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Determinants and clinical outcome of uptitration of ACE-inhibitors and beta-blockers in patients with heart failure: a prospective European study

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Introduction Despite clear guidelines recommendations, most patients with heart failure and reduced ejection–fraction (HFrEF) do not attain guideline-recommended target doses. We aimed to investigate characteristics and for treatment-indication-bias corrected clinical outcome of patients with HFrEF that did not reach recommended treatment doses of ACE-inhibitors/Angiotensin receptor blockers (ARBs) and/or beta-blockers.

Methods and results BIOSTAT-CHF was specifically designed to study uptitration of ACE-inhibitors/ARBs and/or beta-blockers in 2516 heart failure patients from 69 centres in 11 European countries who were selected if they were suboptimally treated while initiation or uptitration was anticipated and encouraged. Patients who died during the uptitration period ($n = 151$) and patients with a LVEF > 40% ($n = 242$) were excluded. Median follow up was 21 months. We studied 2100 HFrEF patients (76% male; mean age 68 ±12), of which 22% achieved the recommended treatment dose for ACE-inhibitor/ARB and 12% of beta-blocker. There were marked differences between European countries. Reaching <50% of the recommended ACE-inhibitor/ARB and beta-blocker dose was associated with an increased risk of death and/or heart failure hospitalization. Patients reaching 50–99% of the recommended ACE-inhibitor/ARB and/or beta-blocker dose had comparable risk of death and/or heart failure hospitalization to those reaching ≥100%. Patients not reaching recommended dose because of symptoms, side effects and non-cardiac organ dysfunction had the highest mortality rate (for ACE-inhibitor/ARB: HR 1.72; 95% CI 1.43–2.01; for beta-blocker: HR 1.70; 95% CI 1.36–2.05).

Conclusion Patients with HFrEF who were treated with less than 50% of recommended dose of ACE-inhibitors/ARBs and beta-blockers seemed to have a greater risk of death and/or heart failure hospitalization compared with patients reaching ≥100%.

Keywords Heart failure • Uptitration • ACE-inhibitor • ARB • Beta-blocker

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Introduction

Current evidence based guidelines of the European Society of Cardiology (ESC) recommends treating patients to recommended or maximum tolerated dose of beta-blockers and angiotensin-converting-enzyme inhibitors (ACE-inhibitors), or angiotensin II receptor blockers (ARBs) when ACE-inhibitors are not tolerated.[1] There is clear evidence from large randomized clinical trials that both ACE-inhibitors and beta-blockers improve clinical outcome in patients with mild to moderate heart failure.[2–12]

In all of these studies, patients were uptitrated to pre-specified doses, and therefore these doses are currently recommended in all guidelines. This recommendation was supported by randomized controlled studies directly comparing low versus high doses, showing (trends towards) superiority of higher doses of ACE-inhibitors and beta-blocker compared with lower doses.[13–15] However, in daily clinical practice, not all patients achieve the recommended doses.[16–18] This might be caused by low blood pressure and/or heart rate, renal dysfunction, and electrolyte disturbances, but may also be related to inadequate prescription adherence.[18]

BIOSTAT-CHF is a European project designed to determine profiles of patients with heart failure that do or do not respond to recommended therapies, regardless of (anticipated) uptitration.[19] This project specifically registered reasons for not achieving recommended dose of ACE-inhibitors/ARBs and beta-blockers. Using the data from BIOSTAT-CHF, we investigated predictors, reasons and clinical outcome of patients that did not reach recommended treatment doses of ACE-inhibitors and beta-blocker.

Methods

Patient population

The design of the study and patients has been described elsewhere.[19] In brief, in BIOSTAT-CHF participated 69 centres from 11 countries, the number of patients included in each centre varied between 1 and 157 with a median of 24 patients. Patients were aged 18 years with symptoms of new-onset or worsening heart failure, confirmed either by a left ventricular ejection fraction (LVEF) of ≤40% or a BNP and/or NT-proBNP plasma levels >400 pg/ml or >2000 pg/ml, respectively. Patients needed to be treated with either oral or intravenous furosemide ≥40 mg/day or equivalent at the time of inclusion. Patients should not have been previously treated with evidence based therapies (ACE-inhibitors/ARBs and beta-blockers) or were receiving ≤50% of the target doses of these drugs at the time of inclusion and with an anticipated initiation or uptitration of ACE-inhibitor/ARB and/or beta-blocker therapy by the treating physician. The first 3 months of treatment were predefined to be the optimization phase after which a stabilization phase of 6 months was defined. During the optimization phase, initiation or uptitration of ACE-inhibitor/ARB and/or beta-blocker was done according to the routine clinical practice of the treating physician, who were encouraged to follow the ESC guidelines at the time of treatment (*Table 1*).[20]

Uptitration

Only patients who reached the end of the 3 months uptitration period were included in this analysis. Patients were considered successfully uptitrated when recommended dose for either ACE-inhibitor/ARB or beta-blocker was achieved after 3 months of uptitration according to current ESC guidelines (*Table 1*).[20] The achieved dose was defined as the highest dose achieved within the uptitration period in percentage of the recommended treatment dose for either ACE-inhibitor/ARB or beta-blocker.

