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Torsemide versus Furosemide in Heart Failure Patients: Insights from Duke University Hospital

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Abstract

Furosemide has historically been the primary loop diuretic in heart failure (HF) patients despite data suggesting potential advantages with torsemide. We used the Duke Echocardiography Lab Database to investigate patients admitted with HF to Duke Hospital from 2000–2010 who were discharged on either torsemide or furosemide. We described baseline characteristics based on discharge diuretic and assessed the relationship with all-cause mortality through 5 years. Of 4,580 patients, 86% (n=3,955) received furosemide and 14% (n=625) received torsemide. Patients receiving torsemide were more likely to be female and had more comorbidities compared with furosemide-treated patients. Survival was worse in torsemide-treated patients (5-yr Kaplan-Meier estimated survival of 41.4% [95% CI: 36.7–46.0] vs. 51.5% [95% CI: 49.8–53.1]). Following risk adjustment, torsemide use was no longer associated with increased mortality (Hazard Ratio 1.16; 95% CI: 0.98–1.38; P=0.0864). Prospective trials are needed to investigate the effect of torsemide vs. furosemide due to the potential for residual confounding.

INTRODUCTION

Loop diuretics including furosemide and torsemide are prescribed for the treatment of symptomatic heart failure (HF)^{1, 2}. Current HF guidelines indicate that loop diuretics are a central treatment for the management of volume overload³. Compared with furosemide, torsemide has increased bioavailability and a longer half-life⁴, yet furosemide remains the most commonly used loop diuretic⁵. Torsemide also has beneficial effects on myocardial fibrosis, the neurohormonal axis, and ventricular structure^{6–11}. Several small studies of torsemide vs. furosemide^{12–14} and a meta-analysis¹⁵ suggest improved clinical outcomes with torsemide. These previous studies had modest sample sizes and were conducted prior to

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the use of contemporary HF therapies. In order to investigate the role of torsemide in current clinical practice, we assessed loop diuretics use at a large, tertiary care hospital over the past decade and evaluated the association with baseline characteristics and post-discharge outcomes.

METHODS

We assessed patients admitted to Duke University Medical Center (DUMC) with a primary discharge diagnosis of HF between 2000 through 2010 that were included in the Duke Echocardiography Lab Database (DELD) and were discharged on either torsemide or furosemide. The DELD is a prospectively maintained digital archive of all clinical echocardiograms performed at DUMC since 1995. For the present analysis, we included patients in the DELD who received an echocardiogram during the HF hospitalization. Patients without an echocardiogram during the hospitalization were not included in the analysis so that we could incorporate recent echocardiographic assessments into our analysis. The first hospitalization for HF between 2000 and 2010 was used for each patient and the discharge date was time 0. Patients were classified according to final in-hospital loop diuretic documentation. Baseline clinical variables for each patient were obtained from the Duke Enterprise Data Unified Content Explorer (DEDUCE) research portal. The DEDUCE research portal is an on-line research tool that allows for investigation of clinical information collected as a by-product of patient care throughout DUMC. Specific examples of available information include laboratory data, ICD-9 diagnostic codes, medications, and billing data. Follow-up data was obtained from patient's medical records as well as via structured processes for patients included in the Duke Databank of Cardiovascular Disease as previously described¹⁶. Patients without outcomes data through these mechanisms had vital status determined through a search of the National Death Index¹⁷. The Duke Institutional Review Board approved this study.

The primary outcome for the present analysis was all-cause mortality through 5 years post-discharge. Secondary outcomes were 30-day all-cause mortality or hospitalization and 30-day hospitalization. Rehospitalization evaluation was limited to the Duke Health system. We were also interested in identifying clinical factors associated with patients being discharged on torsemide as compared with furosemide.

Demographics, medical history, laboratory findings, 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 Wilcoxon rank sum test for continuous variables, and Pearson 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) using backward selection with a p-value of 0.10 to stay in the model. Candidate variables were those included in the baseline characteristics table (Table 1). Year of HF hospitalization was included as an adjustment variable in all models. We assessed linearity of continuous variables and fit interpretable linear splines when necessary.

