Association between up-titration of medical therapy and total hospitalizations and mortality in patients with recent worsening heart failure across the ejection fraction spectrum

***Short title*:** Titration of medical therapies and outcomes in post-worsening HF

Vasiliki Bistola MD, PhD[1]*, Panagiotis Simitsis MD[1]*, John Parissis MD, PhD[1], Wouter Ouwerkerk PhD[2], Dirk J van Veldhuisen MD, PhD[3], John G Cleland MD[4], Stefan D Anker MD, PhD[5], Nilesh J. Samani MD[6], Marco Metra MD[7], Faiez Zannad MD, PhD[8], Eftihia Polyzogopoulou MD PhD[1], Kalliopi Keramida MD PhD[1], Dimitrios Farmakis MD PhD[1], Adriaan A. Voors MD PhD[3], and Gerasimos Filippatos MD[1¶]

*Vasiliki Bistola and Panagiotis Simitsis contributed equally to this manuscript.

Affiliations:

[1]National and Kapodistrian University of Athens, Department of Cardiology, Heart Failure Unit, Attikon University Hospital, Athens, Greece.

[2]National Heart Centre Singapore, Singapore and Dept of Dermatology, Amsterdam UMC, University of Amsterdam, Amsterdam Infection & Immunity Institute, Amsterdam, The Netherlands.

[3]Department of Cardiology, University Medical Centre Groningen, University of Groningen, Hanzeplein 1, 9713 GZ, Groningen, The Netherlands.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/ejhf.2219

[4]National Heart and Lung Institute, Royal Brompton and Harefield Hospitals, Imperial College, London, UK and Robertson Centre for Biostatistics and Clinical Trials, University of Glasgow, Glasgow, UK.

[5]Department of Cardiology (CVK); and Berlin Institute of Health Center for Regenerative Therapies (BCRT); German Centre for Cardiovascular Research (DZHK) partner site Berlin; Charité Universitätsmedizin Berlin, Germany.

[6]Department of Cardiovascular Sciences, University of Leicester, Glenfield Hospital, Leicester, UK and NIHR Leicester Cardiovascular Biomedical Research Unit, Glenfield Hospital, Leicester, LE3 9QP, UK.

[7]Institute of Cardiology, ASST Spedali Civili di Brescia and Department of Medical and Surgical Specialties, Radiological Sciences and Public Health of the University of Brescia, Italy.

[8]Centre d'Investigations Cliniques-Plurithématique 1433, and Institut National de la Santé et de la Recherche Médicale U1116, Centre Hospitalier Regional Universitaire, French Clinical Research Infrastructure Network, Investigation Network Initiative Cardiovascular and Renal Clinical Trialists, Nancy, France.

Total word count: 3435

[¶]Corresponding author:

Gerasimos Filippatos

National and Kapodistrian University of Athens, Department of Cardiology, Heart Failure Unit

Attikon University Hospital

Rimini 1, 12461 Athens, Greece.

Tel +302105832195, email: geros@otenet.gr; gfilippatos@gmail.com

Abstract

Background: The role of neurohormonal inhibition in chronic heart failure is well established. There is limited data on the effect of up-titration of renin angiotensin inhibition (RASi) and beta-blockers (BBs) on clinical outcomes of patients with worsening heart failure (HF) across the left ventricular ejection fraction (LVEF) spectrum.

Methods and results: We analyzed data from 2345 patients from BIOSTAT-CHF (80.9% LVEF<40%), who completed a 3-month up-titration period after recent worsening of HF. Patients were classified by achieved dose (% of recommended): ≥100%, 50-99%, 1-49%, and none. Recurrent event analysis using joint and shared frailty models was used to examine the association between RASi/BBs dose and all-cause and HF hospitalizations. In the 21-months following up-titration, 512 patients died and 879 (37.5%) had ≥1 hospitalization. RASi up-titration was associated, incrementally, with reduced risk of all-cause hospitalization at all achieved dose-levels compared to no treatment [HR (95%CI): ≥100%: 0.60(0.49-0.74), p<0.001; 50-99%: 0.56(0.46-0.68), p<0.001; 1-49%: 0.71(0.59-0.86), p<0.001]. This association was consistent up to an LVEF of 49% (p<0.001), and when considering only HF hospitalizations. Up-titration of BBs was associated with fewer all-cause hospitalizations only when LVEF was <40% (overall p<0.001), but with more HF hospitalizations when LVEF was ≥50%. Up-titration of both RASi/BBs was associated with lower mortality in LVEF up to 49%.

Conclusion: After recent worsening of HF, up-titration of RASi and BBs was associated with a better prognosis in patients with LVEF ≤49%. Up-titration of BBs was associated with a greater risk of HF hospitalization when LVEF was ≥50%.

Keywords: worsening heart failure; renin-angiotensin-system inhibitors; beta-blockers; hospitalizations; mortality.

Introduction

Heart failure (HF) is characterized by high mortality and morbidity[1, 2]. Traditionally, the ability of HF therapies to reduce morbidity has been examined by their effect on time to first unscheduled hospitalization. However, assessment of total hospitalizations could reflect the burden of disease more accurately[3]. Hospitalizations are associated with poorer quality of life and a higher mortality, while they also contribute to over three quarters of HF-related cost [4, 5]. Rates of hospitalizations are highest in the post-discharge period, with up to 30% of patients being re-admitted within 30 days after discharge[6]. The effect of neurohormonal inhibition in patient with recent worsening, especially in those with mildly reduced or preserved ejection fraction, has not been studied. BIOSTAT-CHF is a European prospective study that enrolled patients with worsening HF receiving less than guideline-recommended doses of renin-angiotensin inhibitors (RASi) or beta-blockers (BBs). In a previous analysis, up-titration of RASi and BBs to guideline-recommended doses, if tolerated, was shown to delay the time to first hospitalization and reduce mortality[7]. In the present analysis, we examined whether up-titration of RASi and BBs is associated with reduced total hospitalizations and mortality in patients with worsening HF across the entire LVEF spectrum.

Methods

Study design and characteristics of patients enrolled in the BIOSTAT-CHF study has been described previously[8]. Briefly, BIOSTAT was a prospective, observational study that examined up-titration of RASi (ACEi/ARBs) and BBs in patients with worsening signs or symptoms of HF, either new-onset or with a previous history of HF, from 69 centers in 11 European countries. Patients were either hospitalized or presented at the out-patient HF clinic and were sub-optimally treated with RASi and/or BBs. Drug initiation/up-titration was performed within 3 months post-enrollment (drug optimization phase), in accordance with ESC guidelines [9]. In the subsequent 6 month maintenance period, no further drug optimization was anticipated except if clinical status mandated it. Patients were followed every 6 months for up to 30 months[8]. Institutional Review Board approval was obtained in all countries and all patients provided written informed consent before inclusion. In the present analysis, patients were classified into 4 groups based on the achieved dose of RASi and BBs (% of guideline-recommended): no drug (0%), 1-49%, 50-99% and ≥100% of the recommended dose[9]. Outcomes (events) were total hospitalizations (first and recurrent events) and all-cause death (terminal event) that occurred after completion of drug optimization phase. Among all hospitalizations, only those that were unscheduled and non-fatal were included. Scheduled hospitalizations were discarded and those that led to death were counted once as death events. Per protocol, hospitalizations were adjudicated by the treating physicians and not by a central adjudication committee. Patients followed for less than 3 months and those who died prior to the completion of drug optimization period (defined as 90 days in the present analysis) were excluded from the analysis. Missing value analysis was performed and

only variables with <15% missing values were included. Five complete samples were created using multivariate imputation by chained equations (Gibbs sampling)[10]. Among 3 multiple imputation methods tested (classification and regression trees, random forest algorithm and predictive mean matching), the classification and regression trees method had the best fit.

