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Atrial Fibrillation (AFIB) in the ICU: Incidence, Risk Factors, and Outcomes: The International AFIB-ICU Cohort Study*

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OBJECTIVES: To assess the incidence, risk factors, and outcomes of atrial fibrillation (AF) in the ICU and to describe current practice in the management of AF.

DESIGN: Multicenter, prospective, inception cohort study.

SETTING: Forty-four ICUs in 12 countries in four geographical regions.

SUBJECTS: Adult, acutely admitted ICU patients without a history of persistent/permanent AF or recent cardiac surgery were enrolled; inception periods were from October 2020 to June 2021.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: We included 1,423 ICU patients and analyzed 1,415 (99.4%), among whom 221 patients had 539 episodes of AF. Most (59%) episodes were diagnosed with continuous electrocardiogram monitoring. The incidence of AF was 15.6% (95% CI, 13.8–17.6), of which newly developed AF was 13.3% (11.5–15.1). A history of arterial hypertension, paroxysmal AF, sepsis, or high disease severity at ICU admission was associated with AF. Used interventions to manage AF were fluid bolus 19% (95% CI 16–23), magnesium 16% (13–20), potassium 15% (12–19), amiodarone 51% (47–55), beta-1 selective blockers 34% (30–38), calcium channel blockers 4% (2–6), digoxin 16% (12–19), and direct current cardioversion in 4% (2–6). Patients with AF had more ischemic, thromboembolic (13.6% vs 7.9%), and severe bleeding events (5.9% vs 2.1%), and higher mortality (41.2% vs 25.2%) than those without AF. The adjusted cause-specific hazard ratio for 90-day mortality by AF was 1.38 (95% CI, 0.95–1.99).

CONCLUSIONS: In ICU patients, AF occurred in one of six and was associated with different conditions. AF was associated with worse outcomes while not statistically significantly associated with 90-day mortality in the adjusted analyses. We observed variations in the diagnostic and management strategies for AF.

KEY WORDS: adverse outcomes; critical illness; intensive care units; management; newly developed atrial fibrillation

Atrial fibrillation (AF) is the most common cardiac arrhythmia (1, 2). Research has demonstrated that AF increases the risk of adverse outcomes in hospitalized or outpatient populations (3–6). Data suggest that newly developed AF (NAF) is common in critically ill patients and may negatively affect the short- and long-term outcomes including prolonged hospitalization and increased risk of stroke and death (7–9).

Several treatments are available to manage AF, including antiarrhythmic agents and anticoagulant (AC) therapy. However, previous research has suggested considerable practice variation, and the evidence is limited and derives mainly from noncritically ill patients (7, 10–12).

*See also p. 1255.

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KEY POINTS

- **Question:** What are the incidences, risk factors, adverse outcomes, and management strategies of atrial fibrillation (AF), in particular newly developed episodes of AF (NAF), in ICU patients without a history of persistent or permanent AF?
- **Findings:** In this international cohort, including 1,423 noncardiac ICU patients, the incidence of AF was 15.6%. AF was associated with history of arterial hypertension, paroxysmal AF, sepsis, and high disease severity. AF was associated with increased mortality in crude analyses, but not in the adjusted analyses. We observed variations in the treatments for AF.
- **Meaning:** AF is frequent in the ICU, especially NAF. Different risk factors for AF exist, the prognostic impact is unclear, and no uniform management approach exists.

In this international cohort study, we assessed the incidence of AF including NAF, associated risk factors, used management strategies, and outcomes among adults admitted to the ICU.

We hypothesized that AF is frequent, with specific risk factors, associated with adverse outcomes, and that there is considerable in the clinical practice of AF.

MATERIALS AND METHODS

Study Design and Recruitment

We conducted an international, prospective, inception cohort study with participation of ICUs from Europe, Asia, the Middle East, and Australia/New Zealand. The study was approved by the Danish Patient Safety Authority (31-1521-9) and the Capital Region Knowledge Centre for Data Compliance, Copenhagen, Denmark (P-2020-392). The study received institutional review board approval and ethical committee acceptance from all participating sites (**Supplemental Tables 1** and **2**, http://links.lww.com/CCM/H333). Informed consent was obtained if needed per national laws. All research procedures were conducted according to the Declaration of Helsinki.

The study protocol was published before study completion (13). It was prepared according to the Strengthening the Reporting of Observational Studies in Epidemiology statement (**Supplemental Table 3**, http://links.lww.com/CCM/H333) (14).

Setting

We included patients during one or two inception periods (**Supplemental Table 4**, http://links.lww.com/CCM/H333). Each period consisted of 14 consecutive days. The patient enrolment period was from October 2020 to June 2021.

Study Population

All adults (age ≥18 yr) admitted to the ICU in the inception periods were eligible (**Supplemental Table 5**, http://links.lww.com/CCM/H333). We excluded patients fulfilling any of the following criteria: documented history of persistent or permanent AF, transferred directly from an ICU not participating in the study, elective or planned admission to the ICU, or previously included in the study (Supplemental Table 5, http://links.lww.com/CCM/H333). Furthermore, patients undergoing cardiac surgery were excluded since they were considered not

directly comparable with other ICU populations due to a unique risk factor profile for AF, including direct manipulation of the cardiac tissue, cardiopulmonary bypass, and presence of substantial cardiovascular diseases.

