Torsemide versus Furosemide in Patients with Acute Heart Failure (From the ASCEND-HF Trial)

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Abstract

Furosemide is the most commonly used loop diuretic in heart failure (HF) patients despite data suggesting potential pharmacologic and anti-fibrotic benefits with torsemide. We investigated HF patients in ASCEND-HF who were discharged on either torsemide or furosemide. Using inverse probability weighting to account for the non-random selection of diuretic, we assessed the relation between choice of diuretic at discharge with 30-day mortality or HF hospitalization and 180-day mortality. Of 7,141 patients in the trial, 4,177 patients were included in this analysis, of which 87% (n=3,620) received furosemide and 13% (n=557) received torsemide. Torsemide-treated patients had lower ejection fraction and blood pressure, and higher creatinine and natriuretic peptide level compared with furosemide. Torsemide was associated with similar outcomes on unadjusted analysis and nominally lower events on adjusted analysis [30–day mortality/HF hospitalization OR 0.89, 95% CI: 0.62–1.29, P=0.55 and 180-day mortality HR 0.86, 95% CI: 0.63–1.19, P=0.37]. In conclusion, these data are hypothesis-generating and randomized comparative-effectiveness trials are needed to investigate the optimal diuretic choice.

Keywords

loop diuretics; torsemide; furosemide; heart failure

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Loop diuretics including furosemide and torsemide are prescribed for the majority of symptomatic heart failure (HF) patients[1,2]. Guidelines indicate that the optimal use of diuretics is a cornerstone of HF therapy[3]. However, despite preclinical and clinical data supporting benefits with torsemide, furosemide is the most commonly used loop diuretic[4]. Several small studies of torsemide vs. furosemide[5–7] and a recent meta-analysis[8] suggest a decrease in HF morbidity and potentially mortality with torsemide compared with furosemide. These previous studies were limited by modest sample sizes in cohorts of patients from more than a decade ago. In order to investigate the potential role of torsemide in contemporary clinical practice, we assessed loop diuretics in a large, international acute HF trial and evaluated the association with baseline characteristics and post-discharge outcomes.

METHODS

The design and results of the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) trial have been reported previously[9,10]. Briefly, the trial was an international, double-blind, placebo-controlled study evaluating the effectiveness and safety of nesiritide in addition to standard care among 7,141 patients with acute HF. The trial was conducted from May 2007 through August 2010 at 398 centers in 30 countries throughout the world. Detailed inclusion and exclusion criteria have been described previously[9]. The 2 primary end points were a composite end point of all-cause mortality or HF readmission up to 30 days after randomization and the change in early dyspnea relief after study drug initiation.

Data on patient characteristics were collected during the baseline hospitalization. Loop diuretic use was documented at hospital admission and discharge. Rehospitalization and fatal events within 30 days after randomization were reviewed and categorized by an independent, blinded clinical-events committee. HF hospitalization was classified as previously described[10]. In brief, HF hospitalization required typical clinical manifestations of worsening HF and the addition of or increase in treatment specifically for worsening HF. All-cause mortality was assessed through 180 days.

For the primary analyses, we limited the cohort to patients discharged alive on either furosemide or torsemide. Given significant regional variation in the use of torsemide, we restricted the analyses to those countries having at least 20 patients on either torsemide or furosemide and having some patients on torsemide.

The primary outcome for the present analysis was all-cause mortality or HF hospitalization through 30-days after discharge. Secondary outcomes were 30-day all-cause mortality, 30-day HF hospitalization and 180-day all-cause mortality post-discharge. We were also interested in identifying clinical factors associated with patients being discharged on torsemide as compared with furosemide.

We summarized the patterns of loop diuretic use in ASCEND-HF patients. Demographics, physical and laboratory findings, medical history, and therapies were summarized as frequencies and percentages for categorical variables and by the medians and 25th and 75th

percentiles for continuous variables in patients discharged on either torsemide or furosemide. Baseline characteristics were compared using the Student's t-test or Wilcoxon rank sum test for continuous variables, and chi-square tests for categorical variables as appropriate. We generated a multivariable logistic regression model to determine admission variables associated with discharge torsemide use (over furosemide). We assessed the number of events for the outcomes of interest based on discharge diuretic.

