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# Underuse of heart failure medications and poor long-term prognosis in chronic heart failure patients with polypharmacy – A report from the CHART-2 study

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ABSTRACT

*Background:* In patients with chronic heart failure (CHF), comorbidities are often managed with multiple medications, characterized by polypharmacy, leading to increased risk of potentially inappropriate medication and adverse effects.
*Methods:* We studied 4,876 consecutive patients with CHF (Stage C/D, age 69.0 ± 12.3 years) in the CHART-2 study to evaluate the association among polypharmacy, underuse of HF medications, and all-cause death. Polypharmacy was defined as the daily use of ≥ 8 medications for the survival classification and regression tree analysis.
*Results:* The average number of medications was 10 in the polypharmacy group and 5 in the non-polypharmacy group, respectively. Over a median of 8.3 (4.1–11.7) years, the incidence rate of all-cause death was significantly higher in the polypharmacy group (n = 2,108) than in the non-polypharmacy group (57.3 % vs. 40.6 %; adjusted hazard ratio [aHR] 1.34 (95 %CI, 1.22–1.48), P < 0.001), even in age < 55 years (26.6 % vs. 14.3 %; adjusted hazard ratio [aHR] 1.61 (95 %CI, 1.04–2.50), P = 0.033). In patients with polypharmacy, those without renin-angiotensin system inhibitors (RAS-I) and/or beta-blockers (N = 1,023) were associated with increased incidence of all-cause death as compared with those with both medications (aHR 1.18; 95 %CI 1.04–1.35, P = 0.012).
*Conclusions:* Polypharmacy was associated with poor long-term prognosis, even in younger patients with CHF. Among 4,876 patients with CHF, 1023 (20.9%) with polypharmacy and underuse of RAS-I and/or beta-blocker were associated with increased risk of all-cause death.

## 1. Introduction

More than 26 million individuals suffered from heart failure (HF) along with the society aging worldwide.[1,2] Most of the HF guidelines recommend specific drug classes, including beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and mineralocorticoid receptor antagonists, in order to suppress the activated neurohormonal axes, namely sympathetic and renin-angiotensin-aldosterone (RAAS) systems, with consistent effects to reduce mortality and HF-related hospitalization.[3–5].

The Chronic Heart Failure Analysis and Registry in the Tohoku District 2 (CHART-2) Study is a prospective observational multicenter cohort study.[6] Patients with symptomatic HF, structural cardiac disorder but without HF, or coronary artery disease (CAD) were consecutively enrolled from October 2006 to March 2010, and a total of 10,219 patients have been recruited.[6] The CHART-2 Study has provided real-word evidence and effective strategies to improve the management of CHF in Japan.[7].

The complexity of HF patients is emerging due to progressive aging and multiple comorbidities. Comorbidities are often managed with

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multiple medications, characterized by polypharmacy. However, information on the association of polypharmacy with long-term clinical outcomes in HF patients is limited. Previous studies have shown that polypharmacy is associated with an elevated risk of HF hospitalization in HF patients with preserved ejection fraction (HFpEF) [8] and comorbid medications have been recognized to possess the capacity to both induce and aggravate HF. [9] However, the optimal cutoff number of medications defining polypharmacy in patients with chronic HF and the association between polypharmacy and long-term mortality in the patients with a broad spectrum of EF remain unclear. Furthermore, underuse of HF medications may lead to poor prognosis in general. Especially, HF patients with polypharmacy leads to underprescribing [10], which may cause underuse of drugs against HF and worse prognosis in HF patients. Therefore, it is important to study significance between underuse of anti-HF drugs and long-term prognosis in HF patients with polypharmacy.

In the present study, we thus aimed to evaluate the association between polypharmacy and long-term prognosis in chronic HF patients, with a special reference to age, in the CHART-2 Study. We also examined the association between underuse of HF medications and long-term prognosis in those patients.

