Should torsemide be the loop diuretic of choice in systolic heart failure?

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Furosemide is the most widely prescribed loop diuretic in the setting of systolic heart failure (HF), yet torsemide has been shown to have less inter- and intra-individual variation in bioavailability and a longer duration of action compared with furosemide. Thus, a systematic review and meta-analysis of randomized controlled trials comparing torsemide versus furosemide in patients with systolic HF using OVID MEDLINE, Excerpta Medica (Embase), Web of Science, PubMed and Google Scholar was performed. Extracted data included study design, sample characteristics, intervention, outcomes and control for potential confounding factors. A DerSimonian and Laird random-effects model was used to compute summary risk ratios for HF and cardiovascular (CV) readmission outcomes. Two randomized trials comparing furosemide with torsemide in 471 patients with systolic HF were identified. Compared to furosemide, torsemide significantly reduced total HF readmissions (relative risk (RR): 0.41, 95% CI: 0.28–0.61, p < 0.0001) and HF readmissions (RR: 0.53, 95% CI: 0.33–0.84, p = 0.008) as well as CV readmissions (RR: 0.77, 95% CI: 0.60–0.98, p = 0.03) in patients with "at least 1 readmission." Moreover, compared with furosemide, torsemide caused a 14% reduction in all-cause mortality (RR: 0.86 (0.53–1.39), p = 0.54). Compared with furosemide, torsemide significantly reduces HF and CV-related hospital readmissions in systolic HF. Furthermore, torsemide is associated with a trend in reducing all-cause mortality.

In heart failure (HF), diminished cardiac output causes a decrease in renal blood flow, activating the renin–angiotensin–aldosterone system and the release of arginine vasopressin. This causes preferential retention of free water resulting in pulmonary and peripheral edema. Loop diuretics, such as torsemide and furosemide, are used for the symptomatic treatment of congestive HF (CHF) and are currently recommended for the treatment of chronic HF. Compared with furosemide, torsemide has a longer half-life, a longer duration of action and a higher bioavailability [1]. These favorable effects of torsemide suggest that this agent would be more beneficial than furosemide in patients with systolic HF. Thus, a systematic review and meta-analysis was performed comparing the effects of torsemide to furosemide in patients with systolic HF.

Methods

Data sources & searches

A systematic review of the available literature according to the PRISMA guidelines for the conduct of systematic reviews of intervention studies was performed. Relevant studies were identified through MEDLINE (1959–2012), Excerpta Medica (1959–2012), Web of Science (1959–2012), PubMed (1949–2011) and Google Scholar (1949–2012). To identify further potentially relevant studies missed by the electronic database search, reference lists from identified trials and review articles were manually screened. To ensure the article remained updated, automated weekly email alerts were used.

Study selection

The literature search, data extraction and quality assessment were performed by using a standardized approach. All completed, randomized trials assessing torsemide versus furosemide in systolic HF patients were eligible for inclusion. Only trials that measured mortality, hospital readmissions for HF and hospital readmissions due to cardiovascular (CV) causes were included. An article by Noe *et al.* was excluded due to unbalanced baseline characteristics between torsemide and furosemide [2]. Patients on torsemide were approximately 20 lbs heavier than those on furosemide (p = 0.004), had a higher baseline of angina (44.7 vs 33.6%, p = 0.081), a higher incidence of diabetes (44.7 vs 33.6%, p = 0.081), more previous myocardial infarctions (45.6 vs 38.0%, p = 0.232) and a significantly higher baseline sodium retention score (1.49 vs 0.99,

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■ congestive heart failure ■ furosemide ■ loop diuretics ■ systolic heart failure ■ torsemide

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p = 0.052). Thus, it is apparent that any results from this trial would be significantly biased in furosemide's favor.

Data extraction & quality assessment

The following data elements were extracted from each study: the number of patients per arm, the nature of the intervention, patient selection criteria, diuretic dosing and trial duration. HF readmissions, CV readmissions and mortality were also extracted from each trial. Quality assessment was judged according to concealment of treatment allocation, similarity of both groups at baseline regarding prognostic factors and medication use, broadness of eligibility criteria, blinding of outcome assessors, care providers and patients, completeness of follow-up and intention-to-treat analysis. Overall study quality was quantified using the Jadad score.

Data synthesis & analysis

Summary estimates were computed using a DerSimonian and Laird random-effects model. When either or both treatment groups of study had no events for a particular outcome, they were excluded from the analysis. Heterogeneity across trials was estimated beyond chance alone using the I^2 statistic. As an approximate rule of thumb, I^2 < 30% denotes low heterogeneity, I^2 = 30–50% represents moderate heterogeneity and I^2 > 50% denotes substantial heterogeneity. Publication bias was tested by visually assessing funnel plots for each outcome. A two-tailed p-value of less than 0.05 was considered as statistically significant for all analyses. Cochrane Review Manager (RevManVersion 5.1. The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) was used for all analyses.

Sensitivity analysis

All "hard outcomes" showed no heterogeneity between trials, mortality (I^2 = 0%), HF readmissions (I^2 = 0%) and CV readmissions (I^2 = 0%) (Figures 1–3). Excluding the smallest outcome study was not necessary as it only contributed to approximately 7% of the weight for the risk estimates for HF readmissions and CV readmissions and would not have made the risk estimate for any end point significantly different (Figures 1–3).

Results

Literature search & study characteristics

The literature search yielded 2592 articles, of which 25 were reviewed in full, on the basis of the inclusion criteria (Figure 4). Of these, two studies were eligible for inclusion (Figure 4). Table 1 summarizes the characteristics of the included studies. All trials included systolic HF patients. All patients received the same study medication. All trials had at least 30 days of follow-up and encompassed a minimum of 90 participants. All studies were randomized controlled trials. (Supplementary Table 1, see online at www.future-medicine.com/doi/suppl/10.2217/FCA.12.54).

Supplementary Tables 2 & 3 discuss the number of events accumulated and the quality of each study respectively. All studies scored well on the methodological quality indicators (Table 2). Randomization and concealed allocation were adequately performed in both trials. Trials enrolled a mean of 236 patients with a mean follow-up of 315 days (10.5 months). The mean age of participants was 69 years and 55% of participants were women.

Study outcomes

HF readmissions

Both trials (n = 471) reported hospital readmissions. There was a significant reduction for total HF readmissions with torsemide compared with furosemide, (relative risk [RR]: 0.41; 95% CI: 0.28–0.61, p < 0.0001), I^2 = 0% (Figure 2). Both trials (n = 471) reported hospital readmissions. There was a significant reduction for hospital readmissions with torsemide compared with furosemide (RR: 0.53; 95% CI: 0.33–0.84, p = 0.008), I^2 = 0% in patients with "at least 1 readmission" (Figure 3).

CV readmissions

Both trials (n = 471) reported CV readmissions. There was a significant reduction for CV readmissions with torsemide compared with furosemide (RR: 0.77; 95% CI: 0.60–0.98, p = 0.03), I^2 = 0% in patients with "at least 1 readmission" (Figure 4).

Mortality

Both trials (n = 471) reported mortality. There was a nonsignificant (NS) reduction for mortality with torsemide compared with furosemide (RR: 0.86; 95% CI: 0.53–1.39, p = 0.54), I^2 = 0% (Figure 5).

Pharmacokinetic data

Bioavailability & duration of action

HF results in pulmonary and peripheral edema due to a decrease in cardiac output and retention of free water by the renal tubules. This fluid retention causes dyspnea, orthopnea and fatigue leading to a reduction in exercise capacity and

HF hospitalizations. Therefore, improving cardiac output and fluid retention is vital for the symptomatic treatment of HF.

A diuretics' ability to cause diuresis is directly related to its bioavailability and the ability to reach its site of action (the ascending loop of Henle) [1]. Torsemide has a number of advantages compared with furosemide with regard to these properties. Respectively, torsemide compared with furosemide has as a greater and less variable bioavailability (80–100 vs 10–90%), quicker onset of action (due to a quicker time to maximum concentration [T_{max}] = 1.1 vs 2.4 h) and a longer duration of action (18–24 vs 4–6 h) [1]. Moreover, furosemide's bioavailability is reduced by 30% if taken near the time of a meal, whereas torsemides' bioavailability is not affected by mealtime administration [3].

A postdiuretic sodium chloride retention, called a 'rebound effect' is more prominent in loop diuretics with a shorter duration of action such as furosemide [4]. Torsemide is the first loop diuretic in the pyridine sulfonylurea class. It has a long duration of action (18–24 h) and thus has less likelihood for subtherapeutic concentrations (i.e., less chance for rebound sodium and water retention). Furosemide, due to its shorter duration of action, has a greater chance for causing rebound retention of sodium and water compared with torsemide [4]. Torsemide's long duration of action allows it to be administered just once a day, whereas furosemide is generally given twice daily (b.i.d.). Despite the common practice of prescribing furosemide b.i.d., a more appropriate dosing seems to be four-times a day. This is due to the fact that a reduction in diuresis from baseline occurs 4 h after furosemide administration. Moreover, the once daily (q.d.) dosing of torsemide offers improved patient adherence compared with furosemide, considering that compliance declines by approximately 13% from a q.d. (torsemide) to a b.i.d. (furosemide) regimen [5].

Compared with healthy individuals, the rate of absorption of torsemide (maximum concentration [C_{max}] and T_{max}) and subsequent diuretic effect is not affected in patients with CHF [6,7], whereas the absorption rate and diuretic effect of furosemide and bumetanide are reduced in CHF [8,9]. Furthermore, the diuretic effect of furosemide is significantly reduced in patients with decompensated compared with compensated HF [10]. This has not been observed with torsemide. Another advantage of using torsemide in patients with CHF is less variability in its bioavailability and this allows more consistent drug concentrations in the body, leading to a prolonged diuresis and natriuresis compared with furosemide. In a patient who is nonresponsive to furosemide, a clinician may have difficulty differentiating inappropriate furosemide bioavailability from 'diuretic resistance'. This would be an unlikely scenario in a patient on torsemide. In summary, torsemide retains its pharmacodynamic properties in patients with CHF regardless of the HF severity, whereas furosemide's pharmacodynamics (diuretic and natriuretic effects) are significantly diminished [6–11]. The properties and advantages of torsemide compared with furosemide are summarized in Table 1 & Box 1.

