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Rhythm-control therapy for new-onset atrial fibrillation in critically ill patients: A post hoc analysis from the prospective multicenter observational AFTER-ICU study

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ABSTRACT

Background: Sustained new-onset atrial fibrillation (AF) in the intensive care unit has been reported to be associated with poor outcomes. However, in critical illness, whether rhythm-control therapy can achieve sinus rhythm (SR) restoration is unknown. This study aimed to assess the impact of rhythm-control therapy on SR restoration for new-onset AF in critically ill patients.
Methods: This post-hoc analysis of a prospective multicenter observational study involving 32 Japan intensive care units compared patients with and without rhythm-control therapy for new-onset atrial fibrillation (AF) and conducted a multivariable analysis using Cox proportional hazards regression analysis including rhythm-control therapy as a time-varying covariate for SR restoration.
Results: Of 423 new-onset AF patients, 178 patients (42%) underwent rhythm-control therapy. Among those patients, 131 (31%) underwent rhythm-control therapy within 6 h after AF onset. Magnesium sulphate was the most frequently used rhythm-control drug. The Cox proportional hazards model for SR restoration showed that rhythm-control therapy had a significant positive association with SR restoration (adjusted hazard ratio: 1.46; 95% confidence interval: 1.16–1.85). However, the rhythm-control group had numerically higher hospital mortality than the non-rhythm-control group (31% vs. 23%, p = 0.09).
Conclusions: Rhythm-control therapy for new-onset AF in critically ill patients was associated with SR restoration. However, patients with rhythm-control therapy had poorer prognosis, possibly due to selection bias. These findings may provide important insight for the design and feasibility of interventional studies assessing rhythm-control therapy in new-onset AF.

1. Introduction

New-onset atrial fibrillation (AF) is a common arrythmia in the intensive care unit (ICU) setting [1,2], and may lead to the deterioration of vital signs [3], which has been reported to be associated with longer length of hospital stay, higher incidence of stroke, and greater mortality [4–11]. There are two general approaches to managing AF: rate-control and rhythm-control with pharmacologic interventions, direct-current cardioversion (DC), or both [12]. For general ward settings and postcardiac surgery, interventional studies assessing rhythm-control therapy may not result in any clinical benefit [13,14]. There is no established strategy for managing AF in critical illness because of the lack of clinical research with high quality of evidence [15–18].

Rhythm-control therapy is aimed at shortening the AF duration. However, whether rhythm-control therapy can achieve restoration of the sinus rhythm (SR) in critical illness is unknown. Although a few randomized control trials (RCTs) of pharmacologic interventions were performed in the 1990 s [19–21], they enrolled <50 patients, and their quality of evidence was low because of imprecision and risk of bias [11,15,16]. In observational studies, the

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reported conversion rates were varied [15–18]. For instance, rates with amiodarone administration ranged from 30 to 95%, possibly due to varying dosing regimens, timing of outcome assessment, and definitions of restoration to SR [11,15,22]. New-onset AF was also reported to recur during the ICU stay in about half of patients with initial successful conversion to SR, despite amiodarone use [23]. Furthermore, because new-onset AF often restores to SR spontaneously [24–27], the true effect of rhythm-control therapy on SR restoration is difficult to evaluate. If rhythm-control therapy for AF in critically ill patients has no effect on maintaining SR, we cannot design interventional studies for rhythm-control therapy for AF.

A previous multicenter study reported that sustained new-onset AF was time-dependently associated with hospital mortality [10]. Herein, we aimed to perform a sub-analysis of the previous study in order to assess the impact of rhythm-control therapy for new-onset AF on SR restoration in critically ill patients.

2. Methods

2.1. Study design and setting

This study is a post hoc analysis of the AFTER-ICU study, a prospective observational study that included 423 new-onset AF patients in 32 Japan ICUs [10,28]. Patients admitted to the ICU between April 1, 2017, and March 31, 2018, were enrolled. We followed up all study patients until hospital discharge.

