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Title: Bisoprolol compared with carvedilol and metoprolol succinate in the treatment of patients with chronic heart failure

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Abstract

Aims: Beta-blockers are recommended for the treatment of chronic heart failure (CHF). However, it is disputed whether beta-blockers exert a class effect or whether there are differences in efficacy between agents.

Methods and results: 6,010 out-patients with stable CHF and a reduced left ventricular ejection fraction prescribed either bisoprolol, carvedilol or metoprolol succinate were identified from three registries in Norway, England, and Germany. In three separate matching procedures, patients were individually matched with respect to both dose equivalents and the respective propensity scores for beta-blocker treatment.

During a follow-up of 26,963 patient-years, 302 (29.5%), 637 (37.0%), and 1,232 (37.7%) patients died amongst those prescribed bisoprolol, carvedilol, and metoprolol, respectively. In univariable analysis of the general sample, bisoprolol and carvedilol were both associated with lower mortality as compared with metoprolol succinate (HR 0.80, 95% CI 0.71-0.91, p<0.01, and HR 0.86, 95% CI 0.78-0.94, p<0.01, respectively). Patients prescribed bisoprolol or carvedilol had similar mortality (HR 0.94, 95% CI 0.82-1.08, p=0.37). However, there was no significant association between beta-blocker choice and all-cause mortality in any of the matched samples (HR 0.90; 95% CI 0.76-1.06; p=0.20; HR 1.10, 95% CI 0.93-1.31, p=0.24; and HR 1.08, 95%CI 0.95-1.22, p=0.26 for bisoprolol vs. carvedilol, bisoprolol vs. metoprolol succinate, and carvedilol vs. metoprolol succinate, respectively). Results were confirmed in a number of important subgroups.

Conclusion: Our results suggest that the three beta-blockers investigated have similar effects on mortality amongst patients with CHF.

Words: 235

Key words: beta-blocker, heart failure with reduced ejection fraction, survival, effectiveness

Introduction

Beta-blockers have become one of the mainstays of chronic heart failure (CHF) therapy since they improve both morbidity and mortality in patients with reduced ejection fraction [1-8]. Current guidelines advise the use of bisoprolol, carvedilol and metoprolol succinate interchangeably in the treatment of CHF [1,2]. Given that beta-blockers differ in their selectivity for adrenergic receptors, their lipophilicity and their effects on peripheral circulation [9], there is, however, the question whether beta-blockers exert a class effect or whether any beta-blocker is superior to another [10-13].

As almost all key beta-blocker trials have compared beta-blockers against placebo [3-8], prospective data on the comparative effectiveness of beta-blockers are scarce [14,15]. Since published head-to-head comparisons have not been convincing, a variety of meta-analyses and retrospective studies has been published [12,16-18,13,19-23]. The results, however, were inconclusive. Thus, there is little evidence to inform clinical decisions.

In the present study, we compared the prognosis of patients prescribed bisoprolol, carvedilol or metoprolol succinate in a contemporary multicentre real world cohort of patients with stable CHF from three European countries.

Methods

Databases

Patients' data were extracted from three different European heart failure databases: the Norwegian Heart Failure Registry, the Heart Failure Registry of the Department of Academic Cardiology, University of Hull, UK, and the Heart Failure Registry of the University of Heidelberg, Germany. Recruitment was prospective and continuous for each database and centre. All patients gave their written informed consent for data storage and evaluation. The study conformed to the principles outlined in the Declaration of Helsinki and was approved by the local ethics committees.

The Norwegian Heart Failure Registry was initiated in October 2000 and patients were enrolled from outpatients' clinics of 27 recruiting hospitals well distributed in all regions of Norway ranging in size

and scope from small community to large university hospitals. The participating centres recorded their data using a web-based database.

Patients who attended the community heart failure clinics of the University of Hull, UK, and the University of Heidelberg, Germany, for evaluation of heart failure were offered inclusion into the local heart failure registries. Since both university hospitals are providers of secondary and tertiary care, the registries reflect a broad representation of patients of their respective regions.

