The leading cause of death worldwide is cardiovascular disease. The heart and the kidneys are functionally interdependent, such that dysfunction in one organ may cause dysfunction in the other. By one estimate, more than 60% of patients with congestive heart failure develop chronic kidney disease. Volume overload and congestion are hallmarks of heart failure, and these findings are associated with severe symptoms and poor outcomes. Given the importance of congestion, diuretics remain a cornerstone of heart failure management. However, diuretic treatment remains largely empirical, with little evidence currently available to guide decisions. In this review, we discuss the pathophysiology of cardiorenal syndrome, the pharmacology of loop diuretics, mechanisms of diuretic resistance, and evidence-based treatment paradigms.

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Key Words: Cardiorenal syndrome, Congestive heart failure, Chronic kidney disease, Diuretics, Diuretic resistance

INTRODUCTION
The prevalence of congestive heart failure (CHF) in the United States, as of 2012, was 5.7 million people.1 Patients with CHF exacerbations have the highest rate of hospital readmission, and the National Hospital Discharge Survey recorded 1 million hospitalizations for CHF in 2010.2 Improved mortality because of advances in medical and device therapy has increased the burden of morbidity on the health care system. Diuresis, the mainstay of treatment in cardiorenal syndrome (CRS), carries a class 1 recommendation with level B/C evidence.3,4 Loop diuretics were first approved by the U.S. Food and Drug Administration in 1966 and have become widely prescribed for patients with CHF. In this review, we discuss the pathophysiology of CRS, the mechanism of action of loop diuretics, causes of diuretic resistance, and the most recent evidence-based therapy (Figs. 1–3).

DEFINITION OF CARDIORENAL SYNDROME
CRS encompasses concurrent and interdependent disorders of the heart and kidneys, whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction in the other.7 Another definition proposed by the National Heart, Lung, and Blood Institute is one in which therapy to relieve symptoms of CHF is limited by progressive renal insufficiency.9 There are 5 types of CRS that are defined by the acuity or chronicity of injury to the primary affected organ. CRS is classified as follows: type 1, acute CRS, where acute worsening of cardiac function leads to acute kidney injury (AKI); type 2, chronic CRS, where chronic cardiac depression causes permanent chronic kidney disease; type 3, acute renalocardiogenic syndrome, where AKI causes acute cardiac disorders; type 4, chronic renocardiac syndrome, where chronic kidney disease causes decreased cardiac function and adverse cardiovascular events; and type 5, secondary CRS, where systemic conditions cause acute cardiac and kidney dysfunction (Table 1).7 In decreasing order of prevalence, CRS type 5, 1, 2, 3, and 4 have an estimated prevalence of 38%, 32%, 15%, 8%, and 5%, respectively.7

PATHOPHYSIOLOGY OF CARDIORENAL SYNDROME
There are 4 major mechanisms implicated in CRS: increased renal venous pressure (ie, venous congestion), neurohumoral imbalances, reduced renal perfusion, and right ventricular dilation and dysfunction.

Venous hypertension is thought to result in decreased renal perfusion, raised kidney interstitial pressure, decreased glomerular filtration rate (GFR), maladaptive autoregulatory responses, and other characteristic neurohumoral imbalances. This higher renal venous pressure attenuates glomerular filtration, causes tubule collapse, and may trigger tubulointerstitial fibrosis.10-12 The capacity of the venous system is approximately two-thirds of the total circulatory blood volume, so changing venous capacitance may aggravate or ameliorate heart failure without changes to total body salt, fluid, or weight.13 The importance of congestive kidney failure is highlighted by studies in which kidney function in decompensated heart failure correlated better with right-sided cardiac pressures than with ejection fraction or cardiac index. Elevated central venous pressures also correlate with mortality.11 In one study, kidney function improved when central venous pressures <8 mm Hg were achieved.14

The neurohumoral mechanisms underlying CRS consist of activation of the renin-angiotensin-aldosterone and sympathetic nervous systems as well as increased production of antidiuretic hormone and endothelin 1. These processes increase salt and water retention and systemic vasoconstriction, which in turn decrease renal perfusion.15 Activation of the previously mentioned systems overrides the vasodilatory effects of natriuretic peptides, nitric oxide, prostaglandins, and bradykinin. Chronic and acute exacerbations of CHF are associated with widespread inflammation and high levels of proinflammatory cytokines, which may further boost cardiac, kidney, and other tissue dysfunction.16,17

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Diuretics in the Management of Cardiorenal Syndrome
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Renal perfusion is regulated by adenosine receptors involved with tubuloglomerular feedback (TGF) signaling, and maintain intrarenal vascular tone via a number of pathways which, in CRS, result in afferent arteriolar vasoconstriction and efferent arteriolar dilation.\(^{18-20}\) Actions of adenosine at the macula densa and mesangium depend on angiotensin, renin, nitric oxide, and prostaglandin levels, which are altered in CRS.\(^{21,22}\)

Right ventricular dysfunction increases central venous pressure, which in turn increases renal venous pressure. Right ventricular dilation and dysfunction also reduce left ventricular filling and decrease renal arterial pressure.\(^{11,23}\) The combination of increased renal venous and decreased renal arterial pressures diminishes the pressure gradient across the glomerulus and decreases GFR.