Because the choice of diuretic at discharge was not randomized, we developed a propensity score model to predict the use of furosemide vs. torsemide. The propensity score model was fitted using a logistic regression model with baseline covariates identified in previous ASCEND-HF models[11]. The covariates were country of randomization, age, previous hospitalization for HF, baseline systolic blood pressure (SBP), baseline sodium, baseline BUN, and having a qualifying episode with jugular venous distension (JVD). The estimated propensity scores were used in inverse propensity weighted (IPW) models[12] to assess the association of furosemide or torsemide use with clinical endpoints. IPW methods are a set of statistical techniques that re-weight the data to create a pseudo-population where patient characteristics are independent of treatment received[13]. This condition where there is independence of observed baseline factors and treatment is similar to what would be expected in a randomized study. Thus, IPW is a powerful method for using observational data to compare the effectiveness of 2 or more treatments[13]. This technique offers methodology to address concerns that any observed difference in outcome between 2 groups may reflect inherent differences between the groups (e.g., one group has an increased severity of disease) rather than effects caused by the 2 treatments. In the present analysis, covariate balance was assessed using standardized differences[14]. Logistic regression analyses (for 30-day endpoints) and Cox proportional hazards (for the 180-day endpoint) models were generated to assess the association between loop diuretics and clinical outcomes, weighted by the inverse of the estimated probability of the choice of a particular diuretic. Multivariate regression analysis adjusting for covariates above was also performed as a secondary analysis. Hazard ratios (HRs) for 180-day mortality and Odds Ratios (ORs) for other endpoints were calculated with corresponding 95% confidence intervals (CIs) relative to discharge diuretic. Event rate curves were shown using unadjusted and IPW adjusted Kaplan-Meier estimates. Statistical significance was assessed using 2-sided P values. A P value <0.05 was considered statistically significant. All statistical computations were generated using SAS version 9.4 (SAS Institute Inc., Cary, NC). No extramural funding was used to support this work. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

RESULTS

Figure 1 presents the patients included in this analysis. Of the 7,141 patients in ASCEND, there was discharge diuretic information on 6,398. The majority of patients discharged on a loop diuretic received furosemide (N=5,305; 82.9%). Torsemide was the next most common loop diuretic (N=628; 9.8%) and 267 patients (4.2%) were prescribed bumetanide. There were 72 patients discharged on a combination of loop diuretics and 126 patients (2.0%) who were not discharged on a loop diuretic. The analysis cohort restricted to patients from

countries with at least 20 participants on either torsemide or furosemide and having some patients on torsemide consisted of 4,177 patients from 7 countries: China, India, Korea, Poland, Russia, Ukraine and the United States (Table 1). Of the 4,177 patients in the outcomes analysis cohort, 87% (n=3,620) received furosemide and 13% (n=557) received torsemide. Patients enrolled in the United States constituted nearly half of the overall torsemide cohort (N=265, 47.6%), where there was 11.4% use of torsemide compared to 88.6% use of furosemide.

The baseline patient characteristics by discharge diuretic are presented in Table 1. Patients receiving torsemide had more comorbidities than those receiving furosemide. For instance, torsemide-treated patients had more diabetes mellitus, and atrial and ventricular arrhythmias compared with furosemide-treated patients. The median ejection fraction (EF) was lower in those receiving torsemide. Ischemic etiology was more common in torsemide patients. Torsemide-treated patients had lower systolic blood pressure, and greater creatinine, BUN, and natriuretic peptide level. Patients discharged on torsemide more often received mineralocorticoid receptor antagonists (MRAs) and digoxin on admission compared with furosemide patients. They also had greater baseline use of implantable cardiac devices compared with furosemide-treated patients.

Factors associated with torsemide use at discharge as presented in Table 2. Country was the variable most strongly predictive of baseline torsemide use. Clinical factors associated with torsemide use were higher BUN, lower SBP, and JVD noted during the qualifying episode.

