Application of eligibility criteria from DAPA-HF, EMPEROR-Reduced, and PARADIGM-HF trials to a population with heart failure with reduced ejection fraction at a specialized cardiology Clinic in Medellin, Colombia: A Retrospective Cohort Study

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Abstract

Introduction: The evidence for the pharmacological treatment of heart failure is based on randomized clinical trials with strict inclusion and exclusion criteria. Objectives: To evaluate the proportion of patients with chronic heart failure from an outpatient cohort who would be eligible for the trials DAPA-HF, EMPEROR-reduced, and PARADIGM-HF, and to determine potential differences between study populations.

Methods: Through revision of medical records, we calculated the proportion of patients who would have been eligible for each study and evaluated the incidence of heart failure hospitalizations and all-cause mortality during this period.

Results: A total of 446 patients were included in the cohort. Approximately 75% would be ineligible for the trials, mainly because of their comorbidities. Ineligible patients had a higher all-cause mortality, but a similar incidence of hospitalization.

Conclusion: Approximately 1 in 4 patients from a heart failure clinic in Medellin, Colombia would meet the eligibility criteria for the DAPA-HF, EMPEROR-reduced, and PARADIGM-HF trials. These findings highlight the need to complement randomized clinical trials with real-world data.

Keywords: Heart failure, eligibility, applicability, dapagliflozin, empagliflozin, sacubitril-valsartan.

Introduction: Heart failure (HF) is a disease with a high burden of morbidity and mortality worldwide. Currently, approximately 64 million people worldwide are living with HF, corresponding to a prevalence of 2% (1). Despite implemented treatments, mortality remains around 50% at 5 years (2). According to national and international guidelines, optimal pharmacological management for HF with reduced left ventricular ejection fraction (HFrEF) requires the simultaneous use of Angiotensin Receptor–Neprilysin Inhibitor (ARNI), beta-blockers (BB), mineralocorticoid receptor antagonists (MRAs), and sodium-glucose co-transporter 2 inhibitors (iSGLT2) (3–5). The recommendations for ARNI and iSGLT2 are based on the most representative randomized clinical trials (RCTs) in recent years, such as DAPA-HF, EMPEROR-Reduced (EMPEROR-R), and PARADIGM-HF, which demonstrated a reduction in the composite outcome of cardiovascular mortality and HF hospitalization with the use of dapagliflozin, empagliflozin, and sacubitril-valsartan, respectively (6–8).

Randomized controlled trials (RCTs) are considered the gold standard for assessing the effects of interventions due to their high internal validity. However, characteristics such as inclusion and exclusion criteria can pose challenges in generalizing clinical outcomes to other populations. For instance, the Latin American population may exhibit different responses to medications due to its younger age, distinct socioeconomic, anthropometric, and clinical factors. Adherence to treatments and prescription of therapies according to guideline recommendations also vary. These differences translate into higher mortality rates and frequency of HF hospitalizations (9).

In Colombia, some differences have been described, including a lower proportion of atrial fibrillation (AF), a higher frequency of moderate to severe left ventricular dysfunction, and lower utilization of implantable devices (10). Moreover, the implementation of therapies used in RCTs can take years and may vary based on various clinical and demographic patient characteristics. (11).

Thus, the population enrolled in RCTs may differ from the real-world population, and their external validity requires critical analysis and better patient selection for applying the obtained results. For example, a study that used the Spanish EAHFE registry to assess the applicability of the RELAX-AHF trial found that only 17.4% of patients would be eligible and demonstrated that the Spanish cohort had older patients, a higher proportion in New York Heart Association (NYHA) functional class I-II, and a higher proportion receiving optimal therapy, among other differences (12).

Therefore, this research evaluated the proportion of patients with chronic HFrEF from an outpatient clinic specialized in cardiology who would meet the inclusion and exclusion criteria of the DAPA-HF, EMPEROR-R, and PARADIGM-HF studies. This study also aimed to determine potential differences in clinical-demographic and therapeutic variables between the local cohort and the patients in the original studies. Additionally, the outcomes of mortality and HF hospitalizations were compared between local cohort patients who would have been eligible for the original studies and those who would not have been eligible.

Methods

Study Design, Setting, and Participants: A retrospective cohort study was conducted using an existing administrative database that included all patients admitted to a heart failure clinic in Medellín, Colombia. The study included patients from the registry who were admitted between December 2014 and February 2021. Patients aged 18 years or older with a history of HFrEF (≤40%) and a minimum follow-up of 27 months (based on the longest median follow-up of the three RCTs). Follow-up was conducted by reviewing electronic medical records from the cardiology visits.

Variables and Data Sources: Fifty clinical and demographic variables of patients at the time of admission to the heart failure clinic and at the closest follow-up to 27 months were extracted and included from the electronic medical records, including comorbidities, history of heart failure-related hospitalizations, interventions related to acute myocardial infarction, cardiac devices, relevant laboratory test results closest to clinic admission, and 53 variables related to the prescription and dosage of medications for heart failure management at the beginning and end of the follow-up period. Additionally, the incidence of heart failure hospitalizations was assessed (defined as the record of acutely decompensated heart failure during a hospitalization in the medical records or reported in one of the follow-up outpatient visits). The occurrence of all-cause mortality was also evaluated, with the date of death obtained from the Administrative System for Social Security Resources (ADRES) of the Ministry of Health in Colombia. The cause of death (cardiovascular or non-cardiovascular) was determined by

reviewing the clinical records of patients who died within the institution or through voluntary information obtained by phone calls to family members of the patient.

Finally, the proportion of patients in the local cohort who met the inclusion and exclusion criteria for each of the original studies (DAPA-HF, EMPEROR-R, and PARADIGM-HF) was determined.

Bias Control: To control the quality of collected information, the study personnel underwent training to achieve consistency in data collection and definition of inclusion and exclusion criteria. Any doubts regarding data were resolved through discussion among the investigators. At the end of data collection, outliers or missing data were reviewed and modified if necessary. The final review of inclusion and exclusion criteria for the original studies was conducted through agreement among the principal investigators.

Sample Size: All patients who met the eligibility criteria described constituted the study sample.

Statistical Methods: Categorical variables were summarized as absolute frequencies and percentage estimates, while continuous variables were summarized as means and standard deviations (SD) or medians and interquartile ranges (IQR). The absolute frequency and percentage estimate of patients who fulfilled the characteristics of the original studies were calculated. Using the inclusion and exclusion criteria of each original study, six different cohorts were obtained. Cohorts A (A-DAPA-HF, A-EMPEROR-R, and A-PARADIGM-HF) consisted of patients who met the eligibility criteria for each study, while cohorts B (B-DAPA-HF, B-EMPEROR-R, and B-PARADIGM-HF) included patients who did not meet the criteria. Univariate analysis was then conducted to compare sociodemographic and clinical variables between Cohorts A and the population of each original study and Cohorts B and the population of each original study. Differences between groups were analyzed using the Student's t-test for continuous variables and chi-square test for proportions. Kaplan-Meier survival curves were constructed for the composite outcome of cardiovascular death and heart failure hospitalization, as well as for all-cause mortality and heart failure hospitalization, for cohorts A and B of each study. Data analysis was performed using STATA v17 and “R” v4.1.2; R Core Team 2021. No imputations were done for missing data.

