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Original Article

Continuation of Tolvaptan after Discharge is Associated with an Improved Long-Term Prognosis and a Reduction in Number of Readmissions in Patients with Chronic Heart Failure

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Abstract

Objective : The efficacy of long-term use of tolvaptan after discharge for chronic heart failure (HF) is unclear. The purpose of this study is to clarify the efficacy of long-term use of tolvaptan after discharge from in-hospital admission due to decompensated HF.

Methods and Patients or Materials : We retrospectively analyzed 407 consecutive patients with decompensated HF requiring in-hospital care and their one-year outcomes after discharge. After excluding the 42 patients with in-hospital death or dialysis, 365 patients were investigated.

Results : A multivariable analysis indicated that admission due to decompensated HF at least once in the past year before the index admission (defined as a "frequent flyer"), higher age, a low hemoglobin level, male gender and receiving noninvasive positive pressure ventilation (NPPV) were associated with HF readmissions. We compared HF readmissions rate and a composite endpoint (HF readmissions plus all cause death) rate between the group of continued tolvaptan after discharge and the other group of patients. A propensity matching method was utilized to compare the group of continued tolvaptan (n=37) with the group of others (n=37). The rate of freedom from HF readmissions one year after discharge was tended to be higher in the group of continued tolvaptan than the group of others (p=0.08). The rate of freedom from the composite endpoint (HF readmissions and all-cause death) was higher in the group of continued tolvaptan than the group of others (p=0.04). Change in number of HF admissions one-year before and after the index admission was greater in the group of continued tolvaptan than in the group of others (-1.78 ± 1.05 vs. -1.08 ± 0.82, p=0.002). The same results were obtained in analyzing 59 frequent flyer patients (-2.31 ± 1.08 vs. -1.43 ± 0.80, $p < 0.001$).

Conclusion : These data demonstrated that continuation of tolvaptan after discharge is associated with an improved long-term prognosis and a reduction in number of HF readmissions, suggesting a long-term benefit of tolvaptan in patients with chronic heart failure.

Key words : Continuation of tolvaptan, Heart failure readmissions, Frequent flyer

Introduction

A heart failure (HF) pandemic is already likely. At present, HF is one of the leading causes of morbidity and mortality worldwide[1)~4)] and is a growing public health problem in Japan with the country transitions to a super-aging society[5)~8)].

Several studies and meta-analyses have reported the efficacy of tolvaptan in the acute phase of decompensated HF for improving short-term clinical outcomes[9)~14)]. We recently reported that the early initiation of tolvaptan in congestive HF

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patients shortened the hospital stay and reduced the rate of in-hospital death[15)16)]. However, the efficacy of long-term use of tolvaptan after discharge is unclear. The EVEREST trial, a first prospective randomized control trial of tolvaptan, failed to demonstrate the long-term benefit of tolvaptan[9)]. However, some small studies have shown the efficacy of long-term use of tolvaptan[17)~19)].

In the present study, we investigated whether or not continuing tolvaptan after discharge might have a beneficial effect on the long-term clinical outcomes, such as the number of HF readmissions.

Material and Methods

Study design

This is a single-center, retrospective study investigating the possible effect of continuing tolvaptan after discharge in decompensated HF patients requiring in-hospital care. We retrospectively analyzed 407 consecutive patients with decompensated HF at our hospital. After excluding 42 patients with in-hospital death or dialysis, 365 patients were investigated. We investigated the factors associated with readmissions. We then evaluated the efficacy of continuing tolvaptan after discharge after matching patients' background characteristics using a propensity score matching. The survival after discharge was confirmed from the follow-up records in our hospital or through direct telephone contact with each patient or their family members.

Statistical analyses

All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). This is a modified version of R commander designed to add statistical functions frequently used in biostatistics[20)]. Continuous variables were compared using the unpaired *t*-test or Mann-Whitney test as appropriate. Categorical variables were compared using the chi-squared test or Fisher's exact test as appropriate. An univariate analysis fore related factors to HF readmissions was performed using a Cox proportional hazard analysis. A multivariable analysis was then performed using a Cox proportional hazard analysis when p-value of univariate analysis was less than 0.2. A propensity score-matching analysis was performed after adjusting the HF severity to compare the group of continued tolvaptan to the group of others. Propensity scores of some variables are calculated, then matched. A Kaplan-Meier analysis was performed to assess the rate of HF readmission and all-cause death with a comparison using the log-rank test. A comparison of the parameters before and after tolvaptan use in each group was conducted using a repeated measures analysis of variance (ANOVA). Unless otherwise specified, all data are expressed as mean ± standard deviation or median (95% confidence interval). The probability was two-tailed, with P values of < 0.05 being regarded as statistically significant.