To correct for potential treatment-indication bias due to the non-randomized study design, stabilized inverse probability weights (IPW) were calculated for each patient based on logistic regression models with the probability of receiving the target dose of each drug (BBs or RASi) as the dependent variable and 72 baseline covariates (including second order terms for numeric variables) as predictor[11]. All survival regressions were weighted by the stabilized IPW for each drug.

Survival analysis was performed by fitting shared and joint gamma frailty models using a semi-parametric penalized likelihood estimation on the hazard function, based on the hypothesis that total unscheduled hospitalizations (first and recurrent events) and death (terminal event) are positively correlated[11-13]. For the crude (unadjusted) weighted risk of hospitalizations and death according to drug level, we fitted univariable joint frailty models separately for RASi and BBs. To estimate the adjusted association of the drug dose with hospitalizations and death we fitted a parsimonious multivariable joint frailty model for each drug. Two separate shared frailty models were fitted during the selection process: one for the recurring event (total hospitalizations) and another for the terminal event (death). The log-likelihood, degrees of freedom and likelihood cross-validation criterion (LCV) were calculated for every model. The between-models comparison was performed using the likelihood ratio (LR) test and the LCV, with lower

values of LCV indicating a better fitting model[14]. The final joint frailty model for each drug that linked the effects of covariates on both hospitalizations and death consisted of a formula for the recurring event and a separate formula for the terminal event. The exact process of selection of the final models and other baseline variables that were included in the multivariable joint frailty models are shown in Supplementary Tables 1-4. Shared frailty models were fitted to examine the association of RASi/BBs up-titration with unscheduled hospitalizations due to HF or to cardiovascular causes (HF, cardiac non-HF, renal and vascular causes). Additional information regarding statistical analysis is provided in the Supplementary appendix.

To examine potential differential treatment responses among patients with reduced, mid-range, and preserved LVEF, joint and shared frailty analyses were performed in patient subgroups categorized by baseline LVEF. Poisson regression was used to assess any modification of RASi/BBs relationship with total or HF hospitalizations by LVEF as a continuous variable. To test for heterogeneity of treatment-outcomes associations with respect to other baseline characteristics, p-value of the interaction between baseline characteristics and drug dose levels was calculated using multivariable shared frailty weighted models.

Results

Baseline patient characteristics and up-titration of RASi and BBs

From the total of 2516 patients enrolled in BIOSTAT-CHF, we have analyzed 2345 patients after excluding 171 who died within the 90-day optimization period or were followed for less than 90 days. Excluded patients were older and had a higher comorbidity burden and more severe initial presentation than patients who completed the titration period (Supplementary Table 5). Included patients had a mean age of 70±17 years, 73.6% were males, while 80.9%, 12.6% and 6.6% had baseline LVEF <40%, 40-49% and ≥50%, respectively.

At the end of the drug optimization period, patients who achieved RASi dose ≥100%, 50-99%, 1-49%, or no drug were: 529 (22.6%), 734 (31.3%), 814 (34.7%) and 268 (11.4%), respectively. As to BBs dose, respective patients (n, %) were: 266 (11.3%), 599 (25.5%), 1303 (55.6%) and 177 (7.5%). As shown in Table 1, patients who achieved a high RASi dose (≥50%) were younger, with less frequently atrial fibrillation (AF) and chronic kidney disease (CKD), more frequently diabetes mellitus and arterial hypertension; higher SBP, DBP, and BMI; lower LVEF; more frequently in NYHA class II/III than IV, with better exercise capacity as estimated by 6-minute walking distance (6MWD). Patients who achieved high BB dose (≥50%) were also younger, more frequently males with ischemic HF etiology and AF, but with less frequently chronic obstructive pulmonary disease (COPD); higher SBP, DBP, HR, and BMI; lower LVEF; and, better exercise capacity than patients on lower BB doses.

Outcomes

Among the 2345 patients, 512 died from any cause. A total of 2783 non-fatal hospitalizations were recorded, of which 1996 were unscheduled and occurred in 879 patients (37.5%). Acute HF decompensation was the cause of 914 (45.8%) of unscheduled hospitalizations, while 292 (14.6%) were due to cardiac non-HF causes, 65 (3.3%) to vascular causes, 62 (3.1%) to renal dysfunction, and 663 (33.2%) to non-cardiovascular causes (Supplementary Table 6). Figure 1 shows the frequency distribution of patients with or without clinical events (death or all-cause unscheduled hospitalization) categorized by the number of prior unscheduled hospitalizations.

Association between achieved dose of RASi and BBs with total unscheduled hospitalizations and mortality

The frequencies distribution of hospitalizations and death within patient subgroups categorized according to achieved RASi and BBs dose is shown in Supplementary Table 6.

In the overall population, RASi up-titration was associated with reduced risk of total (univariable $p < 0.001$) hospitalizations and mortality (univariable $p < 0.001$) (Supplementary Table 7). This association was dose-dependent; in patients who achieved either 50-99% or ≥100% of recommended dose, hospitalization risk was significantly reduced compared to patients who achieved 1-49% [50-99% vs 1-49%: HR 0.74, (95% CI) 0.64 – 0.87, $p<0.001$; ≥100% vs 1-49%: HR 0.72, (95%CI) 0.61 – 0.85, $p<0.001$]. Compared to no treatment, the risk was incrementally lower with increasing RASi dose

[HR (95%CI): ≥100%: 0.60(0.49-0.74), p<0.001; 50-99%: 0.56(0.46-0.68), p<0.001; 1-49%: 0.71(0.59-0.86), p<0.001]. There was no difference in hospitalization risk-between patients receiving 50-99% versus ≥100% RASi dose [HR 0.97, (95%CI): 0.81 – 1.15, p=0.701). Up-titration of BBs was not associated with reduction of hospitalization risk in the overall population analysis (univariable p=0.104). After multivariable adjustment, the dose-dependent association of RASi with reduced hospitalization risk remained significant [dose level 1-49% vs no drug: HR 0.71, (95% CI): 0.59 - 0.86, p<0.001; 50-99% vs no drug: HR 0.56, (95% CI): 0.46 - 0.68, p<0.001; ≥100% vs no drug: HR 0.60, (95%CI): 0.49 – 0.74, p<0.001; 50-99% vs 1-49%: HR 0.81, (95%CI): 0.69-0.94, p=0.007] (Supplementary Table 7). BBs remained not associated with reduced hospitalization risk in multivariable analysis (global p-value=0.707). Similar results were obtained in the analysis that included only total HF hospitalizations, where only RASi was associated with reduced hospitalization risk [multivariable model: dose level 1-49% vs no drug: HR 0.72, (95% CI): 0.59 - 0.89, p=0.003; 50-99% vs no drug: HR 0.56, (95% CI): 0.44 - 0.70, p<0.001; ≥100% vs no drug: HR 0.58, (95%CI): 0.45 – 0.74, p<0.001; 50-99% vs 1-49%: HR 0.77, (95%CI): 0.64-0.93, p=0.007]. Similarly to the primary analysis of BIOSTAT-CHF, up-titration of both RASi and BBs was associated with a dose-dependent mortality risk reduction, with dose levels ≥50% achieving statistical significance compared to no treatment in multivariable analysis (Supplementary Table 7).

Survival analyses in subgroups by categories of LVEF confirmed the dose-dependent association of RASi with reduced all-cause hospitalization risk in subgroups with LVEF<40% and ≥40% (p<0.001 in both groups) (Figure 2), as well as in LVEF<50%, but not in the subgroup with LVEF≥50% (Table 2). This relationship was

also apparent in the analysis with LVEF as continuous measure (Figure 3A). Beta blockers were associated with reduced hospitalization risk only in LVEF<40%, whereas there was no significant association in either subgroups with LVEF<50% or ≥50% (Table 2).

