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Original Article

Association between complementary use of Goreisan (a Japanese herbal Kampo medicine) and heart failure readmission: A nationwide propensity score-matched study

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ABSTRACT

Background: Goreisan, a Japanese herbal medicine, possesses aquaretic properties to regulate body fluid homeostasis and may therefore be effective as a complement to standard therapy in improving outcomes in patients with heart failure (HF).

Methods: We retrospectively identified 431,393 patients (mean age 79.2 ± 12.6 years; male 52.3 %) who were admitted for HF for the first time and were discharged alive with standard HF medications between April 2016 and March 2022, using the Japanese Diagnosis Procedure Combination database. We divided patients into two groups according to the prescription of Goreisan at discharge: patients who received standard HF medications plus Goreisan and those who received standard medications alone. We compared the incidence of HF readmission within 1 year after discharge between the groups using propensity score matching.

Results: Overall, Goreisan was prescribed in 1957 (0.45 %) patients at discharge. Patients who received Goreisan were older and received diuretics more frequently than those who did not. One-to-four propensity score matching created a cohort of 1957 and 7828 patients treated with and without Goreisan, respectively. No significant difference was found in the incidence of 1-year HF readmission between the groups [22.1 % vs. 21.7 %; hazard ratio (HR) = 1.02, 95 % confidence interval (CI) = 0.92–1.13]. This result was consistent with that from competing risk analysis (subdistribution HR = 1.02, 95 % CI = 0.92–1.13) and across clinically relevant subgroups except for renal disease. Goreisan use was associated with a lower incidence of HF readmission among patients with renal disease (HR = 0.77, 95 % CI = 0.60–0.97), but not among those without (HR = 1.09, 95 % CI = 0.97–1.23; *p* for interaction = 0.009).

Conclusions: This nationwide propensity score-matched analysis did not demonstrate that complementary Goreisan use at discharge was associated with a lower incidence of 1-year HF readmission in patients with HF receiving standard medications. An ongoing randomized trial is awaited to establish the effectiveness of Goreisan use in patients with HF.

Introduction

Over the past few decades, the number of patients suffering from heart failure (HF) has been rapidly increasing, representing a general pandemic in aging societies worldwide [1–4]. Under such imminent circumstances, medical therapy has evolved in the management of HF, as reflected in major guidelines [5–8], which now include the use of angiotensin receptor–neprilysin inhibitor (ARNI) and sodium–glucose co-transporter 2 inhibitor (SGLT2i). Guideline-directed medical therapy is pivotal for improving outcomes in patients with HF [9–11]. However, repeated HF hospitalizations and the associated costs have posed significant socioeconomic burdens not only in Japan but also in other countries [12–15].

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Despite the effectiveness of guideline-directed medical therapy for HF, there has been a recognized need for complementary and alternative medicine (CAM) in the management of HF worldwide [16]. Kampo medicine, traditional Japanese herbal medicine, represents a form of CAM used to address various symptoms and conditions as a complement or alternative to Western medicine. It is approved under the coverage of the Japanese national health insurance [17,18]. Goreisan is a Kampo formulation composed of five herbal medications and has an aquaretic effect through its action on the aquaporins of the kidney [19,20]. A recent meta-analysis of Chinese randomized trials demonstrated that Wulingsan (Goreisan in China) was effective in reducing brain natriuretic peptide levels and improving left ventricular ejection fraction in patients with chronic HF [21], which suggested that Goreisan may have the potential to treat body fluid imbalances resulting from HF. In addition, Goreisan has been increasingly used in Japan and has been empirically used in some patients with HF [22]. However, clinical evidence of Goreisan use for HF in Japan is limited to case reports [23,24].

We hypothesized that Goreisan, in addition to guideline-directed medical therapy, may be associated with a lower risk of HF readmission in patients admitted with HF. Therefore, the present study aimed to examine the association between complementary use of Goreisan and the risk of HF readmissions using a nationwide database in Japan.

Materials and methods

Study design

The present study was a retrospective cohort analysis using the Japanese Diagnosis Procedure Combination (DPC) database, the details of which were described previously [25]. It was approved by the Institutional Review Board of The University of Tokyo with a waiver of the requirement for informed consent due to the anonymization and de-identification of the registered data [approval number: 3501-(5)].

The DPC database accumulates >7 million hospitalization records from >1000 acute care hospitals located throughout all 47 prefectures in Japan annually (Online methods). While all university hospitals are obliged to participate in the DPC database every year, other hospitals participate voluntarily in each fiscal year. A Japanese fiscal year includes 12 months from April 1 in one calendar year to March 31 in the following year. All diagnoses were recorded using the International Classification of Diseases, Tenth Revision (ICD-10) codes with Japanese text. Diagnostic and therapeutic procedures were recorded using unique Japanese administrative codes. The diagnoses and procedures recorded in the DPC database were previously validated with high accuracy [26,27].

Study cohort and exposure

We identified patients aged ≥20 years who were admitted for the primary diagnosis of HF (ICD-10 code: I50.x) and were discharged alive with prescriptions for any standard HF medications between April 1, 2016, and March 31, 2022. If a patient was hospitalized for HF multiple times at the same hospital during the study period, the first hospitalization was considered the index hospitalization for HF. Standard HF medications included β-blocker, angiotensin-converting enzyme inhibitor (ACE-I), angiotensin receptor blocker (ARB), ARNI, mineralocorticoid receptor antagonist (MRA), SGLT2i, and loop diuretic as per the current HF guidelines [5–8]. The following exclusion criteria were set in line with an ongoing randomized trial of Goreisan for patients with HF [28]: (i) coronary artery bypass grafting, valve surgery/intervention, or cardiac resynchronization therapy within 90 days prior to or during index hospitalization; (ii) ventricular assist device recipients; (iii) heart transplantation recipients; (iv) congenital heart/vascular disease; (v) acute coronary syndrome; (vi) end-stage renal failure (Online Table S1); (vii) mechanical circulatory support during index hospitalization; (viii) pregnancy or delivery within 90 days prior to or during index hospitalization; and (ix) palliative care within 90 days prior to or during index hospitalization. After applying the exclusion criteria, we divided eligible patients into two groups: patients who received Goreisan in addition to standard HF medications (Goreisan group) and those who received standard HF medications alone at discharge (No-Goreisan group).

Covariates

We extracted 67 variables for covariates as potential confounders according to current knowledge and guidelines, previous administrative claims database studies, and clinical relevance in the field of HF (Online Methods and Online Table S2).

