Title: Comparative effectiveness of loop diuretics on mortality in the treatment of patients with chronic heart failure – a multicenter propensity score matched analysis.

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Abstract

Background: Loop diuretics are given to the majority of patients with chronic heart failure (HF). Whether the different pharmacological properties of the three guideline-recommended loop diuretics result in differential effects on survival is unknown.

Methods: 6,293 patients with chronic HF using either bumetanide, furosemide or torasemide were identified in three European HF registries. Patients were individually matched on both the respective propensity scores for receipt of either drug and dose-equivalents thereof.

Results: During a follow-up of 35,038 patient-years, 652 (53.7%), 2,179 (51.9%), and 268 (30.4%) patients died amongst those prescribed bumetanide, furosemide, and torasemide, respectively. In univariable analyses of the general sample, bumetanide and furosemide were both associated with higher mortality as compared with torasemide treatment (HR 1.50, 95% CI 1.31-1.73, p<0.001, and HR 1.34, CI 1.18-1.52, p<0.001, respectively). Mortality was higher in bumetanide users when compared to furosemide users (HR 1.11, 95% CI 1.02-1.20, p=0.01). However, there was no significant association between loop diuretic choice and all-cause mortality in any of the matched samples (bumetanide vs. furosemide, HR 1.03, 95% CI 0.93-1.14, p=0.53; bumetanide vs. torasemide, HR 0.98, 95% CI 0.78-1.24, p=0.89; furosemide vs. torasemide, HR 1.02, 95% CI 0.84-1.24, p=0.82). The results were confirmed in subgroup analyses with respect to age, sex, left ventricular ejection fraction, NYHA functional class, cause of HF, rhythm, and systolic blood pressure.

Conclusions: In patients with HF, mortality is not affected by the choice of individual loop diuretics.

Words: 235

Introduction

Guidelines recommend the use of diuretics to reduce the signs and symptoms of congestion in patients with heart failure (HF) [1, 2]. In addition, diuretics appear to reduce the risk of death and worsening HF compared with placebo [3, 4]. Approximately 60-90% of patients with HF receive at least 1 class of diuretics, particularly a loop diuretic, for the management of acute or chronic HF [5-8]. Furosemide is more commonly used than other loop diuretics [5]. Supplemental table 1 summarizes the pharmacological differences between bumetanide, furosemide and torasemide.

There is some data suggesting potential benefits from longer acting diuretics such as torasemide [9-14] or azosemide [15-17] as compared to furosemide. However, the effects of the few available retrospective [18, 19] and prospective [20-22] comparisons of loop diuretics on mortality are inconsistent. The studies are limited by remarkable heterogeneity, small sample size, poor background HF therapy, or short follow-up duration.

In the present study, we therefore assessed the relative effectiveness in all-cause mortality of the three guideline-recommended loop-diuretics in patients with chronic HF using an international, multicenter, propensity score matched approach.

Methods

Databases

Data were extracted from three different European HF databases: the Norwegian HF Registry, the HF Registry of the Department of Academic Cardiology, University of Hull, UK, and the HF 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 HF Registry was initiated in October 2000 and patients were enrolled from the outpatient 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 HF clinics of the University of Hull, UK, and the University of Heidelberg, Germany, for evaluation of HF were offered inclusion into the local HF 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. Baseline visits of Norwegian patients were performed between 2000 and 2012. For patients from Germany and UK, the respective time periods were 1995-2015 and 2001-2015, respectively. Patients were eligible for the study if they met **all** of the following criteria: a) attendance at the HF outpatient clinic of any of the participating hospitals, b) written informed consent for inclusion into the respective HF registry, c) diagnosis of chronic HF, d) treatment with a loop diuretic, and e) reported daily dose of diuretic treatment.