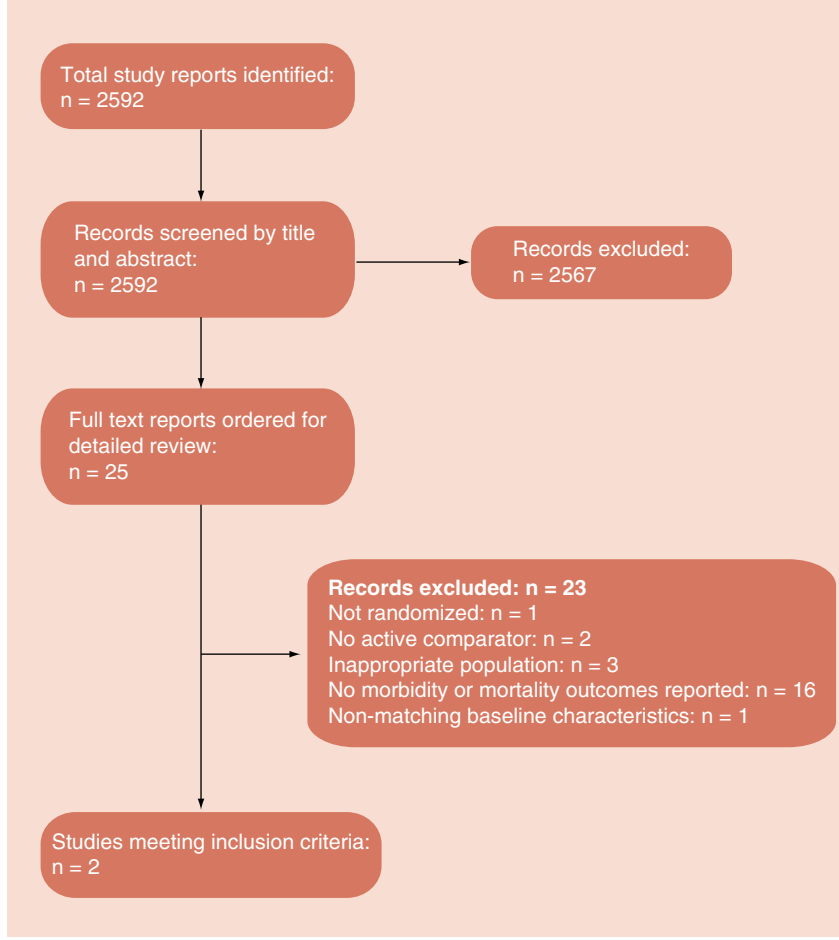

Figure 1. Process for selecting included trials.

Mineralcorticoid receptor antagonism

There is extensive mechanistic, preclinical and clinical data that argue for the importance of inhibiting the mineralcorticoid receptor in patients with HF. In HF, the renin–angiotensin–aldosterone system is upregulated [12]. Inhibition of this system by agents that inhibit aldosterone such as eplerenone and

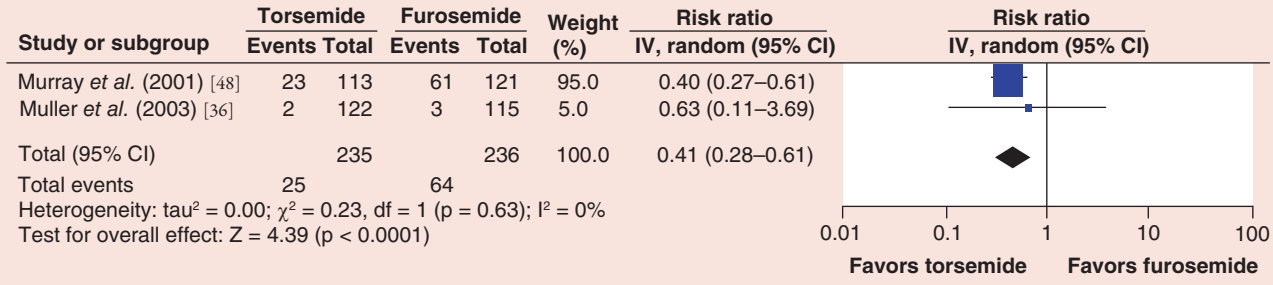

Figure 2. Forest plot of relative risks for total heart failure readmissions.
df: Degrees of freedom; IV: Inverse variance.

spironolactone have been demonstrated to reduce morbidity and mortality in HF patients [13–15]. Furthermore, these agents have been shown to have antifibrotic mechanisms, most likely due to their antialdosterone effects [16,17].

Torsemide, unlike furosemide, has been shown to inhibit myocardial fibrosis [18–21]. These benefits are proposed to be partly due to torsemide's ability to inhibit the binding of aldosterone to its receptor, an effect not shared by furosemide [19,22]. In fact, torsemide but not furosemide was shown to inhibit the transcardiac extraction of aldosterone in patients with CHF [23]. The antialdosterone effects of torsemide also give it a potassium-sparing effect, an effect that is not seen with furosemide [24–26]. Furthermore, torsemide has been shown to inhibit angiotensin II-stimulated vascular smooth muscle cell growth, whereas furosemide has not [20,21]. Torsemide also stimulates antifibrotic factors such as prostacyclin [20] and stimulates the release of prostacyclin to a greater extent than furosemide [20]. These pleiotropic (antialdosterone) effects of torsemide may give it an advantage over furosemide, especially in patients with diastolic HF.

Vasodilatory effects

Torsemide has been shown to lower blood pressure, even at small doses (2.5 mg) where no natriuresis occurs [11]. This action may be due to torsemide's ability to inhibit angiotensin II and endothelin-1-induced vasoconstriction [20,21] or through its ability to increase prostacyclin and nitric oxide [20]. Thus, torsemide may lower blood pressure, mainly through its vasorelaxation properties, an effect not observed with furosemide. The vasodilating and blood pressure-lowering actions of torsemide may also help to lower afterload compared with furosemide, which is a common and perpetuating problem in CHF. In fact, randomized trials have shown significantly greater reductions in blood pressure and afterload (left ventricular systolic volume) and greater improvements in ejection fraction (EF) with torsemide compared with furosemide [27–30].

Side-effect profile

K^+ & Mg^{2+} loss

Long-term treatment with diuretics can lead to hypertrophy of the distal nephron, a phenomenon known as 'diuretic resistance', which causes increased Na^+ and water retention further down the nephron [31]. Thiazide diuretics have been shown to inhibit loop-diuretic resistance and thus some physicians will add a thiazide diuretic on top of a loop diuretic to improve natriuresis and diuresis [32]. However, the addition of

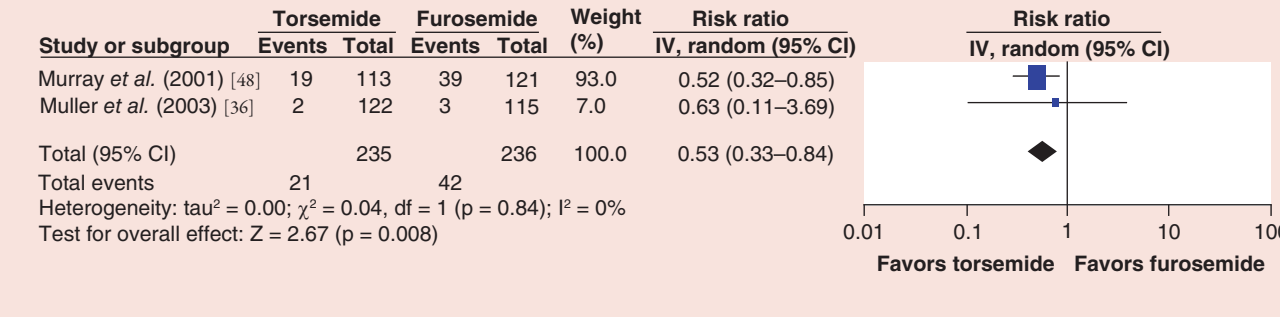

Figure 3. Forest plot of relative risks for heart failure readmissions in patients with "at least 1 readmission".
df: Degrees of freedom; IV: Inverse variance.

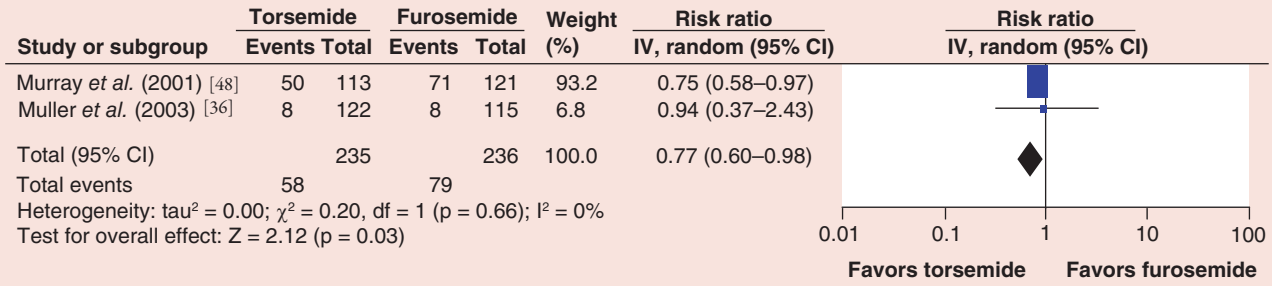

Figure 4. Forest plot of relative risks for cardiovascular readmissions in patients with "at least 1 readmission".
df: Degrees of freedom; IV: Inverse variance.

a thiazide diuretic increases the chance of electrolyte disturbances such as hypokalemia and hypomagnesemia. Despite this fact, the addition of torsemide to hydrochlorothiazide significantly reduced potassium and magnesium loss caused by hydrochlorothiazide, while at the same time increasing natriuresis [33]. This added benefit of torsemide is presumed to be due to its antialdosterone effects, which would not be seen with furosemide [34]. Moreover, torsemide has been shown to cause less hypokalemia compared with furosemide [34]. Thus, the addition of torsemide to hydrochlorothiazide significantly reduces potassium and magnesium loss and at the same time improves natriuresis; an effect that would not be observed with furosemide [33,34].

It is also common for clinicians to add a potassium-sparing diuretic, such as amiloride or triamterene, to a thiazide diuretic to prevent hypokalemia. However, in order for these potassium-sparing diuretics to work there needs to be sufficient luminal calcium at the distal tubule, which does not occur in patients on thiazides due to reduced luminal calcium concentrations caused by the thiazide [32,34]. Thus, potassium-sparing diuretics are not optimal to prevent thiazide-induced hypokalemia [32,34]. However, torsemide has a dual action to prevent thiazide-induced hypokalemia by increasing luminal calcium delivery to the distal tubule, which inhibits the sodium channel and thus decreases K^+ excretion and secondly through its antialdosterone effects [32]. The antialdosterone effects of torsemide may also prevent the normal loop diuretic resistance that occurs with long-term use of these agents; considering that the thiazide sensitive Na^+Cl^- symporter is upregulated in the nephron by aldosterone [11]. In summary, torsemide but not furosemide is a good option to prevent thiazide-induced hypokalemia and hypomagnesemia, which may be due to its antialdosterone effects. Moreover, torsemide may also prevent loop diuretic resistance, whereas these benefits would not be expected to be seen with furosemide. Furthermore, torsemide may be a better option to prevent thiazide-induced hypokalemia compared with a potassium-sparing diuretic such as triamterene or amiloride [33,35]. However, there needs to be more data before this can be confirmed.

Urinary urgency & episodes of micturition

As assessed by treating physicians, overall tolerability of torsemide was rated to be significantly superior (global score: 2.56) to that of furosemide (global score: 2.22, p = 0.0004) in a direct randomized comparison trial in 237 patients with CHF [36]. A higher number of episodes of micturition at various timepoints after diuretic

Table 1. Properties of loop diuretics.

