Optimal Diuretic Strategies for Chronic Heart Failure

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KEYWORDS

• Loop diuretic • Lowest effective dose • Chronic heart failure • Monitoring
• Guideline-directed medical therapy • Torsemide • Furosemide

KEY POINTS

- Loop diuretics are Class I recommended for managing congestion; however, their effects on morbidity and mortality in chronic heart failure remain uncertain due to a lack of large-scale trials.
- Current guidelines emphasize using the lowest effective diuretic dose to achieve and maintain euvolemia, tailoring dosing to individual patient needs to minimize adverse effects.
- Personalized monitoring strategies, including regular clinical monitoring, biomarker-based monitoring and hemodynamic monitoring, is essential for guiding diuretic therapy and assessing volume status.
- Optimal implementation of guideline-directed medical therapy (GDMT)—particularly angiotensin receptor-neprilysin inhibitors, sodium-glucose cotransporter 2 inhibitors, and mineralocorticoid receptor antagonists—may be key to achieving the lowest effective loop diuretic dose in chronic heart failure.
- Optimizing loop diuretic dosing through personalized monitoring strategies and GDMT implementation may be more effective for improving clinical outcomes in heart failure than focusing on the choice of diuretic agent.

INTRODUCTION

Loop diuretics are recommended to alleviate the signs and symptoms of congestion in patients with chronic heart failure (HF).[1,2] Notably, loop diuretics hold a Class I recommendation across all ejection fraction spectrums in the chronic phase of HF. Although HF treatment guidelines have undergone significant revisions over time to incorporate emerging evidence and novel therapies, the recommendations regarding

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Med Clin N Am 109 (2025) 1241–1253
https://doi.org/10.1016/j.mcna.2025.04.004 **medical.theclinics.com**

Abbreviations	
ARNI	angiotensin receptor-neprilysin inhibitor
CI	confidence interval
GDMT	guideline-directed medical therapy
HF	heart failure
HFmrEF	HF with mildly reduced ejection fraction
HFpEF	HF with preserved ejection fraction
HFrEF	HF with reduced ejection fraction
HR	hazard ratio
MRA	mineralocorticoid receptor antagonist
NT-proBNP	N-terminal pro–B-type natriuretic peptide
NYHA	New York Heart Association
OR	odds ratio
RCT	randomized controlled trial
SGLT2i	sodium-glucose cotransporter-2 inhibitor

diuretic use have remained largely unchanged for decades.[1,2] Notably, the effects of loop diuretics on morbidity and mortality in chronic HF have not been evaluated in large-scale randomized controlled trials (RCTs), leaving these outcomes uncertain. Higher doses of loop diuretics and escalating diuretic requirements have been associated with worse prognosis, including increased risks of mortality and HF hospitalization. This highlights the need for careful dose titration to balance symptom relief with potential adverse effects. Furthermore, there is significant ambiguity regarding the choice of diuretic agents for long-term management (eg, torsemide vs furosemide). While many clinical reviews focus on diuretic strategies for *acute* HF, particularly adjunctive therapies for diuretic resistance and their short-term outcomes,[3–7] few have addressed diuretic strategies in the *chronic* phase of HF. In this article, we aim to provide a comprehensive overview of loop diuretic use in chronic HF, exploring the challenges, uncertainties, and future directions for optimizing long-term management strategies.

LIMITED LARGE-SCALE TRIALS OF LOOP DIURETICS ON MORTALITY IN CHRONIC HEART FAILURE

Loop diuretics are recommended as Class I therapy in chronic HF to manage congestion.[1,2] However, their effects on morbidity and mortality in chronic HF have not been studied in large-scale trials and remain uncertain. Some meta-analyses based on data from small trials suggest that conventional diuretics may reduce the risk of death and worsening HF compared to placebo in chronic HF patients. However, these meta-analyses included only small studies with limited follow-up, resulting in uncertain clinician significance and potentially overestimated reductions in events (eg, odds ratio [OR] 0.25, 95% confidence interval [CI] 0.07 to 0.84; $P = .03$ for mortality; OR 0.31, 95% CI 0.15 to 0.62; $P = .010$ for HF hospitalization).[8,9] Furthermore, a key meta-analysis was withdrawn in 2016 after the Cochrane Institute requested an update that was not completed.[10] Observational studies have shown an association between loop diuretic use (compared with no use) and a higher risk of mortality and HF hospitalization.[5] However, it is important to consider the inherent bias in these studies, as patients receiving loop diuretics typically present with more severe disease, which may confound these findings. Importantly, recent landmark trials for chronic HF treatments, including angiotensin receptor-neprilysin inhibitors (ARNI) and sodium-glucose cotransporter-2 inhibitors (SGLT2i), were conducted with a high background use of loop diuretics.[11–15] This suggests that the evidence supporting these newer medications is based on their use in

conjunction with loop diuretic therapy. In summary, while loop diuretics are widely recommended as Class I therapy in chronic HF guidelines and remain a cornerstone of routine clinical practice, their effects on long-term outcomes remain unclear. Further investigation through well-designed, large-scale trials is warranted to better understand their effects on morbidity and mortality in chronic HF patients.