Ethical standards

This human study was approved by the appropriate ethics committee and were therefore performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. This study was approved by the ethics committee of Fukuoka Red Cross Hospital.

Results

Patient Characteristics

We retrospectively analyzed 407 consecutive patients with decompensated HF at our hospital from April 2015 to March 2017. After excluding 42 patients with in-hospital death or dialysis, 365 patients were investigated. Thirty-seven patients continued tolvaptan administration after discharge. The study design is shown in Fig. 1. The patient characteristics are shown in Table 1.

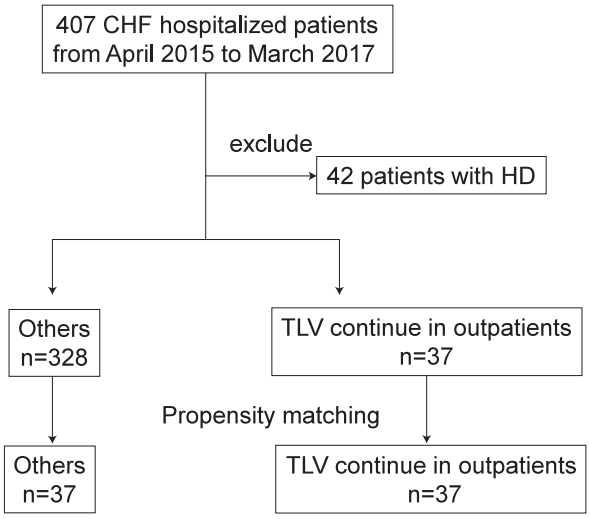

Fig. 1 The illustration of study design.

Others group means patients who did not use tolvaptan after discharge regardless of whether using or not using tolvaptan during admission. We defined patients hospitalized due to decompensated HF within a year before the index admission as frequent flyers.

The factors associated with readmissions due to HF

We performed an univariate and a multivariable analysis for the factors associated with readmissions for HF. A total of 67 of 365 patients were re-hospitalized within one year after their index admission. The result of univariate analysis was shown in Table2. The continuation of tolvaptan was not associated with HF readmission. The multivariable analysis showed that frequent flyers, higher age, a low hemoglobin level, male gender and receiving noninvasive positive pressure ventilation (NPPV) were associated with HF readmissions (Table 2). Whether or not continuing tolvaptan after discharge was not significantly associated with HF readmissions.

Characteristics of the group of continuated tolvaptan and the group of others after propensity matching

We performed propensity score matching based on the backgrounds of the tolvaptan continuing group (n=37) and the others group (n=37). Variables that may affect the prognosis, such as age, hemoglobin level, male gender, NPPV, frequent flyers and the number of HF admission before one year are matched. The characteristics of these groups after propensity score matching are shown in Table 3. After propensity matching, the number of HF admissions within one year before the index admission was comparable between the groups (1.97 ± 1.09 vs. 1.68 ± 0.63, p=0.155). After matching, the dose of loop diuretics was higher in the tolvaptan continuing group.

Effects of tolvaptan continuation after discharge on readmissions due to HF and long-term prognosis

The rate of freedom from HF readmissions one year after discharge was tended to be higher in the continued group than in the other group (p=0.08, Fig. 2A). All-cause death plus HF readmission one year after discharge was higher in the continued group than in the others (p=0.04, Fig. 2B). Ten patients died during the follow up period ; 9 non-cardiac death and 1 cardiac death. The number of admissions due to HF at one-year after discharge was reduced compared to the number of admissions due to HF before the index admission in both groups (Fig. 3A). However, the change in number of readmissions due to HF one-year before and after the index admission were larger in the continued group than in the others (-1.78 ± 1.05 vs. -1.08 ± 0.82, p=0.002 ; Fig. 3B).

