

Methods

Study design and characteristics of patients enrolled in the BIOSTAT-CHF study has been described previously⁸. 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 guidelines⁹. 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 months⁸. 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 $\geq 100\%$ of the recommended dose⁹. 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 or 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 predictor¹¹. 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 correlated¹²⁻¹⁶. Joint frailty models allow studying, jointly, survival processes of recurrent and terminal events, by considering the terminal event as an informative censoring. A common frailty term and its standard error (SE) were calculated for the two event rates (hospitalization and death). Frailty takes into account the heterogeneity in the data associated with unobserved covariates and acts differently for the two rates¹⁴. We examined whether the variance of the frailty term theta of each model was significantly different from 0 using a modified Wald test as a significance test of the random effects distribution occurring on the boundary of the parameter space¹³. Whether the recurrent events were positively associated with mortality

was assessed by the positive value of the coefficient alpha in the joint models. For all survival models, time-to-event was considered as gap time and not calendar time.

Goodness of fit of the shared and joint frailty models was tested by graphical assessment of the martingale residuals that are based on the counting processes theory. Joint frailty models of mortality and all-cause total hospitalization for both RASi and BBs showed significant correlation between recurrent events [θ (SE): 0.956 (0.043), $p < 0.001$, and 0.982 (0.043), $p < 0.001$, respectively] and a positive association between recurrent events and death shown by positive values of the alpha coefficient [α (SE): 0.923 (0.099), $p < 0.001$; and 0.976 (0.099), $p < 0.001$, respectively]. For the crude (unadjusted) risk of hospitalizations and death according to drug level, we fitted univariable joint frailty models separately for RASi and BBs. In these models the only independent covariate was the 4-level factor variable denoting the drug dose levels. To estimate the adjusted association of the drug dose with hospitalizations and death we fitted a parsimonious multivariable joint frailty model for each drug that should have the best fit in terms of predictive accuracy. Thus, we performed an algorithmic forward selection process on shared frailty models with the addition of one baseline variable at a time and comparison with the previous 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 and the degrees of freedom as also the 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 model¹⁷. 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 for RASi and BBs are shown in Supplementary Tables 1 and 2, respectively. Other baseline variables that were included in the multivariable joint frailty models for the association of RASi and BBs with total hospitalizations and mortality are shown in Supplementary Tables 3 and 4, respectively. **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 account potential differential treatment responses among patients with reduced, mid-range, and preserved LVEF, joint frailty analyses were performed in patient subgroups categorized by baseline LVEF, using LVEF cutoffs of either 40% or 50%. 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 using multivariable shared frailty weighted models that included treatment dose, subgroup and treatment by subgroup as fixed factors and the outcome (hospitalizations or death).

Supplementary table 1: Steps of the forward selection algorithm for the final multivariable joint frailty model of the effect of RASi dose level at 3 months on recurrent hospitalizations and death.

| Forward selection algorithm of multivariable shared frailty model for recurrent unscheduled hospitalizations * | | | | | | Forward selection algorithm of multivariable shared frailty model for mortality ** | | | | |
|--|--|-----------------------|--------------|---------|------|--|-----------------------|--------------|---------|------|
| Model number | Model parameters | Comparison with model | LR Statistic | p-value | LC V | Model parameters | Comparison with model | LR statistic | p-value | LC V |
| | Basic model | | | | 3.32 | Basic model | | | | 0.88 |
| Model 1 | Basic model + sex | Basic model | 1.227 | 0.26 | 3.32 | Basic model + sex | Basic model | 0.00 | 0.93 | 0.88 |
| Model 2 | Basic model + age category | Basic model | 15.08 | 0.00 | 3.32 | Basic model + age category | Basic model | 34.1 | <0.0 | 0.88 |
| Model 3 | Model 2 + race (white vs other) | Model 2 | 0.305 | 0.58 | 3.32 | Model 2 + race (white vs other) | Model 2 | 0.55 | 0.45 | 0.88 |
| Model 4 | Model 2 + ischaemic aetiology | Model 2 | 19.55 | <0.0 | 3.31 | Model 2 + ischaemic aetiology | Model 2 | 16.6 | <0.0 | 0.88 |
| Model 5 | Model 4 + hypertensive aetiology | Model 4 | 0.008 | 0.92 | 3.31 | Model 4 + hypertensive aetiology | Model 4 | <0.0 | 0.99 | 0.88 |
| Model 6 | Model 4 + cardiomyopathy | Model 4 | 25.97 | <0.0 | 3.31 | Model 4 + cardiomyopathy | Model 4 | 1.39 | 0.23 | 0.88 |
| Model 7 | Model 6 + valvular heart disease | Model 6 | 6.809 | 0.00 | 3.31 | Model 4 + valvular heart disease | Model 4 | 2.43 | 0.11 | 0.88 |
| Model 8 | Model 7 + history of MI | Model 7 | 5.100 | 0.02 | 3.31 | Model 4 + history of MI | Model 4 | 2.12 | 0.14 | 0.88 |
| Model 9 | Model 8 + history of CABG | Model 8 | 1.383 | 0.24 | 3.31 | Model 4 + history of CABG | Model 4 | 10.4 | 0.00 | 0.88 |
| Model 10 | Model 8 + history of PCI | Model 8 | 0.266 | 0.60 | 3.31 | Model 9 + history of PCI | Model 9 | 2.13 | 0.14 | 0.88 |
| Model 11 | Model 8 + history of AF | Model 8 | 4.309 | 0.03 | 3.31 | Model 9 + history of AF | Model 9 | 5.62 | 0.01 | 0.88 |
| Model 12 | Model 11 + history of stroke | Model 11 | 7.725 | 0.00 | 3.31 | Model 11 + history of stroke | Model 11 | 1.67 | 0.19 | 0.88 |
| Model 13 | Model 12 + history of PAD | Model 12 | 2.118 | 0.14 | 3.31 | Model 11 + history of PAD | Model 11 | 4.40 | 0.03 | 0.88 |
| Model 14 | Model 12 + history of PCM | Model 12 | 1.543 | 0.21 | 3.31 | Model 11 + history of PCM | Model 13 | 0.42 | 0.51 | 0.88 |
| Model 15 | Model 12 + history of ICD | Model 12 | 16.24 | <0.0 | 3.31 | Model 11 + history of ICD | Model 13 | 6.03 | 0.01 | 0.88 |
| Model 16 | Model 15 + history of CRT | Model 15 | 11.99 | 0.00 | 3.31 | Model 15 + history of CRT | Model 15 | 6.23 | 0.01 | 0.88 |
| Model 17 | Model 16 + history of HTN | Model 16 | 0.169 | 0.68 | 3.31 | Model 16 + history of HTN | Model 16 | 0.01 | 0.91 | 0.88 |
| Model 18 | Model 16 + history of smoking | Model 16 | 4.216 | 0.12 | 3.31 | Model 16 + history of smoking | Model 16 | 0.95 | 0.62 | 0.88 |
| Model 19 | Model 16 + Alcohol (current) | Model 16 | 0.477 | 0.49 | 3.31 | Model 16 + Alcohol (current) | Model 16 | 1.41 | 0.23 | 0.88 |
| Model 20 | Model 16 + history of DM | Model 16 | 19.84 | <0.0 | 3.30 | Model 16 + history of DM | Model 16 | 2.49 | 0.11 | 0.88 |
| Model 21 | Model 20 + history of DM on insulin | Model 20 | 1.526 | 0.46 | 3.31 | Model 16 + history of DM on insulin | Model 16 | 4.68 | 0.09 | 0.88 |
| Model 22 | Model 20 + history of COPD | Model 20 | 13.85 | <0.0 | 3.30 | Model 16 + history of COPD | Model 16 | 10.1 | 0.00 | |
| Model 23 | Model 22 + history of CKD | Model 22 | 44.99 | <0.0 | 3.30 | Model 22 + history of CKD | Model 22 | 16 | 1 | 0.87 |
| Model 24 | Model 23 + history of thyroid disease | Model 23 | 0.172 | 0.67 | 3.30 | Model 23 + history of thyroid disease | Model 23 | 29.9 | <0.0 | 0.87 |
| Model 25 | Model 23 + history of malignancy (current) | Model 23 | 11.38 | 0.00 | 3.30 | Model 23 + history of malignancy (current) | Model 23 | 0.56 | 0.45 | 0.87 |
| Model | Model 25 + AF on ECG at | Model | 0.025 | 0.87 | 3.30 | Model 23 + AF on ECG | Model | 0.07 | 0.79 | 0.87 |
| | | | | | | | | 2.52 | 0.11 | 0.87 |

