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ORIGINAL ARTICLE
Myocardial Disease

Effects of Cardioprotective Drugs on 90-Day Mortality or Heart Transplantation in Patients With Fulminant Myocarditis

Shuhei Tara, MD, PhD; Takeshi Yamamoto, MD, PhD, FJCS; Koshiro Kanaoka, MD, PhD; Eiichiro Oka, MD, PhD; Reiko Shiomura, MD, PhD; Junya Matsuda, MD, PhD; Jun Nakata, MD; Hideki Miyachi, MD, PhD; Kenji Onoue, MD, PhD, FJCS; Yoshihiko Saito, MD, PhD, FJCS; Wataru Shimizu, MD, PhD, FJCS; Kuniya Asai, MD, PhD, FJCS, on behalf of the Japanese Registry of Fulminant Myocarditis Investigators

Background: Cardioprotective drugs have not been previously shown to improve the prognosis in patients with fulminant myocarditis presentation (FMP). We aimed to investigate whether cardioprotective drugs, including angiotensin-converting enzyme inhibitor (ACEI)/angiotensin II receptor blocker (ARB) and β-blocker, administered during hospitalization improved the prognosis in patients with FMP.

Methods and Results: This multicenter cohort study conducted in Japan included 755 patients with clinically diagnosed FMP. Those who died within 14 days of admission were excluded, and 588 patients (median age 53 [37–65] years and 40% female) were evaluated. The primary outcome was the composite of 90-day mortality or heart transplantation. The patients were divided into 4 groups according to whether they were administered ACEI/ARB or β-blocker during hospitalization. Administration of ACEI/ARB without β-blocker improved the overall patient outcomes (log-rank test [vs. ACEI/ARB – and β-blocker –]: ACEI/ARB + and β-blocker –, P<0.001; ACEI/ARB – and β-blocker +, P=0.256). Subsequently, a matched cohort of 146 patient pairs was generated for patients with or without ACEI/ARB administration during hospitalization. The outcome-free survival at 90 days was significantly higher in the ACEI/ARB administration group than in the non-administration group (hazard ratio 0.37; 95% confidence interval 0.19–0.71).

Conclusions: Administration of ACEI or ARB during hospitalization was associated with favorable outcomes in terms of 90-day mortality and heart transplantation events in patients with clinically diagnosed FMP.

Key Words: Angiotensin-converting enzyme inhibitor; Angiotensin II receptor blocker; Fulminant myocarditis; Heart transplantation; Mortality

Acute myocarditis is caused by myocardial inflammation due to infection, autoimmunity, or toxicity.[1] Despite being a rare type of acute myocarditis, fulminant myocarditis presentation (FMP) is a fatal condition with sudden hemodynamic collapse and an extremely high risk of death or probability of undergoing heart transplantation (HTx) due to heart failure, cardiogenic shock, or arrhythmias.[2,3] Restoration of hemodynamics using inotropes or mechanical circulatory support (MCS) is the primary management approach for FMP.[1–3] Because it might lead to the deterioration of hemodynamics, administration of cardioprotective drugs such as renin-angiotensin system (RAS) inhibitors and β-blockers in patients with FMP is controversial.[3,4] Therefore, the introduction of cardioprotective drugs is only considered in hemodynamically stable patients with myocarditis,[1,3] and medications are recommended according to the guidelines for heart failure owing to the lack of clinical evidence of these drugs for acute myocarditis.[5] In the present study, we aimed to investigate whether the administration of

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Division of Cardiovascular Intensive Care, Nippon Medical School Hospital, Tokyo (S.T., T.Y., E.O., R.S., J.M., J.N., H.M.); Department of Cardiovascular Medicine, Nippon Medical School, Tokyo (S.T., W.S., K.A.); Department of Cardiovascular Medicine, Nara Medical University, Nara (K.K., K.O., Y.S.); Department of Medical and Health Information Management, National Cerebral and Cardiovascular Center, Osaka (K.K.); and Nara Prefecture Seiwa Medical Center, Nara (Y.S.), Japan

Mailing address: Shuhei Tara, MD, PhD, Division of Cardiovascular Intensive Care, Nippon Medical School Hospital, Department of Cardiovascular Medicine, Nippon Medical School, 1-1-5 Sendagi, Bunkyo-ku, Tokyo 113-8603, Japan. email: s5062@nms.ac.jp and Takeshi Yamamoto, MD, PhD, Division of Cardiovascular Intensive Care, Nippon Medical School Hospital, 1-1-5 Sendagi, Bunkyo-ku, Tokyo 113-8603, Japan. email: yamamoto56@nms.ac.jp

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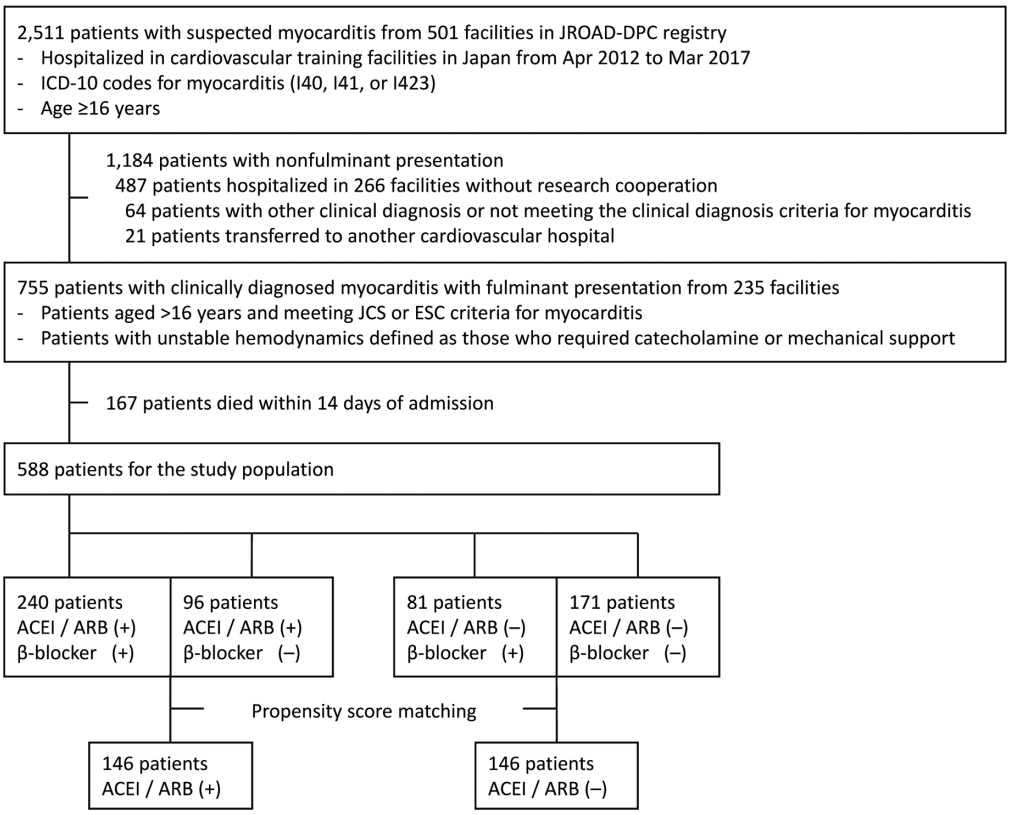