Statistical analysis

To determine predictors of reaching the recommended dose, we developed two prediction models to predict the percentage of achieved recommended dose of ACE-inhibitors/ARBs and beta-blockers using a stepwise backward linear regression model. Both models used 55 clinical and laboratory patient characteristics, all previously reported to be associated with mortality and the composite outcome in heart failure patients (see Supplementary material online, *Table S1*). These methods use the fitted complete model and computes approximate Wald statistics by computing conditional (restricted) maximum likelihood estimates.[21] We also performed 1000 bootstrap analyses to get a robust selection of important patient characteristics associated with reaching recommended dose and achieved dose. We included patient characteristics selected in >40% of the bootstrap analyses.[22] A flow-chart of the steps taken in this analysis is presented in Supplementary material online, *Figure S2*.

In the regression models, for all quantitative patient characteristics, non-linearity was evaluated using restricted cubic splines.[23] For the patient characteristics showing non-linear relations with the *log*Odds for reaching recommended dose or with the achieved dose, Box–Cox transformations were applied.[24,25] We chose the Netherlands as reference country because the uptitration results they included the largest number of patients. Missing values were imputed five times using multi-chain Monte Carlo methods Gibbs sampling.[26] The stepwise regression bootstrap analyses were done 1000 times on all five imputed sets.

Survival curves for mortality starting at 3 months of follow-up, and the first occurrence of death or heart failure related hospitalization in patients reaching recommended ACE-inhibitor/ARB or beta-blocker dose or not were constructed using Kaplan–Meier curves. The predictive value of the achieved dose on survival was evaluated using a Cox regression model. We compared mortality, and the combined outcome of mortality and heart failure related hospitalization between patients who reached recommended dose or not, adjusted for indication-bias, using Kaplan–Meier and Cox regression analysis. Because BIOSTAT-CHF is not a randomized study, the selection of patients and the probability of successful uptitration may be biased due to baseline differences among patients. To adjust for this treatment indication-bias, all analyses of the effect of uptitration on mortality and heart failure hospitalization risk were corrected for the probability of the given treatment (ACE-inhibitor/ARB or beta-blocker). We used four methods for correction: Propensity score matching, a double robust estimation analysis, inverse probability weighting with the probability to reach recommended dose and a multivariate analysis with treatment dose as covariate. Propensity-score matching is used to select patients who were not successfully uptitrated that were similar to patients who were successfully uptitrated with respect to the probability of successful uptitration.[27–29] Double robust estimation combines regression modelling with weighting by the propensity score such that the effect estimator is robust to misspecification of one (but not both) of these models.[30,31] Inverse probability weighting weights each observation by the inverse of the probability of successful uptitration.[32] We only report results of inverse probability weighting because other methods showed similar results. To calculate the probability of successful treatment we used the predictions for successful treatment using a stepwise backward logistic regression models. Predictors of reaching recommended ACE-inhibitor/ARB and beta-blocker dose are presented in Supplementary material online, *Table S2*.

We then compared mortality between patients divided in three groups according to the reasons for (not) reaching recommended doses; (a) those who reached the recommended dose, (b) those who did not reach the recommended dose because of symptoms, side effects or

Table 1 Recommended doses of ACE-inhibitors, ARBs, and beta-blockers in ESC guidelines for patients with LVEF <40%

Drug	Class	Target dose	Total daily dose
Captopril	ACE-inhibitor	50 mg t.i.d.	150 mg
Enalapril	ACE-inhibitor	10 mg b.i.d.	20 mg
Lisinopril	ACE-inhibitor	35 mg q.d.	35 mg
Ramipril	ACE-inhibitor	5 mg b.i.d. or 10 mg q.d.	10 mg
Trandolapril	ACE-inhibitor	4 mg q.d.	4 mg
Perindopril	ACE-inhibitor	8 mg q.d.	8 mg
Candesartan	ARB	32 mg q.d.	32 mg
Valsartan	ARB	160 mg b.i.d.	320 mg
Losartan	ARB	150 mg q.d.	150 mg
Bisoprolol	Beta-blocker	10 mg q.d.	10 mg
Carvedilol	Beta-blocker	25–50 mg b.i.d.	50–100 mg[a]
Metoprolol CR/XL	Beta-blocker	200 mg q.d.	200 mg
Nebivolol	Beta-blocker	10 mg	10 mg

q.d. = once a day; b.i.d.= twice a day; t.i.d. = 3 times a day.
[a]25 mg b.i.d. for patients weighing <75 kg and 50 mg b.i.d. for patients weighing >75 kg.

non-cardiac organ dysfunction, and (c) those who did not reach the recommended dose because of unknown reasons. A Cox regression model was used in comparing these three groups. We constructed survival curves for all three groups using Kaplan–Meier curves.

