A reappraisal of loop diuretic choice in heart failure patients

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The health and economic burden of heart failure is significant and continues to grow each year. Loop diuretics are an integral part of symptom management in heart failure. Furosemide is used disproportionately compared with other loop diuretics, and there is currently no guidance for physicians regarding which agent to choose. However, there exist pharmacologic differences as well as other mechanistic differences that appear to favor torsemide use over furosemide. Compared with furosemide, torsemide improves surrogate markers of heart failure severity such as left ventricular function, plasma brain natriuretic peptide levels, and New York Heart Association functional class and may also reduce hospitalizations, readmissions, and mortality. Data suggest that these benefits could be mediated through torsemide's ability to positively affect the renin-angiotensin-aldosterone system. Specifically, torsemide has been shown to inhibit aldosterone secretion, synthesis, and receptor binding in vitro, as well as decrease transcardiac extraction of aldosterone, myocardial collagen production, and cardiac fibrosis in patients with heart failure. We identified pertinent literature using keyword MEDLINE searches and cross-referencing prior bibliographies. We summarize the available data suggesting potential benefits with torsemide over furosemide, and call attention to the need for a reappraisal of diuretic use in heart failure patients and also for a well-powered, randomized control trial assessing torsemide versus furosemide use. (Am Heart J 2015;169:323-33.)

Despite numerous advances in heart failure (HF) treatment in recent decades, the burden of HF remains significant for patients and the medical system. An estimated 5.1 million adult Americans have HF and with 825 000 new cases annually; by 2030, the prevalence is expected to increase by 46%, resulting in more than 8 million affected adults. In 2012, the total cost for HF was $30.7 billion, and by 2030, it is projected to increase by 127% to $69.7 billion.[1] Much of the cost is attributable to hospitalizations for acute decompensated HF (ADHF), and rates for hospitalization have steadily increased over the last several decades.[2] After hospitalization, the 30-day, 1-year, and 5-year fatality rates remain poor at 10.4%, 22%, and 42.3%, respectively.[1] Furthermore, 30-day readmission rates for patients with an initial diagnosis of HF are nearly 25%, with a median time to readmission of only 12 days, and more than one-third of the readmissions are attributed to recurrent HF symptoms.[3] In the context of this growing burden of HF with high costs, morbidity, and mortality, loop diuretics are a cornerstone of therapy as indicated by published guidelines,[4] and their optimization is an important component of clinical care.

Diuretics are a primary therapy to treat HF patients' symptoms of dyspnea. Loop diuretics serve 2 main purposes, to maintain euvolemia for chronic HF patients and to achieve decongestion in ADHF patients.[4,5] Among hospitalized acute HF patients, 70% were receiving diuretic therapy as an outpatient,[6] and 90% of those admitted for ADHF received intravenous loop diuretics.[7] Challenges to achieving and maintaining decongestion include inadequate diuretic dosing, diuretic resistance, the "breaking phenomenon," and postdiuretic sodium retention or the "rebound effect" as reviewed previously.[8] These challenges, as well as comorbidities such as underlying renal dysfunction, make adequate decongestion difficult to accomplish. Even after aggressive diuretic administration during ADHF hospitalization, many patients have persistent congestive symptoms at discharge.[9] Patients with higher degrees of congestion are not only more likely to be rehospitalized for HF but also have higher rates of mortality.[10] Thus, decongestion is not just an important patient-reported outcome (ie, dyspnea relief), but it also serves as a clinical target for optimization of functional status. Improved decongestion may help to prevent ADHF and the need for

hospitalizations. Current guidelines acknowledge that diuretic effects on morbidity and mortality are unknown, and no specific guidance is provided on loop diuretic choice.[4] There are 3 loop diuretics used in HF patients: furosemide, torsemide, and bumetanide.

In this review, we summarize pharmacologic differences between loop diuretics and review the available data suggesting potential morbidity and mortality benefits with torsemide over furosemide in HF patients. In particular, we discuss the biochemical and molecular effects of torsemide on fibrosis via the renin-angiotensin-aldosterone system (RAAS). We also review previous data regarding cost considerations between torsemide and furosemide, update the data based on contemporary figures, and provide a comparison of direct drug costs to Medicare patients throughout different geographic regions of the United States.

Methods

Publications were identified using MEDLINE searches with keywords that included torsemide, furosemide, bumetanide, loop diuretics, and/or HF, as well as cross-referencing prior bibliographies. Search results included animal and human trials and were filtered by English language. Data for our cost analysis were accessed using the online 2015 Medicare Plan Finder for Health, Prescription Drug and Medigap Plans. We assumed refills for 90 tablets (torsemide 20 mg or furosemide 40 mg daily) at 3-month intervals and selected the 3 prescription drug plans with the lowest estimated annual torsemide drug cost for the 10001, 27707, 34470, 95240, and 99201 ZIP codes. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the manuscript, and its final contents.