Figure 1. Patient enrolment and assignment flowchart. A total of 588 patients with clinically diagnosed FMP from 2,511 patients with suspected myocarditis are enrolled between April 2012 and March 2017. They are grouped according to whether they are administered ACEI/ARB or β-blockers during hospitalization. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ESC, European Society of Cardiology; ICD-10, International Classification of Diseases-10; JCS, Japanese Circulatory Society; JROAD-DPC, Japanese Registry of All Cardiac and Vascular Diseases-Diagnostic Procedure Combination.

cardioprotective drugs, including angiotensin-converting enzyme inhibitor (ACEI)/angiotensin II receptor blocker (ARB) and β-blocker, during hospitalization for treatment in the acute phase was associated with a favorable prognosis in patients with FMP.

Methods

Study Design and Data Collection

We analyzed data from the Japanese Registry of Fulminant Myocarditis (JRFM). This multicenter, retrospective cohort study was conducted in collaboration with 235 cardiovascular training hospitals across Japan. This database is based on the JROAD-DPC (Japanese Registry of All Cardiac and Vascular Diseases-Diagnosis Procedure Combination), a nationwide claims database containing data on cardiac in-patients admitted to the JROAD-registered hospitals in Japan.[6,7] Details of patient enrolment and the selection procedure using the JROAD-DPC database have been previously described.[8] The data of 2,511 patients with suspected myocarditis from 511 facilities in the JROAD-DPC registry between April 2012 and March 2017 were extracted using International Classification of Diseases-10 (ICD-10) codes I40, I41, or I423; individual patient data (retrospective anonymous data) were collected from each facility if joining the registry was allowed and local institutional review board approval was obtained.[8] The study protocol was approved by the Ethics Committee of Nara Medical University (registration no. 2256) in July 2019, Japanese Circulation Society (registration no. 10) in November 2019, and Nippon Medical School (registration no. B-2020-224) in November 2020. An opt-out option by posting the research information in the Nippon Medical School Hospital was utilized instead of obtaining informed consent from each patient, because of the retrospective study design. The present study was conducted in accordance with the principles of the Declaration of Helsinki. This study is registered in the UMIN Clinical Trials Registry (https://www.umin.ac.jp/ctr; UMIN000039763).

The patient data were reviewed for a diagnosis of FMP. Patients diagnosed with other diseases were excluded. Clinically diagnosed acute myocarditis was defined based on the clinical diagnostic criteria of the European Society of Cardiology or the Japanese Circulation Society.[1,9] A total of 755 patients clinically diagnosed with FMP was selected according to their use of catecholamines or MCS during hospitalization (**Figure 1**).[10,11] Because hemodynamic stability is the primary target of treatment in patients with FMP during the inflammatory-acute phase, those who died during this phase were considered to not have had

sufficient time for being treated with cardioprotective drugs to evaluate their effects. Moreover, there could have been an increase in the mortality rate among patients who did not receive these drugs compared with that among patients who received these drugs during the inflammatory-acute phase. To avoid this bias, 167 patients who died within 14 days of hospital admission were excluded. The inflammatory-acute phase within 14 days of admission was defined based on the general clinical course of acute myocarditis[3] and the duration of temporary MCS use in all patients in the present study (95 percentile; intra-aortic balloon pump [IABP], 16 days; veno-arterial extracorporeal membrane oxygenation [VA-ECMO], 13 days). Finally, 588 patients were evaluated in the present study. These patients were divided into 4 groups according to whether they were administered ACEI/ARB and β-blocker during hospitalization to estimate the effect of these drugs on the 90-day mortality or HTx (**Figure 1**). Among these patients, no limitations were placed on the dose or administration duration of these drugs during hospitalization. Patients who were prescribed these drugs at hospital discharge but did not receive them during hospitalization were classified

Table 1. Clinical Characteristics of Patients With Fulminant Myocarditis in the Entire Cohort

