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Published in:
European Journal of Heart Failure

DOI:
[10.1002/ejhf.2219](https://doi.org/10.1002/ejhf.2219)

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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2021

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Bistola, V., Simitsis, P., Parissis, J., Ouwerkerk, W., van Veldhuisen, D. J., Cleland, J. G., Anker, S. D., Samani, N. J., Metra, M., Zannad, F., Polyzogopoulou, E., Keramida, K., Farmakis, D., Voors, A. A., & Filippatos, G. (2021). Association between up-titration of medical therapy and total hospitalizations and mortality in patients with recent worsening heart failure across the ejection fraction spectrum. *European Journal of Heart Failure*, 23(7), 1170–1181. <https://doi.org/10.1002/ejhf.2219>

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

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Received 6 January 2021; revised 6 May 2021; accepted 8 May 2021

Background

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

Methods and results

We analysed 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/BB 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 [hazard ratio (95% confidence interval): ≥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%.

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Conclusion

After recent worsening of HF, up-titration of RASi and BBs was associated with a better prognosis in patients with LVEF $\leq 49\%$. Up-titration of BBs was associated with a greater risk of HF hospitalization when LVEF was $\geq 50\%$.

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 neuro-hormonal inhibition in patients 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 left ventricular ejection fraction (LVEF) spectrum.

Methods

Study design and characteristics of patients enrolled in the BIOSTAT-CHF study have been described previously.⁸ Briefly, BIOSTAT-CHF was a prospective, observational study that examined up-titration of RASi (angiotensin-converting enzyme inhibitors/angiotensin receptor blockers) and BBs in patients with worsening signs or symptoms of HF, either new-onset or with a previous history of HF, from 69 centres in 11 European countries. Patients were either hospitalized or presented at the outpatient HF clinic and were sub-optimally treated with RASi and/or BBs. Drug initiation/up-titration was performed within 3 months post-enrolment (drug optimization phase), in accordance with the European Society of Cardiology 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 four 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 dose.⁹ Outcomes (events) were total hospitalizations (first and recurrent events) and all-cause death (terminal event) that occurred after completion of the 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 the 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 three 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-model 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 online supplementary Tables S1–S4. Shared frailty models were fitted to examine the association of RASi/BB 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 online supplementary material.

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/BB 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 renin–angiotensin system inhibitors and beta-blockers

From the total of 2516 patients enrolled in BIOSTAT-CHF, we have analysed 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 (online supplementary Table S5). Included patients had a mean age of 70 ± 17 years, 73.6% were male, while 80.9%, 12.6% and 6.6% had baseline LVEF <40%, 40–49% and $\geq 50\%$, respectively.

At the end of the drug optimization period, patients who achieved RASi dose $\geq 100\%$, 50–99%, 1–49%, or no drug were: 529 (22.6%), 734 (31.3%), 814 (34.7%) and 268 (11.4%), respectively. As to BB dose, corresponding patients 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 ($\geq 50\%$) were younger, with less frequently atrial fibrillation (AF) and chronic kidney disease, more frequently diabetes mellitus and arterial hypertension; higher systolic and diastolic blood pressure, and body mass index; lower LVEF; more frequently in New York Heart Association class II/III than IV, with better exercise capacity as estimated by 6-min walking distance. Patients who achieved high BB dose ($\geq 50\%$) were also younger, more frequently males with ischaemic HF aetiology and AF, but with less frequently chronic obstructive pulmonary disease; higher systolic and diastolic blood pressure, heart rate, and body mass index; 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 (online supplementary Table S6). 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 renin–angiotensin system inhibitors and beta-blockers with total unscheduled hospitalizations and mortality

The frequency distribution of hospitalizations and death within patient subgroups categorized according to achieved RASi and BB dose is shown in online supplementary Table S6.

In the overall population, RASi up-titration was associated with reduced risk of total (univariable $P < 0.001$) hospitalizations and mortality (univariable $P < 0.001$) (online supplementary Table S7). This association was dose-dependent; in patients who achieved either 50–99% or $\geq 100\%$ of recommended dose, hospitalization risk was significantly reduced compared to patients who achieved 1–49% [50–99% vs. 1–49%: hazard ratio (HR) 0.74 (95% confidence interval-CI 0.64–0.87), $P < 0.001$; $\geq 100\%$ 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): $\geq 100\%$: 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% vs. $\geq 100\%$ 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), $P < 0.001$; $\geq 100\%$ 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), $P = 0.007$] (online supplementary Table S7). 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), $P < 0.001$; $\geq 100\%$ 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 $\geq 50\%$ achieving statistical significance compared to no treatment in multivariable analysis (online supplementary Table S7).