Pharmacology

Loop diuretics inhibit the $Na^+/2Cl^-/K^+$ cotransporter in the thick ascending loop of Henle, resulting in increased excretion of urinary sodium and chloride and subsequent diuresis. Bumetanide and torsemide have consistent bioavailabilities of 80% to 100% compared with the wide range of 10% to 100% for furosemide[8] (Table I).

Torsemide's bioavailability tends to be >90% in patients with renal insufficiency, liver cirrhosis, and HF.[11-15] Unlike furosemide and bumetanide, the bioavailability of torsemide remains unchanged with food intake.[16,17] Oral administration of the 3 agents results in peak serum concentrations within 1 to 2 hours, but torsemide has the longest half-life of about 3.5 hours versus 1 and 2 hours with bumetanide and furosemide, respectively.[15] The pharmacologic properties of torsemide allow for a rapid onset and more predictable diuretic effect in HF patients, particularly when compared with the variable bioavailability of furosemide.[15] Pharmacologic comparisons of furosemide to bumetanide are generally lacking, and most are least 15 years old.[17-20] Within the HF population,

Table I. Pharmacologic properties of loop diuretics

| Property	Furosemide	Torsemide	Bumetanide
Relative potency	1×	2×	40×
Bioavailability (%)	10-100	80-100	80-100
Oral/Intravenous dosing	2:1	1:1	1:1
Time to onset (min)	60	60	30-60
Oral peak serum concentration (h)	1	1	1-2
Absorption affected by food	Yes	No	Yes
Average half-life (h)	2	3.5	1-1.5
Duration of effect (h)	6-8	6-16	4-6
Decreased kaliuresis	No	Yes	No

furosemide and bumetanide have similarly prolonged absorption rates, but consistent with bumetanide's greater bioavailabilty, more of the agent is absorbed overall compared with furosemide.[18] Increased gut edema, as a result of passive venous congestion in HF patients, has classically been considered to be a main contributor to the variable effect of diuretics such as furosemide.[21] Of note, although this concept is commonly referred to in the clinical setting, studies suggest that relatively substantial and sustained decreases in gut blood flow are required to exert a significant change in drug absorption rates.[22] This supports the hypothesis that pharmacologic factors inherent to furosemide may be the primary contributors to a variable diuretic response compared with other loop diuretics. For instance, the bioavailability of furosemide has been shown to be widely variable between different patients and within individual patients in a variety of different health states.[17,23] In contrast, torsemide reliably has a bioavailability >80%, regardless of disease state.[11-14,24]

In addition to pharmacologic differences, genetic differences may also explain, in part, the variable responses to loop diuretics. Analysis of genetic polymorphisms seen in the sodium chloride contransporter, epithelial sodium channel, G nucleotide β-subunit 3, α-adducin, atrial natriuretic peptide precursor, and angiotensin I–converting enzyme (ACE) may explain up to 1/6 of the interpatient variability of loop diuretics on urinary electrolyte excretion, and a resulting 15% variation in urinary volume.[25] Interestingly, none of the polymorphisms affect the $Na^+/2Cl^-/K^+$ cotransporter. The clinical relevance of these observations has yet to be determined.

The RAAS

The role of the RAAS in HF has been extensively studied and reviewed elsewhere.[26] In brief, the RAAS regulates intravascular volume and tissue repair through activation of inflammatory and proliferative mechanisms. Initially, decreased perfusion of the renal juxtaglomerular cells leads to a secretion of renin. Renin cleaves angiotensinogen to angiotensin I which is further cleaved into the

