**Assessing the eligibility criteria in phase III randomized controlled trials of drug therapy in heart failure with preserved ejection fraction: The critical play off between a ‘pure’ patient phenotype and the generalizability of trial findings**

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**Abstract**

**Aims**

To investigate the effect of the different eligibility criteria used by phase III clinical studies in heart failure with preserved ejection fraction (HFpEF) on patient selection, phenotype and survival.

**Methods and Results**

We applied the key eligibility criteria of seven phase III HFpEF studies (DIG-Ancillary, CHARM-Preserved, PEP-CHF, I-PRESERVE, J-DHF, TOPCAT and PARAGON-HF [on-going]) to a typical and well-characterised HFpEF population (n=557) seen in modern European cardiological practice. Follow up was available for a minimum of 24 months in each patient.

Increasing the number of study eligibility criteria identifies a progressively smaller group of patients from real life practice suitable for recruitment into clinical trials; using the J-DHF criteria, 81% of our clinic patients would have been eligible, whereas, the PARAGON-HF criteria significantly reduced this proportion to 32%. The patients identified from our clinical population had similar mortality rates using the different criteria, which were consistently higher than those reported in the actual clinic trials.

**Conclusions**

Trial eligibility criteria have become stricter with time which reduces the number of eligible patients, affecting both generalizability of any findings and feasibility of completing an adequately powered trial. We could not find evidence that the additional criteria employed in more recent randomised trials in HFpEF have identified patients at higher risk of all-cause mortality. **Introduction**

Heart failure with preserved ejection fraction (HFpEF) is common and associated with a high mortality and significant morbidity.[[1](#_ENREF_1)]  Randomized clinical trials have failed to identify any pharmacological therapies that improve survival in this condition.[[2-7](#_ENREF_2)] The probable reason for these neutral trials is that patients were recruited with heterogeneous clinical phenotypes and diverse risk profiles for cardiovascular outcomes.[[8-12](#_ENREF_8)]

The number of eligibility criteria for phase III randomized trials in HFpEF have increased over the past 25 years (Table 1) in an attempt to better identify a disease phenotype that might respond to specific drug therapies.[[13-15](#_ENREF_13)] While tightening eligibility criteria may have the desired effect of selecting a more homogenous group of patients at higher risk of the relevant clinical outcomes (such as death or heart failure hospitalization), this must be balanced against the challenges of patient identification and recruitment.[[16](#_ENREF_16)]

We set out to estimate the effect of the different eligibility criteria used in the phase III randomized trials of drug therapy in HFpEF published to date, and in the on-going PARAGON-HF study (clinicaltrials.gov identifier: NCT01920711) (Table 1) on likely mortality rates and eligibility for enrolment in a typical HFpEF population seen in modern European cardiological practice.

**Methods**

Consecutive patients referred to a diagnostic heart failure clinic at a hospital in South London between January 2005 and November 2012, were studied. This centre provides secondary and tertiary cardiac services for a population of 1.3 million and 3.5 million people, respectively. A diagnosis of heart failure was only made if the patient satisfied the contemporary international heart failure guidelines at the time of consultation based on symptom assessment, clinical evaluation, echocardiography and (in the vast majority) natriuretic peptide level assessment.[[17-22](#_ENREF_17)]. Those that were considered to have heart failure by the consultant heart failure cardiologist in clinic were prospectively entered into a hospital database. This database was used as a sampling frame for this study.

