Period**

Some clinical trials are designed with a run-in period to improve recruitment efficiency and maximize the ability to retain patients on treatment long-term by excluding patients with tolerability issues.35 In clinical trials where a run-in period is used, consideration should be given to the impact on external validity (i.e., rates of intolerance could be higher in clinical practice since in a clinical trial the run-in selects patients who can tolerate the drug), and whether specific labelling is needed. Run-in periods to improve recruitment efficiency may lead to physician concerns that tolerability and efficacy data are overestimated, which may affect uptake and acceptance of the therapy.48-50

**RESEARCH APPROACHES FOR NOVEL THERAPIES**

Novel treatment approaches to the heart failure patient, such as cell-based, gene, and other bioactive agents, have the potential to significantly increase myocardial performance and clinical status. Over the past 15 years, rapid development of numerous products and modes of administration gave rise to the conduct of a many small clinical studies early in the evolution of the field. Unfortunately, progress has been impeded by simultaneous and often independent clinical studies, uncertainty as to product classification and regulatory guidance, and high costs compared to other therapies (often shouldered by small companies). Perhaps most importantly, the absence of a single first-in-class agent upon which to center substantial early development (unlike many novel pharmaceuticals and devices) has led to important questions regarding the appropriateness and relevance of testing these products in the traditional constructs of randomized, controlled trials. The workshop acknowledged the field’s continued promise, as well as the challenges to acquiring meaningful data, including access to adequately trained investigators, maintaining blinding at a time when agent delivery increasingly utilizes sham procedures for control groups, and site-related logistics for dose preparation.

Consensus was reached among participants that the evidentiary requirements for cell-based or other novel therapies should be conceptually similar to other therapies. Both meaningful clinical benefit and safety need to be demonstrated to support approval. A rationale also exists for accepting functional or patient reported outcome endpoints for these therapies, since patients who may be considered as candidates are likely to be those who remain symptomatic after optimization of other guideline-recommended evidence based therapies. Longer term safety assessments (e.g., 5-10 years beyond original licensing) may be necessary to rule out adverse effects. As above, blinding of patients and/or the assessment team is challenging, but it is essential to the scientific validity of the findings and should be implemented whenever possible with plans for maintaining the blind design carefully detailed. Endpoints should be selected considering not only the evidence required for licensing, but also for payers,51 since these therapies are likely to be costly. An endpoint such as freedom from death, transplant, or mechanical circulatory support might be relevant for these therapies, but durability of the effect will be important to assess, especially from the payer’s standpoint.

Observation of a large treatment effect could potentially support acceleration of patient access to the therapy via, for example, conditional approval approach or PRIME if an unmet need can be established. While this has not been warranted based upon current evidence, many treatments for heart failure are in development and establishing a development pathway for advanced cell-based and non-cellular agents is an important step.

**CONCLUSION**

Patients with chronic heart failure have a reduced life expectancy and diminished quality of life, with high healthcare utilization. The composite endpoint of cardiovascular mortality and heart failure hospitalization provides a clinically meaningful assessment of efficacy, and can be used in most pivotal trials of chronic heart failure therapies, with adequate ascertainment of all-cause mortality to confirm safety regarding increased mortality. Patients with worsening heart failure will increasingly receive care in non-hospitalized settings, and it is recognized that outpatient heart failure events may also represent valid endpoints. The possibility of including repeat events in the primary analysis has opened many opportunities to develop and pilot new methods for statistical analyses that may improve the efficiency as well as the clinical relevance of randomized heart failure trials.

A rationale exists for evaluating functional or patient related outcome endpoints as key secondary or supportive endpoints in chronic heart failure trials. This recognition is a call to researchers to generate evidence for determining minimally important difference thresholds and validating these endpoints as meaningful, not only to improve patients’ symptoms and physical limitations, but also as they relate to reduced event rates.

