

Temporal trends of a vasopressin V₂ receptor antagonist in heart failure using a nationwide database in Japan

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Abstract

Aims Real-world data on the use of tolvaptan, an oral selective vasopressin 2 receptor antagonist, for patients with heart failure (HF) are not available in Western countries because tolvaptan is not indicated in the Western countries for volume overload in HF. This study aimed to investigate the current status and recent trends of tolvaptan use for HF in Japan by analysing a nationwide Japanese Diagnosis Procedure Combination database.

Methods and results We retrospectively identified 257 812 patients hospitalized because of HF between 1 April 2008 and 30 November 2018. The diagnosis of HF at admission was based on the International Classification of Diseases, Tenth Revision, and in-hospital treatment. We investigated patient characteristics, in-hospital diuretic treatment, and tolvaptan treatment after discharge. The proportion of patients who were prescribed with tolvaptan for HF increased from 3.2% in 2011 to 39% in 2018. Since 2015, tolvaptan was prescribed within 2 days of hospitalization in >50% of HF cases. At discharge of a patient who was prescribed with tolvaptan, the rate of oral loop diuretic prescription at a dose ≥ 80 mg decreased, while the rate of diuretic prescription at a dose <40 mg increased. After discharge, the rate of tolvaptan prescription gradually increased from 34.0% in 2011 to 69.7% in 2018; however, tolvaptan prescriptions lasting >14 days decreased after 2012.

Conclusions This large-scale survey indicated an increased rate of tolvaptan prescription and an early shift to tolvaptan treatment in patients with HF in Japan. The prognostic effects of this change in HF treatment remain unclear.

Keywords Heart failure; Diuretic therapy; Tolvaptan

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Introduction

Heart failure (HF) is a major healthcare problem because of the associated high morbidity and mortality.^{1,2} The number of patients with acute decompensated HF (ADHF) continues to increase every year.³ In clinical practice, loop diuretics are used for the initial treatment of patients with ADHF to relieve the symptoms of congestion. In the analysis of the Acute Decompensated Heart Failure Syndrome registry, 76.3% of the hospitalized patients with ADHF received intravenous loop diuretics.⁴ However, despite its frequent usage, increasing the dose of loop diuretics may increase the mortality rates associated with HF.^{5,6}

Tolvaptan is an oral selective vasopressin 2 receptor antagonist; it is an aquaretic that acts on the collecting ducts and promotes water diuresis.⁷ Unlike loop diuretics, such as furosemide, tolvaptan promotes the excretion of water without the loss of electrolytes. In Japan, tolvaptan was approved 'volume overload in HF when adequate response is not obtained with other diuretics' since December 2010.⁸ Currently, the indication of fluid retention in HF is accepted mainly in the Asian countries and in several other countries, and tolvaptan is used to manage congestion in patients with HF. In Europe and the USA, tolvaptan is not indicated for volume overload in HF and is mainly used for treating hyponatraemia.

Therefore, real-world data on diuretic therapy with tolvaptan are not available from the Western countries.

In Japan, several studies have reported on the treatment of HF with tolvaptan. The Samsca Post-Marketing Surveillance in Heart Failure (SMILE) study indicated the safety of tolvaptan for patients with HF.^{9–12} However, as this study was a post-marketing survey, it lacked the information regarding the prescribing status, such as changes in the prescription rates or prescription timing after hospitalization. Furthermore, the changes in the use of loop diuretics since tolvaptan was used for HF remain unclear.

To address these gaps in knowledge, we retrospectively evaluated the temporal trends in the treatment of HF with tolvaptan in clinical practice in Japan using a nationwide Diagnosis Procedure Combination (DPC) database. Additionally, we investigated the changes in the concomitant use of loop diuretics within the same cohort.

Methods

Data source

Unlinkable anonymized medical data (DPC) from Medical Data Vision Inc. (Tokyo, Japan) were evaluated in this retrospective study. The data of patients with HF (International Classification of Diseases, Tenth Revision, Codes I50, I11.0, I13.0, and I13.2) and one or more causes of hospitalization between 1 April 2008 and 30 November 2018 were extracted.

The diagnosis of HF was well correlated between DPC data and case review, including clinical laboratory data, with a specificity of 97.5%.¹³

Patient selection

Tolvaptan was launched on 14 December 2010 in Japan. The study cohort was divided into Cohort 1 (1 April 2011 to 30 September 2011) to Cohort 16 (1 October 2018 to 30 November 2018). Cohort 16 data included only short-term follow-up; therefore, we excluded in the analysis as *post hoc* decision. To distinguish from scheduled admission, we defined hospitalization for acute HF as follows: DPC disease segment was 21 (cause of hospitalization), and ICD-10 code was HF; days in hospital were ≥ 0 ; and at least one treatment included injections of loop diuretics, catecholamines, human atrial natriuretic peptide (hANP), phosphodiesterase inhibitors, or cyclic guanosine monophosphate activators or oxygen inhalation therapy (DPC codes: J024, J025, and J027) or artificial ventilation (J026 and J045) or artificial kidney (J038) or intra-aortic balloon pump (K600) during hospitalization.

Outcome

The primary outcome was the prescription rate of tolvaptan for acute HF in each longitudinal cohort. The secondary outcomes were as follows: first and last prescription days of tolvaptan for acute HF; standardized doses of loop diuretics during hospitalization; in-hospital treatment for acute HF; and tolvaptan prescription rate after discharge in the patient with at least three times prescribed in the hospital.

