Determinants and clinical outcome of uptitration of ACE-inhibitor and beta-blocker in patients with heart failure

Ouwerkerk, W.; Voors, A. A.; Anker, S. D.; Cleland, J. G.; Dickstein, K.; Filippatos, G.

Published in:
European Heart Journal

DOI:
10.1093/eurheartj/ehx026

Publication date:
2017

Document Version
Peer reviewed version

European Heart Journal

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

--Manuscript Draft--

Manuscript Number:	EURHEARTJ-D-16-02032R1
Full Title:	Determinants and clinical outcome of uptitration of ACE-inhibitor and beta-blocker in patients with heart failure: a prospective European study
Article Type:	Clinical paper
Keywords:	Heart Failure; uptitration; ACE-inhibitor; ARB; Beta-blocker
Corresponding Author:	Adriaan Alexander Voors, MD,PhD University Hospital Groningen Groningen, NETHERLANDS
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	University Hospital Groningen
Corresponding Author's Secondary Institution:	
First Author:	Wouter Ouwerkerk, MSc
First Author Secondary Information:	
Order of Authors:	Wouter Ouwerkerk, MSc
	Adriaan Alexander Voors, MD,PhD
	Stefan Anker
	John Cleland
	Kenneth Dickstein
	Gerasimos Filippatos
	Pim van der Harst
	Hans Hillege
	Chim Lang
	Jozine ter Maaten
	Leong Ng
	Piotr Ponikowski
	Nilesh Samani
	Dirk van Veldhuisen
	Faiez Zannad
	Marco Metra
	Aeilko Zwinderman
Order of Authors Secondary Information:	
Abstract:	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

	BIOSTAT-CHF was specifically designed to study uptitration of ACE-inhibitors/ARBs and/or beta-blockers in 2516 heart failure patients from 69 centers 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. Results 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%.
Suggested Reviewers:	
Additional Information:	
Question	**Response**
Did you cite ESC guidelines where appropriate?	yes
As Corresponding Author, I take full responsibility for all information declared in this notification.	Yes
As Corresponding Author, I agree to be the principal correspondent with the Editorial Office, review the edited manuscript and proof, and make decisions about releasing manuscript information to the media, federal agencies, etc.	Yes
All persons who have made substantial contributions to the manuscript (e.g. data acquisition, analysis, or writing / editing assistance), but who do not fulfill authorship criteria, are named with their specific contributions in the Acknowledgements Section of the manuscript.	Yes
All persons named in the Acknowledgements Section have provided the Corresponding Author with written permission to be named in the manuscript.	Yes
If an Acknowledgements Section is not included in the paper then no other persons have made substantial contributions to this manuscript.	Yes
Please enter the names of the authors who Conceived and designed the research	All authors
Please enter the names of the authors	Prof Zwinderman

who Performed statistical analysis	Wouter Ouwerkerk
Please enter the names of the authors who Acquired the data	A.A. Voors F. Zannad DJ. van Veldhuisen Ponikowski M. Metra C.C. Lang G. Filippatos K. Dickstein J.G. Cleland S.D. Anker
Please enter the names of the authors who Drafted the manuscript	Adriaan Voors Prof Zwinderman Wouter Ouwerkerk
Please enter the names of the authors who Made critical revision of the manuscript for key intellectual content	All authors
Please enter the names of the authors who did anything else on the manuscript other than what we have listed:	none
This manuscript represents valid and substantiated work.	Yes
If asked, I will provide or fully cooperate in obtaining and providing the original data on which the manuscript is based so the editors or their designates can examine it.	Yes
The paper under question is being submitted by an ESC Working Group.	No
Each person listed as co-author has been entered as contributing to at least one part of the manuscript	Yes

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

W. Ouwerkerk (1), A.A. Voors (2), S.D. Anker, MD (3), J.G. Cleland, MD (4), K. Dickstein, MD (5,6), G. Filippatos, MD (7), P. van der Harst, MD (2), H.L. Hillege, MD (2), C.C. Lang, MD (8), J.M. ter Maaten, MD (2) L.L. Ng, MD (9), P. Ponikowski, MD (10) N.J Samani, MD (9), D.J. van Veldhuisen, MD (2), F. Zannad, MD, PhD (10), M. Metra, MD (13) and A.H. Zwinderman (1)

1. Department of Epidemiology, biostatistics & bioinformatics, Academic Medical Center, Amsterdam, The Netherlands
2. Department of Cardiology, University of Groningen, Groningen, the Netherlands
3. Innovative Clinical Trials, Department of Cardiology & Pneumology, University Medical Center Göttingen (UMG), Göttingen, Germany
4. National Heart & Lung Institute, Royal Brompton & Harefield Hospitals, Imperial College, London, United Kingdom.
5. University of Bergen, Bergen, Norway
6. Stavanger University Hospital, Stavanger, Norway
7. National and Kapodistrian University of Athens, School of Medicine & Department of Cardiology, Heart Failure Unit, Athens University Hospital Attikon, Athens, Greece
8. School of Medicine Centre for Cardiovascular and Lung Biology, Division of Molecular and Clinical Medicine, University of Dundee, Ninewells Hospital & Medical School, Dundee, UK
9. Department of Cardiovascular Sciences, University of Leicester, Glenfield Hospital, Leicester, UK and NIHR Leicester Cardiovascular Biomedical Research Unit, Glenfield Hospital, Leicester, LE3 9QP, UK
10. Department of Heart Diseases, Wroclaw Medical University, Poland and Cardiology Department, Military Hospital, Wroclaw, Poland.
11. Inserm CIC 1433, Université de Lorrain, CHU de Nancy, Nancy, France
12. Institute of Cardiology, Department of medical and surgical specialties, radiological sciences and public health; University of Brescia, Italy

Target journal: Eur Heart J

Corresponding author:
Prof. dr. Adriaan A. Voors
Professor of Cardiology, University Medical Center Groningen
Hanzeplein 1, 9713 GZ Groningen
Phone: +31 (0) 50 361 2355

Abstract

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

BIOSTAT-CHF was specifically designed to study uptitration of ACE-inhibitors/ARBs and/or beta-blockers in 2516 heart failure patients from 69 centers 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.

Results

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%.

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 (2–13).

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 (14–16). However, in daily clinical practice, not all patients achieve the recommended doses (17–19). 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 (19)

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 (20). 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 have been described elsewhere (20). 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 >2,000pg/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 three 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) (21).

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) (21). 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 table S1). These methods uses the fitted complete model and computes approximate Wald statistics by computing conditional (restricted) maximum likelihood estimates (22). 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 (23). A flow-chart of the steps taken in this analysis is presented in figure S2.

