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Identifying optimal doses of heart failure medications in men compared with women: a prospective, observational cohort study

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Abstract

Background: Guideline-recommended doses of angiotensin-converting-enzyme (ACE) inhibitors/angiotensin-receptor blockers (ARBs) and beta-blockers are similar for men and women with heart failure with reduced ejection fraction (HFrEF), even though there are known sex differences in pharmacokinetics of these drugs. We hypothesized that there may be sex differences in the optimal dose of ACE-inhibitors/ARBs and beta-blockers in patients with HFrEF.

Methods: We performed a *post-hoc*-analysis of BIOSTAT-CHF, a prospective study of HF patients in whom initiation and up-titration of ACE-inhibitors/ARBs and beta-blockers was encouraged by protocol. Findings were validated in an independent cohort (ASIAN-HF) of 3,539 men and 961 women with HFrEF.

Findings: Among 1,308 men and 402 women with HFrEF from BIOSTAT-CHF, women were older (74 vs. 70 years, p<0·001), and had lower body weight (72 vs. 85 kg, p<0·001) and height (162 vs. 174 cm, p<0·001) than men, although body mass index did not differ significantly. A similar % of men and women reached guideline-recommended target doses of ACE-inhibitors/ARBs (25 vs. 23%; p=0·61) and beta-blockers (14 vs. 13%; p=0·54). In men, the lowest hazards of death and/or HF-hospitalization occurred at 100% of the recommended dose of ACE-inhibitors/ARBs and beta-blockers, but women showed a ~30% lower risk at only 50% of the recommended doses, with no further decrease in risk at higher dose levels. These sex differences were still present after adjusting for clinical covariates including age and body surface area. In the ASIAN-HF registry, similar patterns were observed for both ACE-inhibitors/ARBs and beta-blockers, with women having a ~30% lower risk at 50% of the recommended doses, with no further benefit at higher dose levels.

Interpretation: This study suggests that women with HFrEF may need lower doses of ACE-inhibitors/ARBs and beta-blockers as compared with men, and brings into question what true 'optimal medical therapy' is for women versus men.

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Keywords: Heart failure – Sex differences – Women – Uptitration – ACE-inhibitor – Beta-blocker

Research in context

Evidence before this study

We searched PubMed from Jan 1, 1980, to Jan 31, 2019. with the search terms “heart failure”, “sex differences”, “gender differences”, “women”, “men”, “outcome”, “mortality”, “hospitalization”, “drugs”, “medication”, “dose”, “angiotensin-converting enzyme inhibitors”, “angiotensin-receptor blockers”, and “beta-blockers”. There were no studies that directly compared the optimal dose levels of current evidence-based drugs on a continuous scale, in relation to clinical outcome of men and women with heart failure with reduced ejection fraction separately.

Added value of this study

To our knowledge, this is the first study to show that there are striking sex differences in the optimal dose levels of angiotensin-converting-enzyme inhibitors/angiotensin-receptor blockers and beta-blockers in patients with heart failure with reduced ejection fraction, where women had the lowest risk of death and/or heart failure hospitalization at half the guideline-recommended doses as compared with men.

Implications of all available evidence

Due to the under-representation of women with heart failure with reduced ejection fraction in all previous clinical drug trials, and in the absence of prospective sex-specific dose-finding clinical trials of current therapies, this is the best available evidence with regards to the optimal dose levels of heart failure medication in men and women separately. These findings should also prompt similar studies in other cardiovascular disease areas.

Introduction

Angiotensin-converting-enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBs) and beta-blockers are the cornerstone of therapy for patients with heart failure with reduced ejection fraction (HFrEF).[1] Current HF guidelines recommend up-titration of ACE-inhibitors/ARBs and beta-blockers to the same target doses in men and women *(Table 1).* These sex-neutral target doses were recommended despite findings from several pharmacological studies indicating that with the same dose, the maximum plasma concentrations of ACE-inhibitors, ARBs and beta-blockers were up to 2·5 times higher in women as compared to men.[2–4] Women generally have lower body weights, a higher proportion of body fat, and a lower plasma volume. This may contribute to a longer duration of action of lipophilic drugs, and higher peak plasma concentrations of hydrophilic drugs in women.[4,5] Moreover, lower cardiac output in women results in lower hepatic flow and lower glomerular filtration rate, and women have lower expression of some drug-specific CYP-isoenzymes, which could also contribute to higher plasma levels of both hydrophilic and lipophilic drugs in women.[6,7] Supporting these considerations, studies with beta-blockers showed different pharmacodynamic effects with a greater reduction in heart rate and blood pressure in women compared to men using similar doses.[8,9] In addition, women have a 50-70% greater risk in experiencing adverse drug reactions compared to men, and these adverse events are generally more serious in women.[4,5,9]

We tested this hypothesis in the prospective multinational European chronic HF cohort of the BIOlogy Study to TAilored Treatment in Chronic Heart Failure (BIOSTAT-CHF), and validated our findings in the independent multinational chronic HF cohort of Asian Sudden Cardiac Death in Heart Failure (ASIAN-HF).

Methods

Patient population and study design

The design and primary results of BIOSTAT-CHF have been previously published.[10,11] Briefly, BIOSTAT-CHF was a multinational, prospective, observational study to evaluate which patients will have a poor clinical outcome despite evidence-based heart failure treatment, in which we have performed a post-hoc analysis. A total of 2,516 patients were included who were on suboptimal HF therapy (not receiving, or receiving ≤50% of target dose of ACE-inhibitors/ARBs and/or beta-blockers) between 2010-2012. Treating physicians were encouraged to initiate and/or up-titrate these drugs during the first three months after inclusion; the optimization phase. Target doses of the individual drugs are summarized in *Supplementary Table 1*.[1] The subsequent six months were considered as the maintenance phase. At nine months, a second study visit was performed in which the use of heart failure medication doses at three and nine months was recorded again. The fraction of the target dose that was achieved after the up-titration period at three months was presented as a percentage ranging from 0 to ≥100%, and further categorized into four groups: 0, 1-49, 50-99% or ≥100% of recommended target dose. We attempted to record the treating physicians' reason for not up-titrating patients to target doses (*Supplementary Material*). Since the European Society of Cardiology guidelines of 2008 only recommended the use of MRA in patients who have been in New York Heart Association (NYHA) class IV in the past 6 months (level of evidence B), no specific MRA up-titration strategy was used in BIOSTAT-CHF. In our analyses, only patients with a left ventricular ejection fraction (LVEF) <40% were included, in accordance with current guideline-recommended therapies (n=1,819).[1] Patients who died within the first three months (the up-titration phase) were excluded (n=109). A flow diagram is displayed in *Supplementary Figure 1.* Baseline characteristics of the patients that were included and excluded for our study is presented in *Supplementary Table 2.* Renal disease was defined as an estimated glomerular filtration rate below 60 mL/min/1·73m^2. Primary outcome was a composite of time to all-cause mortality or HF hospitalization. After the second study visit at nine months, patients were followed either by standard clinic follow-up, or telephone contact every six months until the end of study. The protocol of BIOSTAT-CHF used clear

endpoint definitions, a structured case report form, and source data of all sites were closely monitored. The median follow-up duration for the primary endpoint was 21 months (first and third quartile [Q1-Q3] of 15-27 months).

The results of this study were validated in ASIAN-HF, a prospective observational study of 5,276 patients with symptomatic HF and LVEF≤40% from 11 Asian regions, in which maximally tolerated doses of HF medications were closely recorded and patients were followed up for outcomes (independently adjudicated).[12] Target doses of beta-blockers and ACE-inhibitors/ARBs were defined using the same international standards as for BIOSTAT-CHF. Patients with missing outcome date (n=582) or incomplete data about the dose level of HF medication (n=194) were excluded. Baseline characteristics of patients that were included and excluded from ASIAN-HF for our study is presented in *Supplementary Table 3.*

Both BIOSTAT-CHF and ASIAN-HF comply with the Declaration of Helsinki, and medical ethics committee of participating centers approved the study. All patients provided written informed consent.

Statistical analyses

Normally distributed continuous variables were reported as means ± standard deviation and non-normally distributed variables as median (Q1-Q3). Categorical variables were presented as numbers with percentages. Student's t-tests, Chi-square tests and Mann-Whitney U tests were used for group comparisons. Cox proportional hazard models were used to calculate hazard ratios (HR), adjusted for the effect of potential confounders, with patients using ≥100% of the recommended dose as the reference category. The multivariable risk model of BIOSTAT-CHF for the composite endpoint (death and/or HF hospitalization) was used, which contains age, previous HF hospitalization, systolic blood pressure, presence of peripheral edema, N-terminal pro-brain natriuretic peptide (NT-proBNP), hemoglobin, sodium, high-density lipoprotein, and the use of beta-blockers at baseline.[13] In a separate multivariable model, outcome was adjusted for body surface area (BSA) using the formula of Du Bois & Du Bois.[14] Since the range of 1-49% and 50-99% of recommended dose in the Cox regression models is quite broad, but chosen to keep a sufficient number of patients within all four dose categories, a density plot of the patients using specific dose levels in BIOSTAT-CHF (in blue) and

ASIAN-HF (in red) is displayed as *Supplementary Figure 2*, showing that the large majority of patients in the 50-99% dose category actually uses 50% of recommended dose.

Because BIOSTAT-CHF and ASIAN-HF are not randomized controlled trials, we adjusted for treatment indication bias.[15] All analyses of the effect of up-titration on mortality and/or HF hospitalization risk were inversely weighted with the probability of the given treatment.[16] The given treatment is defined as successful up-titration to ≥50% of European Society of Cardiology–recommended doses for ACE-inhibitor/ARBs or beta-blockers or not.[11] The probability of given treatment for a specific patient was modelled using a penalized (LASSO) logistic regression model.[17] All available covariates were considered as predictor variables for successful up-titration. We averaged the probabilities over five imputation sets. The weights were calculated by the inverse of the probability for those who were successfully treated, or the (1-probability)ˆ-1 for those who were not.