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 $\geq 40\%$ ($P < 0.001$ in both groups) (Figure 2), as well as in LVEF <50%, but not in the subgroup with LVEF $\geq 50\%$ (Table 2). This relationship was also apparent in the analysis with LVEF as a continuous measure (Figure 3A). BBs were associated with reduced hospitalization risk only in LVEF <40%, whereas there was no significant association in either subgroups with LVEF <50% or $\geq 50\%$ (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).

Table 1 Distribution of patient baseline characteristics according to the achieved dose of renin-angiotensin system inhibitors and beta-blockers at 3 months

	RASi				P-value	Beta-blocker				P-value
	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%)	
Demographics										
Male sex	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 (years)	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
<60 years	38 (14.2%)	191 (23.5%)	183 (24.9%)	134 (25.3%)		19 (10.7%)	303 (23.3%)	157 (26.2%)	67 (25.2%)	
60–75 years	99 (36.9%)	332 (40.8%)	316 (43.1%)	255 (48.2%)		68 (38.4%)	560 (43%)	267 (44.6%)	107 (40.2%)	
>75 years	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 hospitalization(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 class 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
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

Table 1 (Continued)

	RASi				Beta-blocker				P-value	≥100%	50–99%	1–49%	50–99%	≥100%	P-value
	0%	1–49%	50–99%	≥100%	0%	1–49%	50–99%	≥100%							
HF drug history															
Hypertension	164 (61.2%)	446 (54.8%)	470 (64%)	381 (72%)	99 (55.9%)	807 (61.9%)	376 (62.8%)	179 (67.3%)	<0.001						0.111
Past smoker	137 (51.1%)	386 (47.4%)	363 (49.5%)	259 (49%)	81 (45.8%)	619 (47.5%)	302 (50.4%)	143 (53.8%)	0.619						0.384
Current smoker	29 (10.8%)	119 (14.6%)	111 (15.1%)	71 (13.4%)	23 (13%)	188 (14.4%)	88 (14.7%)	31 (11.7%)	0.619						0.384
Current alcohol use	72 (26.9%)	213 (26.2%)	204 (27.8%)	165 (31.2%)	44 (24.9%)	319 (24.5%)	190 (31.7%)	101 (38%)	0.240						<0.001
Diabetes	89 (33.2%)	243 (29.9%)	234 (31.9%)	197 (37.2%)	61 (34.5%)	436 (33.5%)	177 (29.5%)	89 (33.5%)	0.042						0.341
Diabetes on insulin	35 (13.1%)	109 (13.4%)	92 (12.5%)	73 (13.8%)	26 (14.7%)	170 (13%)	72 (12%)	41 (15.4%)	0.081						0.535
COPD	52 (19.4%)	141 (17.3%)	124 (16.9%)	76 (14.4%)	45 (25.4%)	213 (16.3%)	97 (16.2%)	38 (14.3%)	0.295						0.012
Chronic kidney disease	135 (50.4%)	235 (28.9%)	160 (21.8%)	84 (15.9%)	53 (29.9%)	338 (25.9%)	157 (26.2%)	66 (24.8%)	<0.001						0.661
Thyroid disease	39 (14.6%)	78 (9.6%)	67 (9.1%)	38 (7.2%)	12 (6.8%)	123 (9.4%)	63 (10.5%)	24 (9%)	0.010						0.508
Malignancy (current)	14 (5.2%)	34 (4.2%)	19 (2.6%)	14 (2.6%)	11 (6.2%)	48 (3.7%)	17 (2.8%)	5 (1.9%)	0.091						0.075
Clinical variables at baseline															
MRA	134 (50%)	469 (57.6%)	378 (51.5%)	274 (51.8%)	81 (45.8%)	752 (57.7%)	306 (51.1%)	116 (43.6%)	0.034						<0.001
Digitalis	42 (15.7%)	178 (21.9%)	142 (19.3%)	93 (17.6%)	31 (17.5%)	254 (19.5%)	121 (20.2%)	49 (18.4%)	0.083						0.845
Systolic BP (mmHg)	120 (25)	120 (25)	121 (30)	130 (25)	120 (27)	120 (28)	125 (30)	125 (23)	<0.001						0.008
Diastolic BP (mmHg)	70 (20)	70 (15)	75 (14)	80 (20)	70 (20)	71 (14)	75 (15)	78 (16)	<0.001						<0.001
Heart rate (bpm)	78 (25)	76 (24)	76 (23)	75 (22)	76 (22)	75 (22)	77 (22)	80 (30)	0.847						<0.001
BMI (kg/m ²)	26.3 (6.3)	26.5 (6.2)	27.4 (6.3)	28.4 (7.6)	26 (7.7)	27 (6.5)	27.8 (6.4)	27.8 (7.1)	<0.001						<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%)							
6MWT (m)	94 (300)	203 (340)	244 (360)	270 (346)	127 (325)	215 (350)	244 (362)	275 (318)	<0.001						<0.001
ECG features at baseline															
AF on ECG	109 (40.7%)	274 (33.7%)	231 (31.5%)	154 (29.1%)	60 (33.9%)	401 (30.8%)	194 (32.4%)	113 (42.5%)	0.009						0.003
RBBB	21 (7.8%)	55 (6.8%)	43 (5.9%)	27 (5.1%)	16 (9%)	79 (6.1%)	37 (6.2%)	14 (5.3%)	0.408						0.410
LBBB	44 (16.4%)	171 (21%)	149 (20.3%)	105 (19.8%)	32 (18.1%)	291 (22.3%)	97 (16.2%)	49 (18.4%)	0.438						0.014
QRS > 130 ms	82 (30.6%)	225 (27.6%)	194 (26.4%)	138 (26.1%)	48 (27.1%)	349 (26.8%)	173 (28.9%)	69 (25.9%)	0.535						0.758
QRS > 150 ms	55 (20.5%)	151 (18.6%)	112 (15.3%)	94 (17.8%)	31 (17.5%)	232 (17.8%)	110 (18.4%)	39 (14.7%)	0.181						0.601
Echo features at baseline															
LVEDD (mm)	59 (14)	62 (12)	60 (11)	61 (12)	60 (11)	61 (13)	61 (12)	60 (12)	<0.001						0.001
LVEF (%)	34 (15)	30 (11)	30 (11)	30 (11)	35 (15)	30 (10)	30 (12)	30 (13)	<0.001						<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%)	73 (41.2%)	602 (46.2%)	280 (46.7%)	111 (41.7%)	0.212						0.327