Results

From the 2516 patients that were included in BIOSTAT-CHF, 151 patients died within the three months uptitration period, 23 patients stopped with the study within three months uptitration period without an event and 242 patients had a LVEF >40% (characteristics are presented in Supplementary material online, *Table S3*). These patients were excluded from the present analysis. Baseline characteristics of the remaining 2100 patients are presented in *Table 2*.

A total of 470 (22%) patients reached recommended dose of ACE-inhibitor/ARB, 16% of patients used an ARB of which 20% reached recommended dose compared to 27% of patients using ACE-inhibitors, and 257 (12%) patients reached recommended beta-blocker dose. We divided the patients in groups of those that reached 0%, 1–49%, 50–99%, and ≥100% of recommended treatment dose of ACE-inhibitor/ARB or beta-blocker. This division was based on the regression slope of the achieved dose on the mortality hazard (Supplementary material online, *Figure S1*).[33] Patient characteristics of patients who reached ACE-inhibitor/ARB or beta-blocker dose of 0%, 1–49%, 50–99%, or ≥100% of recommended dose are presented in *Tables 2* and *3*, respectively.

Predictors for lower dose

Independent predictors for achieving lower percentages of recommended ACE-inhibitor/ARB dose were female sex, country of inclusion, lower BMI and eGFR, and higher alkaline phosphatase values. Predictors for lower beta-blocker doses were higher age, country of inclusion, lower heart rate and diastolic blood pressure (DBP), and more signs of congestion (Supplementary material online, *Table S4*). When the different types of hospitals participating in BIOSTAT-CHF [University hospitals, large teaching hospitals (non-academic), and small non-teaching hospitals], or sites as independent predictors were added to the different models, country differences remained significant.

Marked differences in dose-uptitration were found across Europe. Lower ACE-inhibitor/ARB and beta-blocker doses were achieved in South and Central European countries, while Scandinavian countries achieved higher ACE-inhibitor/ARB and beta-blocker doses (*Figure 1*).

Association between achieved dose and mortality and/or heart failure related hospitalization

After adjusting for indication bias, patients reaching 0% and 1–49% of recommended ACE-inhibitor/ARB dose had a higher risk of mortality (HR 1.76; 95% CI 1.54–1.98, and HR 1.50; 95%CI 1.33–1.67, respectively) and the combined endpoint of death and/or heart failure hospitalization (HR 1.77; 95% CI 1.61–1.94, and 1.23; 95%CI 1.09–1.36, respectively), while patients who reached ACE-inhibitor/ARB doses between 50% and 99% of recommended dose had a similar risk of death and the combined endpoint of death and/or heart failure related hospitalization compared to those reaching ≥100% of recommended treatment dose (HR 0.82; 95% CI 0.62–1.02 and HR 0.86; 95% CI 0.71–1.00, respectively). All hazard ratios are presented in *Table 4*, with the addition of the number of patients in each group and event rate.

Patients reaching 0% and 1–49% of recommended dose of beta-blocker had a higher risk of mortality (HR 2.41; 95% CI 2.13–2.68, and HR 1.91; 95%CI 1.74–2.08, respectively) and the combined endpoint of death and/or heart failure hospitalization (HR 1.51; 95%CI 1.29–1.72, and HR 1.27; 95%CI 1.15–1.39, respectively), while patients who reached beta blocker doses between 50–99% of recommended dose had a similar risk of the combined endpoint of death and/or heart failure related hospitalization (HR 1.04; 95% CI 0.89–1.20), but an increased risk of death (HR 1.29; 95% CI 1.07–1.51)

Table 2 Patient characteristics, with *n* (percentage), mean (SD) or median (interquartile range), at baseline for all patients and for patients who reached 0, 1–49, 50–99, and ≥100% of recommended ACE-inhibitor/ARB dose after uptitration period