Outcome measures

The primary outcome was HF readmission within 1 year after discharge from the index HF hospitalization. The major secondary outcome was a composite of HF readmission and death during all-cause readmissions within 1 year after discharge. The other secondary outcomes included all-cause death during all-cause readmissions, hospitalizations for dehydration, and hospitalizations for acute kidney injury. Readmissions were assessed using a unique identifier assigned to each patient at each hospital in the database. We identified readmissions to the index hospital where a patient was initially admitted for HF and death that occurred during the readmissions. However, we could not follow up on patients if they were admitted to another hospital. We followed up on each patient until 1 year after discharge, death during any-cause readmission, or the last date of the follow-up available in the DPC database, whichever came first. As data from non-university hospitals in the DPC database depended on the voluntary participation of each hospital in each fiscal year, some hospitals occasionally did not submit data to the database for two consecutive fiscal years. If a patient was discharged from a hospital in a fiscal year (fiscal year of discharge; e.g. fiscal year 2016) and the hospital did not participate in the database for the following fiscal year (e.g. fiscal year 2017), the last date of the patient's follow-up was regarded as March 31 in the fiscal year of discharge (e.g. March 31, 2017).

Continuation of Goreisan at the time of readmission

Data on medication continuation/discontinuation and adherence after discharge were unavailable in the database. Instead, in the Goreisan group, we extracted data on whether patients readmitted for HF received Goreisan within two days after readmission and at discharge from the readmission, which could be considered as proxies for the continuation of Goreisan.

Statistical analyses

Propensity score matching was applied at a variable ratio (maximum 1:4) to compare the outcomes between the two groups [29]. Propensity scores were estimated using a logistic regression model, where the aforementioned 67 covariates were included (Online Table S2). Each patient in the Goreisan group was matched with a maximum of four patients in the No-Goreisan group with replacement using the nearest neighbor method within a caliper set as ≤0.2 of the pooled standard deviation of logits of the propensity scores. This method of variable ratio matching is recommended when applicable in statistical literature because it yields higher precision [i.e. narrower confidence intervals (CIs)] than the 1:1 matching at the cost of a slight increase in bias [30,31]. Covariate balance between the groups before and after propensity score matching was examined using standardized mean differences, with the absolute values <0.1 indicating a negligible difference between the two groups [32]. Using the 1:4 propensity score-matched cohort, we used Kaplan–Meier curves to show the cumulative incidence of outcomes with comparisons by the log-rank test. We estimated the hazard ratios (HRs) and 95 % CIs for outcomes of the Goreisan group with

reference to the No-Goreisan group using a Cox proportional hazards model. We checked the proportional hazard assumption using Schoenfeld residuals. We also estimated subdistribution HRs and 95 % CIs on a Fine–Gray subdistribution hazard model to account for competing risk of death [33]. In survival analyses, patients were censored at the date of death during all-cause readmissions or the last date of the follow-up available in the DPC database prior to 1 year after discharge from the first HF hospitalization.

We conducted three sensitivity analyses (Online Methods). First, to evaluate the potential for residual confounding, we examined the association between Goreisan use and two falsification end points (hospitalizations for gastrointestinal bleeding and those for hip fracture; Online Table S1). Second, we calculated E-values using the publicly available website [34] to assess the extent how strongly an unmeasured confounder would have to be associated with both Goreisan use and the outcome to cause a null association between Goreisan use and 1-year HF readmission [35,36]. For the third sensitivity analysis, we performed a complete case analysis to confirm the robustness of the results from our main analysis above where the category of "missing" was used for missing data in the following categorical variables: body mass index, cognitive function, systolic blood pressure at admission, activities of daily living (ADL) at discharge, and home medical care after discharge.

Subgroup analyses for the primary outcome were performed to examine the effect modification in the following clinically relevant subgroups among the propensity score-matched cohort: age (<80 years or ≥80 years), sex, systolic blood pressure at admission, atrial fibrillation, hypertension, renal disease, and concomitant use of tolvaptan at discharge.

Different doses of Goreisan may be associated with the outcomes. While data on the exact dose of Goreisan prescribed at discharge were unavailable, we calculated the approximate daily dose of Goreisan as the total dose of Goreisan divided by the total days of Goreisan used during hospitalization. Using the data, we divided patients in the Goreisan group into two subgroups [standard dose (≥7.5 g/day) and lower dose (<7.5 g/day)] and performed 1:1 propensity score matching to examine the association between the different doses of Goreisan and the outcomes.

We set a two-sided significance level of 0.05 and conducted all statistical analyses using Stata version 18 (StataCorp, College Station, TX, USA).

Results

Study population

We identified 431,393 eligible patients with HF (mean age 79.2 ± 12.6 years; male 52.3 %) from 1495 hospitals, including 1957 (0.45 %) prescribed Goreisan in addition to standard HF medications (Goreisan group) and 429,436 prescribed standard HF medications alone at discharge (No-Goreisan group) (Fig. 1). Patients in the Goreisan group were older (82.9 ± 10.6 years vs. 79.2 ± 12.6 years) and had a higher prevalence of cognitive dysfunction (mild 25.2 % vs. 19.7 %; moderate/severe 16.3 % vs. 12.6 %), renal disease (18.3 % vs. 13.2 %), and anemia (18.8 % vs. 13.5 %) than those in the No-Goreisan group, while they had a lower prevalence of coronary artery disease (22.1 % vs. 29.1 %), hypertension (61.0 % vs. 66.3 %), and dyslipidemia (24.4 % vs. 29.8 %) (Table 1). Patients in the Goreisan group were less frequently admitted by ambulance (29.2 %