Table 3 presents the outcomes data in patients treated with furosemide or torsemide. Torsemide was associated with similar outcomes on unadjusted analysis [30-day mortality/HF hospitalization Odds Ratio (OR) 1.03, 95% Confidence Interval (CI): 0.73–1.45, P=0.88 and 180-day mortality Hazard Ratio (HR) 0.97, 95% CI: 0.73–1.29, P=0.83]. On IPW-adjusted analysis, torsemide use was associated with nominally lower 30-day mortality or HF hospitalization (OR 0.89, 95% CI: 0.62–1.29, P=0.55), 30-day mortality (OR 0.89, 95% CI: 0.40–1.97, P=0.78), 30-day HF hospitalization (OR 0.87; 95% CI: 0.58–1.30, P=0.49) and 180-day mortality (HR 0.86, 95% CI: 0.63–1.19; P=0.37) compared with furosemide. Figures 2 and 3 present the unadjusted and IPW-adjusted event rate curves and Forest Plots, respectively.

DISCUSSION

In a large international acute HF trial, we found that furosemide was the primary loop diuretic used for volume management. There was significant regional variation in the use of other loop diuretics such as torsemide with no use in most countries and comparatively greater use in the Ukraine, Korea, Russia, India and the United States. Patients treated with torsemide tended to have features of more severe disease compared with furosemide-treated patients. After risk-adjustment, torsemide was associated with a non-significant reduction in 30 and 180-day events. These findings support prior data suggesting potential benefits with torsemide and extend the data to the contemporary population hospitalized with acute HF.

A major finding of our analysis was that torsemide-treated patients tended to have features of more severe disease. The clinical factors most strongly associated with torsemide use beyond geographic region were higher BUN, lower SBP, and JVD. These findings suggest that clinicians tend to use torsemide in the setting of refractory volume overload and renal dysfunction. The preferential use of torsemide in these circumstances may be related to torsemide's increased bioavailability, longer half-life (particularly in the setting of renal dysfunction), and maintained absorption in the setting of oral intake and intestinal edema[15]. In fact, the median dose of furosemide equivalents was the same between groups. Importantly, the cause and effect relationship between variables associated with torsemide use is uncertain and requires further investigation. For instance, patients with lower SBP may have more advanced disease leading clinicians to preferentially select torsemide. Alternatively or in parallel, torsemide's pharmacologic profile may lead to more potent diuresis with resultant lower SBP. Similar relationships may be observed with torsemide use and renal function. Torsemide-treated patients also more often received MRA therapy, which influences renal function, but could also be a marker of worse cardiac dysfunction and resultant underlying cardiorenal syndrome. Thus, it is only through prospective, randomized trials that these issues can be adequately assessed.

A primary finding of our analysis was that despite increased severity of disease in the torsemide-treated patients, they had similar outcomes compared to those treated with furosemide. Following risk adjustment, torsemide use was associated with a nominal reduction in 30-day and 180-day events. Interestingly, the adjusted event curves begin to diverge fairly late (i.e., after 90-days post-discharge). One possible explanation is that those patients with more advanced HF die during this early period and are unable to experience any potential beneficial effect of torsemide on underlying fibrosis. On the other hand, those patients who survive the early vulnerable period and have a longer exposure to torsemide may benefit from underlying anti-fibrotic effects[16–21].

Previous studies suggested that torsemide may be associated with better outcomes than furosemide in chronic HF patients[22]. A small (N=234) open-label, randomized study by Murray *et al* compared chronic HF with reduced EF patients receiving torsemide vs. furosemide[5]. All-cause mortality at 12 months was lower with torsemide vs. furosemide (18 vs. 25 deaths), but the difference was not statistically significant (risk ratio 0.77, 95% CI: 0.45–1.33). The TOrasemide In Congestive HF Study investigated torsemide compared with furosemide/other loop diuretics in 1,377 chronic HF patients in an open-label, observational study[6]. Mortality through 12 months was significantly lower in the torsemide group (2.2% vs. 4.5%, P<0.005). These study results as well as another small (N=237) chronic HF study[7] were the focus of a recent meta-analysis by Bikdeli *et al,* which suggested a non-significant trend toward reduced mortality with torsemide compared with furosemide (risk ratio 0.68, 95% CI: 0.39, 1.18)[4]. These prior studies were limited by smaller sample sizes and low event counts (101 total deaths). They also were limited to chronic HF patients and were published between 2001 and 2003. Thus, we provide the first contemporary data related to outcomes in HF patients treated with torsemide vs. furosemide following acute HF hospitalization. These data suggest potential benefits associated with torsemide use even in

the context of current HF therapies. Importantly, these results should be recognized as hypothesis-generating given the observational nature of this analysis.

