Journal of the American Heart Association

ORIGINAL RESEARCH

Associations of Benzodiazepine With Adverse Prognosis in Heart Failure Patients With Insomnia

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BACKGROUND: The prognostic impact of benzodiazepines has been unclear in patients with heart failure (HF).

METHODS AND RESULTS: This was a historical observational cohort study. A total of 826 patients who had been hospitalized for HF and were being treated for insomnia with either benzodiazepines or Z-drugs (zolpidem, zopiclone, or eszopiclone), were enrolled and divided on the basis of their hypnotics: benzodiazepine group (n=488 [59.1%]) and Z group (n=338 [40.9%]). We compared the patient characteristics and postdischarge prognosis between the groups. The primary end points were rehospitalization for HF and cardiac death. The benzodiazepine group was older (age, 72.0 versus 69.0 years; P=0.010), had a higher prevalence of depression (17.4% versus 8.9%; P<0.001), and showed a higher use of loop diuretics (77.9% versus 67.8%; P=0.001). In the laboratory data, the benzodiazepine group demonstrated lower levels of hemoglobin (12.3 versus 13.0 g/dL; P=0.001), sodium (139.0 versus 140.0 mEq/L; P=0.018), and albumin (3.7 versus 3.9 g/dL; P=0.003). Kaplan-Meier analysis showed that both end points were higher in the benzodiazepine group (rehospitalization for HF, log-rank P=0.001; cardiac death, log-rank P=0.043). Multiple Cox proportional hazard analysis revealed that the use of benzodiazepines was an independent predictor of rehospitalization for HF (hazard ratio, 1.530; 95% CI, 1.025–2.284; P=0.038). Furthermore, rehospitalization for HF was higher in the benzodiazepine group after propensity score matching (log-rank P=0.036).

CONCLUSIONS: Benzodiazepine is associated with higher risk of rehospitalization for HF compared with Z-drugs in patients with HF.

Key Words: benzodiazepine ■ heart failure ■ prognosis ■ Z-drugs

Insomnia is one of the major health problems, characterized by poor sleep quality, short sleeping duration, difficulty in falling asleep, difficultly maintaining sleep, or early-morning waking.[1–4] Approximately 6% to 10% of the general population fall under the criteria for insomnia.[1,5–7] Insomnia not only deteriorates quality of life, but also increases risks for comorbidities, such as depression,[8,9] heart failure (HF),[10] and mortality.[11,12]

Benzodiazepine, one of the most commonly prescribed types of hypnotics for patients with insomnia, targets benzodiazepine sites of γ-aminobutyric acid (GABA) type A ($GABA_A$) receptors.[13,14] In addition, benzodiazepines allosterically increase the $GABA_A$ receptors' affinity for GABA, an inhibitory neurotransmitter, and express inhibitory effects in the central nervous system: hypnosis, anxiolysis, seizure suppression, muscle relaxation, and amnesia.[13,14] However, benzodiazepines have risks for tolerance, dependence, and cognitive impairment, as well as falls and fractures.[13,15] According to the current guidelines and other reports, nonbenzodiazepines, called Z-drugs (drugs with names starting with "Z"; zolpidem, zopiclone, and eszopiclone),

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CLINICAL PERSPECTIVE

What Is New?

- Among patients with heart failure (HF) with coexisting insomnia, those receiving benzodiazepines were at higher risk of rehospitalization for HF than those receiving Z-drugs (zolpidem, zopiclone, and/or eszopiclone).
- Benzodiazepines were associated with a 1.5-fold increase in the risk of rehospitalization for HF compared with Z-drugs, and rehospitalization for HF was higher even after propensity score matching.

What Are the Clinical Implications?

- Treatment of insomnia in patients with HF should be optimized because selection of hypnotics is associated with prognosis.
- Treatment of HF also should be optimized to improve sleep and avoid excessive use of hypnotics.

Nonstandard Abbreviations and Acronyms

ACEI	angiotensin-converting enzyme inhibitor
ARB	angiotensin receptor blocker
BNP	B-type natriuretic peptide
CAD	coronary artery disease
CBT-I	cognitive behavioral therapy for insomnia
CNS	central nervous system
CVA	cerebrovascular accident
GABA	γ-aminobutyric acid
$GABA_A$	γ-aminobutyric acid type A
HF	heart failure
HPA	hypothalamic pituitary adrenal
HR	hazard ratio
LVEF	left ventricular ejection fraction
NHYA	New York Heart Association
RAAS	renin-angiotensin-aldosterone system
SAS	sleep apnea syndrome
SNRI	serotonin noradrenalin reuptake inhibitor
SNS	sympathetic nervous system
SSRI	selective serotonin reuptake inhibitor
VTA	ventral tegmental area

which target benzodiazepine sites of $GABA_A$ receptors with higher selectivity compared with benzodiazepines, can be used as alternatives to benzodiazepines.[2,16–18] Z-drugs are relatively safer than benzodiazepines because they have a low abuse potential, and patients do not develop a tolerance to them as rapidly.[18,19]

In patients with HF, the prevalence of insomnia is reported to be high, ranging from 23% to 73%,[20,21] and is associated with adverse prognosis.[21] However, it remains unclear whether the type of hypnotics used affects the prognosis of patients with HF or not. Thus, the aim of the present study was to clarify the associations of benzodiazepines and Z-drugs with prognosis in HF patients with insomnia.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request.

