

## REVIEW ARTICLE

Julie R. Ingelfinger, M.D., *Editor*

## Diuretic Treatment in Heart Failure

David H. Ellison, M.D., and G. Michael Felker, M.D.

From the Oregon Clinical and Translational Research Institute, Oregon Health and Science University and the Veterans Affairs Portland Health Care System, Portland (D.H.E.); and Duke University School of Medicine and Duke Clinical Research Institute, Durham, NC (G.M.F.). Address reprint requests to Dr. Ellison at the Oregon Clinical and Translational Research Institute, SN4N, Oregon Health and Science University, 3181 S.W. Sam Jackson Park Rd., Portland, OR 97239, or at ellisond@ohsu.edu.

This article was updated on February 1, 2018, at NEJM.org.

N Engl J Med 2017;377:1964-75.

DOI: 10.1056/NEJMra1703100

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**M**OST ACCEPTED PHARMACOLOGIC TREATMENTS FOR HEART FAILURE are supported by evidence from large clinical trials. In contrast, evidence from large, well-controlled clinical trials to guide the use of diuretics, among the most frequently used drugs in heart failure, is generally lacking. Fluid retention and congestion are hallmarks of heart failure, and they are associated with both severe symptoms and poor outcomes.<sup>1</sup> Given the centrality of congestion to both symptoms and outcomes, diuretics remain cornerstones of management of heart failure.<sup>2</sup> Although routine diuretic treatment of heart failure may appear to be uncomplicated, questions abound about how best to use diuretics, particularly in patients with acute decompensated heart failure and diuretic resistance. In this review, we discuss current pharmacologic principles of diuretic therapy, integrate data from recent research, and suggest evidence-based approaches to diuretic treatment of heart failure.