In order to compare the non-linear risk of the composite endpoint between men and women along the continuum of fractions of target doses, smoothing natural cubic splines were used. We modelled the composite endpoint in men and women using Cox proportional hazard models with dosages on a continuous scale using natural regression splines added to the sex effects and their interaction. The optimal degrees of freedom were determined based on the Bayesian information criterion defined as: BIC=−2 * log(Likelihood) + number of parameters * log(n), which put a penalty on the number of parameters.[18] The lines in *Figure 1 and 2* are based on the Cox regression models in men and women on that specific dose level, compared to the hazard of the total population (men and women combined) on the median dose.

Further exploratory analysis was performed using subpopulation treatment effect pattern plots (STEPP). STEPP is a robust method for exploring differences in treatment effect between two subgroups (in this study men versus women), and was performed to validate the findings from the cubic splines. STEPP divides the group of men and women into smaller subgroups who use different % of target dose (on the x-axis), and compares every subgroup with overlap of around 100 patients to the next subgroup, until every patient has been included in at least one of the subgroups.[19,20] This approach with overlapping subgroups increases the precision of the estimated treatment effect. The figures display both the individual treatment effect in men and women, combined with a plot below,

showing the ratio of the Relative Risk of women divided by the Relative Risk in men, resulting in a Hazard Ratio for women compared with men, including confidence intervals of this ratio. A two-tailed p-value of <0·05 was considered statistically significant. Statistical analyses were conducted using R, A Language and Environment for Statistical Computing, version 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria).

Role of the funding source

This study was supported by a grant from the European Committee. However, they had no role in the study design; in the collection, analysis, and interpretation of data; in writing of the report; and in the decision to submit the paper for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Clinical characteristics

A total of 1,710 patients from BIOSTAT-CHF were studied, of whom 402 (24%) were women. Baseline characteristics of men and women are presented in *Table 2*. At baseline, women were older (74 versus 70 years, p<0·001), had lower body weight (72 versus 85 kg, p<0·001) and height (162 versus 174 cm, p<0·001), although BMI did not differ significantly (27·3 versus 27·9, p=0·06). Women less often had a history of smoking (28% versus 65%, p<0·001) and less coronary artery disease (35% versus 48%, p<0·001), atrial fibrillation (35% versus 44%, p=0·002), and renal disease (19% versus 25%, p=0·02) as compared with men. Women reported lower quality of life than men (median overall score of 44 versus 54 in men, p<0·001), despite similar levels of NT-proBNP (2,724 versus 2,484 pg/mL in men, p=0·18). The use of MRA was higher in men than in women, both at baseline (59% versus 48% in women, p<0·001), and at follow-up (55% versus 47% in women, p=0·006).

Up-titration of medication

At baseline, there were no significant differences in the use of ACE-inhibitors/ARBs between the sexes, with similarly small proportions already at target doses at baseline *(Table 2)*. Beta-blockers were more frequently used at baseline than ACE-inhibitors/ARBs, and more often in men than in

women, with similarly small proportions already at target dose at baseline. The proportion of men and women who reached the recommended target dose after the first three months of the study was also similar. At the follow-up visit at 9 months, blood pressure and heart rate were similar between men and women *(Supplementary Table 4).* An overview of the most frequently prescribed individual HF drugs in men and women is presented in *Supplementary Table 5*.

With regards to men, the univariable Cox regression model showed the highest risk of death and/or HF hospitalization when they did not receive any dose of ACE-inhibitor/ARBs or beta-blockers, a lower risk when they reached 1-49% or 50-99% of target dose, and lowest risk when they reached ≥100% of target dose (reference category) *(Table 3).* In multivariable analysis, men did not have a survival benefit when they used lower doses as compared to those on target dose. With regards to women, those treated with 50-99% of the recommended target dose had the lowest risk of death and/or HF hospitalization, even compared to those at 100% of the target dose for both ACE-inhibitor/ARBs and beta-blockers, also after multivariable adjustment *(Table 3)*.

Cubic splines and STEPP analyses

Figure 1 shows sex-stratified splines according to dose of beta-blockers and ACE-inhibitors/ARBs, ranging from 1-100%, using the population mean as the reference. For beta-blockers, there was a U-shaped risk curve among women, with an optimal dose level for women around 60% of recommended target dose *(Figure 1A)*. For men using beta-blockers, a lower risk was observed around both 30% and 100% of target dose. For ACE-inhibitors/ARBs, women had the lowest risk of the composite endpoint at around 40% of recommended target dose and no further decrease in risk at higher dose levels, whereas men had the lowest risk at 100% of recommended target dose ($p<0{\cdot}001$, *Figure 1B).*

The STEPP analysis with the fraction of target dose per drug on a continuous scale revealed similar results compared to the Cox regression models and the splines, with men having a lower risk with increasing dose levels of ACE-inhibitors/ARBs and beta-blockers, whereas women had the lowest risk of death and/or HF hospitalization when they used 50% of target dose of ACE-inhibitors/ARBs and *(Supplementary Figure 3).* Both sexes had the highest risk of the composite endpoint when they used no ACE-inhibitors/ARBs or beta-blockers at all.

Validation analysis

Of the 4,500 patients studied from ASIAN-HF, 961 (21%) were women. Both men and women in the validation cohort were younger, and had lower body weight and height compared to the European cohort *(Supplementary Table 6).* The cubic spline for Asian women using doses of beta-blockers showed a steep decline in risk of the composite endpoint around 40-50% of recommended dose, with no further decrease in risk at higher dose levels, whereas the risk in Asian men was lowest when using 100% of recommended target dose of beta-blockers (p<0·001, *Figure 2A*). The spline of Asian women using doses of ACE-inhibitors/ARBs showed a decrease in risk for the composite endpoint around 60% of recommended target dose, and no further protective effect at doses higher than 60% *(Figure 2B).* Asian men did only seem to benefit from ACE-inhibitors/ARBS when using more than 50% of the recommended dose, and on the whole scale of dose levels, men had a significantly higher risk of the composite endpoint as compared with women (P<0·001).

Discussion

Drug therapies are of great importance to patients with HFrEF, and uptitration of these drugs to maximal doses is recommended in current HF guidelines *(Table 1).* The main finding of the present study suggests, however, that these doses may not be appropriate in women. Our multinational observational study showed sex differences in the optimal dose of ACE-inhibitors/ARBs and beta-blockers in patients with HFrEF, where women had the lowest risk of adverse outcomes at lower doses (half the guideline-recommended doses) as compared to men, with no further decrease in risk at higher dose levels.

These findings were found in BIOSTAT-CHF, in which patients were included from 11 European countries, and were validated in an independent HF cohort in which patients were included from 11 Asian regions (ASIAN-HF). These two HF populations did not only differ in ethnic background, but also differed importantly in other baseline characteristics, with patients from ASIAN-HF being younger, and having a much lower body weight, height and BMI as compared to the European cohort. Moreover, known differences in metabolism between Asian and European patients, such as ethnic differences in the incidence of cytochrome P450 polymorphisms, could have resulted in different

findings in the optimal dose levels of patients included in ASIAN-HF as compared to those in the European cohort.[21] Despite differences in baseline characteristics and ethnicity, similar patterns in optimal dose levels for men and women were observed in ASIAN-HF and BIOSTAT-CHF; thus strengthening our hypothesis that there are intrinsic sex differences observed in different regions worldwide.

Important sex differences in relation to the use of heart failure medication has been previously shown by the Digitalis Investigation Group (DIG) trial. This randomized, placebo-controlled trial was first published in 1997, showing less overall- and HF-related hospitalizations in patients using digoxin (versus placebo) in patients with stable HF and LVEF<45%.[22] Therefore, the use of digoxin was recommended in both the United States and the European guidelines. However, a post-hoc subgroup analysis showed a significantly higher absolute risk of death in women, and a non-significant reduction in the risk of death among men (p=0·014 for interaction).[23] Even though men used slightly higher doses of digoxin in this trial (0·0093 mg per unit of body-mass index versus 0·0084 mg in women), higher serum digoxin levels were found in women one month after study entry (0·9 ng/mL versus 0·8 ng/mL, p=0·007). Unfortunately, there was insufficient statistical power to test for an interaction between sex, the use of digoxin, and sex differences in serum digoxin levels, since serum levels of digoxin were only measured in a small subpopulation (less than one third) of the trial participants.[23] There might still be favorable effects of lower doses of digoxin (and accompanying lower serum digoxin levels) in patients with HFrEF using currently recommended therapies, which will be further investigated in a randomized clinical trial.[24]

The randomized trial HEAAL, in which high versus low-doses of losartan in HF were compared, concluded that patients treated with the high dose level had the best clinical outcome.[25] However, a sex-stratified subgroup analysis comparing high versus low dose showed a HR of 0·86 (0·77-0·96) for men in favor of the higher dose of losartan, and no significant difference between the two dose levels in women (HR 1·02, 95% CI 0·85-1·23), with a p-value for interaction of 0·10, even though this study was not powered for subgroup analyses. Moreover, results from ATLAS comparing high and low dose of lisinopril observed that men had significantly lower all-cause mortality using the higher dose levels

(32·5 to 35 mg daily), whereas in women a trend towards better survival in the lower dose (2·5 to 5·0 mg daily) was observed (p-value for interaction was not provided).[26]

As described previously, there are several well-established pharmacokinetic sex differences that could contribute to differences in optimal doses of HF medications for men and women. In our study, women were older, and had a significantly lower body weight and height than men. A study in healthy men and women observed that after administration of one dose of 100mg metoprolol, the area under the concentration-time curve (AUC) was 417 mcg·h/L in men and 867 mcg·h/L in women. The large difference in body weight (83·9 ± 10·7 kg in men and 62·0 ± 7·3 kg in women) and clearance rate between men (253 L/h) and women (101 L/h) seemed to be important contributors to these observed differences in AUC. Based on these findings, a dose reduction for metoprolol of 50% in women was recommended by the authors, which is strikingly similar to the findings in the present study, even after adjustment for BSA.[2]

Another hypothesis is that women are more sensitive, i.e. have a greater clinical response to drugs than men, even if plasma concentrations were similar between the sexes.[4] The effect of sex hormones on specific drugs, but also how drugs effects are being experienced by men and women are still poorly understood, and could potentially contribute to higher reporting rates of adverse events in women.[27]

Sex differences with regards to other HF therapies are previously observed in different responses to cardiac resynchronization therapy (CRT) between men and women, in which women had a better response to CRT than men.[28] However, to our knowledge, no such analyses are available with respect to medical treatment in HF.