Diuretic	Oral bioavailability	Initial dose (mg)	Maintenance dose (mg)	Max dose (mg)	iv. to p.o. conversion	Elimination	Duration of action (h)
Torsemide	80–100%	5–10 q.d.	10–20	200	1:1	80% liver 20% renal[†]	18–24
Furosemide	10–90%	20–40 q.d.–b.i.d.	40–240	600	1:2	50% renal (unchanged)[‡] 50% renal (conjugation)[‡]	4–6
Bumetanide	80–100%	0.5–1 q.d.–b.i.d.	1–5	10	1:1	50% liver[†]	6–8

[†]*More torsemide and bumetanide reaches the tubular fluid in patients with liver disease due to a prolonged half-life.*
[‡]*Furosemide accumulates in renal insufficiency due to a decrease in both urinary excretion and renal conjugation.*
b.i.d.: Twice daily; iv.: Intravenous; p.o.: Per orum*; q.d.: Once daily.*
Data taken from [59–61].

Table 2. Clinical trials on surrogate markers in systolic heart failure: torsemide versus furosemide.

Study (year)	n	Results	Comments	Ref.
Broekhuysen *et al.* (1986)	18	Daily urinary volume increased more with torsemide compared with furosemide ($p < 0.015$). Decline in diuresis was significantly slower after torsemide vs furosemide ($p < 0.05$). Torsemide caused a larger decrease in diastolic blood pressure compared with furosemide in the morning ($p < 0.001$) and in the evening ($p < 0.02$)	During torsemide treatment, diuresis never dropped below baseline values throughout the 24 h interval, whereas diuresis dropped below baseline during the 4–12 h interval in patients assigned to furosemide 40 mg. On a weight basis, torsemide was eight-times more natriuretic and chloruretic than furosemide, but was only three-times more kaliuretic	[27]
Scheen *et al.* (1986)	13	When compared with placebo and furosemide 40 mg, only torsemide 20 mg induced a significant increase in urine volume (68% larger [$2p < 0.001$]), natriuresis (+137% [no p-value given]), urinary chloride excretion (+246% [$2p < 0.02$]) and caused a significant decrease in free water clearance over the 24 h interval (-0.65 ml/min, $2p < 0.02$ vs placebo, -0.51 ml/min, $2p < 0.05$ vs furosemide 40 mg), respectively	A rebound effect of increased sodium and water retention (a decrease in diuresis compared with placebo) was observed 12 h after the administration of furosemide 40 mg, which was not observed with torsemide even after 24 h after administration. In patients with chronic HF, torsemide 20 mg was significantly more effective compared with furosemide 40 mg at increasing diuresis, natriuresis, chloruresis and free water clearance	[40]
Archhammer *et al.* (1988)	111	Within the 4 groups that were switched from furosemide to torsemide body weight significantly decreased ($p < 0.05$). Twenty eight patients had residual edema at the beginning of the study on furosemide vs only five patients at the end of the study, after treatment with torsemide. Thus, 23 patients on furosemide with edema became free of edema after torsemide treatment	There was no significant difference in body weight either before or after treatment between the groups that received either 5 or 10 mg torsemide during the entire study. The 83 patients without edema before starting torsemide remained free of edema throughout the trial	[41]
Herchuelz *et al.* (1988)	18	Daily and fractional Na^+ and CL^- clearances were increased significantly more with torsemide compared with furosemide ($p < 0.0025$ or less). Torsemide decreased blood pressure significantly more than furosemide in the morning ($p < 0.001$) and in the evening ($p < 0.02$)	On a weight basis, torsemide 10 and 20 mg were 6.9- and 9.5-times more natriuretic (mean: 8.2), respectively, than furosemide and 8.2- and 7.3-times more chloruretic (mean: 7.8), respectively, than furosemide ($p < 0.00001$, in favor of torsemide)	[28]
Fiehring *et al.* (1990)	15	Torsemide was the only group to demonstrate a significant decrease in SPAP at 100 watts. The RPP was continuously lower after torsemide at the different watt-steps, whereas it was even higher after furosemide for the 50-, 75- and 100-watt tests, mainly due to a higher heart rate with furosemide	As cardiac demand increases, furosemide becomes less effective at reducing SPAP and DPAP, whereas torsemide becomes more effective. It seems that torsemide lowers energy demand of the heart, whereas furosemide raises energy demand of the heart during increasing levels of exercise	[42]
Stauch *et al.* (1990)	114 enrolled (104 evaluated)	After 4 weeks of treatment with torsemide 10 mg, torsemide 20 mg and furosemide 40 mg, 94, 100 and 79% improved, respectively, from NYHA class III to NYHA class I or II. Thus, almost all patients given torsemide starting with NYHA class III at baseline improved	Torsemide was more effective with respect to symptoms removed or improved. Torsemide 5 and 10 mg are more effective at improving body weight and NYHA functional class compared with furosemide 40 mg	[43]

ACE: Angiotensin-converting enzyme; ARB: Angiotensin receptor blocker; BNP: Brain natriuretic peptide; CHF: Congestive heart failure; CVF: Collagen volume fraction; DcT: Deceleration time; DPAP: Diastolic pulmonary arterial pressure; E/A: Ratio between early and late ventricular filling velocity; EF: Ejection fraction; HF: Heart failure; H/M: Heart to mediastinum ratio; IRT: Isovolemic relaxation time; LVDd: Left ventricular diastolic diameter; LVEDV: Left ventricular end-diastolic volume; LVEF: Left ventricular ejection fraction; LVESV: Left ventricular end-systolic volume; LVMI: Left ventricular mass index; NS: Nonsignificant; NYHA: New York Heart Association; PARC: Plasma active renin concentration; PCP: Procollagen C-proteinase; PCPE: Procollagen type I carboxy-terminal proteinase enhancer; PICP: Procollagen I C-terminal propeptide; PIP: Carboxy-terminal peptide; q.d.: Once daily; RPP: Rate pressure product; SPAP: Systolic pulmonary arterial pressure; TDS: Total defect score; T_{max}: Time to maximum concentration.

Table 2. Clinical trials on surrogate markers in systolic heart failure: torsemide versus furosemide (cont.).

Study (year)	n	Results	Comments	Ref.
Goebel (1993)	70	Mean weight loss in the 10 mg torsemide group was significantly greater than in the 40 mg furosemide group at week 4 (-2.20 kg vs -1.07 kg, p = 0.04). Weight loss was also significantly greater in the 20 mg torsemide group vs the 40 mg furosemide group at weeks 4 and 6 (-2.47 kg vs -1.07 kg and -2.96 kg vs -1.29 kg, p = 0.01), respectively. There was no significant improvement in edema at week 6 in the 40 mg furosemide group (p = 0.118), whereas there was a marginally significant effect for the 10 mg torsemide group (p = 0.057) and a highly significant improvement in the 20 mg torsemide group (p < 0.001). There was no significant improvement in heart size at 6 weeks with the 40 mg furosemide group (p = 0.070), whereas there was a significant improvement in heart size for the 10 mg (p = 0.008) and 20 mg torsemide groups (p = 0.001). There was significantly less edema and pulmonary congestion in the 20 mg torsemide group than in the 10 mg torsemide group (edema, p = 0.003; pulmonary congestion, p = 0.03) and the 40 mg furosemide group (edema, p = 0.001; pulmonary congestion, p = 0.02)	20 mg of torsemide q.d. was significantly more effective than 40 mg of furosemide q.d. in improving CHF symptoms, reducing body weight, reducing pulmonary congestion and reducing edema. Torsemide-treated patients were the only patients to demonstrate a significant improvement in heart size	[44]
Vargo *et al.* (1995)	16	Torsemide was more rapidly absorbed than furosemide (T_{max} = 1.1 vs 2.4 h), respectively. The bioavailability of torsemide was also greater and less variable than that of furosemide (89.3 vs 71.8%, coefficient of variation was 8.9 vs 29.8%), respectively	CHF does not affect the rate or level of absorption of torsemide after oral administration, whereas delayed absorption and lowered bioavailability occurs in CHF patients on furosemide	[1]
Ferrara *et al.* (1997)	40	A statistically significant decrease in diastolic blood pressure from baseline to day 7 was observed with torsemide (-9.8%, p < 0.05), day 14 (-9.1%, p < 0.05) and on day 21 (-8.1%, p < 0.05) of treatment with a similar value at the end of treatment. Furosemide did not significantly decrease diastolic blood pressure. Torsemide significantly increased EF from 35.1 to 40.2% (p < 0.001), whereas furosemide did not. Kaliuresis increased significantly with respect to baseline on days 7, 14, 21 and 28 in patients on furosemide (p < 0.05); no significant increase was found in patients on torsemide	Torsemide has potassium sparing effects and significantly lowers blood pressure and improves EF, whereas furosemide does not	[29]
Yamato *et al.* (2003)	50	At 6 months, in patients treated with torsemide, peak E velocity and E/A ratio were increased (p < 0.001), DcT (p < 0.001) and IRT (p < 0.005) were shortened. Furthermore, LVDd (p < 0.005) and LVMI (p < 0.005) were reduced. The BNP was lowered (p < 0.001), PARC was increased (p < 0.001) and plasma aldosterone was increased (p < 0.001). None of these parameters changed in the furosemide group	LVDd was smaller (p < 0.05), LVMI was smaller (p < 0.05), E/A was greater (p < 0.05), PARC was higher (p < 0.05), plasma aldosterone concentration was higher (p < 0.05), and plasma BNP concentration was lower (p < 0.05) in torsemide treated patients than furosemide treated patients at 6 months	[45]

ACE: Angiotensin-converting enzyme; ARB: Angiotensin receptor blocker; BNP: Brain natriuretic peptide; CHF: Congestive heart failure; CVF: Collagen volume fraction; DcT: Deceleration time; DPAP: Diastolic pulmonary arterial pressure; E/A: Ratio between early and late ventricular filling velocity; EF: Ejection fraction; HF: Heart failure; H/M: Heart to mediastinum ratio; IRT: Isovolemic relaxation time; LVDd: Left ventricular diastolic diameter; LVEDV: Left ventricular end-diastolic volume; LVEF: Left ventricular ejection fraction; LVESV: Left ventricular end-systolic volume; LVMI: Left ventricular mass index; NS: Nonsignificant; NYHA: New York Heart Association; PARC: Plasma active renin concentration; PCP: Procollagen C-proteinase; PCPE: Procollagen type I carboxy-terminal proteinase enhancer; PICP: Procollagen I C-terminal propeptide; PIP: Carboxy-terminal peptide; q.d.: Once daily; RPP: Rate pressure product; SPAP: Systolic pulmonary arterial pressure; TDS: Total defect score; T_{max}: Time to maximum concentration.

Table 2. Clinical trials on surrogate markers in systolic heart failure: torsemide versus furosemide (cont.).

