

New-onset atrial fibrillation in intensive care: epidemiology and outcomes

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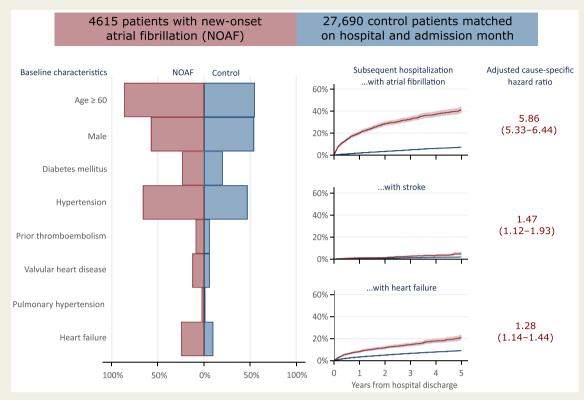
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Aims	New-onset atrial fibrillation (NOAF) is common in patients treated on an intensive care unit (ICU), but the long-term impacts on patient outcomes are unclear. We compared national hospital and long-term outcomes of patients who developed NOAF in ICU with those who did not, before and after adjusting for comorbidities and ICU admission factors.
Methods and results	Using the RISK-II database (Case Mix Programme national clinical audit of adult intensive care linked with Hospital Episode Statistics and mortality data), we conducted a retrospective cohort study of 4615 patients with NOAF and 27 690 matched controls admitted to 248 adult ICUs in England, from April 2009 to March 2016. We examined in-hospital mortality; hospital readmission with atrial fibrillation (AF), heart failure, and stroke up to 6 years post discharge; and mortality up to 8 years post discharge. Compared with controls, patients who developed NOAF in the ICU were at a higher risk of in-hospital mortality [unadjusted odds ratio (OR) 3.22, 95% confidence interval (CI) 3.02–3.44], only partially explained by patient demographics, comorbidities, and ICU admission factors (adjusted OR 1.50, 95% CI 1.38–1.63). They were also at a higher risk of subsequent hospitalization with AF [adjusted cause-specific hazard ratio (aCHR) 5.86, 95% CI 5.33–6.44], stroke (aCHR 1.47, 95% CI 1.12–1.93), and heart failure (aCHR 1.28, 95% CI 1.14–1.44) independent of pre-existing comorbidities.
Conclusion	Patients who develop NOAF during an ICU admission are at a higher risk of in-hospital death and readmissions to hos- pital with AF, heart failure, and stroke than those who do not.

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Baseline characteristics and outcomes of patients in intensive care with new-onset atrial fibrillation compared with patients without atrial fibrillation.

Keywords

Atrial fibrillation • Intensive care • Epidemiology • Critical care • Cohort studies

Introduction

Atrial fibrillation (AF) is common in patients treated on an intensive care unit (ICU).¹ Atrial fibrillation occurring in patients with no prior AF diagnosis (new-onset AF, NOAF) is associated with increased ICU and hospital mortality.^{2,3} The longer-term outcomes for patients who develop NOAF during an ICU admission are unclear.

Atrial fibrillation during critical illness is triggered and maintained by multiple factors involving comorbidities and acute illness severity.^{4,5} Many patients may return to sinus rhythm during resolution of their illness.^{6,7} However, the risks of AF recurring after ICU discharge and the associated sequelae (e.g. stroke) are unclear. There is some evidence that NOAF that develops during hospitalization is associated with a higher risk of future episodes of AF, stroke,⁸ and readmission to hospital.⁹ Outcomes for patients who develop NOAF during an ICU admission require further study. There is no strong evidence to guide NOAF treatment during ICU admission or after ICU discharge.^{10–12} Consequently, current practice varies considerably, particularly in the use of anticoagulation.¹³

This study aimed to compare the outcomes of patients who developed NOAF during an ICU admission to patients without AF.

Methods

Data sources

We published the protocol prior to analysis¹⁴ and report according to the Reporting of studies Conducted using Observational Routinely collected Data (RECORD) guidelines.¹⁵ We analysed patient records from the Risk-II database of anonymized, linked, routinely collected data from (i) the Case Mix Programme (CMP) national clinical audit of adult intensive care,¹⁶ (ii) Hospital Episode Statistics (HES) for England —Admitted Patient Care,¹⁷ and (iii) the Office for National Statistics (ONS) mortality databases.

