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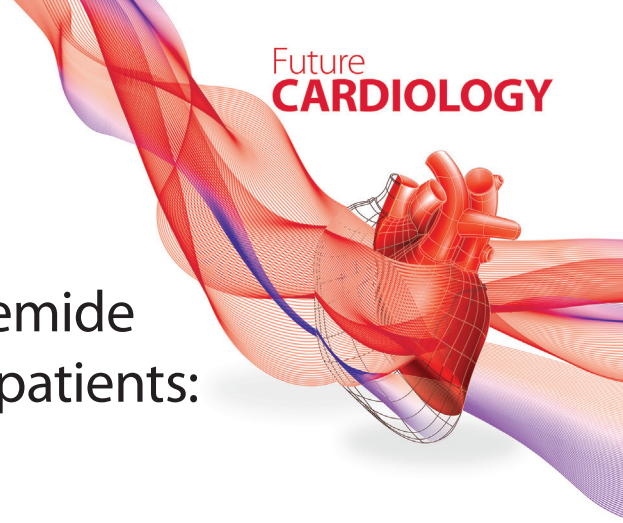

Comparative effectiveness of torsemide versus furosemide in heart failure patients: insights from the PROTECT trial

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Aim: The authors assessed the comparative effectiveness of torsemide versus furosemide in the PROTECT trial. **Methods:** The authors assessed the relationship between loop diuretic at discharge and death or cardiovascular/renal hospitalization within 30 days, and death through 150 days postdischarge using inverse probability weighting. **Results:** Out of 1004 patients, 83.5% received furosemide and 16.5% torsemide. Torsemide patients had higher blood urea nitrogen, and more in-hospital worsening heart failure. Following adjustment, torsemide was associated with similar 30-day outcomes compared with furosemide ($p = 0.93$), but remained associated with increased 150-day death (hazard ratio: 2.26; 95% CI: 1.40–3.66; $p < 0.001$). **Conclusion:** Patients treated with torsemide had features of greater disease severity, similar 30-day outcomes but increased 150-day mortality. Prospective randomized trials are needed to investigate the effect of torsemide versus furosemide.

KEYWORDS
• furosemide • heart failure
• loop diuretics • outcomes
• torsemide

Furosemide has historically been the primary loop diuretic used for the management of volume status in heart failure (HF) patients. However, other loop diuretics such as torsemide have increased half-life and more consistent bioavailability compared with furosemide [1]. Moreover, torsemide may have beneficial effects on myocardial fibrosis, ventricular structure and the neurohormonal milieu [2–7]. Several small observational studies from more than a decade ago [8–10] and a recent meta-analysis [11] suggest a reduction in morbidity and potentially mortality with torsemide compared with furosemide. Despite these data, furosemide remains the most commonly used loop diuretic [12] likely related in part to greater clinician experience with furosemide, historically lower medication cost and a lack of contemporary data supporting a benefit with torsemide. Therefore, the authors assessed the association between loop diuretics and postdischarge outcomes in a large, international acute HF trial. The authors hypothesized that use of torsemide at discharge would be associated with improved outcomes compared with furosemide use.

Methods

• Data source

The international PROTECT trial enrolled 2033 patients admitted to the hospital with acute HF and mild or moderate renal impairment. The design and results of PROTECT have been published [13,14]. Briefly, the inclusion criteria were: prior history of HF treated for at least 14 days with diuretic therapy; hospitalization for worsening breathlessness due to HF requiring intravenous

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diuretic therapy; admission creatinine clearance 20–80 ml/min by the Cockcroft-Gault equation; a brain natriuretic peptide (BNP) level ≥500 pg/ml or N-terminal pro-BNP level ≥2000 pg/ml; and systolic blood pressure (SBP) ≥95 mmHg. Key exclusion criteria were: use of inotropic agents or mechanical support; severe pulmonary disease; significant stenotic valvular disease; recent acute coronary syndrome or significant arrhythmias; and history of seizure/stroke within 2 years. Patients were enrolled from 2007–2009 and randomly assigned to the intravenous administration of the A_1-receptor antagonist rolofylline or placebo. Loop diuretic was documented at baseline and hospital discharge/day 14. Worsening HF (WHF) was defined as a physician-determined assessment of worsening symptoms or signs of HF occurring greater than 24 h after the start of study drug to day 7 or discharge, whichever occurred first, that required institution or an increase in dose of intravenous or mechanical therapy for HF. The primary endpoint for the trial was treatment success (moderate or marked improvement in dyspnea at both 24 and 48 h after rolofylline administration) in the absence of any criterion for treatment failure (death or readmission for HF, WHF, persistent worsening renal function or initiation of dialysis up to and including day 7) or no change in the patient's clinical condition up to and including day 7. Death from any cause or rehospitalization for cardiovascular or renal causes through day 60 was a prespecified secondary endpoint. Vital status was also assessed at 180 days. An independent clinical events committee adjudicated the primary reason for rehospitalization and cause of death through day 60. The investigation conforms with the principles outlined in the Declaration of Helsinki. The PROTECT study was approved by the appropriate regulatory authorities and ethics committees prior to patient enrollment, and written informed consent was obtained from each patient before entry [15,16].

