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ORIGINAL ARTICLE

Real world experience in effect of torsemide vs. furosemide after discharge in patients with HFpEF

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Abstract

Aims Few studies have focused on the effect of torsemide versus furosemide after discharge on prognosis in patients with heart failure with preserved ejection fraction (HFpEF). This single-centre retrospective real-world study was conducted to evaluate the effect of torsemide versus furosemide after discharge on all-cause mortality and rehospitalization for heart failure in patients with HFpEF.

Methods Consecutive patients who were diagnosis with HFpEF after discharge between January 2015 and April 2018 at the First Affiliated Hospital of Dalian Medical University and who had been treated with torsemide or furosemide were included in this study. The primary outcome was all-cause mortality. The second outcome was rehospitalization for heart failure.

Results A total of 445 patients (mean age 68.56 ± 8.07, female 55%) were divided into the torsemide group (*N* = 258) or furosemide group (*N* = 187) based on the treatment course at discharge from the hospital. During a mean follow-up of 87.67 ± 11.15 months, death occurred in 68 of 258 patients (26.36%) in the torsemide group and 60 of 187 patients (30.09%) in the furosemide group [hazard ratio (HR) 0.81, 95% confidence interval (CI) 0.57–1.15, *P* = 0.239]. Rehospitalization for heart failure occurred in 111 of 258 patients (43.02%) in the torsemide groups and 110 of 187 patients (58.82%) in the furosemide group (HR 0.64, 95% CI 0.49–0.85, *P* = 0.002).

Conclusions Compared with furosemide, torsemide did not significantly reduce all-cause mortality, but there was association between torsemide and reduced rehospitalization for heart failure in patients with HFpEF.

Keywords furosemide; heart failure; loop diuretics; preserved ejection fraction; torsemide

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Introduction

In recent decades, heart failure (HF) has become a major and growing public health problem worldwide.[1] The total percentage of the population with HF is projected to increase from 2.4% in 2012 to 3.0% in 2030.[2] Based on the measurement of the left ventricular ejection fraction (LVEF), HF is divided into HF with a reduced ejection fraction (HFrEF, LVEF $\leq$ 40%), HF with a mid-range ejection fraction (HFmrEF, LVEF in the range of 41%–49%) and HF with a preserved ejection fraction (HFpEF, LVEF $\geq$ 50%).[3] The diagnosis of HFpEF includes symptoms and signs of HF, LVEF $\geq$ 50% and objective evidence of cardiac structural and/or functional abnormalities. Secular trends across two decades showed a similar incidence of overall HF but with a declining incidence for HFrEF and an increasing incidence for HFpEF.[4] Unfortunately, there are no other definitive treatments that have been proven to improve the prognosis of HFpEF patients except sodium-glucose cotransporter type 2 inhibitor (SGLT2i).[5,6]

Approximately 65% of patients with HFpEF present with overt congestion, as suggested by clinical signs such as peripheral oedema, ascites, jugular venous distention, S3 gallop sounds or elevated cardiac filling pressures.[7,8]Guidelines indicate that the use of diuretics is a cornerstone of a successful approach to the treatment of congestion in HFpEF patients.[9] Furosemide is the most commonly used loop diuretic for HF.[10] Several small studies have suggested a

decrease in morbidity and potentially mortality with torsemide compared with furosemide.[11,12] However, another study suggested that torsemide was not superior to furosemide in improving functional capacity, diastolic function, quality of life, or neuroendocrine activation.[13] Recently, a randomized clinical trial (the TRANSFORM-HF) revealed that among patients discharged after hospitalization for HF, torsemide compared with furosemide did not result in a significant difference in all-cause mortality over 12 months.[14] However, few studies have focused on the effect of torsemide vs. furosemide after discharge on prognosis in patients with HFpEF. Therefore, we undertook a single-centre, retrospective cohort study to evaluate the effectiveness of torsemide vs. furosemide after discharge on a five-year follow-up prognosis in patients with HFpEF.

Patients and methods

Study design

This was an observational, retrospective, non-interventional real-world study based on data from the First Affiliated Hospital of Dalian Medical University.