Data Management

We developed an electronic case report form in collaboration with Copenhagen Trial Unit (Copenhagen, Denmark) (13). We obtained data on demographics, coexisting morbidities, outpatient medication, disease severity, cardiac rhythm, and the use of organ support at ICU admission (**Supplemental Table 6**, http://links.lww.com/CCM/H333). Specialized hospitals were considered medical centers, including branches of subspeciality care, such as neurosurgery, cardiac surgery, and transplantations.

Daily, during the ICU stay, we registered detected episodes of AF, use of organ support, and AC therapy (**Supplemental Table 7**, http://links.lww.com/CCM/H333). In patients with AF, we assessed the used diagnostic method and interventions (**Supplemental Table 8**, http://links.lww.com/CCM/H333).

We assessed vital status, ischemic stroke, thromboembolic, and severe bleeding events. We defined ischemic stroke and thromboembolic events as the presence of clinically relevant findings and verification by relevant diagnostic modalities. Severe bleeding events were defined as clinical bleeding from any origin requiring the use of a minimum of 3 units of red blood cells within 24 hours (**Supplemental Tables 9** and **10**, http://links.lww.com/CCM/H333) at 90-day follow-up (13).

Definition of AF and NAF

We defined AF as a detected irregular rhythm with the absence of p waves, irregular RR intervals identified by continuous monitoring or 12-lead electrocardiogram (ECG) lasting greater than or equal to 30 seconds, and confirmed as AF by a physician (13). In addition, patients with AF were post hoc subdivided into two groups, those with NAF, and those with previous documented history of paroxysmal AF (PAF) in medical records.

Outcome Measures

The primary outcome was the frequency of AF and NAF in the ICU, defined as the number of patients with at least one detected episode of AF. Secondary outcomes included length of hospital stay, ischemic or thromboembolic events, severe bleeding events, and 90-day mortality (13).

Statistical Methods

We expected a frequency of AF of 10–20% (7, 12, 15). We planned to include at least 1,000 patients to yield an expected 95% CIs of 8–12% if the incidence was 10% or 17–22% if the frequency is 20% (13).

We analyzed data according to the published statistical analysis plan (13). All analyses were performed using R (Version 4.0.2; R Foundation for Statistical Computing, Vienna, Austria; https://www.R-project.org/). Continuous variables are reported as medians with interquartile ranges (IQRs) and categorical variables as numbers with corresponding percentages, stratified according to the presence or absence of AF. The incidence of AF and NAF was reported as the number (%) of study patients with a detected episode of AF.

Baseline and outcome differences between the patients with AF and without AF were evaluated using two-tailed X^2 test, Fisher exact test, or Mann-Whitney U test, as appropriate.

We assessed risk factors for AF by unadjusted and adjusted Cox models with death as a competing event to estimate adjusted cause-specific hazard ratios (HRs) with corresponding 95% CIs. The following variables were included in the adjusted model: sex, history of arterial hypertension, history of diabetes mellitus, history of PAF, history of ischemic heart disease, COVID-19 status at ICU admission, sepsis at ICU admission, trauma at ICU admission, and Simplified Mortality Score (SMS) for the ICU (a severity score ranging from 0 to 42 points and including age as a variable [**Supplemental Table 11**, http://links.lww.com/CCM/H333]) (13, 16). The SMS-ICU was applied to reduce the risk of missing data. Patients with AF at ICU admission were not included in these analyses.

Prognostic Cox models with time since admission to ICU and discharge alive from the ICU as a competing event were used to assess the unadjusted and adjusted HR between AF and all-cause 90-day mortality. AF was handled as a simple time-varying variable. Thus, AF status could change at most once, that is, from status "no AF" to "AF." Patients with AF at ICU admission were assigned the status "AF" at time zero, and patients with the first episode of AF during the ICU admission changed their status from "no AF" to "AF" at the time

point where AF is detected. Accordingly, the HR of the AF time-changing variable is the risk increase at fixed time point since admission when comparing patients that have experienced AF at that time point with patients who have not experienced AF at that time point. The following variables were included in the adjusted model: country, sex, history of ischemic heart disease, septic shock at ICU admission, and SMS-ICU (13).

Used management strategies, ischemic, thromboembolic, and severe bleeding events and length of hospitalization were reported descriptively. Complete case analysis was performed due to few missing data (13).

RESULTS

We included a total of 1,423 patients from 44 ICUs in 12 countries (**Fig. 1**). Fifty-five percentage of the hospitals were specialist hospitals, and 82% of the participating sites were mixed ICUs.

