Outcomes after admission for acute heart failure (AHF) remain extremely poor, especially for patients with decreased renal function or those in whom worsening renal function (WRF) develops during treatment. The Table shows the baseline estimated glomerular filtration rate (GFR) with 30- and 60-day mortality from the Dose Optimization Strategies Evaluation trial in acute Heart Failure (DOSE HF), the CArdioRenal REScue Study in acute Heart Failure (CARRRESS HF), and the Renal Optimization Strategies Evaluation trial in acute Heart Failure (ROSE HF).

GFR at randomization in each of these trials was significantly decreased, and the 60-day mortality of 14.7% in CARRRESS HF (the only study to date requiring documentation of WRF before randomization) is one of the highest yet reported.

WRF may have many causes in the setting of AHF. These include underdiuresis (which may lead to persistent increases in central venous pressure, thereby adversely affecting GFR), direct renal damage from the effects of drugs or procedures, progression of underlying disease, and overdiuresis leading to volume depletion with the subsequent engagement of baroreflex mechanisms and, as a result, a reduction in renal blood flow, GFR, and a fall in cardiac output. WRF may also be caused by a transient reduction in intravascular volume such that the rate at which intravascular volume is replenished from the extravascular space (the so-called plasma refill rate) is exceeded. This can occur despite persistent systemic congestion, as suggested by the results from CARRRESS HF in which serum creatinine increased further during treatment with ultrafiltration, despite clinical evidence of ongoing congestion. Regardless of cause, outcomes in AHF are worse as a function of baseline GFR. Although the threshold for the degree of WRF and outcomes remains poorly defined, an increase in serum creatinine of $\geq 0.3$ mg/dL has also clearly been associated with worse outcomes. Recently, several retrospective analyses from completed trials have suggested that it may be important to consider the time course of WRF and the relationship of WRF to the degree of decongestion achieved, but even in those analyses, the best outcomes are clearly in those patients who achieve clinical decongestion while preserving renal function. Until a prospective trial clearly establishes that any form of WRF is safe during treatment of AHF, it is reasonable to assume that the goal of treatment should be adequate clinical decongestion without causing renal dysfunction (or worsening it if already present). Because reliance on changes in serum creatinine does not distinguish among the various causes of WRF, and because it may be important in particular to know whether true acute kidney injury occurs, the use of new biomarkers, such as cystatin C, KIM 1 (kidney injury molecule-1), and urinary natriuretic peptides, may lead to enhanced understanding of the nature and implication of mechanisms underlying WRF in future trials.

No study to date in AHF with renal function as a primary or secondary end point has demonstrated benefit of any new treatment. It would be difficult to demonstrate meaningful improvement if renal function is normal or nearly normal at the outset, which has been the case in many studies. However, several interventions, including natriuretic peptides, adenosine antagonists, and renal dose dopamine, have failed to improve renal function or to enhance diuresis in patients with significantly compromised renal function at baseline. CARRESS HF, the only trial specifically designed to assess renal function once WRF had occurred on diuretic therapy, failed to show any benefit with substitution of ultrafiltration for diuretics.

Common to many previous studies in AHF (other than CARRESS HF), Relief for Acutely Fluid-Overloaded Patients With Decompensated [RAPID], Ultrafiltration vs. Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Congestive Heart Failure [UNLOAD], Ultrafiltration versus Diuretics vs Ultrafiltration for Clinical, Biohumoral and Haemodynamic Variables in Patients With deCOMPensated [ULTRADISCO] heart failure, and Continuous Ultrafiltration for dECompensated congestive heart failure [CUORE] trials) has been continuous background therapy with high doses of loop diuretics. This class of therapy has intrinsic properties that predispose to WRF by $\geq 3$ mechanisms: direct neurohormonal stimulation, transient depletion of intravascular volume, and frank
overtreatment. Ultrafiltration has not been associated with neurohormonal stimulation but could lead to transient intravascular volume depletion or overdiuresis. In both UNLOAD and CUORE (relatively small studies of ultrafiltration versus diuretics in patients with diminished baseline GFR) renal function neither improved nor significantly deteriorated. The results of both trials contained signals of long-term clinical benefit, a hypothesis now being tested in the much larger AVOID-HF (Aquapheresis versus Intravenous Diuretics and Hospitalizations for Heart Failure) trial. In CARRESS HF, serum creatinine transiently worsened despite persistent congestion, and although the study was not powered for clinical outcomes, there was no difference between the group treated with ultrafiltration and those treated with more intensive diuretic therapy in any clinical measure at discharge, 30 or 60 days. Therefore, the question arises as to whether we should adopt a different approach to these high-risk patients, one that lessens the possibility of aggravating renal dysfunction when present at baseline or of reversing it when WRF occurs.

