Acute heart failure management in the USA and Japan: overview of practice patterns and review of evidence

Toshikazu D. Tanaka¹*¹, Mitsuaki Sawano², Ravi Ramani³, Mark Friedman⁴ and Shun Kohsaka²

¹Division of Cardiology, Department of Internal Medicine, The Jikei University School of Medicine, 3-25-8 Nishi-shimbashi, Minato-ku, Tokyo, 105-8461, Japan; ²Department of Cardiology, Keio University School of Medicine, Tokyo, Japan; ³Heart and Vascular Institute, University of Pittsburgh Medical Center, Pittsburgh, PA, USA; ⁴Section of Cardiology, Sarver Heart Center, Banner University Medical Center, Tucson, AZ, USA

Abstract

Globally, acute heart failure (AHF) remains an ongoing public health issue with its prevalence and mortality increasing in the east and the west. Effective treatment strategies to stabilize AHF are important to alleviate clinical symptoms and to improve clinical outcomes. However, despite the progress in the management of stable and chronic heart failure, no single agent has been proven to play a definitive role in the management of AHF. As a consequence, contemporary treatment strategies for patients with AHF vary greatly by region. This manuscript reviews the medical treatment options for AHF, with an emphasis on the differences between the treatment strategies in the USA and Japan. This information would provide a framework for clinicians to evaluate and manage patients with AHF and highlight the remaining questions to improve clinical outcomes.

Keywords  Acute heart failure; Drug therapy; Regional difference

Received: 21 October 2017; Accepted: 17 April 2018

*Correspondence to: Toshikazu D. Tanaka, MD, PhD, Division of Cardiology, Department of Internal Medicine, The Jikei University School of Medicine, 3-25-8 Nishi-shimbashi, Minato-ku, Tokyo 105-8461, Japan. Tel: +81 3 3433 1111 (ext. 3261); Fax: +81 3 3459 6043. Email: jjuichi@gmail.com

Introduction

Effective treatment strategies for heart failure (HF) are crucial for alleviating symptoms in patients with HF and reducing its mortality. Over the past decades, series of well-designed clinical trials, conducted mainly in the USA and Europe, have led to standardized use of oral beta-blockers, renin–angiotensin–aldosterone system blockers, and mineralocorticoid receptor antagonists for patients with chronic systolic HF. However, no single agent has been shown to play a definitive role in improving survival in patients with acute heart failure (AHF). As a consequence, treatment strategies for patients with AHF vary greatly by institution or region.¹² In Japan, the numbers of clinical trials and observational data analyses related to AHF are increasing, and therefore, guideline recommendations and physicians’ practice patterns are becoming quite unique.

The main purpose of this review is to present an overview of the medical treatment options for AHF [American College of Cardiology/American Heart Association (ACC/AHA) stage C patients], with an emphasis on the differences between the treatment strategies in the USA and Japan. This review is focused on the practice of AHF in the USA and Japan for the following reasons: first is the expectation of overlap between the USA and Europe in terms of clinical practice, contrary to that in Japan due to the degree of heterogeneity. Previous literature reviews, with respect to comparison of key pharmacological therapy, reported that there is generally good agreement between the guidelines from North America and Europe.³⁴ Second, the authors have profound clinical experience in both the USA and Japan but, unfortunately, not in Europe. This information may help to identify public health issues within different populations in each country, which can then be targeted with performance improvement initiatives in order to improve outcomes in patients with AHF.

Diuretics

General comments

Volume overload or redistribution is thought to play a central role in the pathophysiology of congestion in decompensation.⁵ Currently, intravenous loop diuretics are the mainstay
of treatment targeting congestion in AHF. Symptomatic patients with objective evidence of congestion consistent with pulmonary or systemic venous hypertension or oedema typically receive urgent diuretic therapy for rapid relief of dyspnoea. Although no pivotal clinical trial has conclusively demonstrated their effect on reducing morbidity and mortality in patients with HF, it is the preferred drugs in the guidelines of ACC/AHA and the Japanese Circulation Society.

USA

Currently available loop diuretics are furosemide, bumetanide, and torsemide. Bumetanide seems to have an advantage in terms of bioavailability and effective intestinal absorption compared with furosemide (Figure 1). Bumetanide is recommended as the treatment of choice in patients with AHF complicated by intestinal oedema. As for diuretic use in the acute phase, the National Heart, Lung, and Blood Institute Clinical Heart Failure Research Network has addressed the efficacy and safety of furosemide in the Diuretic Optimization Strategies Evaluation trial, which compared high-dose and low-dose administration strategies. Against expectations, there was no significant difference with respect to global assessment of symptoms and renal function when administering by bolus infusion as compared with continuous infusion, or at a high dose as compared with a low dose. The investigators concluded that there was no advantage in symptom relief and protection of kidney function with high dose and bolus administration of diuretics. While this was certainly a noteworthy study, it has not led to improvements in the prognosis for patients hospitalized with AHF nor has it led to a reduction in the costs of their treatment.

Diuretic resistance can generally be overcome by combining different diuretic classes, such as thiazide and loop diuretics. Thiazide diuretics are used as a booster for augmenting the effect of loop diuretics and minimizing the total amount of furosemide. Metolazone is a thiazide-type diuretic widely used in the USA (currently not available in Japan) (Figure 1). Previous research supports the usage of low-dose metolazone in combination with oral loop diuretics as an effective and relatively safe treatment in many outpatients with refractory HF.

Japan

Diuretic therapy is also widely used for the treatment of AHF in Japan. In the acute decompensated heart failure syndromes (ATTEND) registry, 3695 patients (76.3%) were

| Pharmacological mechanism |
|---------------------------|
| **Diuretics**              |
| -Loop diuretics           | Loop diuretics act at the loop of Henle (thus, the term loop diuretics) to increase urinary sodium excretion and decrease signs of fluid retention in patients with heart failure |
| -Thiazide                 | Thiazide, metolazone, and potassium sparing agents (e.g., spironolactone) act in the distal portion of the tubule to increase urinary sodium excretion and decrease signs of fluid retention in patients with heart failure |
| -Metolazone               |
| -Potassium sparing agents |
| **Natriuretic Peptides**  |
| -Nesiritide               | Nesiritide is a recombinant human brain, or B-type, natriuretic peptide that exerts potent effect on vasodilation and natriuresis |
| -Carperilide              | Carperilide is a recombinant human atrium, or A-type, natriuretic peptide that exerts potent effect on vasodilation and natriuresis |
| **Vasodilators**          |
| -Nitroglycerin (NTG)      | NTG and ISDN forms free radical nitric oxide, which produces a vasodilator effect on the peripheral veins and arteries with more prominent effects on the veins |
| -Isosorbide Dinitrate (ISDN) |
| **Tolvaptan**             | Tolvaptan is a selective vasopressin 2 receptor antagonist, facilitates fluid excretion in urine by reducing the expression of aquaporin 2 in the collecting duct via inhibition of vasopressin receptors |
| **Inotrope**              |
| -Dobutamine               | Dobutamine is an intravenous catecholaminergic agent, mainly acts on beta1-adrenergic receptor that exerts an effect on improvement of LV systolic function and decrease in LVEDP despite its slight increase in heart rate |
| -Milrinone                | Milrinone is a non-catecholamine agent with positive inotropic effect for the treatment of severe HF with impaired systolic function. |
treated with diuretics, and almost all (99%) of these patients received furosemide. However, dosage discrepancies have been noted, particularly in the use of furosemide. Recent reports have suggested that higher doses of diuretics might worsen HF prognosis.

- While furosemide was used in up to 90% of patients hospitalized with AHF in the US registry, furosemide was used in about 70% of patients in the Japanese registry.
- Moreover, based on a previous observational study in Japan, the maximum dose of furosemide was less than 200 mg/day, which was less than half the dose of furosemide administered in the USA.

This suggests that, from the standpoint of maximum effective dose, furosemide might have not been administered at adequate amounts in Japan. A possible explanation would be the widespread use of carperitide, an atrial natriuretic peptide that was used as a diuretic in up to 70% of the patients in the Japanese registry. In accordance with the relationship between the maximum in-hospital diuretic dose and mortality, the results suggest a strong dose–response relation with mortality. It appears that the trend of a maximum in-hospital diuretic dose of less than 200 mg/day in Japan might minimize the mortality that worsens in a dose-dependent manner.