This study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology statement [29]. The original study on which this post-hoc study was based was registered at UMIN-CTR (UMIN000026401), and the original study protocol was approved by the Jikei University Institutional Review Board (approval no. 28–200[8443]) and the ethics committees of all other participating hospitals, with an opt-out policy from the patient or proxy.

2.2. Participants

We enrolled patients who developed new-onset AF during their ICU stay. The exclusion criteria were: age < 18 years; history of AF; discharged from the ICU within 24 h after ICU admission; admission to the ICU after cardiac surgery or cardiac arrest; equipped with a pacemaker at AF onset; withheld or withdrew medical therapy at AF onset; declined enrolment in this study. AF was defined as an arrhythmia with irregular R-R intervals without apparent P waves or with F waves that persisted > 5 min or with recurrent episodes within 5 min, as confirmed by 12-lead electrocardiograms or continuous 3-lead electrocardiograms [3,6,14,16,22,30]. Physicians (intensivists or cardiologists) in the participating hospitals made the diagnoses of new-onset AF. Among the various definitions of new-onset AF in critically ill patients reported in previous studies, ranging from 30 s to 1 h [3,6,14,16,22,30], we defined AF lasting longer than 5 min as new-onset AF, which seemed practically sufficiently long to prospectively detect new-onset AF.

2.3. Variables and measurement

To assess the impact of rhythm-control therapy on SR restoration, we compared patients with rhythm-control therapy to those without. We obtained the following information from the AFTER-ICU study: patient demographics, physiological data, and drugs used at AF onset. We also obtained the following information within 7 days after initial AF onset or during the ICU stay, whichever was shorter: timing of DC, drugs used for new-onset AF, adverse events (AEs) (bleeding events or cardiac arrhythmia other than AF), and timing of cardiac rhythm transition. The rhythm-control drugs for new-onset AF were magnesium sulphate, amiodarone, pilsicainide, aprindine, cibenzoline, adenosine triphosphate, disopyramide, flecainide, bepridil, and lidocaine. The rate-control drugs administered were beta-blocking agents (landiolol, bisoprolol, propranolol, and carvedilol), calcium-channel blockers (diltiazem and verapamil), and digoxin. We also defined the use of rhythm-control drugs and/or undergoing DC as rhythm-control therapy.

2.4. Outcomes

Our primary outcome was the last SR restoration within 7 days after the initial AF onset or during the ICU stay, whichever was shorter. SR restoration was defined as sustained SR for > 24 h after the conversion from AF to SR. If the patients were discharged from ICU with SR within 24 h after the conversion of cardiac rhythm from AF to SR, they were also defined as having SR restoration. The secondary outcomes were the patients' cardiac rhythm at ICU discharge, AF duration, ICU length of stay, hospital length of stay, AEs, ICU mortality, hospital mortality, and in-hospital stroke. In-hospital stroke was defined as symptomatic cerebral infarction diagnosed by a neurologist or a neurosurgeon or determined via new computed tomography or magnetic resonance imaging findings [14]. The definitions of the other collected variables are detailed in Table S1.

2.5. Statistical analysis

The study results are presented as median and interquartile range or as absolute numbers with percentage, as appropriate. In all analyses, the number of missing data was reported, and cases with missing data were excluded from each analysis. Comparisons between the two groups were conducted using the chi-square test or Fisher's exact test for categorical variables and the Mann-Whitney *U* test for continuous variables. A p-value < 0.05 was considered statistically significant.