Of the 1,423 patients, data from 1,415 (99.4%) were analyzed (Fig. 1). The median age was 62 years (IQR,

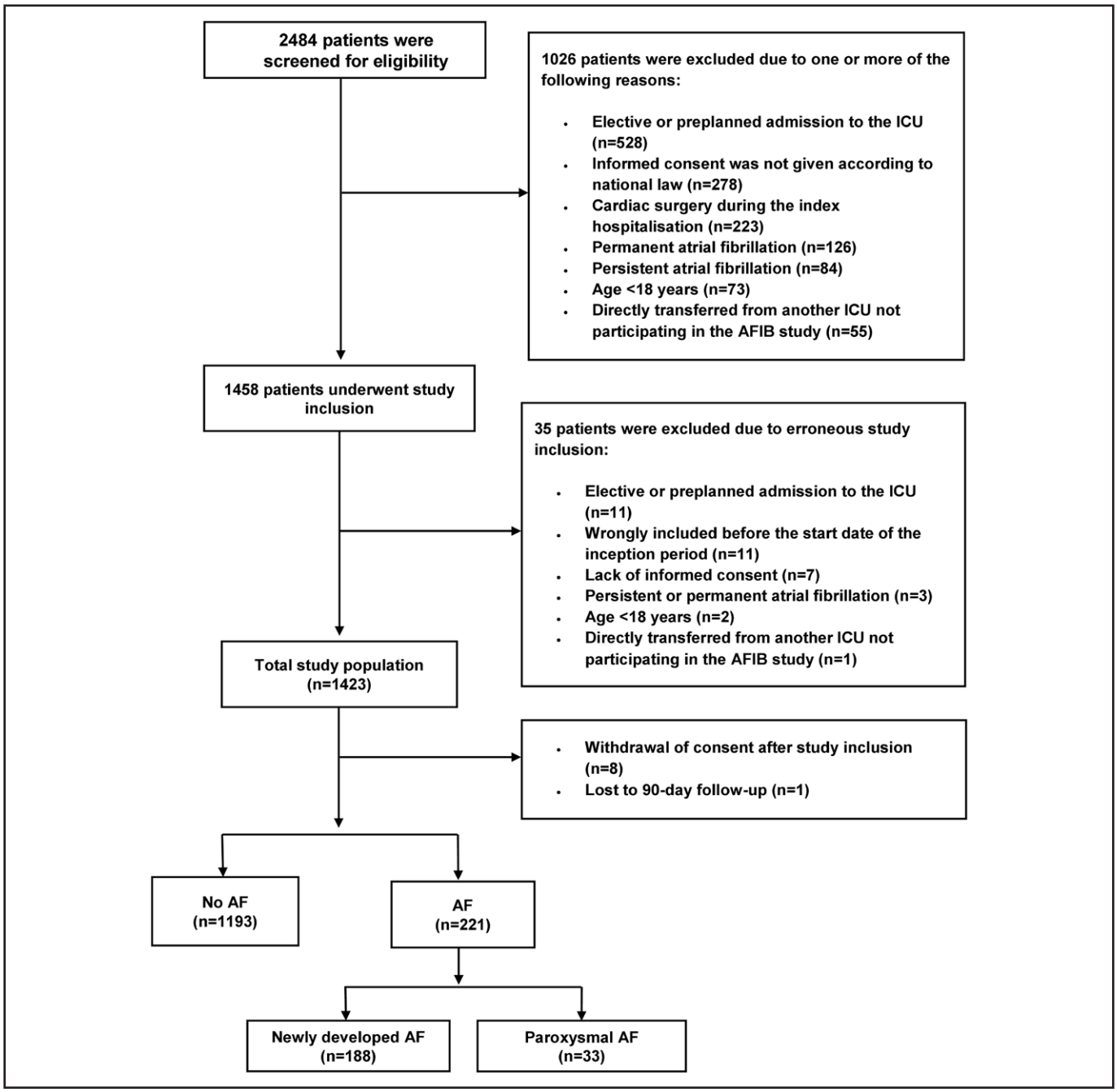

Figure 1. Flowchart of the screening, inclusion, and follow-up processes. AF = atrial fibrillation.

49–72), and SMS-ICU was 14 (10–19) at ICU admission (**Table 1**). Most common comorbidities were arterial hypertension (46%), diabetes mellitus (28%), and ischemic heart disease (14%) (Table 1).

Atrial Fibrillation

A total of 539 AF episodes were detected in 221 patients in the ICU; this was mostly diagnosed on continuous

TABLE 1.
Characteristics of Patients Stratified by the Occurrence of Any Atrial Fibrillation (Newly Developed or Paroxysmal)