In summary, despite the scarcity of clinical evidence, diuretics have been broadly accepted as a primary AHF treatment over the last half century in both the USA and Japan. However, the dosage of furosemide in acute and chronic HF differs substantially between the two countries. While the US guidelines recommend 20 to 40 mg once or twice as the initial daily dose and 600 mg as the maximum total daily dose of furosemide, a daily dose of 40 to 80 mg and a lower maximum dose are used in Japan, even without precisely described in the guidelines. As for the chronic phase of treatment, torsemide and bumetanide are preferred in both countries. Thiazide diuretics seem to be used more frequently in the USA, but their use in Japan seems to be growing owing to the availability of a combination tablet.

Natriuretic peptides: nesiritide and carperitide

General comments

The trends in natriuretic peptide usage seem to be moving in opposite directions in the USA and Japan. According to the Japanese ATTEND registry previously described, carperitide is currently used in more than half of patients with AHF. This agent has both diuretic and vasodilatory effects and contributes to dyspnoea relief and renal protection (Figure 1). In the USA, nesiritide was widely used in the early 2000s because of its effect on haemodynamic function and self-reported symptoms when added to standard care in patients hospitalized with AHF. However, larger clinical endpoint-driven trials have shown more neutral results (Table 1).

USA

With regard to the background of clinical trials related to nesiritide, the Vasodilatation in the Management of Acute Congestive Heart Failure (VMAC) trial found that pulmonary capillary wedge pressure (PCWP) decreased in patients with AHF admission with nesiritide administration at 3 and 24 h. However, the trial did not address the significant improvement of clinical symptoms, and Sackner-Bernstein et al. subsequently suggested that nesiritide might have a negative effect on clinical outcome, such as mortality and renal function.

In order to address this issue, the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) trial was launched. This was a large randomized controlled trial of 7141 patients, and the primary endpoint was the specific clinical outcome. The results indicated that nesiritide used in addition to conventional therapy improved dyspnoea slightly. However, nesiritide did not affect all-cause mortality and the rate of rehospitalization for HF. Moreover, nesiritide was not associated with impairment of renal function, but it was associated with an increase in the rate of hypotension. This article was further commented on in an accompanying editorial article entitled, ‘The Lost Decade of Nesiritide’.

Before the ASCEND-HF trial, the most frequently used intravenous vasoactive agent was nesiritide, which was used in 12% of all patients in the Acute Decompensated Heart Failure National Registry. Nesiritide is currently used as second-line therapy in cases of refractory HF in the USA. Analysis of previous clinical data showed that nesiritide did not increase urine output and did not improve renal function and prognosis.

Japan

In Japan, carperitide, a human atrial natriuretic peptide similar to nesiritide, has been widely accepted and used in clinical practice. Carperitide was used in 69.4% of all patients in the Japanese registry. However, the clinical evidence on the effect of carperitide on clinical endpoints does not seem to be sufficient. The following findings are among the few that support the use of carperitide in Japan:

- In a multicenter randomized controlled study of 49 patients, low-dose carperitide infusion significantly reduced
Table 1  Summary of clinical trials with natriuretic peptides in heart failure

| Country | Year | Study title | Study design | Sample size | Study population | Intervention | Comparator | Primary endpoint | Conclusion |
|---------|------|-------------|--------------|-------------|------------------|--------------|------------|------------------|------------|
| USA     | 2000 | Nesiritide Study Group | RCT, multicenter, and double-blind | 127 | AHF | Nesiritide 0.015 μg/kg/min | Placebo, 6 h | Change from baseline in the PCWP | Nesiritide improves haemodynamic function and clinical status. |
| USA     | 2002 | VMAC | RCT, multicenter, and double-blind | 489 | AHF | Nesiritide 0.01–0.03 μg/kg/min vs. NTG | Placebo | Change in PCWP among catheterized patients and patient self-evaluation of dyspnoea at 3 h after drug initiation | Nesiritide improves haemodynamic function and symptoms more effectively than i.v. NTG or placebo. |
| USA     | 2002 | PRECEDENT | RCT, multicenter, and double-blind | 255 | AHF | Nesiritide 0.015 μg/kg/min vs. nesiritide 0.03 μg/kg/min vs. dobutamine >5 μg/kg/min | None | Dobutamine is associated with substantial proarrhythmic and chronotropic effects in patients with AHF, whereas nesiritide reduces ventricular ectopy or has a neutral effect. |
| USA     | 2005 | N/A | Pooled analysis of RCTs | 862 | AHF | Nesiritide | None | Death within 30 days | Nesiritide may be associated with an increased risk of death. |
| USA     | 2005 | N/A | Pooled analysis of RCTs | 1269 | AHF | Nesiritide | None | Dialysis and medical intervention for WRF | Nesiritide was associated with an increase in serum creatinine >0.5 mg/dL. |
| USA     | 2007 | BNP-CARDS | RCT, multicenter, and double-blind | 75 | AHF with renal dysfunction | Nesiritide 0.01 μg/kg/min | Standard Tx | Rise in serum creatinine by ≥20% and change in serum creatinine | No significant differences in the incidence of a 20% creatinine increase or creatinine change. |
| USA     | 2011 | ASCEND-HF | RCT, multicenter, and double-blind | 7141 | AHF | Nesiritide 0.01 μg/kg/min vs. Standard Tx | Two coprimary endpoints: change in self-reported dyspnoea 6 and 24 h after | Two coprimary endpoints: change in self-reported dyspnoea 6 and 24 h after | No significant effect on dyspnoea was seen. |

(Continues)
| Country   | Year | Study title | Study design          | Sample size | Study population       | Intervention                  | Comparator | Primary endpoint                                                                 | Conclusion                                                                 |
|-----------|------|-------------|------------------------|-------------|------------------------|-------------------------------|------------|---------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| Nesiritide| USA  | ROSE        | RCT, multicenter,      | 360         | AHF with renal dysfunction | Nesiritide 0.005 μg/kg/min (dobutamine) | Standard Tx | Drug initiation and the composite endpoint of rehospitalization for HF and death from any cause during the period from randomization to Day 30 | Neither low-dose dopamine nor low-dose nesiritide enhanced decongestion or improved renal function. |
| Carperitide| Japan | PROTECT     | RCT, multicenter,      | 49          | AHF                    | Carperitide 0.01–0.05 μg/kg/min for 72 h vs. control | Standard Tx | Death and rehospitalization, at 18 months                                         | Significant reductions in mortality and rehospitalization were seen with carperitide. Carperitide monotherapy restored the acute phase and improved the degree of dyspnoea as assessed using the modified Borg scale. |
| Carperitide| Japan | COMPASS     | Prospective observational multicenter | 1832        | AHF                    | Carperitide 0.025–0.05 μg/kg/min | Standard Tx | Improvement in dyspnoea                                                        | Carperitide was used in 69.4% of patients. |
| Carperitide| Japan | ATTEND      | Prospective observational multicenter | 4842        | AHF                    | None                          | None        | None                                                                             | None                                                                         |

AHF, acute heart failure; ASCEND-HF, Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure; ATTEND, acute decompensated heart failure syndromes; BNP-CARDS, B-Type Natriuretic Peptide in Cardiorenal Decompensation Syndrome; COMPASS, Carperitide Effects Observed through Monitoring Dyspnea in Acute Decompensated Heart Failure Study; HF, heart failure; i.v., intravenous; N/A, not applicable; NTG, nitroglycerin; PCWP, pulmonary capillary wedge pressure; PRECEDENT, Prospective Randomized Evaluation of Cardiac Ectopy with Dobutamine or Natrecor Therapy; PROTECT, Prospective Trial of Cardioprotective Effect of Carperitide Treatment; RCT, randomized controlled trial; ROSE, Renal Optimization Strategies Evaluation; Tx, treatment; VMAC, Vasodilatation in the Management of Acute Congestive Heart Failure; WRF, worsening renal failure.
the rates of death and rehospitalization at 18 months in patients with AHF.

• In a prospective observational study of 1524 patients, carperitide monotherapy restored the acute phase and improved the degree of dyspnoea assessed using the modified Borg scale.