To assess the association between rhythm-control therapy and SR restoration, we modelled the time from AF onset to SR restoration using Cox proportional hazards regression. Patients who were later initiated on rhythm-control therapy might have longer time until SR restoration. To address time-related bias, we used the rhythm-control therapy as a time-varying covariate in this model. The following variables were included in this model according to their clinical relevance and importance in previous studies [3–5,8,9,11,18,31,32]: age, history of congestive heart failure (CHF), patient category (non-scheduled surgical, scheduled surgical, and medical), Acute Physiology and Chronic Health Evaluation (APACHE) II scores [33] at ICU admission, infection at AF onset, renal replacement therapy at AF onset, mechanical ventilation at AF onset, administration of drugs (any vasopressors, inotropes, and dexmedetomidine) at AF onset, heart rate (HR) at AF onset, and the laboratory data (potassium and white blood cells [WBC]) before AF onset. To account for the nonlinear effects of age, HR at AF onset, potassium, and WBC on outcomes, the penalized smoothing spline function was incorporated into the Cox proportional hazards model. Patients who were discharged from the ICU or died with remaining AF within 7 days after AF onset were censored because we could not measure their duration until SR restoration. The Cox proportional hazards regression analyses were performed using R version 3.5.1 (The R Foundation for Statistical Computing, Vienna, Austria). All other analyses were performed using Stata version 16 (StataCorp, College Station, TX, USA).

2.6. Sensitivity analysis

Although DC is a rhythm-control therapy, undergoing DC does not result in sustained SR, which is different from the pharmacologic interventions. In addition, magnesium sulphate has not been classified as an antiarrhythmic drug. Therefore, we performed a sensitivity analysis using Cox proportional hazards regression of rhythm-control therapy without DC and magnesium sulphate.

3. Results

3.1. Study population and timing of rhythm-control therapy

In total, 423 patients with new-onset AF were enrolled in the AFTER-ICU study, of these 178 (42%) were treated with the rhythm-control therapy for new-onset AF. The initial timing of rhythm-control therapy during 7 days after AF onset is shown in Fig. 1. Among patients with the rhythm-control therapy, 151 patients (36%) underwent rhythm-control therapy within 24 h after AF onset and 131 patients (31%) within 6 h after AF onset.

3.2. Patients characteristics

The patients' demographic and clinical characteristics are shown in Table 1. Laboratory data are shown in Table S2. Almost two-thirds of the study patients were medical patients and had infection at AF onset. Patients in the rhythm-control group were younger than those in the non-rhythm-control group. The APACHE II score and the proportion of patients who required mechanical ventilation at AF onset were greater in the rhythm-control group than in the non-rhythm-control group. The proportion of those with histories of CHF and ischemic heart disease did not present characteristics with statistically significant differences.

3.3. Physiological data around AF onset

The physiological data before and at AF onset are shown in Table 2. At AF onset, although there was no difference in the mean arterial pressure at AF onset between two groups, the rhythm-control group had higher HR and used vasopressors and inotropes more frequently than the non-rhythm-control group.

3.4. Details of interventions for new-onset AF and outcomes

Interventions for new-onset AF and outcomes are shown in Table 3. The combinations of the interventions for each patient in the rhythm-control group are shown in Fig. S1. Among the patients who had undergone DC for new-onset AF, 37 patients (57%) received rhythm-control drugs. There were a few patients who only used a single drug, and magnesium sulphate was the most frequently used rhythm-control drug. Regarding the rate-control drugs, beta-blocking agents were used more frequently in the rhythm-control group than in the non-rhythm-control group. Although the rhythm-control group had longer AF duration than the non-rhythm-control group, the proportion of patients who with AF at ICU discharge in the rhythm-control group was significantly lower than that in the non-rhythm-control group. Meanwhile, the length of hospital stay, hospital mortality, and frequency of AEs in the rhythm-control group were higher than those in the non-rhythm-control group.

3.5. Impact of rhythm-control on therapy on sinus rhythm restoration

The results of the Cox models for SR restoration after adjustment for the prespecified confounding factors are shown in Table 4 and Fig. S2. Among all covariates included in this model, only rhythm-control therapy had a significant positive association with SR restoration.

3.6. Sensitivity analyses

The sensitivity analyses are shown in Table S3, Table S4, Fig. S3, and Fig. S4. The results of these analyses were similar to those of the main analysis.