• Analysis cohort

For the present analysis, the authors limited the cohort to patients discharged alive on either furosemide or torsemide with follow-up after day 14. Given significant regional variation in the use of torsemide, the authors restricted the analyses to those countries where patients were treated with both furosemide and torsemide.

• Outcomes of interest

The outcomes for the present analysis were death or cardiovascular/renal hospitalization through 30-day postdischarge and death through 150-day postdischarge. The authors used different timepoints compared with the main PROTECT analysis (through 60- and 180-day postrandomization, respectively), since the authors were assessing outcomes associated with discharge loop diuretic rather than use at randomization. Similar methods have been used in previous PROTECT analyses to reduce bias related to shorter follow-up in those patients with longer index hospital length of stay (LOS) [17]. As additional endpoints, index hospital LOS , treatment success/no change/worsening (primary endpoint for the PROTECT trial) and event rates for WHF to 7 days were investigated. The authors were also interested in identifying clinical factors associated with patients being discharged on torsemide as compared with furosemide.

• Statistical methods

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. Diuretic dose was assessed with the conversion of 2 mg furosemide to 1 mg torsemide to present furosemide equivalents as described previously [1]. Patient characteristics were compared between groups using the Wilcoxon rank sum test for continuous variables, and χ^2 or Fisher's mid-P tests for categorical variables as appropriate. The authors assessed the number of events for the outcomes of interest based on discharge diuretic. Cumulative event rates at the end of the study period, and cumulative event rate curves over time postdischarge were estimated using the Kaplan–Meier method.

Because the choice of diuretic at discharge was not randomized, the authors developed a propensity score logistic regression model to predict the use of torsemide versus furosemide. Covariates associated with postdischarge mortality were identified in previous analysis of PROTECT [17,18] and included age, country, hospitalization for HF in the past year, history of diabetes mellitus, history of atrial fibrillation/flutter, baseline measures (BMI, mean blood pressure [BP], blood urea nitrogen [BUN]) and day 14 measures (EQ5D score, congestion score, albumin, ALT, BUN