OPTIMAL DOSE OF LOOP DIURETICS IN CHRONIC HEART FAILURE: FINDING THE LOWEST EFFECTIVE DOSE

In real-world clinical practice, approximately 80% to 90% of patients with chronic HF require a maintenance dose of oral loop diuretics to achieve and maintain euvolemia.[16,17] However, the optimal dose of loop diuretics for chronic HF remains uncertain. While patients with more significant congestion may benefit from higher doses of loop diuretics as maintenance therapy, the use of high doses may lead to adverse effects, including electrolyte disturbances, deleterious neurohormonal activation (eg, heightened activity of the renin-angiotensin-aldosterone system and sympathetic nervous system), worsening renal function, and symptomatic hypotension. Observational studies have also demonstrated an association between higher doses of loop diuretics and increased risks of mortality and HF hospitalization compared with lower doses.[18–22] As a result, current recommendations emphasize the use of the *lowest effective dose of diuretics* to achieve and maintain euvolemia, with dosing tailored to the individual needs of each patient. To guide clinical practice, this article explores strategies to achieve the lowest effective diuretic dose, including personalized monitoring and the implementation of guideline-directed medical therapy (GDMT), based on current best practices and available evidence (**Fig. 1**).

STRATEGIES FOR ACHIEVING THE LOWEST EFFECTIVE DIURETIC DOSE IN CHRONIC HEART FAILURE

Maintaining euvolemia while minimizing diuretic use in patients with chronic HF requires a multifaceted approach. Key strategies include personalized monitoring

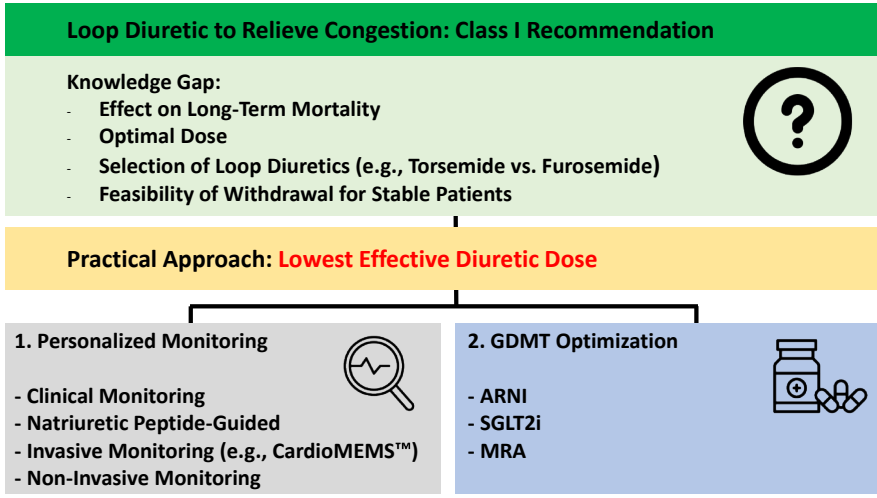

Fig. 1. Optimal diuretic strategies for chronic HF. ARNI, angiotensin receptor-neprilysin inhibitor; GDMT, guideline-directed medical therapy; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium-glucose cotransporter 2 inhibitor.

strategies (eg, regular clinical monitoring, biomarker-based monitoring, and hemodynamic monitoring), and medical management, particularly through initiating and optimizing GDMT. Advances in these areas provide opportunities to tailor treatment, reduce diuretic dependence, and mitigate complications associated with chronic loop diuretic use.[23]

PERSONALIZED MONITORING STRATEGIES

Clinical Monitoring

Clinical monitoring is essential to ensure effective diuretic management. Regular assessment of symptoms, orthostatic blood pressure, and patient-reported outcomes such as the Kansas City Cardiomyopathy Questionnaire helps evaluate volume status.[1] Monitoring electrolyte levels and renal function is also necessary, as excessive diuresis can cause imbalances and worsen kidney function.

