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Diuretic therapy as prognostic enrichment factor for clinical trials in patients with heart failure with reduced ejection fraction

Short title: Diuretic use as enrichment factor

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List of abbreviations

HF: heart failure

LVEF, left ventricular ejection fraction

BNP, B-type natriuretic peptide and

NT-proBNP, N-terminal pro-BNP

EMPHASIS-HF, Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure

HR, hazard ratio

95% CI, 95% confidence interval

CHARM, Candesartan in Heart failure: Reduction in Mortality and morbidity

ReBIC, Rede Brasileira de Estudos em Insuficiência Cardíaca

Abstract (word count 256)

Background: Loop diuretics are the mainstay of congestion treatment in patients with heart failure (HF). We assessed the association between baseline loop diuretic use and outcome. We also compared the increment in risk related to diuretic dose with conventional prognostic enrichment criteria used in the Eplerenone in Patients With Systolic Heart Failure and Mild Symptoms (EMPHASIS-HF) such as prior hospitalization and elevated natriuretic peptides.

Methods: Individual analyses were performed according to baseline loop diuretic usage (furosemide-equivalent dose >40 mg, 1-40 mg, and no furosemide), and according to enrichment criteria adopted in the trial [i.e. recent hospitalization (<30 days or 30 to 180 days prior to randomization) due to HF or other cardiovascular cause, or elevated natriuretic peptides)]. The primary endpoint was a composite of cardiovascular death or HF hospitalization.

Results: Loop diuretic usage at baseline (HR for >40 mg furosemide-equivalent dose =3.16, 95% CI 2.43 to 4.11; HR for 1-40 mg =2.06, 95% CI 1.60 to 2.65) were significantly associated with a higher risk for the primary endpoint in a stepwise manner when compared to no baseline loop diuretic usage. In contrast, the differences in outcome rates were more modest when using history of hospitalization and/or BNP: all HR ranged from 1 (reference, non-HF related CV hospitalization >30 days) to 2.04 (HF hospitalization <30 days). The effect of eplerenone on the primary endpoint was consistent across subgroups in both analyses (P for interaction ≥ 0.2 for all).

Conclusions: Loop diuretic usage (especially at doses >40 mg) identified patients at higher risk than history of HF hospitalization and/or high BNP blood concentrations.

Keywords Heart failure with reduced ejection fraction; eplerenone, loop diuretics, heart failure hospitalization, prognostic enrichment criteria

Introduction

In event-driven trials in heart failure (HF), it has been common to enroll patients at heightened risk of disease-related outcomes by enriching for selected baseline characteristics associated with these outcomes e.g. demographics (such as age), medical history (e.g. of prior HF hospitalization) and laboratory data (e.g. natriuretic peptide blood concentrations). Prognostic enrichment strategies aims at identifying patient subgroups with high event-rate in the course of the clinical study; those procedures considerably reduce the sample sizes needed to show a treatment effect, also increasing the power of the study[1].

Hospitalization for HF is associated with high event-rates in terms of mortality and HF readmissions, independently of left ventricular ejection fraction (LVEF)[2,3]; additionally, an inverse relationship between time from HF hospitalization to randomization and event-rates was also observed.

Higher concentrations of B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP)[4] are associated with higher rates of fatal and non-fatal events during follow-up[5,6], with a steeper increase in cardiovascular compared to non-cardiovascular events [7]. On the other hand, there is no agreed threshold concentration for using these peptides in this way and some comorbidities (e.g. atrial fibrillation) also influence their concentration [7].

Diuretics (especially loop diuretics) play a pivotal role in relieving congestion and related symptoms in patients with HF [8], with a class I recommendation for this indication according to the latest HF guidelines [9,10]. However, many studies have demonstrated that loop diuretic use, especially at high doses, is independently associated with reduced survival in HFrEF patients [11-17]. Thus, higher loop diuretic dosages identify patients with HF at particularly high risk of mortality and dose of diuretic could be considered as another approach to augmenting event rates in clinical trials. However diuretic dose has not been compared to alternative approaches to enriching for risk (such as requiring history of hospitalization/elevated natriuretic peptides).

In the present study we examined the association between loop diuretic use (and diuretic dose) and outcomes and compared these to other current enrichment criteria, using data from the

Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) [18].

Methods

Study design and participants

The design, patient eligibility criteria, study procedures and main results of EMPHASIS-HF have been reported [18]. In brief, in this randomized double-blind trial, patients with NYHA functional class II HF and LVEF no greater than 30% (or, if >30 to 35%, a QRS duration of >130 msec on electrocardiography) were randomly assigned to receive eplerenone (up to 50 mg daily) or placebo, in addition to recommended therapy.

Enrollment criteria in EMPHASIS-HF

In EMPHASIS-HF, all patients either had to have a hospitalization for a cardiovascular reason within 6 months or documentation of elevated plasma natriuretic peptide concentrations (i.e. BNP concentration of at least 250 pg/ml or NT-proBNP of at least 500 pg/ml for males and 750 pg/ml for females, as assessed within 15 days of randomization) [18]. Cardiovascular hospitalization was defined as follows: heart failure (first or subsequent HF hospitalization), acute myocardial infarction, angina pectoris (unstable), cardiac arrhythmia (atrial fibrillation, atrial flutter, supraventricular arrhythmias, or ventricular arrhythmias), stroke/cerebral vascular accident, or other cardiovascular causes (e.g. hypotension, peripheral vascular disease).

Assessment of diuretic use

Use of diuretics was considered part of standard therapy in EMPHASIS-HF, if clinically indicated to minimize fluid retention [19]. Drug name and dose were collected at baseline and during follow-up on case report forms. Furosemide-equivalent doses were calculated, with bumetanide 1 mg or torsemide 20 mg considered equivalent to 40 mg of furosemide [20].

Study outcomes

The primary outcome in the trial was the composite of time to first occurrence of death from cardiovascular causes or hospitalization for HF [18]. Secondary outcomes were the individual components of the primary outcome, all-cause death, cardiovascular hospitalization, and the composite of death or hospitalization for a cardiovascular reason. Adjudication of the outcomes was carried out by an independent committee according to pre-specified criteria [18].