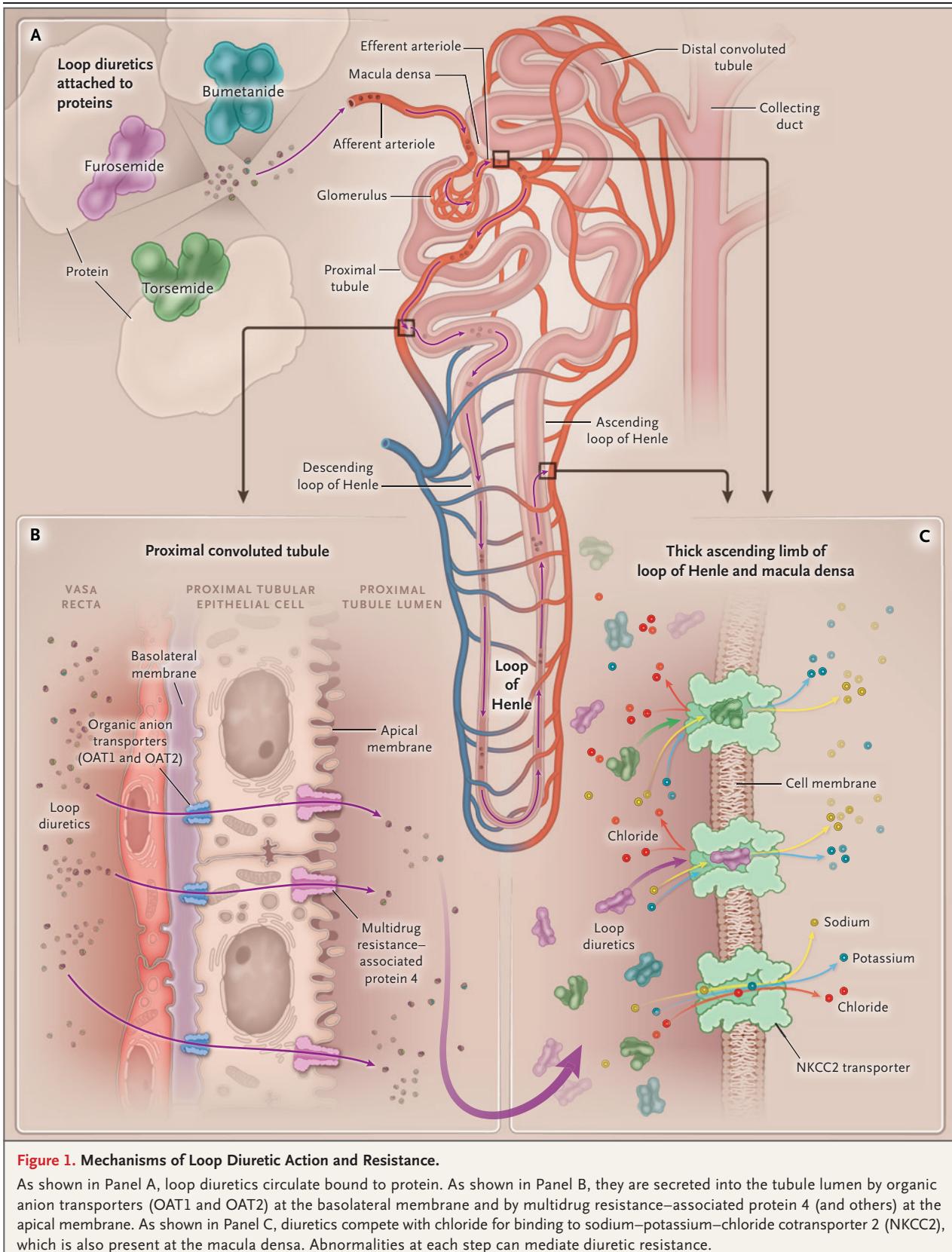
## PHARMACOLOGIC CHARACTERISTICS OF LOOP DIURETICS

Furosemide, bumetanide, and torsemide are prototypical loop diuretics; these agents bind to the translocation pocket at the extracellular surface of sodium-potassium-chloride cotransporters (NKCCs), blocking ion transport directly<sup>3</sup> (Fig. 1). Loop diuretics inhibit the NKCC2 at the apical surface of thick ascending limb cells along the loop of Henle (the gene that encodes this transporter is *SLC12A1*). This transporter reabsorbs (directly and indirectly) up to 25% of filtered sodium and chloride; 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<sup>4</sup> and inhibiting tubuloglomerular feedback, which normally suppresses glomerular filtration when salt delivery to the macula densa increases (Fig. 1).<sup>5</sup> These two additional effects may be both salutary and harmful because elevated plasma renin activity increases the level of angiotensin II, whereas blocking tubuloglomerular feedback helps to maintain the glomerular filtration rate.

These agents also inhibit a second sodium-potassium-chloride symporter isoform, NKCC1 (gene *SLC12A2*), which is widely expressed throughout the body, including in the ear; this probably explains the ototoxicity of loop diuretics.<sup>6</sup> When administered intravenously, loop diuretics cause vasodilation, in part by inhibiting the NKCC1 in vascular smooth-muscle cells.<sup>7</sup> NKCC1 is also expressed by cells of the afferent arteriole and in the extraglomerular mesangium (cells near the macula densa), where it suppresses basal renin secretion<sup>8</sup>; thus, NKCC1 blockade may also contribute to elevation of renin secretion and generation of angiotensin II.

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 long-term use. These diuretics activate the renin-angiotensin-aldosterone system and dilate blood vessels directly, but they also increase the



**Table 1.** Causes of Diuretic Resistance.

Inadequate dose of diuretic
Nonadherence
Not taking drug
High sodium intake
Pharmacokinetic factors
Slow absorption of diuretic because of gut edema
Impaired secretion of diuretic into the tubule lumen
Chronic kidney disease
Aging
Drugs
Nonsteroidal antiinflammatory drugs*
Probenecid
Hypoproteinemia
Hypotension
Nephrotic syndrome
Antinatriuretic drugs
Nonsteroidal antiinflammatory drugs*
Antihypertensive agents
Low renal blood flow
Nephron remodeling
Neurohormonal activation

\* These drugs inhibit the efficacy of loop diuretics through several mechanisms.