Figure 1
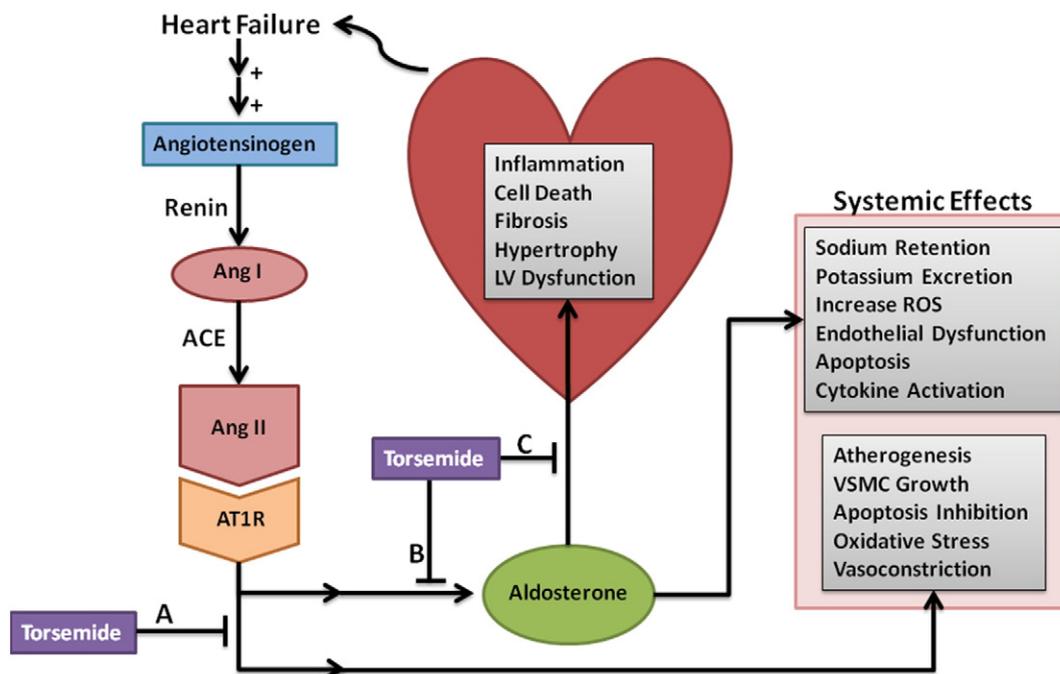
Potential effects of torsemide on the RAAS. Heart failure leads to an up regulation of the RAAS. Renin converts angiotensinogen to Ang I, which is converted to Ang II by ACE. Angiotensin II acts on AT1R leading to downstream effects including increasing aldosterone production and secretion, stimulating atherogenesis, VSMC growth, inhibition of apoptosis, increased oxidative stress, and promoting vasoconstriction. Circulating aldosterone acts on local myocardium receptors leading to myocardial inflammation, cell death, fibrosis, hypertrophy, and LV dysfunction leading to HF. Aldosterone stimulates sodium retention, potassium excretion, an increase in ROS, endothelial dysfunction, apoptosis, and increased cytokine activation. Torsemide may inhibit the downstream effects of Ang II (**A**), the secretion of aldosterone from adrenal cells (**B**), and aldosterone receptor binding (**C**). Abbreviations: Ang I, angiotensin; ROS: reactive oxygen species.

active angiotensin II (Ang II) by ACE. In the final part of this pathway, Ang II promotes aldosterone synthesis and secretion from the adrenal cortex, as well as contributing to ventricular remodeling, myocardial hypertrophy, systemic vasoconstriction, and vascular smooth muscle cell (VSMC) growth via its actions on the Ang II type 1 receptor (AT1R).[27,28] Aldosterone has also been extensively studied and noted to have negative systemic and cardiac effects including promotion of inflammation, fibrosis, hypertrophy, and cell death[29-31] (Figure 1). Loop diuretics have been shown to up-regulate the RAAS.[32,33] These potential adverse effects of loop diuretics have been cited as an explanation for the observation that higher-dose diuretics are associated with worse outcomes.[34] However, these observations may be subject to residual confounding because sicker patients require higher doses of diuretics.

Chronic RAAS activation as seen in HF leads to pathologic remodeling and left ventricular (LV) dysfunction. This process of pathologic remodeling serves as the underlying principle for current guideline recommendations of providing RAAS inhibition with an ACE inhibitor or angiotensin-receptor blockers, unless contraindicated, in all HF patients with a reduced ejection fraction.[4] Guidelines also recommend addition of an aldosterone receptor antagonist in patients with New York Heart Association (NYHA) classes II to IV and LV ejection fraction (LVEF) ≤35%.[4,35,36]

Similar to the guideline-recommended RAAS inhibitors above, studies have suggested potential RAAS benefits with torsemide. When compared with other diuretics, researchers initially noted in animal models that torsemide had longer-lasting diuresis and less urinary potassium excretion,[37] similar to effects seen with aldosterone blockade. These observations led to further studies to assess potential aldosterone antagonist-like activities with torsemide.[38-42] Subsequently, torsemide, but not furosemide, was found to inhibit aldosterone receptor binding in a dose-dependent manner in rat kidneys.[38] It has also been shown that torsemide can directly inhibit aldosterone secretion in animal models.[39] Recently, in vitro studies suggested that torsemide was unable to block aldosterone-mediated receptor translocation in monkey kidney cells.[43] In rat cardiomyocytes, torsemide had a

weak inhibitory effect of aldosterone-mediated transactivation, but specific downstream gene expression was not inhibited.[43] Thus, in vitro data are conflicting and torsemide may exert some effects on both aldosterone production and receptor binding. In contrast, furosemide has been shown to increase circulating aldosterone levels as well as worsen underlying cardiac function in animal models.[44]