| Forward selection algorithm of multivariable shared frailty model for recurrent unscheduled hospitalizations * | | | | | | Forward selection algorithm of multivariable shared frailty model for mortality ** | | | | |
|--|--|-----------------------|--------------|-------------|-------------|--|-----------------------|--------------|-------------|-------------|
| Model number | Model parameters | Comparison with model | LR Statistic | p-value | LCV | Model parameters | Comparison with model | LR statistic | p-value | LCV |
| 26 | baseline | 25 | | 5 | 28 | at baseline | 23 | 3 | 2 | 85 |
| Model 27 | Model 25 + RBBB on ECG at baseline | Model 25 | 1.444 | 0.22 | 3.30 | Model 23 + RBBB on ECG at baseline | Model 23 | 5.24 | 0.02 | 0.87 |
| Model 28 | Model 25 + LBBB on ECG at baseline | Model 25 | 0.011 | 0.91 | 3.30 | Model 27 + LBBB on ECG at baseline | Model 27 | 0.64 | 0.42 | 0.87 |
| Model 29 | Model 25 + QRS >130ms on ECG at baseline | Model 25 | 0.645 | 0.42 | 3.30 | Model 27 + QRS >130ms on ECG at baseline | Model 27 | 0.09 | 0.76 | 0.87 |
| Model 30 | Model 25 + QRS >150ms on ECG at baseline | Model 25 | 3.651 | 0.05 | 3.30 | Model 27 + QRS >150ms on ECG at baseline | Model 27 | 0.06 | 0.79 | 0.87 |
| Model 31 | Model 30 + LVEF category at baseline | Model 25 | 22.99 | <0.01 | 3.30 | Model 27 + LVEF category at baseline | Model 27 | 10.50 | 0.00 | 0.87 |
| Model 32 | Model 31 + MR on echo at baseline | Model 31 | 0.115 | 0.73 | 3.30 | Model 31 + MR on echo at baseline | Model 31 | 1.42 | 0.23 | 0.87 |
| Model 33 | Model 31 + history of ACEi | Model 31 | 0.612 | 0.43 | 3.30 | Model 31 + history of ACEi | Model 31 | 0.02 | 0.87 | 0.87 |
| Model 34 | Model 31 + history of ARB | Model 31 | 0.780 | 0.37 | 3.30 | Model 31 + history of ARB | Model 31 | 0.98 | 0.32 | 0.87 |
| Model 35 | Model 31 + history of BB | Model 31 | 0.004 | 0.95 | 3.30 | Model 31 + history of BB | Model 31 | 0.07 | 0.78 | 0.87 |
| Model 36 | Model 31 + history of MRA | Model 31 | 1.149 | 0.28 | 3.30 | Model 31 + history of MRA | Model 31 | 0.68 | 0.40 | 0.87 |
| Model 37 | Model 31 + history of digoxin | Model 31 | 0.772 | 0.38 | 3.30 | Model 31 + history of digoxin | Model 31 | 0.60 | 0.43 | 0.87 |
| Model 38 | Model 31 + BB at baseline | Model 31 | 7.873 | 0.00 | 3.29 | Model 31 + BB at baseline | Model 31 | 3.25 | 0.07 | 0.87 |
| Model 39 | Model 38 + BB >= 100% target at baseline | Model 38 | 3.812 | 0.05 | 3.29 | Model 31 + BB >= 100% target at baseline | Model 31 | 0.34 | 0.56 | 0.87 |
| Model 40 | Model 38 + ACEi at baseline | Model 38 | 0.109 | 0.74 | 3.29 | Model 31 + ACEi at baseline | Model 31 | 0.71 | 0.39 | 0.87 |
| Model 41 | Model 40 + ACEi >= 100% target at baseline | Model 38 | 0.117 | 0.73 | 3.29 | Model 31 + ACEi >= 100% target at baseline | Model 31 | 0.59 | 0.44 | 0.87 |

* Starting from a basic univariable shared frailty model of the effect of RASi dose level at 3 months on recurrent hospitalisation, the forward selection algorithm consisted of the addition of one baseline variable at a time to the previous model. The log-likelihood and the degrees of freedom as also the likelihood cross-validation criterion (LCV), which is equivalent to the AIC for Cox regression models, were calculated for every model.

The baseline model had 1 explanatory variable, the 1st model had 2 explanatory variables, the 2nd model had 3 explanatory variables and so on. In this way, the ith model had (i+1) explanatory variables. At every step, the ith model (with (i+1) variables) was compared with the (i-1)th model, which had (i+1-1 = i) variables, using the likelihood ratio (LR) test and the absolute difference of their respective LCVs. If the ith model differed significantly from the (i-1)th model then it was selected and served for comparisons with the (i+1)th model, which consisted of (i+1+1 = i+2) variables. If the ith model was not significantly different from the (i-1)th model, then the (i-1)th model remained the selected model and the (i+1)th model was then compared with the (i-1)th model instead of the ith model.

As shown in the Table, the selected shared frailty model for rehospitalizations was Model 38 which differed significantly from Model 31 which had been selected at a previous step (LR test p=0.005) and had a lower LCV value (3.2996 < 3.3003). Model 38 consisted of the variables included in Model 31 plus beta-blockers at baseline. The final shared frailty model for rehospitalizations included the following variables: dose level of RASi at 3 months, age category, ischaemic cause, cardiomyopathic and valvular cause of heart failure, history of myocardial infarction, atrial fibrillation, stroke, ICD, CRT, diabetes, COPD, chronic kidney disease and cancer, LVEF category, and beta-blocker treatment at baseline.

** The same forward selection procedure was followed for the shared frailty model of the effect of beta-blocker dose level at 3 months on mortality. The selected shared frailty model for death was Model 31 which differed significantly from Model 27 that had been previously selected (LR test p=0.005) and had lower LCV value (0.8776 < 8782). Model 31 consisted of the variables included in Model 27 plus LVEF category. The final shared frailty model for mortality included: dose level of RASi at 3 months, age category, ischaemic cause of heart failure, history of CABG, atrial fibrillation, peripheral artery disease, ICD, CRT, COPD, chronic kidney disease, RBBB on ECG at baseline and LVEF category.

The selected final multivariable joint frailty model included jointly the formula of shared frailty model 38 for rehospitalizations and the formula of shared frailty model 31 for mortality. Its formula includes also the inverse probability weights (IPW) for RASi treatment.

Supplementary table 2: Steps of the forward selection algorithm for the final multivariable joint frailty model of the effect of beta-blocker dose level at 3 months on recurrent hospitalizations and death.

| Forward selection algorithm of multivariable shared frailty model for recurrent unscheduled hospitalizations * | | | | | | Forward selection algorithm of multivariable shared frailty model for mortality ** | | | | |
|--|--|-----------------------|--------------|---------|------|--|-----------------------|--------------|---------|------|
| Model number | Model parameters | Comparison with model | LR statistic | P-value | LCV | Model parameters | Comparison with model | LR statistic | P-value | LCV |
| | Basic model | | | | 3.32 | Basic model | | | | 1.05 |
| Model 1 | Basic model + sex | Basic model | 1.565 | 0.211 | 3.33 | Basic model + sex | Basic model | 9.21 | 0.05 | 1.05 |
| Model 2 | Basic model + age category | Basic model | 19.95 | <0.01 | 3.32 | Basic model + age category | Basic model | 38.4 | <0.01 | 1.04 |
| Model 3 | Model 2 + race (white vs other) | Model 2 | 0.357 | 0.550 | 3.32 | Model 2 + race (white vs other) | Model 2 | 0.33 | 0.56 | 1.04 |
| Model 4 | Model 2 + ischaemic aetiology | Model 2 | 18.64 | <0.01 | 3.32 | Model 2 + ischaemic aetiology | Model 2 | 17.2 | <0.01 | 1.04 |
| Model 5 | Model 4 + hypertensive aetiology | Model 4 | 0.115 | 0.734 | 3.32 | Model 4 + hypertensive aetiology | Model 4 | 0.60 | 0.43 | 1.04 |
| Model 6 | Model 4 + cardiomyopathy | Model 4 | 33.15 | <0.01 | 3.32 | Model 4 + cardiomyopathy | Model 4 | 2.50 | 0.11 | 1.04 |
| Model 7 | Model 6 + valvular heart disease | Model 6 | 9.690 | 0.002 | 3.32 | Model 4 + valvular heart disease | Model 4 | 3.08 | 0.07 | 1.04 |
| Model 8 | Model 7 + history of MI | Model 7 | 6.090 | 0.014 | 3.32 | Model 4 + history of MI | Model 4 | 3.10 | 0.07 | 1.04 |
| Model 9 | Model 8 + history of CABG | Model 8 | 2.254 | 0.133 | 3.32 | Model 4 + history of CABG | Model 4 | 13.0 | <0.01 | 1.04 |
| Model 10 | Model 8 + history of PCI | Model 8 | 0.290 | 0.590 | 3.32 | Model 9 + history of PCI | Model 9 | 1.41 | 0.23 | 1.04 |
| Model 11 | Model 8 + history of AF | Model 8 | 5.632 | 0.018 | 3.32 | Model 9 + history of AF | Model 9 | 8.76 | 0.00 | 1.04 |
| Model 12 | Model 11 + history of stroke | Model 11 | 6.783 | 0.009 | 3.32 | Model 11 + history of stroke | Model 11 | 1.21 | 0.27 | 1.04 |
| Model 13 | Model 12 + history of PAD | Model 12 | 2.063 | 0.151 | 3.32 | Model 11 + history of PAD | Model 11 | 3.47 | 0.06 | 1.04 |
| Model 14 | Model 12 + history of PCM | Model 12 | 2.056 | 0.152 | 3.32 | Model 11 + history of PCM | Model 11 | 0.35 | 0.54 | 1.04 |
| Model 15 | Model 12 + history of ICD | Model 12 | 15.04 | <0.01 | 3.31 | Model 11 + history of ICD | Model 11 | 7.52 | 0.00 | 1.04 |
| Model 16 | Model 15 + history of CRT | Model 15 | 16.58 | <0.01 | 3.31 | Model 15 + history of CRT | Model 15 | 10.9 | 0.00 | 1.04 |
| Model 17 | Model 16 + history of HTN | Model 16 | 0.571 | 0.450 | 3.31 | Model 16 + history of HTN | Model 16 | 0.00 | 0.93 | 1.04 |
| Model 18 | Model 16 + history of smoking | Model 16 | 3.746 | 0.154 | 3.31 | Model 16 + history of smoking | Model 16 | 1.01 | 0.60 | 1.04 |
| Model 19 | Model 16 + Alcohol (current) | Model 16 | 0.293 | 0.589 | 3.31 | Model 16 + Alcohol (current) | Model 16 | 1.09 | 0.29 | 1.04 |
| Model 20 | Model 16 + history of DM | Model 16 | 17.30 | <0.01 | 3.31 | Model 16 + history of DM | Model 16 | 1.97 | 0.16 | 1.04 |
| Model 21 | Model 20 + history of DM on insulin | Model 20 | 1.414 | 0.493 | 3.31 | Model 16 + history of DM on insulin | Model 16 | 0 | 0 | 31 |
| Model 22 | Model 20 + history of COPD | Model 20 | 12.93 | <0.01 | 3.31 | Model 16 + history of COPD | Model 16 | 4.73 | 0.09 | 1.04 |
| Model 23 | Model 22 + history of CKD | Model 22 | 64.92 | <0.01 | 3.30 | Model 22 + history of CKD | Model 22 | 9.95 | 0.00 | 1.04 |
| Model 24 | Model 23 + history of thyroid disease | Model 23 | 0.027 | 0.870 | 3.30 | Model 22 + history of thyroid disease | Model 22 | 41.5 | <0.01 | 1.03 |
| Model 25 | Model 23 + history of malignancy (current) | Model 23 | 12.01 | 0.001 | 3.30 | Model 23 + history of malignancy (current) | Model 23 | 0.94 | 0.33 | 1.03 |
| Model 26 | Model 25 + AF on ECG at | Model 25 | 0.101 | 0.750 | 3.30 | Model 23 + AF on ECG | Model 23 | 0.08 | 0.77 | 1.03 |