Patient selection and follow-up

All databases reflect all-comer cohorts. Patients were included after stabilization of both clinical status and medication. Patients were eligible for the study if they met the following criteria: a) attendance at the heart failure outpatient clinic of any of the participating hospitals, b) written informed consent for inclusion into the respective heart failure registry, c) history of heart failure due to left ventricular systolic dysfunction. Medication was at the discretion of the referring physician. For further analyses, we selected patients who were treated with either bisoprolol, carvedilol or metoprolol succinate in conjunction with either an angiotensin-converting-enzyme inhibitor or an angiotensin receptor blocker. The present analysis was restricted to bisoprolol, carvedilol and metoprolol succinate, since their use is recommended by guidelines and they were commonly prescribed in the three heart failure registries (*figure 1*).

Target doses and dose equivalents for beta-blockers were derived from ESC guidelines for the diagnosis and treatment of acute and chronic heart failure [1]. For example, daily doses of 10 mg bisoprolol or 50 mg carvedilol were both considered as 100% dose equivalent, while 5 mg bisoprolol and 25 mg carvedilol were defined as 50% dose equivalent.

The diagnosis of heart failure was established according to guidelines on the basis of typical symptoms and signs associated with an objective abnormality of cardiac structure or function on echocardiography, cardiac magnetic resonance imaging, or left heart catheterisation [1]. All patients included in the present analysis had a left ventricular ejection fraction (LVEF) <45%.

Baseline characteristics included medical history, physical examination, LVEF, blood count and chemistry, and medication. Glomerular filtration rate (GFR) was estimated using the modification of diet in renal disease (MDRD) formula [24].

Surviving patients were followed up for a minimum of six months. Determination of survival status and follow-up were performed by scheduled visits to the outpatient clinic, by telephone calls either to the patients' homes or to their physicians, or by electronic hospital records. For the purpose of the present analysis, patients were censored as "alive" at the date of this last contact. In addition, for the Norwegian Heart Failure Registry, mortality data were obtained at regular intervals from the National Registry and no patients were lost to follow-up. Patients who underwent heart transplantation were followed until transplantation and censored thereafter. All-cause mortality was the predefined endpoint of the study.

Statistical analysis

All tests are two-tailed and a *P*-value of less than 5% was regarded as being statistically significant. Variables are presented as mean ± standard deviation, median [interquartile range], or number [percentages (%)] as appropriate. Chi-squared tests were used to compare frequencies. To test for significant differences between groups, the Kruskal-Wallis test and analysis of variance (ANOVA) tests were used where appropriate.

In order to prevent bias in further statistical analyses due to missing baseline values, we performed a multiple imputation analysis with n=100 repetitions using the Markov chain Monte Carlo method (MCMC). This procedure replaces each missing value with a set of plausible values that represent the uncertainty about the correct value for imputation.

Differences in event-free survival between patients treated with bisoprolol, carvedilol or metoprolol succinate were analysed using Cox proportional hazard models and displayed using the Kaplan-Meier method for survival. To account for possible confounders, patients were matched with respect to beta-blocker treatment using pairwise multi-level propensity score matching as described below. Survival analyses were then repeated in matched cohorts.

Propensity score calculation and matching

Propensity scores were calculated as the single composite variable from a non-parsimonious multivariate logit-linked binary logistic regression of the baseline characteristics. The beta-blocker agent was the dependent variable [25]. In a first step, propensity scores were calculated separately for "bisoprolol vs. carvedilol", "bisoprolol vs. metoprolol succinate", and "carvedilol vs. metoprolol succinate" as dependent variables. Propensity scores were derived from all baseline variables (except beta-blocker dose equivalent) using the multiple imputed baseline data sets. The logits of the probability of receiving a certain beta-blocker according to the respective propensity scores formed the basis of three separate matching procedures. Dose equivalent of the respective beta-blocker was not part of the propensity scores to account separately for one of the main criticisms of the Carvedilol or Metoprolol European Trial (COMET) trial [14,26].

Patients were individually matched for both the propensity of receiving a particular beta-blocker AND their dose equivalents. Each matching procedure was performed in two steps: First, calliper matching of the propensity score was applied with calliper size predefined as 0.2 of the standard deviation of the total sample. In a one-pass procedure starting with a given patient receiving a certain beta-blocker (e.g. bisoprolol), the closest match of a patient receiving a different beta-blocker (e.g. carvedilol) was identified. Second, dose equivalents for the beta-blockers were compared. If doses were equivalent or varied ≤10%, the pair of patients was retained for analysis and removed from the total sample to allow for the next matching cycle to take place. If doses varied >10%, the pair was rejected. Then the first step of the matching process was repeated to identify the next closest match to the given bisoprolol patient of the failed match according to the propensity score. If a further patient on carvedilol was thus identified, the second step was repeated. If no match according to the propensity score AND dose equivalent could be identified, the bisoprolol patient was removed from the total sample and the matching cycle started with the next bisoprolol patient.