It should be noted that previous results from the CHAMP-HF registry showed that women with HFrEF are often not treated with current guideline recommended therapies, in the absence of absolute contraindications to these therapies.[29] Moreover, the TRED-HF trial showed that discontinuation of HFrEF therapies, even in patients with recovered LVEF, have deleterious effects.[30] We therefore emphasize that the findings of the current study should not be misinterpreted as an excuse to undertreat women with HFrEF. Instead, we suggest that a one-size-fits-all approach may not be

optimal in the treatment of men and women with HFrEF, but that the dose levels of HF medication in women should perhaps not be as high as in men.

Limitations

The present study is limited by its post-hoc design. We could not assess dose-related side effects of drugs, despite attempting to record physicians' reasons for lack of up-titration. A greater frequency of adverse drug reactions in women compared to men could impact the maximum tolerated dose and warrants future study. We did not measure serum levels of HF medications, which could have provided more insight into the underlying mechanisms of the present findings. The sample size of women in BIOSTAT-CHF and ASIAN-HF was relatively low as compared to the number of men, which is very common in HFrEF studies. The number of patients reaching target doses of ACE-inhibitors/ARBs and beta-blockers is not comparable to the numbers of patients reaching target doses in randomized clinical trials, since our study reflects real-world up-titration instead of trial protocol targets. We have performed the analyses for ACE-inhibitors/ARBs and beta-blockers, and did not further differentiate between all individual drugs within these drug categories, even though the pharmacokinetic and pharmacodynamic characteristics of the individual drugs within these categories could differ. Even though we have adjusted for multiple potential confounders in our multivariable regression models, we cannot exclude the possibility that our findings could be influenced by other previously described sex differences in baseline characteristics, such as the higher use of MRA in men, or unknown confounding factors. The observation of the lower risk in men that used only ~30% of recommended beta-blocker dose, as was observed in the spline *(Figure 1)* and Cox regression models *(Table 3)*, is not fully understood and might be caused by overfitting of the model. This observation was neither found in the STEPP analysis, nor in the validation cohort of ASIAN-HF.

To our knowledge, this is the first study to describe sex-specific outcome in relation to the prescribed dose levels of HF medications. These findings may have important implications for sex-specific target doses in HF, and should be validated in dose-finding sex-stratified prospective studies. It is, however, unlikely that these sex-specific dose-finding trials of current HFrEF therapies will be performed. This

study also underlines the importance of performing pre-specified sex-specific analyses in all drug trials.

Conclusion

The present study provides evidence supporting the hypothesis that women with HFrEF may have the best outcomes with lower doses of ACE-inhibitors/ARBs and beta-blockers as compared with men, and lower doses than recommended in international HF guidelines. This study brings into question what true 'optimal medical therapy' is for women versus men with HFrEF.

Contributors:

HH, NJS, FZ, KD, CCL, JGC, JMTM, MM, SDA, PVDH, LLN, PVDM, DJVV, CSPL, and AAV were involved in the conception, design, and planning of the research, acquired the data, critically reviewed the manuscript. All others interpreted the results. AAV, CSPL and DJVV handled funding and supervision. AR, JT, VRZ, and SM critically reviewed the manuscript. BTS, WO, and IES performed statistical analyses, wrote and revised the manuscript. The manuscript was approved for submission and publication by all authors.

Declaration of interests:

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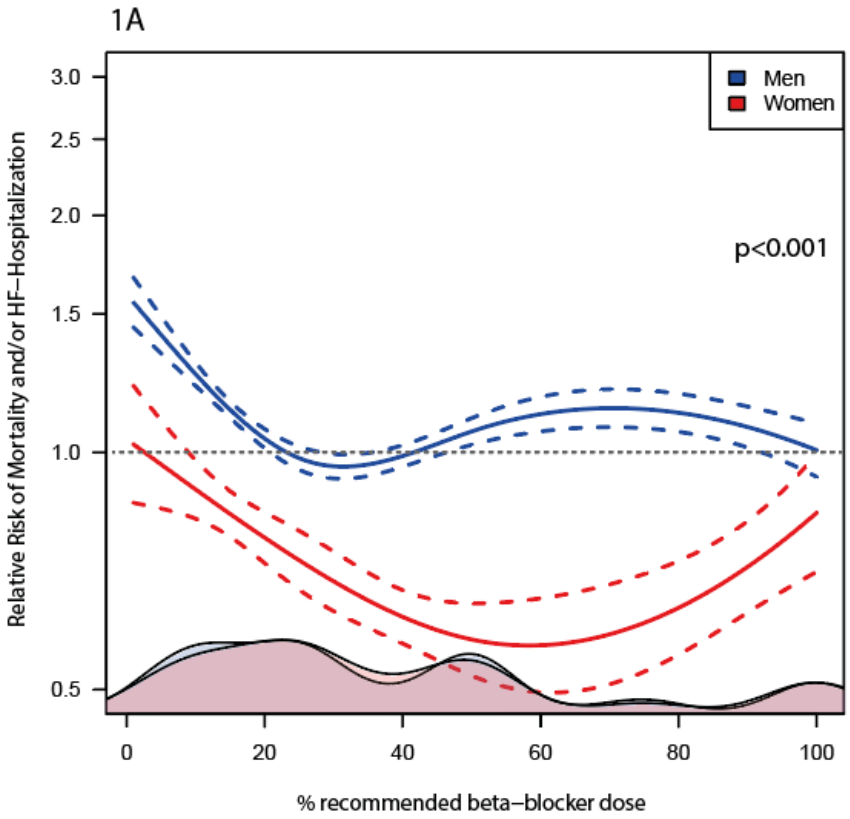
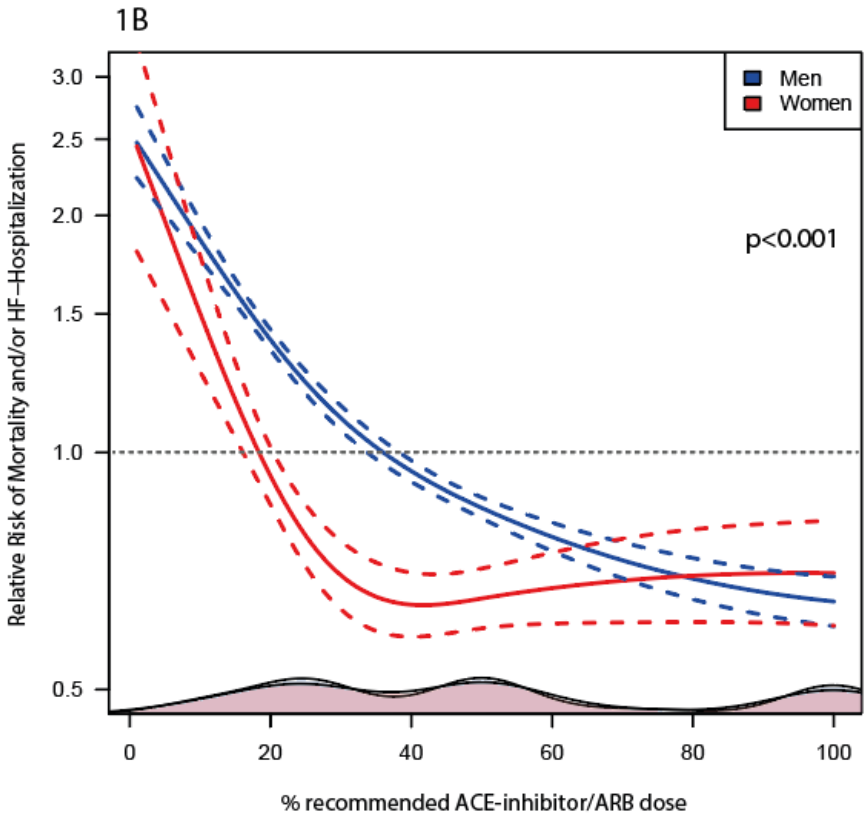
Figure Legend

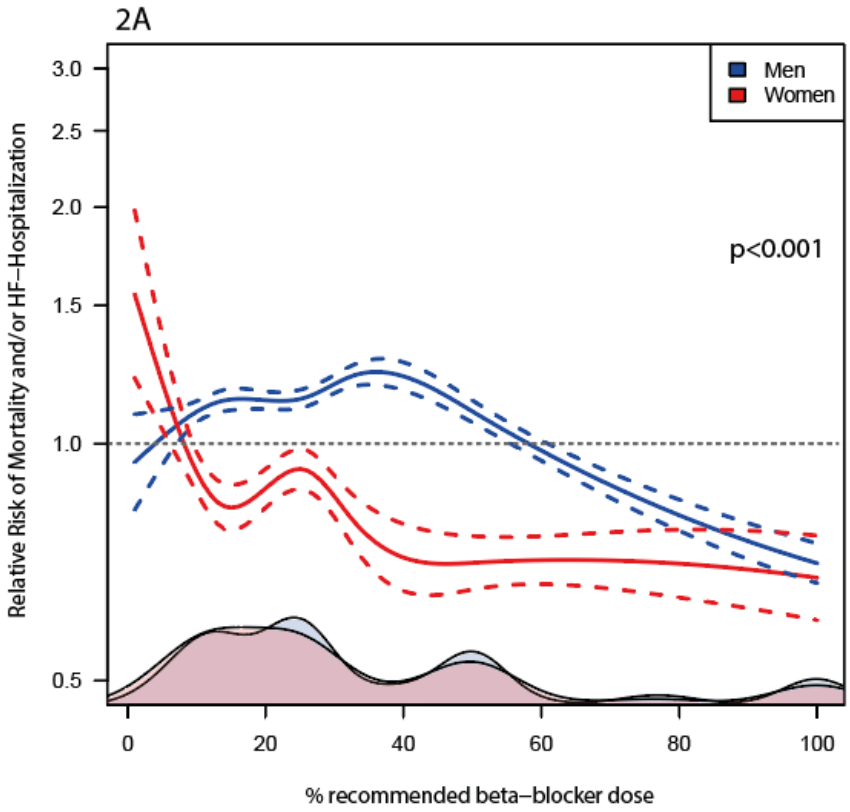
Figure 1. Natural cubic splines showing the optimal beta-blocker (1A) and ACE-inhibitor/ARB dose (1B) ranging from 1-100% of recommended target dose in men and women (BIOSTAT-CHF) for the composite endpoint all-cause mortality and/or HF hospitalization, compared to the hazard of the total population (men and women combined) on the median dose. Median follow-up duration was 21 months (IQR 15-27 months). The smoothened areas at the bottom of both figures represent the density of men (blue) and women (red) taking that specific dose level. The p-value represents the interaction of sex and treatment in the Cox regression model. ACE=angiotensin converting enzyme inhibitor, ARB=angiotensin receptor blocker, HF=heart failure.

