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Polypharmacy and Clinical Outcomes in Hospitalized Patients With Acute Decompensated Heart Failure

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Background: Polypharmacy is a common problem among patients with acute decompensated heart failure (ADHF) who often have multiple comorbidities. **Objective:** The aim of this study was to define the number of medications at hospital discharge and whether it is associated with clinical outcomes at 1 year. **Methods:** We evaluated the number of medications in 2578 patients with ADHF who were ambulatory at hospital discharge in the Kyoto Congestive Heart Failure Registry and compared 1-year outcomes in 4 groups categorized by quartiles of the number of medications (quartile 1, ≤ 5; quartile 2, 6–8; quartile 3, 9–11; and quartile 4, ≥ 12). **Results:** At hospital discharge, the median

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number of medications was 8 (interquartile range, 6–11) with 81.5% and 27.8% taking more than 5 and more than 10 medications, respectively. The cumulative 1-year incidence of a composite of death or rehospitalization (primary outcome measure) increased incrementally with an increasing number of medications (quartile 1, 30.8%; quartile 2, 31.6%; quartile 3, 39.7%; quartile 4, 50.3%; $P < .0001$). After adjusting for confounders, the excess risks of quartile 4 relative to those of quartile 1 remained significant ($P = .01$). **Conclusions:** In the contemporary cohort of patients with ADHF in Japan, polypharmacy at hospital discharge was common, and excessive polypharmacy was associated with a higher risk of mortality and rehospitalizations within a 1-year period. Collaborative disease management programs that include a careful review of medication lists and an appropriate deprescribing protocol should be implemented for these patients.

KEY WORDS: acute decompensated heart failure, older, polypharmacy, prognosis

Polypharmacy is becoming more prevalent in the contemporary, guideline-directed clinical practice in patients with heart failure (HF).[1,2] Multiple medications and eventual polypharmacy entail risks such as adverse drug reactions and a decline in medication adherence, especially in older patients.[3,4] Many of the individual medications for HF have been demonstrated to positively influence patient outcomes when tested against a placebo in randomized controlled trials.[5] However, multimorbid older patients, who are more likely to receive polypharmacy, were excluded from many evidence-generating clinical trials.

In a cross-sectional study of 1.4 million patients in primary care in Scotland, authors reported that HF patients with left ventricular systolic dysfunction had significantly greater comorbidity and polypharmacy.[6] A post hoc analysis of ROCKET-AF study, in which 60% of patients had HF, revealed that 10 or more medications in patients with atrial fibrillation was associated with a higher risk of bleeding but not stroke.[7] However, no previous large-scale study has reported the impact of polypharmacy on clinical outcomes in acute decompensated HF (ADHF) patients.

Thus, in this study, we aimed to evaluate medication use in real-world clinical practice and analyze the association of the number of medications at discharge with 1-year clinical outcomes among hospitalized patients with ADHF using a large Japanese observational registry.

Methods

Study Design

The Kyoto Congestive Heart Failure (KCHF) registry is a physician-initiated, prospective, observational, multicenter cohort study enrolling consecutive patients admitted to hospitals because of ADHF for the first time between October 2014 and March 2016 in 19 secondary and tertiary hospitals in Japan. Details on the study design and patient characteristics in the KCHF registry have been reported previously.[8,9] Briefly, we enrolled all consecutive patients with ADHF as defined by the modified Framingham criteria and those who underwent HF-specific treatment involving intravenous drugs within 24 hours after admission in each participating center. Clinical follow-up information was collected in October 2017. The attending physicians or research assistants at each participating facility collected data on clinical events after the index hospitalization from hospital medical records or patients, relatives, or referring physicians. Patient records were anonymized before the analysis.

The investigation conforms with the principles outlined in the Declaration of Helsinki. The study was approved by the institutional review boards of Kyoto University Graduate School of Medicine and from all the hospital facilities and academic centers involved in this project (please find listed this information in Annex 1). This study was registered with University Hospital Medical Information Network (UMIN identifier: UMIN000015238). A waiver of written informed consent from each patient was granted by the institutional review boards of Kyoto University and each participating center, because the study met the conditions of the Japanese ethical guidelines for Medical and Health Research Involving Human Subjects.[10] We disclosed this study's details to the public as an opt-out method, and this notice informed patients of their right to refuse enrollment.

Definitions and Outcome Measures

The number of oral medications at the time of discharge from the index hospitalization was assessed by drug class according to the Anatomical Therapeutic Chemical Classification System.[11] Therefore, a prescription of 2 types of loop diuretics in 1 patient was counted as 1 medication. Combined products were measured by counting each single-ingredient product separately. We did not collect data on medications administered via injection; medications administered via eye drops, suppositories, ointments, and plasters; or medications that were not taken routinely. We did not collect data of drug schedule. Although we collected the dose of some cardiovascular drugs, we did not collect dose of drugs other than cardiovascular drugs; hence, doses and schedules were not included in the analysis. Detailed definitions of baseline clinical characteristics have been described previously.[8,9]

The primary outcome measure in this study was a composite of death from any cause or rehospitalization at 1 year after hospital discharge. The secondary

outcome measures were all-cause death, cardiovascular death, any rehospitalization, and rehospitalization due to HF.

Study Patients

Among the 4056 enrolled patients in the KCHF registry, 3785 patients (93.3%) were discharged alive after hospitalization for ADHF. We excluded 196 patients for missing data on medications at hospital discharge and 38 patients without follow-up data (Figure 1). We further excluded 942 patients who had a walking disability (ie, wheelchair-bound or bedridden patients) at hospital discharge and 31 patients who had no data on the functional status at discharge because the presence of disability and impairment can reduce patient ability to adhere to recommendations and alter patient preference for treatment or study outcomes.[12] Accordingly, this study's population consisted of 2578 patients with ADHF who were ambulatory at discharge.