The matching procedures of patients treated with bisoprolol vs. metoprolol succinate and carvedilol vs. metoprolol succinate were performed analogously. Owing to this statistical design, the matched patients included in each drug cohort differed between comparisons.

Bias reduction, balance and sensitivity analysis

The balance of baseline covariates before and after matching was assessed using standardised differences [27]. Standardised difference scores are intuitive indexes which measure the effect size between two groups. Compared to a t-test or Wilcoxon rank-sum test, they are independent of sample size. Thus, their use can be recommended for comparing baseline covariates in clinical trials as well as propensity-score matched studies. In addition, we conducted a formal sensitivity analysis to quantify the degree of a hidden bias that would need to be present to invalidate our main conclusions following the method suggested by Love [28].

Subgroups

Analyses were repeated in pre-specified subgroups of the matched samples with respect to age (above vs. below median), sex, LVEF (≤35% vs. >35%), NYHA functional class (I/II vs. III/IV), heart rate (≤75/min vs. >75/min), and rhythm (sinus rhythm yes vs. no). Interaction terms were calculated for each of the predefined subgroups in the propensity matched samples.

<div align="center">

Results

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Of 6,010 patients who met the inclusion criteria outlined above, 4,011 patients were from Norway, 1,171 patients were from Germany, and 728 patients were from England.

Bisoprolol was prescribed for 1,023 patients (17.0%) with a median dose of 5 (2.5-10) mg/d (equivalent to 50 (25-100)% of target dose), carvedilol for 1,721 patients (28.6%) with a median dose of 25 (12.5-50) mg/d (equivalent to 50 (25-100)% of target dose), and metoprolol succinate for 3,266 patients with a median dose of 100 (50-150) mg/d (equivalent to 52.6 (26.3-100)% of target dose).

Baseline characteristics of CHF patients differed with respect to beta-blocker treatment for a substantial number of variables (*table 1*). Overall, patients receiving metoprolol succinate were older and more likely to have NYHA functional class III symptoms than those on carvedilol. In addition, the proportion of patients with ischemic heart disease was higher in the metoprolol succinate group.

Total follow-up was 323,560 patient-months (26,963 patient-years) with a median follow-up duration of 49 (26-76) months. For bisoprolol, median follow-up was 46 (26-72) months, whereas it was 56 (30-84) months and 47 (25-74) months for carvedilol and metoprolol succinate, respectively. During that time 2,171 (36.1%) patients died: 302 (29.5%) on bisoprolol, 637 (37.0%) on carvedilol, and 1,232 (37.7%) on metoprolol succinate.

In univariable analysis of the overall cohort, patients prescribed bisoprolol and carvedilol therapy both had lower mortality when compared with those prescribed metoprolol succinate (HR 0.80, 95% CI 0.71-0.91, p<0.01, and HR 0.86, CI 0.78-0.94, p<0.01, respectively). Survival on bisoprolol was similar to that on carvedilol (HR 0.94, 95% CI 0.82-1.08, p=0.37). Kaplan–Meier curves for 10-year survival of CHF outpatients with respect to beta-blocker treatment are shown in *figure 2*.

The matching procedures identified 839, 986 and 1,380 pairs of patients with similar dose-equivalent for each of the three comparisons (bisoprolol vs. carvedilol, bisoprolol vs. metoprolol succinate and carvedilol vs. metoprolol). Of these, 553 (33%), 554 (28%), and 941 (34%) patients died during 10-year follow-up, respectively. Each of the propensity score matching procedures significantly reduced standardized differences below 10% in the absolute values for most observed covariates, demonstrating an improvement in the covariate balance across the treatment groups. (fFigure 3 a) and b))shows standardised differences of baseline variables before (a) and after (b) matching in each of the 3 matched cohorts. For example, in the overall cohort, the standardized difference of left ventricular ejection fraction between patients treated with bisoprolol and those given carvedilol was ≈20%. However, after matching, the standardized difference of left ventricular ejection fraction was reduced to 0%.