Compared with the ASCEND-HF trial, the size of the study populations was not large enough in these trials to evaluate safety and efficacy thoroughly, with the endpoints set at surrogate markers. There are also studies that report contradictory results.

• In a retrospective cohort study, Sasabuchi et al.31 conducted a database analysis of 47,032 patients and reported that patients treated with carperitide were more likely to receive renal replacement therapy within 21 days of surgery; however, the use of carperitide was not associated with higher or lower in-hospital mortality.

• Matsue et al.32 examined the efficacy of carperitide in 1038 patients with AHF and reported significantly higher in-hospital mortality in the carperitide group compared with the non-carperitide group, and potentially, more harmful effects were observed in elderly patients.

Based on the pharmacological effects of vasodilation, natriuresis, and renin–angiotensin–aldosterone system inhibition, carperitide seems to be useful in patients with pulmonary congestion and patients with refractory HF requiring inotropes, according to current Japanese Circulation Society guidelines. However, because of controversial clinical data, the evidence for the use of carperitide in the setting of AHF in Japan does not appear to be sufficient. Given the consequence of nesiritide in the USA, larger-scale clinical trials evaluating its efficacy and safety are needed in Japan.

### Vasodilators

#### General comments

In the absence of hypotension, vasodilators potently decrease both venous tone (preload) and arterial tone (afterload) (Figure 1). Hence, vasodilators are most frequently administered in combination with intravenous diuretics in the setting of AHF to improve congestive symptoms. The comparison of clinical trials on vasodilators between the USA and Japan is shown in Table 2.

#### USA

Currently available vasodilators include nitroglycerin (NTG), isosorbide dinitrate (ISDN), sodium nitroprusside, and nesiritide. Although vasodilators have been used for the treatment of AHF, no robust evidence confirms their definitive efficacy and safety.

Several studies on ISDN have shown its clinical benefits in patients with AHF. In the Acute Heart Failure Global Survey of Standard Treatment (ALARM-HF) registry, patients admitted with AHF and treated with diuretics and vasodilators had significantly better in-hospital survival compared with patients treated with diuretics alone or those treated with inotropes.33 In addition, Cotter et al.34 showed that high-dose ISDN, given as repeated intravenous boluses after low-dose intravenous furosemide, was safe and effective in controlling severe pulmonary oedema. This treatment regimen was more effective than high-dose furosemide with low-dose ISDN in terms of the need for mechanical ventilation and frequency of myocardial infarction. Finally, Sharon et al.35 demonstrated that high-dose ISDN was safer and better than bi-level positive airway pressure combined with conventional therapy in patients with severe pulmonary oedema.

Contrary to the findings on ISDN, NTG showed conflicting clinical results. In the control arm of the VMAC trial, PCWP was significantly decreased with NTG at 3 h after administration, compared with placebo. However, the effect of NTG was not sustainable, and no significant differences were observed in terms of clinical status and dyspnoea during admission.21 In a subgroup analysis, the onset of the NTG-mediated haemodynamic effect was delayed because of the early development of tolerance despite aggressive up-titrination.36 Following the VMAC trial, Breidthardt et al.37 reported a rapid decrease in serum levels of B-type natriuretic peptide with high-dose subcutaneous or sublingual ISDN administration in addition to conventional therapy, compared with conventional therapy alone. However, this study did not show improvements in 90 day mortality and rehospitalization rates.

Clinical trials of vasodilator therapy in AHF do not provide sufficient evidence to make a definitive conclusion at this time. In light of this situation, Wakai et al.38 integrated the results of previous clinical trials related to vasodilators and analysed the results. Data from 634 patients were combined from four clinical trials of two types of vasodilators (ISDN and NTG). There was no significant difference in terms of effect between furosemide and morphine, furosemide alone, hydralazine, pirenalrol, intravenous nesiritide, and placebo. Given these clinical findings, the use of vasodilators as an adjuvant to diuretic therapy for dyspnoea relief is considered a Class IIb recommendation with evidence level A in the current ACC/AHA guidelines.6

#### Japan

The lack of evidence regarding vasodilators is similar in Japanese practice. As discussed in the previous section, carperitide is the most commonly used vasodilator, followed
### Table 2  Summary of clinical trials with vasodilators in heart failure

| Country | Year | Study title                  | Study design                  | Sample size | Study population                                      | Intervention            | Comparator   | Primary endpoint                                                                 | Conclusion                                                                                                                                   |
|---------|------|------------------------------|--------------------------------|-------------|-------------------------------------------------------|-------------------------|-------------|----------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| ISDN    | USA  | 2004 African-American Heart Failure Trial | RCT, multicenter, and double-blind | 1050        | Black patients who had NYHA Class III or IV HF with dilated ventricles | Fixed dose of ISDN-H   | Placebo     | Composite score made up of weighted values for death from any cause, a first hospitalization for HF, and change in the quality of life | The addition of a fixed dose of ISDN-H to standard therapy for HF including neurohormonal blockers is efficacious and increases survival among Black patients with advanced HF. |
| ISDN    | USA  | 1986 V-HeFT I                | RCT, multicenter, and double-blind | 642         | CHF ISDN-H Prazosin                                   | Mortality               | Prazosin    |                                                                                   |                                                                                   |
| ISDN    | USA  | 1991 V-HeFT II               | RCT, multicenter, and double-blind | 804         | CHF, men receiving digoxin and diuretic therapy for HF ISDN-H | Enalapril               | 2 year mortality |                                                                                   | Further survival benefit with enalapril in the present trial (18%) strengthens the conclusion that vasodilator therapy should be included in the standard treatment for HF. |

CHF, congestive heart failure; HF, heart failure; ISDN, isosorbide dinitrate; ISDN-H, isosorbide dinitrate plus hydralazine; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RCT, randomized controlled trial; V-HeFT I, Vasodilator-Heart Failure Trial I; V-HeFT II, Vasodilator-Heart Failure Trial II.
by NTG, ISDN, and sodium nitroprusside. Mizutani et al.\textsuperscript{39} conducted a clinical trial comparing the effect on haemodynamic change and short-term and long-term prognosis between ISDN and carperitide. There was no significant difference in prognosis, although ISDN improved haemodynamics more effectively than carperitide. Once again, the evidence for carperitide appears insufficient, and careful examination of its efficacy and safety is needed. As for the rest of the vasodilators, their use was low based on the registry data in Japan (ISDN, 9.2%; NTG, 26.0%),\textsuperscript{7} despite strong guideline recommendations.

With respect to frequency of vasodilator use, there does not seem to be a significant discrepancy between the USA and Japan; 26% of patients received vasodilators (70% of them received diuretics) in the Acute Decompensated Heart Failure National Registry (USA),\textsuperscript{19,40} compared with 35% of patients in the ATTEND registry (Japan).\textsuperscript{12} This suggests that vasodilators are not considered standard therapy in AHF at this time. The use of vasodilators was slightly higher in Japan, and this might be due to the implementation of a clinical scenario classification of AHF suggested by Mebazaa et al.\textsuperscript{41} A clinical scenario classification can facilitate the use of vasodilators in AHF, because some AHF patients may predominantly have a volume redistribution issue, rather than hypervolaemia.

**Tolvaptan**

**General comments**

Tolvaptan, one of the selective vasopressin 2 (V\textsubscript{2}) receptor antagonists, facilitates fluid excretion in urine by reducing the expression of aquaporin 2 in the collecting duct via inhibition of vasopressin receptors (Figure 1). The effect of tolvaptan in clinical trials is expected to be different than that of conventional diuretics (Table 3), as it produces water diuresis rather than diuresis with excretion of electrolytes, such as sodium and potassium.

