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REVIEW

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

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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

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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.[1,2] 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.[3,4] 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[6] and the Japanese Circulation Society.[7]

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.[8] 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.[9] 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.[10]

Diuretic resistance can generally be overcome by combining different diuretic classes, such as thiazide and loop diuretics.[6] 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.[11]

Japan

Diuretic therapy is also widely used for the treatment of AHF in Japan.[12,13] In the acute decompensated heart failure syndromes (ATTEND) registry, 3695 patients (76.3%) were

Figure 1 Overview of the pharmacological mechanism of the reviewed medications. HF, heart failure; LV, left ventricular; LVEDP, left ventricular end-diastolic pressure.

	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 -Metolazone -Potassium sparing agents	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
Natriuretic Peptides	
-Nesiritide	Nesiritide is a recombinant human brain, or B-type, natriuretic peptide that exerts potent effect on vasodilation and natriuresis
-Carperitide	Carperitide 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.

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treated with diuretics, and almost all (99%) of these patients received furosemide.[13] 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.[14,15]

- While furosemide was used in up to 90% of patients hospitalized with AHF in the US registry,[16] furosemide was used in about 70% of patients in the Japanese registry.[13]
- 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.[17]

This suggests that, from the standpoint of maximum effective dose, furosemide might have not been administered at adequate amounts in Japan.[8] 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.[13] In accordance with the relationship between the maximum in-hospital diuretic dose and mortality,[14,15] 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.[18]

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.[8,14,19] 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,[6] 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*).[20]

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.[21] However, the trial did not address the significant improvement of clinical symptoms, and Sackner-Bernstein *et al*.[22,23] 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.[20] This article was further commented on in an accompanying editorial article entitled, 'The Lost Decade of Nesiritide'.[24]

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.[25] 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[26] and did not improve renal function[27] and prognosis.[28]

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.[12]

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:[29,30]

- 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
Nesiritide	USA	2000	Nesiritide Study Group	RCT, multicenter, and double-blind	127	AHF	Nesiritide 0.015 μg/kg/min Nesiritide 0.030 μg/kg/min	Placebo, 6 h	Change from baseline in the PCWP	Nesiritide improves haemodynamic function and clinical status.
Nesiritide	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.
Nesiritide	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		Dobutamine is associated with substantial proarrhythmic and chronotropic effects in patients with AHF, whereas nesiritide reduces ventricular ectopy or has a neutral effect.
Nesiritide	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.
Nesiritide	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.
Nesiritide	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.
Nesiritide	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	Nesiritide was not associated with the rate of death and rehospitalization. No significant effect on dyspnoea was seen.

(*Continues*)

Table 1 (continued)

	Country	Year	Study title	Study design	Sample size	Study population	Intervention	Comparator	Primary endpoint	Conclusion
									drug initiation and the composite endpoint of rehospitalization for HF and death from any cause during the period from randomization to Day 30	
Nesiritide	USA	2013	ROSE	RCT, multicenter, and double-blind. 2 × 2	360	AHF with renal dysfunction	Nesiritide 0.005 μg/kg/min (dobutamine)	Standard Tx	Coprimary endpoints included 72 h cumulative urine volume (decongestion endpoint) and the change in serum cystatin C from enrolment to 72 h (renal function endpoint)	Neither low-dose dopamine nor low-dose nesiritide enhanced decongestion or improved renal function.
Carperitide	Japan	2008	PROTECT	RCT, multicenter, and open-label	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	Japan	2008	COMPASS	Prospective observational multicenter	1832	AHF	Carperitide 0.025–0.05 μg/kg/min	Standard Tx	Improvement in dyspnoea	Carperitide monotherapy restored the acute phase and improved the degree of dyspnoea as assessed using the modified Borg scale.
Carperitide	Japan	2016	ATTEND	Prospective observational multicenter	4842	AHF	None	None	None	Carperitide was used in 69.4% of patients.

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-titration.[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, prenalterol, 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	The mortality in the prazosin group was similar to that in the placebo group. LVEF (measured sequentially) rose significantly at 8 weeks and at 1 year in the group treated with hydralazine and ISDN but not in the placebo or prazosin groups.
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 n the standard treatment for HF.

CHF, congestive heart failure; HF, heart failure; ISDN, isosorbide dinitrate; ISDN-H, isosorbide dinitrate plus hydrazaline; 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.