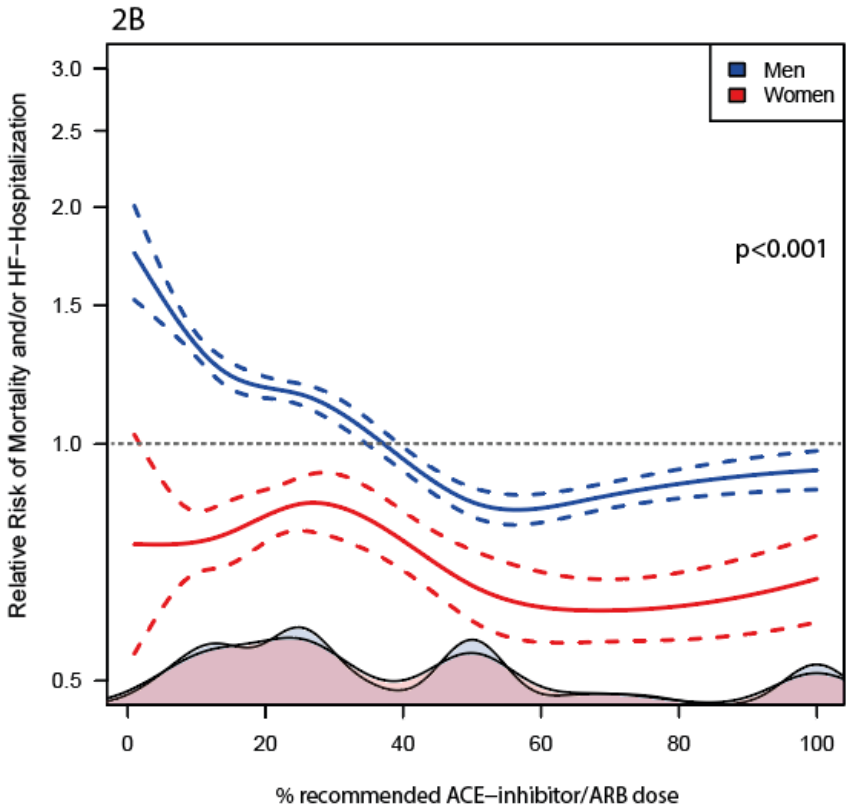
Figure 2. Validation of optimal beta-blocker (2A) and ACE-inhibitor/ARB dose (2B) ranging from 1-100% of recommended target dose in men and women in ASIAN-HF, for the composite endpoint all-cause mortality or HF hospitalization, compared to the hazard of the total population (men and women combined) on the median dose. Median follow-up duration was 14 months (IQR 7-25 months). The smoothened areas at the bottom of both figures represent the density of men (blue) and women (red) taking that specific dose level. The p-value represents the interaction of sex and treatment in the Cox regression model. ACE=angiotensin converting enzyme inhibitor, ARB=angiotensin receptor blocker, HF=heart failure.


1A
Men
Women
p<0.001
Relative Risk of Mortality and/or HF–Hospitalization
3.0
2.5
2.0
1.5
1.0
0.5
0
20
40
60
80
100
% recommended beta–blocker dose


1B
Men
Women
p<0.001
Relative Risk of Mortality and/or HF–Hospitalization
3.0
2.5
2.0
1.5
1.0
0.5
0
20
40
60
80
100
% recommended ACE-inhibitor/ARB dose

1


2A
Men
Women
p<0.001
Relative Risk of Mortality and/or HF−Hospitalization
3.0
2.5
2.0
1.5
1.0
0.5
0
20
40
60
80
100
% recommended beta−blocker dose


2B
Men
Women
p<0.001
Relative Risk of Mortality and/or HF−Hospitalization
3.0
2.5
2.0
1.5
1.0
0.5
0
20
40
60
80
100
% recommended ACE−inhibitor/ARB dose

2

3

4 **Table 1.** Overview of sex-specific details of drug trials on which the international heart failure guidelines are based.

Drug class	Study	Published (year)	Countries	Drug	Target dose	Actual mean dose used	Eligibility criteria	LVEF	Baseline characteristics	Background medication	% women	No. of women	Primary endpoint	Sex-specific outcome
ACE-i	CONSENSUS	1987	Finland, Norway, and Sweden	Enalapril	20mg b.i.d.	9mg b.i.d. 28% on target dose	NYHA IV only,	≤35%	Mean age 71 years, 73% ischaemic heart disease, 50% AF	98% diuretic 93% digoxin 3% b-blocker 55% vasodilator	30	74	Mortality	Significant benefit in men, not in women
	SOLVD-Treatment	1991	U.S.A., Canada, and Belgium	Enalapril	10mg b.i.d.	8·4mg b.i.d. 49% on target dose	<80 years, NYHA I-IV	≤35%	Mean age 61 years, mean LVEF 25%, 71% ischaemic heart disease	85% diuretic 67% digoxin 8% b-blocker 51% vasodilators	20	505	Mortality	Significant benefit in men, trend towards benefit in women
ARB	Val-HeFT	2001	16 countries: U.S.A., Australia, Europe, South Africa	Valsartan	160mg b.i.d.	127 b.i.d. 84% on target dose	NYHA II-IV, Stable, chronic HF	<40%	Mean age 63 years, 57% ischaemic heart disease	93% ACE-i 86% diuretic 67% digoxin 35% b-blocker	20	1,003	Mortality or HF hospitalisation/ ED presentation	Significant benefit in men, trend towards benefit in women
	CHARM-Added	2003	26 countries U.S.A./Europe	Candesartan	32mg q.d.	24mg q.d. 61% on target dose	NYHA II-IV	≤40%	Mean age 64 years, 62% ischaemic heart disease, 77% previous HF hospitalisation	100% ACE-i 90% diuretic 58% digoxin 55% b-blocker 37% vasodilators	21	542	Cardiovascular death or HF hospitalisation	CHARM low-LVEF trials combined: No sex difference in primary endpoint, p for interaction 0·95
	CHARM-Alternative	2003	26 countries U.S.A./Europe	Candesartan	32mg q.d.	23mg q.d. 59% on target dose	NYHA II-IV, ACE-i intolerance	≤40%	Mean age 67 years, 68% ischaemic heart disease, 68% previous HF hospitalisation	0% ACE-i 85% diuretic 55% b-blocker 46% digoxin 43% vasodilators	32	646	Cardiovascular death or HF hospitalisation	
β-blocker	U.S. Carvedilol HF	1996	U.S.A.	Carvedilol	25-50mg b.i.d.	23mg b.i.d. 80% on target dose	Chronic HF, NYHA II-IV	≤35%	Mean age 58 years, mean LVEF 23%	95% ACE-i 95% diuretic 91% digoxin 32% vasodilator	23	256	Mortality	HR 0·41 (0·22-0·80) in men HR 0·23 (0·07-0·69) in women
	CIBIS II	1999	18 European countries	Bisoprolol	10mg q.d.	8·5mg q.d. 63% on target dose	<80 years, NYHA III-IV, stable, chronic HF	≤35%	Mean age 61 years, 50% ischaemic heart disease	96% ACE-i 99% diuretic 52% digoxin 58% vasodilator	19	515	Mortality	Significant benefit in men and women
	MERIT-HF	1999	13 European countries and U.S.A.	Metoprolol	200mg q.d.	159mg q.d. 64% on target dose	Age 40-80, NYHA II-IV, stable, chronic HF	≤40%	Mean age 64 years, 66% ischaemic heart disease	96% ACE-i/ARB 91% diuretic 64% digoxin	23	898	Mortality or all-cause hospitalisation	Significant benefit in men, not in women
	COPERNICUS	2001	21 countries in Europe, Asia, Africa, Australia, U.S.A., and South America	Carvedilol	25mg b.i.d.	18mg b.i.d. 65% on target dose	Low LVEF, inclusion of both inpatient and outpatient clinic	<25%	Mean age 63 years, mean LVEF 20%	97% ACE-i/ARB 99% diuretic 66% digitalis	20	465	Mortality	Significant benefit in men, trend towards benefit in women

	SENIORS	2005	11 European countries	Nebivolol	10 mg q.d.	7·7mg q.d. 68% on target dose	Age ≥70 years, stable, chronic HF	≤35% or HF hospitalisation in the previous year	Mean age 76 years, 68% ischaemic heart disease	82% ACE-I 86% diuretic 39% digoxin	37	785	Mortality or cardiovascular hospital admission	HR 0·93 (0·78-1·11) in men HR 0·72 (0·55-0·93) in women p for interaction 0·11

ACE-i=angiotensin converting enzyme inhibitor, ARB=angiotensin receptor blocker, b.i.d.=bis in die (twice a day), CHARM-Added=Candesartan in heart failure: Assessment of reduction in mortality and morbidity-Added, , CHARM-Alternative= Candesartan in heart failure: Assessment of reduction in mortality and morbidity-Alternative, CIBIS II= Cardiac Insufficiency Bisoprolol Study II, CONSENSUS=Cooperative North Scandinavian Enalapril Survival Study, COPERNICUS= Carvedilol Prospective Randomized Cumulative Survival, ED=emergency department, HF=heart failure, HR=hazard ratio, LVEF=left ventricular ejection fraction, MERIT-HF= Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure, No.=number, NYHA=New York Heart Association, q.d.=quaque die (once a day), SENIORS=Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisations in Seniors with Heart Failure, SOLVD-Treatment=Studies of Left Ventricular Dysfunction, U.S.A.=United States of America, Val-HeFT=Valsartan Heart Failure Trial.