Concomitant disease

The history of disease or concomitant disease was recorded based on the definitive diagnoses on the day or previous date of HF admission. The diseases were classified using ICD-10 codes as follows: hypertension (I10–I15), diabetes mellitus (E1–E4), hyperlipidaemia (E78.0–E78.5), myocardial infarction (I21 and I22), arrhythmia (I48), valvular heart disease (I05–I09, I34–I37, and I39.0–I39.4), cardiomyopathy (I01.2, I09.0, I40–I43, and I51.4), and renal failure (N17 to I19, I12.0, I13.1, and I13.2).

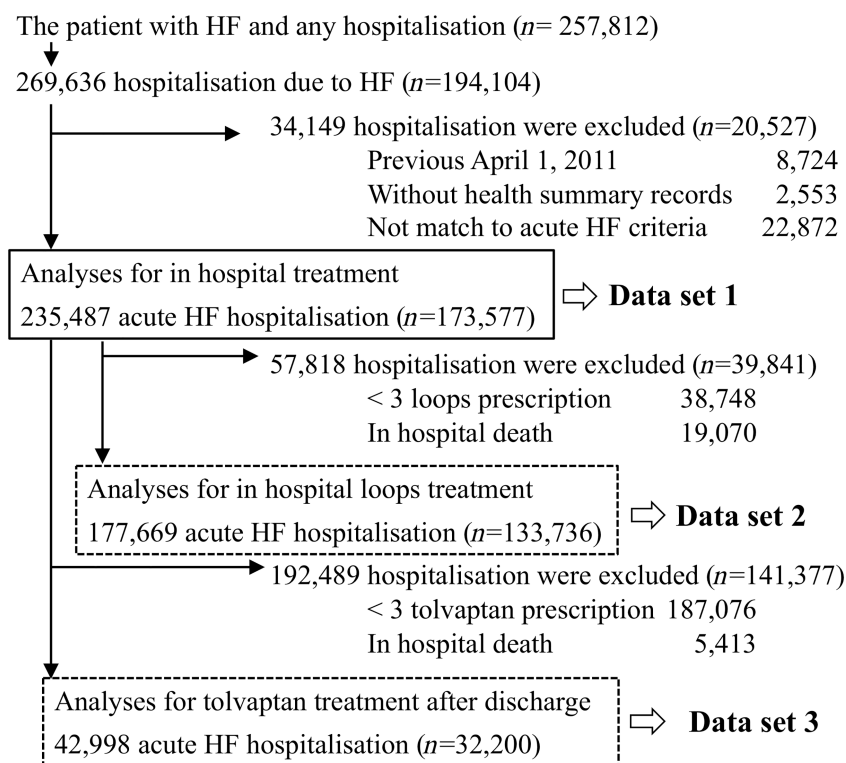
Data analyses

Drugs, routes of administration, and dose were identified based on the trade names. The doses of loop diuretic were converted to equivalent furosemide doses using the standard conversion guidelines (furosemide: $\times 1$; azosemide: $\times 2/3$; torasemide: $\times 5$; bumetanide: $\times 40$; and piretanide: $\times 10$; injection formula was $\times 2$). The first prescription of the drugs was any day the drugs were first prescribed during acute HF. The last prescription date was estimated based on the last prescription data at discharge due to acute HF. Therefore, we used the prescription data of the second last prescription ('last-1'). This algorithm requires at least three prescriptions. We excluded the patients with less than three prescriptions for drugs for acute HF from the analyses. We divided the data into three datasets for each of the following analyses: analyses for in-hospital treatment (Dataset 1); analyses for in-hospital loop diuretic treatment (Dataset 2); and analyses for tolvaptan treatment after discharge (Dataset 3). We summarized the number of hospitalizations per cohort; if a patient was admitted multiple times for HF, he or she was enrolled in the corresponding cohorts. The patient flow chart for each dataset is illustrated in *Figure 1*.

Ethics

Any study using this anonymized data was documented as 'non-covered area' in the 'Ethical Guidelines for

Figure 1 Patient study flow chart. The number indicates the number of patients, and hospitalization indicates the total number of hospitalizations. HF, heart failure.



Epidemiological Research' by the Japanese Government (<https://www.mhlw.go.jp/general/seido/kousei/i-kenkyu/ekigaku/0504sisin.html>, in Japanese). This study was conducted after the study protocols were approved by the ethics committee of the Hyogo Prefectural Amagasaki General Medical Center Ethics Committee.

Statistical analysis

We performed descriptive statistics. Categorical variables were presented as numbers and proportions, and continuous variables were presented as mean \pm standard deviation. Analysis of tolvaptan prescription after discharge for acute HF was performed using the Kaplan–Meier method. Data processing and analyses were performed using R v3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

The study included 235 487 hospitalizations (173 577 patients) in Dataset 1. The patients' demographic characteristics, co-morbidities, and treatment administered during

hospitalization according to the prescription of tolvaptan are summarized in *Table 1A* and *1B*. In each cohort, there was no difference in the sex and age distribution between the patients who were and those who were not prescribed with tolvaptan. However, the proportions of patients with co-morbidities, such as hypertension, diabetes, hyperlipidaemia, ischaemic heart disease, stroke, arrhythmia, hepatic disease, and renal disease, were higher in the tolvaptan-administered group. Particularly, renal failure was consistently noted in >40% of the patients who were prescribed with tolvaptan. Further, the proportion of patients with in-hospital treatments, such as catecholamine injection, pimobendan, thiazides, mineral corticoid receptor antagonists, and beta-blockers, was consistently higher in the tolvaptan-administered group. The use of hANP was higher in the tolvaptan-administered group; however, the prescription rate tended to decrease gradually. The length of hospital stay was consistently longer for patients who were prescribed with tolvaptan.