Medication was at the discretion of the referring physician. As only few patients were treated with azosemide (n=0) or piretanide (n=40), the present analysis was restricted to users of the three guideline-recommended loop diuretics: bumetanide, furosemide, or torasemide (*figure 1*). Dose equivalents were derived from ESC guidelines for the diagnosis and treatment of acute and chronic HF [1], and expressed in mg furosemide. For example, daily oral doses of 10 mg torasemide or 1 mg bumetanide were considered to be equivalent to 40 mg furosemide, while daily oral doses of 20 mg torasemide or 2 mg bumetanide were considered to be equivalent to 80 mg furosemide. Target doses and dose equivalents for angiotensin converting enzyme inhibitors, angiotensin receptor blockers and beta-blockers were also derived from ESC guidelines [1]. For example, daily doses of 10 mg ramipril or 20 mg enalapril were

considered as 100% dose equivalent, while 5 mg ramipril or 10 mg enalapril were defined as 50% dose equivalent. Similarly, daily doses of 10 mg bisoprolol or 50 mg carvedilol were defined as 100% dose equivalent.

The diagnosis of HF was established 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].
Baseline characteristics included medical history, physical examination, left ventricular ejection fraction (LVEF), blood count and chemistry, and medication. Glomerular filtration rate (GFR) was estimated using the Chronic Kidney Disease Epidemiology Collaboration formula (CKD-EPI) [23].

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 HF Registry, mortality data were obtained at regular intervals from the National Statistics Bureau and no patient was lost to follow-up. All-cause mortality was the predefined endpoint of the study. All patients were followed for at least 1 month.

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 [24].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 bumetanide, furosemide, or torasemide were analysed using Cox proportional hazard models and displayed using the Kaplan-Meier method. To account for possible confounders, patients were matched with respect to diuretic treatment using pairwise bi-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 loop diuretic was the dependent variable [25]. In a first step, propensity scores were calculated separately for “bumetanide vs. furosemide”, “bumetanide vs. torasemide”, and “furosemide vs. torasemide” as dependent variables. Propensity scores were derived from all baseline variables except for loop diuretic dose equivalent, estimated GFR (eGFR) and NT-proBNP using the multiple imputed baseline data sets. Dose equivalent of the respective loop diuretic was not part of the propensity scores as it was used as a separate matching criterion. eGFR and NT-proBNP were excluded due to a large number of missing variables. The logits of the probability of receiving a certain loop diuretic according to the respective propensity scores formed the basis of three separate matching procedures.

Patients were individually matched for both the propensity for receiving a particular loop diuretic and their dose equivalents. Each matching procedure was performed in two steps. Firstly, 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 loop diuretic (e.g. bumetanide), the closest match of a patient receiving a different loop diuretic (e.g. furosemide) was identified. Secondly, dose equivalents for the loop diuretics were compared. If doses 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 bumetanide patient of the failed match according to the propensity score. If a further patient on furosemide was thus identified, the second step was repeated. If no match according to the propensity score AND dose equivalent could be identified, the bumetanide patient was removed from the total sample and the matching cycle started with the next bumetanide patient.

The matching procedures of patients treated with bumetanide vs. torasemide and furosemide vs. torasemide 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 [26]. In addition, Chi-squared test, Mann-Whitney-U test, and student's t-test were used to test for differences in baseline variables after matching. As a sensitivity analysis to univariable survival analyses in the matched samples, we performed multivariable Cox regression analyses including significant covariates in the matched samples. Finally, 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 [27].

Subgroups

Analyses were repeated in pre-specified subgroups of the matched samples with respect to age (≤mean vs. >mean), sex, LVEF (≤35 % vs. >35 %), NYHA functional class (I/II vs. III/IV), cause of HF (ischaemic vs. non-ischaemic), eGFR (≤60 ml/min/1.73m² vs. >60 ml/min/1.73m²), serum potassium level (≤mean vs. >mean) and systolic blood pressure (≤120 mmHg vs. >120 mmHg). Interaction terms were calculated for each of the predefined subgroups in the propensity matched sample.