4. Discussion

4.1. Key findings

This post-hoc analysis of a prospective multicenter observational study assessed the impact of rhythm-control therapy on SR restoration in critically ill patients. Among 423 new-onset AF patients, 178 patients (42%) were treated with rhythm-control

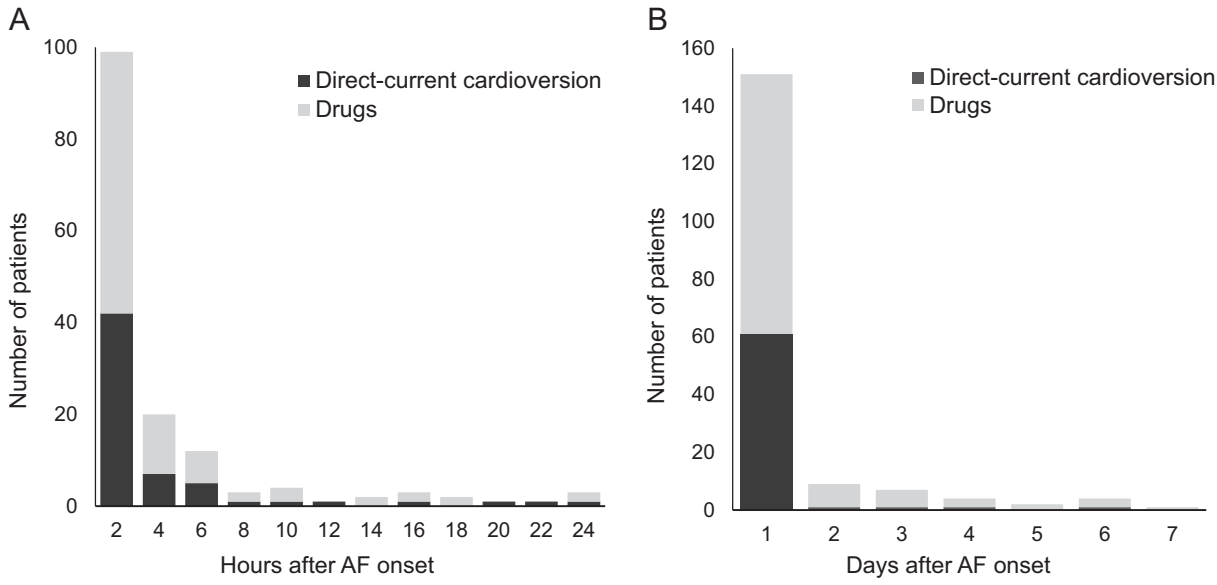

Fig. 1. Timing of rhythm-control therapy initiated for new-onset atrial fibrillation (AF) (A) within 24 h and (B) within 7 days after AF onset.

Table 1
Comparison of demographic and clinical characteristics: Non-rhythm-control vs. Rhythm-control.

	Non-rhythm-control (n = 245)	Rhythm-control (n = 178)	p value
Age, years	75 (67–82)	73 (66–80)	0.02
Male sex, n (%)	162 (66.1)	124 (69.7)	0.46
Body mass index, kg/m^2 [a]	23 (20–25)	22 (19–25)	0.56
Hypertension, n (%)	130 (53.1)	69 (38.8)	0.004
Diabetes, n (%)	60 (24.5)	52 (29.2)	0.32
Congestive heart failure, n (%)	25 (10.2)	18 (10.1)	1.00
Ischemic heart disease, n (%)	20 (8.2)	23 (12.9)	0.14
Prior stroke or TIA, n (%)	28 (11.4)	17 (9.6)	0.63
CHADS2 score	1 (1–2)	1 (0–2)	0.07
Chronic hemodialysis, n (%)	10 (4.1)	14 (7.9)	0.13
Previous medication			
Calcium-channel blockers, n (%)	100 (40.8)	41 (23.0)	<0.001
β-blocking agents, n (%)	36 (14.7)	20 (11.2)	0.31
ACE inhibitors, n (%)	15 (6.1)	7 (3.9)	0.38
ARBs, n (%)	54 (22.0)	35 (19.7)	0.63
Antidiabetic agents, n (%)	57 (23.3)	40 (22.5)	0.91
Anticoagulants, n (%)	17 (6.9)	14 (7.9)	0.71
Antiarrhythmic drugs, n (%)	4 (1.6)	1 (0.6)	0.40
Patient category			
Non-scheduled surgical, n (%)	61 (24.9)	34 (19.1)	
Scheduled surgical, n (%)	36 (14.7)	25 (14.0)	0.27
Medical, n (%)	148 (60.4)	119 (66.9)	
APACHE II score at ICU admission	23 (16–28)	25 (20–30)	0.002
SOFA at AF onset [b]	7 (4–10)	7 (5–11)	0.09
Infection at AF onset, n (%)	163 (66.5)	132 (74.2)	0.11
MV at AF onset, n (%)	134 (54.7)	121 (68.0)	0.007
RRT at AF onset, n (%)	54 (22.0)	50 (28.1)	0.17