Pre-clinical and clinical data suggest potential mechanisms for improved outcomes with torsemide compared with furosemide as recently reviewed[22]. In brief, torsemide also has beneficial effects on aldosterone production, myocardial fibrosis, sympathetic activation, and ventricular remodeling[16–21]. Animal studies of torsemide demonstrated reduced aldosterone production and inhibition of aldosterone receptor binding that were not seen with furosemide[17,18]. Since aldosterone blockade is a primary treatment for reduced EF, these observations are highly relevant. In chronic HF patients, torsemide has been shown to decrease myocardial fibrosis as a result of reduced collagen synthesis and cross-linking, whereas furosemide has not[20,23,24]. Of note, none of the patients included in these earlier studies received MRAs. Nonetheless, data suggest that torsemide acts at a different level than MRAs to interfere with the myocardial fibrotic process[25]. Importantly, conflicting data have recently been presented suggesting that torsemide may not block aldosterone receptor binding[26] such that co-administration of torsemide and an MRA may be warranted. A small randomized trial of torsemide vs. furosemide in patients with renal failure found that the diuretics had similar effects on fluid and sodium excretion, but torsemide led to less renin-angiotensin-aldosterone system activation[16]. A study by Yamato *et al* compared torsemide and furosemide therapy in 50 chronic HF patients[27]. At 6 months, study parameters were unchanged in the furosemide group, whereas the torsemide group had a smaller left ventricular (LV) diameter, improved LV filling parameters, and decreased natriuretic peptide levels. Additional benefits with torsemide over furosemide include less urinary potassium loss[28,29] with the potential for reduced arrhythmia burden and improved compliance due to less frequent dosing, and decreased urinary urgency and micturition episodes[7].

We did not find that torsemide use was associated with significantly improved outcomes. However, the point estimates for the adjusted association between torsemide and outcomes favored torsemide for each endpoint. The lack of a significant association may be due to type 2 error. Alternatively, the lack of a significant association may have been related, in part, due to the complex interaction of a number of factors that influence early post-discharge outcomes. For instance, HF rehospitalization rates are subject to significant regional variation[30].

In sum, outside the context of a randomized trial, we do not believe these findings warrant a change in current clinical practice regarding loop diuretic selection. However, these data provide further rationale for such a trial and suggest potential clinical advantages to using torsemide in acute HF patients.

This was a retrospective analysis from a clinical trial. Given the significant regional variation in the use of torsemide, our sample size was reduced for the present analysis and results should be viewed as hypothesis-generating. We used adjustment covariates that have been used in prior ASCEND-HF analyses as one strategy to minimize bias via a consistent variable selection process. Despite IPW adjustment, other measured and unmeasured variables may have influenced these results. Nonetheless, it is interesting to note that the

torsemide-treated patients tended to have features of more severe disease, and despite this, had similar outcomes on unadjusted analysis and a nominal reduction in events following adjustment with the ASCEND risk model variables. However, outside of the context of a randomized clinical trial, the effect of torsemide as compared with furosemide cannot be established. The analysis population was not a new-user design given the common use of both diuretics and a requirement for the care of symptomatic heart failure patients. Furthermore, data were not available regarding post-discharge diuretic changes (e.g., crossover between furosemide and torsemide). These data should be viewed as exploratory.

Acknowledgments

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Highlights

- Furosemide is the most commonly used loop diuretic in heart failure (HF) patients despite data suggesting potential pharmacologic and anti-fibrotic benefits with torsemide.

- In this large international acute HF trial, a minority of patients received torsemide and commonly had indicators of more severe disease.

