Review Article

TRANSFORM-HF Trial: Choice of loop diuretic in acute heart failure does not matter!

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Abstract

The major clinical manifestations of heart failure (HF) are due to fluid retention and congestion, and thus, therapy targeting congestion plays a central role in HF management. Furosemide is by far the most commonly prescribed loop diuretic. However, data primarily derived from observational and small randomized trials point toward potential advantages with torsemide use including improvement in functional status, survival, and hospitalization for HF. The TRANSFORM-HF study aimed to answer a pragmatic query faced by physicians managing HF – Does the choice of loop diuretic matter in HF? There was no benefit of torsemide over furosemide in this large study of >2800 patients for mortality, hospitalization, and quality of life. Though, there were a few shortcomings of the study, the results are in sync with current HF guidelines which do not advocate the use of one loop diuretic or other. Hence, the focus in acute HF should be on optimizing the diuretic dose and other guideline-based therapies rather than the type of diuretics. Recent trials of acetazolamide and other diuretics have shown benefits when used in conjunction with loop diuretics. Since the primary care physician is often the first point of medical contact, the manuscript aims to provide insights into their practice. The message is clear that in acute heart failure, there is no benefit of choosing the type of loop diuretic and impetus should be on adding other class diuretics if needed as well as initiating other guideline-directed medical therapies.

Keywords: ADVOR, congestion, furosemide, mortality, weight loss

Introduction

The major clinical manifestations of heart failure (HF) are due to fluid retention and congestion, and thus, therapy targeting congestion plays a central role in HF management. Furosemide is by far the most commonly prescribed loop diuretic. Data primarily derived from observational and small randomized trials point toward potential advantages with torsemide use including improvement in functional status, survival, and hospitalization for HF (HHF). The TRANSFORM-HF study aimed to answer a pragmatic query faced by physicians managing HF for quite some time – Does the choice of diuretic matter in HF in short term or long term? The trial recruited hospitalized heart failure patients regardless of ejection fraction (EF) and evaluated hard cardiovascular outcomes. Since the primary care physician is often the first point of medical contact, the study results have implications for them too. The manuscript aims to provide insights into the choice of diuretics in acute HF.

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Trial Summary

The TRANSFORM-HF trial was a multicenter, open-label, and randomized trial across 60 centers in USA.[1] It enrolled 2859 patients hospitalized with a diagnosis of HF, irrespective of their EF and whether it was the first episode of HF (de novo) or a recurrent one. Patients with LVEF >40% needed additional natriuretic peptide elevation. In addition, all patients were anticipated to need long-term diuretics on an outpatient basis. Comorbidities were generally not an exclusion, except end-stage renal failure and short life expectancy. The primary outcome

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was all-cause mortality as analyzed by a time-to-event method. The three clinical secondary outcomes were a composite of all-cause mortality or all-cause hospitalization at 30 days and 12 months and total hospitalizations at 12 months. Two additional secondary end points were related to quality of life (QOL): Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score (KCCQ-CSS) and Patient Health Questionnaire-2 (PHQ-2) over 12 months.[2] The randomization was 1:1, and the dosing/frequency of the diuretic was adjusted at the local sites. The planned duration of follow-up was 30 months for death and 12 months for HHF. The median age of patients was 65 years, and the proportion of women and blacks stood at 36.9% and 33.9%, respectively. The coverage of guideline-directed medical therapy (GDMT) was also high: beta blocker, 81%; RAAS blocker, 67.5%; and mineralocorticoid receptor antagonist, 45%.

At study completion, all-cause death occurred similarly in both groups [26.1 vs 26.2% in torsemide and furosemide; hazard ratio (HR) 1.02, $P = 0.76$]. Similarly, over 12 months, there was no difference in all-cause death or all-cause hospitalization rates (47.3% vs 49.3%; HR 0.92 $P = 0.92$), although the numbers were numerically lower in the torsemide arm. With respect to total hospitalizations and all-cause death or all-cause hospitalization rates at 30 days, there were numerically lower numbers in the torsemide arm, but results did not reach statistical significance. The results were consistent across various subgroups like race, sex, age, LVEF, e-GFR, NYHA class, duration of heart failure, presence of diabetes, and systolic BP values. A post hoc analysis employing a competing risk model did find 12% reduction in all-cause hospitalization at 12 months in patients on treatment at 30 days and at discharge. Thus, the strategy of utilizing torsemide appears to have similar effectiveness compared with a strategy of furosemide for alleviation of adverse outcomes in patients hospitalized with HF. Here, it should be noted that the trial was plagued by a high crossover rate (7% from torsemide to furosemide), nonadherence (almost 10% were not taking diuretics at 6 months), and loss to follow-up. Being an event-driven trial, when the trial was stopped, the sample size achieved was only half of the original plan. Also, no analysis was done on safety and metabolic side effects, which might have thrown some light on choosing particular diuretics in specific situations.

