JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 75, NO. 10, 2020

PUBLISHED BY ELSEVIER

THE PRESENT AND FUTURE

JACC STATE-OF-THE-ART REVIEW

Diuretic Therapy for Patients With Heart Failure

JACC State-of-the-Art Review

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CME/MOC/ECME Objective for This Article: Upon completion of this activity, the learner should be able to: 1) understand the role of loop diuretics pharmacokinetics and pharmacodynamics in the response to loop diuretics in heart failure; 2) understand the pathophysiology of diuretic resistance in heart failure and available treatment approaches; and 3) understand the best approaches for optimizing chronic oral diuretic therapy in heart failure.

CME/MOC/ECME Editor Disclosure: *JACC* CME/MOC/ECME Editor Ragavendra R. Baliga, MD, FACC, has reported that he has no financial relationships or interests to disclose.

Author Disclosures: Dr. Felker has received research grants from the National Heart, Lung, and Blood Institute, American Heart Association, Amgen, Merck, Cytokinetics, and Roche Diagnostics; and has received consulting income from Novartis, Amgen, Bristol-Myers Squibb, Cytokinetics, Medtronic, Cardionomic, Relypsa, V-Wave, Myokardia, Innolife, EBR Systems, Arena, Abbott, Sphingotec, Roche Diagnostics, Alnylam, LivaNova, Windtree Therapeutics, Rocket Pharma, and SC Pharma. Dr. Cox has received research grants from Otsuka Pharmaceuticals. Dr. Testani has received grants from Sequana Medical, Bristol-Myers Squibb, 3ive Labs, Boehringer Ingelheim, Otsuka, Sanofi, FIRE1, and Abbott; has received consulting fees from Sequana Medical, AstraZeneca, Novartis, 3ive Labs, Boehringer Ingelheim, MagentaMed, Reprieve, Sanofi, FIRE1, and W.L. Gore; and has received personal fees from Cardionomic and Renalguard. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Medium of Participation: Print (article only); online (article and quiz).

CME/MOC/ECME Term of Approval

Issue Date: March 17, 2020
Expiration Date: March 16, 2021

Listen to this manuscript's audio summary by Editor-in-Chief Dr. Valentin Fuster on JACC.org.

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ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2019.12.059

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ABSTRACT

Expansion of extracellular fluid volume is central to the pathophysiology of heart failure. Increased extracellular fluid leads to elevated intracardiac filling pressures, resulting in a constellation of signs and symptoms of heart failure referred to as congestion. Loop diuretics are one of the cornerstones of treatments for heart failure, but in contrast to other therapies, robust clinical trial evidence to guide the use of diuretics is sparse. A nuanced understanding of renal physiology and diuretic pharmacokinetics is essential for skillful use of diuretics in the management of heart failure in both the inpatient and outpatient settings. Diuretic resistance, defined as an inadequate quantity of natriuresis despite an adequate diuretic regimen, is a major clinical challenge that generally portends a poor prognosis. In this review, the authors discuss the fundamental mechanisms and physiological principles that underlie the use of diuretic therapy and the available data on the optimal use of diuretics. (J Am Coll Cardiol 2020;75:1178–95) © 2020 by the American College of Cardiology Foundation.

Expansion of extracellular fluid volume is central to the pathophysiology of heart failure (HF). Increased extracellular fluid leads to elevated intracardiac filling pressures, resulting in a constellation of signs and symptoms of HF (edema, dyspnea, orthopnea) commonly referred to as congestion (1). Given the central role of volume expansion in the pathogenesis of congestion, diuretic agents are among the cornerstones of treatments for HF.

Most pharmacological treatments for HF, at least for HF with reduced ejection fraction, are supported by evidence from large clinical trials demonstrating improved mortality and/or HF hospitalization. The integrated sum of these data have led to the concept of guideline-directed medical therapy, a set of treatments with clear outcome benefits that form the basis for HF standard of care. By contrast, robust clinical trial evidence to guide the use of diuretic agents is sparse. Although routine diuretic treatment of patients with HF may appear uncomplicated, questions abound about how best to use diuretic agents, particularly in settings of acute decompensation and diuretic resistance. In this review, we discuss the fundamental mechanisms and physiological principles that underlie the use of diuretic therapy and the available clinical trial data on the optimal use of diuretic agents. This review will primarily focus on loop diuretic agents as the mainstays of diuretic therapy for HF, but will also discuss other adjuncts to loop diuretic therapy such as thiazides that are primarily used when there is diuretic resistance.

RENAL PHYSIOLOGY AND DIURETIC RESPONSE

The kidney is the target organ for diuretic therapy, and as such, a detailed appreciation of renal physiology is essential for understanding diuretic effects. Chronic kidney disease (CKD) is strong predictor of adverse outcome in HF (2), and CKD impairs the

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Manuscript received September 11, 2019; revised manuscript received November 15, 2019, accepted December 2, 2019.

ABBREVIATIONS AND ACRONYMS

ACE = angiotensin converting enzyme

ADHF = acute decompensated heart failure

AVP = arginine vasopressin

CKD = chronic kidney disease

eGFR = estimated glomerular filtration rate

GFR = glomerular filtration rate

HF = heart failure

IV = intravenous

NKCC = Na^+-K^+-$2Cl^-$ cotransporter

NSAID = nonsteroidal anti-inflammatory drug

RBF = renal blood flow

"reserve" available for the kidneys to respond to the insult posed by congestion. A summary of key renal mechanisms related to diuretic response.

GLOMERULUS AND PROXIMAL TUBULES. In normal circumstances, renal blood flow (RBF) is around 20% of cardiac output and mainly determined by differences in renal arterial and venous pressure. Glomerular filtration rate (GFR) is determined by the number of functional glomeruli as well as hydrostatic and colloid osmotic pressure differences between glomerular capillaries and Bowman's space (Starling forces). The kidney acts to preserve a "normal GFR" and has several mechanisms to do so in the face of changes in renal blood flow (3). Importantly, all these mechanisms will eventually alter the ratio of GFR/RBF (also known as the filtration fraction [4] [**Figure 1**]). Hence, 2 patients with similar GFR can exhibit a different filtration fraction, which will significantly influence renal tubular Na^+ absorption.

Numerous factors can impair GFR in HF. Aside from fewer functionally active glomeruli, increased neurohumoral activation reduces RBF. In addition, increased central venous pressure is associated with decreased RBF and deterioration of GFR, and clinical observations confirm that effective decongestion may improve renal function (5,6). All of this contributes to low RBF resulting in a high filtration fraction. Additionally, increased intra-abdominal pressure, reduced capacitance of the splanchnic vasculature, congestion of abdominal organs, and aggressive decongestive therapy resulting in intravascular underfilling all may contribute to further deterioration of GFR (7).

The renal circulation consists of 2 distinct capillary beds in series: a high-pressure system in the glomerular capillaries that favors filtration and a low-pressure system in the peritubular capillaries that favors absorption. In normal circumstances, the reabsorbed fraction of filtered Na^+ in the proximal tubules is kept stable secondary to glomerulotubular balance (8). When blood is filtered in the glomerulus, the hydrostatic pressure will gradually drop while the oncotic pressure increases over the length of the glomerular capillaries. Depending on the filtration fraction as well as the neurohumoral status (vasoconstriction vs. vasodilatation of the glomerular arterioles), changes in hydrostatic and osmotic pressure in the renal interstitium and peritubular capillaries will determine Na^+ and water reabsorption in the proximal tubules.