- After risk-adjustment, torsemide was associated with a non-significant reduction in 30 and 180-day events.
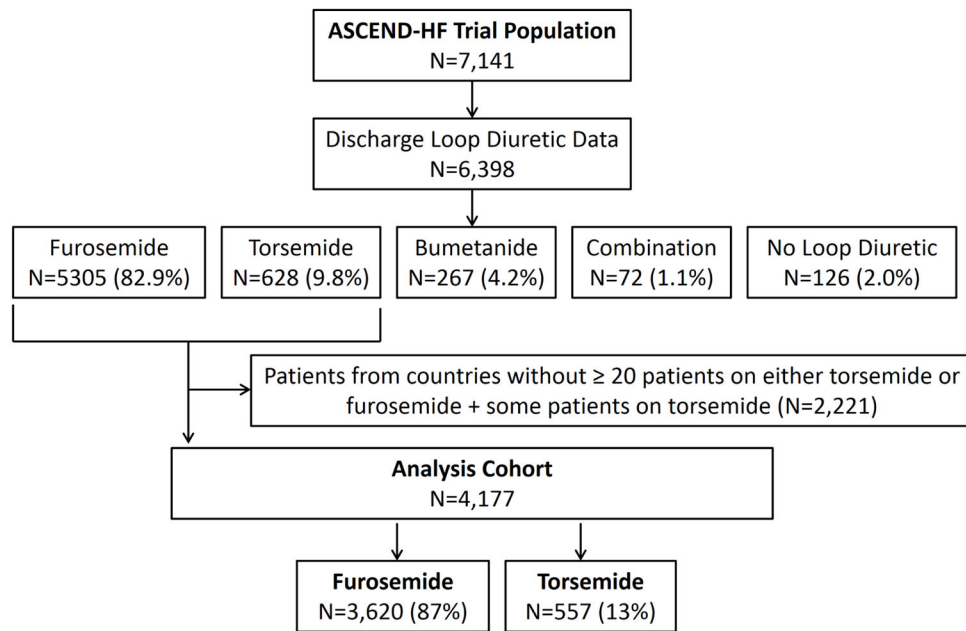
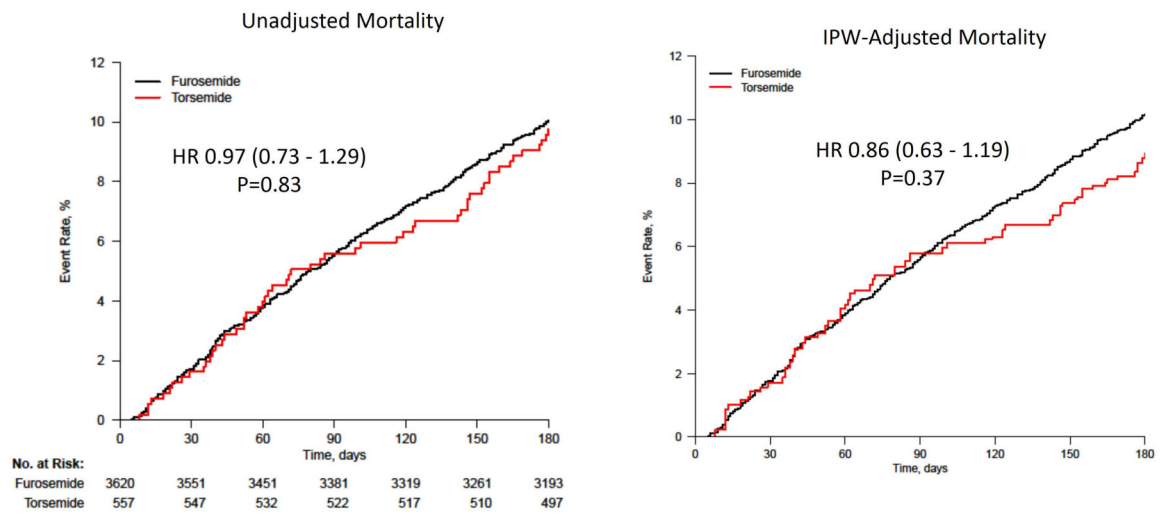**Figure 1.**
Study population.

Figure 2.
Unadjusted (A) and IPW adjusted (B) event rate curves by discharge loop diuretic*.