Patients diagnosed with heart failure who had an ejection fraction (EF) >40% derived from echocardiography (the threshold used in the CHARM-Preserved, PEP-CHF and J-DHF trials) were used as the sample ‘typical’ HFpEF population. Two cardiologists retrospectively reviewed the history and investigations of all these patients and identified those who would fulfil the key select recruitment criteria of the phase III studies. These key select criteria were EF, previous hospitalization, markers of diastolic dysfunction and natriuretic peptide concentration as inclusion criteria and age, renal dysfunction and presence of other cardiomyopathies (hypertrophic/restrictive/dilated, recovered heart failure with reduced ejection fraction, left sided valvular heart disease and pulmonary hypertension not related to left heart disease) as exclusion criteria as detailed in Table 1 and Supplementary Appendix-S1. The trials did have other criteria (Supplementary Appendix-S2), which were not adopted by our study as they were either unique to one of the trials e.g. PEP-CHF specified that patients should be able to walk without assistance of another, or involved investigations that would not routinely be performed in all heart failure patients.

A previous history of heart failure admission was defined as any hospital admission with heart failure symptoms and signs requiring treatment with intravenous diuretics- this was ascertained from review of the clinical notes and investigations performed.

Diastolic dysfunction formed part of the inclusion criteria for PEP-CHF, I-Preserve and PARAGON-HF. Each trial had a combination of varying criteria to define diastolic dysfunction, which we have simplified in this study to markers of cardiac structural disease consistent with left ventricular diastolic dysfunction; namely left atrial dilatation (left atrial diameter ≥38mm or left atrial area ≥ 20cm2) and/or left ventricular hypertrophy (LVH) defined as septal or posterior wall thickness ≥11mm, in keeping with recent guidelines[[23](#_ENREF_23)] and the PARAGON-HF criteria.

Follow-up survival data were comprehensively available for all patients for at least 24 months via electronic data linkage with the United Kingdom Office of National Statistics. Twenty-four months was the minimum length of time of complete follow-up as this was the period between November 2012 (the last date we included heart failure patients from the clinic into this study) and the censoring date we used to obtain mortality data from the Office of National Statistics.

The electronic patient records were retrospectively reviewed at the censor date to determine the number of heart failure hospitalizations at our centre following initial assessment in the diagnostic heart failure clinic.

This study complies with the Declaration of Helsinki and was given institutional NHS ethical approval.

**Statistical analysis**

Continuous variables are presented as mean ± standard deviation (SD) and compared by analysis of variance. Non parametric data were log transformed prior to statistical testing. Categorical variables are reported as number (percentage) and compared by chi-square test (using the exact method where feasible). Differences in variances of continuous variables were assessed using Levene’s test.

All-cause mortality was presented as event/1000 patient years and calculated as: ([number of deaths/population of patients] x [1000/mean years of follow up]). For the clinic data, we opted to display annualized mortality rates based on two years of follow-up; to calculate the event rate of the individual phase III studies we used the data presented in the primary results paper using the median/mean follow-up described. Several sensitivity analyses were performed to investigate the effect of adopting more stringent criteria to diagnose heart failure and lengthening the follow-up time on mortality rates. Annualized mortality rates were calculated: 1) on patients who only had either a previous heart failure hospitalization or were on diuretics (sensitivity analysis 1); 2) on patients who had a previous heart failure hospitalization and were on diuretics (sensitivity analysis 2); and 3) over a mean of three, four and five years follow-up.

Hospitalized heart failure rate was presented as admissions/patient year and calculated as: (number of hospitalizations for heart failure/ population of patients/ mean years of follow-up).

A P value of <0.05 was considered statistically significant. The patient populations selected by the different criteria were each compared to DIG-Ancillary (the first phase III study in HFpEF). Post hoc multiple comparisons were performed using Newman-Keuls correction for continuous variables and Bonferroni corrected z-tests for categorical data. Data were analysed using SPSS (IBM v22).