Case Mix Programme data are collected for the purpose of service evaluation and quality improvement in critical care. The CMP includes admission records for each participating adult high dependency or ICU in England, Wales, or Northern Ireland.¹⁶ Not all ICUs participated during the study period though coverage reached 100% in the final year. The CMP was used to identify the study cohort, extract patient demographics, and provide dates for the start and end of hospital admission and critical care.

Hospital Episode Statistics data are collected for the purpose of reimbursing National Health Service (NHS) hospitals for provision of services. The HES 'Admitted Patient Care' section contains records for each 'episode of care' under one consultant during a hospital admission. The HES Admitted Patient Care database includes all NHS hospital

Graphical Abstract

admissions with associated diagnostic and procedure coding. We used the diagnostic coding to identify AF during or prior to ICU admission; comorbidities recorded in the index or prior hospitalizations; and subsequent hospitalizations with AF, stroke, or heart failure.

The ONS mortality database contains information on all deaths registered in the UK and was used to identify mortality after hospital discharge.

The anonymized Risk-II database is maintained by the Intensive Care National Audit and Research Centre (ICNARC) and includes links to HES and ONS by NHS Digital using a deterministic algorithm that uses patients' NHS number (a unique patient identifier), date of birth, post-code, and sex. The RISK-II database was generated under HRA approval 15-WA-0256, allowing secondary analysis of the anonymized data.

Participants

The Risk-II database includes CMP records from 1 April 2009 to 31 March 2016, HES records from 1 April 2004 to 31 March 2016, and ONS records from 1 April 2009 to 31 October 2018. We excluded admissions to cardiothoracic ICUs but did not exclude patients treated for cardiac conditions on general ICUs. We also excluded admissions lasting <4 h, and patients aged under 16 at the time of ICU admission.

Identification of atrial fibrillation

Codes used for identifying diagnoses are summarized in Supplementary material online, *Table S1*.

Pre-existing AF was identified where a HES record containing a diagnostic code for AF preceded an ICU admission (CMP record). This included all HES records from previous hospital admissions and any care episodes that preceded ICU admission. Additionally, if any HES record relating to the same hospital admission contained a procedure code for atrial ablation, pacemaker insertion, or direct current cardioversion, then AF was classified as pre-existing.

We defined NOAF as AF occurring during an ICU admission when a new diagnosis of AF was contained within a HES record that overlapped in time with a CMP record, in the absence of pre-existing AF.

For some patients, overlaps between CMP and HES records created uncertainty about whether AF developed prior, during, or after ICU admission. Rules for handling these ambiguities are summarized in Supplementary material online, *Table S2*. Where there was ambiguity about whether AF developed prior to or during ICU admission, we assumed that AF developed prior. Where there was ambiguity about whether AF developed during or after ICU admission (but while in hospital), these patients were excluded from the primary analysis. We conducted a sensitivity analysis including the latter group of patients; the primary analysis therefore favoured specificity, whereas our sensitivity analysis adopted broader criteria for classifying NOAF.

Outcomes

Date and cause of death were obtained from ONS and status at hospital discharge from CMP. Subsequent deaths were classified as 1–90 days, 91 days to 1 year, or >1 year after hospital discharge. Hospital readmission involving AF, ischaemic stroke, or heart failure was identified from diagnosis codes (see Supplementary material online, *Table S1*) in linked HES records. Matching of patients on calendar month of admission and use of time-to-event analysis with censoring of patients at the end of the relevant data set's observation window (see below), allowed for patients to be followed for up to 8 years (mortality) or 6 years (hospital readmission) post-discharge.

Comorbidities

Comorbidities were identified from HES records prior to ICU admission that contained a diagnosis code for diabetes mellitus, hypertension, thromboembolism (including stroke), valvular heart disease, dilating cardiomyopathy, pulmonary hypertension, or heart failure (see Supplementary material online, *Table S1*).