Statistical Analysis

Among the 2578 study patients, 81.5% received a prescription of more than 5 medications and 27.8% received more than 10 medications. The median number of medications was 8 (interquartile range, 6–11; range, 0–24) (Figure 2). As most patients received 6 or more medications, that is, the most commonly cited definition for polypharmacy, we did not use this criteria. Instead, we categorized patients into 4 groups based on the quartiles of the number of medications at hospital discharge (quartile 1, ≤5; quartile 2, 6–8; quartile 3, 9–11; and quartile 4, ≥12). We compared the baseline characteristics and clinical outcomes of patients across the quartiles using the χ^2 test for categorical variables and 1-way analysis of variance for continuous variables. To assess the trend across the quartiles, we used

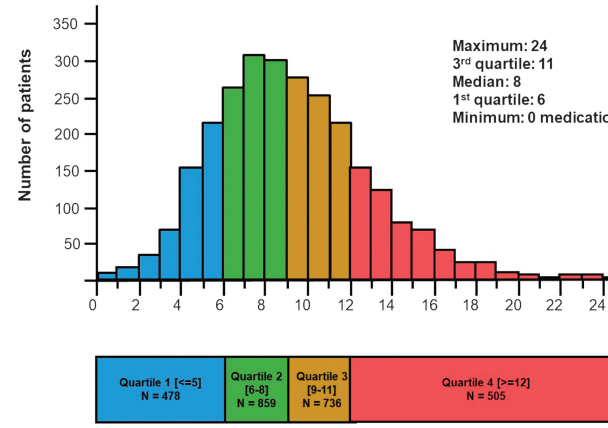


FIGURE 2. *Number of medications at discharge from the index hospitalization.*

the Cochran-Armitage trend test for categorical variables and the Jonckheere-Terpstra test for continuous variables.

We regarded the date of hospital discharge as time 0 for the clinical follow-up. Cumulative incidences were estimated by the Kaplan-Meier method and compared using the log-rank test. We used a multivariable Cox proportional hazards model to estimate the risk of quartiles 2, 3, and 4 relative to that of quartile 1 (reference) for primary and secondary outcome measures. Results were expressed as hazard ratios (HRs) with the corresponding 95% confidence intervals (CIs). To adjust for potential confounders, we included both the quartiles based on the number of medications and the 20 clinically relevant risk-adjusting variables: being 80 years or older, women, body mass index (BMI) less than 22 kg/m^2, acute coronary syndrome, nonacute coronary syndrome, atrial fibrillation or flutter, hypertension, diabetes mellitus, previous stroke, chronic lung disease, current smoking, living alone, systolic blood pressure less than 90 mm Hg

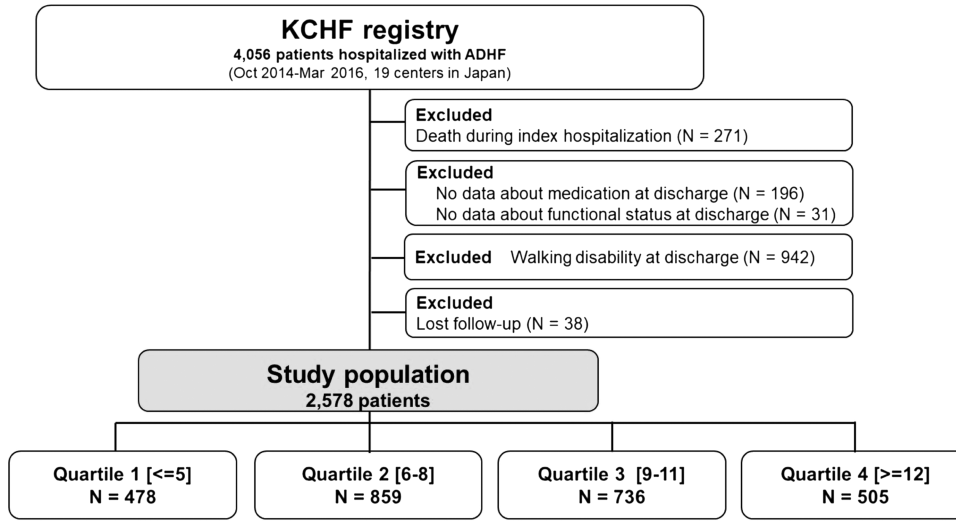


FIGURE 1. *Study flowchart. ADHF, acute decompensated heart failure; KCHF, Kyoto Congestive Heart Failure.*

at admission, heart rate less than 60/min at admission, estimated glomerular filtration rate less than 30 mL/min per 1.73 m^2, anemia, serum albumin less than 3 g/dL, and HF with reduced ejection fraction, consistent with a previous study.[8] Proportional hazard assumptions for quartiles were assessed on plots of log (time) versus log [–log (survival)] stratified by the risk variables and were verified to be acceptable. Missing values were

