Effects of mokuboito, a Japanese Kampo medicine, on long-term clinical outcomes in patients with heart failure

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ABSTRACT

Aim: We previously reported that oral administration of mokuboito (a Japanese Kampo medicine) significantly improved symptoms in hospitalized patients with heart failure (HF). However, it remains unclear whether mokuboito treatment affects the long-term clinical prognosis in patients with HF.

Methods: We retrospectively investigated the long-term prognosis in 40 patients who participated in our previous study. Patients were allocated randomly to Group S (standard therapy alone) or Group M (oral administration of mokuboito plus standard therapy). The primary outcome was the composite endpoint of major adverse cardiovascular events (MACE; death from any cause, myocardial infarction or unstable angina, and readmission due to worsening HF) during 2 years.

Results: MACE were respectively observed in 13 and 5 patients in Group S and Group M (incidence rate per 100 person-years, 57.7 versus 17.3; \(P = 0.02\)), and the hazard ratio (HR) was 0.32 (95% CI 0.12–0.91; \(P = 0.02\)). Death from any cause was respectively observed in seven and three patients in Group S and Group M (incidence rate per 100 person-years, 22.6 versus 9.00; \(P = 0.18\)), and the HR was 0.41 (95% CI 0.11–1.58; \(P = 0.18\)). Readmission due to worsening HF was respectively observed in 11 and 5 in Group S and Group M (incidence rate per 100 person-years, 44.4 versus 16.8; \(P = 0.08\)), and the HR was 0.39 (95% CI 0.13–1.12; \(P = 0.07\)).

Conclusions: Oral administration of mokuboito significantly improved long-term clinical outcomes in patients hospitalized for HF during 2 years after discharge.

KEY WORDS: chronic heart failure, Japanese Kampo medicine, major adverse cardiovascular events, mokuboito

LIST OF ABBREVIATIONS

HF heart failure
MACE major adverse cardiovascular events
HR hazard ratio
CI confidence interval
ACEI angiotensin-converting enzyme inhibitor
ARB angiotensin II receptor blocker
MRA mineral corticoid receptor antagonist
ADHF acute decompensated heart failure
BNP brain natriuretic peptide
T-Bil total bilirubin
AST aspartate amino transferase
ALT alanine amino transferase
Cr creatinine
Na sodium
K potassium
LVEF left ventricular ejection fraction
LVDd end-diastolic left ventricular diameter
IVCd maximum inferior vena cava diameter
SD standard deviation
BMI body mass index

INTRODUCTION

Recent progress in treatments for heart failure (HF) has improved patients’ long-term prognosis. The benefits of beta-blockers [1–3], angiotensin-converting enzyme inhibitors (ACEIs) [4,5], angiotensin II receptor blockers (ARBs) [6,7], and mineral corticoid receptor antagonists (MRAs) [8,9] in the treatment of HF have been established on the basis of accumulating evidence. In addition to the above, ivabradine [10], an angiotensin–neprilysin inhibitor [11],
and sodium–glucose cotransporter 2 inhibitors [12,13] have been recently reported as emerging therapies for chronic HF.

Nonpharmacological treatments, such as cardiac resynchronization therapy [14], adaptive servo ventilation [15,16], and cardiac rehabilitation [17], also reportedly improve symptoms and reduce readmission due to worsening HF. However, in real-world clinical settings, even with adequate standard therapies, patients with HF often suffer from symptoms due to excessive body fluid and congestion, which generally require hospital admission for bed rest and intravenous administration of diuretics. Loop diuretics help to rapidly reduce congestion; however, at high doses, they reportedly lead to worsening renal function and higher mortality [18,19]. Although aquaretic efficacy and safety were reportedly demonstrated for tolvaptan [20], we have to take care that it does not induce hypernatremia and, therefore, frequent blood tests are needed.

In a search for novel strategies against HF with congestion, we focused on Kampo medicines (Japanese traditional herbal medicines) and previously reported that short-term oral administration of mokuboito significantly improved symptoms in hospitalized patients with acute decompensated heart failure (ADHF) without any significant adverse effects [21]. These benefits were presumably due to reduction of congestion and cardiac preload. We also observed that less tolvaptan was used in the subjects treated with mokuboito as compared with those under standard therapy alone [21]. However, it remains unclear whether mokuboito has long-term favorable clinical outcomes in patients with HF, and we therefore retrospectively investigated this in the patients who participated in the previous study.