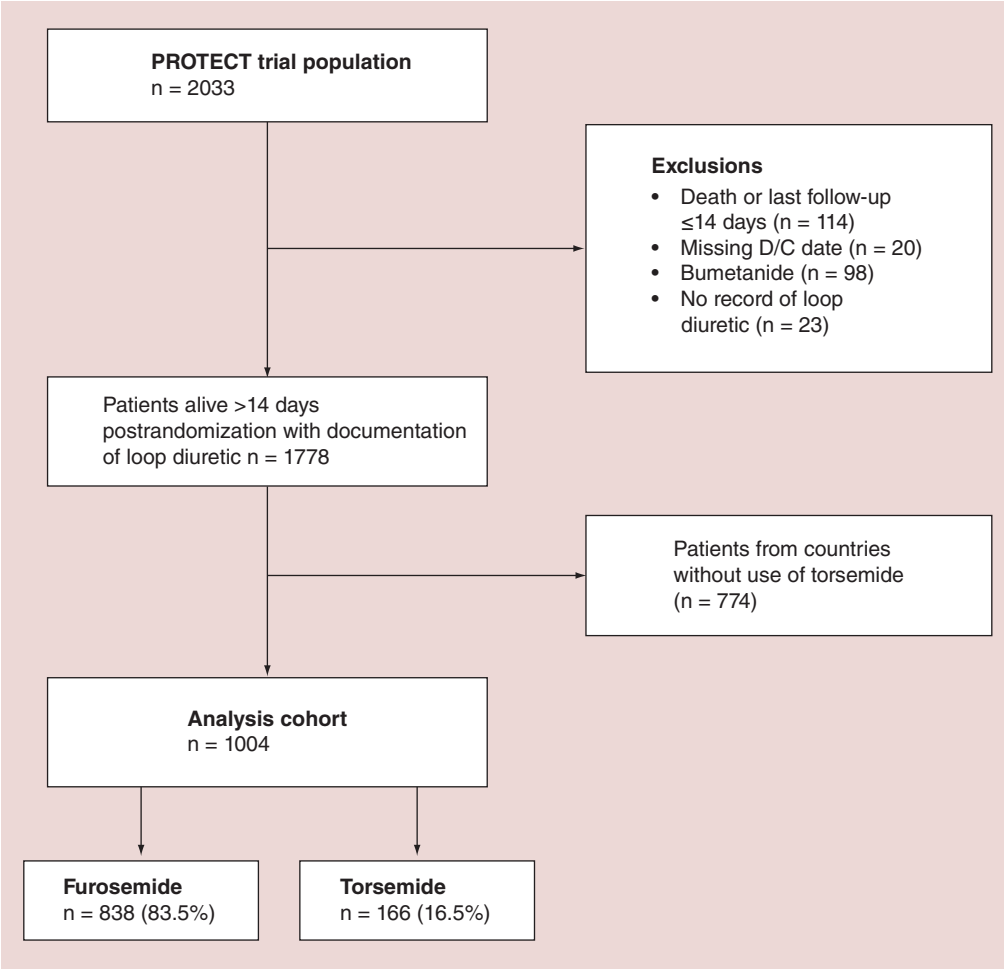

Figure 1. Study population.
D/C: Indicates discharge.

and total cholesterol). Cox proportional hazards models were generated to assess the association between loop diuretic use at discharge and subsequent clinical outcomes. Hazard ratios (HRs) for torsemide versus furosemide were calculated with corresponding 95% CIs. The estimated propensity scores were used for inverse propensity weighting (IPW) of observations in these models [19]. IPW methods reweight the data to create a pseudo-population where, under the assumption that important confounders have been accounted for, patient characteristics are independent of treatment received [20]. Multivariate regression analysis adjusting for covariates above was also performed as a secondary analysis. Statistical significance was assessed using two-sided p-values ($p < 0.05$ was considered statistically significant). All statistical computations were generated by Duke Clinical Research Institute (Durham, NC, USA) using SAS version 9.2 or higher (SAS Institute Inc., Cary, NC, USA). 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. Out of 2033 patients in the PROTECT trial, 1876 patients were discharged on a loop diuretic. Furosemide was used in 1612 patients (86.0%), torsemide in 166 patients (8.8%) and bumetanide in only 98 patients (5.2%). The 11 enrolling countries with no use of torsemide at discharge were Belgium (total n = 6), France (n = 72), The Netherlands (n = 13), Sweden (n = 6), UK (n = 22), Czech Republic (n = 157), Hungary (n = 24), Romania (n = 86), Argentina (n = 52), Israel (n = 303) and Canada (n = 33). In the outcomes analysis, patients were included

from six countries that discharged patients on both furosemide and torsemide: the USA, Poland, Russia, Germany, Italy and the Ukraine (Table 1). Out of the 1004 patients discharged alive on either furosemide or torsemide, from countries in which both drugs were used, 83.5% (n = 838) received furosemide and 16.5% (n = 166) received torsemide. Patients enrolled in Germany and the USA constituted the majority of the overall torsemide cohort (n = 87) where there was 61.8 and 13.1% use of torsemide, respectively. The median daily dose in the patients discharged on torsemide was 15 mg (IQR: 10–40), which is 30 mg (IQR: 20–80) when converted to furosemide equivalents, compared with 80 mg (IQR: 40–80) in the patients discharged on furosemide. Patient characteristics by discharge diuretic are presented in Table 1. Patients discharged on torsemide were more likely to have an HF hospitalization in the previous year and had more atrial fibrillation than patients discharged on furosemide. Torsemide patients had worse congestion as evidenced by more severe dyspnea on exertion, greater elevation in jugular venous pressure (JVP) and worse orthopnea compared with furosemide-treated patients. Patients receiving torsemide had higher BMI and BUN as well as lower mean blood pressure compared with patients discharged on furosemide. In general, HF medication use was similar in both patient groups, while implantable cardioverter defibrillator (ICD) use was greater in the torsemide patients. The baseline characteristics of patients excluded due to the lack of torsemide use in the enrolling country are presented in Supplementary Table 1. Compared with the analysis cohort, patients excluded from the analysis were older, had more diabetes and ICD use, higher blood pressure and worse renal function.