Table 2. Baseline characteristics of men and women in BIOSTAT-CHF.

	Men	Women	p-value
	(n=1,308)	**(n=402)**	
Clinical			
Age	70 ± 12	74 ± 12	<0·001
Weight (kg)	85 ± 18	72 ± 16	<0·001
Height (cm)	174 ± 8	162 ± 7	<0·001
BMI (kg/m2)	27·9 ± 5·2	27·3 ± 5·8	0·06
NYHA (%)			0·27
I	120 (10)	34 (10)	
II	639 (55)	172 (49)	
III	372 (32)	130 (37)	
IV	38 (3)	12 (3)	
LVEF, %	27 ± 7	29 ± 6	<0·001
Systolic blood pressure, mmHg	123 ± 20	126 ± 23	0·002
Diastolic blood pressure, mmHg	76 ± 12	75 ± 13	0·21
Pulse pressure, mmHg	47 ± 15	52 ± 17	<0·001
Heart rate, beats/min	82 ± 21	83 ± 20	0·32
Smoking (%)			<0·001
Never	371 (28)	245 (61)	
Past	725 (56)	114 (28)	
Current	210 (16)	43 (11)	
History of (%)			
Coronary artery disease*	631 (48)	139 (35)	<0·001
Valvular surgery	95 (7)	25 (6)	0·55
Atrial fibrillation	574 (44)	140 (35)	0·002
Stroke	111 (9)	30 (8)	0·58
Peripheral art. disease	140 (11)	22 (6)	0·002
Hypertension	759 (58)	253 (63)	0·10
Diabetes mellitus	431 (33)	109 (27)	0·03
COPD	236 (18)	52 (13)	0·02
Renal disease	332 (25)	78 (19)	0·02
Physical examination (%)			
Rales	638 (50)	205 (52)	0·44
Edema	595 (55)	175 (54)	0·75
Orthopnea	388 (30)	137 (34)	0·10
Hepatomegaly	206 (16)	40 (10)	0·005
Quality of life			
Functional status score	57 [36, 77]	46 [29, 64]	<0·001
Clinical summary score	52 [33, 71]	42 [27, 60]	<0·001
Overall score	54 [36, 71]	44 [31, 60]	<0·001
Laboratory data			
NT-proBNP (pg/mL)	2484 [1073, 5032]	2724 [1193, 5906]	0·18
Hemoglobin (g/dL)	13·9 [12·4, 14·9]	12·8 [11·8, 13·8]	<0·001
Creatinine (µmol/L)	106 [88, 130]	88 [72, 109]	<0·001
Sodium (mmol/L)	140 [137, 142]	140 [138, 142]	0·12

Potassium (mmol/L)	4·3 [4·0, 4·6]	4·2 [3·8, 4·6]	<0·001
Medication (%)			
Baseline			
ACE or ARB	988 (76)	291 (72)	0·23
B-Blocker	1123 (86)	328 (82)	0·045
MRA	775 (59)	191 (48)	<0·001
Diuretics	1302 (100)	401 (100)	0·90
Patients on target dose at baseline			
ACE or ARB	170 (13)	59 (15)	0·44
B-Blocker	66 (5)	21 (5)	0·99
Median dose at baseline			
ACE or ARB	0·25 [0·05, 0·50]	0·25 [0·00, 0·50]	0·814
B-Blocker	0·25 [0·06, 0·47]	0·25 [0·04, 0·38]	0·612
Follow-up			
ACE or ARB	1186 (91)	365 (91)	0·92
B-Blocker	1235 (94)	366 (91)	0·05
MRA	722 (55)	190 (47)	0·006
Patients on target dose at follow-up			
ACE or ARB	304 (23)	99 (25)	0·61
B-Blocker	168 (13)	57 (14)	0·54
Median dose at follow-up			
ACE or ARB	0·50 [0·25, 0·75]	0·50 [0·25, 0·75]	0·502
B-Blocker	0·25 [0·12, 0·50]	0·25 [0·12, 0·50]	0·536

* Coronary artery disease: previous myocardial infarction, percutaneous coronary intervention (PCI) and/or coronary artery bypass graft (CABG). BMI=body mass index, NYHA=New York Heart Association, LVEF=left ventricular ejection fraction, BP = blood pressure, COPD=chronic obstructive pulmonary disease, NT-proBNP=N-terminal pro-B-type natriuretic peptide, ACE=angiotensin converting enzyme inhibitor, ARB=angiotensin receptor blocker, MRA=mineralocorticoid receptor antagonist

Table 3. Risk of death or heart failure hospitalization for men and women who received 0, 1-49, 50-99% or ≥100% of recommended ACE-inhibitor/ARB and beta-blocker dose in BIOSTAT-CHF.

ACE-inhibitor/ARBs	**Men**				**Women**			
	0%	1-49%	50-99%	≥100%	0%	1-49%	50-99%	≥100%
	n=122	n=476	n=406	n=304	n=37	n=136	n=130	n=99
Hazard ratio (univariable)	2·29 (2·06-2·55)	1·87 (1·69-2·08)	1·19 (1·06-1·33)	Ref.	1·45 (1·18-1·79)	1·04 (0·85-1·26)	0·79 (0·64-0·98)	Ref.
Hazard ratio (multivariable)*	2·18 (1·95-2·43)	1·82 (1·64-2·02)	1·17 (1·04-1·30)	Ref.	1·30 (1·05-1·60)	0·85 (0·70-1·05)	0·67 (0·54-0·84)	Ref.
Hazard ratio (multivariable)**	1·09 (0·97-1·23)	1·24 (1·12-1·38)	0·99 (0·88-1·10)	Ref.	0·79 (0·63-0·99)	0·90 (0·74-1·11)	0·66 (0·53-0·83)	Ref.
Beta-Blockers	**Men**				**Women**			
	0%	1-49%	50-99%	≥100%	0%	1-49%	50-99%	≥100%
	n=73	n=751	n=339	n=145	n=36	n=229	n=91	n=46
Hazard ratio (univariable)	1·55 (1·39-1·73)	1·11 (1·00-1·23)	1·16 (1·03-1·29)	Ref.	1·15 (0·94-1·42)	0·73 (0·59-0·89)	0·63 (0·51-0·79)	Ref.
Hazard ratio (multivariable)*	1·46 (1·31-1·63)	1·08 (0·98-1·20)	1·14 (1·03-1·27)	Ref.	1·08 (0·87-1·35)	0·79 (0·65-0·98)	0·74 (0·59-0·92)	Ref.
Hazard ratio (multivariable)**	1·14 (1·03-1·28)	0·95 (0·86-1·06)	1·01 (0·9-1·13)	Ref.	1·02 (0·83-1·26)	0·84 (0·69-1·03)	0·76 (0·61-0·95)	Ref.

*Multivariable model 1: adjusted for body surface are (BSA).

**Multivariable model 2: adjusted for BIOSTAT-CHF model for death and/or heart failure hospitalization including age, heart failure hospitalization in previous year, systolic blood pressure, presence of peripheral edema, NT-proBNP, hemoglobin, sodium, high-density lipoprotein, and the use of beta-blockers at baseline.

Supplementary Appendix

Table S1. Recommended doses of ACE-inhibitors, ARBs, and beta-blockers in ESC guidelines for patients with LVEF <40%.

Drug	Class	Total daily dose
Captopril	ACE-inhibitor	150 mg
Enalapril	ACE-inhibitor	20 mg
Lisinopril	ACE-inhibitor	35 mg
Ramipril	ACE-inhibitor	10 mg
Trandolapril	ACE-inhibitor	4 mg
Perindopril	ACE-inhibitor	8 mg
Candesartan	ARB	32 mg
Valsartan	ARB	320 mg
Losartan	ARB	150 mg
Bisoprolol	Beta-blocker	10 mg
Carvedilol	Beta-blocker	50–100 mg*
Metoprolol	Beta-blocker	200 mg
Nebivolol	Beta-blocker	10 mg

*A maximum dose of 50mg twice daily can be administered to patients weighting over 85 kg.

Table S2. Baseline characteristics of included and excluded patients (BIOSTAT-CHF).

	Included	Excluded	p-value
	n=1710	n=806	
Clinical			
Age	71 ± 12	76 ± 11	<0·001
Women (%)	402 (24)	268 (33)	<0·001
Weight (kg)	82 ± 18	81 ± 19	0·46
Height (cm)	172 ± 9	170 ± 9	<0·001
BMI (kg/m2)	27·8 ± 5·4	28·1 ± 5·8	0·15
NYHA (%)			0·06
I	154 (10)	80 (12)	
II	811 (54)	330 (48)	
III	502 (33)	248 (36)	
IV	50 (3)	32 (5)	
LVEF, %	27 ± 7	64 ± 31	<0·001
Systolic blood pressure, mmHg	124 ± 21	127 ± 24	<0·001
Diastolic blood pressure, mmHg	75 ± 13	74 ± 15	0·001
Heart rate, beats/min	82 ± 21	83 ± 22	0·37
History of (%)			
Coronary artery disease*	770 (45)	361 (45)	0·94
Valvular surgery	120 (7)	59 (7)	0·85
Atrial fibrillation	714 (42)	429 (53)	<0·001
Peripheral art. disease	162 (10)	111 (14)	0·002
Hypertension	1012 (59)	557 (69)	<0·001
Diabetes mellitus	540 (32)	279 (35)	0·14
COPD	288 (17)	148 (18)	0·38
Renal disease	410 (24)	286 (36)	<0·001
Physical examination (%)			
Rales	843 (50·3)	448 (58)	<0·001
Edema	770 (54·8)	486 (70)	<0·001
Orthopnea	525 (30·7)	354 (44)	<0·001
Hepatomegaly	246 (14·4)	112 (14)	0·813
Quality of life			
Overall score	51 [34, 69]	43 [27, 59]	<0·001
Laboratory data			
NT-proBNP (pg/mL)	2550 [1103, 5178]	3135 [1369, 6717]	<0·001
Hemoglobin (g/dL)	13·6 [12·2, 14·7]	12·70 [11·3, 13·9]	<0·001
Creatinine (µmol/L)	101 [83, 125]	105 [86, 142]	<0·001
Sodium (mmol/L)	140 [137, 142]	139 [136, 141]	<0·001
Potassium (mmol/L)	4·2 [3·9, 4·6]	4·2 [3·9, 4·6]	0·09
Baseline medication (%)			
ACE or ARB	1279 (75)	541 (67)	<0·001
B-Blocker	1451 (85)	642 (80)	0·001
MRA	966 (57)	373 (46)	<0·001
Diuretics	1703 (100)	801 (99)	0·68

* Coronary artery disease: previous myocardial infarction, percutaneous coronary intervention (PCI) and/or coronary artery bypass graft (CABG). BMI=body mass index, NYHA=New York Heart Association, LVEF=left ventricular ejection fraction, BP = blood pressure, COPD=chronic obstructive pulmonary disease, NT-proBNP=N-terminal pro-B-type natriuretic peptide, ACE=angiotensin converting enzyme inhibitor, ARB=angiotensin receptor blocker, MRA=mineralocorticoid receptor antagonist.