Statistical analysis

For the present analysis, patients were grouped into 3 subgroups according to the main enrichment criterion met at baseline: i) HF-related or, ii) non-HF related (i.e. due to other cardiovascular causes) prior cardiovascular hospitalization, iii) elevated natriuretic peptide blood concentrations. Timing of prior hospitalization for HF or for other cardiovascular causes before enrollment (i.e. within 6 months according to inclusion criteria) was categorized as follows: i) <30 days or ii) 30-180 days prior to randomization. Additionally, patients were grouped according to furosemide-equivalent dose as follows: i) no baseline loop diuretic, ii) furosemide-equivalent 1 to 40 mg, iii) furosemide-equivalent >40 mg[16,21]. Patients were also grouped according to loop and thiazide diuretic use [i.e. 1) no baseline diuretic, 2) thiazide use, 3) furosemide 1-40 mg, 4) furosemide 1-40 mg + thiazide use, 5) furosemide >40 mg, and 6) furosemide >40 mg + thiazide use], and to additional furosemide dosage subgroups (i.e. no loop diuretic, 1-20 mg, 21-40 mg, 41-80, and >80 mg).

Continuous variables are expressed as mean (\pm standard deviation) or median (25th–75th percentiles); categorical variables as numbers and percentages. Baseline characteristics were defined in the whole cohort according to the respective enrichment criteria at baseline (i.e. prior HF or cardiovascular hospitalization, elevated natriuretic peptides), and furosemide-equivalent dose. Characteristics were compared among enrichment criteria subgroups, between timing categories within hospitalization subgroups, and among furosemide-equivalent subgroups. Additionally, proportions of furosemide-equivalent dose categories were defined according to

enrichment criteria at baseline and their timing. Comparisons of baseline characteristics were performed by using Student's t-test, Mann–Whitney, ANOVA, and chi-square test for trend, as appropriate.

Risk probabilities for the primary outcome according to enrichment criteria, furosemide-equivalent categories, and furosemide-thiazide combinations were calculated in distinct analyses using the Kaplan–Meier method and plotted as survival curves; respective associations with the primary outcome were assessed by univariable Cox proportional hazards models and the subgroup with the lowest event rate were taken as reference. Additionally, associations of enrichment criteria and loop diuretic use with primary and secondary outcomes were also assessed. Multivariable Cox analyses were also performed. Multicollinearity was checked using R function “check_multicollinearity” from Performance package, and obtained variance inflation factors indicated no significant collinear relationship. The treatment effect of eplerenone according to enrichment criteria (and their timing), furosemide-equivalent dose, and loop-thiazide diuretic combinations on primary and secondary outcomes were assessed in separate analyses by introducing an interaction term within univariable models. Harrell's C-statistics for time-to-event data were used to assess the ability of furosemide to predict the primary outcome, in the total cohort, and in subgroups according to study enrichment criteria.

Associations were expressed as hazard ratios and their 95% confidence interval (HR, 95% CI). A P-value <0.05 was considered statistically significant. Statistical analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, North Carolina) the R software (R Foundation for Statistical Computing).

Results

Patient characteristics

Of the 2737 patients randomized in EMPHASIS-HF, 2722 (99.5%) and 2715 (99.2%) had information available for the prespecified enrichment criteria and furosemide-equivalent

dose, respectively, at baseline. The main baseline characteristics are outlined in *Table 1* and *Table 2*.

The overlap between furosemide subgroups and selected prognostic enrichment criteria are illustrated in Fig. S1 in Supplementary material.

When compared to patients with a prior hospitalization (HF-related or for other cardiovascular causes), the subgroup enrolled on the basis of elevated natriuretic peptide blood concentrations were more likely to be male, and had a worse clinical profile, including a higher prevalence of diabetes and lower diastolic blood pressure and LVEF at randomization (all P-values <0.03) (*Table 1*). Patients in the subgroup enrolled on the basis of a prior HF hospitalization were more likely to be on a loop diuretic (furosemide-equivalent dose 1-40, >40 mg, and >40 mg + thiazide/thiazide-like diuretic), and less likely to be on a beta-blocker compared to the other patients (all P-values <0.01). Finally, the subgroup with a prior non-HF related cardiovascular hospitalization was more likely to have HF of an ischemic etiology, to be on an thiazide/thiazide-like diuretic, or to have worse renal function as compared to other subgroups (all P-values <0.03).

In the subgroup with a prior HF hospitalization, patients with HF hospitalization <30 days were more likely to have HF due to an ischemic cause, to be on an angiotensin-converting enzyme inhibitors, an angiotensin II receptor blockers or a thiazide/thiazide-like diuretic, to have lower systolic blood pressure and higher LVEF as compared to those with a less recent HF hospitalization; they were also less likely to be on a loop diuretic (furosemide-equivalent dose 1-40 mg) compared to the other HF hospitalization subgroup (all P-values <0.04). There were few imbalances in baseline risk factor relative to the timing of non-HF related cardiovascular hospitalization before randomization (*Table 1*)

Patients treated with a loop diuretic at baseline (especially those with furosemide-equivalent dose >40 mg) were older, more likely to be obese, diabetic, and have an implantable device, but less likely to have an ischemic etiology or to be on a thiazide/thiazide-like diuretic, compared to patients not treated with a loop diuretic at baseline. Patients treated with a loop

diuretic also had lower blood pressure and LVEF, and a higher heart rate, compared to those not treated with a loop diuretic (all P-values <0.04) (*Table 2*).

Patients with loop diuretic at baseline were more likely to have had a previous HF hospitalization when compared to patients not treated with loop diuretic [66.7% (438/657) for furosemide >40 mg, and 58.4% (824/1411) for furosemide 1-40 mg, versus 34.3% (222/647) in patients without diuretics, P-value <0.0001] (*Table 2, Fig. S1 in Supplementary Material*). With regard to non-HF related cardiovascular hospitalization, the opposite trend was observed [18.4% (121/657) for furosemide >40 mg, and 32.7% (400/1411) for furosemide 1-40 mg, versus 58.8% (317/647) in patients without diuretics, P-value <0.0001]. Differences in terms of elevated natriuretic peptide at baseline were not statistically significant across furosemide subgroups (P-value =0.2) (*Table 2*).

Impact of conventional prognostic enrichment criteria and loop diuretic use on outcomes

After 2 years of follow-up, the risk of cardiovascular death or HF hospitalization was highest among patients with a prior HF hospitalization: 28.5% [95% CI 24.7-32.1%] in those with hospitalization <30 days and 27.5% (95% CI 23.9-30.9%) in those with hospitalization 30-180 days before randomization (*Fig. 1A*). Lower event rates were observed in patients enrolled using natriuretic peptide (24.0%, 95% CI 17.0-30.5%) or non-HF related cardiovascular hospitalization criteria (20.0% [95% CI 14.2-25.4%] and 14.8% [95% CI 11.5-17.9%] for hospitalization <30 days and 30-180 days before randomization, respectively) (*Fig. 1A*). When taking patients randomized within 30-180 days of non-HF related cardiovascular hospitalization as reference, a prior HF hospitalization within 30 days (HR 2.04, 95% CI 1.60 to 2.62), or within 30-180 days (HR 1.82, 95% CI 1.42 to 2.33) were both associated with significantly higher risks of the primary outcome (*Fig. 2A*).