Variable	Overall[a] (*n* = 1,415)	No AF (*n* = 1,194)	AF Episode[b] (*n* = 221)	Newly Developed AF (*n* = 188)	Paroxysmal AF (*n* = 33)
Age, yr, median (IQR)	62 (49–72)	60 (46–70)	72 (63–80)	71 (61–79)	79 (71–83)
Male, gender	816 (58)	688 (58)	128/221 (58)	109/188 (58)	19/33 (58)
Elective surgery	115 (8)	98 (8)	17/221 (8)	14/188 (7)	3/33 (9)
Acute surgery within 24 hr before ICU admission	230 (16)	189 (16)	41/221 (19)	32/188 (17)	9/33 (27)
Simplified Mortality Score for the ICU, median (IQR)	14 (10–19)	13 (9–19)	18 (14–23)	18 (14–22)	21 (17–25)
Sepsis	258 (18)	192 (16)	66/221 (30)	57/188 (30)	9/33 (27)
Septic shock	135 (52)	100 (8)	35/66 (53)	31/57 (54)	4/33 (12)
Trauma	110 (8)	99 (8)	11/221 (5)	10/188 (5)	1/33 (<1)
COVID-19	244 (17)	209 (18)	35/221 (16)	30/188 (16)	5/33 (15)
Medical history					
Hypertension	653 (46)	517 (43)	136/221 (62)	114/188 (61)	22/33 (67)
Ischemic heart disease	196 (14)	151 (13)	45/221 (20)	35/188 (19)	10/33 (30)
Cardiac surgery	53 (4)	39 (3)	14/221 (6)	11/188 (6)	3/33 (9)
Cardiac valve dis.	50 (3)	34 (3)	16/221 (7)	11/188 (6)	5/33 (15)
Diabetes mellitus	394 (28)	320 (27)	74/221 (33)	59/188 (31)	15/33 (45)
Hematological malignancy/metastatic cancer	149 (11)	127 (11)	22/221 (10)	18/188 (10)	4/33 (12)
Paroxysmal AF	54 (4)	21 (2)	33/221 (15)	-	33/33 (100)
Tachyarrhythmia	32 (2)	25 (2)	7/221 (3)	4/188 (2)	3/33 (9)
Previous venous thromboembolism/peripheral vascular disease	125 (9)	101 (9)	24/221 (11)	18/188 (10)	6/33 (18)
Thyroid disease	99 (7)	83 (6)	16 (7)	12/188 (6)	4/33 (12)
Regular outpatient medications					
Beta-blockers	314 (22)	231 (19)	83/221 (38)	66/188 (35)	17/33 (52)
Calcium channel blockers	276 (20)	214 (18)	62/221 (28)	53/188 (28)	9/33 (27)
Digoxin	13 (1)	4 (<1)	9/221 (4)	4/188 (2)	5/33 (15)
Amiodarone	7 (<1)	4 (<1)	3/221 (1)	1/188 (<1)	2/33 (6)
Other[c]	0 (-)	0 (-)	0 (-)	-	0 (-)
Anticoagulants	110 (8)	79 (7)	31/221 (14)	14/188 (7)	17/33 (52)
Antiplatelet agents	252 (18)	201 (17)	51/221 (23)	44/188 (23)	7/33 (21)

AF = atrial fibrillation, IQR = interquartile range.

[a]Values are numbers (percentages) unless stated otherwise.

[b]Patients with one or more detected episode of AF at ICU admission and during the ICU stay are included.

[c]Others include propafenone, dronedarone, and flecainide.

cardiac rhythm monitors 59% (95% CI, 54.9–63.3) or continuous monitors combined with 12-lead ECGs 28% (95% CI, 24.4–32.2) (**Table 2**).

The frequency of AF in the ICU was 15.6% (95% CI, 13.8–17.6), of which 13.3% had NAF and 2.3% a previous history of PAF, respectively (Table 2). Of the 54 patients with a history of PAF, 33 (61%) developed AF in the ICU (Table 1). The median time from ICU admission to the first detected episode of AF was 2 days (IQR, 1–4 d).

Patients with AF were older and had higher SMS-ICU scores than patients without AF. Sepsis, diabetes mellitus, and a history of cardiovascular comorbidities, including PAF, were frequent in ICU patients with AF (Table 1).

TABLE 2.

Use of Organ-Supporting Interventions and Anticoagulant Therapy During ICU Stay Stratified by the Occurrence of Any Atrial Fibrillation (Newly Developed or Paroxysmal)

Cardiac Rhythm at ICU Admission	Number of Patients ($n = 1,415$)[a,b]
Sinus rhythm	1,083 (76.5)
Sinus tachycardia	202 (14.3)
AF	57 (4.0)
Bradyarrhythmia	42 (2.9)
Other supraventricular tachyarrhythmia	24 (1.7)
Ventricular arrhythmia	6 (0.4)
Nonshockable rhythms	1 (0.07)
Detected AF events in the ICU ($n = 221$)	
No. of patients with AF at ICU admission or during ICU stay	221 (15.6)
No. of patients with newly developed AF	188 (13.3)
No. of patients with a previous history of paroxysmal AF	33 (2.3)
Total number of detected AF episodes	539
Diagnostic method used to detect AF episodes ($n = 539$)	
Use of continuous monitor screen	319 (59.2)
Use of 12-lead ECG	39 (7.2)
Use of both monitor and confirmed by 12-lead ECG	152 (28.2)
Unclear	29 (5.4)

AF = atrial fibrillation, ECG = electrocardiogram.
[a]Values are numbers (percentages) unless stated otherwise.
[b]We had no missing data for any of the registered variables in Table 2.

