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EDITORIAL

Heart failure epidemiology and novel treatments in Japan: facts and numbers

Masaaki Konishi[1]*, Junichi Ishida[1], Jochen Springer[1], Stephan von Haehling[1], Yoshihiro J. Akashi[2], Hiroaki Shimokawa[3] and Stefan D. Anker[1]

[1]*Innovative Clinical Trials, Department of Cardiology and Pneumology, University of Göttingen Medical School, Göttingen, Germany;* [2]*Division of Cardiology, Department of Internal Medicine, St. Marianna University School of Medicine, Kawasaki, Japan;* [3]*Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan*

Abstract

Japan has the highest proportion of older people in the world, 25.9% of the population were aged 65 or above in 2014. Although there have been no population-based studies that precisely examined the prevalence of heart failure in Japan, one report estimated the number of Japanese outpatients with left ventricular dysfunction was 979, 000 (0.8% of total population), which was projected to increase gradually as the population ages, reaching 1.3 million by 2030. Ischemic etiology was less frequently observed in Japan (31–47%) than in western population (54–57%). The prevalence of HF with preserved ejection fraction was similar between Japan (34–68%) and western countries (34–51%). Non-cardiac co-morbidities such as chronic obstructive pulmonary diseases and anemia were observed in 6–9% in Japan and 19–31% in western countries, and 35–58% in Japan and 37–56% in western countries, respectively. The definition of chronic kidney disease widely differed among studies. A relatively good survival prognosis in Japanese patients has been discussed. One-year mortality after discharge from initial hospitalization was 9–12%, which seems to be better than the western cohort. Although length of stay was remarkably longer in Japan (15–21 days) than western countries (4–9 days), it will have to be shortened, as Japan is now being faced with an upcoming HF pandemic. Some treatments in Japan are not approved outside Japan. Such treatments include carperitide infusion (used in 58% of hospitalized HF), nicorandil infusion (9.6%), and oral pimobendan (5%). More recently, landiolol and tolvaptan have been approved. Although these drugs might have a potential to be an effective therapeutic option, lack of corroborating evidence in many of such treatments would emphasize the need for larger clinical trials.

*Correspondence to: Masaaki Konishi, Innovative Clinical Trials, Department of Cardiology and Pneumology, University Medical Centre Göttingen, Robert-Koch-Str. 40 37075 Göttingen, Germany. Tel: +49 551 39 8133; Fax: +49 551 39 20911. Email: m_koni524@hotmail.com

Introduction

Japan has the highest proportion of older people in the world, 25.9% of the population were aged 65 or above in 2014.[1] On the other hand, heart failure is a major public health problem in developed countries, in terms of a disease, which binds enormous medical resources.[2] As the incidence of heart failure increases with age,[3] the heart failure pandemic is expected to be evident in Japan by 2030.[4,5] Here we show the facts and numbers in heart failure clinical practice in Japan. The experiences and knowledge gained in Japan may help other countries, where the over ageing problem will follow that of Japan.

Epidemiology of heart failure in Japan

A recent review has shown a relatively low prevalence of heart failure in Japan ($<1\%$) in comparison with that in other developed countries in North America and Europe (1–2%).[6] However, there have been no population-based studies that precisely examined the prevalence of heart failure in Japan as far as we know, although one report estimated the number of Japanese outpatients with left ventricular dysfunction was 979 000 in 2005 (0.8% of total population), which was projected to increase gradually as the population ages, reaching 1.3 million by 2030.[4] According to registry data of hospitalized heart failure patients, ischemic aetiology was less

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Table 1. Characteristics and outcomes of heart failure patients in Japanese and Western registries