Ethical considerations: The study adhered to the principles of the Helsinki Declaration (13). The project was approved by the ethics committee of the institution. Since no direct interventions were performed on patients and participant identities were protected, informed consent was not required.

Results

Participants: The database consisted of 1,741 potentially eligible patients, of whom 1,295 were excluded and ultimately, 446 patients were included (Figure 1).

Of the 446 patients in the study cohort, 119 (26.7%) would meet the eligibility criteria for the DAPA-HF study, 112 (25.1%) for PARADIGM-HF, and 112 (25.1%) for EMPEROR-R. The main reasons of ineligibility included hypotension at admission, acute myocardial infarction (AMI) within 3 months of admission, and comorbidities such as pulmonary disease, cancer, or renal dysfunction, (Figure 2).

Descriptive data

Baseline characteristics*:* The study cohort patients had a mean age of 65 years (SD 13.9), 35.8% were female, had an average body mass index (BMI) of 24.8, ischemic etiology of heart failure was present in 45%, and the majority had NYHA class II at admission (49.3%) with an average ejection fraction of 27%. The median N-terminal pro-B-type natriuretic peptide (NT-proBNP) level was 2,230 pg/mL, mean glomerular filtration rate (GFR) measured by CKD-EPI was 67 ml/min/m². The most common comorbidity was hypertension (65%), followed by diabetes (35.2%) (Table 1).

At admission to the clinic, 88% of patients had prescription of an ACE inhibitor/angiotensin receptor blocker /ARNI (ACEI/ARB /ARNI), 97.5% were using beta-blockers, 78.2% mineralocorticoid receptor antagonists (MRA), 3.4% SGLT2 inhibitors, and 72.6% furosemide. Among the patients who did not use an ACEI during the follow-up period, intolerance was reported in only 1.4%, while the remaining patients did not have a specified cause for not receiving them. The use of all medications at admission and during the final follow-up is shown in Table 2.

Comparisons

In the local cohort, compared to the original studies, there was a higher representation of women (35.8% vs 23.8% for DAPA-HF, 23.5% for EMPEROR-R, and 21% for PARADIGM-HF), a higher frequency of NYHA I (24% vs 0% for DAPA-HF and EMPEROR-R, and 4% for PARADIGM-HF), a lower prevalence of ischemic etiology of HF (45% vs 55% for DAPA-HF, 52% for EMPEROR-R, and 59% for PARADIGM-HF), a higher

prevalence of prior hospitalization for HF compared to DAPA-HF and EMPEROR-R (52.2% vs 47% and 31% respectively), but a lower prevalence of prior hospitalization compared to PARADIGM (52.2% vs 62%).

Regarding medications, there was a higher use of ACEI/ARB compared to DAPA-HF and EMPEROR-R (85% vs 68.9% and 70% respectively), similar use of beta-blockers compared to all three studies (97% vs 96% in DAPA-HF, 94.7% in EMPEROR-R, and 93.1% in PARADIGM-HF), and lower use of digitalis compared to DAPA-HF and PARADIGM-HF (5.2% vs 18.8% and 29% respectively).

Regarding devices, there was a lower use of implantable cardioverter-defibrillator (ICD) compared to DAPA-HF and EMPEROR-R (18.8% vs 26.2% in DAPA-HF, 31% in EMPEROR-R), but a higher use of cardiac resynchronization therapy (CRT) (15.9% vs 8% in DAPA-HF, 11.8% in EMPEROR-R, 7% in PARADIGM-HF).

Below, the resulting cohorts (meeting eligibility criteria = A and not meeting eligibility criteria = B) are compared to their respective original studies and among themselves:

DAPA-HF (Table 3): Patients in cohort A-DAPA-HF, compared to those in the original study, had a lower left ventricular ejection fraction (LVEF) (27.4% vs 31.2%), a lower frequency of previous hospitalizations for HF (39.5% vs 47.4%), and a higher average estimated glomerular filtration rate (eGFR) (71.7 vs 66 ml/min/m².).

On the other hand, patients in cohort B-DAPA-HF, compared to those in the original study, had a higher frequency of NYHA class I (33% vs 0%), a lower LVEF (27.2% vs 31.2%), and a higher frequency of previous hospitalizations for HF (56.9% vs 47.4%).

Patients in cohort B-DAPA-HF, compared to those in cohort A-DAPA-HF, had a higher frequency of NYHA class I (33% vs 0%), a higher average NT-proBNP (3240 pg/mL vs 1750 pg/mL), a higher history of hospitalizations (56.9% vs 39.5%), a lower eGFR (65 vs 71 ml/min/m²), and lower use of ACEI/ARB (82% vs 94.1).

EMPEROR-R (Table 4): Patients in cohort A-EMPEROR-HF, compared to those in the original study, had a higher frequency of NYHA class III (31.3% vs. 24.4%), a higher incidence of previous hospitalizations for HF (50% vs. 31%), a lower prevalence of diabetes (37.5% vs. 72.4%), a higher average eGFR (70.6 vs. 61.8 ml/min/m²), a higher use of ACEI /ARB (94.6% vs. 70.5%), and a higher use of ARMs (82.9% vs. 70.1%).

Patients in cohort B-EMPEROR-HF, compared to those in the original study, had a higher frequency of NYHA class I (32.3% vs. 0%), a higher incidence of previous hospitalizations for HF (53% vs. 31%), a higher eGFR (66.1 vs. 61.8), and a higher use of ACEI/ARB (82% vs. 70.5%).

When comparing patients in cohort B-EMPEROR-HF with their respective cohort A, a higher frequency of NYHA class I (32.3% vs. 0%), a lower eGFR (66.1 vs. 70.6 ml/min/m²), a higher average NT-proBNP (2730 vs. 1170 pg/mL), and a lower use of ACEI/ARB (82% vs. 94.6%) were found.

PARADIGM-HF (Table 5): Patients in cohort A-PARADIGM-HF, compared to those in the original study, had a higher frequency of NYHA class III (31.3% vs. 23.1%), a lower incidence of previous hospitalizations (48.2% vs. 62.3%), a lower LVEF (25.7% vs. 29.6%), a lower use of ACEI (53% vs. 78%), but a higher use of ARM (82.1% vs. 54.2%).