In the analyses that considered total HF and total cardiovascular hospitalizations, RASi titration was associated with incrementally lower risk in patients with LVEF up to <50% (Figure 3B, Table 3). BBs showed a dose-independent association with reduced risk only in patients with LVEF<40% in univariable weighted analysis but not after multivariable adjustment. On the contrary, an increased risk was detected with maximal and supra-maximal BB doses (≥100% of target) in patients with LVEF≥50% (Figure 3C-D, Table 3 and Supplementary Table 8). Up-titration of BBs was associated with less pronounced heart rate (HR) reduction in patients with history of AF at baseline compared to those without [HR at 9 months in the subgroup of ≥100% of target BBs dose (mean±SD): AF history, 78±18; no AF history, 68±12, F test $p_{interaction}$= 0.006).

Regarding mortality, categorical analyses by LVEF showed that both BBs and RASi were associated with reduced mortality risk in patients with LVEF up to 49% (p<0.001 for both drug classes in both analyses), while no benefit was seen with either drug class in LVEF≥50% (Table 2).

Subgroup analysis

Subgroup analysis by other baseline characteristics showed no significant interactions between RASi/BBs dose and hospitalizations or mortality risk, except for: history of

myocardial infarction (p=0.042), chronic kidney disease (p=0.041) and baseline treatment with RASi (p=0.02) that interacted with the association of RASi with mortality; mitral regurgitation that interacted with BBs association with mortality (p= 0.007); and primary etiology of cardiomyopathy (p= 0.04) and previous RASi therapy (p=0.002) that interacted with BBs association with hospitalizations risk (Supplementary Table 9).

We also analyzed the association of RASi and BBs up-titration with total and HF hospitalizations risk according to index HF worsening event (outpatients versus hospitalized at enrollment). Risk of both outcomes was significantly reduced with RASi in both subgroups. However, BBs were associated with reduced risk only in hospitalized patients with LVEF<40% but not in the subgroup enrolled as outpatients (Supplementary Tables 10, 11).

Discussion

Recurrent hospitalizations are frequent in HF patients, with the highest risk observed in the vulnerable period after an episode of worsening[15]. Assessment of total hospitalizations could present a more relevant clinical trial end-point of HF morbidity than time to first hospitalization because it might reflect better the true burden of the syndrome and suggest a long-lasting effect of the intervention[3]. In the present analysis, we have shown that up-titration of first-line HF medical therapy RASi to ≥50% of maximal recommended doses was associated with reduced risk of total unscheduled hospitalization in patients with HF worsening. Importantly, this association was observed in patients with a wide range of LVEF from <40% up to approximately 50%.

The present results are consistent with previously published post-hoc analyses of clinical trials and recently published data from registries regarding the effect of RASi on total HF hospitalizations[16, 17]. An analysis of the CHARM trial, which compared candesartan over placebo in chronic HF with LVEF of the entire spectrum, has shown that candesartan reduced the rate of total HF admissions both in patients with reduced (CHARM-alternative) and preserved LVEF (CHARM-preserved), by 35% and 25%, respectively[18]. Recently, the neprilysin inhibitor/RASi sacubitril/valsartan was shown to reduce recurrent hospitalizations by a further 23% compared to enalapril[19]. Therefore, it appears that RAS inhibition could be efficacious in decreasing the frequency of acute exacerbations of HF, possibly due to the reduction of congestion and intracardiac pressures by promoting natriuresis, diuresis and vasodilation[20].

Regarding the association of RASi dose and total hospitalizations risk, published data are limited. A post-hoc analysis of ATLAS trial, which compared the efficacy of low

versus high-dose lisinopril in chronic HFrEF, has shown that maximal lisinopril dose was superior to very low doses in reducing total hospitalizations[21]. The present analysis may extend the findings from ATLAS to patients with worsening HF of both reduced and mid-range LVEF. In addition, the favorable association of RASi dosing was observed not only with maximal but also with intermediate doses that were at least 50% of guideline recommended. Moreover, the present results adds to previously published data showing an association of up-titration of first-line HF therapies with better mortality/morbidity (in a time to first hospitalization analysis) in the HFrEF sub-population of BIOSTAT-CHF[7, 22].

Contrary to RASi, BBs up-titration was not associated with reduction of hospitalizations risk in a wide LVEF spectrum but only in patients with reduced LVEF, On the other hand, BBs dose of ≥50% of maximal recommended was associated with reduced mortality risk in LVEF up to 49%. Interestingly, an increased risk of HF hospitalizations was found with maximal and supra-maximal BBs doses in LVEF ≥50%. The differential association of BBs with mortality versus hospitalizations is consistent with the findings of the primary analysis of BIOSTAT-CHF, where the magnitude of reduced mortality risk by BBs was greater than the combined endpoint (mortality/hospitalization). On the other hand, the magnitude of the association between RASi up-titration and mortality or mortality/morbidity risk reduction was similar[7]. Although a clear explanation for this finding is not obvious, it may be hypothesized that whereas BBs primarily reduce cardiovascular mortality through suppression of arrhythmic sudden cardiac death, RASi also effectively prevent congestion-driven worsening[20]. The finding of increased HF hospitalization risk with ≥100% BBs dose in

preserved LVEF appears to be in accordance with a recent post-hoc analysis of TOPCAT trial (spironolactone versus placebo in HF with preserved LVEF), where BBs were associated with increased risk of HF hospitalizations in LVEF≥50%, but an opposite albeit nonsignificant association was seen in LVEF 45-49% [23]. Moreover, the present results are in accordance with a recent meta-analysis of HF randomized trials across the LVEF spectrum, which showed a beneficial effect of BBs on all-cause and CV mortality in LVEF up to 49%, whereas the benefit of BBs on CV hospitalizations was exerted in LVEF up to <40% but not ≥40%[24]. Of note, the benefits of BBs were observed only in patients with sinus rhythm but not in those with AF[24, 25]. In our study, although AF at baseline was more frequent among patients who achieved higher BBs dose, up-titration of BBs was associated with a less pronounced effect on HR in patients with a history of AF. Therefore, we consider it unlikely that the greater risk of HF hospitalization with higher doses of BBs were due to an adverse effect of low HR in the subset with AF[26]. Furthermore, previous studies in HFpEF have shown increased natriuretic peptide (NP) levels in patients treated with BBs, while one study showed marked reduction of NPs after BBs discontinuation in stable HFpEF[27, 28]. The effect of BBs in HFpEF might be explained by increases in left ventricular filling pressures due to prolongation of the diastolic period[29]. However, as subgroups with LVEF 40-49% and ≥50% were small (295 and 154 patients, respectively), we cannot exclude the possibility of chance findings and therefore results should be interpreted cautiously.

Our study has several limitations. First, BIOSTAT-CHF is nonrandomized study and therefore unidentified confounding factors may not have been corrected sufficiently in the present analysis despite statistical adjustments. Second, we have used only one

method (joint frailty) to examine association of therapies dosing and total events, despite the fact that no gold standard has been adopted. Whereas several methods have been proposed to analyze recurrent events, each of them addressing differently the potential bias of competing risks, joint frailty may give more unbiased estimates of the risk of recurrent events when the recurrent and terminal events are correlated. Potential limitations include the *a priori* assumption that events are positively correlated and the possible divergence between conditional (subject's level) recurrent event risk calculated by joint frailty and marginal risk (population's level) if there is a significant treatment effect on mortality. However, in a recent analysis of the PARADIGM-HF, four different statistical methods of analysis of recurrent events (including joint frailty) yielded similar reductions in HR for hospitalizations with sacubitril/valsartan over enalapril despite the positive effect of sacubitril/valsartan on mortality[19]. Although we have corrected for potential treatment-indication bias with IPW method, we cannot exclude any residual bias due to the nonrandomized design of BIOSTAT-CHF study. The study was conducted before the introduction of sacubitril/valsartan, thus the present analysis could not examine its association with risk of unscheduled hospitalizations in this real world setting. Last, as patients with LVEF>40% consisted a minority (19%) of the study population, analysis by LVEF deserves some caution and confirmation in future studies.