Location Cohort	Japan HIJC-HF	Japan JCARE-CARD	Japan ATTEND	Japan CHART-2 [e]	Europe EHFS II	USA OPTIMIZE-HF	USA ADHERE
No. of patients	2808[22]	1692[8, 12,13, 21,29]	4842[7, 17]	4736	3580[10, 15]	41267[17, 23, 26]	105388[11, 24, 25, 30]
Mean age, years	70	71	73	69	70	73	72
Female sex, %	41	40	42	32	39	52	52
Ischemic aetiology, %	34	32	31	47	54	23	57
HFPEF, %	34	42	46	69	34	51	51
cut-off in LVEF, %	> 50	> = 40	> = 40	> = 50	> = 45	> = 40	> 40
Comorbidity							
Hypertension, %	54	53	69	74	63	71	77
COPD, %	NA	6	9	NA	19	28	31
CKD, %	23	11.3	69	47	17	20	20
Definition of CKD	Cr > =1.5	Cr > 2.5	eGFR < 60		Cr > 2	NA	Cr > 2
Anaemia (WHO criteria), %	44	57	58	35	37, 47 [a]	51 [b]	56,51 [c]
Outcome							
Length of stay (median), days	NA	15	21	NA	9	4	4
In-hospital mortality, %	NA	5.6	6.4	NA	6.7	3.8	4.0
Long-term mortality	11.0	8.9, 11.6 [d]	17.0	4.2	20.5	8.3	NA
Settings	1 year after discharge	1 year after discharge	1 year after admission	1 year at outpatient clinics	1 year after discharge	60–90 days after discharge	
References	22	8, 12, 13, 21, 29	7, 27	9, 19, 20, 28	10, 15	17, 23, 26	11, 24, 25, 30

ADHERE, The Acute Decompensated Heart Failure National Registry; ATTEND, the acute decompensated heart failure syndromes; CHART-2, the Chronic Heart failure Analysis and Registry in Tohoku district 2; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; Cr, serum creatinin; eGFR, estimated glomerular filtration rate; EHFS II, EuroHeart Failure Survey II; HFPEF, heart failure with preserved ejection fraction; HIJC-HF, the Heart Institute of Japan—Department of Cardiology-Heart Failure; JCARE-CARD, Japanese Cardiac Registry of Heart Failure in Cardiology; LVEF, left ventricular ejection fraction; NA, not available; OPTIMIZE-HF, the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure; WHO, World Health Organization.

[a]37% for patients with age of <80 and 47% for patients with age of > =80.

[b]Patients with Hb <12.1 g/dL.

[c]56% in men and 51% in women.

[d]8.9% in patients with preserved and 11.6% in patients with reduced LVEF.

[e]79.5% of participants in the CHART-2 Study (Stage A/B/C/D, N = 10,219) were outpatients.

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frequently observed in Japan [31% in the acute decompensated heart failure syndromes (ATTEND), 32% in the Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD),[7,8] and 47% in the Chronic Heart failure Analysis and Registry in Tohoku disrict (CHART)-2 [9]] than in European [54% in EuroHeart Failure Survey (EHFS) II[10]] and USA [57% in The Acute Decompensated Heart Failure National Registry (ADHERE) [11]] populations (*Table 1*), although the rate has been increasing in recent years.[9] Hypertension is similarly observed among these three populations (53–74% in Japan, 77% in USA, and 63% in Europe).[7–11] A relatively good survival prognosis in Japanese heart failure patients has been discussed.[12] One year mortality 'after discharge from initial hospitalization' for heart failure was 8.9–11.6% (with respect to preserved or reduced EF) in JCARE-CARD registry[13], whereas that 'after the day of admission' in ATTEND registry was 17.0%.[14] Mortality in both of these studies seems to be better than European cohort in EHFS II registry (20.5% of mortality 'after discharge from initial hospitalization' with 6.7% in-hospital mortality[10,15]) and Finnish Acute Heart Failure Study registry (27% 'after the day of admission'[16]) and possibly better than that in US population [The Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure (OPTIMIZE-HF) registry], representing 3.8% in-hospital mortality followed by 8.3% 60–90 day mortality.[17] In addition, prognosis of Japanese heart failure patients has been improved in dilated cardiomyopathy[18] as well as in symptomatic heart failure patients,[19] along with implementation of evidence-based strategies. As far as outpatients are concerned, 1-year mortality in the CHART-2 study was only 4.2%.[20] One of the most remarkable features of Japanese heart failure patients is their longer length of stay in comparison with the western population.[21] The median length of stay was 15–21 days in Japan, whereas it was 4–9 days in western countries (*Table 1*).[21] Although such differences are likely to be the result of the difference in the healthcare systems; longer length of hospitalization might provide patients with more opportunities for optimal treatment. Even though it seems beneficial, it is likely that length of stay in Japan will have to be shortened, as the Japanese health care system is now being challenged with an upcoming heart failure pandemic.