Study (year)	n	Results	Comments	Ref.
Lopez *et al.* (2004)	39	CVF after treatment was significantly lower in the torsemide group compared with the furosemide group ($p < 0.005$). Furosemide did not significantly affect CVF in the overall population, patients with systolic or diastolic HF (7.29 vs 6.47%, p = NS, 6.66%, p = NS, and 6.10%, p = NS, respectively). Torsemide was associated with a significant reduction in serum PIP (143 vs 111 ug/l, $p < 0.01$), whereas serum PIP did not change in the furosemide group (133 vs 133 ug/l, p = NS). Serum PIP was lower after torsemide treatment compared with furosemide treatment ($p < 0.01$). The number of patients deomonstrating improvement of at least one grade in NYHA functional class was greater in the torsemide group compared with the furosemide group ($p < 0.05$). EF and left ventricular chamber stiffness had trends towards improvement with torsemide but not furosemide	Torsemide but not furosemide improves myocardial fibrosis in CHF patients and causes a significantly greater improvement in NYHA functional class	[20]
Tsutamoto *et al.* (2004)	60	Plasma aldosterone level in the coronary sinus was significantly lower than that in the aortic root (73.1 vs 56.9 pg/ml; $p < 0.001$) on furosemide, whereas there was no difference in plasma aldosterone levels between the carotid sinus and aortic root in the torsemide group (85.4 vs 83.1 pg/ml). Plasma procollagen type III aminoterminal peptide (a biochemical marker of fibrosis) in the carotid sinus was significantly lower in the torsemide group than in the furosemide group (0.52 vs 0.67 U/ml; $p < 0.05$)	The transcardiac gradient (aortic root to carotid sinus) of aldosterone and the extraction ratio of aldosterone in the aortic root were significantly lower in the torsemide group than those in the furosemide group. Torsemide has aldosterone receptor antagonist abilities in the heart	[18]
Naganuma *et al.* (2005)	32	When furosemide (average 41 mg) taken daily for at least 4 months was switched to torsemide (average 8.1 mg) daily for 3 months, the break point in double product vs work rate relationship was significantly improved from 25 watts to 29 watts; p = 0.004) and peak exercise improved from 36 to 39 watts; p = 0.003). Moreover, torsemide significantly improved left ventricular EF (from 45 to 47%; p = 0.016) and showed a trend towards a decrease in BNP (from 142 to 116 pg/ml; p = 0.08). Average heart rate over 24 h significantly decreased once switched to torsemide (from 80 to 76 beats/min; p = 0.011)	Chronic congestive heart failure (NYHA classes II and III) patients that were pretreated with ACE inhibitors (88%), β-blockers (53%), digitalis (47%). Switching chronic HF patients on furosemide to torsemide (at 1/5th the furosemide dose) provides additional beneficial effects	[46]
Kasama *et al.* (2006)	40	In patients receiving torsemide, TDS decreased from 44 to 36 ($p < 0.001$), H/M ratio increased from 1.61 to 1.77 ($p < 0.001$), washout rate decreased from 52 to 41% (p = 0.001), LVEDV decreased from 173 to 147 ml ($p < 0.001$), LVESV decreased from 117 to 95 ml ($p < 0.001$) and LVEF tended to increase (from 31 to 34%, NS). These parameters did not change significantly in patients receiving furosemide. NYHA functional class of patients in the torsemide group was improved significantly more than in the furosemide group ($p < 0.05$)	Compared with furosemide, torsemide can improve cardiac sympathetic nerve activity and attenuate left ventricular remodeling in patients with CHF	[30]

ACE: Angiotensin-converting enzyme; ARB: Angiotensin receptor blocker; BNP: Brain natriuretic peptide; CHF: Congestive heart failure; CVF: Collagen volume fraction; DcT: Deceleration time; DPAP: Diastolic pulmonary arterial pressure; E/A: Ratio between early and late ventricular filling velocity; EF: Ejection fraction; HF: Heart failure; H/M: Heart to mediastinum ratio; IRT: Isovolemic relaxation time; LVDd: Left ventricular diastolic diameter; LVEDV: Left ventricular end-diastolic volume; LVEF: Left ventricular ejection fraction; LVESV: Left ventricular end-systolic volume; LVMI: Left ventricular mass index; NS: Nonsignificant; NYHA: New York Heart Association; PARC: Plasma active renin concentration; PCP: Procollagen C-proteinase; PCPE: Procollagen type I carboxy-terminal proteinase enhancer; PICP: Procollagen I C-terminal propeptide; PIP: Carboxy-terminal peptide; q.d.: Once daily; RPP: Rate pressure product; SPAP: Systolic pulmonary arterial pressure; TDS: Total defect score; T_{max}: Time to maximum concentration.

Table 2. Clinical trials on surrogate markers in systolic heart failure: torsemide versus furosemide (cont.).

Study (year)	n	Results	Comments	Ref.
Lopez *et al.* (2007)	22	There were significantly more patients in the torsemide group showing an improvement of at least 1 grade in NYHA functional class compared with the furosemide group ($p < 0.01$). CVF significantly decreased in the torsemide group ($p < 0.01$) but remained unchanged in the furosemide group. The difference between the change in myocardial fibrosis from baseline between torsemide and furosemide was significantly in favor of torsemide (-43.20 vs -4.11%; $p < 0.05$), respectively. Torsemide caused a significant reduction in PICP, whereas there was no change with furosemide ($p < 0.01$). Furthermore, serum PICP at 8 months was significantly lower in the torsemide group compared with the furosemide group ($p < 0.05$, -19.30 vs -4.12%; $p < 0.05$ for the difference in change from baseline)	Torsemide has the ability to interfere with the myocardial PCP/PCPE system, which may contribute to its antifibrotic mechanism in the heart. These benefits were shown on top of ACE-inhibitors and ARBs. PCP activation significantly decreased in the torsemide group ($p < 0.05$), whereas there was no change in the furosemide group. Moreover, the expression of PCP zymogen and PCP active form significantly increased in the furosemide group ($p < 0.05$), whereas there was no change in the torsemide group	[21]
Senzaki *et al.* (2008)	102	HF index showed a trend for improvement in patients on torsemide (7.4–6.8; $p = 0.07$). BNP significantly decreased (50–45 pg/dl) on torsemide. 24-h urinary output significantly increased (298–346 ml) when furosemide was switched to torsemide (no p-value). Potassium increased from 4.2 to 4.3 mEq/l and HF symptoms showed a trend for improvement on torsemide. None of these parameters were significantly affected by furosemide	Torsemide improves signs and symptoms of HF while having a potassium-sparing effect; this was not seen with furosemide	[47]

ACE: Angiotensin-converting enzyme; ARB: Angiotensin receptor blocker; BNP: Brain natriuretic peptide; CHF: Congestive heart failure; CVF: Collagen volume fraction; DcT: Deceleration time; DPAP: Diastolic pulmonary arterial pressure; E/A: Ratio between early and late ventricular filling velocity; EF: Ejection fraction; HF: Heart failure; H/M: Heart to mediastinum ratio; IRT: Isovolemic relaxation time; LVDd: Left ventricular diastolic diameter; LVEDV: Left ventricular end-diastolic volume; LVEF: Left ventricular ejection fraction; LVESV: Left ventricular end-systolic volume; LVMI: Left ventricular mass index; NS: Nonsignificant; NYHA: New York Heart Association; PARC: Plasma active renin concentration; PCP: Procollagen C-proteinase; PCPE: Procollagen type I carboxy-terminal proteinase enhancer; PICP: Procollagen I C-terminal propeptide; PIP: Carboxy-terminal peptide; q.d.: Once daily; RPP: Rate pressure product; SPAP: Systolic pulmonary arterial pressure; TDS: Total defect score; T_{max}: Time to maximum concentration.

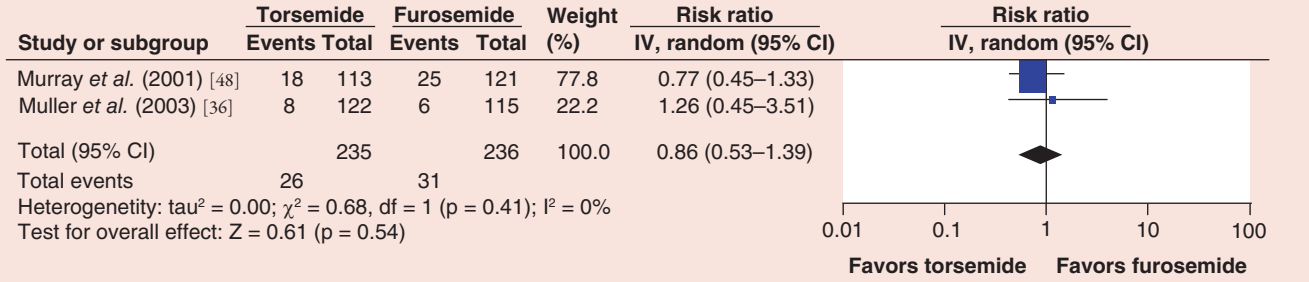

Figure 5. Forest plot of relative risks for mortality.
df: Degrees of freedom; IV: Inverse variance.

intake was recorded in the furosemide than in the torsemide group throughout the whole study period. The number of episodes of micturition after torsemide and furosemide in the 3-, 6- and 12-h time periods were 2.75 vs 3.36 ($p < 0.001$), 4.23 vs 4.85 ($p < 0.001$) and 5.61 vs 6.45 ($p < 0.001$), respectively. Patients treated with furosemide had a stronger urinary urgency (global score: 2.00) than those on torsemide (global score: 1.66, $p < 0.0001$). Patients on torsemide also felt significantly less restricted in their daily lives than patients on furosemide throughout the whole study period ($p = 0.0005$). Lastly, patients on torsemide had a greater improvement in their quality of daily life (0.88 for global score) than furosemide patients (global score: 0.43, $p = 0.0002$, in favor of torsemide). In summary, torsemide significantly improves functional and social limitation compared with furosemide, leading to an improvement in quality of life. The improved quality of life with torsemide compared with furosemide is most likely due to a decrease in urinary urgency and urinations throughout the day [36].

Ototoxicity

Torsemide is mainly metabolized in the liver (80%) with minimal renal excretion (20%), whereas furosemide is mainly metabolized through the kidneys. Therefore, torsemide's half-life is relatively unaffected by renal dysfunction. However, furosemide's half-life is significantly increased in renal dysfunction [37]. Of note, furosemide is also metabolized in the kidneys leading to accumulation of furosemide in renal dysfunction; this is not observed with torsemide. The resulting increased accumulation of furosemide in patients with lowered kidney function results in an increased risk of ototoxicity with furosemide compared with torsemide. Min *et al.* concluded that the order of risk for ototoxicity from lowest to highest was as follows: torsemide < bumetanide < furosemide < ethacrynic acid [38].

These data come from reports of ototoxicity of 6.4% with furosemide compared with 1 and <1% for bumetanide and torsemide, respectively [38].

Acute kidney failure is an unpredictable event that can occur at any time in a patient for multiple reasons (e.g., infection, kidney stones, surgery, radio contrast dye) and would lead to an increased risk of ototoxicity in a patient on furosemide. In summary, lowered kidney function is common, especially among patients with CHF. Furosemide has a much higher risk of accumulation and subsequent ototoxicity compared with torsemide in patients with lowered renal function. Since acute kidney failure is an upredictable event that can occur at any time, can have multiple underlying causes (e.g., infection and kidney stones) and predisposes to an increased risk of ototoxicity [37].

Drug interactions unique to torsemide

Torsemide has been demonstrated to increase warfarin International Normalized Ratio [39]. Potential mechanisms for an increase in the anticoagulation effect of warfarin may be competition for the CYP2C9 enzyme and thus decreased warfarin metabolism or protein-binding displacement of warfarin from albumin (increasing free warfarin concentrations) [39]. Probenecid, β-lactam and sulphonamide antibiotics, methotrexate, cimetidine, valproic acid and antiviral agents can compete with loop diuretics for tubular section and decrease their effectiveness [37].