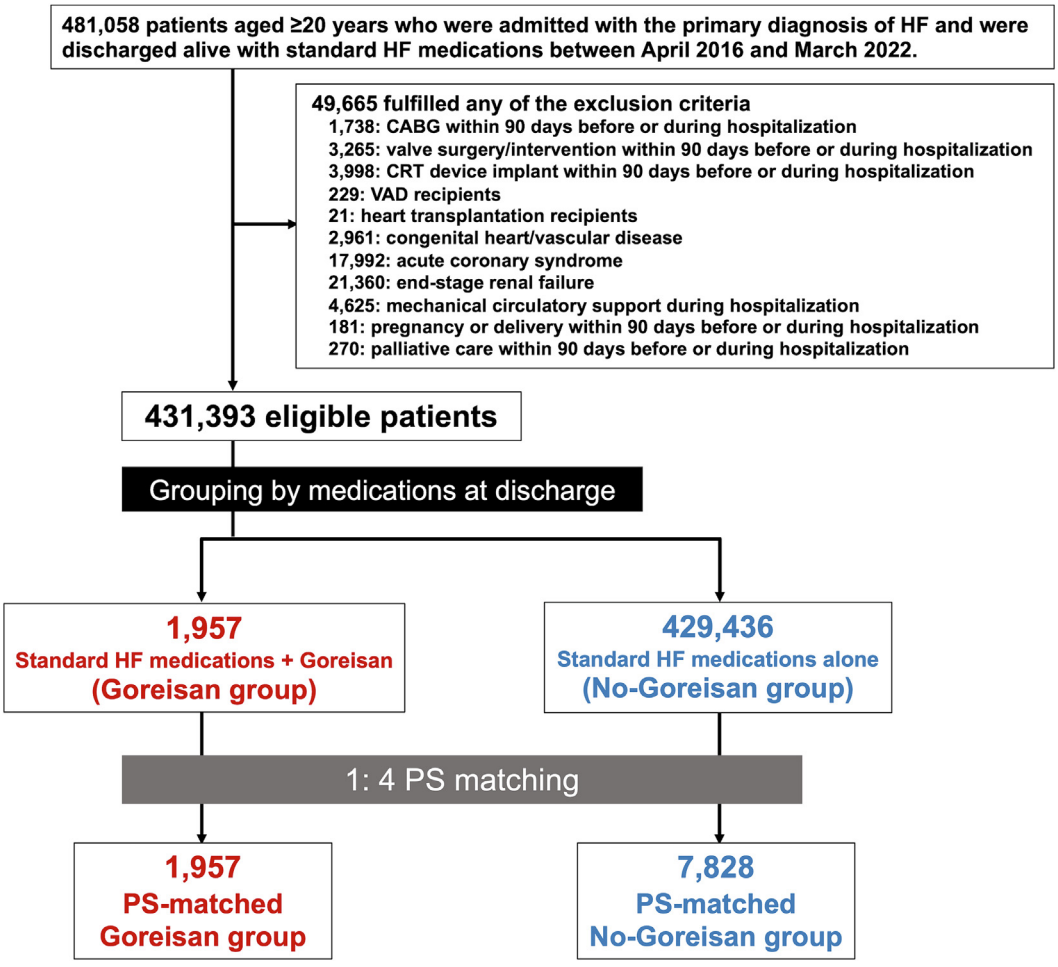

Fig. 1. Flow of patient selection.
CABG, coronary artery bypass grafting; CRT, cardiac resynchronization therapy; HF, heart failure; PS, propensity score; VAD, ventricular assist device.

Table 1
Patient characteristics in the unmatched and PS-matched cohorts.