| Forward selection algorithm of multivariable shared frailty model for recurrent unscheduled hospitalizations * | | | | | | Forward selection algorithm of multivariable shared frailty model for mortality ** | | | | |
|--|--|-----------------------|--------------|--------------|-------------|--|-----------------------|--------------|-------------|-------------|
| Model number | Model parameters | Comparison with model | LR statistic | P-value | LCV | Model parameters | Comparison with model | LR statistic | P-value | LCV |
| | baseline | 25 | | | 64 | at baseline | 23 | 4 | 0 | 75 |
| Model 27 | Model 25 + RBBB on ECG at baseline | Model 25 | 1.837 | 0.175 | 3.30 | Model 23 + RBBB on ECG at baseline | Model 23 | 4.52 | 0.03 | 1.03 |
| Model 28 | Model 25 + LBBB on ECG at baseline | Model 25 | 0.012 | 0.914 | 3.30 | Model 27 + LBBB on ECG at baseline | Model 27 | 0.27 | 0.60 | 1.03 |
| Model 29 | Model 25 + QRS >130ms on ECG at baseline | Model 25 | 0.566 | 0.452 | 3.30 | Model 27 + QRS >130ms on ECG at baseline | Model 27 | 0.11 | 0.73 | 1.03 |
| Model 30 | Model 25 + QRS >150ms on ECG at baseline | Model 25 | 4.298 | 0.038 | 3.30 | Model 27 + QRS >150ms on ECG at baseline | Model 27 | 0.10 | 0.75 | 1.03 |
| Model 31 | Model 30 + LVEF category at baseline | Model 30 | 29.73 | <0.01 | 3.30 | Model 27 + LVEF category at baseline | Model 27 | 12.7 | 0.00 | 1.03 |
| Model 32 | Model 31 + MR on echo at baseline | Model 31 | 0.120 | 0.729 | 3.30 | Model 31 + MR on echo at baseline | Model 31 | 1.80 | 0.17 | 1.03 |
| Model 33 | Model 31 + history of ACEi | Model 31 | 0.552 | 0.457 | 3.30 | Model 31 + history of ACEi | Model 31 | 0.00 | 0.96 | 1.03 |
| Model 34 | Model 31 + history of ARB | Model 31 | 0.809 | 0.368 | 3.30 | Model 31 + history of ARB | Model 31 | 1.09 | 0.29 | 1.03 |
| Model 35 | Model 31 + history of BB | Model 31 | 0.145 | 0.703 | 3.30 | Model 31 + history of BB | Model 31 | <0.01 | 0.98 | 1.03 |
| Model 36 | Model 31 + history of MRA | Model 31 | 0.534 | 0.465 | 3.30 | Model 31 + history of MRA | Model 31 | 0.77 | 0.37 | 1.03 |
| Model 37 | Model 31 + history of digoxin | Model 31 | 0.584 | 0.445 | 3.30 | Model 31 + history of digoxin | Model 31 | 0.73 | 0.39 | 1.03 |
| Model 38 | Model 31 + BB at baseline | Model 31 | 6.176 | 0.013 | 3.30 | Model 31 + BB at baseline | Model 31 | 1.84 | 0.17 | 1.03 |
| Model 39 | Model 38 + BB >= 100% target at baseline | Model 38 | 1.402 | 0.236 | 3.30 | Model 31 + BB >= 100% target at baseline | Model 31 | 1.81 | 0.17 | 1.03 |
| Model 40 | Model 38 + ACEi at baseline | Model 38 | 4.248 | 0.039 | 3.30 | Model 31 + ACEi at baseline | Model 31 | 2.23 | 0.13 | 1.03 |
| Model 41 | Model 40 + ACEi >= 100% target at baseline | Model 40 | 0.201 | 0.654 | 3.30 | Model 31 + ACEi >= 100% target at baseline | Model 31 | 0.41 | 0.51 | 1.03 |

* Starting from a basic univariable shared frailty model of the effect of beta-blocker dose level at 3 months on recurrent hospitalisation, the forward selection algorithm consisted of the addition of one baseline variable at a time to the previous model. The log-likelihood and the degrees of freedom as also the likelihood cross-validation criterion (LCV), which is equivalent to the AIC for Cox regression models, were calculated for every model. The baseline model had 1 explanatory variable, the 1st model had 2 explanatory variables, the 2nd model had 3 explanatory variables and so on. In this way, the ith model had (i+1) explanatory variables. At every step, the ith model (with (i+1) variables) was compared with the (i-1)th model, which had (i+1-1 = i) variables, using the likelihood ratio (LR) test and the absolute difference of their respective LCVs. If the ith model differed significantly from the (i-1)th model then it was selected and served for comparisons with the (i+1)th model, which consisted of (i+1+1 = i+2) variables. If the ith model was not significantly different from the (i-1)th model, then the (i-1)th model remained the selected model and the (i+1)th model was then compared with the (i-1)th model instead of the ith model.

As shown in the Table, the selected shared frailty model for rehospitalizations was Model 40 which differed significantly from Model 38 which had been selected at a previous step (LR test p=0.039) and had a lower LCV value (3.3022 < 3.3025). Model 40 consisted of the variables included in Model 38 plus RASi at baseline. The final shared frailty model for rehospitalizations included the following variables: dose level of beta-blocker at 3 months, age category, ischaemic cause, cardiomyopathic and valvular cause of heart failure, history of myocardial infarction, atrial fibrillation, stroke, ICD, CRT, diabetes, COPD, chronic kidney disease and cancer, duration of QRS >150ms, LVEF category, beta-blocker and RASi treatment at baseline.

** The same forward selection procedure was followed for the shared frailty model of the effect of beta-blocker dose level at 3 months on mortality. The selected shared frailty model for death was Model 31 which differed significantly from Model 27 that had been previously selected (LR test p=0.002) and had lower LCV value (1.0363 < 1.0373). Model 31 consisted of the variables included in Model 27 plus LVEF category. The final shared frailty model for mortality included: dose level of beta-blocker at 3 months, age category, ischaemic cause of heart failure, history of CABG, atrial fibrillation, ICD, CRT, COPD, chronic kidney disease, RBBB on ECG at baseline and LVEF category.

The selected final multivariable joint frailty model included jointly the formula of shared frailty model 40 for rehospitalizations and the formula of shared frailty model 31 for mortality. Its formula includes also the inverse probability weights (IPW) for beta-blocker treatment.