	All patients	0%	1–49%	50–99%	≥100%	*P*-value
n	2100	305	686	639	470	
Sex (Male)	1589 (76%)	234 (77%)	520 (76%)	474 (74%)	361 (77%)	0.73
Race (Caucasian)	2078 (99%)	304 (100%)	677 (99%)	634 (99%)	463 (99%)	0.53
Age (years)	68 (12)	70 (12)	68 (12)	67 (12)	67 (12)	0.001
Ischemic aetiology	1154 (55%)	181 (59%)	373 (54%)	356 (56%)	244 (52%)	0.22
Previous Hospitalization in past year before baseline	669 (32%)	120 (39%)	239 (35%)	185 (29%)	125 (27%)	0.0003
HF duration (years)	8 (3.6–13.3)	5.7 (2.3–101)	8.7 (5.3–13.7)	8.6 (4.6–13.5)	8.5 (4–14.1)	0.14
Atrial Fibrillation	901 (43%)	147 (48%)	316 (46%)	248 (39%)	190 (40%)	0.01
Diabetes mellitus	676 (32%)	102 (33%)	201 (29%)	198 (31%)	175 (37%)	0.03
Hypertension	1277 (61%)	177 (58%)	366 (53%)	399 (62%)	335 (71%)	<0.00001
Body mass index (kg/m^2)	28 (5.52)	27.5 (5.25)	27.1 (5.08)	28.1 (5.34)	29.4 (6.21)	<0.00001
Heart rate (beats/min)	79 (19)	78 (17)	81 (20)	80 (19)	80 (21)	0.52
Systolic blood pressure (mmHg)	124 (21)	119 (22)	119 (20)	126 (20)	133 (22)	<0.00001
Diastolic blood pressure (mmHg)	76 (13)	72 (12)	73 (12)	77 (13)	80 (14)	<0.00001
LVEF (%)	30 (25–35)	30 (25–35)	27 (21–33)	30 (25–35)	30 (25–35)	0.001
NT-proBNP (ng/L)	4138 (2249–8220)	5947 (2955–11788)	4565.5 (2509–8859)	4131 (2081–7529)	3274 (2015–5847)	0.00001
eGFR (ml/min/1.73m^2)	66.7 (23.66)	56.8 (25.11)	65 (23.79)	69.9 (22.2)	71 (22.35)	<0.00001
% ACE-inhibitor/ARB target dose	50 (25–75)	0 (0–0)	25 (14.3–25)	50 (50–50)	100 (100–100)	<0.00001
% beta-blocker target dose	25 (12.5–50)	25 (12.5–50)	25 (12.5–50)	25 (12.5–50)	50 (25–75)	<0.00001

eGFR, estimated glomerular filtration rate; HF, heart failure; LVEF, Left ventricular ejection fraction; *n*, Number of patients; NT-proBNP, N-terminal pro B-type natriuretic peptide.

Table 3 Patient characteristics, with *n* (percentage), mean (SD), or median (interquartile range), at baseline for all patients and for patients who reached 0, 1–49, 50–99, and ≥100% of recommended beta-blocker dose after uptitration period

	All patients	0%	1–49%	50–99%	≥100%	*P*-value
n	2100	200	1062	581	257	
Sex (Male)	1589 (76%)	136 (68%)	823 (78%)	444 (76%)	186 (72%)	0.02
Race (Caucasian)	2078 (99%)	199 (100%)	1050 (99%)	575 (99%)	254 (99%)	0.90
Age (years)	68 (12)	70 (12)	68 (12)	67 (12)	67 (13)	0.02
Ischemic aetiology	1154 (55%)	103 (52%)	604 (57%)	318 (55%)	129 (50%)	0.18
Previous Hospitalization in past year before baseline	669 (32%)	70 (35%)	326 (31%)	181 (31%)	92 (36%)	0.32
HF duration (years)	8 (3.6–13.3)	8.8 (4.4–13.9)	6.7 (3.3–11.7)	8.3 (3.7–13.4)	9 (4.7–18)	0.49
Atrial Fibrillation	901 (43%)	85 (43%)	432 (41%)	255 (44%)	129 (50%)	0.05
Diabetes mellitus	676 (32%)	68 (34%)	356 (34%)	169 (29%)	83 (32%)	0.29
Hypertension	1277 (61%)	105 (53%)	654 (62%)	359 (62%)	159 (62%)	0.09
Body mass index (kg/m^2)	28 (5.52)	27.9 (5.91)	28 (5.32)	28.1 (5.7)	27.9 (5.67)	0.85
Heart rate (beats/min)	80 (19)	76 (18)	78 (18)	81 (20)	86 (23)	<0.00001
Systolic blood pressure (mmHg)	124 (21)	121 (21)	123 (21)	127 (22)	126 (20)	0.001
Diastolic blood pressure (mmHg)	76 (13)	71 (12)	75 (12)	78 (14)	78 (13)	<0.00001
LVEF (%)	30 (25–35)	30 (25–35)	30 (24–35)	30 (25–35)	30 (25–35)	0.97
NT-proBNP (ng/L)	4138 (2249–8220)	3282 (1542–8522)	4534 (2503–8806)	3953 (2337–7494)	3676 (2040–7541)	0.04
eGFR (ml/min/1.73 m^2)	66.7 (23.66)	64.5 (22.82)	66.4 (23.68)	66.6 (23.17)	69.3 (25.13)	0.05
% ACE-inhibitor/ARB target dose	50 (25–75)	25 (15.8–50)	38 (13–50)	50 (25–100)	50 (25–100)	<0.00001
% beta-blocker target dose	25 (12.5–50)	0 (0–0)	25 (12.5–25)	50 (50–50)	100 (100–100)	<0.00001

eGFR, estimated glomerular filtration rate; HF, heart failure; LVEF, Left ventricular ejection fraction; *n*, Number of patients; NT-proBNP, N-terminal pro B-type natriuretic peptide.