Subjects and Study Protocol

This was a historical observational cohort study of 2213 patients who had been hospitalized in Fukushima Medical University Hospital for decompensated HF between January 2010 and December 2017. The diagnosis of HF was made by each patient's attending cardiologist using the Framingham criteria and/or current guidelines.[22–24] The definition of insomnia was in accordance with that described previously.[21] In brief, insomnia was diagnosed on the basis of direct interviews using a questionnaire by the attending physicians and medical staff for patients or caregivers. The topics discussed were as follows: (1) usual use of hypnotics ("Do you take hypnotics >3 times per week?" with the response options of yes/no) or (2) presence of either insomnia symptoms, grades 3 or 4, accompanied by impairment of daytime function.[4,10] The second topic was assessed using the following items: difficulty initiating sleep ("Do you have difficulties falling asleep?" with the response options 1, never; 2, occasionally; 3, often; or 4, almost every night); difficulty maintaining sleep and/or early morning awakenings ("Do you wake up in the early hours, unable to get back to sleep?" with the response options 1, never; 2, occasionally; 3, often; or 4, almost every night); and nonrestorative sleep ("How often do you suffer from poor sleep?" with the response options 1, never or a few times a year; 2, 1 to 2 times per month; 3, about once a week; or 4, more than once a week).[21] This questionnaire was based on a modified International Classification of Sleep Disorders, second edition criteria,[4,10] supported by the American Academy of Sleep Medicine and the Japanese Society of Sleep Research, which are used widely in Japanese clinical practice. Insomnia was defined as (1) the use of hypnotics >3 times per week and/or (2) the presence of either insomnia symptoms, grade 3 or 4, accompanied by impairment of daytime function, as described above. On admission, pharmacists at our hospital who were blind to this study checked the