Table S3. Baseline characteristics of included and excluded patients (ASIAN-HF).

	Included	Excluded	p-value
	n=4500	n=776	
Clinical			
Age	60 ± 13	60 ± 13	0·27
Women (%)	961 (21)	192 (25)	0·039
Weight (kg)	68 ± 16	66 ± 16	0·06
Height (cm)	164 ± 9	163 ± 9	0·006
BMI (kg/m2)	24·9 ± 5·1	24·7 ± 5·4	0·29
NYHA (%)			<0·001
I	556 (14)	57 (8)	
II	2116 (52)	387 (55)	
III	1154 (28)	223 (32)	
IV	255 (6)	36 (5)	
LVEF, %	27 ± 7	27 ± 7	0·63
Systolic blood pressure, mmHg	118 ± 20	121 ± 21	<0·001
Diastolic blood pressure, mmHg	72 ± 12	74 ± 13	<0·001
Heart rate, beats/min	81 ± 19	84 ± 20	<0·001
History of (%)			
Coronary artery disease*	2289 (51)	339 (45)	0·005
Atrial fibrillation	831 (19)	110 (15)	0·014
Stroke	302 (7)	36 (5)	0·06
Peripheral art. disease	157 (4)	22 (3)	0·51
Hypertension	2323 (52)	396 (59)	0·59
Diabetes mellitus	1841 (41)	279 (37)	0·06
COPD	367 (8)	67 (9)	0·52
Physical examination (%)			
Rales	726 (16)	153 (20)	0·004
Edema	1012 (23)	229 (31)	<0·001
Hepatomegaly	238 (5)	48 (6)	0·25
Quality of life			
Overall score	67 [47, 84]	65 [44, 81]	0·004
Laboratory data			
Hemoglobin (g/dL)	13·2 [11·7, 14·6]	13·1 [11·6, 14·6]	0·860
Creatinine (mg/dL)	1·1 [0·90, 1·44]	1·2 [0·9, 1·6]	0·001
Sodium (mmol/L)	139 [136, 141]	138 [135, 140]	<0·001
Potassium (mmol/L)	4·2 [3·9, 4·6]	4·2 [3·8, 4·5]	0·021
Baseline medication (%)			
ACE or ARB	3236 (72)	417 (74)	0·44
B-Blocker	3497 (79)	442 (70)	<0·001
MRA	2685 (60)	313 (40)	<0·001
Diuretics	3696 (82)	490 (76)	<0·001

* Coronary artery disease: previous myocardial infarction, percutaneous coronary intervention (PCI) and/or coronary artery bypass graft (CABG), BMI=body mass index, NYHA=New York Heart Association, LVEF=left ventricular ejection fraction, BP = blood pressure, COPD=chronic obstructive pulmonary disease, ACE=angiotensin converting enzyme inhibitor, ARB=angiotensin receptor blocker, MRA=mineralocorticoid receptor antagonist.

Table S4. Clinical characteristics of men and women at 9 months in BIOSTAT-CHF.

	Men	Women	p-value
Follow-up visit			
Weight (kg)	86 ± 19	73 ± 16	<0·001
Systolic blood pressure, mmHg	124 ± 20	125 ± 21	0·32
Diastolic blood pressure, mmHg	75 ± 12	75 ± 12	0·48
Heart rate, beats/min	72 ± 15	73 ± 14	0·55

Table S5. Overview of individual drug intake by men and women.

	Men *n*, %	Women *n*, %
ACE-inhibitor		
Ramipril	565 (47)	143 (39)
Enalapril	163 (14)	48 (13)
Perindopril	162 (14)	61 (17)
Lisinopril	36 (3)	9 (3)
Fosinopril	38 (3)	8 (2)
Trandolapril	17 (1)	3 (1)
Quinapril	14 (1)	3 (1)
Captopril	15 (1)	1 (1)
ARB		
Candesartan	58 (5)	30 (8)
Valsartan	46 (4)	22 (6)
Losartan	31 (3)	18 (5)
Irbesartan	18 (2)	6 (2)
Telmisartan	9 (1)	4 (1)
Beta-blocker		
Carvedilol	495 (40)	119 (32)
Bisoprolol	448 (36)	144 (39)
Metoprolol	229 (19)	84 (23)
Nebivolol	52 (4)	19 (5)
Atenolol	5 (1)	1 (1)

ACE=angiotensin converting enzyme inhibitor, ARB=angiotensin receptor blocker.

Table S6. Baseline characteristics of men and women in ASIAN-HF.

	Men	Women	p-value
	(n=3,539)	**(n=961)**	
Clinical			
Age	60 ± 13	61 ± 14	0·006
Weight (kg)	70 ± 15	59 ± 13	<0·001
Height (cm)	167 ± 7	155 ± 7	<0·001
BMI (kg/m2)	25·1 ± 5·0	24·5 ± 5·2	0·006
NYHA (%)			<0·001
I	467 (15)	89 (10)	
II	1668 (52)	448 (52)	
III	884 (28)	270 (31)	
IV	195 (6)	60 (7)	
LVEF, %	27 ± 7	29 ± 7	<0·001
Systolic blood pressure, mmHg	118 ± 20	119 ± 21	0·12
Diastolic blood pressure, mmHg	72 ± 12	71 ± 12	<0·001
Pulse pressure, mmHg	45 ± 15	48 ± 16	<0·001
Heart rate, beats/min	81 ± 19	82 ± 19	0·009
Smoking (%)			<0·001
Never	1613 (46)	876 (91)	
Past	1364 (39)	60 (6)	
Current	560 (16)	25 (3)	
History of (%)			
Coronary artery disease*	1953 (55)	336 (35)	<0·001
Atrial fibrillation	670 (19)	161 (17)	0·14
Stroke	243 (7)	59 (6)	0·47
Peripheral art. disease	133 (4)	24 (3)	0·07
Hypertension	1854 (52)	469 (49)	0·05
Diabetes mellitus	1470 (42)	371 (39)	0·11
COPD	293 (8)	74 (8)	0·61
Physical examination (%)			
Rales	587 (17)	139 (15)	0·12
Edema	797 (23)	215 (22)	0·95
Hepatomegaly	199 (6)	39 (4)	0·07
Quality of life			
Clinical summary score	74 [55, 90]	69 [50, 86]	<0·001
Overall score	68 [49, 84]	64 [43, 81]	<0·001
Laboratory data			
Hemoglobin (g/dL)	13·4 [11·9, 14·8]	12·2 [10·8, 13·4]	<0·001
Creatinine (mg/dL)	1·14 [0·92, 1·48]	0·94 [0·75, 1·24]	<0·001
Sodium (mmol/L)	139 [136, 141]	139 [136, 141]	0·02
Potassium (mmol/L)	4·2 [3·9, 4·6]	4·2 [3·9, 4·6]	0·34
Medications (%)			
ACE or ARB	2559 (72)	677 (70)	0·27
B-Blocker	2779 (79)	718 (75)	0·009
MRA	2141 (61)	544 (57)	0·03

Diuretics	2901 (82)	795 (83)	0·62

* Coronary artery disease: previous myocardial infarction, percutaneous coronary intervention (PCI) and/or coronary artery bypass graft (CABG), BMI=body mass index, NYHA=New York Heart Association, LVEF=left ventricular ejection fraction, BP = blood pressure, COPD=chronic obstructive pulmonary disease, ACE=angiotensin converting enzyme inhibitor, ARB=angiotensin receptor blocker, MRA=mineralocorticoid receptor antagonist.

Table S7. Baseline characteristics of men and women using 0-49% versus 50-≥100% of recommended target doses of ACE-inhibitors/ARBs.

	Men			Women		
	0-49% of target dose	50-≥100% of target dose	p-value	0-49% of target dose	50-≥100% of target dose	p-value
	n=598	n=710		n=173	n=229	
Clinical						
Age	70 ± 12	69 ± 11	0·02	74 ± 13	74 ± 11	0·81
Weight (kg)	82 ± 16	88 ± 18	<0·001	70 ± 17	73 ± 16	0·07
Height (cm)	174 ± 7	175 ± 8	0·004	162 ± 7	162 ± 7	0·71
BMI (kg/m2)	27·2 ± 4·8	28·6 ± 5·5	<0·001	26·8 ± 6·0	27·8 ± 5·6	0·08
NYHA (%)			0·15			0·09
I	57 (11)	63 (10)		9 (6)	25 (13)	
II	274 (51)	365 (58)		75 (50)	97 (49)	
III	187 (35)	185 (29)		57 (38)	73 (37)	
IV	18 (3)	20 (3)		8 (5)	4 (2)	
LVEF, %	26 ± 7	27 ± 7	0·006	28 ± 6	30 ± 6	0·005
Systolic blood pressure, mmHg	118 ± 19	127 ± 20	<0·001	121 ± 23	130 ± 22	<0·001
Diastolic blood pressure, mmHg	73 ± 12	78 ± 12	<0·001	72 ± 13	77 ± 13	<0·001
Heart rate, beats/min	83 ± 20	81 ± 22	0·12	81 ± 19	84 ± 21	0·11
Smoking (%)			0·91			0·75
Never	173 (29)	198 (28)		109 (63)	136 (59)	
Past	328 (55)	397 (56)		47 (27)	67 (29)	
Current	96 (16)	114 (16)		17 (10)	26 (11)	
History of (%)						
Coronary artery disease*	294 (49)	337 (48)	0·58	75 (43)	64 (28)	0·002
Valvular surgery	56 (9)	39 (6)	0·01	16 (9)	9 (4)	0·05
Atrial fibrillation	289 (48)	285 (40)	0·004	67 (39)	73 (32)	0·19
Peripheral art. disease	67 (11)	73 (10)	0·65	16 (9)	6 (3)	0·008
Hypertension	299 (50)	460 (65)	<0·001	106 (61)	147 (64)	0·62