Similarly, taking the subgroup without loop-diuretic at baseline as reference, both patients with a furosemide-equivalent dose >40 mg (HR 3.16, 95% CI 2.43 to 4.11) and 1-40 mg (HR 2.06, 95% CI 1.60 to 2.65) displayed a significantly higher risk of the primary outcome (*Figs 1B*

and 2A). Importantly, patients with a furosemide-equivalent dose >40 mg had a very high-risk for event (32.9% at 2 years) which was comparable to or higher than that of patients with a HF hospitalization <30 days (28.5% at 2 years). Similar results were observed by multivariable analyses for both original study inclusion criteria and loop-diuretic subgroups (*Fig. S2 in Supplementary material*). Additionally, the prognostic accuracy of furosemide use as assessed by Harrell's C-index is statically significant in the total cohort as well as in risk subgroups according to original study enrichment inclusion criteria, with superimposable results (*Table 1 in Supplementary material*)

When taking into account subgroups according to loop and thiazide diuretic combinations, thiazide/thiazide-like diuretic use does not seem to modify the risk of adverse outcome conferred by loop diuretic alone, for both furosemide >40 mg (thiazide =32.7% vs. no thiazide 33.0%, HR \approx 3.3), and furosemide 1-40 mg (thiazide =27.9% vs. no thiazide 24.4%, HR \approx 2.2). The risk associated with thiazide diuretic use alone is comparable to that of patients taking no diuretics (*Figs 1C and 2B*). Finally, a fair stepwise increase in the risk of primary outcome was observed when considering furosemide 1-20, 21-40, 41-80, and >80 mg subgroups (*Fig. 1D*)

Without taking into account timing of hospitalization or loop-diuretic dose, a prior HF hospitalization (non-HF related cardiovascular hospitalization subgroup as reference; HRs >1.15, all P-values <0.001) and loop diuretic use (no baseline loop diuretic as reference; HRs >1.70, all P-values <0.0001) were both significantly associated with the primary and all secondary outcomes (*Fig. S3 in Supplementary material*). Recent (versus less recent – considered as reference) non-HF related cardiovascular or HF hospitalization were overall not significantly associated with worse prognosis. (*Fig. S3 in Supplementary material*).

Effect of eplerenone according to conventional prognostic enrichment criteria and baseline loop-diuretic use

According to enrichment criteria categories, the treatment effect of eplerenone on the primary outcome was significant in both patients randomized within 30 days of an HF

hospitalization (HR 0.53, 95% CI 0.40 to 0.70) as well as in patients with natriuretic peptide criteria (HR 0.54, 95% CI 0.30 to 0.95) (*Fig. 3A*); no significant interaction between treatment effect of eplerenone and enrichment criteria was observed (interaction P-value =0.20) (*Fig. 3A*).

Both patients with a furosemide-equivalent dose >40 mg (HR 0.65, 95% CI 0.50 to 0.86) and 1-40 mg (HR 0.63, 95% CI 0.51 to 0.79) significantly benefitted from eplerenone treatment with respect to the primary outcome; as for the enrichment criteria analysis, the interaction did not reach statistical significance (interaction P =0.64) (*Fig. 3A*). Similar results were observed when considering loop-diuretic/thiazide diuretic combinations (interaction P =0.51; *Fig. 3B*)

Overall, interaction analyses between treatment effect of eplerenone and enrichment criteria, loop diuretic (use and dosage), or timing of prior cardiovascular hospitalization (non-HF-related) were not significant for all studied primary and secondary outcomes (*Table 2 in Supplementary materials*).

Discussion

In this post hoc analysis of the EMPHASIS-HF study, we found that, among patients with HFrEF and mild symptoms, loop diuretics usage (especially at high doses) identified participants with a 2-3 fold greater risk of cardiovascular death or HF hospitalization, which is a similar or greater increment in risk than that conferred by a well-established risk-enrichment criteria such as prior HF hospitalization. The higher risk related to loop diuretic use was consistent for all secondary endpoints, and the treatment effect of eplerenone was not influenced by this background diuretic use or dose.

Prognostic enrichment strategies in heart failure clinical trials

For event-driven studies, prognostic enrichment strategies usually involve identification of patients with a higher probability of having a disease-related endpoint. This approach is intended to permit a smaller sample size as a result of the higher event rate, but assumes that the proportional reduction in events with treatment is maintained [1]. These risk-enhancing variables

usually include clinical and laboratory measurements, medical history, genomic and proteomic measurements.

The concept that a recent hospitalization for HF can identify a high-risk patient population is well-described [3,2], and confirmed in recent HF studies [22]. Findings from the Candesartan in Heart failure: Reduction in Mortality and morbidity (CHARM) Program (enrolling 7599 HF patients with or without systolic dysfunction) showed that the magnitude of increased risk of cardiovascular death or HF hospitalization in HF_rEF with a prior HF hospitalization before randomization was approximately 60%, and that the time interval between hospitalization and randomization was inversely associated with adverse outcome[2]. Another post hoc analysis on the same cohort taking into account HF hospitalizations occurring during study follow-up found similar results in terms of mortality [3].

Due to differences in statistical methodology between our study and the above post hoc analyses from the CHARM Program (i.e. different reference category, comparison among multiple enrichment criteria), a direct comparison cannot be made. However, even in a worst-case scenario as in the present study (i.e. a prior cardiovascular but not HF-related hospitalization as reference category), our results demonstrated that HF hospitalization within 6 months prior to randomization was associated with a 75% higher risk for the combined outcome, with an inverse relationship between timing of hospitalization and risk of adverse outcome (*Fig. 3 in Supplementary material*).

On the other hand, the assumption that a previous HF hospitalization would carry higher risk in HF trials was not confirmed in the TOPCAT trial, showing marked regional differences in terms of primary combined endpoint event-rates between patients randomized from Eastern Europe compared with those enrolled from the Americas (respectively, 14.7 vs. 2.4 per 100 patient-years)[23]. This suggest that, although HF hospitalization is generally seen as an objective enrollment criterion, non-adjudicated qualifying hospitalization can lead to inclusion of different patient populations, and subsequent treatment effect heterogeneity[23].