MATERIALS AND METHODS

Study population

Forty patients participated in the previous study that investigated the effects of mokuboito in patients with ADHF. We obtained their clinical data after discharge from medical charts or using a telephone questionnaire.

In the previous study, 40 consecutive patients admitted to the Tokorozawa Heart Center due to ADHF were prospectively included. They were those who satisfied the inclusion criteria of needing admission for ADHF and giving written informed consent, and did not meet the exclusion criteria. The main exclusion criteria were: (i) younger than 20 years old, (ii) communication not possible owing to bronchial intubation or shock vital signs, (iii) pregnancy, (iv) inability to take oral medicine, (v) inability to undergo examinations (e.g., body weight measurement) due to orthopnea, and (vi) having a doctor who did not agree to participate in the study.

Study design

This study retrospectively investigated patients who participated in the previous study, a randomized control, open-label pilot study in a single center. ADHF was diagnosed by each physician according to the 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic HF.

In the previous study, after obtaining informed consent, the subjects were assigned to receive standard therapy alone (Group S) or mokuboito in addition to standard therapy (Group M), within 24 h of admission, and, except for mokuboito, the respective physicians in charge of them could independently decide on the medication they would use. The subjects were randomized in a 1:1 fashion to Group S and Group M via a minimization method using a software cloud service.

We collected 2 years (104 weeks) of clinical data after entry to the previous study. The data were obtained from medical charts for patients who had regularly visited our hospital; otherwise, we used a telephone questionnaire.

The primary endpoint was the composite endpoint of major adverse cardiovascular events (MACE) during 2 years. We defined MACE as death from any cause, myocardial infarction or unstable angina, and readmission due to worsening HF. Secondary endpoints were changes from baseline levels to those at 2 years after randomization of brain natriuretic peptide (BNP), total bilirubin (T-Bil), aspartate amino transferase (AST), alanine amino transferase (ALT), creatinine (Cr), sodium (Na), and potassium (K) in blood samples, and echocardiographic parameters. The data obtained at day 10 or discharge if earlier in the previous short-term study were used as the baseline data in this long-term study. These biochemical or echocardiographic data were collected only for patients who had regularly visited our institute.

The previous study was registered with the University Hospital Medical Information Network-Clinical Trials registry (UMIN-CTR number UMIN000026621). The Ethics Committee of Tokorozawa Heart Center approved the study protocol (no. H28-3) in accordance with the Declaration of Helsinki, and all patients gave written informed consent to participate. In the present study, informed consent was obtained in the form of opt-out on the following website: http://oukai.or.jp/thc.com/wordpress/wp-content/uploads/2020/10/%E6%9C%A8%E9%98%B2%E5%B7%B2%E6%B9%AF%E9%95%B7%E6%9C%F%E4%BA%88%E5%BE%8C%E3%82%AA%E3%83%95%E3%82%A7%E3%83%88%E2%82%A2%E3%82%A6%E3%83%88%E8%A8%88%E7%94%BB%E6%9B%B20210121Final.pdf.

Mokuboito

We used TSUMURA dried extract of mokuboito granules, 7.5 g of which contains 1.5 g of the dried extract of the following mixed crude drugs: The Japanese Pharmacopeia (JP) Gypsum 10.0 g, JP Sinomenium Stem 4.0 g, JP Cinna-mon Bark 3.0 g, and JP Ginseng 3.0 g. Mokuboito was administered orally with lukewarm water before every meal.

Echocardiography

Standard 2D Doppler echocardiography (HD15 High Definition Ultrasound Systems, Royal Philips, Amsterdam,
Nederland; Philips Electronics Japan, Tokyo, Japan) was performed. In the previous study, we obtained echocardiographic parameters at 10 days after admission or discharge if earlier, which were left ventricular ejection fraction (LVEF) by the Teichholz method, end-diastolic left ventricular diameter (LVDd), E/e’ (E, early wave of mitral inflow; e’, peak early diastolic mitral annular velocity of the septal wall side), and maximum inferior vena cava diameter (IVCd). We used these data as baseline data in the present study. The data after 2 years from entry to the previous study were collected from medical charts if available.