Because the choice of diuretic at discharge was not randomized, a multivariable model was used to estimate propensity scores – individual probabilities of torsemide use at discharge. Logistic (for 30-day endpoints) and Cox proportional hazards regression (for mortality through 5 years) models assessed the association between discharge loop diuretics and clinical outcomes using inverse probability weighting (IPW). In brief, patients are weighted by the inverse of their estimated probability of diuretic actually received. Covariate balance under IPW was assessed using standardized differences¹⁸. A covariate-adjusted model was also evaluated to assess to association of torsemide use with clinical endpoints. We assessed linearity and proportional hazards assumptions for adjustment covariates and discharge medications and applied appropriate transformations as needed. No violations were detected for loop diuretics. Hazard ratios (HRs) for long-term 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 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 9.2 or higher (SAS Institute Inc., Cary, NC).

RESULTS

We identified 7,442 unique patients with a HF admission to DUMC between Jan 1, 2000 and Dec 31, 2010 who were discharged alive. Of these, 4580 patients had an echocardiogram prior to discharge and were discharged on either torsemide or furosemide. Of 4,580 patients, 86% (n=3,955) received furosemide and 14% (n=625) received torsemide. Figure 1 presents the percentage of HF patients discharged on furosemide vs. torsemide over the study period. Torsemide use began to increase in 2006 and rose to approximately 30% of loop diuretic use in 2010. Table 1 presents the baseline characteristics of the study population based on discharge loop diuretic. Patients receiving torsemide were more likely to be female and had more comorbidities compared with furosemide-treated patients. Torsemide-treated patients had a higher creatinine, BUN and NT-proBNP, more severe tricuspid regurgitation and worse right ventricular (RV) function. Patients discharged on torsemide less often received ACE-inhibitors and beta-blockers but more often received aldosterone antagonists compared with furosemide patients.

Factors associated with torsemide use at discharge in a multivariable model are presented in Table 2. Clinical factors independently associated with torsemide use were younger age, female sex, higher EF, renal dysfunction, RV dilatation and tricuspid regurgitation.

Figure 2 presents the unadjusted mortality curve for patients receiving torsemide vs. furosemide. Survival was worse in patients who received torsemide (5-yr Kaplan-Meier estimated survival of 41.4% [95% CI: 36.7–46.0] vs. 51.5% [95% CI: 49.8–53.1]). Table 3 presents the Kaplan-Meier estimates of mortality and mortality or hospitalization based on discharge diuretic. At 6 months patients who received torsemide had higher mortality (Kaplan-Meier estimated survival of 82.0% [95% CI: 78.8–84.8] vs. 86.2% [95% CI: 85.1–87.3]) and higher incidence of mortality or hospitalization (Kaplan-Meier estimated survival of 65.2% [95% CI: 61.3–68.8] vs. 73.5% [95% CI: 72.1–74.9]). The same trend was observed at 1 year for mortality (Kaplan-Meier estimated survival of 73.5% [95% CI: 69.9–

76.8] vs. 79.5% [95% CI: 78.2–80.7]) and mortality or hospitalizations (Kaplan-Meier estimated survival of 52.8% [95% CI: 48.8–56.7] vs. 64.3% [95% CI: 62.8–65.8]).

Table 4 presents the outcomes data in patients treated with furosemide or torsemide. On unadjusted analysis, torsemide was also associated with increased 30-day mortality or hospitalization, 30-day hospitalization, and long-term mortality. Following risk adjustment, there was no longer an association between torsemide and increased 30-day mortality or hospitalization (Odds Ratio 1.30; 95% CI: 0.98–1.72; $P=0.0687$), or long-term mortality (Hazard Ratio 1.16; 95% CI: 0.98–1.38; $P=0.0864$). The association between torsemide and increased 30-day hospitalization alone was attenuated but remained significant after risk adjustment.