TABLE 1 Patient Characteristics

Variables	All Patients (N = 2578)	No. Medications at Discharge: Quartile 1 (≤5) (N = 478, 18.5%)	Quartile 2 (6–8) (N = 859, 33.3%)	Quartile 3 (9–11) (N = 736, 28.5%)	Quartile 4 (≥12) (N = 505, 19.5%)	*P* for Trend
Clinical characteristics						
Age, y	77 (69–84)	75 (65–83)	78 (67–84)	78 (71–84)	77 (70–83)	.014
Age ≥ 80 y[a]	1078 (41.8)	163 (34.1)	381 (44.4)	327 (44.4)	207 (41.0)	.06
Women[a]	1026 (39.8)	209 (43.7)	334 (38.8)	300 (40.8)	183 (36.2)	.06
BMI	23.3 ± 4.5	22.7 ± 4.2	23.3 ± 4.8	23.4 ± 4.4	23.8 ± 4.6	<.0001
BMI < 22 (kg/m^2)[a]	1053 (42)	213 (46.2)	358 (43.0)	304 (42.5)	178 (35.7)	.002
Body weight	58.6 ± 14.8	56.9 ± 14.3	59.1 ± 15.9	58.3 ± 13.8	60.0 ± 14.6	.006
Origin						
Coronary artery disease	850 (33.0)	56 (11.7)	240 (27.9)	292 (39.7)	262 (51.9)	<.0001
ACS[a]	146 (5.7)	18 (3.8)	49 (5.7)	53 (7.2)	26 (5.2)	.2
Non-ACS[a]	704 (27.3)	38 (8.0)	191 (22.2)	239 (32.5)	236 (46.7)	<.0001
Previous myocardial infarction	581 (22.5)	30 (6.3)	144 (16.8)	206 (28.0)	201 (39.8)	<.0001
Hypertensive heart disease	640 (24.8)	145 (30.3)	232 (27.0)	169 (23.0)	94 (18.6)	<.0001
Valvular heart disease	456 (17.7)	100 (20.9)	162 (18.9)	125 (17.0)	69 (13.7)	.002
Cardiomyopathy	433 (16.8)	106 (22.2)	166 (19.3)	100 (13.6)	61 (12.1)	<.0001
Medical history						
Previous heart failure hospitalization[a]	875 (33.9)	88 (18.4)	229 (26.7)	291 (39.5)	267 (52.9)	<.0001
Atrial fibrillation or flutter[a]	1073 (41.6)	154 (32.2)	361 (42.0)	336 (45.7)	222 (44.0)	<.0001
Hypertension[a]	1852 (71.8)	289 (60.5)	617 (71.8)	570 (77.5)	376 (74.5)	<.0001
Diabetes mellitus[a]	992 (38.5)	78 (16.3)	281 (32.7)	342 (46.5)	291 (57.6)	<.0001
Previous stroke[a]	335 (13.0)	32 (6.7)	103 (12.0)	122 (16.6)	78 (15.5)	<.0001
Malignancy	359 (13.9)	67 (14.0)	103 (12.0)	114 (15.5)	75 (14.6)	.25
Chronic lung disease[a]	336 (13.0)	52 (10.9)	91 (10.6)	97 (13.2)	96 (19.0)	<.0001
Current smoking[a]	388 (15.3)	92 (19.6)	132 (15.6)	97 (13.4)	67 (13.5)	.005
Social background						
Dementia	236 (9.2)	36 (7.5)	79 (9.2)	79 (10.7)	42 (8.3)	.46
Living alone[a]	577 (22.4)	108 (22.6)	191 (22.2)	172 (23.4)	106 (21.0)	.72
Unemployed	2133 (82.7)	370 (77.4)	683 (79.5)	629 (85.5)	451 (89.3)	<.0001
Public assistance	152 (5.9)	20 (4.2)	39 (4.5)	47 (6.4)	46 (9.1)	.0002
Use of long-term care insurance at discharge	568 (22.0)	67 (14.0)	151 (17.6)	206 (28.0)	144 (28.5)	<.0001
Vital signs and symptoms at admission						
Systolic blood pressure <90 mm Hg[a]	66 (2.6)	14 (2.9)	22 (2.6)	13 (1.8)	17 (3.4)	.95
Systolic blood pressure (continuous)	149.4 ± 35.5	153.0 ± 36.2	150.3 ± 36.3	149.2 ± 34.8	144.8 ± 34.0	.0006
Heart rate < 60/min[a]	159 (6.2)	42 (8.9)	45 (5.3)	35 (4.8)	37 (7.4)	.35
NYHA class III/VI	2194 (85.4)	391 (82.5)	738 (86.1)	634 (86.3)	431 (85.7)	.20
Tests at admission						
eGFR[a] < 30 mL/min per 1.73 m^2	597 (23.2)	59 (12.4)	175 (20.4)	190 (25.8)	173 (34.3)	<.0001
Anemia[a]	1588 (61.7)	261 (55.0)	473 (55.1)	491 (66.7)	363 (72.0)	—
Serum albumin < 3 g/dL[a]	256 (10.3)	36 (7.7)	95 (11.5)	67 (9.3)	58 (11.9)	
LVEF, %	45.5 ± 16.1	46.3 ± 16.6	45.2 ± 15.5	45.5 ± 16.0	45.3 ± 16.7	
Classification of HF according to LVEF						.0006
HFrEF (LVEF, <40%)[a]	1015 (39.5)	177 (37.3)	338 (39.4)	299 (40.7)	201 (40.0)	.35
HFmrEF (LVEF, 40%–49%)	487 (19.0)	83 (17.5)	168 (19.6)	137 (18.6)	99 (19.7)	.202
HFpEF (LVEF, ≥50%)	1068 (41.6)	215 (45.3)	351 (41.0)	299 (40.7)	203 (40.4)	

Continuous variables are presented as mean ± standard deviation or median with interquartile range. Categorical variables are presented as number (percentage).

Abbreviations: ACS, acute coronary syndrome; BMI, body mass index; eGFR, estimated glomerular filtration rate; HFmrEF, heart failure with midrange ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, heart rate; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

[a]Risk-adjusting variables selected for the multivariable Cox proportional hazards models.

handled without imputation and excluded from the fully adjusted model. As a sensitivity analysis, we also explored whether there is a stepwise increase in the risk for clinical outcome measures from quartile 1 to quartile 4 using continuous variables (0 for quartile 1, 1 for quartile 2, 2 for quartile 3, and 3 for quartile 4) in the multivariable model.

We also performed the subgroup analysis for the primary outcome measure stratified by age, sex, BMI, left ventricular ejection fraction (LVEF), and presence or absence of anemia. We evaluated the interaction between the subgroup factors and the effects of the quartiles of the number of medications on the primary outcome measure.

All statistical analyses were conducted by physicians (N.O. and T.K.) and a statistician (T.M.) using JMP 14.0 or SAS 9.4 (both SAS Institute Inc, Cary, North Carolina). Two-tailed *P* values less than .05 were considered significant.

Results

Patient Characteristics

Among the 2578 study patients, median age was 77 (interquartile range, 69–84; 18–103) years, and women accounted for 40%; 2004 patients (77.7%) received renin-angiotensin-aldosterone system (RAAS) inhibitors, and 1843 patients (71.5%) received β-blockers (Tables 1 and 2). Patients who received more medications had a greater BMI; more often had a history of HF admission, coronary artery disease, atrial fibrillation or flutter, diabetes mellitus, chronic kidney disease, anemia, and chronic lung disease; were more often unemployed; and more often used public assistance and long-term care insurance at hospital discharge than those who received fewer medications (Table 1). No significant difference was found in the LVEF, presence or absence of dementia, and living status according to the number of medications between these patients.