*Hazard Ratio (95% Confidence Interval) is for torsemide compared with furosemide.
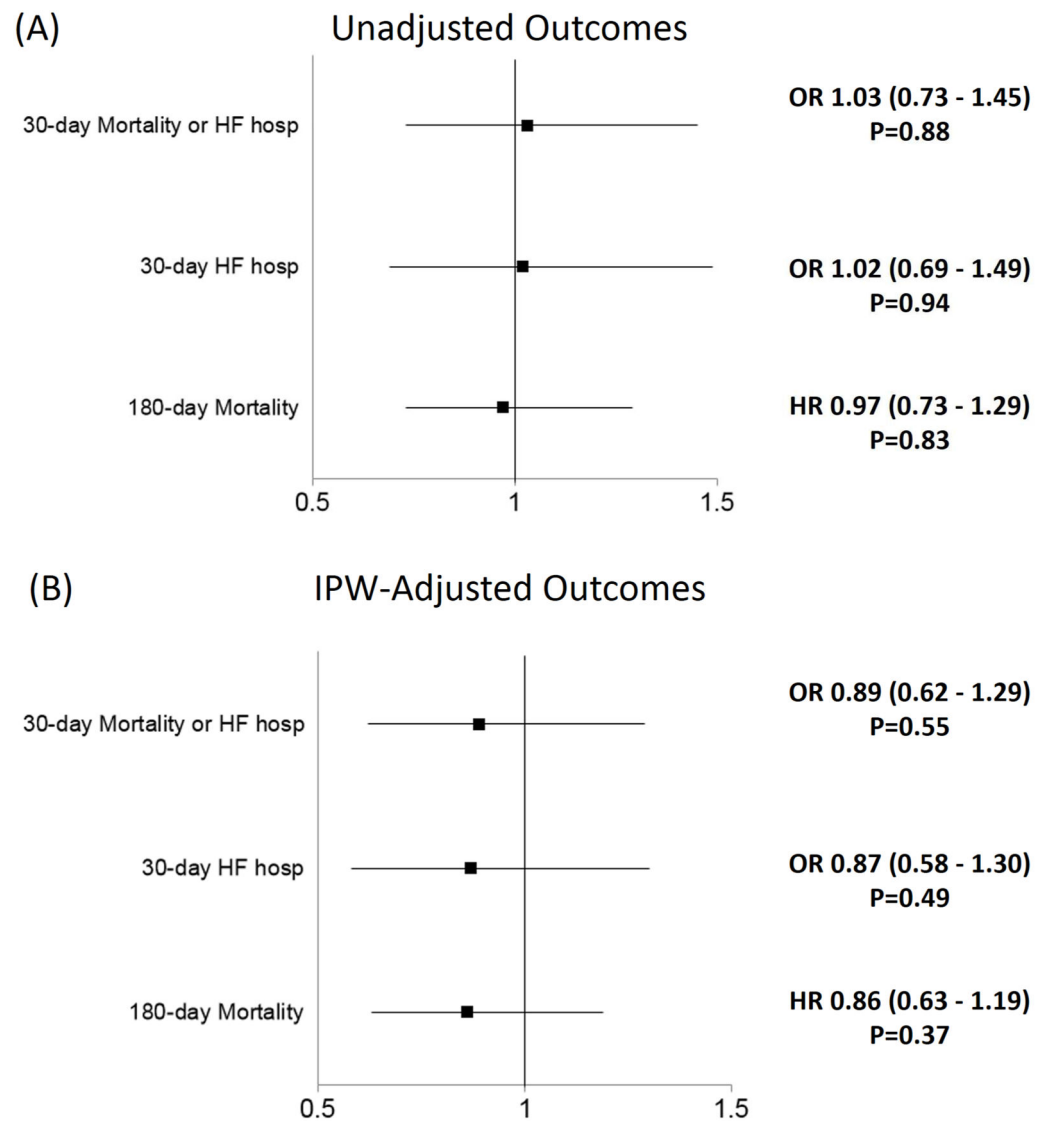
Figure 3.
(A) Unadjusted and (B) IPW-Adjusted Outcomes associated with torsemide use at discharge (reference=furosemide).