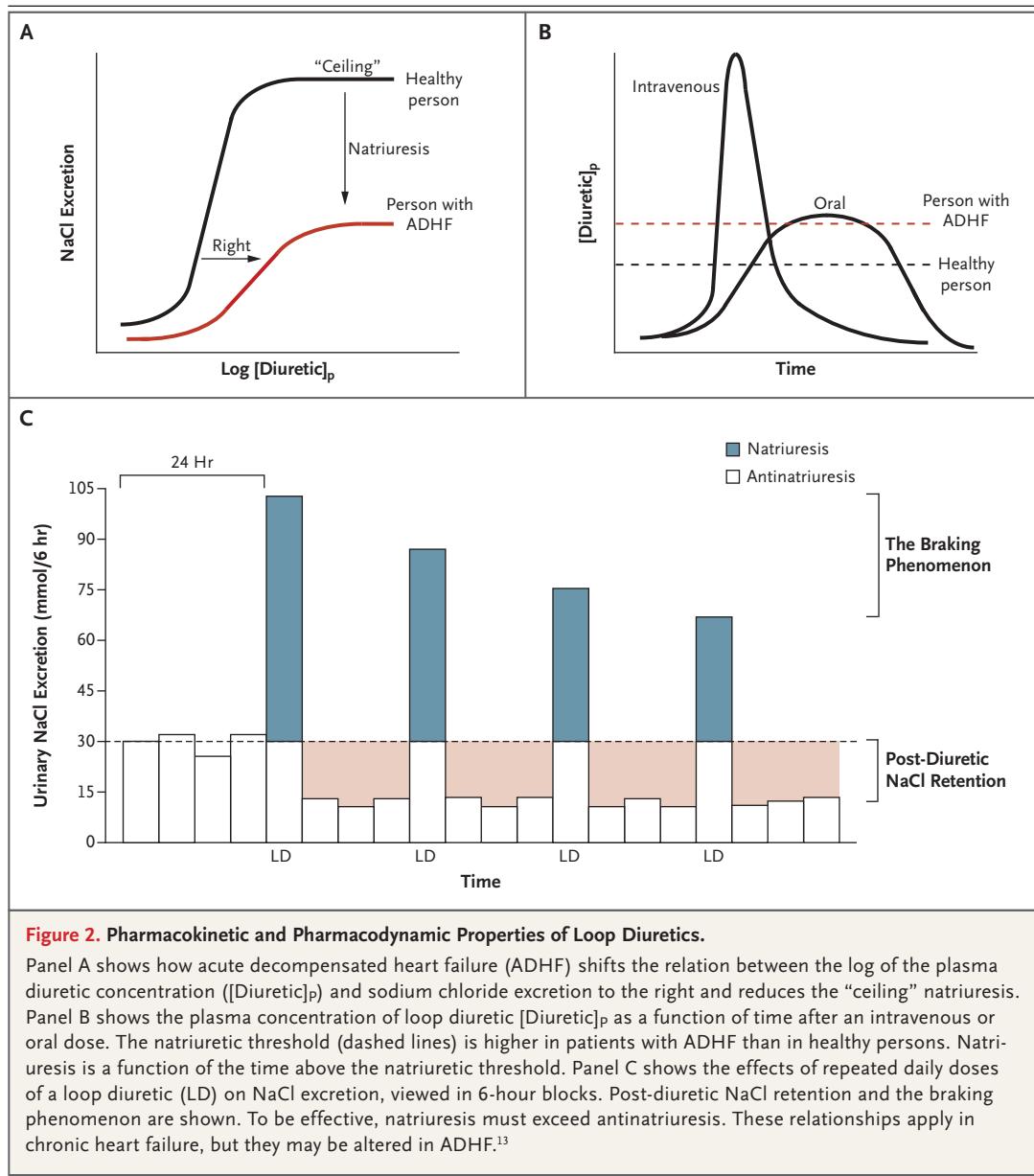
level of vasodilatory prostaglandins and the pressure within the proximal tubule.<sup>7</sup> Some of these effects counteract each other; accordingly, high-dose intravenous loop diuretics can decrease or increase arterial pressure, increase or decrease stroke volume,<sup>9</sup> and decrease renal blood flow. It is difficult to predict which effects will predominate in a given patient.

Loop diuretics are organic anions that circulate bound to proteins (>90%), limiting their volumes of distribution. Thus, loop diuretics do not enter tubular fluid by means of glomerular filtration but, rather, require secretion across proximal tubular cells, through organic anion transporters and the multidrug resistance-associated protein 4 (Fig. 1).<sup>10</sup> Genetic deletion of organic anion transporters in mice leads to diuretic resistance,<sup>11,12</sup> a phenomenon mimicked in humans, when nonsteroidal antiinflammatory drugs or endogenous uremic anions compete for loop diuretic secretion through transporters (Table 1).

## PHARMACOKINETIC CHARACTERISTICS OF LOOP DIURETICS

Loop diuretics have steep dose-response curves, with plateaus often reached at commonly used doses (Fig. 2A). These agents are often called threshold drugs, suggesting that increasing doses beyond a “ceiling” will not increase their effect. Although this is true of natriuretic efficiency, Figure 2B shows that increasing the dose above this nominal “ceiling” can cause additional natriuresis by increasing the time during which the plasma diuretic concentration exceeds the natriuretic threshold, which makes it appear as if a ceiling does not exist. When administered orally, furosemide has limited and highly variable bioavailability (mean, approximately 50%; range, 10 to 90).<sup>14</sup> Food intake delays furosemide absorption,<sup>15</sup> reducing its peak concentration. Since the half-life of furosemide excretion is shorter than its gastrointestinal rate of absorption, the drug has absorption-limited pharmacokinetic features,<sup>15</sup> meaning that the apparent half-life after oral use is longer than the excretion half-life. In patients with preserved kidney function, intravenous doses of furosemide 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 become even more effective than an oral dose (Fig. 2B). Although gut edema and low duodenal blood flow do not typically affect oral bioavailability (the amount absorbed relative to the amount ingested), they slow absorption, thereby reducing peak plasma levels and contributing to diuretic resistance (Fig. 2B).<sup>16</sup>