In the regression models, for all quantitative patient characteristics, non-linearity was evaluated using restricted cubic splines (24). 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 (25,26). We chose the Netherlands as reference country because the uptitration results they included the largest number of patients. Missing values were imputed 5 times using multi-chain Monte Carlo methods Gibbs sampling (27). The stepwise regression bootstrap analyses were done 1000 times on all 5 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 (28–30). 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 (31,32). Inverse probability weighting weights each observation by the inverse of the probability of successful uptitration (33). 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 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 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 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 figure S1) (34). 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 table 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 table S4). When the different types of hospitals participating in BIOSTAT-CHF (Uuniversity 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 50-99% 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) 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 supplementary 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 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 and beta-blockers are presented in supplementary 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 (4–9,35–38). 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 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 (39). 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 centers, only 25% of patients reached and maintained guideline-recommended target doses of bisoprolol/carvedilol after 12 weeks treatment (40). In a UK primary care cohort study of 12493 patients, only 17.8% reached the recommended beta-blocker dose (18). 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 was achieved (41). 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 dose 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 (42–46). 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 (47,48). 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 (2,6,8,16,49–51). 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 (11,12) and V-HeFT II (13) trials have clearly shown benefit of ACE-inhibitors at high doses. The NETWORK trial (50) 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 (14) 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 to 35 mg daily (93%-100% of the recommended dose). The HEAAL trial (16) compared 33% to 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 (52) 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 (53).

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/ARB 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 (54). 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 three different methods (propensity score matching, double robust estimation, and inverse probability weighting). 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.

Funding

This work was supported by a grant from the European Commission [FP7-242209-BIOSTAT-CHF; EudraCT 2010-020808-29]

Declaration of interests (alphabetical order):

Anker reports consultancy for Thermo Fisher, and Consultancy and Research Support from Vifor Pharma

Cleland: none reported

Dickstein: none reported

Filippatos: none reported

van der Harst: none reported

Hillege: none reported

Lang: none reported

ter Maaten: none reported

Metra: Consulting honoraria from Amgen, Bayer, Novartis, Servier

Ng: none reported

Ouwerkerk: none reported

Ponikowski: none reported

Samani: none reported

Van Veldhuisen: none reported

Voors: none reported

Zannad: none reported

Zwinderman: none reported

References

1. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur J Heart Fail. 2016;10
2. The Solvd Investigators. Effect of Enalapril on Survival in Patients with Reduced Left Ventricular Ejection Fractions and Congestive Heart Failure. N Engl J Med. 1991;325:293-302
3. Garg R, Yusuf S, Bussmann WD, Sleight P, Uprichard A, Massie B, et al. Overview of Randomized Trials of Angiotensin-Converting Enzyme Inhibitors on Mortality and Morbidity in Patients With Heart Failure. JAMA J Am Med Assoc. 1995;273:1450
4. Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, et al. The Effect of Carvedilol on Morbidity and Mortality in Patients with Chronic Heart Failure. N Engl J Med. 1996;334:1349–55.
5. Hjalmarson A, Goldstein S, Fagerberg B, Wedel H, Waagstein F, Kjekshus J, et al. Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the Metoprolol CR/XL Randomized Intervention Trial in congestive heart failure (MERIT-HF). MERIT-HF Study Group. JAMA. 2000;283:1295–302
6. Packer M, Coats AJS, Fowler MB, Katus HA, Krum H, Mohacsi P, et al. Effect of Carvedilol on Survival in Severe Chronic Heart Failure. N Engl J Med. 2001;344:1651–8.
7. Poole-Wilson P a, Swedberg K, Cleland JG, Di Lenarda A, Hanrath P, Komajda M, et al. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial. Lancet. 2003;362:7–13.
8. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet. 1999;353:9–13.
9. Flather MD, Shibata MC, Coats AJS, Van Veldhuisen DJ, Parkhomenko A, Borbola J, et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). Eur Heart J. 2005;26:215–25.
10. The CONSENSUS Trial Study Group*. Effects of Enalapril on Mortality in Severe Congestive Heart Failure. N Engl J Med. 1987;316:1429–35.
11. The SOLVD Investigators*. Effect of Enalapril on Survival in Patients with Reduced Left Ventricular Ejection Fractions and Congestive Heart Failure. N Engl J Med. 1991;325:293–302.
12. The SOLVD Investigators*. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. N Engl J Med. 1992;327:685–91.
13. Cohn JN, Johnson G, Ziesche S, Cobb F, Francis G, Tristani F, et al. A Comparison of Enalapril with Hydralazine–Isosorbide Dinitrate in the Treatment of Chronic Congestive Heart Failure. N Engl J Med. 1991;325(5):303–10.
14. Packer M, Poole-Wilson P a., Armstrong PW, Cleland JGF, Horowitz JD, Massie BM, et al. Comparative Effects of Low and High Doses of the Angiotensin-Converting Enzyme Inhibitor, Lisinopril, on Morbidity and Mortality in Chronic Heart Failure. Circulation. 1999;100(23):2312–8.
15. Bristow MR, Gilbert EM, Abraham WT, Adams KF, Fowler MB, Hershberger RE, et al. Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. Circulation. 1996;94:2807–16.
16. Konstam MA, Neaton JD, Dickstein K, Drexler H, Komajda M, Martinez FA, et al. Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAL study): a randomised, double-blind trial. Lancet. 2009;374:1840–8.
17. Cleland JG. Contemporary management of heart failure in clinical practice. Heart. 2002;88:Suppl 2 ii5-8.
18. Komajda M, Follath F, Swedberg K, Cleland J, Aguilar JC, Cohen-Solal A, et al. The EuroHeart Failure Survey programme--a survey on the quality of care among patients with heart failure in Europe. Part 2: treatment. Eur Heart J. 2003;24:464–74.
19. Kalra PR, Morley C, Barnes S, Menown I, Kassianos G, Padmanabhan S, et al. Discontinuation of beta-blockers in cardiovascular disease: UK primary care cohort study. Int J Cardiol. 2013;167:2695–9.
20. Voors AA, Anker SD, Cleland JG, Dickstein K, Filippatos G, van der Harst P, et al. A systems BIOlogy Study to TAilored Treatment in Chronic Heart Failure: rationale, design, and baseline characteristics of BIOSTAT-CHF.