Table 1

Baseline characteristics of the study population by discharge diuretic.

Characteristic	Furosemide (N=3620)	Torsemide (N=557)	P-Value
Age (years)	65 (54–75)	65 (54–74)	0.34
Women	1255 (34.7%)	179 (32.1%)	0.24
Race			<.001
White	1750 (48.3%)	257 (46.1%)	
Black	814 (22.5%)	86 (15.4%)	
Asian	1027 (28.4%)	207 (37.2%)	
Other	29 (0.8%)	7 (1.3%)	
Country[*]			<.001
China	182 (90.6%)	19 (9.4%)	
India	730 (81.3%)	168 (18.7%)	
Korea	99 (84.6%)	18 (15.4%)	
Poland	224 (93.7%)	15 (6.3%)	
Russia	211 (86.8%)	32 (13.2%)	
Ukraine	117 (74.5%)	40 (25.5%)	
United States	2057 (88.6%)	265 (11.4%)	
Heart failure history			
HF hospitalization within prior year	1476 (40.8%)	239 (42.9%)	0.35
Ischemic etiology	2228 (61.5%)	38 (69.5%)	<.001
Ejection fraction (%)	30 (20–35)	25 (20–35)	0.025
Ejection fraction 50%	346 (9.6%)	52 (9.3%)	0.87
NYHA Class			0.12
I	77 (2.6%)	8 (1.7%)	
II	501 (17.0%)	79 (16.6%)	
III	1572 (53.5%)	238 (50.0%)	
IV	791 (26.9%)	151 (31.7%)	
Past medical history			
Hypertension	2667 (73.7%)	383 (68.8%)	0.015
Diabetes mellitus	1537 (42.5%)	271 (48.7%)	0.006
Hyperlipidemia	1473 (40.7%)	233 (41.8%)	0.62
Coronary artery disease	2025 (56.0%)	361 (64.8%)	<.001
Myocardial infarction	1267 (35.0%)	223 (40.0%)	0.021
Atrial fibrillation or flutter	1206 (33.3%)	214 (38.4%)	0.018
Ventricular tachycardia	340 (9.4%)	73 (13.1%)	0.006
Cerebrovascular disease	445 (12.3%)	65 (11.7%)	0.68
Peripheral vascular disease	393 (10.9%)	65 (11.7%)	0.57
Chronic respiratory disease	595 (16.4%)	101 (18.1%)	0.32
Prior percutaneous coronary intervention	604 (16.7%)	101 (18.1%)	0.40
Prior coronary bypass	643 (17.8%)	129 (23.2%)	0.002
Qualifying Episode Symptoms			

Characteristic	Furosemide (N=3620)	Torsemide (N=557)	P-Value
Dyspnea			0.50
At Rest	2148 (59.3%)	339/557 (60.9%)	
With Minimal Activity	1472 (40.7%)	218/557 (39.1%)	
Orthopnea	2723 (75.3%)	424/556 (76.3%)	0.63
Weight Gain	2333 (64.6%)	387/557 (69.5%)	0.026
Physical Examination			
BMI (kg/m^2)	28 (24–33)	28 (24–34)	0.70
Systolic BP (mmHg)	125 (110–140)	120 (110–131)	<.001
Diastolic BP (mmHg)	76 (68–85)	72 (66–80)	<.001
Heart rate (bpm)	82 (72–95)	82 (72–94)	0.36
Elevated JVP documented	1968 (54.4%)	340 (61.0%)	0.003
S3 gallop	971 (26.8%)	144 (25.9%)	0.63
Mitral regurgitation	983 (27.2%)	170 (30.5%)	0.098
Pulmonary edema	3072 (84.9%)	450 (80.9%)	0.018
Peripheral edema	2641 (73.0%)	431 (77.4%)	0.028
Laboratories and imaging			
Sodium (mmol/L)	139 (136–141)	138 (135–141)	<.001
Creatinine (mg/dL)	1.2 (1.0–1.5)	1.3 (1.1–1.6)	0.002
Blood urea nitrogen (mg/dL)	23 (17–34)	28 (19–39)	<.001
Hemoglobin (g/dL)	12.6 (11.3–13.9)	12.5 (11.2–14.0)	0.54
NT-proBNP (pg/mL)	4307 (2112–8770)	5345 (2661–9315)	0.006
X-ray indicating pulmonary congestion	2560 (78.1%)	329 (70.0%)	<.001
Baseline medications and devices			
Furosemide-equivalent dose (mg)	40 (40, 80)	40 (20, 80)	0.0013
ACE-inhibitor or ARB	2145 (59.3%)	332 (59.6%)	0.88
Beta blocker	2133 (58.9%)	336 (60.3%)	0.54
Aldosterone antagonists	969 (26.8%)	199 (35.7%)	<.001
Oral or Topical Nitrates	843 (23.3%)	170 (30.5%)	<.001
Digoxin or Digitalis Glycoside	973 (26.9%)	195 (35.0%)	<.001
Hydralazine	311 (8.6%)	55 (9.9%)	0.32
Implantable Cardioverter Defibrillator	685 (18.9%)	143 (25.7%)	<.001
Biventricular pacemaker	325 (9.0%)	74 (13.3%)	0.001

