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Diuretic Treatment in Heart Failure--from Physiology to Clinical Trials

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INTRODUCTION

Most accepted pharmacologic treatments for heart failure are supported by evidence from large clinical trials. In contrast, diuretics, among the most frequently used drugs in heart failure, generally lack such evidence to guide their use. Fluid retention and congestion are hallmarks of heart failure, and are associated with both more severe symptoms and worse outcomes.¹ Given the centrality of congestion to both symptoms and outcomes, diuretics remain cornerstones of heart failure management despite very limited controlled data.² Although routine diuretic treatment of heart failure may appear uncomplicated, questions abound about how best to utilize diuretics, particularly in settings of acute decompensated heart failure (ADHF) and diuretic resistance. In this review, we update pharmacological principles of diuretic therapy, integrate data from recent research, and suggest evidence-based approaches to diuretic treatment of heart failure.

Loop Diuretics--Pharmacology

Furosemide, bumetanide, and torsemide are prototypic loop diuretics; they bind to the translocation pocket at the extracellular surface of sodium-potassium-chloride symporters (NKCCs), blocking ion transport directly³ (Fig. 1). These drugs inhibit a sodium-potassium-chloride symporter at the apical surface of thick ascending limb cells along the loop of Henle (NKCC2, gene *SLC12A1*). This transporter reabsorbs (directly and indirectly) up to 25% of filtered salt; its blockade is responsible for most natriuretic effects of loop diuretics.

Loop diuretics also inhibit the same symporter at the apical membrane of macula densa cells, stimulating renin secretion,⁴ and inhibiting tubuloglomerular feedback.⁵ These effects may be both salutary and harmful, because elevated plasma renin activity increases angiotensin II, while blocking tubuloglomerular feedback helps to maintain the glomerular filtration rate.

Loop diuretics also inhibit a second sodium-potassium-chloride symporter isoform, NKCC1 (Gene *SLC12A2*), which is widely expressed throughout the body, including in the ear, likely explaining their ototoxicity.⁶ When administered intravenously, loop diuretics vasodilate, in part by inhibiting NKCC1 in vascular smooth muscle cells.⁷ NKCC1 is also expressed by cells of the afferent arteriole and extraglomerular mesangium in the kidney, where it suppresses basal renin secretion.⁸ Blockade may contribute to elevation of renin secretion and angiotensin II generation.

Loop diuretics have complex effects on renal and systemic hemodynamics, which are influenced by the dose and route of administration, concomitant disease and treatment, and chronicity of use. As noted, loop diuretics activate the renin-angiotensin-aldosterone system and dilate blood vessels directly, but they also increase vasodilatory prostaglandins, and the pressure within the proximal tubule.⁷ The results of these sometimes counteracting effects are that high dose intravenous loop diuretics can decrease or increase arterial pressure, increase or decrease stroke volume,⁹ and decrease renal blood flow. It is difficult to predict, in an individual patient, which effects will predominate.

Loop diuretics are organic anions, which circulate bound to proteins (>90%), limiting their volumes of distribution. Thus, loop diuretics do not enter tubule fluid by glomerular filtration, but require secretion across the proximal tubule, via organic anion transporters and the Multidrug Resistance–Associated Protein 4 (Fig. 1).¹⁰ Genetic deletion of organic anion transporters in mice leads to diuretic resistance,^{11,12} a phenomenon mimicked in humans, when non-steroidal anti-inflammatory drugs or endogenous uremic anions, compete for loop diuretic secretion (see Table 1).

Loop Diuretic Pharmacokinetics

Loop diuretics exhibit steep dose response curves, with plateaus often reached at commonly employed doses (Fig. 2). They are often called *threshold drugs*, suggesting that raising doses beyond a ‘ceiling’ will not increase their effect. While this is true of natriuretic efficiency, Figure 2 demonstrates that raising the dose above this nominal ‘ceiling’ causes additional natriuresis by increasing the time during which the plasma diuretic concentration exceeds the natriuretic threshold; this makes it appear as if a ceiling does not exist. When administered orally, furosemide exhibits limited and highly variable bioavailability (mean~50%, range 10–90%).¹³ Food intake delays furosemide absorption,¹⁴ reducing its peak concentration. As the furosemide excretion half-life is shorter than its gastrointestinal absorption rate, the drug exhibits absorption-limited pharmacokinetics,¹⁴ meaning that the apparent half-life following oral use is longer than the excretion half-life. For individuals with preserved kidney function, intravenous furosemide doses are approximately twice as potent on a per milligram basis as oral doses. In contrast, when sodium retention is more avid, as in acute decompensated heart failure, a higher *peak* level may be required and an intravenous dose may be more effective (Fig. 2). Although gut edema and low duodenal blood flow do not typically affect oral bioavailability (amount absorbed/amount ingested), they slow absorption, thereby reducing peak plasma levels, and contributing to diuretic resistance (Fig. 2B).¹⁵