Selection of matched controls

To align different observational windows and the associated varying degrees of follow-up, we created a control cohort, matched to our NOAF cohort on hospital, month, and year of admission to ICU. Control patients were selected from all available ICU admissions with no evidence of pre-existing or new-onset AF in their linked HES records. Matching was performed to maximize the size of the control cohort while ensuring that at least 99% of patients with NOAF were included.

Statistical analysis

We estimated odds ratios (ORs) for hospital mortality using logistic regression. We estimated hazard ratios (HRs) for mortality after hospital discharge using Cox proportional hazard regression. For subsequent hospitalization with AF, stroke, and heart failure, we estimated unadjusted and adjusted cause-specific HRs (CHRs) using non-parametric methods to account for the competing risk of death.^{18,19} Each of these models were estimated before and after adjustment for age, sex, and comorbidities. We additionally adjusted mortality outcomes for ICU admission factors. These included illness severity as measured by a modified ICNARC physiology score²⁰ with heart rate contribution removed, cardiopulmonary resuscitation prior to admission, admission type, and reason for ICU admission. The proportional hazard assumption was tested by visual inspection of Schoenfeld residual plots. Age was modelled continuously using a restricted cubic spline.²¹

Results for the primary analysis were compared with a sensitivity analysis employing the broader definition for NOAF, as detailed in Supplementary material online, *Table S2*.

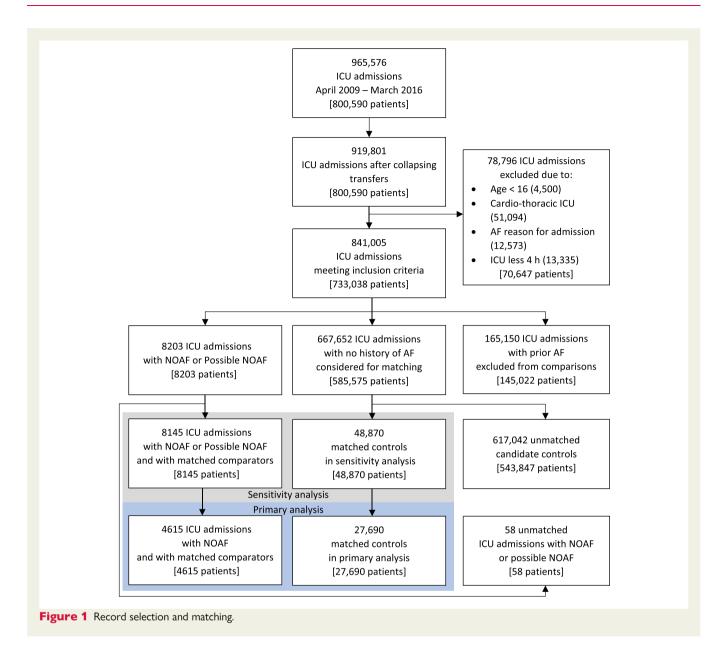
Results

We identified 965 576 admissions to 248 ICUs in England between April 2009 and March 2016, comprising 800 590 individual patients. After excluding admissions to cardiothoracic units, admissions lasting <4 h, or where admission age was <16 years, 841 005 admissions from 241 ICUs were available for analysis.

Of these admissions, we identified 4615 patients with NOAF along with 27 690 matched controls for the primary analysis. For our sensitivity analysis, we identified 8145 patients with NOAF along with 48 870 matched controls (*Figure 1*).

On average, patients who developed NOAF were older, with a greater number of previous hospitalizations involving hypertension, heart failure, or valvular heart disease. They were less likely to be elective/scheduled surgical admissions, and appeared sicker on average, with higher ICNARC physiology scores (*Table 1*).

Median follow-up time was 2.8 years (interquartile range 1.3–4.6 years) from ICU admission. Kaplan–Meier survival plots for each outcome are illustrated in *Figures 2* and *3*. Compared with controls, patients with NOAF had an elevated risk of death in hospital [unadjusted OR 3.22, 95% confidence interval (CI) 3.02–3.44] and during the first 90 days after hospital discharge (unadjusted HR 2.11, 95% CI 1.83–2.44; *Table 2*). Approximately half of this excess risk was explained by patient characteristics and comorbidities



(adjusted OR for death in hospital 2.32, 95% CI 2.16–2.48, and adjusted HR for death during the first 90 days after hospital discharge 1.46, 95% CI 1.26–1.70). After adjusting for ICU admission factors including illness severity, NOAF remained associated with hospital mortality (adjusted OR 1.50, 95% CI 1.38–1.63), but was no longer significantly associated with death during the first 90 days after hospital discharge (adjusted HR 1.10, 95% CI 0.95–1.29).