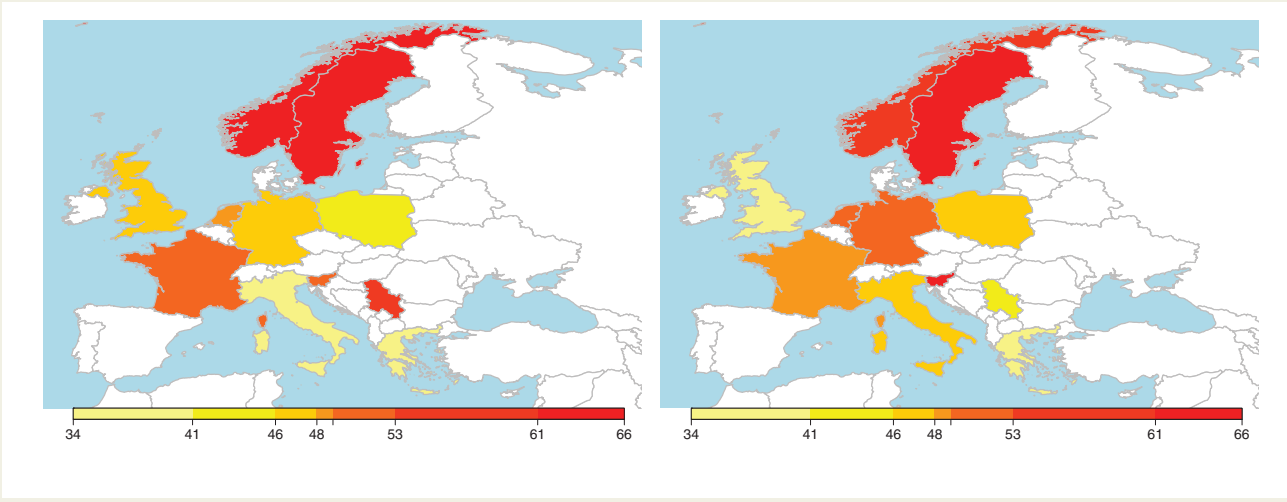

Figure 1 Average percentage achieved of the recommended dose of ACE-inhibitor/ARB (left), and beta-blocker (right) per country.

Table 4 Hazard ratios and number of events of achieving four different levels of recommended treatment dose (0, 1–49 50–99, and ≥100%) for mortality, heart failure related hospitalization, and the first occurrence of death or heart failure related hospitalization

	ACE-inhibitor/ARB				Beta-blocker			
	0%	1–49%	50–99%	≥100%	0%	1–49%	50–99%	≥100%
n	305	686	639	470	200	1062	581	257
Mortality rate, % (n)	29% (89)	25% (172)	14% (92)	15% (70)	27% (53)	22% (233)	16% (93)	17% (44)
Mortality and/or HF-hospitalization rate, % (n)	50% (152)	39% (267)	29% (185)	29% (137)	41% (82)	36% (286)	31% (182)	35% (91)
HR Mortality	1.76 (1.54–1.98)	1.50 (1.33–1.67)	0.82 (0.61–1.02)	–	2.41 (2.13–2.68)	1.91 (1.74–2.08)	1.29 (1.07–1.51)	–
HR Mortality and/or HF-hospitalization	1.77 (1.61–1.94)	1.23 (1.09–1.36)	0.86 (0.71–1.00)	–	1.51 (1.29–1.72)	1.27 (1.15–1.39)	1.04 (0.89–1.20)	–

CI, confidence interval; HF, heart failure; HR, hazard ratio; n, Number of patients.

compared to those reaching ≥100% of recommended treatment dose. Kaplan–Meier survival curves for achieving 0%, 1–49%, 50–99%, and ≥100% of recommended ACE-inhibitor/ARB and beta-blocker dose are presented in *Figure 2*. In *Figure 3*, Kaplan–Meier curves are presented for patients achieving ≥100% recommended dose for both ACE-inhibitor/ARB and beta-blocker, ≥50% recommended ACE-inhibitor and beta-blocker dose, ≥50% of at least ACE-inhibitor/ARB or beta-blocker recommended dose, and for patients achieving <50% of recommended ACE-inhibitor/ARB and beta-blocker dose.

Reasons for not achieving recommended doses and their effect on mortality

BIOSTAT specifically recorded reasons for not achieving recommended doses (Supplementary material online, *Table S5*). We divided the patients in three groups: (a) those who reached the recommended dose, (b) those who did not reach the recommended dose because of symptoms, side effects or non-cardiac organ dysfunction, and (c) those who did not reach the recommended dose because of other/unknown/not specified reasons.