The rate of tolvaptan-administered patients gradually increased to 3.2% in Cohort 1; 9.8%, Cohort 3; 14.5%, Cohort 5; 20.1%, Cohort 7; 24.7%, Cohort 9; 28.8%, Cohort 11; 35.5%, Cohort 13; and 39.0%, Cohort 15 (*Figure 2*). We noted that the prescription of drugs was gradually initiated

Table 1A Patient's characteristics and in-hospital treatment divided by tolvaptan prescription

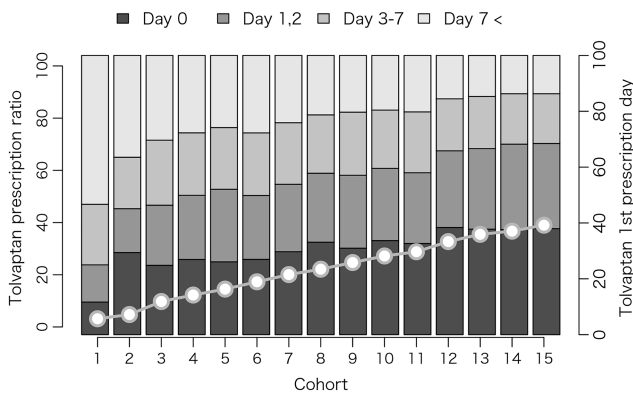
Cohort	1st		3rd		5th		7th	
	(-)	(+)	(-)	(+)	(-)	(+)	(-)	(+)
Tolvaptan	3688	120	4207	455	7386	1254	10468	2629
n	1880 (51.0)	66 (55.0)	2095 (49.8)	260 (57.1)	3761 (50.9)	670 (53.4)	5294 (50.6)	1463 (55.6)
Male gender, n (%)	78.3 ± 12.6	78.6 ± 11.1	78.5 ± 12.3	78.3 ± 11.1	78.4 ± 12.5	78.8 ± 11.5	79.0 ± 12.4	78.0 ± 12.1
Age (years)	In-hospital treatment							
Length of stay (days)	26.7 ± 41.9	46.6 ± 31.4	25.0 ± 33.3	39.7 ± 36.1	24.4 ± 33.0	37.1 ± 38.1	22.9 ± 26.2	35.5 ± 42.1
Tolvaptan start day (days)	13.8 ± 17.1	13.8 ± 17.1		8.5 ± 15.2				6.2 ± 11.3
Catecholamine, n (%)	820 (22.2)	66 (55.0)	910 (21.6)	173 (38.0)	1382 (18.7)	414 (33.0)	1696 (16.2)	872 (33.2)
cGMP activator, n (%)	1145 (31.0)	26 (21.7)	1319 (31.4)	110 (24.2)	2590 (35.1)	346 (27.6)	3642 (34.8)	701 (26.7)
hANP, n (%)	1922 (52.1)	72 (60.0)	2059 (48.9)	270 (59.3)	3307 (44.8)	677 (54.0)	4354 (41.6)	1405 (53.4)
Loop diuretics, n (%)	3399 (92.2)	119 (99.2)	3818 (90.8)	449 (98.7)	6615 (89.6)	1218 (97.1)	9354 (89.4)	2572 (97.8)
ACEI, n (%)	725 (19.7)	36 (30.0)	851 (20.2)	102 (22.4)	1605 (21.7)	335 (26.7)	2393 (22.9)	635 (24.2)
ARB, n (%)	1326 (36.0)	36 (30.0)	1531 (36.4)	171 (37.6)	2509 (34.0)	411 (32.8)	3286 (31.4)	787 (29.9)
MRA, n (%)	1786 (48.4)	69 (57.5)	2018 (48.0)	248 (54.5)	3292 (44.6)	721 (57.5)	4369 (41.7)	1458 (55.5)
Beta-blocker, n (%)	1619 (43.9)	66 (55.0)	1951 (46.4)	247 (54.3)	3742 (50.7)	733 (58.5)	5337 (51.0)	1587 (60.4)
Artificial kidney, n (%)	252 (6.8)	8 (6.7)	270 (6.4)	38 (8.4)	494 (6.7)	75 (6.0)	669 (6.4)	174 (6.6)
Co-morbidities or medical history	Co-morbidities or medical history							
Hypertension, n (%)	2902 (78.7)	97 (80.8)	3428 (81.5)	378 (83.1)	5962 (80.7)	1056 (84.2)	8510 (81.3)	2272 (86.4)
Diabetes mellitus, n (%)	1427 (38.7)	57 (47.5)	1683 (40.0)	247 (54.3)	3041 (41.2)	639 (51.0)	4291 (41.0)	1343 (51.1)
Hyperlipidaemia, n (%)	520 (14.1)	24 (20.0)	676 (16.1)	79 (17.4)	1437 (19.5)	287 (22.9)	1931 (18.4)	621 (23.6)
Myocardial infarction, n (%)	700 (19.0)	29 (24.2)	804 (19.1)	91 (20.0)	1379 (18.7)	265 (21.1)	1828 (17.5)	628 (23.9)
Arrhythmia, n (%)	1497 (40.6)	57 (47.5)	1769 (42.0)	219 (48.1)	2984 (40.4)	660 (52.6)	4418 (42.2)	1416 (53.9)
Valvular heart disease, n (%)	1100 (29.8)	50 (41.7)	1221 (29.0)	170 (37.4)	2103 (28.5)	435 (34.7)	2982 (28.5)	948 (36.1)
Cardiomyopathy, n (%)	288 (7.8)	10 (8.3)	375 (8.9)	53 (11.6)	556 (7.5)	159 (12.7)	795 (7.6)	311 (11.8)
Renal failure, n (%)	968 (26.2)	61 (50.8)	1173 (27.9)	202 (44.4)	2021 (27.4)	503 (40.1)	2989 (28.6)	1166 (44.4)

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; cGMP, cyclic guanosine monophosphate; hANP, human atrial natriuretic peptide; MRA, mineralocorticoid antagonist.

