Can Torsemide and Combination of Loop Diuretics Improve Mortality in Patients with Chronic Heart Failure After Discharge?

Insights from Fuwai Hospital

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Summary

The aim of this study was to investigate the effect on mortality of torsemide and a combination of loop diuretics (furosemide + torsemide) in contemporary practice in patients with chronic heart failure (HF).

We investigated patients with HF in the Heart Failure Center of Fuwai Hospital from 2009 to 2013 who were discharged on furosemide, torsemide, or a combination of the 2 drugs. Using inverse probability weighting (IPW) to account for nonrandom selection of diuretic strategies, we assessed the association between different diuretic strategies and mortality.

Among 956 patients, 19.7% (n = 188) received furosemide, 36.6% (n = 350) torsemide, and 43.7% (n = 418) the combination therapy. The torsemide-treated and combination-treated patients had worse heart function and higher furosemide equivalent. Univariable Cox proportional hazards models showed that the combination group had worse outcomes (all-cause HR = 2.044, P = 0.008; CV HR = 1.988, P = 0.011), while torsemide was associated with an outcome (all-cause HR = 1.640, P = 0.078; CV HR = 1.509, P = 0.147) similar to that of furosemide. After IPW, torsemide was associated with a nominally lower mortality compared with furosemide (all-cause HR = 0.738, P = 0.222; CV HR = 0.667, P = 0.110), and the association between the combination treatment and increased mortality was no longer statistically significant (all-cause HR = 1.207, P = 0.470; CV HR = 1.174, P = 0.540).

We found that torsemide and the combination strategy had similar outcomes when compared with furosemide. However, considering the lack of diuretic randomized clinical trials (RCTs) conducted with the aim of exploring the effect on mortality of different diuretic treatments, prospective trials are needed to investigate the effect of different diuretic strategies in chronic HF.

Key words: Contemporary practice, Inverse probability weighting, Different diuretic strategies, All-cause mortality, CV mortality

The health burden of heart failure (HF) is significant and continues to grow in China. Loop diuretics play an essential role in the management of volume overload symptoms. A meta-analysis showed that diuretic use was associated with reduced mortality and improved exercise capacity in HF. However, another study found that use of loop diuretics at discharge was an independent predictor for rehospitalization. Current guidelines indicate that loop diuretics are the cornerstone for the management of volume overload. Furosemide and torsemide are two of the most commonly used loop diuretics in clinical practice. A review showed that torsemide had the ability to positively affect the renin-angiotensin-aldosterone system and result in better outcomes, as compared with furosemide. In the meantime, the phenomenon of diuretic resistance requires the logic of using combinations of different diuretics, but the association of a combination of loop diuretics with mortality in chronic HF is still unclear. Yet, the effect of different loop diuretic therapy on chronic HF outcomes has not been studied in large randomized clinical trials (RCTs). Previous studies had modest sample sizes and were conducted prior to the use of contemporary HF therapy. To investigate the role of torsemide and a combination of loop diuretics (furosemide + torsemide) in contemporary practice, we assessed different diuretic strategies at a large, tertiary hospital with contemporary therapy of heart failure over the past several years and evaluated the association with different kinds of diuretic strategies and post-discharge one-year mortality, using inverse probability weighting (IPW).
Methods

We assessed patients admitted to the Heart Failure Center of Fuwai Hospital with a primary discharge diagnosis of heart failure between 2009 and 2013 that were included in the Fuwai Electronic Medical Record System (FEMRS) and were discharged on furosemide, torsemide, or a combination of these 2 drugs. All patients had to be at least 18 years old and both echocardiogram data and a NYHA classification prior to discharge were available. For patients with multiple admissions, only the first admission was included in this study. All patients provided written informed consent and the ethics committee of Fuwai Hospital approved this study.

Adverse events with respect to one-year all-cause death and cardiovascular (CV) death were ascertained every 3 months via electronic hospital record follow-up or conversation with the patient or their family by telephone. Cardiovascular (CV) death included progressive heart failure death (progressive deterioration of HF in the absence of another cause), sudden death (unexpected and witnessed death in a stable patient without evidence of specific cause of death), death due to myocardial infarction or stroke, or other CV death (such as mortal complications of cardiac surgery, rupture of an aneurysm, pulmonary embolism, and aortic dissection).

