Impact of Rhythm-control Therapy for New-onset Atrial Fibrillation in Critically ill Patients : A Post Hoc Analysis From the Prospective Observational AFTER-ICU study

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Research

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Abstract

Background

Sustained new-onset atrial fibrillation (AF) is time-dependently associated with hospital mortality. However, whether rhythm-control therapy can achieve sinus rhythm (SR) restoration in critically ill patients is unknown. This study aimed to assess the impact of rhythm-control therapy on SR restoration in critically ill patients with new-onset AF.

Methods

This study is a post hoc analysis of the AFTER-ICU study, a prospective observational study of patients with new-onset AF in 32 Japan intensive care units. This study included patients with and without rhythm-control therapy with new-onset AF. A multivariable analysis was performed using Cox proportional hazards regression analysis including rhythm-control therapy as a time-varying covariate for SR restoration.

Results

Of 423 patients with new-onset AF, 178 (42%) underwent rhythm-control therapy. Among those patients, 131 (31%) underwent rhythm-control therapy within 6 hours after AF onset. Magnesium sulfate 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). The rhythm-control group had 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.

Trial registration

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Background

New-onset atrial fibrillation (AF) is a common arrhythmia in critically ill patients [1,2], and it may lead to the deterioration of vital signs in the clinical context [3]. The development of both new-onset and sustained new-onset AF was reported to be possibly 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 cardioversion, or both [12]. For general ward settings and postcardiac surgery, interventional studies assessing rhythm-control therapy could not show clinical benefit [13,14]. There is no established strategy for managing AF in critically ill patients because of a lack of clinical research with high quality of evidence [15–18].

Rhythm-control therapy for AF is aimed at shortening the AF duration. However, whether rhythm-control therapy can achieve sinus rhythm (SR) restoration in critically ill patients is unknown. Although there were a few randomized control trials (RCTs) for pharmacologic interventions in the 1990s [19–21], they enrolled fewer than 50 patients, and their quality of evidence was low or very low because of imprecision and risk of bias [11,15,16]. In observational studies, the reported conversion rates with pharmacologic interventions were varied [15–18]. For instance, the conversion rates for using amiodarone ranged from 30% to 95%, possibly due to various dosing regimens, timing of outcome assessment, and definitions of restoration to SR [11,15,22]. Furthermore, because new-onset AF often restores to SR spontaneously [23–26], 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 SR restoration, we cannot design interventional studies for rhythm-control therapy for AF.

A previous multicenter study described the epidemiology after identification of new-onset AF [27], and another study also reported that sustained new-onset AF was time-dependently associated with hospital mortality [10]. In this study, we aimed to perform a sub-analysis of the AFTER-ICU study in order to assess the impact of rhythm-control therapy on SR restoration in critically ill patients with new-onset AF.

**Materials And Methods**

*Study design and setting*

This study is a post hoc analysis of the AFTER-ICU study, a prospective observational study that included 423 patients with new-onset AF in 32 Japan intensive care units (ICUs) [10,27]. 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 [28].

*Participants*

We enrolled patients who developed new-onset AF during their ICU stay. The exclusion criteria were as follows: age <18 years; history of AF; discharged from the ICU within 24 hours after ICU admission; admitted to the ICU after cardiac surgery or cardiac arrest; with a pacemaker at AF onset; withheld or withdrew medical therapy at AF onset; declined enrollment in this study. AF was defined as an arrhythmia with irregular R-R intervals without apparent P waves or with F waves that persisted longer than 5 minutes or with recurrent episodes within 5 minutes, as confirmed by 12-lead electrocardiograms or continuous 3-lead electrocardiograms [3,6,14,16,22,29]. Physicians (intensivists or cardiologists) in the participating hospitals made the diagnoses of new-onset AF.
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 ICU stay, whichever was shorter: timing of direct-current cardioversion, drugs used for new-onset AF, adverse events (bleeding events or cardiac arrhythmia other than AF), and timing of cardiac rhythm transition. The rhythm-control drugs for new-onset AF were magnesium sulfate, amiodarone, pilsicainide, aprindine, cibenzoline, adenosine triphosphate, disopyramide, flecainide, bepridil, and lidocaine. The rate control drugs 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 direct-cardioversion as rhythm-control therapy.