In order to address the remaining unmet medical needs in heart failure patients, we should endeavor to refine the target patient populations and develop novel therapies. Collaboration among regulators, industry, clinical trialists, cardiologists, payers, and patient organizations will be critical to ensure that scientifically robust and practical solutions to developing new therapeutics in this patient population are implemented.

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References

1. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2016;**18**:891-975.

2. van Riet EE, Hoes AW, Wagenaar KP, Limburg A, Landman MA, Rutten FH. Epidemiology of heart failure: the prevalence of heart failure and ventricular dysfunction in older adults over time. A systematic review. *Eur J Heart Fail* 2016;**18**:242-252.

3. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014;**371**:993-1004.

4. Thorvaldsen T, Benson L, Dahlstrom U, Edner M, Lund LH. Use of evidence-based therapy and survival in heart failure in Sweden 2003-2012. *Eur J Heart Fail* 2016;**18**:503-511.

5. Crespo-Leiro MG, Anker SD, Maggioni AP, Coats AJ, Filippatos G, Ruschitzka F, Ferrari R, Piepoli MF, Delgado Jimenez JF, Metra M, Fonseca C, Hradec J, Amir O, Logeart D, Dahlstrom U, Merkely B, Drozdz J, Goncalvesova E, Hassanein M, Chioncel O, Lainscak M, Seferovic PM, Tousoulis D, Kavoliuniene A, Fruhwald F, Fazlibegovic E, Temizhan A, Gatzov P, Erglis A, Laroche C, Mebazaa A. European Society of Cardiology Heart Failure Long-Term Registry (ESC-HF-LT): 1-year follow-up outcomes and differences across regions. *Eur J Heart Fail* 2016;**18**:613-625.

6. Kaitin KI, Dimasi JA. Pharmaceutical innovation in the 21st century: new drug approvals in the first decade, 2000-2009. *Clin Pharmacol Ther* 2011;**89**:183-188.

7. Jackson N, Atar D, Borentain M, Breithardt G, van Eickels M, Endres M, Fraass U, Friede T, Hannachi H, Janmohamed S, Kreuzer J, Landray M, Lautsch D, Le Floch C, Mol P, Naci H, Samani N, Svensson A, Thorstensen C, Tijssen J, Vandzhura V, Zalewski A, Kirchhof P. Improving clinical trials for cardiovascular diseases: a position paper from the Cardiovascular Roundtable of the European Society of Cardiology. *Eur Heart J* 2016;**37**:747-754.

8. DeMets DL, Pocock SJ, Julian DG. The agonising negative trend in monitoring of clinical trials. *Lancet* 1999;**354**:1983-1988.

9. Massie BM, Berk MR, Brozena SC, Elkayam U, Plehn JF, Kukin ML, Packer M, Murphy BE, Neuberg GW, Steingart RM, . Can further benefit be achieved by adding flosequinan to patients with congestive heart failure who remain symptomatic on diuretic, digoxin, and an angiotensin converting enzyme inhibitor? Results of the flosequinan-ACE inhibitor trial (FACET). *Circulation* 1993;**88**:492-501.

10. Packer M, Narahara KA, Elkayam U, Sullivan JM, Pearle DL, Massie BM, Creager MA. Double-blind, placebo-controlled study of the efficacy of flosequinan in patients with chronic heart failure. Principal Investigators of the REFLECT Study. *J Am Coll Cardiol* 1993;**22**:65-72.

11. European Medicines Agency Committee for Medicinal Products for Human Use (CHMP). Guideline on clinical investigation of medicinal products for the treatment of chronic heart failure. <http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/02/WC500201772.pdf>

12. Anker SD, Schroeder S, Atar D, Bax JJ, Ceconi C, Cowie MR, Crisp A, Dominjon F, Ford I, Ghofrani HA, Gropper S, Hindricks G, Hlatky MA, Holcomb R, Honarpour N, Jukema JW, Kim AM, Kunz M, Lefkowitz M, Le FC, Landmesser U, McDonagh TA, McMurray JJ, Merkely B, Packer M, Prasad K, Revkin J, Rosano GM, Somaratne R, Stough WG, Voors AA, Ruschitzka F. Traditional and new composite endpoints in heart failure clinical trials: facilitating comprehensive efficacy assessments and improving trial efficiency. *Eur J Heart Fail* 2016;**18**:482-489.