Diabetes mellitus	182 (30)	249 (35)	0·09	46 (27)	63 (28)	0·93
COPD	123 (21)	113 (16)	0·04	18 (10)	34 (15)	0·24
Renal disease	195 (33)	137 (19)	<0·001	45 (26)	33 (14)	0·005
Physical examination (%)						
Rales	339 (57)	299 (43)	<0·001	95 (56)	110 (50)	0·28
Edema	292 (58)	303 (53)	0·10	75 (53)	100 (54)	0·92
Orthopnea	195 (33)	193 (27)	0·04	69 (40)	68 (30)	0·04
Hepatomegaly	120 (20)	86 (12)	<0·001	20 (12)	20 (9)	0·43
Quality of life						
Overall score	50 [31, 67]	57 [40, 74]	<0·001	42 [27, 56]	46 [32, 62]	0·04
Laboratory data						
NT-proBNP (pg/mL)	2983 [1267, 6425]	2122 [912, 4359]	<0·001	3056 [1399, 7673]	2430 [937, 4771]	0·002
Hemoglobin (g/dL)	13·6 [12·2, 14·8]	14·0 [12·8, 15·1]	<0·001	12·8 [11·5, 13·6]	13·0 [12·1, 14·0]	0·03
Creatinine (µmol/L)	109 [91, 143]	102 [86, 123]	<0·001	95 [76, 121]	83 [71, 104]	<0·001
Sodium (mmol/L)	139 [137, 141]	140 [137, 142]	0·02	140 [138, 142]	140 [138, 142]	0·13
Potassium (mmol/L)	4·3 [4·0, 4·6]	4·3 [4·0, 4·6]	0·63	4·2 [3·9, 4·7]	4·1 [3·7, 4·5]	0·12
Baseline medication (%)						
ACE or ARB	416 (70)	572 (81)	<0·001	113 (65)	178 (78)	0·008
B-Blocker	509 (85)	614 (87)	0·53	143 (83)	185 (81)	0·73
MRA	369 (62)	406 (57)	0·11	95 (55)	96 (42)	0·01
Diuretics	594 (99)	708 (100)	0·53	173 (100)	228 (100)	1·00

* Coronary artery disease: previous myocardial infarction, percutaneous coronary intervention (PCI) and/or coronary artery bypass graft (CABG), BMI=body mass index, NYHA=New York Heart Association, LVEF=left ventricular ejection fraction, BP = blood pressure, COPD=chronic obstructive pulmonary disease, ACE=angiotensin converting enzyme inhibitor, ARB=angiotensin receptor blocker, MRA=mineralocorticoid receptor antagonist.

Table S8. Baseline characteristics of men and women using 0-49% versus 50-≥100% of recommended target doses of β-blockers.

	Men			Women		
	0-49% of target dose	50-≥100% of target dose	p-value	0-49% of target dose	50-≥100% of target dose	p-value
	n=824	n=484		n=265	n=137	
Clinical						
Age	70 ± 12	69 ± 12	0·33	74 ± 12	74 ± 12	0·68
Weight (kg)	83 ± 18	88 ± 18	<0·001	70 ± 16	76 ± 16	0·001
Height (cm)	174 ± 7	176 ± 8	<0·001	161 ± 7	164 ± 7	<0·001
BMI (kg/m2)	27·6 ± 5·1	28·4 ± 5·4	0·007	27·0 ± 5·8	28·0 ± 5·6	0·10
NYHA (%)			0·53			0·47
I	72 (10)	48 (11)		19 (8)	15 (13)	
II	406 (56)	233 (53)		115 (49)	57 (50)	
III	234 (32)	138 (32)		90 (39)	40 (35)	
IV	20 (3)	18 (4)		9 (4)	3 (3)	
LVEF, %	27 ± 7	27 ± 7	0·12	29 ± 6	28 ± 7	0·27
Systolic blood pressure, mmHg	122 ± 20	124 ± 21	0·09	126 ± 23	128 ± 23	0·46
Diastolic blood pressure, mmHg	75 ± 12	77 ± 13	<0·001	74 ± 13	76 ± 14	0·15
Heart rate, beats/min	81 ± 20	83 ± 22	0·04	81 ± 19	86 ± 21	0·02
Smoking (%)			0·91			0·09
Never	232 (28)	139 (29)		171 (65)	74 (54)	
Past	456 (55)	269 (56)		66 (25)	48 (35)	
Current	135 (16)	75 (16)		28 (11)	15 (11)	
History of (%)						
Coronary artery disease*	412 (50)	219 (45)	0·11	83 (31)	56 (41)	0·07
Valvular surgery	58 (7)	37 (8)	0·77	16 (6)	9 (7)	1·00
Atrial fibrillation	334 (41)	240 (50)	0·002	80 (30)	60 (44)	0·009
Peripheral art. disease	107 (13)	33 (7)	0·001	13 (5)	9 (7)	0·64
Hypertension	477 (58)	282 (58)	0·94	167 (63)	86 (63)	1·00
Diabetes mellitus	281 (34)	150 (31)	0·27	74 (28)	35 (26)	0·70

COPD	153 (19)	83 (17)	0·57	38 (14)	14 (10)	0·31
Renal disease	213 (26)	119 (25)	0·66	52 (20)	26 (19)	0·98
Physical examination (%)						
Rales	433 (54)	205 (43)	0·001	137 (53)	68 (51)	0·85
Edema	387 (57)	208 (53)	0·23	111 (53)	64 (56)	0·71
Orthopnea	271 (33)	117 (24)	0·001	87 (33)	50 (37)	0·55
Hepatomegaly	141 (17)	65 (13)	0·09	30 (11)	10 (7)	0·27
Quality of life						
Overall score	53 [34, 70]	55 [38, 73]	0·05	43 [30, 58]	46 [32, 64]	0·15
Laboratory data						
NT-proBNP (pg/mL)	2527 [1132, 5003]	2435 [957, 5087]	0·40	2637 [1157, 5640]	2938 [1417, 6756]	0·21
Hemoglobin (g/dL)	13·8 [12·3, 14·8]	14·0 [12·7, 15·1]	0·03	12·9 [11·8, 13·9]	12·8 [11·8, 13·8]	0·84
Creatinine (µmol/L)	106 [88, 132]	103 [88, 128]	0·16	88 [72, 108]	88 [71, 113]	0·78
Sodium (mmol/L)	140 [137, 142]	140 [138, 142]	0·02	140 [138, 142]	140 [138, 142]	0·87
Potassium (mmol/L)	4·3 [4·0, 4·6]	4·3 [4·0, 4·6]	0·80	4·2 [3·8, 4·6]	4·2 [3·7, 4·5]	0·39
Baseline medication (%)						
ACE or ARB	619 (75)	369 (76)	0·70	192 (73)	99 (72)	1·00
B-Blocker	674 (82)	449 (93)	<0·001	205 (77)	123 (90)	0·004
MRA	513 (62)	262 (54)	0·005	129 (49)	62 (45)	0·59
Diuretics	818 (99)	484 (100)	0·15	265 (100)	136 (99)	0·74

* Coronary artery disease: previous myocardial infarction, percutaneous coronary intervention (PCI) and/or coronary artery bypass graft (CABG), BMI=body mass index, NYHA=New York Heart Association, LVEF=left ventricular ejection fraction, BP = blood pressure, COPD=chronic obstructive pulmonary disease, ACE=angiotensin converting enzyme inhibitor, ARB=angiotensin receptor blocker, MRA=mineralocorticoid receptor antagonist.

Table S9. The number of men and women reaching specific dose level combinations of ACE-inhibitors/ARBs and β-blockers in BIOSTAT-CHF and ASIAN-HF.

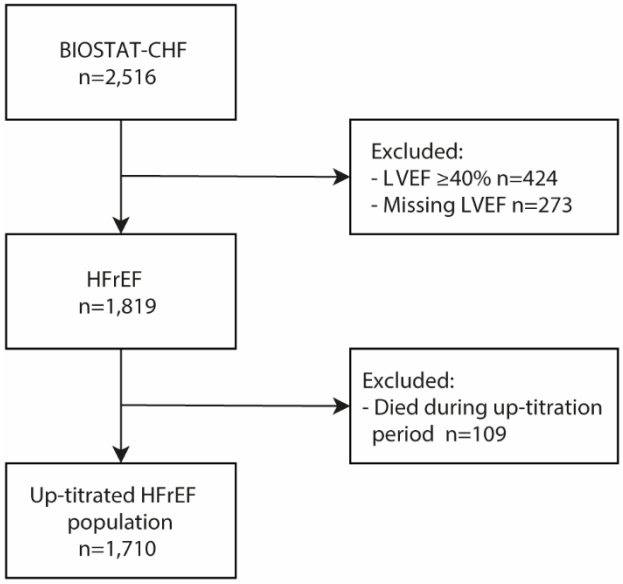
BIOSTAT-CHF		**Men** n=1,308	**Women** n=402
ACE-i/ARB dose:	**β-blocker dose:**		
Target dose	Target dose	58 (4%)	19 (5%)
50-100%	50-100%	317 (24%)	88 (22%)
50-100%	0-49%	393 (30%)	141 (35%)
0-49%	50-100%	167 (13%)	49 (12%)
0-49%	0-49%	431 (33%)	124 (31%)
ASIAN-HF		**Men** n=3,539	**Women** n=961
ACE-i/ARB dose:	**β-blocker dose:**		
Target dose	Target dose	77 (2%)	22 (2%)
50-100%	50-100%	384 (11%)	103 (11%)
50-100%	0-49%	724 (20%)	194 (20%)
0-49%	50-100%	584 (17%)	135 (14%)
0-49%	0-49%	1790 (51%)	516 (54%)

Table S10. Overview of the reasons why men and women were not using target doses of ACE-inhibitors/ARBs and β-blockers after the up-titration period of BIOSTAT-CHF.