Bumetanide and torsemide, two other loop diuretics, have higher and more consistent oral bioavailability than furosemide (>90%), and they do not have absorption-limited kinetics, making oral and intravenous doses similar. Although bumetanide and torsemide are both well absorbed, torsemide has a longer half-life in patients with heart failure (6 hours) than furosemide (2.7 hours, although this half-life is prolonged in patients with chronic kidney disease<sup>17</sup>) or bumetanide (1.3 hours).<sup>18</sup> Since a longer half-life reduces the time during which a diuretic level is below the natriuretic threshold (Fig. 2C), one might expect that torsemide should be more ef-



fective during typical dosing regimens; however, data to support this possibility are limited.<sup>19</sup> A systematic analysis of the effectiveness of torsemide as compared with furosemide suggested that torsemide reduced hospital readmissions for heart failure.<sup>20</sup> However, available data are limited, and the question is well suited for definitive clinical trials.<sup>21</sup>

The goal of loop-diuretic treatment in heart failure is not simply to increase urinary excretion of sodium chloride, but rather to achieve negative short-term sodium chloride and water

balance (here termed decongestion) and, in the longer term, to reduce extracellular fluid volume. Because the half-lives of loop diuretics are shorter than typical dosing intervals (often twice daily), and because these agents inhibit solute transport primarily along only one of several sodium-reabsorbing nephron segments, their effects on extracellular fluid volume are complex.

A dose of a loop diuretic increases urinary excretion of sodium chloride for several hours, but this is then followed by a period of very low sodium excretion, often termed “post-diuretic

sodium retention.” To induce negative sodium chloride balance, the excretion of sodium chloride during 24 hours must exceed its intake. When dietary sodium chloride intake is high, post-diuretic sodium retention will offset the initial natriuresis, especially if the dosing interval is long. In contrast, low intake of sodium chloride permits urinary sodium excretion to exceed intake (Fig. 2C). The difference in these effects on extracellular fluid volume underscores the importance of dietary intake of sodium chloride, the drug half-life, and the dosing interval, especially in patients with chronic heart failure.<sup>22</sup>

When extracellular fluid volume declines, a second type of adaptation occurs, during which the natriuretic response to each dose of diuretic decreases; this is frequently termed the “braking phenomenon” (Fig. 2C), and it may involve activation of the sympathetic nervous system, activation of the renin–angiotensin–aldosterone system, nephron remodeling (hypertrophy of the distal nephron, as discussed below), and depletion of extracellular fluid volume itself.<sup>23</sup> If braking did not occur, long-term diuretic treatment would cause relentless contraction of extracellular fluid volume, but when this occurs in patients with persistent congestion, it contributes to diuretic resistance. Thus, the same mechanisms may contribute to both diuretic resistance and diuretic adaptation.

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#### USE OF LOOP DIURETICS IN PATIENTS WITH ACUTE DECOMPENSATED HEART FAILURE

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The limited evidence to guide diuretic use in patients with heart failure in general is reflected in contemporary practice guidelines, which give diuretics a class I recommendation, but it is based on level B or level C evidence.<sup>24,25</sup> Furthermore, high doses of diuretics, which stimulate the renin–angiotensin–aldosterone and sympathetic nervous systems, have been associated with poor outcomes, raising the possibility that high doses should be avoided.<sup>26–28</sup> The Diuretic Optimization Strategies Evaluation (DOSE) trial evaluated the approach to diuretic dosing and the route of administration in patients with acute decompensated heart failure.<sup>29</sup> With the use of a 2-by-2 factorial design, 308 patients with acute decompensated heart failure were randomly assigned

to receive furosemide administered intravenously as twice-daily boluses or as a continuous infusion, and to either “low doses” (equivalent to the patient’s previous oral dose) or “high doses” (2.5 times the previous oral dose). Furthermore, all patients received both intravenous boluses every 12 hours and a continuous infusion, one of which contained furosemide and the other a saline placebo (in a factorial double-dummy design).<sup>29</sup>

