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Potential advantages of torsemide in patients with heart failure: more than just a 'water pill'?

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Heart failure (HF) with preserved ejection fraction (HFpEF) is a growing public health problem that accounts for approximately half of the 38 million cases of HF worldwide.[1,2] Despite this enormous HFpEF population with clinical outcomes comparable to HF with reduced ejection fraction (HFrEF), therapeutic advancement in HFpEF has been near absent. Indeed, with the possible exception of spironolactone, contemporary management of HFpEF remains devoid of evidence-based therapy, with treatment limited to the optimization of comorbidities and use of diuretics to manage congestion.[3] This lack of proven therapy is particularly alarming in the face of current epidemiologic trends forecasting a continued rise in HFpEF prevalence to become the more common form of HF in coming years.[4] Thus, despite remarkable progress in the treatment of HFrEF, contemporary care faces the humbling possibility of having no definitively proven therapy for the majority of patients with HF.

Given the unmet therapeutic need, HFpEF research has continued to focus on understanding the pathophysiology of the condition and identifying potential targets for therapy. In this respect, myocardial fibrosis has garnered much attention.[5] Broadly defined, myocardial fibrosis reflects interstitial expansion from excess collagen formation, and carries potential for mediating a wide array of cardiac abnormalities, including impairment of the microvascular, mechanical, electrical and metabolic function of the heart.[5] Examination of HFpEF cohorts suggests that myocardial fibrosis may be highly prevalent, associated with clinical outcomes, and potentially reversible.[5–8] Indeed, the extracellular matrix of HFpEF patients contains greater collagen content compared to patients with HFrEF and healthy controls, largely contributing to the HFpEF hallmarks of ventricular stiffness and impaired relaxation.[9] Accordingly, these data support the hypothesis that agents with potent anti-fibrotic abilities may represent effective HFpEF therapies.[5] In this context, previous work with torsemide, a loop diuretic available for routine use across the spectrum of HF, suggests that the medication may exert favourable biochemical and molecular effects on myocardial fibrosis.[10,11] Conceivably, such properties may make torsemide a particularly helpful drug in HFpEF, whereby a single agent could control congestion while simultaneously attenuating (or reversing) changes in myocardial fibrosis. Thus, confirmation of added anti-fibrotic and clinical outcome benefits of torsemide beyond its symptomatic role as a diuretic would

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differentiate it from other loop diuretics, highlighting it as the clear choice in HFpEF and potentially other forms of HF.

In this issue of the Journal, Trippel *et al.* present the small, double-blinded, randomized controlled DROP-PIP trial investigating the effects of torsemide and furosemide on serum C-terminal propeptide of procollagen type I (PIP), a biomarker reflective of collagen synthesis and myocardial fibrosis burden.[12] Eligible patients met the guideline definition of HFpEF, had type 2 diabetes mellitus (DM), and had either baseline PIP of ≥110ng/mL or the combination of PIP ≥70ng/mL and left atrial enlargement. In total, 35 patients were randomized to torsemide 5mg/day vs. furosemide 20 mg/day and followed for assessment of the primary endpoint defined as the percentage change in PIP value from baseline to 9 months. Trial results showed no significant difference between the two groups in the longitudinal change in PIP and a negligible change from baseline in each study arm. Results were consistent irrespective of intention-to-treat or per-protocol analysis. Similarly, there were no significant differences in any secondary endpoints, including measures of functional capacity, echocardiographic surrogates of diastolic dysfunction, quality of life, natriuretic peptide level, and renal function.[12]

Although the investigators are to be congratulated for a well executed clinical trial, several limitations of this work should be highlighted.[12] First, although each study arm experienced small changes in PIP over time, the small sample size and single-centre nature of the trial limited power to detect significant differences between treatment arms for any of the primary or secondary endpoints. This limitation of a small study cohort was compounded by the dropout of nearly one in five patients during follow-up due to refractory congestion or other reasons. Second, the authors do not justify their choice of drug dosing and it is possible that higher doses of torsemide might have produced different results. Specifically, some prior studies have used a 2:1 ratio with regard to potency of torsemide vs. furosemide, and it is possible that testing effects of 10 mg torsemide against those of 20 mg furosemide would have produced different results.[13] Third, as highlighted by the authors, baseline PIP levels were imbalanced across the study arms and were significantly higher in patients randomized to furosemide. Such imbalances are inherent risks in the execution of small studies with biomarker-based endpoints and, in this circumstance, suggest the possibility of regression to the mean as hindering detection of incremental PIP lowering with torsemide. Fourth, questions can be raised regarding the disease severity of the current cohort and it remains unclear if a population enriched with more severe derangements in traditional risk markers, or a higher inclusion cutoff for baseline PIP, would have yielded different results. For example, although only a minority of patients were labelled New York Heart Association class I status and all patients had DM, baseline levels of N terminal pro-B-type natriuretic peptide (NT-proBNP) were nearly within the normal range (i.e. mean: 174 pg/mL) and echocardiographic E/e' ratios were only modestly elevated (i.e. mean: 1 4.1). Similarly, inclusion in the trial mandated a ≥ 5-day washout period from any loop diuretic prior to randomization, and tolerance of such a washout period and marginal baseline NT-proBNP levels despite diuretic absence suggests a low-risk patient phenotype with minimal congestion. Thus, although the research question assessed in the present study is of major importance, the limitations outlined above prohibit any conclusive insights on the anti-fibrotic potential and clinical utility of torsemide in HFpEF.