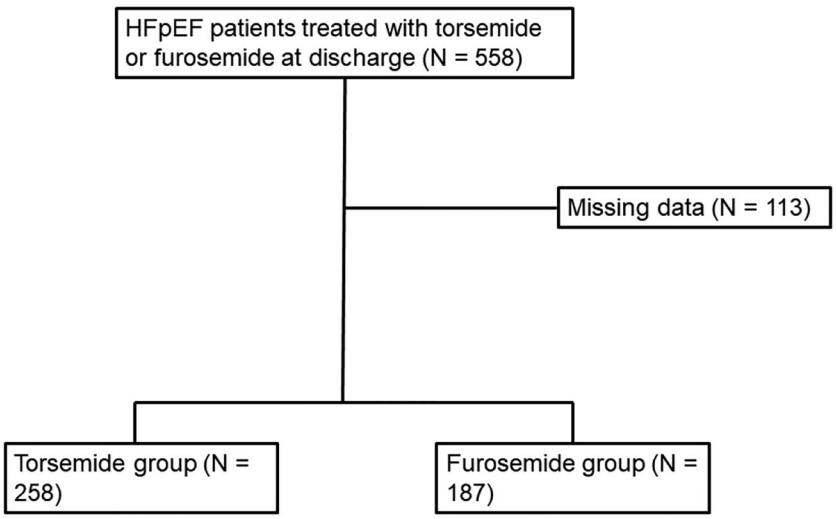
Study population

The study was approved by the institutional review board of Dalian Medical University, and informed consent was obtained from the subjects. Consecutive patients who were diagnosed with HFpEF after discharge from January 2015 to April 2018 at the First Affiliated Hospital of Dalian Medical University who had been treated with torsemide or furosemide were included in this study. All patients were first hospitalized for HF. None of the patients were treated with either torsemide or furosemide. All patients received standard HF treatment during hospitalization and were significantly better off when discharged. The dosage of torsemide or furosemide depends on the patient's condition at the time of discharge, and they will maintain this dosage for a long time. A total of 558 patients were included; however, 113 patients were excluded due to loss to follow-up, and the remaining 445 patients were divided into the torsemide group (N = 258) or furosemide group (N = 187) based on the treatment at discharge from the hospital (*Figure* 1).

Clinical definitions

HFpEF was diagnosed according to the 2021 European Society of Cardiology (ESC) guidelines for the diagnosis and treatment of acute and chronic HF. The diagnostic criteria included the following: (i) symptoms or signs of HF; (ii) LVEF $\geq$ 50%; (iii) objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of left ventricular (LV) diastolic dysfunction/increased LV filling pressures, including an LV mass index $\geq$95 g/m^2 (female) or $>$115 g/m^2 (male), a relative wall thickness $>$0.42, an LA volume index $>$34 mL/m^2 [sinus rhythm, (SR)] or $>$40 mL/m^2 [atrial fibrillation (AF)], an E/e' ratio at rest $>$9, an N-terminal pro-B-type natriuretic peptide (BNP) $>$125 (SR) or $>$365 (AF) pg/mL, a BNP $>$ 35 (SR) or $>$105 (AF) pg/mL, a pulmonary artery systolic pressure $>$35 mmHg, and a tricuspid regurgitation velocity at rest $>$2.8 m/s. The exclusion criteria

Figure 1 Flow chart of the study.



were severe valvular disease, specific type of cardiomyopathy (such as hypertrophic cardiomyopathy or restrictive cardiomyopathy), end-stage renal failure [estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2] or systemic inflammatory disease.[3]

Study outcomes

The primary outcome was all-cause mortality. The second outcome was first rehospitalization for HF.

Follow-up

Most of the enrolled patients were required to return to the outpatient clinic every year. Nevertheless, if the patients did not appear at their scheduled clinic, they were to be interviewed by telephone annually. During the follow-up period, there was no switching between medication groups or any dosage changes, which we would end our follow-up if it had occurred. The cut-off was April 2023 for the occurrence of study outcomes. The mean follow-up duration was 87.67 months (*Figure* 2).

Statistical analysis

Qualitative variables are expressed as percentages (%), and the χ^2 test was used for comparisons between groups. Normally distributed data are expressed as the mean (standard deviation), and non-normally distributed data are expressed as the median (inter-quartile range). A paired *t* test was used to detect differences between two groups with normally distributed data. For other data with non-normal distributions, the Mann–Whitney test was used to detect differences between two groups. Kaplan–Meier analysis and multivariate Cox regression analysis were used to describe the cumulative incidence of adverse events. *P* values <0.05 were considered to indicate statistically significant. The χ^2 test, *t* test, Mann–Whitney test and multivariate Cox regression analysis were performed using Statistical Package for Social Sciences, Version 24.0 (SPSS Inc., Chicago, IL, USA). Kaplan–Meier analysis was performed using GraphPad Prism 9.