History of beta-blockers, digoxin, and ACs as outpatient medication was more common in patients with AF at ICU admission, especially in the PAF group, compared with patients with NAF (Table 1). Use of organ support was more frequent in patients with AF, for example, use of respiratory support, inotropes/vasopressors, and renal replacement therapy (**Table 3**).

In the adjusted analyses, history of arterial hypertension (adjusted HR, 1.57; 95% CI, 1.13–2.20), PAF (adjusted HR, 2.89; 1.57–5.33), sepsis at ICU admission (adjusted HR, 1.57; 1.09–2.24), and higher SMS-ICU (adjusted HR, 1.08; 1.06–1.11) were associated with AF during the ICU stay (**Supplemental Tables 12** and **13*A*** and ***B***, http://links.lww.com/CCM/H333).

Management Strategies

The most used interventions to correct modifiable factors included fluid bolus 19% (95% CI, 16–23), magnesium 16% (13–20), and potassium 15% (12–19) (**Fig. 2**). Amiodarone 51% (47–55), beta-1 selective blockers 34% (30–38), calcium channel blockers 4% (2–6), and digoxin 16% (12–19) were the most frequently used pharmacological agents (Fig. 2; and **Supplemental Table 14**, http://links.lww.com/CCM/H333). Direct current cardioversion was only applied in 24 patients 4% (2–6). Among patients receiving nonselective beta-blockers, none received sotalol (Fig. 2).

Seventy-one percent were anticoagulated during the ICU stay, mainly using prophylactic dosing strategies for the total (**Table 3**). Initiation of therapeutic ACs due to AF was only reported in 44/539 (8%) of the cases. The most used agents were low-molecular-weight heparins (22/44), direct oral ACs (10/44), and unfractionated heparin (5/44).

Outcomes

The all-cause 90-day mortality was 27.7% (95% CI, 25.4–30.1) (**Table 4**); in patients with AF, mortality was 41.2% compared with 25.2% in those without AF. The unadjusted and adjusted HRs were of 1.67 (1.17–2.37) and 1.38 (0.95–1.99), respectively (Table 4 and **Supplemental Table 15**, http://links.lww.com/CCM/H333).

Overall, there was a higher rate of ischemic or thromboembolic events in the AF group and relative risk 1.64 (95% CI, 1.11–2.42). The frequency of ischemic stroke