	Patients with available data ACEI or ARB / β-blocker (–/–), (–/+), (+/–), (+/+)	ACEI or ARB (–) and β-blocker (–) (n=171)	ACEI or ARB (–) and β-blocker (+) (n=81)	ACEI or ARB (+) and β-blocker (–) (n=96)	ACEI or ARB (+) and β-blocker (+) (n=240)	P value
Demographic findings						
Age (years)	171, 81, 96, 240	49 (35–64)	58 (39–69)	47 (31–62)	55 (40–65)	0.005
Female	171, 81, 96, 240	80 (47)	28 (35)	30 (31)	98 (41)	0.060
Medical history						
Hypertension	171, 81, 96, 240	29 (17)	18 (22)	20 (21)	61 (25)	0.235
Diabetes	171, 81, 96, 240	15 (8.8)	5 (6.2)	10 (10)	29 (12)	0.428
Chronic kidney disease	171, 81, 96, 240	3 (1.8)	4 (4.9)	1 (1.0)	10 (4.2)	0.235
Medications before admission						
β-blocker	171, 81, 96, 240	6 (3.5)	12 (15)	1 (1.0)	13 (5.4)	<0.001
ACEI or ARB	171, 81, 96, 240	16 (9.4)	4 (4.9)	14 (15)	39 (16)	0.026
Clinical findings at admission						
BMI (kg/m^2)	160, 75, 92, 236	22.2 (19.9–24.6)	21.9 (19.5–23.4)	22.4 (19.9–24.6)	22.0 (19.8–24.6)	0.783
Heart rate (beats/min)	169, 79, 95, 237	101 (80–120)	100 (89–120)	98 (77–111)	101 (80–119)	0.27
Body temperature (°C)	154, 74, 92, 219	36.9 (36.3–37.9)	36.7 (36.2–37.4)	36.5 (36.2–37.3)	36.7 (36.3–37.3)	0.035
SBP <90 mmHg or CPA* on admission	167, 79, 95, 236	64 (38)	22 (28)	21 (22)	75 (32)	0.046
Advanced AV block on the first day	171, 81, 96, 240	37 (22)	13 (16)	16 (17)	43 (18)	0.636
VT or VF on the first day	171, 81, 96, 240	39 (23)	18 (22)	11 (11)	47 (20)	0.138
Laboratory findings at admission						
White blood cells (/mm^3)	171, 81, 95, 240	9,500 (7,270–13,875)	9,920 (7,300–12,500)	9,200 (6,900–12,550)	10,105 (7,090–13,400)	0.783
Hemoglobin (g/dL)	169, 80, 92, 240	13.5 (11.9–14.6)	13.1 (11.4–14.3)	13.8 (12.7–15.1)	13.2 (11.7–14.9)	0.019
Albumin (g/dL)	165, 76, 90, 228	3.3 (2.8–3.8)	3.4 (3.0–3.7)	3.5 (3.2–3.9)	3.3 (3.0–3.7)	0.011
eGFR (mL/min/1.73 m^2)	171, 81, 95, 240	59.0 (37.0–83.0)	52.0 (34.0–69.0)	66.0 (44.0–80.0)	54.5 (35.0–76.5)	0.068
CRP (mg/dL)	170, 94, 80, 238	4.8 (1.5–11.0)	5.5 (1.9–12.3)	4.0 (1.9–10.5)	4.0 (1.4–9.5)	0.417
BNP (pg/mL)	137, 68, 82, 190	524 (254–922)	615 (269–1,289)	493 (270–855)	608 (318–1,294)	0.054
Nt-proBNP (pg/mL)	23, 11, 15, 48	10,816 (1,945–26,264)	12,776 (9,184–21,497)	7,224 (2,131–17,278)	7,469 (3,709–21,775)	0.351
Creatinine kinase-Mb (IU/L)	150, 70, 86, 221	57 (28–103)	50 (22–78)	43 (24–86)	46 (19–89)	0.186
Elevated troponin†	154, 69, 85, 218	132 (86)	61 (88)	77 (91)	197 (90)	0.514
Lactate (mmol/L)	110, 54, 69, 166	2.8 (1.6–5.2)	3.0 (1.6–9.8)	1.8 (1.2–3.3)	2.4 (1.3–4.3)	0.008
ECG findings on admission						
Sinus rhythm	170, 80, 96, 240	129 (76)	55 (69)	79 (82)	175 (73)	0.175
QRS duration (ms)	159, 72, 87, 217	118 (92–139)	122 (103–144)	108 (89–130)	108 (90–138)	0.230
ST elevation	169, 78, 96, 238	120 (71)	47 (60)	62 (65)	135 (57)	0.030

(**Table 1** continued the next page.)

	Patients with available data ACEI or ARB / β-blocker (–/–), (–/+), (+/–), (+/+)	ACEI or ARB (–) and β-blocker (–) (n=171)	ACEI or ARB (–) and β-blocker (+) (n=81)	ACEI or ARB (+) and β-blocker (–) (n=96)	ACEI or ARB (+) and β-blocker (+) (n=240)	P value
Echocardiography findings on admission						
LVEF (%)	162, 78, 91, 229	30 (20–44)	30 (23–46)	42 (30–49)	30 (20–43)	<0.001
LVDd (mm)	124, 61, 81, 196	46 (42–49)	48 (43–54)	46 (42–49)	47 (43–51)	0.070
Pericardial effusion	156, 73, 91, 220	74 (47)	40 (55)	44 (48)	99 (45)	0.545
Coronary angiography						
Coronary artery stenosis ≥75%	149, 68, 83, 219	3 (2.0)	1 (1.5)	12 (14)	6 (2.7)	<0.001
Endomyocardial biopsy						
Left ventricular biopsy	78, 44, 55, 165	54 (69)	31 (70)	35 (64)	121 (73)	0.585
Histological diagnosis	77, 43, 55, 165					0.812
Lymphocytic		55 (71)	32 (74)	37 (67)	117 (71)	
Eosinophilic		13 (17)	4 (9.3)	10 (18)	21 (13)	
Giant cell		4 (5.2)	3 (7.0)	1 (1.8)	10 (6.1)	
Damaged cardiomyocytes						
Severe (≥50%)	57, 30, 48, 123	27 (47)	13 (43)	12 (25)	40 (33)	0.069
Medications during hospitalization						
Mineralocorticoid receptor antagonist	171, 81, 96, 240	24 (14)	29 (36)	26 (27)	135 (56)	<0.001
Intravenous steroids	171, 81, 96, 240	81 (47)	41 (51)	36 (38)	126 (53)	0.093
Intravenous immunoglobulin	171, 81, 96, 240	56 (33)	26 (32)	26 (27)	87 (36)	0.445
Inotropes	171, 81, 96, 240	167 (98)	78 (96)	91 (95)	229 (95)	0.604
Temporary MCS devices						
Intra-aortic balloon pump	171, 81, 96, 240	118 (69)	62 (77)	68 (71)	192 (80)	0.059
VA-ECMO	171, 81, 96, 240	89 (52)	39 (48)	20 (21)	105 (44)	<0.001
Ventricular assist device	171, 81, 96, 240	13 (7.6)	10 (12)	0 (0)	21 (8.8)	0.011
Invasive-mechanical support devices						
Mechanical ventilator	171, 81, 96, 240	50 (29)	31 (38)	23 (24)	104 (43)	0.002
Renal replacement therapy	171, 81, 96, 240	56 (33)	30 (37)	8 (8.3)	67 (28)	<0.001
Discharge prescription‡						
β-blocker	125, 63, 93, 220	1 (0.8)	41 (65)	1 (1.1)	174 (79)	<0.001
ACEI or ARB	125, 63, 93, 220	3 (2.4)	0 (0)	70 (75)	162 (74)	<0.001

Values are presented as median (interquartile range) or n (%). ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; AV, atrioventricular; BMI, body mass index; BNP, B-type natriuretic peptide; CPA, cardiopulmonary arrest; CRP, C-reactive protein; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; LVDd, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; MCS, mechanical circulatory support; Nt-proBNP, N-terminal pro-B-type natriuretic peptide; SBP, systolic blood pressure; VA-ECMO, veno-arterial extracorporeal membrane oxygenation; VF, ventricular fibrillation; VT, ventricular tachycardia. *CPA is defined as loss of spontaneous respiration, loss of carotid artery pulse, or asystole, ventricular fibrillation, pulseless ventricular tachycardia, or pulseless electrical activity on ECG monitoring. †Elevated troponin level is defined as ≥0.02 ng/mL or qualitative test positive of troponin T or troponin I. ‡Data for in-hospital mortality are excluded.

into the non-administration during hospitalization groups.

