Fluid removal is an important component of heart failure treatment to relieve signs and symptoms of edema and to improve oxygenation. In this regard, diuretic therapy should be initiated without delay, and indeed early intervention has been associated with better outcomes for patients hospitalized with acute decompensated heart failure (ADHF). Loop diuretics have a 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 first-line treatment for ameliorating symptoms in the management of ADHF. At the same time, diuretic treatment can cause worsening renal function (WRF) or acute kidney injury (AKI), and may contribute to increased length of stay, increased readmission rate and decreased short- and long-term survival. The Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial showed a strict correlation between diuretic dose and 6-month mortality, with higher doses failing to produce greater reductions in body weight in 395 hospitalized HF patients. The ESCAPE investigators revealed that diuretic dose predicted mortality even after adjustment for multiple confounders. However, we should pay close attention to the fact that the median furosemide equivalent maximal daily dose in this population was 400 mg/day to achieve the median weight loss of 2.8 kg, and that dose-dependent worsening of 6-month mortality does not seem to be observed in patients who receive a maximal in-hospital diuretic dose less than 200 mg/day (Figure 1). Considering the fact that the maximal in-hospital diuretic dose in Japan is generally lower than 200 mg/day, we should recognize that causal interrelations between the dose of loop diuretics and clinical outcomes in populations of Japanese patients warrants further investigation.
matched analysis revealed that urine volumes on days 1 and 2 were significantly higher in the TLV group, despite carperitide being administered significantly less often (24.3% vs. 54.1%), and the dose of continuous intravenous furosemide during the first 48 h was significantly lower (30.0 [15.0–47.5] mg vs. 63.3 [25.0–180.0] mg) than those in the conventional treatment group. Interestingly, there were significantly fewer patients with worsening AKI in the TLV group than in the conventional group. The results of the multivariate logistic regression model for worsening AKI found that the only specific medication associated with AKI was TLV. The Kaplan-Meier curves showed that the all-cause death rate was significantly lower in the TLV group compared with the conventional group. Finally, the multivariate Cox regression model indicated that TLV therapy was an independent predictor of 180-day mortality. These data suggest that immediate and short-term TLV administration additional to furosemide can be beneficial for the treatment of ADHF. Treatment with TLV is generally not recommended in unconscious or sedated patients. Therefore, TLV was administered only to patients for whom the treatment was determined by the physician to be safe, which may lead to patient selection bias. Indeed, endotracheal intubation were less frequently used in the TLV group, even after propensity matching, indicating that more severe decompensated patients were included in the conventional therapy group despite similar NYHA classes between the 2 groups. Prospective and randomized clinical trials are needed to confirm the beneficial effects of TLV in the treatment of ADHF.

Intravenous infusion of carperitide, a synthetic alpha-human atrial natriuretic peptide, has been widely used in Japan as a first-line treatment of ADHF.3,13 It has a short half-life that allows rapid titration, has potent natriuretic and vasodilating properties, and inhibits the activity of the renin-angiotensin-aldosterone system. These kinetic and pharmacological properties of carperitide are in contradistinction to those of TLV. There-
fore, it is worth further investigating whether the combined use of these agents achieves volume control without neurohumoral activation and prevents WRF, minimizes the dosage of loop diuretic, and therefore improves patient prognosis.

In summary, Shirakabe et al. demonstrate that TLV administration in addition to intravenous furosemide therapy successfully managed ADHF and provided better mid-term outcomes. Their methods and results are worth referencing in future studies.

References