## 2. Methods

### 2.1. Study design

The CHART-2 Study is a multicenter, prospective, observational study for chronic HF in Japan, and the details have been described previously (NCT00418041).[6] Briefly, a total of 10,219 consecutive stable patients aged ≥ 20 years with coronary artery disease (N = 928), asymptomatic structural heart disease (Stage B, N = 4,405), and a current or past history of HF (Stage C/D, N = 4,876) were registered from the 24 participating hospitals between October 2006 and March 2010. [6] The diagnosis of HF was made by attending experienced cardiologists based on the criteria of the Framingham study[11] and stages of HF were determined according to the ACC/AHA guidelines.[12] All patient information, including demography, medical history, laboratory, echocardiography, and angiography data, were recorded at the time of enrollment, and annually thereafter by trained clinical research coordinators. In the present study, we finally enrolled 4,876 consecutive CHF patients with symptomatic Stage C/D after excluding 10 patients with data unavailable (Fig. 1). The study outcome was all-cause death with a median follow-up of 8.3 (4.1–11.7) years. The study protocol was approved by the local ethics committee of each participating hospital and written informed consent was obtained from all patients.

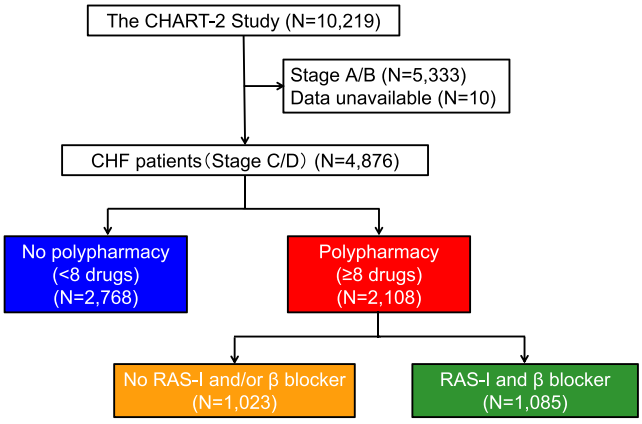


**Fig. 1.** Study flowchart.

### 2.2. Statistical analysis

We determined a cut-off point for polypharmacy using the results from survival classification and regression trees (CART) [13] analysis, performed with the 'rpart' and the 'survival' packages of the R software. CART analysis provides a binary decision tree for classification and regression, based on recursive partitioning of the data space. It sequentially determines conditioning variables and their splitting points for partitioning, to fit a simple prediction model within each partition. [13] Survival CART is the CART analysis that considers survival time as an outcome.[14] We defined polypharmacy as the long-term use of ≥ 8 medications for the survival CART analysis. We did not collect data on over-the-counter (OTC) medicines. We compared the baseline characteristics and the prognosis of patients with polypharmacy to those without it. Descriptive statistics were reported, including mean ± SD and frequency (percentage) for continuous and categorical data, respectively, according to polypharmacy category. B-type natriuretic peptide (BNP), C-reactive protein (CRP), and triglyceride were described as median (IQR) due to their skewed distribution. We used Welch's *t*-test for continuous variables and Fisher's exact test for categorical variables to compare group differences. Kaplan-Meier survival curves were plotted with two-sided log-rank test. Cox regression modeling was used including the following variables as the potential confounders; age, sex, body mass index (BMI), heart rate, smoking, hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, stroke, cancer, ischemic heart disease, left ventricular ejection fraction (LVEF), blood chemistry data (serum levels of hemoglobin, creatinine, and BNP), and New York Heart Association (NYHA) classification. Subgroup analyses were performed including age, sex, systolic blood pressure, ischemic heart disease, chronic kidney disease, and LVEF. Among the patients with polypharmacy, the relationship between renin-angiotensin system (RAS) inhibitor and beta-blocker and long-term prognosis was examined with Kaplan-Meier procedure and multivariable Cox proportional hazards models. Two-sided $P < 0.05$ was considered to be statistically significant. These statistical analyses were performed using the open-source statistics computing R software (version 3.5.3) (R Foundation for Statistical Computing, Vienna, Austria).

## 3. Results

### 3.1. Patient characteristics

Of 4,876 patients, 2,108 (43.2 %) were with polypharmacy (use of ≥ 8 medications) and 2,768 (56.8 %) without polypharmacy (Fig. 1, **Figure S1**). The percentage of polypharmacy increased with age (**Figure S2**). In the overall cohort, the average number of medications was 7 with a maximum of 22 medications (**Figure S3**). The average number of drugs prescribed was 10 in the polypharmacy group and 5 in the non-polypharmacy group. Table 1 shows baseline characteristics stratified by polypharmacy status. The patients with polypharmacy were characterized by older age and higher prevalence of ischemic heart disease, hypertension, diabetes, dyslipidemia, atrial fibrillation, and renal dysfunction as expected. In addition, patients with polypharmacy were more likely to have a history of stroke, higher BNP, lower EF, and larger LVDd.