**Results**

1366 patients were identified as having heart failure during the study period. Of these 809 (59.2%) had heart failure with a reduced ejection fraction (HFrEF), the remaining 557 (40.8%) had an EF> 40% and this population of HFpEF is more fully described in Table 2 and Supplementary Appendices- S3-5). The median NT-proBNP in this population was 2899 pg/mL (interquartile range 1045-7760) (data missing in 30 patients) (Supplementary Appendices- S3 and S4). Only seven patients had an initial clinic NT-proBNP <125 pg/mL (the threshold for non-acute onset heart failure in recent international guidelines [[17](#_ENREF_17)]). The case notes of these seven patients were further reviewed to confirm whether the diagnosis of heart failure was accurate: 3 had a cardiomyopathy (restrictive/hypertrophic), 2 had a dilated cardiomyopathy and 2 had recovered HFrEF (see Supplementary Appendix- S1). Three hundred and sixty-seven (65.8%) of the patients had a preceding hospitalization for heart failure decompensation requiring intravenous diuretic therapy. Four hundred and twelve (73.8%) of the cohort with an EF>40% had evidence of diastolic dysfunction with either left atrial dilatation or left ventricular hypertrophy. Three hundred and ninety-three (74%) patients were on a diuretic (loop, thiazide or aldosterone receptor antagonist); data were missing in 24 patients (Supplementary Appendix- S3).

The estimated population from this outpatient clinic that fulfilled eligibility criteria for different phase III HFpEF trials (Table 1) are described in Figure 1 and Supplementary Appendix-S3. Increasing the number of entry criteria reduced the percentage of eligible patients from as high as 81.1% using the Japanese Diastolic Heart Failure (J-DHF) trial criteria to as low as 30.7% using PARAGON-HF criteria.

Compared to the patients selected using the DIG-Ancillary criteria, an older cohort was selected using the criteria of PEP-CHF, I-PRESERVE and PARAGON-HF (Table 2, Supplementary Appendix-S3). PEP-CHF criteria also identified a population with a greater proportion of atrial fibrillation.

The age and past medical history of patients who were included in each of the published trials were compared with the patients who meet the eligibility criteria in our ‘real-world’ HF register (Table 2). Applying the different trial criteria identified different patient subgroups within our total population. Overall, our population was older, more likely to have AF, and less likely to have diabetes and hypertension than those that fulfilled the criteria for the trials listed (Table 2).

All-cause mortality standardised to 1000 patient years for the population in the published phase III studies and our HFpEF population from clinic are presented in Figure 2. There is a significant difference in survival between those who were enrolled in the published trials and those patients from our clinic population with the latter systematically having a higher mortality rate (+59.2 deaths/1000 patient years, 95% confidence interval: 36.8, 81.6, p<0.001). However, there were no differences in mortality rates across the seven different clinic populations filtered by trial criteria (Figure 2). The sensitivity analyses showed that when the phase III trial criteria were applied to a more refined subset of our clinic population (1. those with either a heart failure hospitalization or being treated with diuretics; and 2. those that had a history of heart failure hospitalization and were concurrently on diuretics) that the annualized all-cause mortality event rate increased (statistically non-significant) and remained significantly higher than those reported in the phase III clinical trials (Supplementary Appendix-S6). Similarly increasing the length of follow-up in our clinic population did not significantly alter event rate (Supplementary Appendix-S7).

The cause of death, as stated on death certification was available in 39 out of 126 (31.0%) deceased HFpEF patients. Of these 39 deaths, 10 (25.6%) were cardiac (heart failure or sudden cardiac) in origin.

Hospitalized heart failure rates were calculated over an average follow-up period of 3.9 years. The hospitalization rate varied from 0.58-1.09 admissions/year depending on which selection trial criteria were applied (Figure 3).

**Discussion**

The main findings of this study are: 1) real-world clinic patients with HFpEF have a significantly higher rate of all-cause mortality than those recruited into phase III clinical trials and 2) tighter eligibility criteria greatly reduces the feasibility of recruitment and the potential generalizability of any findings without increasing trial event rates (all-cause mortality).