Statistical analysis

Baseline characteristics and changes in various parameters were reported as number and proportion or mean ± standard deviation (SD), as appropriate. Differences in continuous variables between groups were analyzed using a paired or unpaired Student’s t-test for parametrically distributed variables and Mann–Whitney test for nonparametrically distributed variables. Af, atrial fibrillation; BMI, body mass index; CS, Clinical Scenario of acute decompensated heart failure; CKD, chronic kidney disease; DM, diabetes mellitus; DCM, dilated cardiomyopathy; Group S, standard therapy alone; Group M, oral administration of mokuboito plus standard therapy; HFref, heart failure with reduced ejection fraction; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HTN, hypertension; IHD, ischemic heart disease; MRA, mineralocorticoid receptor antagonist; NYHA, New York heart Association Functional Classification; Nohria, Nohria–Stevenson classification of acute heart failure syndrome; RAS, renin–angiotensin system.

Table 1 | Baseline patient characteristics

|                         | Group S | Group M | P value |
|-------------------------|---------|---------|---------|
| Number of patients      | 21      | 19      |         |
| Age, years              | 78.2 ± 9.1 | 78.5 ± 7.7 | 0.97* |
| Gender, male, no. (%)   | 15 (71.4) | 13 (68.4) | 1.00   |
| BMI, kg/m²              | 23.6 ± 2.2 | 22.4 ± 2.6 | 0.14* |

Classification of heart failure severity, no. (%)

| NYHA | 1 | 2 | 3 | 4 |       |
|------|---|---|---|---|-------|
| S    | 0 (0) | 5 (23.8) | 7 (33.3) | 9 (42.9) |       |
| M    | 0 (0) | 5 (26.3) | 8 (42.1) | 6 (31.6) |       |
| P value | 0.79 | 0.66 | 0.08 | 0.27 |       |

| Nohria A | 1 | 2 | 3 | 4 |       |
|----------|---|---|---|---|-------|
| S        | 0 (0) | 7 (33.3) | 2 (9.5) |       |
| M        | 0 (0) | 4 (21.1) | 3 (15.8) |       |
| P value | 0.27 |       |       |       |

Risk factors, no. (%)

| HTN      | 17 (81.0) | 4 (21.1) |       |
| DM       | 13 (61.9) | 5 (26.3) |       |
| CKD      | 13 (61.9) | 8 (42.1) |       |
| Current smoker | 3 (14.3) | 1 (5.3) |       |
| P value | <0.01 |       |       |

Prior medication, no. (%)

| RAS inhibitor | 13 (61.9) | 12 (63.2) |       |
| Beta-blocker  | 14 (66.7) | 13 (68.4) |       |
| MRA           | 2 (10.0)  | 5 (26.3)  |       |
| Digitalis     | 1 (4.76)  | 2 (10.5)  |       |
| P value |        |       |       |

Table 1 (continued)

|                         | Group S | Group M | P value |
|-------------------------|---------|---------|---------|
| Diuretics               | 13 (61.9) | 11 (57.9) | 1.00   |
| Pimobendan              | 3 (14.3)  | 6 (31.6)  | 0.26   |
| Tolvaptan               | 3 (14.3)  | 0 (0)    | 0.23   |
| Amiodarone              | 2 (9.5)   | 4 (21.1)  | 0.40   |

P value was calculated using Fisher’s exact test unless otherwise indicated.

*P value was analyzed using Student’s t-test for parametrically distributed variables and Mann–Whitney test for nonparametrically distributed variables.

Af, atrial fibrillation; BMI, body mass index; CS, Clinical Scenario of acute decompensated heart failure; CKD, chronic kidney disease; DM, diabetes mellitus; DCM, dilated cardiomyopathy; Group S, standard therapy alone; Group M, oral administration of mokuboito plus standard therapy; HFref, heart failure with reduced ejection fraction; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HTN, hypertension; IHD, ischemic heart disease; MRA, mineralocorticoid receptor antagonist; NYHA, New York heart Association Functional Classification; Nohria, Nohria–Stevenson classification of acute heart failure syndrome; RAS, renin–angiotensin system.

Age and BMI are presented as mean ± SD.
used in this analysis. Model 1 was a univariate model, including oral administration of mokuboito as the explanatory variable. Model 2 was adjusted for sex and age. Model 3 was adjusted for known prognostic factors for HF: sex, age, atrial fibrillation, LVEF < 40%, diabetes mellitus, CKD, use of MRA, and use of diuretics.