Supplementary table 3: Variables included in the multivariable joint frailty survival model for the effect of RASi dose level at 3 months on hospitalizations and mortality in the overall population.

| Variable | Hospitalizations * | | Mortality ** | |
|---------------------------------------|--------------------|---------|--------------------|---------|
| | HR (95% CI) | p-value | HR (95% CI) | p-value |
| RASi <50% vs 0% target at 3 months | 0.71 (0.59 - 0.86) | <0.001 | 0.96 (0.73 - 1.27) | 0.792 |
| RASi =50-99% vs 0% target at 3 months | 0.56 (0.46 - 0.68) | <0.001 | 0.58 (0.43 - 0.79) | 0.001 |
| RASi ≥100% vs 0% target at 3 months | 0.60 (0.49 - 0.74) | <0.001 | 0.57 (0.41 - 0.80) | 0.001 |
| Age =60-75y vs <60y | 0.96 (0.81 - 1.14) | 0.655 | 1.13 (0.84 - 1.50) | 0.420 |
| Age >75y vs <60y | 1.11 (0.93 - 1.32) | 0.259 | 1.54 (1.15 - 2.06) | 0.004 |
| Ischemic vs other cause of HF | 1.12 (0.95 - 1.33) | 0.183 | 1.36 (1.10 - 1.69) | 0.005 |
| Cardiomyopathy vs other cause of HF | 0.73 (0.64 - 0.84) | <0.001 | N/A | N/A |
| Valvular vs other cause of HF | 1.21 (1.07 - 1.37) | 0.003 | N/A | N/A |
| History of myocardial infarction | 1.14 (0.97 - 1.35) | 0.118 | N/A | N/A |
| History of CABG | N/A | N/A | 1.38 (1.09 - 1.75) | 0.008 |
| History of atrial fibrillation | 1.11 (0.98 - 1.26) | 0.105 | 1.26 (1.04 - 1.54) | 0.020 |
| History of peripheral artery disease | N/A | N/A | 1.24 (0.95 - 1.61) | 0.112 |
| History of stroke | 1.22 (1.01 - 1.48) | 0.037 | N/A | N/A |
| Implanted ICD | 1.72 (1.39 - 2.12) | <0.001 | 1.62 (1.18 - 2.23) | 0.003 |
| Implanted CRT | 1.46 (1.18 - 1.79) | <0.001 | 1.52 (1.13 - 2.05) | 0.006 |
| History of diabetes | 1.28 (1.13 - 1.45) | <0.001 | N/A | N/A |
| History of COPD | 1.34 (1.14 - 1.56) | <0.001 | 1.46 (1.16 - 1.84) | 0.001 |
| History of chronic kidney disease | 1.68 (1.46 - 1.93) | <0.001 | 1.86 (1.51 - 2.28) | <0.001 |
| History of Malignancy | 1.60 (1.21 - 2.11) | 0.001 | N/A | N/A |
| RBBB on ECG at baseline | N/A | N/A | 1.39 (1.01 - 1.91) | 0.041 |
| LVEF <40% vs ≥50% at baseline | 0.69 (0.53 - 0.89) | 0.004 | 0.76 (0.52 - 1.12) | 0.171 |
| LVEF =40-49% vs ≥50% at baseline | 0.60 (0.49 - 0.74) | <0.001 | 0.60 (0.43 - 0.83) | 0.002 |
| Beta-blocker treatment at baseline | 0.84 (0.72 - 0.98) | 0.023 | N/A | N/A |

The effects of the model variables are expressed as hazard ratios (HR) with their respective 95% confidence intervals (95% CI). All effects were calculated using the multivariable joint frailty survival model that fitted jointly the terminal event rate (death) and the recurrent event rate (unscheduled non-fatal all-cause hospitalizations). The joint frailty model included two separate formulas: one for the rehospitalizations and another for mortality. The time between events (gap time) was used. The model was weighted by the inverse probability weights (IPW) for treatment with RASi at 3 months.

* The risk of rehospitalizations was fitted by a formula that included 16 variables: dose level of RASi at 3 months, age category, ischaemic cause, cardiomyopathic and valvular cause of heart failure, history of myocardial infarction, atrial fibrillation, stroke, ICD, CRT, diabetes, COPD, chronic kidney disease and cancer, LVEF category, and beta-blocker treatment at baseline.

** The risk of death was fitted by a separate formula that included 12 variables: dose level of RASi at 3 months, age category, ischaemic cause of heart failure, history of CABG, atrial fibrillation, peripheral artery disease, ICD, CRT, COPD, chronic kidney disease, RBBB on ECG at baseline and LVEF category.

RASi, renin-angiotensin-inhibitors; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronisation therapy; HF, heart failure; LVEF, left ventricular ejection fraction.

Supplementary table 4: Variables included in the multivariable joint frailty survival model for the effect of beta-blocker dose level at 3 months on hospitalizations and mortality.

| Variable | Rehospitalizations * | | Mortality ** | |
|---|----------------------|---------|--------------------|---------|
| | HR (95% CI) | p-value | HR (95% CI) | p-value |
| Beta-blocker <50% vs 0% target at 3 months | 0.98 (0.75 - 1.29) | 0.089 | 1.00 (0.69 - 1.43) | 0.002 |
| Beta-blocker =50-99% vs 0% target at 3 months | 0.94 (0.71 - 1.26) | 0.285 | 0.59 (0.39 - 0.88) | <0.001 |
| Beta-blocker ≥100% vs 0% target at 3 months | 1.20 (0.87 - 1.64) | 0.013 | 0.74 (0.47 - 1.16) | 0.181 |
| Age =60-75y vs <60y | 0.95 (0.80 - 1.14) | 0.610 | 1.06 (0.79 - 1.42) | 0.711 |
| Age >75y vs <60y | 1.10 (0.91 - 1.34) | 0.324 | 1.48 (1.10 - 2.00) | 0.013 |
| Ischemic vs other cause of HF | 1.12 (0.94 - 1.32) | 0.195 | 1.36 (1.10 - 1.70) | 0.005 |
| Cardiomyopathy vs other cause of HF | 0.72 (0.62 - 0.83) | <0.001 | N/A | N/A |
| Valvular vs other cause of HF | 1.23 (1.08 - 1.40) | 0.001 | N/A | N/A |
| History of myocardial infarction | 1.15 (0.97 - 1.36) | 0.096 | N/A | N/A |
| History of CABG | N/A | N/A | 1.45 (1.15 - 1.84) | 0.002 |
| History of atrial fibrillation | 1.12 (0.98 - 1.27) | 0.080 | 1.30 (1.07 - 1.59) | 0.009 |
| History of stroke | 1.20 (1.00 - 1.45) | 0.057 | N/A | N/A |
| Implanted ICD | 1.74 (1.41 - 2.15) | <0.001 | 1.70 (1.24 - 2.35) | 0.001 |
| Implanted CRT | 1.44 (1.16 - 1.79) | 0.001 | 1.67 (1.23 - 2.26) | 0.001 |
| History of diabetes | 1.26 (1.11 - 1.43) | <0.001 | N/A | N/A |
| History of COPD | 1.35 (1.15 - 1.58) | <0.001 | 1.43 (1.14 - 1.81) | 0.003 |
| History of chronic kidney disease | 1.80 (1.57 - 2.06) | <0.001 | 2.09 (1.70 - 2.56) | <0.001 |
| History of Malignancy | 1.64 (1.24 - 2.16) | <0.001 | N/A | N/A |
| QRS duration ≥150ms vs <150ms at baseline | 1.21 (1.04 - 1.42) | 0.015 | N/A | N/A |
| RBBB on ECG at baseline | N/A | N/A | 1.42 (1.03 - 1.95) | 0.035 |
| LVEF <40% vs ≥50% at baseline | 0.66 (0.50 - 0.87) | 0.004 | 0.71 (0.48 - 1.06) | 0.098 |
| LVEF =40-49% vs ≥50% at baseline | 0.58 (0.46 - 0.73) | <0.001 | 0.55 (0.39 - 0.77) | 0.001 |
| Beta-blocker treatment at baseline | 0.85 (0.71 - 1.01) | 0.225 | N/A | N/A |
| RASi treatment at baseline | 0.89 (0.78 - 1.02) | 0.095 | N/A | N/A |

The effects of the model variables are expressed as hazard ratios (HR) with their respective 95% confidence intervals (95% CI). All effects were calculated using the multivariable joint frailty survival model that fitted jointly the terminal event rate (death) and the recurrent event rate (unscheduled non-fatal all-cause hospitalizations). The joint frailty model included two separate formulas: one for the rehospitalizations and another for mortality. The time between events (gap time) was used. The model was weighted by the inverse probability weights (IPW) for treatment with beta-blockers at 3 months.

* The risk of rehospitalizations was fitted by a formula that included 18 variables: dose level of beta-blocker at 3 months, age category, ischaemic cause, cardiomyopathic and valvular cause of heart failure, history of myocardial infarction, atrial fibrillation, stroke, ICD, CRT, diabetes, COPD, chronic kidney disease and cancer, QRS >150ms on ECG at baseline, LVEF category, beta-blocker and RASi treatment at baseline.

** The risk of death was fitted by a separate formula that included 11 variables: dose level of beta-blocker at 3 months, age category, ischaemic cause of heart failure, history of CABG, atrial fibrillation, ICD, CRT, COPD, chronic kidney disease, RBBB on ECG at baseline and LVEF category.

RASi, renin-angiotensin-inhibitors; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronisation therapy; HF, heart failure; LVEF, left ventricular ejection fraction.