	Unmatched cohort			1:4 PS-matched cohort		
	Goreisan	No Goreisan	SMD	Goreisan	No Goreisan	SMD
	n = 1957	n = 429,436		n = 1957	n = 7828	
Age, years, mean ± SD	82.9 ± 10.6	79.2 ± 12.6	0.323	82.9 ± 10.6	83.1 ± 10.5	−0.012
Male	930 (47.5)	224,643 (52.3)	−0.096	930 (47.5)	3764 (48.1)	−0.011
Ambulance use for admission	571 (29.2)	152,329 (35.5)	−0.135	571 (29.2)	2233 (28.5)	0.014
BMI						
<18.5 kg/m^2	275 (14.1)	56,845 (13.2)	0.024	275 (14.1)	1115 (14.2)	−0.005
18.5–24.9 kg/m^2	1011 (51.7)	227,776 (53.0)	−0.028	1011 (51.7)	4049 (51.7)	−0.001
25.0–29.9 kg/m^2	402 (20.5)	84,337 (19.6)	0.023	402 (20.5)	1617 (20.7)	−0.003
≥30 kg/m^2	138 (7.1)	30,564 (7.1)	−0.003	138 (7.1)	532 (6.8)	0.010
Missing	131 (6.7)	29,914 (7.0)	−0.011	131 (6.7)	515 (6.6)	0.005
Cognitive function						
Normal	1127 (57.6)	283,707 (66.1)	−0.175	1127 (57.6)	4475 (57.2)	0.009
Mild dysfunction	494 (25.2)	84,493 (19.7)	0.134	494 (25.2)	1967 (25.1)	0.003
Moderate/severe dysfunction	319 (16.3)	53,999 (12.6)	0.106	319 (16.3)	1335 (17.1)	−0.020
Missing	17 (0.9)	7237 (1.7)	−0.073	17 (0.9)	51 (0.7)	0.025
Systolic BP at admission						
>140 mmHg	580 (29.6)	146,539 (34.1)	−0.096	580 (29.6)	2307 (29.5)	0.004
100–140 mmHg	885 (45.2)	178,569 (41.6)	0.073	885 (45.2)	3478 (44.4)	0.016
<100 mmHg	140 (7.2)	28,982 (6.7)	0.016	140 (7.2)	585 (7.5)	−0.012
Missing	352 (18.0)	75,346 (17.5)	0.012	352 (18.0)	1458 (18.6)	−0.017
Cardiac disease						
Atrial fibrillation	769 (39.3)	175,166 (40.8)	−0.031	769 (39.3)	3090 (39.5)	−0.004
CAD	432 (22.1)	124,843 (29.1)	−0.161	432 (22.1)	1726 (22.0)	0.001
DCM	34 (1.7)	10,697 (2.5)	−0.052	34 (1.7)	150 (1.9)	−0.012
MR	105 (5.4)	25,728 (6.0)	−0.027	105 (5.4)	447 (5.7)	−0.015
AS	92 (4.7)	18,920 (4.4)	0.014	92 (4.7)	401 (5.1)	−0.020
AR	47 (2.4)	11,260 (2.6)	−0.014	47 (2.4)	193 (2.5)	−0.004
Complete AV block	27 (1.4)	5607 (1.3)	0.006	27 (1.4)	90 (1.1)	0.020
VT	30 (1.5)	9418 (2.2)	−0.049	30 (1.5)	113 (1.4)	0.007
Comorbidity						
Charlson comorbidity index						
1	579 (29.6)	148,375 (34.6)	−0.107	579 (29.6)	2321 (29.6)	−0.001
2	540 (27.6)	124,137 (28.9)	−0.029	540 (27.6)	2186 (27.9)	−0.007
3	436 (22.3)	83,999 (19.6)	0.067	436 (22.3)	1721 (22.0)	0.007
≥4	402 (20.5)	72,925 (17.0)	0.091	402 (20.5)	1600 (20.4)	0.003
Hypertension	1194 (61.0)	284,867 (66.3)	−0.111	1194 (61.0)	4719 (60.3)	0.015
Diabetes mellitus	572 (29.2)	123,949 (28.9)	0.008	572 (29.2)	2296 (29.3)	−0.002
Dyslipidemia	477 (24.4)	127,762 (29.8)	−0.121	477 (24.4)	1873 (23.9)	0.010
Prior stroke	150 (7.7)	26,324 (6.1)	0.061	150 (7.7)	556 (7.1)	0.022
Renal disease	359 (18.3)	56,876 (13.2)	0.140	359 (18.3)	1400 (17.9)	0.013
Liver disease	72 (3.7)	13,151 (3.1)	0.034	72 (3.7)	304 (3.9)	−0.011
Chronic pulmonary disease	188 (9.6)	41,820 (9.7)	−0.004	188 (9.6)	757 (9.7)	−0.002
Malignancy	144 (7.4)	27,192 (6.3)	0.041	144 (7.4)	590 (7.5)	−0.007
Anemia	367 (18.8)	58,121 (13.5)	0.142	367 (18.8)	1459 (18.6)	0.003
In-hospital management						
ICU admission	54 (2.8)	26,404 (6.1)	−0.165	54 (2.8)	217 (2.8)	−0.001
HCU admission	126 (6.4)	37,652 (8.8)	−0.088	126 (6.4)	468 (6.0)	0.017
Dobutamine	184 (9.4)	39,989 (9.3)	0.003	184 (9.4)	765 (9.8)	−0.013
Dopamine	82 (4.2)	14,057 (3.3)	0.048	82 (4.2)	336 (4.3)	−0.005
Noradrenaline	49 (2.5)	12,162 (2.8)	−0.020	49 (2.5)	165 (2.1)	0.025
PDE III inhibitor	19 (1.0)	3774 (0.9)	0.010	19 (1.0)	73 (0.9)	0.004
Carperitide	412 (21.1)	108,181 (25.2)	−0.098	412 (21.1)	1619 (20.7)	0.009
Intravenous nitrate	371 (19.0)	145,399 (33.9)	−0.343	371 (19.0)	1407 (18.0)	0.023
PCI	33 (1.7)	13,966 (3.3)	−0.101	33 (1.7)	130 (1.7)	0.002
PPM/ICD implantation	20 (1.0)	4671 (1.1)	−0.006	20 (1.0)	76 (1.0)	0.005
Red cell transfusion	173 (8.8)	25,724 (6.0)	0.109	173 (8.8)	716 (9.1)	−0.012
Cardiac rehabilitation	1044 (53.3)	223,682 (52.1)	0.025	1044 (53.3)	4091 (52.3)	0.022
Concomitant medications at discharge						
ACE-I/ARB	946 (48.3)	234,296 (54.6)	−0.125	946 (48.3)	3797 (48.5)	−0.003
ARNI	76 (3.9)	9747 (2.3)	0.094	76 (3.9)	288 (3.7)	0.012
MRA	901 (46.0)	199,850 (46.5)	−0.010	901 (46.0)	3517 (44.9)	0.022
β-Blocker	963 (49.2)	253,403 (59.0)	−0.198	963 (49.2)	3793 (48.5)	0.015
SGLT2 inhibitor	209 (10.7)	32,868 (7.7)	0.105	209 (10.7)	817 (10.4)	0.008
Loop diuretic	1739 (88.9)	366,293 (85.3)	0.106	1739 (88.9)	6954 (88.8)	0.001
Thiazide	149 (7.6)	18,659 (4.3)	0.138	149 (7.6)	604 (7.7)	−0.004
Tolvaptan	710 (36.3)	91,100 (21.2)	0.338	710 (36.3)	2821 (36.0)	0.005
Digitalis	79 (4.0)	19,114 (4.5)	−0.021	79 (4.0)	298 (3.8)	0.011
Ivabradine	5 (0.3)	963 (0.2)	0.006	5 (0.3)	17 (0.2)	0.008
Vericiguat	1 (0.1)	77 (0.0)	0.018	1 (0.1)	6 (0.1)	−0.014
Amiodarone	78 (4.0)	21,778 (5.1)	−0.052	78 (4.0)	293 (3.7)	0.012
Calcium channel blocker	723 (36.9)	138,589 (32.3)	0.098	723 (36.9)	2867 (36.6)	0.007
DOAC	639 (32.7)	140,958 (32.8)	−0.004	639 (32.7)	2546 (32.5)	0.003
Warfarin	285 (14.6)	54,201 (12.6)	0.057	285 (14.6)	1159 (14.8)	−0.007

(continued on next page)

Table 1 (*continued*)