In conclusion, this analysis of BIOSTAT-CHF suggests that up-titration of RASi to doses at least 50% of those recommended in guidelines is associated with reduced risk of total unscheduled hospitalizations in patients with recent worsening HF and an LVEF ≤49%. Up-titration of BBs was associated with reduced hospitalization risk only in patients with an LVEF <40%. These results suggest that the well documented benefits of

up-titration of disease-modifying therapies in stable chronic HF extend to less stable patients with a recent exacerbation.

Funding

This project was funded by a grant from the European Commission (FP7-242209-BIOSTAT-CHF; EudraCT 2010-020808-29).

Disclosures

Dr. Bistola reports honoraria for lectures from AstraZeneca, Novartis, and Pfizer. Dr. Parissis reports horonaria for lectures and advisory boards from Novartis, Pfizer, Servier, Orion Pharma and Roche Diagnostics. Dr. van Veldhuisen has received board membership fees or travel expenses from Novartis, Johnson & Johnson, and Vifor. Dr. Metra has received personal honoraria for participation to trials' committees, advisory boards or speeches at sponsored symposia from Abbott vascular, Amgen, Astra Zeneca, Bayer, Vifor Pharma, Servier, WindTree Therapeutics. Dr. Zannad has received personal fees from Janssen, Novartis, Bayer, Boston Scientific, Amgen, CVRx, Boehringer Ingelheim, AstraZeneca, Vifor Fresenius, Cardior Pharmaceuticals, Cerno Pharmaceuticals, Applied Therapeutics, and Merck; and has received other payments from CVCT and Cardiorenal. Dr. Farmakis reports speaker honoraria or consultation fees from Abbott Laboratories, Bayer, Boehringer Ingelheim, Menarini, Novartis, Orion Pharma and Roche Diagnostics. Dr. Voors received consultancy fees or research grants from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Cytokinetics, Merck, Myokardia,

Novartis, Novonordisk, Roche Diagnostics. Dr. Filippatos reports committee membership in trials and/or registries sponsored by Amgen, Bayer, Novartis, BI, Medtronic, Vifor, Servier. All other authors have nothing to disclose.

References

1. Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, de Ferranti SD, Floyd J, Fornage M, Gillespie C, Isasi CR, Jimenez MC, Jordan LC, Judd SE, Lackland D, Lichtman JH, Lisabeth L, Liu S, Longenecker CT, Mackey RH, Matsushita K, Mozaffarian D, Mussolino ME, Nasir K, Neumar RW, Palaniappan L, Pandey DK, Thiagarajan RR, Reeves MJ, Ritchey M, Rodriguez CJ, Roth GA, Rosamond WD, Sasson C, Towfighi A, Tsao CW, Turner MB, Virani SS, Voeks JH, Willey JZ, Wilkins JT, Wu JH, Alger HM, Wong SS, Muntner P, American Heart Association Statistics C and Stroke Statistics S. Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association. *Circulation*. 2017;135:e146-e603.

2. Butler J, Yang M, Manzi MA, Hess GP, Patel MJ, Rhodes T and Givertz MM. Clinical Course of Patients With Worsening Heart Failure With Reduced Ejection Fraction. *J Am Coll Cardiol*. 2019;73:935-944.

3. Anker SD and McMurray JJ. Time to move on from 'time-to-first': should all events be included in the analysis of clinical trials? *Eur Heart J*. 2012;33:2764-5.

4. Santas E, Valero E, Mollar A, Garcia-Blas S, Palau P, Minana G, Nunez E, Sanchis J, Chorro FJ and Nunez J. Burden of Recurrent Hospitalizations Following an Admission for Acute Heart Failure: Preserved Versus Reduced Ejection Fraction. *Rev Esp Cardiol (Engl Ed)*. 2017;70:239-246.

5. Jackson SL, Tong X, King RJ, Loustalot F, Hong Y and Ritchey MD. National Burden of Heart Failure Events in the United States, 2006 to 2014. *Circ Heart Fail*. 2018;11:e004873.

6. Jencks SF, Williams MV and Coleman EA. Rehospitalizations among patients in the Medicare fee-for-service program. *N Engl J Med*. 2009;360:1418-28.

7. Ouwerkerk W, Voors AA, Anker SD, Cleland JG, Dickstein K, Filippatos G, van der Harst P, Hillege HL, Lang CC, Ter Maaten JM, Ng LL, Ponikowski P, Samani NJ, van Veldhuisen DJ, Zannad F, Metra M and Zwinderman AH. Determinants and clinical outcome of uptitration of ACE-inhibitors and beta-blockers in patients with heart failure: a prospective European study. *Eur Heart J*. 2017;38:1883-1890.

8. Voors AA, Anker SD, Cleland JG, Dickstein K, Filippatos G, van der Harst P, Hillege HL, Lang CC, Ter Maaten JM, Ng L, Ponikowski P, Samani NJ, van Veldhuisen DJ, Zannad F, Zwinderman AH and Metra M. A systems BIOlogy Study to TAilored Treatment in Chronic Heart Failure: rationale, design, and baseline characteristics of BIOSTAT-CHF. *Eur J Heart Fail*. 2016;18:716-26.

9. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, Stromberg A, van Veldhuisen DJ, Atar D, Hoes AW, Keren A, Mebazaa A, Nieminen M, Priori SG, Swedberg K and Guidelines ESCCfP. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur Heart J*. 2008;29:2388-442.

10. van Buuren S and Groothuis-Oudshoorn K. mice: Multivariate Imputation by Chained Equations in R. *2011*. 2011;45:67.

11. Hernan MA and Robins JM. *Causal Inference*: Taylor & Francis; 2019.

12. Rondeau V, Marzroui Y and Gonzalez JR. frailtypack: An R Package for the Analysis of Correlated Survival Data with Frailty Models Using Penalized Likelihood Estimation or Parametrical Estimation. *Journal of Statistical Software; Vol 1, Issue 4 (2012)*. 2012.

13. Rogers JK, Yaroshinsky A, Pocock SJ, Stokar D and Pogoda J. Analysis of recurrent events with an associated informative dropout time: Application of the joint frailty model. *Stat Med*. 2016;35:2195-205.

14. Commenges D, Joly P, GÉGout-Petit A and Liquet B. Choice between Semi-parametric Estimators of Markov and Non-Markov Multi-state Models from Coarsened Observations. *Scandinavian Journal of Statistics*. 2007;34:33-52.

15. Desai AS and Stevenson LW. Rehospitalization for heart failure: predict or prevent? *Circulation*. 2012;126:501-6.

16. Scalvini S, Bernocchi P, Villa S, Paganoni AM, La Rovere MT and Frigerio M. Treatment prescription, adherence, and persistence after the first hospitalization for heart failure: A population-based retrospective study on 100785 patients. *Int J Cardiol*. 2021.

17. Wirtz HS, Sheer R, Honarpour N, Casebeer AW, Simmons JD, Kurtz CE, Pasquale MK and Globe G. Real-World Analysis of Guideline-Based Therapy After Hospitalization for Heart Failure. *J Am Heart Assoc*. 2020;9:e015042.