Results

We identified 9,289 HF patients in the three databases. *Figure 1* shows the composition and selection flow with respect to the different loop diuretics in our study population. Of 6,293 patients who met the inclusion criteria outlined above, 3,844 patients (61.1%) were from Norway, 1,120 patients (17.8%) were from Germany, and 1,329 patients (21.1%) were from England.

Bumetanide was prescribed for 1,215 patients (19.3%) with a median dose of 1 (1-2) mg/d (equivalent to 40 (40-80) mg furosemide per day), furosemide for 4,197 patients (66.7%) with a median dose of 40 (40-80) mg/d, and torasemide for 881 patients with a median dose of 20 (10-20) mg/d (equivalent to 80 (40-80) mg furosemide per day). Baseline characteristics of HF patients differed with respect to loop diuretic treatment for a number of variables (*table 1*). Overall, patients receiving torasemide were younger and more likely to be in NYHA functional class I than those on bumetanide and furosemide. In addition, the majority of patients using torasemide suffered from HF of non-ischaemic origin, while ischaemic HF was common in bumetanide and furosemide users. NT-proBNP levels were lower in the torasemide group, whereas mean LVEF was <35% in all three treatment groups. In patients using torasemide, systolic blood pressure was significantly lower as compared to patients on bumetanide or furosemide.

Total follow-up was 420,467 patient-months (35,038 patient-years) with a median follow-up duration of 61 (27-99) months. For bumetanide, median follow-up was 59 (26-98) months, whereas it was 67 (31-105) months and 36 (18-69) months for furosemide and torasemide, respectively. During that time 3,099 (49.2%) patients died: 652 (53.7%) of those on bumetanide, 2,179 (51.9%) of those on furosemide, and 268 (30.4%) of those on torasemide.

In univariable analyses of the overall cohort, patients prescribed bumetanide and furosemide both had higher mortality compared with those prescribed torasemide (HR 1.50, 95% CI 1.31-

1.73, p<0.001, and HR 1.34, CI 1.18-1.52, p<0.001, respectively). Mortality was higher in bumetanide users compared to furosemide users (HR 1.11, 95% CI 1.02-1.20, p=0.01). Kaplan–Meier curves for 10-year survival with respect to loop diuretic treatment are shown in *figure 2 a)*.

The matching procedures identified 1,175 pairs, 313 pairs, and 522 pairs patients with similar dose-equivalents for each of the three comparisons (bumetanide vs. furosemide, bumetanide vs. torasemide and furosemide vs. torasemide). Of these, 1,495 (63.6%), 301 (48.1%), and 443 (42.4%) patients died during 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 a substantial improvement in the covariate balance across the treatment groups (*supplemental figure 1 a) and b)*). However, matched patients treated with bumetanide or furosemide differed with respect to beta-blocker dose equivalents, while matched patients using bumetanide or torasemide varied with respect to heart rhythm, treatment with angiotensin converting enzyme inhibitors/ angiotensin receptor blockers, and beta-blocker dose equivalents. Matched patients with furosemide or torasemide treatment varied with respect to height, rhythm, and eGFR. The apparent statistical significance of the differences in baseline variables in the matched cohorts may result from large sample sizes and might thus not be biologically significant. Detailed descriptions of the matched samples are available in *supplemental tables 2-4*.

Univariable Cox proportional hazard analyses did not find any significant association between the particular loop diuretics prescribed and all-cause mortality in any of the matched samples (bumetanide vs. furosemide, HR 1.03, 95% CI 0.93-1.14, p=0.53; bumetanide vs. torasemide, HR 0.98, 95% CI 0.78-1.24, p=0.89; furosemide vs. torasemide, HR 1.02, 95% CI 0.84-1.24, p=0.82). Results were confirmed after adjusting for significant covariates in the matched samples (bumetanide vs. furosemide, HR 1.0121, 95% CI 0.91-1.1214, p=0.85; bumetanide vs. torasemide, HR 1.02, 95% CI 0.78-1.33, p=0.89; and furosemide vs. torasemide, HR 1.08,

95% CI 0.84-1.39, p=0.57). The Kaplan–Meier curves for survival of matched HF patients with respect to loop diuretic treatment are presented in *figures 2 b)-d).*

Subgroup analyses essentially confirmed that none of the loop diuretics was superior to one of the others, with the exception that furosemide was superior to bumetanide in patients with NYHA class III/IV HF symptoms, whereas bumetanide was superior to furosemide in NYHA class I/II patients. The relevant plot is shown in *figure 3*.