Trials measuring surrogate markers

Broekhuysen *et al.* (1986)

A total of 18 edematous patients (11 CHF, three corpulmonale and four hepatic cirrhosis) were randomized to a double-blind treatment of either torsemide 10 mg, torsemide 20 mg

or furosemide 40 mg as a single morning dose during a 5-day period, which was preceded and followed by 2-day control periods [27]. There was no difference between the three groups of patients with respect to age, body weight, blood pressure, cause of underlying disease and laboratory data before the start of the study. During torsemide treatment, diuresis remained above baseline values throughout the 24-h interval, whereas diuresis dropped below baseline during the 4–12-h interval in patients assigned to furosemide 40 mg. Daily urinary volume increased more with torsemide compared with furosemide ($p < 0.015$). Torsemide 10 and 20 mg, and furosemide 40 mg increased mean daily diuresis by 95, 114 and 62%, respectively. Decline in diuresis was significantly slower after torsemide versus furosemide ($p < 0.05$). Torsemide 10 mg and 20 mg induced more weight loss compared with furosemide 40 mg (2.9, 2.8 and 2.3 kg), respectively. The 10- and 20-mg doses of torsemide were two- and four-times more effective than 40 mg of furosemide on the relative clearance of sodium and chloride ($p < 0.025$ and $p < 0.0025$), respectively. On a weight basis, torsemide was eight-times more natriuretic and chloruretic

Box 1. Advantages of torsemide versus furosemide.

Pharmacological properties

- Longer duration of action
- Quicker onset of action
- Greater and less variable bioavailability
- Food decreases fuorsemide's but not torsemide's diuretic activity (bioavailability, T_{max} and C_{max})
- Potassium-sparing effect
- Magnesium-sparing effect
- Less postdiuretic 'rebound effect' of sodium and water retention
- Less chance of ototoxicity: furosemide but not torsemide is metabolized by the kidneys and thus in renal dysfunction furosemide will accumulate, increasing the risk of ototoxicity
- Inhibition of the RAAS system: inhibition of angiotensin-II and aldosterone
- Greater binding to luminal tubular receptors
- Bioavailability is not affected by CHF or renal dysfunction
- On a milligram-to-milligram basis, the natriuretic and chloruretic effects of torsemide are approximately eight-times that of furosemide
- Torsemide is 97–99% protein bound whereas furosemide is 95% protein bound. A loop diuretic with greater than 95% protein binding limits its glomerular filtration. This allows the diuretic to stay trapped in the vascular space (bound to serum proteins) so that it can be consistently delivered to secretory sites of proximal tubule cells (i.e., more torsemide is delivered to the site of action versus furosemide due to higher protein binding)
- Hypoalbuminemic states (celiac disease, Crohn's disease, short bowel syndrome, liver dysfunction such as hepatitis, cirrhosis or hepatic carcinoma or nephrotic syndrome). A decrease in systemic albumin decreases the amount of medication bound to albumin in the blood, allowing more of the loop diuretic to be trapped in the interstitial space. This leads to less drug reaching the site of action in the tubular lumen. Furthermore, hypoalbuminemia increases renal glucuronidation and this increases furosemides metabolism (this will not occur with torsemide)

Clinical effects

- Greater effects on blood pressure
- Greater reduction in HF- and CV-related hospital readmissions
- Decreased length of hospital stay
- Better quality of life: less nocturia, micturition and urinary urgency
- Greater improvement in NYHA functional class (fatigue, heart size, leg edema, pulmonary congestion and ejection fraction are all improved significantly more with torsemide)
- Inhibits the sympathetic nervous system (norepinephrine): shows improvement in myocardial 123-iodine metaiodobenzylguanidine uptake and improves total defect score, washout rate and heart to mediastinum ratio
- Decreases cardiac fibrosis: offers the potential advantage of decreased sudden death from arrhythmias (due to cardiac fibrosis), improvement in cardiac function and improvements in NYHA functional class especially in patients with diastolic dysfunction (who are more affected by cardiac fibrosis)
- Increased compliance: once daily vs twice daily dosing
- Reduces thiazide diuretic induced potassium and magnesium loss
- Increased diuresis and natriuresis
- Increased glomerular filtration rate

CHF: Congestive heart failure; CV: Cardiovascular; HF: Heart failure; NYHA: New York Heart Association: RAAS: Renin–angiotensin–aldosterone system.

than furosemide but was only three-times more kaliuretic. Thus, torsemide causes less potassium loss than furosemide for the same natriuresis/choruresis. Torsemide also significantly increased calcium and phosphate clearance compared with furosemide ($p < 0.025$). Torsemide had no effect on blood chemistry or hematology, whereas furosemide caused a significant decrease in blood hematocrit, red cell count and hemoglobin by approximately 10% ($p < 0.05$). Torsemide caused a larger decrease in diastolic blood pressure compared with furosemide in the morning ($p < 0.001$) and in the evening ($p < 0.02$) [27]. In summary, torsemide is a longer and more potent loop diuretic compared with furosemide with K-sparing benefits (Table 2).

Scheen *et al.* (1986)

In a double-blind crossover trial, two doses of torsemide (10 and 20 mg) were compared with furosemide 40 mg and placebo [40]. A rebound effect of increased sodium and water retention (a decrease in diuresis compared with placebo) was observed 12 h following the administration of furosemide 40 mg, which was not seen with torsemide, even after 24 h after administration. During the 4–12 h period after administration, torsemide 20 mg was the only treatment to demonstrate a significant increase in diuresis when compared with placebo. From 12 to 24 h, diuresis was significantly lower with furosemide 40 mg compared with placebo or torsemide 20 mg. When compared with placebo and furosemide 40 mg, only torsemide 20 mg induced a significant increase in urine volume (68% larger [2p < 0.001]), natriuresis (137% increase [no p-value given]), urinary chloride excretion (246% increase [2p < 0.02]) and caused a significant decrease in free water clearance over the 24 h interval (-0.65 ml/min, 2p < 0.02 vs placebo, -0.51 ml/min, 2p < 0.05 vs furosemide 40 mg), respectively. In conclusion, in patients with chronic HF, torsemide 20 mg was significantly more effective compared with furosemide 40 mg at increasing diuresis, natriuresis, chloruresis and free water clearance [40].

Archhammer *et al.* (1988)

A double-blind multicenter trial was undertaken comparing 5 or 10 mg of torsemide daily in patients who were pretreated with 40 mg of furosemide with compensated chronic CHF with edema [41]. Compensated patients receiving furosemide 40 mg for at least 4 weeks were switched over to either 5 mg or 10 mg torsemide q.d. for 6 months. The study evaluated 111 patients over 24 weeks. A total of 54 patients started with 5 mg torsemide and 35 of them continued on this dose until the end of the study. In the remaining 19 patients, the dose was increased to 10 mg torsemide. A total of 57 patients started with 10 mg and 42 continued on 10 mg until the end of the study; in 15 patients the dose was increased to 20 mg. Weight significantly decreased ($p < 0.05$) in all torsemide groups (regardless of the dose) when patients switched over from furosemide therapy. There was no significant difference in body weight either before or after treatment between the 5 mg and 10 mg torsemide groups throughout the study. A total of 23 of the 28 patients having residual edema at the beginning of the study (on furosemide) became free of edema on torsemide. The 83 patients without edema remained free of edema on torsemide throughout the trial. In summary, when compensated CHF patients are switched from 40 mg of furosemide to 5–10 mg of torsemide, there is a significant improvement in weight (most likely due to improved diuresis) and edema [41].

Herchuelz *et al.* (1988)

This was a randomized, double-blind controlled study in 18 patients with edema of various origins (11 CHF, three corpulmonale and four hepatic cirrhosis) [28]. There was no difference between baseline characteristics with respect to age, body weight and underlying disease. Patients were randomly assigned to either 10 mg torsemide, 20 mg torsemide or 40 mg furosemide regimens. The diuretics were given by mouth as a single morning dose for 5 days (with 2 days of a control period afterwards). Daily and fractional Na^+ and Cl^- clearances were increased significantly more with torsemide compared with furosemide ($p < 0.0025$ or less). On a weight basis, torsemide 10 mg and 20 mg were 6.9- and 9.5-times more natriuretic (mean: 8.2), respectively than furosemide and 8.2- and 7.3-times more chloruretic (mean: 7.8), respectively than furosemide ($p < 0.00001$, in favor of torsemide). The natriuretic effect of torsemide 10 mg, 20 mg and furosemide 40 mg on the first day of treatment lasted 8, 19.3 and 10 h, respectively. The chloruretic effect of torsemide 10 mg, 20 mg and furosemide 40 mg lasted 20, 22 and 13.3 h, respectively. Torsemide 10 mg and 20 mg significantly increased the Na^+/K^+ ratio over baseline compared with furosemide over the 5 days of treatment (+2.22, +3.77 vs +1.84, respectively, $p < 0.025$). Torsemide also increased calcium and phosphate clearances

significantly more compared with furosemide ($p < 0.025$). Torsemide decreased blood pressure significantly more than furosemide in the morning ($p < 0.001$) and in the evening ($p < 0.02$). In the furosemide group, blood hematocrit, red cell count and hemoglobin decreased by approximately 10% ($p < 0.05$). These decreases were thought to be due to cirrhosis with gastroduodenal ulcer or to possible infections, which were identified in all patients demonstrating a decrease in hematological values, except in one patient. T_{max} was 1 h in the torsemide 10 and 20 mg groups with an elimination half-life of 3.8 h. The duration of action of torsemide on urinary volume, sodium and chloride clearance was 2-, 1.4- and 1.6-times longer, respectively, than that of furosemide. Torsemide was also more potassium sparing than furosemide. Torsemide 10 and 20 mg increased the basal Na^+/K^+ ratio 1.4- and 2.2-times that of furosemide. In summary, torsemide has potassium-sparing abilities with a more potent and longer lasting diuretic effect compared with furosemide [28].

Fiehring *et al.* (1990)

A single intravenous (iv.) 10 mg dose of torsemide was compared with 20 mg iv. furosemide (equal to 40 mg *per orem* [p.o.] furosemide) in 15 patients in a controlled, double-blind, randomized clinical trial in patients with CHF [42]. All patients in the torsemide group had left ventricular HF (n = 8), whereas five patients had left ventricular and 2 patients had right ventricular HF in the furosemide group. There were significant differences in body weight and height between patients at baseline. A Swan–Ganz catheter was inserted for measuring the pulmonary mean, systolic and diastolic arterial pressure and right atrial pressure (mean pulmonary arterial pressure, systolic pulmonary arterial pressure, diastolic pulmonary arterial pressure and right atrial pressure). Each patient underwent three bicycle exercise tests in the supine position. After verification of a pathological increase in intracardiac pressure the patients received the iv. loop diuretics after the elevated pressures had decreased to baseline values. The second exercise test began 5 min after injection. Torsemide was the only group to show a significant decrease in systolic pulmonary arterial pressure at 100 watts with systolic pulmonary arterial pressure being lowered for the 25–75 watts in both groups. Diastolic pulmonary arterial pressure was significantly lowered in the 75- and 100-watt periods with torsemide, whereas it was lowered in the 25- and 50-watt periods in the furosemide group. The rate pressure product (RPP) was continuously lower after torsemide at the different watt-steps, whereas it was even higher after furosemide for the 50, 75 and 100 watt tests, mainly due to a higher heart rate. The RPP before and after 10 mg torsemide and 20 mg furosemide for the 25, 50, 75 and 100 watt tests was (150–140 vs 134–131, 195–166 vs 156–160, 199–189 vs 170–196 and 255–238 vs 185–216), respectively. The RPP is a measure of stress placed on the cardiac muscle based on the number of times the heart needs to beat per minute and the systolic blood pressure that it is working against. RPP is a direct measure of the energy demand (consumption) of the heart (i.e., higher RPP with furosemide suggests increased energy consumption of the heart). Thus, it seems that torsemide lowers the energy demand of the heart, whereas furosemide raises the energy demand of the heart during increasing levels of exercise. The interpretation of this trial is confounded due to the higher degree of HF in the torsemide group compared with the furosemide group (due to a higher right ventricular resting pressure, which is already above normal in the torsemide group, whereas it was still normal in the furosemide group). However, the presence of exercise-induced HF was verified in all patients due to the pressures achieved during the control period [42].