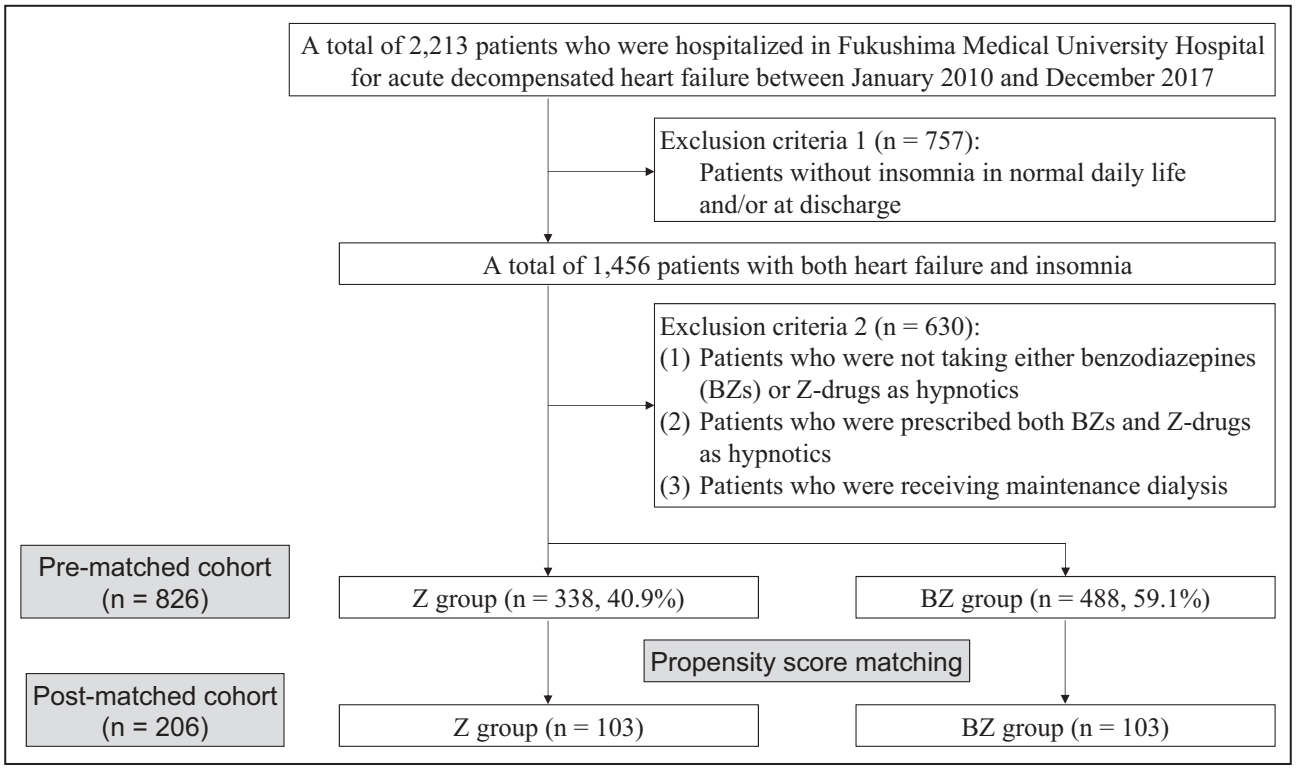

Figure 1. Patient flow chart.
BZ indicates benzodiazepine; and Z, zolpidem, zopiclone, or eszopiclone.

type of hypnotics, if said hypnotics were prescribed to patients by their family physicians. Each attending physician then kept prescribing the same hypnotics during hospitalization and at discharge.

A patient flow chart is shown in Figure 1. First, patients without insomnia in their normal daily life (n=757) were excluded. Other patients who were excluded (n=630) were as follows: (1) patients who were not taking either benzodiazepines or Z-drugs as hypnotics; (2) patients who were prescribed both benzodiazepines and Z-drugs as hypnotics; and (3) patients who were receiving maintenance dialysis. Finally, a total of 826 patients were included in this study. We divided these patients on the basis of the type of hypnotics at discharge: patients with benzodiazepines (the benzodiazepine group, n=488 [59.1%]) and those with Z-drugs (the Z group, n=338 [40.9%]). We compared the patients' characteristics and postdischarge prognosis. The patients' characteristics included demographic data and medication at the time of discharge. Blood samples and echocardiographic data were obtained within 1 week before discharge. This study had 2 primary end points: (1) rehospitalization for HF on the basis of the Framingham criteria and/or current guidelines[22–24]; and (2) cardiac death. Cardiac death was defined as death caused by worsening HF, ventricular fibrillation documented by ECG or implantable devices, or acute coronary syndrome. Status and dates of end points were obtained from the patients' medical records. If these data were unavailable, the patient's status was ascertained by a telephone call to his/her referring hospital physician. These follow-ups were performed annually.

Comorbidities were defined in accordance with those described previously.[21] Hypertension was defined as the recent use of antihypertensive drugs, a systolic blood pressure of ≥140 mm Hg, and/or a diastolic blood pressure of ≥90 mm Hg. Diabetes mellitus was defined as the recent use of antidiabetic drugs, a fasting glucose value of ≥126 mg/dL, a casual glucose value of ≥200 mg/dL, and/or hemoglobin A1c (National Glycohemoglobin Standardization Program) of ≥6.5%. Dyslipidemia was defined as the recent use of cholesterol-lowering drugs, a triglyceride value of ≥150 mg/dL, a low-density lipoprotein cholesterol value of ≥140 mg/dL, and/or a high-density lipoprotein cholesterol value of <40 mg/dL. Atrial fibrillation was identified by an ECG performed during hospitalization and/or from medical records. Chronic kidney disease was defined as an estimated glomerular filtration rate of <60 mL/min per 1.73 cm^2 using the modified Modification of Diet in Renal Disease equation.[25] Depression was diagnosed on the basis of medical history and/or a Center for Epidemiological Studies-Depression score of ≥16.[26] Sleep apnea syndrome was defined as an apnea-hypopnea index of ≥5, and included both central and obstructive sleep apnea.[27]

Written informed consent was obtained from all patients. The study protocol was approved by the ethical committee of Fukushima Medical University, the investigation conforms with the principles outlined in the Declaration of Helsinki, and reporting of the study conforms to STROBE (Strengthening the Reporting of Observational studies in Epidemiology) along with references to STROBE and the broader EQUATOR (Enhancing the Quality and Transparency Of health Research) guidelines.[28]

Statistical Analysis

Normality was confirmed using the Shapiro-Wilk test in each group. Normally distributed variables are presented as mean±SD, nonnormally distributed variables are presented as median (25th percentile, 75th percentile), and categorical variables are expressed as counts and percentages. Normally distributed variables were compared using the Student *t* test, nonnormally distributed variables were compared using the Mann-Whitney *U* test, and the χ^2 test was used for comparisons of categorical variables in the prematched cohort. Kaplan-Meier analysis was used to assess the 2 primary end points, and a log-rank test was used for initial comparisons. Cox proportional hazard analyses were used to evaluate benzodiazepines as predictors of the 2 end points. Univariable Cox proportional hazard analysis was followed by a multivariable analysis adjusted for factors that differed significantly between the 2 groups. To prepare for the heterogeneity of HF, interaction *P* values between hypnotic type and age (below versus above the median) or left ventricular ejection fraction (LVEF) category (LVEF of <50% versus ≥50%) were obtained by entering the type of hypnotics, age, or LVEF category, and each interaction.