Eur J Heart Fail. 2016;18:716–26.
21. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJV, Ponikowski P, Poole-Wilson PA, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart. Eur Heart J. 2008;29:2388–442.
22. Lawless JF, Singhal K. Efficient Screening of Nonnormal Regression Models. Biometrics. 1978;34:318.
23. Altman DG, Andersen PK. Bootstrap investigation of the stability of a Cox regression model. Stat Med. 1989;8:771–83.
24. Harrell, Jr FE. Regression Modeling Strategies. 2nd ed. Cham: Springer International Publishing; 2015. XXIV, 572. (Springer Series in Statistics).
25. Box GEP, Cox DR. An Analysis of Transformations Revisited, Rebutted. J Am Stat Assoc. 1982;77:209.
26. Clark JE, Osborne JW, Gallagher P, Watson S. A simple method for optimising transformation of non-parametric data: an illustration by reference to cortisol assays. Hum Psychopharmacol Clin Exp. 2016;31:259–67.
27. Buuren S van, Groothuis-Oudshoorn K. mice : Multivariate Imputation by Chained Equations in R. J Stat Softw. 2011;45:1--67.
28. Adelson JL. Reducing Selection Bias with Propensity Scores. Pract Assessment, Res Eval. 2013;18.
29. Holland PW. Statistics and Causal Inference. J Am Stat Assoc. 1986;81:945–60.
30. Rubin DB. Causal Inference Using Potential Outcomes. J Am Stat Assoc. 2005;100:322–31.
31. Robins JM, Rotnitzky A, Zhao LP. Estimation of Regression Coefficients When Some Regressors are not Always Observed. J Am Stat Assoc. 1994;89:846–66.
32. Zetterqvist J, Sjölander A. Doubly Robust Estimation with the R Package drgee. Epidemiol Method. 2015;4.
33. Wal WM van der, Geskus RB. ipw : An R Package for Inverse Probability Weighting. J Stat Softw. 2011;43:1–23.
34. Eilers PHC, Marx BD. Flexible smoothing with B -splines and penalties. Stat Sci. 1996;11:89–121.
35. Willenheimer R, Veldhuisen DJ van, Silke B, Erdmann, Follath F, Krum H, et al. Effect on Survival and Hospitalization of Initiating Treatment for Chronic Heart Failure With Bisoprolol Followed by Enalapril, as Compared With the Opposite Sequence: Results of the Randomized Cardiac Insufficiency Bisoprolol Study (CIBIS) III. Circulation. 2005;112:2426–35.
36. Chatterjee S, Biondi-Zoccai G, Abbate A, D'Ascenzo F, Castagno D, Van Tassell B, et al. Benefits of β blockers in patients with heart failure and reduced ejection fraction: network meta-analysis. BMJ. 2013;346:f55.
37. Deedwania PC, Gottlieb S, Ghali JK, Waagstein F, Wikstrand JCM. Efficacy, safety and tolerability of beta-adrenergic blockade with metoprolol CR/XL in elderly patients with heart failure. Eur Heart J. 2004;25:1300–9.
38. Swedberg K, Komajda M, Böhm M, Borer JS, Ford I, Dubost-Brama A, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. Lancet. 2010;376:875–85.
39. Maggioni AP, Anker SD, Dahlström U, Filippatos G, Ponikowski P, Zannad F, et al. Are hospitalized or ambulatory patients with heart failure treated in accordance with European Society of Cardiology guidelines? Evidence from 12 440 patients of the ESC Heart Failure Long-Term Registry. Eur J Heart Fail. 2013;
40. Düngen HD, Apostolović S, Inkrot S, Tahirović E, Töpper A, Mehrhof F, et al. Titration to target dose of bisoprolol vs. carvedilol in elderly patients with heart failure: The CIBIS-ELD trial. Eur J Heart Fail. 2011;
41. Persson H, Erntell H, Eriksson B, Johansson G, Swedberg K, Dahlström U. Improved pharmacological therapy of chronic heart failure in primary care: A randomized Study of NT-proBNP guided management of heart failure - SIGNAL-HF (Swedish intervention study - Guidelines and NT-proBNP analysis in heart failure). Eur J Heart Fail. 2010;
42. Brenyo A, Barsheshet A, Kutyifa V, Ruwald A-C, Rao M, Zareba W, et al. Predictors of spontaneous reverse remodeling in mild heart failure patients with left ventricular dysfunction. Circ Hear Fail. 2014;7:565–72.
43. Goldenberg I, Moss AJ, McNitt S, Zareba W, Hall WJ, Andrews ML. Inverse Relationship of Blood Pressure Levels to Sudden Cardiac Mortality and Benefit of the Implantable Cardioverter-Defibrillator in Patients With Ischemic Left Ventricular Dysfunction. J Am Coll Cardiol. 2007;49:1427–33.

44. Güder G, Frantz S, Bauersachs J, Allolio B, Wanner C, Koller MT, et al. Reverse Epidemiology in Systolic and Nonsystolic Heart Failure: Cumulative Prognostic Benefit of Classical Cardiovascular Risk Factors. Circ Hear Fail. 2009;2:563–71.
45. Merlo M, Pyxaras SA, Pinamonti B, Barbati G, Di Lenarda A, Sinagra G. Prevalence and Prognostic Significance of Left Ventricular Reverse Remodeling in Dilated Cardiomyopathy Receiving Tailored Medical Treatment. J Am Coll Cardiol. 2011;57:1468–76.
46. Güder G, Störk S, Gelbrich G, Brenner S, Deubner N, Morbach C, et al. Nurse-coordinated collaborative disease management improves the quality of guideline-recommended heart failure therapy, patient-reported outcomes, and left ventricular remodelling. Eur J Heart Fail. 2015;17:442–52.
47. Sokol SI, Cheng A, Frishman WH, Kaza CS. Cardiovascular drug therapy in patients with hepatic diseases and patients with congestive heart failure. J Clin Pharmacol. 2000;40:11–30.
48. Alvarez A, Mukherjee D. Liver Abnormalities in Cardiac Diseases and Heart Failure. Int J Angiol. 2011;20:135–42.
49. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet. 1999;353:2001–7.
50. The NETWORK investigators. Clinical outcome with enalapril in symptomatic chronic heart failure; a dose comparison. Eur Heart J. 1998;19:481–9.
51. Massie BM, Armstrong PW, Cleland JG, Horowitz JD, Packer M, Poole-Wilson PA, et al. Toleration of high doses of angiotensin-converting enzyme inhibitors in patients with chronic heart failure: results from the ATLAS trial. The Assessment of Treatment with Lisinopril and Survival. Arch Intern Med. 2001;161:165–71.
52. Clement DL, De Buyzere M, Tomas M, Vanavermaete G. Long-term effects of clinical outcome with low and high dose in the Captopril in Heart Insufficient Patients Study (CHIPS). Acta Cardiol. 2000;55:1–7.
53. Nanas JN, Alexopoulos G, Anastasiou-Nana MI, Karidis K, Tirologos A, Zobolos S, et al. Outcome of patients with congestive heart failure treated with standard versus high doses of enalapril: a multicenter study. High Enalapril Dose Study Group. J Am Coll Cardiol. 2000;36:2090–5.
54. Dobre D, van Veldhuisen DJ, Mordenti G, Vintila M, Haaijer-Ruskamp FM, Coats AJS, et al. Tolerability and dose-related effects of nebivolol in elderly patients with heart failure: Data from the Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure (SENIORS) trial. Am Heart J. 2007;154:109–15.