ACE-inhibitors/ARBs reason (%)	Men n=1308	Women n=402	p-value
On target dose	304 (23)	99 (25)	0·61
Not on target dose	1004 (77)	303 (75)	
Symptoms/side effects/non-cardiac organ dysfunction	118 (12)	48 (16)	0·039
Not-specified/unknown	886 (88)	255 (84)	
β-blockers reason (%)			
On target dose	168 (13)	57 (14)	0·54
Not on target dose	1140 (87)	345 (86)	
Symptoms/side effects/non-cardiac organ dysfunction	103 (9)	36 (10)	0·13
Not-specified/unknown	1037 (91)	309 (90)	

ACE=angiotensin converting enzyme inhibitor, ARB=angiotensin receptor blocker.

Figure S1. Flow diagram of selected patients.



BIOSTAT-CHF= the BIOlogy Study to TAilored Treatment in Chronic Heart Failure, LVEF=left ventricular ejection fraction, HFrEF=heart failure with reduced ejection fraction.

Figure S2. Density plot of the dose levels used in BIOSTAT-CHF (blue) and ASIAN-HF (red).

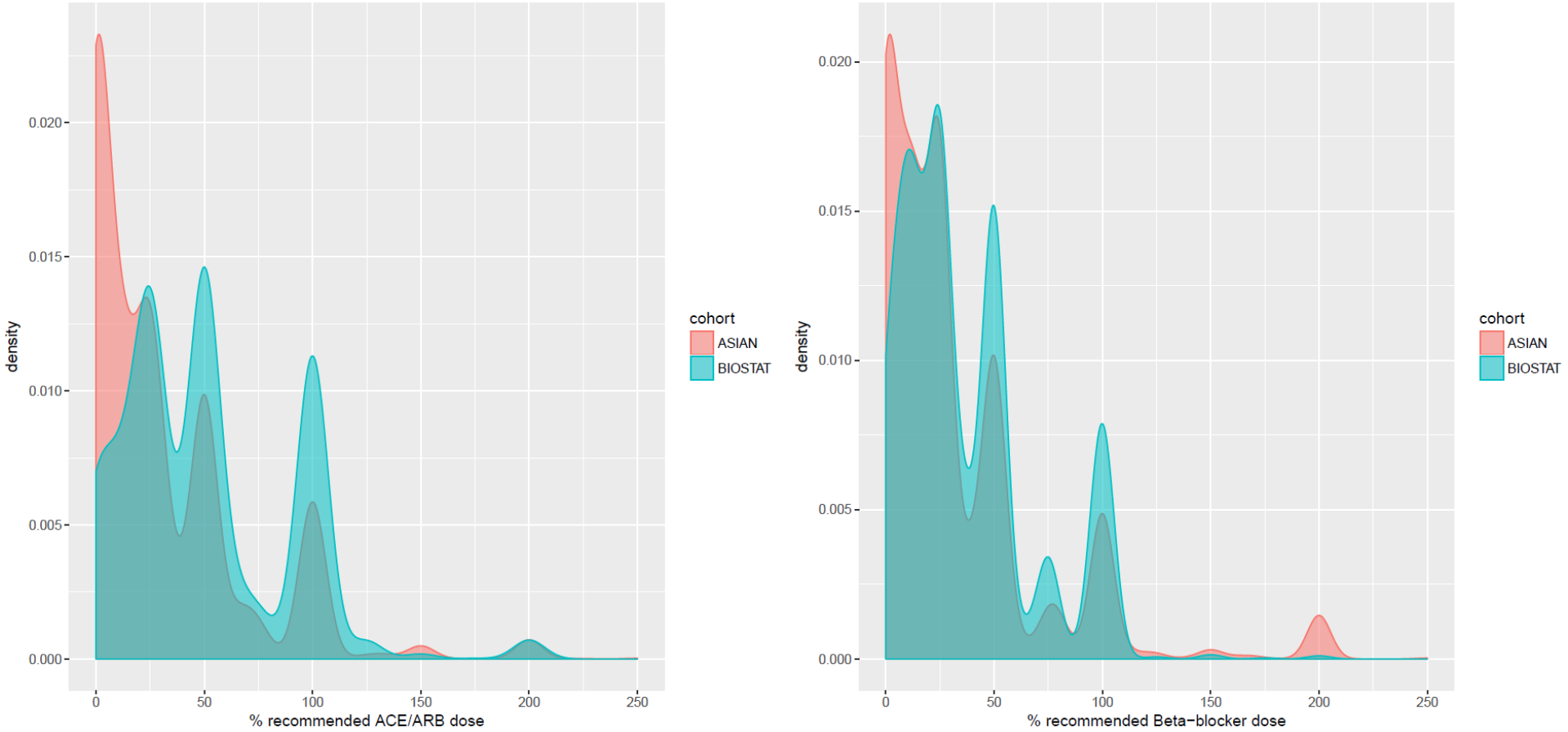
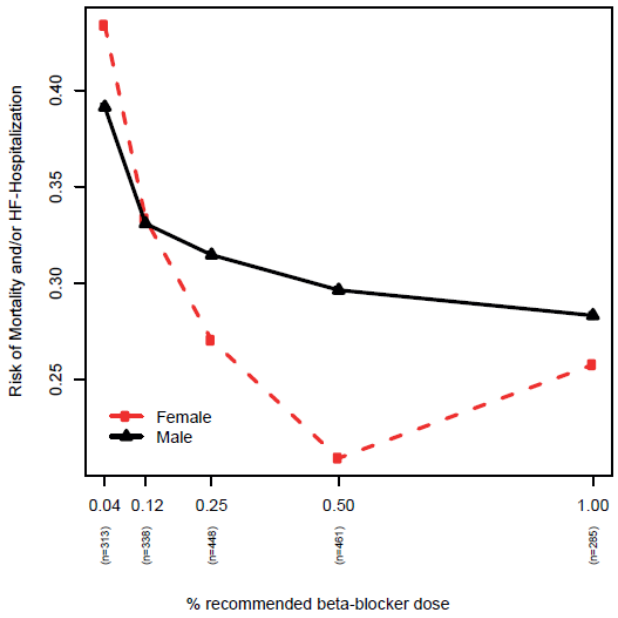
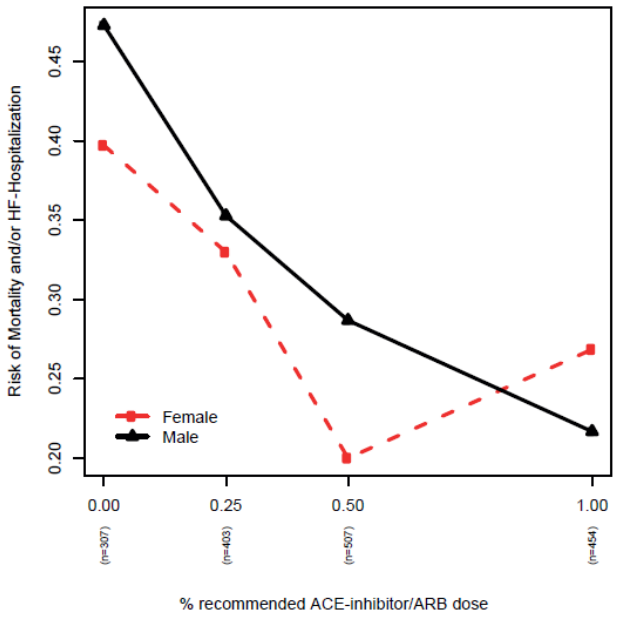


Figure S3. Subpopulation treatment effect pattern plot (STEPP) of men and women per % of recommended beta-blockers (3A) and ACE-inhibitors/ARBs (3B) dose in BIOSTAT-CHF, and the ratio of the relative risk of women divided by the relative risk in men for beta-blockers (3C) and ACE-inhibitors/ARBs (3D), resulting in a hazard ratio for women compared with men, including confidence intervals of this ratio.

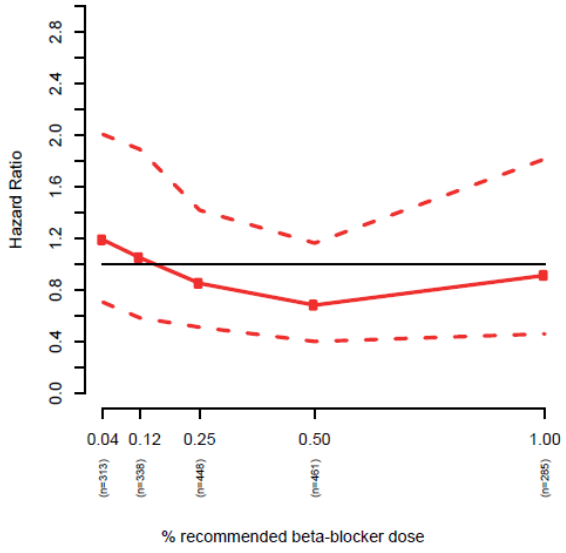
3A



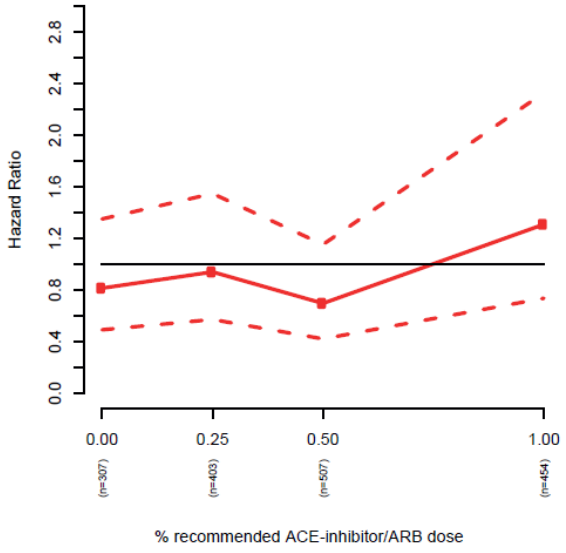
3B



3C



3D



Appendix S1.

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