Statistical significance was defined as probability of less than 0.05 for two-sided tests. The descriptive assessments

| Table 2 | Primary outcome between groups |
|---------|-------------------------------|
|         | Group S                        | Group M                        | P value |
|         | No. incidence rate (per 100 person-years) | No. incidence rate (per 100 person-years) |
| MACE    | 13 57.7 (33.5, 99.4)           | 5 17.3 (7.2, 41.5)             | 0.02    |
| Death from any cause | 7 22.6 (10.8, 47.5)           | 3 9.00 (2.9, 27.9)             | 0.18    |
| Readmission for heart failure | 11 44.4 (23.9, 82.5)          | 5 16.8 (7.0, 40.3)             | 0.08    |

Cl, confidence interval; MACE, major adverse cardiovascular events. P values were analyzed using Poisson regression model. Incidence rates are shown with 95% confidence intervals.

Figure 1 | Kaplan–Meier curves for probability of primary endpoint. (a) Kaplan–Meier analysis of probability of combined endpoint (death from any cause, acute myocardial infarction and unstable angina, readmission for worsening HF) (—) Group S and (—) Group M. (b) Kaplan–Meier analysis of probability of death from any cause (—) Group S and (—) Group M. (c) Kaplan–Meier analysis of probability of readmission for worsening HF (—) Group S and (—) Group M.
and analytical statistics were performed with STATA/IC 15.1 (StataCorp LLC, College Station, TX, USA).

RESULTS

Baseline characteristics

The baseline characteristics of each group (Group S and Group M) are presented in Table 1. There were no differences between the groups in terms of age, sex, BMI, clinical classification of HF using LVEF, prior medications, or severity of HF as evaluated using the New York Heart Association Functional Classification, clinical scenario of acute heart failure syndrome [22], and Nohria–Stevenson classification [23] (Table 1). However, percentages of subjects in Group S were significantly higher than those in Group M for ischemic heart disease (IHD), hypertension, and diabetes mellitus (Table 1).

In Group M, two patients discontinued taking mokuboito according to physician’s decision in charge. We do not have detailed information on another two patients because they stopped visiting our hospital. Fifteen patients (78.9%) continued taking mokuboito throughout their observation period. Mean administration period was 581.6 ± 259.3 days. All patients were administrated 7.5 g of mokuboito. In the retrospective investigation, there was no unfavorable effect of mokuboito and no patient who discontinued owing to side effects.

Primary endpoint

The clinical event data of 37 patients were obtained from medical charts or by telephone questionnaire. We obtained incomplete information for three patients because they stopped visiting our hospital (last visit: one patient in Group S at 53 weeks, two patients in Group M at 50 and 103 weeks, respectively). MACE were observed in 13 patients (57.7/100 person-years) in Group S and 5 patients (17.3/100 person-years) in Group M (P = 0.02, Table 2), respectively, and the hazard ratio (HR) was 0.32 (95% confidence interval (CI) = 0.12–0.91, P = 0.02, Fig. 1). Death from any cause was observed in seven patients (22.6/100 person-years) in Group S and in three patients (9.00/100 person-years) in Group M (P = 0.18, Table 2), and the HR was 0.41 (95% CI 0.11–1.58, P = 0.18, Fig. 1). There were no patients who suffered from myocardial infarction or unstable angina in the study period. Readmission for HF was observed in 11 patients (44.4/100 person-years) in Group S and 5 patients (16.8/100 person-years) in Group M (P = 0.08, Table 2), respectively, and the HR was 0.39 (95% CI 0.13–1.12, P = 0.07, Fig. 1). The Kaplan–Meier curves are shown in Fig. 1.

To further investigate whether use of mokuboito was an independent predictor of the primary endpoint, we performed multivariate analysis regarding MACE (Table 3). The models for multivariate analysis were selected as described in Methods. Model 1 was a crude model, and model 2 was adjusted for sex and age. Model 3 was adjusted for known prognostic factors selected according to the proportional-hazard assumption. In all models, use of mokuboito was an independent predictor of significantly decreased MACE. The analysis according to model 3 suggested that low LVEF and use of MRA were independent predictors of a potentially significant increase in the incidence of MACE.

Secondary endpoints

Biochemical and echocardiographic parameters 2 years after randomization were obtained in 19 and 17 patients, respectively. Among biochemical parameters, there were no differences between baseline [21] and 2 years after randomization in both groups. Serum K levels were significantly lower in Group S than Group M at baseline; however, this difference was not observed at 2 years after randomization (Table 4). Regarding echocardiographic parameters, LVDd was significantly reduced at 2 years in Group S, but in contrast, we observed no change in Group M. Regarding other cardiac echo data, there were no differences in individual parameters.