Results

Baseline characteristics

The baseline characteristics of patients with HFpEF stratified by torsemide versus furosemide are presented in *Table* 1. Regarding patient demographics, the two groups had similar ages, gender ratios and body mass indexes. In terms of comorbidities, patients treated with torsemide were more likely to have a history of stable angina (18.22% vs. 11.23%, $P = 0.046$) and AF (61.63% vs. 39.57%, $P < 0.001$). Other comorbidities were similar between the two groups.

Clinical characteristics

The clinical characteristics of patients with HFpEF stratified by torsemide versus furosemide are presented in *Table* 2. Most of the New York Heart Association (NYHA) classes in the torsemide group and furosemide group were NYHA class III (56.20% and 59.89%, respectively) or NYHA class IV (32.17%

Figure 2 Study design. The study period was between January 2015 and 30 April 2023, and the inclusion period was between January 2015 and April 2018; the follow-up period was between January 2016 and April 2023. All patients were followed up for at least 12 months.

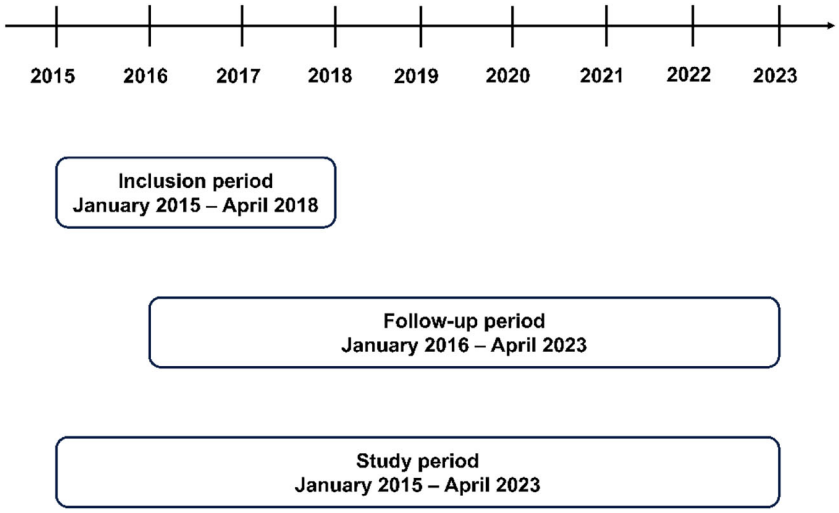


Table 1 Baseline characteristics in patients with heart failure with preserved ejection fraction stratified by torsemide versus furosemide.

	Torsemide	Furosemide	*P*
Total	258	187	
Ages; median (IQR)	70 (64–74)	70 (64–76)	0.081
Men; n (%)	114 (44.19)	84 (44.92)	0.923
Height (cm); mean (*SD*)	162.74 (7.60)	163.48 (7.59)	0.300
Weight (kg); mean (*SD*)	70.00 (13.57)	72.28 (13.74)	0.082
BMI (kg/m^2); mean (*SD*)	26.34 (4.33)	26.91 (3.92)	0.154
Hypertension; *n* (%)	206 (79.84)	147 (78.61)	0.813
Stable angina; *n* (%)	47 (18.22)	21 (11.23)	0.046
Myocardial infarction; *n* (%)	62 (24.03)	48 (25.67)	0.739
PCI/CABG; *n* (%)	34 (13.18)	23 (12.30)	0.886
Diabetes mellitus; *n* (%)	134 (51.98)	88 (47.06)	0.337
Atrial fibrillation; *n* (%)	159 (61.63)	74 (39.57)	<0.001
Previous stroke; *n* (%)	19 (7.36)	19 (10.16)	0.308
Pacemaker; *n* (%)	8 (3.10)	8 (4.28)	0.608

Abbreviations: BMI, body mass index; CABG: coronary artery bypass grafting; IQR, inter-quartile range; PCI, percutaneous coronary intervention; *SD*, standard deviation.

Table 2 Clinical characteristics in patients with heart failure with preserved ejection fraction stratified by torsemide versus furosemide.