Table 1: Recommended doses of ACE-inhibitors, ARBs and beta-blockers in ESC guidelines for patients with LVEF <40%. q.d.=once a day; b.i.d.=twice a day; t.i.d.=3 times a day

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*
Metoprolol CR/XL	Beta-blocker	200 mg q.d.	200 mg
Nebivolol	Beta-blocker	10 mg	10 mg

*25 mg b.i.d. for patients weighing <75 kg and
50 mg b.i.d. for patients weighing >75 k

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 (2.3-10.1)	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/1.73m^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

Table 4: Hazard ratios and number of events of achieving 4 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

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

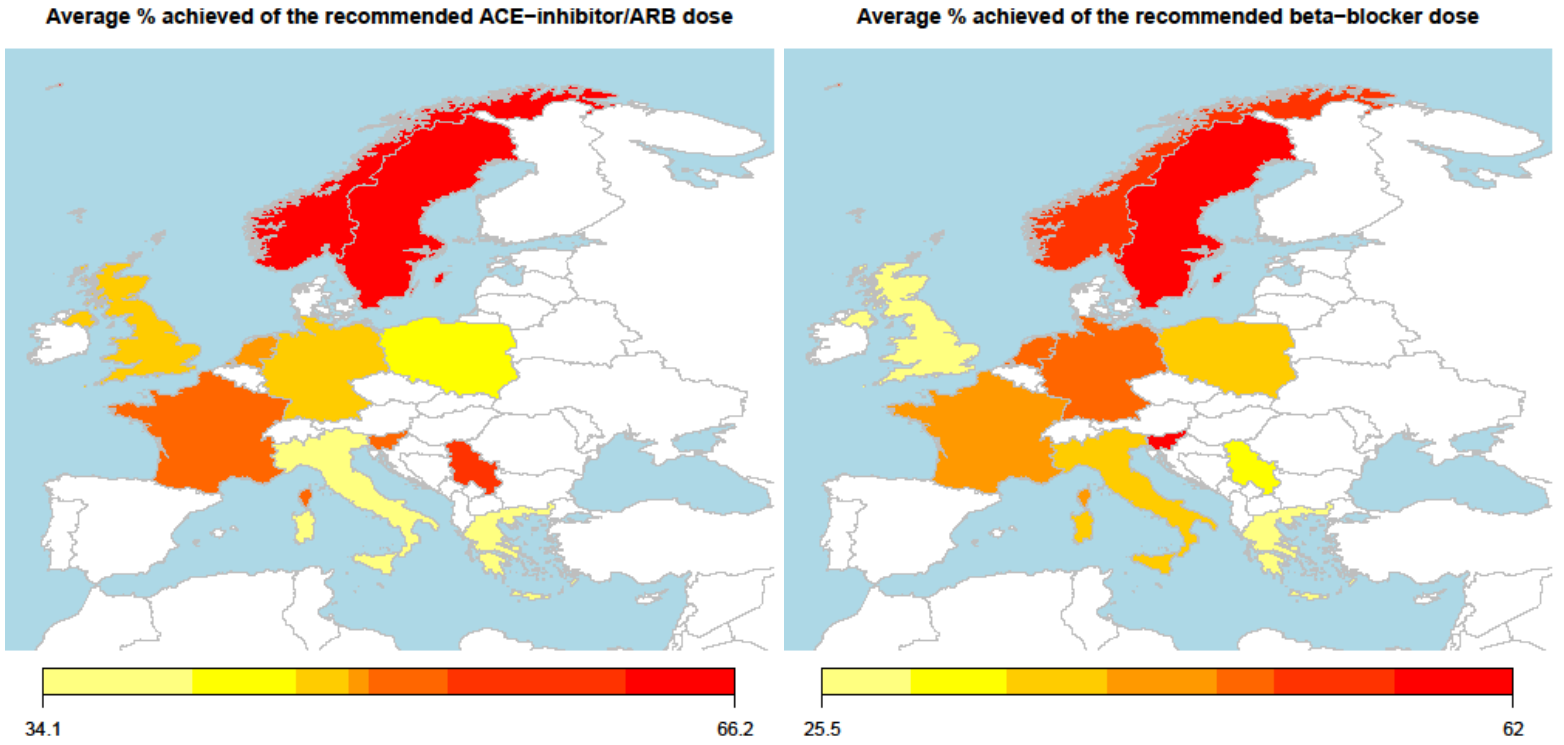
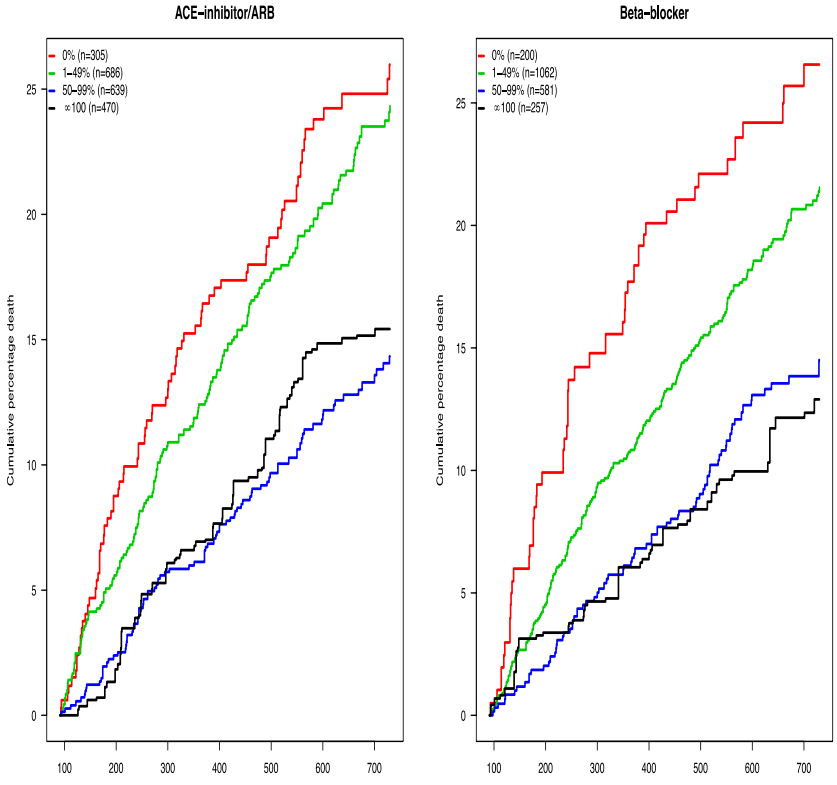


Figure 2: Adjusted mortality rate for patients receiving 0%, 1-49%, 50-00% or ≥100% of the recommended ACE-inhibitor/ARBs or beta-blocker dose, together with the risk set sizes at each time point.