HIGHLIGHTS

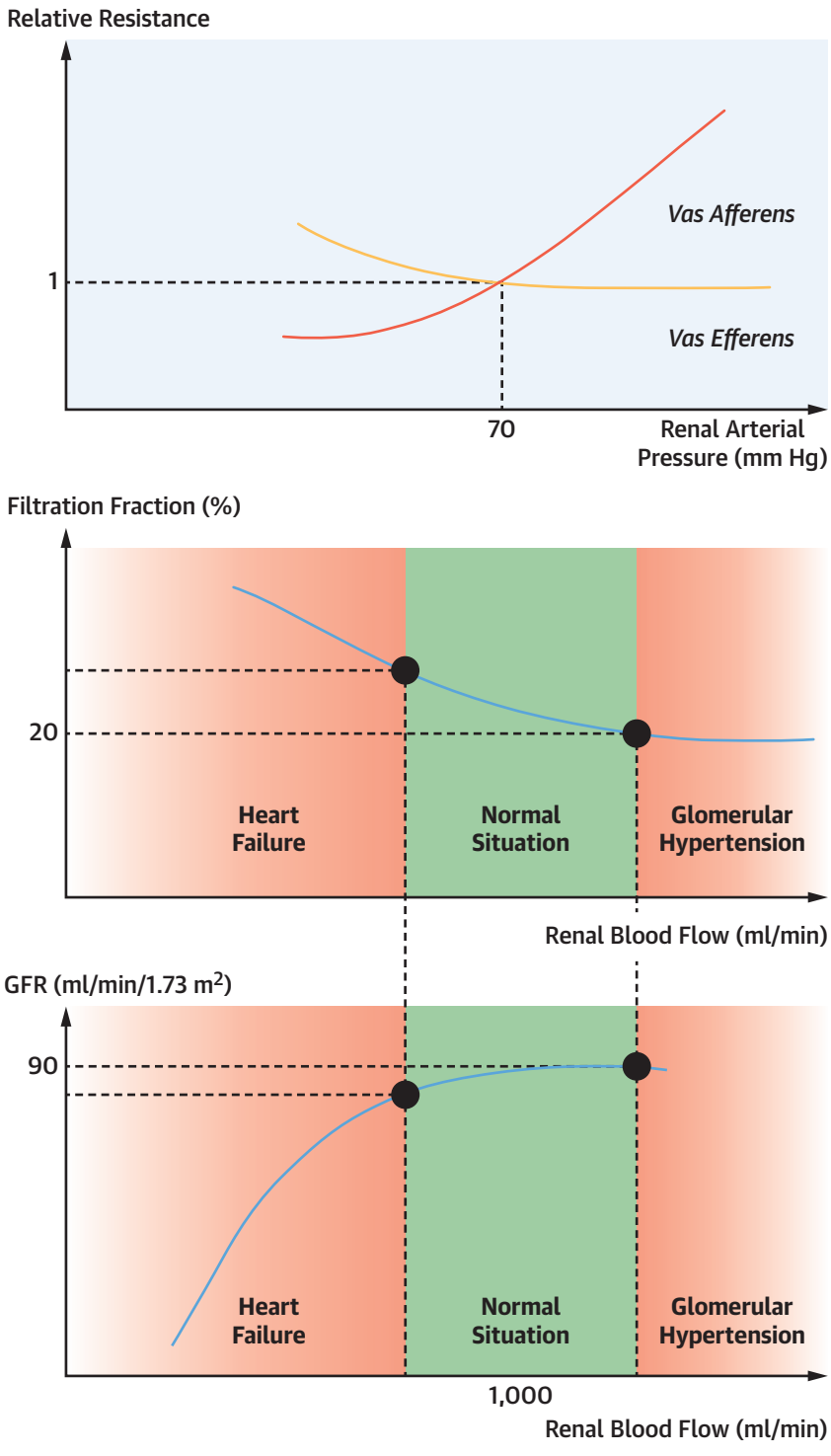
- Loop diuretics are one of the cornerstones of treatments for heart failure, but there is sparse robust clinical trial evidence to guide use.
- Understanding renal physiology and loop diuretic pharmacology is key to successful diuretic therapy. Loop diuretics have steep dose-response curves, meaning there is little effect until a threshold level is reached, then an upper threshold of effect.
- Diuretic resistance is a complex clinical problem with poor prognosis and ill-defined treatment options, clearly in need of further study.
- Novel approaches to diuretic delivery such as subcutaneous furosemide may enable new treatment algorithms in heart failure.

HF facilitates Na^+ and water reabsorption proximally. First, the increased filtration fraction as a consequence of decreased RBF and increased venous pressures raises peritubular capillary oncotic pressure (as more water is filtered, the concentration of proteins in the peritubular capillaries that determine oncotic pressure increases) (9). Second, interstitial proteins will be washed out by increased lymphatic flow, further promoting passive Na^+ reabsorption as oncotic pressure in peritubular capillaries is high (10,11). Third, angiotensin II levels (elevated in HF) are an important neurohormonal signal for proximal Na^+ reabsorption (12). In sum, significantly less Na^+ will be delivered to the more distal parts of the nephron, with important therapeutic implications for the use of loop diuretic agents.

THE LOOP OF HENLE. Normally, one-third of the filtered volume reaches the loop of Henle, which plays an essential role in concentration of urine through the creation of a hypertonic gradient by removing more NaCl than water from the tubular fluid. This process is facilitated by a very slow rate of countercurrent blood flow and enhanced urea transport into the interstitium. Whether the final urine is diluted or concentrated depends on water permeability of the distal nephron segments, which is determined by the activity of aquaporin-2 channels.

In HF, both natriuresis and maximal free water excretion are decreased. First, less tubular fluid will be provided to the loop of Henle as more is

FIGURE 1 **Relationship Between Filtration Fraction and the GFR**



The kidney tries to preserve the glomerular filtration rate (GFR) with changes in filtration fraction over a wide range of arterial pressures by altering the resistance of the afferent and efferent arterioles. Reprinted with permission from Mullens et al. (5).

TABLE 1 Pharmacokinetic and Pharmacodynamic Properties of Common Loop Diuretics

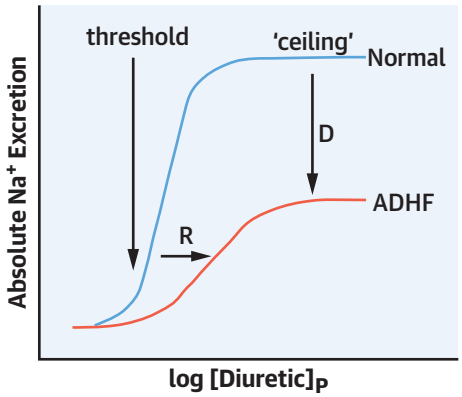
	Furosemide	Bumetanide	Torsemide
Relative IV potency, mg	40	1	20
PO to IV conversion, approximate	2:1	1:1	1:1
Bioavailability, %	10–100 (average = 50)	80–100	80–100
Initial outpatient PO dose, mg	20–40	0.5–1	5–10
Maintenance outpatient PO dose, mg	40–240	1–5	10–20
Maximum daily IV dose, mg*	600	10	200
Onset, min			
Oral	30–60	30–60	30–60
IV	5	2–3	10
Peak serum concentration after PO administration, h	1	0.5–2	0.5–2
Affected by food	Yes	Yes	No
Metabolism	50% renal conjugation	50% hepatic	80% hepatic
Half-life, h			
Normal	1.5–2	1	3–4
Renal dysfunction	2.8	1.6	4–5
Hepatic dysfunction	2.5	2.3	8
HF	2.7	1.3	6
Average duration of effect, h	6–8	4–6	6–8

Dose escalation is generally limited by the risk of ototoxicity. Some centers may use higher loop diuretic doses than listed here.

HF = heart failure; IV = intravenous; PO = per orem (orally).

reabsorbed proximally. Second, increased neurohumoral activation further stimulates active Na^+ reabsorption in the ascending parts (13). Third, poor blood flow increases the renal interstitial oncotic pressure by preventing washout of solutes from the renal medulla, further limiting the potential to excrete water (14,15).