	Torsemide	Furosemide	*P*
NYHA class; *n* (%)			
I	/	/	—
II	30 (11.63)	21 (11.23)	
III	145 (56.20)	112 (59.89)	
IV	83 (32.17)	54 (28.88)	
Blood pressure			
SBP (mmHg); mean (*SD*)	143.01 (27.70)	142.13 (22.58)	0.720
DBP (mmHg); mean (*SD*)	80.63 (16.93)	80.18 (13.71)	0.765
ECG			
Heart rate (BPM); mean (*SD*)	82.92 (20.94)	78.88 (21.32)	0.047
QRS (ms); mean (*SD*)	96.86 (26.17)	96.23 (23.41)	0.818
QTc (ms); mean (*SD*)	465.39 (51.69)	455.43 (52.09)	0.076
UCG			
LAD (mm); mean (*SD*)	43.65 (6.80)	40.85 (6.59)	<0.001
LVDD (mm); mean (*SD*)	47.24 (7.39)	47.33 (7.33)	0.907
LVEF (%);mean (*SD*)	56.50 (2.74)	56.55 (3.99)	0.883
E/e'; mean (*SD*)	12.70 (5.96)	11.69 (5.84)	0.110
EDT (ms); mean (*SD*)	181.78 (53.06)	187.11 (51.56)	0.322

Abbreviations: DBP, diastolic blood pressure; ECG, electrocardiogram; EDT, E wave deceleration time; LAD, left atrium diameter; LVDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SBP, systolic blood pressure; SD, standard deviation; UCG, ultrasound cardiogram.

and 28.88%, respectively). Both groups had a high incidence of hypertension (79.84% vs. 78.61%), and both had elevated systolic blood pressure at discharge, but there was no significant difference between the two groups (143.01 ± 27.70 mmHg vs. 142.13 ± 22.58 mmHg, $P = 0.720$). On electrocardiogram, the torsemide group had a greater heart rate than did furosemide group (82.92 ± 20.94 bpm vs. 78.88 ± 21.32 bpm, $P = 0.047$). According to the echocardiogram, the LVEF was greater than 50% in both groups, and the left atrium diameter was greater in the torsemide group (LAD, 43.65 ± 6.80 mm vs. 40.85 ± 6.59 mm, $P < 0.001$).

Table 3 Drug therapy in patients with heart failure with preserved ejection fraction stratified by torsemide versus furosemide.

	Torsemide	Furosemide	*P*
Loop diuretic doses; mg (*SD*)	11.16 (0.25)	21.97 (0.56)	—
MRAs; *n* (%)	186 (72.09)	121 (64.71)	0.098
AECi; *n* (%)	80 (31.01)	53 (28.34)	0.600
ARB; *n* (%)	79 (30.62)	52 (27.81)	0.529
CCB; *n* (%)	101 (39.15)	89 (47.59)	0.081
Beta-blockers; *n* (%)	206 (79.84)	136 (72.73)	0.088
Digoxin; *n* (%)	31 (12.02)	14 (7.49)	0.151
Statins; *n* (%)	156 (60.47)	119 (63.64)	0.553
Antiplatelet drugs; *n* (%)	113 (43.80)	91 (48.66)	0.336
Anticoagulants; *n* (%)	85 (32.95)	56 (29.95)	0.536
Metformin; *n* (%)	120 (46.51)	85 (45.45)	0.848
SGLT2i; *n* (%)	25 (9.69)	14 (7.49)	0.498

Abbreviations: ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; CCB, calcium channel blockers; MRAs, mineralocorticoid receptor antagonists; SGLT2i, sodium-glucose cotransporter type 2 inhibitor.

Drug therapy

The results of drug therapy in patients with HFpEF stratified by torsemide versus furosemide are presented in *Table* 3. The loop diuretic dose was 11.16 ± 0.25 mg in the torsemide group and 21.97 ± 0.56 mg in the furosemide group at discharge. The most commonly used medications in the torsemide group and furosemide group were beta-blockers (79.84% and 72.73%, respectively) and mineralocorticoid receptor antagonists (MRAs, 72.09% and 64.70%, respectively). For all drug therapies (MRA, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers, beta-blockers, digoxin, statins, antiplatelet drugs, anticoagulants, metformin and SGLT2i), there were no significant differences between the two groups.

Laboratory tests

The results of laboratory tests in patients with HFpEF stratified by torsemide versus furosemide are presented in *Table* 4. All the laboratory findings of patients were collected at the first admission. Compared with the furosemide group, the torsemide group had elevated BNP [368.54 (209.68–696.04) pg/mL vs. 207.05 (93.67–438.37) pg/mL, $P < 0.001$; in patients with AF, 483.92 (225.38–1184.94) pg/mL vs. 267.71 (168.67–445.97) pg/mL, $P < 0.001$; in patients without AF, 318.52 (204.01–566.48) pg/mL vs. 118.83 (61.92–431.04) pg/mL, $P < 0.001$], D-dimer [635.00 (307.50–1370.50) μg/L vs. 540.00 (260.00–990.00) μg/L, $P = 0.039$] and uric acid (UA, 459.19 ± 158.40 μmol/L vs.