	100	200	300	400	500	600	700
Red	303	276	261	245	214	161	128
Green	683	645	601	579	500	420	302
Blue	636	622	594	581	492	407	313
Black	470	461	442	431	377	307	230

	100	200	300	400	500	600	700
Red	199	180	168	157	135	111	90
Green	1057	1009	946	913	778	641	478
Blue	580	569	546	533	467	374	272
Black	256	246	238	233	203	169	133

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.

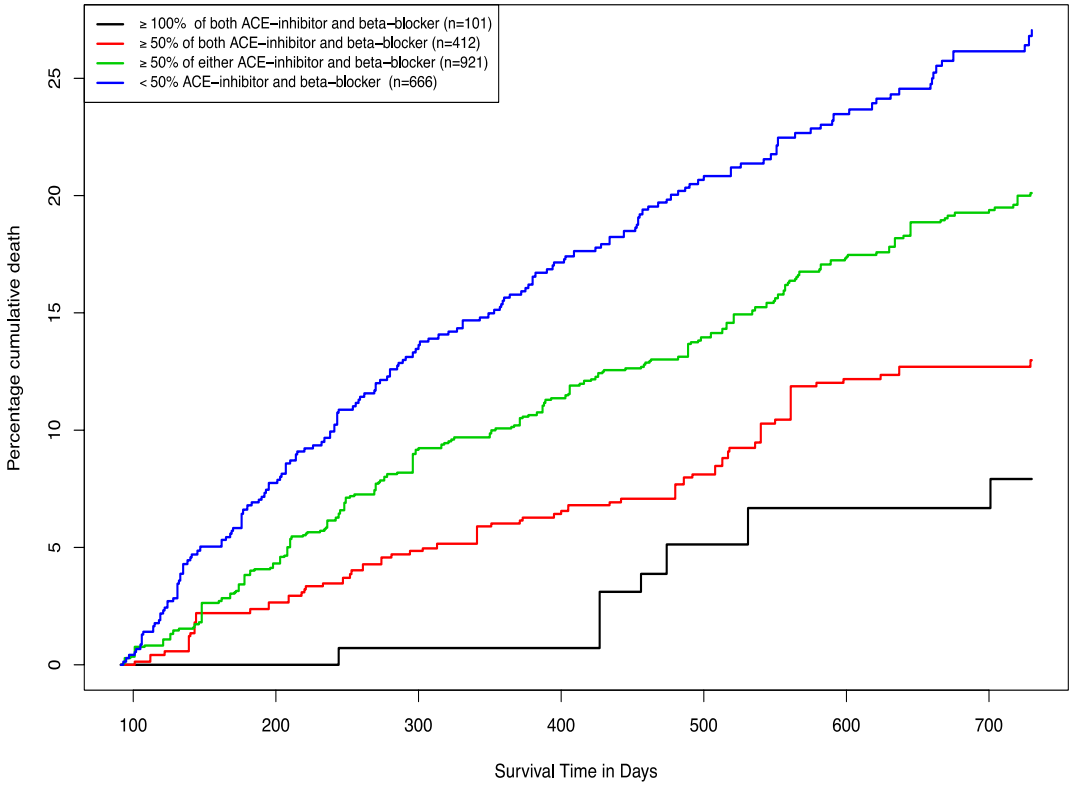
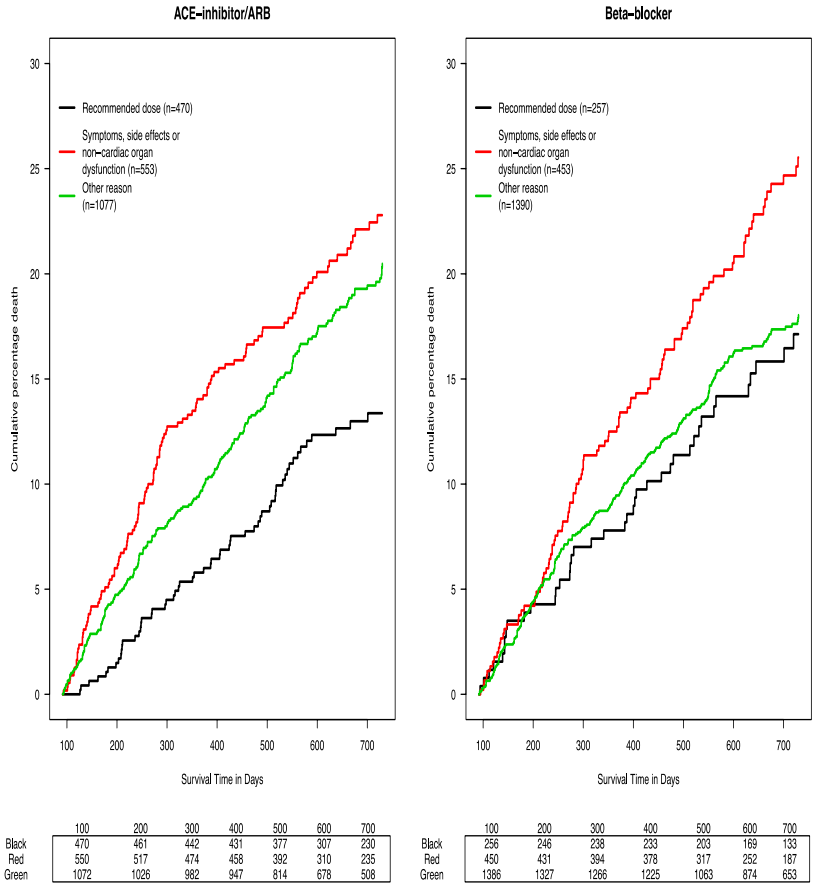


Figure 4: Adjusted mortality rate for patients a) receiving recommended dose; b) reached less than recommended dose due to symptoms, side effects or non-cardiac organ failure and c) reached less than recommended dose for other reasons, together with the risk set sizes at each time point.