Cox proportional hazard analyses did not find any significant association between the particular beta-blocker prescribed and all-cause mortality in any of the matched samples (bisoprolol vs. carvedilol, HR 0.90, 95% CI 0.76-1.06, p=0.20; bisoprolol vs. metoprolol succinate HR 1.10, 95% CI 0.93-1.31, p=0.24; carvedilol vs. metoprolol succinate HR 1.08, 95% CI 0.95-1.22, p=0.26). The Kaplan–Meier curves for survival of matched CHF patients with respect to beta-blocker treatment are presented in *figures 4-6.*

Subgroup analyses mainly confirmed that none of the beta-blockers was inferior to any other with two exceptions: in patients without sinus rhythm, there was a survival benefit of metoprolol succinate over carvedilol (p=0.03), and in patients with a resting heart rate ≤75/min, there was a marginally significant benefit of carvedilol over bisoprolol (p=0.05). The interaction terms indicated that there was no significant interaction between subgroups and individual beta-blocker agents. The relevant plot is shown in *figure 7*.

The formal sensitivity analyses indicate only a small residual bias. The respective Γ-values were 0.93, 0.65, and 0.78 for bisoprolol vs. carvedilol, bisoprolol vs. metoprolol succinate, and carvedilol vs. metoprolol succinate (no residual bias at Γ=1.0). This means that in order to attribute a possible survival benefit to an unobserved covariate rather than the receipt of e.g. bisoprolol (vs. carvedilol), that unobserved covariate would only need to produce a 7% increase in the odds of receipt of bisoprolol while being a weak predictor of all-cause mortality.

Discussion

We found no evidence for a difference in survival amongst patients prescribed bisoprolol, carvedilol, or metoprolol succinate and all-cause mortality in a large contemporary international cohort of patients with stable CHF and reduced ejection fraction. The finding was consistent through a range of important subgroups including patients in sinus rhythm for whom the benefits of beta-blockers are best established. Our results support the view that the reduction in mortality compared to placebo was similar across landmark trials that used these three beta-blockers [4,7,3,8].

Our results contrast to the Carvedilol or Metoprolol European Trial (COMET) that is the only adequately powered randomised head-to-head comparison of two beta-blockers. In COMET, carvedilol was associated with better survival than metoprolol tartrate in 3,029 patients with CHF symptoms (NYHA II-IV) and LVEF <35% [14]. However, metoprolol was used at a lower dose and with a different formulation than that proved to reduce mortality [8,4]. A network meta-analysis of 8 randomized beta-blocker trials including 4,563 patients reported a potential benefit in favour of carvedilol over beta 1-receptor selective blockers [13], but 94% of the deaths derived from the

COMET trial. The results must therefore be interpreted with caution. Our analysis supports results from other observational studies [16,17,22] and meta-analyses [12,19,23] that found carvedilol and metoprolol similarly effective. Some of these studies included metoprolol tartrate [16,12] and did not account for beta-blocker dose [19,17]. Our study therefore adds important evidence to current knowledge.

In patients who were not in sinus rhythm, however, we noted a benefit of metoprolol succinate over carvedilol, although this may have been a chance finding reflecting the number of comparisons being made. However, this again contrasts with a post-hoc analysis from the COMET trial that reported additional benefits on mortality and morbidity of carvedilol relative to metoprolol tartrate in patients with CHF whether or not they were in atrial fibrillation. We have previously reported similar effectiveness of carvedilol and metoprolol succinate in 1,480 matched patients irrespective of the underlying heart rhythm [22]. Prior meta-analyses have questioned the prognostic benefit of beta-blockers in patients with CHF in atrial fibrillation [29,30]. Here it is important to note that our results merely indicate equal effectiveness of the beta-blockers concerned but – in the absence of an alternative comparator – cannot assess overall effectiveness.