Table 4 Laboratory test in patients with heart failure with preserved ejection fraction stratified by torsemide versus furosemide.

	Torsemide	Furosemide	*P*
WBC ($\times 10^9$/L); mean (*SD*)	6.83 (2.56)	6.94 (1.95)	0.619
Hb (g/L); mean (*SD*)	122.26 (25.41)	126.86 (25.88)	0.069
PLT ($\times 10^9$/L); mean (*SD*)	198.94 (64.92)	206.42 (67.08)	0.249
BNP (pg/mL); median (IQR)	368.54 (209.68–696.04)	207.05 (93.67–438.37)	<0.001
AF	483.92 (225.38–1184.94)	267.71 (168.67–445.97)	<0.001
Without AF	318.52 (204.01–566.48)	118.83 (61.92–431.04)	<0.001
Hs-cTnI (μg/L); median (IQR)	0.02 (0.01–0.05)	0.02 (0.01–0.04)	0.019
D-dimer (μg/L); median (IQR)	635.00 (307.50–1370.50)	540.00 (260.00–990.00)	0.039
ALT (U/L); median (IQR)	19.00 (12.50–29.35)	21.00 (14.00–31.00)	0.248
AST (U/L); median (IQR)	21.00 (16.50–27.50)	20.00 (16.00–27.50)	0.766
Cre (μmol/L); median (IQR)	82.00 (66.00–112.75)	76.00 (61.18–98.75)	0.057
eGFR (mL/min); median (IQR)	67.93 (45.53–88.51)	70.50 (50.58–92.70)	0.196
UA (μmol/L); mean (*SD*)	459.19 (158.40)	418.24 (126.83)	0.005
TC (mmol/L); median (IQR)	4.25 (3.54–5.13)	4.55 (3.71–5.31)	0.050
TG (μmol/L); median (IQR)	1.17 (0.86–1.53)	1.36 (0.97–1.90)	0.002
LDL-C (mmol/L); mean (*SD*)	2.46 (0.81)	2.62 (0.91)	0.050
HDL-C (mmol/L); mean (*SD*)	1.10 (0.31)	1.16 (0.39)	0.077
Sodium (mmol/L); mean (*SD*)	141.34 (4.04)	141.38 (4.14)	0.907
Potassium (mmol/L); mean (*SD*)	3.99 (0.58)	3.99 (0.49)	0.946

Abbreviations: AF, atrial fibrillation; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BNP, B-type natriuretic peptide; Cre, creatinine; eGFR, estimated glomerular filtration rate; Hb, haemoglobin; HDL-C, high-density lipoprotein cholesterol; Hs-cTnI, high-sensitivity cardiac troponin I; IQR, inter-quartile range; LDL-C, low-density lipoprotein cholesterol; PLT, platelet count; SD, standard deviation; TC, total cholesterol; TG, triglycerides; UA, uric acid; WBC, white blood cell count.

418.24 ± 126.83 μmol/L, *P* = 0.005). Reduced total cholesterol (TC, 4.25 [3.54–5.13] mmol/L vs. 4.55 [3.71–5.31] mmol/L, *P* = 0.050), triglycerides (TG, 1.17 [0.86–1.53] mmol/L vs. 1.36 [0.97–1.90] mmol/L, *P* = 0.002) and low-density lipoprotein cholesterol (LDL-C, 2.46 ± 0.81 mmol/L vs. 2.62 ± 0.91 mmol/L, *P* = 0.050) were detected. For other laboratory tests (white blood cell count, haemoglobin, platelet count, high-sensitivity cardiac troponin I, alanine aminotransferase, aspartate aminotransferase, creatinine, eGFR, high-density lipoprotein cholesterol, sodium and potassium), there were no significant differences between the two groups.

Primary outcome and secondary outcomes

During a mean follow-up of 87.67 ± 11.15 months, 68 of 258 patients (26.36%) died in the torsemide group and 60 of 187 patients (30.09%) died in the furosemide group [hazard ratio (HR) 0.81, 95% confidence interval (CI) 0.57–1.15, *P* = 0.239] (*Table* 5 and *Figure* 3). In terms of secondary outcomes, rehospitalization for HF occurred in 111 of 258 patients (43.02%) in the torsemide group and 110 of 187 patients (58.82%) in the furosemide group (HR 0.64, 95% CI 0.49–0.85, *P* = 0.002) (*Table* 5 and *Figure* 4).