Ageing and heart failure—heart failure with preserved ejection fraction and non-cardiac co-morbidities

Heart failure with preserved ejection fraction (HFpEF) and high prevalence of non-cardiac co-morbidities are two major problems in old heart failure patients. In Japan, the prevalence of HFpEF ranges from 34% to 46% according to HFpEF definition and mean age of overall cohort[7,13,22](*Table 1*). In the CHART-1 and CHART-2 studies, which also included patients without hospitalization, HFpEF accounted for 51 and 68% of overall cohort, respectively.[9] In western countries, HFpEF was observed in 51% in OPTIMIZE-HF,[23] 34% in EHFS-II,[10] and 51% in ADHERE,[24] suggesting similar prevalence in Japanese and western heart failure populations. Regarding non-cardiac co-morbidities, chronic obstructive pulmonary diseases (COPD), chronic kidney disease (CKD), and anaemia are the most frequently described in these large cohort studies. COPD was observed 9% in ATTEND,[7] 5.8% in JCARE-CARD,[21] whereas 31% in ADHERE,[25] 28% in OPTIMIZE-HF,[26] and 19% in EHFS II.[10] CKD was observed in 47–69% (defined by estimated glomerular filtration rate < 60 mL/min/1.73 m^2)[9,27] or 11.3% (defined by serum creatinine (Cr) > 2.5 mg/dL or dialysis),[21] whereas 30% (as reported) and 20% (defined by Cr >2 mg/dL) in ADHERE,[11] 17% (defined by Cr >2 mg/dL, renal transplant, or dialysis) in EHFS II.[10] No clear explanation for the difference in prevalence of COPD among these studies have been given, whereas CKD prevalence may differ among these studies due to lack of a standard definition of CKD. Anaemia as defined by the World Health Organization criteria was observed in 35% in CHART-2,[28] 58% in ATTEND,[27] 57% in JCARE-CARD,[29] whereas 51% for women and 56% for men in ADHERE,[30] and 37% for younger (< 80) and 47% for older patients ($> = 80$) in EHFS II.[31]

Unique characteristics of heart failure treatment in Japan

Some treatments in Japan, including pharmacological and non-pharmacological ones, are not approved outside Japan. Some of them might have the potential to be effective treatment options for some subpopulation in heart failure, if appropriately designed trials are performed in the future. On the other hand, some of non-pharmacological treatments are less prevalent in Japan than western countries. For example, the numbers of heart transplantations are limited and waiting times are long.[32] Cardiac rehabilitation has not been frequently performed either,[33] although precise numbers in Japanese heart failure population have not been reported so far.

Carperitide

Carperitide is an intravenous recombinant atrial natriuretic peptide which is approved only in Japan at present, for acute heart failure treatment, whereas nesiritide (a recombinant B-type natriuretic peptide) is available in USA, Argentina, Columbia, Switzerland, and Israel. The expected cardiovascular effects of carperitide are vasodilation and sympathetic tone reduction in the peripheral vasculature.[34] Based on a class IIa recommendation in The Japanese Society of Cardiology guidelines for treatment of acute heart failure,[35] carperitide was used in 58% of acute heart failure patients

in ATTEND registry.[7] In spite of the high number of carperitide infusions in Japan, supporting clinical evidence is mainly based on a relatively small randomized study.[36] Carperitide has also been reported as renoprotective,[37,38] but on the other hand, the association between carperitide use and high mortality has been reported in a recent propensity score matched analysis.[39] Larger randomized clinical trials to determine the safety and effectiveness are warranted.