The primary outcome in the present study was a composite of all-cause mortality and HTx at a follow up of 90 days. Follow-up data were obtained from either medical records or telephone interviews. Secondary outcomes were a composite of: all-cause mortality and HTx at a follow up of 1 year; in-hospital mortality; length of hospital stay; and duration of MCS use, including IABP and VA-ECMO, during hospitalization in patients who were discharged alive. We also assessed the changes in the echocardiography left ventricular ejection fraction (LVEF) at discharge and 6–12 months after discharge in both groups.

Statistical Analysis

Clinical characteristics of the patients are described as numbers and percentages for dichotomous variables or median and interquartile range (IQR) for continuous variables. The Fisher's exact probability and Mann-Whitney U tests were used to compare dichotomous and continuous variables, respectively, between the 2 groups. For comparisons among multiple groups, data for continuous and dichotomous variables were evaluated using the non-parametric Kruskal-Wallis and Pearson's χ^2 tests, respectively.

The Kaplan-Meier method was used to estimate the cumulative incidence of death or HTx at 90 days, and the differences between groups were compared using the log-rank test. We performed propensity score matching analysis to adjust for potential selection bias in the treatment assignment. Propensity scores were generated using a multivariate logistic regression model in patients receiving ACEI or ARB. The matching variables in this model included: age; sex; medical histories of hypertension, diabetes, and chronic kidney disease; clinical conditions at admission such as shock vitals, including systolic blood pressure (SBP) <90 mmHg or cardiopulmonary arrest (CPA) on admission; occurrence of advanced atrioventricular

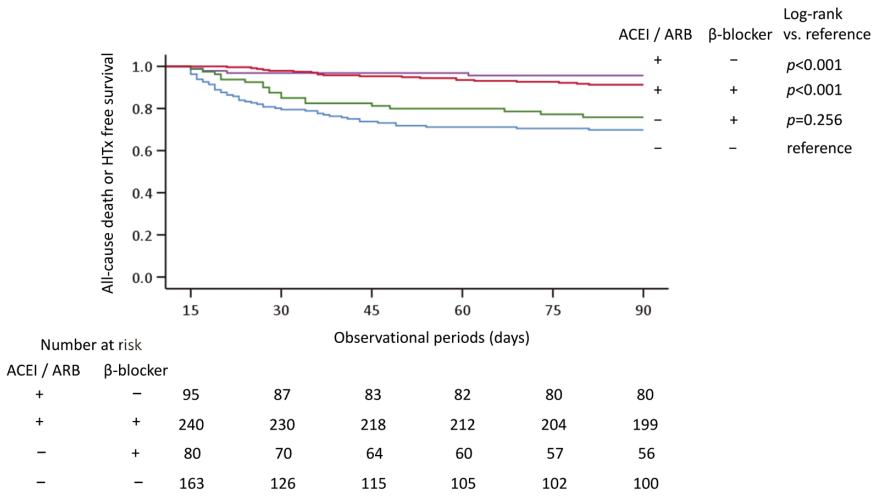

Figure 2. Cumulative event-free survival in the entire cohort. Patients are divided into 4 groups according to whether they are administered ACEI/ARB or β-blocker during hospitalization. These groups are compared based on the cumulative event (all-cause death or HTx)-free survival at 90 days using the Kaplan-Meier method with log-rank test. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; HTx, heart transplantation.

Table 2. Clinical Characteristics of Patients With Fulminant Myocarditis in the Matched Cohort

	Patients with available data ACEI or ARB (+, –)	ACEI or ARB (+) (n=146)	ACEI or ARB (–) (n=146)	Standardized difference
Demographic findings				
Age (years)	146, 146	54 (38–64)	51 (34–68)	0.004
Female	146, 146	62 (43)	61 (42)	0.014
Medical history				
Hypertension	146, 146	28 (19)	29 (20)	0.017
Diabetes	146, 146	11 (7.5)	10 (6.8)	0.027
Chronic kidney disease	146, 146	4 (2.7)	5 (3.4)	0.040
Medications before admission				
β-blocker	146, 146	4 (2.7)	14 (9.6)	0.288
ACEI or ARB	146, 146	19 (13)	12 (8.2)	0.156
Clinical findings at admission				
BMI (kg/m^2)	141, 142	21.9 (19.4–24.1)	21.8 (19.4–24.1)	0.073
Heart rate (beats/min)	144, 145	98 (80–111)	98 (78–119)	0.083
Body temperature (°C)	136, 136	36.6 (36.3–37.2)	36.9 (36.3–37.6)	0.212
SBP <90 mmHg or CPA* on admission	146, 146	38 (26)	39 (27)	0.016
Advanced AV block on the first day	146, 146	27 (19)	28 (19)	0.018
VT or VF on the first day	146, 146	27 (19)	30 (21)	0.052
Laboratory findings at admission				
White blood cells (/mm^3)	146, 146	9,695 (6,550–12,968)	9,550 (7,408–12,675)	0.024
Hemoglobin (g/dL)	146, 146	13.4 (11.8–14.9)	13.6 (11.9–14.8)	0.040
Albumin (g/dL)	146, 146	3.5 (3.1–3.7)	3.5 (3.1–3.8)	0.031
eGFR (mL/min/1.73 m^2)	146, 146	61.0 (38.0–76.0)	62.0 (39.0–82.0)	0.126
CRP (mg/dL)	144, 145	3.4 (1.9–9.5)	4.4 (1.3–10.5)	0.032
BNP (pg/mL)	115, 122	546 (289–1,034)	474 (231–844)	0.126
Nt-proBNP (pg/mL)	36, 19	7,469 (2,438–17,892)	10,424 (6,844–16,192)	0.184
Creatinine kinase-Mb (IU/L)	134, 127	43 (19–89)	43 (24–75)	0.021
Elevated troponin†	141, 130	127 (90)	114 (88)	0.076
Lactate (mmol/L)	99, 94	2.0 (1.3–3.7)	3.0 (1.5–5.9)	0.326

(**Table 2** continued the next page.)