Patients in cohort B-PARADIGM-HF, compared to those in the original study, had a higher frequency of NYHA class I (32.3% vs. 4.3%), higher creatinine levels (1.39 vs. 1.13 mg/dL), and a lower number of previous hospitalizations for HF (53.6% vs. 62.3%). Patients in cohort B-PARADIGM-HF, compared to their respective cohort A, had a higher frequency of NYHA class I (32.3% vs. 0%), a higher average NT-proBNP (2730 vs. 1750 pg/mL), higher creatinine levels (1.39 vs. 1.1 mg/dL), a lower use of ACEI (44.3% vs. 53.6%), and a lower use of ARM (76.9% vs. 82.1%).

Outcomes

Mortality and Hospitalizations: In the study cohort, during a follow-up time of 918 person-years, with a median of 27 months (range 0-65 months), the all-cause mortality rate was 26.7%; 36.8% of patients experienced at least one hospitalization due to HF and 41.9% experienced either cardiovascular death or hospitalization due to HF. In subgroup analysis, mortality was higher in all B cohorts (around 30%) compared to all A cohorts (around 18%) (Table 6). Among all deaths, cardiovascular causes were more predominant in cohort A-DAPA-HF (59%) and A-PARADIGM-HF (68.2%) compared to cohorts B-DAPA-HF and B-PARADIGM-HF (51% and 49.5%, respectively). (Table 7). The frequency of hospitalizations was also similar when comparing A and B cohorts across all three studies (Table 8). The composite outcome of cardiovascular death and heart failure is presented in Table 9. Kaplan-Meier curves are shown in Figures 3-8.

Discussion

Main Findings: The most important finding of this study was that approximately 75% of the patients would not have been eligible for the original trials, mainly because of low systolic blood pressure, severe lung disease, hyperkalemia, history of stroke or transient ischemic attack, device implantation or acute coronary syndrome within the last 90 days, and low GFR.

The baseline clinical and demographic characteristics of the study cohort were similar to national and international heart failure registries (10, 11, 13). When comparing the study cohort with the targeted RCTs, there was a higher representation of women, a lower prevalence of ischemic etiology, a higher frequency of patients in NYHA functional classes I and II, and a higher use of guideline-directed medical therapy and cardiac resynchronization therapy. The underrepresentation of women in cardiovascular disease RCTs has been widely described and is influenced by logistical and medical practice-related factors (14–16). The higher frequency of patients with better functional class is attributed to the exclusion of NYHA class I patients in the primary RCTs and the fact that some patients in the local cohort were already receiving treatment for HF at the first visit. Additionally, it is noteworthy that the use of cardiac resynchronization therapy devices was similar to the ESC-HF-LT registry in both cohorts (13).

Furthermore, the eligible patients from the local cohorts, compared to the original trials, had lower body mass index, higher prescription of optimal therapy, lower left ventricular ejection fraction and systolic blood pressure, and higher average heart rate. Among the patients who would have been ineligible for the RCTs, compared to the patients from the original trials, there was a higher frequency of NYHA functional class I and IV and a lower frequency of atrial fibrillation and diabetes (except when comparing to PARADIGM-HF patients). Additionally, the GFR was lower in these patients compared to DAPA-HF and PARADIGM-HF.

Also, when comparing the ineligible patients to the eligible patients from the local cohort, significant differences were found, including a higher prevalence of ischemic etiology, lower use of optimal medical therapy, higher use of digitalis, more hospitalization history, and worse renal function. Interestingly, there was a higher use of implantable cardioverter-defibrillator and cardiac resynchronization therapy (except for A-PARADIGM-HF vs. B-PARADIGM-HF cohorts).

It is noteworthy that, although the incidence of HF hospitalizations was similar between eligible and ineligible patients in the local cohorts, the prognosis of the patients who would have been excluded was worse. There was a higher all-cause mortality during the follow-up period, and higher cardiovascular mortality in the A-DAPA-HF and A-PARADIGM-HF cohorts compared to their respective B cohorts. This could be associated with the higher burden of comorbidities in the non-included patients, but these findings should be explored in further studies.

Regarding the prescription of pharmacological treatment for HF, the use of iSGLT2 and ARNI was initially low but increased over time, likely because of evolving knowledge, after the publication of PARADIGM-HF results. On the other hand, the use of other guideline-directed medical therapy decreased at the time of the last follow-up, with a remarkably high prescription of ARB without a clear reason, as intolerance was only reported in 1.4% of patients who did not receive ACEI.

Although the explanation for this phenomenon is beyond the scope of this study, a lower use of guideline-directed medical therapy has been described in populations with poorer prognosis, who are more likely to benefit from these treatments. This is known as the "risk-treatment paradox" (17). Besides, similar difficulties regarding the use and titration of HF treatment have been described in other cohorts such as CHAMP-HF and BIOSTAT-CHF (11, 18).

Interpretation: This study demonstrated that most patients with HFrEF attending the outpatient clinic of a high-complexity institution in Medellín, Colombia, would not have been eligible for enrollment in the DAPA-HF, EMPEROR-R, and PARADIGM-HF trials. However, it is important to note that some patients met transient exclusion criteria (dependent on the timing of an event relative to the clinic admission) and could become candidates for the trials during follow-up. The study also revealed two fundamental differences between the local cohort and the population of the clinical trials. The first difference was observed in various sociodemographic, therapeutic, and baseline clinical variables mentioned before, while the second was the poorer prognosis of patients who would not have been eligible for these trials. These findings are consistent with those of various studies. For example, Wang et al. found that, when evaluating the eligibility criteria of RELAX-AHF, only two out of every ten patients in their cohort would have met the criteria (19). Furthermore, in a literature review conducted by Kennedy-Martin et al., which examined twenty cardiology studies assessing

the applicability of clinical trials to real-world settings, it was found that in most of these studies, over 50% of patients were ineligible, and typically, these were the most comorbid, elderly, female, and undertreated individuals according to guideline recommendations (20). Regarding similar comparisons with DAPA-HF and EMPEROR-HF, a study in Sweden described that 52% and 39% of their HFrEF patients would meet eligibility criteria, respectively (21), which is considerably higher than our cohort but still far from ideal. However, in the Swedish Heart Failure Registry, with strict criteria, only 35% would have qualified for DAPA-HF, and only 31% for EMPEROR-HF (22), which is closer to our findings. Additionally, in relation to PARADIGM, Norberg et al. found that only 24% of their HFrEF patients with EF <35% would have been eligible for inclusion (23).

Despite randomized controlled trials (RCTs) being considered the gold standard of evidence (24), they have disadvantages due to their strict inclusion and exclusion criteria, high cost, and challenges in long-term follow-up (25). This explains the gap between efficacy (demonstrated in RCTs) and effectiveness (evaluated in observational studies) of an intervention (26). Consequently, there is an increasing number of real-world studies being published, which assess the clinical outcomes of drugs in a less restrictive context and with a greater diversity of patients. For example, Ganesananthan et al. evaluated the results of transitioning to sacubitril-valsartan management between 2017 and 2019 in patients at the University Hospital of Wales. They demonstrated improvement in functional class, quality of life, ejection fraction, and left ventricular end-diastolic diameter at 3 months of follow-up (27). Furthermore, a systematic review of 68 real-world studies examined outcomes in patients treated with sacubitril-valsartan, comparing it to standard therapy (typically ACE inhibitors/ARBs). The review found a reduction in heart failure hospitalizations, all-cause hospitalizations, and all-cause mortality, consistent with the results of the PARADIGM-HF trial, with a discontinuation rate of 10.3% (28).