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 longer than 24 hours after the conversion from AF to SR. If the patients were discharged from ICU with SR within 24 hours after the conversion of cardiac rhythm from AF to SR, they were also defined as those with SR restoration. The secondary outcomes were the patients’ cardiac rhythm at ICU discharge, AF duration, ICU length of stay, hospital length of stay, adverse events, 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 definition of the other collected variables is detailed in Additional table 1.

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 chi-square test or Fisher's exact test for categorical variables and Mann-Whitney U test for continuous variables. P<0.05 was considered statistically significant.

To assess the association between rhythm-control therapy and SR restoration, we modeled 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 [3–5,8,9,11,18,30,31]: age, previous history of congestive heart failure, patient category (nonscheduled surgical, scheduled surgical, and medical), Acute Physiology and Chronic Health Evaluation (APACHE) II scores [32] 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 at AF onset, and the laboratory data (potassium and white blood cells) before AF onset. To account for the nonlinear effects of age, heart rate at AF onset, potassium, and white blood cells 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).

Sensitivity analyses

Although direct-current cardioversion is a rhythm-control therapy, undergoing DC direct-current cardioversion does not have the effect of sustained SR, which is different from the pharmacologic interventions. Therefore, we performed sensitivity analysis using Cox proportional hazards regression for the rhythm-control therapy without direct-current cardioversion.

Results

A total of 423 patients with new-onset AF were enrolled in the AFTER-ICU study, of whom 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 (36%) underwent rhythm-control therapy within 24 hours after AF onset and 131 (31%) within 6 hours after AF onset.

The patients’ demographic and clinical characteristics are shown in Table 1. Laboratory data are shown in Additional table 2. 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 those in the non-rhythm-control group. The proportion of those with previous histories of congestive heart failure and ischemic heart disease did not statistically differ between the two groups.

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 heart rate and used vasopressors and inotropes more frequently than the non-rhythm-control group.

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 Additional fig. 1. Among the patients who had undergone direct-current cardioversion for new-onset AF, 37 (57%) received rhythm-control drugs. There were a few patients who only used a single drug, and magnesium sulfate 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 remained in 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 adverse events in the rhythm-control group were higher than those in the non-rhythm-control group.

The results of the Cox models for SR restoration after adjustment for the prespecified confounding factors are shown in Table 4 and Additional fig. 2. Among all covariates included in this model, only rhythm-control therapy had a significant positive association with SR restoration.

The sensitivity analyses are shown in Additional table 3 and fig.3. The results of these analyses were similar to those of the main analysis.

**Discussion**

**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 patients with new-onset AF, 178 (42%) were treated with rhythm-control 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 hours after AF onset, magnesium sulfate 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.

**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 sulfate and amiodarone has been evaluated for new-onset AF in a few interventional studies conducted in the 2000s [15,16,21,33]. For example, a single-center RCT with 60 patients with AF compared the efficacy of amiodarone with that of diltiazem [33]. They reported that amiodarone tended to be more effective than diltiazem on SR restoration at 4 hours after AF onset (42.5% vs. 30%, P=0.34). Another single-center RCT with 42 patients with AF without hemodynamic instability reported that sulfate magnesium was better than amiodarone for SR restoration at 24 hours after AF
onset (78% vs. 50%) [21]. Moreover, a prospective single-arm study reported that the combination of amiodarone and magnesium sulfate might have a high probability of SR restoration (90% at 24 hours after AF onset) [22]. Consistent with these previous studies, we found that rhythm-control therapy, including magnesium sulfate and amiodarone, was associated with SR restoration. Our current analyses took into account 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 for evaluation of rhythm-control therapy, especially for observation time points of cardiac rhythms (mainly at 24 hours) [15–18]. Such specific observation time points cannot consider the time-varying nature of rhythm-control therapy, often called “immortal bias” [34–36]. Because rhythm-control therapy is generally initiated for sustained AF, patients with 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 common in critical care research [34,36]. These findings suggest the importance of appropriately treating time-varying covariates for conducting observational studies in critical care setting.

**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 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 for the initiation of rhythm-control therapy, rhythm-control drug options, proportion of patients who remained in AF, and frequency of adverse events. These findings may provide important insight for the design and feasibility of interventional studies assessing rhythm-control therapy in new-onset AF.