AF: atrial fibrillation, TIA: transient ischemic attack, CHADS2: one point: recent congestive heart failure, hypertension, age older than 75 years, diabetes mellitus; two points: transient ischemic attack or a prior stroke, ACE: angiotensin converting enzyme, ARBs: angiotensin II receptor blockers, APACHE II: Acute Physiology and Chronic Health Evaluation II, SOFA: Sequential Organ Failure Assessment, MV: mechanical ventilation, RRT: renal replacement therapy.
[a] One missing data.
[b] Eleven missing data.

Table 2
Physiological data and interventions: Non-rhythm-control vs. Rhythm-control.

	Non-rhythm-control (n = 245)	Rhythm-control (n = 178)	P-value
Physiological data before AF onset			
Heart rate, per minute	95 (84–106)	96 (82–107)	0.61
Mean arterial pressure, mmHg	80 (71–94)	81 (70–91)	0.61
Physiological data at AF onset			
Heart rate, per minute	125 (105–143)	136 (120–155)	<0.001
Mean arterial pressure, mmHg	77 (65–91)	74 (63–88)	0.11
Drugs at AF onset			
Vasopressors, n (%)[a]	99 (40.4)	93 (52.2)	0.02
Inotropes, n (%)[b]	22 (9.0)	30 (16.9)	0.02
Anticoagulants, n (%)[c]	54 (22.0)	29 (16.3)	0.17
Dexmedetomidine, n (%)	42 (17.1)	42 (23.6)	0.11
Propofol, n (%)	41 (16.7)	46 (25.8)	0.03
Midazolam, n (%)	27 (11.0)	20 (11.2)	1.00
Diltiazem, n (%)	3 (1.2)	1 (0.6)	0.64
β-blocking agents, n (%)	11 (4.5)	23 (12.9)	0.002
Amiodarone, n (%)	1 (0.4)	2 (1.1)	0.58

AF: atrial fibrillation, DC: direct current cardioversion, ICU: intensive care unit.
[a] Noradrenaline, adrenaline, dopamine, and vasopressin.
[b] Dobutamine and PDE inhibitors.
[c] Heparin subcutaneous injection, heparin intravenous injection, warfarin, and direct oral anticoagulants

therapy. Patients in the rhythm-control group had higher APACHE II score and more frequently required mechanical ventilation, vasopressors, and inotropes at AF onset than those in the non-rhythm-control group. ICU and hospital mortality in the rhythm-control group were also greater than those in the non-rhythm-control group. Among the rhythm-control drugs, many of which were administered within 6 h after AF onset, magnesium sulphate was the most frequently used. Although the total AF duration in the rhythm-control group was longer than that in the non-rhythm-control group, the patients in the rhythm-control group remained in AF at ICU discharge less frequently than those in the non-rhythm-control group. Moreover, the multivariable Cox regression analysis that included the rhythm-control therapy as a time-varying covariate confirmed the association between rhythm-control therapy and SR restoration.