	Patients with available data ACEI or ARB (+, –)	ACEI or ARB (+) (n=146)	ACEI or ARB (–) (n=146)	Standardized difference
ECG findings on admission				
Sinus rhythm	146, 146	111 (76)	114 (78)	0.049
QRS duration (ms)	127, 139	112 (91–135)	118 (90–138)	0.027
ST elevation	146, 146	100 (69)	95 (65)	0.073
Echocardiography findings on admission				
LVEF (%)	146, 146	34 (23–46)	33 (25–49)	0.076
LVDd (mm)	129, 107	46 (42–51)	47 (43–50)	0.009
Pericardial effusion	136, 138	59 (43)	74 (54)	0.206
Coronary angiography				
Coronary artery stenosis ≥75%	131, 125	12 (9.2)	2 (1.6)	0.34
Endomyocardial biopsy				
Left ventricular biopsy	94, 71	68 (72)	50 (70)	0.042
Histologic diagnosis	94, 71			0.322
Lymphocytic		66 (70)	53 (76)	
Eosinophilic		11 (12)	9 (13)	
Giant cell		6 (6.4)	3 (4.3)	
Medications during hospitalization				
Mineralocorticoid receptor antagonist	146, 146	46 (32)	45 (31)	0.015
β-blocker	146, 146	72 (49)	68 (47)	0.055
Intravenous steroids	146, 146	69 (47)	68 (47)	0.014
Intravenous immunoglobulin	146, 145	50 (34)	44 (30)	0.084
Inotropes	146, 146	141 (97)	143 (98)	0.084
Temporary MCS devices				
Intra-aortic balloon pump	146, 146	104 (71)	102 (70)	0.030
VA-ECMO	146, 146	54 (37)	63 (43)	0.126
Ventricular assist device	146, 146	10 (6.8)	12 (8.2)	0.052
Invasive-mechanical support devices				
Mechanical ventilator	146, 146	45 (31)	50 (34)	0.073
Renal replacement therapy	146, 146	40 (27)	33 (23)	0.111
Discharge prescription‡				
β-blocker	136, 120	54 (40)	34 (28)	0.242
ACEI or ARB	136, 120	107 (79)	2 (1.7)	2.538

Values are presented as median (interquartile range) or n (%). Abbreviations as in Table 1. *CPA is defined as loss of spontaneous respiration, loss of carotid artery pulse or asystole, VF, pulseless ventricular tachycardia, or pulseless electrical activity on ECG monitoring. †Elevated troponin is defined as ≥0.02 ng/mL or qualitative test positive of troponin T or troponin I. ‡Data for in-hospital mortality are excluded.

(AV) block and ventricular tachycardia (VT)/ventricular fibrillation (VF) on the first day of admission; laboratory findings at admission such as white blood cells, hemoglobin, albumin, and estimated glomerular filtration rate (eGFR); electrocardiogram (ECG) findings at admission such as rhythm (sinus or not) and ST elevation (with/without); echocardiography LVEF at admission; administrations of β-blocker and mineralocorticoid receptor antagonist during hospitalization; temporary use of MCS devices such as IABP, VA-ECMO, and ventricular assist device (VAD); and the use of invasive mechanical support devices such as mechanical ventilator and renal replacement therapy (RRT). Among these matching variables, older age, non-sinus rhythm, admission LVEF <40%, and VT or VF on the first day were identified as factors associated with 90-day mortality or HTx in patients with FMP in our previous report.[8] We used 1-to-1 and nearest-neighbor methods with a caliper set at 0.2 of the standard deviation of the logit of the propensity score. Standardized differences were calculated to compare the differences in patient characteristics between the matched groups.

We performed Cox regression analysis to determine the association of ACEI/ARB and β-blocker administration during hospitalization with the 90-day mortality or HTx in the entire cohort. In this model, the following confounders were used with the forced entry method: age; female sex; SBP <90 mmHg or CPA on admission; non-sinus rhythm and QRS duration >120 ms on admission ECG; echocardiography LVEF <40% at admission; eGFR on admission; occurrence of advanced AV block and sustained VT or VF during hospitalization; MCS use, including IABP, VA-ECMO, and VAD; use of mechanical ventilator; and implementation of RRT. A Cox proportional hazards model was also used for evaluation of the post-discharge prognosis, and covariates including age, sex, eGFR at discharge, sustained VT or VF during hospitalization, and use of VA-ECMO were selected according to statistical significance in a univariate analysis.

All statistical tests were 2-sided, and a P value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS (version 25; IBM Corp., Armonk, NY, USA).

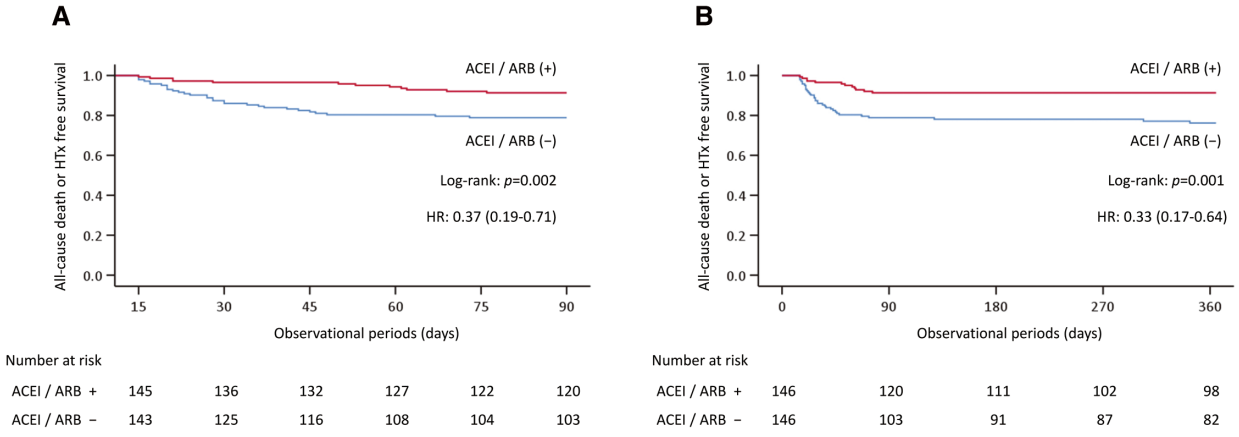

Figure 3. Cumulative event-free survival in the matched cohort. A matched cohort of 146 pairs is generated using propensity score matching between the 2 groups of patients with or without ACEI/ARB administration during hospitalization. These groups were compared based on the cumulative event (all-cause death or HTx)-free survival at (**A**) 90 days and (**B**) 360 days using Kaplan-Meier method with log-rank test. Hazard ratios (HR) and 95% confidence intervals for the risk of outcome are determined using univariate analysis with Cox proportional hazards modeling. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; HTx, heart transplantation.