When sodium reabsorption is blocked in the ascending loop of Henle after administration of a loop diuretic, sodium concentration increases in the fluid bathing the macula densa. This triggers the release of renin, which may stimulate sympathetic nervous system activity, and the release of arginine vasopressin, leading to vasoconstriction. Although formal dose–response studies of neurohormonal activation and loop diuretic dosing are lacking, the process may not be dose dependent in view of the underlying mechanism. Recent data from the DOSE trial show that increases in plasma renin were similar with both low- and high-dose furosemide administration. A decongestive strategy that significantly reduces reliance on loop diuretics, might, therefore, be desirable.

In theory, one might avoid WRF because of excessively rapid, if transient, reductions in intravascular volume or frank overdiuresis by applying loop diuretics or ultrafiltration at a lower intensity level for longer periods of time. Another approach would be to utilize aquaretic therapy with antagonists to the V2 receptor for arginine vasopressin. This approach would be feasible and potentially desirable because these agents may be less likely to engage any of the 3 mechanisms by which loop diuretics and ultrafiltration may lead to WRF.

Studying the effect of varying intensities of decongestive therapy on renal function with either loop diuretics or ultrafiltration is possible. The DOSE trial demonstrated that patients given higher doses of furosemide experienced greater symptomatic benefit, more weight loss, and had no worse 60-day outcomes, despite a slight excess of WRF. It is an open question as to whether lower doses of furosemide in a DOSE-like study might have a better effect on renal function or on outcomes. Randomizing patients to even lower doses of furosemide might be problematic, however, given better symptom relief in the higher intensification arm of DOSE and in view of the signal from the retrospective analysis of ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) suggesting that more intensive decongestion was associated with improved long-term outcomes. At a minimum, a low-dose loop diuretic regimen would likely require longer hospital stays.

No dose–response trials with ultrafiltration have been conducted with primary renal end points. The rate of ultrafiltration used in CARRESS HF was lower than that in RAPID, UNLOAD, ULTRADISCO, and CUORE in which WRF was not seen; however, the duration of treatment in CARRESS HF was longer than in some of the other ultrafiltration trials. The mechanism responsible for the transient increase in creatinine after ultrafiltration in CARRESS HF is uncertain although, given what we know about potential mechanisms, it seems likely that transient intravascular volume depletion played a role. Why this was not seen in the other studies is not clear, but the patient populations were different with decreased but potentially more stable renal function at entry. Interestingly, plasma renin was higher in CARRESS HF with ultrafiltration than with intensified medical treatment. In this population at the rate of therapy applied, ultrafiltration may therefore not be as neurohormonally neutral as in previous studies. Although it is possible to conduct a study of low rates of ultrafiltration versus the rate used in previous studies in high-risk patients, such studies would be challenging because of the need for prolonged use of ultrafiltration, exposing the patient to greater risk (and expense). As with a trial of a low dose of furosemide, length of stay would almost certainly be increased, which would be problematic in the United States from a financial point of view. It is interesting to speculate, however, whether to improve overall outcomes in AHF, a longer length of stay would be required. In other countries, longer lengths of stay are associated with lower readmission rates, although whether this is related to the nature of decongestive treatment regimens is unknown.

The alternative approach to testing the effect of more prolonged courses of lower doses of loop diuretics or a less intensive ultrafiltration prescription would be to base decongestive therapy on drugs having less intrinsic possibility of causing WRF by any of the likely mechanisms operative with our current therapy. On mechanistic grounds, such an approach might plausibly rely on antagonists to the V2 receptor for arginine vasopressin. There are also some empirical data to support this approach. Both conivaptan (a balanced V1a/V2 antagonist) and tolvaptan have been shown to enhance diuresis safely and significantly when added to loop diuretics without causing WRF or either acutely or over long periods of time as shown in the

Table. Baseline Estimated Glomerular Filtration Rate and 30- and 60-Day Mortality Rates From the DOSE Trial, the ROSE Trial, and the CARRESS in Acute Heart Failure Trial Recently Conducted by the National Heart, Lung, and Blood Institute Heart Failure Network

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>GFR at Baseline (mL/min/1.73 m²)</th>
<th>30 d Mortality %</th>
<th>60 d Mortality %</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOSE</td>
<td>308</td>
<td>54.20±24.12</td>
<td>5.26</td>
<td>10.45</td>
</tr>
<tr>
<td>ROSE</td>
<td>360</td>
<td>42.68±13.68</td>
<td>4.02</td>
<td>9.52</td>
</tr>
<tr>
<td>CARRESS</td>
<td>186</td>
<td>33.97±11.94</td>
<td>7.85</td>
<td>14.70</td>
</tr>
</tbody>
</table>