### Table 3 | Multivariate analysis of prognostic factors

| Model | HR | 95% CI | P value |
|-------|----|--------|---------|
| Model 1 | Use of mokuboito | 0.32 | 0.12–0.91 | 0.03 |
| | Proportional hazards assumption | | | |
| Model 2 | HR | 95% CI | P value |
| Use of mokuboito | 0.30 | 0.11–0.84 | 0.02 |
| Male gender | 2.69 | 0.78–9.34 | 0.12 |
| Age/10 | 1.59 | 0.88–2.88 | 0.13 |
| | Proportional hazards assumption | | | |
| Model 3 | HR | 95% CI | P value |
| Use of mokuboito | 0.16 | 0.04–0.64 | 0.01 |
| Male gender | 2.85 | 0.66–12.3 | 0.16 |
| Age/10 | 1.21 | 0.60–2.44 | 0.59 |
| Atrial fibrillation | 1.14 | 0.33–3.97 | 0.84 |
| LVEF < 40% | 4.49 | 1.20–16.8 | 0.03 |
| Diabetes mellitus | 1.00 | 0.33–3.07 | 0.99 |
| CKD | 2.90 | 0.72–11.7 | 0.13 |
| Use of MRA | 4.80 | 1.21–25.8 | 0.03 |
| Use of diuretics | 3.00 | 0.78–11.6 | 0.11 |

P values were analyzed using Cox proportional hazards model. CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio; MRA, mineralocorticoid receptor antagonist.
between the two groups both at baseline and 2 years after randomization (Table 4).

**DISCUSSION**

We investigated long-term effects of mokuboito in hospitalized patients with ADHF for 2 years after discharge. The present study revealed a significantly greater reduction in 2-year MACE in the subjects treated with mokuboito (Group M) as compared with those who underwent only standard therapy (Group S). Although there were no significant differences in death from any cause between the groups, the rate for readmission for worsening HF tended to be lower in Group M than in Group S (Table 2), indicating that this effect should be confirmed in future population studies.

**Table 4 | Changes in various parameters 2 years after randomization**

| Parameters          | Group S                       | Group M                       | Group S versus Group M baseline (P value #) | Group S versus Group M 2 years after randomization (P value #) |
|---------------------|-------------------------------|-------------------------------|-------------------------------------------|---------------------------------------------------------------|
| Biochemical parameters |                               |                               |                                           |                                                               |
| BNP, pg/mL          | 355 ± 524                     | 243 ± 315                     | 0.65                                      | 0.61                                                          |
| T-Bil, mg/dL        | 0.61 ± 0.24                   | 0.65 ± 0.16                   | 0.36                                      | 0.73                                                          |
| AST, U/L            | 22.6 ± 12.6                   | 20.7 ± 5.06                   | 0.31                                      | 0.65                                                          |
| ALT, U/L            | 22.4 ± 26.2                   | 12.8 ± 3.46                   | 0.47                                      | 0.24                                                          |
| Cr, mg/dl           | 1.53 ± 0.82                   | 1.26 ± 0.52                   | 0.19                                      | 0.41                                                          |
| Na, mEq/L           | 140 ± 3.81                    | 141 ± 2.06                    | 0.48                                      | 0.78                                                          |
| K, mEq/L            | 3.78 ± 0.59                   | 4.55 ± 0.47                   | 0.27                                      | <0.01                                                         |
| Echocardiographic parameters |                           |                               |                                           |                                                               |
| LVEF, %             | 44.9 ± 12.4                   | 52.9 ± 15.9                   | 0.59                                      | 0.27                                                          |
| LVd, mm             | 55.6 ± 6.93                   | 51.0 ± 8.49                   | 0.57                                      | 0.24                                                          |
| E/e'                | 15.6 ± 5.45                   | 15.4 ± 3.71                   | 0.45                                      | 0.93                                                          |
| IVCd, mm            | 15.5 ± 4.75                   | 15.4 ± 3.47                   | 0.19                                      | 0.98                                                          |
| LAD, mm             | 43.4 ± 4.10                   | 44.8 ± 7.00                   | 0.79                                      | 0.63                                                          |

*P value was analyzed using paired t-test.

**P value was analyzed using Student’s t-test.

AST, aspartate amino transferase; ALT, alanine amino transferase; BNP, brain natriuretic peptide; Cr, creatinine; E/e', early wave of mitral inflow/peak early diastolic mitral annular velocity of septal wall side; IVCd, maximum diameter of inferior vena cava; K, potassium; LAD, left atrium diameter; LVEF, left ventricular ejection fraction; LVd, left ventricular end-diastolic diameter; Na, sodium; T-Bil, total bilirubin.