Factors associated with torsemide use at discharge are presented in Table 2. Country was the primary factor associated with torsemide use. The odds for torsemide use were highest in the Ukraine and Germany compared with the USA. Clinical factors associated with torsemide use included HF hospitalization in the previous year, mean blood pressure at baseline and congestion score at day 14.

In-hospital outcomes by loop diuretic use at discharge are presented in Table 3. Index hospitalization length of stay was similar between the two groups. The event rate for in-hospital WHF was significantly higher in the patients that were later discharged on torsemide compared with the furosemide-treated group (14.5 vs 9.1%, p = 0.034). During index hospitalization, patients who were eventually discharged on torsemide had a higher percentage of treatment failure or unchanged status and less treatment success for the primary outcome of the original clinical trial of rolofylline compared with those patients discharged on furosemide.

Table 4 presents postdischarge outcomes in patients treated with furosemide or torsemide. Death or cardiovascular/renal hospitalization through 30-day and 150-day death were increased in patients discharged on torsemide compared with furosemide (19.1 vs 15.1% [p = 0.25] and 18.7 vs 9.1% [p < 0.001], respectively). Figure 2 displays the unadjusted event rate curves. Following adjustment for treatment propensity, torsemide use was associated with similar 30-day outcomes compared with furosemide (HR: 1.02; 95% CI: 0.64–1.63; p = 0.93), and increased 150-day death (HR: 2.26; 95% CI: 1.40–3.66; p < .001). Multivariate regression analysis yielded similar results to those with IPW methodology. Additional adjustment for index hospitalization length of stay and in-hospital WHF yielded similar results.

Discussion

In a large international acute HF trial, the authors found that furosemide was the primary loop diuretic used in most countries (>85% use), except for Germany and the Ukraine which used greater than 60% torsemide. The observation that no patients in 11 of the countries that enrolled in PROTECT had any patients discharged on torsemide and only 5% of patients were discharged on bumetanide, highlights the substantial regional variation in the availability, cost and use of alternative loop diuretics. The furosemide equivalent dose was lower in the patients discharged on torsemide. Patients discharged on torsemide tended to have features of more severe disease, particularly prior HF hospitalization, worse congestion, higher BUN and more in-hospital WHF and overall in-hospital treatment failure compared with furosemide-treated patients. After adjustment for treatment propensity, torsemide was associated with similar 30-day outcomes but increased 150-day mortality compared with furosemide. Due to the potential for residual confounding, these data, which conflict with earlier studies [21], provide the equipoise for a prospective randomized trial that is adequately powered to investigate the effect of torsemide versus furosemide on clinical outcomes.

A primary finding of our analysis was that patients discharged on torsemide had features of

Table 1. Characteristics of the study population by discharge diuretic.

Characteristic	Torsemide (n = 166)	Furosemide (n = 838)	p-value
Age (years)	70 (60; 77)	69 (60; 77)	0.745
Male sex	118 (71.1)	574 (68.5)	0.510
Country:			<0.001
– Germany (n = 89, 8.9%)	55 (61.8)	34 (38.2)	
– Italy (n = 51, 5.1%)	4 (7.8)	47 (92.2)	
– Poland (n = 323, 32.2%)	23 (7.1)	300 (92.9)	
– Russia (n = 267, 26.6%)	31 (11.6)	236 (88.4)	
– Ukraine (n = 30, 2.9%)	21 (70.0)	9 (30.0)	
– USA (n = 244, 24.3%)	32 (13.1)	212 (86.9)	
HF history:			
– HF hospitalization within prior year	102 (61.4)	440 (52.5)	0.035
– Ischemic etiology	112 (67.5)	593 (70.8)	0.397
– Ejection fraction (%)	30 (23, 41)	28 (20, 38)	0.236
– Ejection fraction <40%	64 (69.6)	302 (76.6)	0.156
–NYHA class 1 month prior:			0.003
• None/I/II	40 (24.1)	115 (13.7)	
• III	62 (37.3)	364 (43.5)	
• IV	64 (38.6)	358 (42.8)	
– EQ-5D utility score (day 14)	0.78 (0.57; 0.84)	0.79 (0.63; 0.85)	0.011
Past medical history			
– Hypertension	137 (82.5)	680 (81.1)	0.675
– Diabetes mellitus	81 (48.8)	353 (42.1)	0.113
– Atrial fibrillation or flutter	107 (64.5)	443 (53.2)	0.008
– Stroke or PVD	31 (18.8)	164 (19.6)	0.811
Signs and symptoms of HF on latest of days 5–14:			
–Dyspnea on exertion:			0.008
• None	4 (2.4)	88 (10.6)	
• Mild	73 (44.0)	362 (43.5)	
• Moderate	81 (48.8)	348 (41.8)	
• Severe	8 (4.8)	34 (4.1)	
– Edema:			0.054
• 0	102 (61.4)	587 (70.5)	
• 1+	40 (24.1)	176 (21.1)	
• 2+	19 (11.4)	54 (6.5)	
• 3+	5 (3.0)	16 (1.9)	
–Rales:			0.129
• No rales	132 (79.5)	711 (85.4)	
• Rales <1/3	31 (18.7)	115 (13.8)	
• Rales 1/3–2/3	3 (1.8)	7 (0.8)	
– JVP:			<0.001
• <6 cm	72 (55.0)	571 (75.3)	
• 6–10 cm	43 (32.8)	157 (20.7)	
• >10 cm	16 (12.2)	30 (4.0)	