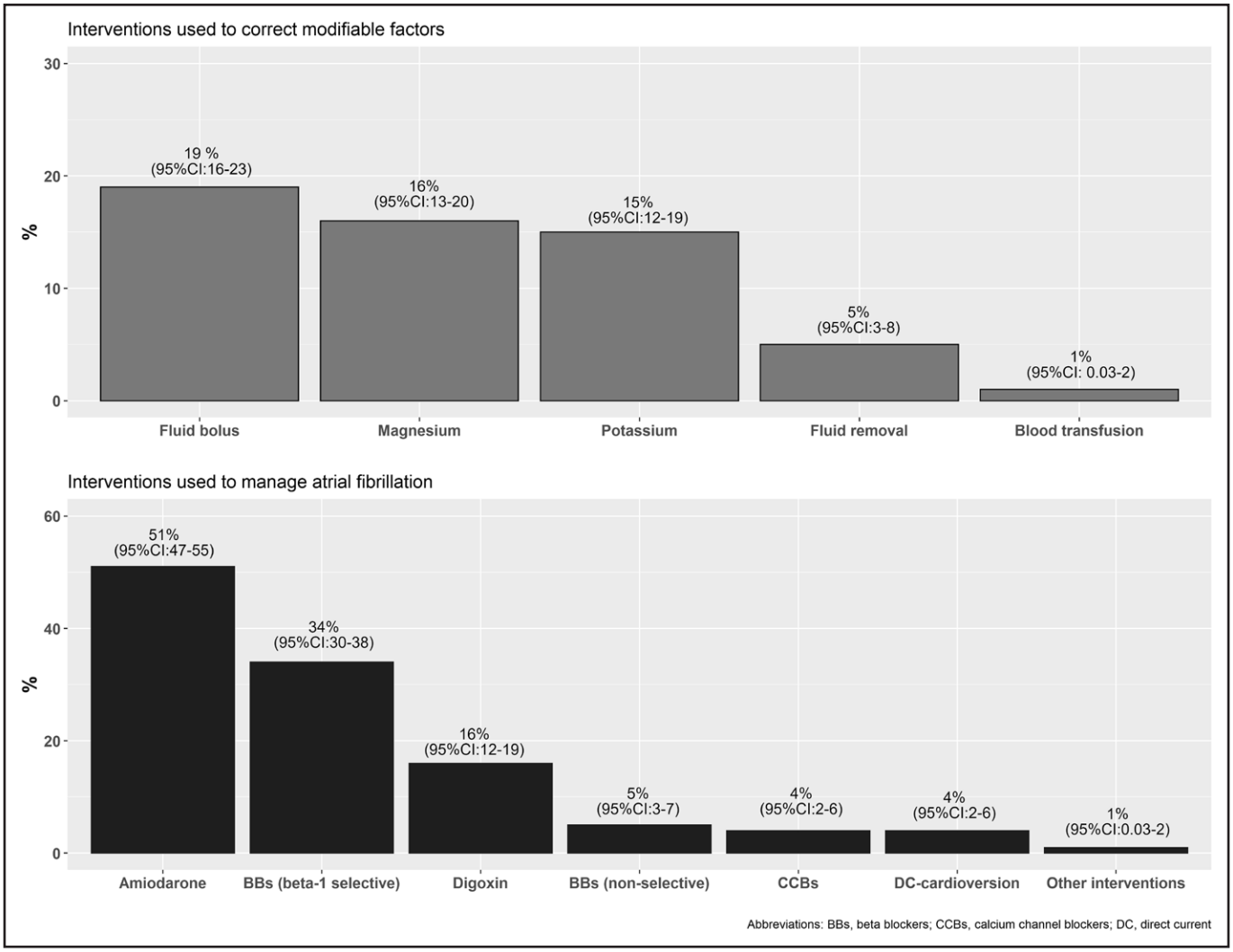

Figure 2. Used pharmacological and nonpharmacological interventions to manage atrial fibrillation in the ICU. BBs = beta-blockers, CCBs = calcium channel blockers, DC = direct current.

was 3% (1–5) among patients with AF compared with 2% (1–3) in those without AF (Table 4). We observed similar numbers of myocardial infarctions and pulmonary embolisms (Table 4). We also observed a higher number of severe bleeding episodes among patients with AF than among those without AF (5.9% vs 2.7%) (Table 4).

DISCUSSION

In this prospective cohort study, we observed an overall frequency of AF of 15.6% in ICU patients, of whom 85% represented NAF and 15% PAF, respectively. Risk factors associated for AF included a history of arterial hypertension, PAF, sepsis at ICU admission and higher disease severity. The most used interventions to manage AF were amiodarone, beta-1 selective blockers, fluid bolus, and magnesium. On the contrary, use of direct current cardioversion was limited. AF was not statistically significant associated with 90-day mortality in the adjusted analysis. Overall, patients with AF had higher frequencies of ischemic, thromboembolic, and severe bleeding events.

We aimed to report the incidence of AF as diagnosed by the treating clinicians. Currently, there is no consensus regarding the definition of NAF in critical care settings (7, 10). We choose a pragmatic definition of AF and NAF encompassing different diagnostic methods to assess used diagnostic tools in clinical practice. The diagnosis was mainly made using continuous monitors. Our AF incidence of 15.6% is in line with previous findings (7). However, variation exists due to differences in study design, detection methods, and definitions (7, 17). Higher incidences of NAF are

TABLE 3.
Cardiac Rhythm in All Patients and Diagnostic Method Used for Atrial Fibrillation

Use of Organ-Supporting Interventions	Overall[a,b] (*n* = 1,415)	No AF (*n* = 1,194)	AF[c] (*n* = 221)	Newly developed AF (*n* = 188)	Paroxysmal AF (*n* = 33)
Use of respiratory support	899 (63.5)	727 (60.9)	172 (78)	151 (80.3)	21 (63.6)
No. of days, median (IQR)	4 (2–8)	3 (2–7)	6 (2–14)	6 (2–14)	2 (2–6)
Use of vasopressor/inotropes	750 (53.0)	579 (48.5)	171 (77.8)	148 (78.7)	23 (69.6)
No. of days, median (IQR)	3 (2–5)	3 (2–4)	4 (2–8)	5 (3–8)	3 (2–7)
Use of renal replacement therapy	190 (13.4)	136 (11.4)	54 (24.4)	48 (25.5)	6 (18.1)
No. of days, median (IQR)	3 (2–7)	3 (2–5)	6 (2–9)	6 (2–10)	3 (2–7)
Anticoagulant therapy					
Use of anticoagulant therapy	1,004 (70.9)	818 (68.5)	186 (84.1)	160 (85.1)	26 (78.7)
No. of days, median (IQR)	4 (2–8)	4 (2–7)	6 (3–14)	7 (4–15)	3 (2–6)
Anticoagulant dosing strategy					
No. of days on prophylactic dose (%)	78.8	80.4	74.5	74.9	65.8
No. of days on therapeutic dose (%)	21.2	19.6	25.5	25.1	34.2
Use of antiplatelet therapy	260 (18.4)	209 (17.5)	51 (23.1)	48 (25.5)	3 (9.1)
No. of days, median (IQR)	3 (2–5)	3 (2–4)	3 (2–7)	3 (2–7)	3 (2–3)

IQR = interquartile range.

[a]Values are numbers (percentages) unless stated otherwise.

[b]We had no missing data for any of the registered variables in Table 3.