Data on two QOL outcomes were published separately.[2] There was no significant difference between the arms at 12 months regarding change in KCCQ-CCS from baseline. Similarly, the proportion of patients with PHQ-2 score >3 at 12 months was also not significantly different between both diuretic arms. Hence, use of torsemide did not result in better symptoms or QOL compared to furosemide.

Implications for practice

HF is a major public health burden globally.[3,4] It is associated with high morbidity and mortality.[5,6] However, despite continued advances in therapy, the prognosis of HF remains poor.[5,6]

Diuretics in HF

The main clinical manifestations of HF are due to fluid retention and congestion, and thus, therapy targeting congestion plays a central role in HF management. The first loop diuretic to gain U.S. Food and Drug Administration (FDA) approval around 50 years ago was furosemide.[7] The three loop diuretics in vogue (furosemide, torsemide, and bumetanide) have been instrumental in achieving decongestion of HF patients across the globe. Diuretics are used to achieve and maintain an euvolemic state. In general, loop diuretics, such as furosemide, are the mainstay of diuretic therapy in HF due to their great effectiveness. Indeed, loop diuretics result in more intense and shorter diuresis than thiazides, which results in more gentle and prolonged diuresis. The practice guidelines therefore recommend loop diuretics as the primary medications (Class I indication) to control fluid retention in HF.[5,6] This is despite the fact that limited data exist regarding their effects on morbidity and mortality. A Cochrane database review of 14 studies including 525 patients reported that diuretics decrease the odds of death and hospitalization compared to ACE inhibitor and digoxin.[8] But the publication was withdrawn subsequently.

Torsemide versus furosemide

Furosemide is by far the most commonly prescribed oral loop diuretic, but patients with resistance to oral furosemide therapy may benefit from second-generation oral loop diuretics (bumetanide and torsemide). These may be more efficacious as they have higher oral bioavailability and potency.

In the prospective Torsemide In Chronic heart failure (TORIC) study, the use of torsemide was associated with lower mortality than furosemide in 1377 patients with HF (2.2% vs 4.5%; $P = 0.05$).[9] The NYHA class improvement was significantly better with torsemide, while hypokalemia episodes were less frequent. Torsemide also improved diastolic functions of LV better compared to furosemide.[10] Other observational, small randomized trials and meta-analyses have suggested torsemide may reduce HF hospitalization, improve functional status, and improve survival, as compared with furosemide.[11-14]

Torsemide has a better pharmacological profile compared to the ubiquitous furosemide. It has 2 to 4 times more potency, higher bioavailability of 80–100% irrespective of food intake, and a longer half-life and duration of effect [Figure 1].[7,9,11] An additional advantage of torsemide remains the ability to downregulate the activity of the renin-angiotensin-aldosterone system through both inhibition of aldosterone release and aldosterone antagonist-like blockade of the receptor.[10,15,16] This antialdosterone effect is one of the putative mechanisms of benefit of torsemide on mortality on HF.

Subsequent studies demonstrated that torsemide was seen to attenuate left ventricular fibrosis in patients with HF to a greater extent than furosemide by decreasing the amount of type I procollagen.[15-18] Though evidence favors torsemide over

furosemide, there is dominance of furosemide in the treatment of HF.[19] This is because there are many examples where despite basic science and favorable preclinical, observational, and small randomized studies, large clinical trials can show negative results. Thus, despite the Class I indication for use of diuretic agents in HF, treatment guidelines appropriately do not provide a specific recommendation for routine use of any specific agent.[5,6] The TRANSFORM-HF trial was designed to answer this pivotal question plaguing clinicians across the globe – can the use of torsemide in HF lead to improvement outcomes? The results of TRANSFORM-HF trial have clearly shown that there is almost no difference in terms of all-cause mortality and HF hospitalization between furosemide and torsemide and the results were superimposable. There was also no difference in total hospitalizations among the two groups. Failure of the study could be attributed to methodological issues described earlier. Additionally, the evolving pharmacotherapy and management of HF over the last decade since the TORIC and small studies of torsemide in early 2000s could have played a part.