Values presented as median (IQR), mean ± SD or N (percentage); the denominator is noted when different from the overall number of individuals in the group.

[*] For country, the data are presented as the number of patients (%) on each medication such that the row adds up to 100% for each country.

Abbreviations: NYHA indicates New York Heart Association; BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; BNP, brain natriuretic peptide; ACE, angiotensin converting enzyme and ARB, angiotensin receptor blocker.

Table 2

Variables associated with torsemide use at discharge.

Variable	OR (95% CI)	P-value
Country (reference=US)		<.001
China	0.94 (0.57 – 1.56)	
Korea	1.62 (0.92 – 2.84)	
Poland	0.44 (0.23 – 0.86)	
Russia	1.22 (0.80 – 1.85)	
Ukraine	3.74 (2.48 – 5.63)	
India	1.61 (1.28 – 2.03)	
BUN (per doubling)	1.37 (1.21 – 1.55)	<.001
Baseline systolic BP (per 10 mmHg increase)	0.87 (0.83 – 0.92)	<.001
Prior HF hospitalization	1.15 (0.94 – 1.40)	0.175
Qualifying episode JVD	1.29 (1.05 – 1.59)	0.015

Abbreviations: BUN indicates blood urea nitrogen; BP, blood pressure; HF, heart failure; JVD, jugular venous distension.

Table 3

Unadjusted and Adjusted* Outcomes associated with torsemide use at discharge (reference=furosemide).

Endpoint	Number of Events/Sample Size (%)		Odds Ratio or Hazard Ratio (95% Confidence Interval)	P-value
	Furosemide	Torsemide		
30-day Mortality or HF hospitalization	262/3526 (7.4%)	41/538 (7.6%)		
Unadjusted			1.03 (0.73 – 1.45)	0.88
Adjusted IPW			0.89 (0.62 – 1.29)	0.55
Covariate Adjustment			0.86 (0.60 – 1.24)	0.43
30-day Mortality	62/3613 (1.7%)	9/556 (1.6%)		
Unadjusted			0.94 (0.47 – 1.91)	0.87
Adjusted IPW			0.89 (0.40 – 1.97)	0.78
Covariate Adjustment			0.78 (0.38 – 1.62)	0.51
30-day HF hospitalization	207/3525 (5.9%)	32/537 (6.0%)		
Unadjusted			1.02 (0.69 – 1.49)	0.94
Adjusted IPW			0.87 (0.58 – 1.30)	0.49
Covariate Adjustment			0.87 (0.58 – 1.31)	0.49
180-day Mortality	360/3620 (9.9%)	54/557 (9.7%)		
Unadjusted			0.97 (0.73 – 1.29)	0.83
Adjusted IPW			0.86 (0.63 – 1.19)	0.37
Covariate Adjustment			0.86 (0.64 – 1.15)	0.30

*
Adjustment variables: country of randomization, age, hospitalization for heart failure within the prior year, qualifying episode of JVP, baseline systolic BP, baseline sodium, and BUN (log).

Abbreviations: HF indicated heart failure; IPW, inverse probability weighted.