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

19. Mogensen UM, Gong J, Jhund PS, Shen L, Kober L, Desai AS, Lefkowitz MP, Packer M, Rouleau JL, Solomon SD, Claggett BL, Swedberg K, Zile MR, Mueller-Velten G and McMurray JJV. Effect of sacubitril/valsartan on recurrent events in the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF). *Eur J Heart Fail*. 2018;20:760-768.

20. Jobs A, Abdin A, de Waha-Thiele S, Eitel I, Thiele H, de Wit C and Vonthein R. Angiotensin-converting-enzyme inhibitors in hemodynamic congestion: a meta-analysis of early studies. *Clin Res Cardiol*. 2019;108:1240-1248.

21. Packer M, Poole-Wilson PA, Armstrong PW, Cleland JG, Horowitz JD, Massie BM, Ryden L, Thygesen K and Uretsky BF. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. ATLAS Study Group. *Circulation*. 1999;100:2312-8.

22. Santema BT, Ouwerkerk W, Tromp J, Sama IE, Ravera A, Regitz-Zagrosek V, Hillege H, Samani NJ, Zannad F, Dickstein K, Lang CC, Cleland JG, Ter Maaten JM, Metra M, Anker SD, van der Harst P, Ng LL, van der Meer P, van Veldhuisen DJ, Meyer S, Lam CSP, investigators A-H and Voors AA. Identifying optimal doses of heart failure medications in men compared with women: a prospective, observational, cohort study. *Lancet*. 2019;394:1254-1263.

23. Silverman DN, Plante TB, Infeld M, Callas PW, Juraschek SP, Dougherty GB and Meyer M. Association of beta-Blocker Use With Heart Failure Hospitalizations and Cardiovascular Disease Mortality Among Patients With Heart Failure With a Preserved

Ejection Fraction: A Secondary Analysis of the TOPCAT Trial. *JAMA Netw Open*. 2019;2:e1916598.

24. Cleland JGF, Bunting KV, Flather MD, Altman DG, Holmes J, Coats AJS, Manzano L, McMurray JJV, Ruschitzka F, van Veldhuisen DJ, von Lueder TG, Bohm M, Andersson B, Kjekshus J, Packer M, Rigby AS, Rosano G, Wedel H, Hjalmarson A, Wikstrand J, Kotecha D and Beta-blockers in Heart Failure Collaborative G. Beta-blockers for heart failure with reduced, mid-range, and preserved ejection fraction: an individual patient-level analysis of double-blind randomized trials. *Eur Heart J*. 2018;39:26-35.

25. Kotecha D, Holmes J, Krum H, Altman DG, Manzano L, Cleland JG, Lip GY, Coats AJ, Andersson B, Kirchhof P, von Lueder TG, Wedel H, Rosano G, Shibata MC, Rigby A, Flather MD and Beta-Blockers in Heart Failure Collaborative G. Efficacy of beta blockers in patients with heart failure plus atrial fibrillation: an individual-patient data meta-analysis. *Lancet*. 2014;384:2235-43.

26. Filippatos G and Farmakis D. How to Use Beta-Blockers in Heart Failure With Reduced Ejection Fraction and Atrial Fibrillation. *J Am Coll Cardiol*. 2017;69:2897-2900.

27. Bergstrom A, Andersson B, Edner M, Nylander E, Persson H and Dahlstrom U. Effect of carvedilol on diastolic function in patients with diastolic heart failure and preserved systolic function. Results of the Swedish Doppler-echocardiographic study (SWEDIC). *Eur J Heart Fail*. 2004;6:453-61.

28. Nambiar L, Silverman D, Vanburen P, LeWinter M and Meyer M. Beta-Blocker Cessation in Stable Outpatients With Heart Failure With a Preserved Ejection Fraction. *J Card Fail*. 2019.

29. Meyer M and LeWinter MM. Heart Rate and Heart Failure With Preserved Ejection Fraction: Time to Slow beta-Blocker Use? *Circ Heart Fail*. 2019;12:e006213.

Legends

Figure legend 1. Frequency distribution of patients with or without clinical events (death or all-cause unscheduled hospitalization) by the number of prior unscheduled hospitalizations.

Figure legend 2. Predicted survival plots according to LVEF cut-off (LVEF ≥40% versus LVEF <40%) and RASi dose at 3 months for the outcomes of all-cause unscheduled hospitalizations (top two panels) and all-cause mortality (bottom two panels).

Figure legend 3. Incidence rate ratio of total all-cause (A, C) and heart failure (B, D) hospitalizations between different dose levels of RASi (A, B) and BBs (C, D) as a function of left ventricular ejection fraction (red, ≥100% of guideline recommended; blue, 50-99%; green, no RASi/BBs; reference, 1-49%). Shaded areas represent 95% confidence intervals.

Table 1. Distribution of patient baseline characteristics according to the achieved dose of RASi and BBs at 3 months.