Notwithstanding the neutral findings of Trippel and colleagues, the preponderance of available data has generated the hypothesis that torsemide has unique advantages over furosemide (Table 1). Aside from the above mentioned potential effects on myocardial fibrosis, torsemide may exert favourable effects on the renin-angiotensin-aldosterone system (RAAS).[13] Although the utility of RAAS inhibition in HFrEF is well established, definitive benefits with aldosterone antagonism in HFpEF might have been shown in the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) trial had adequate quality control been ensured.[14] Pre-clinical and small clinical studies have suggested that torsemide down-regulates RAAS activity by modulating aldosterone activity by both aldosterone antagonist-like blockade of the receptor and inhibition of aldosterone release.[13] Indeed, favourable neurohormonal modulation has been implicated as the mechanism by which torsemide possibly reduces myocardial fibrosis and fosters reverse ventricular remodelling.[15] In contrast, although data are mixed, furosemide may up-regulate the RAAS and such a phenomenon is cited as a potential explanation for the progression of HF and the observation that higher-dose diuretics are associated with worse patient outcomes.[16]

In addition to its potential neurohormonal benefits, the pharmacologic properties of torsemide differentiate it from other loop diuretics for the purposes of controlling signs and symptoms of congestion. Compared with furosemide, torsemide is 2 to 4 times more potent, offers consistent 80–100% bioavailability irrespective of food intake, provokes less hypokalaemia, and carries a longer half-life and duration of effect.[13] In combination, these properties provide torsemide with a more robust and predictable diuretic effect, particularly in comparison with the variable bioavailability of furosemide. Although not definitively proven, in the context of data identifying worsening congestion as the primary reason for HF hospitalization and diuretic resistance as a strong predictor of adverse outcomes, it is plausible that the more consistent diuretic effect of torsemide would be helpful in reducing the need for HF hospitalization and facilitating easier outpatient HF management.

Despite the anti-fibrotic, neurohormonal and pharmacological benefits of torsemide over furosemide cited above, there has been no translation of this evidence into a definitive, randomized, clinical outcomes trial. The most recent meta-analysis of available clinical data found trends towards improved functional class and lower mortality with torsemide, but statistical significance was not met and studies suffered from remarkable heterogeneity.[17] In light of the limited data, current HF guidelines acknowledge that diuretic effects on morbidity and mortality are unknown and offer no specific recommendations on choice of loop diuretic.[3] Given that loop diuretics are used by nearly 80% of all chronic HF patients and represent the long-established cornerstone of symptomatic management, better evidence identifying the diuretic agent of choice is surely needed.[18] In this context, the US National Heart, Lung, and Blood Institute recently approved funding for the TRANSFORM-HF (Torsemide Comparison with Furosemide for Management of Heart Failure) trial (clinicaltrials.gov identifier: NCT03296813), a robustly powered, 6000-patient, prospective comparative-effectiveness study of torsemide vs. furosemide in the treatment of HF This pragmatic trial will randomize HF patients to torsemide or oral furosemide prior to hospital discharge to assess the long-term impact of diuretic choice on the primary endpoint of 12-month all-cause mortality. The trial will be inclusive of both HFrEF and HFpEF patients,

but, given the differences in pathophysiology and the potential of torsemide to interact differently in each group, efficacy analysis by subgroup is prespecified.

In conclusion, the article by Trippel *et al.* points to the heart of a key, but underappreciated, question in cardiovascular medicine: what is the best diuretic to use in a HF patient? In aggregate, a wealth of basic, pre-clinical, observational, and small randomized trials have highlighted a compelling rationale for the use of torsemide as the diuretic of choice for HF Such enthusiasm is particularly tempting in HFpEF subjects, a patient population in which the bar is low and a drug need only beat placebo to represent a major therapeutic breakthrough. However, the history of cardiology and HF has been plagued by instances in which confidence in 'common sense' mechanisms and surrogate endpoints is subsequently shattered by neutral or negative effects on morbidity and mortality. Thus, for now, clinical equipoise for the routine use of torsemide vs. furosemide must persist and definitive outcomes data are eagerly awaited. In the meantime, clinicians and patients with HF are left to wonder if that daily loop diuretic prescribed for years can serve as anything more than 'just a water pill'.

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Table 1

Potential advantages of torsemide over furosemide in the treatment of heart failure

Pharmacologic properties better suited for managing congestion
• More predictable and reliable diuretic effect
- Near 100% bioavailability compared with variable furosemide bioavailability (i.e. 10–100%)
- Absorption not affected by food
- 2–4 times more potent than furosemide
- May be less vulnerable to diuretic resistance
• Longer half-life (3.5h vs. 2h) and duration of effect (6–16h vs. 6–8h) than furosemide
• Less prone to hypokalaemia
Favourable effects on neurohormones
• Renin-angiotensin-aldosterone system inhibition
- Decreased aldosterone secretion from adrenal cells
- Aldosterone antagonist-like blockade of aldosterone receptors
- Inhibition of downstream effects of angiotensin II
• Decreased sympathetic activation
Favourable effects on cardiac remodelling
• Slows or reverses development of myocardial fibrosis
• Attenuates progressive ventricular dilation and hypertrophy