**Strengths and limitations**

To the best of our knowledge, the current 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]. With the 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. First, because it 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 [15,29]. Second, we could not determine the best timing of rhythm control for SR restoration. In our study, almost 70% of all rhythm-control therapies were initiated within 6 hours after AF onset, which may be the appropriate duration for initiating the treatment in future interventional studies. Third, 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. Fourth, we did not distinguish direct-current cardioversion from other pharmacologic interventions as rhythm-control therapy because whether there is any difference in impact on SR restoration between those interventions is unknown. However, our sensitivity analyses without direct-current cardioversion showed similar results as the primary findings. An analysis focused on direct-current cardioversion using our database seems warranted. Finally, we could not identify a specific intervention in favor of SR restoration because of the various rhythm-control drugs used. Sulfate magnesium, which appears to have a low risk of adverse events [15,18,39], was the most frequently used among the rhythm-control drugs. This drug may be promising for future interventional studies assessing rhythm-control therapy.

**Conclusion**

This study showed that rhythm-control therapy was associated with SR restoration for new-onset AF in critically ill patients. 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.

**Abbreviations**

AF: atrial fibrillation, APACHE: Acute Physiology and Chronic Health Evaluation, ICU: intensive care unit, RCT: randomized control trial, SR: sinus rhythm.

**Declarations**

**Ethics approval and consent to participate:** The AFTER-ICU 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 for publication:** Not applicable.

**Availability of data and materials:** The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Competing interests:** The authors declare that they have no competing interests.
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Authors' contributions: TY has full access to all the data in the study and takes responsibility for the integrity of the data. Study concept and design: TY, SU, MK, TI, HI, and YS. Acquisition of data: TY and SU. Analysis and interpretation of data: TY, SU, MK, TI, HI, and YS. Drafting of the manuscript: TY and SU. Critical revision of the manuscript for important intellectual content: TY, SU, MK, TI, HI, and YS.

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Tables

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

AF, atrial brillation; TIA, transient ischemic attack; CHADS2, 1 point: recent congestive heart failure, hypertension, age older than 75 years, diabetes mellitus; 2 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 (n = 245) | Rhythm control (n = 178) | P value |
|--------------------------------------|------------------------------|--------------------------|---------|
| Physiological data before AF onset   |                              |                          |         |
| Heart rate (bpm)                     | 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 (bpm)                     | 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 a                        | 99 (40.4)                    | 93 (52.2)                | 0.02    |
| Inotropes b                          | 22 (9.0)                     | 30 (16.9)                | 0.02    |
| Anticoagulants c                     | 54 (22.0)                    | 29 (16.3)                | 0.17    |
| Dexmedetomidine                      | 42 (17.1)                    | 42 (23.6)                | 0.11    |
| Propofol                             | 41 (16.7)                    | 46 (25.8)                | 0.03    |
| Midazolam                            | 27 (11.0)                    | 20 (11.2)                | 1.00    |
| Diltiazem                            | 3 (1.2)                      | 1 (0.6)                  | 0.64    |
| β-Blocking agents                    | 11 (4.5)                     | 23 (12.9)                | 0.002   |
| Amiodarone                           | 1 (0.4)                      | 2 (1.1)                  | 0.58    |
Values are presented as median [interquartile range] or n (%).

AF, atrial fibrillation; DC, direct current cardioversion; ICU, intensive care unit.

a Noradrenaline, adrenaline, dopamine, and vasopressin.

b Dobutamine and phosphodiesterase inhibitors.

c Subcutaneous and intravenous heparin injections, warfarin, and direct oral anticoagulants.