Stauch *et al.* (1990)

Torsemide 5 mg and 10 mg p.o. were compared with furosemide 40 mg p.o. in 114 patients with New York Heart Association (NYHA) class II or III HF presenting with peripheral edema in a controlled, double-blind, group-comparative multicenter study [43]. Patients had not been treated with diuretics for at least 4 weeks. Weight loss of at least 2.5 kg in the torsemide 10 mg, torsemide 20 mg and furosemide 40 mg groups occurred in 70.6, 76.5 and 61.1% of patients, respectively (changes were significant in each group, but differences between groups were not significant). The study groups did not significantly differ with respect to sex, age and body weight at baseline. Digoxin was used in the torsemide 10 mg, torsemide 20 mg and furosemide 40 mg groups in 65, 79 and 83% of patients, respectively. After 4 weeks of treatment with torsemide 10 mg, torsemide 20 mg and furosemide 40 mg, 94, 100 and 79% of patients, respectively, improved from NYHA class III to NYHA class I or II. Thus, almost all patients given torsemide starting with NYHA class III HF at baseline improved. Improvement

from NYHA class II at the beginning to NYHA class I occurred in 25, 35 and 29% of patients treated with torsemide 5 mg, torsemide 10 mg and furosemide 40 mg, respectively. Torsemide was more effective with respect to symptoms removed or improved. Tolerance was 97, 91 and 89% in the torsemide 5 mg, torsemide 10 mg and furosemide 40 mg groups, respectively. In summary, torsemide 5 and 10 mg are more effective at improving body weight and NYHA functional class compared with furosemide 40 mg [43].

Goebel (1993)

A total of 70 patients with CHF who had been maintained on 40 mg of furosemide q.d. for at least 2 weeks were randomized in a double-blind, multicenter trial comparing 10 mg torsemide, 20 mg torsemide and 40 mg furosemide q.d. for 6 weeks [44]. None of the patients withdrew from the trial prematurely and the mean duration of therapy was 43 days. Mean weight loss in the 10 mg torsemide group was significantly greater than in the 40 mg furosemide group at week 4 (-2.20 vs -1.07 kg, p = 0.04). Weight loss was also significantly greater in the 20 mg torsemide group versus the 40 mg furosemide group at weeks 4 and 6 (-2.47 vs -1.07 kg and -2.96 vs -1.29 kg, p = 0.01), respectively. Torsemide was more effective compared with furosemide in reducing edema. There was no significant improvement in edema at week 6 in the 40 mg furosemide group (p = 0.118), whereas there was a marginally significant effect for the 10 mg torsemide group (p = 0.057) and a highly significant improvement in the 20 mg torsemide group (p < 0.001). There was no significant improvement in heart size at 6 weeks with the 40 mg furosemide group (p = 0.07), whereas there was a significant improvement in heart size for the 10 mg (p = 0.008) and 20 mg torsemide groups (p = 0.001). There was significantly less edema and pulmonary congestion in the group receiving 20 mg torsemide than in the group receiving 10 mg torsemide (edema, p = 0.003; pulmonary congestion, p = 0.03) and the group receiving 40 mg furosemide (edema, p = 0.001; pulmonary congestion, p = 0.02). All groups improved pulmonary congestion from baseline, but the effects were greater in patients treated with torsemide 10 and 20 mg compared with furosemide 40 mg (p = 0.013, p <0.001 and p = 0.035, respectively) [44]. In summary, 20 mg of torsemide q.d. was significantly more effective than 40 mg of furosemide q.d. in improving CHF symptoms, reducing body weight, reducing pulmonary congestion and reducing edema. Torsemide 10- and 20-mg-treated patients were the only patients to demonstrate a significant improvement in heart size [44].

Vargo *et al.* (1995)

In this study, 16 patients with compensated CHF were given torsemide (10 mg p.o. and iv.) and furosemide (40 mg p.o. and 20 mg iv.) in a randomized crossover clinical trial. Torsemide was more rapidly absorbed than furosemide (T_{max} = 1.1 vs 2.4 h), respectively [1]. The bioavailability of torsemide was also greater and less variable than that of furosemide (89.3 vs 71.8%, coefficient of variation was 8.9 vs 29.8%), respectively. In summary, CHF did not affect the rate or completeness of absorption of torsemide after oral administration, whereas delayed absorption and lowered bioavailability of furosemide was observed [1].

Ferrara *et al.* (1997)

In this study, 40 cardiopathic patients (27 men and 13 women, mean age: 62.9 years) with CHF (NYHA functional class II and III) of stable clinical condition and absence of diuretic therapy during the week preceding the study were randomized to a double-masked trial (20 patients were administered torsemide 10 mg and 20 patients were given furosemide 25 mg) q.d. for 28 days [29]. Two patients in the torsemide and one patient in the furosemide group were withdrawn from treatment as a result of adverse reactions. There was a statistically significant decrease in diastolic blood pressure from baseline to day 7 with torsemide (-9.8%, p < 0.05), day 14 (-9.1%, p < 0.05), and on day 21 (-8.1%, p < 0.05) of treatment with a similar value at the end of treatment. Furosemide did not significantly decrease diastolic blood pressure. Torsemide demonstrated a trend toward a reduction in end-diastolic volume after 28 days of treatment (150.9 vs 144.32 ml, p = NS) and a significant reduction in end-systolic volume (97.8 vs 75.9 ml, p < 0.001). Torsemide significantly increased EF from 35.1 to 40.2% (p < 0.001) and increased systolic function from 25.3 to 28.6% (p = NS). Furosemide caused a statistically significant decrease in both end-diastolic volume and end-systolic volume from 140.8 to 131.9 ml (p < 0.001) and from 95.32 to 68.2 ml (p = 0.05), respectively. However, furosemide did not significantly increase EF or systolic function (37.1 vs 43.2% [NS] and 26.5 vs 30.6% [NS], respectively). Kaliuresis increased significantly with respect to baseline on days 7, 14,

21 and 28 in patients on furosemide ($p < 0.05$); no significant increase was found in patients on torsemide. Kaliuresis was significantly higher on days 14, 21 and 28 with furosemide versus torsemide (92.4 vs 60.2 mEq, 99.0 vs 62.7 mEq and 113 mEq vs 61.1 mEq, respectively, $p < 0.05$). A statistically significant decrease in serum potassium levels was found on days 21 and 28 in patients on furosemide (4.2–4.0 and 4.2–3.9 mEq/l, respectively, $p < 0.05$). A statistically significant difference in serum potassium levels was observed between torsemide and furosemide on day 21 (4.2 vs 4.0 mEq/l, $p < 0.05$) and on day 28 (4.2 vs 3.9 mEq/l, $p < 0.05$). In fact, torsemide slightly increased serum potassium levels from baseline to day 28 (4.1–4.2 mEq/l). Fifteen patients on torsemide and 16 patients on furosemide completed the study. There was good compliance in each group when urinary sodium levels were compared. In summary, torsemide has potassium-sparing effects and significantly lowers blood pressure and improves EF, whereas furosemide does not [29].

Yamato *et al.* (2003)

Fifty patients who had chronic HF and symptoms (NYHA class II–III), despite long-term therapy with both low-dose furosemide and angiotensin-converting enzyme inhibitors (ACE-Is) were randomized to a 6-month, open-label trial [45]. Baseline and follow-up echocardiograms and neurohumoral assays were obtained in 25 patients on furosemide (continued same dose of oral furosemide at 20–40mg/day) and in 25 patients on torsemide (received 4–8mg/day in place of furosemide). At 6 months, in patients treated with torsemide, peak E velocity and E/A ratio were increased ($p <0.001$), deceleration time ($p < 0.001$) and isovolemic relaxation time ($p < 0.005$) were shortened. Furthermore, left ventricular diastolic diameter ($p < 0.005$) and left ventricular mass index ($p < 0.005$) were reduced. BNP was lowered ($p < 0.001$), plasma active renin concentration was increased ($p < 0.001$) and plasma aldosterone was increased ($p < 0.001$). None of these parameters changed in the furosemide group. Consequently, left ventricular diastolic diameter was smaller ($p < 0.05$) left ventricular mass index was smaller ($p < 0.05$), E/A was greater ($p < 0.05$), plasma active renin concentration was higher ($p < 0.05$), plasma aldosterone concentration was higher ($p < 0.05$), and plasma BNP concentration was lower ($p < 0.05$) in torsemide-treated patients compared with furosemide-treated patients at 6 months [45].

Lopez *et al.* (2004)

In this study, 39 Caucasian patients with different cardiomyopathies (previous diagnosis of NYHA functional class II to IV HF) who had been receiving standard HF treatment (loop diuretic plus ACE-Is or angiotensin type I receptor antagonist (angiotensin receptor blocker [ARB] plus β-blocker) for the previous 6 months were randomized to receive either torsemide (n = 20)at a dose of 10–20 mg/day or furosemide (n = 19) at a dose of 20–40 mg/day for 8 months [20]. The primary end point was the change in the fraction of myocardial volume occupied by collagen, or collagen volume fraction (CVF) measured from endomyocardial biopsies from baseline to 8 months. This was a randomized, open-label, parallel-group pilot study. Aldosterone antagonists were not permitted and a salt intake restriction of 4 g/day and concomitant CHF medication were continued during the study. Mean daily dose in the torsemide group (n = 19) at the end of the treatment period and the furosemide group (n = 17) were 10.6 and 32.2 mg, respectively. Baseline clinical characteristics were comparable for patients who completed the study. CVF significantly decreased in the torsemide group (7.96 vs 4.48%, $p < 0.01$). CVF after treatment was significantly lower in the torsemide group compared with the furosemide group ($p < 0.005$). Moreover, torsemide had a significantly greater effect on CVF in patients with diastolic CHF (final value: 4.37%, $p < 0.001$) than in patients with systolic CHF (final value: 4.81%, $p < 0.05$). Furosemide did not significantly affect CVF in the overall population, patients with systolic or diastolic HF (7.29 vs 6.47%, p = NS; 6.66%, p = NS and 6.10%, p = NS), respectively. Serum concentrations of carboxy-terminal peptide of procollagen type I (PIP) reflects the rate of extracellular synthesis of collagen type I. Torsemide was associated with a significant reduction in serum PIP (143 vs 111 ug/l, $p < 0.01$), whereas serum PIP did not change in the furosemide group (133 vs 133 ug/l, p = NS). Serum PIP was lower after torsemide treatment compared with furosemide treatment ($p < 0.01$). The number of patients showing improvement of at least one grade in NYHA functional class was greater in the torsemide group compared with the furosemide group ($p < 0.05$). EF and left ventricular chamber stiffness had trends toward improvement with torsemide but not furosemide. In summary, torsemide but not furosemide improves myocardial fibrosis in CHF patients and causes a significantly greater improvement in NYHA functional class [20].