Baseline clinical variables at discharge, including demographic characteristics, co-morbidities, laboratory data, echocardiogram data, and medications were obtained from FEMRS (Table I). Torsemide was converted to the furosemide equivalent dose: 1 mg of oral torsemide was considered equivalent to 2 mg of oral furosemide, and 1 mg of oral bumetanide was considered equivalent to 40 mg of oral furosemide. Data were summarized by the medians and 25th and 75th percentiles (IQR) for continuous variables, and as percentages for categorical variables. For the purpose of this analysis, the patients were divided into 3 groups according to different diuretic treatments at discharge: furosemide, torsemide, and a combination of these 2 drugs. The combination group was treated with furosemide and torsemide on alternating days. Baseline characteristics were compared using the Wilcoxon rank-sum test for continuous variables and the Pearson chi-square test for categorical variables.

We generated two multivariable logistic regression models (Models 1 and 2) to determine baseline variables associated with discharge torsemide use or combination treatment (over furosemide), using backward selection with a P value of 0.10 to stay in the models. Candidate variables were those included in the baseline characteristics table (Table I).

Because the choice of diuretic strategy at discharge was not randomized, two multivariable logistic models (using the variables in Model 1 or 2, and some variables which were probably associated with torsemide use or combination therapy in clinical practice) were used to estimate propensity scores.

One-year cumulative mortality curves were prepared using unadjusted Kaplan-Meier estimates (Figure 1). Cox proportional hazards models were used to assess the association between different kinds of diuretic strategies and outcome, using inverse probability weighting (IPW). IPW methods are a set of statistical techniques that reweight the data to create a pseudo-population in which patient characteristics are independent of the treatment received. Covariate-adjusted models were also used to assess the association of different diuretic strategies with outcome. Furosemide equivalent was included as an adjustment variable in all models. Hazard ratios (HR) with 95% confidence intervals (CIs) were calculated, along with the corresponding P value.

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.

Results

Figure 2 presents the patients included in this analysis. Of 1511 HF patients hospitalized in the Heart Failure Center of Fuwai Hospital between 2009 and 2013 who were discharged, 956 patients were discharged on loop diuretics, and had echocardiogram data and a NYHA classification prior to discharge. Furosemide was administered to 19.7% (n = 188), torsemide to 36.6% (n = 350), and a combination of both loop diuretics to 43.7% (n = 418). Bumetanide was also used by 13 patients in the furosemide group and 22 patients in the torsemide group. Eight patients in the furosemide group and 2 patients in the torsemide group also used hydrochlorothiazide. The baseline characteristics of the study cohort by discharge diuretic strategies are presented in Table I. Patients receiving torsemide had higher incidences of atrial fibrillation/flutter, pulmonary artery hypertension (PAH), and anemia, but less coronary heart disease and diabetes mellitus compared with furosemide-treated patients. Torsemide-treated patients received less ACEI/ARB, beta blockers, spironolactone and statins, but more warfarin and digoxin after discharge compared with patients treated with furosemide. Both the torsemide-treated and combination-treated patients had worse NYHA classification, more hyponatremia, and higher BUN, UA, and NT-proBNP levels compared with the furosemide-treated patients. The median daily dose of furosemide equivalent in patients discharged on torsemide and combination were 40 mg (IQR: 20-40) and 40 mg (IQR: 30-40) respectively, compared with 20 mg (IQR: 20-27.5) in the patients discharged on furosemide.

Factors associated with torsemide and combination treatment at discharge are presented in Table II. Clinical factors independently associated with torsemide use were NYHA classification, serum chloride, UA, anemia, spironolactone, warfarin, and statin. The clinical factors independently associated with combination treatment were NYHA classification and UA.