Guidelines do not specify the exact frequency for laboratory testing,[1] but expert recommendations suggest assessing renal function and electrolytes about 3 times per year in stable patients.[24] More frequent monitoring is needed when adjusting diuretic therapy or in patients at higher risk, such as those with chronic kidney disease or those on high-dose diuretics or renin-angiotensin-aldosterone system inhibitors. Laboratory tests should be repeated after any dose adjustment, with timing based on the patient's condition and treatment changes.

While daily weight monitoring and fluid restrictions have traditionally been recommended, their role in guiding diuretic therapy remains uncertain. The 2022 American Heart Association (AHA)/American College of Cardiology (ACC)/Heart Failure Society of America (HFSA) guidelines do not mandate strict fluid restriction but suggest it may be useful in selected patients.[1] A tailored approach combining symptom tracking and laboratory monitoring can help optimize diuretic therapy while avoiding unnecessary restrictions.

Biomarker-Based Monitoring

Serial measurements of natriuretic peptides have been proposed as a tool to guide GDMT titration, improve clinical outcomes, and adjust diuretic dosing. However, clinical studies evaluating this strategy have yielded mixed results.[25–31] The GUIDE-IT trial, a multicenter RCT, evaluated whether natriuretic peptide-guided therapy improves clinical outcomes compared with usual care in high-risk patients with HF with reduced ejection fraction (HFrEF).[32] Patients in the natriuretic peptide-guided group had therapy titrated to achieve N-terminal pro–B-type natriuretic peptide (NT-proBNP) levels below 1000 pg/mL, while the usual care group received standard treatment without routine NT-proBNP monitoring. The trial was stopped early for futility after enrolling 894 patients, with no significant difference in the primary endpoint of HF hospitalization or cardiovascular mortality (hazard ratio [HR] 0.98, 95% CI 0.79 to 1.22; $P = .88$). Notably, natriuretic peptide guided management did not lead to a reduction in diuretic use. These findings suggest that natriuretic peptide-guided therapy does not provide additional benefits over guideline-directed care in optimizing diuretic strategies.

Invasive Monitoring

Among invasive monitoring strategies, the CardioMEMS Heart Sensor has demonstrated efficacy in reducing HF-related hospitalizations through pulmonary artery pressure monitoring. The CHAMPION trial, a multicenter RCT, evaluated the effectiveness of a wireless implantable hemodynamic monitoring system in patients with New York Heart Association (NYHA) class III HF and a prior HF hospitalization.[33]

The study enrolled 550 patients and found that pulmonary artery pressure-guided management significantly reduced HF-related hospitalizations at 6 months compared to standard care (HR 0.72, 95% CI 0.60–0.85), with a sustained 37% reduction over the entire follow-up period (HR 0.63, 95% CI 0.52–0.77). In addition to reducing hospitalization rates, the CHAMPION trial reported an increase in the number of medication adjustments, including diuretics, based on pulmonary artery pressure data. Notably, dose increases were more common than reductions, highlighting the role of this monitoring strategy in optimizing volume management rather than minimizing diuretic use.

The GUIDE-HF trial also used hemodynamic-guided management and expanded on these findings by including a broader HF population (NYHA class II–IV) with either recent HF hospitalization or elevated natriuretic peptides.[34] The trial enrolled 1,022 patients but found no significant reduction in the primary composite endpoint of all-cause mortality and total HF events (HR 0.88, 95% CI 0.74–1.05). A pre-coronavirus disease 2019 (COVID-19) analysis suggested a reduction in HF events (HR 0.76, 95% CI 0.61–0.95), primarily driven by fewer HF hospitalizations (HR 0.72, 95% CI 0.57–0.92). The MONITOR-HF trial, conducted in the Netherlands, evaluated pulmonary artery pressure-guided management in 348 patients with NYHA class III HF.[35] The study demonstrated improvements in quality of life and a 44% reduction in HF hospitalizations (HR 0.56, 95% CI 0.38–0.84). While these trials assessed pulmonary artery pressure monitoring for HF management, neither GUIDE-HF nor MONITOR-HF specifically evaluated its effect on diuretic use.

Noninvasive Monitoring

Several noninvasive monitoring strategies have emerged and received US Food and Drug Administration approval, with additional technologies currently under development.[36] Approved devices include the Bodyport cardiac scale, remote dielectric sensing, Sensinel cardiopulmonary management system, and ZOLL heart failure management system. However, none have demonstrated a reduction in diuretic requirements.[37–40] Further research is needed to clarify whether such strategies influence diuretic dosing and volume management in HF.