This trial indicates that torsemide inhibits the extracellular synthesis of collagen type I. Torsemide's ability to inhibit the cardiac synthesis of collagen type I may be due to its ability to reduce myocardial fibrosis (CVF) in CHF patients. ACE-Is/ARBs and β-blockers were balanced between groups at baseline and thus the benefits on cardiac fibrosis with the use of torsemide seem to be in addition to other medications commonly used in CHF (ACE-Is, β-blockers and ARBs). Fibrosis most likely plays an important role in diastolic and systolic dysfunction and is a structural change that promotes arrhythmias [20]. Thus, a reduction in fibrosis with torsemide but not furosemide may offer a potential advantage of decreased sudden death from arrhythmias and may explain why there were better improvements in cardiac function and NYHA functional class with torsemide compared with furosemide [20]. The inhibition of myocardial fibrosis with torsemide may be especially important in patients with diastolic dysfunction.

Tsutamoto *et al.* (2004)

In this study, 60 patients with CHF (left ventricular EF [LVEF] <45%) were treated with either torsemide 8 mg or furosemide 40 mg/day for 1 month [18]. There was no difference in baseline characteristics between the two groups. Plasma aldosterone level in the coronary sinus was significantly lower than that in the aortic root (73.1 vs 56.9 pg/ml; p < 0.001) on furosemide, whereas there was no difference in plasma aldosterone levels between the carotid sinus and aortic root in the torsemide group (85.4 vs 83.1 pg/ml). Moreover, plasma procollagen type III aminoterminal peptide (a biochemical marker of fibrosis) in the carotid sinus was significantly lower in the torsemide group than in the furosemide group (0.52 vs 0.67 U/ml, p < 0.05). The transcardiac gradient (aortic root to carotid sinus) of aldosterone and the extraction ratio of aldosterone in the aortic root were significantly lower in the torsemide group than those in the furosemide group. The transcardiac extraction of aldosterone is a potential marker of aldosterone action in the heart [18]. This study indicates that torsemide can act as an aldosterone receptor antagonist in the heart.

Table 3. Murray and Muller *et al.* trials.

End point	Torsemide versus furosemide
HF readmissions	60% reduction (p < 0.01)
Cardiovascular readmissions	34% reduction (p < 0.02)
All-cause mortality	23% reduction (p = 0.54)
Hospital stay	64% reduction (106 vs 294 days, p = 0.02)
Tolerability	p = 0.0001
Improvement in daily restrictions	p = 0.0002
The number of urinations at 3, 6 and 12 h after diuretic intake	p < 0.001, improvement at all times points with torsemide vs furosemide
Improvement in NYHA functional class	p < 0.014, only significant with torsemide
Fatigue scores at 2, 8 and 12 months	p < 0.05

HF: Heart failure; NYHA: New York Heart Association.
Data taken from [36,48].

Naganuma *et al.* (2005)

A total of 32 patients with chronic congestive HF (NYHA classes II and III) that were pretreated with ACE-Is (88%), β-blockers (53%), digitalis (47%) and furosemide (100%) 20–120mg (41mg average) daily for at least 4 months were switched to torsemide (average 8.1 mg) daily for 3 months [46]. After the switch, the break point in double product versus work rate relationship was significantly improved from 25 watts to 29 watts (p = 0.004) and peak exercise improved from 36 to 39 watts (p = 0.003). Moreover, torsemide significantly improved LVEF (from 45 to 47%, p = 0.016) and showed a trend toward a decrease in BNP (from 142 to 116 pg/ml, p = 0.08). Average heart rate over 24 h significantly decreased once switched to torsemide (from 80 to 76 beats/min, p = 0.011). In summary, switching chronic HF patients on furosemide to torsemide (at one-fifth the furosemide dose) significantly improves exercise tolerance, heart rate and LVEF with a trend for reduction in BNP [46].

Kasama *et al.* (2006)

A total of 40 patients with nonischemic CHF (LVEF <45%) were randomly assigned to torsemide (4–8 mg/day; n = 20) or furosemide (20–40 mg/day; n = 20) [30]. All patients were also treated with ACE-Is. After 6 months of treatment, in patients receiving torsemide, total defect score decreased from 44 to 36 (p < 0.001), heart:mediastinum ratio increased from 1.61 to 1.77 (p < 0.001), washout rate decreased from 52 to 41% (p = 0.001), left ventricular end-diastolic volume decreased from 173 to 147 ml (p < 0.001), left vetricular end-systolic volume decreased from 117 to 95 ml (p < 0.001) and LVEF showed a trend for improvement (from 31 to 34%, p = NS). These parameters did not significantly change in patients receiving furosemide. NYHA functional class in the torsemide group was improved significantly more than in

Table 4. Clinical trials on hard end points: torsemide versus furosemide.

Study	n	Results	Comments	Ref.
Murray *et al.* (2001)	234	Compared to furosemide, torsemide caused less readmissions for HF (19 [17%] vs 39 [32%], p = 0.01), CV causes (50 [44%] vs 71 [59%], p = 0.03) in 'patients with at least 1 readmission' and less readmission for HF (23 vs 61, p < 0.01) and for all CV causes (78 vs 130, p = 0.02) when total readmissions were analyzed. Furthermore, patients on torsemide had significantly fewer hospital days for HF (106 vs 296 days, p = 0.02) and a trend for less hospital days due to CV causes (364 vs 614, p = 0.06)	After 12 months of follow-up. ACE-inhibitor use at baseline was 81% and 77% for the torsemide and furosemide groups, respectively. Average daily dose of 136 mg of furosemide and 72 mg of torsemide. Torsemide also significantly improved fatigue scores at months 2, 8 and 12 compared with furosemide	[48]
Muller *et al.* (2003)	237	Two and three HF hospitalizations in the torsemide and furosemide groups (RR: 0.63 [95% CI: 0.11–3.69]), respectively. Eight hospitalizations due to CV causes in both groups (RR: 0.94 [95% CI: 0.37–2.43]. Eight and six deaths in the torsemide and furosemide groups (RR: 1.26 [95% CI: 0.45–3.51]), respectively	After 9 months of follow-up. Mean doses for torsemide and furosemide were 11.36 and 40.04 mg, respectively. All patients (100%) were on ACE-inhibitors. A total of 194 patients completed the trial	[36]

ACE: Angiotensin-converting enzyme; CV: Cardiovascular; HF: Heart failure; RR: Relative risk.

the furosemide group (p < 0.05). The change from baseline to 6 months in the amount of patients in NYHA functional class I (in the torsemide and furosemide groups) was 0–7 versus 0–2, NYHA class II (7–12 vs 8–13) and NYHA class III (13–1 vs 12–5). BNP decreased significantly more with torsemide vs furosemide at 6 months (244–154 vs 239–218 pg/ml). The mean dose of enalapril was 7.3 mg/day in the torsemide group versus 7.4 mg/day in the furosemide group (NS). The mean dose of perindopril was 3.1 mg/day in the torsemide group versus 3.0 mg/day in the furosemide group (NS). The mean dose of carvedilol was 14 mg/day in the torsemide group versus 13 mg/day in the furosemide group (NS). The dose of digitalis was 0.25 mg/day in both groups [30]. These findings indicate that, compared with furosemide, torsemide can improve cardiac sympathetic nerve activity and attenuate left ventricular remodeling in patients with CHF [45].

Lopez *et al.* (2007)

Procollagen C-proteinase (PCP) has been found in fibroblasts and in the interstitial space [20]. PCP and procollagen type I carboxy-terminal proteinase enhancer (PCPE) have been found in cardiomyocytes upon endomyocardial biopsy from patients with CHF [21]. The PCP/PCPE system plays an important role in collagen type I synthesis and deposition [21]. Myocardial fibrosis has been shown to be a major cause of left ventricular dysfunction leading to or worsening HF. PCP stimulates the formation of cross-links between collagen type I molecules forming collagen type I fibrils and its activity is increased tenfold by PCPE [21]. PCP is also involved in the cleavage of procollagen type I C-terminal propeptide (PICP). Serum PICP has been proposed as a reliable index of collagen type I synthesis within the human myocardium [21]. PICP may be a specific biomarker of the activity of myocardial PCP in patients with chronic HF.

Torsemide 10.9 mg and furosemide 34.5 mg was administered to a total of 22 patients. No significant differences were observed at baseline for clinical or echocardiographic characteristics, myocardial fibrosis or collagen type I synthesis and degradation between groups. PCP activation tended to be higher in the torsemide group (2.59) compared with the furosemide group (2.14). Left ventricular end-diastolic volume demonstrated a trend toward a decrease in the torsemide group, whereas the furosemide group showed no change. LVEF tended to increase in the torsemide group but not in the furosemide group. There were significantly more patients in the torsemide group demonstrating an improvement of at least one grade in NYHA functional class compared with the furosemide group (p < 0.01). CVF significantly decreased in the torsemide group (p < 0.01) but remained unchanged in the furosemide group. The difference between the change in myocardial fibrosis from baseline between torsemide and furosemide was significantly in favor of torsemide (-43.20 vs -4.11%, p < 0.05). Torsemide caused a significant reduction in PICP, whereas there was no change with furosemide (p < 0.01). Furthermore, serum PICP at 8 months was significantly lower in the torsemide group compared with the furosemide group (p < 0.05, -19.30 vs -4.12%, p < 0.05 for the difference in change from baseline). PCP activation

Table 5. Torsemide versus furosemide in systolic heart failure.

Outcome	Trials	n	Results, RR (95% CI)	p-value	NNT (10.5 months)
HF readmissions	Two active-controlled	471	0.41 (0.28, 0.61)	<0.0001	6†
Cardiovascular readmissions	Two active-controlled	471	0.77 (0.60, 0.98)	0.03	9‡ 11§

†Data from total HF readmissions.
‡Data from total cardiovascular readmissions.
§Data from patients with at least one cardiovascular readmission, p-value for patients with at least one cardiovascular readmission.
HF: Heart failure; NNT: Number needed to treat; RR: Relative risk.

significantly decreased in the torsemide group ($p < 0.05$), whereas there was no change in the furosemide group. Moreover, the expression of PCP zymogen and the active form of PCP significantly increased in the furosemide group ($p < 0.05$), whereas there was no change in the torsemide group. The 36-kDa PCPE fragment significantly decreased in the torsemide group ($p < 0.05$), whereas it remained unchanged in the furosemide group. In summary, torsemide has the ability to interfere with the myocardial PCP/PCPE system, which may contribute to its antifibrotic mechanism in the heart. These benefits were shown on top of ACE-Is and ARBs [21].