Effects of tolvaptan continuation on readmissions among frequent flyers

Frequent flyer was strongly associated with HF readmissions in the present study. Thus, we investigated the effect of tolvaptan continuation in the population of frequent flyers strongly associated with HF readmissions. Of the 365 patients examined, 59 were defined as frequent flyers.

Table 1 Characteristics of all patients

	Others	TLV continue	p
n	328	37	
	Backgrounds		
age	76.6 ± 13.8	78.9 ± 13.4	0.336
male（%）	189（57.6）	20（54.1）	0.754
BNP	801.8 ± 802.3	1300.7 ± 936.7	0.0006
EF	43.5 ± 17.8	41.4 ± 16.4	0.503
NYHA3,4（%）	261（79.6）	29（78.4）	0.832
Frequent flyer（%）	37（11.3）	22（59.5）	＜0.001
IHD（%）	103（31.4）	20（54.1）	0.0009
sBP	145.2 ± 36.1	138.5 ± 32.1	0.284
dBP	83.6 ± 23.2	77.1 ± 22.6	0.108
HR	86.0［30.0, 170.0］	75.0［50.0, 120.0］	0.012
BMI	22.1［13.8, 47.4］	22.4［14.2, 27.7］	0.39
Hospital stay	18.5［2.0, 120.0］	21.0［6.0, 101.0］	0.351
	Comorbidity		
AF（%）	145（44.2）	16（43.2）	1
DM（%）	101（30.8）	9（24.3）	0.457
COPD（%）	26（7.9）	3（8.1）	1
pneumonia（%）	46（14.0）	3（8.1）	0.447
	Labo data		
BUN	27.7 ± 14.5	32.3 ± 13.5	0.066
Cr	1.38 ± 0.99	1.70 ± 0.83	0.055
eGFR	47.2 ± 22.1	36.3 ± 21.2	0.0047
UA	6.8 ± 2.4	6.8 ± 2.3	0.89
Na	140.0［123.6, 147.4］	138.9［121.5, 145.9］	0.07
K	4.34 ± 0.65	4.15 ± 0.57	0.086
Hb	12.0［4.8, 19.4］	11.6［7.7, 15.6］	0.098
Alb	3.7［1.1, 5.0］	3.6［2.6, 4.2］	0.211
	At discharge		
ACEI/ARB（%）	274（83.5）	32（86.5）	0.815
BB（%）	256（78.0）	33（89.1）	0.137
MRA（%）	179（54.6）	22（59.5）	0.605
Loop at discharge（%）	189（57.6）	29（78.4）	0.02
Loop dose at discharge	14.8 ± 16.4	21.4 ± 15.5	0.022
	In hospital use		
Loop（%）	188（57.3）	28（75.7）	0.104
TLV（%）	56（17.1）	37（100）	＜0.001
Carperitide（%）	87（26.5）	9（24.3）	0.846
Cathecolamine（%）	48（14.6）	5（13.5）	1
NPPV（%）	53（16.2）	2（5.4）	0.092
CRT/ICD（%）	6（1.8）	2（5.4）	0.19

Data are given as n (%), the mean ± SD or the median plus confidence interval Abbreviations are described in the manuscript