The formal sensitivity analyses indicate only a small residual bias. The respective Γ-values were 0.76, 0.73, and 0.84 for bumetanide vs. furosemide, bumetanide vs. torasemide, and furosemide vs. torasemide (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. furosemide (vs. torasemide), that unobserved covariate would need to produce a 16% increase in the odds of receipt of bumetanide while being a weak predictor of all-cause mortality.

Discussion

In this European multicentre cohort study of outpatients with chronic HF, we analysed the association of treatment with any of the three guideline-recommended loop diuretics bumetanide, furosemide, or torasemide and long-term survival. Our main findings are that

- patient characteristics were different between treatment groups and nations. Torasemide users were younger, had lower NT-proBNP levels and a higher eGFR than bumetanide and furosemide users. In addition, torasemide users more often had non-ischaemic HF, comorbidities such as hypertension and diabetes and were less often in sinus rhythm.
- treatment with torasemide appeared associated with lower mortality when compared to bumetanide and furosemide therapy in univariable analyses of the general sample, only.

- after controlling for confounders and loop diuretic dose, no difference in survival was noted between the three individual loop diuretics.
- results were consistent through a range of important subgroups.

Loop diuretics are an integral part of symptom management in patients with chronic HF. There is strong evidence that diuretics relieve symptoms, reduce episodes of decompensation and increase exercise capacity in patients with chronic HF [3, 4]. In the present analysis, a total of 73% of patients included in the three HF registries was treated with a loop diuretic. This number is lower when compared to data from hospitalized HF patients included in the US American Perspective database [5] but rather similar to other samples of patients with chronic HF [6, 7]. In line with previous reports [5, 18], the majority of patients was treated with furosemide. However, the proportion of patients using bumetanide or torasemide was higher when compared to other available registry data [5, 18].

In the present study, patients on torasemide were significantly younger and predominantly suffered from HF of non-ischaemic origin as compared to patients receiving bumetanide or furosemide. In addition, torasemide users tended to have features of less severe HF, leading to better survival in an unadjusted model as compared to those treated with bumetanide or furosemide. This contrasts to data from other retrospective analyses which reported more advanced HF in patients treated with torasemide as compared to furosemide users [18, 19, 28]. Although the majority of torasemide users had concomitant arterial hypertension, systolic blood pressure was significantly lower in patients on torasemide. The cause and effect relationship between variables associated with torasemide use is uncertain and requires further investigation. For example, patients with low blood pressure may lead clinicians to prefer torasemide since its longer half-life may increase tolerability of diuretic treatment. Alternatively, low blood pressure may result from the use of higher median diuretic doses and/or more extensive background HF or antihypertensive therapy in torasemide users.

Preclinical and clinical data suggest that there may be beneficial pharmacological and disease-specific effects with long-acting loop diuretics such as torasemide as compared to short-acting

furosemide [9-15, 29-36]. In brief, there is evidence that torasemide reduces aldosterone production, myocardial fibrosis, sympathetic activation, and ventricular remodelling [10-12, 14, 15, 31-33, 36]. In the present study, however, these potential benefits did not translate into improved survival with long-acting loop diuretics after risk adjustment.