	Unmatched cohort			1:4 PS-matched cohort		
	Goreisan	No Goreisan	SMD	Goreisan	No Goreisan	SMD
	n = 1957	n = 429,436		n = 1957	n = 7828	
Aspirin	343 (17.5)	90,524 (21.1)	−0.090	343 (17.5)	1363 (17.4)	0.003
P2Y12 inhibitor	183 (9.4)	48,803 (11.4)	−0.066	183 (9.4)	698 (8.9)	0.014
Statin	526 (26.9)	120,954 (28.2)	−0.029	526 (26.9)	2065 (26.4)	0.011
Goshajinkigan	14 (0.7)	859 (0.2)	0.076	14 (0.7)	49 (0.6)	0.013
Saireito	2 (0.1)	179 (0.0)	0.023	2 (0.1)	5 (0.1)	0.014
Boiogito	5 (0.3)	108 (0.0)	0.062	5 (0.3)	15 (0.2)	0.017
Bofutsushosan	1 (0.1)	102 (0.0)	0.014	1 (0.1)	4 (0.1)	0.000
Tokishakuyakusan	3 (0.2)	86 (0.0)	0.045	3 (0.2)	12 (0.2)	0.000
Mokuboito	6 (0.3)	69 (0.0)	0.072	6 (0.3)	9 (0.1)	0.048
Discharge status						
ADL at discharge						
Independence	727 (37.1)	225,895 (52.6)	−0.315	727 (37.1)	2865 (36.6)	0.011
Partial dependence	756 (38.6)	126,319 (29.4)	0.195	756 (38.6)	2987 (38.2)	0.010
Total dependence	239 (12.2)	37,570 (8.7)	0.113	239 (12.2)	978 (12.5)	−0.009
Missing	235 (12.0)	39,652 (9.2)	0.090	235 (12.0)	998 (12.7)	−0.022
Length of hospital stay, days, median (IQR)	20.0 (13.0–32.0)	17.0 (12.0–25.0)	0.258	20.0 (13.0–32.0)	19.0 (13.0–30.0)	0.031
Discharge to home	1604 (82.0)	375,264 (87.4)	−0.151	1604 (82.0)	6464 (82.6)	−0.017
Home medical care after discharge						
No	1704 (87.1)	388,833 (90.5)	−0.110	1704 (87.1)	6782 (86.6)	0.013
Yes	226 (11.5)	36,808 (8.6)	0.099	226 (11.5)	945 (12.1)	−0.016
Missing	27 (1.4)	3795 (0.9)	0.047	27 (1.4)	101 (1.3)	0.008
Hospital characteristics						
University hospital	134 (6.8)	33,976 (7.9)	−0.041	134 (6.8)	515 (6.6)	0.010
Annualized hospital volume of HF admissions (cases/year)						
≤67	788 (40.3)	142,351 (33.1)	0.148	788 (40.3)	3196 (40.8)	−0.011
68–119	686 (35.1)	143,678 (33.5)	0.034	686 (35.1)	2743 (35.0)	0.000
≥120	483 (24.7)	143,407 (33.4)	−0.193	483 (24.7)	1889 (24.1)	0.013
Fiscal year						
2016	282 (14.4)	86,559 (20.2)	−0.152	282 (14.4)	1097 (14.0)	0.011
2017	233 (11.9)	75,981 (17.7)	−0.164	233 (11.9)	905 (11.6)	0.011
2018	281 (14.4)	72,356 (16.8)	−0.069	281 (14.4)	1135 (14.5)	−0.004
2019	286 (14.6)	64,377 (15.0)	−0.011	286 (14.6)	1182 (15.1)	−0.014
2020	391 (20.0)	67,134 (15.6)	0.114	391 (20.0)	1594 (20.4)	−0.010
2021	484 (24.7)	63,029 (14.7)	0.255	484 (24.7)	1915 (24.5)	0.006

Values are presented as n (%) unless indicated otherwise.

ACE-I, angiotensin-converting enzyme inhibitor; ADL, activities of daily living; AR, aortic regurgitation; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; AS, aortic stenosis; AV, atrioventricular; BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; DCM, dilated cardiomyopathy; DOAC, direct oral anticoagulant; IQR, interquartile range; HCU, high care unit; HF, heart failure; ICD, implantable cardioverter defibrillator; ICU, intensive care unit; MR, mitral regurgitation; MRA, mineralocorticoid receptor antagonist; PCI, percutaneous coronary intervention; PDE, phosphodiesterase; PPM, permanent pacemaker; PS, propensity score; SD, standard deviation; SMD, standardized mean difference; SGLT2, sodium-glucose cotransporter 2; VT, ventricular tachycardia.

vs. 35.5 %) and to the intensive care unit (2.8 % vs. 6.1 %). They also received intravenous nitrate less frequently during hospitalization (19.0 % vs. 33.9 %). Regarding concomitant medications at discharge, patients in the Goreisan group were more likely to receive diuretics [loop diuretic (88.9 % vs. 85.3 %), thiazide (7.6 % vs. 4.3 %), tolvaptan (36.3 % vs. 21.2 %)] and SGLT2i (10.7 % vs. 7.7 %), while they received ACE-I/ARB (48.3 % vs. 54.6 %) and β-blocker (49.2 % vs. 59.0 %) less frequently. Furthermore, patients in the Goreisan group had a longer hospital stay (median 20.0 days vs. 17.0 days) and more impaired ADL at discharge (partial dependence, 38.6 % vs. 29.4 %; total dependence, 12.2 % vs. 8.7 %), and they were discharged home less frequently (82.0 % vs. 87.4 %). Goreisan was used more frequently at hospitals with a lower volume of HF admissions. After propensity score matching, patient characteristics were well-balanced between the two groups. Distributions of propensity scores are shown in Online Fig. S1. The comparison between the overall (unmatched) and propensity score-matched cohorts is shown in Online Table S4.

Outcomes

In the propensity score-matched cohort, Goreisan was not significantly associated with the incidence of 1-year HF readmission (22.1 % vs. 21.7 %; HR 1.02, 95 % CI 0.92–1.13, $p = 0.73$) or composite outcome (24.8 % vs. 24.5 %; HR 1.01, 95 % CI 0.92–1.12, $p = 0.79$) (Fig. 2 and Table 2). The result from the Fine–Gray model accounting for competing risk of death was a subdistribution HR of 1.02 (95 % CI 0.92–1.13) for 1-year HF readmission, which was consistent with the result from the Cox model. Moreover, Goreisan was not significantly associated with the incidence of the secondary outcomes (Table 2 and Online Fig. S2).

In the Goreisan group, 433 patients were readmitted with HF within 1 year after the first episode of HF. Among them, 230 (53.1 %) patients received Goreisan within two days after readmission. Moreover, among 370 patients discharged alive from readmission, 183 (49.5 %) were prescribed Goreisan at the time of discharge from the readmission.

Sensitivity analyses

As the first sensitivity analysis, the falsification end points of gastrointestinal bleeding and hip fracture demonstrated no statistically significant difference between the Goreisan and No-Goreisan groups (Table 2). As the second sensitivity, we calculated E-values by assuming the true HR of Goreisan use on a lower incidence of 1-year HF readmission as ranging from 0.6 to 0.9 (Table 3). The smallest E-value to explain the null association between Goreisan use and 1-year HF readmission was 1.40. We believe that such an unmeasured factor so strongly associated with both Goreisan use and 1-year HF readmission would be unlikely. For the third sensitivity analysis, we performed the complete case analysis and found the results consistent with the main analysis (Online Tables S5, S6, and Online Fig. S3).