Table 2 Association with heart failure readmissions

Univariate analysis

	HR	95% confidence interval	p-value	AUC
		Backgrounds		
age	1.024	1.003-1.045	0.021	0.551
male（%）	1.684	1.005-2.821	0.047	0.482
BNP	1.000	0.997-1.000	0.896	0.715
EF	1.004	0.990-1.018	0.559	0.532
NYHA3,4（%）	1.085	0.592-1.989	0.790	0.494
Frequent flyer（%）	3.036	1.822-5.058	< 0.001	0.741
IHD（%）	1.574	0.970-2.551	0.066	0.613
sBP	0.999	0.992-1.006	0.795	0.548
dBP	0.990	0.979-1.002	0.102	0.583
HR	0.997	0.988-1.006	0.594	0.626
Hospital stay	1.002	0.986-1.016	0.840	0.547
		Comorbidity		
AF（%）	0.793	0.485-1.296	0.355	0.495
DM（%）	1.225	0.740-2.029	0.429	0.468
COPD（%）	1.817	0.900-3.68	0.095	0.499
pneumonia（%）	0.761	0.348-1.667	0.496	0.47
		Labo data		
BUN	1.009	0.993-1.025	0.237	0.622
Cr	1.080	0.876-1.331	0.470	0.653
eGFR	0.992	0.981-1.003	0.169	0.651
UA	0.962	0.868-1.067	0.470	0.591
Na	1.008	0.948-1.072	0.792	0.496
K	0.995	0.687-1.442	0.981	0.584
Hb	0.879	0.799-0.967	0.008	0.583
Alb	0.736	0.503-1.078	0.115	0.563
		At discharge		
ACEI/ARB（%）	0.856	0.458-1.600	0.627	0.515
BB（%）	0.831	0.474-1.457	0.518	0.556
MRA（%）	0.946	0.585-1.530	0.823	0.524
Loop at discharge（%）	1.139	0.694-1.869	0.606	0.604
Loop dose at discharge	1.009	0.995-1.023	0.203	0.626
TLV continue	1.070	0.489-2.341	0.865	0.502
		In hospital use		
Loop（%）	0.993	0.609-1.619	0.979	0.59
TLV（%）	1.283	0.760-2.165	0.351	0.915
Carperitide（%）	0.794	0.447-1.411	0.432	0.489
Cathecolamine（%）	1.051	0.536-2.058	0.884	0.494
NPPV（%）	1.562	0.866-2.815	0.137	0.446
CRT/ICD（%）	3.287	1.195-9.039	0.021	0.518

Multivariable analysis

	HR	95% confidential interval	p
age	1.024	1.001-1.049	0.045
Frequent flyer	2.63	1.478-4.681	0.001
Hb	0.867	0.782-0.962	0.007
male	2.191	1.234-3.889	0.007
NPPV	2.119	1.106-4.057	0.023

Univariate and Multivariable analysis about association with HF readmissions was performed.
Abbreviations are described in the manuscript

Table 3 Characteristics after propensity score matching

	Others	TLV continue	p
n	37	37	
	Backgrounds		
age	81.6 ± 11.6	78.9 ± 13.4	0.353
male（%）	20（54.1）	20（54.1）	1
BNP	929.4 ± 922.3	1300.7 ± 936.7	0.095
EF	45.4 ± 16.6	41.4 ± 16.4	0.295
NYHA3,4（%）	31（83.8）	29（78.4）	0.768
Frequent flyer（%）	22（59.5）	22（59.5）	1
No. of HF admissions before 1year	1.68 ± 0.63	1.97 ± 1.09	0.155
IHD（%）	17（45.9）	20（54.1）	0.642
sBP	145.9 ± 38.5	138.5 ± 32.1	0.372
dBP	80.2 ± 25.5	77.1 ± 22.6	0.578
HR	83.0［51.0, 140.0］	75.0［50.0, 120.0］	0.075
BMI	20.3［15.4, 47.3］	22.4［14.2, 27.7］	0.196
Hospital stay	21.0［7.0, 85.0］	21.0［6.0, 101.0］	0.766
	Comorbidity		
AF（%）	13（35.1）	16（43.2）	0.634
DM（%）	15（40.5）	9（24.3）	0.214
COPD（%）	3（8.1）	3（8.1）	1
pneumonia（%）	6（16.2）	3（8.1）	0.479
	Labo data		
BUN	32.4 ± 15.5	32.3 ± 13.5	0.959
Cr	1.69 ± 1.55	1.70 ± 0.83	0.955
eGFR	40.9 ± 21.5	36.3 ± 21.2	0.353
UA	6.8 ± 2.4	6.8 ± 2.3	0.89
Na	139.9［130.9, 146.5］	138.9［121.5, 145.9］	0.378
K	4.29 ± 0.57	4.15 ± 0.57	0.282
Hb	10.7［7.8, 15.8］	11.6［7.7, 15.6］	0.254
Alb	3.6［1.7, 4.2］	3.6［2.6, 4.2］	0.434
	At discharge		
ACEI/ARB（%）	29（78.4）	32（86.5）	0.543
BB（%）	29（78.4）	33（89.1）	0.345
MRA（%）	20（54.1）	22（59.5）	0.815
Loop at discharge（%）	23（62.2）	29（78.4）	0.203
Loop dose at discharge	14.8 ± 16.4	21.4 ± 15.5	0.022
	In hospital use		
Loop（%）	23（62.2）	28（75.7）	0.315
TLV（%）	7（18.9）	37（100）	＜0.001
Carperitide（%）	7（18.9）	9（24.3）	0.778
Cathecolamine（%）	6（16.2）	5（13.5）	1
NPPV（%）	3（8.1）	2（5.4）	1
CRT/ICD（%）	3（8.1）	2（5.4）	1