Values presented as median (IQR) or n (percentage of group), except where indicated otherwise.

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.

†The congestion score is an equally weighted aggregate of the scores for edema, rales, JVP, orthopnea and dyspnea on exertion.

‡eGFR calculated from central lab using MDRD formula.

ARB: Angiotensin receptor blocker; BP: Blood pressure; BUN: Blood urea nitrogen; EF: Ejection fraction; eGFR: Estimated glomerular filtration rate; EQ-5D: EuroQol questionnaire measuring health outcome; HF: Heart failure; JVP: Jugular venous pressure; NYHA: New York Heart Association; PVD: Peripheral vascular disease.

Table 1. Characteristics of the study population by discharge diuretic (cont.).

Characteristic	Torsemide (n = 166)	Furosemide (n = 838)	p-value
– Orthopnea:			0.002
• None	45 (27.1)	353 (42.4)	
• One pillow (10 cm)	69 (41.6)	298 (35.8)	
• Two pillows (20 cm)	40 (24.1)	144 (17.3)	
• >30 degrees	12 (7.2)	38 (4.6)	
– Congestion score†	3.5 (2.0; 6.5)	3.0 (2.0; 4.0)	<0.001
Physical examination:			
– BMI (kg/m^2)	29.9 (25.7; 33.9)	27.9 (24.4; 32.7)	0.006
– Systolic BP (mmHg)	120 (110; 140)	124 (110; 140)	0.274
– Diastolic BP (mmHg)	72 (63; 80)	76 (70; 80)	0.024
– Mean BP (mmHg)	89.5 (81.3; 97.7)	91.7 (83.3; 100.0)	0.045
– Heart rate (bpm)	80 (70; 91)	80 (70; 94)	0.151
Laboratories on day 1:			
– Sodium (mmol/l)	140 (138; 142)	140 (137; 143)	0.512
– Creatinine (mg/dl)	1.4 (1.2; 1.8)	1.3 (1.1; 1.7)	0.094
– eGFR‡ (ml/min/1.73 m^2)	47.6 (34.8; 58.0)	49.6 (37.1; 62.1)	0.061
– BUN (mg/dl)	32 (25; 41)	27 (21; 38)	<0.001
– Hemoglobin (g/dl)	12.5 (11.2; 13.9)	12.9 (11.5; 14.3)	0.088
– Albumin (g/dl)	3.8 (3.6; 4.1)	3.8 (3.6; 4.1)	0.320
– Total cholesterol (mg/dl)	144 (117; 175)	142 (118; 175)	0.723
– ALT (U/l)	19 (15; 33)	23 (15; 34)	0.158
Latest laboratories of days 5–14:			
– Sodium (mmol/l)	139 (136; 142)	139 (136; 142)	0.693
– Creatinine (mg/dl)	1.4 (1.2; 1.8)	1.3 (1.1; 1.8)	0.151
– eGFR‡ (ml/min/1.73 m^2)	47.0 (33.8; 59.0)	48.9 (35.5; 64.8)	0.080
– BUN (mg/dl)	35 (25; 45)	30 (22; 43)	0.024
– Hemoglobin (g/dl)	12.7 (11.1; 14.4)	13.2 (11.7; 14.9)	0.016
– Albumin (g/dl)	4.0 (3.7; 4.3)	4.0 (3.7; 4.3)	0.633
– Total cholesterol (mg/dl)	150.5 (119.0; 191.0)	156.0 (126.0; 189.0)	0.392
– ALT (U/l)	22 (16; 30)	23 (16; 32)	0.767
Baseline medications (two weeks prior to admission) and devices:			
– ACE-inhibitor or ARB	131 (78.9)	610 (72.8)	0.101
– β-blocker	133 (80.1)	626 (74.7)	0.138
– Aldosterone antagonists	69 (41.6)	377 (45.0)	0.418
– Nitrates	41 (24.7)	227 (27.1)	0.525
– Digoxin	60 (36.1)	261 (31.1)	0.207
– Implantable cardioverter defibrillator	44 (26.5)	141 (16.8)	0.003
– Biventricular pacemaker	19 (11.4)	77 (9.2)	0.369
Medications at discharge (or day 7 if earlier):			
– ACE-inhibitor or ARB	138 (83.1)	723 (86.3)	0.290
– β-blocker	146 (88.0)	737 (87.9)	0.999
– Aldosterone antagonists	104 (62.7)	541 (64.6)	0.639
– Nitrates	28 (16.9)	189 (22.6)	0.102
– Digoxin	67 (40.4)	313 (37.4)	0.472