### 3.2. Prognostic significance of polypharmacy

The number of medications was linearly associated with all-cause death (**Figure S4**). Over a median of 8.3 (4.1–11.7) years, the patients with polypharmacy had poor prognosis than those without it (adjusted HR 1.34, 95 %CI 1.22–1.48, $P < 0.001$) (Fig. 2, **Table S1**). Importantly, subgroup analysis showed that the relationship between polypharmacy and mortality differ by age and atrial fibrillation (**Figure S5**). Polypharmacy was associated with higher all-cause mortality in patients with < 55 years (aHR 1.61, 95 %CI, 1.04–2.50, $P = 0.033$), <65 years

**Table 1**
Baseline patient characteristics of heart failure patients by polypharmacy.

| | Without polypharmacy (N = 2,768) | With polypharmacy (N = 2,108) | P value |
|---|---|---|---|
| Age (years) | 67.71 ± 13.03 | 70.64 ± 10.99 | < 0.001 |
| Female, n (%) | 870 (31.4) | 686 (32.5) | 0.42 |
| BMI (kg/m$^2$) | 23.79 ± 3.84 | 23.77 ± 3.9 | 0.879 |
| Smoking, n (%) | 1211 (46.5) | 922 (46.1) | 0.789 |
| Etiology of CHF, n (%) | | | |
| Ischemic heart disease | 1177 (42.5) | 1302 (61.8) | < 0.001 |
| Dilated cardiomyopathy | 407 (14.7) | 223 (10.6) | < 0.001 |
| Hypertrophic cardiomyopathy | 88 (3.2) | 30 (1.4) | < 0.001 |
| Hypertensive heart disease | 604 (21.8) | 302 (14.3) | < 0.001 |
| Valvular heart disease | 295 (10.7) | 155 (7.4) | < 0.001 |
| Clinical history, n (%) | | | |
| Hypertension | 2452 (88.6) | 1954 (92.7) | < 0.001 |
| Diabetes mellitus | 881 (31.8) | 1089 (51.7) | < 0.001 |
| Dyslipidemia | 2162 (78.1) | 1852 (87.9) | < 0.001 |
| Atrial fibrillation | 1102 (39.8) | 903 (42.8) | 0.034 |
| Stroke | 471 (17) | 530 (25.1) | < 0.001 |
| Cancer | 357 (12.9) | 314 (14.9) | 0.049 |
| NYHA III/IV class (%) | 221 (8.0) | 333 (15.8) | < 0.001 |
| Hemodynamics | | | |
| Systolic BP (mmHg) | 126.66 ± 18.41 | 125.56 ± 20.02 | 0.047 |
| Diastolic BP (mmHg) | 72.91 ± 11.85 | 71.16 ± 11.97 | < 0.001 |
| Heart rate (bpm) | 72.46 ± 15.22 | 72.23 ± 14.37 | 0.6 |
| LVEF (%) | 58.03 ± 14.69 | 54.81 ± 15.9 | < 0.001 |
| LVDd (mm) | 51.13 ± 8.82 | 53.35 ± 9.56 | < 0.001 |
| Laboratory data | | | |
| LDL-C (mg/dL) | 109.12 ± 31.21 | 102.35 ± 30.37 | < 0.001 |
| HDL-C (mg/dL) | 52.49 ± 15.46 | 49.83 ± 15.17 | < 0.001 |
| Triglyceride (mg/dL) | 107 (77, 153) | 109 (80, 154.25) | 0.1 |
| Hemoglobin (g/dL) | 13.44 ± 1.93 | 12.79 ± 2.02 | < 0.001 |
| Creatinine (mg/dL) | 0.96 ± 0.72 | 1.18 ± 0.9 | < 0.001 |
| Total protein (g/dL) | 7.15 ± 0.6 | 7.14 ± 0.65 | 0.618 |
| Albumin (g/dL) | 4.1 ± 0.46 | 4 ± 0.51 | < 0.001 |
| HbA1c (%) | 6.16 ± 0.9 | 6.46 ± 1.06 | < 0.001 |
| BNP (pg/ml) | 86.8 (33.2, 211.9) | 130.2 (56.825, 269) | < 0.001 |
| CRP (mg/dL) | 0.1 (0.1, 0.3) | 0.2 (0.1, 0.4) | < 0.001 |
| Medical treatment, n (%) | | | |
| ACE-I/ARB | 1834 (66.3) | 1757 (83.3) | < 0.001 |
| Beta-blocker | 1157 (41.8) | 1245 (59.1) | < 0.001 |
| Calcium channel blocker | 906 (32.7) | 983 (46.6) | < 0.001 |
| Digitalis | 572 (20.7) | 588 (27.9) | < 0.001 |
| MRA | 483 (17.4) | 718 (34.1) | < 0.001 |
| Diuretics | 1285 (46.4) | 1502 (71.3) | < 0.001 |
| Statin | 762 (27.5) | 1104 (52.4) | < 0.001 |
| Antiplatelet drugs | 1393 (50.3) | 1576 (74.8) | < 0.001 |
| Warfarin | 927 (33.5) | 967 (45.9) | < 0.001 |
| Nitrates | 542 (19.6) | 752 (35.7) | < 0.001 |
| Antidiabetic agents | 161 (5.8) | 484 (23.0) | < 0.001 |
| NSAIDs | 47 (1.7) | 77 (3.7) | < 0.001 |
| Number of drugs | 5.02 ± 1.67 | 10.1 ± 2.16 | < 0.001 |