Supplementary table 5. Baseline characteristics of patients who did not completed the 3-month drug titration period and were excluded from the analysis.

| | Patients included in the analysis (N=2345) | Patients excluded from the analysis (N=171) | p-value |
|---|---|--|----------------|
| <i>Demographics</i> | | | |
| Sex (Male) | 1726 (73.6%) | 119 (69.6%) | 0,247 |
| Race (Caucasian) | 2321 (99.0%) | 168 (98.2%) | 0,370 |
| Age (y) | 70 (17) | 74 (11) | <0.001 |
| <60y | 546 (23.3%) | 24 (14.0%) | 0,005 |
| 60-75y | 1002 (42.7%) | 57 (33.3%) | 0,016 |
| >75y | 797 (34.0%) | 90 (52.6%) | <0.001 |
| <i>Cause of HF</i> | | | |
| <i>Primary</i> | | | |
| Ischaemic | 1051 (44.8%) | 83 (48.5%) | 0,303 |
| Hypertensive | 245 (10.4%) | 15 (8.8%) | 0,530 |
| Cardiomyopathy | 617 (26.3%) | 33 (19.3%) | 0,071 |
| Valvular | 173 (7.4%) | 20 (11.7%) | 0,034 |
| <i>Primary or contributory</i> | | | |
| Ischaemic | 1266 (54%) | 102 (60.4%) | 0,123 |
| Hypertensive | 1279 (54.5%) | 90 (52.6%) | 0,718 |
| Cardiomyopathy | 950 (40.5%) | 60 (35.1%) | 0,246 |
| Valvular | 872 (37.2%) | 84 (49.1%) | 0,001 |
| <i>HF history</i> | | | |
| Previous hospitalization(s) in past year before baseline | 731 (31.2%) | 61 (35.7%) | 0,230 |
| NYHA prior to enrolment | | | |
| NYHA I | 256 (10.9%) | 7 (4.1%) | 0,015 |
| NYHA II | 1218 (51.9%) | 61 (35.7%) | 0,008 |
| NYHA III | 783 (33.4%) | 65 (38.0%) | 0,015 |
| NYHA IV | 88 (3.8%) | 13 (7.6%) | 0,001 |
| <i>Comorbidities</i> | | | |
| Myocardial infarction | 884 (37.7%) | 76 (44.4%) | 0,086 |
| CABG | 391 (16.7%) | 41 (24.0%) | 0,015 |
| PCI | 510 (21.7%) | 32 (18.7%) | 0,339 |
| AF | 1054 (44.9%) | 91 (53.2%) | 0,034 |
| Stroke | 214 (9.1%) | 19 (11.1%) | 0,387 |
| Peripheral artery disease | 252 (10.7%) | 21 (12.3%) | 0,533 |
| Pacemaker | 160 (6.8%) | 24 (14.0%) | <0.001 |

| | | | |
|---------------------------------------|--------------|-------------|--------|
| ICD | 190 (8.1%) | 14 (8.2%) | 0,984 |
| CRT | 206 (8.8%) | 16 (9.4%) | 0,799 |
| Hypertension | 1461 (62.3%) | 107 (62.6%) | 0,953 |
| Past smoker | 1145 (48.8%) | 78 (45.6%) | 0,436 |
| Current smoker | 330 (14.1%) | 20 (11.7%) | 0,363 |
| Current alcohol use | 654 (27.9%) | 49 (28.8%) | 0,773 |
| Diabetes | 763 (32.5%) | 54 (31.6%) | 0,779 |
| Diabetes on insulin | 309 (13.2%) | 21 (12.3%) | 0,935 |
| COPD | 393 (16.8%) | 44 (25.7%) | 0,003 |
| Chronic kidney disease | 614 (26.2%) | 81 (47.4%) | <0.001 |
| Thyroid disease | 222 (9.5%) | 29 (17.0%) | 0,002 |
| Malignacy (current) | 81 (3.5%) | 16 (9.4%) | <0.001 |
| <i>HF-drug history</i> | | | |
| MRA | 1255 (53.5%) | 83 (48.5%) | 0,204 |
| Digitalis | 455 (19.4%) | 38 (22.2%) | 0,355 |
| <i>Clinical variables at baseline</i> | | | |
| Systolic BP (mmHg) | 125 (22) | 119 (21) | 0,001 |
| Diastolic BP (mmHg) | 75 (13) | 70 (12) | <0.001 |
| Heart rate (bpm) | 79 (19) | 81 (19) | 0,169 |
| NYHA | | | |
| NYHA I | 56 (2.4%) | 0 (0%) | 0,041 |
| NYHA II | 852 (36.3%) | 39 (22.8%) | 0,001 |
| NYHA III | 1166 (49.7%) | 96 (56.1%) | 0,047 |
| NYHA IV | 271 (11.6%) | 29 (17.0%) | 0,026 |
| 6MWT (m) | 214 (173) | 111 (138) | <0.001 |
| <i>ECG features at baseline</i> | | | |
| AF on ECG | 768 (32.8%) | 63 (37.1%) | 0,225 |
| RBBB | 146 (6.2%) | 23 (13.7%) | 0,011 |
| LBBB | 469 (20.0%) | 48 (28.6%) | 0,042 |
| QRS>130ms | 639 (27.2%) | 67 (39.2%) | <0.001 |
| QRS>150ms | 412 (17.6%) | 41 (24.0%) | 0,021 |
| <i>LVEF category at baseline</i> | | | |
| LVEF \geq50% | 154 (6.6%) | 15 (8.8%) | 0,066 |
| LVEF 40-49% | 295 (12.6%) | 17 (9.9%) | 0,587 |
| LVEF <40% | 1896 (80.9%) | 111 (64.9%) | 0,025 |

Supplementary Table 5 6: Frequency distribution of total hospitalizations and death according to the level of achieved RASi or BBs dose at 3 months.

| | RASi | | | | Beta-blockers | | | | Total |
|--|----------------|----------------|----------------|----------------|--------------------|-----------------|----------------|--------------------|-----------------|
| | 0% | 1–49% | 50–99% | ≥100% | 0% | 1–49% | 50–99% | ≥100% | |
| Patients, 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%) | 2345 |
| Number of deaths, n (%) | 93 (34.7%) | 219 (26.9%) | 122 (16.6%) | 78 (14.7%) | 48 (27.1%) | 313 (24.0%) | 97 (16.2%) | 54 (20.3%) | 512 (21.8%) |
| Total hospitalizations | 514 | 967 | 754 | 548 | 228 | 1435 | 730 | 390 | 2783 |
| Total unscheduled hospitalizations | 418 | 714 | 504 | 360 | 174 | 1059 | 492 | 271 | 1996 |
| Mean total unscheduled hospitalizations | 1.56 | 0.88 | 0.69 | 0.68 | 0.98 | 0.81 | 0.82 | 1.02 | 0.85 |
| <i>By cause</i> | | | | | | | | | |
| Cardiac - non HF, events (%) | 52 (12.4%) | 104 (14.6%) | 76 (15.1%) | 60 (16.7%) | 20 (11.5%) | 153 (14.4%) | 85 (17.3%) | 34 (12.5%) | 292 (14.6%) |
| HF, events (%) | 202 (48.3%) | 338 (47.3%) | 226 (44.8%) | 148 (41.1%) | 71 (40.8%) | 496 (46.8%) | 226 (45.9%) | 121 (44.6%) | 914 (45.8%) |
| Vascular, events (%) | 10 (2.4%) | 24 (3.4%) | 18 (3.6%) | 13 (3.6%) | 7 (4.0%) (3.5%) | 37 (3.5%) | 17 (3.5%) | 4 (1.5%) (3.3%) | 65 (3.3%) |
| Renal Dysfunction, events (%) | 19 (4.5%) | 19 (2.7%) | 12 (2.4%) | 12 (3.3%) | 3 (1.7%) (3.2%) | 34 (3.2%) | 15 (3.0%) | 10 (3.7%) | 62 (3.1%) |
| Non Cardiovascular, events (%) | 135 (32.3%) | 229 (32.1%) | 172 (34.1%) | 127 (35.3%) | 73 (42.0%) | 339 (32.0%) | 149 (30.3%) | 102 (37.6%) | 663 (33.2%) |
| <i>Patients with no. of hospitalization, n (%)</i> | | | | | | | | | |
| 0 | 119 (44.4%) | 509 (62.5%) | 483 (65.8%) | 355 (67.1%) | 96 (54.2%) | 837 (64.2%) | 371 (61.9%) | 162 (60.9%) | 1466 (62.5%) |
| 1 | 49 (18.3%) | 149 (18.3%) | 148 (20.2%) | 90 (17.0%) | 37 (20.9%) | 241 (18.5%) | 116 (19.4%) | 42 (15.8%) | 436 (18.6%) |
| 2 | 37 (13.8%) | 49 (6.0%) | 44 (6.0%) | 33 (6.2%) | 20 (11.3%) | 76 (5.8%) | 41 (6.8%) | 26 (9.8%) | 163 (7.0%) |
| 3 | 31 (11.6%) | 48 (5.9%) | 24 (3.3%) | 27 (5.1%) | 12 (6.8%) | 72 (5.5%) | 35 (5.8%) | 11 (4.1%) | 130 (5.5%) |
| >3 | 32 (11.9%) | 59 (7.2%) | 35 (4.8%) | 24 (4.5%) | 12 (6.8%) | 77 (5.9%) | 36 (6.0%) | 25 (9.4%) | 150 (6.4%) |
| Any event | 149 (55.6%) | 305 (37.5%) | 251 (34.2%) | 174 (32.9%) | 81 (45.8%) | 466 (35.8%) | 228 (38.1%) | 104 (39.1%) | 879 (37.5%) |