One of the first human studies to assess RAAS activation with torsemide compared with furosemide measured aldosterone levels and plasma active renin concentration (PARC) in 50 patients with NYHA class II or III symptoms and LVEF ≤45% who were taking 20 or 40 mg of furosemide daily, in a 6 month crossover design.[40] Blockade of the RAAS through aldosterone receptor antagonism with spironolactone has reliably been shown to produce elevated aldosterone levels and PARC,[41,45] likely through the loss of feedback inhibition. Investigators found that similar to spironolactone, torsemide led to an increase in aldosterone and PARC.[40] Although preclinical studies have suggested that torsemide may inhibit aldosterone release, these findings may suggest that the more dominant mechanism in HF patients is likely its potential aldosterone receptor inhibition. Furthermore, torsemide improved clinical markers of HF severity in a dose-dependent manner as noted by a decrease in plasma brain natriuretic peptide (BNP) and improved echocardiographic measurements of LV function when compared with furosemide.[40] These observations with torsemide are similar to those seen in HF patients receiving spironolactone,[45] which are thought to be mediated through direct myocardial aldosterone receptor inhibition. Several studies have provided evidence for torsemide's ability to block myocardial aldosterone receptors. Early studies indicated that cardiac dysfunction results in greater uptake of circulating aldosterone by myocardial cells when compared with healthy controls,[46] leading to further LV dysfunction and pathologic remodeling.[46,47] Torsemide has been shown to reduce this myocardial aldosterone extraction compared with furosemide within HF patients,[42] suggesting that torsemide may directly antagonize the cardiac aldosterone receptors. Thus, in addition to torsemide's potential effects on reducing aldosterone production and secretion, it may inhibit myocardial extraction of deleterious aldosterone from circulation. However, it is worth noting that despite the above studies, the clinical importance of any potential effect of torsemide on aldosterone or aldosterone receptors remains to be proven.

Although the majority of data regarding torsemide's potential effect on RAAS inhibition have focused on aldosterone modulation, studies have also assessed potential benefits via effects on Ang II. Torsemide was found to inhibit the downstream effects of Ang II–induced protein synthesis during in vitro studies with rat VSMC, whereas furosemide had no such effect.[48] Although this single, in vitro study is limited in extrapolating results to humans, it is suggestive

that modulation of the systemic effect of Ang II may provide yet another mechanism by which torsemide provides benefit via RAAS inhibition. For instance, the blockade of the AT1R has proven mortality benefit within HF patients.[49,50]
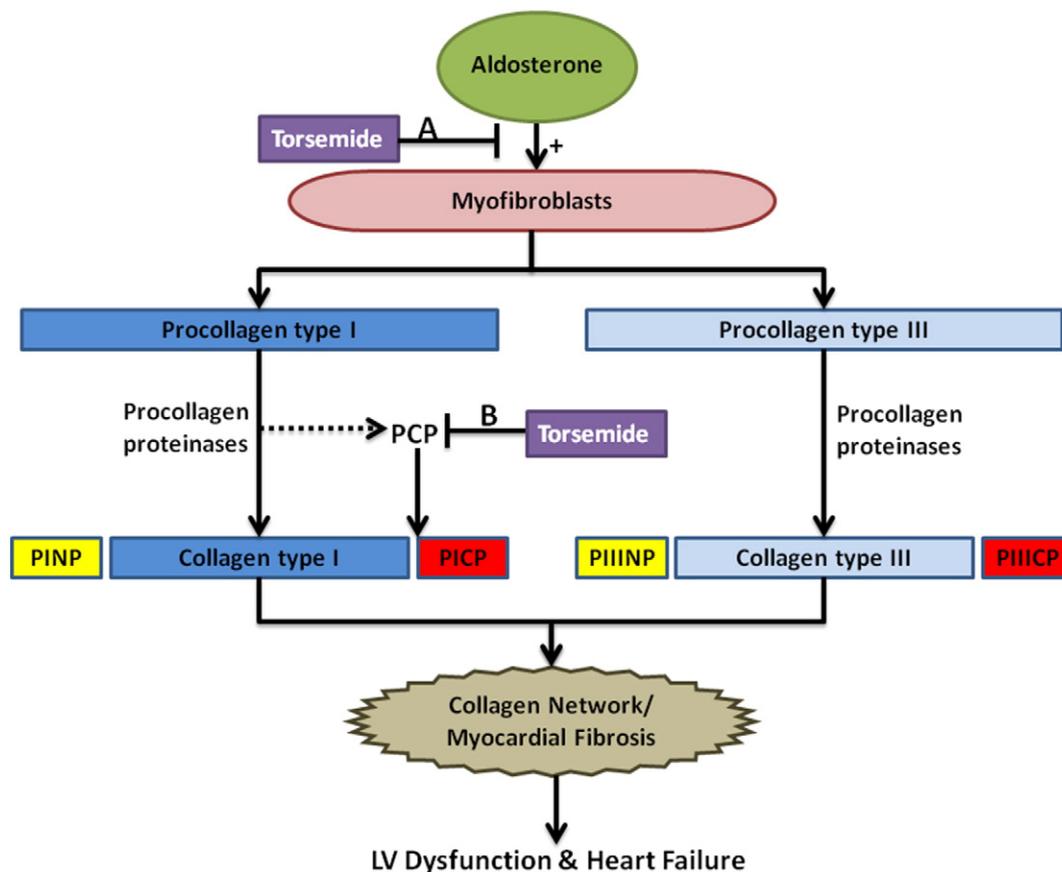
Cardiac fibrosis