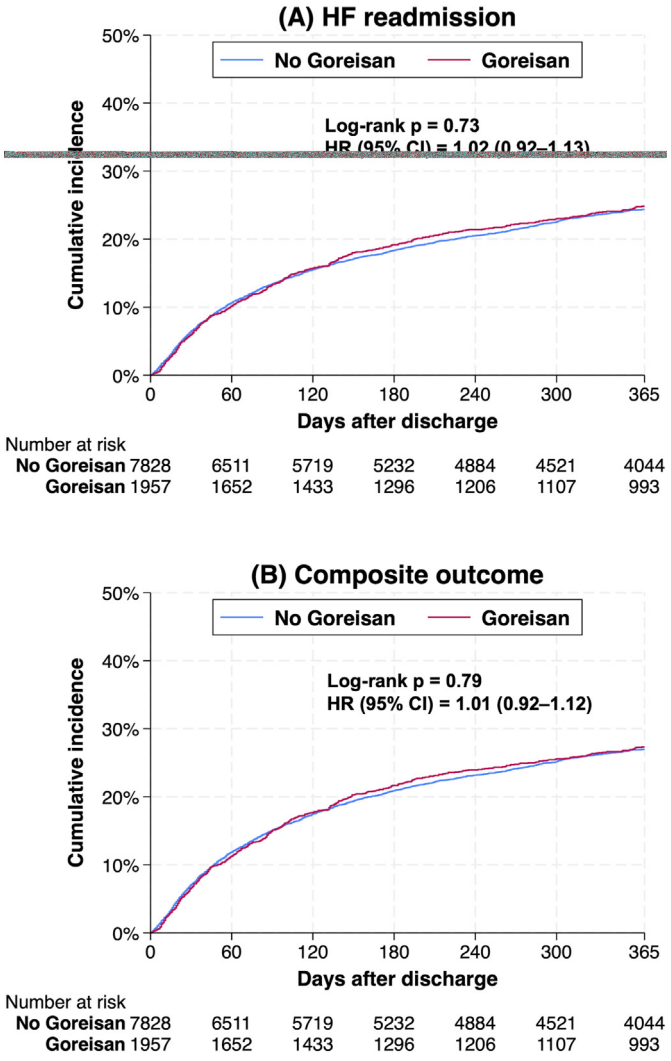

Fig. 2. Kaplan–Meier curves comparing the cumulative incidence of the primary and major secondary outcomes between the Goreisan and No-Goreisan groups in the propensity score-matched cohort. (A) HF readmission and (B) composite outcome of HF readmission and death. CI, confidence interval; HF, heart failure; HR, hazard ratio.

Subgroup analysis

There were no effect modifications in the association between Goreisan use and 1-year HF readmission in the subgroups stratified by age, sex, systolic blood pressure at admission, atrial fibrillation, hypertension, and concomitant use of tolvaptan at discharge (Fig. 3). However, an effect modification was observed in the subgroups stratified by renal disease (p for interaction = 0.009). In the subgroup with renal disease, patients prescribed Goreisan at discharge had a lower incidence of 1-year HF readmission than those without a Goreisan prescription (22.3 % vs 28.1 %; HR 0.77, 95 % CI 0.60–0.97). Meanwhile, there was no significant difference in the subgroup without renal disease (22.1 % vs 20.3 %; HR 1.09, 95 % CI 0.97–1.23) (Fig. 4).

Table 3
E-value analyses for the association between Goreisan use and 1-year HF readmission.

	Hypothetical estimates for possible true association between Goreisan use and 1-year HF readmission			
	HR = 0.6	HR = 0.7	HR = 0.8	HR = 0.9
E-value for point estimates	2.24	1.92	1.65	1.40
E-value for confidence interval	2.02	1.71	1.44	1.14

The smallest E-value was 1.40, indicating that an unmeasured confounder had to be associated with both Goreisan use and 1-year HF readmission by 1.40-fold when the true HR of Goreisan use on the incidence of 1-year HF readmission was 0.9.
HF, heart failure; HR, hazard ratio.

Different doses of Goreisan and outcomes

In 1957 patients in the Goreisan group, the median dose of Goreisan during hospitalization was 7.50 (interquartile range: 5.38–7.50) g/day. We divided the patients into two subgroups according to the daily dose: 1084 patients with a standard dose (≥7.5 g/day) and 873 patients with a lower dose (<7.5 g/day) (Online Table S7). One-to-one propensity score-matching created 771 pairs, where no significant difference was observed in the 1-year HF readmission (20.9 % vs. 21.4 %; HR 0.98, 95 % CI 0.79–1.22, p = 0.84), composite outcome (23.6 % vs. 23.9 %; HR 0.99, 95 % CI 0.81–1.22, p = 0.93), or other outcomes (Online Table S8 and Online Fig. S4).

Discussion

This retrospective nationwide study did not demonstrate a significant association between complementary Goreisan use as a medication at discharge and a reduced risk of 1-year HF readmission after the first episode of HF hospitalization. This lack of significant association was consistent across clinically relevant subgroups except for renal disease.

Current status of Goreisan use in the management of HF

In Japan, Kampo medicine has been integrated into clinical practice for over 40 years to address a variety of symptoms such as fatigue,

Table 2
1-year outcomes.

	Unmatched cohort		1:4 PS-matched cohort					
	Goreisan	No Goreisan	Goreisan	No Goreisan	Cox model		Fine-Gray model	
	n = 1957	n = 429,436	n = 1957	n = 7828	HR (95 % CI)	p-Value	sHR (95 % CI)	p-Value
Primary outcome								
HF readmission	433 (22.1)	84,567 (19.7)	433 (22.1)	1698 (21.7)	1.02 (0.92–1.13)	0.73	1.02 (0.92–1.13)	0.73
Major secondary outcome								
Composite outcome	486 (24.8)	94,193 (21.9)	486 (24.8)	1915 (24.5)	1.01 (0.92–1.12)	0.79	NA	
Other secondary outcomes								
Death during readmissions	147 (7.5)	24,468 (5.7)	147 (7.5)	580 (7.4)	1.01 (0.84–1.21)	0.91	NA	
Hospitalization for dehydration	48 (2.5)	9423 (2.2)	48 (2.5)	216 (2.8)	0.88 (0.65–1.21)	0.44	0.88 (0.65–1.21)	0.44
Hospitalization for acute kidney injury	17 (0.9)	3265 (0.8)	17 (0.9)	60 (0.8)	1.13 (0.66–1.94)	0.66	1.13 (0.66–1.94)	0.65
Falsification end points								
Hospitalization for gastrointestinal bleeding	11 (0.6)	2869 (0.7)	11 (0.6)	59 (0.8)	0.74 (0.39–1.41)	0.37	0.74 (0.39–1.42)	0.37
Hospitalization for hip fracture	14 (0.7)	2376 (0.6)	14 (0.7)	62 (0.8)	0.90 (0.50–1.61)	0.72	0.90 (0.50–1.61)	0.72

Values are presented as n (%) unless indicated otherwise.
CI, confidence interval; HF, heart failure; HR, hazard ratio; NA, not applicable; PS, propensity score; sHR, subdistribution hazard ratio.