Patients not reaching recommended dose because of symptoms, side effects and non-cardiac organ dysfunction (group b) had the highest mortality rate as presented in *Figure 4*. For ACE-inhibitor/ARB, the hazard for not reaching recommended dose because of symptoms, side effects and non-cardiac organ dysfunction was 1.72; 95% CI 1.43–2.01 and the HR for 'other reasons' was 1.46; 95% CI 1.19–1.73 (*P*-value for difference between these groups = 0.1457). Not reaching the recommended dose of beta-blockers because of symptoms, side effects and non-cardiac organ dysfunction was associated with an increased mortality risk (HR 1.70; 95% CI 1.36–2.05) while the mortality risk was not increased in patients who did not reach the recommended dose for 'other reasons' (HR 1.18; 95% CI 0.86–1.50; *P*-value for difference between these groups = 0.0001). Patient characteristics of all three groups for ACE-inhibitors/ARBs

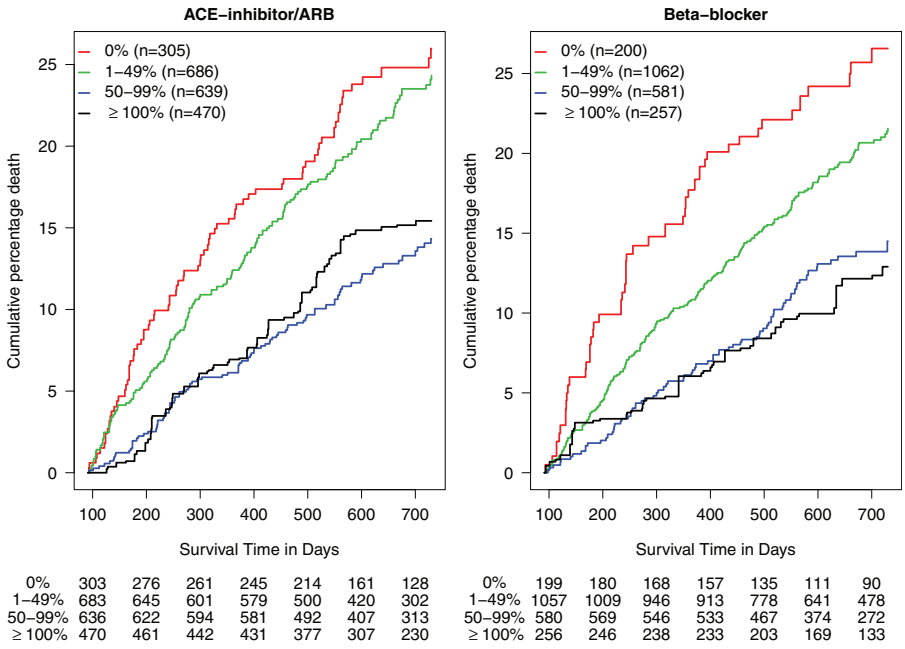

Figure 2 Adjusted mortality rate for patients receiving 0, 1–49, 50–99% or ≥ 100% of the recommended ACE-inhibitor/ARBs or beta-blocker dose, together with the risk set sizes at each time point.

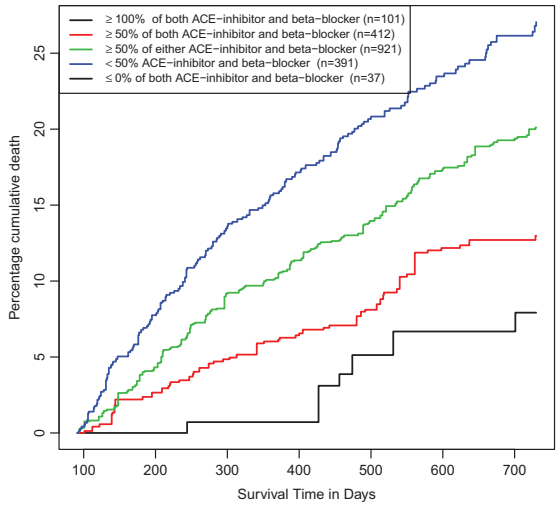

Figure 3 Adjusted mortality rate for patients achieving or ≥ 100% for both ACE-inhibitor/ARB and beta-blocker recommended dose, ≥50% recommended ACE-inhibitor and beta-blocker dose, ≥50% of at least ACE-inhibitor/ARB or beta-blocker recommended dose, and for patients achieving <50% of recommended ACE-inhibitor/ARB and beta-blocker dose.

and beta-blockers are presented in Supplementary material online, *Table S6*. Patients not reaching recommended ACE-inhibitor/ARB and beta-blocker dose because of symptoms, side effects or non-cardiac organ dysfunction had significantly higher LVEF ($P = 0.04$, and $P = 0.04$, respectively) and NT-proBNP ($P = 0.0005$, and $P = 0.02$, respectively) compared to patients not reaching recommended dose because of other/unknown reasons. Additionally, patients not reaching beta-blocker dose were somewhat older ($P = 0.08$), had were longer diagnosed with heart failure ($P = 0.07$), had more AF ($P = 0.06$) and lower DBP ($P = 0.08$).