Although differences in the patients’ global assessment of symptoms (a coprimary end point) did not reach statistical significance, the high-dose group had more favorable outcomes with regard to several prespecified secondary measures, including relief from dyspnea, change in weight, and net fluid loss. Worsening renal function (the other coprimary end point), defined as an increase in the serum creatinine level of more than 0.3 mg per deciliter (26.5 μmol per liter) within 72 hours after randomization, tended to occur more often in the high-dose group than in the low-dose group; however, the subsequently published results of a post hoc analysis suggested that an initial increase in the serum creatinine level in that trial was associated with better, rather than worse, long-term clinical outcomes.<sup>30</sup>

Other data sets have also suggested that worsening renal function during therapy for heart failure may not portend a poor prognosis when it occurs in patients with effective decongestion.<sup>31–33</sup> Although activation of the renin–angiotensin–aldosterone system has been suggested to be an adverse consequence of use of high-dose diuretics, randomization to the high-dose regimen in the DOSE trial did not lead to greater activation of the renin–angiotensin–aldosterone system than randomization to the low-dose regimen, although the analysis was limited by lack of standardization of timing and the inherent variability of measurements of plasma renin activity.<sup>34</sup> Thus, although observational data suggest that high doses of diuretics are associated with increased mortality among patients with heart failure,<sup>27</sup> the DOSE trial suggests that such an approach to the treatment of heart failure is reasonable. Although the DOSE trial was the largest randomized trial assessing diuretic strategies in patients with heart failure, it was a single modestly sized study that was not powered to evaluate clinical outcomes.

In the DOSE trial, there was no significant

difference between the bolus and continuous approaches with respect to the primary end points: the patients' global assessment of symptoms and the change in the serum creatinine level at 72 hours; these findings were confirmed in a subsequent smaller trial.<sup>35</sup> Thus, these data alone do not provide support for the use of continuous infusions of diuretics for acute decompensated heart failure. However, several caveats should be mentioned. In the DOSE trial, continuous infusions were not routinely preceded by loading doses, which speed the achievement of a steady-state level.<sup>18</sup> In addition, the initial rates of furosemide infusion averaged 5 mg per hour (the low-dose regimen) and 10 mg per hour (the high-dose regimen), which are lower than often recommended<sup>18</sup> (Table 2). Furthermore, the population studied was not selected for resistance to diuretics and had a mean serum creatinine level of 1.5 mg per deciliter (132.6  $\mu$ mol per liter); thus, these patients did not have marked kidney dysfunction. Therefore, although initial treatment with furosemide at a daily dose of 2.5 times the previous oral dose administered as twice-daily boluses is a reasonable initial strategy for most patients, ongoing assessment of clinical response is imperative, and patients with specific clinical scenarios (e.g., as diuretic resistance, the cardio-renal syndrome, and severe right ventricular dysfunction) may have a better response to continuous infusion therapy than to boluses, as discussed below.

#### ADJUNCTS TO DIURETIC TREATMENT

Although retention of renal sodium chloride is the major determinant of congestion in heart failure, hyponatremia, indicating water accumulation, is common and portends a poor prognosis.<sup>38</sup> The oral vasopressin-2 receptor antagonist tolvaptan inhibits the action of antidiuretic hormone and increases excretion of free water (aquaresis).<sup>39</sup> The large-scale Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study with Tolvaptan (EVEREST), which evaluated patients who were hospitalized for heart failure (with or without hyponatremia), did not show superiority of tolvaptan over placebo with respect to long-term clinical outcomes, although potentially beneficial effects with respect to volume status and symptoms were observed in the

Table 2. Stepped-Care Pharmacologic Approach.*				
Level	Furosemide		Metolazone†	
	Previous Oral Dose‡	Bolus	Infusion Rate	Oral Dose
1	≤80 mg	40 mg	5 mg/hr	NA
2	81–160 mg	80 mg	10 mg/hr	5 mg daily
3	161–240 mg	80 mg	20 mg/hr	5 mg twice daily
4	>240 mg	80 mg	30 mg/hr	5 mg twice daily

\* The goal of treatment is a daily urine volume of 3 to 5 liters until clinical euvolemia is reached. The initial approach may involve the intravenous administration (in two doses) of 2.5 times the patient's previous oral daily dose of furosemide or alternatively the infusion approach described above. The diuretic level can be increased daily to achieve urinary output between 3 and 5 liters per day by moving to the next step if the urinary output remains less than 3 liters. NA denotes not applicable.

† Hydrochlorothiazide (at a dose of 50 mg twice daily) or chlorthalidone (at a dose of 50 mg daily) may be substituted for metolazone. Adapted from Grodin et al.<sup>36</sup> and Bart et al.<sup>37</sup> The full algorithm includes additional considerations for vasodilator, inotropic, or mechanical therapy in patients who do not have a response within 48 hours.