DISCUSSION

In a large single center HF cohort, we found that furosemide was the primary loop diuretic used for volume management. Patients treated with torsemide tended to have features of more severe disease compared with furosemide-treated patients. In particular, patients who received torsemide tended to have right-sided valvular regurgitation and multiorgan dysfunction with concomitant chronic kidney disease. On unadjusted analysis, torsemide use was associated with increased short-term morbidity and mortality at 30-days, 6 months, and 1 year, along with worse long-term survival. Following risk adjustment, the association between torsemide and increased long-term mortality was attenuated and no longer reached statistical significance. Importantly, while the association between increased events with torsemide versus furosemide was attenuated following risk adjustment, the nominal difference continued to trend toward worse outcomes with torsemide. Therefore, these findings should be viewed as hypothesis generating. Given the potential for residual confounding, these data combined with prior observational data suggesting benefits with torsemide provide the equipoise for a prospective trial that is adequately powered to investigate the effect of torsemide vs. furosemide on clinical outcome.

The primary finding of our analysis was that torsemide-treated patients had features of more severe disease compared with furosemide-treated patients. Clinical factors strongly associated with torsemide use were renal disease and RV dilatation. Right-sided valvular regurgitation was more common in torsemide-treated patients. These findings suggest that clinicians use torsemide in the setting of refractory volume overload and renal failure. The preferential use of torsemide in these circumstances may be related to torsemide's consistent bioavailability even in the setting of intestinal edema⁴.

Despite preclinical and clinical data suggesting beneficial pharmacologic and disease-specific benefits with torsemide over furosemide^{6–11}, we did not demonstrate improved outcomes with torsemide. There are several potential explanations for these findings. First, despite multiple adjustment models, other measured and unmeasured variables may have influenced these results. Outside the context of a randomized clinical trial, the effect of torsemide as compared with furosemide cannot be established. Alternatively, while earlier studies suggested anti-fibrotic effects with torsemide^{10, 19, 20}, it remains unclear whether these effects translate into clinically meaningful benefits for patients. Loop diuretics have

not previously been shown to be associated with improved clinical outcomes in prospective evaluations³. Third, previous studies suggesting an association between torsemide and outcomes were conducted in the chronic HF populations¹³ rather than those recently hospitalized with HF. There may be important clinical differences between the chronic stable HF population and those with acute HF with respect to the benefit of different therapies^{21, 22}. Furthermore, data are not available for this cohort regarding whether or not there was equivalent dosing in torsemide vs. furosemide treated patients.

With a sample size of 4,580 patients, this is largest analysis to date comparing torsemide to furosemide use in the HF population. When considering risk adjustments, our analysis was inclusive of echocardiographic data allowing for adjustments based on more objective variables as compared to prior analyses that incorporated subjective measures such as NYHA class. Furthermore, prior studies of mortality and hospitalization comparing torsemide vs. furosemide-treated patients averaged <1 year of follow-up, while our analysis provides data on long-term mortality with a follow-up interval of 5 years.

The dramatic increase in the use of torsemide over the past several years highlights the importance of obtaining prospective data comparing these 2 loop diuretics. There is an unmet need to empirically test the potential benefits of torsemide that have been identified in earlier studies^{10, 19, 20}. At present, the preferential use of furosemide is likely due to furosemide being first to market in 1966 compared with torsemide which was FDA-approved in 1993 and became generic in 2002. We observed that the use of torsemide at our institution began to increase several years later in 2005–2006. There is no preferred diuretic at our institution and diuretic choice is left to the discretion of the treating provider. Clinicians tend to have greater experience with furosemide and it has historically been less expensive. These 2 drugs now have comparable costs. Studies that were conducted even prior to the widespread availability of generic torsemide²³ suggest that despite a previously higher acquisition cost, torsemide may be associated with a reduction in total cost per patient. Randomized trial data comparing loop diuretic strategies would provide an opportunity to improve HF management and reduce health care expenditures with currently available therapies.

There are several limitations to our study. First, this was a retrospective analysis from a single tertiary referral center. The analysis cohort required that patients had an echocardiogram during hospitalization. We included patients with both preserved EF and reduced EF. The generalizability of these results to HF populations with different baseline characteristics is unclear. Data were not consistently available regarding post-discharge loop diuretic adjustments. Thus, there is the potential for crossover between furosemide and torsemide which could confound these results. The analysis population was not a new-user design given the routine use of loop diuretics in clinical practice in order to manage volume overload. Rehospitalization data were limited to those within the Duke Health System. These data may provide the rationale for an appropriately powered clinical trial of the comparative-effectiveness of furosemide vs. torsemide in HF patients.

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Figure 1.
Use of loop diuretics over the study period.