Senzaki *et al.* (2008)

A total of 102 children with chronic HF who had received oral torsemide were analyzed. Sixty two patients were newly diagnosed as having HF and were given torsemide as a diuretic [47]. The remaining 40 patients (replacement group) had been given furosemide for 3 months before the study, and furosemide was then replaced with torsemide. Clinical signs and symptoms of HF (assessed as the HF index), humoral factors and serum potassium concentrations before torsemide treatment were compared with those obtained 3–4 weeks after torsemide treatment. The clinical signs and symptoms of HF were assessed by the modified New York University Pediatric HF Index. This HF index showed a trend for improvement in patients on torsemide(7.4–6.8, $p = 0.07$). BNP significantly decreased (50–45 pg/dl) on torsemide. The 24 h urinary output significantly increased (298–346 ml) when furosemide was switched to torsemide (no p-value). Serum potassium levels significantly increased from 4.2 to 4.3 mEq/l and HF symptoms showed a trend for improvement on torsemide. None of these parameters were significantly affected by furosemide [47]. In summary, torsemide improves signs and symptoms of HF while having a potassium-sparing effect, which was not seen with furosemide.

Trials measuring hospitalizations for HF & CV events

Murray *et al.* (2001)

Treatment randomization was stratified by study site (Wishard Hospital [IN, USA], n = 193; Roudebush VA Hospital [IN, USA], n = 41) and by patients' primary admitting diagnosis (HF or other) (Table 3) [48]. Investigators were blinded as to drug assignment, but the drugs were open label, with no placebo 'dummies'. Baseline NYHA functional class was 2.8 and 2.6 for torsemide and furosemide, respectively. Compared with furosemide, torsemide caused less readmissions for HF (39 [32%] vs 19 [17%], $p < 0.01$) and for all CV causes (71 [59%] vs 50 [44%], $p = 0.03$) in 'patients with at least 1 readmission' and fewer readmissions for HF (61 vs 23, $p < 0.01$) and for all CV causes (78 vs 130, $p = 0.02$) when total readmissions were analyzed. Patients on torsemide had significantly fewer hospital days for HF (106 vs 296 days, $p = 0.02$) and a trend for less hospital days due to CV causes (364 vs 614, $p = 0.06$). All-cause mortality was also lower with torsemide vs furosemide (18 and 25 deaths, respectively (RR: 0.77 [95% CI: 0.45–1.33]). Torsemide also significantly improved fatigue scores at months 2, 8 and 12 compared with furosemide. In summary, compared with furosemide, torsemide causes significantly fewer readmissions for HF and all CV causes with a NS trend for reduced all-cause mortality. Moreover, HF patients were significantly less fatigued and had a shorter hospital stay on torsemide compared with furosemide (Tables 3 & 4) [48].

Muller *et al.* (2003)

This study was a prospective, multicenter, randomized and unblinded trial [36]. Baseline NYHA functional class was 2.5 and 2.4 for the torsemide (n = 122) and furosemide (n = 115) groups, respectively. There was a mean NYHA class decrease of 0.48 in patients treated with torsemide (from 2.47 to 1.99) compared with a mean decrease by 0.39 with furosemide (from 2.37 to 2.01, [NS] vs torsemide) [36]. Of the torsemide-treated patients, 40.2% improved by at least one NYHA class, 38.5% were unchanged and 21.3% worsened. In the furosemide group, 30.7% improved, 46.5% remained unchanged and 22.8% worsened. The overall trend for NYHA functional class improvement was only significant with torsemide ($p = 0.014$), but not

with furosemide (p = 0.269). Tolerability and improvement in daily restrictions were significantly higher with torsemide compared with furosemide (p = 0.0001 and p = 0.0002), respectively. The number of episodes of micturition at 3, 6 and 12 h after diuretic intake and urgency to urinate was significantly lower in the torsemide versus the furosemide group (p < 0.001 at all time points and p < 0.0001), respectively. In summary, torsemide significantly improves NYHA functional status compared with furosemide, most likely due to an improvement in diuresis and pulmonary congestion. Moreover, torsemide causes a greater improvement in quality of life compared with furosemide due to a dual benefit on clinical status and social function (Tables 3 & 4) [36].

Conclusion

In this comprehensive systematic review of randomized controlled trials, which included a total number of 471 patients, torsemide significantly reduced HF and CV-related hospital readmissions compared with furosemide. However, the results have some limitations. Of particular note, trials were randomized but not double-blind. Both trials were multicentered and included a few hundred patients. This systematic review evaluated 471 patients, encompassing 89, 137 and 57 HF and CV readmissions and deaths, respectively (Figure 5).

In 2006, the annual US healthcare cost for treating patients with HF was US$29.6 billion [49]. At least 70% of this cost was due to HF readmissions, with an estimated cost of $20.72 billion [50]. Taking into account the results of this meta-analysis (RR: 59% reduction in HF readmissions), switching patients on furosemide to torsemide could save the US healthcare system approximately $12.22 billion/year in HF readmissions alone [49–51]. This does not include the money that would be saved from a reduction in CV readmissions, which would be expected to be substantial.

HF results in a decrease in cardiac output with subsequent activation of the renin–angiotensin–aldosterone system in order to maintain target-organ blood flow [52]. Furthermore, arginine vasopressin (antidiuretic hormone) is released by the posterior pituitary gland causing free water retention by the kidneys [53]. Thus, many HF patients are placed on loop diuretics to prevent pulmonary and peripheral edema, which helps to keep them out of the hospital.

Furosemide is the most commonly used loop diuretic for systolic HF patients. However, torsemide has distinct features giving additional benefits beyond a natriuretic and diuretic effect [18–22]. These pleiotropic effects seem to give torsemide an advantage compared with furosemide, such as a significant reduction in HF and CV hospitalizations compared with furosemide [36,48]. More importantly, the TORIC trial showed that torsemide is more efficacious at improving NYHA functional class and is associated with a greater than 50% reduction in mortality compared with furosemide and other diuretics [53]. The results of this systematic review and the TORIC trial should encourage a large multicentered clinical trial to confirm that torsemide improves morbidity and mortality in patients with systolic HF.

HF consensus guidelines do not distinguish one loop diuretic from another [54,55]. However, it is clear that torsemide is a different loop diuretic compared with furosemide with greater evidence to support its use [36,48,53]. Compared with furosemide, the 10.5-month number needed to prevent one HF or CV readmission with torsemide was six and nine, respectively (Table 5).

Loop diuretics such as torsemide and furosemide are used for the symptomatic treatment of CHF [53], and are currently recommended for the treatment of chronic HF [53–55]. Compared with furosemide, torsemide has a longer half-life, longer duration of action and a higher and less variable bioavailability [1]. This article demonstrates that compared with furosemide, torsemide improves hard outcomes as well as cardiac function and humoral factors. Thus, torsemide should be the loop diuretic of choice in patients with HF compared with furosemide.

In direct randomized comparison trials, torsemide improves fatigue, hospitalizations for HF and CV causes, decreases hospital stay, improves exercise tolerance, quality of life, urinations, urinary urgency, left ventricular function, humoral factors, cardiac sympathetic nerve activity, myocardial fibrosis, left ventricular remodeling, hypokalemia, diuresis, natriuresis, pulmonary congestion, edema, blood pressure and weight compared with furosemide, yet furosemide is the most prescribed loop diuretic. Taking into account the previously mentioned benefits, torsemide not furosemide should be the loop diuretic of choice in patients with HF.

Future perspective

This article found that torsemide compared with furosemide significantly reduces HF and

CV-related hospital readmissions as well as length of hospital stay in patients with systolic HF [35,47]. Thus, torsemide should be a first-line loop diuretic compared with furosemide in this patient population. The use of torsemide instead of furosemide could save the healthcare system billions of dollars. In fact, it was shown that a patient switched from furosemide to torsemide lowers healthcare costs by over $500 per patient per year [55]. A larger, double-blind, multicentered trial should be performed to confirm these results.

Torsemide is the only loop diuretic to have antialdosterone, vasodilating and antifibrotic properties. These properties lead to improvements in heart function and blood pressure compared with furosemide [40,44]. Furthermore, the blood pressure-lowering effect of torsemide is seen at low doses (2.5 mg) where there are minimal effects on sodium, potassium and magnesium excretion [56]. Therefore, a next logical step would be to determine whether torsemide reduces CV events in hypertensive patients at high risk of CV disease or in patients with chronic kidney disease (CKD).

Thiazide diuretics are currently recommended by The Joint National Committee (JNC 7) on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, as a first-line treatment for high blood pressure but these agents have a higher risk of metabolic side effects such as hypokalemia, hypomagnesemia, hyponatremia, hyperglycemia, hyperuricemia and hypercholesterolemia compared with torsemide [57,58]. Thiazide diuretics also lose their ability to reduce blood pressure in patients with CKD (glomerular filtration rate <40 ml/min). However, torsemide's bioavailability and blood pressure-lowering effects are not lowered in CKD. Moreover, torsemide has the additional benefit of inhibiting aldosterone, which is generally elevated in CKD [48]. Furthermore, primary aldosteronism is a major cause of resistant hypertension and torsemide may be suited in these hard-to-treat hypertensives that cannot tolerate spironolactone, or already have high potassium levels. In summary, a large double-blind trial should be performed in patients with CKD as well as hypertensive patients at high risk for CV disease to investigate whether torsemide reduces CV events in these patient populations. If proven effective, torsemide may be an appropriate alternative to thiaizde diuretics as a first-line treatment for hypertension.

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Executive summary

- A systematic review of randomized trials using OVID MEDLINE, Excerpta Medica, Web of Science, PubMed and Google Scholar was performed. Two randomized trials comparing furosemide with torsemide in 471 patients with systolic heart failure (HF) were identified. Compared with furosemide, torsemide significantly reduced HF readmissions (relative risk: 0.53, 95% CI: 0.33–0.84) and cardiovascular readmissions (relative risk: 0.77, 95% CI: 0.60–0.98) in patients with "at least 1 readmission".
- In direct comparison trials, torsemide significantly improves fatigue, reduces HF and cardiovascular-related hospital readmissions, reduces hospital stay, improves exercise tolerance, quality of life, urinations, urinary urgency, left ventricular function, humoral factors, cardiac sympathetic nerve activity, myocardial fibrosis, left ventricular remodeling, hypokalemia, diuresis, natriuresis, pulmonary congestion, edema, blood pressure and weight compared with furosemide.
- On a milligram-to-milligram basis, the natriuretic and chloruretic effects of torsemide are approximately eight-times that of furosemide.
- Compared to furosemide, torsemide has a longer half-life, longer duration of action, and a higher and less variable bioavailability.
- Compared to furosemide, torsemide significantly reduced total heart failure readmissions (relative risk: 0.41, 95% CI: 0.28–0.61; $p < 0.0001$), $I^2 = 0\%$.
- Compared to healthy individuals, the rate of absorption of torsemide and the subsequent diuretic effect, are not affected by congestive HF (CHF), whereas the absorption rate and diuretic effect of furosemide and bumetanide are reduced in CHF. Thus, torsemide retains its pharmacodynamic properties in patients with CHF regardless of the HF severity, whereas furosemide's pharmacodynamics (diuretic and natriuretic effects) are significantly diminished.
- Furosemide is metabolized in the kidneys leading to accumulation of furosemide but not torsemide in renal dysfunction. The resulting increased accumulation of furosemide in patients with lowered kidney function results in an increased risk of ototoxicity with furosemide compared with torsemide.
- Torsemide has antialdosterone, antifibrotic and vasodilatory properties. These properties are not shared by furosemide.
- Torsemide should be the loop diuretic of choice compared with furosemide in patients with systolic HF.

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