Table 1 (Continued)

	RASi			Beta-blocker					P-value	≥100%	50–99%	1–49%	≥100%	P-value	
	0%	1–49%	50–99%	≥100%	P-value	0%	1–49%	50–99%							
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/1.73 m ²)	48.9 (34.6)	66.2 (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					
6MWT, 6-min walk test; AF, atrial fibrillation; BMI, body mass index; BNP, B-type natriuretic peptide; BP, blood pressure; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; Hb, haemoglobin; HF, heart failure; ICD, implantable cardioverter-defibrillator; LBBB, left bundle branch block; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; RASi, renin–angiotensin system inhibitor; RBBB, right bundle branch block.															

6MWT, 6-min walk test; AF, atrial fibrillation; BMI, body mass index; BNP, B-type natriuretic peptide; BP, blood pressure; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; Hb, haemoglobin; HF, heart failure; ICD, implantable cardioverter-defibrillator; LBBB, left bundle branch block; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; RASi, renin–angiotensin system inhibitor; RBBB, right bundle branch block.

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 online supplementary Table S8). Up-titration of BBs was associated with less pronounced heart rate reduction in patients with history of AF at baseline compared to those without [HR at 9 months in the subgroup of ≥100% of target BB dose (mean ± standard deviation): AF history, 78 ± 18; no AF history, 68 ± 12, F test $P_{\text{interaction}} = 0.006$].

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/BB 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 BB association with mortality ($P = 0.007$); and primary aetiology of cardiomyopathy ($P = 0.04$) and previous RASi therapy ($P = 0.002$) that interacted with BB association with hospitalization risk (online supplementary Table S9).

We also analysed the association of RASi and BB up-titration with total and HF hospitalization risk according to index HF worsening event (outpatients vs. hospitalized at enrolment). The 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 (online supplementary Tables S10 and S11).

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 endpoint 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 hospitalizations 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

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

Figure 2 Predicted survival plots according to left ventricular ejection fraction (LVEF) cut-off (LVEF $\geq 40\%$ vs. LVEF $< 40\%$) and renin-angiotensin system inhibitor dose at 3 months for the outcomes of all-cause unscheduled hospitalizations (top panels) and all-cause mortality (bottom panels). ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Table 2 Shared frailty recurrent event analysis for total all-cause hospitalizations and all-cause mortality in subgroups by baseline left ventricular ejection fractionF

Drug dose at 3 months (% target)	RASi			Beta-blockers			LVEF <40%			LVEF <50%			LVEF ≥50%		
	LVEF <40%	HR (95% CI)	P-value	LVEF <40%	HR (95% CI)	P-value	LVEF <40%	HR (95% CI)	P-value	LVEF <40%	HR (95% CI)	P-value	LVEF <40%	HR (95% CI)	P-value
Total all-cause unscheduled hospitalizations (n = 1996 events)															
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
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
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
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
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
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
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
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
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
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
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
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
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
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
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
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
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
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

CI, confidence interval; HR, hazard ratio; LVEF, left ventricular ejection fraction; RASi, renin–angiotensin system inhibitor.

