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CLINICAL INVESTIGATION

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New-onset atrial fibrillation in the intensive care unit: Protocol for an international inception cohort study (AFIB-ICU)

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Abstract

Introduction: New-onset atrial fibrillation (NOAF) is frequently observed in critically ill patients and may be associated with prolonged hospital stay and increased mortality. Considerable variation exists in the reported frequencies of NOAF due to the lack of a standardised definition and detection method. Importantly, there are limited data on NOAF in the intensive care unit (ICU). Thus, we aim to provide contemporary epidemiological data on NOAF in the ICU.

Methods and Analysis: We have designed an international inception cohort study including at least 1,000 consecutive adult patients acutely admitted to the ICU without prior history of persistent or permanent AF. We will present data on the incidence, risk factors, used management strategies and outcomes of NOAF. We will register

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data daily during stay in the ICU for a maximum of 90 days after admission. The incidence of NOAF and management strategies used will be presented descriptively, and we will use Cox regression analyses including competing risk analyses to assess risk factors for NOAF and any association with 90-day mortality.

Conclusion: The outlined international AFIB-ICU inception cohort study will provide contemporary data on the incidence, risk factors, used management strategies and outcomes of NOAF in adult ICU patients.

Ethics and dissemination: This observational study poses no risk to the included patients. All participating sites will obtain relevant approvals according to national laws before patient enrollment. Funding sources will have no influence on data handling, analyses or writing of the manuscript. The study report(s) will be submitted to an international peer-reviewed journal.

1 | BACKGROUND

New-onset atrial fibrillation (NOAF) is frequently observed in critically ill patients, but the reported frequencies vary considerably, likely due to varying populations, and the used detection methods and monitoring intensities.[1] NOAF may lead to hemodynamic instability, heart failure and stroke,[2,3] and some studies suggest an association between NOAF and increased mortality in critically ill patients.[4-7] However, uncertainty exists, as the body of evidence consists of a limited number of studies with low methodological quality and conflicting results.[8] Therefore, it is difficult to draw any firm conclusions regarding the clinical implications of NOAF in critically ill patients. Numerous pharmacological and non-pharmacological management strategies of NOAF have been suggested based on physiological understanding and data from non-critically ill patients.[8,9] However, the evidence base for intensive care unit (ICU) patients is very limited, and the balance between the benefits and harms of these interventions is largely unknown in this population.[8,10] To move forward, contemporary data from ICU patients are needed, including data on the incidence of NOAF, risk factors, management strategies and outcome. Concurrently, this study will provide data to inform future clinical trials.

1.1 | Objectives

We aim to assess the incidence of NOAF and its risk factors in a contemporary cohort of adult ICU patients. Moreover, we will provide details on the currently used treatment strategies and assess the outcomes of ICU patients with NOAF. We hypothesise that NOAF is common with considerable variation in the used treatment strategies, specific risk factors for NOAF exist, and that NOAF is associated with adverse outcomes including stroke and death.

1.2 | Research questions

1. What is the incidence of NOAF and what are important risk factors for NOAF in the ICU?
2. What pharmacological and non-pharmacological interventions are used for managing NOAF in the ICU?
3. What is the outcome of ICU patients with NOAF?

2 | METHODS

2.1 | Study design and recruitment

We will conduct an inception cohort study in ICUs in Europe, Asia, the Middle East and Australia/New Zealand. We expect to include at least 1000 patients from 50 to 80 participating ICUs. Patients will be included within inception periods of 14 consecutive days with follow-up 90 days after ICU admission. At each individual site, the local investigator will choose two 14-day inception periods if possible. All patients admitted to the ICU during the inception period will be actively screened for inclusion.

All included ICU patients will be checked for documented episodes of NOAF during the ICU stay. The relevant approvals will be obtained by the national or local investigator according to national laws before study start. It is approved by the Danish Patient Safety Authority 31-1521-9, the Capital Region Knowledge Centre for Data Compliance (P-2020-392) and will be approved by all required authorities in other participating countries before study start. Informed consent from patients or surrogates will be obtained if needed as per national laws.

2.2 | Inclusion criteria

We will screen all adults (age ≥18 years) who are acutely admitted to the ICU within the inception period for inclusion. Patients who are in the ICU before the start of the inception period will not be screened.

2.3 | Exclusion criteria

We will exclude patients who meet any of the following criteria:

1. Previously included in the AFIB-ICU study.
2. Transferred directly from a non-participating ICU
3. Have undergone emergency or scheduled cardiac surgery during the current hospital admission, defined as any surgery including stent procedures such as percutaneous coronary interventions or other angioplasty procedures done on the heart muscle, valves or thoracic arteries including the thoracic part of the aorta.
4. Planned admission to the ICU, defined as a planned transfer to the ICU, eg, after elective surgery or other planned procedures.
5. Documented history of persistent AF, defined as recurrent episodes of AF that last 7 days or more.[11]
6. Documented history of permanent AF, defined as existing AF with failed previous strategies for maintaining sinus rhythm and not further pursued.[11]

2.4 | Study timeline and closure

The AFIB-ICU study began participant enrolment in October 2020 and is currently recruiting (544 patients included, March 11, 2021). The study will be closed when the 90-day follow-up period has ended for all included patients. We expect recruitment to end in the summer of 2021.