	RASi					Beta-blocker				
:	**0%**	**1–49%**	**50–99%**	**≥100%**	**p-value**	**0%**	**1–49%**	**50–99%**	**≥100%**	**p-value**
n (%)	268 (11.4%)	814 (34.7%)	734 (31.3%)	529 (22.6%)		177 (7.5%)	1303 (55.6%)	599 (25.5%)	266 (11.3%)	
Demographics										
Sex (Male)	186 (69.4%)	605 (74.3%)	538 (73.3%)	397 (75%)	0.354	115 (65%)	964 (74%)	460 (76.8%)	187 (70.3%)	0.009
Race (Caucasian)	265 (98.9%)	805 (98.9%)	728 (99.2%)	523 (98.9%)	0.930	176 (99.4%)	1289 (98.9%)	594 (99.2%)	262 (98.5%)	0.749
Age (y)	75 (16)	71 (17)	69 (17)	68 (15)	<0.001	75 (16)	70 (17)	69 (17)	70 (18)	<0.001
Age category					<0.001					<0.001
<60y	38 (14.2%)	191 (23.5%)	183 (24.9%)	134 (25.3%)		19 (10.7%)	303 (23.3%)	157 (26.2%)	67 (25.2%)	
60-75y	99 (36.9%)	332 (40.8%)	316 (43.1%)	255 (48.2%)		68 (38.4%)	560 (43%)	267 (44.6%)	107 (40.2%)	
>75y	131 (48.9%)	291 (35.7%)	235 (32%)	140 (26.5%)		90 (50.8%)	440 (33.8%)	175 (29.2%)	92 (34.6%)	
Cause of HF										
Primary										
Ischaemic	135 (50.4%)	354 (43.5%)	342 (46.6%)	220 (41.6%)	0.367	61 (34.5%)	599 (46%)	289 (48.2%)	102 (38.3%)	0.016
Hypertensive	21 (7.8%)	65 (8%)	78 (10.6%)	81 (15.3%)	<0.001	20 (11.3%)	137 (10.5%)	52 (8.7%)	36 (13.5%)	0.157
Cardiomyopathy	40 (14.9%)	234 (28.7%)	196 (26.7%)	147 (27.8%)	<0.001	37 (20.9%)	366 (28.1%)	148 (24.7%)	66 (24.8%)	0.205
Valvular	33 (12.3%)	72 (8.8%)	44 (6%)	24 (4.5%)	<0.001	21 (11.9%)	90 (6.9%)	44 (7.3%)	18 (6.8%)	0.035
Primary or contributory										
Ischaemic	153 (57.1%)	436 (53.6%)	406 (55.3%)	271 (51.2%)	0.356	75 (42.4%)	725 (55.6%)	334 (55.8%)	132 (49.6%)	0.003
Hypertensive	132 (49.3%)	384 (47.2%)	415 (56.5%)	348 (65.8%)	<0.001	85 (48%)	712 (54.6%)	328 (54.8%)	154 (57.9%)	0.235
Cardiomyopathy	62 (23.1%)	361 (44.3%)	295 (40.2%)	232 (43.9%)	<0.001	60 (33.9%)	558 (42.8%)	238 (39.7%)	94 (35.3%)	0.027
Valvular	114 (42.5%)	306 (37.6%)	279 (38%)	173 (32.7%)	0.044	62 (35%)	510 (39.1%)	217 (36.2%)	83 (31.2%)	0.079
Previous hospitalisation(s) in past year before baseline	104 (38.8%)	271 (33.3%)	210 (28.6%)	146 (27.6%)	0.002	49 (27.7%)	409 (31.4%)	184 (30.7%)	89 (33.5%)	0.628
NYHA prior to enrolment					0.288					0.025
I	33 (12.3%)	79 (9.7%)	91 (12.4%)	53 (10%)		20 (11.3%)	142 (10.9%)	70 (11.7%)	24 (9%)	
II	134 (50%)	408 (50.1%)	384 (52.3%)	292 (55.2%)		79 (44.6%)	689 (52.9%)	322 (53.8%)	128 (48.1%)	
III	92 (34.3%)	296 (36.4%)	227 (30.9%)	168 (31.8%)		71 (40.1%)	435 (33.4%)	181 (30.2%)	96 (36.1%)	
IV	9 (3.4%)	31 (3.8%)	32 (4.4%)	16 (3%)		7 (4%)	37 (2.8%)	26 (4.3%)	18 (6.8%)	
Medical History										
Myocardial infarction	110 (41%)	314 (38.6%)	273 (37.2%)	187 (35.3%)	0.413	50 (28.2%)	499 (38.3%)	249 (41.6%)	86 (32.3%)	0.003
CABG	65 (24.3%)	134 (16.5%)	117 (15.9%)	75 (14.2%)	0.003	28 (15.8%)	218 (16.7%)	106 (17.7%)	39 (14.7%)	0.724
PCI	64 (23.9%)	182 (22.4%)	163 (22.2%)	101 (19.1%)	0.365	31 (17.5%)	282 (21.6%)	138 (23%)	59 (22.2%)	0.477
AF	150 (56%)	385 (47.3%)	297 (40.5%)	222 (42%)	<0.001	82 (46.3%)	551 (42.3%)	278 (46.4%)	143 (53.8%)	0.005
Stroke	29 (10.8%)	78 (9.6%)	66 (9%)	41 (7.8%)	0.502	17 (9.6%)	125 (9.6%)	52 (8.7%)	20 (7.5%)	0.714
Peripheral artery disease	40 (14.9%)	84 (10.3%)	81 (11%)	47 (8.9%)	0.072	19 (10.7%)	153 (11.7%)	57 (9.5%)	23 (8.6%)	0.319

	RASi					Beta-blocker				
	0%	1–49%	50–99%	≥100%	p-value	0%	1–49%	50–99%	≥100%	p-value
Pacemaker	26 (9.7%)	59 (7.2%)	44 (6%)	31 (5.9%)	0.152	14 (7.9%)	102 (7.8%)	28 (4.7%)	16 (6%)	0.071
ICD	22 (8.2%)	76 (9.3%)	63 (8.6%)	29 (5.5%)	0.079	16 (9%)	102 (7.8%)	51 (8.5%)	21 (7.9%)	0.921
CRT	31 (11.6%)	91 (11.2%)	46 (6.3%)	38 (7.2%)	0.001	11 (6.2%)	99 (7.6%)	71 (11.9%)	25 (9.4%)	0.012
Hypertension	164 (61.2%)	446 (54.8%)	470 (64%)	381 (72%)	<0.001	99 (55.9%)	807 (61.9%)	376 (62.8%)	179 (67.3%)	0.111
Past smoker	137 (51.1%)	386 (47.4%)	363 (49.5%)	259 (49%)	0.619	81 (45.8%)	619 (47.5%)	302 (50.4%)	143 (53.8%)	0.384
Current smoker	29 (10.8%)	119 (14.6%)	111 (15.1%)	71 (13.4%)	0.619	23 (13%)	188 (14.4%)	88 (14.7%)	31 (11.7%)	0.384
Current alcohol use	72 (26.9%)	213 (26.2%)	204 (27.8%)	165 (31.2%)	0.240	44 (24.9%)	319 (24.5%)	190 (31.7%)	101 (38%)	<0.001
Diabetes	89 (33.2%)	243 (29.9%)	234 (31.9%)	197 (37.2%)	0.042	61 (34.5%)	436 (33.5%)	177 (29.5%)	89 (33.5%)	0.341
Diabetes on insulin	35 (13.1%)	109 (13.4%)	92 (12.5%)	73 (13.8%)	0.081	26 (14.7%)	170 (13%)	72 (12%)	41 (15.4%)	0.535
COPD	52 (19.4%)	141 (17.3%)	124 (16.9%)	76 (14.4%)	0.295	45 (25.4%)	213 (16.3%)	97 (16.2%)	38 (14.3%)	0.012
Chronic kidney disease	135 (50.4%)	235 (28.9%)	160 (21.8%)	84 (15.9%)	<0.001	53 (29.9%)	338 (25.9%)	157 (26.2%)	66 (24.8%)	0.661
Thyroid disease	39 (14.6%)	78 (9.6%)	67 (9.1%)	38 (7.2%)	0.010	12 (6.8%)	123 (9.4%)	63 (10.5%)	24 (9%)	0.508
Malignancy (current)	14 (5.2%)	34 (4.2%)	19 (2.6%)	14 (2.6%)	0.091	11 (6.2%)	48 (3.7%)	17 (2.8%)	5 (1.9%)	0.075
HF-drug history										
MRA	134 (50%)	469 (57.6%)	378 (51.5%)	274 (51.8%)	0.034	81 (45.8%)	752 (57.7%)	306 (51.1%)	116 (43.6%)	<0.001
Digitalis	42 (15.7%)	178 (21.9%)	142 (19.3%)	93 (17.6%)	0.083	31 (17.5%)	254 (19.5%)	121 (20.2%)	49 (18.4%)	0.845
Clinical variables at baseline										
Systolic BP (mmHg)	120 (25)	120 (25)	121 (30)	130 (25)	<0.001	120 (27)	120 (28)	125 (30)	125 (23)	0.008
Diastolic BP (mmHg)	70 (20)	70 (15)	75 (14)	80 (20)	<0.001	70 (20)	71 (14)	75 (15)	78 (16)	<0.001
Heart rate (bpm)	78 (25)	76 (24)	76 (23)	75 (22)	0.847	76 (22)	75 (22)	77 (22)	80 (30)	<0.001
BMI (kg/m^2)	26.3 (6.3)	26.5 (6.2)	27.4 (6.3)	28.4 (7.6)	<0.001	26 (7.7)	27 (6.5)	27.8 (6.4)	27.8 (7.1)	<0.001
NYHA class					<0.001					0.217
I	6 (2.2%)	19 (2.3%)	18 (2.5%)	13 (2.5%)		6 (3.4%)	35 (2.7%)	9 (1.5%)	6 (2.3%)	
II	63 (23.5%)	288 (35.4%)	280 (38.1%)	221 (41.8%)		61 (34.5%)	449 (34.5%)	240 (40.1%)	102 (38.3%)	
III	141 (52.6%)	416 (51.1%)	354 (48.2%)	255 (48.2%)		88 (49.7%)	653 (50.1%)	293 (48.9%)	132 (49.6%)	
IV	58 (21.6%)	91 (11.2%)	82 (11.2%)	40 (7.6%)		22 (12.4%)	166 (12.7%)	57 (9.5%)	26 (9.8%)	
6-MWT (m)	94 (300)	203 (340)	244 (360)	270 (346)	<0.001	127 (325)	215 (350)	244 (362)	275 (318)	<0.001
ECG features at baseline										
AF on ECG	109 (40.7%)	274 (33.7%)	231 (31.5%)	154 (29.1%)	0.009	60 (33.9%)	401 (30.8%)	194 (32.4%)	113 (42.5%)	0.003
RBBB	21 (7.8%)	55 (6.8%)	43 (5.9%)	27 (5.1%)	0.408	16 (9%)	79 (6.1%)	37 (6.2%)	14 (5.3%)	0.410
LBBB	44 (16.4%)	171 (21%)	149 (20.3%)	105 (19.8%)	0.438	32 (18.1%)	291 (22.3%)	97 (16.2%)	49 (18.4%)	0.014
QRS >130ms	82 (30.6%)	225 (27.6%)	194 (26.4%)	138 (26.1%)	0.535	48 (27.1%)	349 (26.8%)	173 (28.9%)	69 (25.9%)	0.758
QRS >150ms	55 (20.5%)	151 (18.6%)	112 (15.3%)	94 (17.8%)	0.181	31 (17.5%)	232 (17.8%)	110 (18.4%)	39 (14.7%)	0.601
Echo features at baseline										
LVEDD (mm)	59 (14)	62 (12)	60 (11)	61 (12)	<0.001	60 (11)	61 (13)	61 (12)	60 (12)	0.001