As shown in Figure 1, to eliminate imbalances in the measurement of baseline characteristics because of selection bias associated with the use of Z-drugs or benzodiazepines, we used 2 approaches: multiple Cox regression analysis in the prematched cohort (n=826) and propensity score matching analysis (postmatched cohort, n=206).[29] Among the patients who had been prescribed hypnotics (Z-drugs, n=338; benzodiazepines, n=488), the propensity score for treatment with benzodiazepines was estimated for each patient by logistic regression analysis, with the clinically relevant variables associated with the introduction of benzodiazepines. A propensity score model was estimated using the logistic regression model, which was adjusted for the patients' characteristics, as listed in Table 1 (age, sex, body mass index, systolic blood pressure, New York Heart Association functional class III or IV, prior HF admission, hypertension, diabetes mellitus, dyslipidemia,

Table 1. Patient Characteristics: Prematched Cohort (n=826)

Characteristic	Z Group (n=338)	Benzodiazepine Group (n=488)	*P* Value
Demographic data			
Age, y	69.0 (60.0, 77.0)	72.0 (62.0, 79.0)	0.010
Male sex, n (%)	221 (65.4)	273 (55.9)	0.007
Body mass index, kg/m^2	23.0 (20.7, 26.0)	22.6 (20.2, 24.9)	0.009
Systolic blood pressure, mm Hg	122.0 (108.0, 142.0)	121.0 (104.0, 145.5)	0.656
NYHA functional class III or IV, n (%)	16 (4.7)	23 (4.7)	0.989
Medical history, n (%)			
Prior HF admission	115 (35.0)	164 (34.7)	0.934
Hypertension	238 (70.4)	348 (71.3)	0.780
Diabetes mellitus	140 (41.4)	208 (42.6)	0.731
Dyslipidemia	247 (73.1)	357 (73.2)	0.980
Atrial fibrillation	143 (42.3)	207 (42.4)	0.975
CAD	102 (30.2)	179 (36.7)	0.052
CVA	58 (17.2)	83 (17.0)	0.955
Chronic kidney disease	183 (54.1)	289 (59.2)	0.147
Depression	30 (8.9)	85 (17.4)	<0.001
Sleep apnea syndrome	181 (89.2)	196 (76.6)	<0.001
Medications, n (%)			
β Blockers	249 (73.7)	386 (79.1)	0.069
ACEIs/ARBs	250 (74.0)	367 (75.2)	0.687
Loop diuretics	229 (67.8)	380 (77.9)	0.001
SSRIs/SNRIs	8 (2.4)	15 (3.1)	0.544
Laboratory data			
BNP, pg/mL	217.3 (83.4, 528.7)	282.8 (104.3, 627.1)	0.094
Creatinine, mg/dL	0.92 (0.77, 1.15)	0.93 (0.72, 1.25)	0.829
Blood urea nitrogen, mg/dL	18.0 (15.0, 23.0)	19.0 (14.0, 26.0)	0.314
Hemoglobin, g/dL	13.0 (11.5, 14.3)	12.3 (10.6, 13.9)	0.001
Sodium, mEq/L	140.0 (137.0, 142.0)	139.0 (137.0, 141.0)	0.018
Albumin, g/dL	3.9 (3.5, 4.2)	3.7 (3.3, 4.1)	0.003
Echocardiographic data			
LVEF, %	51.2 (37.3, 63.0)	53.5 (40.0, 63.0)	0.325
LVEF of <50%, n (%)	133 (47.7)	157 (42.3)	0.174

Data are given as median (25th percentile, 75th percentile), unless otherwise indicated. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BNP, B-type natriuretic peptide; CAD, coronary artery disease; CVA, cerebrovascular accident; HF, heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SNRI, serotonin noradrenalin reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; and Z, zolpidem, zopiclone, or eszopiclone.

atrial fibrillation, coronary artery disease, cerebrovascular accident, chronic kidney disease, sleep apnea syndrome, β blockers, angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers, loop diuretics, B-type natriuretic peptide, creatinine, blood urea nitrogen, hemoglobin, sodium, albumin, and LVEF), as these variables were considered to be important in prognostic prediction in other studies.[21,23,24,27] Presence of depression and the use of selective serotonin reuptake inhibitors and/or serotonin noradrenalin reuptake inhibitors were excluded from the logistic regression model because these covariates were considered to be more strongly associated with exposure than with the end points.[17,29,30] Propensity score matching was then performed, using the nearest neighbor matching without replacement. A caliper width of 0.2 of the SD of the logit of the propensity score was used for the developed propensity score.[31,32] In the postmatched cohort, normally distributed variables were compared using the paired *t* test, and nonnormally distributed variables were compared using the Wilcoxon signed rank test. Differences in the 1-, 2-, and 3-year primary outcomes were evaluated by the McNemar test. $P<0.05$ was considered statistically significant. All analyses were performed using a statistical software package (SPSS version 25; IBM, Armonk, NY).