Values presented as median (IQR) or n (percentage of group), except where indicated otherwise.

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.

†The congestion score is an equally weighted aggregate of the scores for edema, rales, JVP, orthopnea and dyspnea on exertion.

‡eGFR calculated from central lab using MDRD formula.

ARB: Angiotensin receptor blocker; BP: Blood pressure; BUN: Blood urea nitrogen; EF: Ejection fraction; eGFR: Estimated glomerular filtration rate; EQ-5D: EuroQol questionnaire measuring health outcome; HF: Heart failure; JVP: Jugular venous pressure; NYHA: New York Heart Association; PVD: Peripheral vascular disease.

Table 2. Variables associated with torsemide use at discharge.

Covariate	Multivariable odds ratio	95% CI	χ^2	p-value
Age (5-year increase)	0.96	0.88–1.06	0.597	0.440
Country (vs USA):			140.91	<.001
– Germany	15.6	8.18–29.6		
– Italy	0.49	0.15–1.55		
– Poland	0.67	0.36–1.25		
– Russia	1.39	0.74–2.60		
– Ukraine	30.8	11.2–84.2		
Hospitalization for HF in past year (yes vs no)	1.77	1.17–2.68	7.196	0.007
History of diabetes mellitus (yes vs no)	0.83	0.54–1.29	0.679	0.410
History of atrial fib/flutter (yes vs no)	1.50	0.98–2.30	3.504	0.061
BMI at baseline (5 kg/m^2 increase)	1.03	0.88–1.20	0.126	0.723
Mean BP at baseline (20 mmHg increase)	0.65	0.45–0.94	5.377	0.020
BUN at baseline (10 mg/dl increase)	1.15	0.99–1.34	3.292	0.070
BUN at day 14 (10 mg/dl increase)	0.97	0.86–1.10	0.171	0.679
Albumin at day 14 (0.5 g/dl increase)	1.14	0.89–1.47	1.081	0.298
ALT at day 14, U/l below 200 (10 U/l increase)	1.05	0.96–1.15	1.266	0.260
Total cholesterol at day 14 (10 mg/dl increase)	0.99	0.94–1.04	0.236	0.627
EQ5D utility score at day 14 (0.1 unit increase)	0.99	0.89–1.09	0.067	0.795
Congestion score at day 14 (1 unit increase)	1.10	1.00–1.20	4.151	0.042

BP: Blood pressure; BUN: Blood urea nitrogen; EQ-5D: EuroQol EQ-5D questionnaire measuring health outcome; HF: Heart failure.

more severe disease compared with furosemide patients. In particular, patients who received torsemide tended to have more significant congestion as well as higher BMI and BUN, and lower mean blood pressure. BUN captures renal dysfunction as well as metabolic status and neurohormonal activation suggesting worse systemic perturbations in patients treated with torsemide. Patients discharged on torsemide also were more likely to have been hospitalized for HF in the preceding year and had an increased comorbidity burden including atrial fibrillation. Prior HF hospitalization is a strong predictor of increased risk for future adverse events [22]. In addition, in-hospital WHF, which has been associated with worse long-term outcomes [23], was seen more often in the patients that were discharged on torsemide compared with those treated with furosemide. Interestingly, other HF medication use was similar between the two groups, while ICD therapy was increased in the torsemide group. This finding may have been related to between-group differences in the New York Heart Association (NYHA) class, prior HF hospitalizations and/or regional differences in the implantation rates of devices. Thus, despite similar background HF therapy in the torsemide and furosemide treated patients, patients discharged on torsemide had a high-risk profile including prior HF hospitalizations and in-hospital WHF.