	RASi					Beta-blocker				
	0%	**1–49%**	**50–99%**	**≥100%**	**p-value**	**0%**	**1–49%**	**50–99%**	**≥100%**	**p-value**
LVEF (%)	34 (15)	30 (11)	30 (11)	30 (11)	<0.001	35 (15)	30 (10)	30 (12)	30 (13)	<0.001
LVEF category					<0.001					<0.001
LVEF ≥50%	43 (16%)	46 (5.7%)	43 (5.9%)	22 (4.2%)		24 (13.6%)	71 (5.4%)	41 (6.8%)	18 (6.8%)	
LVEF 40-49%	41 (15.3%)	90 (11.1%)	93 (12.7%)	71 (13.4%)		30 (16.9%)	151 (11.6%)	73 (12.2%)	41 (15.4%)	
LVEF<40%	184 (68.7%)	678 (83.3%)	598 (81.5%)	436 (82.4%)		123 (69.5%)	1081 (83%)	485 (81%)	207 (77.8%)	
MR on echo	128 (47.8%)	387 (47.5%)	328 (44.7%)	223 (42.2%)	0.212	73 (41.2%)	602 (46.2%)	280 (46.7%)	111 (41.7%)	0.327
Labs at baseline										
Hb (g/dL)	12.6 (2.5)	13.3 (2.6)	13.6 (2.5)	13.7 (2.5)	<0.001	12.9 (2.7)	13.4 (2.5)	13.5 (2.5)	13.4 (2.5)	0.006
Sodium (mmol/L)	139 (5)	139 (5)	140 (5)	140 (4)	<0.001	139 (5)	140 (5)	140 (4)	140 (3)	<0.001
eGFR (ml/min/1.73m^2)	48.9 (34.6)	62.2 (32)	64.6 (29.1)	66.2 (30)	<0.001	58.6 (27.3)	63.1 (31.2)	62.7 (30.3)	64.6 (32.4)	0.167
Urea (mmol/L)	15.1 (14.4)	12.9 (11.1)	11 (9.4)	9.6 (9.3)	<0.001	11.8 (10.5)	12.5 (11.5)	10.9 (8.9)	10.4 (10.1)	<0.001
NT-proBNP (ng/L)	5289 (8301)	4532 (6316)	3999 (5372)	3324 (3788)	<0.001	3486 (6012)	4305 (6263)	3949 (4892)	3691 (5136)	0.085
BNP (ng/L)	265 (477)	243 (366)	210 (328)	165 (281)	<0.001	223 (366)	220 (363)	206 (334)	249 (357)	0.130

Table 2: Shared frailty recurrent event analysis for a) total all-cause hospitalizations and b) all-cause mortality in subgroups by baseline LVEF.

	RASi						Beta-blockers					
	LVEF<40%		LVEF<50%		LVEF≥50%		LVEF<40%		LVEF<50%		LVEF≥50%	
Drug dose at 3 months (% target)	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Total all-cause unscheduled hospitalizations *(N events = 1996)*												
Univariable weighted shared frailty model												
Dose 1-49% vs 0% target	0.58 (0.45 – 0.75)	<0.001	0.57 (0.45 – 0.72)	<0.001	0.83 (0.52 – 1.31)	0.413	0.67 (0.48-0.92)	0.013	0.76 (0.57 – 1.01)	0.063	1.18 (0.69 – 2.02)	0.548
Dose 50-99% vs 0% target	0.41 (0.31-0.53)	<0.001	0.42 (0.33 – 0.53)	<0.001	0.62 (0.38 – 1.01)	0.053	0.62 (0.44-0.87)	0.006	0.71 (0.52 – 0.96)	0.028	1.11 (0.62 – 1.99)	0.721
Dose 50-99% vs 1-49% target	0.72 (0.59-0.87)	<0.001	0.75 (0.62 – 0.89)	0.001	0.75 (0.46 – 1.22)	0.247	0.95 (0.79-1.15)	0.616	0.94 (0.79 – 1.12)	0.520	0.94 (0.61 – 1.45)	0.793
Dose ≥100% vs 0% target	0.38 (0.29-0.51)	<0.001	0.39 (0.30 – 0.50)	<0.001	0.89 (0.51 – 1.54)	0.674	0.81 (0.55-1.18)	0.268	0.86 (0.61 – 1.21)	0.393	1.28 (0.64 – 2.59)	0.486
Dose ≥100% vs 1-49% target	0.68 (0.55-0.84)	<0.001	0.69 (0.57 – 0.84)	<0.001	1.08 (0.62 – 1.87)	0.786	1.24 (0.96-1.60)	0.105	1.15 (0.91 – 1.45)	0.230	1.09 (0.61 – 1.95)	0.774
Dose ≥100% vs 50-99% target	0.98 (0.79-1.23)	0.895	0.95 (0.78 – 1.17)	0.639	1.44 (0.81 – 2.54)	0.212	1.37 (1.03-1.82)	0.031	1.26 (0.98 – 1.63)	0.074	1.16 (0.62 – 2.16)	0.649
Multivariable weighted shared frailty model												
Dose 1-49% vs 0% target	0.72 (0.60-0.86)	0.000	0.74 (0.63 - 0.87)	<0.001	0.83 (0.60 - 1.15)	0.257	0.75 (0.59-0.96)	0.023	0.83 (0.67 - 1.04)	0.114	1.21 (0.78 - 1.88)	0.390
Dose 50-99% vs 0% target	0.57 (0.47-0.69)	0.000	0.61 (0.51 - 0.72)	<0.001	0.60 (0.42 - 0.86)	0.005	0.73 (0.56-0.95)	0.021	0.80 (0.63 - 1.03)	0.080	1.15 (0.72 - 1.86)	0.555
Dose 50-99% vs 1-49% target	0.82 (0.72-0.93)	0.002	0.82 (0.72 - 0.94)	0.005	0.73 (0.52 - 1.04)	0.079	0.97 (0.84-1.13)	0.714	0.97 (0.85 - 1.10)	0.597	0.96 (0.69 - 1.32)	0.791
Dose ≥100% vs 0% target	0.60 (0.49-0.74)	0.000	0.62 (0.51 - 0.74)	0.000	0.98 (0.65 - 1.48)	0.939	0.86 (0.64-1.15)	0.316	0.91 (0.69 - 1.18)	0.469	1.72 (0.99 - 3.00)	0.055
Dose ≥100% vs 1-49% target	0.85 (0.74-0.98)	0.024	0.84 (0.72 - 0.98)	0.023	1.20 (0.80 - 1.79)	0.376	1.14 (0.95-1.38)	0.158	1.09 (0.92 - 1.29)	0.330	1.43 (0.91 - 2.23)	0.118
Dose ≥100% vs 50-99% target	1.06 (0.89-1.26)	0.518	1.02 (0.87 - 1.20)	0.792	1.64 (1.06 - 2.55)	0.027	1.18 (0.96-1.45)	0.118	1.13 (0.94 - 1.36)	0.196	1.51 (0.95 - 2.40)	0.085
Death *(N = 512 events)*												
Univariable Cox model												
Dose 1-49% vs 0% target	0.74 (0.56-1.00)	0.047	0.84 (0.64 – 1.10)	0.205	1.29 (0.67 – 2.52)	0.446	0.74 (0.52-1.06)	0.100	0.82 (0.59 – 1.14)	0.241	3.00 (1.17 – 7.68)	0.022
Dose 50-99% vs 0% target	0.43 (0.31-0.60)	<0.001	0.49 (0.37 – 0.67)	<0.001	1.09 (0.54 – 2.22)	0.803	0.50 (0.34-0.75)	0.001	0.54 (0.37 – 0.78)	0.001	1.82 (0.64 – 5.12)	0.259
Dose 50-99% vs 1-49% target	0.58 (0.45-0.75)	<0.001	0.59 (0.46 – 0.74)	<0.001	0.94 (0.48 – 1.86)	0.866	0.68 (0.52-0.88)	0.004	0.66 (0.51 – 0.84)	<0.001	0.65 (0.34 – 1.26)	0.204
Dose ≥ 100% vs 0% target	0.40 (0.28-0.57)	<0.001	0.45 (0.33 – 0.63)	<0.001	0.73 (0.29 – 1.85)	0.502	0.55 (0.35-0.88)	0.012	0.62 (0.41 – 0.95)	0.029	2.05 (0.63 – 6.70)	0.234
Dose ≥100% vs 1-49% target	0.53 (0.40-0.72)	<0.001	0.54 (0.41 – 0.70)	<0.001	0.63 (0.25 – 1.58)	0.322	0.75 (0.52-1.06)	0.101	0.76 (0.56 – 1.04)	0.086	0.74 (0.31 – 1.76)	0.491
Dose ≥100% vs 50-99% target	0.92 (0.66-1.28)	0.617	0.91 (0.68 – 1.23)	0.558	0.75 (0.29 – 1.96)	0.561	1.10 (0.74-1.64)	0.638	1.16 (0.81 – 1.66)	0.417	1.29 (0.48 – 3.49)	0.614