Thus, it can be concluded that torsemide and furosemide have similar effectiveness in terms of clinical outcomes of mortality and repeat hospitalizations in patients admitted with HF. It should be at the treating physician's discretion to administer whichever loop diuretic he deems suitable. Nevertheless, the primary focus in HF should be rather on appropriate diuretic dosing and prioritizing guideline-directed medical therapy (GDMT) initiation/titration rather than the choice of loop diuretic.

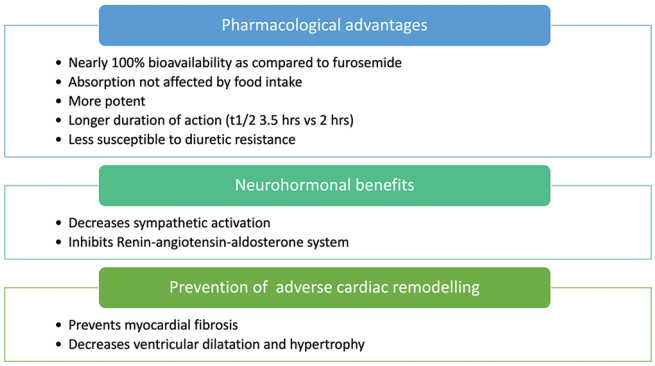

Figure 1: Various potential advantages of torsemide over furosemide

Looking beyond loop diuretics

Acetazolamide belongs to a different class of diuretics which inhibit the carbonic anhydrase enzyme in proximal tubules and are generally not utilized for decongestion in acute HF. However, a multicenter, randomized, and placebo-controlled trial of acetazolamide (**ADVOR** Study) in acute HF with clinical signs of congestion has shown that the addition of acetazolamide to loop-diuretic therapy was associated with higher incidence of successful decongestion (primary end point).[20] There was also higher urine volume and natriuresis with acetazolamide. However, as in TRANSFORM-HF study, the risk of death from any cause or rehospitalization for HF (secondary composite end point) did not differ. A noteworthy point is that the risk of death or hospitalization in the study (30% at 90 days) was considerably lower than that in the DOSE trial (50% at 60 days) and in the Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF; 40% at 60 days).[21,22] A substudy of ADVOR trial showed that higher bicarbonate levels (HCO3-) at baseline predicted better response to acetazolamide including better decongestion, natriuresis, urine output, and hospital stay.[23] A loop diuretic only strategy (placebo arm) led to higher bicarbonate levels, which was attenuated by acetazolamide, thereby providing some mechanistic insights into loop diuretic resistance and treatment.

The recently published **CHOLROTIC** trial evaluated the role of hydrochlorothiazide (HCTZ) over and above loop diuretics in 230 patients with acute HF.[24] Addition of HCTZ to loop diuretics led to significantly greater weight loss and natriuresis, but there was no effect on patient-related dyspnea. Similar to previous trials, mortality or hospitalization was not affected. More patients in HCTZ arm had impaired renal functions but not hypokalemia.

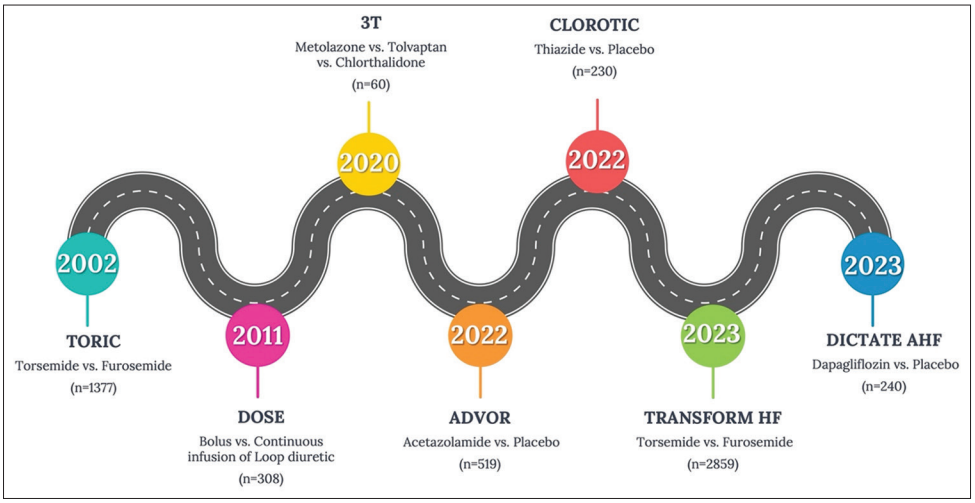

Figure 2: The major diuretic trials in Heart failure in the past two decades. The numbers in the parentheses represent the sample size of the respective study

The **3T** trial aimed to find the best regimen to overcome I/V loop diuretic resistance.[25] Around 60 patients with acute HF and proven diuretic resistance were randomized to metolazone, IV chlorothiazide, or tolvaptan in addition to I/V loop diuretics. All the three regimens produced weight loss, increased urine output, and improved diuretic efficacy. There was no difference between groups, but tolvaptan group had attenuated decline in serum sodium.