**USA**

Currently, two ‘vaptans’ have been approved in the USA. The first agent approved by the Food and Drug Administration is conivaptan, a non-selective, V\textsubscript{1a}/V\textsubscript{2} receptor antagonist. In order to examine the effect of the second agent, tolvaptan, the Acute and Chronic Therapeutic Impact of a Vasopressin-2 Antagonist in Congestive Heart Failure trial was conducted. The trial revealed dose-independent loss of body weight (BW), improvement of signs and symptoms of HF, and lower mortality in patients with renal impairment from severe congestion in the tolvaptan group, compared with placebo.\textsuperscript{42} Finally, in the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan trial, the effect of tolvaptan in HF patients with left ventricular ejection fraction of less than 40% was compared with placebo. This trial reported greater improvement of symptoms, such as dyspnoea and BW loss in the 24 h after drug administration. However, it did not show an improvement in overall symptom scores nor an effect on long-term clinical outcomes, such as mortality and readmission rate.\textsuperscript{43,44}

Yet, in addition to a post hoc analysis revealing more improvement with tolvaptan compared with placebo in patients with lower serum sodium,\textsuperscript{45} tolvaptan seems to have a potentially beneficial effect on volume status and AHF symptoms in the initial treatment days.\textsuperscript{44,46} In light of these findings, the Targeting Acute Congestion with Tolvaptan in Congestive Heart Failure Study (TACTICS-HF) and Short Term Clinical Effects of Tolvaptan in Patients Hospitalized for Worsening Heart Failure with Challenging Volume Management (Study to Evaluate Challenging Responses to Therapy in Congestive Heart Failure) were performed.\textsuperscript{47} In the former prospective, double-blind, placebo-controlled trial of 257 patients with AHF, the addition of tolvaptan to a standardized furosemide regimen did not improve dyspnoea, a primary endpoint.\textsuperscript{48} In the latter randomized, double-blind, placebo-controlled study of 250 patients with AHF, tolvaptan was not associated with greater early improvement in dyspnoea, in spite of rapid and persistent weight loss.\textsuperscript{49}

**Japan**

In Japan, clinical evidence regarding the efficacy and safety of tolvaptan has been accumulated in recent years.

- In the AHF volume control multicenter randomized trial in 109 patients with AHF, the results suggest that tolvaptan might be efficacious and safe compared with carperitide because of significantly higher urine output even with thirst, lower incidence of renal impairment and hypotension requiring drug discontinuation, and lower cost.\textsuperscript{50}
- Shirakabe et al.\textsuperscript{51} investigated 183 patients admitted to the intensive care unit with AHF, which revealed a significant reduction in the total amount of furosemide, prevention of acute renal impairment, and improvement in 180 day mortality with tolvaptan administration compared with conventional treatment.
- Kinugawa et al.\textsuperscript{52} reported the improvement of congestion and significant BW loss 7 and 14 days after tolvaptan administration in patients with insufficient response to loop diuretics in the post-marketing surveillance of tolvaptan in Japan. These findings support the results of the previous study reported by Shirakabe et al.\textsuperscript{51}
- Matsue et al.\textsuperscript{53} reported the answering question on tolvaptan’s efficacy for patients with acute decompensated heart failure and renal failure study, a prospective,
multicenter, randomized, open-label, parallel-group study, which found that tolvaptan in addition to conventional therapy achieved more diuresis and symptom relief in AHF patients with renal impairment than conventional therapy alone.

Currently, tolvaptan has been broadly used as a diuretic with a new mechanism of action in Japan since its approval as a drug for HF in 2010. In contrast, tolvaptan is approved only for the treatment of hyponatraemia in the USA based on the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan trial, which did not show an improvement of long-term outcomes, such as cardiovascular mortality and readmission rate. Based on the finding of tolvaptan on TACTICS-HF and Study to Evaluate Challenging Responses to Therapy in Congestive Heart Failure, the discussion seems to be moving towards the next stage of development of better strategies for the treatment of AHF, as there does not appear to be a justification for additional studies in acute or chronic HF. Moreover, the use of tolvaptan is discouraged in an editorial on the TACTICS-HF based on efficacy and cost.54

Inotropes

Between the USA and Japan, there seems to be no significant difference in the view of inotropes as a ‘necessary evil’ for cases involving acutely decompensated HF. Because levosimendan is not available in Japan, we will cover the topic of classic inotropic agents, such as dobutamine and milrinone and their use in end-stage HF (Table 4). We will also exclude the discussion of any haemodynamic support such as Impella or extracorporeal membrane oxygenation.

Dobutamine

General comments
Dobutamine is an intravenous catecholaminergic agent, introduced in the late 1970s, that mainly acts on the beta-1 adrenergic receptor (and has a slight effect on the beta-2 and alpha-1 adrenergic receptors) (Figure 1). Dobutamine is known to decrease left ventricular end-diastolic pressure with a slight increase in heart rate.55

USA
Although there is concern regarding the relationship between a continuous infusion of dobutamine for more than 72 h and haemodynamic tolerance,56 dobutamine was used for short-term infusion and subsequent chronic home or outpatient infusions because of the evidence of a potential clinical benefit.57–61 A subanalysis from the Floplan International Randomized Survival Trial has altered the clinical benefit of dobutamine, as it was demonstrated that dobutamine was associated with worse survival and clinical outcomes and did not improve quality of life during or after the infusions.62 Despite this observational data, substantial experience has verified that the use of inotropic therapy for the treatment of severe HF is associated with reduced survival. However, previous clinical studies differed considerably from modern practice in regard to patient selection and contemporary HF therapy including beta-blockers, aldosterone antagonists, defibrillators, or cardiac resynchronization. There are no recent trials on chronic inotropic use, and given the clinical uncertainty and controversy over their use, there is wide variation in inotrope use among institutions. In light of this background, a recent retrospective study has shown that survival on inotropes for patients who were not candidates for transplant or left ventricular assist device remained poor.63

Japan
- The effect on pulmonary artery diastolic pressure and PCWP was higher with dobutamine than with dopamine in an earlier crossover trial. Dobutamine was also more effective in improving congestion.
- Despite no evidence of the superiority of dobutamine to milrinone in previous clinical trials, dobutamine appeared to be the preferable inotrope for in-hospital management compared with milrinone (dobutamine 12.7% vs. milrinone 2.8%) within the ATTEND registry in Japan.

Milrinone

General comments
Milrinone is a non-catecholaminergic agent with a positive inotropic effect that was introduced in the early 1990s for the treatment of severe HF with impaired systolic function (Figure 1). Milrinone has also exhibited a similar inotropic effect with dobutamine in a different mechanism; however, no head-to-head clinical trials have been conducted between the two agents.

USA
Prospective Randomized Milrinone Survival Evaluation and Outcomes of Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure are two of the largest and most representative studies to examine milrinone therapy available to date. Prospective Randomized Milrinone Survival Evaluation enrolled 1088 patients with New York Heart Association III or IV HF, randomized them to placebo or oral milrinone, and demonstrated that the milrinone group had a 28% higher mortality at 6.1 months.64 Outcomes of Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure evaluated in-hospital inotrope use in 958 patients with HF exacerbation. The primary endpoint was the number of days hospitalized for cardiovascular causes within 60 days.65 There was more hypotension and...
| Study title                              | Design                          | Country | Year | Sample size | Study population | Intervention                                 | Comparator | Primary endpoint | Conclusion                                                                 |
|-----------------------------------------|---------------------------------|---------|------|-------------|------------------|----------------------------------------------|------------|-----------------|---------------------------------------------------------------------------|
| Tolvaptan Japan 2013 N/A                | Prospective observational study | Japan   | 2013 | 114         | ADHF at high risk of WRF | Tolvaptan 15 mg once daily plus conventional Tx | Conventional Tx | UOP at 24 and 48 h | UOP at 24 and 48 h was higher, and incidence of WRF was lower with tolvaptan. Early administration of tolvaptan could prevent exacerbation of AKI and may improve the prognosis for ADHF patients. |
| Tolvaptan Japan 2014 N/A                | Prospective observational study | Japan   | 2014 | 183         | ADHF              | Tolvaptan 7.5 mg with continuous i.v. furosemide and additionally at 12 h intervals until HF was compensated | Conventional Tx | In-hospital mortality and WRF | Early administration of tolvaptan could prevent exacerbation of AKI and may improve the prognosis for ADHF patients. |
| Tolvaptan Japan 2014 N/A                | Prospective cohort (post-marketing surveillance) | Japan   | 2014 | 1840        | CHF               | Tolvaptan 3.75–15 mg/day                       | N/A        | Decrease in BW and hypernatraemia | Tolvaptan demonstrated aquaretic efficacy in HF patients with diuretic-resistant volume overload. Fewer adverse events (e.g. worsening HF and hypotension requiring drug discontinuation) were observed with tolvaptan. |
| Tolvaptan Japan 2013 AVCMA               | RCT, multicenter, and open-label | Japan   | 2013 | 109         | ADHF              | Tolvaptan 3.75–15 mg/day                       | Carperitide 0.0125–0.025 μg/kg/min | Increase in urine volume | Fewer adverse events (e.g. worsening HF and hypotension requiring drug discontinuation) were observed with tolvaptan. Adding tolvaptan achieved more diuresis and symptom relief in AHF patients with renal impairment. |
| Tolvaptan Japan 2016 AQUAMARINE         | RCT, multicenter, and open-label | Japan   | 2016 | 220         | ADHF with renal dysfunction (eGFR 15 to 60 mL/min/1.72 m²) | Tolvaptan plus conventional Tx | Conventional Tx | UOP within 48 h | Adding tolvaptan achieved more diuresis and symptom relief in AHF patients with renal impairment. |
| Conivaptan USA 2001 N/A                 | RCT, multicenter, and double-blind | USA     | 2001 | 142         | Symptomatic HF (NYHA class III and IV) | Single i.v. dose (10, 20, or 40 mg) conivaptan | Conventional Tx | Increase in PCWP 3 to 6 h, AUC for the change from baseline PCWP | Conivaptan resulted in modest decreases in filling pressures concurrent with an increase in UOP. |