With regard to eplerenone treatment effect, a previous post hoc analysis of EMPHASIS-HF showed that the beneficial effect of eplerenone on outcomes was unaffected by the timing of the qualifying cardiovascular hospitalization [24]. Similarly, we found no significant overall interaction between eplerenone treatment effect and enrichment criteria.

Diuretic therapy as enrichment factor in heart failure with reduced ejection fraction clinical trials

Loop diuretics are used for relieving congestive HF symptoms and signs, with 80% of HF patients being prescribed this medications [25]. Although diuretics have long been acknowledged as having positive effects on chronic HF patients, several retrospective studies have highlighted that their use, especially in high doses, is associated with adverse outcome [25]. As suggested by the current European Guidelines[10], diuretics might be temporarily discontinued in selected asymptomatic patients without signs of congestion. To this purpose, the Rede Brasileira de Estudos em Insuficiência Cardíaca (ReBIC trial), a multicentre double-blind randomized study which enrolled a cohort of 188 apparently euvolaemic HF outpatients (LVEF \leq 45%) on stable low dose of furosemide (40 up to 80 mg/day), recently demonstrated that diuretic withdrawal do not significantly impact on the self-perception of dyspnea and use of additional diuretics up to 90 after randomization[26]. However, the study was underpowered to assess the effect of such a strategy on hard clinical endpoints, and larger trials with long-term follow-up are needed.

Despite growing data, the causal relationship between diuretics use and adverse outcome have been challenged on the grounds that a high diuretic dose more likely reflects the severity of the disease rather than a true risk factor among patients with HF and systolic dysfunction (i.e. “the sicker the patient, the higher the diuretic dose”) [27].

In this respect, Pellicori et al, in a cohort of 1190 HF outpatient with mixed LVEF, demonstrated that loop diuretics did not independently predict adverse outcome at long-term

follow-up by multivariable analyses, but rather identifies patients with more advanced HF and level of congestion, which may account for their worse prognosis[28].

In any case, the primary aim of our study was not focused on adding further evidence on the prognostic impact of diuretic therapy (which was already demonstrated in several studies as reported above), but rather to directly compare the baseline risk associated with loop-diuretic therapy with that of other baseline factors usually adopted as prognostic enrichment criteria (i.e. prior HF hospitalization or natriuretic peptide blood concentrations).

Although diuretic dose may be a powerful, simple prognostic enrichment criteria in HFrEF trials, care should be taken to avoid investigators deliberately prescribing the dose required to fit the inclusion criteria, or at least reporting that they have done so. This is also the case for history of HF hospitalization as highlighted above. This may potentially be mitigated by a policy of quality control and data ascertainment. Our results demonstrate that the risk associated with loop-diuretic at least matches or even exceeds that associated with history of HF hospitalization.

On the other hand, it should be noted that “greater risk” does not equal “greater modifiable risk”, and a proportion of patients with more advanced HF may be refractory to the benefits of a particular therapy. Clinical trialists should keep from enrolling patients with very high event rates, but rather target intermediate risk populations (the so-called “sweet-spot”), associated with larger treatment effects[29,6].

Finally, we showed how the stepwise increase in the risk of adverse outcome associated with furosemide use appears to be unaffected by the concomitant use of thiazide; indeed, the risk associated with a given dosage of furosemide (i.e. furosemide >40 and 1-40 mg) is quite comparable to that of respective subgroups contemporarily taking thiazide diuretics (Fig. 1C).

Of note, the risk-rate of adverse outcome associated with thiazide use alone is comparable to that of patients without diuretics at baseline (about 12.0% at 2-year follow-up); that risk is, respectively, about half and one third of that observed in subgroups with furosemide 1-40 and >40 mg (Fig. 1C). This HFrEF subgroup, not taking loop diuretics regularly (or taking only thiazide diuretics) represents about 25% of our total cohort, and similar proportions are observed

in more contemporary study[30]. Further studies are needed to assess whether is still suitable to include that low-risk subgroup in forthcoming HFrEF trial design.

Limitations

This is a post hoc analysis of a randomized clinical trial that was not powered to identify differences in terms of outcomes according loop diuretic use. Additionally, in EMPHASIS-HF, elevated natriuretic peptides were requested only in the absence of a recent cardiovascular hospitalization [18], otherwise their concentration was not routinely assessed.

Conclusions

Dose of loop diuretics (especially at high doses) identifies a subset of HF patients with high risk of adverse clinical outcomes, a risk similar or greater in magnitude than the risk conferred by other well-established prognostic enrichment factors, namely HF hospitalization and raised natriuretic peptide concentrations. We believe that including diuretic dose as an additional enrichment criterion can be useful in designing future HF trials

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Figure captions

Fig. 1 A-B-C-D: Kaplan Meier curves for enrichment criteria - Survival curves for cardiovascular death or HF hospitalization according to enrichment criteria (non-HF related CVH within 30 days or 30 to 180 days prior to randomization, HFH within 30 days or 30 to 180 days prior to randomization or elevated natriuretic peptides; panel A), to furosemide subgroups (3 subgroups, panel B), to furosemide-thiazide combination subgroups (panel C), and to 5 furosemide subgroups (panel D)

HF, heart failure; CVH, cardiovascular hospitalization; HFH, heart failure hospitalization.

Fig. 2A-B: Enrichment factors and risk of primary outcome - Association of enrichment criteria (CVH within 30 days or 30 to 180 days prior to randomization, HFH within 30 days or 30 to 180 days prior to randomization or elevated natriuretic peptides) and loop diuretic use (Panel A), and of furosemide-thiazide combination subgroups (Panel B) with rates of cardiovascular death or HF hospitalization (unadjusted hazard ratios). See Figure 1 for abbreviations.

Fig. 3A-B: Effect of eplerenone according to enrichment criteria - Forest plot for treatment effect on cardiovascular death or hospitalization for heart failure according to enrichment criteria and loop diuretic use (Panel A), and to furosemide-thiazide combination subgroups (Panel B).

Supplementary materials

Fig. 1 Venn diagram showing the overlap between furosemide subgroups (>40 mg, 1-40 mg) and selected prognostic enrichment criteria (i.e. previous heart failure hospitalization and elevated natriuretic peptide concentrations). The subgroup no diuretic/non-HF CVH is not taken into account. See Figure 1 for abbreviations.

Fig. 2 Multivariable Cox proportional hazards models for study enrichment criteria and loop-diuretic subgroups

Fig. 3 Enrichment factors and outcome - Association of enrichment criteria (non-HF related CVH within 30 days or 30 to 180 days prior to randomization, HFH within 30 days or 30 to 180 days prior to randomization or elevated natriuretic peptides) and diuretic use with rates of cardiovascular death or HF hospitalization and secondary outcomes. See Figure 1 for abbreviations.