Data are given as n (%), the mean ± SD or the median plus confidence interval
Abbreviations are described in the manuscript

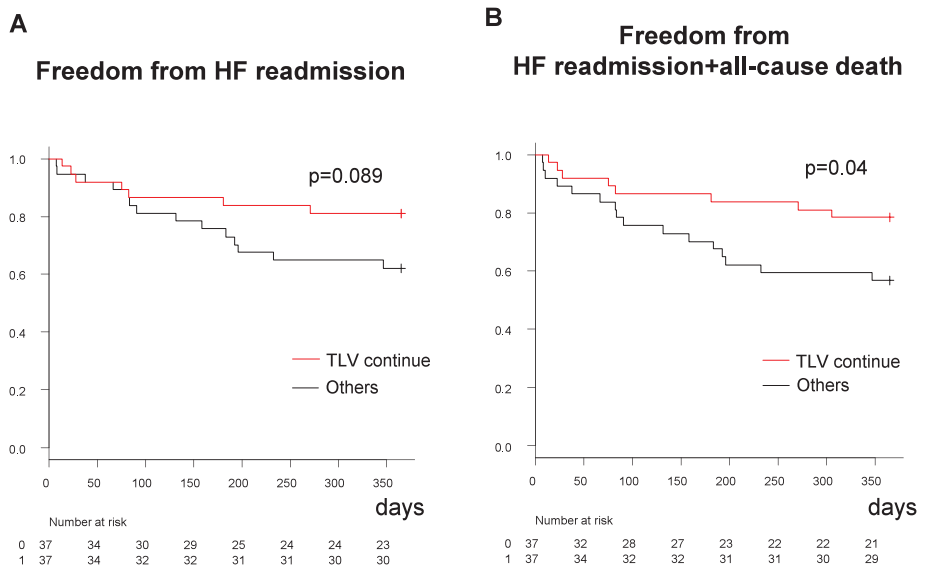

Fig. 2 Survival curves of freedom from HF readmission (A) and HF readmissions and all-cause death (B) between the patients who continued tolvaptan and others by a Kaplan-Meier analysis.

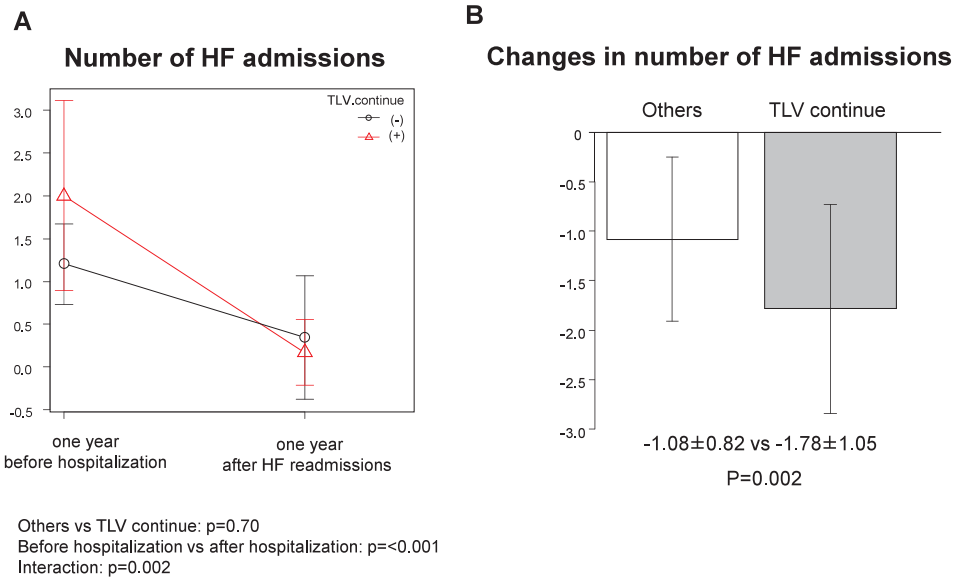

Fig. 3 A comparison of number of HF admissions (A) and changes in number of HF admissions (B) between the patients with continued tolvaptan and others. The data are presented as the mean ± SD.