Clinical Outcomes

The median length of follow-up was 492 (interquartile range, 374–666) days. The cumulative 1-year composite incidence of death or rehospitalization increased incrementally with an increasing number of medications (quartile 1 [≤5], 30.8%; quartile 2 [6–8], 31.6%; quartile 3 [9–11], 39.7%; quartile 4 [≥12], 50.3%; log-rank $P < .0001$) (Figure 3A). After adjusting for confounders, the excess risk of quartile 4 relative to that of quartile 1 remained significant for the primary outcome measure (HR, 1.30; 95% CI, 1.04–1.61; $P = .01$) (Table 3). The cumulative 1-year incidence of all-cause death was significantly higher in quartile 3 and quartile 4 than in quartile 1 (Figure 3B). However, the excess adjusted risk of quartile 3 and quartile 4 relative to that of quartile 1 was no longer significant for all-cause death (Table 3). The cumulative 1-year incidences of any rehospitalization and HF rehospitalization were also significantly higher in quartile 3 and quartile 4 than in quartile 1 (Figure 3C and 3D). The excess adjusted risk of quartile 4 relative to that of quartile 1 remained significant for any rehospitalization, and the excess adjusted risk of quartile 3 and quartile 4 relative to that of quartile 1 remained significant for HF rehospitalization (Table 3). Although detailed information of the causes of readmissions and deaths was not available in this study, we found that cardiovascular death was accounted in 162 subjects (6.5%) so, approximately in two-thirds (61.3%) of this group, the mortality may be attributable to cardiac causes (Table 3).

In a sensitivity analysis, we observed a significant excess risk for the primary outcome measure per quartile of the number of medications (HR, 1.12; 95% CI, 1.05–1.20; $P = .0008$). The excess risk for HF rehospitalization per quartile of number of medications was also significant (HR, 1.18; 95% CI, 1.05–1.29; $P = .0005$).

Subgroup Analysis

Significant interactions were found between those subgroup factors such as age and anemia and the association of the number of medications on the primary outcome measure. In patients younger than 80 years, but not in those 80 years or older, there was significant excess adjusted risk of quartile 3 and quartile 4 relative to that of quartile 1 for the primary outcome measure. In patients without anemia, but not in those with anemia, there was significant excess adjusted risk of quartile 4 relative to that of quartile 1 for the primary outcome measure. No significant interactions were observed between factors such as sex, BMI, LVEF, and the effect of the number of medications on the primary outcome measure (Figure 4).

Discussion

The main findings of this real-world study, evaluating polypharmacy and clinical outcomes in patients hospitalized for ADHF, were as follows. First, the median number of medications at hospital discharge was 8, and 81.5% of patients received prescriptions for more than 5 medications. Second, patients receiving more medications had more complex medical history and social background than those receiving fewer medications. Finally, in patients receiving 12 or more medications, the adjusted risk for death or any hospitalization during the first year after discharge was significantly higher than in patients receiving 5 or less medications. However, it might be noteworthy that the excess risk of a greater number of medications for the primary outcome measure was not significant in patients 80 years or older and patients with anemia. Unmeasured factors such as poor compliance may be accountable for this discrepancy. As discussed

TABLE 2 Medication at Hospital Discharge

Variables	All Patients (N = 2578)	No. Medications at Discharge: Quartile 1 (≤5) (N = 478, 18.5%)	Quartile 2 (6–8) (N = 859, 33.3%)	Quartile 3 (9–11) (N = 736, 28.5%)	Quartile 4 (≥12) (N = 505, 19.5%)	*P* for Trend
Medications at discharge						
No. medications	8 (6–11)	4 (3–5)	7 (6–8)	10 (9–11)	13 (12–15)	—
RAAS inhibitors	2004 (77.7)	318 (66.5)	669 (77.9)	601 (81.7)	416 (82.4)	<.0001
MRAs	1217 (47.2)	179 (37.5)	421 (49.0)	366 (49.7)	251 (49.7)	.0004
ACEi or ARB	1615 (62.7)	250 (52.3)	529 (61.6)	492 (66.9)	344 (68.1)	<.0001
ACEi	687 (26.7)	127 (26.6)	238 (27.7)	185 (25.1)	137 (27.1)	.79
ARB	942 (36.5)	126 (26.4)	294 (34.2)	308 (41.9)	214 (42.4)	<.0001
BB	1843 (71.5)	288 (60.3)	607 (70.7)	556 (75.5)	392 (77.6)	<.0001
Diuretics						
Loop diuretics[a]	2113 (82.0)	334 (69.9)	683 (79.5)	643 (87.4)	453 (89.7)	<.0001
Thyazide diuretics	140 (5.4)	12 (2.5)	30 (3.5)	47 (6.4)	51 (10.1)	<.0001
Tolvaptan	239 (9.3)	10 (2.1)	49 (5.7)	75 (10.2)	105 (20.8)	<.0001
Vasodilators						
CCBs[a]	897 (34.8)	116 (24.3)	255 (29.7)	304 (41.3)	222 (44.0)	<.0001
Nitrates	297 (11.5)	9 (1.9)	52 (6.1)	111 (15.1)	125 (24.8)	<.0001
Inotropic agents						
Digitalis	151 (5.9)	13 (2.7)	35 (4.1)	53 (7.2)	50 (9.9)	<.0001
Pimopendane	129 (5.0)	7 (1.5)	23 (2.7)	40 (5.4)	59 (11.7)	<.0001
Antidysrhythmics						
Amiodarone	197 (7.6)	12 (2.5)	55 (6.4)	62 (8.4)	68 (13.5)	<.0001
Antidysrhythmics other than amiodarone	150 (5.8)	14 (2.9)	38 (4.4)	50 (6.8)	48 (9.5)	<.0001
Antithrombotic agents						
Triple antithrombotic agents	386 (15.0)	9 (1.9)	90 (10.5)	139 (18.9)	148 (29.3)	<.0001
Dual antithrombotic agents	1013 (38.3)	68 (14.2)	290 (33.8)	352 (47.8)	303 (60.0)	<.0001
Aspirin	1013 (39.3)	68 (14.2)	290 (33.8)	352 (47.8)	303 (60.0)	<.0001
Other antiplatelet agents	646 (25.1)	32 (6.7)	178 (20.7)	226 (30.7)	210 (41.6)	<.0001
Warfarin	678 (26.3)	54 (11.3)	204 (23.8)	230 (31.3)	190 (37.6)	<.0001
DOAC	578 (22.4)	114 (23.9)	216 (25.2)	158 (21.5)	90 (17.8)	.005
Glucose-lowering drugs						
Insulin	205 (8.0)	9 (1.9)	48 (5.6)	71 (9.7)	77 (15.3)	<.0001
Metformin	76 (3.0)	4 (0.8)	15 (1.8)	29 (3.9)	28 (5.5)	<.0001
DPP4 inhibitors	444 (17.2)	15 (3.1)	104 (12.1)	167 (22.7)	158 (31.3)	<.0001
SGLT2 inhibitors	13 (0.5)	1 (0.2)	2 (0.2)	6 (0.8)	4 (0.8)	.07
NSAIDs	52 (2.0)	3 (0.6)	12 (1.4)	18 (2.5)	19 (3.8)	.0001
Others	3 (2–5)	1 (0–1)	3 (2–3)	4 (3–5)	7 (6–9)	<.0001