FIGURE 2 Pharmacodynamics of Loop Diuretic Pharmacology



Loop diuretics have steep dose-response curves, meaning that there is little effect until a threshold is achieved, beyond which a ceiling of effect is reached. In patients with heart failure, the dose-response curve is shifted downward and to the right. Note that the x-axis for diuretic dose is on the log scale, suggesting that substantial increases in diuretic dosing are required to achieve an increase in diuretic effect. ADHF = acute decompensated heart failure.

MACULA DENSA. The final part of the loop of Henle contains the macula densa and endocrine cells in close relation to the afferent arteriole. RBF and GFR are autoregulated by 3 major mechanisms: the myogenic response, the macula densa tubuloglomerular feedback, and renin secretion (16). The myogenic response reduces the tension of vascular smooth muscles along the afferent arteriole when pressure there declines. The more delayed tubuloglomerular feedback response, sensed via the loop diuretic-sensitive Na^+-K^+-$2Cl^-$ cotransporter (NKCC-2), also helps to maintain the GFR when tubule solute delivery declines, as occurs in HF. Additionally, a decrease in intratubular solute delivery to the macula densa, also acting via the loop diuretic-sensitive NKCC-2, triggers renin release that will further stimulate angiotensin II production, thereby increasing vasoconstriction of predominantly the efferent arterioles. All 3 of these processes serve to maintain the GFR constant, but at the expense of renin-angiotensin-aldosterone system activation.

DISTAL CONVOLUTED TUBULE AND COLLECTING DUCT. Although almost 90% of the filtered Na^+ has already been reabsorbed before reaching the distal parts, the distal fractional Na^+ reabsorption will determine the final urinary Na^+ concentration and osmolality. Reabsorption depends on the tubular flow rate and aldosterone and arginine vasopressin (AVP) levels (17–19). Although thiazide-sensitive Na^+/Cl^- symporter and aldosterone-sensitive epithelial Na^+ channels can increase solute absorption, insertion of aquaporin channels, expressed when AVP is high, promotes water absorption (20,21).

HF is characterized by a low distal tubular flow secondary to increased fractional reabsorption in the proximal parts of the tubules and often concomitantly decreased GFR. Moreover, high aldosterone further stimulates reabsorption of remaining tubular Na^+. In addition, the presence of a high interstitial oncotic pressure, as well as high AVP levels, also promotes water retention (22).

DIURETIC PHARMACOLOGY AND PHARMACODYNAMICS

Effective diuretic action requires 4 discrete steps: 1) ingestion and gastrointestinal absorption (if given orally); 2) delivery to the kidney; 3) secretion into the tubule lumen; and 4) binding to the transport protein. The resulting tendency to increase NaCl excretion by inhibition of NaCl reabsorption along one segment of the nephron, however, is

counterbalanced by compensatory processes that favor NaCl retention as detailed in the preceding text. The net natriuresis results from the balance of the two.

GASTROINTESTINAL ABSORPTION OF DIURETIC AGENTS. Loop diuretic agents are absorbed relatively quickly from the gastrointestinal tract, but there are important differences between agents (**Table 1**); further, disease processes may alter rates of absorption and sometimes bioavailability. Furosemide's absorption is slower than its elimination half-life, a phenomenon called "absorption-limited" or "flip-flop" kinetics (23,24); its mean net bioavailability is 50%, but absorption is quite variable and may be influenced by food intake. Bumetanide and torsemide are absorbed rapidly (25), reaching peak concentrations within 0.5 to 2 h after an oral dose; absorption of these agents is more complete (typically >80%), when compared with furosemide. Although HF can slow furosemide and bumetanide absorption (26,27), torsemide absorption is better preserved in this situation (28).

Although the low bioavailability of furosemide has led to the suggestion that its dose should be doubled when switching from intravenous (IV) to oral administration (25), there are few clinical data that directly support this, and a fixed conversion cannot be given; it is better to determine doses on the basis of response (29,30). Doses of bumetanide and torsemide are usually maintained when a patient is switched between the IV and oral routes of administration, but again, response should be the determinant.

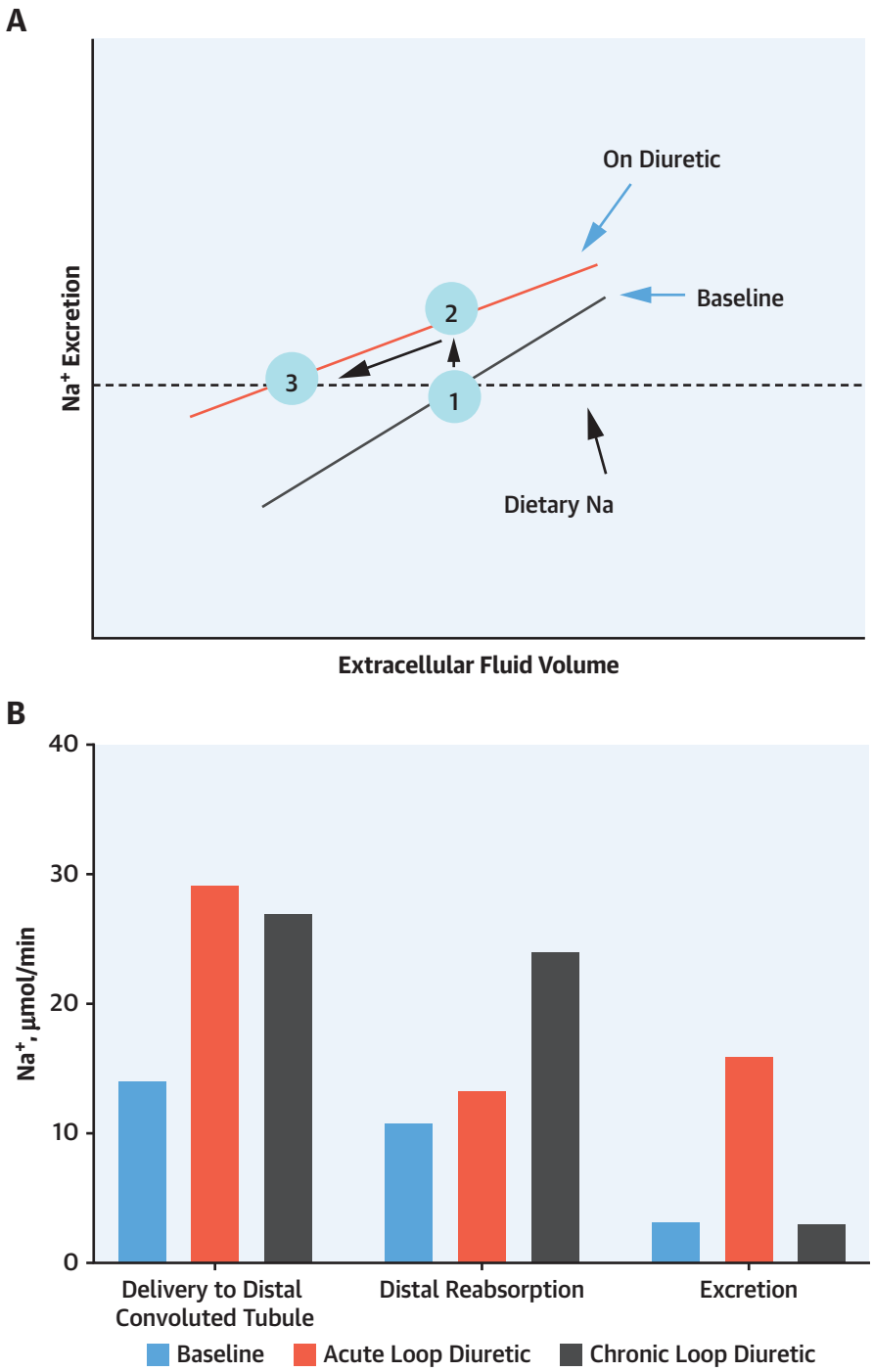
Loop diuretic agents have steep dose-response curves, meaning that there is little effect until a threshold is reached, beyond which the response rapidly approaches a maximum, sometimes called a ceiling (**Figure 2**). Although such relationships are typically plotted as the logarithm of the diuretic concentration or dose, clinicians typically think of dose ranges in linear terms. The logarithmic relation underlies the common recommendation to double the dose, if no response is obtained with an initial dose. Once the ceiling is reached, increasing diuretic doses to achieve higher peak levels will not increase the maximal rate of natriuresis. Yet, increasing a dose above the ceiling will likely have an additional natriuretic effect, because a higher dose will maintain serum diuretic concentrations above the threshold for longer (see further discussion in the following text).