RESULTS

The comparisons of patient characteristics between the Z and benzodiazepine groups of the prematched cohort (n=826) are summarized in Table 1. The benzodiazepine group was older (age, 72.0 versus 69.0 years; $P=0.010$), had a lower prevalence of male sex (55.9% versus 65.4%; $P=0.007$), and had a lower body mass index (22.6 versus 23.0 kg/m^2; $P=0.009$). With respect to medical history, the prevalence of depression was higher (17.4% versus 8.9%; $P<0.001$) and that of sleep apnea syndrome was lower (76.6% versus 89.2%; $P<0.001$) in the benzodiazepine group. In contrast, other comorbidities, such as prior HF admission, atrial fibrillation, coronary artery disease, and cerebrovascular accident, were comparable

Table 2. Cox Proportional Hazard Analysis for Rehospitalization for HF and Cardiac Death

Variable	HR	95% CI	*P* Value
Rehospitalization for HF (event n=244/826)			
Benzodiazepines (vs Z-drugs)	1.555	1.184–2.042	0.001
Benzodiazepines (vs Z-drugs)*	1.516	1.152–1.994	0.003
Benzodiazepines (vs Z-drugs)†	1.530	1.025–2.284	0.038
Cardiac death (event n=140/826)			
Benzodiazepines (vs Z-drugs)	1.448	1.010–2.075	0.044
Benzodiazepines (vs Z-drugs)*	1.357	0.944–1.951	0.099

HF indicates heart failure; HR, hazard ratio; and Z, zolpidem, zopiclone, or eszopiclone.
*Adjusted for age and sex.
†Adjusted for age, sex, body mass index, depression, sleep apnea syndrome, loop diuretics, hemoglobin, sodium, and albumin.

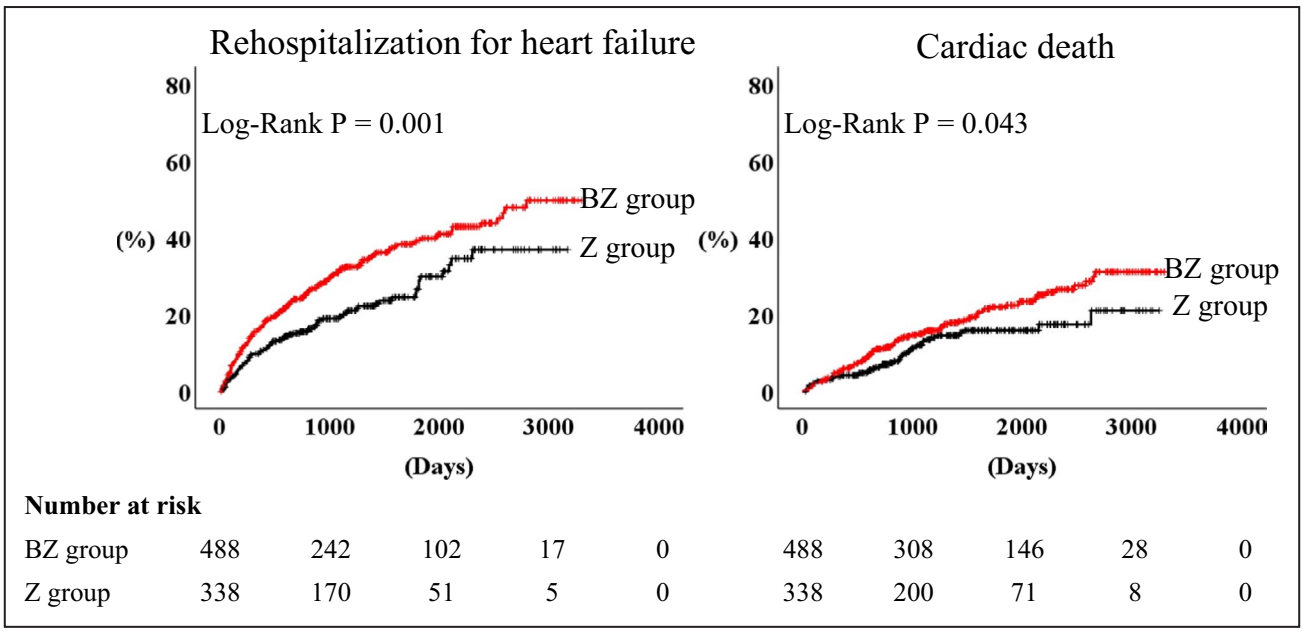

Figure 2. Kaplan-Meier analysis: prematched cohort (n=826).
BZ indicates benzodiazepine; and Z, zolpidem, zopiclone, or eszopiclone.

between the 2 groups. Both groups received similar medication for HF, except for a higher use of loop diuretics in the benzodiazepine group (77.9% versus 67.8%; *P*=0.001). In the laboratory data, levels of hemoglobin, sodium, and albumin were lower in the benzodiazepine group (hemoglobin, 12.3 versus 13.0 g/dL, *P*=0.001; sodium, 139.0 versus 140.0 mEq/L, *P*=0.018; albumin, 3.7 versus 3.9 g/dL, *P*=0.003). In contrast, there were no significant differences in levels of B-type natriuretic peptide, creatinine, or blood urea nitrogen. According to the echocardiography, LVEF was similar between the 2 groups.