4.2. Relationship with previous studies

For an interventional study to assess whether rhythm-control therapy can improve patient outcomes, we need the premise that rhythm-control therapy is effective for SR restoration. In critically ill patients, the efficacy of magnesium sulphate and amiodarone has been evaluated for new-onset AF in a few interventional studies conducted in the 2000 s [15,16,21,34]. For example, a single-center RCT with 60 AF patients compared the efficacy of amiodarone with that of diltiazem [34]. They reported that amiodarone tended to be more effective than diltiazem for SR restoration at 4 h after AF onset (42.5% vs. 30%, p = 0.34). Another single-center RCT with 42 AF patients without hemodynamic instability reported that sulphate magnesium was better than amiodarone for SR restoration at 24 h after AF onset (78% vs. 50%) [21]. Moreover, a prospective single-arm study reported that the combination of amiodarone and magnesium sulphate might have a high probability of SR restoration (90% at 24 h after AF onset) [22]. Consistent with these previous studies, we found that rhythm-control therapy, including magnesium sulphate and amiodarone, was associated with SR restoration. Our current analysis considered the duration until the last SR restoration from all AFs (including recurrent AF) within 7 days after AF onset. Moreover, among variables included in the multivariable regression analysis, only rhythm-control therapy showed a significant positive impact on SR restoration. Therefore, our study highlighted the importance of rhythm-control therapy for SR restoration from new-onset AF in critically ill patients.

Previous observational studies for rhythm-control therapy had methodological problems in their evaluation of rhythm-control therapy, especially for observation time points of cardiac rhythms (mainly at 24 h) [15–18]. Such specific observation time points cannot consider the time-varying nature of rhythm-control therapy, often called "immortal bias" [35,36]. Because rhythm-control therapy is generally initiated for sustained AF, patients receiving rhythm-control therapy may have longer AF duration and lower chance of SR restoration at a specific time point than those without rhythm-control. In fact, in our study, although the rhythm-control group had a longer AF duration in the univariable analysis, the multivariable analysis, which used rhythm-control therapy as a time-varying covariate, showed the significant impact of the therapy on SR restoration. This statistical approach is less

Table 3
Interventions and outcomes: Non-rhythm-control vs. Rhythm-control.

	Non-rhythm-control (n = 245)	Rhythm-control (n = 178)	P-value
Timing of rhythm-control, hours		1.5 (0.4–6.7)	–
Direct-current cardioversion, n (%)	–	65 (36.9)	–
Pharmacological intervention, n (%)			
Rhythm-control drugs, n (%)	–	150 (84.3)	–
Magnesium sulphate, n (%)	–	76 (42.7)	–
Amiodarone, n (%)	–	50 (28.1)	–
Pilsicainide, n (%)	–	42 (23.6)	–
Others, n (%)[a]	–	35 (19.7)	–
Rate-control drugs, n (%)	150 (61.2)	132 (74.2)	0.007
Beta blocking agents, n (%)	98 (40.0)	105 (59.0)	<0.001
Landiolol, n (%)	80 (32.7)	92 (51.7)	<0.001
Bisoprolol, n (%)	35 (14.3)	35 (19.7)	0.15
Propranolol, n (%)	1 (0.4)	1 (0.6)	1.00
Carvedilol, n (%)	5 (2.0)	3 (1.7)	1.00
Calcium-channel blockers, n (%)	74 (30.2)	53 (29.8)	1.00
Diltiazem, n (%)	50 (20.4)	24 (13.5)	0.07
Verapamil, n (%)	26 (10.6)	32 (18.0)	0.03
Digoxin, n (%)	5 (2.0)	9 (5.1)	0.10
Anticoagulants, n (%)	102 (41.6)	71 (39.9)	0.76
Heparin injection			
intravenous, n (%)	74 (30.2)	50 (28.1)	0.67
subcutaneous, n (%)	28 (11.4)	14 (7.9)	0.25
DOAC, n (%)	7 (2.9)	13 (7.3)	0.04
Warfarin, n (%)	3 (1.2)	2 (1.1)	1.00
ICU length of stay[b], days	4.9 (2.0–9.3)	6.8 (3.4–13.0)	<0.001
Hospital length of stay[c], days	24.9 (11.9–46.2)	27.4 (14.2–54.7)	0.12
ICU mortality, n (%)	25 (10.2)	29 (16.3)	0.08
Hospital mortality, n (%)	57 (23.3)	55 (30.9)	0.09
Stroke after AF onset, n (%)	12 (4.9)	7 (4.0)	0.81
Days from AF to stroke, days	2.2 (1.4–7.5)	21.3 (1.3–31.8)	0.13
Initial AF duration[d], hours	13.9 (3.8–50.1)	14.8 (3.5–34.9)	0.42
Total AF duration[e], hours	16.0 (4.0–59.9)	23.9 (8.0–45.0)	0.29
AF at ICU discharge[f], n (%)	47 (21.4)	15 (10.1)	0.004
Adverse events			
Bleeding, n (%)	12 (4.9)	18 (10.1)	0.05
Arrhythmias other than AF, n (%)	3 (1.2)	10 (5.6)	0.02