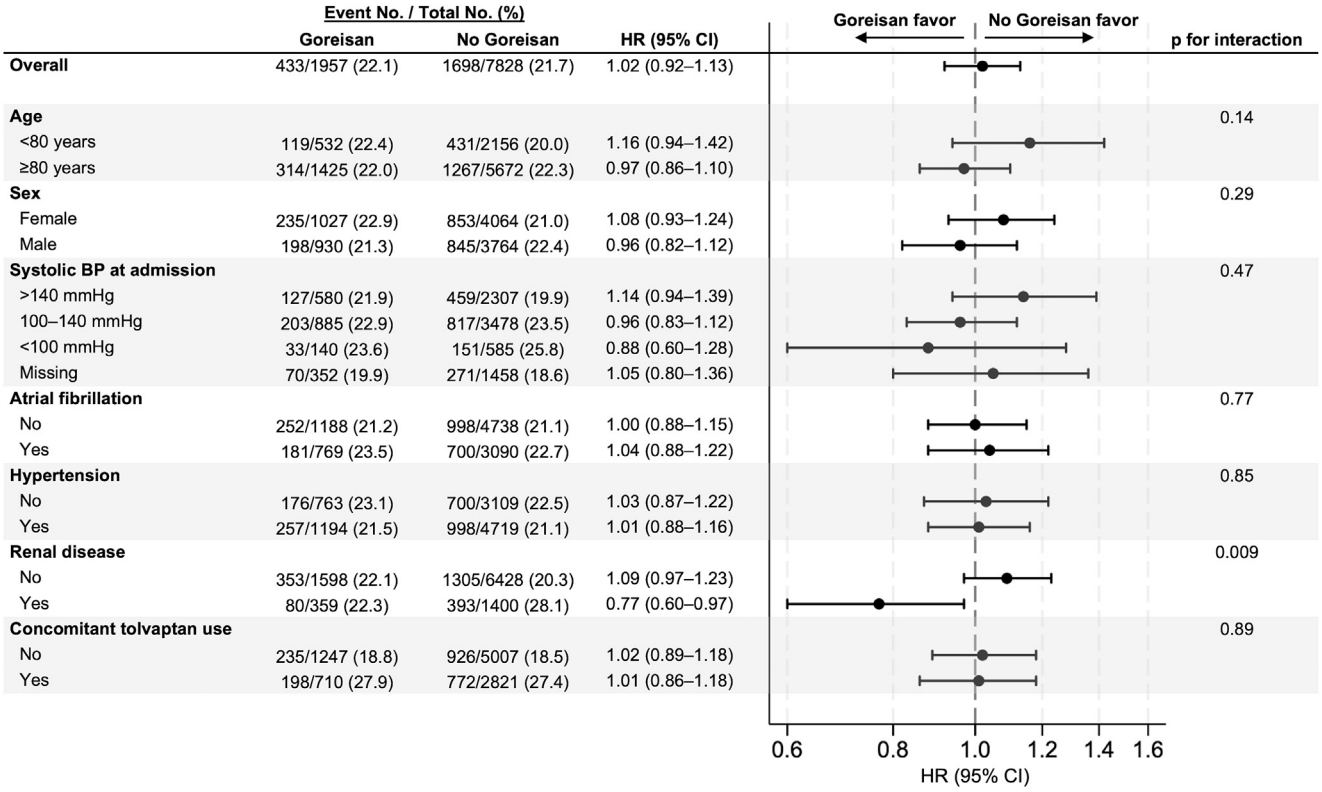

Fig. 3. Subgroup analysis for heart failure readmission in the propensity score-matched cohort.
BP, blood pressure; CI, confidence interval; HR, hazard ratio.

frailty, muscle cramps, general malaise, decreased appetite, constipation, and leg edema [37]. Goreisan is recognized for its effectiveness in treating fluid regulation disorders and is among the most commonly used Kampo formulations in the contemporary era in Japan [38]. Observational studies demonstrated that Goreisan was associated with a reduced incidence of postoperative recurrence of chronic subdural hematoma [39,40], a finding corroborated by a recent randomized trial [41]. Moreover, a small observational study reported that Goreisan was associated with improvement in postoperative abdominal lymphedema [42]. Furthermore, our recent nationwide trend analysis demonstrated an increasing number of hospitalized patients with HF receiving Goreisan over the past decade [22]. However, in the present study, Goreisan was not commonly used for patients hospitalized with HF, accounting for only ~0.5 % of patients. This could be attributed to the lack of evidence and guideline recommendations [8,43,44]. In the unmatched cohort of the present study, Goreisan was used more frequently in older patients treated with other diuretics, particularly tolvaptan. This may suggest that Goreisan is utilized in patients experiencing fluid retention despite receiving standard diuretic therapy.

Association between Goreisan and HF readmission

The present study did not demonstrate that Goreisan use, in addition to standard HF medications, was associated with a lower incidence of