During the postdischarge follow-up period of a median of 1254 days, there were 244 cases of rehospitalization for HF, and 140 cardiac deaths. In the Kaplan-Meier analysis (Figure 2), both end points were higher in the benzodiazepine group than in the Z group (rehospitalization for HF, log-rank *P*=0.001; cardiac death, log-rank *P*=0.043). The results of the Cox proportional hazard analysis are described in Table 2. In the univariable Cox proportional hazard analysis, the use of benzodiazepines was associated with both rehospitalization for HF (hazard ratio, 1.555; 95% CI, 1.184–2.042; *P*=0.001) and cardiac death (hazard ratio, 1.448; 95% CI, 1.010–2.075; *P*=0.044). In the multivariable Cox proportional hazard analysis, use of benzodiazepines was associated with rehospitalization for HF (hazard ratio, 1.530; 95% CI, 1.025–2.284; *P*=0.038), but not with cardiac death. There were no interactions between hypnotic type and either age (age of <71 versus ≥71 years; rehospitalization for HF, interaction *P*=0.468; cardiac death, interaction *P*=0.301) or LVEF category (LVEF of <50% versus ≥50%; rehospitalization for HF, interaction *P*=0.320; cardiac death, interaction *P*=0.139).

In addition, we performed propensity score matching. The SD of the logit of the propensity score was 0.28, and the caliper width was set at 0.06. In the postmatched cohort (n=206), the demographic, laboratory, and echocardiographic data were equivalent between the 2 groups (Table 3). For matched pairs, 1- and 2-year rehospitalization for HF tended to be higher, and 3-year rehospitalization was significantly higher in the benzodiazepine group. Differences in the primary outcomes during the total follow-up period are shown in Figure 3. Rehospitalization for HF rate was higher in the benzodiazepine group than in the Z group (log-rank *P*=0.036), and the rate of cardiac death did not significantly differ between the groups.

Table 3. Patient Characteristics: Postmatched Cohort (n=206)

Characteristic	Z Group (n=103)	Benzodiazepine Group (n=103)	*P* Value
Demographic data			
Age, y	67.0 (60.0, 75.0)	68.0 (60.0, 75.0)	0.951
Body mass index, kg/m^2	23.2 (20.4, 26.0)	23.0 (21.1, 24.8)	0.341
Systolic blood pressure, mm Hg	118.0 (102.5, 134.0)	112.0 (103.0, 134.0)	0.326
Laboratory data			
BNP, pg/mL	243.1 (95.1, 565.9)	247.7 (112.3, 562.6)	0.944
Creatinine, mg/dL	0.89 (0.75, 1.04)	0.93 (0.71, 1.14)	0.645
Blood urea nitrogen, mg/dL	18.0 (14.0, 22.0)	19.0 (14.0, 24.5)	0.776
Hemoglobin, g/dL	12.8±1.9	12.8±2.2	0.950
Sodium, mEq/L	140.0 (137.5, 142.0)	139.0 (137.0, 141.0)	0.555
Albumin, g/dL	3.9 (3.5, 4.2)	3.8 (3.5, 4.2)	0.729
Echocardiographic data			
LVEF, %	46.1 (31.9, 63.1)	51.8 (36.7, 60.8)	0.853
Rehospitalization for HF, n (%)			
1 y	10 (9.7)	19 (18.4)	0.078
2 y	16 (15.5)	27 (26.2)	0.082
3 y	20 (19.4)	36 (35.0)	0.015
Cardiac death, n (%)			
1 y	4 (3.9)	6 (5.8)	0.754
2 y	6 (5.8)	10 (9.7)	0.454
3 y	10 (9.7)	13 (12.6)	0.678

Data are given as median (25th percentile, 75th percentile) or mean±SD, unless otherwise indicated. BNP indicates B-type natriuretic peptide; HF, heart failure; LVEF, left ventricular ejection fraction; and Z, zolpidem, zopiclone, or eszopiclone.

DISCUSSION

To the best of our knowledge, the present study was the first to show that the use of benzodiazepine was associated with higher risk of rehospitalization for HF in patients with HF, using multivariable analysis and propensity score matching analysis. These findings are pivotal because insomnia itself and the selection of prescribed hypnotics are modifiable factors.