Our finding in chronic stable patients is supported by two large retrospective analyses comparing furosemide and torasemide following acute decompensation HF [18, 19]. To date, there are no adequately powered randomized controlled trials comparing the long-term prognostic effects of different loop diuretics. Unlike bumetanide for which there is a dearth of clinical studies, a few small prospective studies have compared the effects of torasemide versus furosemide. Two open-label, randomized studies showed no difference in mortality between torasemide and furosemide users [21, 22], whereas the TOrasemide In Congestive HF (TORIC) study suggested a survival benefit with torasemide [20, 37]. However, TORIC was an open-label, non-randomised, post-marketing surveillance study with a median follow-up duration of only 5.9 months and a low use of standard HF therapies. The Japanese Multicenter Evaluation of LOng- versus short-acting Diuretics In Congestive heart failure (J-MELODIC) trial is a randomized, open, blinded endpoint trial that compared azosemide with furosemide in 320 patients with chronic HF [17]. Although azosemide significantly reduced the primary composite endpoint of cardiovascular death and unplanned admission to hospital for congestive HF after two years of follow-up, no statistically significant differences in cardiovascular mortality or all-cause death were noted. Again, the trial was not adequately powered to provide statistically robust results. In contrast, the present study is the largest analysis to date comparing torasemide to furosemide use in a population with chronic HF and the only study that provides data on bumetanide use.

In subgroup analyses of matched patients taking bumetanide or furosemide, we found that bumetanide was beneficial in patients with NYHA I/II symptoms, while furosemide was superior in NYHA class III/IV patients. There are no other studies against which to compare this finding. As bumetanide and furosemide share many pharmacological features, the reason for the

heterogeneity of the relative effectiveness over NYHA class subgroups remains unclear. Given the number of subgroup analyses being made, we cannot exclude a random result. Prospective trials are warranted to clarify the relative effectiveness of loop diuretics in patients with HF.

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. For example, data on the concurrent use of other diuretics such as thiazides were lacking and thus may have biased our results. Due to the retrospective design of the present analysis, we cannot comment on the specific reasons for selection of a particular loop diuretic nor on medication adherence. In this context, it must be noted that torasemide was only used in German patients, while bumetanide was only available in Norway and the UK. Young torasemide users are underrepresented in the matched samples since patients on bumetanide or furosemide were significantly older than torasemide users. Therefore, our conclusions may be transferred to younger torasemide users with caution. Our data do not allow identification of patients who either switched from one diuretic to another or changed diuretic dosing during follow-up. Also, we cannot comment on changes of other covariates over time. Follow-up duration in torasemide users was significantly shorter than in furosemide or bumetanide users which may bias outcome analyses. However, our data result from comprehensive outpatient databases with continuous, prospective inclusion, and close surveillance. The detailed characterization of patients allows consideration of various potential confounders through the use of comprehensive propensity score and multivariable Cox regression models. The large sample size, long-term follow-up and prospective inclusion of patients from three European countries are obvious strengths of the present study. The results are therefore likely to be generalizable to other chronic HF populations. However, final

evidence regarding the comparative effectiveness of loop diuretics is only possible through an adequately powered prospective randomised trial.

While the available evidence on the comparative prognostic effects of loop diuretics in chronic HF is scarce, some studies suggest advantages in HF symptoms and quality of life with the use of long-acting diuretics [17, 21, 22, 38]. As follow-up data on hospitalisation rates and clinical status were not available in the present study, we cannot comment on these endpoints. Due to the low number of patients receiving piretanide or azosemide, our study was restricted to patients using bumetanide, furosemide or torasemide. Results may not be transferable to patients taking other diuretics than those included in the present analysis.

There is an on-going debate whether treatment with diuretics has an impact on the prognosis of HF patients per se. Due to a lack of adequately powered randomised controlled trials, current guidelines acknowledge that diuretic effects on morbidity and mortality are unknown, and no specific guidance is provided on loop diuretic choice [1, 2]. While a Cochrane meta-analysis suggests that conventional diuretics may reduce the risk of death and worsening HF compared to placebo [3, 4], post-hoc analyses from large HF trials as well as a number of retrospective studies have reported adverse outcomes in HF patients prescribed loop diuretics [39-44]. As our study only included patients receiving loop diuretics, we cannot comment on the overall prognostic effect of loop diuretic treatment.