(Continues)
| Country | Year | Study title | Study design | Sample size | Study population | Intervention | Comparator | Primary endpoint | Conclusion |
|---------|------|-------------|--------------|-------------|------------------|--------------|------------|------------------|------------|
| Tolvaptan USA | 2003 | | RCT, multicenter, and double-blind | 254 | LVEF <40% and hospitalized for HF with persistent signs and symptoms of systemic congestion despite standard Tx | Tolvaptan 30, 45, and 60 mg/day for 25 days | Conventional Tx | over the 12 h evaluation period | Decrease in BW By Day 1, BW decreased in tolvaptan group, but no further decreases were noted after Day 1. Median BW at 24 h decreased in all patients in the tolvaptan group but no difference in worsening HF at 60 days. |
| Tolvaptan USA | 2003 | ACTIV in CHF | RCT, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging, phase 2 trial | 319 | AHF | Tolvaptan 30, 60, and 90 mg/day for 60 days | Conventional Tx | Change in BW at 24 h after randomization | |
| Tolvaptan USA | 2007 | MENTOR | RCT, multicenter, and double-blind | 240 | AHF | Tolvaptan 30 mg | Conventional Rx | LVEDVI, subject-assessed symptom scales, and Minnesota questionnaire | Tolvaptan did not have a significant effect on LVEDVI. No significant differences in symptoms or QOL measures. Patients with AHF can derive short-term benefit from tolvaptan. |
| Tolvaptan USA | 2008 | ECLIPSE | RCT, multicenter, and double-blind | 181 | AHF, symptomatic NYHA Classes III and IV HF for at least 3 months with LV systolic dysfunction and LVEF of <40% HFrEF | Tolvaptan 15, 30, or 60 mg | Placebo | PCWP | |
| Tolvaptan USA | 2007 | EVEREST-Outcomes | RCT, multicenter, and double-blind | 4133 | HFrEF | Tolvaptan 30 mg/day | Conventional Tx | All-cause mortality, composite CV mortality or HF hospitalization Dyspnœa improvement measured by Likert scale at 8 and 24 h | Addition of tolvaptan to a standardized furosemide regimen did not improve the number of responders |
| Tolvaptan USA | 2016 | TACTICS-HF | RCT, multicenter, and double-blind | 257 | AHF | Tolvaptan (given at 0, 24, and 48 h) | Conventional Tx | |

(Continues)
atrial arrhythmias in the milrinone group and no difference in the primary outcome or survival. These two findings led to the conclusion that milrinone should only be administered to specific types of patients and continued over only a short period of time. More recently, a large observational study demonstrated significant differences in the patterns of use of positive inotropic agents among a diverse group of hospitals in the USA. This study identified various hospital patterns based on the type of agents: dobutamine predominant (29% of hospitals), dopamine predominant (25%), milrinone predominant (1%), mixed dobutamine and dopamine pattern (32%), and mixed pattern including all three agents.66

Japan

In Japan, the effects of milrinone on AHF have been investigated in a multicenter, double-blind clinical trial,67 which revealed that the time of onset of action was prompt with intravenous administration and the effect on haemodynamic improvement was dose dependent. In the AHF guidelines of the Japanese Circulation Society, milrinone is approved as Class IIa and evidence level of A; however, the use of milrinone should be confined to carefully selected patients with low blood pressure and reduced cardiac output who can have their blood pressure and heart rhythm monitored closely.

Inotropes in palliative care (home inotrope therapy vs. oral inotrope therapy)

The general role of inotropes in current practice is to treat acutely decompensated HF and maintain end-organ function in transplant or left ventricular assist device candidates, or to be used as palliative therapy.68 Home inotrope therapy has been shown to shorten length of hospital stay69 and to increase cardiovascular death.70

The incidence of new-onset HF in the elderly population (>65 years) in Japan is 23.0% in 2010, with an estimated incidence of 29.1% in 2020 and 31.6% in 2030.71 Given the age limit on advanced HF therapy of less than 65 years of age in Japan, the number of patients with end-stage HF who are potential candidates for home inotrope therapy is increasing. At present, home inotrope therapy is not officially approved for patients, and an oral inotropic agent is frequently prescribed as an alternative in Japan. There appear to be some cases involving oral inotrope use in patients who require an improvement of quality of life in end-stage HF,72 and this enables a weaning of the intravenous agents. The evidence of the use of oral inotrope in Japan is based on the Effects of Pimobendan on Chronic Heart Failure Study. This study identified the effect of pimobendan as an oral inotrope on significantly lowered morbidity and improved the physical activity of patients with mild to moderate congestive heart failure (CHF) compared with placebo.

Table 3 (continued)

| Country | Year | Study title | Study design | Sample size | Study population | Intervention | Comparator | Primary endpoint | Conclusion |
|---------|------|-------------|--------------|-------------|------------------|--------------|------------|------------------|-----------|
| USA     | 2016 | SECRET of CHF | RCT, multicenter, and placebo-controlled | 250 AHF | 250 AHF | Tolvaptan 30 mg/day | Placebo | The change in self-assessed dyspnoea score at 8 and 16 h by a 7-point Likert scale | Tolvaptan was not associated with greater early improvement in dyspnoea in patients with AHF who were selected for greater potential benefit from vasopressin receptor inhibition. |
| Country  | Year | Study title | Study design | Sample size | Study population | Intervention | Comparator | Primary endpoint | Conclusion |
|----------|------|-------------|--------------|-------------|------------------|--------------|------------|------------------|------------|
| Dobutamine | USA 1999 | FIRST | RCT, multicenter, and double-blind | 471 | Patients with advanced HF | Dobutamine | No dobutamine | Worsening HF, need for vasoactive medications, resuscitated cardiac arrest, MI, and total mortality | Dobutamine use at the time of randomization was associated with a higher 6 month mortality rate. Levosimendan may be better than dobutamine for treating patients with a history of CHF or those on beta-blocker therapy when they are hospitalized with ADHF. Despite its beneficial haemodynamic actions, long-term therapy with oral milrinone increases the morbidity and mortality of patients with severe CHF. Milrinone may have a bidirectional effect based on aetiology in decompensated HF. Milrinone may be deleterious in ischaemic HF but neutral to beneficial in NICM. Pimobendan is effective in patients with CHF but is less effective in patients with OMI than in patients with DCM or other heart diseases. |
| Dobutamine | USA 2009 | SURVIVE | RCT, multicenter, and double-blind | 1327 | Critically ill patients hospitalized with low-output HF | Dobutamine | Levosimendan | All-cause mortality over 180 days | |
| Milrinone | USA 1991 | PROMISE | RCT, multicenter, and double-blind | 1088 | Severe CHF (NYHA Class III or IV) and advanced LV dysfunction | Oral milrinone 40 mg daily | Placebo | All-cause mortality | |
| Milrinone | USA 2003 | OPTIME-CHF | RCT, multicenter, and double-blind | 949 | HF systolic dysfunction and decompensated HF | 48 to 72 h of intravenous milrinone | Placebo | Hospitalized from cardiovascular causes within 60 days | |
| Pimobendan | Japan 2001 | None | Prospective observational multicenter | 34 | Mild to moderate CHF | Pimobendan, 2.5 mg/day for 12 months | None | HF symptoms | |

ADHF, acute decompensated heart failure; CHF, chronic heart failure; DCM, dilated cardiomyopathy; FIRST, Flolan International Randomized Survival Trial; HF, heart failure; LV, left ventricular; MI, myocardial infarction; NICM, non-ischaemic cardiomyopathy; NYHA, New York Heart Association; OMI, old myocardial infarction; OPTIME-CHF, Outcomes of Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure; PROMISE, Prospective Randomized Milrinone Survival Evaluation; RCT, randomized controlled trial; SURVIVE, Survival of Patients with Acute Heart Failure in Need of Intravenous Inotropic Support.
The use of oral inotrope in patients with end-stage HF has fallen out of favour in the USA because most of the clinical trials related to oral inotropes have generated negative results. In addition, a recent retrospective study demonstrated that there were no mortality differences between chronic intravenous dobutamine or milrinone in patients with stage D HF being discharged from the hospital.