Gastrointestinal absorption of any loop diuretic agent may be altered during exacerbations of HF, although total bioavailability is typically maintained (26). Even with maintained bioavailability, however, slowed absorption can impair natriuresis, especially when the natriuretic threshold is increased, such as in acute decompensated heart failure (ADHF) (31). As an example, the areas under the curve for arbitrary IV and oral furosemide doses may be similar, but the areas under the curve that lie above the natriuretic threshold may differ. This is likely the explanation for the common observation that IV doses of loop diuretic agents, which achieve higher peak levels, may be effective when oral doses lose their efficacy, especially if the natriuretic threshold is increased.

DIURETIC SECRETION INTO THE TUBULE LUMEN. Loop diuretic agents exert their natriuretic actions primarily by binding to NKCC along the luminal membrane of thick ascending limb cells. Even though loop diuretics are small molecules, they circulate tightly bound to proteins, such as albumin, preventing delivery to the tubule lumen by glomerular filtration. To gain access to the tubular fluid and therefore to their sites of activity, they must be secreted across the proximal tubule. Peritubular uptake is mediated by the organic anion transporters OAT1 and OAT3, whereas the apically located multidrug resistance-associated protein 4 (Mrp-4) appears to mediate at least a portion of secretion into the tubular fluid (32,33).

Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit diuretic secretion and alter diuretic responsiveness, and because of their frequent use, are a well-recognized cause of ADHF (34). Diuretic secretion into the tubular lumen is also compromised in CKD (35), shifting the natriuretic dose-response curve to the right. A rightward shift in the dose-response curve can be overcome by using higher diuretic doses. Yet, both NSAIDS and CKD also shift the ceiling natriuresis downward when the natriuretic response is expressed as absolute sodium excretion. The mechanism for resistance attributable to NSAIDs is complex. As noted in the preceding text, loop diuretic inhibition of NaCl reabsorption at the macula densa stimulates production of prostaglandins, via cyclooxygenase-2 (36). Prostaglandin E2 feeds back on tubules, contributing to the resulting natriuresis by inhibiting NaCl transport along the thick ascending limb and collecting duct (37,38). NSAIDs block this prostaglandin-mediated anti-natriuresis. When used long term, NSAIDs increase the abundance and activity of NKCC-2 along the thick ascending limb (39). Additionally, loop diuretic agents inhibit a second isoform of the cotransporter called NKCC-1. This

CENTRAL ILLUSTRATION **Fundamentals of Loop Diuretic Adaptation**



Felker, G.M. et al. J Am Coll Cardiol. 2020;75(10):1178–95.

(A) In patients treated with diuretic agents, Na^+ excretion initially increases (from **point 1 to point 2**) but then declines with renal adaptation (from **point 2 to point 3**), resulting in a new steady state but at a lower extracellular fluid volume **(point 3)**. **(B)** Adaption occurs via increased reabsorption in the distal tubule with long-term exposure, resulting in a gradual decrease in net Na+ excretion (the braking phenomenon).

TABLE 2 Diuretic Tips for the Clinician

Initial loop diuretic dosing in patients hospitalized with HF and congestion: For patients on long-term loop diuretic agents, 2.5× their outpatient dose on a mg per mg basis, demonstrated safety and efficacy in the DOSE trial. For example, for patients taking 40 mg of oral furosemide twice daily as an outpatient, initial IV dosing would be 100 mg of furosemide IV twice daily. For patients not receiving long-term loop diuretics agents, 40–80 mg IV BID of furosemide or the equivalent is a reasonable empiric starting dose. Due to post-dosing Na^+ retention, IV loop diuretic agents should usually be given at least twice daily.
Adjustment of diuretic dosing: Subsequent doses of loop diuretic agents should be guided by clinical response to initial doses. For a sufficient dose of loop diuretic agent, urine output should measurably increase within 2 h. If there is not an adequate response to initial dose, there is no need to wait until the next scheduled dose to increase dosing. Because the dose-response curve (**Figure 2**) to loop diuretic agents is logarithmic, substantial increases in dose (i.e., doubling) are usually required for improved diuretic response. Urine Na^+ monitoring may also be an effective strategy to guide diuretic dosing, although not yet tested in large studies (**Figure 4**).
Responding to increasing serum creatinine during diuretic therapy for congestion: Although clinical context is key, increases in serum creatinine (up to a 0.5 mg/dl increase) during diuretic treatment are common and do not always necessitate stopping or decreasing loop diuretic dosing, especially if congestion is persistent. Clinical trial data suggest that such changes are usually transient and associated with similar or even better long-term outcomes in the setting of effective decongestion.
Dealing with diuretic resistance: Identification of the resistance mechanism(s) can facilitate individualized strategies to improve diuretic response. Combination nephron blockade by adding at thiazide-like diuretic agent (most often metolazone) to loop diuretic agents often results in robust diuresis, but there is substantial risk of electrolyte abnormalities with this approach. The dose of loop diuretic agent at which combination nephron blockade should be initiated is an area of uncertainty.
Adjusting chronic loop diuretic dosing during optimization of GDMT: In general, the goal of long-term dosing is use of the lowest dose that permits effective maintenance of volume status. Optimization of GDMT may allow reduction in loop diuretic dosing, and dose reduction may be required to mitigate the risk of hypotension or volume depletion (i.e., after initiation of sacubitril-valsartan).

BID = twice daily; DOSE = Diuretic Optimization Strategies Evaluation study; GDMT = guideline-directed medical treatment; IV = intravenous.

protein is expressed by vascular smooth muscle cells, such as those in the afferent arteriole; loop diuretic agents contribute to afferent arteriolar vasodilation by blocking this transporter (40). Again, this compensatory adaptation is largely dependent on prostaglandin production and can be blocked by NSAIDs.

CKD also impairs the natriuretic response to diuretic agents through a different mechanism. The maximal natriuretic capacity of loop diuretic agents is frequently described as preserved in CKD, when natriuresis is measured as a fraction of filtered load. Yet the maximal absolute natriuretic effect of diuretic agents is reduced in CKD because, as the filtered sodium load decreases, kidneys maintain urinary salt excretion by suppressing sodium reabsorption along the nephron. Thus, there is less NaCl reabsorption occurring, and less NaCl reabsorption to inhibit in CKD.

VOLUMES OF DISTRIBUTION, METABOLISM, AND HALF-LIVES. Loop diuretic agents are organic anions that circulate tightly bound to albumin (>90%). Thus, their volumes of distribution are low, except during extreme hypoalbuminemia (41). Despite this, there is little evidence to suggest that albumin infusion enhances natriuretic efficacy as long as serum albumin in >2 g/dl) (42).