‡ A dose of 40 mg of furosemide is considered to be equivalent to 1 mg of bumetanide or 20 mg of torsemide.

initial days of treatment.<sup>40</sup> Subsequently, smaller trials, which focused on the use of tolvaptan in patients with lower plasma sodium levels than those in EVEREST in order to achieve short-term decongestion, did not show a significant reduction in symptoms or an improvement in clinical outcomes, although these patients had greater weight and fluid loss than those in EVEREST.<sup>41,42</sup>

Low renal blood flow contributes to sodium retention in acute decompensated heart failure by limiting sodium filtration, increasing sodium reabsorption, and reducing renal delivery of diuretics to the proximal tubule. Since dopamine increases renal blood flow and excretion of urinary sodium at low doses,<sup>43,44</sup> it might therefore augment natriuresis. Similar considerations apply to natriuretic peptides. In the Renal Optimization Strategies Evaluation in Acute Heart Failure (ROSE-AHF) trial, 360 patients who were hospitalized for acute decompensated heart failure with impaired renal function were randomly assigned to furosemide plus dopamine infusion (at a dose of 2  $\mu$ g per kilogram of body weight per minute), nesiritide (at a dose of 0.005  $\mu$ g per kilogram per minute), or placebo.<sup>45</sup> Neither active drug affected the coprimary end points of urine volume or change in cystatin C level during the ensuing 72 hours. Furthermore, despite the low dose, dopamine infusion was associated

with tachycardia (7% in the dopamine group vs. 1% in the placebo group,  $P<0.001$ ). A post hoc subgroup analysis suggested that the effects of low-dose dopamine differed according to subtype of heart failure. In patients who had heart failure with reduced ejection fraction, dopamine may have enhanced decongestion and improved the prognosis; this provides an impetus to further study.<sup>46</sup>

Although nearly all patients with heart failure with reduced ejection fraction receive drugs that block the renin–angiotensin–aldosterone system, aldosterone breakthrough is common.<sup>47</sup> Mineralocorticoid antagonists such as spironolactone decrease mortality among patients who have heart failure with reduced ejection fraction, but they are used at low doses (e.g., 25 mg) to avoid hypokalemia. Several small studies suggested that higher “natriuretic doses” of mineralocorticoid antagonists might decrease congestion in acute decompensated heart failure.<sup>48</sup> In the ATHENA-HF study (Study of High-dose Spironolactone vs. Placebo Therapy in Acute Heart Failure), 360 patients with acute decompensated heart failure and congestion were randomly assigned to spironolactone (at a dose of 100 mg daily) for 96 hours or placebo (low-dose spironolactone was continued).<sup>49</sup> Spironolactone did not improve the primary end point of decongestion (as measured according to the change in the N-terminal pro-B-type natriuretic peptide level) or secondary end points, including improvement in symptoms and decongestion. The plasma potassium concentration was not affected, however, suggesting incomplete mineralocorticoid receptor blockade.

When diuretics do not achieve decongestion despite the use of maximal doses, the patient is typically said to be diuretic resistant. Single doses of furosemide (250 mg) are often considered to be maximal, although recommendations vary.<sup>50</sup> Diuretic-resistant patients are at high risk for illness and death,<sup>51</sup> and this scenario, which is frequently associated with kidney dysfunction, is often termed the cardiorenal syndrome. Several causes and potential approaches to such diminution of efficacy of loop diuretics can be deduced by considering the pharmacokinetic and pharmacodynamic factors discussed above and listed in Table 1.<sup>52</sup>

#### NEPHRON REMODELING

The nephron comprises a set of anatomically and molecularly distinct segments, arranged in