The development of cardiac fibrosis in HF patients is mediated by myofibroblasts that respond to aldosterone, among other factors, by increasing the synthesis and secretion of fibrillar collagen precursors[51] (Figure 2). Two of the more abundant precursors in the heart are collagen types I and III, which are preceded by triple-helix procollagen precursors that require cleavage of terminal propeptides before integration into the collagen molecule.[51] The carboxy-terminal propeptide of procollagen type I (PICP) can be quantified and used as a measurement of the amount of collagen, and thus myocardial fibrosis, produced.[52] The correlation of increased PICP levels and myocardial fibrosis has been demonstrated in biopsy studies.[53]

Prior studies have suggested potential benefits on fibrosis with torsemide. A randomized study of 39 patients with NYHA class II to IV symptoms and average LVEF ranging from 38% to 44% found that after 8 months, those receiving torsemide (10-20 mg daily) had less myocardial collagen on septal biopsy and lower concentrations of PICP did than those receiving furosemide (20-40 mg daily).[54] Other investigators have used the aminoterminal propeptide of procollagen type III (PIIINP) as a surrogate marker of myocardial fibrosis. Unlike PICP, PIIINP does not have a 1:1 ratio of the number of molecules released to the number of collagen molecules produced.[51] Still, it has been suggested that in HF patients, PIIINP levels positively correlate with cardiac aldosterone extraction,[46] and PIIINP levels are reduced in patients receiving torsemide, along with the previously noted reduction in aldosterone extraction.[42] These data provide further support that torsemide has antifibrotic effects mediated through inhibition of aldosterone.

Another antifibrotic mechanism for torsemide has been described by Lopez et al.[55] The investigators found that activation of the enzyme responsible for cleavage of the PICP, procollagen type I carboxy-terminal proteinase (PCP), was decreased in a sample of 22 patients taking torsemide and unchanged in furosemide-treated patients. Although inhibition of PCP may explain lower levels of PICP in torsemide-treated patients, there needs to be further investigation to elucidate whether this is a direct action or downstream effect of torsemide.

The largest study completed to date investigating torsemide's antifibrotic effects was TORAFIC,[56] a multicenter study of 155 HF patients randomized to torsemide or furosemide. In contrast to prior data, the investigators found no significant differences between the 2 groups in changes of PICP levels.[56] Several potential confounding

Figure 2

Potential effects of torsemide on myocardial fibrosis. Aldosterone, as well as other cytokines, growth factors, and hormones, stimulates myofibroblasts to synthesize and secrete 2 main collagen precursors within the heart, procollagen type I, and procollagen type III. Procollagen proteinases are enzymes that process the procollagen into collagen molecules by cleaving the terminal propeptides. The cleaved propeptides of procollagen type I (PINP and PICP) and procollagen type III (PIIINP and PIIICP) are released into circulation and can be quantified as an indirect measurement of collagen production. The mature collagen molecules are further processed and eventually form the collagen network responsible for myocardial fibrosis, subsequently leading to pathologic remodeling, LV dysfunction, and HF. Torsemide is thought to mainly inhibit downstream collagen synthesis through its inhibition at the level of the aldosterone receptor (**A**), but torsemide may also decrease the activity of the PCP enzyme, the procollagen proteinase responsible for cleavage of PICP (**B**). Abbreviations: PINP, procollagen type I amino-terminal propeptide; PIIICP, procollagen type III carboxy-terminal propeptide.

variables could explain the negative data. The TORAFIC study had a disproportionately large number of mild, or early-stage, HF patients, as evidenced by baseline characteristics revealing a low prevalence of baseline edema, and most patients had NYHA class II symptoms (96.1% and 89.7% in the torsemide and furosemide groups, respectively), no patients had NYHA class IV symptoms, and the average LVEF was 54.4% and 50.7% in the torsemide and furosemide groups, respectively. Comparatively, Lopez et al[54] had a patient population with baseline NYHA class III-IV symptoms in ~58% of the torsemide group and ~70% of the furosemide group, with an associated average LVEF of 40% and 38% in the torsemide and furosemide groups, respectively. Thus,

arguably the TORAFIC study's patient population had less severe HF at baseline compared with prior study data, possibly explaining the low baseline serum levels of PICP noted and limiting the investigators ability to detect a significant change.