Clinical factors strongly associated with torsemide use included prior HF hospitalization,

Table 3. Summary of in-hospital outcomes by loop diuretic use at discharge.

Outcomes	Overall (n = 1004)	Torsemide (n = 166)	Furosemide (n = 838)	p-value[†]
Index hospitalization length of stay (days; IQR)	10 (7, 15)	9 (7, 15)	10 (6, 15)	0.43
WHF through 7 days; n (%)	100 (10.0)	24 (14.5)	76 (9.1)	0.034
Treatment success outcome; n (%)				0.002
– Failure	166 (16.5)	33 (19.9)	133 (15.9)	
– Unchanged	431 (42.9)	85 (51.2)	346 (41.3)	
– Success	407 (40.5)	48 (28.9)	359 (42.8)	

[†]p-value for length of stay from Wilcoxon test. p-value for WHF from χ^2 test. p-value for treatment success outcome from nonparametric ANOVA test.
IQR: median; WHF: Worsening heart failure.

Table 4. Outcomes associated with torsemide use at discharge (reference = furosemide).

Endpoint	Number of events/sample size (KM%)		HR (95% CI)	p-value
	Torsemide	*Furosemide*		
Death or CV/renal hospitalization through 30-day postdischarge:	31/165 (19.1%)	126/836 (15.1%)		
– Unadjusted			1.261 (0.851–1.868)	0.248
– Adjusted IPW[†]			1.020 (0.640–1.626)	0.932
– Covariate adjusted[‡]			0.860 (0.540–1.368)	0.523
Death through 150-day postdischarge:	31/166 (18.7%)	76/838 (9.1%)		
– Unadjusted			2.184 (1.438–3.316)	<0.001
– Adjusted IPW[†]			2.259 (1.396–3.657)	<0.001
– Covariate adjusted[‡]			2.141 (1.307–3.507)	0.002

[†]IPW adjustment using propensity score model listed in **Table 2**.
[‡]Adjusted using regression analysis, including the covariates listed in **Table 2**.
CV: Cardiovascular; HR: Hazard ratio; IPW: Inverse probability weighted; KM: Kaplan–Meier.

congestion score and BUN. These findings suggest that clinicians use torsemide in the setting of perceived failure to respond to furosemide with refractory volume overload. Interestingly, the furosemide equivalent dose was lower in those patients discharged on torsemide. Torsemide has more consistent bioavailability compared with furosemide including in patients with intestinal edema [1]. Despite these pharmacologic advantages with torsemide, furosemide remains the most commonly used loop diuretic in most world regions given greater clinical experience and a historical patient-level cost advantage with furosemide. These two drugs now have comparable costs given the availability of generic torsemide. In fact, studies prior to the widespread availability of generic torsemide [24] suggested that torsemide may be associated with a reduction in total cost per patient due to reduced rehospitalization. However, the authors did not observe a rehospitalization benefit associated with torsemide use in their analysis.

Despite earlier studies demonstrating potential benefits with torsemide over furosemide [2–7], the authors did not observe improved outcomes associated with discharge torsemide prescription. As recently reviewed [21], studies have suggested beneficial effects of torsemide related to inhibition of aldosterone secretion and/or receptor binding and reduced myocardial collagen production. The authors did not observe a beneficial association with torsemide use in the present analysis, the specific reasons for which are unclear. The