**Differences in socio-economic background**

Considering the differences between the treatment strategies for AHF in the USA and Japan, a discussion of the socio-economic background seems inevitable.

**USA**

In the USA, despite recent changes, universal coverage is lacking. This puts a significant financial burden on uninsured patients, who often receive only emergency and not longitudinal care. That is, such patients present in AHF to the emergency rooms and are managed in the inpatient setting. However, because of financial and other constraints, such patients often have poor follow-up post-discharge and have difficulty in paying for medications. They thus present again as emergency cases, at enormous expense to the system, and with worse results.

In addition, even if patients are insured, they generally have copays for prescription medications. Branded and on-patent medications almost always have significantly higher copays; increasingly, patients request generics or older medications to minimize financial impact. This does affect choices in the acute setting for medications that will be continued in the outpatient setting. Finally, there is increased cost consciousness in recent years. Inpatient formularies vary from hospital to hospital, with medication prices playing significant roles in decisions to maintain and/or restrict access to certain medications. For example, tolvaptan, an expensive medication, in many hospitals is restricted to nephology service use alone.

Thus, market forces may play a bigger role in the management of HF in the USA compared with Japan.

**Japan**

Two unique characteristics of the Japanese medical system warrant consideration. The first is that a universal healthcare system has been in place since 1961, and it ensures relative equality of medical service and access. This system has achieved good health across the population at low cost, with increased equality between different population groups. However, at times, the cost of medical care becomes secondary as Japan’s basic policy has been a laissez-faire approach to how services are provided. For instance, clinicians in Japan generally can determine treatment strategy and provide any drug for patients with AHF, no matter how much it costs.

Second, the concept of the ‘benevolent act’, which implies that caregivers should provide the care without expecting a financial return, is heavily emphasized in Japan. As a consequence, expensive drugs, which have not been shown to justify their cost based on outcomes, might be overused in the care of AHF patients in Japan. Careful attention should also be paid to the cost–benefit issue in terms of medical treatment of patients with AHF.

**Conclusions**

Despite the accumulation of clinical data discussed earlier, there is still less conclusive information on AHF treatment than there is for CHF treatment. Recently, the increase in the number of patients with AHF and CHF has become one of the most pressing medical issues facing both industrialized and developing nations. Therefore, when developing new drugs and medical devices to treat these conditions, it is essential to consider economic factors and the relevant insurance systems.

**Conflict of interest**

None declared.

**References**

1. Teixeira A, Parenica J, Park JJ, Ishihara S, AlHabib KF, Laribi S, Maggioni A, Miró Ò, Sato N, Kajimoto K, Cohen-Solal A, Fairman E, Lassus J, Mueller C, Peacock WF, Januzzi JL, Choi D-J, Plaisance P, Spinar J, Mebazaa A, Gayat E, GREAT (Global Research on Acute Conditions Team) Network. Clinical presentation and outcome by age categories in acute heart failure: results from an international observational cohort. *Eur J Heart Fail* 2015; 17: 1114–1123.

2. Shah MR, Hasselblad V, Tasissa G, Christenson RH, Binay C, O’Connor CM, Ohman EM, Stevenson LW, Calif RM. Rapid assay brain natriuretic peptide and troponin I in patients hospitalized with decompensated heart failure.
(from the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effective Trial). *Am J Cardiol* 2007; 100: 1427–1433.

3. McMurray J, Swedberg K. Treatment of chronic heart failure: a comparison between the major guidelines. *Eur Heart J* 2006; 27: 1773–1777.

4. Rajadurai J, Tse H-F, Wang C-H, Yang N-I, Zhou J, Sim D. Understanding the epidemiology of heart failure to improve management practices: an Asia-Pacific perspective. *J Card Fail* 2017; 23: 327–339.

5. Gheorghiade M, Follath F, Ponikowski P, Barsuk JH, Blair JEA, Cleland JG, Dickstein K, Drazner MH, Fornarow GC, Jaarsma T, Jondeau G, Sendon JL, Mebazaa A, Metra M, Nieminen M, Pang PS, Seferovic P, Stevenson LW, van Veldhuisen DJ, Zannad F, Anker SD, Stevenson LW, Tang WHW, Califf RM, Adams KF. Relation between dose of loop diuretics and outcomes in a randomized controlled trial. *Eur J Heart Fail* 2011; 13: 797–805.

6. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Drazner MH, Fornarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JVF, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WHW, Califf RM, Adams KF. Relation between dose of loop diuretics and outcomes in a heart failure population: results of the ESCAPE trial. *Eur J Heart Fail* 2007; 9: 1064–1069.

7. Peacock WF, Costanzo MR, De Marco T, Lopatin M, Wynn J, Mills RM, Emerman CL, ADHERE Scientific Advisory Committee and Investigators. Impact of intravenous loop diuretics on outcomes of patients hospitalized with acute decompensated heart failure: insights from the ADHERE registry. *Circulation* 2009; 113: 12–19.

8. Dohi K, Ito M. Immediate and short-term use of tolvaptan for acute decompensated heart failure. *Circ J* 2014; 78: 829–831.

9. Dohi K, Ito M. Novel diuretic strategies for the treatment of heart failure in Japan. *Circ J* 2014; 78: 1816–1823.

10. Yancy CW, Lopatin M, Stevenson LW, De Marco T, Fornarow GC, ADHERE Scientific Advisory Committee and Investigators. Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated heart failure with preserved systolic function: a report from the Acute Decompensated Heart Failure National Registry (ADHERE) Database. *J Am Coll Cardiol* 2006; 47: 76–84.

11. O’Connor CM, Starling RC, Hernandez AF, Armstrong PW, Dickstein K, Hasselblad V, Heizer GM, Komajda M, Massie BM, McMurray JVF, Nieminen MS, Reisin EJ, Rouleau JL, Swedberg K, Adams KF, Anker SD, Atar D, Bhattler A, Botero R, Bohidar NR, Butler J, Clausell N, Corbalán R, Costanzo MR, Dahlstrom U, Deckelbaum LJ, Diaz R, Dunlap ME, Ezekowitz JA, Feldman D, Felker GM, Fornarow GC, Gennevois D, Gottlieb SS, Hill JA, Hollandier JE, Howlett JG, Hudson MP, Kociol RD, Krum H, Laoux-Cevicis A, Levy WC, Méndez GF, Metra M, Mittal S, Oh BH, Pereira NL, Ponikowski P, Tang WH, Tanomsup S, Teerlink JR, Tripodiadis FF, Troughton RW, Voors AA, Whellan DJ, Zannad F, Califf RM. Effect of nesiritide in patients with acute decompensated heart failure. *N Engl J Med* 2011; 365: 32–43.

12. Publication Committee for the V-MAC Investigators (Vasodilatation in the Management of Acute CHF). Intravenous nesiritide vs nitroglycerin for treatment of decompensated congestive heart failure: a randomized controlled trial. *JAMA* 2002; 287: 1531–1540.

13. Sackker-Bernstein JD, Skopicki HA, Aaronson KD. Risk of worsening renal function with nesiritide in patients with acutely decompensated heart failure. *Circulation* 2005; 111: 1487–1491.