13. O'Connor CM, Gattis WA, Ryan TJ. The role of clinical nonfatal end points in cardiovascular phase II/III clinical trials. *Am Heart J* 2000;**139**:S143-S154.

14. Swedberg K, Komajda M, Bohm M, Borer JS, Ford I, Dubost-Brama A, Lerebours G, Tavazzi L. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet* 2010;**376**:875-885.

15. Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, Vincent J, Pocock SJ, Pitt B. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med* 2011;**364**:11-21.

16. Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, Michelson EL, Olofsson B, Ostergren J, Yusuf S, Pocock S, CHARM Investigators and Committees. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. *Lancet* 2003;**362**:759-766.

17. Zannad F, Garcia AA, Anker SD, Armstrong PW, Calvo G, Cleland JG, Cohn JN, Dickstein K, Domanski MJ, Ekman I, Filippatos GS, Gheorghiade M, Hernandez AF, Jaarsma T, Koglin J, Konstam M, Kupfer S, Maggioni AP, Mebazaa A, Metra M, Nowack C, Pieske B, Pina IL, Pocock SJ, Ponikowski P, Rosano G, Ruilope LM, Ruschitzka F, Severin T, Solomon S, Stein K, Stockbridge NL, Stough WG, Swedberg K, Tavazzi L, Voors AA, Wasserman SM, Woehrle H, Zalewski A, McMurray JJ. Clinical outcome endpoints in heart failure trials: a European Society of Cardiology Heart Failure Association consensus document. *Eur J Heart Fail* 2013;**15**:1082-1094.

18. DeVore AD, Allen LA, Eapen ZJ. Thinking Outside the Box: Treating Acute Heart Failure Outside the Hospital to Improve Care and Reduce Admissions. *J Card Fail* 2015;**21**:667-673.

19. Maru S, Byrnes J, Carrington MJ, Chan YK, Thompson DR, Stewart S, Scuffham PA. Cost-effectiveness of home versus clinic-based management of chronic heart failure: Extended follow-up of a pragmatic, multicentre randomized trial cohort - The WHICH? study (Which Heart Failure Intervention Is Most Cost-Effective & Consumer Friendly in Reducing Hospital Care). *Int J Cardiol* 2015;**201**:368-375.

20. Stewart S, Jenkins A, Buchan S, McGuire A, Capewell S, McMurray JJ. The current cost of heart failure to the National Health Service in the UK. *Eur J Heart Fail* 2002;**4**:361-371.

21. Skali H, Dwyer EM, Goldstein R, Haigney M, Krone R, Kukin M, Lichstein E, McNitt S, Moss AJ, Pfeffer MA, Solomon SD. Prognosis and response to therapy of first inpatient and outpatient heart failure event in a heart failure clinical trial: MADIT-CRT. *Eur J Heart Fail* 2014;**16**:560-565.

22. Okumura N, Jhund PS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Swedberg K, Zile MR, Solomon SD, Packer M, McMurray JJ. Importance of Clinical Worsening of Heart Failure Treated in the Outpatient Setting: Evidence From the Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial (PARADIGM-HF). *Circulation* 2016;**133**:2254-2262.

23. Mallick A, Gandhi PU, Gaggin HK, Ibrahim N, Januzzi JL. The Importance of Worsening Heart Failure in Ambulatory Patients: Definition, Characteristics, and Effects of Amino-Terminal Pro-B Type Natriuretic Peptide Guided Therapy. *JACC Heart Fail* 2016.