As a result, RCTs have a high ability to control confounding factors and biases, adding internal validity to their results, which allows for replicability within the same population. However, studies like ours demonstrate differences in sociodemographic, clinical, and prognostic factors among patients, which could affect the external validity of the results. Hence, the results of clinical trials should be complemented with information provided by pragmatic and real-world studies that consider the particularities of clinical practice. This could enable individualized interventions and possibly a better risk-benefit profile of therapies.

Strengths and limitations of the study: This is the first study to evaluate the inclusion and exclusion criteria of the three major recent RCTs for the treatment of HF in a Latin American population. The study has inherent limitations due to its retrospective design and because of being conducted in a specialized institution for cardiac diseases, there is a risk of referral bias. However, the broad inclusion criteria used allows the studied population to be representative of other Latin American patients attending HF outpatient clinics. BNP and NT-proBNP levels are part of the inclusion criteria for the DAPA-HF, PARADIGM-HF, and EMPEROR-R trials, however, these criteria were not considered in the present study to determine applicability due to infrequent measurement in our setting, mainly due to availability and costs. There are limited data on patients' height and BMI, which limited the evaluation of obesity as a comorbidity. Considering obesity as a primary risk factor for HF, there is a call to give more attention to metabolic comorbidities and anthropometric measurements as a standard of care in the management of these patients.

Conclusion: It was found that 3 out of 4 patients with HFrEF attending a specialized HF clinic in a cardiology hospital in Medellín, Colombia, would not have been eligible for the DAPA-HF, EMPEROR-R, and PARADIGM-HF trials. This suggests that the invaluable evidence provided by RCTs for the pharmacological management of HF should be enhanced and complemented with pragmatic or real-world studies, where effectiveness and safety outcomes can be evaluated in a more heterogeneous population that resembles the patients encountered in daily clinical practice.

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Legends

Figure 1. Flowchart of Included Patients.

Figure 2. Reasons for non-elibility of local cohort patients from the original studies.

SBP: Systolic Blood Pressure ADHF: Acute Decompensated Heart Failure ACS: Acute Coronary Syndrome Stroke: Stroke TIA: Transient Ischemic Attack ACEi/ARB: Angiotensin-Converting Enzyme Inhibitor/Angiotensin Receptor Blocker SGLT2i: Sodium-Glucose Cotransporter 2 Inhibitor GFR: Glomerular Filtration Rate.

*SBP < 95 for DAPA-HF and PARADIGM-HF, and <100 for EMPEROR-R. †GFR < 30 for DAPA-HF and PARADIGM-HF, and <20 for EMPEROR-R.

Figure 3. Composite outcome and mortality from all causes of local eligible and ineligible cohorts for each original trial.

Table 1. Baseline clinical, demographic, and laboratory characteristics

*The number corresponds to the patients in whom the variable could be evaluated.

BMI: body mass index; HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; NYHA: New York Heart Association; GFR: glomerular filtration rate; TSAT: transferrin saturation; LVEF: left ventricular ejection fraction; BNP: brain natriuretic peptide; NT-proBNP: N-terminal pro-brain natriuretic peptide; Hb: hemoglobin; AMI: Acute myocardial infarction; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting; TIA: transient ischemic attack; ICD: implantable cardioverter-defibrillator; CRT: cardiac resynchronization therapy; CRT-D: cardiac resynchronization therapy with defibrillator.

Table 2. Use of medical therapy at baseline and follow-up.

ACEI: Angiotensin-Converting Enzyme Inhibitor; ARB: Angiotensin Receptor Blocker; ARNI: Angiotensin Receptor Neprilysin Inhibitor; MRA: Mineralocorticoid receptor antagonist; SGLT2-I: Sodium-Glucose Cotransporter 2 Inhibitor.

Table 3. DAPA-HF trial comparison with local cohorts A-DAPA-HF and B-DAPA-HF.

*P corresponds to Cohort A-DAPA-HF vs. Original Cohort DAPA-HF †P corresponds to Cohort B-DAPA-HF vs. Original Cohort.

BMI: Body Mass Index; HR: Heart Rate; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; NYHA: New York Heart Association; GFR: Estimated Glomerular Filtration Rate; LVEF: Left Ventricular Ejection Fraction; AF: atrial fibrillation; NT-proBNP: N-terminal pro-B-type natriuretic peptide; CDI: Cardioverter Defibrillator Implantation; CRT: cardiac resynchronization therapy; CRT-D: cardiac resynchronization therapy with defibrillator; ACEI: Angiotensin-Converting Enzyme Inhibitor; ARB Angiotensin Receptor Blocker; BB: Beta Blocker; ARM: Mineralocorticoid Receptor Antagonist; ARNI: Angiotensin Receptor Neprilysin Inhibitor; ISGLT2: Sodium-Glucose Cotransporter 2 Inhibitor; DPP4i: Dipeptidyl Peptidase-4 Inhibitor; GLP-1RA: Glucagon-Like Peptide-1 Receptor Agonist.

Table 4. PARADIGM-HF trial comparison with local cohorts A-PARADIGM-HF and B-PARADIGM-HF.

*P corresponds to Cohort A-PARADIGM-HF vs. Original Cohort; †P corresponds to Cohort B-PARADIGM-HF vs. Original Cohort.

BMI: Body Mass Index; HR: Heart Rate; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; NYHA: New York Heart Association; GFR: Estimated Glomerular Filtration Rate; LVEF: Left Ventricular Ejection Fraction; BNP: Brain Natriuretic Peptide; NT-proBNP: N-terminal pro-B-type natriuretic peptide; AF: atrial fibrillation; CDI: Cardioverter Defibrillator Implantation; CRT: cardiac resynchronization therapy; CRT-D: cardiac resynchronization therapy with defibrillator; ACEI: Angiotensin-Converting Enzyme Inhibitor; ARB: Angiotensin Receptor Blocker; BB: Beta Blocker; ARM: Mineralocorticoid Receptor Antagonist; ARNI: Angiotensin Receptor Neprilysin Inhibitor.

Table 5. EMPEROR-R trial comparison with local cohorts A-EMPEROR-R and B-EMPEROR-R

*P corresponds to Cohort A vs. Original Cohort; †P corresponds to Cohort B vs. Original Cohort.