3 | OUTCOME MEASURES

3.1 | Definition of NOAF

NOAF is defined as an irregular rhythm with absence of *p* waves and irregular RR intervals identified by continuous monitoring or 12-lead ECG lasting at least 30 seconds if confirmed as AF by the treating doctor.[11]

We will define NOAF as an episode (one or more) of supraventricular arrhythmia documented as AF by the treating doctor. All participants fulfilling these criteria will be classified as having NOAF because we exclude patients with permanent or persistent AF.

3.2 | Primary outcome

The primary outcome is the incidence of NOAF in the ICU. We will define the incidence as the number of participants with at least one detected episode of NOAF either at ICU admission or developed during the ICU stay.

3.3 | Secondary outcomes

1. Ninety-day mortality defined as death within 90 days after ICU admission.
2. Ischaemic and/or thromboembolic events within 90 days after ICU admission.
3. Severe bleeding episodes within 90 days after ICU admission.
4. Length of stay in hospital for a maximum period of 90 days.
5. Length of stay in the ICU for a maximum period of 90 days.

According to national law by the participating countries, the 90-day follow-up will be performed by assessing medical records, national registers or phone call according to national law.

We will use the following definitions:

A Acute myocardial ischaemia: increase in serum cardiac biomarker values and at least one of the following criteria: (1) symptoms of ischaemia, (2) new or presumed significant ST segment or T wave ECG changes, (3) new left bundle branch block, development of pathological Q waves on ECG, (4) radiological or echocardiographic evidence of new loss of viable myocardium or regional wall motion abnormality or (5) identification of an intracoronary thrombus at angiography or autopsy.[12] The acute myocardial ischaemia diagnosis must be confirmed by the doctor as myocardial ischaemia based on the above mentioned clinical and laboratory criteria.

B Ischaemic stroke: clinical signs of neurological dysfunction and verified by computed tomography (CT) or magnetic resonance imaging (MRI)[13]

C Intestinal ischaemia: verified clinically, or by endoscopy, catheter angiography ultrasound, CT-angiography or MRI.[14]

D Acute limb ischaemia: clinical signs, Doppler ultrasound and need of open/percutaneous vascular intervention, amputation or antithrombotic treatment.[15]

E Pulmonary embolism: verified by CT-scan, ventilation–perfusion (VQ) scan or initiation of therapy due to suspected pulmonary embolism.[16]

F Deep venous thrombosis: verified by ultrasound, CT-scan, MRI venography, phlebography or initiation of therapy due to suspected deep venous thrombosis.[16]

G Severe bleeding episodes within 90 days defined a clinical bleeding from any origin AND the use of ≥3 units of red blood cells (RBC) within 24 hours.[17]

3.4 | Data management

Data will be continuously collected in a unique electronic case report form (eCRF) from medical records and laboratory reports by

the local investigator(s) at each participating site. A clinical data management plan for the study will be provided to the local investigators and other authorised research personnel, which includes used definitions, electronic case report form (eCRF) instructions and data handling procedures. The entered data from the eCRF will be exported into an electronic database and securely stored, as required by the national data protection authorities.

We will use the system OpenClinica,[18] which is hosted by the Copenhagen Trial Unit (CTU), Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen University Hospital. All study participants are assigned a unique trial identification number and data will be handled according to applicable laws. The local investigators are responsible for the data collection and their accuracy. In addition, the local investigators will ensure the completeness of the eCRF after the follow-up period. The site investigators will only have access to their own site participants using a personal username and password to log in to the database. No analyses will be performed before data accuracy has been assured.

4 | STATISTICAL METHODS

4.1 | Sample size estimation

Based on an estimated incidence of NOAF of 10%–20% in critically ill patients in general ICUs using continuous monitoring and/or ECG,[8] we plan to include at least 1000 patients to yield an expected 95% confidence interval (CI) for the incidence of NOAF of 8%–12% if the incidence is 10% or 17%–22% if the incidence is 20%.

4.2 | Population to be analysed

We will analyse all included participants and present baseline data in the full cohort stratified by development of NOAF or not during the ICU stay (included in the supplement). Continuous variables will be expressed as medians with interquartile ranges (IQRs) and categorical variables as numbers with corresponding percentages.

4.3 | The incidence of NOAF

The incidence of NOAF will be reported as the number (%) of participants with one or more episodes of NOAF with corresponding 95% CI.

4.4 | Risk factors for NOAF

We will use multivariable Cox models with time since admission as the time-axis and death as a competing risk to compute hazard ratios with 95% CIs to assess the crude and adjusted (for all other variables listed in the following) association between NOAF and the following independent variables: sex, history of hypertension, history of diabetes mellitus, history of paroxysmal AF, history of ischaemic heart disease, COVID-19 status at ICU admission, sepsis at ICU admission, trauma at ICU admission and Simplified Mortality Score for the Intensive Care Unit (SMS-ICU, a severity score).[19,20] Patients with NOAF at admission will not be included in this analysis.