GUIDELINE-DIRECTED MEDICAL THERAPY OPTIMIZATION

Optimizing GDMT is another key strategy to minimize loop diuretic use in chronic HF. GDMT consists of 3 primary classes of medications that have been shown to influence diuretic dosing: (1) ARNI—enhances natriuresis and diuresis through neprilysin inhibition while reducing neurohormonal activation, potentially decreasing the reliance on loop diuretics; (2) SGLT2i—promote osmotic diuresis and natriuresis, leading to reduced fluid retention and potentially lowering diuretic requirements; (3) Mineralocorticoid receptor antagonists (MRAs)—improve sodium excretion and reduce aldosterone-mediated fluid retention, which may contribute to a lower need for loop diuretics. Several studies in patients with HFrEF, HF with mildly reduced ejection fraction (HFmrEF), and HF with preserved ejection fraction (HFpEF) have demonstrated the potential for GDMT to reduce loop diuretic requirements.

Angiotensin Receptor-Neprilysin Inhibitors

The PARADIGM-HF trial (n = 8,399) compared sacubitril/valsartan with enalapril in HFrEF patients and assessed loop diuretic dose requirements over time.[41] Patients receiving sacubitril/valsartan were more likely to reduce their diuretic dose, with dose reductions of 2.0% at 6 months, 4.1% at 12 months, and 6.1% at 24 months. A post

hoc analysis of the PARAGON-HF trial (n = 4,796) suggested a trend toward reduced new diuretic initiation with sacubitril/valsartan compared to valsartan in HFpEF, although mean loop diuretic dose and discontinuation rates remained unchanged.[42]

Sodium-Glucose Cotransporter-2 Inhibitors

In the EMPEROR-Reduced trial (n = 3,730), empagliflozin reduced the need for diuretic intensification compared to placebo (297 vs 414, HR 0.67 [95% CI 0.56–0.78]).[43] Similarly, the DAPA-HF trial (n = 4,616) found that patients receiving dapagliflozin were more likely to experience a reduction in diuretic dose (12.4% vs 8.7%) and less likely to require dose intensification (10.2% vs 14.2%).[44] In HFpEF, a post hoc analysis of the EMPEROR-Preserved trial (n = 5,988) demonstrated that empagliflozin was associated with a decreased likelihood of diuretic intensification (HR 0.74, 95% CI 0.65–0.84) and an increased likelihood of de-escalation (HR 1.15, 95% CI 1.02–1.30).[45] The DELIVER trial (n = 6,263) in patients with HFpEF showed that dapagliflozin was associated with a 32% reduction in new diuretic initiation (HR 0.68, 95% CI 0.55–0.84), though it did not significantly influence diuretic discontinuation.[46] Of note, patients who did have dose reductions or diuretic discontinuation were more likely to be in the dapagliflozin arm (14.7% vs 16.5%, $P<.001$) with a net reduction in furosemide equivalent dose of −6.5% (CI, −9.4 to −3.6).

Mineralocorticoid Receptor Antagonists

The EPHESUS trial (n = 6,632) evaluated the effect of eplerenone, in addition to standard medical therapy, on loop diuretic use in patients with systolic dysfunction following myocardial infarction. At the 180-day follow-up, 14.2% of patients in the placebo group required furosemide equivalent doses greater than 40 mg/day, compared to 11.6% in the eplerenone group, with this difference persisting at 270 and 360 days.[47] The RALES trial, which demonstrated significant reductions in mortality and hospitalization with spironolactone in patients with HFrEF, did not specifically report whether MRA use led to a reduction in loop diuretic doses.

In summary, although no RCTs have specifically evaluated the strategy of minimizing loop diuretic doses through the optimization of GDMT, post hoc analyses of trial datasets suggest that the appropriate use and titration of GDMT—particularly ARNI, SGLT2i, and MRA—may be effective in achieving the lowest effective loop diuretic dose in chronic HF.