BMI: Body Mass Index; HR: Heart Rate; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; NYHA: New York Heart Association; GFR: Estimated Glomerular Filtration Rate; LVEF: Left Ventricular Ejection Fraction; AF: atrial fibrillation; NT-proBNP: N-terminal pro-B-type natriuretic peptide; CDI:

Cardiodesfibrillator Implantation; CRT: cardiac resynchronization therapy; CRT-D: cardiac resynchronization therapy with defibrillator; ACEI: Angiotensin-Converting Enzyme Inhibitor; ARB: Angiotensin Receptor Blocker; BB: Beta Blocker; MRA: Mineralocorticoid Receptor Antagonist; ARNI: Angiotensin Receptor Neprilysin Inhibitor.

Table 6. Total and cohort-specific all-cause mortality in the study

Table 7. Cause-specific mortality by cohort and study

Table 8. New hospitalizations for heart failure during the follow-up period, discriminated by cohort and study

Table 9. Composite outcome of heart failure hospitalization and cardiovascular cause mortality, discriminated by cohort and study.

Tables and figures

Figure 1. Flowchart of Included Patients.

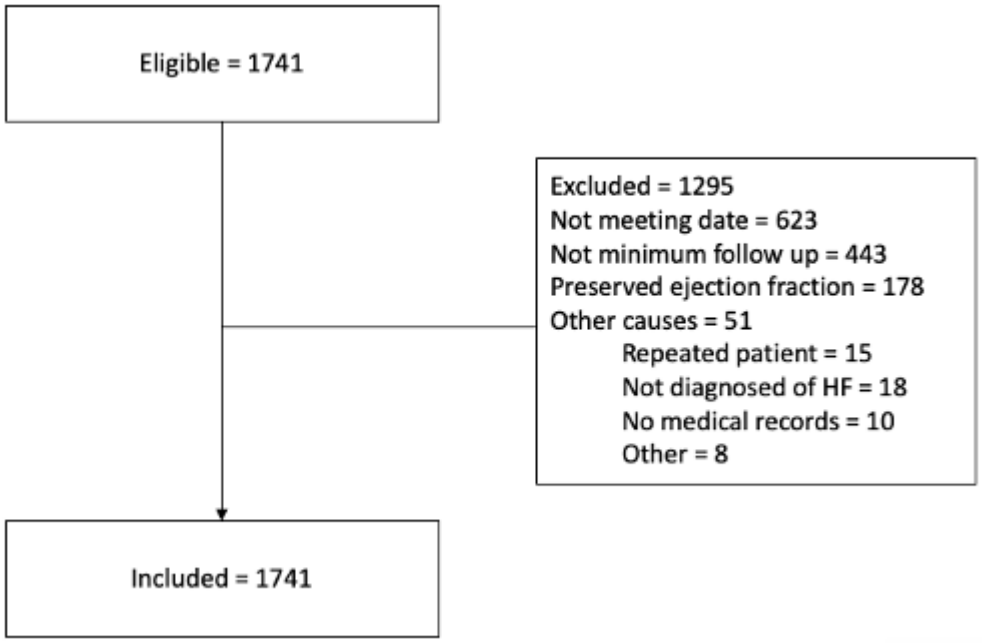

Figure 2. Reasons for non-elibility of local cohort patients from the original studies.

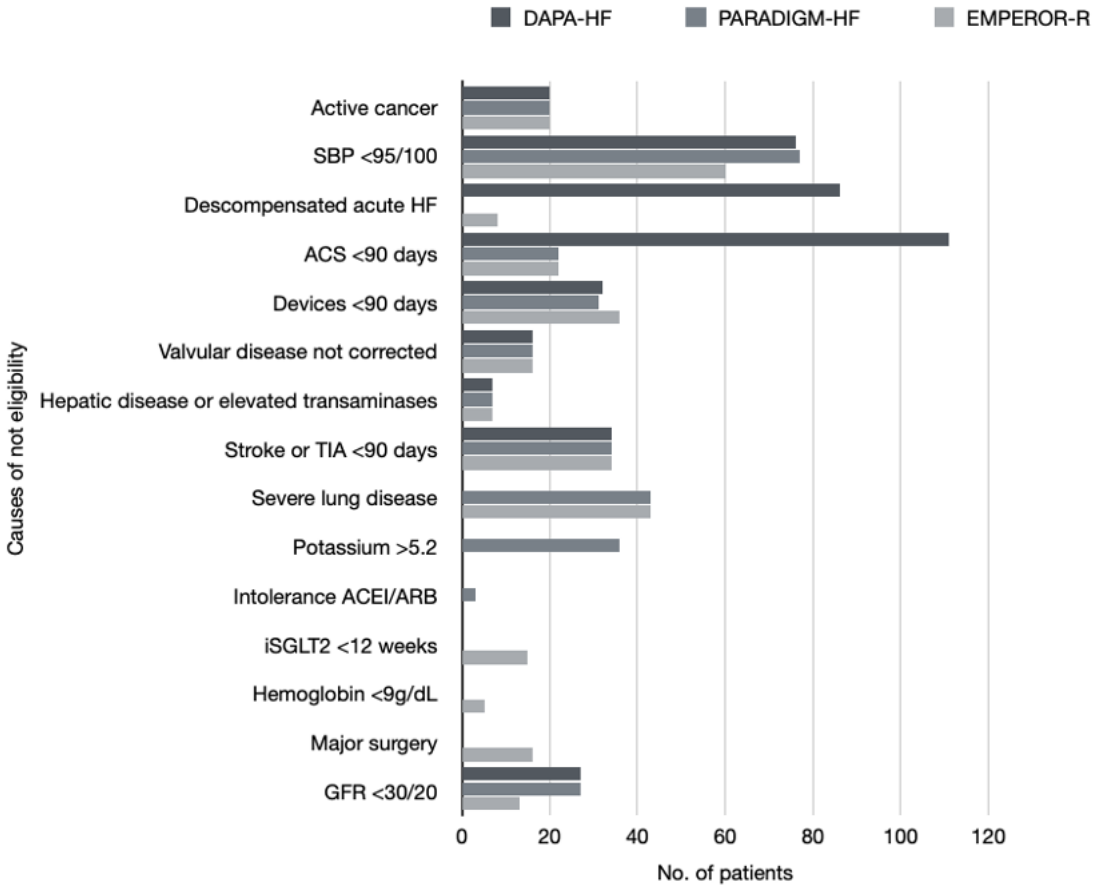

Figure 3. Composite outcome and mortality from all causes of local eligible and ineligible cohorts for each original trial.