24. Hicks KA, Tcheng JE, Bozkurt B, Chaitman BR, Cutlip DE, Farb A, Fonarow GC, Jacobs JP, Jaff MR, Lichtman JH, Limacher MC, Mahaffey KW, Mehran R, Nissen SE, Smith EE, Targum SL. 2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Cardiovascular Endpoints Data Standards). *J Am Coll Cardiol* 2015;**66**:403-469.

25. Zachariah D, Taylor J, Rowell N, Spooner C, Kalra PR. Drug therapy for heart failure in older patients-what do they want? *J Geriatr Cardiol* 2015;**12**:165-173.

26. European Medicines Agency. Adaptive pathways to patients: report on the initial experience of the pilot project. <http://www.ema.europa.eu/docs/en_GB/document_library/Report/2014/12/WC500179560.pdf>

27. European Medicines Agency Committee for Medicinal Products for Human Use (CHMP). Enhanced early dialogue to facilitate accelerated assessment of PRIority MEdicines (PRIME). <http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2016/03/WC500202636.pdf>

28. Nathan SD, du Bois RM, Albera C, Bradford WZ, Costabel U, Kartashov A, Noble PW, Sahn SA, Valeyre D, Weycker D, King TE, Jr. Validation of test performance characteristics and minimal clinically important difference of the 6-minute walk test in patients with idiopathic pulmonary fibrosis. *Respir Med* 2015;**109**:914-922.

29. Galie N, Hoeper MM, Humbert M, Torbicki A, Vachiery JL, Barbera JA, Beghetti M, Corris P, Gaine S, Gibbs JS, Gomez-Sanchez MA, Jondeau G, Klepetko W, Opitz C, Peacock A, Rubin L, Zellweger M, Simonneau G. Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). *Eur Heart J* 2009;**30**:2493-2537.

30. Taichman DB, Ornelas J, Chung L, Klinger JR, Lewis S, Mandel J, Palevsky HI, Rich S, Sood N, Rosenzweig EB, Trow TK, Yung R, Elliott CG, Badesch DB. Pharmacologic therapy for pulmonary arterial hypertension in adults: CHEST guideline and expert panel report. *Chest* 2014;**146**:449-475.

31. American Thoracic Society. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002;**166**:111-117.

32. Pocock SJ, Clayton TC, Stone GW. Design of Major Randomized Trials: Part 3 of a 4-Part Series on Statistics for Clinical Trials. *J Am Coll Cardiol* 2015;**66**:2757-2766.

33. Rogers JK, Pocock SJ, McMurray JJ, Granger CB, Michelson EL, Ostergren J, Pfeffer MA, Solomon SD, Swedberg K, Yusuf S. Analysing recurrent hospitalizations in heart failure: a review of statistical methodology, with application to CHARM-Preserved. *Eur J Heart Fail* 2014;**16**:33-40.

34. Rogers JK, Jhund PS, Perez AC, Bohm M, Cleland JG, Gullestad L, Kjekshus J, van Veldhuisen DJ, Wikstrand J, Wedel H, McMurray JJ, Pocock SJ. Effect of rosuvastatin on repeat heart failure hospitalizations: the CORONA Trial (Controlled Rosuvastatin Multinational Trial in Heart Failure). *JACC Heart Fail* 2014;**2**:289-297.

35. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz M, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR. Baseline characteristics and treatment of patients in prospective comparison of ARNI with ACEI to determine impact on global mortality and morbidity in heart failure trial (PARADIGM-HF). *Eur J Heart Fail* 2014;**16**:817-825.

36. Greenberg B, Butler J, Felker GM, Ponikowski P, Voors AA, Desai AS, Barnard D, Bouchard A, Jaski B, Lyon AR, Pogoda JM, Rudy JJ, Zsebo KM. Calcium upregulation by percutaneous administration of gene therapy in patients with cardiac disease (CUPID 2): a randomised, multinational, double-blind, placebo-controlled, phase 2b trial. *Lancet* 2016;**387**:1178-1186.