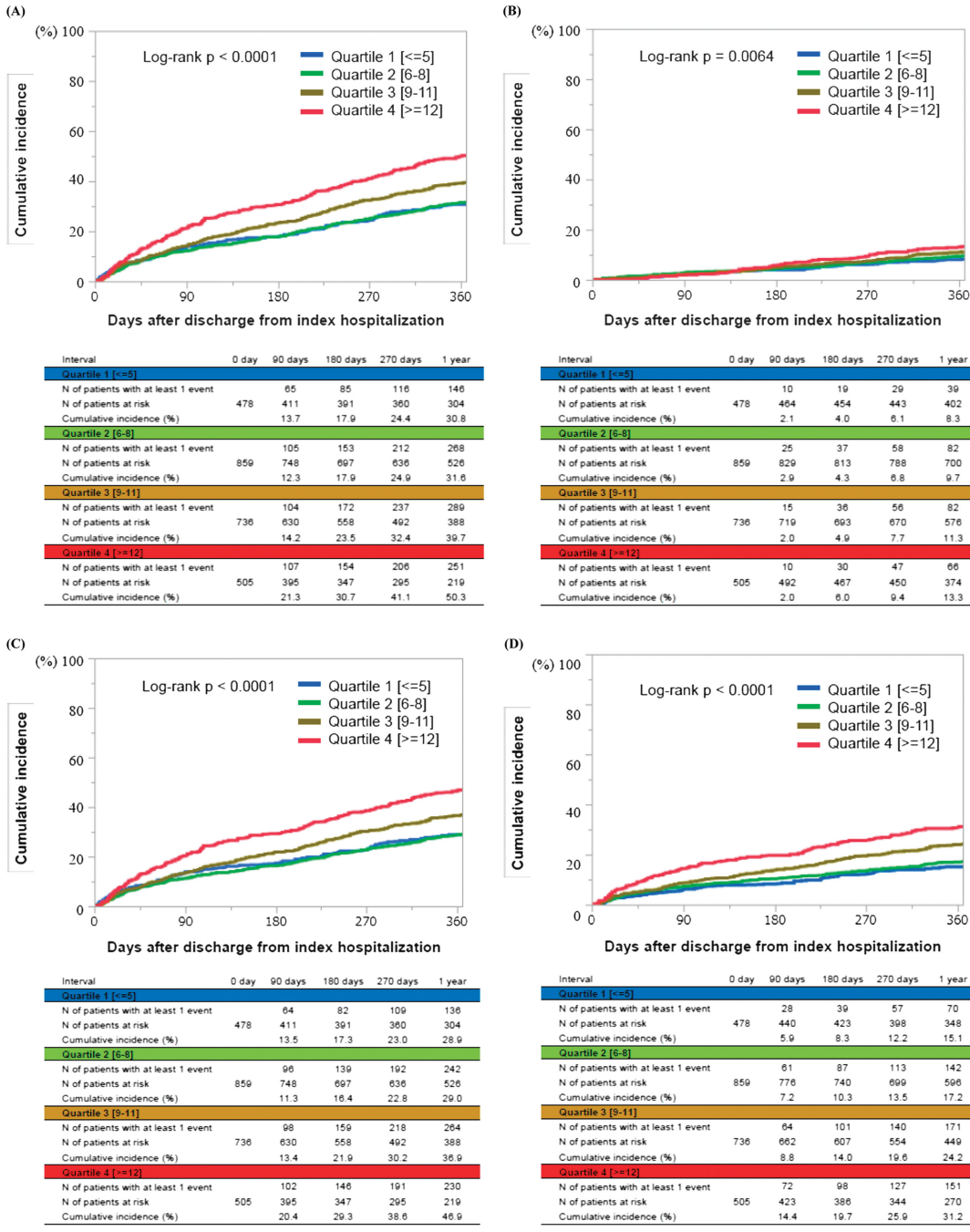
Categorical variables are presented as number (percentage). Dual and triple antithrombotic agents at hospital discharge were defined as taking 2 and 3 antithrombotic drugs (aspirin, other antiplatelet, warfarin, and direct oral anticoagulant), respectively.

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; BB, β-blockers; CCBs, calcium channel blockers; DOAC, direct oral anticoagulants; DPP4, dipeptidyl peptidase-4 inhibitors; MRAs, mineralocorticoid receptor antagonists; NSAIDs, nonsteroidal anti-inflammatory drugs; RAAS, renin-angiotensin-aldosterone system; SGLT2, sodium glucose cotransporter 2.

[a]Drugs counted as 1 medicine.

in the Limitations section, compliance was not evaluated in this study.