Figure 1

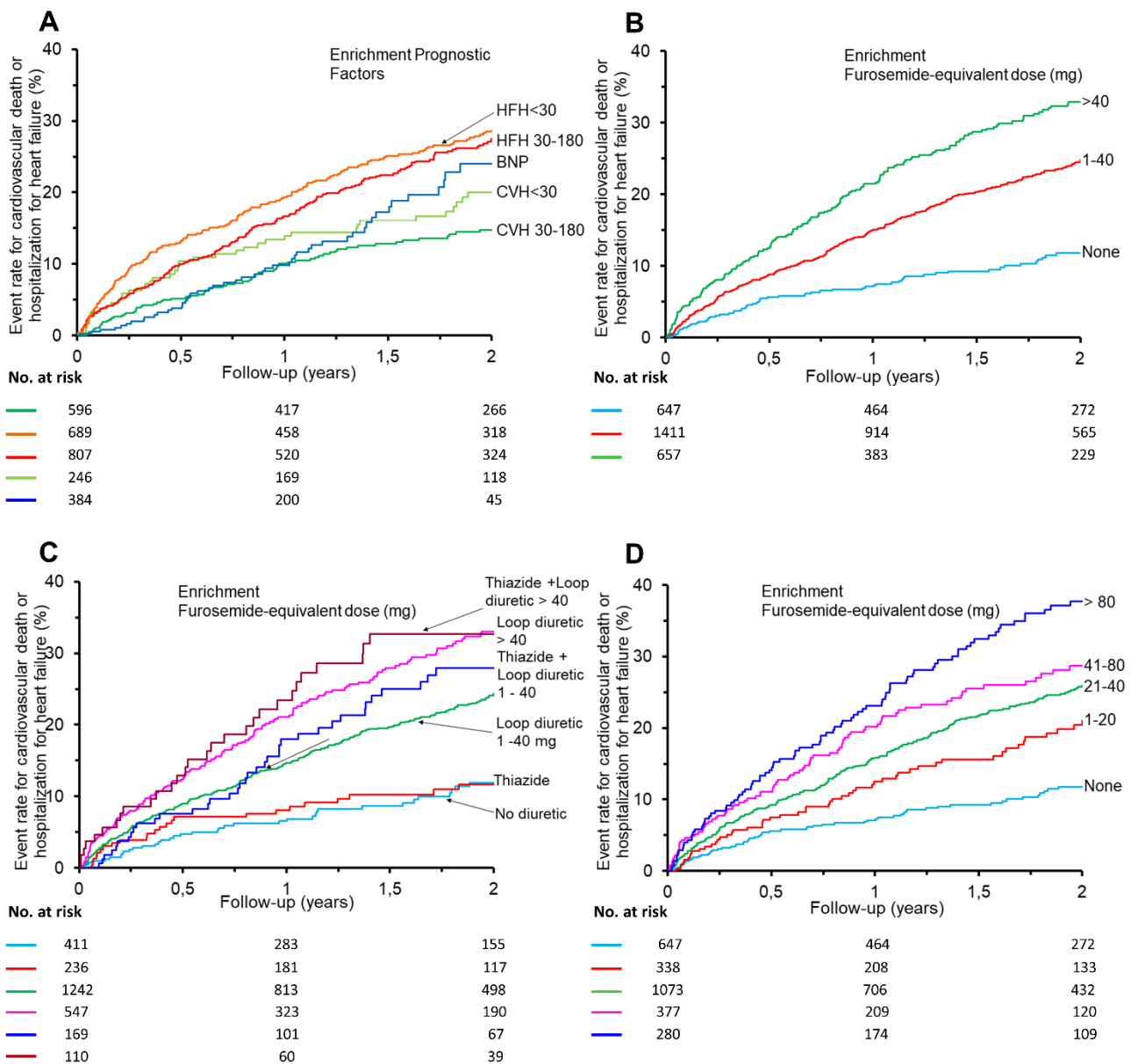


Figure 2

Cardiovascular death or hospitalization for heart failure

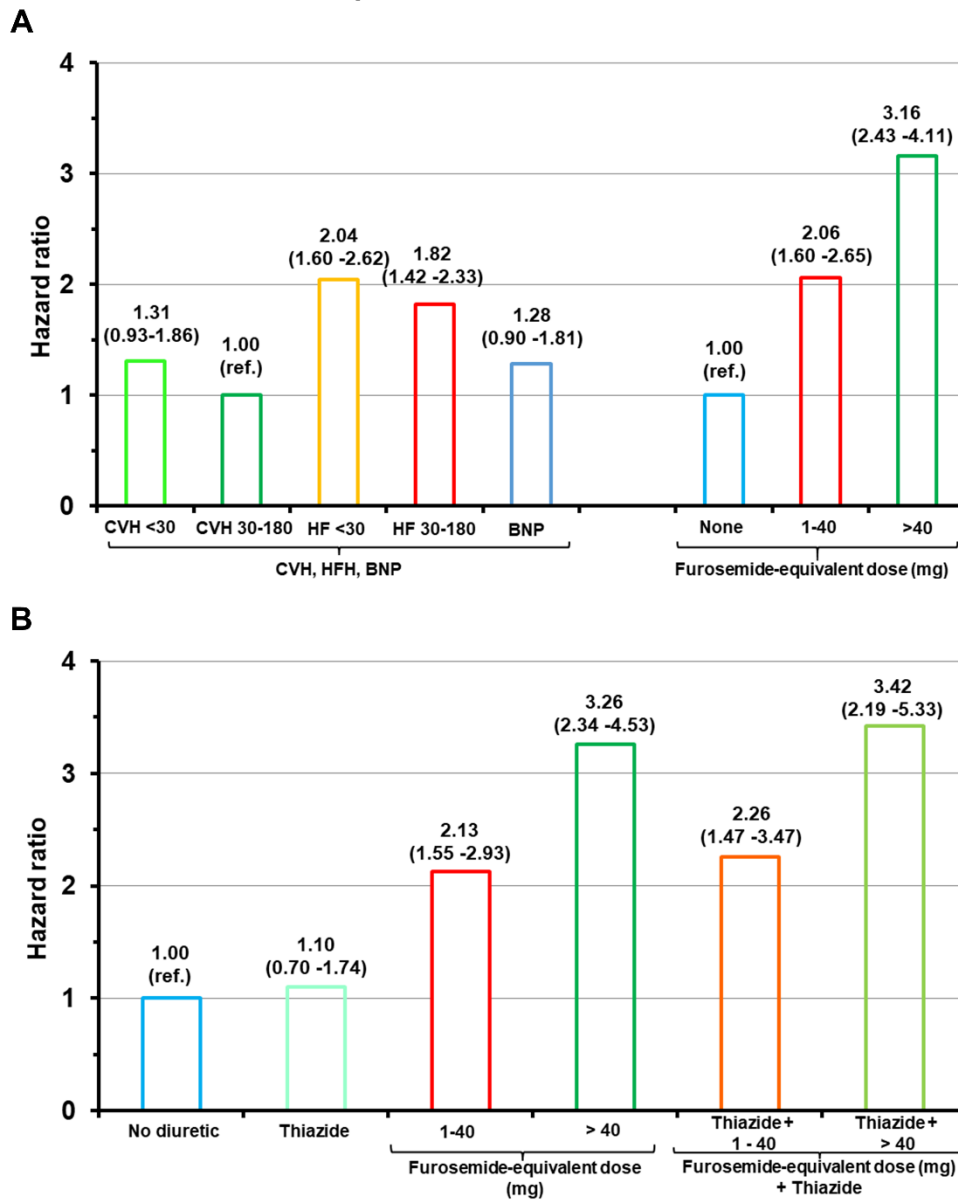
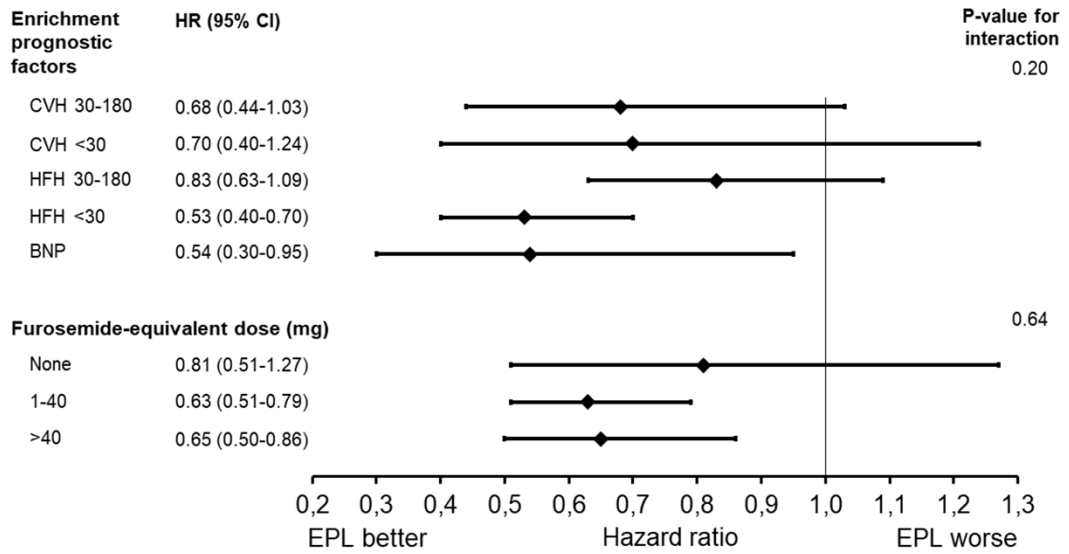


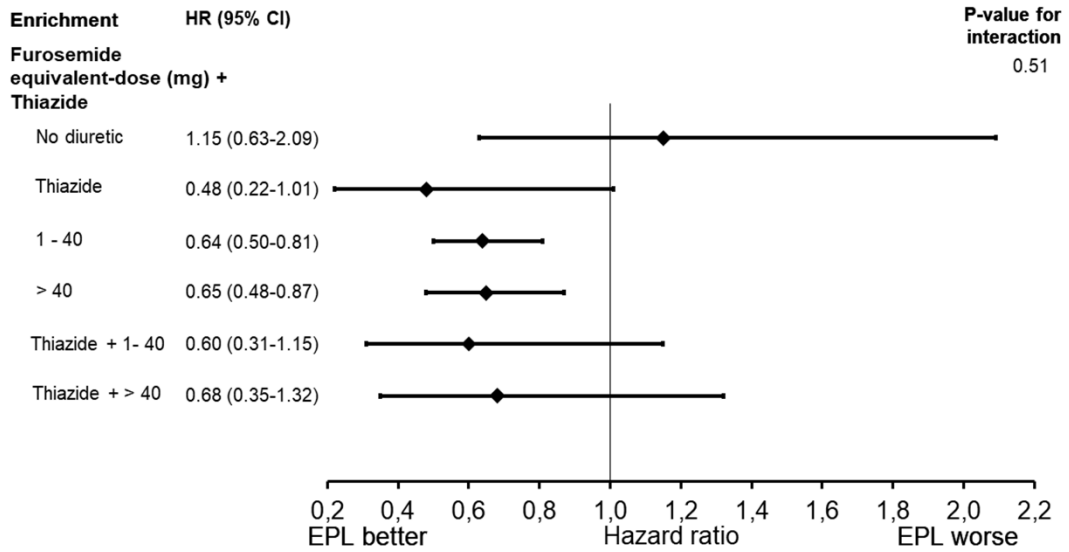
Figure 3

Cardiovascular death or hospitalization for heart failure

A



B



Graphical abstract

Diuretic therapy as prognostic enrichment factor for clinical trials in patients with heart failure with reduced ejection fraction

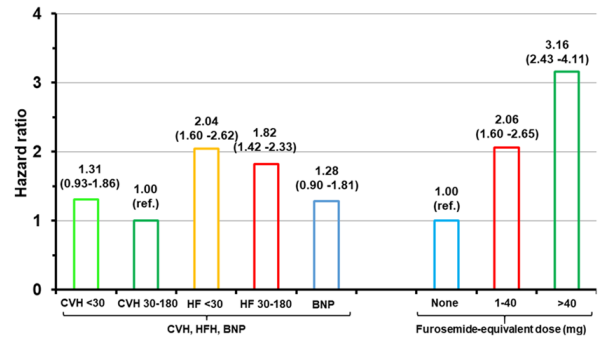
Aims

Compare the increment in risk related to **diuretic dose vs. conventional prognostic criteria** (prior hospitalization and elevated natriuretic peptides) used in the Eplerenone in Patients With Systolic Heart Failure and Mild Symptoms (EMPHASIS-HF).