	100	200	300	400	500	600	700
Black	470	461	442	431	377	307	230
Red	550	517	474	458	392	310	235
Green	1072	1026	982	947	814	678	508

	100	200	300	400	500	600	700
Black	256	246	238	233	203	169	133
Red	450	431	394	378	317	252	187
Green	1386	1327	1266	1225	1063	874	653

Supplementary data

Table S1: Baseline patient characteristics. All were used in regression analyses. Given in either numbers (percentages), mean (sd), median (interquartile range)

Description of baseline patient characteristics	
n	2100
Sex (Male)	1589 (76%)
Age (years)	68 (12)
Country	
Netherlands	276 (13%)
Germany	84 (4%)
France	195 (9%)
Greece	278 (13%)
Italy	289 (14%)
Norway	93 (4%)
Poland	244 (12%)
Serbia	366 (17%)
Slovenia	22 (1%)
Sweden	96 (5%)
United Kingdom	157 (8%)
Smoking	
no	772 (37%)
past	1026 (49%)
current	302 (14%)
Alcohol usage	595 (28%)
Body Mass Index (kg/m^2)	28 (5.52)
Heart Rate (bpm)	80 (19)
Systolic Blood Pressure (mmHg)	124 (21)
Diastolic Blood Pressure (mmHg)	76 (13)
Left ventricular ejection fraction (%)	29 (7.5)
NYHA Class	
I	54 (3%)
II	760 (37%)
III	1004 (49%)
IV	232 (11%)
Ischemic heart disease	1154 (55%)
Hospitalization in past year before baseline	669 (32%)
HF duration (years)	8 (3.6-13.3)
Atrial Fibrillation	901 (43%)
Diabetes	676 (32%)
eGFR (ml/min/1.73m^2)	66.7 (23.66)
Myocardial Infarction	822 (39%)
Coronary Artery Bypass Graft	344 (16%)
Coronary artery disease	957 (46%)
Percutaneous Coronary Intervention	473 (23%)
Stroke	187 (9%)
Peripheral Arterial Disease	214 (10%)
Chronic Obstructive Pulmonary Disease	344 (16%)

Pulmonary congestion	
Single base	260 (13%)
Bi-basilar	756 (37%)
Peripheral oedema	988 (47%)
Elevated Jugular venous pressure	442 (30%)
Hepatomegaly	291 (14%)
3*rd* Heart Tone	220 (11%)
Rales > 1/3 up lung fields	183 (18%)
Orthopnea present	678 (32%)
Baseline Medication	
Haematocrit (%)	40.5 (5.26)
Blood urea nitrogen (mmol/L)	10.8 (7.3-17.17)
N-terminal pro b-type natriuretic peptide e (pg/ml)	4138 (2249-8220)
Haemoglobin (g/L)	13.4 (1.85)
Sodium (mmol/L)	139.2 (3.83)
Potassium (mmol/L)	4.3 (0.55)
B-type natriuretic peptide (BNP) (pg/ml)	637 (291-1197)
Bilirubin (μmol/L)	14 (9.92-20.61)
Total-cholesterol (mmol/L)	4.3 (1.36)
HDL-cholesterol (mmol/L)	1.1 (0.39)
HEPC	6.5 (2.3-17)
Soluble Transferrin Receptor (mg/L)	1.5 (1.14-2.02)
Free Thyroxine (FT4) pmol/L)	15.8 (13.16-18.9)
HBA1C	6.3 (5.74-7.12)
ASAT (U/L)	25 (17-38)
ALAT (U/L)	25 (19-35)
TSH (mU/L)	1.8 (1.19-2.9)
Proteinuria (mg/dL)	5 (0-19.25)
Gamma-GT (U/L)	54 (28-103)
Alkaline Phophatase (ug/L)	84 (64.98-117)
TnI (pg/mL)	12.2 (6.56-25.87)
ET-1 (pg/mL)	5.2 (3.93-6.93)
bio-ADM (pg/mL)	31.8 (21.95-49.67)
Troponin (ug/L)	0.04 (0.01-0.1)

Table S2: Results of logistic regression for reaching recommended ACE-inhibitor/ARB or beta-blocker dose. These results are used for predicting the probabilities of receiving recommended treatment in the inverse probability weighting. Negative estimates represent a negative relation, so Norwegian patients have a higher probability of being uptitrated, while patients from Italy low compared to patient from the Netherlands.

	ACE-inhibitor/ARB			Beta-Blocker		
	Estimate	Std. Error	*p*-value	Estimate	Std. Error	*p*-value
Intercept	-6.38	0.48	<0.0001	-2.48	0.339	<0.0001
Country						
Netherlands	-	-	-	-	-	-
Germany	-0.32	0.345	0.36	-1.08	0.453	0.02
France	0.23	0.233	0.32	-0.13	0.241	0.58
Greece	-0.81	0.245	0.001	-2.02	0.371	<0.0001
Italy	-0.22	0.224	0.32	-0.51	0.236	0.03
Norway	1.19	0.269	<0.0001	0.27	0.279	0.33
Poland	-0.41	0.234	0.08	-1.06	0.284	<0.0001
Serbia	0.26	0.195	0.18	-1.58	0.293	<0.0001
Slovenia	0.33	0.497	0.5076	0.91	0.472	0.05
Sweden	1.25	0.265	<0.0001	0.9	0.265	<0.0001
United Kingdom	0.19	0.254	0.45	-1.86	0.443	<0.0001
Body mass index (kg/m^2)	0.06	0.01	<0.0001			
Systolic blood pressure (per 10 mmHg)	0.22	0.026	<0.0001			
eGFR (per 10 ml/min/1.73m^2)	0.1	0.024	<0.0001			
Heart rate (per 10 bpm)				0.13	0.033	<0.0001

Table S3: Patient characteristics of the included patients and excluded patients, those with LVEF>40%, died within 3 months of up-titration period, and who stopped with the study within three months up-titration period without an event

		Excluded patients			
	included patients	LVEF>40%	died	right censored	p-value
n	2100	242	151	23	
Sex (Male)	1589 (75.7%)	135 (55.8%)	105 (69.5%)	17 (73.9%)	<0.0001
Race (Caucasian)	2078 (99%)	240 (99.2%)	150 (99.3%)	21 (91.3%)	<0.0001
Age (years)	67.7 (11.95)	76 (9.12)	74.4 (10.77)	67.8 (10.29)	<0.0001
Ischemic aetiology	1154 (55%)	100 (41.3%)	90 (59.6%)	14 (60.9%)	0.0003
Previous Hospitalization in past year before baseline	669 (31.9%)	62 (25.6%)	53 (35.1%)	10 (43.5%)	0.09
HF duration (years)	8 (3.55-13.27)	8.9 (3.97-15.16)	11.1 (3.08-14.7)	0	0.83
Artrial Fibrilation	901 (42.9%)	151 (62.4%)	82 (54.3%)	9 (39.1%)	<0.0001
DM	676 (32.2%)	87 (36%)	49 (32.5%)	7 (30.4%)	0.69
Hypertension	1277 (60.8%)	182 (75.2%)	96 (63.6%)	14 (60.9%)	0.0002
Body mass index (kg/m^2)	28 (5.52)	28 (5.71)	26.4 (4.83)	26.7 (3.37)	0.004
Heart rate (beats/min)	79.8 (19.43)	80 (20.11)	82.5 (19.62)	77.7 (15.35)	0.3
Systolic blood pressure (mmHg)	124.2 (21.24)	132.7 (25.98)	119.3 (21.25)	122.3 (19.88)	0.83
Diastolic blood pressure (mmHg)	75.5 (13.05)	72.5 (16.02)	70.6 (11.65)	74.2 (14.92)	<0.0001
LVEF (%)	30 (25-35)	50 (45-57.5)	30 (21.5-38)	30 (27.5-35)	<0.0001
NT-proBNP (ng/L)	4138 (2249-8220)	3810 (2440-7391)	9326 (4139.5-16415.75)	5188.5 (2781.75-13837.5)	<0.0001
eGFR (ml/min/1.73m^2)	66.7 (23.66)	60.6 (22.95)	52.2 (23.78)	65.5 (19.89)	<0.0001
% ACE target dose	50 (25-75)	25 (0-50)	13 (0-44)	25 (13.6-50)	<0.0001
% BB target dose	25 (12.5-50)	38 (12.5-50)	12 (0-37.5)	25 (12.5-50)	<0.0001

Table S4: Results of linear regression for achieving lower percentages of recommended ACE-inhibitor/ARB or beta-blocker doses. Negative values represent higher percentage of recommended dose, while positive values are associated with achieving lower recommended doses.