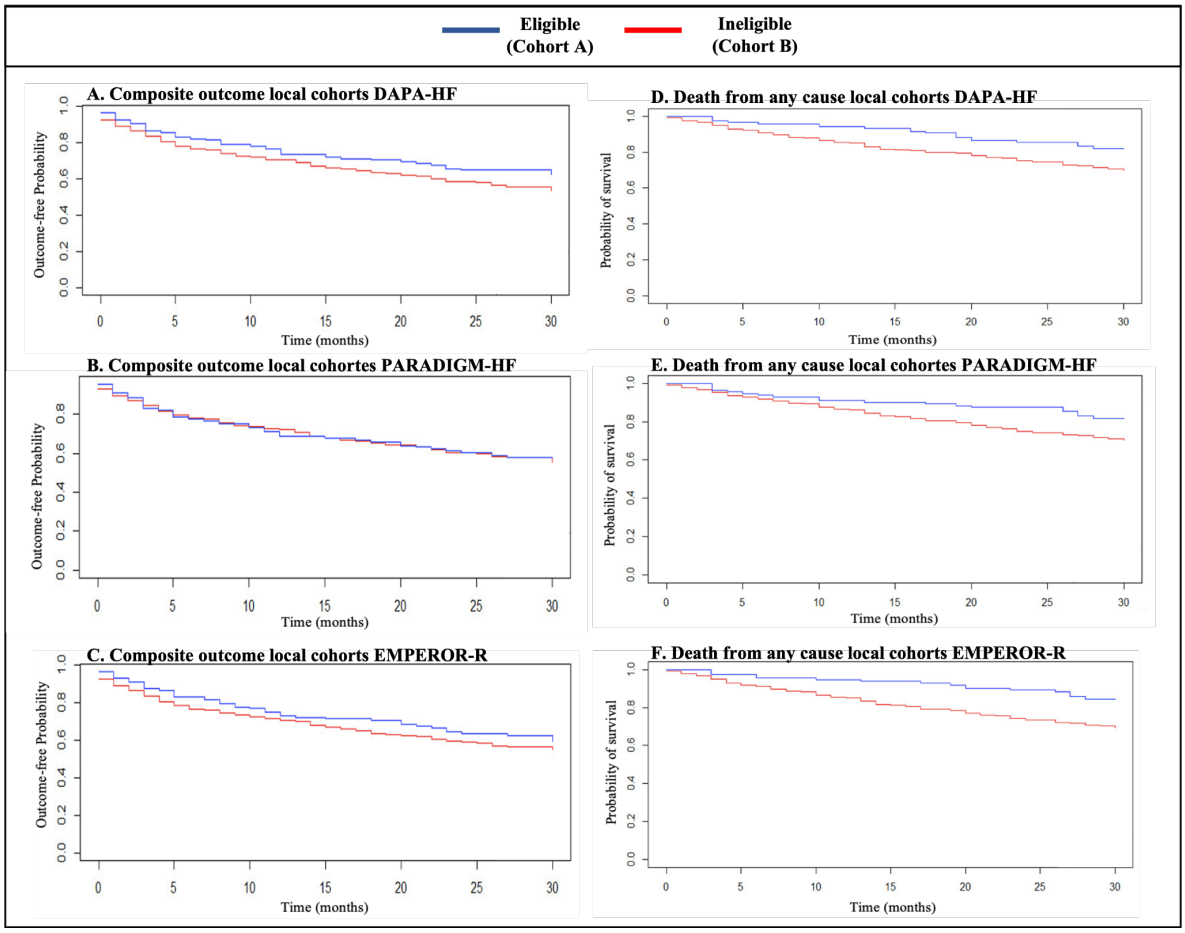
Eligible
(Cohort A)
Ineligible
(Cohort B)
A. Composite outcome local cohorts DAPA-HF
Outcome-free Probability
Time (months)
D. Death from any cause local cohorts DAPA-HF
Probability of survival
Time (months)
B. Composite outcome local cohortes PARADIGM-HF
Outcome-free Probability
Time (months)
E. Death from any cause local cohortes PARADIGM-HF
Probability of survival
Time (months)
C. Composite outcome local cohorts EMPEROR-R
Outcome-free Probability
Time (months)
F. Death from any cause local cohorts EMPEROR-R
Probability of survival
Time (months)

Table 1. Baseline clinical, demographic, and laboratory characteristics

Characteristics	**Local cohort, N = 446**
Average age ± SD – years	65.2 ± 13.9
Female sex– no. (%)	155 (35.8)
Average weight ± SD – Kg, (n = 411*)	68.1 ± 13.8
Average Height ± SD – cm, (n = 73*)	163.5 ± 10.1
Average BMI ± SD – kg/m2, (n = 72*)	24.8 ± 3.83
Average HR ± SD – beats/minute	74.9 ± 13.6
Average SBP ± SD – mmHg	112 ± 19.2
Average DBP ± SD – mmHg	68.9 ± 11.4
NYHA at admission – no. (%)	
I	108 (24.2)
II	220 (49.3)
III	114 (25.5)
IV	4 (0.08)
NYHA at last follow-up – no. (%)	
I	143 (32)
II	193 (43.3)
III	86 (19.3)
IV	24 (5.4)
Average Creatinine ± SD – mg/dl, (n = 444*)	1.3 ± 1,1
Average GFR ± SD – ml/min/m2, (n = 444*)	67 ± 24.3
Patients with GFR <60 – no. (%), (n = 444*)	177 (39.7)
Average BUN ± SD – mg/dL, (n = 435*)	25.9 ± 13.3
Average Hemoglobin ± SD – g/dL, (n = 425*)	13.4 ± 1.7
Average Potassium ± SD – mEq/L, (n = 437*)	4.4 ± 0.54
Average Sodium ± SD – mEq/L, (n = 432*)	139.2 ± 3.5

Average Ferritin ± SD – ng/ml, (n = 73*)	186 ± 190.4
Average TSAT ± SD – %, (n = 53*)	44.4 ± 60.2
Average LVEF at admission ± SD – %	27 ± 7.9
Average LVEF at last follow-up ± SD – %	35 ± 12.7
Median NT-proBNP (IQR) – pg/mL, (n = 46*)	2230 (759 - 4540)
Average HbA1c ± SD – % (n = 182*)	6.55 ± 1.28
Etiology – no. (%)	
Ischemic	201 (45)
Dilated idiopathyc	80 (17.9)
Primary valve	34 (7.6)
Tachycardiomyopathy	31 (6.9)
Hypertensive	23 (5.1)
Chemotherapy induced	10 (2.2)
Others	67 (15)
Background - No. (%)	
Arterial hypertension	291 (65)
Diabetes	157 (35.2)
Type I	4 (0.8)
Type II	119 (26.6)
Prediabetes	34 (7.6)
Malignancy	20 (4.4)
Aortic valve disease	6 (1.3)
Mitral valve disease	10 (2.2)
Atrial fibrillation	136 (30.5)
AMI	173 (38.7)
PCI	93 (20.8)
CABG	35 (7.8)

Medical therapy	35 (7.8)
PCI+CABG	10 (2.2)
Stroke or TIA	34 (7.6)
Cirrhosis	4 (0.9)
Major surgery within 3 months	16 (3.58)
Abnormal liver profile, (n=129*)	3 (0.6)
Enfermedad pulmonar	43 (9.6)
Previous hospitalization for HF	233 (52.2)
Devices- No. (%)	192 (43)
Pacemaker	35 (7.8)
ICD	84 (18.8)
CRT	20 (4.5)
CRT-D	51 (11.4)

Table 2. Use of medical therapy at baseline and follow-up.