Table 5 Clinical outcome in patients with heart failure with preserved ejection fraction stratified by torsemide versus furosemide.

	Torsemide	Furosemide	*P*	HR	95% CI
All-cause mortality	68	60	0.239	0.81	0.57–1.15
Rehospitalization for heart failure	111	110	0.002	0.64	0.49–0.85

Abbreviations: CI, confidence interval; HR, hazard ratio.

Multivariate Cox regression analysis

We conducted multivariate Cox regression analysis to exclude the influence of bias on the results (*Table*s 6 and 7). Multivariate Cox regression revealed that compared with furosemide, torsemide did not reduce all-cause mortality (HR = 0.93, *P* = 0.818, 95% CI: 0.51–1.71); however, it reduced rehospitalization for HF (HR = 0.57, *P* = 0.008, 95% CI: 0.37–0.87). Other factors, such as AF, co-medication and laboratory findings had no effect on all-cause mortality or rehospitalization for HF (all $P > 0.05$).

Discussion

Loop diuretic doses are closely related to symptoms in patients with HFpEF. A 'high dose' of loop diuretics may be associated with residual congestion.[15] Notably, in our study, the doses of loop diuretic used were quite low (11 mg of torsemide and approximately 20 mg of furosemide), considering that the majority of patients had NYHA III–IV symptoms. The possible reason for this finding is related to do with Chinese regulations, where patients are diagnosed based on their condition at the time of admission. In fact, after systematic treatment during hospitalization, the vast majority of NYHA III–IV patients can recover to NYHA II at discharge.

Figure 3 All-cause mortality in patients with heart failure with preserved ejection fraction stratified by torsemide versus furosemide. CI, confidence interval; HR, hazard ratio.

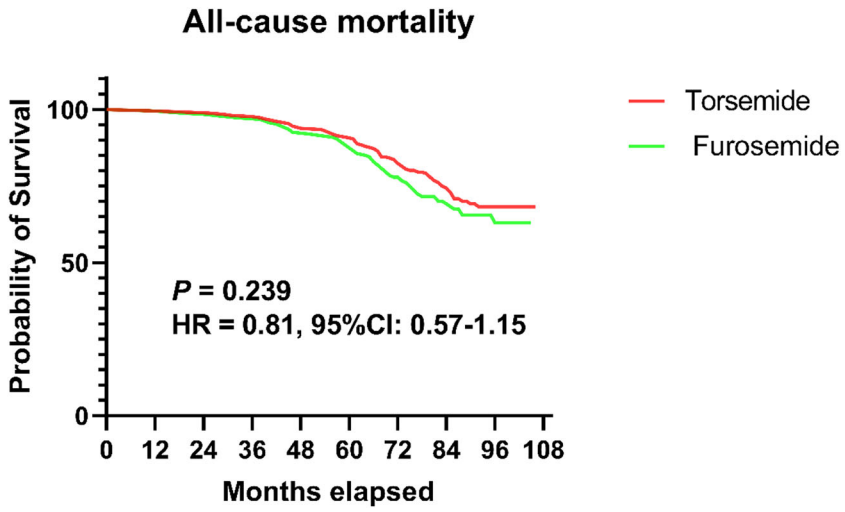
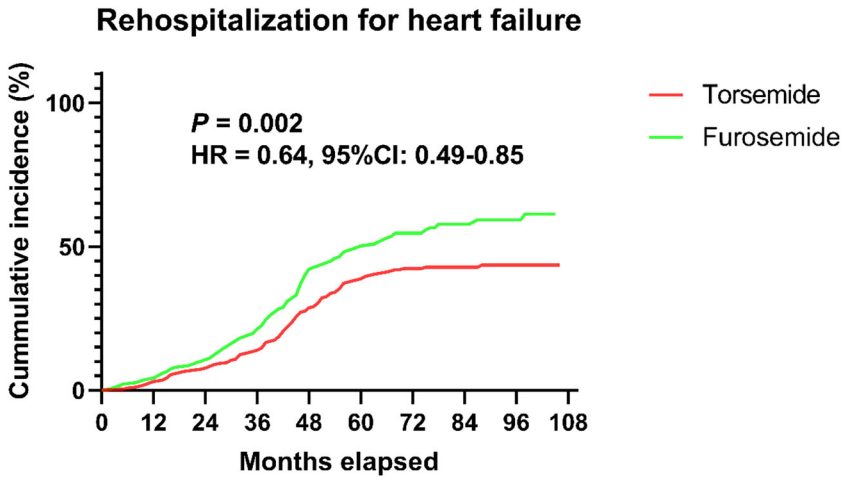


Figure 4 Rehospitalization for heart failure in patients with heart failure with preserved ejection fraction stratified by torsemide versus furosemide. CI, confidence interval; HR, hazard ratio.