Smaller increases in risk of death >90 days after hospital discharge were entirely explained by patients' characteristics and medical history (death 91 days to 1 year after discharge unadjusted HR 1.38, 95% CI 1.20–1.59, adjusted HR 0.99, 95% CI 0.86–1.15; death >1 year after discharge unadjusted HR 1.66, 95% CI 1.53–1.79, adjusted HR 1.04, 95% CI 0.96–1.12).

Compared with controls, patients with NOAF were at 10 times the risk of subsequent hospitalization with AF (20.2 vs. 1.9%, unadjusted CHR 9.77, 95% CI 8.91–10.70) and over twice the risk of

subsequent hospitalization with stroke (1.2 vs. 0.5%, unadjusted CHR 2.31, 95% CI 1.77–3.02) or heart failure (7.8 vs. 2.8%, unadjusted CHR 2.68, 95% CI 2.39–2.99). Approximately half of these excesses in risk were explained by patients' characteristics and medical history (adjusted CHR for subsequent hospitalization with AF 5.86, 95% CI 5.33–6.44; stroke 1.47, 95% CI 1.12–1.93; and heart failure 1.28, 95% CI 1.14–1.44). Cumulative incidence of events at 1, 3, and 5 years are summarized in Supplementary material online, *Table S3* and the cumulative incidence of death, by cause of death, in Supplementary material online, *Table S4*.

When the classification of NOAF was relaxed for the sensitivity analysis to include patients where there was uncertainty about whether NOAF developed in ICU or on the ward after ICU discharge, patient characteristics and comorbidities remained similar (see Supplementary material online, *Table S5*). However, hospital mortality reduced from 43.3% among patients with NOAF in the

Table 1Patient characteristics

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	NOAF (<i>N</i> = 4615)	Control ^a (N = 27 690)						
Age, years, mean (SD)	71.5 (11.3)	59.1 (17.8)						
Sex, male, <i>n</i> (%)	2646 (57.3%)	15 008 (54.2%)						
Ethnicity								
White, <i>n</i> (%)	4332 (93.9%)	25 157 (90.9%)						
Mixed, n (%)	7 (0.2%)	113 (0.4%)						
Asian, <i>n</i> (%)	86 (1.9%)	854 (3.1%)						
Black, n (%)	48 (1.0%)	564 (2.0%)						
Other, <i>n</i> (%)	35 (0.8%)	294 (1.1%)						
Not stated, n (%)	107 (2.3%)	708 (2.6%)						
Obesity (body mass	1085 (26.5%)	5926 (24.4%)						
index \geq 30 kg/m ²), <i>n</i> (%)								
Previous hospitalization with:								
Hypertension, n (%)	3050 (66.1%)	13 056 (47.2%)						
Heart failure, n (%)	1146 (24.8%)	2791 (10.1%)						
Diabetes mellitus, n (%)	1085 (23.5%)	5691 (20.6%)						
lschaemic heart disease, n (%)	1450 (31.4%)	5741 (20.7%)						
Valvular heart disease, n (%)	578 (12.5%)	1720 (6.2%)						
Thromboembolism (including	418 (9.1%)	1715 (6.2%)						
stroke), n (%)								
Peripheral artery disease, n (%)	782 (16.9%)	3435 (12.4%)						
Pulmonary hypertension, n (%)	121 (2.6%)	322 (1.2%)						
Dilating cardiomyopathy, n (%)	30 (0.7%)	141 (0.5%)						
Reasons for admission to ICU								
Surgical: elective/scheduled								
Cardiac, n (%)	10 (0.2%)	77 (0.3%)						
Other, n (%)	448 (9.7%)	6524 (23.6%)						
Surgical: emergency/urgent								
Cardiac, n (%)	5 (0.1%)	32 (0.1%)						
Trauma, <i>n</i> (%)	346 (7.5%)	1572 (5.7%)						
Other, n (%)	695 (15.1%)	3792 (13.7%)						
Medical								
Cardiac, n (%)	294 (6.4%)	1106 (4.0%)						
Other, n (%)	2817 (61.0%)	14 587 (52.7%)						
CPR in 24 h prior to ICU	5 (0.1%)	32 (0.1%)						
admission, n (%)								
Physiology during first 24 h of ICU admission								
Lowest systolic blood pressure (mmHg), mean (SD)	91 (18)	97 (20)						
Highest temperature (°C), mean (SD)	37.7 (1.0)	37.6 (1.0)						
Lowest respiratory rate (min ⁻¹), mean (SD)	14.0 (4.4)	13.0 (4.0)						
Urine output (mL), mean (SD)	1417 (1141)	1887 (1403)						
PaO_2/FiO_2 (kPa), mean (SD)	26.2 (13.6)	33.9 (16.3)						
Lowest pH, mean (SD)	7.28 (0.12)	7.31 (0.12)						
Highest urea (mmol/L), mean (SD)		9.6 (9.1)						
		Continued						