37. Greene SJ, Fonarow GC, Solomon SD, Subacius H, Maggioni AP, Bohm M, Lewis EF, Zannad F, Gheorghiade M. Global variation in clinical profile, management, and post-discharge outcomes among patients hospitalized for worsening chronic heart failure: findings from the ASTRONAUT trial. *Eur J Heart Fail* 2015;**17**:591-600.

38. Blair JE, Zannad F, Konstam MA, Cook T, Traver B, Burnett JC, Jr., Grinfeld L, Krasa H, Maggioni AP, Orlandi C, Swedberg K, Udelson JE, Zimmer C, Gheorghiade M. Continental differences in clinical characteristics, management, and outcomes in patients hospitalized with worsening heart failure results from the EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study with Tolvaptan) program. *J Am Coll Cardiol* 2008;**52**:1640-1648.

39. Kristensen SL, Kober L, Jhund PS, Solomon SD, Kjekshus J, McKelvie RS, Zile MR, Granger CB, Wikstrand J, Komajda M, Carson PE, Pfeffer MA, Swedberg K, Wedel H, Yusuf S, McMurray JJ. International geographic variation in event rates in trials of heart failure with preserved and reduced ejection fraction. *Circulation* 2015;**131**:43-53.

40. Mentz RJ, Kaski JC, Dan GA, Goldstein S, Stockbridge N, Alonso-Garcia A, Ruilope LM, Martinez FA, Zannad F, Pitt B, Fiuzat M, O'Connor CM. Implications of geographical variation on clinical outcomes of cardiovascular trials. *Am Heart J* 2012;**164**:303-312.

41. Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, Clausell N, Desai AS, Diaz R, Fleg JL, Gordeev I, Harty B, Heitner JF, Kenwood CT, Lewis EF, O'Meara E, Probstfield JL, Shaburishvili T, Shah SJ, Solomon SD, Sweitzer NK, Yang S, McKinlay SM. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med* 2014;**370**:1383-1392.

42. Wedel H, DeMets D, Deedwania P, Fagerberg B, Goldstein S, Gottlieb S, Hjalmarson A, Kjekshus J, Waagstein F, Wikstrand J. Challenges of subgroup analyses in multinational clinical trials: experiences from the MERIT-HF trial. *Am Heart J* 2001;**142**:502-511.

43. Pocock SJ, Assmann SE, Enos LE, Kasten LE. Subgroup analysis, covariate adjustment and baseline comparisons in clinical trial reporting: current practice and problems. *Stat Med* 2002;**21**:2917-2930.

44. Yusuf S, Wittes J, Probstfield J, Tyroler HA. Analysis and interpretation of treatment effects in subgroups of patients in randomized clinical trials. *JAMA* 1991;**266**:93-98.

45. Assmann SF, Pocock SJ, Enos LE, Kasten LE. Subgroup analysis and other (mis)uses of baseline data in clinical trials. *Lancet* 2000;**355**:1064-1069.

46. Pocock SJ, Lubsen J. More on subgroup analyses in clinical trials. *N Engl J Med* 2008;**358**:2076-2077.

47. Wang R, Lagakos SW, Ware JH, Hunter DJ, Drazen JM. Statistics in medicine--reporting of subgroup analyses in clinical trials. *N Engl J Med* 2007;**357**:2189-2194.

48. Lainscak M, Coats AJ. The PARADIGM of ARNI's: Assessing reasons for non-implementation in heart failure. *Int J Cardiol* 2016;**212**:187-189.

49. Dec GW. LCZ696 (sacubitril/valsartan): can we predict who will benefit? *J Am Coll Cardiol* 2015;**66**:2072-2074.

50. Filippatos G, Farmakis D, Parissis J, Lekakis J. Drug therapy for patients with systolic heart failure after the PARADIGM-HF trial: in need of a new paradigm of LCZ696 implementation in clinical practice. *BMC Med* 2015;**13**:35.

51. Eichler HG, Hurts H, Broich K, Rasi G. Drug Regulation and Pricing--Can Regulators Influence Affordability? *N Engl J Med* 2016;**374**:1807-1809.