Table 3. Shared frailty recurrent event analysis for total heart failure hospitalizations in subgroups by baseline LVEF.

	Total unscheduled heart failure hospitalizations											
	(N events = 914)											
Drug dose at 3 months (% target)	**RASi**						**Beta-blockers**					
	LVEF < 40% (n=1896)		**LVEF < 50% (n=2191)**		**LVEF ≥ 50% (n=154)**		**LVEF < 40% (n=1896)**		**LVEF < 50% (n=2191)**		**LVEF ≥ 50% (n=154)**	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Univariable weighted shared frailty model												
Dose 1-49% vs 0% target	0.59 (0.46 - 0.77)	0,000	0.58 (0.46 - 0.74)	0,000	0.99 (0.63 - 1.55)	0,959	0.62 (0.45 - 0.86)	0,004	0.70 (0.52 - 0.95)	0,020	2.04 (1.33 - 3.13)	0,001
Dose 50-99% vs 0% target	0.40 (0.31 - 0.53)	0,000	0.41 (0.32 - 0.53)	0,000	0.80 (0.50 - 1.31)	0,380	0.57 (0.40 - 0.81)	0,002	0.64 (0.46 - 0.89)	0,008	2.12 (1.29 - 3.50)	0,003
Dose 50-99% vs 1-49% target	0.69 (0.55 - 0.85)	0,001	0.71 (0.58 - 0.87)	0,001	0.83 (0.51 - 1.35)	0,447	0.92 (0.74 - 1.14)	0,435	0.92 (0.76 - 1.12)	0,411	1.05 (0.67 - 1.65)	0,827
Dose >=100% vs 0% target	0.38 (0.28 - 0.51)	0,000	0.39 (0.30 - 0.51)	0,000	0.69 (0.35 - 1.35)	0,276	0.64 (0.43 - 0.95)	0,026	0.68 (0.47 - 0.98)	0,041	2.73 (1.38 - 5.41)	0,004
Dose >=100% vs 1-49% target	0.65 (0.51 - 0.82)	0,000	0.67 (0.54 - 0.84)	0,001	0.71 (0.36 - 1.39)	0,316	1.03 (0.78 - 1.36)	0,859	0.98 (0.76 - 1.27)	0,871	1.35 (0.71 - 2.57)	0,361
Dose >=100% vs 50-99% target	0.95 (0.73 - 1.23)	0,687	0.95 (0.75 - 1.21)	0,683	0.86 (0.44 - 1.69)	0,666	1.12 (0.83 - 1.53)		1.07 (0.80 - 1.42)	0,641	1.31 (0.68 - 2.49)	0,418
Multivariable weighted shared frailty model												
Dose 1-49% vs 0% target	0.67 (0.52 - 0.86)	0,001	0.69 (0.55 - 0.87)	0,001	0.86 (0.51 - 1.48)	0,593	0.80 (0.56 - 1.12)	0,192	0.85 (0.62 - 1.17)	0,325	1.92 (0.76 - 4.81)	0,167
Dose 50-99% vs 0% target	0.49 (0.37 - 0.64)	0,000	0.52 (0.41 - 0.67)	0,000	0.76 (0.43 - 1.35)	0,345	0.73 (0.50 - 1.06)	0,094	0.79 (0.56 - 1.12)	0,192	2.25 (0.85 - 5.95)	0,102
Dose 50-99% vs 1-49% target	0.74 (0.60 - 0.91)	0,004	0.76 (0.62 - 0.93)	0,007	0.87 (0.51 - 1.51)	0,629	0.91 (0.74 - 1.12)	0,395	0.93 (0.77 - 1.13)	0,474	1.17 (0.67 - 2.02)	0,584
Dose >=100% vs 0% target	0.52 (0.39 - 0.69)	0,000	0.55 (0.42 - 0.72)	0,000	0.70 (0.32 - 1.54)	0,379	0.85 (0.56 - 1.30)	0,458	0.87 (0.59 - 1.28)	0,479	4.11 (1.43 - 11.79)	0,009
Dose >=100% vs 1-49% target	0.78 (0.61 - 0.99)	0,039	0.80 (0.64 - 1.00)	0,053	0.81 (0.39 - 1.70)	0,576	1.08 (0.82 - 1.41)	0,600	1.02 (0.80 - 1.32)	0,855	2.12 (1.03 - 4.37)	0,040
Dose >=100% vs 50-99% target	1.06 (0.82 - 1.37)	0,639	1.06 (0.84 - 1.34)	0,623	0.92 (0.42 - 2.00)	0,835	1.19 (0.88 - 1.60)	0,267	1.10 (0.84 - 1.46)	0,480	1.81 (0.83 - 3.94)	0,136