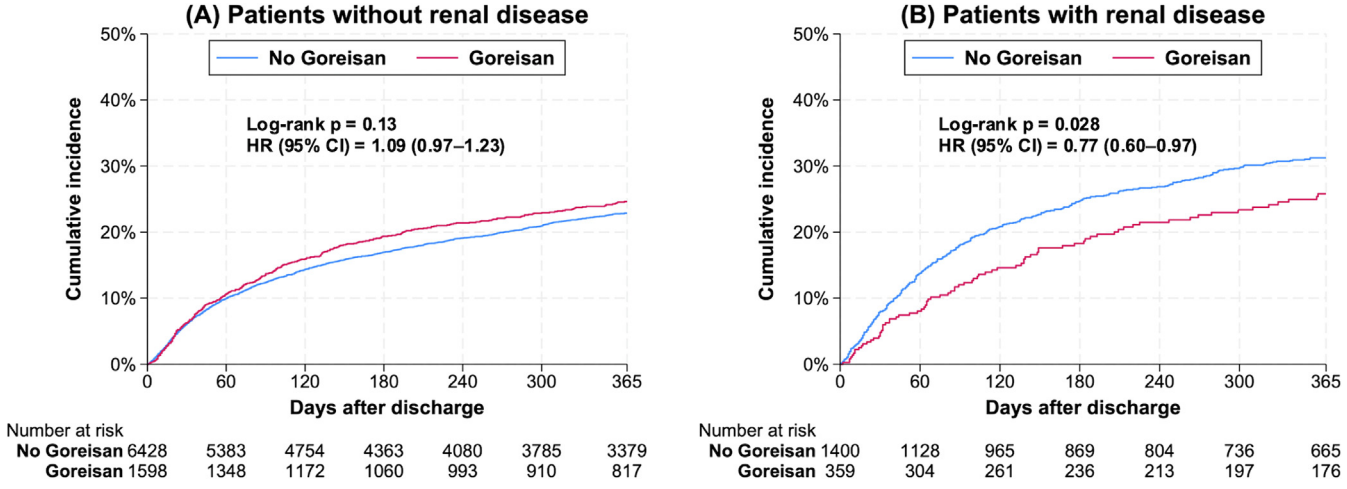

Fig. 4. Kaplan–Meier curves illustrating the cumulative incidence of heart failure readmission in the subgroups stratified by the presence or absence of renal disease in the propensity score-matched cohort.
CI, confidence interval; HR, hazard ratio.

1-year HF readmission in patients with HF. This finding may be consistent with previous studies indicating that other types of diuretics were not associated with improved prognosis. Prior studies reported that loop diuretic was not associated with improved prognosis in patients with HF [45–48]. Moreover, randomized trials failed to demonstrate that tolvaptan (vasopressin V2 receptor antagonist) improved long-term outcomes in patients with HF, although it did improve HF-related symptoms [49]. In this context, our finding may be reasonable because Goreisan appears to have no or few beneficial effects on the sympathetic nervous or the renin-angiotensin-aldosterone systems closely related to HF development and deterioration, similar to other diuretics.

Interestingly, renal disease had an effect modification on the association between Goreisan use and 1-year HF readmission in the present study, where Goreisan use was associated with a lower incidence of 1-year HF readmission in patients with renal disease but not in those without renal disease. A previous experimental study suggested a potential effect of Goreisan (Wulingsan) in ameliorating renal damage caused by diabetic nephropathy [50]. Recently, another experimental study demonstrated that Goreisan reduced inflammation, oxidative stress, and renal fibrosis in a mouse model of folic acid-induced chronic kidney disease [51]. Taken together, Goreisan use may exert a beneficial effect in patients with HF and renal disease, warranting further investigations.

In the present study, the continuation rate of Goreisan may be low according to the proportion (53.1 %) of patients who received Goreisan within two days after readmission, which may have affected the results of the association between Goreisan and HF readmission. Given the retrospective observational nature of the present study, a well-powered randomized trial with data on medication continuation/discontinuation and adherence is warranted to examine the clinical effectiveness of Goreisan in patients with HF receiving standard HF medications.

Improving health-related quality of life is one of the major goals in the management of cardiovascular diseases [43,44]. In current guidelines, diuretics are recommended to alleviate symptoms in patients with HF and symptoms of congestion [5,6,8,44]. Goreisan may have the potential to mitigate HF-related symptoms in a similar way to tolvaptan [52]. In this regard, patient-reported outcomes for Goreisan need to be examined in randomized trials to assess the efficacy of Goreisan. The ongoing GOREISAN-HF trial (NCT04691700) will examine the efficacy of Goreisan on both prognosis and patient-reported outcomes in patients who receive standard HF medications [28], the results of which are awaited.

Study limitations

The present study had several limitations. First, it is a retrospective analysis using an administrative claims database. The DPC database lacked clinical data such as symptoms, degree of congestion, cardiac dimensions and functions assessed by echocardiography, hemodynamics, renal function, hemoglobin, albumin, and electrolyte levels, and cause of death. In particular, the lack of data on left ventricular ejection fraction, estimated glomerular filtration rate, brain natriuretic peptide, and N-terminal pro-brain natriuretic peptide may be a considerable limitation in administrative database studies given their prognostic values. Although we adjusted for measured confounders using propensity score matching to balance the patient status and severity of HF between the groups, unmeasured factors may have acted as residual confounders in estimating the relationship between Goreisan and outcomes. Nonetheless, our sensitivity analyses suggested that an unmeasured confounder would be unlikely to mask the association between Goreisan use and 1-year HF readmission. Second, diagnoses of diseases were based on ICD-10 codes and may therefore be subject to misclassification bias mainly due to low sensitivities [26,27]. For example, the prevalence of renal disease in the overall cohort seemed lower than that reported in other studies with laboratory data available [53,54]. Third, the present analysis was unable to account for potential crossovers between the two groups during follow-up. Fourth, some patients may have been readmitted for HF to hospitals that were different from the index hospital or did not participate in the database, which may have resulted in the underestimation of readmissions. We were unable to identify deaths that occurred out-of-hospital (e.g. deaths at home or non-hospital facilities) or during readmissions to a hospital different from the index hospital. However, we assumed that this limitation would not impact our results if such readmissions and deaths occurred at similar rates in both groups. Fifth, although we handled missing data as the category of "missing" in our main analysis and confirmed the results consistent with a complete case analysis, the results may be subject to residual biases related to missing data.

Conclusions

This nationwide cohort study did not demonstrate that the complementary use of Goreisan in addition to standard HF medications at discharge from the first HF hospitalization, was associated with a lower incidence of 1-year HF readmission.

Data availability

The data used in the present study are not publicly available owing to contracts with hospitals that provide data to the database.

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Declaration of competing interest

Drs Isogai and Miyawaki have an academic affiliation with the Department of Health Services Research, which is a cooperative program between The University of Tokyo and Tsumura & Company. Drs Michihata, Matsui, and Jo had an academic affiliation with the Department of Health Services Research. Dr. Okada has an academic affiliation with the Department of Prevention of Diabetes and Lifestyle-Related Diseases, which is a cooperative program between The University of Tokyo and the Asahi Mutual Life Insurance Company. Tsumura & Company and the Asahi Mutual Life Insurance Company played no roles in the design of the study; the collection, analysis, or interpretation of the data; the writing of the manuscript; or the decision to publish the results. The other authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jjcc.2024.09.010.

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