Approximately 50% of an administered furosemide dose is excreted unchanged into the urine. The remainder appears to be eliminated by glucuronidation, predominantly also in the kidney. Torsemide and bumetanide are eliminated both by hepatic processes and urinary excretion, although hepatic metabolism may predominate, especially for torsemide. The differences in metabolic fate mean that the half-life of furosemide is prolonged in kidney failure, whereas the half-lives of torsemide and bumetanide tend to be preserved in CKD (43). Although the ratio of equipotent doses of furosemide to bumetanide is 40:1 in normal individuals, that ratio declines as kidney dysfunction progresses (44).

Although this apparent increase in furosemide potency with a low GFR may seem beneficial, it also increases the toxic potential of furosemide, especially in the setting of acute kidney injury. Deafness and tinnitus from loop diuretic agents appear to result primarily from high serum concentrations, which inhibit the NKCC isoform (NKCC-1) in the ear (45,46). Deafness and tinnitus occur when very large bolus doses of loop diuretic agents have been employed, especially in the setting of acute kidney injury (47).

Loop diuretic agents are characterized by relatively short half-lives. Thus, the initial natriuresis typically wanes within 3 to 6 h, so that a single daily dose allows some 16 to 21 h for the kidneys to reverse salt and water losses. For individuals in steady state, the phenomenon of post-diuretic NaCl retention defines the reduction in urinary NaCl excretion below baseline after the diuretic effect wears off. This is

TABLE 3 Comparison of Low-Dose and High-Dose Arms of the DOSE-AHF Study

	Low Dose	High Dose	p Value
Primary endpoints			
Patient global assessment VAS AUC at 72 h	4,171	4,430	0.06
Change in creatinine at 72 h, mg/dl	0.04	0.08	0.21
Secondary endpoints			
Dyspnea VAS AUC at 72 h	4,478	4,668	0.041
% free from congestion at 72 h	11	18	0.091
Change in weight in pounds at 72 h	−6.1	−8.7	0.011
Net volume loss at 72 h, ml	3,575	4,899	0.001
Change in NT-proBNP at 72 h, pg/ml	−1,194	−1,882	0.06
% with creatinine increase >0.3 mg/dl by 72 h	14	23	0.041
Median length of stay, days	6	5	0.55

AUC = area under the curve; DOSE-AHF = Determining Optimal Dose and Duration of Diuretic Treatment in People With Acute Heart Failure study; NT-proBNP = N-terminal pro–B-type natriuretic peptide; VAS = visual analog scale.

typically present until another dose of diuretic agent is administered (29) and accounts for the usual recommendation to use loop diuretic agents twice daily; clearly, this imperative is most important when using bumetanide and least so with torsemide, which is often administered once daily. Yet, a recent study in healthy subjects noted that natriuresis lasted only 4 h with torsemide; in comparison, an extended-release preparation of the same drug led to a natriuretic effect that was twice as much (48).

Although these considerations apply to patients with stable HF, where daily urine NaCl excretion matches daily NaCl intake, they are altered when patients become decompensated. Decompensation is typically preceded by a decline in urinary sodium excretion (49), indicating that diuretic agents lose their effectiveness before decompensation. Possible mechanisms responsible are described in the following text.

DIURETIC ADAPTATIONS AND NEPHRON REMODELING. One feature of diuretic action that complicates their effectiveness derives from the structure of the nephron itself. The nephron comprises a set of molecularly and functionally distinct segments, arranged in series, each contributing to net NaCl reabsorption (although NaCl secretion also occurs along some) (50). Loop diuretic agents primarily inhibit NaCl reabsorption along the thick ascending limb, but the resulting increase in NaCl excretion does not match the increased NaCl delivery from the thick ascending limb, as secondary effects, primarily along segments distal to the thick ascending limb, supervene. When diuretic agents are used chronically, proximal factors may also contribute to salt retention, both directly, and by elaborating paracrine factors that act distally (51). Net salt excretion during diuretic treatment, then, reflects a balance between inhibition of reabsorption at the primary site of diuretic action and stimulation of reabsorption distally (and perhaps proximally).

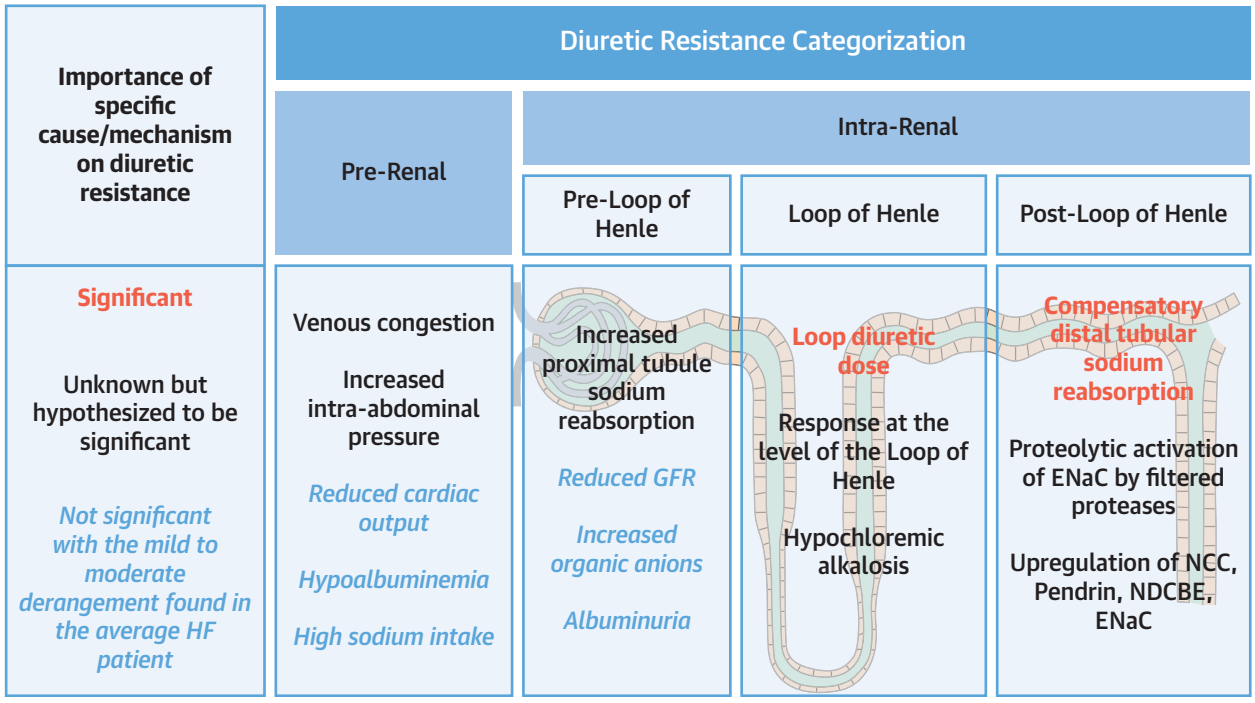
Loop diuretic agents, therefore, greatly increase the luminal NaCl concentration in fluid entering the distal convoluted tubule. Although this increase stimulates NaCl reabsorption downstream (52), this is relatively modest, accounting for the marked natriuretic capacity of these drugs. However, chronic diuretic treatment greatly increases the capacity of the distal nephron to reabsorb delivered NaCl, leading to the secondary decline in natriuresis (the "braking phenomenon") (53) (**Central Illustration**). This process occurs in every patient given a diuretic agent, as net NaCl excretion returns to equal NaCl intake at steady state; when this occurs despite persistent congestion, these same mechanisms contribute to diuretic resistance (further discussed later in the text).

Secondary increases in NaCl absorptive capacity are associated with remarkable nephron remodeling, with hypertrophy of the distal convoluted tubule, connecting tubule, and collecting duct (54,55). One signaling pathway contributing to nephron remodeling is the renin-angiotensin-aldosterone system. Activation of NaCl transport during chronic furosemide infusion is partially aldosterone mediated (56), 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 (57). A third mechanism involves systemic metabolic effects, including metabolic alkalosis (58) and hypokalemia, which strongly activate the sodium-chloride cotransporter (59–62). It seems likely that distal convoluted tubule remodeling is a consequence of increased NaCl movement through cells, because it also occurs when genetic mutations activate NCC (63).