Continuous variables are expressed as mean ± standard deviation, except, BNP, CRP levels, and Triglyceride, which are expressed as median with interquartile range. Abbreviations: ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blockers; BMI, body mass index; BNP, brain natriuretic peptide; BP, blood pressure; CHF, chronic heart failure; CRP, C-reactive protein; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein-cholesterol; LVDd, left ventricular diastolic dimension; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonists; NSAIDs, non-steroidal anti-inflammatory drugs; NYHA, New York Heart Association.

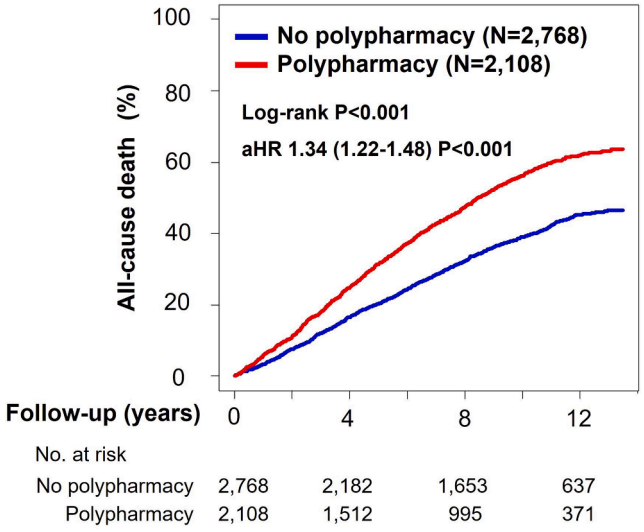


**Fig. 2.** Kaplan-Meier curves and adjusted hazard ratio by multivariable Cox proportional regression analysis for all-cause death among HF patients by polypharmacy.Abbreviations: aHR, adjusted hazard ratio.

(aHR 1.56, 95 %CI, 1.22–1.99, P < 0.001), and < 75 years (aHR 1.46, 95 %CI, 1.26–1.69, P < 0.001). In patients with atrial fibrillation, polypharmacy was associated with poor prognosis (HR 1.51, 95 %CI, 1.31–1.74, P < 0.001). In contrast, sex, blood pressure, ischemic heart disease, diabetes, CKD, or LVEF status (LVEF ≥ 50 %, <50 %) did not influence the association between polypharmacy and all-cause death (Figure S5). In overall cohort, mortality rates (/1000 person-years) were 39.0 in the patients taking RAS-I and beta-blockers without polypharmacy, and 53.1 in those not taking RAS-I and/or beta-blockers without polypharmacy. In the patients with polypharmacy, the rates were 68.2 in those taking RAS-I and beta-blockers, and 91.0 in those not taking RAS-I and/or beta-blockers. When stratifying by LVEF < 40 % or ≥ 40 %, mortality rates in LVEF < 40 % were 92.9 in patients taking RAS-I and beta-blockers, and 134.8 in those not taking RAS-I and/or beta-blockers. The mortality rates in LVEF ≥ 40 % were 59.9 in the patients taking RAS-I and beta-blockers, and 86.3 in those not taking

RAS-I and/or beta-blockers (Table S2).