ICU: intensive care unit, AF: atrial fibrillation.
[a] Other drugs are following drugs: aprindine, cibenzoline, adenosine triphosphate, disopyramide, flecainide, bepridil, lidocaine.
[b] Length from the initial AF onset to ICU discharge.
[c] Length from the initial AF onset to hospital discharge.
[d] AF duration from the initial onset to the initial sinus restoration or the end of observation period, whichever is shorter.
[e] Total AF duration within seven days after AF onset or during ICU stay, whichever is shorter.
[f] Patients who survived at ICU discharge

Table 4
Multivariable Cox proportional hazard analysis for sinus rhythm restoration.

	Adjusted hazard ratio (95% CI)	P-value
MV at AF onset	0.69 (0.53–0.89)	0.004
RRT at AF onset	0.82 (0.61–1.09)	0.17
Inotropes[a]	0.90 (0.63–1.26)	0.53
Congestive heart failure	0.93 (0.62–1.40)	0.73
Patient category		
Scheduled surgical	Ref.	–
Non-scheduled surgical	1.00 (0.67–1.48)	0.99
Medical	0.91 (0.62–1.32)	0.61
Infection at AF onset	0.95 (0.71–1.27)	0.72
APACHE II, point	1.01 (0.99–1.02)	0.38
Vasopressors at AF onset[b]	1.15 (0.90–1.47)	0.25
Dexmedetomidine	1.16 (0.88–1.54)	0.29
Rhythm-control therapy	**1.46 (1.16–1.85)**	**0.001**

Age, heart rate at AF onset, potassium, and white blood cells were also included in this model as non-linear variables (Fig.S2).
CI: confidence interval, AF: atrial fibrillation, MV: mechanical ventilation, RRT: renal replacement therapy, APACHE II: Acute Physiology and Chronic Health Evaluation II.
[a] Administering any of the following inotropes at AF onset: dobutamine and phosphodiesterase inhibitors
[b] Administering any of the following vasopressors at AF onset: noradrenaline, adrenaline, vasopressin, and dopamine.

common in critical care research [36]. These findings suggest the importance of appropriately treating time-varying covariates when conducting observational studies in the critical care setting.

4.3. Significance and implications

Despite the lack of evidence, rhythm-control therapy for AF has been generally indicated in hemodynamically unstable patients [17,18,37]. Therefore, the rhythm-control group in observational studies might have poor outcomes [38]. Indeed, we found that the rhythm-control group had greater ICU and hospital mortality with greater severity scores and a higher proportion of patients requiring mechanical ventilation and vasopressors at AF onset. To avoid this confounder, RCTs for the assessment of rhythm-control therapy are warranted. In addition, we also presented the timing of the initiation of rhythm-control therapy, rhythm-control drug options, proportion of patients who remained in AF, and frequency of AEs. These findings may provide important insight for the design and feasibility of interventional studies assessing rhythm-control therapy in new-onset AF.