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by NTG, ISDN, and sodium nitroprusside. Mizutani *et al*.[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%),[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),[19,40] compared with 35% of patients in the ATTEND registry (Japan).[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*.[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_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_{1a}/V_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.[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 vs. 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.[43,44]

Yet, in addition to a *post hoc* analysis revealing more improvement with tolvaptan compared with placebo in patients with lower serum sodium,[45] tolvaptan seems to have a potentially beneficial effect on volume status and AHF symptoms in the initial treatment days.[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.[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.[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.[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.[50]
- Shirakabe *et al*.[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*.[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*.[51]
- Matsue *et al*.[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 intoropes 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 Flolan 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

Table 3 Summary of clinical trials with vasopressin receptor antagonists in heart failure

	Country	Year	Study title	Study design	Sample size	Study population	Intervention	Comparator	Primary endpoint	Conclusion
Tolvaptan	Japan	2013	N/A	Prospective observational study	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.
Tolvaptan	Japan	2014	N/A	Prospective observational study	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)	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.
Tolvaptan	Japan	2013	AVCMA	RCT, multicenter, and open-label	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.
Tolvaptan	Japan	2016	AQUAMARINE	RCT, multicenter, and open-label	220	ADHF with renal dysfunction (eGFR 15 to 60 mL/min/1.72 m^2)	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	142	Symptomatic HF (NYHA class III and IV)	Single i.v. dose (10, 20, or 40 mg) conivaptan	Conventional Tx	(i) Peak change from baseline (the average of two qualifying baseline values) in PCWP at 3 to 6 h (ii) AUC for the change from baseline PCWP	Conivaptan resulted in modest decreases in filling pressures concurrent with an increase in UOP.

(*Continues*)

Table 3 (continued)

	Country	Year	Study title	Study design	Sample size	Study population	Intervention	Comparator	Primary endpoint	Conclusion
									over the 12 h evaluation period	
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	Decrease in BW	By Day 1, BW decreased in tolvaptan group, but no further decreases were n oted after Day 1.
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	Median BW at 24 h decreased in all patients in the tolvaptan group but no difference in worsening HF at 60 days.
Tolvaptan	USA	2007	MENTOR	RCT, multicenter, and double-blind	240	AHF	Tolvaptan 30 mg	Conventional Tx	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.
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%	Tolvaptan 15, 30, or 60 mg	Placebo	PCWP	Patients with AHF can derive short-term benefit from tolvaptan.
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	
Tolvaptan	USA	2016	TACTICS-HF	RCT, multicenter, and double-blind	257	AHF	Tolvaptan (given at 0, 24, and 48 h)	Conventional Tx	Dyspnoea 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

(*Continues*)

Table 3 (continued)

	Country	Year	Study title	Study design	Sample size	Study population	Intervention	Comparator	Primary endpoint	Conclusion
Tolvaptan	USA	2016	SECRET of CHF	RCT, multicenter, double-blind, and placebo-controlled	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	at 24 h despite greater BW loss and fluid loss. 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.

ACTIV in CHF, Acute and Chronic Therapeutic Impact of a Vasopressin-2 Antagonist in Congestive Heart Failure; ADHF, acute decompensated heart failure; AKI, acute kidney insufficiency; AQUAMARINE, answering question on tolvaptan's efficacy for patients with acute decompensated heart failure and renal failure; AUC, area under the curve; AVCMA, acute heart failure volume control multicenter randomized; BW, body weight; CV, cardiovascular; ECLIPSE, Effect of Tolvaptan on Hemodynamic Parameters in Subjects with Heart Failure; eGFR, estimated glomerular filtration rate; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; MENTOR, Multicenter Evaluation of Tolvaptan Effects on Left Ventricular Remodeling; N/A, not applicable; PCWP, pulmonary capillary wedge pressure; QOL, quality of life; SECRET of CHF, Study to Evaluate Challenging Responses to Therapy in Congestive Heart Failure; TACTICS-HF, Targeting Acute Congestion with Tolvaptan in Congestive Heart Failure; Tx, treatment; UOP, urine output; WRF, worsening renal failure.

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 (13%).[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 stay[69] 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.

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Table 4 Summary of clinical trials with inotropes in heart failure

	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.
Dobutamine	USA	2009	SURVIVE	RCT, multicenter, and double-blind	1327	Critically ill patients hospitalized with l ow-output HF	Dobutamine	Levosimendan	All-cause mortality over 180 days	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.
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	Despite its beneficial haemodynamic actions, long-term therapy with oral milrinone increases the morbidity and mortality of patients with severe CHF.
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	Milrinone may have a bidirectional effect based on aetiology in decompensated HF. Milrinone may be deleterious in i schaemic HF but neutral to beneficial in NICM.
Pimobendan	Japan	2001	None	Prospective observational multicenter	34	Mild to moderate CHF	Pimobendan, 2.5 mg/day for 12 months	None	HF symptoms	Pimobendan is effective in patients with CHF but is less effective in patients with OMI than in patients with DCM or other heart diseases.

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.[64,73] 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.[74]

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.[75] This puts a significant financial burden on uninsured patients, who often receive only emergency and not longitudinal care.[76] 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,[77] 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.[78] 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.[79] The first is that a universal healthcare system has been in place since 1961, and it ensures relative equality of medical service and access.[80] This system has achieved good health across the population at low cost, with increased equality between different population groups.[81] 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.[82] 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,[48,49,54] 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.

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