Lastly, it is arguable that the creation of three individually matched comparisons may yield slightly different results as no direct triplets (and thus within triplet comparisons) were formed. Therefore, hierarchical chains (if A is superior to B and B to C then A must be superior to C) as an alternative sensitivity analysis to our results were not feasible. We preferred individual pairwise comparison over triplet comparison as it allows for substantially more patients to be matched thus increasing statistical power of each group comparison. This argument, however, is purely theoretical as all pairwise comparisons found similar prognostic relevance for all loop-diuretics examined.

Conclusion

In this European multicentre cohort study of patients with HF, we found no difference in all-cause mortality for patients treated with bumetanide, furosemide, or torasemide after adjustment for covariates and loop diuretic dose. This finding was consistent through a number of important subgroups.

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Table 1: Baseline characteristics of patients with HF stratified by use of loop diuretics

	All patients (n = 6,293)	**Bumetanide (n = 1,215)**	**Furosemide (n = 4,197)**	**Torasemide (n = 881)**	**p-value**
Age, *years (n=6,293)*	68.9 ± 12.2	70.6 ± 11.3	70.2 ± 11.3	60.2 ± 12.8	*<0.001*
Female, *n (%) (n=6,293)*	1,704 (27.1)	352 (28.9)	1,151 (27.4)	201 (22.8)	*0.006*
BMI, *kg/m²* *(n=5,823)*	27.4 ± 5.3	27.7 ± 5.3	27.1 ± 5.2	28.6 ± 5.4	*<0.001*
SBP, *mmHg* *(n=6,200)*	123 ± 22	123 ± 22	125 ± 22	114 ± 19	*<0.001*
HR, *1/min* *(n=6,207)*	70 ± 14	70 ± 14	70 ± 14	71 ± 13	*0.029*
Sinus rhythm, *n (%)* *(n=6,071)*	3,687 (58.6)	716 (58.9)	2,533 (60.4)	438 (49.7)	*<0.001*
LVEF, *% (n=5,848)*	32 ± 11	33 ± 11	32 ± 11	31 ± 13	*<0.001*
Cause of HF, *n (%)* *(n=6,132)*					*<0.001*
ischaemic	3,276 (54.6)	640 (54.7)	2,323 (56.9)	313 (35.6)	
non-ischaemic	2,855 (45.4)	530 (45.3)	1,760 (43.1)	565 (64.4)	
NYHA class, *n (%)* *(n=6,212)*					*<0.001*
I	804 (12.9)	113 (9.4)	478 (11.6)	213 (24.2)	
II	3,157 (50.8)	624 (51.9)	2,218 (53.7)	315 (35.8)	
III	2,174 (35.0)	446 (37.1)	1,385 (33.5)	343 (39.0)	
IV	76 (1.2)	18 (1.5)	49 (1.2)	9 (1.0)	