[c]Patients with one or more detected episode of atrial at ICU admission and during the ICU stay are included.

reported in studies using continuous monitoring or wearable monitors (7, 15, 18, 19).

We found that ICU patients with AF were older, had higher disease severity, and required organ support more frequently. Using Cox regression to adjust for potential clinical confounders and competing events, we found that arterial hypertension, history of PAF, sepsis, and high disease severity increased the risk of AF. The transient and multifactorial natures of AF make it difficult to determine the impact of the individual risk factors (20). Observational data suggest that AF is associated with different factors, including male gender, cardiovascular comorbidities, older age, and use of organ-supporting interventions (7, 20). Our study findings are in concordance with previous data (7, 20, 21). Better evidence on risk factors can guide clinicians in identifying individuals at higher risk of developing AF through validated scoring systems.

Larger clinical trials conducted in noncritically ill patients have not demonstrated advantages of rhythm control compared with rate control (22–25). Guidelines recommend beta-blockers or calcium channel antagonists to achieve rate control (2, 26), but these guidelines are not specific for ICU patients. Amiodarone or digoxin may be alternatives in patients with impaired left ventricular function. Rhythm control may be preferred in younger patients, NAF, cardiomyopathies, or signs of circulatory shock (2). We found that amiodarone, beta-1 selective blockers, and digoxin were the most used interventions. Reviews highlight that management strategies of AF in critically ill patients are based on limited evidence. This may explain the observed practice variation (10, 27). Antiarrhythmics have serious adverse reactions, which may affect outcome. Amiodarone appears to be safe in acute settings but have well-known long-term adverse effects (28, 29). Safety data are mainly derived from noncritically ill patients with chronic forms of AF rather than critically ill patients who are likely more susceptible to adverse events (7, 10). Furthermore, considering the heterogeneity of ICU patients concerning disease severity, comorbidities, and the need for different interventions, it is likely that the optimal management strategies vary between subgroups of ICU patients.

TABLE 4.
Clinical Outcomes Stratified by the Occurrence of Any Atrial Fibrillation (Newly Developed or Paroxysmal)

Outcome Measure[a,b]	Overall (*n* = 1,414)	No AF (*n* = 1,193)	Any AF (*n* = 221)	Newly Developed AF (*n* = 188)	Paroxysmal AF (*n* = 33)
All-cause 90-d mortality	392 (27.7)	301 (25.2)	91 (41.2)	77 (40.9)	14 (42.4)
ICU LOS, d, median (IQR)	4 (3–9)	4 (2–8)	7 (4–14)	8 (4–16)	3 (3–7)
Hospital LOS, d, median (IQR)	15 (8–30)	14 (7–29)	20 (11–36)	22 (12–40)	11 (7–24)
Ischemic or thromboembolic episodes during the 90 d study period					
Total number of events	124 (8.8)	94 (7.9)	30 (13.6)	29 (15.4)	1 (3.0)
Acute myocardial infarction	30 (2.1)	20 (1.7)	10 (4.5)	10 (5.3)	0 (-)
Ischemic stroke	29 (1.9)	23 (1.9)	6 (2.7)	6 (3.2)	0 (-)
Intestinal ischemia	8 (0.6)	5 (0.4)	3 (1.4)	3 (1.6)	0 (-)
Acute limb ischemia	4 (0.3)	3 (0.3)	1 (0.4)	1 (0.5)	0 (-)
Deep venous thrombosis	28 (2.0)	25 (2.1)	3 (1.4)	2 (1)	1 (3.0)
Portal vein thrombosis	1 (3.6)	1 (4.0)	0	0 (-)	0 (-)
Mesenteric venous thrombosis	0 (-)	0 (-)	0	0 (-)	0 (-)
Renal venous thrombosis	0 (-)	0 (-)	0	0 (-)	0 (-)
Other	0 (-)	0 (-)	0	0 (-)	0 (-)
Pulmonary embolism	25 (1.8)	18 (1.5)	7 (3.2)	7 (3.7)	0 (-)
Severe bleeding episodes during the 90 d study period					
Severe bleeding episodes	38 (2.7)	25 (2.1)	13 (5.9)	13 (7)	0 (-)
Adjusted Association Between AF and the 90-d Mortality Assessed by Cause-Specific Hazard Ratio					
Variable		Adjusted hazard ratios (95% CI)		*p*	
AF[c]		1.38 (0.95–1.99)		0.09	
Male		0.97 (0.74–1.27)		0.81	
History of ischemic heart disease		0.93 (0.63–1.37)		0.72	
COVID-19 at ICU admission		1.16 (0.81–1.65)		0.42	
Septic shock		1.04 (0.69–1.58)		0.84	
Country[d]					
Australia		0.46 (0.18–1.16)		0.10	
China		0.94 (0.58–1.51)		0.79	
Finland		0.53 (0.27–1.05)		0.07	
India		2.20 (1.44–3.36)		< 0.001	
Netherlands		0.81 (0.25–2.60)		0.71	
New Zealand		0.84 (0.33–2.14)		0.72	
Norway		0.49 (0.12–2.04)		0.33	
Poland		1.37 (0.75–2.48)		0.31	
Saudi Arabia		1.05 (0.65–1.71)		0.84	
Sweden		1.08 (0.62–1.89)		0.78	
Switzerland		0.94 (0.44–2.02)		0.87	