Although it is recognised that the mortality rate of patients with HFpEF is higher in registry and observational studies compared to phase III clinical studies, the populations studied have been derived using different definitions of HFpEF and hence are not easily comparable.[[11](#_ENREF_11), [15](#_ENREF_15)] We have addressed this shortcoming by comparing crude mortality rates from clinical trials to those of a heart failure cohort derived by applying similar definitions of HFpEF and found that the reported mortality rate in clinical trials was approximately half of that seen in the cohort derived from a heart failure clinic using the same key eligibility criteria. The underlying reasons for this have been previously debated and in our population are likely to be related to the large disparity in age between the patients recruited into clinical trials and the clinic patients (Table 2).[[24](#_ENREF_24), [25](#_ENREF_25)] Interestingly, applying the different trial criteria to our clinic patients, selects different cohorts of varying ages, prevalence of co-morbidities and risk of further heart failure hospitalization. The data in Table 2 suggests that older patients are more prone to atrial fibrillation, which is unsurprising. Our reported one-, two- and three-year annualized mortality rates were comparable to those reported in a meta-analysis of 31 heart failure studies (24 of which were observational) and included 10, 347 patients with HFpEF (12%, 23%, 31% vs. 11%, 18% and 25%; clinic patients satisfying DIG-Ancillary criteria vs. MAGGIC group).[[26](#_ENREF_26)]

Geographical variation in mortality rate has been demonstrated in clinical trials. In the placebo arm of the TOPCAT trial, patients recruited from Russia/Georgia had a 2-3 fold lower mortality rate than those from the Americas.[[27](#_ENREF_27)] There were important differences in patient characteristics and responses to spironolactone between the two regions. A possible contributor to this discrepancy was that the majority (90%) of patients recruited from Russia/Georgia satisfied the recent heart failure hospitalization inclusion criterion, which was unadjudicated and may have led to the recruitment of patients without heart failure as opposed to the more objective alternative of an elevated natriuretic peptide level.

To increase the likelihood of recruiting only patients with heart failure, trialists are increasingly adopting stricter and more objective entry criteria with the aim of identifying a ‘purer’ phenotype. However, increasing the number of study eligibility criteria identifies a progressively smaller group of patients from real life practice; using the PARAGON-HF criteria, less than one third of our clinic patients would have been eligible. This diminishes the generalizability of any findings and subsequent implementation of any positive results into routine practice.[[24](#_ENREF_24), [28](#_ENREF_28)] This is not unique to the HFpEF population and has also been reported in the HFrEF population who actually have evidence-based therapies that improve cardiovascular endpoints.[[17](#_ENREF_17)] Qualitative research has identified physician concerns regarding the generic translation of trial findings to subgroups of their heart failure patient population that were not well represented in clinical trials (in particular the elderly and those with multiple co-morbidities) as a barrier to implementation of the trial findings.[[29-31](#_ENREF_29)]

Another undesirable effect of increasing the number of eligibility criteria is that it makes recruitment more challenging. On reviewing the previous phase III HFpEF studies, PEP-CHF and J-DHF were prematurely stopped due to difficulty in recruitment and hence were underpowered [[3](#_ENREF_3), [6](#_ENREF_6)], whereas I-PRESERVE and TOPCAT, which had adaptive trial designs, compensated for a slower than expected enrolment rate by increasing the follow up period to ensure the required number of events occurred to adequately power the trials.[[4](#_ENREF_4), [12](#_ENREF_12), [32](#_ENREF_32)]