The other loop diuretics, bumetanide and torsemide, exhibit higher and more consistent oral bioavailability (>90%), and do not exhibit absorption-limited kinetics, making oral and intravenous doses more comparable. While bumetanide and torsemide are both well absorbed, torsemide has a longer half-life in heart failure (6 hours) compared furosemide (2.7 hours, although prolonged in chronic kidney disease¹⁶) or bumetanide (1.3 hours)¹⁷. As a longer half-life reduces the time during which a diuretic level is below the natriuretic threshold (see Fig. 2C), one might expect that torsemide should be more effective during typical dosing regimens, but data to support this suggestion are limited.¹⁸ A systematic analysis of torsemide versus furosemide comparative effectiveness suggested that torsemide reduced heart failure readmissions,¹⁹ but available data are limited and the question is well-suited for definitive clinical trials.²⁰

The goal of loop diuretic treatment of heart failure is not simply to increase urinary salt excretion, but rather to achieve negative salt and water balance over the short term (decongestion), and reduce extracellular fluid volume chronically. Because loop diuretic half-lives are shorter than typical dosing intervals (often twice daily), and because they inhibit solute transport primarily along only one of several sodium-reabsorbing nephron segments, their effects on extracellular fluid volume are complex. A loop diuretic dose increases urine sodium excretion for several hours, but this is followed a period of very low sodium excretion, often termed 'post-diuretic Na⁺ retention'. To induce negative Na⁺ balance, salt excretion during 24 hours must exceed salt intake. When dietary salt intake is high, post-diuretic Na⁺ retention will offset the initial natriuresis, especially if the dosing interval is long. In contrast, low salt intake permits urinary Na⁺ excretion to exceed intake (Fig. 2C), emphasizing the importance of dietary salt intake, drug half-life, and dosing interval, especially for chronic heart failure.²¹

When extracellular fluid volume declines, a second type of adaptation occurs, during which the natriuretic response to each dose falls; this is frequently termed the 'braking phenomenon' (Fig. 2C), and may involve activation of the sympathetic nervous and renin-angiotensin-aldosterone systems, nephron remodeling and extracellular fluid volume depletion itself.²² If braking did not occur, long term diuretic treatment would cause relentless extracellular fluid volume contraction, but when this occurs in the setting of persistent congestion, it contributes to diuretic resistance. Thus, the same mechanisms may contribute to both diuretic resistance and diuretic adaptation.

Loop Diuretic Use in Acute Decompensated Heart Failure

The limited evidence to guide diuretic use in heart failure is reflected in contemporary practice guidelines, which give diuretics a class I recommendation but based on level B or C evidence.^{23,24} Furthermore, high diuretic doses, which stimulate the renin-angiotensin-aldosterone and sympathetic nervous systems, have been associated with worse outcomes, raising the possibility that they should be avoided.^{25–27} The Diuretic Optimization Strategies Evaluation (DOSE) study evaluated the optimal approach to diuretic dosing and route of administration for patients with acute decompensated heart failure.²⁸ Using a 2 × 2 factorial 'double dummy' design, DOSE randomized 308 acute decompensated heart failure patients

to furosemide, given as twice daily intravenous boluses or continuous infusion, and either 'low doses' (equal to the patient's home oral dose) or 'high doses' (2.5 times the oral dose).

For comparison of high and low doses, differences in the patient's global assessment of symptoms did not reach statistical significance, but the high dose group had more favorable outcomes with regard to several pre-specified secondary measures, including relief of dyspnea, change in weight, and net fluid loss. Worsening renal function (defined as increase in serum creatinine >0.3 mg/dl within 72 hours) occurred more often in the high dose arm, but a *post hoc* analysis found that an initial rise in serum creatinine was associated with better, rather than worse, clinical outcomes.²⁹ This has been recognized in other datasets, as well.³⁰ Although renin-angiotensin-aldosterone system activation has been suggested to be an adverse consequence of high dose diuretic use, randomization to the high dose regimen in the DOSE study did not lead to greater activation of the renin-angiotensin-aldosterone system compared to the low dose regimen, although this analysis is limited by lack of standardization of timing and the inherent variability of plasma renin activity measurements.³¹ Thus, while observational data suggest that high diuretic doses are associated with higher mortality in heart failure,²⁶ the DOSE study provides reassurance about the safety and utility of this approach in heart failure, with the caveat that DOSE was not powered to evaluate clinical outcomes.