4.4. Strengths and limitations

The present study included a larger number of critically ill patients with new-onset AF than that of previous studies that assessed the impact of rhythm-control therapy [4,5,15,16]. Using multivariable regression analysis considering time-related bias, we showed a significant impact of rhythm-control therapy on SR restoration. However, this study also has several limitations to be considered. First, because the study was conducted only in Japan, our findings may have limited generalizability. However, the rate of SR restoration at ICU discharge in the rhythm-control group was 85%, which was within the range found in previous studies [15,30]. Second, we manually detected new-onset AF without using automatic systems; thus, we may have missed some new-onset AF cases that could not be clinically recognized [39]. However, a retrospective cohort study involving automated analysis of continuous electrocardiography to detect AF reported that subclinical AF (detected by the algorithm but missed by clinicians) was not associated with poor hospital outcomes [7]. Third, we could not determine the optimal timing of rhythm-control for SR restoration. In our study, almost 70% of all rhythm-control therapies were initiated within 6 h after AF onset, which may be the appropriate duration for initiating the treatment in future interventional studies. Fourth, most patients with rhythm-control therapy also received rate-control therapy, which might have contributed to SR restoration. Future studies that include a specific protocol for drug usage are needed. Fifth, we did not distinguish DC from other pharmacological interventions as rhythm-control therapy because whether there is any difference in impact on SR restoration between those interventions is unknown. However, our sensitivity analysis without DC showed similar results as the primary find-

ings. An analysis focused on DC using our database seems warranted. Sixth, we could not identify a specific intervention that is particularly favorable for SR restoration because of the various combinations and timings of rhythm-control drugs (Fig S1). Seventh, we did not collect echocardiographic information, ECG data, or cardiac biological data, which might have been confounding factors in the assessment of rhythm-control therapy. However, a history of CHF was not associated with SR restoration in our multivariable Cox proportional hazard analysis. Ninth, because the proportion of patients requiring mechanical ventilation and vasopressors at AF onset in the rhythm-control group was higher than that in the non-rhythm-control group, rhythm-control therapy for AF might be preferred in generally unstable patients. Because of these characteristics of our study, we might underestimate the impact of rhythm-control therapy on restoration of SR. Finally, we could not control for unknown confounding factors because of the study's observational nature. To resolve these problems, RCTs assessing the objective outcomes of rhythm-control therapy are strongly warranted.

5. Conclusion

This study showed that rhythm-control therapy for new-onset AF in critically ill patients was associated with SR restoration. Because patients treated with rhythm-control in observational studies may have poor outcomes due to selection bias (i.e., patients with hemodynamic instability tend to get the treatment), further interventional studies for rhythm-control therapy are strongly warranted to avoid this confounder.

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Ethics approval: This study is a post hoc analysis of a prospective observational study. The original study was registered at UMIN-CTR (UMIN000026401), and the original study protocol was approved by the Jikei University Institutional Review Board (approval no. 28–200[8443]) and the ethics committees of all other participating hospitals, with an opt-out policy from the patient or proxy.

Consent to participate: Informed consent was obtained via an opt-out policy from the patient or proxy included in the study.

Consent for publication: The participant has consented to the submission of this original article to the journal via an opt-out policy.

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CRediT authorship contribution statement

Takuo Yoshida: Conceptualization, Methodology, Formal analysis, Investigation, Resources, Data curation, Writing - original draft, Visualization, Supervision, Project administration, Funding acquisition. **Shigehiko Uchino:** Conceptualization, Methodology, Investigation, Resources, Data curation, Writing - review & editing. **Yusuke Sasabuchi:** Conceptualization, Methodology, Formal analysis, Writing - review & editing. **Michihito Kyo:** Conceptualization, Formal analysis, Writing - review & editing. **Takashi Igarashi:** Conceptualization, Formal analysis, Writing - review & editing. **Haruka Inoue:** Conceptualization, Formal analysis, Writing - review & editing. **:** .

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 data

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