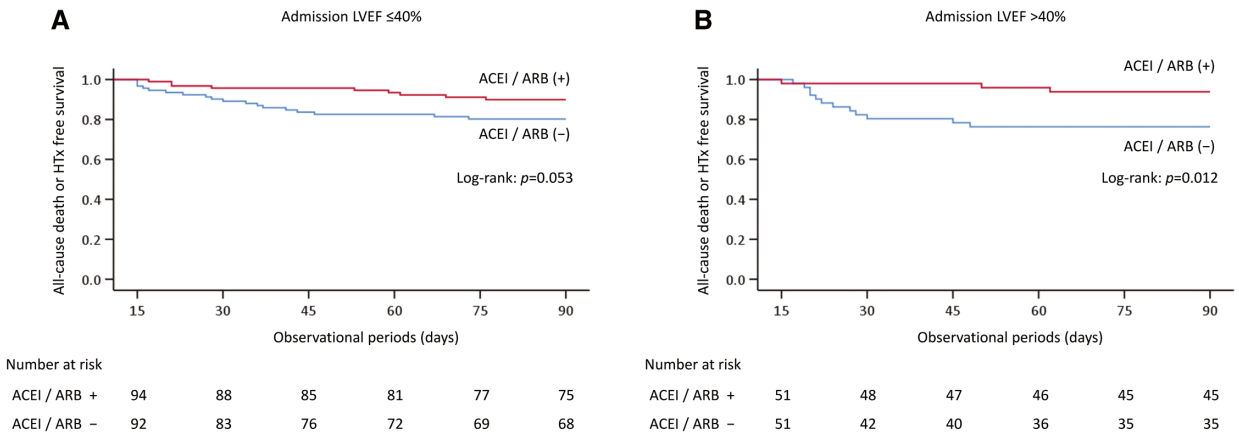

Figure 4. Cumulative event-free survival in the subgroups in the matched cohort. Patients in the matched cohort of the 2 groups of patients with or without ACEI/ARB administration during hospitalization were divided into 2 subgroups by (**A**) admission LVEF ≤40% and (**B**) admission LVEF >40%. These groups were compared based on the cumulative event (all-cause death or HTx)-free survival at 90 days using Kaplan-Meier method with log-rank test in each subgroup. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; HTx, heart transplantation.

Results

Ninety-Day Mortality or HTx With or Without ACEI/ARB and β-Blocker in the Entire Cohort

The characteristics of patients in the 4 groups are shown in **Table 1**. The 90-day mortality and HTx in the 4 groups were compared using the log-rank test. With patients receiving neither ACEI/ARB nor β-blocker as a reference, the administration of ACEI/ARB was associated with better outcomes regardless of the co-administration status of a β-blocker (log-rank test: ACEI/ARB + and β-blocker −, P<0.001; ACEI/ARB + and β-blocker +, P<0.001; ACEI/ARB − and β-blocker +, P=0.256; **Figure 2**). Multivariable analysis with Cox regression modeling using the data of the entire cohort demonstrated that administration of ACEI or ARB during hospitalization independently reduced the risk of 90-day mortality or HTx after adjusting for confounders (adjusted hazard ratio [HR] 0.41; 95% confidence interval [CI] 0.22–0.75; P=0.004) and had a greater impact on outcomes than β-blockers (adjusted HR 0.47; 95% CI 0.27–0.83; P=0.009).

Mortality or HTx With or Without ACEI/ARB in the Matched Cohort

After dividing the 588 patients into 2 groups according to the administration status of ACEI/ARB during hospital-

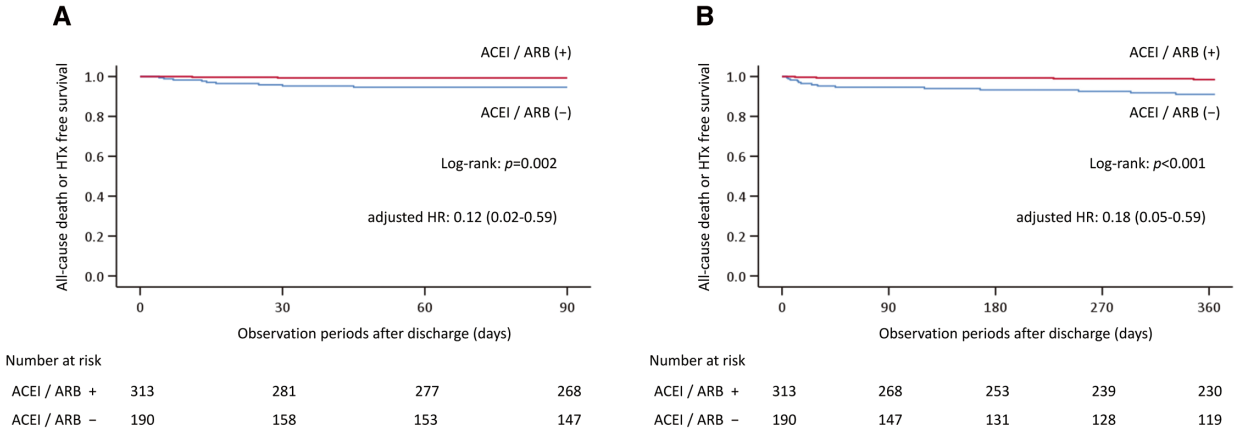

Figure 5. Cumulative event-free survival after discharge in the entire cohort. Patients who were discharged alive from the entire cohort were divided into 2 groups according to the administration of ACEI/ARB during hospitalization and were followed up starting from the day of discharge. The cumulative event (all-cause death or HTx)-free survival at (**A**) 90 days and (**B**) 365 days was compared between groups using the Kaplan-Meier method with the log-rank test. Hazard ratios (HR) and 95% confidence intervals for the risk of outcome were determined using multivariate analysis with Cox proportional hazards modeling, and covariates including age, sex, estimated glomerular filtration rate at discharge, sustained ventricular tachycardia or ventricular fibrillation during hospitalization, and use of veno-arterial extracorporeal membrane oxygenation were selected through a univariate analysis. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; HTx, heart transplantation.