The Multistep Administration of bisoprolol IN Chronic Heart Failure II (MAIN-CHF II) trial prospectively compared bisoprolol and carvedilol in the treatment of Japanese patients with mild to moderate CHF [15]. The trial, however, recruited only 59 patients and therefore lacks statistical power to test non-inferiority of bisoprolol vs. carvedilol. An observational study of 217 patients with CHF and NYHA functional class III/ IV symptoms reported no significant differences in the survival and cardiac event-free rates between treatment groups [18]. In addition, prospective trials found comparable tolerability of bisoprolol and carvedilol [31,32]. Similarly, our study does not find any evidence of superiority of carvedilol over bisoprolol while including a much larger cohort of contemporary CHF patients.

Bisoprolol and metoprolol succinate are both lipophilic beta 1-receptor selective blockers. However, their relative beta 1/ beta 2-affinities differ, being varying between 2.3 and 35 for metoprolol succinate and 13.5-18 for bisoprolol [9,33,34]. The difference may be of clinical relevance, but there are no

prospective trials on the comparative effectiveness of bisoprolol vs. metoprolol succinate in patients with CHF. An indirect head-to-head comparison using Bayesian network meta-analysis of randomized beta-blocker trials as well as an analysis from the Danish Heart Failure Registry did not find any statistical evidence for the superiority of bisoprolol vs. metoprolol [12,21]. However, the inclusion of both metoprolol succinate and metoprolol tartrate trials limits the informative value of the analyses. Moreover, the proportion of bisoprolol users in the Danish study was rather small (11.2%), and it is unclear how many patients received target doses of beta-blockers. In contrast, our study was performed with particular focus on equal dosing of beta-blockers.

Limitations

As with any non-randomized, observational design, the present study may be subject to unmeasured confounders. Sensitivity analyses cannot prove or rule out the presence of such an unmeasured confounder. However, our data result from comprehensive outpatient databases with continuous inclusion and close surveillance. The detailed characterization of patients allows consideration of various potential confounders through the use of comprehensive propensity score models. The large sample size and inclusion of patients from three European countries are obvious strengths of the present study. The results are therefore likely to be generalizable to other CHF populations. We observed substantial differences in patient characteristics between countries. However, as patient characteristics were used for propensity score calculation and matching, we expect that this should not have an impact on our results in the matched cohorts. We further cannot comment on the specific reasons for the selection of a particular beta-blocker, nor on medication adherence. In addition, our data do not allow identification of patients who either switched from one beta-blocker to another or changed the beta-blocker dose during follow-up. As inclusion into the analyses of our study was performed after stabilization of both clinical status and medication in an ambulatory setting, however, this may reduce the necessity for further modulation of beta-blocker treatment.

From this observational study, we can infer that there is no association between the beta-blocker prescribed and mortality but we cannot be sure that the lack of observed difference truly reflects similar benefit. Ideally, our results should be confirmed in a large-scale, randomized head-to-head

comparison of beta-blockers. Given the required sample size and associated costs, such a trial may never be done.

Conclusion

In an international, real-world cohort of CHF patients with reduced ejection fraction, we found no difference in all-cause mortality for patients treated with bisoprolol, carvedilol or metoprolol succinate. The finding was consistent in subgroups with respect to age, sex, LVEF, NYHA functional class, heart rate, and rhythm. In accordance with current guidelines, this analysis suggests that bisoprolol, carvedilol, and metoprolol succinate may be used interchangeably in the treatment of patients with CHF.

Conflict of interest: The authors declare that they have no conflict of interest.

All patients gave their written informed consent for data storage and evaluation. The study conformed to the principles outlined in the Declaration of Helsinki and was approved by the local ethics committees. Patients' data were pseudonymised for analyses.

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Figure legends

Fig. 1 Inclusion of beta-blocker users in study cohort

Fig. 2 Kaplan–Meier curves for 10-year survival for hospital outpatients with chronic heart failure receiving bisoprolol, carvedilol and metoprolol succinate, respectively

Fig. 3 a and b Absolute standardized differences before (a) and after (b) propensity score matching comparing covariate values for hospital outpatients with chronic heart failure receiving bisoprolol vs. carvedilol, bisoprolol vs. metoprolol succinate, and carvedilol vs. metoprolol succinate, respectively

Legend: ACEi, angiotensin converting enzyme; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate using the Modification of Diet in Renal Disease equation; HR, heart rate; BPsys, systolic blood pressure; LVEF, left ventricular ejection fraction; aHT, arterial hypertension; OPD, obstructive pulmonary disease; NYHA, New York Heart Association functional class; BMI, body mass index