Our study focused on the long-term effects of oral diuretics on symptoms and mortality in these patients after discharge.

Compared with furosemide, torsemide did not significantly affect all-cause mortality among patients discharged after hospitalization in our study. This result is consistent with the TRANSFORM-HF trial and KCHF study.[14,16] There was no association between changes in loop diuretic dose from admission to discharge and the all-cause mortality. Some preclinical and clinical data suggest that torsemide has increased bioavailability and a longer half-life or has more beneficial effects on myocardial fibrosis than dose furosemide; however, there was no evidence that the effects of torsemide improved all-cause mortality in patients with HFpEF compared with those of furosemide in our study. It should be noted that patients in this study were included from January 2015 to April 2018, when SGLT2i was not used to treat HFpEF. The EMPEROR-Preserved trial and DELIVER trial demonstrated that empagliflozin or dapagliflozin reduced the combined risk of cardiovascular death or hospitalization for HF in patients with HFpEF, regardless of the presence or absence of diabetes.[5,6] However, in the TRANSFORM-HF trial, the percentage of patients treated with SGLT2i was only 6.4% in the torsemide group and 5.9% in the furosemide group. In this study, the percentage of patients treated with

Table 6 Cox multivariate analysis for all-cause mortality in heart failure with preserved ejection fraction patients.

	HR	*P*	95% CI
BMI	0.93	0.125	0.85–1.02
Stable angina	0.79	0.662	0.79–4.42
Atrial fibrillation	0.88	0.711	0.43–1.78
NYHA class			
NYHA II	0.67	0.820	0.02–22.25
NYHA III	1.68	0.767	0.05–52.26
NYHA IV	0.70	0.837	0.02–22.10
Heart rate	0.99	0.418	0.98–1.01
LAD	0.96	0.178	0.90–1.02
MRAs	1.05	0.876	0.58–1.91
CCB	0.89	0.736	0.47–1.71
β-blocker	1.50	0.289	0.71–3.16
BNP	1.00	0.137	0.99–1.00
Hs-TnI	0.98	0.735	0.88–1.10
D-dimer	1.00	0.117	1.00–1.00
Cre	0.99	0.311	0.99–1.00
UA	0.99	0.439	0.99–1.00
TC	0.64	0.215	0.31–1.30
TG	0.75	0.210	0.48–1.17
LDL-C	1.85	0.229	0.68–5.03
Torsemide or furosemide	0.93	0.818	0.51–1.71

Abbreviations: BMI, body mass index; BNP, B-type natriuretic peptide; CCB, calcium channel blockers; CI, confidence interval; Cre, creatinine; HR, hazard ratio; Hs-cTnI, high-sensitivity cardiac troponin I; LAD, left atrium diameter; LDL-C, low-density lipoprotein cholesterol; MRAs, mineralocorticoid receptor antagonists; NYHA, New York Heart Association; TC, total cholesterol; TG, triglycerides; UA, uric acid.

Table 7 Cox multivariate analysis for rehospitalization for heart failure in heart failure with preserved ejection fraction patients.

	HR	*P*	95% CI
BMI	0.97	0.296	0.91–1.03
Stable angina	0.50	0.086	0.22–1.11
Atrial fibrillation	1.37	0.197	0.85–2.23
NYHA class			
NYHA II	0.42	0.549	0.02–7.24
NYHA III	0.67	0.784	0.04–11.38
NYHA IV	0.32	0.431	0.02–5.44
Heart rate	0.99	0.471	0.99–1.01
LAD	1.00	0.926	0.97–1.04
MRAs	1.27	0.264	0.84–1.93
CCB	0.85	0.446	0.57–1.28
β-blocker	1.15	0.566	0.71–1.86
BNP	1.00	0.077	0.99–1.00
Hs-TnI	0.98	0.528	0.90–1.06
D-dimer	1.00	0.209	1.00–1.00
Cre	0.99	0.404	0.99–1.00
UA	1.00	0.972	0.99–1.00
TC	0.96	0.590	0.82–1.12
TG	1.16	0.288	0.89–1.51
LDL-C	1.24	0.165	0.92–1.66
Torsemide or furosemide	0.57	0.009	0.37–0.87

Abbreviations: BMI, body mass index; BNP, B-type natriuretic peptide; CCB, calcium channel blockers; CI, confidence interval; Cre, creatinine; HR, hazard ratio; Hs-cTnI, high-sensitivity cardiac troponin I; LAD, left atrium diameter; LDL-C, low-density lipoprotein cholesterol; MRAs, mineralocorticoid receptor antagonists; NYHA, New York Heart Association; TC, total cholesterol; TG, triglycerides; UA, uric acid.