14. Sackker-Bernstein JD, Kowalski M, Fox M, Aaronson K. Short-term risk of death after treatment with nesiritide for decompensated heart failure: a pooled analysis of randomized controlled trials. *JAMA* 2005; 293: 1900–1905.

15. Topol EJ. The last decade of nesiritide. *N Engl J Med* 2011; 365: 81–82.

16. Fornarow GC, Corday E, ADHERE Scientific Advisory Committee. Overview of acutely decompensated heart failure clinical trials. *Am J Cardiol* 2013; 111: 1177–1185.

17. van Beurden VM, Hernandez AF, Stebbins A, Hasselblad V, Ezekowitz JA, Califf RM, O’Connor CM, Starling RC, Hernandez AF. Effects of nesiritide and predictors of urine output in acute decompensated heart failure: results from ASCEND-HF (acute study of clinical effectiveness of nesiritide and decompensated heart failure). *Heart Fail Rev* 2004; 9: 179–185.

18. Gottlieb SS, Stebbins A, Voors AA, Hasselblad V, Ezekowitz JA, Califf RM, Gottlieb SS, O’Connor CM, Starling RC, Hernandez AF. Nesiritide, renal function, and associated outcomes during hospitalization for acute decompensated heart failure: results from the Acute Study of Clinical Effectiveness of Nesiritide and Decompensated Heart Failure (ASCEND-HF). *Circulation* 2014; 130: 958–965.

19. Patel PA, Heizer G, O’Connor CM, Schulte PJ, Dickstein K, Ezekowitz JA, Armstrong PW, Hasselblad V, Mills RM, McMurray JVF, Starling RC, Tang WHW, Califf RM, Hernandez AF. Hypertension during hospitalization for acute heart failure is independently associated with 30-day mortality: findings from ASCEND-HF. *Circ Heart Fail* 2014; 7: 918–925.

20. Hata N, Seino Y, Tsutamoto T, Hiramitsu S, Kaneko N, Yoshikawa T, Yokoyama H, Tanaka K, Mizuno K, Nejima J, Kinoshita T.D. Tanaka et al.
M. Effects of carperitide on the long-term prognosis of patients with acute decompensated chronic heart failure: the PROTECT multicenter randomized controlled study. *Circ J* 2008; 72: 1787–1793.

30. Nomura F, Kurobe N, Mori Y, Hikita A, Kawai M, Suwa M, Okutani Y. Multicenter prospective investigation on efficacy and safety of carperitide as a first-line drug for acute heart failure syndrome with preserved blood pressure: COMPaSS: Carperitide Effects Observed through Monitoring Dyspnea in Acute Decompensated Heart Failure Study. *Circ J* 2008; 72: 1777–1786.

31. Sasabuchi Y, Yasunaga H, Matsui H, Lefor AK, Fushimi K, Sanui M. Carperitide increases the need for renal replacement therapy after cardiovascular surgery. *J Cardiothorac Vasc Anesth* 2015; 29: 1426–1431.

32. Matsue Y, Yoshida N, Kume T, Okura H, Suzuki M, Matsamura A, Yoshida K, Hashimoto Y. Carperitide is associated with increased in-hospital mortality in acute heart failure: a propensity score-matched analysis. *J Card Fail* 2015; 21: 859–864.

33. Mebazaa A, Parissis J, Porcher R, Gayat E, Nikolau M, Boas FV, Delgado JF, Pollath F. Short-term survival by treatment among patients hospitalized with acute heart failure: the global ALARM-HF registry using propensity scoring methods. *Intensive Care Med* 2011; 37: 290–301.

34. Cotter G, Metzker E, Kaluski E, Faienna G, Miller R, Simovitz A, Shaham O, Marghityan D, Koren M, Blatt A, Moshkovitz Y, Zaidenberg R, Golik A. Randomised trial of high-dose isosorbide dinitrate plus low-dose furosemide versus high-dose furosemide in severe pulmonary oedema. *Lancet* 1998; 351: 389–395.

35. Sharon A, Shpier I, Kaluski E, Moshkowitz Y, Milovanov O, Polak R, Blatt A, Simovitz A, Shaham O, Faienna G, Metzger M, Stav D, Yoge V, Golik R, Krakover R, Vered Z, Cotter G. High-dose intravenous isosorbide-dinitrate is safer and better than Bi-PAP ventilation combined with conventional treatment for severe pulmonary edema. *J Am Coll Cardiol* 2000; 36: 832–837.

36. Elkayam U, Akhter MW, Singh H, Khan S, Usman A. Comparison of effects on left ventricular filling pressure of intravenous nesiritide and high-dose nitroglycerin in patients with decompensated heart failure. *Am J Cardiol* 2004; 93: 237–240.

37. Breidhardt T, Noveanu M, Potocki M, Reichlin T, Egli P, Hartweg S, Socrates T, Namay E, Christ M, Mebazaa A, Mueller C. Impact of a high-dose nitrate strategy on cardiac stress in acute heart failure: a pilot study. *J Intern Med* 2010; 267: 322–330.

38. Wakai A, McCabe A, Kidney R, Brooks SC, Seupaul RA, Diersch DB, Salter N, Fermann GJ, Pospisil C. Nitrates for acute heart failure syndromes. Cochrane Heart Group, ed. *Cochrane Database Syst Rev* 2013; 4: CD005151.

39. Mizutani T, Inomata T, Watanabe N, Maekawa E, Yanagisawa T, Shinagawa H, Koitabashi T. Takeuchi I, Izumi T. Comparison of nitrite compounds and carperitide for initial treatment of acute decompensated heart failure. *Int Heart J* 2011; 52: 114–118.

40. Adams KF, Fonarow GC, Edmister CM, Adams KF, Elkayam U, Barbagelata A, Ghali JK, Benza RL, McGrew FA, Toller P, Rolland E, Nieminen M, Komajda M, Parkhomenko I, Muzi A, Grinfeld L, Konstam MA, Kostic D, Krisa HB, Maggioni A, Ouyang J, Swedberg K, Zannad F, Zannor D, Udelson JE, EVEREST Investigators. Clinical course of patients with hyponatraemia and decompensated systolic heart failure and the effect of vasopressin receptor antagonism with tolvaptan. *J Card Fail* 2013; 19: 390–397.

41. Pang PS, Konstam MA, Krasa HB, Swedberg K, Zannad F, Blair JEA, Zimmr C, Teerlink JR, Maggioni AP, Burnett JC, Grinfeld L, Ouyang J, Udelson JE, Gheorghiade M, Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) Investigators. Effects of tolvaptan on dyspnoea relief from the EVEREST trials. *Eur J Heart* 2009; 30: 2223–2240.

42. Felker GM. Tolvaptan in patients hospitalized with acute heart failure. *Circ Heart Fail* 2015; 8: 997–1005.

43. Felker GM, Rentz RJ, Cole RT, Adams KF, Egnaeyck GF, Fuziat M, Patel CB, Echols M, Khourri MG, Taurus JM, Gupta D, Mondi P, Roberts R, O’Connor CH. Efficacy and safety of tolvaptan in patients hospitalized with acute heart failure. *J Am Coll Cardiol* 2017; 69: 1399–1406.

44. Konstam MA, Kiernan M, Chandler A, Dhingra R, Mody FY, Eisen H, Haught WH, Wagoner L, Gupta D, Patten R, Gorlin P, Korr K, Fileccia R, Pressler SJ, Gregory D, Wedge P, Dowling D, Romeling M, Konstam JM, Massaro JM, Udelson JE, SECRET of CHF Investigators, Coordinators, and Committee Members. Short-term effects of tolvaptan in patients with acute heart failure and volume overload. *J Am Coll Cardiol* 2017; 69: 1409–1419.

45. Suzuki S, Yoshihisa A, Yamaki T, Sugimoto K, Kunii H, Nakazato K, Abe Y, Saito T, Ohwada T, Suzuki H, Saitho S-I, Kubota I, Takeishi Y, AVCA Investigators. Acute heart failure with control multicenter randomized (AVCA) trial: comparison of tolvaptan and carperitide. *J Clin Pharmacol* 2013; 53: 1277–1285.

46. Shirakabe A, Hata N, Yamamoto M, Kobayashi N, Shinada T, Tomita K, Tsurumi M, Matsushita M, Okazaki H, Yamamoto Y, Yokoyama S, Asai K, Shimizu W. Immediate administration of tolvaptan prevents the exacerbation of acute kidney injury and improves the mid-term prognosis of patients with severely decompensated acute heart failure. *Circ J* 2014; 78: 911–921.