	ACE-inhibitor/ARB			Beta-blocker		
	Estimate	Std. Error	*p*-value	Estimate	Std. Error	*p*-value
Intercept	92.46	4.692	<0.0001	71.46	6.199	<0.0001
Age (per 10 years)				1.7	0.532	0.001
Gender (female)	4.39	1.708	0.01			
Country						
Netherlands	-	-	-	-	-	-
Germany	2.12	4.075	0.60	0.29	3.582	0.9347
France	-0.38	3.05	0.90	2.17	2.652	0.4127
Greece	10.58	2.782	<0.0001	22.41	2.43	<0.0001
Italy	15.88	2.754	<0.0001	6.85	2.416	0.005
Norway	-13.58	3.908	<0.0001	-2.96	3.383	0.38
Poland	11.26	2.879	<0.0001	12.39	2.521	<0.0001
Serbia	-4.66	2.609	0.07	16.19	2.328	<0.0001
Slovenia	-2.54	7.215	0.73	-11.7	6.265	0.06
Sweden	-18.69	3.858	<0.0001	-13.18	3.381	<0.0001
United Kingdom	3.17	3.269	0.33	17.41	2.836	<0.0001
Diastolic blood pressure (per 10 mmHg)				-2.63	0.498	<0.0001
Body mass index (kg/m^2)	-0.95	0.13	<0.0001			
Heart rate (per 10 bmp)				-1.62	0.344	<0.0001
Alkaline Phosphatase (per 10 μg/L)	0.26	0.119	0.07			
eGFR (per 10 ml/min/1.73m^2)	-2.79	0.309	<0.0001			
Pulmonary congestion						
No				-	-	-
Single base				4.21	1.953	0.03
Bi-basilar				5.31	1.383	<0.0001

Table S5: CRF page of ACE-inhibitor/ARB and Beta-blocker to fill in uptitration result

ACE-inhibitor/ARB

Drug name*	Total daily dose (mg)	Start date (dd/mm/yyyy)	End date (dd/mm/yyyy)	Ongoing at 9 month visit	Reason #	Specify reason

Beta-blocker

Drug name*	Total daily dose (mg)	Start date (dd/mm/yyyy)	End date (dd/mm/yyyy)	Ongoing at 9 month visit	Reason #	Specify reason

*also include drugs stopped within 3 months before inclusion

reasons #

1=Non optimal dose acc. to ESC guidelines;

2=Symptoms;

3=Side effects ;

4=Non-cardiac organ dysfunction;

99=Other, specify

Table S6: Patient characteristics, with n (percentage), mean (sd) or median (interquartile range), at baseline for all patients and 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 for ACE-inhibitor/ARBs and beta-blockers

		ACE-inhibitor/ARB				Beta-blocker			
	All patients	recommended dose	symptoms, side effects or non-cardiac organ dysfunction	other/unknown/not specified reasons	p-value	recommended dose	symptoms, side effects or non-cardiac organ dysfunction	other/unknown/not specified reasons	p-value
n	2100	470	553	1077		257	453	1390	
Sex (Male)	1589 (76%)	361 (77%)	408 (74%)	820 (76%)	0.46	186 (72%)	333 (74%)	1070 (77%)	0.14
Race (Caucasian)	2078 (99%)	463 (99%)	550 (100%)	1065 (99%)	0.27	254 (99%)	451 (100%)	1373 (99%)	0.69
Age (years)	68 (12)	67 (12)	68 (12)	68 (12)	0.08	67.2 (13)	68.6 (12)	67.5 (12)	0.17
Ischemic aetiology	1154 (55%)	244 (52%)	309 (56%)	601 (56%)	0.32	129 (50%)	254 (56%)	771 (56%)	0.26
Previous Hospitalization in past year before baseline	669 (32%)	125 (27%)	180 (33%)	364 (34%)	0.02	92 (36%)	147 (33%)	430 (31%)	0.29
HF duration (years)	8 (3.6-13.3)	9.6 (2.6-16.3)	8 (2.3-14.5)	7.6 (2.3-16.1)	0.01	8.7 (2.6-16.3)	9 (2.4-16.7)	7.7 (2.3-15.2)	0.13
Artrial Fibrilation	901 (43%)	190 (40%)	245 (44%)	466 (43%)	0.43	129 (50%)	207 (46%)	565 (41%)	0.01
Diabetes mellitus	676 (32%)	175 (37%)	169 (31%)	332 (31%)	0.03	83 (32%)	148 (33%)	445 (32%)	0.97
Hypertension	1277 (61%)	335 (71%)	311 (56%)	631 (59%)	<0.0001	159 (62%)	267 (59%)	851 (61%)	0.64
Body mass index (kg/m^2)	28 (5.52)	29.4 (6.21)	27.7 (5.17)	27.5 (5.28)	<0.0001	27.9 (5.64)	28.1 (5.51)	28 (5.5)	0.90
Heart rate (beats/min)	80 (19)	80 (21)	80 (20)	80 (19)	0.88	86 (23)	78 (19)	79 (19)	<0.0001
Systolic blood pressure (mmHg)	124 (21)	133 (22)	121 (21)	122 (20)	<0.0001	126 (20)	123 (20)	124 (22)	0.26
Diastolic blood pressure (mmHg)	76 (13)	80 (14)	74 (13)	74 (12)	<0.0001	78 (13)	74 (13)	76 (13)	0.003
LVEF (%)	30 (25-35)	30 (25-35)	30 (24-35)	29 (25-35)	0.0004	30 (25-35)	30 (25-35)	30 (25-35)	0.11
NT-proBNP (ng/L)	4138 (2249-8220)	3110 (1611-5796)	4500 (2495-8831)	3620 (2033-7506)	<0.0001	3582 (2037-6754)	3968 (2364-7637)	3545 (2009-7384)	0.04
eGFR (ml/min/1.73m^2)	66.7 (23.66)	70.9 (22.46)	64.2 (23.28)	66.1 (24.12)	<0.0001	69.1 (25.28)	65.9 (22.67)	66.5 (23.64)	0.19
% ACE target dose	50 (25-75)	100	25 (12.5-50)	25 (13-50)	<0.0001	50 (25-100)	50 (16.7-62.5)	50 (25-62.5)	<0.0001
% BB target dose	25 (12.5-50)	50 (25-75)	25 (12.5-50)	25 (12.5-50)	<0.0001	100	25 (12.5-50)	25 (12.5-50)	<0.0001

eGFR: estimated glomerular filtration rate; LVEF: Left ventricular ejection fraction; NT-proBNP: N-terminal pro B-type natriuretic peptide

Figure S1: Flow-chart of the steps taken in model development phase and in the subsequent development of the Cox-models.