The burden of HF falls disproportionately on older people, who are often simultaneously afflicted with many comorbidities. In this study, the median age of study patients was 77 years, and conditions such as diabetes (38.5%), hypertension (71.8%), renal failure (23.2%), chronic lung disease (13.0%), previous stroke (13.0%), previous myocardial infarction (22.5%), and atrial fibrillation or flutter (41.6%) were prevalent. Thus, practitioners typically face the challenge of managing not a single but multiple conditions. Consequently, multiple medications and polypharmacy are almost inevitable for these patients. Notably, the median age of 77 years in the present registry was much higher than that reported in previous large registries on HF. With the aging population, this scenario will become more common. Underuse of cardioprotective drugs such as RAAS inhibitors and β-blockers may increase hospital admissions or death because of exaggeration of HF, whereas excessive polypharmacy (ie, 10 medications) has been reported to be strongly associated with inappropriate medication use and adverse drug events.[12,13] Adverse drug events include an increased risk of nonadherence, drug-drug interactions, adverse drug reactions, and preventable medication-related hospital admissions or death. Hypotension due to antihypertensive drugs, hyperkalemia and renal failure due



Interval	0 day	90 days	180 days	270 days	1 year
Quartile 1 [<=5]					
N of patients with at least 1 event		65	85	116	146
N of patients at risk	478	411	391	360	304
Cumulative incidence (%)		13.7	17.9	24.4	30.8
Quartile 2 [6-8]					
N of patients with at least 1 event		105	153	212	268
N of patients at risk	859	748	697	636	526
Cumulative incidence (%)		12.3	17.9	24.9	31.6
Quartile 3 [9-11]					
N of patients with at least 1 event		104	172	237	289
N of patients at risk	736	630	558	492	388
Cumulative incidence (%)		14.2	23.5	32.4	39.7
Quartile 4 [>=12]					
N of patients with at least 1 event		107	154	206	251
N of patients at risk	505	395	347	295	219
Cumulative incidence (%)		21.3	30.7	41.1	50.3

Interval	0 day	90 days	180 days	270 days	1 year
Quartile 1 [<=5]					
N of patients with at least 1 event		10	19	29	39
N of patients at risk	478	464	454	443	402
Cumulative incidence (%)		2.1	4.0	6.1	8.3
Quartile 2 [6-8]					
N of patients with at least 1 event		25	37	58	82
N of patients at risk	859	829	813	788	700
Cumulative incidence (%)		2.9	4.3	6.8	9.7
Quartile 3 [9-11]					
N of patients with at least 1 event		15	36	56	82
N of patients at risk	736	719	693	670	576
Cumulative incidence (%)		2.0	4.9	7.7	11.3
Quartile 4 [>=12]					
N of patients with at least 1 event		10	30	47	66
N of patients at risk	505	492	467	450	374
Cumulative incidence (%)		2.0	6.0	9.4	13.3

Interval	0 day	90 days	180 days	270 days	1 year
Quartile 1 [<=5]					
N of patients with at least 1 event		64	82	109	136
N of patients at risk	478	411	391	360	304
Cumulative incidence (%)		13.5	17.3	23.0	28.9
Quartile 2 [6-8]					
N of patients with at least 1 event		96	139	192	242
N of patients at risk	859	748	697	636	526
Cumulative incidence (%)		11.3	16.4	22.8	29.0
Quartile 3 [9-11]					
N of patients with at least 1 event		98	159	218	264
N of patients at risk	736	630	558	492	388
Cumulative incidence (%)		13.4	21.9	30.2	36.9
Quartile 4 [>=12]					
N of patients with at least 1 event		102	146	191	230
N of patients at risk	505	395	347	295	219
Cumulative incidence (%)		20.4	29.3	38.6	46.9

Interval	0 day	90 days	180 days	270 days	1 year
Quartile 1 [<=5]					
N of patients with at least 1 event		28	39	57	70
N of patients at risk	478	440	423	398	348
Cumulative incidence (%)		5.9	8.3	12.2	15.1
Quartile 2 [6-8]					
N of patients with at least 1 event		61	87	113	142
N of patients at risk	859	776	740	699	596
Cumulative incidence (%)		7.2	10.3	13.5	17.2
Quartile 3 [9-11]					
N of patients with at least 1 event		64	101	140	171
N of patients at risk	736	662	607	554	449
Cumulative incidence (%)		8.8	14.0	19.6	24.2
Quartile 4 [>=12]					
N of patients with at least 1 event		72	98	127	151
N of patients at risk	505	423	386	344	270
Cumulative incidence (%)		14.4	19.7	25.9	31.2

FIGURE 3. *Kaplan-Meier curves for clinical outcomes according to the quartiles based on the number of medications at discharge from the index hospitalization. A, All-cause death or any rehospitalization. B, All-cause death. C, Any rehospitalization. D, Heart failure rehospitalization.*

to RAAS inhibitors, hyponatremia and/or hypokalemia due to diuretics, hemorrhagic events due to antithrombotic drugs, QT prolongation and ventricular dysrhythmia due to various drugs, and hypoglycemia due to hypoglycemic drugs are frequently observed adverse drug events in patients with HF. Notably, the number of drugs not listed in Table 2 are remarkably high in the study patients. Thus, noncardiovascular drugs may also cause adverse drug events in these patients. Use of the FORTA ("Fit fOR The Aged") list has been reported to be helpful for improving pharmacotherapy in the multimorbid, older patients. This approach may also have the potential to improve future clinical outcomes in patients with HF.[14]

In addition to the medical history, we were interested in describing the social background of patients with HF. The presence of dementia, living without family support, and a low-income status complicate the management of HF. In this study, there was a substantial number of patients with dementia (9.2%), patients living