This group was divided into two groups : the group with continued tolvaptan (n=22) and the others (n=37). The characteristics of these groups were similar (Table 4). Among the frequent flyers, number of admissions due to HF one-year after discharge was reduced compared to the number of admissions due to HF before the index admission in both groups (Fig. 4A). However, the change in number of admissions due to HF one-year before and after the index admission (−2.31 ± 1.08 vs. −1.43 ± 0.80, $p < 0.001$) were larger in the tolvaptan continued group than the other group (Fig. 4B).

Table 4 Characteristics of frequent flyer patients

	Others	TLV continue	p
n	37	22	
	Backgrounds		
age	79.5 ± 10.3	80.5 ± 9.1	0.72
male（%）	23（62.2）	13（59.1）	1
BNP	1102.7 ± 1053.1	1276.9 ± 820.0	0.516
EF	41.9 ± 17.2	39.5 ± 14.2	0.568
NYHA3,4（%）	29（78.4）	21（95.5）	0.134
IHD（%）	16（43.2）	13（59.1）	0.288
sBP	140.8 ± 40.3	143.3 ± 37.5	0.819
dBP	76.5 ± 22.9	80.6 ± 23.5	0.514
HR	86.8 ± 22.5	81.7 ± 19.8	0.377
BMI	21.2 ± 4.1	21.8 ± 3.5	0.569
Hospital stay	19.2 ± 17.9	18.6 ± 14.9	0.903
Comorbidity			
AF（%）	12（32.4）	8（36.4）	0.783
DM（%）	12（32.4）	7（31.8）	1
COPD（%）	1（2.7）	2（9.1）	0.549
pneumonia（%）	6（16.2）	0（0.0）	0.075
Labo data			
BUN	32.3 ± 14.8	33.3 ± 12.1	0.793
Cr	1.20［0.65, 9.23］	1.71［0.53, 3.45］	0.237
eGFR	39.47（22.76）	33.35（20.79）	0.307
UA	6.33 ± 1.59	6.68 ± 1.62	0.428
Na	139.2 ± 3.9	138.9 ± 3.9	0.867
K	4.40 ± 0.65	4.01 ± 0.63	0.031
Hb	10.9 ± 2.1	11.2 ± 1.9	0.721
Alb	3.60［1.70, 4.40］	3.60［2.60, 4.20］	0.857
At discharge			
ACEI/ARB（%）	30（81.1）	18（81.8）	1
BB（%）	32（86.5）	20（90.9）	0.702
MRA（%）	18（48.6）	14（63.6）	0.293
Loop at discharge（%）	24（64.9）	16（72.7）	0.578
Loop dose at discharge	19.2 ± 17.9	18.6 ± 14.9	0.903
In hospital use			
Loop（%）	23（62.2）	15（68.2）	0.781
TLV（%）	7（18.9）	22（100.0）	＜0.001
Carperitide（%）	8（21.6）	7（31.8）	0.537
Cathecolamine（%）	8（21.6）	4（18.2）	1
NPPV（%）	2（5.4）	0（0.0）	0.524
CRT/ICD（%）	3（8.1）	2（9.1）	1

Data are given as n (%), the mean ± SD or the median plus confidence interval
Abbreviations are described in the manuscript