Supplementary Table 67: Effect of ACE-inhibitors/ARB and beta-blockers level of dose at 3 months on total hospitalizations and mortality based on univariable and multivariable joint frailty survival models (overall population).

| Drug dose | Beta-blockers | | ACE-inhibitors/ARB | |
|-------------------------------|--------------------|---------|--------------------|---------|
| | HR (95% CI) | p-value | HR (95% CI) | p-value |
| Total hospitalizations | | | | |
| Unadjusted effect | | | | |
| Dose < 1-49% vs 0% target | 0.82 (0.65 - 1.05) | 0.113 | 0.56 (0.46 - 0.67) | <0.001 |
| Dose = 50-99% vs 0% target | 0.78 (0.61 - 1.01) | 0.061 | 0.42 (0.34 - 0.51) | <0.001 |
| Dose = 50-99% vs 1-49% target | 0.97 (0.84 - 1.12) | 0.653 | 0.74 (0.64 - 0.87) | <0.001 |
| Dose ≥ 100% vs 0% target | 0.94 (0.71 - 1.25) | 0.690 | 0.40 (0.33 - 0.49) | <0.001 |
| Dose ≥ 100% vs 1-49% target | 1.16 (0.96 - 1.41) | 0.122 | 0.72 (0.61 - 0.85) | <0.001 |
| Dose ≥ 100% vs 50-99% target | 1.25 (1.01 - 1.54) | 0.042 | 0.97 (0.81 - 1.15) | 0.701 |
| Adjusted effect | | | | |
| Dose < 1-49% vs 0% target | 0.98 (0.75 - 1.29) | 0.902 | 0.71 (0.59 - 0.86) | <0.001 |
| Dose = 50-99% vs 0% target | 0.94 (0.71 - 1.26) | 0.697 | 0.56 (0.46 - 0.68) | <0.001 |
| Dose = 50-99% vs 1-49% target | 0.97 (0.84 - 1.13) | 0.724 | 0.81 (0.69 - 0.94) | 0.007 |
| Dose ≥ 100% vs 0% target | 1.20 (0.87 - 1.64) | 0.268 | 0.60 (0.49 - 0.74) | <0.001 |
| Dose ≥ 100% vs 1-49% target | 1.23 (1.01 - 1.50) | 0.037 | 0.87 (0.73 - 1.03) | 0.109 |
| Dose ≥ 100% vs 50-99% target | 1.32 (1.06 - 1.63) | 0.013 | 1.12 (0.93 - 1.34) | 0.233 |
| Death | | | | |
| Unadjusted effect | | | | |
| Dose < 1-49% vs 0% target | 0.85 (0.59 - 1.21) | 0.361 | 0.69 (0.52 - 0.92) | 0.011 |
| Dose = 50-99% vs 0% target | 0.53 (0.36 - 0.79) | 0.002 | 0.39 (0.29 - 0.53) | <0.001 |
| Dose = 50-99% vs 1-49% target | 0.64 (0.50 - 0.82) | <0.001 | 0.56 (0.44 - 0.72) | <0.001 |
| Dose ≥ 100% vs 0% target | 0.63 (0.40 - 0.99) | 0.043 | 0.33 (0.23 - 0.46) | <0.001 |
| Dose ≥ 100% vs 1-49% target | 0.75 (0.54 - 1.04) | 0.086 | 0.47 (0.36 - 0.63) | <0.001 |
| Dose ≥ 100% vs 50-99% target | 1.21 (0.84 - 1.76) | 0.306 | 0.84 (0.62 - 1.14) | 0.254 |
| Adjusted effect | | | | |
| Dose < 1-49% vs 0% target | 1.00 (0.69 - 1.43) | 0.980 | 0.96 (0.73 - 1.27) | 0.792 |
| Dose = 50-99% vs 0% target | 0.59 (0.39 - 0.88) | 0.010 | 0.58 (0.43 - 0.79) | 0.001 |
| Dose = 50-99% vs 1-49% target | 0.59 (0.47 - 0.76) | <0.001 | 0.62 (0.48 - 0.78) | <0.001 |
| Dose ≥ 100% vs 0% target | 0.74 (0.47 - 1.16) | 0.186 | 0.57 (0.41 - 0.80) | 0.001 |
| Dose ≥ 100% vs 1-49% target | 0.75 (0.54 - 1.03) | 0.073 | 0.60 (0.46 - 0.80) | <0.001 |
| Dose ≥ 100% vs 50-99% target | 1.28 (0.89 - 1.86) | 0.181 | 1.00 (0.74 - 1.35) | 0.986 |

The effects of the drug dose are expressed as hazard ratios (HR) with their respective 95% confidence intervals (95% CI). All effects were estimated using joint frailty survival models (separate for each drug) that fitted jointly the terminal event rate (death) and the recurrent event rate (unscheduled non-fatal all-cause hospitalizations). The time between events (gap time) was used. All frailty models (univariable and multivariable) were weighted by the inverse probability weights (IPW) that had been calculated for each drug separately.

The unadjusted effect was calculated using univariable joint frailty models for each drug. In these models the only independent covariate is the 4-level factor variable denoting the dosage levels of the drug in question.

The adjusted effect was calculated using multivariable joint frailty models for each drug. These models were selected based on algorithmic forward selection process on shared frailty models with the addition of one baseline variable at a time and comparison with the previous model based on likelihood ratio test. For each drug, two separate shared frailty models were fitted during the selection process: one for the recurrent event (hospitalizations) and another for the terminal event (death). Thus, the final joint model for each drug that links the effects of covariates on both hospitalizations and death consists of one formula for the recurrent event and another different formula for the terminal event.

Supplementary table 8. Shared frailty survival analysis for total cardiovascular hospitalizations in subgroups by baseline LVEF.