Baseline data were obtained 10 days after admission or discharge if earlier in the previous short-term study.

Values are presented as mean ± SD.

T-Bil levels and LVd detected by echocardiography, which have been accepted as indirect indicators of organ congestion and cardiac preload, respectively, in patients with HF [24]. Moreover, tolvaptan, a diuretic, was less used in Group M than Group S under the condition that the physicians in charge independently decided on the use of diuretics and other medications in our previous study [21], providing further support for the concept that mokuboito has a beneficial effect in cardiac preload reduction. In contrast to the diuretics, mokuboito might reduce cardiac preload not only by attenuating intravenous volume overload, but also by an endothelium-independent vasodilative effect as previously reported by Nishida et al. [25,26]. In the experiments on vasodilation, they used rat aorta, not vein. However, it is possible that mokuboito exerts an effect on veins by relaxing vascular smooth muscle cells, similarly to nitroglycerin, leading to vasodilation, which in turn results in preload reduction. Regarding other mechanisms, a previous case report stated that mokuboito treatment increased cardiac output 20 min after administration as compared with baseline in an 80-year-old male patient with HF due to aortic regurgitation [27]. However, this effect should be confirmed in future population studies.
From a Kampo medical point of view, Gypsum together with Sinomenium Stem are known to have a water-utilizing effect in Chinese traditional medicine. In the ‘Jin Gui Yao Lue’, a classic clinical text of traditional Chinese medicine, mokuboito is described as relieving the hardness in the epigastric region and upper abdomen. Using modern scientific terms, this means that mokuboito is effective at relieving the symptom of hepatomegaly caused by congestive heart failure. Indeed, the finding that mokuboito significantly reduced serum T-Bil levels raises the possibility that this property contributed to the favorable effects observed in patients with ADHF [21].

Our two studies on mokuboito revealed that it improved not only short-term HF-related symptoms, but also long-term prognosis in patients who had been hospitalized for HF. Although mokuboito treatment had favorable effects over the short term, such as reducing serum T-Bil levels and LVDd, and did not cause harmful hypokalemia, as compared with the standard therapy alone [21], there were no changes in the secondary endpoints of biochemical and echocardiographic parameters, between just before and 2 years after discharge (Table 4) in Group M. In contrast, LVDd and serum K levels in Group S were respectively reduced and increased 2 years after randomization. These findings suggest that mokuboito has beneficial effects in the acute phase of HF when patients are hospitalized, and that they are maintained over a long period of time. Multivariate analysis confirmed the benefits of mokuboito for the long-term prognosis of HF patients after hospitalization (Table 3). It also revealed that low LVEF was associated with a poor prognosis, which was not surprising because this has been widely established through accumulating evidence. In this study, multivariate analysis showed that mokuboito was still an independent predictor of MACE, including low LVEF as a moderator variable. In contrast, it is difficult to explain why treatment with an MRA was associated with an increase in MACE despite several clinical trials having demonstrated favorable outcomes for MRAs in patients with HF [8,9]. Since the number of patients treated with the MRA was relatively small (Table 1), further clinical trials should be performed to confirm this unexpected finding.

The present study has several limitations. First, it was a single-center, retrospective, observational study conducted by analyzing data from the small number of participants in our previous study. A large-scale multicenter prospective study will be needed in the future. Second, it should have used a placebo to obtain a more robust conclusion; however, it is difficult to prepare a placebo since Kampo preparations have a unique smell and flavor. Third, regarding secondary endpoints, data were limited because they were obtained only from the patients who had regularly visited our institute. This might produce selection bias and affect the results. Finally, Group S included more subjects with ischemic heart disease, hypertension, and diabetes mellitus, and such bias might also impact the results.

CONCLUSIONS
Oral administration of mokuboito significantly reduced 2-year MACE in patients who had been hospitalized with ADHF. The observations of this study provide the basis for a novel therapeutic strategy using mokuboito in HF patients.

ACKNOWLEDGMENTS
We appreciate Mr. Alexander Cox for English proofreading of our manuscript.

FUNDING
This research received no grant from any public, commercial, or nonprofit funding organization.

DISCLOSURES
The authors declare no conflicts of interest associated with this manuscript.

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