Novel Diuretic Strategies for the Treatment of Heart Failure in Japan
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Fluid management is of paramount importance in the treatment strategy of heart failure (HF), but the therapeutic efficacy of loop diuretic-based treatment for HF patients is limited by insufficient response and adverse effects. Clinical data establishing the efficacy and safety of tolvaptan, a selective oral vasopressin V2 receptor antagonist that induces aquaresis, have recently been accumulated over 3 years of daily clinical experience in Japan. Intravenous infusion of carperitide, a synthetic a-human atrial natriuretic peptide, has also been widely used as acute-phase therapy for acute decompensated HF in Japan. Combination therapy using loop diuretics, tolvaptan, and carperitide with differing and complementary mechanisms of action may maximize therapeutic activity, to minimize the dosage of loop diuretics and thereby reduce the adverse effects not only for volume removal but also for the stability of cardiorenal hemodynamics. (Circ J 2014; 78: 1816–1823)

Key Words: Diuretics; Heart failure; Japanese

Decongestion Therapy in ADHF
Aggressive fluid removal therapy is strongly recommended for symptom relief and hemodynamic improvement in ADHF. The ATTEND registry, a total of 4,842 patients enrolled at 52 hospitals from April 2007 to December 2011 in Japan, demonstrated that the number of cardiac deaths was highest during the first 7 days after admission and then declined over time. Hence, hemodynamic stabilization of patients with HF, including rapid decongestion during the acute phase, is undoubtedly important to minimize the incidence of in-hospital cardiac death. At the same time, several previous clinical studies demonstrated that rapid decongestion can cause worsening renal function (WRF), and may contribute to increased length of stay, increased readmission rate and decreased short- and long-term survival. These apparently contradictory observations raise the question of whether aggressive decongestion therapy takes precedence over concerns about WRF and truly improves clinical outcomes. Metra et al followed up 594 patients who were hospitalized because of ADHF, and divided them into 4 groups according to the development or not of WRF during hospitalization and the persistence of more than 1 sign of congestion at discharge. They demonstrated that patients with WRF and no congestion had similar outcomes to those with no WRF and no congestion, whereas the risk of death or of death or HF readmission was increased in patients with persistent congestion alone and in those with both WRF and congestion. Those results indicate that persistent fluid overload during hospitalization is one of the most important prognostic factors for poor outcomes, and WRF secondary to successful fluid removal does not lead to harmful clinical outcomes. In the Ultrafiltration vs. Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Congestive Heart Failure (UNLOAD) trial, greater weight loss and a trend toward WRF by ultrafiltration compared with conventional diuretic therapy were associated with a reduced rate of rehospitalization for HF. Therefore,
Loop Diuretics

Loop diuretics have high natriuretic potency by blocking the luminal Na-K-2Cl transporter in the thick ascending limb of the loop of Henle, and they remain the frontline treatment for ameliorating symptoms in the management of ADHF. However, multiple clinical observations have suggested an association between loop diuretic use and worsening outcomes in patients with HF. Specifically, higher doses of loop diuretics contribute directly to adverse outcomes, with higher doses failing to produce greater reductions in body weight in 395 hospitalized HF patients.

In the ESCAPE trial, investigators revealed that loop diuretic dose predicted mortality even after adjustment for multiple confounders. However, it remains unknown whether higher diuretic requirements are simply a marker of higher risk or whether higher doses of loop diuretics contribute directly to adverse outcomes. In addition, we should pay close attention to the fact that dose-dependent worsening of 6-month mortality did not seem to be observed in patients receiving a maximal in-hospital diuretic dose of less than 300 mg/day (Figure 1). Considering that the maximal in-hospital diuretic dose in Japan is generally lower than 200 mg/day, we should recognize that the causal relationship between the dose of loop diuretics and clinical outcomes in Japanese populations warrants further investigation.