Insomnia and HF adversely affect each other; insomnia increases the risk of incident HF, and symptoms of HF (eg, paroxysmal nocturnal dyspnea and/or orthopnea) disrupt sleep.[10,33] The mechanisms that underlie insomnia, hypnotics, and the prognosis of patients with HF are not yet fully understood. Although the current hypothesis remains a matter of speculation, one plausible explanation is the shared common pathophysiological features: activation of the sympathetic nervous system, the hypothalamic pituitary adrenal axis, and the renin-angiotensin-aldosterone system.[1,10,21]

$GABA_A$ receptors consist of various subunits (α1–6, β1–3, and γ1–3) and variants.[13,14] The benzodiazepine

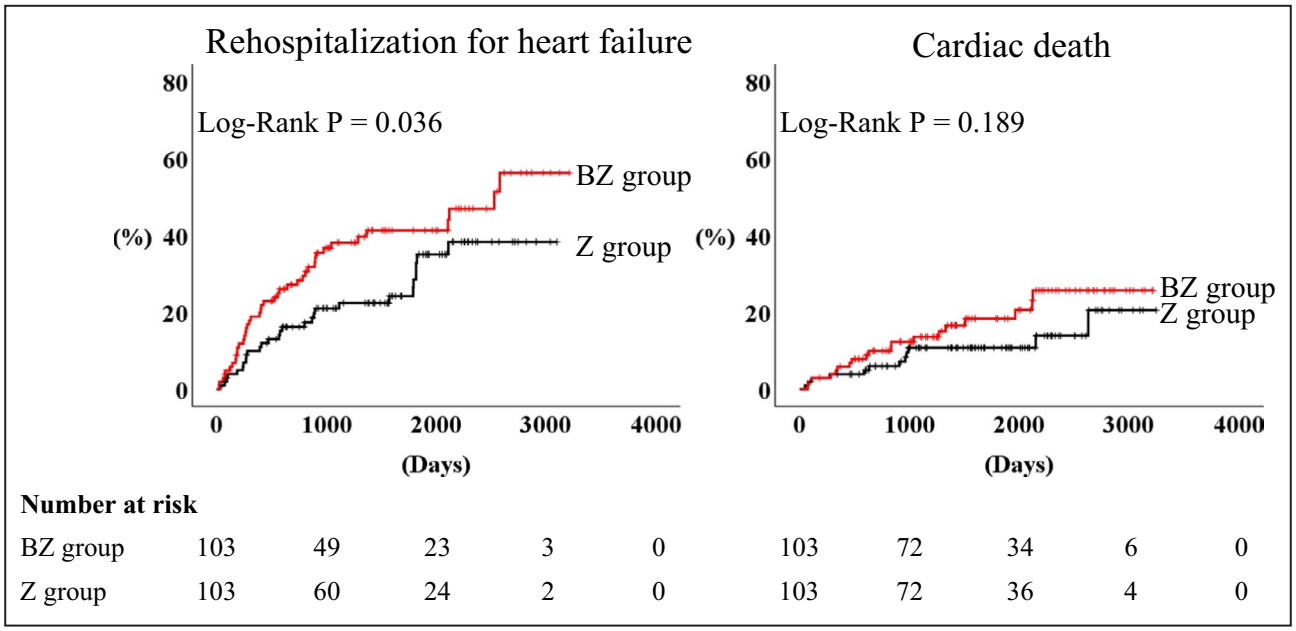

Figure 3. Kaplan-Meier analysis: postmatched cohort (n=206).
BZ indicates benzodiazepine; and Z, zolpidem, zopiclone, or eszopiclone.