Table 1 Continued

	NOAF (N = 4615)	Control ^a (N = 27 690)
Lowest white blood cell count (×10 ⁹ /L), mean (SD)	12.5 (11.4)	11.9 (8.6)
Highest creatinine (mg/dL), mean (SD)	2.0 (2.1)	1.5 (1.8)
Highest serum sodium mmol/L), mean (SD)	139 (6)	139 (5)
ICNARC physiology score ^b	20 (1527)	14 (9.20)

AF, atrial fibrillation; SD, standard deviation.

^aNo documented AF prior to or during ICU stay.

 $^{\mathrm{b}}\mathrm{Customized}$ version of the ICNARC physiology score excluding heart rate component.

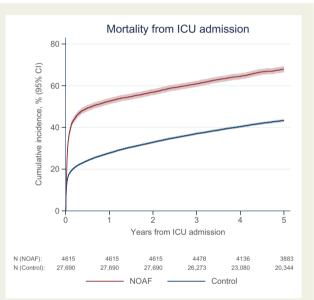


Figure 2 Cumulative incidence of mortality from intensive care unit admission. Cumulative incidence of mortality estimated using the Kaplan–Meier method.

primary analysis to 34.1% in the sensitivity analysis (see Supplementary material online, *Table S5*). Accordingly, after accounting for comorbidities and ICU admission factors, there was no longer an association between NOAF and in-hospital mortality (adjusted OR 1.02, 95% CI 0.96–1.09), although a small increase was observed in the first 90 days post-discharge (adjusted OR 1.22, 95% CI 1.10–1.35; see Supplementary material online, *Table S6*). Consistent with the primary analysis, risks of hospital readmission remained elevated in the NOAF cohort (adjusted CHR for readmission with AF 6.41, 95% CI 5.99–6.85; stroke 1.59, 95% CI 1.32–1.91, and heart failure 1.25, 95% CI 1.15–1.35). Unadjusted cumulative incidence of events at 1, 3, and 5 years in the sensitivity analysis cohort is summarized in Supplementary material online, *Table S7*.

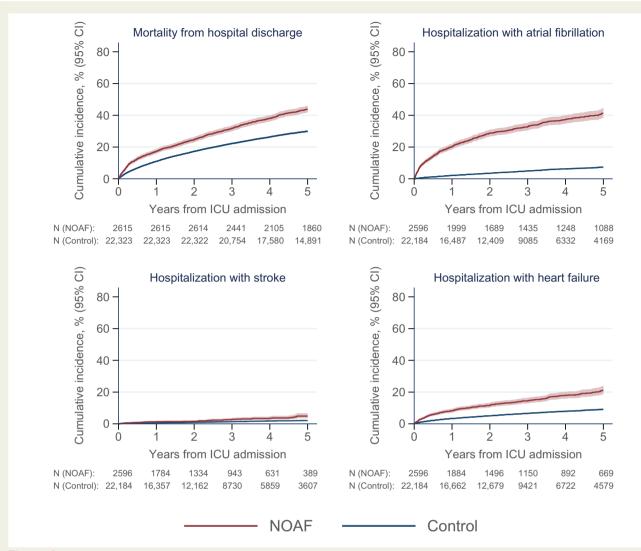


Figure 3 Cumulative incidence of mortality and hospitalization after hospital discharge. Cumulative incidence of mortality estimated using the Kaplan–Meier method. Cumulative incidences of hospital admission with atrial fibrillation, stroke, and heart failure estimated using non-parametric methods to account for competing risk of death.