LOOP DIURETICS DURING HOSPITALIZATION FOR HF

Parenteral loop diuretic agents are the mainstay of the treatment of patients hospitalized for HF (64). As noted previously, despite their ubiquitous use in clinical practice, the evidence base for appropriate use of loop diuretic agents stands in stark contrast to many other areas of HF care. These limitations are reflected in current guidelines, which give diuretic agents a Class I recommendation in a variety of clinical circumstances, but based on no higher than Level of Evidence: B or C (65,66). General questions that

FIGURE 3 Renal Mechanisms of Diuretic Resistance



The specific transporters/channels responsible for distal tubular sodium reabsorption are not yet elucidated and may include multiple pathways. Transporters under current investigation are listed in this table but are not inclusive of all potential mechanisms. GFR = glomerular filtration rate; HF = heart failure; ENaC = epithelial sodium channel; NCC = sodium-chloride co-transporter; NDCBE = sodium-dependent chloride/bicarbonate exchanger. Adapted with permission from Cox et al. (122).

arise in approaching patients hospitalized for HF with signs of congestion include picking an initial dose of loop diuretic agent, whether it is preferable to give intermittent boluses or continuous infusions, and how to change therapy if the initial diuretic response is inadequate (i.e., diuretic resistance). Some practical guidance on these issues in clinical practice is provided in **Table 2**.

THE DOSE STUDY. The DOSE (Diuretic Optimization Strategies Evaluation) study was designed to address 2 of the aforementioned questions about IV loop diuretic therapy in hospitalized patients with HF: first, whether higher-dose furosemide therapy is preferable to lower dose, and secondly, whether continuous infusion of furosemide is preferable to intermittent IV boluses. Although prior observational studies have suggested an association of poor outcomes with higher doses of diuretic agents, such data are highly confounded by indication (i.e., patients requiring higher doses of diuretic agents are generally sicker) (67). This study randomized 308 patients hospitalized with HF and signs and symptoms of congestion using a 2 × 2 factorial design. Patients were randomized to either IV boluses every 12 h or as a continuous infusion, and to either low doses (numerically equal to the patient's home daily oral dose) or high doses (numerically equal to 2.5 times the home daily oral dose). Although differences in the patient's global assessment of symptoms (a coprimary endpoint) did not reach statistical significance, 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 (**Table 3**) (68). Worsening renal function (defined as increase in plasma creatinine >0.3 mg/dl within 72 h) occurred more often in the high-dose arm, although subsequent analyses showed that an initial rise in plasma creatinine was associated with better, rather than worse, long-term clinical outcomes (69). These data suggest that more aggressive approach to loop diuretic dosing is generally preferred to cautious dosing in ADHF.

From a pharmacodynamic view, there are several advantages of continuous infusion over intermittent dosing, specifically the maintenance of a furosemide concentration about the diuretic threshold while

avoiding high peak levels (that could cause toxicity). Small studies have suggested potential clinical benefits from this approach (47,70). However, in the substantially larger DOSE study, there were no differences observed in clinical endpoints for the comparison of twice-daily IV bolus versus continuous furosemide infusion; no difference was observed for either of the primary endpoints or key secondary endpoints. Whether continuous infusion of loop diuretic agents may be more effective or safer in other clinical situations remains uncertain.

DIURETIC RESISTANCE

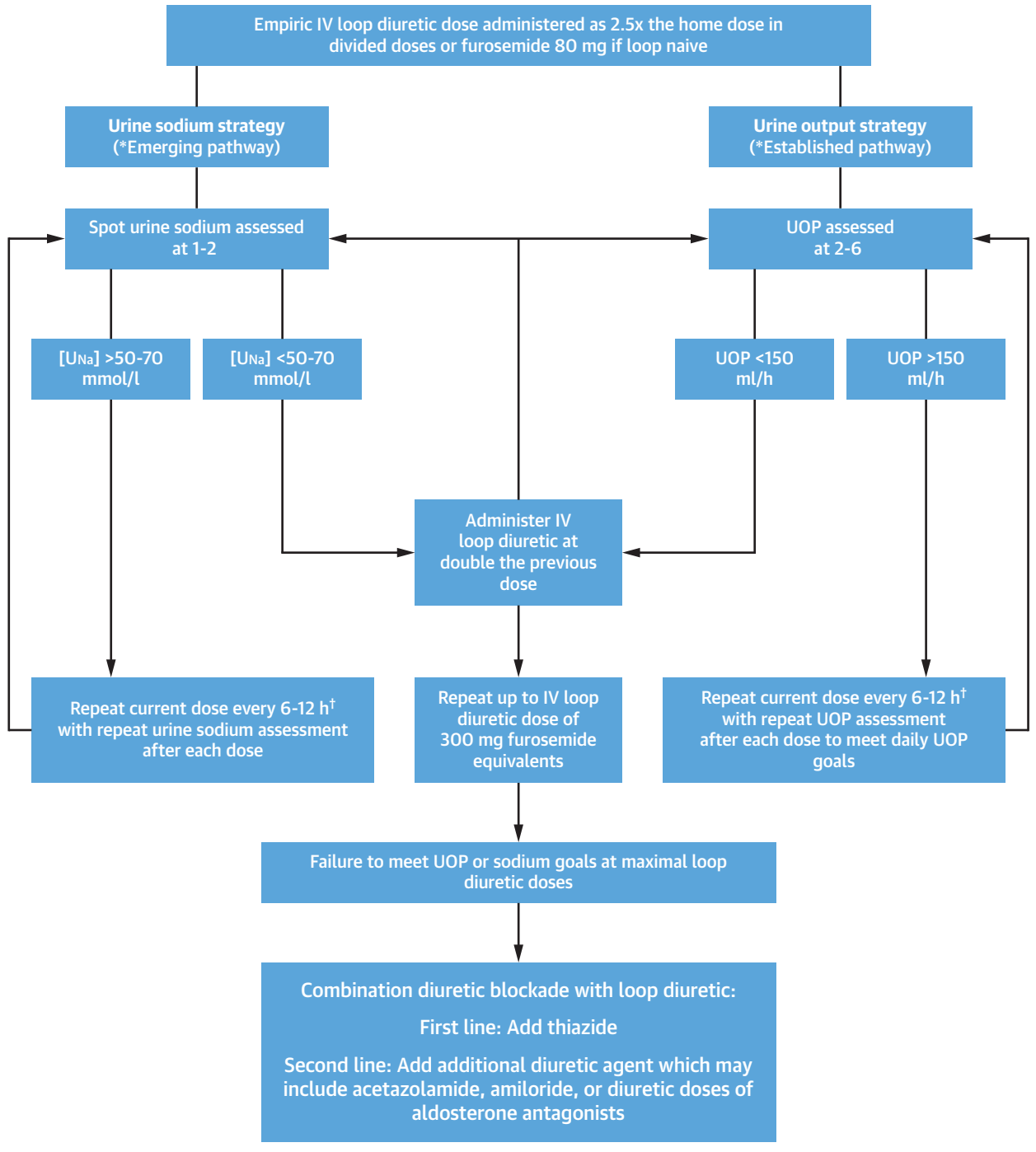
A quantitative definition of diuretic resistance with utility in both clinical and research scenarios remains elusive. Qualitatively, diuretic resistance can be described as an inadequate rate/quantity of natriuresis despite an *adequate* diuretic regimen (29). A major problem in transitioning from a qualitative to a useful quantitative definition is that an adequate diuretic regimen is subjective and varies with the clinical context. Diuretic efficiency (also referred to as "diuretic response") is one attempt to integrate the diuretic response in context of the loop diuretic dose, expressed as fluid output, weight change, or sodium output adjusted for the quantity of diuretic agent administered (71). In general, patients with low diuretic efficiency have worse outcomes, with those exhibiting low diuretic efficiency on high-dose loop diuretic agents having the worst prognosis. Diuretic efficiency has been validated in multiple populations and is additive to other prognostic markers (72–74). The majority of studies using diuretic efficacy have not incorporated the log-linear relationship between dose and response. For example, a 20-mg increment in dose from 20 mg to 40 mg will produce a much larger increase in diuresis than 220 mg to 240 mg, requiring a logarithmic transformation of the dose to correct for this issue (75).