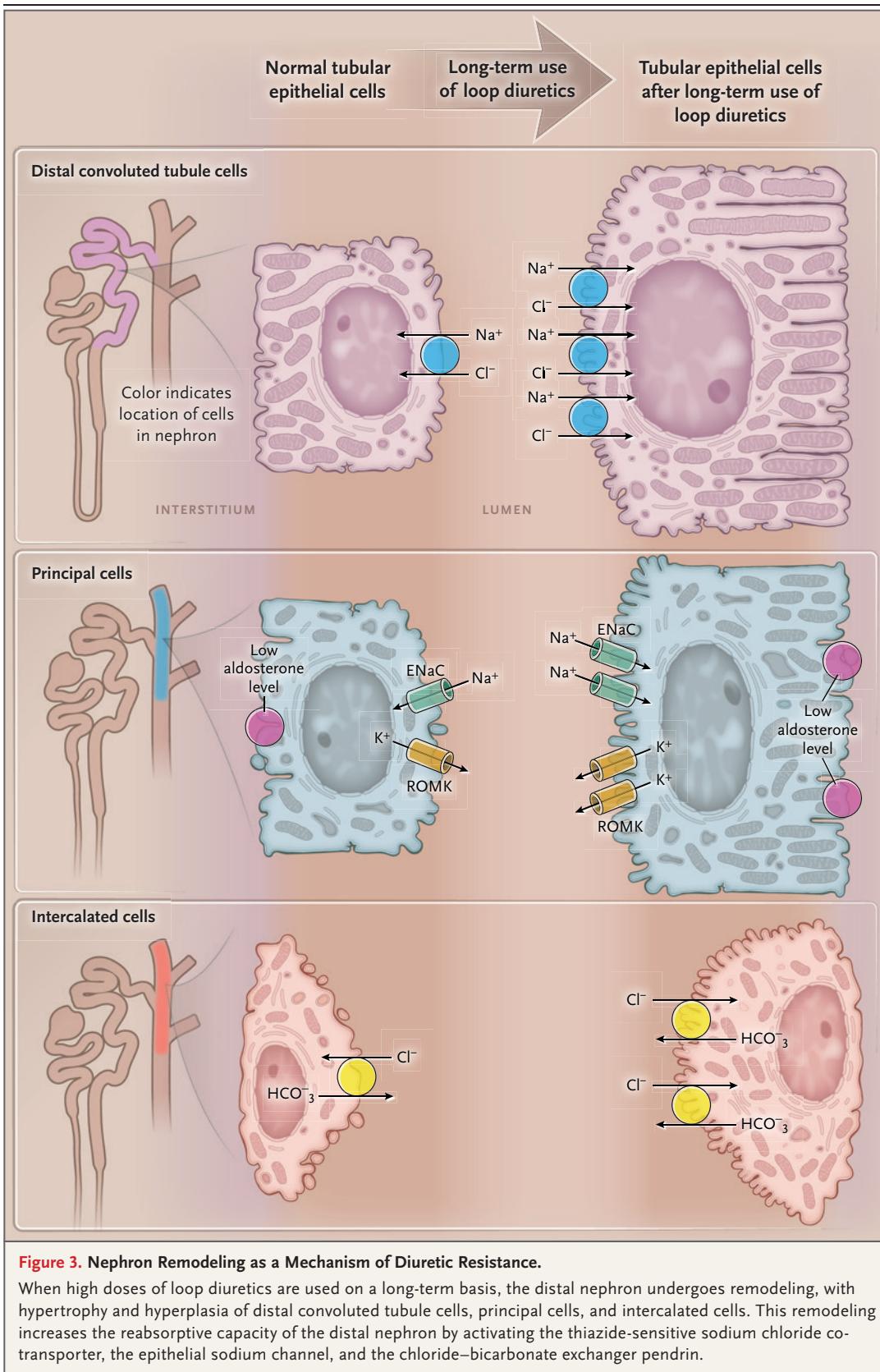
a series, each contributing to net sodium ion reabsorption (Fig. 3). Loop diuretics primarily inhibit salt reabsorption along the thick ascending limb, but they do not increase excretion of sodium chloride as much as they inhibit transport of sodium chloride because they indirectly stimulate distal nephron segments to augment their rates of reabsorption. Net excretion of sodium chloride, then, reflects the balance between inhibition at the primary site of diuretic action and stimulation distally (and perhaps proximally).

Additional changes occur with sustained use of diuretics, including remarkable distal tubular remodeling, with hypertrophy of the distal convoluted tubule,<sup>53,54</sup> the connecting tubule, and the collecting duct (Fig. 3). These effects involve cells that classically transport sodium ion, but they also involve intercalated cells,<sup>55</sup> which participate in chloride reabsorption and acid–base homeostasis. New potential biomarkers for remodeling have been identified.<sup>56,57</sup>