Fig. 4 Kaplan–Meier curves for 10-year survival regarding all-cause mortality in the propensity and dose-equivalent matched cohort for hospital outpatients with chronic heart failure receiving bisoprolol or carvedilol

Fig. 5 Kaplan–Meier curves for 10-year survival regarding all-cause mortality in the propensity and dose-equivalent matched cohort for hospital outpatients with chronic heart failure receiving bisoprolol or metoprolol succinate

Fig. 6 Kaplan–Meier curves for 10-year survival regarding all-cause mortality in the propensity and dose-equivalent matched cohort for hospital outpatients with chronic heart failure receiving carvedilol or metoprolol succinate

Fig. 7 Cox regression analyses for all-cause mortality regarding beta-blocker use in the predefined subgroups for the propensity score matched cohorts

Legend: LVEF, left ventricular ejection fraction; NYHA, New York Heart Association functional class. *P for interaction refers to subgroups of each propensity matched sample.

Table 1: Baseline characteristics of CHF patients with respect to beta-blocker treatment

	All patients n = 6,010	Bisoprolol n = 1,023	Carvedilol n = 1,721	Metoprolol succinate n = 3,266	p-value	p-value*
Age, *y [n = 6,010]*	67 ± 13	67 ± 13	65 ± 13	69 ± 13	*<0.001*	*<0.001*
Men, *n (%) [n = 6,010]*	4,377 (72.8)	725 (70.9)	1,313 (76.3)	2,339 (71.6)	*<0.001*	0.06
BMI, *kg/m² [n = 5,543]*	27 ± 5	28 ± 5	27 ± 5	27 ± 5	*<0.001*	*<0.001*
Heart Failure Registry *[n = 6,010]*					*<0.001*	*n.a.*
Norway, *n (%)*	4,111 (68.4)	473 (46.2)	853 (49.6)	2,785 (85.3)		
Heidelberg, *n (%)*	1,171 (19.5)	277 (27.1)	443 (25.7)	451 (13.8)		
Hull, *n (%)*	728 (12.1)	273 (26.7)	425 (24.7)	30 (0.9)		
Cause of CHF *[n = 6,008]*					*<0.001*	*<0.001*
CHD, *n (%)*	3,130 (52.1)	498 (48.8)	834 (48.4)	1,798 (55.0)		
dCMP, *n (%)*	1,357 (22.6)	256 (25.1)	547 (31.8)	554 (17.0)		
Other, *n (%)*	1,521 (25.3)	267 (26.1)	340 (19.8)	914 (28.0)		
NYHA, *n (%) [n = 5,936]*					*<0.001*	*<0.001*
I	1,105 (18.6)	209 (20.5)	379 (22.3)	517 (16.1)		
II	3,117 (52.5)	511 (50.2)	908 (53.4)	1,698 (52.7)		
III	1,685 (28.4)	293 (28.8)	406 (23.9)	986 (30.6)		
IV	29 (0.5)	5 (0.5)	6 (0.4)	18 (0.6)		
LVEF, *% [n = 5,380]*	33 ± 11	33 ± 12	31 ± 11	33 ± 12	*<0.001*	*<0.001*
BPsys, *mmHg [n = 5,957]*	123 ± 21	124 ± 22	122 ± 21	124 ± 20	*0.01*	*<0.001*
Sinus rhythm, *n (%) [n = 5,120]*	3,263 (63.7)	507 (63.5)	947 (68.4)	1,809 (61.6)	*<0.001*	*<0.001*
HR, *1/min [n = 5,943]*	68 ± 12	67 ± 13	69 ± 13	67 ± 12	*<0.001*	*<0.001*
NT-proBNP, *pg/mL [n =*	982	1,059	939	981	0.18	*<0.001*