Figure 3 Incidence rate ratio of total all-cause (A, C) and heart failure (B, D) hospitalizations between different dose levels of renin–angiotensin system inhibitors (A, B) and beta-blockers (C, D) as a function of left ventricular ejection fraction (LVEF) ($\geq 100\%$ of guideline-recommended; 50–99% of guideline-recommended; no renin–angiotensin system inhibitors/beta-blockers; reference 1–49%). Shaded areas represent 95% confidence intervals. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

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 angiotensin receptor–neprilysin inhibitor sacubitril/valsartan was shown to reduce recurrent hospitalizations by a further 23% compared to enalapril.¹⁹ Therefore, it appears that renin–angiotensin system 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 vasodilatation.²⁰

Regarding the association of RASi dose and total hospitalization risk, published data are limited. A post-hoc analysis of the ATLAS trial, which compared the efficacy of low vs. high-dose lisinopril in chronic HF with reduced ejection fraction (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 favourable 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, BB up-titration was not associated with reduction of hospitalization risk in a wide LVEF spectrum but only in patients with reduced LVEF. On the other hand, BB $\geq 50\%$ of maximal recommended dose 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 BB doses in LVEF $\geq 50\%$. The differential association of BBs with mortality vs. 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 $\geq 100\%$ BB dose in preserved LVEF appears to be in accordance with a recent post-hoc analysis of the TOPCAT trial (spironolactone vs. placebo in HF

Table 3 Shared frailty recurrent event analysis for total heart failure hospitalizations ($n = 914$ events) in subgroups by baseline left ventricular ejection fraction

Drug dose at 3 months (% target)	RASI	Beta-blockers											
		LVEF <40% (n = 1896)						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		
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)	0.641	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	

CI, confidence interval; HR, hazard ratio; LVEF, left ventricular ejection fraction; RASi, renin-angiotensin system inhibitor.

with preserved LVEF), where BBs were associated with increased risk of HF hospitalizations in LVEF $\geq 50\%$, but an opposite albeit non-significant 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 cardiovascular mortality in LVEF up to 49%, whereas the benefit of BBs on cardiovascular hospitalizations was exerted in LVEF up to $<40\%$ but not $\geq 40\%$.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 BB dose, up-titration of BBs was associated with a less pronounced effect on heart rate in patients with a history of AF. Therefore, we consider it unlikely that the greater risk of HF hospitalization with higher doses of BBs was due to an adverse effect of low heart rate in the subset with AF.²⁶ Furthermore, previous studies in HF with preserved ejection fraction (HFpEF) have shown increased natriuretic peptide levels in patients treated with BBs, while one study showed a marked reduction of natriuretic peptides after BB 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 $\geq 50\%$ 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 a non-randomized 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 analyse 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 non-randomized design of BIOSTAT-CHF. 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 $\leq 49\%$. 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.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Funding

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

Conflict of interest: V.B. reports honoraria for lectures from AstraZeneca, Novartis, and Pfizer. J.P. reports honoraria for lectures and advisory boards from Novartis, Pfizer, Servier, Orion Pharma and Roche Diagnostics. D.J.v.V. has received board membership fees or travel expenses from Novartis, Johnson & Johnson, and Vifor. M.M. has received personal honoraria for participation in trial committees, advisory boards or speeches at sponsored symposia from Abbott Vascular, Amgen, AstraZeneca, Bayer, Vifor Pharma, Servier, WindTree Therapeutics. F.Z. 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. D.F. reports speaker honoraria or consultation fees from Abbott Laboratories, Bayer, Boehringer Ingelheim, Menarini, Novartis, Orion Pharma and Roche Diagnostics. A.A.V. received consultancy fees or research grants from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Cytokinetics, Merck, Myokardia, Novartis, Novonordisk, Roche Diagnostics. G.F. reports committee membership in trials and/or registries sponsored by Amgen, Bayer, Novartis, BI, Medtronic, Vifor, Servier. All other authors have nothing to disclose.

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