Table 1B Patient's characteristics and in-hospital treatment divided by tolvaptan prescription

Cohort	9th		11th		13th		15th	
	(-)	(+)	(-)	(+)	(-)	(+)	(-)	(+)
Tolvaptan								
n	11733	3846	13119	5311	14082	7749	13656	8729
Male gender, n (%)	5903 (50.3)	2115 (55.0)	6528 (49.8)	2816 (53.0)	7207 (51.2)	4196 (54.1)	6923 (50.7)	4655 (53.3)
Age (years)	78.6 ± 13.0	78.9 ± 11.8	79.2 ± 12.9	79.4 ± 11.8	79.4 ± 12.7	79.6 ± 11.8	79.3 ± 13.0	80.1 ± 11.9
In-hospital treatment								
Length of stay (days)	22.8 ± 27.2	32.3 ± 32.4	21.9 ± 23.9	32.2 ± 36.9	21.2 ± 22.9	29.6 ± 27.3	20.2 ± 18.8	27.9 ± 23.8
Tolvaptan start day (days)		5.1 ± 11.5		5.0 ± 9.6		3.8 ± 8.0		3.4 ± 6.8
Catecholamine, n (%)	1899 (16.2)	1231 (32.0)	2048 (15.6)	1556 (29.3)	2103 (14.9)	2233 (28.8)	1934 (14.2)	2408 (27.6)
cGMP activator, n (%)	4155 (35.4)	1099 (28.6)	4465 (34.0)	1385 (26.1)	4946 (35.1)	2122 (27.4)	4740 (34.7)	2292 (26.3)
hANP, n (%)	4454 (38.0)	1878 (48.8)	4327 (33.0)	2322 (43.7)	3945 (28.0)	3122 (40.3)	3476 (25.5)	3258 (37.3)
Loop diuretics, n (%)	10436 (88.9)	3765 (97.9)	11676 (89.0)	5233 (98.5)	12635 (89.7)	7672 (99.0)	12093 (88.6)	8619 (98.7)
ACEI, n (%)	2724 (23.2)	1030 (26.8)	3086 (23.5)	1424 (26.8)	3549 (25.2)	2187 (28.2)	3372 (24.7)	2518 (28.8)
ARB, n (%)	3612 (30.8)	1180 (30.7)	3831 (29.2)	1550 (29.2)	4610 (32.7)	2423 (31.3)	3138 (23.0)	1841 (21.1)
MRA, n (%)	4859 (41.4)	2125 (55.3)	5554 (42.3)	2842 (53.5)	6239 (44.3)	4308 (55.6)	5909 (43.3)	4776 (54.7)
Beta-blocker, n (%)	6194 (52.8)	2417 (62.8)	7050 (53.7)	3412 (64.2)	8193 (58.2)	5251 (67.8)	7983 (58.5)	5925 (67.9)
Artificial kidney, n (%)	744 (6.3)	191 (5.0)	874 (6.7)	196 (3.7)	1021 (7.3)	275 (3.5)	1129 (8.3)	281 (3.2)
Co-morbidities or medical history								
Hypertension, n (%)	9682 (82.5)	3300 (85.8)	10719 (81.7)	4568 (86.0)	11330 (80.5)	6595 (85.1)	10985 (80.4)	7362 (84.3)
Diabetes mellitus, n (%)	4851 (41.3)	2038 (53.0)	5386 (41.1)	2664 (50.2)	5896 (41.9)	3949 (51.0)	5789 (42.4)	4521 (51.8)
Hyperlipidaemia, n (%)	2386 (20.3)	941 (24.5)	2657 (20.3)	1349 (25.4)	2954 (21.0)	1958 (25.3)	2877 (21.1)	2235 (25.6)
Myocardial infarction, n (%)	2091 (17.8)	894 (23.2)	2301 (17.5)	1239 (23.3)	2382 (16.9)	1722 (22.2)	2309 (16.9)	1847 (21.2)
Arrhythmia, n (%)	5101 (43.5)	2160 (56.2)	5931 (45.2)	2955 (55.6)	6253 (44.4)	4374 (56.4)	6071 (44.5)	4878 (55.9)
Valvular heart disease, n (%)	3371 (28.7)	1365 (35.5)	3764 (28.7)	1960 (36.9)	3895 (27.7)	2884 (37.2)	3910 (28.6)	3189 (36.5)
Cardiomyopathy, n (%)	895 (7.6)	404 (10.5)	994 (7.6)	528 (9.9)	887 (6.3)	845 (10.9)	901 (6.6)	869 (10.0)
Renal failure, n (%)	3454 (29.4)	1579 (41.1)	3676 (28.0)	2169 (40.8)	3888 (27.6)	3142 (40.5)	3950 (28.9)	3675 (42.1)

Figure 2 The longitudinal changes of tolvaptan prescription rate and start date in acute heart failure. The line graph showed the tolvaptan prescription rate. The odd cohorts were 1 April to 30 September, and even cohorts were 1 October to 31 May from 2011 to 2018 (1st: 1 April 2011 to 30 September 2011; 15th: 1 April 2018 to 30 September 2018).



earlier over time. After Cohort 9, tolvaptan was prescribed within 2 days of hospitalization for more than 50% of the patients.