Primary endpoint

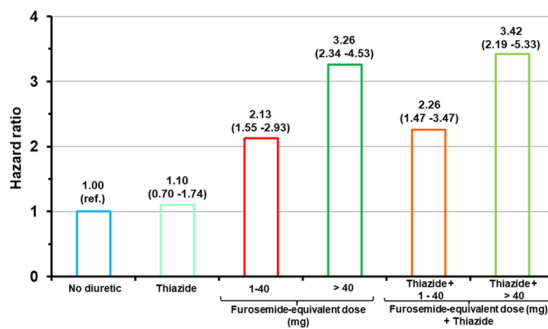
Composite of CV death or HF hospitalization.

Association of loop diuretic dose and conventional prognostic enrichment criteria with CV death or HF hospitalization



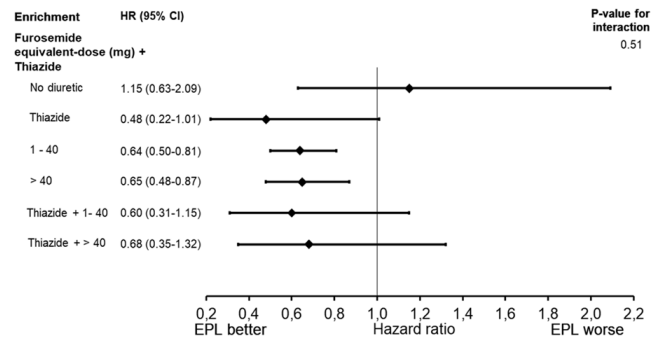
Loop diuretic usage at baseline is more associated with the primary endpoint (HR 2.0 to 3.2) than history of hospitalization and/or BNP: (HR ranging from 1.3 to 2)

Interplay of loop diuretic dose and thiazide use with regards to CV death or HF hospitalization



Thiazide use does not seem to modify the risk of adverse outcome conferred by loop diuretic alone

Effect of eplerenone according to diuretic use



Eplerenone effect is overall consistent across subgroups. The estimated effect in patients without diuretics was neutral (HR 1.15)

Loop diuretic usage identified patients at higher risk than history of HF hospitalization and/or high BNP blood concentrations.

Including diuretic dose as an additional enrichment criterion can be useful in designing future HF trials.

Table 1 Patient characteristics according to enrichment criteria (history of HFH within 30 days or between 30 and 180 days prior to randomization, history of CVH within 30 days or between 30 and 180 days prior to randomization, and elevated natriuretic peptide concentrations)

Characteristic	History of HFH (1)				History of non-HF related CVH (2)				Elevated natriuretic peptides (3)	P-value for trend (1) vs. (2) vs. (3)
	within 180 days (n=1496)	Within 30 days (n=689) (1 a)	Between 30-180 (n=807) (1 b)	P (1 b vs. 1 a)	within 180 days (n=842)	Within 30 days (n=246) (2 a)	Between 30-180 (n=596) (2 b)	P (2 a vs. 2 b)	StatBNP (n=384)	
Age (years)	68.7 ± 7.7	68.8 ± 7.3	68.7 ± 8.0	0.73	68.4 ± 7.4	67.8 ± 6.8	68.7 ± 7.6	0.16	68.8 ± 8.1	0.68
Male sex	1141 (76.3 %)	535 (77.6 %)	606 (75.1 %)	0.25	658 (78.1 %)	185 (75.2 %)	473 (79.4 %)	0.18	318 (82.8 %)	0.022
SBP (mmHg)	124 ± 17	122 ± 16	125 ± 17	0.001	125 ± 17	125 ± 16	125 ± 17	0.99	124 ± 1	0.11
DBP (mmHg)	75 ± 10	75 ± 10	75 ± 10	0.92	75 ± 10	75 ± 10	75 ± 10	0.96	72 ± 11	< 0.0001
HR (bpm)	71 (64 - 80)	7 (64 - 80)	70 (64 - 80)	0.18	70 (62 - 78)	70 (63 - 79)	70 (62 - 78)	0.33	68 (60 - 76)	< 0.0001
LVEF (%)	27 (23 - 30)	27 (24 - 30)	26 (23 - 30)	0.01	28 (25 - 30)	28 (25 - 30)	28 (25 - 30)	0.79	25 (21 - 30)	< 0.0001
eGFR <60	979 (65.4 %)	433 (62.8%)	546 (67.6 %)	0.053	598 (71.0 %)	165 (67.1 %)	433 (72.7 %)	0.11	238 (62.0 %)	0.002
Non ischemic HF	556 (37.3 %)	218 (31.6 %)	338 (42.1 %)	< 0.0001	155 (18.4 %)	52 (21.1 %)	103 (17.3 %)	0.19	128 (33.3 %)	< 0.0001
Ischemic HF	936 (62.7 %)	471 (68.4 %)	465 (57.9 %)	< 0.0001	687 (81.6 %)	194 (78.9 %)	493 (82.7 %)	0.19	256 (66.7 %)	< 0.0001
BMI >30	390 (26.2 %)	173 (25.2 %)	217 (27.1 %)	0.42	236 (28.2 %)	78 (31.7 %)	158 (26.7 %)	0.14	109 (28.6 %)	0.47
Previous MI	636 (42.5 %)	314 (45.6 %)	322 (39.9 %)	0.027	533 (63.3 %)	147 (59.8 %)	386 (64.8 %)	0.17	206 (53.6 %)	< 0.0001
Previous HF Hosp.	890 (59.5 %)	409 (59.4 %)	481 (59.6 %)	0.92	361 (42.9 %)	136 (55.3 %)	225 (37.8 %)	< 0.0001	180 (46.9 %)	< 0.0001
Diabetes	507 (33.9 %)	232 (33.7 %)	275 (34.1 %)	0.87	227 (27.0 %)	62 (25.2 %)	165 (27.7 %)	0.46	118 (30.7 %)	0.002
ICD	94 (6.3 %)	40 (5.8 %)	54 (6.7 %)	0.48	157 (18.6 %)	33 (13.4 %)	124 (20.8 %)	0.012	111 (28.9 %)	< 0.0001
Pacemaker	165 (11.0 %)	78 (11.3 %)	87 (10.8 %)	0.74	136 (16.2 %)	28 (11.4 %)	108 (18.1 %)	0.016	92 (24.0 %)	< 0.0001
Thiazide/thiazide like diuretic	275 (18.4 %)	147 (21.3 %)	128 (15.9 %)	0.006	182 (21.6 %)	61 (24.8 %)	121 (20.3 %)	0.15	59 (15.4 %)	0.024
ACE inhibitor	1163 (78.2 %)	546 (79.7 %)	617 (76.9 %)	0.2	670 (80.0 %)	212 (86.5 %)	458 (77.2 %)	0.002	279 (73.0 %)	0.025
ARB	276 (18.6 %)	125 (18.2 %)	151 (18.8 %)	0.77	149 (17.8 %)	28 (11.4 %)	121 (20.4 %)	0.002	99 (25.9 %)	0.002
ACE inhibitor or ARB	1401 (94.2 %)	655 (95.6 %)	746 (93.0 %)	0.032	789 (94.2 %)	236 (96.3 %)	553 (93.3 %)	0.085	354 (92.7 %)	0.51
Beta-blocker	1264 (85.0 %)	579 (84.5 %)	685 (85.4 %)	0.63	751 (89.6 %)	219 (89.4 %)	532 (89.7 %)	0.89	345 (90.3 %)	0.0009
No furosemide	221 (14.9 %)	119 (17.4 %)	102 (12.8 %)	0.013	317 (37.8 %)	91 (37.3 %)	226 (38.0 %)	0.84	102 (26.9 %)	< 0.0001
Furosemide 1-40 mg	824 (55.6 %)	356 (52.0 %)	468 (58.6 %)	0.01	400 (47.7 %)	116 (47.5 %)	284 (47.8 %)	0.94	181 (47.8 %)	0.0003
Furosemide 1-40 mg + thiazide	103 (7.0 %)	49 (7.2 %)	54 (6.8 %)	0.77	46 (5.5 %)	17 (7.0 %)	29 (4.9 %)	0.23	20 (5.3 %)	0.26
Furosemide >40 mg	438 (29.5 %)	210 (30.7 %)	228 (28.6 %)	0.38	121 (14.4 %)	37 (15.2 %)	84 (14.1 %)	0.70	96 (25.3 %)	< 0.0001
Furosemide >40 mg + thiazide	76 (5.1 %)	42 (6.1 %)	34 (4.3 %)	0.10	18 (2.2 %)	7 (2.9 %)	11 (1.9 %)	0.36	15 (4.0 %)	0.002