TABLE 3 Postdischarge Clinical Outcomes by Number of Medications at Discharge

	No. Patients With Event and Cumulative 1-y Incidence, %	Crude HR	95% CI	*P*	Adjusted HR	95% CI	*P*
All-cause death or any rehospitalization							
Quartile 1 (≤5)	146 (30.8)	Reference			Reference		
Quartile 2 (6–8)	268 (31.6)	1.01	0.84–1.21	.85	0.89	0.73–1.09	.46
Quartile 3 (9–11)	289 (39.7)	1.36	1.13–1.62	.0008	1.09	0.89–1.33	.26
Quartile 4 (≥12)	251 (50.3)	1.81	1.50–2.18	<.0001	1.30	1.04–1.61	.01
All-cause death							
Quartile 1 (≤5)	39 (8.3)	Reference			Reference		
Quartile 2 (6–8)	82 (9.7)	1.22	0.89–1.68	.21	1.10	0.78–1.56	.55
Quartile 3 (9–11)	82 (11.3)	1.43	1.04–1.97	.03	1.21	0.85–1.74	.28
Quartile 4 (≥12)	66 (13.3)	1.72	1.23–2.40	.001	1.30	0.88–1.92	.18
Cardiovascular death							
Quartile 1 (≤5)	22 (4.7)	Reference			Reference		
Quartile 2 (6–8)	53 (6.3)	1.02	0.91–1.15	.62	1.02	0.90–1.17	.66
Quartile 3 (9–11)	49 (6.9)	1.06	0.97–1.20	.29	1.06	0.93–1.22	.21
Quartile 4 (≥12)	38 (7.9)	1.16	1.02–1.33	.02	1.10	0.94–1.29	.22
Any rehospitalization							
Quartile 1 (≤5)	136 (28.9)	Reference			Reference		
Quartile 2 (6–8)	242 (29.0)	0.98	0.82–1.20	.98	0.87	0.71–1.08	.23
Quartile 3 (9–11)	264 (36.9)	1.33	1.10–1.61	.002	1.07	0.86–1.32	.53
Quartile 4 (≥12)	230 (46.9)	1.81	1.49–2.20	<.0001	1.29	1.02–1.63	.03
Rehospitalization for HF							
Quartile 1 (≤5)	70 (15.1)	Reference			Reference		
Quartile 2 (6–8)	142 (17.2)	1.18	0.90–1.54	.22	1.03	0.76–1.37	.88
Quartile 3 (9–11)	171 (24.2)	1.79	1.38–2.31	<.0001	1.37	1.03–1.84	.03
Quartile 4 (≥12)	151 (31.2)	2.29	1.76–2.99	<.0001	1.50	1.10–2.05	.009

Abbreviations: CI, confidence interval; HF, heart failure; HR, hazard ratio.

alone (22.4%), and unemployed patients (82.7%). It is difficult to directly compare our findings with those of previous studies because of differences in the definitions; however, dementia, social isolation, and unemployment are generally associated with poor medication adherence.[13,15] Approximately one-fifth of patients used long-term care insurance at discharge, a unique Japanese healthcare system to support the daily living of older patients. We could not clarify the effect of long-term care insurance itself in this study; however, such a healthcare system is crucial for older patients with HF to support their lives and maintain medication adherence. It may also have the potential to improve future clinical outcomes in these patients.

Our study emphasizes the need for physicians to be careful and judicious when caring for patients with HF. However, little evidence is available to guide polypharmacy in patients with HF and multiple comorbidities. Previous studies have indicated that it could be beneficial to decrease the number of medications among multimorbid patients to reduce the risk of medication-related harm.[16,17] A survey among multimorbid older adults in Denmark revealed that 41% of patients 65 years or older with 10 or more prescribed medications were interested in a consultation at an outpatient clinic specializing in polypharmacy.[16] To reduce inappropriate medication use, it would be required to provide medication reviews and to prioritize those drugs for possible discontinuation that have the lowest benefit-harm ratio and lowest likelihood of adverse withdrawal reactions or disease rebound syndromes in each patient before hospital discharge.[18] Development of learning healthcare systems, which include cardiovascular disease care innovations in informatics, patient-clinician partnerships, incentives, and development of a continuous learning culture, has been drawing attention to improve the quality and efficacy of medication in patients with cardiovascular diseases.[19] One of the learning healthcare systems available at present is outpatient cardiac rehabilitation; however, a poor participation rate is reported, with overall participation rates less than 50% during recent decades in Japan despite international recommendations.[20,21] Efforts to increase the participation rate for cardiac rehabilitation and the development of new learning healthcare systems are necessary. Whenever possible, patients with HF, particularly those with multiple competing comorbidities and polypharmacy, need to be enrolled in such programs.

Limitations

This study has several notable limitations. First, there was potential for residual confounding due to the observational study design. Despite extensive adjustments, residual confounding may have influenced the observed association. Second, we did not have data on