Discussion

This study demonstrates that patients who develop NOAF during an ICU stay are older and have more comorbidities than those who do not. After controlling for these differences, patients with NOAF still have substantially higher mortality in hospital, and have higher rates of subsequent hospitalization with AF, stroke, and heart failure than those who do not. In patients who survive to hospital discharge, the excess risk of death associated with ICU-acquired NOAF was accounted for by differences in patient demographics, comorbidities, and ICU admission factors including illness severity.

Our study findings are limited by the sensitivity of diagnostic records, that is, NOAF may have been present but not have been recorded, or it may be ambiguous as to whether AF that was recorded was new-onset or pre-existing. We adopted a NOAF definition that favoured specificity over sensitivity. We prioritized confidence in a NOAF diagnosis at the expense that not all cases of NOAF would be identified. Our methods explain the low reported incidence of NAOF compared with existing literature. Comparison with other data sources suggests that we identified a subset of all patients who developed NOAF who likely represent those patients for whom their AF was of sufficient clinical importance to be documented in their clinical notes. It is likely, therefore, that our NOAF cohort does not contain patients who had brief episodes of self-limiting, or easily treated AF.

Furthermore, the sensitivity of our outcomes may be limited, for example, our outcome of hospitalized ischaemic stroke may miss extremes of severity where mild strokes were managed in an outpatient setting, or where death occurred prior to hospital admission. Potentially relevant information that was not available in the linked data sources includes some risk factors (e.g. dyslipidaemia, smoking, and alcohol use) and anticoagulation therapy during or after critical care admission. Lastly, we did not analyse the outcomes of patients with pre-existing AF.

Table 2 Outcomes

Outcomes	NOAF	Control ^a	NOAF vs. control		
During hospital admission	Events/N (%)		Unadjusted OR (95% CI)	Adjusted OR (95% Cl) ^b	Adjusted OR (95% CI) ^c
Death	2000/4615 (43.3)	5367/27 690 (19.4)	3.22 (3.02–3.44)	2.32 (2.16–2.48)	1.50 (1.38–1.63)
After hospital discharge	Events/person-years (IR)		Unadjusted HR (95% CI)	Adjusted HR (95% Cl) ^b	Adjusted HR (95% Cl) ^c
Death					
1–90 days after discharge	213/609 (35.0)	907/5400 (16.8)	2.11 (1.83–2.44)	1.46 (1.26–1.70)	1.10 (0.95–1.29)
91 days—1 year after discharge	227/2250 (10.1)	1512/20 688 (7.3)	1.38 (1.20–1.59)	0.99 (0.86–1.15)	0.91 (0.79–1.06)
>1 year after discharge	736/9548 (7.7)	4675/96 268 (4.9)	1.66 (1.53–1.79)	1.04 (0.96–1.12)	0.96 (0.88–1.04)
Subsequent hospital admission with:			Unadjusted CHR (95% Cl)	Adjusted CHR (95% CI) ^b	_
Atrial fibrillation	855/4231 (20.2)	1017/53 458 (1.9)	9.77 (8.91–10.70)	5.86 (5.33-6.44)	_
Stroke	68/5574 (1.2)	283/54 509 (0.5)	2.31 (1.77–3.02)	1.47 (1.12–1.93)	_
Heart failure	395/5087 (7.8)	1462/52 907 (2.8)	2.68 (2.39–2.99)	1.28 (1.14–1.44)	_

Hazard ratios estimated using Cox proportional hazards regression \pm adjustment for the same factors. Cause-specific hazard ratios estimated using Cox proportional hazards regression with censoring at death \pm adjustment for the same factors.