Now, we revisit the underlying mechanisms that provide the strongest relationship between loop diuretic dosage and dismal outcomes. Testani et al. independently analyzed 2 cohorts: (1) consecutive admissions at the University of Pennsylvania (Penn) with a primary discharge diagnosis of HF (n=657) and (2) patients in the ESCAPE data set (n=390); diuretic efficiency (DE) was estimated as the net fluid output produced per 40 mg of furosemide equivalents, then dichotomized into high vs. low DE based on the median value. They found that low DE was associated with worse survival even after adjusting for in-hospital diuretic dose and fluid output, in addition to baseline characteristics (Penn: hazards ratio [HR], 1.36; 95% confidence interval [CI], 1.04–1.78; P=0.02; ESCAPE: HR, 2.86; 95% CI, 1.53–5.36; P=0.001). In The Diuretic Optimization Strategies Evaluation (DOSE) study, a total of 308 patients with ADHF were randomly assigned, in a 1:1:1:1 ratio, to either a low-dose strategy (total intravenous furosemide dose equal to their total daily oral loop diuretic dose in furosemide equivalents) or a high-dose strategy (total daily intravenous furosemide dose 2.5-fold their total daily oral loop diuretic dose in furosemide equivalents) and to administration of furosemide by either intravenous bolus every 12 h or continuous intravenous infusion. In the comparison of the high-dose and low-dose strategies, there was a nonsignificant trend toward greater improvement in patient global assessment of symptoms (mean area under the curve 4,430±1,401 vs. 4,171±1,436, P=0.06). There was a transient WRF with high-dose diuretics, but this disappeared by the time of discharge. Although the study was not powered to detect differences in clinical outcomes, the incidence of the 60-day outcome of death, rehospitalization, or emergency department visit was lower in the high-dose than in the low-dose arm (HR=0.83, P=0.28). These 2 recent studies suggest that transient WRF secondary to volume de-
showed an association with increased survival only in patients with high levels of carbohydrate antigen 125 (>35U/ml), a reliable surrogate of systemic congestion, and high blood urea nitrogen (≥24.8 mg/dl), a surrogate of renal dysfunction/neurohormonal activation, at a median follow-up of 21 months in 1,389 consecutive patients discharged for acute HF. Their results suggest that aggressive decongestion would result in a net positive prognostic effect in patients with renal dysfunction associated with systemic and renal congestion. Their findings may underscore the importance of identifying patients who can benefit from HDLDs.

The use of long-acting rather than short-acting loop diuretics may provide better prognoses in patients with chronic HF. Sustained natriuretic action of long-acting loop diuretics may contribute to minimizing neurohumoral activation and rebound sodium retention, which could favorably influence cardiac remodeling and patient prognoses.

**Thiazide Diuretics**

Thiazide diuretics can antagonize the renal adaptation to chronic loop diuretic therapy by blocking distal tubule sodium reabsorption, and potentially improve diuretic resistance because of rebound sodium retention. However, combined loop-thiazide diuretic therapy can lead to powerful neurohormonal activation and therefore clinically important adverse effects are common, requiring careful monitoring of serum electrolytes and renal function. Hyponatremia can occur because the increase in urine sodium excretion is greater than the increase in urine water excretion, with more hypertonic urine after combined loop-thiazide diuretic therapy than after loop diuretic alone. Importantly, hyponatremia is independently associated with adverse outcomes in patients with HF. Therefore, minimum necessity use of loop/thiazide diuretics can prevent hyponatremia in HF management.

**Tolvaptan Therapy**

The therapeutic efficacy of loop diuretic-based treatment is limited by insufficient response and adverse effects. Conventional pharmacological strategies to overcome the ineffectiveness of loop diuretics in the management of volume overload often presented as patients with high levels of carbohydrate antigen 125 (>35U/ml), a reliable surrogate of systemic congestion, and high blood urea nitrogen (≥24.8 mg/dl), a surrogate of renal dysfunction/neurohormonal activation, at a median follow-up of 21 months in 1,389 consecutive patients discharged for acute HF. Their results suggest that aggressive decongestion would result in a net positive prognostic effect in patients with renal dysfunction associated with systemic and renal congestion. Their findings may underscore the importance of identifying patients who can benefit from HDLDs.

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Diuretic Strategy in HF

We previously examined the short-term effects of tolvaptan treatment in patients with chronic HF and excess fluid retention despite receiving appropriate medical therapy including loop and/or thiazide diuretics. A 7-day tolvaptan treatment at a dose of 7.5 mg/day significantly increased urinary volume and decreased body weight (Figure 3) without affecting systemic blood pressure and heart rate. Notably, no patients developed overt symptomatic hypernatremia during treatment, mainly because of fluid shift from the interstitial to the intravascular space following adequate water diuresis. Importantly, most patients showed hemodynamic improvement, assessed using right heart catheterization (Figure 4). Matsue et al in Japan demonstrated that tolvaptan therapy achieved more diuresis without WRF in patients at high risk for WRF in a prospective observational study. This finding is consistent with previous experimental and clinical data.