sites are formed by one of several α subunits (α1, α2, α3, and α5) and a γ subunit.[13] These subtypes contribute to the pharmacological effects of benzodiazepines and Z-drugs. For instance, α1 is associated with sedation, addiction, and amnesia, whereas α2 is related to anxiolysis, antidepression, and myorelaxation.[13,34] The ventral tegmental area and nucleus accumbens are located in the mesolimbic area, and are known as the central nervous system reward system.[35] Benzodiazepine dependence is caused by activation of dopaminergic neurons in the ventral tegmental area by modulating α1-containing $GABA_A$ receptors expressed in nearby interneurons.[36] Thus, the differences in α subunit selectivity between benzodiazepines and Z-drugs contribute to benzodiazepine dependence.[14,36] From real-world evidence, the risk of a patient becoming dependent on Z-drugs is lower than that of benzodiazepines.[37,38] Although both benzodiazepines and Z-drugs show inhibitory effects through $GABA_A$ receptors in the central nervous system,[13,14] Z-drugs are superior in that it takes longer for patients to build a tolerance to them.[19] Downregulation in $GABA_A$ receptors after long-term exposure to benzodiazepines leads to tolerance.[39] Thus, benzodiazepine tolerance could result in increased sympathetic nervous system, hypothalamic pituitary adrenal axis, and renin-angiotensin-aldosterone system. In the current study, the benzodiazepine group showed lower levels of sodium, indicating increased neurohormonal activation, which was consistent with this hypothesis.[40,41] These neurohormonal activations may be a plausible explanation for poor prognosis.[42] Insomnia is described as hyperarousal of the central nervous system.[1,3,4,21] Patients taking benzodiazepines may be at higher risk of rebound insomnia and withdrawal symptoms compared with those taking Z-drugs.[19] Psychological withdrawal symptoms can lead to emotional stress, such as anxiety, nervousness, depression, and irritability.[14] Stress activates the amygdala, a brain region associated with stress, and causes cardiovascular disease through increased bone marrow activity and arterial inflammation.[43] Furthermore, a new pathway, called the neuroimmune axis, outside the sympathetic nervous system has been attracting great interest recently.[44] Fragmented sleep reduces production of orexin in the hypothalamus, which, in turn, activates the production of monocytes in the bone marrow, resulting in greater atherosclerosis.[44] With respect to comorbid disorders, sleep apnea syndrome is one of the major comorbidities of insomnia and HF.[27,45] Because benzodiazepines may suppress respiratory drive and have muscle-relaxing effects, they may possibly deteriorate the patient's ability to breathe during sleep.[17] Thus, benzodiazepines can be a risk factor of cardiovascular events.[27] These pleiotropic unfavorable effects suggest that the use of benzodiazepines adversely affects HF beyond insomnia itself.

A standard treatment for HF patients with insomnia has yet to be established, although in general, all patients should receive cognitive behavioral therapy for insomnia as first-line treatment.[2–4] Collaboration with specialists, such as psychiatrists, should be considered. When pharmacotherapy is added, the decision becomes which hypnotics to prescribe. Clinicians

should select hypnotics according to symptom pattern, treatment goals, past treatment responses, patient preference, cost, availability of other treatments, comorbid conditions, contraindications, concurrent medication interactions, and adverse effects.[4] To date, there have been no direct comparisons of the effectiveness of hypnotics.[46] The results of the current study suggest that Z-drugs, rather than benzodiazepines, should be considered to avoid rehospitalization for HF in patients with HF. It is also necessary to optimize medical therapy for HF. For example, the use of diuretics at night should be avoided not to disrupt sleep. However, insufficient decongestion is also undesirable, because it causes paroxysmal nocturnal dyspnea and/or orthopnea. In addition, cardiac rehabilitation might be useful for improving insomnia, as well as exercise capacity and prognosis.[21,47,48]

STUDY STRENGTHS AND LIMITATIONS

This present study had several strengths. First, we focused on the modifiable prognostic factors. Insomnia can be ameliorated by cognitive behavioral therapy for insomnia alone or in combination with pharmacotherapy, and the choice of hypnotics is modifiable.[1–4,16,17,46] Second, we clearly distinguished benzodiazepines from Z-drugs. Although sometimes benzodiazepines and Z-drugs are considered to be in the same category by researchers or public health officials, we found a robust and significant difference between these 2 types of medication for prognosis. This finding is pivotal not only for clinical practice, but also for health policy. Third, we performed multiple Cox proportional hazard analysis and propensity score matching. Because this was a historical cohort study, these methods effectively strengthened the reliability of our results.

On the other hand, there were several limitations to the current study. First, as a single-center study with a relatively small number of patients, our results should be considered preliminary. Second, because the study population was divided on the basis of the type of hypnotics at discharge, neither doses nor changes in hypnotic treatment after discharge were taken into account. Third, considering the historical aspects of hypnotics (ie, Z-drugs are newer than benzodiazepines) and higher age demonstrated in the benzodiazepine group, we could not completely exclude selection bias and some remaining possible confounding factors. Fourth, we focused on only Z-drugs and benzodiazepines; we did not investigate the effectiveness or safety of other hypnotics (eg, ramelteon, suvorexant, and melatonin) for patients with HF.

CONCLUSIONS

Benzodiazepine is associated with higher risk of rehospitalization for HF in patients with HF. Z-drugs might be superior to benzodiazepines as hypnotics in patients with HF.

ARTICLE INFORMATION

Received July 18, 2019; accepted February 21, 2020.

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Acknowledgments

The authors thank Ms Kumiko Watanabe, Ms Hitomi Kobayashi, and Ms Tomiko Miura for their technical assistance, as well as Dr Hajime Iwasa (Department of Public Health, Fukushima Medical University) for his advice on medical statistics.

Sources of Funding

This study was supported in part by a grant-in-aid for scientific research (No. 16K09447) from the Japan Society for the Promotion of Science.

Disclosures

Drs Yoshihisa and Misaka belong to the Department of Advanced Cardiac Therapeutics at Fukushima Medical University, which is supported by Fukuda-denshi Co, Ltd. This company is not associated with the contents of this study. The remaining authors have no disclosures to report.

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