There was no difference in the DOSE study between bolus and infusion approaches for the primary endpoints, patient global assessment of symptoms and change in serum creatinine at 72-hours, findings confirmed in a smaller trial.³² Although these data do not support using continuous diuretic infusions for acute decompensated heart failure, several caveats should be mentioned. Continuous infusions were not routinely preceded by loading doses in the DOSE trial, which speed achievement of steady state.¹⁷ The initial furosemide infusion rates averaged 5 (for low dose) and 14 mg/hour (for high dose), which are lower than often recommended (¹⁷, and Table 2); Finally, the population studied was not selected for resistance to diuretics, and did not have substantial kidney dysfunction (mean plasma creatinine concentration 1.5 mg/dL). Thus, while initial treatment with furosemide at a daily dose of $2.5 \times$ the home dose given as twice daily boluses is an appropriate initial strategy for most patients, ongoing assessment of clinical response is imperative, and specific clinical scenarios (such as diuretic resistance, cardiorenal syndrome, and severe right ventricular dysfunction) may respond better to continuous infusion therapy, as discussed below.

Adjuncts to Diuretic Treatment

Although renal salt retention is the major determinant of congestion in heart failure, hyponatremia, reflecting water accumulation, is common and portends a poor prognosis.³³ The oral vasopressin-2 receptor antagonist tolvaptan inhibits the action of anti-diuretic hormone and increases free water excretion (aquaresis).³⁴ The large-scale Efficacy of Vasopressin Antagonist in Heart Failure Outcome Study with Tolvaptan (EVEREST), which evaluated patients hospitalized for heart failure (with or without hyponatremia) did not demonstrate superiority of tolvaptan over placebo in terms of long-term clinical outcomes, although potentially beneficial effects on volume status and symptoms were observed in the initial treatment days.³⁵ Subsequently, smaller trials, which focused on the use of tolvaptan

in patients with lower serum sodium levels in order to achieve short term decongestion, did not show significant improvement in symptoms or clinical outcomes, despite leading to greater weight and fluid loss.^{36,37}

Low renal blood flow contributes to sodium retention in acute decompensated heart failure by limiting Na^+ filtration, increasing Na^+ reabsorption, and reducing renal diuretic delivery to the proximal tubule. As dopamine increases renal blood flow and urinary Na^+ excretion at low doses,^{38,39} it might therefore augment natriuresis. Similar considerations apply to natriuretic peptides. The Renal Optimization Strategies Evaluation in Acute Heart Failure (ROSE-AHF) study randomized 360 patients hospitalized for acute decompensated heart failure with impaired renal function to furosemide plus either dopamine infusion (2 $\mu\text{g}/\text{kg}/\text{min}$), nesiritide (0.005 $\mu\text{g}/\text{kg}/\text{min}$), or placebo.⁴⁰ Neither drug affected the co-primary endpoints of urine volume or change in cystatin C level during 72 hours; despite the low dose, dopamine infusion was, however, associated with tachycardia (7% for dopamine vs. 1% for placebo, $p > 0.001$). A post hoc subgroup analysis suggested that the effects of low dose dopamine differed by heart failure subtype; in patients with heart failure with reduced ejection fraction dopamine may have enhanced decongestion and improved prognosis, providing an impetus to further study.⁴¹

Although nearly all patients with heart failure with reduced ejection fraction receive drugs that block the renin-angiotensin-aldosterone system, aldosterone breakthrough is common.⁴² Mineralocorticoid antagonists such as spironolactone improve mortality in heart failure with reduced ejection fraction, but are used at low doses (25 mg) to avoid hyperkalemia. Several small studies suggested that higher “natriuretic doses” of mineralocorticoid antagonists might improve decongestion in acute decompensated heart failure.⁴³ The ATHENA study randomized 360 patients with acute decompensated heart failure and congestion to 96 hours of spironolactone (100mg daily) or placebo (low dose spironolactone was continued)[ref when available]. Spironolactone did not improve the primary endpoint of decongestion (as measured by change in NT-proBNP) or secondary endpoints, including symptom improvement and decongestion; plasma potassium concentration was not affected, however, suggesting incomplete mineralocorticoid receptor blockade.