FEASIBILITY OF DIURETIC WITHDRAWAL FOR STABLE PATIENTS

The potential for diuretic withdrawal in select HF patients warrants consideration to support pharmacotherapy optimization. In certain euvolemic, clinically stable individuals, tapering or discontinuing diuretics may be a viable approach. A prospective study involving 50 ambulatory HF patients, who had been on stable neurohormonal blockade and diuretic therapy for at least 3 months without signs of volume overload, assessed the feasibility of loop diuretic down-titration and withdrawal.[48] The criterion for successful down-titration was maintaining a reduced diuretic dose for 30 days without weight gain exceeding 1.5 kg or the emergence of HF symptoms. At the 30-day follow-up, 62% of patients successfully maintained the lower dose, suggesting that diuretic reduction is feasible in a subset of stable chronic HF patients.

Additionally, an RCT conducted in Brazil involving 188 patients further explored this strategy.[49] In individuals characterized as low-risk—defined by an oral furosemide dose of lesser than 80 mg daily, absence of recent HF hospitalizations, and optimized GDMT—loop diuretic withdrawal did not lead to worsening symptoms or a need for

diuretic reinstatement when compared to continued diuretic use over a 90-day follow-up period. Although these findings are limited by small sample sizes, they indicate that carefully monitored diuretic withdrawal may be a safe and feasible approach in select HF patients. Further research is needed to refine patient selection criteria and establish best practices for diuretic tapering in clinical settings.

SELECTION OF LOOP DIURETICS IN CHRONIC HEART FAILURE

The optimal choice of loop diuretic in chronic HF remains uncertain, particularly between furosemide and torsemide. Although furosemide is more commonly prescribed, torsemide offers pharmacokinetic advantages, including more predictable gastrointestinal absorption, higher bioavailability (80%–100%), a longer half-life, and extended duration of action.[50–52] These properties contribute to more sustained diuresis and potentially lower rates of hypokalemia. Additionally, torsemide has been suggested to exert neurohormonal effects, including aldosterone inhibition, which may improve cardiac remodeling and reduce myocardial fibrosis.[53–56] Observational studies and small trials have reported that torsemide may reduce HF hospitalizations and improve survival compared to furosemide.[57–60] However, no large-scale RCTs had confirmed these benefits until the TRANSFORM-HF trial, which aimed to determine whether torsemide's pharmacokinetic advantages translate into improved clinical outcomes (**Table 1**).[61]

TRANSFORM-HF was an open-label, pragmatic RCT that randomized 2,859 hospitalized HF patients to either torsemide or furosemide, with dosing determined by treating clinicians. The trial found no significant difference in all-cause mortality between torsemide and furosemide (HR 1.02, 95% CI 0.89–1.18) over a median follow-up of 17.4 months. Similarly, there was no significant difference in all-cause mortality or hospitalization at 12 months (HR 0.92, 95% CI 0.83–1.02) or total hospitalizations (rate ratio 0.94, 95% CI 0.84–1.07). A subanalysis assessing patient-reported symptoms and quality of life also demonstrated no significant differences.[62] These findings suggest that, rather than focusing on the choice between torsemide and furosemide, clinical efforts should be directed toward optimizing loop diuretic dosing and prioritizing GDMT implementation to improve long-term outcomes in HF patients.

SUMMARY AND FUTURE DIRECTIONS

This article provides a comprehensive evaluation of loop diuretic use in chronic HF, highlighting persistent uncertainties and challenges in optimizing long-term management of loop diuretics. Notably, the effects of loop diuretics on morbidity and mortality remain unexamined in large-scale trials, leaving their effect on clinical outcomes uncertain. While loop diuretics play a crucial role in managing congestion, their use must be carefully balanced against potential adverse effects, such as electrolyte disturbances, neurohormonal activation, and renal dysfunction.

Current recommendations advocate for the lowest effective diuretic dose tailored to individual patient needs. However, the optimal dosing strategy remains undefined, highlighting the need for further research. The feasibility of diuretic withdrawal in stable chronic HF patients also warrant investigation, as emerging data suggest that some patients may maintain clinical stability without chronic diuretic use.

Minimizing loop diuretic use through the optimization of GDMT—particularly with ARNIs, SGLT2i, and MRAs—represents a promising approach to improving volume management and long-term outcomes. Additionally, advancements in monitoring strategies, including biomarkers, CardioMEMS, and remote patient monitoring, may