Analyses of in-hospital loop diuretic treatment

We examined the use of diuretics in 177 669 hospitalizations (133 736 patients) in Dataset 2. *Tables 2* and *A1* depict the use of loop diuretics according to tolvaptan prescription. The average oral dose of diuretics (in terms of furosemide equivalents) was higher on both the first day and the last-1 day in the tolvaptan-administered group (Cohort 15: 40.5 and 39.1 mg, respectively) than that in the group that was not administered with tolvaptan (Cohort 15: 33.2 and 30.0 mg, respectively). In patients treated with tolvaptan, a temporal trend of slight decrease in both the first and last-1 oral doses of diuretics was observed from Cohort 1 (55.3 and 58.7 mg, respectively) to Cohort 15 (40.5 and 39.1 mg, respectively). A similar trend was observed for the last-1 oral dose of diuretics in patients who did not receive tolvaptan (Cohort 1, 36.8 mg; Cohort 15, 30.0 mg). *Figure 3* illustrates the prescription of oral doses on the last-1 day; the prescription rate of furosemide equivalents ≥ 80 mg was reduced, and the prescription of tolvaptan increased for patients receiving furosemide equivalents < 40 mg. The prescription rate of intravenous loop diuretics on the day of admission was approximately 75% in the overall cohorts. hANP was prescribed to nearly 50% of patients in Cohorts 1–7. In the subsequent cohorts, hANP prescription rates tended to decline; however, hANP was still prescribed to approximately 40% of patients in the tolvaptan group.

Analyses for tolvaptan treatment after discharge

We evaluated tolvaptan prescription after discharge in 42 998 hospitalizations (32 200 patients) in Dataset 3. The proportion of patients who received tolvaptan at discharge was 34.0% [95% confidence interval (CI): 23.3–49.4] for Cohort 1, which gradually increased to approximately 69.7% (95% CI: 68.5–70.9) for Cohort 15. At 14 days after discharge, the tolvaptan prescription rate decreased from Cohort 3 onwards. At 56 days after discharge, approximately 30% of patients in Cohorts 12–15 were prescribed with tolvaptan. In Cohort 13, 17.3% (95% CI: 16.3–18.3) of patients were prescribed with tolvaptan for > 168 days (*Figure 4* and *Table A2*).

Discussion

The present study reported the longitudinal epidemiological data on the trends in the treatment of acute HF, including the use of loop diuretics and tolvaptan, based on a nationwide hospital claims database. We found that tolvaptan was often prescribed for patients with acute HF and multiple co-morbidities. The tolvaptan prescription rates for acute HF increased gradually, and tolvaptan was being prescribed earlier than that noted previously. The rate of prescription of high-dose loop diuretics decreased, and the tolvaptan prescription rates increased at discharge.

Patients' background

Tolvaptan has been approved for patients with HF with persistent fluid retention despite the use of conventional diuretics in Japan. Therefore, it is necessary to carefully consider the differences in the background characteristics of the patients according to the use of tolvaptan. Previous prospective observational studies on patients with acute HF reported that tolvaptan-administered patients had poorer renal function and lower ejection fraction.^{14,15} However, large data on the patients' demographic characteristics and co-morbidities have not been previously investigated. In this study, there were no apparent differences in the sex or age distribution between patients according to the prescription of tolvaptan. However, we noted a higher prevalence of co-morbidities, especially renal failure, longer lengths of hospital stay, and increased use of inotropic drugs in tolvaptan-administered patients. In summary, tolvaptan has been used in daily clinical practice for patients with more refractory HF.

Table 2 Prescription of oral loop diuretics in patients divided by tolvaptan prescription

Cohort Term	1st		5th		9th		13th		15th	
	First	Last-1	First	Last-1	First	Last-1	First	Last-1	First	Last-1
<i>n</i>	2709		5265		8414		10340		9837	
Without tolvaptan										
Dose (mg)	36.4 ± 27.1	36.8 ± 28.2	34.7 ± 23.2	35.1 ± 25.6	34.1 ± 24.3	32.8 ± 23.9	32.3 ± 23.3	30.4 ± 20.9	33.2 ± 24.1	30.0 ± 20.8
~80	632 (23.3)	1945 (71.8)	1187 (22.5)	3855 (73.2)	1885 (22.4)	6010 (71.4)	2826 (27.3)	7820 (75.6)	2622 (26.7)	7354 (74.8)
>80	32 (1.2)	93 (3.4)	36 (0.7)	132 (2.5)	45 (0.5)	137 (1.6)	75 (0.7)	142 (1.4)	73 (0.7)	126 (1.3)
Cohort	1st		5th		9th		13th		15th	
<i>n</i>	75		965		3040		6365		7197	
With tolvaptan										
Dose (mg)	53.3 ± 44.5	58.7 ± 36.9	48.6 ± 35.0	45.6 ± 32.5	40.8 ± 29.7	43.4 ± 33.6	42.1 ± 33.0	40.4 ± 30.6	40.5 ± 30.9	39.1 ± 30.2
~80	13 (17.3)	54 (72.0)	232 (24.0)	682 (92.4)	796 (26.2)	2179 (71.7)	2022 (31.8)	4801 (75.4)	2245 (31.2)	5410 (75.2)
>80	2 (16.0)	8 (12.7)	22 (2.3)	56 (5.8)	50 (1.6)	168 (5.5)	144 (2.3)	283 (4.4)	145 (2.0)	287 (4.0)

Data are presented as the mean value ± standard deviation or *n* (%). The doses of loop diuretic were converted to equivalent furosemide doses using the standard conversion guidelines (furosemide: ×1; azosemide: ×2/3; torasemide: ×5; bumetanide: ×40; and piretanide: ×10; injection formula was ×2).