In our cohort, all-cause mortality through one-year was increased in patients discharged on torsemide (14.3%) and combination treatment (17.5%) compared with furosemide (9%). Figures 1, 3 show the unadjusted mortality curves for patients receiving loop diuretics. Table III presents the outcomes in patients treated with different diuretic strategies. Univariable Cox proportional hazards
models showed that torsemide-treated patients had similar outcomes (all-cause HR = 1.640, 95%CI: 0.946-2.843, \(P = 0.078\); CV HR = 1.509, 95%CI: 0.865-2.631, \(P = 0.147\), while combination-treated patients had worse out-
comes (all-cause HR = 2.044, 95%CI: 1.206-3.465, \(P = 0.008\); CV HR = 1.988, 95%CI: 1.171-3.374, \(P = 0.011\)), compared with furosemide, respectively. Following adjustment for risk factors, torsemide was associated with nominally decreased mortality (all-cause HR = 0.767, 95%CI: 0.415-1.415, \(P = 0.396\); CV HR = 0.689, 95%CI: 0.370-1.285, \(P = 0.241\)). However, the association of combination treatment with worse outcome no longer remained (all-cause HR = 1.433, 95%CI: 0.824-2.491, \(P = 0.203\); CV HR = 1.398, 95%CI: 0.802-2.435, \(P = 0.237\)) after risk factor adjustment. On IPW-adjusted analysis, torsemide use was associated with nominally lower mortality (all-cause HR = 0.738, 95%CI: 0.452-1.020, \(P = 0.222\); CV HR = 0.667, 95%CI: 0.406-1.096, \(P = 0.011\)) compared with furosemide. Also, the association between combination treatment and increased one-year all-cause and CV mortality was no longer statistically significant (all-cause HR = 1.207, 95%CI: 0.725-2.011, \(P = 0.470\); CV HR = 1.174, 95%CI: 0.703-1.959, \(P = 0.540\)) compared with furosemide.

It is noteworthy that regardless of whether a multivariable Cox model or IPW-adjusted model was used, a higher furosemide equivalent was associated with increased mortality.

**Discussion**

In this single center heart failure cohort in China, we found that torsemide and a furosemide-torsemide combination treatment were more commonly used than furosemide at discharge. This was different from the reports of previous studies. Both the torsemide and combination groups had higher NYHA classification, more hypotension, and higher furosemide equivalent compared with the furosemide group. Combination-treated patients had higher Cr and BUN compared with furosemide. Torsemide-treated patients had slightly higher incidences of atrial fibrillation/flutter, PAH and anemia, but less coronary artery disease and diabetes mellitus compared with the furosemide patients. In particular, patients who received torsemide tended to receive less drugs (such as ACEI/ARB, beta blockers, and spironolactone) which could improve outcomes in heart failure. We did not find any differences in Cr and eGFR between the torsemide and furosemide groups at baseline, although BUN was significantly higher in the torsemide-treated patients.

In logistic analysis, we found that clinical factors associated with torsemide use were higher NYHA classification, anemia, less use of spironolactone and statins, and higher UA. Higher NYHA classification and UA were also associated with combination treatment. These findings suggest that clinicians use torsemide/combination in the setting of severe heart failure at discharge. The sub-preferential use of furosemide in these circumstances may be related to the higher frequency of furosemide’s side effects. On the contrary, because of the pharmacological advantage of torsemide, torsemide could more efficiently maintain water balance and caused less side effects, com-

**Figure 1.** Kaplan-Meier curve of all-cause mortality: furosemide versus torsemide.

![Kaplan-Meier curve of all-cause mortality: furosemide versus torsemide.](image)
Figure 2. Study population.

Table II. Variables Associated with Torsemide and Combination Treatment at Discharge

<table>
<thead>
<tr>
<th>Variable</th>
<th>Torsemide (Model 1) Odds Ratio (95% CI)</th>
<th>P value</th>
<th>Combination (Model 2) Odds Ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA III/IV</td>
<td>2.514 (1.564-4.040)</td>
<td>&lt; 0.001</td>
<td>2.258 (1.483-3.438)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Warfarin</td>
<td>1.974 (1.197-3.256)</td>
<td>0.008</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>1.926 (1.166-3.179)</td>
<td>0.010</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UA</td>
<td>1.003 (1.001-1.004)</td>
<td>0.001</td>
<td>1.003 (1.001-1.004)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Cl</td>
<td>0.916 (0.868-0.966)</td>
<td>0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statin</td>
<td>0.584 (0.394-0.866)</td>
<td>0.008</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spirolactone</td>
<td>0.429 (0.258-0.715)</td>
<td>0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NYHA indicates New York Heart Association; UA, uric acid; and Cl, chlorine.

pared with furosemide.6,7)

Although not designed as a mortality study, TORIC suggested a lower mortality among chronic HF patients treated with torsemide compared with furosemide.7) Another open-label randomized trial found that compared with furosemide, torsemide treatment could reduce readmission for heart failure and for cardiovascular causes.6) However, these previous studies had modest sample sizes and were conducted without contemporary HF therapy. In recent years, two retrospective studies with large sample sizes suggested that torsemide was associated with similar outcomes compared with furosemide.12,13) We did not observe significantly improved outcomes with torsemide use in our HF cohort, the specific reason for which remains unclear. Compared with previous studies6,7) that were conducted decades ago, our study cohort had higher usage rates for ACEI/ARB, beta blockers, and spirolactone, which could inhibit the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system. Although it had been reported that torsemide also has the ability to
block the RAAS and sympathetic nervous system, the potential advantages of torsemide might become negligible in cases of contemporary therapy of heart failure with RAAS inhibitors and beta blockers. Importantly, while the associations between decreased mortality and torsemide in two retrospective studies and our study were not statistically significant, after adjustment the value of point estimation continued to trend towards a better outcome with torsemide in these 3 studies.