Statistical comparisons have not been made across the 3 trials. Mortality was highest in CARRESS heart failure, in which the entry criteria required an increase in serum creatinine of ≥0.3 mg/dL while on diuretic therapy in the presence of persistent clinical congestion. CARRESS indicates CardioRenal REScue Study; DOSE, Dose Optimization Strategies Evaluation; GFR, glomerular filtration rate; ROSE, Renal Optimization Strategies Evaluation.
Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) study. Conivaptan has been shown to potentiate the natriuretic effect of furosemide. Tolvaptan does not cause neurohormonal stimulation; although in EVEREST, plasma vasoppressin levels rose slightly, presumably because of the slight increase in osmolality. A similar rise in vasopressin levels was seen in a study by Udelsan et al in which tolvaptan was compared with furosemide as monotherapy for up to a week. In this trial, aldosterone levels were lower in the tolvaptan arm, however, presumably because of diuresis without stimulation of renin secretion. Tolvaptan also had a beneficial effect on renal blood flow and GFR when compared with furosemide in patients with stable chronic heart failure. Regarding clinical results, in the aforementioned study by Udelson et al, tolvaptan produced equivalent weight loss to that with furosemide without WRF. A recent small study in patients with AHF and low baseline GFR showed that tolvaptan, when added to furosemide, was associated with superior decongestion and considerably less WRF with lower doses of furosemide. In the EVEREST trial, patients randomized to tolvaptan also were given lower doses of furosemide, despite persistent lower body weight, stable renal function, and no other safety concerns. The available clinical data along with the mechanistic issues, therefore, suggest that a larger, longer term trial of this drug in patients with AHF and WRF would be feasible at this time.

V2 antagonists acutely produce a free-water diuresis and an increase in serum osmolality which, as shown in the Figure, would be expected to have a beneficial effect on the oncotic forces leading to tissue congestion. This effect is very different from that produced by furosemide or ultrafiltration in which the primary driver of fluid movement from the extravascular to intravascular compartment is a fall in hydrostatic pressure after fluid removal from the intravascular space. Neither loop diuretics nor ultrafiltration produces a change in serum osmolality; as a result, there is an inherently greater tendency to produce WRF by the mechanism related to plasma refill rate. In the EVEREST trial, there was an early improvement in dyspnea in the patients randomized to tolvaptan in addition to loop diuretics, which may have been because of the early shift of fluid caused by changes in oncotic pressure. In the long-term phase of EVEREST, body weight remained lower and serum sodium remained higher, suggesting that an osmotic diuresis may have been sustained. Another potential advantage of aquaretics as alternatives to loop diuretics in AHF is their comparative hemodynamic neutrality.

A potential drawback to reliance on aquaretics would be the need to produce a natriuresis because sodium retention contributes to the expansion of intra- and extracellular fluid volume in patients with HF. To an extent, strict sodium restriction would obviate this problem, but in reality that may not always be achieved. In view of this concern, it might be that the most important benefit of an aquaretic-based regimen would be to reduce the doses drastically needed for furosemide rather than replace this drug entirely. However, given the fact that tolvaptan, after several days, actually did lead to an increase in urinary sodium in the study already cited by Udelsan et al (presumably because of ongoing osmotic diuresis), it might be possible to design trials relying solely on this agent with only rescue furosemide permitted in the tolvaptan arm. Clearly, there is an unmet need to improve outcomes in patients with AHF, particularly those with impaired renal function or those in whom renal function deteriorates with current treatment. Although we will need to pay more attention to the mechanisms underlying WRF in future trials, it is plausible that decongestive therapies that aggravate neurohormonal

Figure. A and B, Schematic depiction of the key forces favoring the formation and resolution of edema and the expected effects of a V2 antagonist on these forces. Either or both an increase in intracapillary hydrostatic pressure or a decrease in plasma oncotic pressure will favor edema formation. Conversely, a decrease in intracapillary hydrostatic pressure and an increase in oncotic pressure will favor edema resolution. The primary effect of a V2 antagonist would be to increase oncotic pressure because plasma oncotic pressure increases in response to free-water diuresis. Some decrease in hydrostatic pressure would also occur if intravascular volume and pressure gradually decline during a net loss of fluid. The net effect would be to produce a sustained movement of fluid from the extravascular to the vascular space without disrupting renal function. These effects differ from those of loop diuretics or ultrafiltration, in which, a rapid reduction in intravascular volume and pressure diminishes intracapillary hydrostatic pressure, no effect occurs on oncotic pressure. The result may be either a transient or an ongoing imbalance in fluids, residing in the intravascular and extravascular compartments such that the plasma refill rate is exceeded, in turn leading to an increase in serum creatinine.
imbalance and rapidly deplete intravascular volume are counterproductive. Although additional dose–response trials of furosemide or ultrafiltration can be considered, our preference, based on both practical and mechanistic considerations, would be to pursue studies based on aquaretics. We have the study models available to us—ROSE HF for the prevention of WRF and CARRRESS HF for treatment—as well as a Food and Drug Administration–approved agent. Evaluation of tolvaptan instead of dopamine, nesiritide, and ultrafiltration in trials similar to ROSE HF and CARRRESS HF would tell us whether a radically different approach to decongestion confers renal benefit in patients with AHF. If it did, the stage would be set for appropriately powered outcomes studies.

Disclosures

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