Temporal trends in tolvaptan treatment

Our findings suggested that the tolvaptan prescription rates gradually increased over time. This temporal trend may be affected by both clinical experience and findings of the SMILE study. The SMILE study reported that tolvaptan can be safely prescribed; however, data on the timing of initiating tolvaptan prescription are unclear. The present findings indicated that the gradual trend was to prescribe tolvaptan earlier during hospitalization. Recent observational studies have indicated that the early use of tolvaptan during hospitalization could prevent deterioration in renal function and reduce the duration of hospitalization and in-hospital deaths.^{14,16}

In contrast, the prescription rate of hANP decreased gradually in this study. These results suggest that the strategy to prescribe tolvaptan early is commonly used across several medical institutions and that it might have altered the management strategies for conventional HF. However, sufficient evidence for the early use of tolvaptan in patients with HF is not available, particularly with respect to improved long-term prognosis; therefore, further discussions and studies are warranted.

Temporal trends for loop diuresis treatment in acute heart failure

Loop diuretics are the first-line drugs for HF. However, they are known to have serious side effects, such as electrolyte imbalances, decreased renal function, and activation of the renin-angiotensin system.¹⁷ Several observational studies have reported that high-dose loop diuretics are associated with poor prognoses in patients with HF.^{18–21} A recent Swedish nationwide cohort study reported a trend of decreased prescription rates and dose of loop diuretics for the patients with chronic HF.²² The SMILE study demonstrated that the baseline dose of oral diuretics decreased from 69.3 to 54.9 mg between 2011 and 2015.¹¹ Similarly, in our study, the baseline dose of oral loop diuretics (in furosemide equivalents) gradually decreased between Cohort 1 and Cohort 15. Furthermore, when focusing on oral loop diuretics before discharge, our findings suggested that the proportion of patients receiving furosemide equivalent >80 mg/day decreased and that of those receiving furosemide equivalent <40 mg/day increased among the tolvaptan-prescribed patients. The prescription rate of intravenous loop diuretics on the day of admission was only 75% in all the cohorts. The prescription rate is lower in Japan than in Western countries because hANP is often used as a vasodilator and as a diuretic without loop diuretics. In fact, in the Kyoto Congestive Heart Failure registry, between 2014 and 2016, intravenous loop diuretics and hANP were used in 84% and 37% of cases, respectively, within 24 h of admission.²³ The usage of hANP was observed to decrease from 2007 to 2015 in the other

Figure 3 The longitudinal changes with and without tolvaptan in standardized oral furosemide dose of loop diuretics at previous prescription for in-hospital any last prescription. The odd cohorts were 1 April to 30 September, and even cohorts were 1 October to 31 May from 2011 to 2018 (1st: 1 April 2011 to 30 September 2011; 15th: 1 April 2018 to 30 September 2018).

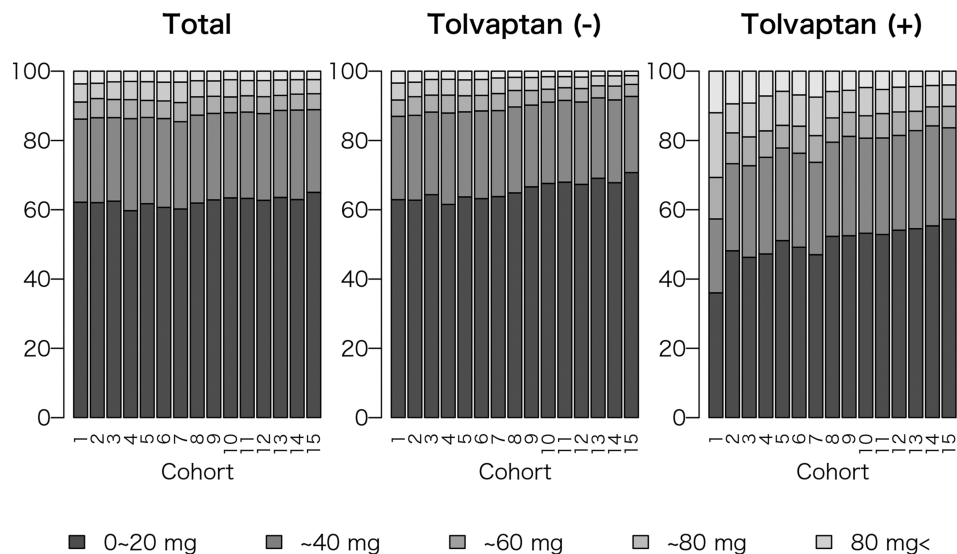
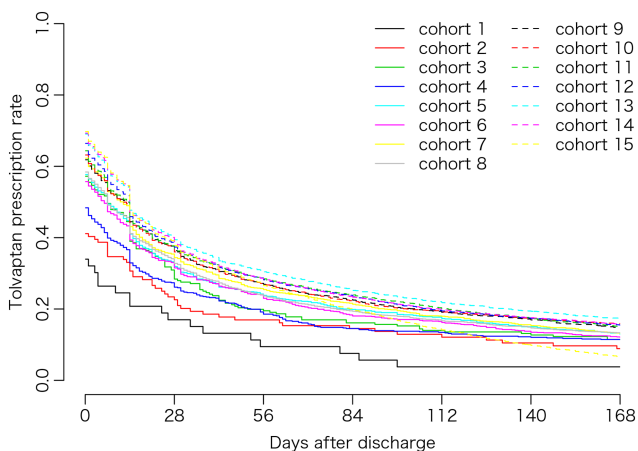


Figure 4 The prescription rate of tolvaptan after discharge. The odd cohorts were 1 April to 30 September, and even cohorts were 1 October to 31 May from 2011 to 2018 (1st: 1 April 2011 to 30 September 2011; 15th: 1 April 2018 to 30 September 2018).



three large Japanese HF registries. However, it was reported that the usage was still high in the acute phase; between 2007 and 2011, 2011 and 2015, and 2014 and 2015, the rates were 58.3%, 52.1%, and 45.6%, respectively.²⁴ In the present study, a trend towards decreasing the use of hANP was observed after 2014; nevertheless, it continued to be frequently used in patients with HF. We believe that the lower rate of use of intravenous loop diuretics is because of the unique Japanese usage of hANP. However, we could not determine

whether the declining trend in the doses of loop diuretics and use of hANP was related to the increased prescription rate of tolvaptan to avoid high-dose loop diuretics because there were no data on congestion in this study. In addition, it is unclear whether the decrease in the use of loop diuretics had an impact on clinical outcomes. Further studies on concomitant diuretic therapy are required to further elucidate the efficacy of these therapies.