Figure 2.
Kaplan-Meier unadjusted mortality estimated by discharge loop diuretic. Abbreviations:
Furo.=furosemide; Tors.=torsemide

Table 1

Baseline characteristics of the study population by discharge diuretic.

Characteristic	FUROSEMIDE (n=3955)	TORSEMIDE (n=625)	P-value
Age(years)	65 (54–76)	64 (53–74)	0.076
Gender			<.001
Male	2197 (55.6%)	299 (47.8%)	
Female	1756 (44.4%)	326 (52.2%)	
Hypertension	3328 (84.1%)	547 (87.5%)	0.030
Diabetes	1886 (47.7%)	334 (53.4%)	0.007
Prior myocardial infarction	1520 (38.4%)	221 (35.4%)	0.141
Prior cerebrovascular disease	891 (22.5%)	168 (26.9%)	0.016
Renal failure	749 (18.9%)	288 (46.1%)	<.001
Hyperlipidemia	2253 (57.0%)	351 (56.2%)	0.705
Atrial fibrillation	1608 (40.7%)	304 (48.6%)	<.001
Chronic obstructive pulmonary disease	478 (12.1%)	81 (13.0%)	0.535
Liver disease	147 (3.7%)	48 (7.7%)	<.001
History of smoking	1951 (49.3%)	238 (38.1%)	<.001
Creatinine(mg/dL)	1.20 (1.00–1.60)	1.40 (1.00–2.00)	<.001
BUN (mg/dL)	23 (17–35)	27 (18–45)	<.001
NT-proBNP [n](pg/mL)	[1879] 3501 (1379–8488)	[404] 4214 (1725–9499)	0.026
Echocardiographic Details^a			
Days from echo to discharge	4 (2–7)	6 (3–10)	<.001
Left ventricular ejection fraction			0.113
<15%	382 (9.7%)	64 (10.3%)	
15–24%	388 (9.9%)	58 (9.3%)	
25–34%	527 (13.4%)	76 (12.2%)	
35–44%	378 (9.6%)	56 (9.0%)	
45–54%	416 (10.6%)	90 (14.4%)	
>=55%	1843 (46.8%)	279 (44.8%)	
RV Size			<.001
Mildly enlarged	650/3893 (16.7%)	111/618 (18.0%)	
Moderately enlarged	264/3893 (6.8%)	68/618 (11.0%)	
Severely enlarged	75/3893 (1.9%)	39/618 (6.3%)	
RV Contraction			<.001
Mild global decrease	570/3881 (14.7%)	114/616 (18.5%)	
Moderate global decrease	369/3881 (9.5%)	78/616 (12.7%)	
Severe global decrease	165/3881 (4.3%)	50/616 (8.1%)	
RV Systolic Pressure (mmHg)	43 (35–54)	45 (36–56)	0.004
Mitral regurgitation	985 (27.3%)	146 (25.4%)	0.343
Aortic regurgitation	138 (3.8%)	27 (4.6%)	0.362
Aortic stenosis	300 (8.2%)	61 (10.4%)	0.078

Characteristic	FUROSEMIDE (n=3955)	TORSEMIDE (n=625)	P-value
Pulmonic regurgitation	140/2379 (5.9%)	37/347 (10.7%)	<.001
Tricuspid regurgitation	899 (24.6%)	201 (33.9%)	<.001
Left ventricular hypertrophy	806 (21.0%)	144 (23.5%)	0.167
Concurrent Medication Use			
ACE-inhibitor	2725 (68.9%)	296 (47.4%)	<.001
ARB	726 (18.4%)	168 (26.9%)	<.001
Beta-blocker	3460 (87.5%)	528 (84.5%)	0.037
Aldosterone antagonist	1467 (37.1%)	286 (45.8%)	<.001

Data presented as median (interquartile range) or N (percentage).

The sample size is noted when different from the overall number of individuals in the group.

^aFor echocardiographic data, variables represent moderate to severe disease.

Definitions: Hypertension, renal failure, hyperlipidemia, and liver disease were based on documentation of these clinical diagnoses in the medical history.