Preclinical data and surrogate markers with torsemide

Given the potential pharmacologic, RAAS, and anti-fibrotic benefits of torsemide over furosemide, several studies have directly compared these agents in an attempt to quantify effects on HF status and severity. Preclinical data are limited, but investigators demonstrated several differences between 2 groups of HF-induced rats that were randomized to receive varying doses of torsemide

and furosemide.[57] After 4 weeks, 100% of the rats receiving torsemide remained alive compared with only 64.3% in the control group and 75% of the furosemide groups.[57] The torsemide group also had improved LV end-diastolic pressures based on echocardiography and decreased myocardial fibrosis and collagen deposition compared with furosemide-treated rats.[57]

Early clinical studies comparing torsemide with furosemide focused mainly on the diuretic effect and noted that patients receiving torsemide had more diuresis and subsequent weight loss compared with furosemide.[58,59] In a prospective, multicenter trial of 237 HF patients randomized to torsemide or furosemide, investigators found that torsemide was superior for improvements in patient-reported quality of life and there was a trend for greater improvement in NYHA class.[60] Others studies have also demonstrated improvement in symptoms such as fatigue with torsemide over furosemide,[61] but these studies were limited due to the lack of adequate blinding.[60,61] Kasama et al[62] similarly found improvements in NYHA functional class in a small, randomized sample of 40 HF patients treated with torsemide compared with furosemide after 6 months of therapy. Furthermore, the torsemide-treated group had improvements in other surrogate measures such as decreased LV end-diastolic and systolic volumes, decreased levels of BNP, and improved sympathetic nerve activity.[62] Several other studies have noted greater improvement in NYHA functional class with torsemide compared with furosemide,[54,55,63] whereas only the aforementioned TORAFIC study found no significant difference in functional improvement. These data suggest relative concordance across multiple studies that torsemide improves surrogate markers of HF severity to a greater extent than furosemide.

Torsemide versus furosemide—morbidity and mortality

Trial data assessing morbidity and mortality of different loop diuretics are limited (Table II). As such, a recent systematic review identified just 25 randomized trials comparing the 2 agents, and only 2 (total N = 471) were included in the analysis because of limited data on clinical outcomes.[64] The landmark TORIC study, which was the largest study to date comparing torsemide to furosemide, was not included in the above analysis as it was not a randomized controlled trial.[63] TORIC was principally designed for postmarket surveillance of safety and tolerability. The original data analysis found a significant relative risk reduction in death among the torsemide group. This led to the post hoc analysis that included adult patients with NYHA class II-IV symptoms, who had at least one follow-up visit, and who had few exclusion criteria, even allowing for concomitant use of other diuretics. The main exclusion criteria were patients with torsemide hypersensitivity, significant electrolyte disturbances, severe ventricular arrhythmia, complete atrioventricular block, dyspnea due to lung disease, or protocol violations. The analysis included 1,377 patients

and found that after an average of 9 months, there was a significant 51.5% reduction in the risk of overall mortality, 59.7% reduction in cardiac mortality, and significant improvement in functional status within the torsemide group.[63] However, the results remain limited by the study design and sample population because the cohort of patients was rural and non–hospital based, and the use of other standard HF-pharmacotherapies such as β-blockers and ACE inhibitors was low (~9.5% and ~30%, respectively). Nevertheless, the mortality benefit observed was significant and TORIC remains at the center of the discussion regarding torsemide's mortality benefit.

One of the first randomized trials to address questions of morbidity and mortality was an open-label trial of 234 HF patients given torsemide or furosemide for up to 1 year.[61] The study was powered for a primary end point of HF-related readmissions. They found that patients given torsemide were less likely to be readmitted for HF or any cardiovascular event and had less HF-related hospital days (106 vs 296 days).[61] Analysis of secondary end points found that the torsemide group had reduced all-cause mortality (18 vs 25 deaths), but it was not statistically significant.[61] One interesting difference between the baseline characteristics of the 2 groups was that patients randomized to torsemide had significantly more HF hospitalizations in the year preceding enrollment.[61] Thus, the observation of reduced HF readmissions and a trend toward reduced mortality with torsemide, even in the context of a potentially higher risk population,[3] was another early observation supporting potential clinical benefits with torsemide. Furthermore, the study was not powered to detect differences in patient mortality, and the study population from 2 hospital centers within the same city may not be generalizable to the broad HF population.

Another study randomized 237 HF patients to torsemide or furosemide with a primary end point of overall hospitalizations.[60] After 9 months, the torsemide group had significantly fewer in-hospital days related to HF and cardiovascular disease combined (95 vs 146 days). There was no difference in hospitalizations due to ADHF or cardiovascular disease alone, or all-cause mortality. The investigators indicated that the difference in hospitalization days was mainly due to a single patient in the furosemide group with a prolonged stay. Furthermore, the estimated sample size needed in each group for adequate power was 120, but only 237 patients were randomized and 194 completed the study. Although this study and the previous study by Murray et al[61] had similar sample sizes and end points, several key differences exist. Compared with the prior study, the patients in the study population of Müller et al[60] had lower baseline NYHA functional class and were required to be on an ACE inhibitor. They also had less total follow-up days and had only 14 deaths in the entire study, further limiting their ability to detect a mortality difference between treatment groups.