The solutions to these problems are likely to be multifaceted but a change in strategy for patient selection is needed for future HFpEF trials.[[9](#_ENREF_9), [10](#_ENREF_10), [12-14](#_ENREF_12), [24](#_ENREF_24)] Current opinion supports using criteria that will identify pathophysiologically distinct populations (e.g. HFpEF characterised by right ventricular dysfunction and pulmonary hypertension) with an investigational intervention that targets the key abnormality in question (e.g. soluble guanylate cyclase stimulators).[[12](#_ENREF_12), [14](#_ENREF_14)] Patients with co-morbidity and advanced age should not automatically be excluded if heart failure is objectively present. Furthermore, endpoints should be chosen that are clinically meaningful for the HFpEF population and are likely to be affected by the investigational drug. Three such endpoints are cardiovascular mortality (as opposed to all-cause mortality, which includes non-cardiac deaths that are unlikely to be improved by cardiovascular medications), heart failure hospitalization and quality of life. However, these changes may make recruitment harder, prolong study duration and increase trial costs, all which are undesirable. A possible solution to these problems is adoption of novel trial designs such as the registry- based randomized clinical trial, which combines the benefits of lower cost, larger scale and improved generalizability of observational registries with the scientific rigor of prospective randomization.[[33](#_ENREF_33), [34](#_ENREF_34)] Currently this very promising research method, which has already been used in the acute myocardial infarction setting,[[35](#_ENREF_35)] is feasible only in countries which have a well-developed, comprehensive and universal electronic health care environment such as in Scandinavia or Scotland.

**Limitations**

This is a retrospective, single-centre study, which is subject to selection bias that may affect the external validity of any conclusions. A key limitation is that we applied only selected eligibility criteria of the phase III HFpEF trials to our clinic population and hence we cannot accurately demonstrate the consequences of the different eligibility criteria used by the various trials.

The strengths of our data are that they are real-world, comprehensive and our patients are well characterised and the majority had natriuretic peptide levels measured. All-cause mortality was the main outcome studied as this is well defined and comprehensively ascertainable in our population. Other endpoints, such as heart failure hospitalization and cardiovascular mortality are often preferred as primary outcomes in modern HFpEF trials but we do not have complete or adjudicated data on these endpoints in our clinic population. The heart failure hospitalization rate we have presented may be an underestimate as patients may have been hospitalized at other institutes and we had no access to these data. We were unable to confidently ascertain the cause of death in the majority of our patients as they died either at home or at other hospitals.

**Conclusion**

In conclusion, there is a large discrepancy between mortality rates in phase III HFpEF trials and a clinic population chosen using similar criteria. Trial eligibility criteria have become stricter with time, which has reduced the number of eligible patients and this has a consequence on both generalizability of trial findings and the feasibility of completing an adequately powered study. We could not find evidence that the additional criteria employed in more recent randomised trials in HFpEF have identified patients at higher risk of mortality.

**Funding**

HP, CH, CDM and MRC are in part supported by the NIHR Cardiovascular Biomedical Research Unit at the Royal Brompton Hospital and National Heart and Lung Institute, Imperial College.

**Conflicts of interest**

Prof. Cowie reports personal fees from Novartis, during the conduct of the study; personal fees from Servier, grants and personal fees from Bayer, grants and personal fees from ResMed, personal fees from St Jude Medical, personal fees from Boston Scientific, personal fees from Medtronic, personal fees from Pfizer, personal fees from Daiichi-Sankyo, outside the submitted work. Prof. Di Mario reports grants from Medtronic, personal fees from Medtronic, outside the submitted work. All other authors report no conflicts of interests.

**Legends**

**Figure 1: The effect of increasing eligibility criteria used in phase III trials of heart failure with preserved ejection fraction on identifying suitable patients for inclusion from a heart failure clinic.** Dig-A- Dig-Ancillary.

**Figure 2: Annualized all-cause mortality event rate/1000 patient years in patients meeting the entry criteria for various phase III trials from a heart failure (HF) clinic and from the published trial data.** The global P value compares event rates between the published trial data and the clinic population satisfying the eligibility criteria of each trial.

**Figure 3: Heart failure hospitalization rate per patient year in patients meeting the entry criteria for various phase III trials from a heart failure (HF) clinic.** \* denotes significant difference (P<0.05) in hospitalization rate compared to the clinic population satisfying the eligibility criteria of the DIG-Ancillary trial.

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Figure 1



Figure 2



Figure 3