Defining diuretic resistance is further complicated by the fact that the standard metrics by which we quantify diuresis and natriuresis in clinical practice are poor. Agreement between weight loss and net urine output, which should correlate nearly perfectly, is remarkably poor even in the setting of rigorous clinical trials of diuretic therapy (76). Additionally, urine- and weight-based metrics only capture changes in total body water, whereas the upstream cause of extracellular volume expansion is accumulation of sodium (77). As a result of these issues, quantification of diuretic response by urinary sodium output has gained recent attention. Notably, in the ROSE-AHF (Renal Optimization Strategies Evaluation in Acute Heart Failure) trial of diuretic strategies in hospitalized patients at risk for diuretic resistance, a positive sodium balance occurred in 28% of patients and was strongly associated with increased 6-month mortality, even in patients who achieved a net negative fluid balance (78). Because direct measurement of cumulative 24-h sodium output may be challenging, several recent studies have focused on urine sodium concentrations in spot urine samples following diuretic administration. A post-diuretic spot urine sodium <50 to 70 mmol/l is associated with higher risk of worsening kidney function, worsening HF, and long-term adverse events (79–83). One small, single-center study demonstrated that prediction of the cumulative 6-h sodium output from a spot urine sodium and creatinine 2 h after diuretic administration is also possible and demonstrated excellent correlation with measured 6-h sodium output. This approach overcomes many of the practical issues with cumulative urine collections but is in need of validation in larger populations (84).

MECHANISMS OF DIURETIC RESISTANCE. When considering diuretic resistance, we must first appreciate that the ability of the kidney to mount a resistance to diuretic agents is the only reason that loop diuretic agents are not prohibitively unsafe. If the initial, normal loop diuretic response of excreting ≥20% of filtered sodium persisted, a continuous loop diuretic infusion would result in the loss of ~280 g of NaCl and ~50 l of urine in a patient with normal renal function. Diuretic braking, the mechanisms of which are described earlier in the text, prevents what would otherwise likely be a fatal diuresis. It is unknown, but quite likely, that many of the mechanisms underlying pathological diuretic resistance are the same as these potentially beneficial braking effects.

Unlike the umbrella term *diuretic braking*, an anatomically based categorization of diuretic resistance mechanisms facilitates recognition of common mechanisms and may ultimately aid clinicians in choosing therapeutic strategies to overcoming resistance. Diuretic resistance can broadly be dichotomized as: pre-renal and intrarenal diuretic resistance, with the latter further divided on the basis of the anatomic nephron segments in which the resistance mechanism arises (**Figure 3**). The majority of what we currently know about the mechanisms for diuretic resistance is derived from animal models or human studies primarily performed in euvolemic healthy controls or patients with hypertension or chronic kidney disease (85,86). There is a paucity of studies in HF patients on contemporary evidence-based medical

FIGURE 4 **A Proposed Algorithm for Diuretic Titration**



A proposed algorithm for titrating diuretic strategies in patients with persistent congestion and diuretic resistance, on the basis of urine sodium measurement and urine output, is shown. *Diuretic titration to UOP has minimal trial evidence and clear limitations, yet substantial clinical experience exists. Data are accumulating to support urine sodium-based diuretic titration, but evidence and clinical experience remain limited. †IV loop diuretic doses exceeding >1,000 mg of furosemide equivalents/day have limited safety data and should be used cautiously. Bumetanide may confer less risk at higher doses because it has demonstrated reduced ototoxicity risk in animal models. [UNa] = urine sodium concentration; IV = intravenous; UOP = urine output. Algorithm adapted in part from Mullens et al. (1).

therapy, and a growing appreciation that mechanisms may differ on the basis of the clinical context and population.

Pre-renal diuretic resistance. Similar to pre-renal classification of acute kidney injury, hemodynamic cardio-renal interactions can contribute to diuretic resistance. However, pre-renal mechanisms appear to be proportionately less important in patients with HF where intrarenal mechanisms dominate. Although often traditionally viewed as a significant mechanism, mild-to-moderate aberrations in cardiac output are not a prominent driver of cardiorenal syndrome and diuretic resistance in most patients (87,88). Treatment with vasodilators, dopamine, and milrinone failed to augment diuresis, weight loss, or urine sodium output in patients with ADHF without severe hemodynamic profiles (89–92). Temporary cessation of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers with the goal of improving renal function may actually worsen diuretic response in the absence of clinically manifest hypotension. Randomized trials and observational data found angiotensin-converting enzyme inhibitors/angiotensin receptor blockers used with IV loop diuretic agents were associated with increased natriuresis and diuretic efficiency without worsening kidney function (93,94). In summary, clinically significant hemodynamic derangements such as hypotension or low-output HF should be addressed, and may very well improve diuretic response. However, on a population level, most diuretic resistance does not appear to be driven by hemodynamic derangements and adding inotropes with the sole purpose of improving diuresis in the absence of a definable hemodynamic target is generally ineffective.

Traditional paradigms consider high sodium intake to be a cause of pre-renal pseudo-diuretic resistance (95). Multiple studies have demonstrated that in euvolemic volunteers on a high-salt diet, post-diuretic sodium reabsorption completely compensates for the loop diuretic-induced natriuresis, resulting in no net sodium loss (95,96). The relationship between sodium intake and diuresis in HF patients appears to be much more complex (97). Carefully conducted comparisons of high- versus low-sodium diets in ADHF have demonstrated equivalent diuretic outcomes with high-sodium intake (98). Hypertonic saline combined with high-dose loop diuretic agents has been reported to produce greater natriuresis and urine volume than high-dose loop diuretic agents alone among ADHF patients with diuretic resistance, although these studies have not been widely replicated (99,100).

Intrarenal diuretic resistance. Renal dysfunction has historically been considered a dominant driver of diuretic resistance in HF, as it is in the CKD population (85). However, estimates of GFR are not well correlated with the net diuretic responsiveness in patients with HF (71,74). Patients with lower estimated glomerular filtration rate (eGFR) tend to have less tubular resistance than patients with higher eGFR and excreted approximately twice as much sodium per nephron (75). Thus, patients with HF and low eGFR compensated for a lower number of nephrons by each nephron excreting more salt.

It has long been established that induction of a hypochloremic metabolic alkalosis with sodium bicarbonate will substantially reduce diuretic response, and hypochloremic alkalosis may be an important factor associated with diuretic resistance in hospitalized ADHF patients (101). The mechanisms for this finding may include reduction of luminal chloride concentration or direct effects of reduced intracellular chloride on regulatory elements governing sodium avidity.

Research is ongoing to understand which nephron segment(s) contribute most to tubular resistance in HF and the corresponding mechanisms responsible. Although most filtered sodium is reabsorbed in the proximal tubule and loop of Henle, most data from animal models and current human literature indicates post-loop of Henle tubular mechanisms have the greater contribution to diuretic resistance in HF in patients receiving adequate doses of loop diuretic agents, with implications for treatment (102).

STRATEGIES TO OVERCOME DIURETIC RESISTANCE.