Comorbidity, *n (%)* *(n=6,293)*					
Diabetes mellitus	1,469 (23.3)	280 (23.0)	882 (21.0)	307 (34.8)	*<0.001*
Hypertension	2,582 (41.0)	428 (35.2)	1,426 (33.9)	728 (82.7)	*<0.001*
COPD/ asthma	816 (12.9)	176 (14.5)	554 (13.2)	86 (9.8)	*0.006*
Smoker, *n (%)* *(n=6,293)*					*<0.001*
ever	2,182 (34.7)	368 (29.5)	1,385 (33.0)	429 (48.8)	
never	4,111 (66.3)	847 (70.5)	2,812 (67.0)	451 (51.2)	
Sodium, *mmol/L* *(n=5,936)*	139 ± 3	139 ± 3	140 ± 3	139 ± 3	*<0.001*
Potassium, *mmol/L* *(n=5,938)*	4.4 ± 0.5	4.4 ± 0.5	4.4 ± 0.5	4.4 ± 0.5	*0.002*
NTproBNP, *ng/L* *(n=2,761)*	1,387 (541-3,178)	1,463 (634-3,248)	1,514 (636-3,248)	1,146 (361-2,849)	*<0.001*
eGFR, *ml/min/1.73m²* *(n=3,630)*	59 (45-78)	57 (44-73)	58 (44-73)	68 (49-89)	*<0.001*
Treatment					
ACEI, *n (%)* *(n=6,293)*	4,574 (72.7)	871 (71.7)	3,068 (73.1)	635 (72.2)	0.635
ARB, *n (%)* *(n=6,292)*	1,294 (20.6)	244 (20.1)	760 (18.1)	290 (32.9)	*<0.001*
ACEI and/or ARB, *n (%)* *(n=6,293)*	5,714 (90.8)	1,098 (90.4)	3,777 (90.0)	839 (95.3)	*<0.001*

ACEI/ARB dose equivalent, *% (n=6,278)*	50 (50-100)	50 (50-100)	50 (50-100)	75 (50-100)	*<0.001*
Beta-blocker, *n (%) (n=6,293)*	5,330 (84.7)	1,054 (86.7)	3,444 (82.1)	832 (94.5)	*<0.001*
Beta-blocker dose equivalent, *% (n=6,124)*	50 (25-100)	50 (25-100)	50 (13-79)	75 (50-100)	*<0.001*
MRA, *n (%) (n=6,291)*	2,302 (36.6)	515 (42.4)	1,176 (28.0)	611 (69.4)	*<0.001*
Loop diuretic dose, *mg furosemide (n=6,293)*	40 (40-80)	40 (40-80)	40 (40-80)	80 (40-80)	*<0.001*
Anticoagulants, *n (%) (n=6,293)*	3,071 (48.8)	586 (48.2)	1,889 (45.0)	596 (67.7)	*<0.001*
ASA, *n (%) (n=6,293)*	2,590 (41.2)	503 (41.4)	1,885 (44.9)	202 (22.9)	*<0.001*
Statin, *n (%) (n=6,293)*	3,305 (52.5)	628 (51.7)	2,091 (49.8)	586 (66.6)	*<0.001*

HF, heart failure; BMI, body mass index; SBP, systolic blood pressure; HR, heart rate; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; COPD, chronic obstructive pulmonary disease; NTproBNP, N-terminal pro brain natriuretic peptide; eGFR, estimated glomerular filtration rate using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist; ASA, acetylsalicyl acid. Significant p-values are written in italics. Numbers in italics show the number of patients with available information on the respective variable.

Figures

Figure 1: Selection of patients for inclusion in the present analyses

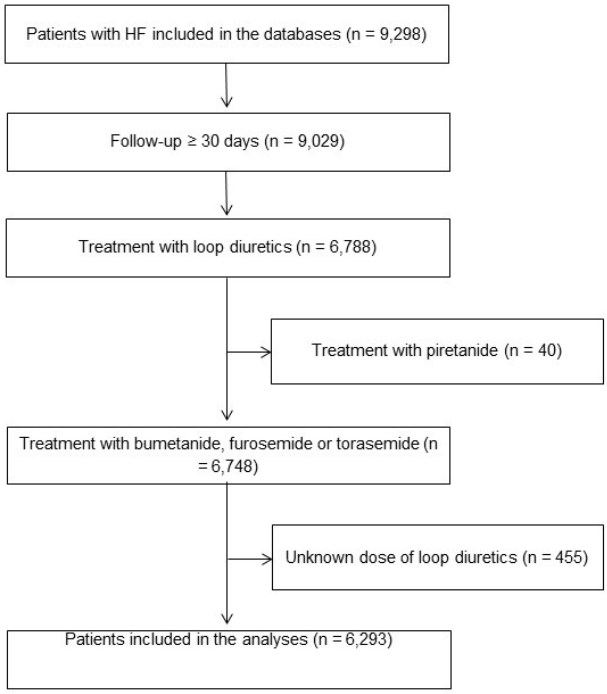

Figure 2: Kaplan–Meier curves for 10-year survival for hospital outpatients with chronic heart failure receiving bumetanide, furosemide, and torasemide, respectively: a) general sample, b) matched patients with bumetanide or furosemide treatment, c) matched patients with furosemide or torasemide treatment, d) matched patients with bumetanide or torasemide treatment.