HF, heart failure; CVH, cardiovascular hospitalization; HFH, heart failure hospitalization; BNP, B-type natriuretic peptide; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; LVEF, left ventricular ejection fraction; eGFR, Estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter defibrillator; BMI, body mass index; MI, myocardial infarction; ACE, angiotensin converting enzyme; ARB, Angiotensin II receptor blockers

Table 2 Baseline patient characteristics according to furosemide-equivalent dose

Characteristic	Furosemide-equivalent dose		None		1-40 mg		>40 mg		P-value for trend
	n	m ± SD/ median (Q1-Q3) /n(%) (n=647)	n	m ± SD/ median (Q1-Q3)/ n(%) (n=1411)	n	m ± SD/ median (Q1-Q3)/ n(%) (n=657)			
Age (Years)	647	68.0 ± 7.4	1411	69.0 ± 7.8	657	68.5 ± 7.4	0.037		
Male gender	647	507 (78.4 %)	1411	1083 (76.8 %)	657	519 (79.0 %)	0.47		
SBP (mmHg)	646	128 ± 16	1411	124 ± 17	657	121 ± 17	< 0.0001		
DBP (mmHg)	646	76 ± 10	1411	75 ± 10	657	73 ± 10	< 0.0001		
HR (bpm)	646	68.0 (62.0 - 76.0)	1410	70.0 (63.0 - 80.0)	657	72.0 (64.0 - 80.0)	< 0.0001		
LVEF (%)	612	28.0 (25.0 - 30.0)	1342	27.0 (24.0 - 30.0)	614	25.0 (21.0 - 30.0)	< 0.0001		
eGFR <60	647	513 (79.3 %)	1409	926 (65.7 %)	655	369 (56.3 %)	< 0.0001		
Non ischemic HF	646	160 (24.8 %)	1409	454 (32.2 %)	655	223 (34.0 %)	0.0004		
Ischemic HF	646	486 (75.2 %)	1409	955 (67.8 %)	655	432 (66.0 %)	0.0004		
BMI >30	647	180 (27.8 %)	1401	349 (24.9 %)	652	205 (31.4 %)	0.008		
Previous MI	647	362 (56.0 %)	1411	709 (50.2 %)	657	299 (45.5 %)	0.0008		
Previous HFH	647	248 (38.3 %)	1411	755 (53.5 %)	657	420 (63.9 %)	< 0.0001		
Diabetes	647	153 (23.6 %)	1411	438 (31.0 %)	657	262 (39.9 %)	< 0.0001		
ICD	647	89 (13.8 %)	1411	162 (11.5 %)	657	106 (16.1 %)	0.012		
Pacemaker	647	75 (11.6 %)	1411	208 (14.7 %)	657	108 (16.4 %)	0.039		
Thiazide/thiazide like diuretic	647	236 (36.5%)	1411	169 (12.0 %)	657	110 (16.7 %)	<0.0001		
ACE-inhibitor	631	500 (79.2 %)	1411	1118 (79.2 %)	657	487 (74.1 %)	0.023		
ARB	631	108 (17.1 %)	1411	277 (19.6 %)	657	141 (21.5 %)	0.14		
ACE-inhibitor or ARB	631	594 (94.1 %)	1411	1337 (94.8 %)	657	608 (92.5 %)	0.14		
Beta-blocker	631	553 (87.6 %)	1411	1235 (87.5 %)	657	567 (86.3 %)	0.7		
Non-HF CVH≤180	647	317/647 (58.8 %)	1411	400/1411 (32.7 %)	657	121/657 (18.4 %)	< 0.0001		
Non-HF CVH 30-180	647	226/647 (34.9%)	1411	284/1411 (20.1 %)	657	84/657 (12.8 %)	0.93		
Non-HF CVH <30	647	91/647 (14.1 %)	1411	116/1411 (8.2 %)	657	37/657 (5.6 %)	0.93		
HFH≤180 (n=1496)	647	222/647 (34.3 %)	1411	824/1411 (58.4 %)	657	438/657 (66.7 %)	< 0.0001		
HFH 30-180	647	102/647 (15.8%)	1411	468/1411 (33.2 %)	657	228/657 (34.7 %)	0.013		
HFH<30	647	119/647 (18.4 %)	1411	356/1411 (25.2 %)	657	210/657 (32.0 %)	0.013		
BNP (n=385)	647	102/647 (15.8 %)	1411	182/1411 (12.9 %)	657	96/657 (14.7 %)	0.2		

See Table 1 for abbreviations