### 3.3. Underuse of HF medications in patients with polypharmacy

The group that did not take either RAS-I and/or beta-blockers (underuse of HF medications, N = 1,023) was older and had a higher prevalence of women, hypertensive heart disease, and valvular heart diseases (**Table S3**). This group also tended to have higher prevalence of history of stroke and had higher LVEF, lower BNP, and higher use of calcium channel blockers (**Table S3**). The group also had increased incidence of all-cause death as compared with that with both medications (adjusted HR 1.18; 95 %CI 1.04–1.35, P = 0.012) (Fig. 3). This trend remained consistent regardless of LVEF (**Table S4**). Furthermore, the HFrEF (LVEF < 40 %) patients taking RAS-I, MRA and beta-blocker had a lower mortality rate (64.8 %) compared to a 70.6 % in those not taking RAS-I, MRA and/or beta-blocker (**Table S5**).

## 4. Discussion

In the present study, we examined the prognostic influence of polypharmacy and underuse of HF medication in chronic HF patients in our CHART-2 Study. We determined cutoff number of 8 for polypharmacy in HF patients using CART analysis given the patients with HF tend to have more medications. The novel findings of the present study were as follows; First, 43.2 % of the patients had polypharmacy and its prevalence increased with age. Second, polypharmacy was associated with poor prognosis not only in elderly but also in younger patients. Third, even in patients with polypharmacy, underuse of HF medications (RAS-I and/or beta-blockers) was associated with increased risk of all-cause death, indicating the importance of appropriate medications in HF practice. [15].

A previous *meta*-analysis study including 54 studies with various definitions of polypharmacy revealed that the pooled estimated prevalence of polypharmacy was 37 % (95 % CI: 31–43 %).[16] Although we defined polypharmacy as the use of 8 or more drugs in the present study, the present result with 43 % prevalence indicates that polypharmacy is a common important issue among chronic HF patients. In the present study, polypharmacy was associated with increased risk for all-cause death not only in elderly but also in younger patients. In general population, polypharmacy in the elderly was associated with increased risks, such as inappropriate prescription, poor adherence, and drug interactions.[17] Other studies showed that polypharmacy was associated with poor clinical outcomes in HF patients.[8,18] Sunada et al. reported that the number of medications on admission was associated with mortality in 193 patients with acute HF with a median age of 81 years, during an average follow-up period of 12 months.[18] Minamisawa et al. also reported that polypharmacy (≥10 medications) was associated with elevated risk of hospitalization in 1,758 HF patients with preserved ejection fraction during a median follow-up period of 2.9 years.[8] As compared with these previous studies, the strength of the present study is a larger sample size with longer follow-up period (a median of 8.3 years).

We found that polypharmacy was associated with 16.7 % increase in all-cause mortality, suggesting the prognostic significance of polypharmacy. Our findings further highlight the prognostic relevance of polypharmacy in younger HF patients (<55 years), extending the understanding that polypharmacy from elderly to younger population. Polypharmacy in HF patients may reflect the progression of systemic diseases, as they often have multiple comorbidities. In addition, the decreased medication adherence associated with polypharmacy may increase the incidence of adverse events and increase mortality rates. [19].

Professional guidelines recommend combination therapy with ACE inhibitors or ARBs, and beta-blockers for improving the prognosis of HF. [3–5] Furthermore, HF patients have multiple comorbidities, such as hypertension, diabetes, dyslipidemia, myocardial ischemia, and atrial fibrillation,[20] which can increase the number of medications. Polypharmacy potentially increases the risk of underuse of effective medications, which may lead to poor prognosis. The present results demonstrated that in patients with polypharmacy, underuse of either RAS-I and/or beta-blocker was associated with increased risk of all-cause death. In contrast, “appropriate polypharmacy” is defined as