47. Kinugawa K, Sato N, Inomata T, Shimakawa T, Iwatate N, Mizuguchi K. Efficacy and safety of tolvaptan in heart failure patients with volume overload. *Circ J* 2014; 78: 844–852.

48. Matsue Y, Suzuki M, Tiori S, Yamaguchi S, Fagamizu S, Ono Y, Fuji H, Kitai T, Nishio T, Sugii K, Onishi Y, Noda M, Kagiyama N, Sato Y, Yoshida K, Goldsmith SR. Clinical effectiveness of tolvaptan in patients with acute heart failure.
failure and renal dysfunction. J Card Fail 2016; 22: 423–432.

54. Starling RC, Young JB. Tolvaptan in acute heart failure: time to move on. J Am Coll Cardiol 2017; 69: 1407–1408.

55. Akhtar N, Mikulic E, Cohn JN, Chaudhry MH. Hemodynamic effect of dobutamine in patients with severe heart failure. Am J Cardiol 1975; 36: 202–205.

56. Unverferth DA, Blanford M, Kates RE, Leier CV. Tolerance to dobutamine after a 72 hour continuous infusion. Am J Med 1980; 69: 262–266.

57. Unverferth DV, Magorien RD, Lewis RP, Leier CV. Long-term benefit of dobutamine in patients with congestive cardiomyopathy. Am J Heart 1980; 100: 622–630.

58. Liang CS, Sherman LG, Doherty JY, Wellington K, Lee VW, Hood WB. Sustained improvement of cardiac function in patients with congestive heart failure after short-term infusion of dobutamine. Circulation 1984; 69: 113–119.

59. Collins JA, Skidmore MA, Melvin DB, Engel PJ. Home intravenous dobutamine therapy in patients awaiting heart transplantation. J Heart Transplant 1994; 13: S126–S129.

60. Miller LW, Merkle EJ, Jennison SH. Outpatient use of dobutamine to support patients awaiting heart transplantation. J Heart Lung Transplant 1994; 13: 885–900.

61. O'Connor CM, Gattis WA, Uretsky BF, Adams KF, McNulty SE, Grossman SH, McKenna WJ, Zannad F, Swedberg K, Gheorghiade M, Califf RM. Continuous intravenous dobutamine is associated with an increased risk of death in patients with advanced heart failure: insights from the Floran International Randomized Survival Trial (FIRST). Am Heart J 1999; 138: 78–86.

62. Hashim T, Sanam K, Revilla-Martinez M, Morgan CJ, Tallaj JA, Pamboukian SV, Loyaga-Rendon RY, George JF, Acharya D. Clinical characteristics and outcomes of intravenous inotropic therapy in advanced heart failure. Circ Heart Fail 2015; 8: 880–886.

63. Packer M, Carver JR, Rodeheffer RJ, Ivanhoe RJ, DiBianco R, Zeldis SM, Hendrix GH, Bommer WJ, Elkayam U, Kukin ML, The PROMISE Study Research Group. Effect of oral milrinone on mortality in severe chronic heart failure. N Engl J Med 1991; 325: 1468–1475.

64. Cuffe MS, Califf RM, Adams KF, Benza R, Bourge R, Colucci WS, Massie BM, O'Connor CM, Pina I, Quigg R, Silver MA, Gheorghiade M. Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) Investigators. Short-term intravenous milrinone for acute exacerbation of chronic heart failure: a randomized controlled trial. JAMA 2002; 287: 1541–1547.

65. Partovian C, Gleich SR, Moisy PS, Li S-X, Wang H, Strait KM, Allen LA, Lagu T, Normand S-LT, Krumholz HM. Hospital patterns of use of positive inotrope agents in patients with heart failure. J Am Coll Cardiol 2012; 60: 1402–1409.

66. Seino Y, Momomura S, Takano T, Hayakawa H, Katoh K. Japanese Intravenous Milrinone Investigators. Multicenter, double-blind study of intravenous milrinone for patients with acute heart failure in Japan. Crit Care Med 1996; 24: 1490–1497.

67. Allen LA, Stevenson LW, Grady KL, Goldstein NE, Matlock DD, Arnold RM, Cook NR, Feller GM, Francis GS, Hauptman PJ, Havranek EP, Krumholz HM, Mancini D, Riegel B, Spertus JA. On behalf of the American Heart Association Council on Quality of Care and Outcomes Research, Council on Cardiovascular Nursing, Council on Clinical Cardiology, Council on Cardiovascular Radiology and Intervention, and Council on Cardiovascular Surgery and Anesthesia. Decision making in advanced heart failure: a scientific statement from the American Heart Association. Circulation 2012; 125: 1928–1952.

68. Hauptman PJ, Mikolajczak P, George A, Mohr CJ, Hoover R, Swindle J, Schnitzer MA. Chronic inotropic therapy in end-stage heart failure. Am Heart J 2006; 152: 1096.e1–e8.

69. Thackray S, Eastwood J, Freemantle N, Moreton S, Cland JG. The effectiveness and relative effectiveness of intravenous inotropic drugs acting through the adrenergic pathway in patients with heart failure—a meta-regression analysis. Eur J Heart Fail 2002; 4: 515–529.

70. Shimokawa H, Miura M, Nochioka K, Sakata Y. Heart failure as a general pandemic in Asia. Eur J Heart Fail 2015; 17: 884–892.

71. Sasayama S, Asahni H, Kihara Y, Yokawa S, Terada Y, Yoshida S, Ejiri M, Horikoshi I. Clinical effects of long-term administration of pimobendan in patients with moderate congestive heart failure. Heart Vessels 1994; 9: 113–120.

72. Cohn JN, Goldstein SO, Greenberg BH, Lorell BH, Bourge RC, Jaski BE, Gottlieb SO, McGrew F, DeMets DL, White BG, Vessaaninone Trial Investigators. A dose-dependent increase in mortality with vesseaninone among patients with severe heart failure. N Engl J Med 1998; 339: 1810–1816.

73. Gorodeski EZ, Chu EC, Reese JR, Shishibehor MH, Hsich E, Starling RC. Proposis on chronic dobutamine or milrinone infusions for stage D heart failure. Circ Heart Fail 2009; 2: 320–324.

74. Sommers BD, Gunja MW, Finegold K, Musco T. Changes in self-reported insurance coverage, access to care, and health under the Affordable Care Act. JAMA 2015; 314: 366–374.

75. Sommers BD, Gawande AA, Baicker K. Health insurance coverage and health—what the recent evidence tells us. N Engl J Med 2017; 377: 586–593.

76. Miller S. The effect of insurance on emergency room visits: an analysis of the 2006 Massachusetts health reform. J Public Econ 2012; 96: 893–908.

77. Yancy CW, Januzzi JL, Allen LA, Butler J, Davis LL, Fonarow GC, Ibrahim NE, Jessup M, Lindenfeld J, Maddox TM, Masoud FA, Motiwala SR, Patterson JH, Walsh MN, Wasserman A. 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment: answers to 10 pivotal issues about heart failure with reduced ejection fraction: a report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. J Am Coll Cardiol 2018; 71: 201–230.

78. Reich MR, Shibuya K. The future of Japan’s health system—sustaining good health with equity at low cost. N Engl J Med 2015; 373: 1793–1797.

79. Ikemage N, Yoo S-K, Hashimoto H, Matsumoto M, Ogata H, Babazono A, Watanabe R, Shibuya K, Yang Y-J, Reich MR, Kobayashi Y. Japanese universal health coverage: evolution, achievements, and challenges. Lancet 2011; 378: 1106–1115.

80. Shibuya K, Hashimoto H, Ikemage N, Nishi A, Tanimoto T, Miyata H, Takemi K, Reich MR. Future of Japan’s system of good health at low cost with equity: beyond universal coverage. Lancet 2011; 378: 1265–1273.

81. Hashimoto H, Ikemage N, Shibuya K, Izumi N, Nomuchi H, Yasunaga H, Miyata H, Aoyin JM, Reich MR. Cost containment and quality of care in Japan: is there a trade-off? Lancet 2011; 378: 1174–1182.