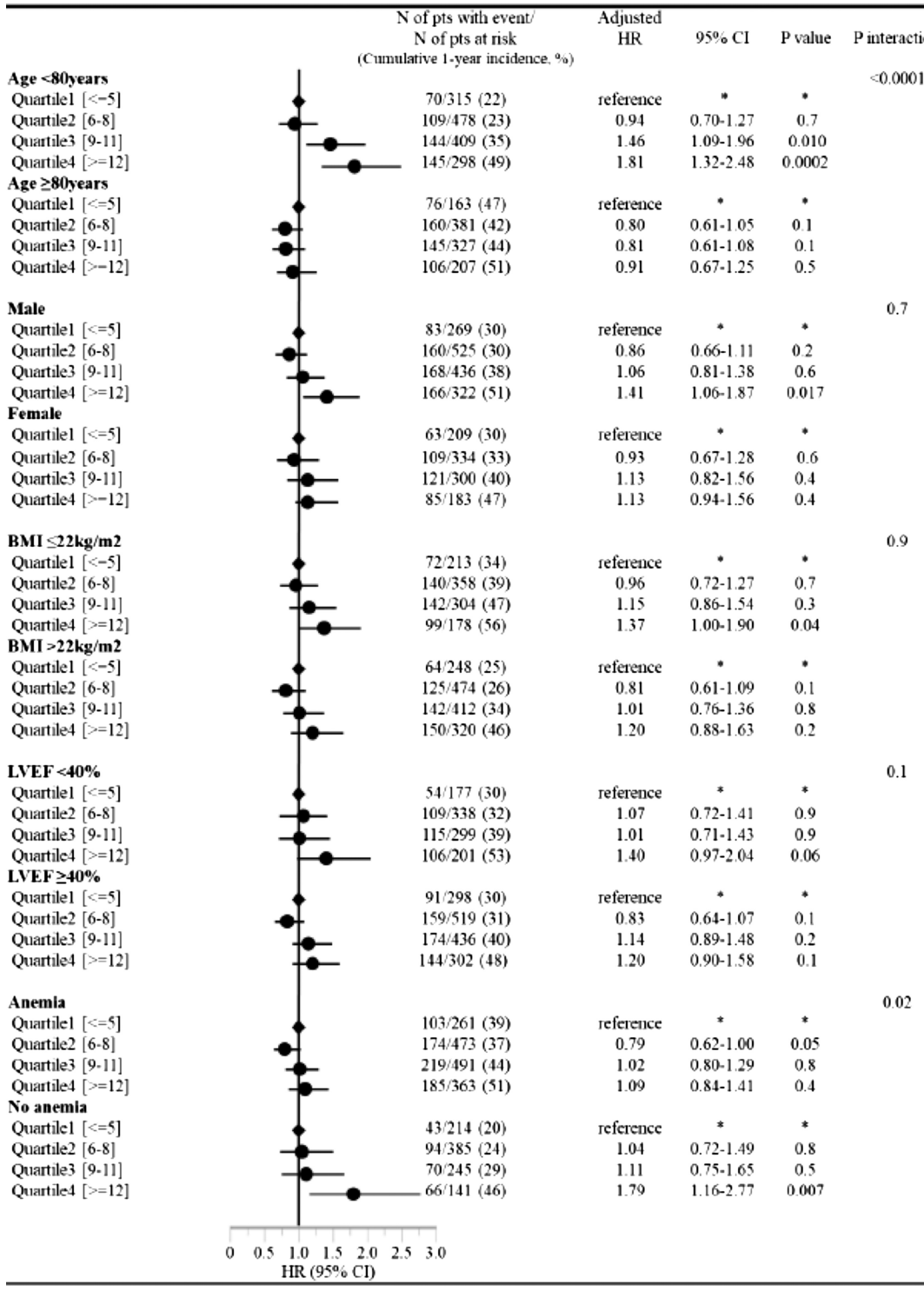


FIGURE 4. *Forrest plots for the subgroup analyses on the primary outcome measure (all-cause death or any rehospitalization) at 1 year after discharge from the index hospitalization. BMI, body mass index; CI, confidence interval; HR, hazard ratio; and LVEF, left ventricular ejection fraction.*

patient adherence to medications in this study. Although we excluded patients with walking disability at discharge, unmeasurable reasons for reducing patient ability to adherence to recommendations may affect the number of medications. A deprescribing protocol was not proposed in any hospitals that participated during the study period; however, it can be assumed that some of the attending physicians did not prescribe a prophylactic drug for very older patients or high-risk patients for ADEs.[22] Third, the data were limited to

What's New and Important

- Patients with ADHF are prescribed multiple medications at hospital discharge in the real-word clinical practice, and the number of medications is independently associated with a higher risk of mortality and rehospitalizations. The excess risks of multiple medications were independently observed when the number of medications become 12 or more.
- Our study underscore the importance in patients with ADHF to implement a comprehensive management program that includes a careful review of medication lists at discharge and perform an appropriate deprescribing protocol in the follow-up.
- We consider that cardiac rehabilitation programs, regrettably underused in Japan and in many other countries, may be ideally used as an important component of this postdischarge program.

prescriptions at hospital discharge, and we did not have data on the doses of medications or the prescriptions after hospital discharge. However, patients with polypharmacy driven by chronic medical conditions do not often have dramatic changes in the doses or number of medications they are taking. Fourth, the data did not include over-the-counter medicines, and complementary and alternative medicines after hospital discharge. However, because the public health insurance system in Japan is adopted for all citizens, patients with HF rarely need over-the-counter or complementary and alternative medicines because they are expensive. Fifth, although we investigated the number of all medications, we did not collect data to differentiate each drug except those listed in Table 2. Authors of a recent study who analyzed medication data using 558 older patients with HF hospitalization from the REGARD study indicated that most medications prescribed were noncardiovascular medications, such as proton pump inhibitors and electrolyte supplements.[23] Sixth, we investigated the number of medications administered orally, but some types of drugs administered parenterally are often available in the current clinical practice. Therefore, the actual status and adverse effects of polypharmacy in patients with ADHF may have been underestimated in this study. Finally, as already mentioned in the Clinical Outcomes section, detailed information was not available for the specific cause of readmissions or death. Moreover, increasing medication use has been associated with a higher risk of ADEs, especially in older patients.[24,25] Future studies are needed to examine the association of polypharmacy with ADEs in patients with ADHF.

Conclusions

In the contemporary cohort of patients with ADHF, polypharmacy at hospital discharge was common, and excessive polypharmacy was associated with a higher risk of mortality and rehospitalizations 1 year after discharge. Cardiac rehabilitation and collaborative disease management programs that include the careful review of medication lists and an appropriate deprescribing protocol should be implemented for these patients.

Annex 1:

The study was approved by the institutional review boards of Kyoto University Graduate School of Medicine (approval no. E2311), Shiga General Hospital (approval no. 20141120-01), Tenri Hospital (approval no. 640), Kobe City Medical Center General Hospital (approval no. 14094), Hyogo Prefectural Amagasaki General Medical Center (approval no. Rinri 26-32), National Hospital Organization Kyoto Medical Center (approval no. 14-080), Mitsubishi Kyoto Hospital (approved December 10, 2014), Okamoto Memorial Hospital (approval no. 201503), Japanese Red Cross Otsu Hospital (approval no. 318), Hikone Municipal Hospital (approval no. 26-17), Japanese Red Cross Osaka Hospital (approval no. 392), Shimabara Hospital (approval no. E2311), Kishiwada City Hospital (approval no. 12), Kansai Electric Power Hospital (approval no. 26-59), Shizuoka General Hospital (approval no. Rin14-11-47), Kurashiki Central Hospital (approval no. 1719), Kokura Memorial Hospital (approval no. 14111202), Kitano Hospital (approval no. P14-11-012), and Japanese Red Cross Wakayama Medical Center (approval no. 328).

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