Pharmacological therapy formulation– no. (%) (n=446)				
ACEI			225 (50.4)	
ARB			210 (47.1)	
BB			441 (98.8)	
MRA			377 (84.5)	
SGLT2-I			56 (12.5)	
ARNI			70 (15.7)	
Furosemide			357 (80)	
Digitalis			28 (6.3)	
Drug	Initial		Last follow-up	
	Frequency no. (%)	Dose Mean ± SD	frequency no. (%)	Dose Mean ± SD
Enalapril	207 (46)	11.9 ± 11.4	140 (31.4)	13.7 ± 13.4
Losartan	159 (35.6)	68.4 ± 35.3	162 (36.3)	69.9 ± 34.2
Valsartan	1 (0.2)	160	2 (0.4)	320
Carvedilol	333 (74.6)	23 ± 119.6	278 (62.3)	33.9 ± 25.6
Metoprolol S.	79 (17.7)	79.8 ± 52.8	120 (26.9)	117 ± 74.3
Nebivolol	1 (0.2)	5	1 (0.2)	10
Bisoprolol	10 (2.2)	4.3 ± 2.4	13 (2.9)	8.1 ± 5.9
Spironolactone	338 (75.7)	24.6 ± 11.8	291 (65.2)	23.1 ± 7.9
Eplerenone	11 (2.4	34.7 ± 15	25 (5.6)	33.5 ± 13.7
ARNI	14 (3.1)	107.4 ± 43.2	65 (14.5)	190.8 ± 118.2
Dapagliflozin	3 (0.6)	10	29 (6.5)	9.8 ± 0.94
Empagliflozin	12 (2.6)	20.2 ± 7.1	23 (5.1)	17.6 ± 7.6
Furosemide	324 (72.6)	54.2 ± 27.8	284 (63.7)	58.7 ± 35.1
Digitalis	23 (5.2)	0.15 ± 0.06	10 (2.2)	0.12 ± 0.04

Table 3. DAPA-HF trial comparison with local cohorts A-DAPA-HF and B-DAPA-HF.

Characteristics	Dapa-HF, N=2373 (%)	Cohort A-DAPA-HF, N=119 (%)	P value*	Cohort B-DAPA-HF, N=327 (%)	P value†
Age	66.2 ± 11	64.4 ± 12.9	< 0.05	65.9 ± 14.4	6.719
Female	564 (23.8)	44 (36.9)	< 0.001	111 (33.9)	< 0.001
BMI (N=15)	28.2 ± 6	26.9 ± 3.7	< 0.001	24.3 ± 3.7	< 0.001
NYHA			2.151		< 0.001
I	0	0		108 (33)	
II	1606 (67.7)	77 (64.7)		143 (43.7)	
III	747 (31.5)	42 (35.3)		72 (22)	
IV	20 (0.8)	0		4 (1.2)	
HR	71.5 ± 11.6	75.1 ± 14.5	< 0.001	74.8 ± 13.3	< 0.001
SBP	122.0 ± 16.3	118.4 ± 18.3	< 0.001	110.2 ± 19	< 0.001
NT-proBNP (N=18)	1428 (857–2655)	1475 (157-2680)		3240 (1540-5460)	
LVEF	31.2±6.7	27.7 ± 7.8	< 0.001	27.2 ± 8.1	< 0.001
Etiology			< 0.001		< 0.05
Ischemic	1316 (55.5)	43 (36.1)		158 (48.3)	
Not ishemic	857 (36.1)	65 (54.6)		142 (43.4)	
Unknown	200 (8.4)	11 (9.2)		27 (8.3)	
Background					
Hospitalization	1124 (47.4)	47 (39.5)	0.786	186 (56.9)	< 0.001
AF	916 (38.6)	38 (31.9)	1.736	98 (29.9)	< 0.05
Diabetes	993 (41.8)	39 (32.8)	2.414	118 (36.1)	< 0.05
GFR					
Media (N=118)	66.0±19.6	71.7 ± 21.2	< 0.001	65.6 ± 25.2	4.280
<60	962/2372 (40.6)	41 (34.5)	3.032	136 (41.6)	6.697

Dispositivos					
CDI	622 (26.2)	22 (18.5)	0.786	62 (20)	< 0.05
CRT/CRT-D	190 (8.0)	15 (12.6)	< 0.001	56 (17.1)	< 0.001
Medication					
Diuretic	2216 (93.4)	82 (73.2)	< 0.001	244 (74.6)	< 0.001
ACEI/ARB	1286 (68.9)	112 (94.1)	< 0.001	268 (82)	< 0.001
ACEI	1332 (56.1)	59 (49.6)	1.397	149 (45.6)	< 0.001
ARB	675 (28.4)	53 (44.5)	< 0.001	119 (36.4)	< 0.05
ARNI	250 (10.5)	3 (2.5)	< 0.05	11 (3.4)	< 0.001
BB	2278 (96.0)	119 (100)	< 0.05	317 (96.9)	6.788
MRA	1696 (71.5)	105 (88.2)	< 0.05	253 (77.4)	1.071
Digitalis	445 (18.8)	3 (2.5)	< 0.001	26 (7.9)	< 0.001
Diabetes medication					
Biguanide	504/993 (50.8)	26/39 (66.7)	< 0.05	57/118 (48.3)	5.616
Sulfonilurea	228/993 (23.0)	0/39 (0)	< 0.001	1/118 (0.8%)	< 0.001
iDPP4	161/993 (16.2)	6/39 (15.4)	6.720	24/118 (20.3%)	977
aGLP1	11/993 (1.1)	1/39 (2.6)	< 0.05	3/118 (2.5%)	1.823
Insulina	274/993 (27.6)	13/39 (33.3)	< 0.05	38/118 (32.2%)	2.219

Table 4. PARADIGM-HF trial comparison with local cohorts A-PARADIGM-HF and B-PARADIGM-HF.