When diuretics fail to achieve decongestion despite maximal doses, the patient is typically deemed *diuretic resistant*. Single doses of furosemide of 250 mg are often considered to be maximal, although recommendations vary.⁴⁴ Diuretic resistant patients are at high risk for morbidity and mortality,⁴⁵ and this scenario is frequently associated with kidney dysfunction, often termed the *cardiorenal syndrome*. Several causes of, and potential approaches to, this diminution of loop diuretic efficacy can be deduced by considering the pharmacokinetic and pharmacodynamics factors discussed above (Table 1).⁴⁶

Nephron Remodeling—The nephron comprises a set of molecularly distinct segments, arranged in series, each contributing to net Na^+ reabsorption (Fig. 3). Loop diuretics primarily inhibit salt reabsorption along the thick ascending limb, but they do not increase Na^+ excretion as much as they inhibit salt transport because they indirectly stimulate distal segments to augment their reabsorptive rates. Net salt excretion, then, reflects the balance

between inhibition at the primary site of diuretic action and stimulation distally (and perhaps proximally).

When diuretic use is chronic, additional changes occur, including remarkable distal remodeling, with hypertrophy of the distal convoluted tubule,^{47,48} connecting tubule and collecting duct (Fig. 3). These effects involve not only classical Na⁺ transporting cells, but also intercalated cells,⁴⁹ which participate in chloride reabsorption as well as acid base homeostasis; novel biomarkers for remodeling have been suggested.^{50,51}

One signaling pathway contributing to nephron remodeling is the renin-angiotensin-aldosterone system. Activation of thiazide-sensitive NaCl cotransporter (NCC) during chronic furosemide infusion is partially aldosterone mediated,⁵² and aldosterone classically activates the epithelial sodium channel. A second mechanism involves increased luminal solute and fluid delivery to distal segments, which increases transepithelial solute flux and obligates new protein synthesis.⁵³ A third mechanism involves systemic metabolic effects, including metabolic alkalosis⁵⁴ and hypokalemia. Even modest declines in plasma potassium concentration are associated with worse prognosis;⁵⁵ this pathway strongly activates the sodium-chloride symporter,^{56–59} and is tightly linked to distal convoluted tubule remodeling.⁶⁰ Finally, circulating proteases filtered in heart failure and kidney disease may directly activate the epithelial sodium channel.⁶¹

Treatment of Diuretic Resistance—Diuretic resistance is defined as failure to achieve decongestion, with low urine sodium concentration, despite the use of maximal recommended doses. Continuous infusion diuretic therapy is frequently employed in this setting. A *post hoc* analysis has suggested that a stepped care pharmacological approach (Table 2) focused on aggressive diuretic therapy titrated to produce urine volume of 3–5 L/day may be superior to standard decongestive therapy in patients with cardiorenal syndrome.^{62,63} Although limited, these data represent a reasonable structured approach to this challenging clinical scenario.

Activation of the renin-angiotensin-aldosterone system contributes to the shifted diuretic response curve observed in acute decompensated heart failure (Fig. 2), making this system a tempting target. Yet, the effects of angiotensin converting enzyme inhibitors and angiotensin receptor blockers are complex; the drugs have direct natriuretic effects, because they inhibit Na⁺ reabsorption along the nephron, and can inhibit natriuresis, because they lower arterial pressure. In heart failure with reduced ejection fraction, their effects on afterload commonly dominate and they are typically continued. In contrast, renin-angiotensin-aldosterone blockade may be detrimental with preserved ejection fraction, where afterload reduction does not increase cardiac output.⁶⁴

Nephron remodeling may also be a therapeutic target. Testani and colleagues⁶⁵ used fractional sodium and lithium clearances to show that up to 75% of diuretic resistance in acute decompensated heart failure could be attributed to activation of salt transport along the distal nephron. Given this, drugs that block salt reabsorption there (such as metolazone or other thiazide type drugs) should be useful, although the efficacy and safety of this approach (termed “sequential nephron blockade”) has not been evaluated in adequately powered

clinical trials.⁴⁶ Combining the two diuretic classes can sometimes lead to massive natriuresis and kaliuresis, however, warranting careful monitoring during chronic treatment. Small studies suggest that oral metolazone is as effective as intravenous chlorothiazide.^{66,67} Amiloride might also prove useful to block activated sodium channels,⁶¹ and carbonic anhydrase inhibitors, which inhibit the chloride/bicarbonate exchanger pendrin,⁷⁴ may be especially useful when metabolic alkalosis occurs.⁷³

The optimal timing of sequential nephron blockade in heart failure remains uncertain. Traditionally, a second class of diuretic is added after resistance has developed, by which time the distal nephron is extensively remodeled. An alternative approach would be to introduce low dose sequential blockade earlier,⁶⁸ although supportive data are lacking. Sodium glucose cotransporter (SGLT2) inhibitors reduce the incidence of heart failure and are subjects of ongoing clinical investigation.⁶⁹

Other Approaches and Future Directions

Mechanical ultrafiltration is theoretically attractive to remove salt and water, with less stimulation of the renin-angiotensin-aldosterone system and a lower risk for rehospitalization^{70,71}. A trial comparing ultrafiltration versus a stepped pharmacologic approach (Table 2) in heart failure and cardiorenal syndrome showed similar fluid removal but more renal dysfunction and adverse events with ultrafiltration.⁶³ A larger trial was stopped early by the study sponsor.⁷² At present, ultrafiltration in heart failure patients seems indicated primarily as part of comprehensive dialytic treatment of combined heart and kidney failure.