### LOOP DIURETICS IN CONGESTIVE HEART FAILURE

Extracellular fluid volume reduction in patients with CHF returns hemodynamics to a more optimal position on the Frank-Starling curve. Reducing volume overload improves renal perfusion pressure by decreasing central venous pressure, renal venous pressure, and right ventricular dilation, which improves right and left ventricular performance.\(^{24}\)

These beneficial effects are achieved by diuretics, typically loop diuretics, by increasing urinary sodium excretion, thereby causing net negative salt and water balance and reduction in the extracellular fluid volume. Several classes of diuretics are available (see Table 2), but the most effective and commonly used in CHF are those that act in the loop of Henle.

The most commonly used loop diuretics are furosemide, torsemide, and bumetanide. Torsemide and bumetanide have greater and more consistent oral bioavailability (90%) than furosemide (10%-90%).\(^{25}\) Loop diuretics cause natriuresis by blocking the sodium-potassium-chloride symporter (NKCC2) present in the thick ascending limb of the loop of Henle, which is responsible for reabsorption of 25% of the filtered load of sodium. The NKCC2 transporters in the macula densa are also inhibited by loop diuretics, thus stimulating renin secretion and inhibiting TGF, which in turn enhances diuresis.\(^{26-28}\) The activation of the renin-angiotensin-aldosterone system causes vasoconstriction and increases prostaglandins levels.\(^{29}\) These effects lead to decreased renal blood flow, but effects on systemic arterial pressure and cardiac stroke volume are variable.\(^{30}\)

Loop diuretics have complex effects on systemic and renal hemodynamics, which are affected by the route of administration, diuretic dose, comorbid conditions, and duration of use. High-dose intravenous (IV) bolus loop diuretic therapy improves cardiopulmonary congestion, net fluid loss, and weight more effectively than low-dose therapy.\(^{31}\) Continuous loop diuretic infusions are not more effective than frequently administered bolus loop diuretics. Among the loop diuretics, torsemide has the longest half-life (6 hours) compared with furosemide (2.7 hours) and bumetanide (1.3 hours).\(^{25,32}\)

IV furosemide, because of its higher bioavailability compared with the oral formulation, is recommended for inpatient treatment of acute decompensated heart failure. Twice-daily IV furosemide that is 2.5 times the daily oral equivalent dose is a reasonable starting point for therapy, as demonstrated in the Diuretic Optimization Strategies Evaluation (DOSE) trial (see subsequently).\(^{31}\)

### DIURETIC RESISTANCE

Diuretic resistance was defined by Krämer and colleagues\(^{33}\) as a clinical state in which diuretic response is diminished or lost before the therapeutic goal of relief from edema has been reached. This definition translates into the failure of the chosen diuretic to resolve congestion, which is manifested by low urine sodium concentration despite use of the maximal diuretic dose. Common causes of diuretic resistance are listed in Table 3. Loop diuretics are threshold drugs, which means that increasing the dose of the drug beyond an individualized ceiling will not increase efficacy. Conversely, insufficient diuresis may result from insufficient dose or duration of drug administration. To achieve negative sodium balance, sodium excretion must be greater than sodium intake.

Diuretic resistance can occur for several reasons. Loop diuretics are protein-bound anions that require organic anion transporters for secretion into the proximal tubules, after which the drugs are carried in the nascent urine to their site of action in the thick ascending limb.\(^{35}\) Therefore, urinary secretion of diuretics by organic anion transporters can be competitively inhibited by exogenous anions, such as nonsteroidal anti-inflammatory drugs and endogenous anions such as bile acids, fatty acids, and uremic toxins. In addition, because diuretics circulate bound to protein, lower effective doses of drug are delivered to the nephron in the setting of decreased protein production or increased protein loss, such as nephrotic syndrome or protein-losing enteropathy. Finally, although gut edema may not affect overall bioavailability, it may slow diuretic absorption, causing decrease in the peak plasma drug level.\(^{25}\)

One mechanism of diuretic resistance that deserves special mention is the braking phenomenon, whereby