Table II. Torsemide vs furosemide studies: hospitalizations and mortality

Study (year)	N	Patients	Design	Avg follow-up	Comparison	Outcomes (torsemide vs furosemide)	Limitations
TORIC (2002)	1377	• Spanish-based	Open-label, nonrandomized, post-marketing surveillance	9.2 mo (~276 d)	Torsemide avg dose 8.2 mg/d vs furosemide avg dose 35 mg/d + other diuretics	• 51.5% RR reduction in total mortality (17 vs 27 deaths)	• Nonrandomized
		• Avg age ~68 y				• 59.7% RR reduction in cardiac mortality (11 vs 27 deaths)	• Greater concurrent use of other diuretics in furosemide group
		• NYHA class II-IV				• Greater improvement in ≥ 1 NYHA class	• Low use of standard HF therapies
		• 50% female					• Rural non–hospital-based population
							• No report of hospitalization rates
Müller et al (2003)[60]	237	• Switzerland-based	Open-label, randomized, prospective	239 d in torsemide arm; 250 d in furosemide arm	Torsemide avg dose 11.36 mg/d vs furosemide avg dose 40.04 mg/d	• No difference in mortality (8 vs 6 deaths)	• Small sample size
		• Avg age ~74 y				• No difference in number of HF and CV-disease hospitalizations (10 vs 11)	• Sample sizes in each group were not adequately powered
		• NYHA classes II-IV				• Fewer combined HF and CV-related hospital days (95 vs 146)	• Furosemide group had more renal insufficiency
		• Required ACE inhibitor use				• Greater improvement in ≥ 1 NYHA class	• Concurrent ACE inhibitor therapy was required
		• ~57% female					• Hospitalization data skewed by a single furosemide-treated patient with prolonged hospital stay
							• Lack of blinding and subjective data
Murray et al (2001)[61]	234	• Indianapolis, USA-based	Open-label, randomized, prospective	324 d in torsemide arm; 318 d in furosemide arm	Torsemide avg dose 72 mg/d vs furosemide avg dose 136 mg/d	• No difference in mortality	• Small sample size
		• Avg age ~64 y				• 52% decrease in HF readmission rate	• Torsemide group had more pretrial HF hospitalizations in prior 1 y
		• NYHA classes II-III				• 34% decrease in all CV-related readmission risk	• High reported daily doses of loop diuretics
		• Excluded LV diastolic dysfunction only				• Less HF-related hospital d (106 vs 296)	
		• ~53% female					

Abbreviations: *avg*, Average; *RR*, relative risk; *CV*, cardiovascular.

Table III. Estimated 2015 Medicare patient average annual drug costs differences: torsemide vs furosemide

Location		Costs with no extra insurance		Costs with medicaid dual eligible	
ZIP code	City, state	Retail, mean (range)	Mail order, mean (range)	Retail, mean (range)	Mail order, mean (range)
10001	Manhattan, NY	$32.00 ($0-$63)	$24.30 ($0-$73)	$1.70 ($0-$5)	$1.70 ($0-$5)
27707	Durham, NC	$32.30 ($0-$64)	$24.70 ($0-$74)	$0.00 ($0-$0)	$0.00 ($0-$0)
34470	Ocala, FL	$21.70 ($0-$33)	$0.00 ($0-$0)	$1.70 ($0-$5)	$1.70 ($0-$5)
95240	Lodi, CA	$35.30 ($0-$73)	$28.30 ($0-$85)	$1.70 ($0-$5)	$0.00 ($0-$0)
99201	Spokane, WA	$47.00 ($38-$64)	$38.70 ($6-$74)	$0.00 ($0-$0)	$0.00 ($0-$0)
Total average costs differences (range)		$33.70 ($0-$73)	$23.20 ($0-$85)	$1.00 ($0-$5)	$0.70 ($0-$5)

More recently, a meta-analysis of the existing studies[55,56,60-63] found a trend toward improvement in NYHA class functional status (risk ratio 0.93, 95% CI 0.82-1.06) and all-cause death (risk ratio 0.68, 95% CI 0.39-1.18) in torsemide-treated compared with furosemide-treated patients.[65] However, the meta-analysis was limited by the quality of the included studies, and each end point had at least moderate degrees of heterogeneity (NYHA class I^2 = 46%; mortality I^2 = 48%) across the studies. The limitations of the above-mentioned studies may have further limited the ability to detect a significant difference in either end point. Nevertheless, the data are suggestive of a potential benefit with torsemide over furosemide in regard to morbidity and mortality.