Dapagliflozin, a sodium glucose cotransporter (SGLT-2) inhibitor, has been shown to improve CV outcomes in chronic heart failure. Although not a diuretic *per se*, these classes of drugs produce diuresis and natriuresis in kidney and this is one of their multiple mechanisms of benefits for CV outcomes. Recently, the impact of dapagliflozin on decongestion in acute HF was evaluated in **DICTATE AHF** study.[26] The study results revealed that dapagliflozin use led to higher efficiency and a lesser dose of loop diuretics and higher weight loss. There was better natriuresis, diuresis, early transition oral diuretics, and shorter hospital stay with dapagliflozin. Figure 2 depicts the landmark diuretic trials in heart failure in recent decades.

Implications for clinical practice

The primary care physician is often the first point of contact for a majority of patients in both urban and rural settings alike. Dyspnea is a common symptom for which patients with HF seek care in both the setting of an emergency visit or an outpatient visit. Diuretics are often the mainstay for management of dyspnea in acute and chronic settings. In the setting of acute HF, loop diuretics are the first-line agents due to their brisk onset of action and proven efficacy for symptom alleviation for past 5 decades. Furosemide and torsemide are the two agents in vogue with torsemide boasting of superior efficacy and safety based on preclinical, observational, and small nonrandomized studies. The physician/clinician was often faced with the dilemma of choosing one agent over the other given the lack of large RCTs. TRANSFORM-HF aimed to solve this clinical conundrum, and the results demonstrate that despite having a better pharmacological and safety profile, the use of torsemide in acute HF does not result in superior clinical outcomes. There was also no improvement in surrogate markers either. Hence, pending a larger clinical trial, there is no benefit of choosing one loop diuretic over the other and personal experience, cost, and availability might be the deciding factors. On the contrary, recent studies have demonstrated utility of other classes of diuretics in acute HF like acetazolamide, hydrochlorothiazide, and dapagliflozin (though not strictly a diuretic by definition!). In nutshell, the goal in acute HF should be utilization of other classes of diuretics in conjunction with loop diuretics if needed rather than being argy-bargy over the type of loop diuretic.

Conclusion

The TRANSFORM-HF trial failed to demonstrate the superiority of torsemide over furosemide to improve cardiovascular outcomes in acute HF. This is despite the fact that torsemide has a better pharmacological profile, favorable effects on ventricular remodeling, and positive CV outcomes in small randomized studies. The focus in Acute HF should be on early initiation of GDMT and proper dosing of loop diuretics. Acetazolamide and dapagliflozin have shown promise for decongestion in acute HF, while HCTZ, tolvaptan, and thiazide-like diuretics can be utilized in conjunction with loop diuretics to decrease their resistance.

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Conflicts of interest

There are no conflicts of interest.

References

1. Mentz RJ, Anstrom KJ, Eisenstein EL, Sapp S, Greene SJ, Morgan S, *et al.* Effect of torsemide vs furosemide after discharge on all-cause mortality in patients hospitalized with heart failure: The TRANSFORM-HF randomized clinical trial. JAMA 2023;329:214-23.
2. Greene SJ, Velazquez EJ, Anstrom KJ, Clare RM, DeWald TA, Psotka MA, *et al.* Effect of torsemide versus furosemide on symptoms and quality of life among patients hospitalized for heart failure: The Transform-HF randomized clinical trial. Circulation 2023;148:124-34.
3. Shahim B, Kapelios CJ, Savarese G, Lund LH. Global public health burden of heart failure: An updated review. Card Fail Rev 2023;9:e11.
4. Writing Committee Members; ACC/AHA Joint Committee Members. 2022 AHA/ACC/HFSA guideline for the management of heart failure. J Card Fail 2022;28:e1-167.
5. Mc Donagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, *et al.* 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2021;42:3599-726.
6. Guha S, Harikrishnan S, Ray S, Sethi R, Ramakrishnan S, Banerjee S, *et al.* CSI position statement on management of heart failure in India. Indian Heart J 2018;70(Suppl 1):S1-72.
7. Greene SJ, Velazquez EJ, Anstrom KJ, Eisenstein EL, Sapp S, Morgan S, *et al.* Pragmatic design of randomized clinical trials for heart failure: Rationale and design of the TRANSFORM-HF trial. JACC Heart Fail 2021;9:325-35.
8. Faris RF, Flather M, Purcell H, Poole-Wilson PA, Coats AJ. Diuretics for heart failure. Cochrane Database Syst Rev 2012:CD003838. doi: 10.1002/14651858.CD003838.pub3.
9. Cosin J, Diez J. TORIC Investigators. Torasemide in chronic heart failure: Results of the TORIC study. Eur J Heart Fail 2002;4:507–13.
10. Yamato M, Sasaki T, Honda K, Fukuda M, Akutagawa O, Okamoto M, *et al.* Effects of torasemide on left ventricular function and neurohumoral factors in patients with chronic heart failure. Circ J 2003;67:384-90.
11. Murray MD, Deer MM, Ferguson JA, Dexter PR, Bennett SJ, Perkins SM, *et al.* Open-label randomized trial of torsemide compared with furosemide therapy for patients with heart failure. Am J Med 2001;111:513–20.