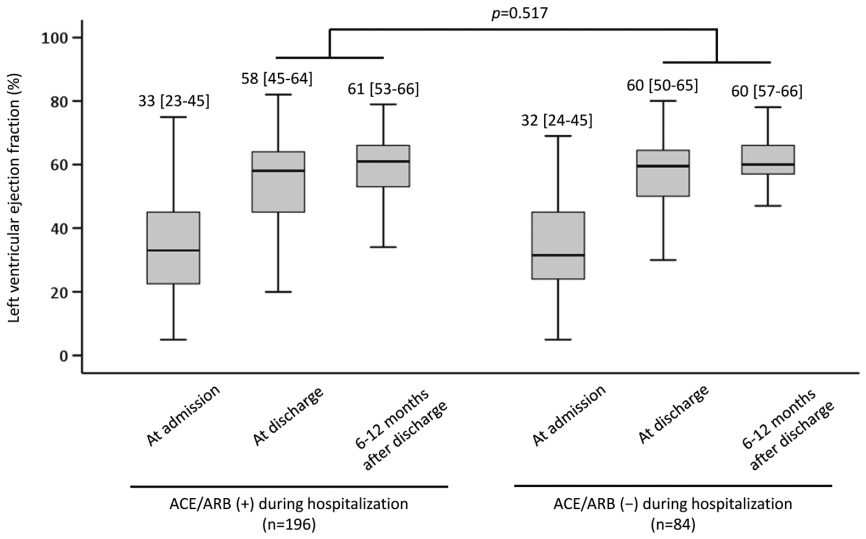

Figure 6. Changes in echocardiography left ventricular ejection fraction (LVEF) over the clinical course of the entire cohort. Among the patients who were followed for 6–12 months after discharge, those who received ACEI or ARB during hospitalization and those who did not were assessed for changes in the echocardiography LVEF at admission, discharge, and 6–12 months after discharge. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

ization, a matched cohort of 146 pairs was created with a C-statistic of 0.781 and a caliper of 0.049. Of the 146 patients in the ACEI/ARB administration group, 128 (88%) and 28 (19%) were administered ACEI and ARB, respectively. Characteristics of patients in the 2 groups in the matched cohort are shown in **Table 2**.

During the 90-day follow up, 12 primary outcomes (all-cause death 12; HTx 0) occurred in the matched ACEI/ARB administration group and 30 (all-cause death 30; HTx 0) in the matched non-administration groups. The cumulative event (all-cause death or HTx)-free survival at 90 days in the ACEI/ARB administration group was higher than that in the non-administration groups (log-rank test P=0.002; HR 0.37; 95% CI 0.19–0.71; **Figure 3A**). When the observational period was extended to 1 year, the ACEI/ARB administration group also had higher cumulative event-free survival than the non-administration groups (log-rank test P=0.001; HR 0.33; 95% CI 0.17–0.64; **Figure 3B**).

Furthermore, we classified the patients in the matched cohort into 2 subgroups based on the LVEF at admission (LVEF ≤40% [n=188] and LVEF >40% [n=104]) and evaluated the cumulative event-free survival. Only in the subgroup with LVEF >40% was the cumulative event-free survival in the ACEI/ARB administration group signifi-

cantly higher than that in the non-administration groups (log-rank P=0.003; **Figure 4**).

In-Hospital Outcomes

The in-hospital mortality in the ACEI/ARB administration group was lower than that in the non-administration group in the matched cohort (6.8% vs. 18%, respectively; P=0.007; **Supplementary Table 1**). After excluding the in-hospital mortality cases from the matched cohort, we evaluated the in-hospital outcomes (**Supplementary Table 1**). The length of hospital stay was significantly longer in the ACEI/ARB administration group than in the non-administration group (28 [18–47] vs. 22 [15–42] days, respectively; P=0.017). No difference was observed in the duration of temporary MCS use in either IABP or VA-ECMO between the groups (IABP 5 [4–8] vs. 5 [3–9] days, respectively; P=0.824; VA-ECMO 1 [1–3] vs. 1 [1–2] days, respectively; P=0.683). There was no difference in the echocardiography LVEF at discharge between the groups (58% [47–65] vs. 60% [49–64], respectively; P=0.643).

Post-Discharge Analysis

From the entire cohort, patients who were discharged alive were divided into 2 groups according to the administration of ACEI/ARB during hospitalization (ACEI/ARB administration group [n=313] and ACEI/ARB non-administration group [n=190]) and were followed up starting from the day of discharge. Medication rates for ACEI or ARB during the clinical course in the 2 groups are shown in **Supplementary Table 2**. During the 90-day follow up, the primary outcome was achieved for 2 (all-cause death 2; HTx 0) patients in the ACEI/ARB administration group and 9 (all-cause death 9; HTx 0) patients in the non-administration group. The cumulative event (all-cause death or HTx)-free survival at 90 days was higher in the ACEI/ARB administration group than in the non-administration group (log-rank test P=0.002; adjusted HR 0.12; 95% CI 0.02–0.59; **Figure 5A**). When the observational period was extended to 1 year, the primary outcome was achieved for 4 (all-cause death 4; HTx 0) patients in the ACEI/ARB administration group and 14 (all-cause death 14; HTx 0) patients in the non-administration group. The ACEI/ARB administration group also showed a higher cumulative event-free survival rate than the non-administration group (log-rank test P<0.001; adjusted HR 0.18; 95% CI 0.05–0.59; **Figure 5B**).

Among the patients who were followed for 6–12 months after discharge, those who received ACEI or ARB during hospitalization (n=196) and those who did not (n=84) were assessed for changes in the echocardiography LVEF at discharge and 6–12 months after discharge. Although the LVEF in both groups was maintained at 6–12 months after discharge without a statistically significant between-group difference (P=0.517; **Figure 6**), the LVEF for 5.7% (14 of 196 in the ACEI/ARB administration during hospitalization group and 2 of 84 in the ACEI/ARB non-administration during hospitalization group) of patients with FMP showed a decrease of ≥10% at 6–12 months after discharge.