In our logistic analysis, we found that a higher NYHA classification and higher UA were associated with combination treatment. There are several potential reasons for the preference of combination treatment. First, torsemide had a pharmacological advantage over furosemide, and combination treatment could reduce the use of furosemide. Second, it is common for clinicians to use multiple diuretics to deal with diuretic resistance. Third, since torsemide is more expensive than furosemide in China, combination treatment may reduce the cost for HF patients compared with torsemide and have potential benefits compared with furosemide. It is noteworthy that we assessed the associations between combination treat-
ment and one-year all-cause and CV mortality compared with furosemide for the first time. On unadjusted analysis, combination treatment was associated with increased one-year all-cause and CV mortality. After multivariable and IPW adjustment, we found that there was a nominal increase but not a statistically significant increase in one-year mortality. There are several potential explanations for this finding. First, despite multivariable and IPW adjustment models, other measured and unmeasured factors may influence the result. Second, patient compliance with combination treatment may be lower than single loop diuretic use. Patients may switch to one of these two loop diuretics during follow-up and this behavior may affect the results of the study. Third, the calculations of furosemide equivalent dose were different in different studies.9,11,18 Therefore, it was unclear whether the calculation of furosemide equivalent dose (1 mg of oral torsemide was considered to be equivalent to 2 mg of oral furosemide) was reasonable. Unreasonable conversion in clinical practice may result in insufficient diuresis or excessive diuresis which had an adverse impact on prognosis. Although our analysis showed that combination treatment was associated with similar outcomes compared with furosemide, it also provided an insight into its potential disadvantage.

We also found that regardless of whether multivariable Cox models or IPW adjusted models were used, a higher furosemide equivalent dose was associated with increased one-year mortality and these findings were consistent with previous studies.10,21 The furosemide equivalent dose in our study cohort was lower than those of the PROTECT trial and ASCEND-HF trial,11,12 and this finding expanded the understanding of diuretic use in patients with chronic heart failure in China. Diuretics stimulate the RAAS and sympathetic nervous system by depleting the circulating blood volume, contributing to further HF progression.21 In a prospective, randomized study (n = 40) in which the patients were treated with optimal oral doses of HF medication, it was found that the dose of diuretic can be safely lowered in patients with stable and chronic HF, and there was a tendency toward better outcomes associated with the decrease in the dose of diuretics.20

In summary, our study provides further rationale for clinical practice regarding diuretic strategy selection in chronic HF patients after discharge. Furosemide, torsemide, and a combination treatment of these 2 drugs are 3 optional strategies for chronic heart failure patients. Although there were no differences in outcomes between furosemide and torsemide in our study, we still suggest that torsemide should be the preferred diuretic drug for chronic heart failure patients if possible because of its potential pharmacological benefits and fewer side effects. Combination treatment may be another option if the furosemide equivalent dose can be correctly identified. In patients with stable and chronic HF, it is better to reduce the dose of diuretic to an extent that will not affect the HF treatment effect.

There are several limitations in our study. First, this was a retrospective analysis from a single tertiary hospital. We excluded patients without an echocardiogram at discharge and included patients with both preserved and reduced EF. Therefore, the generalizability of the results to HF patients with different characteristics is unclear. Data about the compliance to diuretic strategies and dose were not available. Thus, it is possible to change the diuretic strategy during follow-up, which could confound these results. Despite IPW adjustment, there were still few variables unbalanced between the study group and control group, and other measured and unmeasured variables may have influenced our results. Thus, these data should be regarded as exploratory.

Conclusion

We found that torsemide was not associated with significantly decreased one-year all-cause mortality and CV mortality, and the combination strategy was associated with a similar outcome compared with furosemide. However, considering the lack of diuretic RCTs conducted for the aim of exploring the effect on mortality of different diuretic treatments, and what is a reasonable calculation of furosemide equivalent for chronic heart failure patients, prospective trials are needed to investigate the effect of different diuretic strategies in chronic HF.

Disclosures

Conflicts of interest: None.

References

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