12. Müller K, Gamba G, Jaquet F, Hess B. Torasemide vs. furosemide in primary care patients with chronic heart failure NYHA II to IV--efficacy and quality of life. Eur J Heart Fail 2003;5:793-801.
13. Wargo KA, Banta WM. A comprehensive review of the loop diuretics: Should furosemide be first line? Ann Pharmacother 2009;43:1836-47.
14. Di Nicolantonio JJ. Should torsemide be the loop diuretic of choice in systolic heart failure? Future Cardiol 2012;8:707-28.
15. Kasama S, Toyama T, Hatori T, Sumino H, Kumakura H, Takayama Y, *et al*. Effects of torasemide on cardiac sympathetic nerve activity and left ventricular remodelling in patients with congestive heart failure. Heart 2006;92:1434–40.
16. .Bikdel Lopez B, Querejeta R, Gonzalez A, Sánchez E, Larman M, Díez J, *et al*. Effects of loop diuretics on myocardial fibrosis and collagen type I turnover in chronic heart failure. J Am Coll Cardiol 2004;43:2028.
17. Lopez B, Gonzalez A, Beaumont J, Querejeta R, Larman M, Diez J. Identification of a potential cardiac antifibrotic mechanism of torasemide in patients with chronic heart failure. J Am Coll Cardiol 2007;50:859–67.
18. TORAFIC Investigators Group. Effects of prolonged-release torasemide versus furosemide on myocardial fibrosis in hypertensive patients with chronic heart failure: A randomized, blinded-end point, active-controlled study. Clin Ther 2011;33:1204-13.e3.
19. Bikdeli B, Strait KM, Dharmarajan K, Partovian C, Coca SG, Kim N, *et al*. Dominance of furosemide for loop diuretic therapy in heart failure: Time to revisit the alternatives? J Am Coll Cardiol 2013;61:1549–50.
20. Mullens W, Dauw J, Martens P, Verbrugge FH, Nijst P, Meekers E, *et al*. Acetazolamide in acute decompensated heart failure with volume overload. N Engl J Med 2022;387:1185-95.
21. Felker GM, Lee KL, Bull DA, Redfield MM, Stevenson LW, Goldsmith SR, *et al*. Diuretic strategies in patients with acute decompensated heart failure. N Engl J Med 2011;364:797-805.
22. Bart BA, Goldsmith SR, Lee KL, Redfield MM, Felker GM, O'Connor CM, *et al*. Cardiorenal rescue study in acute decompensated heart failure: Rationale and design of CARRESS-HF, for the Heart Failure Clinical Research Network. J Card Fail 2012;18:176-82.
23. Martens P, Verbrugge FH, Dauw J, Nijst P, Meekers E, Augusto SN, *et al*. Pre-treatment bicarbonate levels and decongestion by acetazolamide: The ADVOR trial. Eur Heart J 2023;44:1995-2005.
24. Trullàs JC, Morales-Rull JL, Casado J, Carrera-Izquierdo M, Sánchez-Marteles M, Conde-Martel A, *et al*. Combining loop with thiazide diuretics for decompensated heart failure: The CLOROTIC trial. Eur Heart J 2023;44:411-21.
25. Cox ZL, Hung R, Lenihan DJ, Testani JM. Diuretic strategies for loop diuretic resistance in acute heart failure: The 3 T trial. JACC Heart Fail 2020;8:157–68.
26. Cox ZL, Collins SP, Aaron M, Hernandez GA, Iii ATM, Davidson BT, *et al*. Efficacy and safety of dapagliflozin in acute heart failure: Rationale and design of the DICTATE-AHF trial. Am Heart J 2021;232:116-24.