Discussion

In this multicenter cohort study that included patients from 235 cardiovascular hospitals across Japan, we demonstrated that cardioprotective ACEI or ARB administration was associated with favorable outcomes in terms of 90-day mortality or HTx in patients with clinically diagnosed FMP. Interventions targeted at hemodynamic compromise and depressed myocardial function are crucial in the acute phase of FMP.[12] Indications for MCS, especially VA-ECMO, and administration of inotropes are established strategies for hemodynamically compromised patients with FMP, although these strategies cannot treat myocarditis. However, there is no clinical evidence that supports the cardioprotective effects of RAS inhibitors or β-blockers in acute myocarditis.[4] During the acute phase of FMP, inflammation and cellular damage occur in the myocardium resulting in cardiac dysfunction.[12] Both ACEI and ARB reportedly prevented inflammation and myocardial damage in animal models of myocarditis,[13,14] possibly because of a reduction in angiotensin II-mediated inflammatory processes.[15] Moreover, an animal experimental model demonstrated that early ACEI administration led to a significant inflammatory reduction in myocarditis.[16] Our results recommend the administration of ACEI or ARB during hospitalization in patients with FMP; however, the ideal time for initiating the treatment remains unclear.

In the present study, we clinically diagnosed FMP. In our previous report, using the same database from the JRFM, we analyzed the patients with histologically proven FMP and showed that the severity of histological damage was associated with a worse 90-day prognosis in patients with lymphocytic myocarditis.[8] Endomyocardial biopsy provides a definitive diagnosis of myocarditis, determines the treatment strategy, and contributes to the estimation of prognosis.[3] However, this is not feasible in some patients because of the lack of an appropriate environment and operators for this procedure. In these cases, the diagnosis of acute myocarditis can be clinically performed based on the symptoms, clinical signs, a course suggestive of acute myocarditis, and other examinations.[1,3,9] In the clinical setting, the treatment strategies for heart failure and cardiogenic shock in acute myocarditis are consistent, regardless of the histological type. Therefore, we extended the definition of FMP in the present study from histologically proven cases to clinically diagnosed cases.

Administration of ACEI or ARB during hospitalization was shown in the present study to be effective in patients with FMP whose LVEF was preserved (>40%) at the time of admission. Because FMP is generally characterized as acute pump failure,[10] patients with preserved LVEF on admission are considered to have preserved LVEF at the early stage of onset and declined LVEF subsequently after admission. Moreover, it is unclear whether LVEF in patients with FMP was preserved or reduced when ACEI or ARB was administered. Thus, our results do not indicate the effectiveness of ACEI or ARB only in patients with FMP whose LVEF is preserved. Furthermore, it is unclear why ACEI or ARB was effective in patients with the clinical course of decreased LVEF after admission. In contrast, ACEI or ARB was not effective in patients with FMP whose LVEF was reduced (≤40%) at the time of admission in the present study. This might be attributed to the fact that reduced LVEF from the early stage of onset in FMP increases the risk of hemodynamic deterioration due to the drugs and is associated with various cardiovascular events with or without ACEI or ARB.

In cases where LVEF is preserved in the early stages of FMP onset, it is unclear whether the early administration of cardioprotective drugs contributes to the prevention of worsening cardiac function.[3,17] In contrast, our results indicated that those patients whose admission LVEF was

preserved were the candidates for ACEI or ARB administration. In both groups, the LVEF recovered during hospitalization and was maintained after discharge. However, more than 5% of patients showed a 10% or more decrease in LVEF 6–12 months after discharge. Persistent inflammation can cause chronic active myocarditis, which in turn leads to LV dysfunction. Heart failure relapse occurred in 40% of the cases in which LVEF showed improvements when pharmacological treatment was withdrawn in the patients with dilated cardiomyopathy.[18] Regardless of the LVEF status at discharge, it is important to monitor the cardiac condition in patients with FMP even after discharge and consider continuing ACEI/ARB therapy.

Study Limitations

This study has several limitations. First, this was a retrospective cohort study, and the time point at which the introduction of cardioprotective drugs was considered varied among the patients. Furthermore, the administration of cardioprotective drugs may have been avoided in the patients who had a poor prognosis, although we excluded those who died within 14 days of hospital admission. Thus, the reverse causality between ACEI/ARB administration and improved prognosis in patients with FMP might have affected the results of this study. Second, unmeasured confounders might have affected the results. The clinical profiles of the patients treated with and without cardioprotective drugs showed a considerable difference. To minimize potential selection bias due to cardioprotective drug use, we applied propensity score matching after classifying patients into 2 groups according to ACEI or ARB administration during hospitalization. However, some variables, such as lactate level at admission, presence of pericardial effusion, frequency of coronary artery stenosis, and histological diagnosis, were not adequately matched between the 2 groups. To address these challenges, randomized controlled trials that investigate the impact of cardioprotective drugs on clinical outcomes are warranted. Third, several types of medications have cardioprotective effects, and the association of these medications with the prognosis was not determined in this study. Furthermore, the overall effect of all cardioprotective drugs, including ACEI/ARB and β-blocker, on the outcome was not analyzed in order to prioritize evaluation of the effect of individual drugs. Fourth, we extended the observation period for patients with FMP to 1 year. Landmark analysis of the time point set at 90 days is considered necessary to evaluate the remote effect (>90 days). However, the incidence of outcomes in the chronic phase (later than 90 days) was very low to permit comparisons between the 2 groups. Thus, our results did not show that ACEI/ARB administration had a positive effect on the remote prognosis; however, it showed that a favorable association of ACEI/ARB administration with the prognosis was maintained after 90 days.

Conclusions

The administration of ACEI or ARB during hospitalization was associated with a lower incidence of 90-day mortality and HTx in patients with clinically diagnosed FMP. Although it is still unclear at what time point these drugs should be administered initially, our results recommend the administration of ACEI or ARB during hospitalization in patients with FMP.

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Disclosures

The authors declare that they no conflicts of interest.

IRB Information

The study protocol was approved by the Ethics Committee of Nara Medical University (registration no. 2256), Japanese Circulation Society (registration no. 10), and Nippon Medical School (registration no. B-2020-224).

Data Availability

The deidentified participant data will not be shared.

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Supplementary Files

Please find supplementary file(s);
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