Nicorandil

Nicorandil has been originally developed as an anti-anginal drug which activates adenosine triphosphate-sensitive potassium channels and has a vasodilation effect on veins and arteries. In 2007, nicorandil injection was supplementally approved for acute heart failure treatment in Japan. In ATTEND registry, 9.6% of acute heart failure patients were treated with intravenous infusion of nicorandil.[7] A meta-analysis of five small randomized controlled trials has shown the reduction in mortality with a hazard ratio of 0.35 (95% CI: 0.16–0.54, $P < 0.001$) in comparison with nitrate, standard therapy, and placebo.[40] As a reason for favourable outcome in nicorandil groups, several kinds of cardioprotective effects, including anti-inflammatory and anti-endothelial dysfunction effects, have been discussed.[40]

Landiolol

Landiolol is a short-acting intravenous β-1 selective adrenergic receptor blocker that is rapidly metabolized with a half-life of approximately 4 min. In response to the result from the J-Land study,[41] which was conducted to compare the efficacy and safety of landiolol with those of digoxin for swift control of tachycardia in atrial fibrillation/flutter in patients with left ventricular dysfunction, landiolol was approved for 'tachyarrhythmia in patients with cardiac dysfunction' in 2013. Landiolol might be a novel therapeutic option in heart failure patients with complicating atrial fibrillation, whose numbers have been increasing in the heart failure population and also have been reported to have poor prognosis.[42]

Tolvaptan

Tolvaptan is an oral, non-peptide vasopressin V2 receptor antagonist, which has shown to induce free water excretion without increasing urine sodium. The Phase III Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study with Tolvaptan trial has shown improved short-term signs and symptoms of heart failure[43] but no effect on long-term heart failure-related morbidity or mortality on hospitalized heart failure patients.[44] Following these results, in 2010, tolvaptan was approved in Japan. However, many researchers have been concerned about heart failure subpopulations such as CKD,[45] hypoalbuminemia,[46] early-admission setting,[47] and low blood pressure.[48]

Pimobendan

Pimobendan is a positive inotropic agent through its calcium-sensitizing and phosphodiesterase inhibiting effect. Although oral pimobendan increased mortality of chronic heart failure patients in European countries (Pimobendan in Congestive Heart Failure study),[49] in 306 Japanese patients pimobendan improved the physical activity without increasing mortality in the effects of pimobendan on chronic heart failure study.[50] Pimobendan is used in 5% of patients to improve physical activity[7] and might be a possible add-on option for symptomatic heart failure patients even with the optimal medical therapy.

Waon therapy

Waon therapy is a form of thermal therapy using a far infrared-ray dry sauna with temperature maintained at 60 °C followed by a rest on a bed outside the sauna for 30 min.[51] During the therapy, the deep body temperature is increased by 1.0 °C, resulting in improvement of acute hemodynamics including cardiac output, mean pulmonary artery wedge pressure, and systemic vascular resistance. A prospective, multicenter trial has confirmed that 2 weeks of Waon therapy is safe, improves clinical symptoms, cardiac function, and decreases cardiac size in chronic heart failure patients.[52] Further trials are still expected to confirm the long-term safety and efficacy.

Conclusions

Here we show the facts and numbers regarding the epidemiology and novel treatments of heart failure in Japan. Although the number of heart failure patients is projected to increase as the population ages, there have been no population-based studies that precisely examine the prevalence of heart failure in Japan so far. Whereas the clinical background of heart failure demonstrated in large clinical registries does not differ remarkably between Japanese and western populations, a relatively good prognosis has been suggested in Japanese patients. Although their longer length of hospital stay is one of the most remarkable features of Japanese heart failure patients, it is obvious that the length of stay in Japan needs to be shortened, because Japan is now facing an upcoming heart failure pandemic. Some treatments commonly used in Japan are not approved outside Japan; however, these might still have the potential to be effective

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therapeutic options for some subpopulations in heart failure. Lack of corroborating evidence in many such treatments emphasizes the need for larger clinical trials.

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Conflicts of interest

S. von Haehling has been a paid consultant to Vifor, Respicardia, Pfizer, Novartis, Roche, Sorin, and Thermo Fisher Scientific. He has received lecture fees from Amgen and Sanofi. H. Shimokawa has received lecture fees from Bayer Yakuhin, Ltd. (Osaka, Japan) and Daiichi Sankyo Co., Ltd. (Tokyo, Japan). S. Anker has been a paid consultant to Bayer, Relypsa, Thermo Fisher Scientific, Novartis, LoneStar Heart, and Vifor; he has received speaker fees from Novartis and Vifor; and his institution has received a research grant from Vifor Pharma and Abbott Vascular. M. Konishi, J. Ishida, J. Springer, and Y. J. Akashi declare that they have no conflict of interest.

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