SGLT2i was 9.89% in the torsemide group and 7.04% in the furosemide group, even the incidence of diabetes in the two groups was 52.10% and 46.01%, respectively. This could be because the patients we included were discharged from 2015 to 2018, and dapagliflozin was not approved for the treatment of type 2 diabetes in China until 2017. We wondered whether torsemide or furosemide combined with SGLT2i improved the prognosis of patients with HFpEF.

Rehospitalization is common in patients with HFpEF. In some studies, patients with HFpEF were hospitalized an average of 1.39 times per year after diagnosis.[17] In another study, at 5 years after hospitalization for HFpEF, the rehospitalization rate was approximately 80%.[18] In general, the proportion of cardiovascular hospitalizations is greater in patients with HFpEF enrolled in clinical trials.[19,20] In our study, the rehospitalization rates were 43.02% in the torsemide group and 58.82% in the furosemide group, which seem to be much lower than that in other studies. We think that this is related to the fact that the populations included in our study all received loop diuretic therapy, and we already know that loop diuretics are a cornerstone of a successful approach to the treatment of congestion in HFpEF patients, which might lead to a reduction in rehospitalization for HF. In addition, most of the enrolled patients were required to return to the outpatient clinic every year. Nevertheless, if the patients did not appear at their scheduled clinic, they were to be interviewed by telephone annually. The medication was adjusted as the patient's condition changed. This may also have contributed to the lower rate of rehospitalization rate in our study.

We found that compared with furosemide, torsemide was associated with lower rehospitalization for HF (HR 0.64, 95% CI 0.49–0.85, $P = 0.002$), even though the torsemide group was more likely to have a larger LAD (43.65 ± 6.80 mm vs. 40.85 ± 6.59 mm, $P < 0.001$) and a higher level of BNP [368.54 (209.68–696.04) pg/mL vs. 207.05 (93.67–438.37) pg/mL, $P < 0.001$], which means that the torsemide group may indicate greater disease severity. To explain this result, we suggest the following possible explanations: (i) torsemide has increased bioavailability and a longer half-life than furosemide[21]; (ii) torsemide may also have beneficial effects on myocardial fibrosis, aldosterone production, sympathetic activation, ventricular remodelling and natriuretic peptides.[22,23] However, the lack of a significant difference in all-cause mortality caused by torsemide versus furosemide due to torsemide does not interfere with the major pathophysiological mechanisms that drive the underlying cause of HFpEF, such as systemic inflammation, oxidative stress and neurohormonal activation, thereby reducing the incidence of adverse cardiovascular events. Additional research is needed to confirm these benefits and explore the underlying mechanisms involved.

Limitations

Nevertheless, we must note that this study has several limitations. First, this was a retrospective study, which inevitably resulted in selection bias and recall bias. Second, this was a single-centre study with relatively few subjects; therefore, a larger multi-centre clinical study is needed. Third, due to the complexity of loop diuretic use during hospitalization, we may not able to provide accurate data on the usage of loop diuretics before discharge. Fourth, we cannot rule out the effect of loop diuretic doses on the study results. Even KCHF study found that there was no association between starting loop diuretics from admission to discharge and all-cause mortality; however, not all patients included in KCHF study with a LVEF $\geq$ 50%. Future work should be conducted to explore different dose conversions and time-varying analyses should be carried out to better understand the implications of differences for each dose in patients with HFpEF. Finally, few patients included in this study were treated with SGLT2i, unless they had diabetes mellitus.

Conclusions

Compared with furosemide, torsemide did not significantly reduce all-cause mortality, but there was an association between torsemide and reduced rehospitalization for HF in patients with HFpEF.

Conflicts of interest statement

The authors declared that they have no conflicts of interest to this work.

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Consent to participate

Informed consent was obtained from all individual participants included in the study.

Consent for publication

All authors approved the final manuscript and the submission to this journal.

Data availability statement

Not available.

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