Very recently, Shirakabe et al prospectively enrolled 183 patients with ADHF who were admitted to the intensive care unit and examined whether the immediate and short-term administration of tolvaptan reduced the amount of furosemide required, prevented worsening acute kidney injury (AKI), and led to a better outcome for patients with severe ADHF. Patients were assigned to receive either tolvaptan (7.5 mg administered within 12 h of hospitalization and then every 12 h until the HF was compensated) or conventional treatment with continuous intravenous furosemide administration at the physician’s discretion. Propensity-matched analysis revealed that urine volumes on days 1 and 2 were significantly higher in the tolva-
Vasodilators such as intravenous nitroglycerin are recommended first-line treatment of ADHF associated with elevated systemic blood pressure at presentation. Intravenous infusion of carperitide, a synthetic α-human ANP, has been widely used as an acute-phase therapy for ADHF, because of its diuretic and vasodilatory effects, and diuretic therapy using carperitide is recommend in the current Japanese guidelines (Class IIa, Level of Evidence: B). ANP binds and activates natriuretic peptide receptor-A (NPRA), which is located in the proximal tubules, as well as in the cortical and inner medullary collecting ducts, and ANP/NPRA signaling promotes the excretion of sodium and water, inhibits RAAS, and enhances the glomerular filtration rate and renal plasma flow in the kidneys. Therefore, administration of carperitide can overcome diuretic resistance as well as loop diuretic-induced RAAS activation and WRF. One of the most striking differences in the management of ADHF is the higher use of carperitide in Japanese (34–69%) compared with lower use of nesiritide, a synthetic human brain natriuretic peptide, in the United States (8–11%). Carperitide elicits natriuretic, diuretic, and vasorelaxant effects, all of which are directed to the reduction of body fluid and the maintenance of blood pressure homeostasis, which consequently increases cardiac output without direct inotropic effects. We previously demonstrated that carperitide infusion increased cGMP generation, decreased afterload and preload, and improved left ventricular systolic and diastolic function in in patients with congestive HF. Because hyponatremia is not only a marker of increased morbidity and mortality, but also a promising therapeutic target in the treatment of HF, it is worth investigating whether long-term administration of tolvaptan has prognostic benefits and identifying the most appropriate dosing strategy in Japanese populations, especially in HF with hyponatremia.

Role of Intravenous Carperitide Infusion

Consistent with the results from the clinical studies described, post-marketing prospective multicenter surveillance, which enrolled more than 1,000 HF patients with insufficient response to loop diuretics, demonstrated that tolvaptan therapy decreased body weight by ~2.3±2.5 kg, and ~3.5±4.1 kg at days 7 and 14, respectively, from baseline, with statistical significance associated with improvement of congestive symptoms. Accordingly, tolvaptan has marked capacity for aquaretics in HF patients with diuretic-resistant volume overload in real-world clinical settings. Although hyponatremia is a potential complication, and indeed 3.8% of patients experienced it, predictive factors of hyponatremia were found to be the starting dosage of tolvaptan (15 mg/day), serum sodium level (≥142 mEq/L) and serum potassium level (<3.8 mEq/L) at baseline. Therefore, physicians should administer a lower dose of tolvaptan in patients with normonatremia and hypokalemia to prevent hyponatremia. Indeed, two-thirds of patients received low-dose tolvaptan equal to or less than 7.5 mg/day in this post-marketing prospective multicenter surveillance.

The clinical benefits of chronic tolvaptan therapy have not yet been clearly demonstrated. The Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) trial failed to demonstrate clear benefits of long-term tolvaptan treatment in either morbidity or mortality during a median follow-up of 9.9 months, despite sustained improvements in serum sodium levels, overall fluid balance and congestive symptoms. Because hyponatremia is not only a marker of increased morbidity and mortality, but also a promising therapeutic target in the treatment of HF, it is worth investigating whether long-term administration of tolvaptan has prognostic benefits and identifying the most appropriate dosing strategy in Japanese populations, especially in HF with hyponatremia.
Concomitant and aggressive vasodilatation therapy with diuretics is necessary especially in ADHF patients without hypotension. Concomitant use of low-dose carperitide can be useful in addition to water-sodium excretion therapy using loop diuretics and tolvaptan. It is worth investigating further whether the combined use of loop diuretics, tolvaptan, and carperitide may achieve volume control without neurohumoral activation and prevent WRF, minimize the dosage of loop diuretic, and therefore improve patient prognosis. Pharmacological inhibition of the V2/AQP-2 system that induces aquarexis without direct activation of the RAAS and sympathetic nervous system, and activation of ANP/NPRA signaling that induces natriuresis and RAAS inhibition, could constitute a novel strategy for HF therapy in Japan (Figure 6). The economic effect of this therapeutic strategy for ADHF remains unclear. Up-front costs are definitely greater with this strategy than with incremental doses of loop diuretics alone; but total longitudinal costs could be lower if the length of hospital stay and/or rehospitalization rate is reduced.

Patients with HF and advanced stages of chronic kidney disease (CKD) frequently manifest diuretic resistance. Because both carperitide and tolvaptan have potential protective effects on renal function in the treatment of ADHF in individuals with CKD and/or at high risk for WRF, future clinical trials should be performed to confirm the efficacy and safety of combination therapy with these 2 agents with different mechanisms of action in the management of HF at various clinical stages of CKD.

**Conclusions**

Although many questions remain unanswered about the best approach to using diuretics, they remain an important part of the ADHF armamentarium. Combination therapy with tolvaptan and carperitide with differing and complementary mechanisms of action may maximize therapeutic activity, to minimize the dosage of loop diuretics and therefore reduce the side effects not only for volume removal but also for the stability of cardioenal hemodynamics. Future clinical trials from Japan should be performed to confirm the efficacy and safety of this strategy.
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