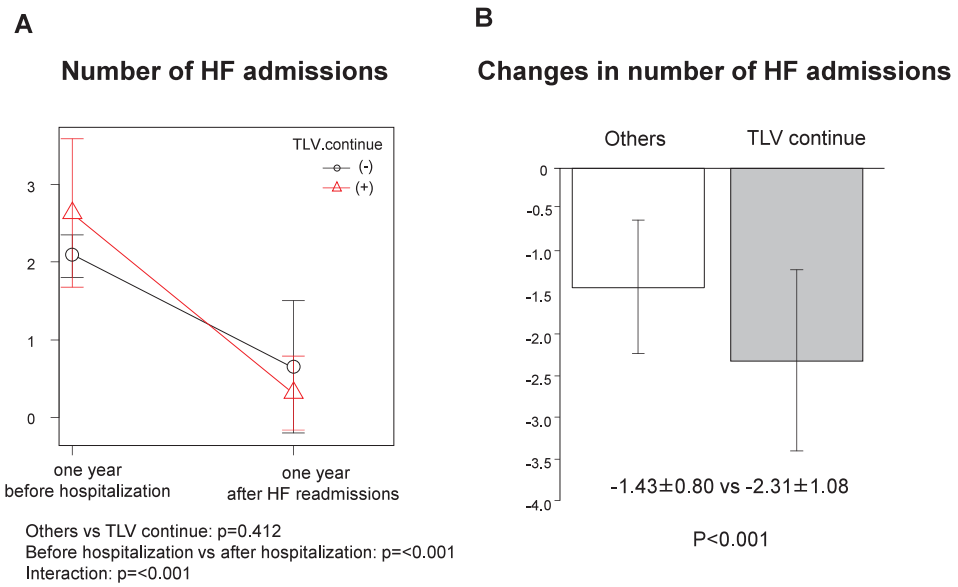

Fig. 4 A comparison of number of HF admissions (A) and changes in number of HF admissions (B) between the frequent flyer patients with continued tolvaptan and the others. The data are presented as the mean ± SD.

Discussion

The present study demonstrated that continuing tolvaptan after discharge was associated with an improved long-term prognosis in HF patients. Furthermore, continuing tolvaptan was associated with a reduction in number of HF readmissions. The beneficial effects of tolvaptan in the acute phase of decompensated HF have been described and established in several previous reports. We also previously reported an efficacy of early use of tolvaptan in decompensated HF patients[15)16)].

However, evidence regarding the efficacy of chronic use of tolvaptan in HF patients has been insufficient. The EVEREST trial, the first prospective randomized control trial of tolvaptan, failed to demonstrate a long-term benefit of tolvaptan, although some observational studies have suggested its long-term beneficial effects[9)]. Imamura et al. reported that responders to tolvaptan had a higher rate of freedom from HF readmissions for two years[17)]. They also showed that tolvaptan therapy significantly reduced the two-year readmission rate both in HF with reduced ejection fraction (HFrEF) and in HF with preserved EF (HFpEF) populations[18)]. Furthermore, Uemura et al. demonstrated that continuing tolvaptan resulted in a reduction of cardiac-related death or HF-related admissions in patients with HF and chronic kidney disease for one year[19)]. We have experienced favorable clinical outcomes with a long-term use of tolvaptan, thus we intended to clarify the outcomes of long-term use of tolvaptan in the present study.

We investigated 365 consecutive decompensated HF patients without in-hospital death or dialysis in the present study. Sixty-seven of 365 patients (18.3%) were re-hospitalized during one year after discharge in the present study. First, we clarified the related clinical factors to HF readmissions. Result from multivariable analysis showed that frequent flyer, higher age, a low hemoglobin level, male gender and receiving noninvasive positive pressure ventilation (NPPV) were associated with HF readmissions. We speculated that HF severity in patients with NPPV but not NPPV use itself was relevant to the HF readmissions. Continuing tolvaptan after discharge was not significantly related to the incidence of HF readmissions.

Only 10% patients continued tolvaptan after discharge, although 93 patients received tolvaptan during the admissions. This result was affected by each physician decision whether or not to continue tolvaptan after discharge. Physicians might have decided to continue tolvaptan in only severe patients, as the tolvaptan continuation group included patients with a higher BNP level and a larger proportion of frequent flyers. Given these discrepancies in the background characteristics, we performed a propensity score matching analysis. Both group included a large but equal number of frequent flyer patients after the propensity score matching. The result demonstrated that continuation of tolvaptan after discharge was associated with favorable long-term prognosis and less HF readmissions in HF patients. These results are consistent with some previous reports[17)~19)]. Furthermore, the present study demonstrated that continuation of tolvaptan after discharge was related to a reduction in number of HF readmissions in HF patients as well as frequent flyers. These results were firstly reported to report in the present study. These results suggested that continuing tolvaptan after discharge helped prevent worsening of HF in the studied patients. Taken together with the previous studies, a clinical benefit of long-term use of tolvaptan was suggested. In this study, continuing tolvaptan reduced all cause death. However, ten patients died during the follow up period ; 9 non-cardiac death and 1 cardiac death. We speculate this result is due to not direct effect of tolvaptan but indirect effect. Decongestion by tolvaptan reduced symptoms of HF, such as shortness of breath, leg edema and so on leading to improve the quality of life (QOL). Improving the QOL might lead to better prognosis.