| Total cardiovascular hospitalizations | | | | | | | | | | | | | | | | |
|---|----------------------------------|---------------------|---|---------------------|---|---------------------|---|---------------------|----------------------------------|---------------------|---|---------------------|---|---------------------|---|---------------------|
| <i>(N events = 1333)</i> | | | | | | | | | | | | | | | | |
| Drug dose at 3 months (% target) | ACEi/ARB | | | | | | | | Beta-blockers | | | | | | | |
| | All patients (N=2345) | | Patients with LVEF < 40% (N=1896) | | Patients with LVEF < 50% (N=2191) | | Patients with LVEF ≥ 50% (N=154) | | All patients (N=2345) | | Patients with LVEF < 40% (N=1896) | | Patients with LVEF < 50% (N=2191) | | Patients with 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 | HR (95% CI) | p- value | HR (95% CI) | p- value |
| <i>Univariable weighted shared frailty model</i> | | | | | | | | | | | | | | | | |
| Dose 1-49% vs 0% target | 0.64 (0.54) | 0,000 | 0.62 (0.50) | 0,000 | 0.61 (0.50) | 0,000 | 1.05 (0.70) | 0,798 | 0.80 (0.63) | 0,061 | 0.65 (0.49) | 0,002 | 0.74 (0.57) | 0,016 | 1.83 (1.10) | 0,019 |
| | - | | - | | - | | - | | - | | - | | - | | - | |
| | 0.76) | | 0.77) | | 0.74) | | 1.58) | | 1.01) | | 0.85) | | 0.95) | | 3.04) | |
| Dose 50-99% vs 0% target | 0.49 (0.40) | 0,000 | 0.44 (0.35) | 0,000 | 0.46 (0.38) | 0,000 | 0.89 (0.58) | 0,608 | 0.79 (0.62) | 0,069 | 0.64 (0.48) | 0,003 | 0.71 (0.55) | 0,013 | 2.08 (1.22) | 0,007 |
| | - | | - | | - | | - | | - | | - | | - | | - | |
| | 0.59) | | 0.55) | | 0.56) | | 1.37) | | 1.02) | | 0.86) | | 0.93) | | 3.56) | |
| Dose 50-99% vs 1-49% target | 0.77 (0.66) | 0,001 | 0.70 (0.59) | 0,000 | 0.76 (0.64) | 0,001 | 0.85 (0.56) | 0,448 | 0.99 (0.86) | 0,941 | 1.00 (0.84) | 0,961 | 0.97 (0.83) | 0,692 | 1.14 (0.79) | 0,478 |
| | - | | - | | - | | - | | - | | - | | - | | - | |
| | 0.89) | | 0.84) | | 0.89) | | 1.29) | | 1.15) | | 1.18) | | 1.13) | | 1.64) | |
| Dose ≥100% vs 0% target | 0.46 (0.38) | 0,000 | 0.42 (0.33) | 0,000 | 0.43 (0.35) | 0,000 | 1.03 (0.63) | 0,896 | 0.82 (0.62) | 0,173 | 0.66 (0.48) | 0,015 | 0.73 (0.54) | 0,040 | 2.36 (1.26) | 0,008 |
| | - | | - | | - | | - | | - | | - | | - | | - | |
| | 0.57) | | 0.54) | | 0.54) | | 1.70) | | 1.09) | | 0.92) | | 0.99) | | 4.43) | |
| Dose ≥100% vs 1-49% target | 0.73 (0.61) | 0,000 | 0.68 (0.55) | 0,000 | 0.71 (0.60) | 0,000 | 0.98 (0.60) | 0,947 | 1.03 (0.85) | 0,772 | 1.03 (0.82) | 0,804 | 0.99 (0.80) | 0,935 | 1.29 (0.79) | 0,310 |
| | - | | - | | - | | - | | - | | - | | - | | - | |
| | 0.87) | | 0.82) | | 0.85) | | 1.61) | | 1.25) | | 1.30) | | 1.22) | | 2.12) | |
| Dose ≥100% vs 50-99% target | 0.96 (0.80) | 0,623 | 0.96 (0.78) | 0,739 | 0.95 (0.78) | 0,585 | 1.16 (0.70) | 0,574 | 1.04 (0.84) | 0,721 | 1.04 (0.81) | 0,760 | 1.03 (0.82) | 0,821 | 1.14 (0.69) | 0,621 |
| | - | | - | | - | | - | | - | | - | | - | | - | |
| | 1.15) | | 1.19) | | 1.15) | | 1.91) | | 1.29) | | 1.34) | | 1.29) | | 1.88) | |
| <i>Multivariable weighted shared frailty model</i> | | | | | | | | | | | | | | | | |
| Dose 1-49% vs 0% target | 0.75 (0.63) | 0,001 | 0.70 (0.57) | 0,001 | 0.71 (0.59) | 0,000 | 0.87 (0.56) | 0,545 | 0.93 (0.73) | 0,592 | 0.75 (0.57) | 0,051 | 0.83 (0.64) | 0,163 | 1.77 (0.85) | 0,124 |
| | - | | - | | - | | - | | - | | - | | - | | - | |
| | 0.89) | | 0.86) | | 0.85) | | 1.36) | | 1.20) | | 1.00) | | 1.08) | | 3.67) | |
| Dose 50-99% vs 0% target | 0.60 (0.50) | 0,000 | 0.52 (0.42) | 0,000 | 0.56 (0.46) | 0,000 | 0.75 (0.47) | 0,228 | 0.91 (0.70) | 0,472 | 0.73 (0.54) | 0,044 | 0.79 (0.60) | 0,108 | 2.03 (0.94) | 0,070 |
| | - | | - | | - | | - | | - | | - | | - | | - | |
| | 0.72) | | 0.65) | | 0.68) | | 1.20) | | 1.18) | | 0.99) | | 1.05) | | 4.35) | |
| Dose 50-99% vs 1-49% target | 0.80 (0.69) | 0,005 | 0.75 (0.63) | 0,001 | 0.80 (0.68) | 0,005 | 0.86 (0.56) | 0,513 | 0.97 (0.84) | 0,695 | 0.97 (0.82) | 0,718 | 0.96 (0.82) | 0,557 | 1.14 (0.75) | 0,545 |
| | - | | - | | - | | - | | - | | - | | - | | - | |
| | 0.94) | | 0.89) | | 0.94) | | 1.34) | | 1.12) | | 1.14) | | 1.11) | | 1.74) | |
| Dose ≥100% vs 0% target | 0.64 (0.52) | 0,000 | 0.57 (0.45) | 0,000 | 0.60 (0.48) | 0,000 | 0.88 (0.49) | 0,663 | 0.96 (0.71) | 0,772 | 0.79 (0.56) | 0,187 | 0.84 (0.61) | 0,274 | 2.98 (1.31) | 0,009 |
| | - | | - | | - | | - | | - | | - | | - | | - | |
| | 0.78) | | 0.72) | | 0.74) | | 1.58) | | 1.29) | | 1.12) | | 1.15) | | 6.78) | |
| Dose ≥100% vs 1-49% target | 0.85 (0.72) | 0,059 | 0.81 (0.67) | 0,031 | 0.85 (0.71) | 0,065 | 1.01 (0.58) | 0,979 | 1.03 (0.85) | 0,794 | 1.05 (0.84) | 0,647 | 1.01 (0.83) | 0,914 | 1.67 (0.94) | 0,078 |
| | - | | - | | - | | - | | - | | - | | - | | - | |
| | 1.01) | | 0.98) | | 1.01) | | 1.75) | | 1.24) | | 1.32) | | 1.24) | | 2.97) | |
| Dose ≥100% vs 50-99% target | 1.06 (0.89) | 0,524 | 1.09 (0.88) | 0,438 | 1.06 (0.88) | 0,539 | 1.17 (0.65) | 0,600 | 1.06 (0.86) | 0,581 | 1.09 (0.85) | 0,482 | 1.06 (0.85) | 0,606 | 1.47 (0.82) | 0,194 |
| | - | | - | | - | | - | | - | | - | | - | | - | |
| | 1.27) | | 1.34) | | 1.28) | | 2.10) | | 1.30) | | 1.39) | | 1.32) | | 2.63) | |
| Cardiovascular hospitalizations: they include hospitalizations due to cardiac non-HF, HF, vascular or renal dysfunction causes | | | | | | | | | | | | | | | | |

Supplementary Table 7 9: Interaction between baseline characteristics and BBs or RASi dose on risk of unscheduled non-fatal hospitalizations and mortality based on multivariable shared frailty models.

| Subgroup | Multivariable shared frailty models * | | | |
|--|--|-------|---|-------|
| | Global p-values for the interaction with BBs dose at 3 months ** | | Global p-values for the interaction with RASi dose at 3 months ** | |
| | Hospitalizations | Death | Hospitalizations | Death |
| Demographics | | | | |
| Age category | 0.932 | 0.501 | 0.544 | 0.435 |
| Heart failure aetiology | | | | |
| Ischaemic | 0.231 | 0.724 | 0.221 | 0.233 |
| Hypertensive | 0.172 | 0.432 | 0.312 | 0.267 |
| Cardiomyopathy | 0.040 | 0.473 | 0.166 | 0.055 |
| Valvular | 0.192 | 0.344 | 0.076 | 0.189 |
| Medical History | | | | |
| Myocardial infarction | 0.244 | 0.958 | 0.309 | 0.042 |
| CABG | 0.183 | 0.167 | 0.779 | 0.121 |
| PCI | 0.462 | 0.385 | 0.479 | 0.739 |
| Atrial fibrillation | 0.372 | 0.424 | 0.206 | 0.385 |
| Stroke | 0.966 | 0.267 | 0.147 | 0.533 |
| Peripheral artery disease | 0.590 | 0.317 | 0.190 | 0.715 |
| Pacemaker | 0.933 | 0.671 | 0.791 | 0.672 |
| ICD | 0.908 | 0.233 | 0.063 | 0.507 |
| CRT | 0.787 | 0.475 | 0.861 | 0.532 |
| Hypertension | 0.581 | 0.118 | 0.287 | 0.433 |
| Smoking | 0.694 | 0.586 | 0.530 | 0.412 |
| Current alcohol use | 0.404 | 0.197 | 0.337 | 0.464 |
| Diabetes | 0.359 | 0.830 | 0.432 | 0.135 |
| COPD | 0.430 | 0.088 | 0.935 | 0.540 |
| Chronic kidney disease | 0.744 | 0.120 | 0.385 | 0.041 |
| Thyroid disease | 0.374 | 0.893 | 0.544 | 0.123 |
| Malignancy (current) | 0.189 | 0.945 | 0.619 | 0.126 |
| Medication History | | | | |
| ACEi | 0.002 | 0.587 | 0.866 | 0.482 |
| Beta-blockers | 0.522 | 0.802 | 0.464 | 0.051 |
| MRA | 0.626 | 0.610 | 0.467 | 0.262 |
| Digoxin | 0.237 | 0.417 | 0.812 | 0.110 |
| Clinical variables at baseline | | | | |
| Atrial fibrillation on ECG | 0.700 | 0.229 | 0.063 | 0.330 |
| RBBB on ECG | 0.059 | 0.733 | 0.406 | 0.853 |
| LBBB on ECG | 0.616 | 0.102 | 0.942 | 0.646 |
| QRS >130ms on ECG | 0.670 | 0.056 | 0.682 | 0.488 |
| QRS >150ms on ECG | 0.928 | 0.111 | 0.716 | 0.714 |
| LVEF category | 0.106 | 0.295 | 0.260 | 0.321 |
| Mitral regurgitation | 0.776 | 0.007 | 0.075 | 0.517 |
| Prognostic drugs at baseline | | | | |
| Beta-blockers vs no beta-blockers | 0.242 | 0.584 | 0.587 | 0.460 |
| Optimal beta-blocker dose vs suboptimal or no beta-blocker | 0.113 | 0.169 | 0.208 | 0.558 |
| RASi vs no RASi | 0.920 | 0.400 | 0.324 | 0.020 |
| Optimal RASi dose vs suboptimal or no RASi | 0.798 | 0.117 | 0.752 | 0.219 |

Supplementary Table 7 9: Interaction between baseline characteristics and BBs or RASi dose on risk of unscheduled non-fatal hospitalizations and mortality based on multivariable shared frailty models.