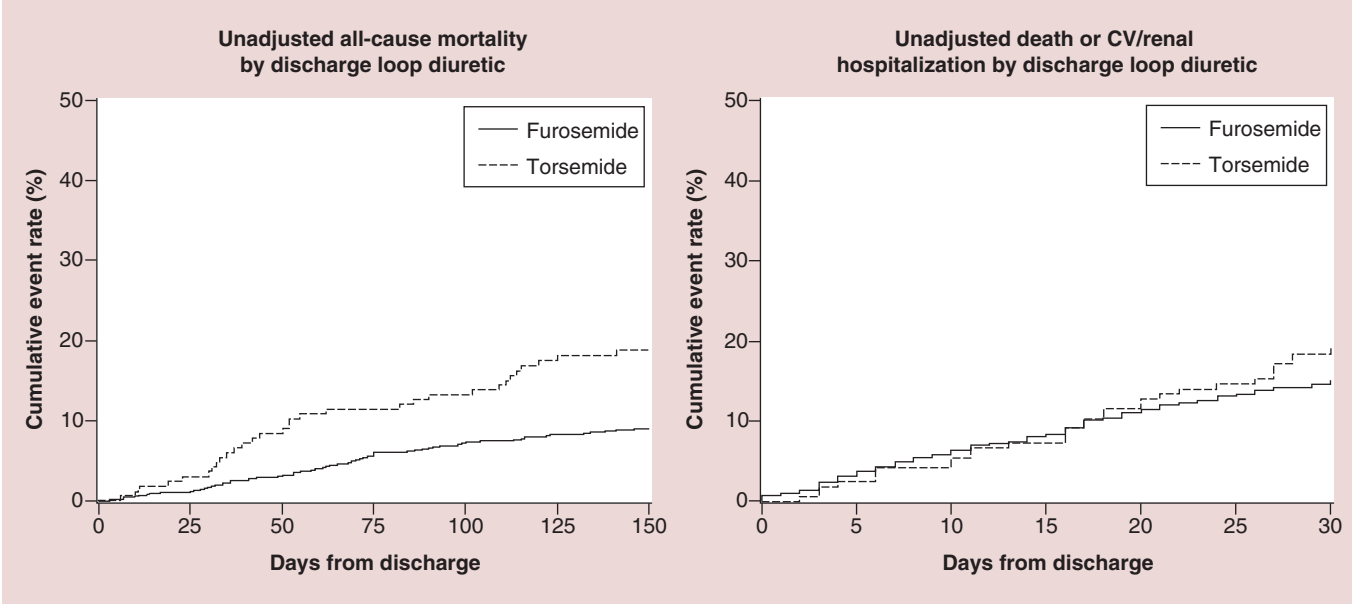

Figure 2. Unadjusted event rate curves by discharge loop diuretic.

authors hypothesize that measured and unmeasured variables may have influenced these results and that the statistical methods were not able to adequately adjust for the increased severity of disease in torsemide patients. It is also possible that the antifibrotic effects that were observed in earlier studies with torsemide [6,25–26] may not result in improved clinical outcomes until there is a longer duration of exposure, particularly in the setting of contemporary guideline-directed HF medications including mineralocorticoid receptor antagonists. Additionally, the implications of a differential furosemide equivalent dose between the two study groups may have influenced the findings. A higher dose of torsemide than that used in this patient population (median dose of 15 mg torsemide; or 30 mg furosemide equivalent) may be necessary to mediate the beneficial effects. Previous studies have not demonstrated improved outcomes in association with diuretic therapies for HF patients [27]. Furthermore, data are not available for this cohort regarding medication crossover following discharge. Moreover, given the strong association between country and diuretic choice, these data may be confounded by international differences as has been described previously in the PROTECT trial [28] and additional recent heart failure trials including TOPCAT [29].

• Limitations

This was a retrospective analysis from a clinical trial and patients met specific entry criteria. These data may not apply to patients with different clinical characteristics to those included in the PROTECT trial. In particular, the regional variation in the use of torsemide is a major potential confounder [28]. Despite IPW adjustment, other measured and unmeasured variables may have influenced these results. The analysis population receiving torsemide was relatively modest in size and the analysis may have been underpowered. It was not a new-user design given the common use of diuretics to treat symptoms of volume overload. Furthermore, data were not available regarding postdischarge diuretic changes including medication type and dose. Thus, these data should be viewed as exploratory.

Conclusion

In a large international HF trial, patients discharged on torsemide had features of greater disease severity. After adjustment for treatment propensity, torsemide was associated with similar 30-day outcomes but increased 150-day mortality compared with furosemide.

Future perspective

Despite prior observational data suggesting improved outcomes with torsemide compared with furosemide, a relationship between torsemide use and clinical benefits was not observed in the present analysis. Randomized trials would be needed to support the preferential use of torsemide over furosemide.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/full/10.2217/fca.15.56

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

EXECUTIVE SUMMARY

- In a large international heart failure trial, patients discharged on torsemide had features of greater disease severity than those discharged on furosemide.
- After adjustment for treatment propensity, torsemide was associated with similar 30-day outcomes but increased 150-day mortality compared with furosemide.
- These data provide the rationale for an appropriately powered randomized clinical trial of the comparative–effectiveness of furosemide versus torsemide in heart failure patients.

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