The combination of hypertonic saline with high loop diuretic doses has been proposed to mitigate renal dysfunction and promote natriuresis,⁷⁵ although this has not yet been tested in a robust trials. Finally, furosemide has been reformulated for subcutaneous delivery, which may allow delivery of “IV-like” diuresis outside of the hospital setting, with potentially important implications for care delivery and cost. This approach is now being tested in a multi-center randomized controlled trial (NCT02877095).

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Figure 1.

Mechanisms of loop diuretic action and resistance. Loop diuretics circulate bound to protein, and are secreted into the tubule lumen by organic anion transporters (OAT1 and OAT2) at the basolateral membrane, and Multidrug Resistant Protein-4 (and others) at the apical membrane. Diuretics compete with chloride for binding to NKCC2, which is also present at the macula densa. Enhanced salt absorption along proximal tubules limits diuretic-sensitive transport. Each step can mediate diuretic resistance (see text). PT: proximal tubule; TAL: thick ascending limb; MD: macula densa; DCT: distal convoluted tubule; CD: collecting duct; G: glomerulus.

Figure 2. Pharmacokinetic and Pharmacodynamic properties of loop diuretics. Panel A: acute decompensated heart failure shifts the dose-response curve to the right (R) and reduces the maximal natriuresis (D). B: plasma concentration of loop diuretic $[\text{Diuretic}]_p$, as a function of time after intravenous (IV) or oral dose. The natriuretic threshold (as in A) in normal individuals and in acute decompensated heart failure is shown. Note that a higher concentration may be required for patients with acute decompensated heart failure. C: effects of repeated daily doses of loop diuretic (LD) on Na^+ excretion comparing post-diuretic Na^+ retention and the braking phenomenon. To be effective, natriuresis (dotted area)

must exceed antinatriuresis (hatched area). These relationships may be altered, however, in acute decompensated heart failure.⁷⁶

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Figure 3. Nephron remodeling as a mechanism of diuretic resistance. When high doses of loop diuretics are used chronically, the distal nephron undergoes remodeling, with hypertrophy and hyperplasia of distal convoluted tubule cells, principal cells and intercalated cells. This increases the reabsorptive capacity of the distal nephron, through mechanisms discussed in the text.

Table 1

Causes of Diuretic Resistance

- Inadequate Dose
- Non Adherence
  - Not taking drug
  - High NaCl Intake
- Pharmacokinetic
  - Slow absorption (gut edema)
  - Impaired secretion into the tubule lumen
  - Chronic kidney disease
  - Aging
- Drugs
  - Non-steroidal anti-inflammatory drugs[§]
  - Probenecid
- Hypoproteinemia
- Hypotension
- Nephrotic syndrome
- Antinatriuretic drugs
  - Non-steroidal anti-inflammatory drugs[§]
  - Hypotensive agents
- Low renal blood flow
- Nephron remodeling
- Neurohormonal Activation

[§]these drugs inhibit loop diuretic efficacy through several mechanisms.

Table 2
Stepped Pharmacological Care Algorithm

Goal: daily volume urine volume of 3–5 liters until clinical euvolemia is reached.

Initial Approach: $2.5 \times$ daily home furosemide * dose, given intravenously, divided into two doses.

Diuretic protocol (adjusted daily to achieve urine output between 3–5 liters daily) :

Level	Current Daily Furosemide * Dose	Bolus	Infusion Rate	Metolazone [§] (oral)
1	80 mg	40 mg	5 mg/hour	0
2	81–160 mg	80 mg	10 mg/hour	5 mg daily
3	161–240 mg	80 mg	20 mg/hour	5 mg twice daily
4	240 mg	80 mg	30 mg/hour	5 mg twice daily

* Diuretic equivalents: 40 mg furosemide is considered equivalent to 1 mg bumetanide and 20 mg torsemide.

[§]Hydrochlorothiazide (50 mg twice daily) or chlorthalidone (50 mg daily) may be substituted for metolazone. Adapted from. ^{62,63} The full algorithm includes additional considerations for vasodilator, inotropic, or mechanical therapy for patients who fail to respond within 48 hours.