4.5 | The association between NOAF and 90-day mortality

We will assess the association between NOAF and all-cause 90-day survival by Cox hazard modelling (time since admission as time-axis). We will handle NOAF as a binary time-dependent variable adjusting for the time to the first detected episode of NOAF.[21] The following variables will be used in the adjusted analysis: sex, country, history of ischaemic heart disease, septic shock at ICU admission and SMS-ICU.[19] Discharged alive from the ICU will be considered as a competing event.[22,23]

4.6 | Descriptive data

We will descriptively report the following secondary outcomes in participants with and without one or more episodes of NOAF in the following:

- Length of ICU stay (continuous outcome)
- Length of hospital stay (continuous outcome)
- Ischaemic or thromboembolic events (dichotomous outcome)
- Severe bleedings episodes (dichotomous outcome)

Moreover, we will descriptively present the used interventions or treatment strategies for patients with one or more episode of NOAF, including the used anticoagulant therapy. Numerical data will be presented using medians with IQRs and categorical data will be presented as numbers with percentages.

4.7 | Handling of missing data

We expect a low proportion of missing data but will report missingness as numbers with percentages. If 5% or more of the patients have missing data, we will use multiple imputated data for all analyses including patients with at least 5% missing data for all variables included in said analysis.[24,25] We will create 25 imputed datasets under the assumption that data are 'missing at random' and use predictive mean matching and logistic regression methods for numerical and categorical variables, respectively.[26] Where multiple imputations are used, the primary results of the applicable analyses will be based on these data. In addition, the corresponding complete case analyses will be presented in the supplementary material. We will solely use complete case analysis (excluding patients with missing

data) for analyses where the number of patients with missing data for all included variables is less than 5%.[25-27] Any additional details on missing data handling, selection and exclusion of observations and handling of statistical analysis will be provided in the manuscript.

5 | ADMINISTRATIVE ASPECTS

5.1 | Confidentiality

The obtained data and other information from the included participants will be held in strict confidence by the investigators, research staff and the study sponsor.

No information or data concerning the study will be released by any unauthorised third party, without a prior written approval of the sponsoring institution. Authorised representatives from the sponsor may inspect all documents and records required to be maintained by the investigator. All reports that leave the site will be identified only by the subject identification number to ensure confidentiality.

6 | PUBLICATION POLICY

The management committee holds the primary responsibility for a transparent reporting of the protocol and the study results. When the study has been completed, the main manuscript will be reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement[28] and submitted to an international peer-reviewed journal. All participating principal site investigators are obliged to declare any conflicts of interest, including financial. Any deviations from this protocol will be described along with reasoning in the study report.

6.1 | Authorship and dissemination

Members of the management committee, national and site investigators will be granted authorship according to the guidelines from the International Committee for Medical Journal Editors (ICMJE; http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html). All other research personnel or persons contributing to the study will be acknowledged as 'AFIB-ICU cohort study collaborators' in a supplementary appendix to the main paper. Funding sources will have no influence on data handling or analyses or writing of the manuscript. Publication of data from substudies will be encouraged after the approval by the Management Committee of a written protocol for such a study.

7 | DISCUSSION

AF is the most common tachyarrhythmia worldwide and evidence derived from non-critically ill populations has associated AF with worse outcomes.[29] The evidence base in the critical care setting is weak due to lack of studies with appropriate methodology, considerable heterogeneity and conflicting results.[8] Furthermore, currently used management strategies or interventions used against NOAF in the ICU are supported by low/very low-quality evidence.[8,10] Consequently, prospective observational studies are warranted to describe clinical practice and provide important epidemiological data for the planning future of trials in this area. The AFIB-ICU inception cohort study will have several strengths. The study has been planned and designed in accordance with the STROBE statement.[28] including a predefined statistical analysis plan, prespecified variables and outcomes of interest, thereby increasing the internal validity and transparency of the study. The international design and participation of ICUs in different countries allow us to assess geographical and interregional differences in management strategies of NOAF, thereby providing data with external validity.

We have chosen a pragmatic approach to diagnose NOAF, which we believe reflects clinical practice in many ICUs. We are not able to retrospectively assessing all recorded heart rhythm by continuous cardiac monitoring during the ICU, which may lead to an underestimation of the incidence of NOAF. Inherent limitations include the risk of missing data, patients lost to follow-up and incomplete data collection, which may lower the precision of the data and introduce bias.

In addition, the multifactorial nature of AF and known heterogeneity among ICU patients makes this study prone to residual confounding.

In conclusion, the AFIB-ICU inception cohort study will provide important information about NOAF in adult ICU patients, and the results will inform future randomised clinical trials on the optimal management strategy in these patients.

CONFLICT OF INTEREST

The Department of Intensive Care, Rigshospitalet, has received funds for other research projects from the Novo Nordisk Foundation and Pfizer.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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