Discussion

The aim of this study was to establish characteristics and clinical outcomes of non-successful uptitration of recommended therapies in patients with heart failure. After an uptitration phase, only in 22% of patients the recommended doses of ACE-inhibitors/ARBs, and in 12% of patients the recommended doses of the beta-blockers were achieved. These numbers are lower compared with clinical trials, but similar to heart failure registries.[4–9,34–37] Higher success rates were mainly achieved in studies in mild to moderate CHF patients in clinical trial settings. Trial setting results might overestimate uptitration success in daily clinical patient population, since generally more motivated patients will accept trial participation and close monitoring of clinical trials will lead to better application of the guidelines. Data

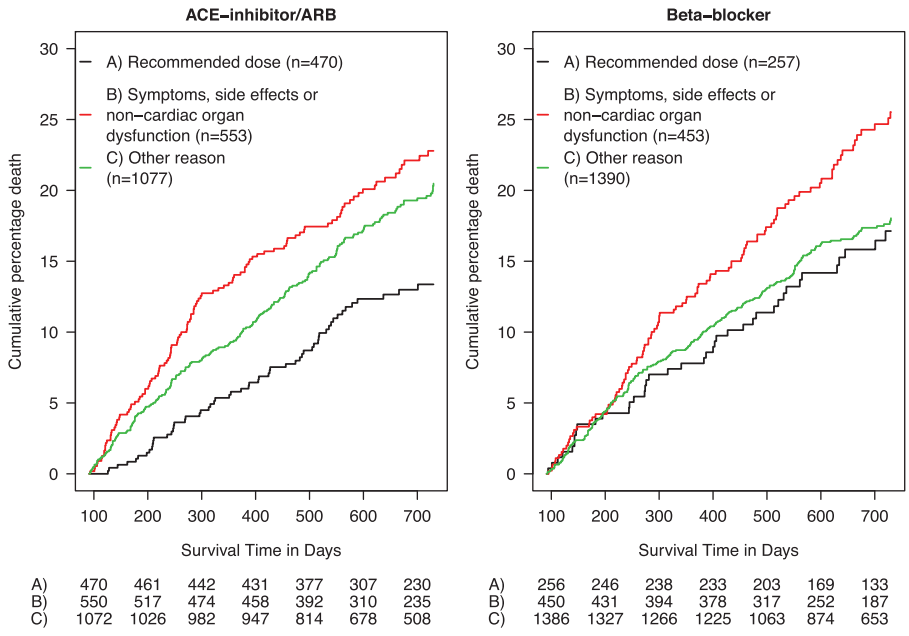

Figure 4 Adjusted mortality rate for patients (*A*) receiving recommended dose; (*B*) reached less than recommended dose due to symptoms, side effects or non-cardiac organ failure; and (*C*) reached less than recommended dose for other reasons, together with the risk set sizes at each time point.

from the European Society of Cardiology Heart Failure Pilot Survey showed that ramipril and enalapril were the most prescribed ACE-inhibitors; the target dose of these drugs was achieved in 38 and 46% of the cases, respectively.[38] The target dose of carvedilol, bisoprolol, and metoprolol was reached in 37, 21, and 21% of patients. In the CIBIS-ELD study, elderly patients from 41 cardiology centres, only 25% of patients reached and maintained guideline-recommended target doses of bisoprolol/carvedilol after 12 weeks treatment.[39] In a UK primary care cohort study of 12493 patients, only 17.8% reached the recommended beta-blocker dose.[17] Using a structured treatment of CHF according to guidelines in a Swedish trial with heart failure patients in the primary care setting, a marked increase in the recommended doses of ACE-inhibitors and beta-blockers were achieved.[40] BIOSTAT-CHF was not a clinical trial, but patients were still younger and more often male compared with the general heart failure population. This is related to the inclusion criteria of the study and the setting of cardiology clinics. It should be noted that patients could only enter the study if they were receiving ≤50% of the target doses of these drugs at the time of inclusion and with an anticipated initiation or uptitration of ACE-inhibitor/ARB and/or beta-blocker therapy by the treating physician.

Patients more likely to achieve lower ACE-inhibitor/ARB doses were female, had lower BMI and eGFR, higher alkaline phosphatase values and were more often treated in South and Central European countries. Patients more likely to achieve lower beta-blocker doses were older had lower heart rates and DBP, more signs of congestion and were also more often treated in South and Central European countries. The relationship between BMI, eGFR and prognosis and uptitration dose is previously reported.[41–45] It is not clear why female patient achieved lower ACE-inhibitor/ARB doses, this might be because they have lower body weight. Similarly, it is not clear why elevated alkaline phosphatase is associated with lower achieved doses. Some of the ACE-inhibitors and ARBs (enalapril, ramipril, fosinopril, trandolapril, quinapril, benazepril, moexipril, and losartan) are prodrugs, and require transformation by the liver into active metabolites. With liver dysfunction, decreases in prodrug transformation and inactivation of active drug may occur, although this is highly speculative.[46,47] The ESC guidelines advices to reduce beta-blocker dose when patients have low heart rate (<50 b.p.m.) or asymptomatic low blood pressure and increasing congestion,[1] this is in line with our findings of predictors for lower beta-blocker doses. Differences found between European countries were remarkable. The most pronounced difference is between the Scandinavian countries and the Southern European countries. These differences might be a reflection of differences in national health systems and different local practice or differences in patient characteristics.