The present study demonstrated that being a frequent flyer was strongly associated with readmission for HF (HR 2.627). Frequent flyers who are repeatedly admitted due to HF is a serious problem in the management of HF and continuing tolvaptan in the outpatient care could be an useful therapeutic strategy especially for those patients. Thus, it can be said that this study was performed only in the population with severe backgrounds.

Several limitations in the present study should be mentioned. First, this study was a single-center retrospective observational study, and the number of patients with continued tolvaptan was small. We therefore performed a propensity score matching in order to improve the statistical credibility. Although most of the clinical variables were well matched in this method, the dose of loop diuretics at discharge was larger in the tolvaptan continuing group. Second, as mentioned above, this study might include some degree of selection bias. Third, we compared the long-term effects of tolvaptan between the group that continued tolvaptan after discharge and the group without tolvaptan use after discharge regardless of the in-hospital medication regimen. Fourth, number of HF admissions before the index admission tended to be higher in the group of continued tolvaptan in the frequent flyer analysis. We cannot deny the possibility that the results in frequent flyers of reduction in number of HF admissions may be affected by a 'regression to the mean' phenomenon. Further prospective randomized studies should be conducted to establish the effect of long-term use of tolvaptan in HF patients.

Conclusions

In conclusion, this study demonstrated that continuing tolvaptan after discharge is associated with a favorable long-term prognosis in HF patients. Furthermore, it was accompanied by a reduction in number of HF readmissions in all HF patients, as well as in frequent flyers. These data suggest that continuing tolvaptan after discharge may have a beneficial effect in a selected group of patients with chronic HF.

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（和文抄録）

トルバプタンの外来継続はうっ血性心不全患者の長期予後改善と，心不全による再入院回数の減少に関連する

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目的：慢性心不全に対するトルバプタンの退院後の長期使用の効果は明らかではなく，この研究ではその効果についての検討を行った．

方法：我々は連続 407 名の入院を必要とするうっ血性心不全患者の退院後 1 年間の予後について検討，42 名の院内死亡，透析患者を除いた 365 名について解析を行った．

結果：多変量解析を行うと，入院前 1 年間に少なくとも 1 回以上の心不全入院歴のある患者（frequent flyer と定義），高齢であること，貧血があること，男性であること，NPPV による治療を受けたことなどが 1 年間の心不全再入院と関連が強い因子として残った．我々は続いて退院後にトルバプタンを継続したことと心不全再入院についての関連について調べた．トルバプタン継続群とそれ以外で，心不全再入院と関連する交絡因子を含めた背景を揃えるためにプロペンシティマッチングを行い，それぞれ 37 名ずつでの解析を行った．1 年間の心不全再入院回避率はトルバプタン継続群で高い傾向にあった（p=0.08）．心不全再入院回避率と全死亡回避率を合わせた複合アウトカムはトルバプタン継続群で有意に高かった（p=0.04）．さらに，対象入院前の 1 年間の心不全入院回数と退院後 1 年間の再入院回数の変化を比べたところトルバプタン継続群で入院回数の減少率は有意に高かった（−1.78 ± 1.05 vs. −1.08 ± 0.82, p=0.002）．さらに，59 名の frequent flyer の患者だけで比べても同様の結果が得られた（−2.31 ± 1.08 vs. −1.43 ± 0.80，$p < 0.001$）．

結論：これらの結果から退院後のトルバプタン継続はうっ血性心不全患者の長期予後を改善し，心不全再入院回数を減少させる可能性が示唆された．

キーワード：トルバプタン外来継続，心不全再入院，Frequent flyer