Although the strategies employed will depend on the mechanisms of diuretic resistance in the individual patient, the overarching goals are to relieve signs and symptoms of congestion and achieve a net negative sodium balance. The following guidelines suggest strategies to employ in hemodynamically stable, hypervolemic patients with HF exhibiting diuretic resistance.

It is unknown whether a strategy maximizing loop diuretic doses or combination diuretic therapy is superior. Most experts recommend delaying combination therapy until the loop diuretic dose is optimized, though no consensus exists on the magnitude of titration required before adding a thiazide. Although using combination diuretic approaches is physiologically attractive, there are substantial risks of electrolyte abnormalities that may be quite severe (103). In a retrospective observational analysis employing propensity matching, combination diuretic therapy with metolazone was associated

with increased risk of hypokalemia, hyponatremia, worsening renal function, and mortality (104). A stepwise diuretic titration algorithm combining loop diuretic uptitration with the addition of thiazide therapy compared favorably to ultrafiltration in a randomized trial and is frequently suggested as an algorithm for addressing diuretic resistance, although this has not been studied directly against other diuretic strategies (105). This area remains in need of more randomized data to guide treatment decisions.

The adequacy of an empirically chosen loop diuretic dose can be evaluated by urine output and potentially urinary sodium. A flowchart suggesting a generalized approach to treatment for the patient with diuretic resistance is shown in **Figure 4**. An IV loop diuretic dose that produces a spot urine sodium <50 mmol/l or a urine output <150 ml/h at 2 h is inadequate and should generally be doubled until a maximal dose is reached (not clearly defined but often up to a bolus dose of 200 to 300 mg of furosemide equivalents) and urine sodium or output remeasured (1). Once an adequate natriuretic/diuretic response is achieved, the dose can be repeated every 6 to 12 h to achieve the goal net negative sodium balance or urine output.

If congestion is persistent despite adequate doses of loop diuretic agents, sequential nephron blockade with a thiazide (or thiazide-like agent) is generally the next step in treatment. Although metolazone is often empirically chosen, other types of thiazides or thiazide-like diuretic agents appear to have equal efficacy at equipotent doses without evidence of superiority for one agent, even in patients with low eGFR (103). Intravenous chlorothiazide was not superior to oral metolazone when added to loop diuretic agents in a recent prospective trial of strategies for treating diuretic resistance (106).

Other combination diuretic strategies with loop diuretic agents may be tried in patients refractory to standard approaches. Acetazolamide is currently being investigated in combination with IV loop diuretic agents in the ADVOR (Acetazolamide in Decompensated Heart Failure With Volume Overload; NCT03505788) trial (107). Diuretic doses of mineralocorticoid receptor antagonists (>50 mg) have natriuretic effects that might make them attractive adjuncts to loop diuretic agents, but the ATHENA-HF (Study of High-dose Spironolactone vs. Placebo Therapy in Acute Heart Failure) trial in patients with ADHF found no difference in secondary diuretic outcomes such as net urine output or weight change with high doses of spironolactone (108). However, the population studied did not exhibit diuretic resistance, and the 96-h time period might be insufficient to measure the effects of spironolactone's major active metabolite, canrenone (half-life ~17 h). Finally, a variety of other adjuncts to diuretic agents have been evaluated in patients with or at risk for diuretic resistance, including low-dose dopamine (109), low-dose nesiritide (109), and vasopressin antagonists such as tolvaptan (110). Although low-dose dopamine did not show a clinical benefit in the ROSE-AHF study, subgroup analysis did suggest the possibility of benefit in patients with low ejection fraction (109). The sodium-glucose cotransporter 2 inhibitors (SGLT-2i) have diuretic effects and have improved outcomes in a recent clinical trial in chronic HF, but their impact on diuretic resistance per se is a topic of ongoing study (111).

LOOP DIURETIC USE IN CHRONIC HF

Most patients with chronic HF require a maintenance dose of an oral loop diuretic agent to maintain euvolemia and clinical stability. The ideal choice of loop diuretic agent for patients with chronic HF is uncertain. As noted in the preceding text, other than torsemide, the commonly used loop diuretic agents (furosemide and bumetanide) are short acting (<3 h). For this reason, loop diuretic agents usually are more effective when dosed twice daily (as opposed to daily dosing) to minimize periods where the concentration in the tubular fluid declines below a therapeutic level, which may produce post-diuretic sodium retention as described earlier in the text (29). Torsemide and bumetanide also have better and predictable bioavailability than furosemide, another theoretical advantage. Whether there are other advantages of one diuretic agent over another beyond just pharmacokinetic factors is in uncertain. In addition to its more favorable pharmacology, there are data to suggest that torsemide has other favorable effects (in comparison to furosemide) with regard to mitigation of cardiac fibrosis, an important mechanism of HF progression (112). Uncontrolled data and a small randomized trial have suggested the possibility that torsemide may be associated with improved outcomes over furosemide (113,114). An ongoing large, pragmatic outcomes trial called TRANSFORM-HF (Torsemide Comparison With Furosemide for Management of Heart Failure; NCT03296813) is comparing the impact of torsemide versus furosemide on all-cause mortality in a broad population of patients with HF.

WITHDRAWAL OF DIURETIC AGENTS. Observational data suggest that HF patients who can be managed

chronically without a loop diuretic agent generally have a good prognosis (115). One question that arises clinically, but for which there are very little data, is whether oral diuretic agents can be withdrawn in patients with HF who are clinically stable. A recently presented randomized clinical trial of 188 patients from centers in Brazil demonstrated that in patients with low-risk features (oral furosemide dose ≤80 mg daily, no recent HF hospitalizations, and optimized HF therapy, withdrawal of loop diuretic agents was not associated with worsening symptoms or the need to reinstitute diuretic therapy compared with continuation of diuretic agents (116). Although limited by sample size, these data suggest that diuretic withdrawal may be feasible in selected patients with careful clinical follow-up.

FUTURE DIRECTIONS

With ongoing changes in health care delivery, there is increased interest in strategies for managing volume overload and worsening HF outside the hospital setting (117). Driven in part by financial penalties for HF readmissions, many centers in the United States have developed specialized multidisciplinary outpatient clinics in efforts to facilitate early treatment of congestion and decrease hospitalizations (118,119). Although systematic study of this approach is lacking, this strategy of using intermittent IV loop diuretic agents in the outpatient setting may be appropriate in selected high-risk patients.

What about alternative routes of administration of parenteral loop diuretic agents? The recent development of subcutaneous furosemide has garnered significant interest. Early data with subcutaneous treatment using reformulated (buffered) furosemide suggests that this can provide therapeutic levels of furosemide with the anticipated diuretic response (120,121). Although data on clinical outcomes are lacking, ongoing development of delivery systems designed for use outside the hospital could provide an important alternative to hospitalization for patients with volume overload refractory to oral diuretic agents (and without other indications for hospitalization).

Finally, there is substantial unmet need to both better define and treat diuretic resistance. Strategies such as incorporating physiological data (such as urinary Na^+) into diuretic titration decisions are physiologically sound but in need of prospective clinical data. Further investigation of novel diuretic combination strategies with loop diuretic agents to restore diuretic efficacy are needed and may include SGLT2i, acetazolamide, epithelial sodium channel inhibitors, or novel ion transporter inhibitors.

CONCLUSIONS

The skillful use of diuretic therapy remains fundamental to HF management. An understanding of the physiological effects, as well as the pharmacokinetic and pharmacodynamic properties, of these drugs is key for safe and effective use. Despite the long-standing clinical experience with loop diuretic agents, ongoing research (both fundamental and clinical trials) is providing insights into more effective diuretic use and how these agents can best be used to improve outcomes for patients with HF.

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KEY WORDS congestion, diuretics, heart failure, pharmacology

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