We found that reaching less than 50% of the recommended doses of both ACE-inhibitor/ARBs and beta-blockers resulted in significant poorer survival. This is in line with previous published trials.[2,6,8,15,48–50] Because BIOSTAT-CHF patients were systematically uptitrated to recommended treatment or maximum tolerated doses according to the guidelines, it enabled us to compare the effects of achieved dose on mortality, and mortality and/or heart failure related hospitalization.

Patients who achieved doses 50–99% of the recommended dose for beta-blockers had significantly worse survival than patient

reaching recommended dose, but a similar risk of the combined endpoint of mortality and/or heart failure related hospitalization. For ACE-inhibitors/ARB, patients reaching 50–99% of recommended dose a similar rates of mortality and the combined endpoint of mortality and/or heart failure related hospitalization. Although highly speculative, this would suggest that the optimal treatment dose for ACE-inhibitor/ARB could be less than the recommended dose, and may vary between 50 and 100% of the current recommended dose. There is little known about the comparison of 0%, 1–49%, 50–99%, and ≥100% of recommended ACE-inhibitors/ARBs doses. The Results of CONSENSUS,[10] SOLVD,[2,11] and V-HeFT II[12] trials have clearly shown benefit of ACE-inhibitors at high doses. The NETWORK trial[49] compared 25, 50, and 100% of recommended enalapril dose, although there was a trend in mortality reduction they did not find any significant difference in mortality and heart failure related hospitalizations. The ATLAS trial[13] suggests that higher doses does reduce heart failure related hospitalizations ($P = 0.002$). They compared 2.5–5 mg daily lisinopril (7–14% of the recommended lisinopril dose) to 32.5–35 mg daily (93%-100% of the recommended dose). The HEAAL trial[16] compared 33–100% of the recommended losartan dose. They found a significant difference in all-cause mortality and/or heart failure related hospitalization ($P = 0.027$). The CIPS trial[51] evaluated 33% versus 66% of the recommended captopril dose and did only find a trend toward reduction of heart failure related hospitalization, but this trial only included 298 patients and did not have enough power. Nanas et al. compared recommended enalapril dose to high (300%) dose, but did not found significant differences in survival.[52]

BIOSTAT-CHF was specifically designed to record reasons for not achieving the recommended doses. Only in 26 and 22% of the patients for ACE-inhibitors/ARBs and beta-blockers, this was caused by intolerance to the drug, either because of organ dysfunction (e.g. renal dysfunction) or it was related to symptoms and/or side effects (e.g. dizziness). Patients who could not be uptitrated because of symptoms, side effects and non-cardiac organ dysfunction had the highest mortality rate, both with regards to the ACE-inhibitors/ARBs and beta-blockers. This supports previous findings of a post-hoc analysis of the SENIORS trial, patients intolerant to any dose of nebivolol had a markedly higher risk of death or CV hospitalization compared with placebo.[53] In the majority of patients, no specific reason was provided. This high percentage of 'other reasons' could have many causes. Perhaps the 3-month period for uptitration was too short, and physicians were still uptitrating treatment dose when the 3 months of uptitration period passed. Another reason might be lack of patient compliance. A third reason might be related to non-compliance of physicians to the recommendation provided in the guidelines. The observation that patients in which recommended doses of ACE-inhibitor/ARB and beta-blocker was not achieved because of drug intolerance had a higher mortality than patients for which no reason was specified.

Regardless of the design of BIOSTAT-CHF and efforts to record all reasons for dose change, we lack further specification of reasons for not achieving recommended dose other than 'unknown'.

In this manuscript, we corrected for indication bias using four different methods (propensity score matching, double robust estimation, inverse probability weighting and a multivatiate analysis with treatment dose as covariate). All of these methods gave similar results. This strengthens the belief we adequately corrected for indication bias, but whether we corrected sufficiently for all bias is unfortunately not testable.

Conclusion

Despite the encouragement to follow the ESC Heart Failure Guidelines, only 22% patients reached recommended dose of ACE-inhibitor/ARB and 12% of patients achieved recommended dose for beta-blocker. Independent predictors of reaching lower ACE-inhibitor/ARB doses were country of inclusion, female gender, lower BMI and eGFR, and higher alkaline phosphatase, while predictors for lower doses of beta-blockers were higher age, country of inclusion and lower DBP, heart rate and more signs of congestion. Reaching less than 50% of the recommended dose of ACE-inhibitor/ARB and beta-blocker doses was associated with worse survival. In most patients, no specific reason for not reaching the recommended dose could be provided. Patients who did not reach the recommended ACE-inhibitor/ARB or beta-blocker dose because of intolerance had worse survival compared to patients when there was another reason for not reaching recommended dose.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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