(*Continued*)

TABLE 4. (*Continued*)

Clinical Outcomes Stratified by the Occurrence of Any Atrial Fibrillation (Newly Developed or Paroxysmal)

Outcome Measure[a,b]	Overall (*n* = 1,414)	No AF (*n* = 1,193)	Any AF (*n* = 221)	Newly Developed AF (*n* = 188)	Paroxysmal AF (*n* = 33)
One point increase in Simplified Mortality Score for the ICU		1.06 (1.04–1.08)			< 0.001

AF = atrial fibrillation, IQR = interquartile range, LOS = length of stay.

[a]Values are numbers (percentages) unless stated otherwise.

[b]One patient was lost to the 90-d follow-up corresponding to a missingness of 0.07%.

[c]AF was computed as a binary time-dependent variable allowing a change in the AF status from "no AF" to "AF" during the ICU stay.

[d]Denmark is used as reference group for the variable "Country" in the analysis.

AC therapy reduces stroke risk in patients with AF (30). Still, the risk-benefit profile of AC therapy during and beyond the ICU stay is uncertain among critically ill patients who develop AF (10, 31). The clinical dilemma is underscored in our data, as the incidences of both thromboembolic and bleeding events were increased in patients with AF. We observed a higher use and longer duration of AC therapy in patients with AF than in those without AF. Interestingly, less than 10% of AF episodes led to a therapeutic dosing strategy in the ICU. However, we had no data on the AC therapy after ICU discharge, which may have affected the observed ischemic, thromboembolic, and bleeding events at 90-day follow-up. Uncertainty exists regarding the optimal dosing strategy of ACs during the ICU stay and follow-up regimen among patient with critical illness-related AF (11, 32, 33). AC therapy is challenging with dynamic changes in the stroke and bleeding risks among critically ill patients due to multiorgan failure, polypharmacy, and other underlying pathophysiological conditions (20). The evidence around the risk of stroke and the overall benefits of using therapeutic AC therapy over prophylactic during critical illness is very limited (7, 27).

Previous evidence is inconclusive regarding whether AF is a risk factor for poor outcome (34–39). Like other study results, we observed a higher crude mortality rate in ICU patients with AF (7). The association was statistically significant in the unadjusted analysis but not in the adjusted analysis. Previous studies have mainly assessed the effects of AF using logistic or Cox regression analyses without taking competing events into account, potentially resulting in biased estimates due to informative censoring and residual confounding (40–43). Our analysis suggests that AF is associated with worse outcomes but does not statistically significantly affect the 90-day mortality when adjusting for other risk factors. However, these findings may be impacted by the burden of AF and different pathophysiological aspects in critically ill patients.

The strengths of this cohort study include a published protocol (13, 14). The participation of ICUs in different regions increases the external validity. We chose a pragmatic definition of NAF and included patients with a previous history of PAF. Patients with PAF may have a lower threshold for developing new AF events compared with patients with first-ever diagnose of AF, but the diagnostic workup and initial management strategy in the ICU are likely to be same. We also accounted for competing events in our prespecified Cox models to lower the risk of biased estimates.

Our study has limitations. First, we could not evaluate all recorded cardiac rhythms. Second, only 35% of the AF events were assessed by 12-lead ECG, increasing the risk of misclassification. Third, approximately 25% of all the patients with AF had their first AF episode detected at ICU admission. Thus, we cannot rule out that some patients had an undiagnosed persistent AF at ICU admission due to the uncertainty regarding the AF duration upon ICU admission. Fourth, we did not have data on echocardiographic parameters, statin use, or the different subtypes of calcium channel blockers why we may miss some important aspects regarding the management of AF. Fifth, our preplanned statistical models included a limited number of variables. The inclusion of more detailed data on subtypes of cardiovascular disease, echocardiographic evaluation, and laboratory tests may have produced more valid results. The predictors identified in the models may be used to identify patients at high risk of poor

outcomes but may only represent associations and not causal relationships. Finally, our test of the proportional hazard assumption indicated issues with control variables in the 90-day mortality analysis, but not the AF variable. Together with the simplified inclusion of AF in the model (allowing one shift only), the validity and estimates from the Cox model may have been affected. Thus, these results should be interpreted with caution.

CONCLUSIONS

In this international prospective cohort, the frequency of AF and NAF in ICU patients was 15.6% and 13.3%, respectively. Risk factors for AF included arterial hypertension, PAF, sepsis, and high disease severity at ICU admission. We observed variations in the diagnostic and management strategies for AF and few patients were fully anticoagulated during the ICU stay. AF was associated with worse outcomes, while not statistically significantly associated with 90-day mortality in the adjusted analyses.

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