One signaling pathway contributing to nephron remodeling is the renin–angiotensin–aldosterone system. Activation of the thiazide-sensitive sodium chloride cotransporter (NCC) during long-term furosemide infusion is partially mediated by aldosterone,<sup>58</sup> and aldosterone classically activates the epithelial sodium channel. A second mechanism involves increased delivery of luminal solute and fluid to distal nephron segments, which increases transepithelial solute flux and, according to experimental studies, results in evidence of increased transcription in those segments.<sup>59</sup> A third mechanism involves systemic metabolic effects from diuretic use, including metabolic alkalosis<sup>60</sup> and hypokalemia. Even slight decreases in the plasma potassium concentration are associated with a poor prognosis<sup>61</sup>; hypokalemia strongly activates the sodium–chloride cotransporter<sup>62–65</sup> and is tightly linked to distal convoluted tubule remodeling.<sup>66</sup> Finally, circulating proteases that are filtered by the glomerulus in patients with heart failure, such as furin, plasmin, and plasminogen, may directly activate the epithelial sodium channel.<sup>67</sup>

#### TREATMENT OF DIURETIC RESISTANCE

Diuretic resistance is defined as the failure of diuretics to achieve decongestion, which is manifest by a low urine sodium concentration, despite the use of maximal recommended doses. Continuous infusion of diuretic therapy is frequently used in such patients. A post hoc analysis has



suggested that a stepped-care pharmacologic approach (Table 2) that is focused on aggressive diuretic therapy and is adjusted to produce a urine volume of 3 to 5 liters per day may be superior to standard “decongestive therapy,” consisting of standard high-dose loop diuretics, in patients with the cardiorenal syndrome.<sup>36,37</sup> Although evidence is limited, such an approach seems reasonable in patients with diuretic resistance.

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; these drugs have direct natriuretic effects because they inhibit sodium reabsorption along the nephron, and they can inhibit natriuresis because they lower arterial pressure. In heart failure with reduced ejection fraction, their effectiveness in increasing cardiac output commonly dominates and they are typically continued. In contrast, renin–angiotensin–aldosterone blockade may be detrimental in patients with heart failure with preserved ejection fraction, in whom afterload reduction may not increase cardiac output.<sup>68</sup>

Nephron remodeling may also be a useful therapeutic target. Ter Maaten and colleagues<sup>69</sup> 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 sodium chloride transport along the distal nephron. Given this, drugs that block sodium chloride reabsorption there (e.g., metolazone or other thiazide-type drugs) should be useful, although the efficacy and safety of this approach (termed “sequential nephron blockade”) have not been evaluated in adequately powered clinical trials.<sup>52</sup> The combination of loop and thiazide-type diuretics can sometimes lead to massive natriuresis and kaliuresis, however, and careful monitoring during long-term treatment is warranted. Small studies suggest that oral metolazone, when combined with a loop diuretic, is as effective as intravenous chlorothiazide in reducing congestion.<sup>70,71</sup> Amiloride might also prove useful in blocking activated sodium channels, as noted above,<sup>67</sup> and carbonic anhydrase inhibitors, which inhibit the chloride-

bicarbonate exchanger pendrin,<sup>72</sup> may be especially useful when metabolic alkalosis occurs.<sup>73</sup>

The timing of sequential nephron blockade in heart failure remains uncertain. Traditionally, a second class of diuretic is added after resistance to a first class has developed, by which time the distal nephron is extensively remodeled. An alternative approach would be to introduce low-dose sequential blockade earlier,<sup>74</sup> although supportive data are lacking.

#### OTHER APPROACHES AND FUTURE DIRECTIONS

The use of extracorporeal ultrafiltration is a theoretically attractive method with which to remove sodium chloride and water, with less stimulation of the renin–angiotensin–aldosterone system and a lower risk of rehospitalization than the risk associated with the use of diuretics.<sup>75,76</sup> A trial comparing ultrafiltration with a stepped-care pharmacologic approach (Table 2) in patients with heart failure and the cardiorenal syndrome showed similar fluid removal but more renal dysfunction and adverse events with ultrafiltration.<sup>37</sup> A larger such trial was discontinued early by the study sponsor because of slower-than-expected trial enrollment.<sup>77</sup> At present, ultrafiltration in patients with heart failure appears to be indicated primarily when dialytic treatment is indicated in patients with combined heart failure and kidney failure.

The combination of hypertonic saline with high doses of loop diuretics has been proposed to mitigate renal dysfunction and promote natriuresis,<sup>78</sup> although that approach has not yet been tested in robust trials. Finally, furosemide has been reformulated for subcutaneous delivery, which may allow delivery of “intravenous-like” diuretics outside the hospital setting, with potentially important implications for care delivery and cost. This approach is now being tested in a multicenter, randomized, controlled trial (ClinicalTrials.gov number, NCT02877095).

In summary, the skillful use of diuretic therapy remains fundamental to the successful management of heart failure. 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 diuretics, ongoing research in both fundamental and clinical trials is providing insights into more effective diuretic use, with the

goal of improving the care of patients with heart failure.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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