**Table 3: interventions and outcomes**
|                              | Non-rhythm control (n = 245) | Rhythm control (n = 178) | P value |
|------------------------------|-----------------------------|--------------------------|---------|
| Timing of rhythm control (hours) | 1.5 [0.4–6.7]               | 65 (36.9)                | □       |
| Direct-current cardioversion | □                           | 65 (36.9)                | □       |
| Pharmacologic intervention   | □                           | 150 (84.3)               | □       |
| Rhythm-control drugs         | □                           | 150 (84.3)               | □       |
| Magnesium sulfate            | □                           | 76 (42.7)                | □       |
| Amiodarone                   | □                           | 50 (28.1)                | □       |
| Pilsicainide                 | □                           | 42 (23.6)                | □       |
| Others a                     | □                           | 35 (19.7)                | □       |
| Rate-control drugs           | 150 (61.2)                  | 132 (74.2)               | 0.007   |
| β-Blocking agents            | 98 (40.0)                   | 105 (59.0)               | <0.001  |
| Landiolol                    | 80 (32.7)                   | 92 (51.7)                | <0.001  |
| Bisoprolol                   | 35 (14.3)                   | 35 (19.7)                | 0.15    |
| Propranolol                  | 1 (0.4)                     | 1 (0.6)                  | 1.00    |
| Carvedilol                   | 5 (2.0)                     | 3 (1.7)                  | 1.00    |
| Calcium-channel blockers     | 74 (30.2)                   | 53 (29.8)                | 1.00    |
| Diltiazem                    | 50 (20.4)                   | 24 (13.5)                | 0.07    |
| Verapamil                    | 26 (10.6)                   | 32 (18.0)                | 0.03    |
| Digoxin                      | 5 (2.0)                     | 9 (5.1)                  | 0.10    |
| Anticoagulants               | 102 (41.6)                  | 71 (39.9)                | 0.76    |
| Heparin injection            | □                           | □                        | □       |
| Intravenous                  | 74 (30.2)                   | 50 (28.1)                | 0.67    |
| Subcutaneous                 | 28 (11.4)                   | 14 (7.9)                 | 0.25    |
| DOAC                         | 7 (2.9)                     | 13 (7.3)                 | 0.04    |
| Warfarin                     | 3 (1.2)                     | 2 (1.1)                  | 1.00    |
| ICU length of stay (days) b  | 4.9 [2.0–9.3]               | 6.8 [3.4–13.0]           | <0.001  |
| Hospital length of stay (days) c | 24.9 [11.9–46.2]         | 27.4 [14.2–54.7]         | 0.12    |
| ICU mortality                | 25 (10.2)                   | 29 (16.3)                | 0.08    |
|                                     | Control (n=243) | Case (n=186) | p-value |
|-------------------------------------|-----------------|--------------|---------|
| Hospital mortality                  | 57 (23.3)       | 55 (30.9)    | 0.09    |
| Stroke after AF onset               | 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 (hours)         | 13.9 [3.8–50.1] | 14.8 [3.5–34.9] | 0.42 |
| Total AF duration (hours)           | 16.0 [4.0–59.9] | 23.9 [8.0–45.0] | 0.29 |
| AF at ICU discharge                 | 47 (21.4)       | 15 (10.1)    | 0.004   |

**Adverse events**

|                                     | Control (n=243) | Case (n=186) | p-value |
|-------------------------------------|-----------------|--------------|---------|
| Bleeding                            | 12 (4.9)        | 18 (10.1)    | 0.05    |
| Arrhythmias other than AF           | 3 (1.2)         | 10 (5.6)     | 0.02    |

Values are presented as median [interquartile range] or n (%).

DC, direct current cardioversion; ICU, intensive care unit; AF, atrial fibrillation.

a Other drugs: aprindine, cibenzoline, adenosine triphosphate, disopyramide, flecainide, bepridil, and 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 7 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**
| Patient category               | 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<sup>a</sup>         | 0.90 (0.63–1.26)               | 0.53    |
| Congestive heart failure      | 0.93 (0.62–1.40)               | 0.73    |
| Patient category              |                                |         |
| Scheduled surgical            | Ref                            |         |
| Nonscheduled 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<sup>b</sup> | 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 nonlinear variables [Additional fig. 2].

CI, confidence interval; AF, atrial fibrillation; MV, mechanical ventilation; RRT, renal replacement therapy; APACHE II, Acute Physiology and Chronic Health Evaluation II.

<sup>a</sup> Administration any of the following inotropes at AF onset: dobutamine and phosphodiesterase inhibitors.

<sup>b</sup> Administration any of the following vasopressors at AF onset: noradrenaline, adrenaline, vasopressin, and dopamine.

**Figures**
Figure 1

Timing of rhythm-control therapy initiated for new-onset atrial fibrillation (AF) (a) Within 24 hours. (b) Within 7 days after AF onset.

Supplementary Files

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- AFTERrhythmcontrolsupplementCC20201008.docx