Tolvaptan treatment after discharge

In the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan, long-term tolvaptan therapy did not improve the mortality rates compared with the placebo.²⁵ Nevertheless, 43.6% of patients received tolvaptan for >2 weeks after discharge in the SMILE study.⁹ Our findings also indicated that the rate of continuing tolvaptan after discharge has been increasing. A recent study suggested the benefits of long-term tolvaptan treatment in patients with several risk factors for HF readmission.²⁶ Another retrospective study suggested that long-term tolvaptan therapy in patients with acute HF and chronic renal failure was safe and reduced the readmission rates due to HF.²⁷ Furthermore, a prospective randomized study reported improvements in the quality of life and a decrease in the readmission rates for HF due to the 6 month tolvaptan therapy.²⁸ Therefore, long-term tolvaptan therapy for suitable patients may be acceptable with careful follow-up.

Limitations

There are several limitations of this study. First, this study was a retrospective analysis using a secondary administrative database. HF diagnosis based on the DPC database is generally less validated compared with that based on planned prospective studies. Furthermore, we could not assess the appropriateness of the treatment because this was not an interventional trial. Second, this study did not cover all the participating DPC hospitals; it only included data obtained from the Medical Data Vision Inc.'s medical database, which covers 18% of the DPC hospitals. This data source does not include other hospitals or national and private university hospitals. Furthermore, because the volume of data provided is gradually increasing every year, the number of data points varies each year. Therefore, there is potential for bias with respect to patient selection; therefore, the results of the study should be generalized cautiously. Third, this study did not include significant clinical data, such as the ejection fraction, systolic blood pressure, and biomarkers such as serum brain natriuretic peptide levels. In particular, another considerable limitation is the unavailability of physiological findings of congestion, such as lower limb oedema and jugular vein distension. Therefore, the severity of HF could not be determined. We could not assess the differences between the patients with reduced, preserved, and mid-range ejection fraction. Fourth, the data could not be used to confirm whether tolvaptan was used only for refractory fluid retention resistant to conventional diuretics. Fifth, the treatment history was not traced if a patient moved to other hospitals. Therefore, some data may be underestimated. Particularly, the decrease in the continuous prescription rate of tolvaptan after discharge may be because tolvaptan was prescribed at another hospital. Additionally, the patients who were not actually taking the medication as prescribed were also included.

Conclusions

Our study reported on the temporal trends of HF treatment, including tolvaptan use, in Japan. In clinical practice, the prescription rate of tolvaptan has increased compared with that noted previously, and tolvaptan is prescribed earlier than that noted previously. The initial protocol included tolvaptan therapy only during hospitalization; however, tolvaptan therapy was commonly continued after discharge in many hospitals. In Japan, tolvaptan is indicated for fluid retention in HF, and accumulation of additional data is necessary. Finally, as the number of patients with HF is increasing, our results may help in updating our clinical knowledge of HF therapy.

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Conflict of interest

None declared.

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Appendix

Table A1 Prescription of loop diuretics in patients divided by tolvaptan prescription