Cost analysis

Historically, the acquisition cost of furosemide has been less than torsemide, but since torsemide became generic in 2002, that difference has been minimized. Despite the higher acquisition cost, economic analyses while torsemide was on-patent found a reduction in total cost per patient compared with furosemide.[66] This difference was observed largely due to decreased hospital admissions in the torsemide group.[66] Another analysis of 240 randomized HF patients found no difference in average medical costs related to HF or cardiovascular-related diseases in torsemide-treated patients.[67] The above studies and several others have been reviewed previously[68] and suggest that torsemide compared with furosemide decreases, or at a minimum does not increase, total health care costs despite the higher acquisition costs.[68]

Müller et al[60] present the more recent and conservative data of the 2 trials reporting HF-related hospital days while comparing torsemide and furosemide[60,61] (Table II). Using the unadjusted data in Müller et al, we estimated the 90-day inpatient cost difference between the torsemide and furosemide groups using the 2013 average reimbursement for Medicare's diagnosis-related group weight unit of $5,774. We calculated a total daily cost of $1,252.27 using the most conservative of Medicare's diagnosis-related group HF-related weight unit from 2014. At 90 days, there were 0.05 less hospital days per patient

in the torsemide group, accounting for $63 less total cost per patient. Based on local Wal-Mart pharmacy pricing, the difference in cost of obtaining a 90-day supply of torsemide 10 mg versus furosemide 20 mg daily is $52.28. Thus, when considering the difference in acquisition costs and using conservative hospitalization and reimbursement rates, data suggest that torsemide use does not increase total medical costs.

Although total medical costs may be similar, a potential barrier to patient compliance with torsemide use may be higher direct costs to the patient. We estimated the average annual drug cost differences for Medicare patients taking torsemide 20 mg compared with furosemide 40 mg daily. The 2015 estimated Medicare costs were collected from 5 separate geographic regions across the United States and were adjusted based on delivery method (retail vs mail order) and presence or absence of financial assistance with Medicaid dual eligibility (Table III). The average annual drug costs differences to patients taking torsemide compared with furosemide without extra insurance was $33.70 ($0.094/d) for retail and $23.20 ($0.064/d) for mail order. Although the average annual drug cost differences for patients with Medicaid dual eligibility was $1.00 ($0.003/d) for retail and $0.70 ($0.002/d) for mail order. There was minimal variation across geographic regions. Thus, the cost increment for torsemide versus furosemide use is less than $3 per month for Medicare patients not receiving financial assistance, and there is no difference for patients with dual Medicare and Medicaid eligibility. Limitations of our cost analysis include the lack of inclusivity of all geographic regions, furosemide availability on $4 formularies may be less than some copayments, and choices of prescription drug plans may be influenced by medications not included in our analysis.

Conclusion

There is significant room for improvement in regard to preventing hospitalizations and reducing mortality within the HF patient population. Most studies that directly compared torsemide to furosemide have been small, underpowered, and with limited end points. Nonetheless,

Table IV. Potential benefits of torsemide compared with furosemide

Preclinical data	Clinical data
• Improved diuresis	• Improved diuresis and weight reduction
• Decreased kaliuresis	• Decreased transcardiac aldosterone extraction
• Decreased aldosterone secretion	• Less RAAS activation
• Inhibition of aldosterone receptor*	• Decreased myocardial collagen
• Inhibition of Ang II effects	• Decreased levels of PICP† and PIIINP (collagen surrogates)Decreased PCP activity
• Improved LV function	• Decreased levels of plasma BNP
• Decreased myocardial collagen	• Improved LV function
• Increased survival rate	• Improved NYHA class†
	• Improved subjective quality of life
	• Decreased all-cause‡ and cardiac-associated mortality
	• Decreased rates of hospitalization‡
	• Decreased length of hospital stay related to HF

* Gravez et al[43] found no receptor inhibition.
† TORAFIC study[56] found no difference between variables.
‡ Müller et al[60] found no difference between variables.

most have suggested benefits with torsemide use, including improved NYHA functional class, improved LV function, decreased myocardial fibrosis, decreased rates of hospitalizations, and potentially a reduction in mortality (Table IV). However, there remains a need for a prospective, large, randomized controlled trial directly comparing torsemide to furosemide within the HF population that is adequately powered for such end points.

Current guidelines recommend diuretic use without providing guidance on therapy choice,[4] and despite all of the preclinical and clinical differences noted, clinicians commonly use furosemide over other loop diuretics.[65] The preferential use of furosemide is likely due to furosemide being first to market in 1966 such that clinicians tend to have experience with its use and it generally has lower acquisition costs. In comparison, torsemide was not Food and Drug Administration approved until 1993 and tends to be reserved for patients refractory to furosemide or those with renal failure or suspected intestinal edema. The above data suggesting comparative clinical benefits with torsemide over furosemide and the availability of generic torsemide coupled with economic analyses finding similar total medical costs and minimal differences in direct patient drug costs suggest that clinicians should consider torsemide use first over furosemide and, at the very least, emphasize a need for a reappraisal of current diuretic use in HF patients.

Disclosures

The authors report no relevant conflicts of interest.

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