2,671]	(338-2,367)	(365-2,617)	(342-2,216)	(316-2,348)		
Creatinine, *μmol/L [n = 5,826]*	97 (80-121)	97 (81-120)	97 (80-124)	96 (80-120)	0.42	*<0.001*
eGFR, *mL/min/1.73m² [n = 5,826]*	65 (49-83)	63 (48-81)	64 (47-84)	66 (51-83)	*0.01*	*<0.001*
Sodium, *mmol/L [n =5,808]*	140 ± 3	140 ± 3	139 ± 3	140 ± 3	*<0.001*	*<0.001*
Potassium, *mmol/L [n = 5,813]*	4.4 ± 0.5	4.4 ± 0.5	4.4 ± 0.5	4.4 ± 0.4	*0.007*	*<0.001*
Haemoglobin, *g/dL [n = 3,689]*	13.7 ± 1.6	13.7 ± 1.6	13.5 ± 1.6	13.7 ± 1.5	*0.001*	*0.02*
Comorbidities, *n (%)*						
OPD *[n = 6,010]*	708 (11.8)	232 (22.7)	123 (7.1)	353 (10.8)	*<0.001*	*<0.001*
aHT *[n = 5,962]*	2,405 (40.3)	473 (47.1)	632 (37.1)	1,300 (39.9)	*<0.001*	*<0.001*
Hyperlipidaemia *[n = 5,219]*	3,098 (59.4)	445 (61.2)	701 (55.2)	1,952 (60.5)	*0.003*	*0.03*
Active smoker *[n = 5,882]*	884 (15.0)	137 (14.1)	226 (13.4)	521 (16.1)	*0.002*	*<0.001*
Stroke *[n = 5,282]*	437 (8.3)	51 (6.8)	72 (5.6)	314 (9.7)	*<0.001*	0.52
PVD *[n = 5,282]*	436 (8.3)	88 (11.7)	96 (7.4)	252 (7.8)	*0.001*	*<0.001*
Diabetes *[n = 5,919]*	1,171 (19.8)	222 (22.5)	343 (20.3)	606 (18.7)	*0.026*	*<0.001*
Treatment						
Beta-blocker dose equivalent, *% [n = 6,010]*	52.6 (26.3-100)	50 (25.0-100)	50 (25.0-100)	52.6 (26.3-100)	*<0.001*	*<0.001*
ACEi, *n (%) [n = 6,010]*	4,459 (74.2)	718 (70.2)	1,305 (75.8)	2,436 (74.6)	*0.004*	*<0.001*
ACEi dose equivalent,	100	100	100	100	*0.01*	*<0.001*

% [n = 4,457]	(50-100)	(50-100)	(50-100)	(50-100)		
ARB, n (%) [n = 5,997]	1,212 (20.2)	240 (23.6)	337 (19.6)	635 (19.5)	0.01	<0.001
ACEi and/or ARB, n (%) [n = 6,010]	5,184 (86.3)	831 (81.2)	1,453 (84.4)	2,900 (88.8)	<0.001	<0.001
ACEi/ ARB dose equivalent, % [n = 5,495]	100 (50-100)	75 (50-100)	100 (50-100)	100 (50-100)	0.003	<0.001
MRA, n (%) [n = 6,003]	2,002 (33.3)	351 (34.3)	739 (43.0)	912 (28.0)	<0.001	<0.001
Loop diuretic, n (%) [n = 6,010]	4,468 (74.3)	702 (68.6)	1,350 (78.4)	2,416 (74.0)	<0.001	<0.001
Loop diuretic dose, mg furosemide [n = 4,460]	40 (20-80)	40 (40-80)	40 (20-80)	40 (20-80)	0.02	<0.001
Aspirin, n (%) [n = 6,010]	2,562 (42.6)	390 (38.1)	607 (35.3)	1,565 (47.9)	<0.001	<0.001
Statin, n (%) [n = 6,010]	3,209 (53.4)	575 (56.2)	946 (55.0)	1,688 (51.7)	0.01	<0.001

Values shown are mean ± SD or median (interquartile range). p-values <0.05 are written in italics. *p-values refer to comparisons between countries. n, number; BMI, body mass index; CHF, chronic heart failure; CHD, coronary heart disease; dCMP, dilated cardiomyopathy; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; BPsys, systolic blood pressure; HR, heart rate; eGFR, estimated glomerular filtration rate calculated using the Modification of Diet in Renal Disease equation; OPD, obstructive pulmonary disease; aHT, arterial hypertension; PVD, peripheral vascular disease; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor antagonist; MRA, mineralocorticoid receptor antagonist. Dose equivalent represent percentage achieved of the individual drug with respect to the guideline recommended target dose.