Characteristics	PARADIGM-HF, N= 4187 (%)	Cohort A-PARADIGM-HF, N =112 (%)	P value*	Cohort B-PARADIGM-HF, N=334	P value†
Age	63.8±11.5	62.7 ± 12.9	8.283	65.5 ± 14.4	< 0.001
Female	879 (21.0)	40 (35.7)	< 0.001	115 (34.4)	< 0.001
BMI (N=16)	28.1±5.5	26.2 ± 4.1	< 0.001	24.4 ± 3.7	< 0.001
NYHA			< 0.05		< 0.05
I	180 (4.3)	0		108 (32.3)	
II	2998 (71.6)	76 (67.9)		144 (43.1)	
III	969 (23.1)	35 (31.3)		79 (23.7)	
IV	33 (0.8)	1 (0.9)		3 (0.9)	
HR	72±12	75.9 ± 14.4	< 0.001	74.6 ± 13.4	< 0.001
SBP	122±15	117 ± 16.4	< 0.001	110.6 ± 19.7	< 0.001
BNP (N=0)	255 (155–474)	Sin dato		dic-67	
NT-proBNP (N=16)	1631 (885–3154)	1750 (422-4190)		2730 (1090-4540)	
LVEF	29.6±6.1	25.7 ± 6.7	< 0.001	27.9 ± 8.3	< 0.001
Etiology					
Ischemic	2506 (59.9)	43 (38.4)	< 0.001	158 (47.4)	< 0.001
Background					
Hospitalization	2607 (62.3)	54 (48.2)	< 0.001	179 (53.6)	< 0.05
AF	1517 (36.2)	33 (29.5)	3.345	103 (30.8)	191
HTA	2969 (70.9)	69 (61.6)	< 0.05	222 (66.5)	800
Diabetes	1451 (34.7)	38 (33.9)	6.932	119 (35.6)	9.727
Creatinine mg/dl	1.13±0.3	1.1 ± 0.3	< 0.001	1.39 ± 1.2	< 0.001

(N=111)					
Devices					
CDI	623 (14.9)	23 (20.5)	< 0.05	61 (18.3)	1.117
CRT/CRT-D	292 (7.0)	18 (16.1)	< 0.001	53 (15.9)	< 0.001
Medication					
Diuretic	3363 (80.3)	89 (79.5)	5.713	247 (74)	< 0.05
ACEI	3266 (78.0)	60 (53.6)	< 0.001	148 (44.3)	< 0.001
ARB	929 (22.2)	46 (41.1)	< 0.001	126 (37.7)	< 0.001
ARNI	0	5 (4.5)	< 0.001	9 (2.7)	< 0.001
BB	3899 (93.1)	112 (100)	< 0.001	324 (97)	267
MRA	2271 (54.2)	92 (82.1)	< 0.001	257 (76.9)	< 0.001
Digitalis	1223 (29.2)	3 (2.7)	< 0.001	26 (7.8)	< 0.001

Table 5. EMPEROR-R trial comparison with local cohorts A-EMPEROR-R and B-EMPEROR-R

Characteristics	EMPEROR-R, N=1863 (%)	Cohort A-EMPEROR-R, N=112 (%)	P value*	Cohort B-EMPEROR-R, N=334 (%)	P value†
Age	67.2±10.8	64.7 ± 12.5	< 0.001	65.5 ± 14.4	1.026
Female	437 (23.5)	39 (34.8)	< 0.05	116 (34.7)	< 0.001
BMI (N=15)	28.0±5.5	27.1 ± 3.7	< 0.001	24.3 ± 3.7	< 0.001
NYHA			< 0.05		< 0.001
I	0	0		108 (32.3)	
II	1399 (75.1)	76 (67.9)		144 (43.1)	
III	455 (24.4)	35 (31.3)		79 (23.7)	
IV	9 (0.5)	1 (0.9)		3 (0.9)	
HR	71.0±11.7	74 ± 10.8	< 0.001	75.2 ± 14.5	< 0.001
SBP	122.6±15.9	116.5 ± 14.8	< 0.001	110.9 ± 20.3	< 0.001
NT-proBNP (N=12)	1887 (1077–3429)	1170 (155-2645)		2730 (1440-5400)	
LVEF	27.7±6.0	27.3 ± 7.4	< 0.05	27.3 ± 8.2	8.054
Etiology			< 0.05		< 0.05
Ischemic	983 (52.8)	43 (38.4)		158 (47.3)	
Not ischemic	880 (47.2)	69 (61.6)		176 (52.7)	
Background					
Hospitalization	577 (31.0)	56 (50)	< 0.001	177 (53)	< 0.001
AF	664 (35.6)	32 (28.6)	4.034	104 (31.1)	< 0.05
HTA	1349 (72.4)	74 (66)	< 0.05	217 (65)	< 0.05
Diabetes	927 (72.4)	42 (37.5)	< 0.001	115 (34.4)	< 0.001
GFR					
Media (N=112)	61.8±21.7	70.6 ± 21.6	< 0.001	66.1 ± 25.1	< 0.05

<60	893/1862 (48.0)	42 (37.5)	990	135 (40.4)	< 0.05
Devices					
ICD	578 (31.0)	17 (15.2)	< 0.05	67 (20.1)	< 0.001
CRT/CRT-D	220 (11.8)	16 (14.3)	< 0.05	55 (16.5)	1.077
Medication					
ACEI/ARB	1314 (70.5)	106 (94.6)	< 0.001	274 (82)	< 0.001
ACEI		61 (54.5)		147 (44)	
ARB		45 (40.2)		127 (38)	
ARNI	340 (18.3)	4 (3.6)	< 0.001	10 (3%)	< 0.001
BB	1765 (94.7)	112 (100)	< 0.05	324 (97)	2.300
MRA	1306 (70.1)	98 (87.5)	< 0.05	333 (99.7)	561

Table 6. Total and cohort-specific all-cause mortality in the study

All-cause mortality	Cohort A - N (%)	Cohort B - N (%)
DAPA-HF	22 (18.5)	97 (29.7)
PARADIGM-HF	22 (19,6)	97 (29,1)
EMPEROR-reduced	19 (16.9)	100 (29.9)

Table 7. Cause-specific mortality by cohort and study

Cause of death	**Cohort A, N (%)**	**Cohort B, N (%)**
DAPA-HF	N = 22	N = 97
Cardiovascular	13 (59)	50 (51.5)
Not cardiovascular	2 (9.1)	11 (11.3)
Unknown	7 (31.8)	36 (37.1)
PARADIGM-HF	N = 22	N = 97
Cardiovascular	15 (68,2)	48 (49.5)
Not cardiovascular	2 (9.1)	11 (11,3)
Unknown	5 (22.7)	38 (39.2)
EMPEROR-R	N = 19	N = 100
Cardiovascular	10 (52.6)	53 (53)
Not cardiovascular	2 (10.5)	11 (11)
Unknown	7 (36.8)	36 (36)

Table 8. New hospitalizations for heart failure during the follow-up period, discriminated by cohort and study

HF hospitalizations	Cohort A - N (%)	Cohort B - N (%)
DAPA-HF	41 (34,5)	123 (37.6)
PARADIGM-HF	44 (39,3)	120 (35.9)
EMPEROR-R	42 (37,5)	122 (36.5)

Table 9. Composite outcome of heart failure hospitalization and cardiovascular cause mortality, discriminated by cohort and study.

Composite outcome	Cohort A - N (%)	Cohort B - N (%)
DAPA-HF	45 (37.8)	142 (43.4)
PARADIGM-HF	48 (42.9)	139 (41.6)
EMPEROR-R	44 (39)	143 (42.8)