Cohort Term	1st		5th		9th		13th		15th	
	First	Last-1	First	Last-1	First	Last-1	First	Last-1	First	Last-1
<i>n</i>	2709		5265		8414		10340		9837	
Without tolvaptan										
Injection treatment										
Furosemide	2049 (75.6)	255 (9.4)	3892 (73.9)	510 (9.7)	6294 (74.8)	815 (9.7)	7870 (76.1)	889 (8.6)	7619 (77.5)	938 (9.5)
Others	6 (0.2)	0 (0.0)	10 (0.2)	2 (0.0)	21 (0.2)	4 (0.0)	12 (0.1)	0 (0.0)	6 (0.1)	1 (0.0)
Dose (mg)	72.0 ± 101.0	66.4 ± 86.0	67.8 ± 76.0	60.1 ± 65.2	67.5 ± 78.7	63.4 ± 63.3	64.6 ± 54.1	59.0 ± 50.3	63.9 ± 58.9	58.5 ± 44.5
~80	1776 (65.6)	229 (8.5)	3416 (64.9)	471 (8.9)	5510 (65.5)	738 (8.8)	6869 (66.4)	825 (8.0)	6703 (68.1)	871 (8.9)
~160	189 (7.0)	19 (0.7)	322 (6.1)	27 (0.5)	539 (6.4)	58 (0.7)	719 (7.0)	36 (0.3)	658 (6.7)	45 (0.5)
~320	63 (2.3)	4 (0.1)	125 (2.4)	10 (0.2)	185 (2.2)	15 (0.2)	239 (2.3)	19 (0.2)	212 (2.2)	17 (0.2)
>320	27 (1.0)	3 (0.1)	38 (0.7)	4 (0.1)	71 (0.8)	8 (0.1)	44 (0.4)	9 (0.1)	46 (0.5)	5 (0.1)
Sum of loop diuretics										
<i>n</i>	2393 (88.3)		4547 (86.4)		7347 (87.3)		9278 (89.7)		8909 (90.6)	
Dose (mg)	71.9 ± 96.5	40.8 ± 41.0	67.5 ± 73.5	38.7 ± 35.1	66.9 ± 76.1	37 ± 34.7	64.9 ± 54.6	33.9 ± 28.5	64.7 ± 58.9	34.0 ± 28.0
~80	2004 (74.0)	2127 (78.5)	3883 (73.8)	4209 (79.9)	6282 (74.7)	6762 (80.4)	7845 (75.9)	8435 (81.6)	7616 (77.4)	7975 (81.1)
~160	284 (10.5)	107 (3.9)	486 (9.2)	170 (3.2)	775 (9.2)	230 (2.7)	1089 (10.5)	204 (2.0)	974 (9.9)	206 (2.1)
~320	77 (2.8)	16 (0.6)	138 (2.6)	24 (0.5)	215 (2.6)	35 (0.4)	295 (2.9)	32 (0.3)	270 (2.7)	38 (0.4)
>320	28 (1.0)	3 (0.1)	40 (0.8)	5 (0.1)	75 (0.9)	9 (0.1)	49 (0.5)	9 (0.1)	49 (0.5)	5 (0.1)
Cohort	1st 75		5th 965		9th 3040		13th 6365		15th 7197	
With tolvaptan										
Injection treatment										
Furosemide	54 (72.0)	5 (6.7)	630 (65.3)	88 (9.1)	2090 (68.8)	242 (8.0)	4456 (70.0)	459 (7.2)	5203 (72.3)	578 (8.0)
Others	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	4 (0.1)	1 (0.0)	1 (0.0)	0 (0.0)
Dose (mg)	71.3 ± 53.2	72.0 ± 52.2	73.0 ± 84.3	84.3 ± 71.5	75.6 ± 92.1	76.3 ± 119.7	72.7 ± 81.5	80.7 ± 110.6	72.7 ± 71.7	92.7 ± 129.6
~80	43 (57.3)	4 (5.3)	538 (55.8)	64 (6.6)	1727 (56.8)	215 (7.1)	3763 (59.1)	396 (6.2)	4359 (60.6)	465 (6.5)
~160	9 (12.0)	1 (1.3)	66 (6.8)	17 (1.8)	233 (7.7)	16 (0.5)	447 (7.0)	29 (0.5)	550 (7.6)	55 (0.8)
~320	3 (4.0)	0 (0.0)	16 (1.7)	5 (0.5)	102 (3.4)	8 (0.3)	190 (3.0)	20 (0.3)	229 (3.2)	32 (0.4)
>320	0 (0.0)	0 (0.0)	10 (1.0)	2 (0.2)	30 (1.0)	3 (0.1)	56 (0.9)	14 (0.2)	65 (0.9)	26 (0.4)
Sum of loop diuretics										
<i>n</i>	62 (82.7)		769 (79.7)		2502 (82.3)		5499 (86.4)		6294 (87.5)	
Dose (mg)	76.1 ± 55.3	60.6 ± 38.1	75.8 ± 81.3	51.0 ± 44.3	77.0 ± 88.3	47.4 ± 51.4	75.5 ± 80.8	44.8 ± 46.5	75.5 ± 72.5	45.3 ± 55.9
~80	45 (60.0)	57 (76.0)	614 (63.6)	720 (74.6)	1965 (64.6)	2327 (76.5)	4359 (68.5)	5010 (78.7)	4958 (68.9)	5656 (78.6)
~160	13 (17.3)	9 (12.0)	117 (12.1)	76 (7.9)	372 (12.2)	177 (5.8)	810 (12.7)	330 (5.2)	953 (13.2)	334 (4.6)
~320	4 (5.3)	1 (1.3)	28 (2.9)	7 (0.7)	131 (4.3)	31 (1.0)	263 (4.1)	54 (0.8)	309 (4.3)	74 (1.0)
>320	0 (0.0)	0 (0.0)	10 (1.0)	3 (0.3)	34 (1.1)	5 (0.2)	67 (1.1)	14 (0.2)	74 (1.0)	33 (0.5)

Data are presented as the mean value ± standard deviation or *n* (%). The doses of loop diuretic were converted to equivalent furosemide doses using the standard conversion guidelines (furosemide: x1; azosemide: x2/3; torasemide: x5; bumetanide: x40; and piretanide: x10; injection formula was x2).

Table A2 Prescription rate of tolvaptan after discharge

Day	Cohort 1		Cohort 3, 5		Cohort 7, 9		Cohort 11, 13		Cohort 15	
	Estimated	95% CI	Estimated	95% CI	Estimated	95% CI	Estimated	95% CI	Estimated	95% CI
0	34.0	23.3–49.4	57.6	54.6–60.7	62.0	60.5–63.5	67.2	66.2–68.2	69.7	68.6–70.9
7	26.4	16.9–41.4	49.5	46.5–52.6	53.1	51.6–54.6	56.4	55.4–57.5	59	57.8–60.3
14	20.8	12.3–35.1	40.5	37.6–43.7	43.9	42.4–45.5	46.5	45.5–47.5	47.2	45.9–48.4
28	17	9.4–0.8	31.1	28.4–34.1	35.5	34.1–37.0	38.2	37.2–39.3	37.8	36.6–39.1
56	17	9.4–30.8	22.8	20.4–25.5	26.3	25.0–27.7	29.6	28.7–30.6	26.6	25.5–27.7
83	7.6	2.9–19.4	19	16.7–21.6	22	20.8–23.3	24.7	23.8–25.6	19.8	18.8–20.8
168	3.8	1.0–14.7	12.5	10.7–14.7	14.2	13.2–15.3	16.4	15.6–17.2	6.4	5.8–7.1

CI, confidence interval.

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