All-cause total hospitalizations

| Multivariable shared frailty models * | | | | |
|--|---|--------------|--|--------------|
| Subgroup | Global p-values for the interaction with BBs dose at 3 months ** | | Global p-values for the interaction with RASi dose at 3 months ** | |
| | Hospitalizations | Death | Hospitalizations | Death |
| | | | | |

* Multivariable shared frailty survival models were fitted separately for each outcome (hospitalizations and death) and each drug (beta-blockers and RASi). Shared frailty models take into account the existence of correlation within subject for the relapse times but do not link the two different outcomes (as opposed to joint frailty models). The independent linear predictor of each survival model consisted of the main effect of the baseline variable, the main effect of the drug (RASi or beta-blocker) dose level at 3 months (4 levels) and their interaction term. All models are weighted by the inverse probability weights of receiving the respective drug at 3 months.

** The p-values in the table represent the global p-values of the interaction terms of the models due to the fact that the term that denotes the effect of the drug dose level at 3 months is a 4-level factor term and some of the baseline variables are higher level factors and not binary.

RASi: renin-angiotensin-inhibitor; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronisation therapy; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; PCI, percutaneous coronary intervention.

| Drug dose at 3 months (% target) | <i>(N events = 1996)</i> | | | | | | | |
|---|--------------------------------|---------|------------------------------------|---------|--------------------------------|---------|------------------------------------|---------|
| | ACEi/ARB | | | | Beta-blockers | | | |
| | Hospitalized on baseline visit | | Not hospitalized on baseline visit | | Hospitalized on baseline visit | | Not hospitalized on baseline visit | |
| | HR (95% CI) | p-value | HR (95% CI) | p-value | HR (95% CI) | p-value | HR (95% CI) | p-value |
| <i>All patients (N=2345)</i> | | | | | | | | |
| Dose 1-49% vs 0% target | 0.66 (0.56 - 0.77) | 0,000 | 0.67 (0.45 - 0.98) | 0,037 | 0.77 (0.63 - 0.95) | 0,012 | 0.83 (0.52 - 1.33) | 0,441 |
| Dose 50-99% vs 0% target | 0.54 (0.46 - 0.64) | 0,000 | 0.48 (0.33 - 0.71) | 0,000 | 0.78 (0.63 - 0.98) | 0,032 | 0.81 (0.50 - 1.32) | 0,399 |
| Dose >=100% vs 0% target | 0.53 (0.44 - 0.65) | 0,000 | 0.47 (0.31 - 0.69) | 0,000 | 0.81 (0.62 - 1.05) | 0,107 | 1.10 (0.66 - 1.84) | 0,710 |
| <i>Patients with LVEF<40% (N=1896)</i> | | | | | | | | |
| Dose 1-49% vs 0% target | 0.66 (0.54 - 0.81) | 0,000 | 0.64 (0.42 - 0.99) | 0,045 | 0.66 (0.52 - 0.85) | 0,001 | 0.70 (0.41 - 1.20) | 0,194 |
| Dose 50-99% vs 0% target | 0.52 (0.42 - 0.65) | 0,000 | 0.45 (0.29 - 0.71) | 0,000 | 0.67 (0.51 - 0.88) | 0,004 | 0.74 (0.42 - 1.28) | 0,279 |
| Dose >=100% vs 0% target | 0.52 (0.41 - 0.67) | 0,000 | 0.43 (0.28 - 0.68) | 0,000 | 0.70 (0.51 - 0.96) | 0,029 | 0.98 (0.55 - 1.75) | 0,942 |
| <i>Patients with LVEF<50% (N=2191)</i> | | | | | | | | |
| Dose 1-49% vs 0% target | 0.66 (0.55 - 0.79) | 0,000 | 0.64 (0.44 - 0.95) | 0,027 | 0.75 (0.60 - 0.95) | 0,016 | 0.79 (0.48 - 1.29) | 0,343 |
| Dose 50-99% vs 0% target | 0.54 (0.45 - 0.66) | 0,000 | 0.47 (0.31 - 0.70) | 0,000 | 0.75 (0.59 - 0.97) | 0,026 | 0.79 (0.47 - 1.31) | 0,357 |
| Dose >=100% vs 0% target | 0.52 (0.42 - 0.65) | 0,000 | 0.44 (0.29 - 0.65) | 0,000 | 0.74 (0.56 - 0.99) | 0,044 | 1.10 (0.65 - 1.87) | 0,728 |
| <i>Patients with LVEF≥50% (N=154)</i> | | | | | | | | |
| Dose 1-49% vs 0% target | 0.83 (0.62 - 1.11) | 0,218 | 1.35 (0.70 - 2.59) | 0,370 | 1.01 (0.76 - 1.35) | 0,934 | 2.31 (1.09 - 4.87) | 0,028 |
| Dose 50-99% vs 0% target | 0.71 (0.51 - 0.98) | 0,040 | 0.74 (0.35 - 1.58) | 0,441 | 1.10 (0.79 - 1.54) | 0,563 | 1.68 (0.71 - 3.95) | 0,238 |
| Dose >=100% vs 0% target | 0.88 (0.60 - 1.30) | 0,513 | 1.10 (0.58 - 2.11) | 0,764 | 1.30 (0.86 - 1.95) | 0,214 | 2.92 (0.62 - 13.76) | 0,176 |

Supplementary table 10. Shared frailty analysis of total all-cause hospitalizations by index HF worsening event (outpatients vs hospitalized at enrollment).

Supplementary table 11. Shared frailty analysis of total HF hospitalizations by index HF worsening event (outpatients vs hospitalized at enrollment).

| Total heart failure hospitalizations | | | | | | | | |
|---|---------------------------------------|----------------|---|----------------|---------------------------------------|----------------|---|----------------|
| Drug dose at 3 months (% target) | <i>(N events = 914)</i> | | | | | | | |
| | ACEi/ARB | | | | Beta-blockers | | | |
| | Hospitalized on baseline visit | | Not hospitalized on baseline visit | | Hospitalized on baseline visit | | Not hospitalized on baseline visit | |
| | HR (95% CI) | p-value | HR (95% CI) | p-value | HR (95% CI) | p-value | HR (95% CI) | p-value |
| <i>All patients (N=2345)</i> | | | | | | | | |
| Dose 1-49% vs 0% target | 0.61 (0.48 - 0.77) | 0,000 | 0.75 (0.42 - 1.36) | 0,350 | 0.83 (0.61 - 1.14) | 0,252 | 0.71 (0.37 - 1.34) | 0,290 |
| Dose 50-99% vs 0% target | 0.46 (0.36 - 0.59) | 0,000 | 0.50 (0.27 - 0.91) | 0,023 | 0.83 (0.59 - 1.17) | 0,283 | 0.63 (0.32 - 1.23) | 0,174 |
| Dose >=100% vs 0% target | 0.46 (0.34 - 0.61) | 0,000 | 0.45 (0.24 - 0.83) | 0,011 | 0.89 (0.61- 1.31) | 0,563 | 0.72 (0.35 - 1.51) | 0,388 |
| <i>Patients with LVEF<40% (N=1896)</i> | | | | | | | | |
| Dose 1-49% vs 0% target | 0.60 (0.51 - 0.71) | 0,000 | 0.75 (0.40 - 1.40) | 0,363 | 0.68 (0.58 - 0.79) | 0,000 | 0.63 (0.31 - 1.28) | 0,203 |
| Dose 50-99% vs 0% target | 0.42 (0.34 - 0.52) | 0,000 | 0.53 (0.28 - 0.99) | 0,047 | 0.65 (0.52 - 0.82) | 0,000 | 0.58 (0.28 - 1.23) | 0,158 |
| Dose >=100% vs 0% target | 0.44 (0.34 - 0.57) | 0,000 | 0.46 (0.24 - 0.88) | 0,019 | 0.73 (0.53 - 1.00) | 0,051 | 0.70 (0.31 - 1.55) | 0,375 |
| <i>Patients with LVEF<50% (N=2191)</i> | | | | | | | | |
| Dose 1-49% vs 0% target | 0.58 (0.45 - 0.75) | 0,000 | 0.76 (0.42 - 1.35) | 0,345 | 0.75 (0.54 - 1.05) | 0,091 | 0.66 (0.34 - 1.27) | 0,212 |
| Dose 50-99% vs 0% target | 0.43 (0.33 - 0.57) | 0,000 | 0.50 (0.28 - 0.91) | 0,024 | 0.74 (0.51 - 1.05) | 0,093 | 0.58 (0.29 - 1.17) | 0,127 |
| Dose >=100% vs 0% target | 0.45 (0.33 - 0.61) | 0,000 | 0.44 (0.24 - 0.80) | 0,008 | 0.77 (0.51 - 1.16) | 0,210 | 0.69 (0.33 - 1.46) | 0,331 |
| <i>Patients with LVEF >=50% (N=154)</i> | | | | | | | | |
| Dose 1-49% vs 0% target | 0.86 (0.52 - 1.43) | 0,572 | 1.48 (0.77 - 2.83) | 0,240 | 1.79 (1.11 - 2.89) | 0,017 | 2.77 (1.42 - 5.42) | 0,003 |
| Dose 50-99% vs 0% target | 0.81 (0.47 - 1.41) | 0,465 | 0.59 (0.26 - 1.35) | 0,214 | 2.05 (1.17 - 3.60) | 0,012 | 2.22 (0.93 - 5.32) | 0,073 |
| Dose >=100% vs 0% target | 0.44 (0.17 - 1.17) | 0,101 | 1.03 (0.50 - 2.12) | 0,939 | 2.53 (1.22 - 5.23) | 0,013 | 4.88 (1.09 - 21.81) | 0,038 |