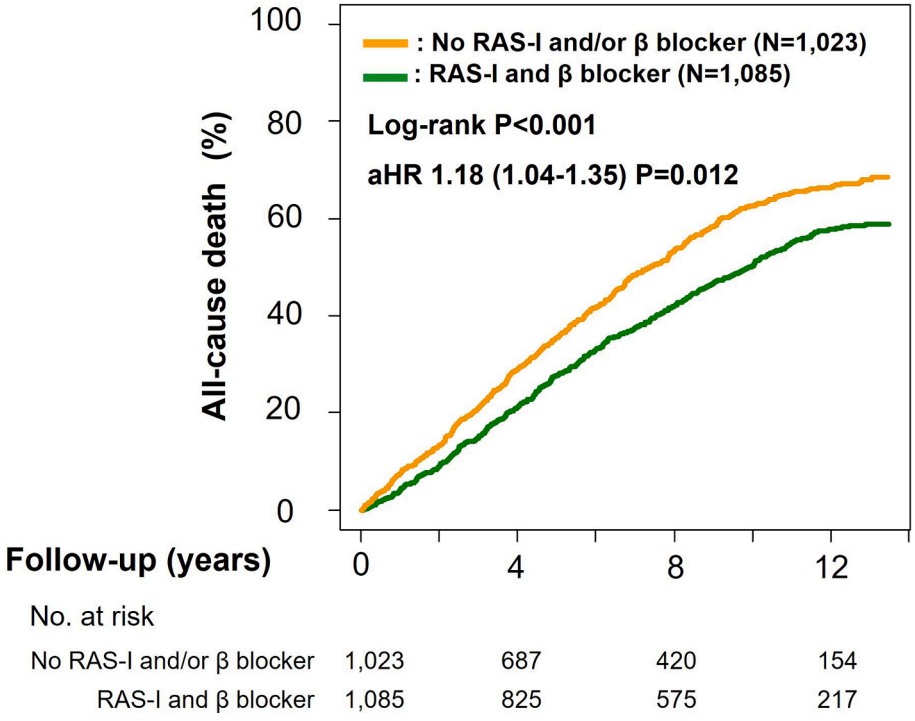


**Fig. 3.** Kaplan-Meier curves and adjusted hazard ratio by multivariable Cox proportional regression analysis for all-cause death by daily use of RAS-I and/or beta-blocker.Abbreviations: aHR, adjusted hazard ratio; RAS, renin-angiotensin system.

prescription for an individual according to best evidence.[21] Given by the higher risk of worsening clinical outcomes by discontinuation of RAS-I or beta-blocker in patients with HF,[22] these medications should not be easily withdrawn in HF patients for appropriate polypharmacy. Our findings indicate that even in polypharmacy status, medication for HF should be used for the patients. The CHAMP-HF study [23] reported that even in the new era of HF pharmacotherapy, beta-blocker and RAS-I including angiotensin receptor neprilysin inhibitor (ARNI) are still underuse. Our results encourage the clinicians to add on these standard HF medications for HF patients even in those with polypharmacy.

### 4.1. Study limitations

Several limitations should be mentioned for the present study. First, since the CHART-2 Study is an observational study for CHF in Japan, there needs a caution when generalizing the present findings to other populations in different countries. In particular, since the CHART-2 Study enrolled stable CHF population, validation studies are warranted in patients with acute HF or those with CHF in more severe clinical conditions. Second, our study definition was based on the number of medications, and we were unable to evaluate the difference between the dose of HF medications and prognosis. Third, there were no data available on drug interactions or adverse drug effects. Forth, medication use was assessed only at the enrollment and changes in medications were not examined during the follow-up period. Furthermore, as the CHART-2 launched in 2006, the prescription rates for digitalis and beta-blockers may be higher than those in current practice.

## 5. Conclusions

Polypharmacy, defined as the use of 8 or more drugs, are associated with underuse of guidelines-recommended medications and poor prognosis in CHF patients.

IRB Information

The present study was approved by Ethics Committee Tohoku University Graduate School of Medicine. Reference number: 2022-1-671.

Clinical trial registration

URL: http://www.clinicaltrials.gov. Unique identifier: NCT00418041.

## CRediT authorship contribution statement

**Takahide Fujihashi:** Writing – original draft, Visualization, Software, Resources, Methodology, Formal analysis, Data curation. **Kotaro Nochioka:** Writing – review & editing, Project administration, Methodology, Conceptualization. **Satoshi Yasuda:** Writing – review & editing, Supervision. **Yasuhiko Sakata:** Methodology, Conceptualization. **Hideka Hayashi:** Resources, Investigation, Data curation. **Takashi Shiroto:** Writing – review & editing. **Jun Takahashi:** Writing – review & editing. **Satoshi Miyata:** Software, Formal analysis. **Hiroaki Shimokawa:** Writing – review & editing, Supervision, Conceptualization, Funding acquisition.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary material

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