Table 1
Summary of the TRANSFORM-HF trial

Rationale for the potential advantages of torsemide over furosemide	Consistent and predictable absorption pattern, with a bioavailability of 80%–100% regardless of food intake Longer half-life (3.5 vs 2.0 h for furosemide) and an extended duration of action (6–16 h vs 6–8 h for furosemide) Potential favorable effects on neurohormonal activation Possible reduction in myocardial fibrosis and improvement in cardiac remodeling
Study aim	To compare the treatment strategy of torsemide vs furosemide on long-term clinical outcomes among patients hospitalized with HF.
Trial design	An open-label, pragmatic trial conducted at 60 centers in the US from 2018-2022, enrolling 2,859 patients with HF who were randomized 1:1 to a loop diuretic strategy of torsemide or furosemide. The median follow-up duration was 17.4 mo.
Primary endpoint	All- cause mortality
Secondary endpoints	• Composite of all-cause mortality or all-cause hospitalization • Total hospitalizations assessed over 12 mo
Results	• *No significant difference in all -cause mortality:* 26.1% in the torsemide group vs 26.2% in the furosemide group (HR 1.02, 95% CI 0.89–1.18) • *No significant difference in all-cause mortality or all-cause hospitalization:* 47.3% in the torsemide group vs 49.3% in the furosemide group (HR, 0.92, 95% CI 0.83–1.02) • *No significant difference in total hospitalizations* 940 events in the torsemide group vs 987 in the furosemide group (rate ratio, 0.94, 95% CI 0.84–1.07) • *No significant improvement in symptoms or quality of life with torsemide over furosemide*
Clinical implications	A torsemide-based strategy demonstrated similar effectiveness to a furosemide-based strategy in terms of mortality and hospitalization outcomes in patients with HF. Clinical focus should be placed on optimizing diuretic dosing and prioritizing the initiation and titration of GDMT rather than selecting between torsemide and furosemide.

facilitate individualized diuretic adjustments to ensure euvolemia with the lowest effective dose.

The selection of loop diuretics remains a topic of debate. While prior studies suggested pharmacologic advantages of torsemide over furosemide, the TRANSFORM-HF trial found no significant differences in mortality, hospitalization rates, symptoms, or quality of life between the 2 agents. These findings indicate that clinical focus should shift away from diuretic selection and instead prioritize appropriate diuretic dosing and GDMT implementation.

Future research should refine diuretic dosing strategies and explore the role of combination therapies within the broader framework of GDMT-driven chronic HF management.

In conclusion, loop diuretics remain essential in chronic HF management, but their role must be redefined within the context of optimized GDMT and personalized care. Shifting the clinical focus toward minimizing loop diuretic use through GDMT

optimization and personalized treatment approaches, rather than diuretic selection, may lead to improved long-term outcomes in chronic HF patients.

CLINICS CARE POINTS

- Loop diuretics are Class I recommended for managing congestion; however, their effects on morbidity and mortality in chronic heart failure remain uncertain due to a lack of large-scale trials.
- Current guidelines emphasize using the lowest effective diuretic dose to achieve and maintain euvolemia, tailoring dosing to individual patient needs to minimize adverse effects.
- Personalized monitoring strategies, including regular clinical monitoring, biomarker-based monitoring and hemodynamic monitoring, is essential for guiding diuretic therapy and assessing volume status.
- Routine renal function and electrolyte monitoring help prevent adverse effects of diuretics. While guidelines do not specify exact intervals, expert recommendations suggest testing approximately three times per year in stable patients and more frequently after dose adjustments or in high-risk individuals.
- Optimal implementation of guideline-directed medical therapy (GDMT)—particularly angiotensin receptor-neprilysin inhibitors, sodium-glucose cotransporter 2 inhibitors, and mineralocorticoid receptor antagonists—may be key to achieving the lowest effective loop diuretic dose in chronic heart failure.
- Torsemide and furosemide show no significant differences in mortality, hospitalization, symptoms, or quality of life, as demonstrated in the TRANSFORM-HF trial.
- Optimizing loop diuretic dosing through personalized monitoring strategies and GDMT implementation may be more effective for improving clinical outcomes in heart failure than focusing on the choice of diuretic agent.

DECLARATION OF AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

During the preparation of this work the author(s) used Gen AI. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

SOURCE OF FUNDING

None.

DISCLOSURES

Dr R.J. Mentz has received research support and/or honoraria from Novartis, Abbott, American Regent, United States, Amgen, United States, AstraZeneca, United Kingdom, Bayer, Germany, Boehringer Ingelheim, United States, Boston Scientific, Cytokinetics, United States, Fast BioMedical, Gilead, United States, Innolife, Eli Lilly, Medtronic, Medable, Merck, United States, Novo Nordisk, Denmark, Pharmacosmos, Relypsa, United States, Respicardia, United States, Roche, Switzerland, Sanofi, United States, Vifor, Windtree Therapeutics, United States, and ZOLL, United States.

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