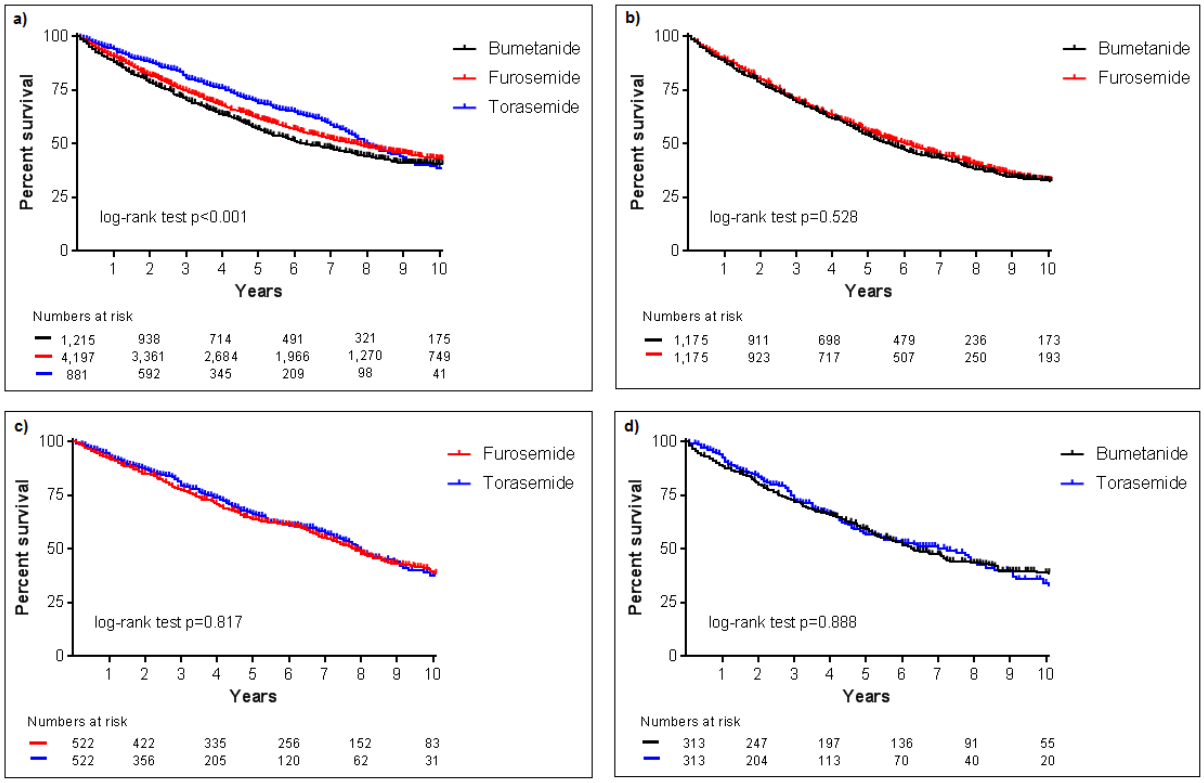

Figure 3: Cox regression analyses for all-cause mortality regarding loop diuretic use in the predefined subgroups for the propensity score matched cohorts.

Legend: SBP, systolic blood pressure; HF, heart failure; eGFR; estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association functional class. **P* for interaction refers to subgroups of each propensity matched sample.