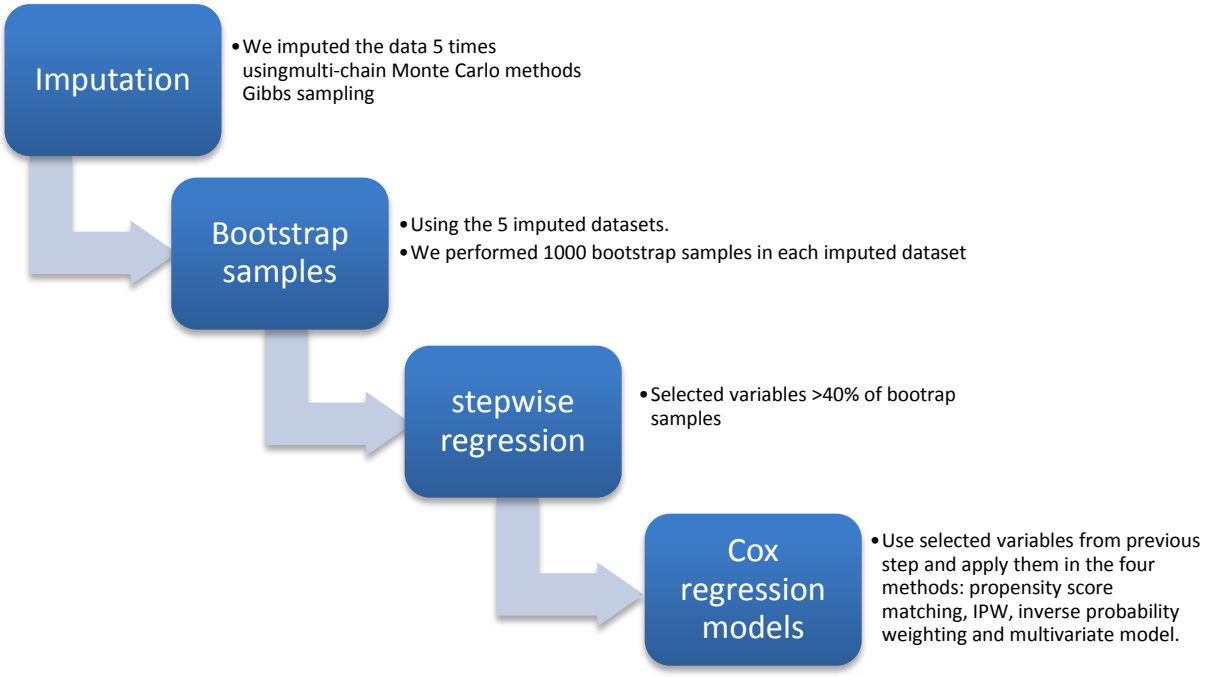
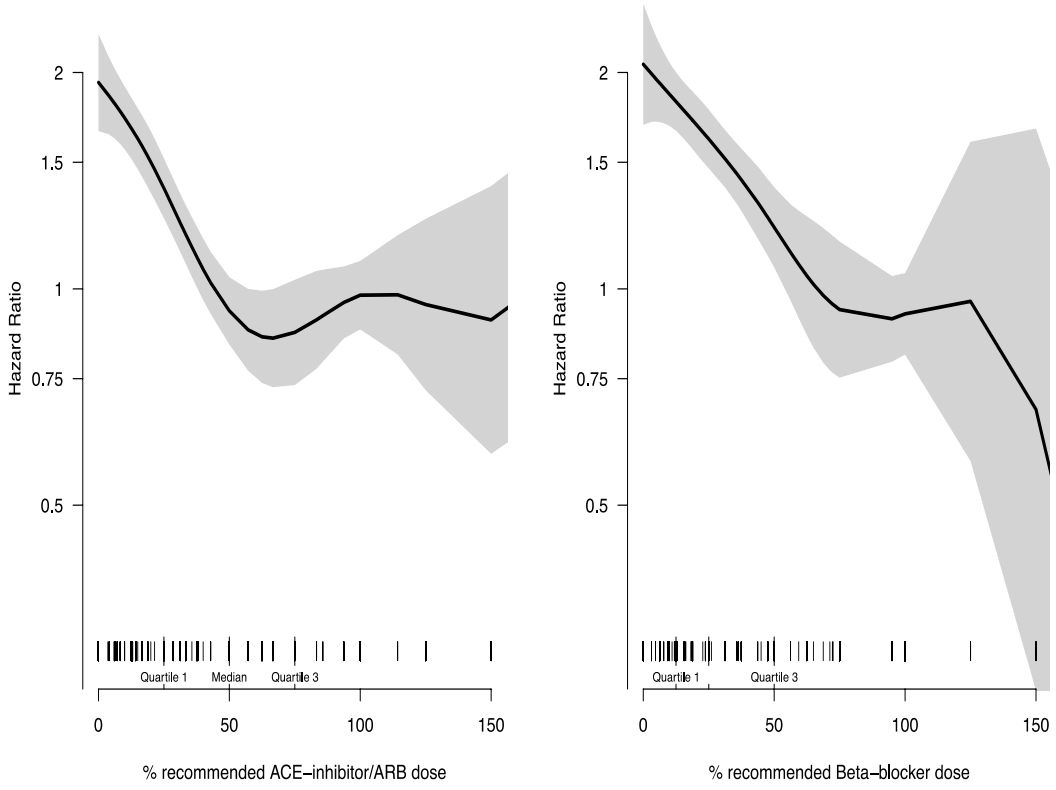


Figure S2: Hazard ratio curve for achieved ACE-inhibitor/ARB and beta-blocker doses. These hazard curves are comparing achieved doses to achieving recommended doses using a pspline function.



Word count: 3795 words

Permissions information

The authors do hereby declare that all illustrations and figures in the manuscript are entirely original and do not require reprint permission

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

BIOSTAT-CHF was specifically designed to study uptitration of ACE-inhibitors/ARBs and/or beta-blockers in 2516 heart failure patients from 69 centers 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.

Results

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%.