Abbreviations: ACE=angiotensin converting enzyme; ARB=angiotensin receptor blocker; BNP=brain natriuretic peptide; BUN=blood urea nitrogen

Table 2

Key variables associated with torsemide use at discharge.

Characteristic	Odds Ratio (95% CI)	p-value
Age (per 5 years)	0.92 (0.89 – 0.96)	<.0001
Female sex	1.44 (1.17 – 1.77)	0.0005
Chronic kidney disease	1.55 (1.20 – 2.01)	0.0008
ACE-Inhibitors	0.78 (0.63 – 0.95)	0.0151
Aldosterone antagonists	1.97 (1.59 – 2.44)	<.0001
Ejection fraction (per 5% increase)	1.10 (1.07 – 1.14)	<.0001
Right ventricular size (reference=normal)		0.0049
Mildly enlarged	1.08 (0.82 – 1.41)	.
Moderately enlarged	1.25 (0.88 – 1.78)	.
Severely enlarged	2.46 (1.49 – 4.04)	.
Tricuspid regurgitation (reference=none)		0.0065
Mild	1.20 (0.95 – 1.53)	.
Moderate	1.27 (0.94 – 1.72)	.
Severe	1.91 (1.33 – 2.75)	.
Creatinine (per 0.1 mg/dL up to 2.0) *	1.06 (1.03 – 1.09)	<.0001

Abbreviations: ACE=angiotensin converting enzyme; CI=confidence interval

* There was evidence of non-linearity for creatinine such that fit interpretable linear splines were used. There was insufficient evidence to suggest an association between creatinine and torsemide use when the creatinine value was >2.0 mg/dL.

Definitions: Chronic kidney disease was based on documentation of these clinical diagnoses in the medical history.

Table 3

Kaplan-Meier Estimate for outcomes based on discharge diuretic.

Outcome	Furosemide		Torsemide	
	Number At Risk	KM Estimated Survival (95%CI)	Number At Risk	KM Estimated Survival (95%CI)
Mortality or Hospitalization				
0.5 years	2891	0.735 (0.721 – 0.749)	406	0.652 (0.613 – 0.688)
1 year	2461	0.643 (0.628 – 0.658)	295	0.528 (0.488 – 0.567)
3 years	1448	0.445 (0.429 – 0.461)	100	0.340 (0.298 – 0.383)
5 years	830	0.335 (0.319 – 0.351)	32	0.218 (0.173 – 0.266)
Mortality				
0.5 years	3401	0.862 (0.851 – 0.873)	511	0.820 (0.788 – 0.848)
1 year	3128	0.795 (0.782 – 0.807)	456	0.735 (0.699 – 0.768)
3 years	2286	0.623 (0.607 – 0.638)	266	0.554 (0.513 – 0.594)
5 years	1493	0.515 (0.498 – 0.531)	94	0.414 (0.367 – 0.460)

Abbreviations: CI=confidence interval; KM=Kaplan-Meier

Table 4

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

Endpoint	Sample Size	Odds Ratio or Hazard Ratio (95% CI)	P-value
30-day Mortality or hospitalization		Odds Ratio (95% CI)	
Unadjusted	4580	1.38 (1.06 – 1.80)	0.018
Adjusted ^a	4555	1.22 (0.91 – 1.64)	0.1769
Adjusted IPW ^a	4555	1.30 (0.98 – 1.72)	0.0687
30-day hospitalization		Odds Ratio (95% CI)	
Unadjusted	4580	1.52 (1.11 – 2.09)	0.0099
Adjusted ^a	4555	1.29 (0.91 – 1.83)	0.1607
Adjusted IPW ^a	4555	1.45 (1.04 – 2.02)	0.0283
Mortality through 5 years		Hazard Ratio (95% CI)	
Unadjusted	4580	1.33 (1.17 – 1.51)	<.0001
Adjusted ^a	4555	1.09 (0.95 – 1.24)	0.2279
Adjusted IPW ^a	4555	1.16 (0.98 – 1.38)	0.0864

^a Adjustment variables: age, sex, chronic kidney disease, creatinine, ejection fraction, right ventricular size, aortic stenosis, mitral stenosis, tricuspid regurgitation, aldosterone antagonists, and ACE-inhibitors

Abbreviations: CI=confidence interval; IPW=inverse probability weighted.