AF, atrial fibrillation; CHR, cause-specific hazard ratio; CI, confidence interval; HR, hazard ratio; IR, incidence rate; NOAF, new-onset atrial fibrillation; OR, odds ratio.

^aNo documented AF prior to or during ICU stay. Odds ratios estimated using logistic regression. ^bAdjusted for age (using a restricted cubic spline with knots at positions 25, 54, 68, and 84 years), sex, diabetes mellitus, hypertension, prior thromboembolism, valvular heart disease, pulmonary hypertension, and heart failure.

^cAdjusted for comorbidities listed under footnote b in addition to CPR prior to admission, illness severity (customized version of the ICNARC physiology score excluding heart rate component), admission type (medical admission/admission following elective surgery/admission following emergency surgery), and reason for ICU admission [system level: cardiovascular, gastrointestinal, genito-urinary, neurological (including eyes), respiratory, and others].

We found that even after accounting for pre-existing comorbidities, the occurrence of NOAF during an ICU stay was associated with a considerably increased risk of hospital readmission with AF. Recurrence of AF during the same ICU admission appears to be common, with around one-third of patients developing AF again in the ICU after initial successful treatment.^{6,7} Our study extends these findings by suggesting persistence of AF after hospital discharge. This is indicated by persistent elevation of risk of readmission with AF. One previous Korean study found 34% of those who developed NOAF during an ICU admission had recurrent AF documented in hospital claims in the following 6 months.²² Together, this suggests that much of the NOAF associated with critical illness does not resolve with treatment of the underlying condition. Our study provides the evidence to support current guidelines stating that patients developing NOAF secondary to a potentially 'reversible' condition should receive careful follow-up,²³ countering the notion in previous guidelines that successful treatment of the underlying condition often eliminates AF.²⁴

Our finding of important AF recurrence/persistence gives weight to our finding of increased stroke risk in patients who develop NOAF during critical illness. Limited prior evidence exists to support our finding. In a Korean retrospective analysis of patients who survived for >6 months after an ICU admission, NOAF during an ICU stay was associated with an increased risk of subsequent stroke or systemic embolism in age and comorbidity propensity-matched groups over 3 years of follow-up.²² A retrospective study in the USA of hospitalized patients with sepsis demonstrated that patients who developed NOAF during their hospital admission are at increased risk of ischaemic stroke compared with those who did not over the 5 years post-hospital discharge, despite accounting for comorbidities and certain sepsis-severity variables.⁹ Together these findings suggest that some patients who develop NOAF during critical illness may benefit from follow-up and anticoagulation for stroke prophylaxis where indicated. The optimal subgroups and timing of anticoagulation initiation is unclear, with practice variable within and across ICUs.^{13,25} Prospective studies are needed of monitoring and follow-up strategies to identify the timing of AF recurrence, and patients at highest risk, most likely to benefit from anticoagulation.

We found elevated hospital mortality rates in those patients developing ICU-acquired NOAF. There are plausible mechanisms to explain the association between NOAF and early mortality. Organized atrial activity contributes to ventricular filling and cardiac output. New-onset atrial fibrillation, therefore, detrimentally affects haemodynamic status, and results in a reduction in blood pressure and increased need for vasoactive medications²⁶ and precedes organ failure²⁷ in patients in an ICU. New-onset atrial fibrillation is also associated with early thromboembolic complications during critical illness that may contribute to mortality.²⁸ Notably, in our sensitivity analysis including patients who may have developed NOAF in hospital after ICU discharge, there was no association between NOAF and in-hospital mortality. These findings give weight to the hypothesis that NOAF during critical illness confers most mortality risk when patients are most unwell, on an ICU, where haemodynamic impact is likely to be most marked.

A causal association between ICU-acquired NOAF and longerterm mortality is less clear. Previous evidence has suggested that developing NOAF during an ICU stay is associated with increased allcause mortality after hospital discharge. One single-centre study in The Netherlands found a 26% 1-year mortality in patients who developed NOAF in the ICU, vs. 4.6% in propensity-matched patients who did not develop NOAF. A study of patients with sepsis also identified an increased risk of mortality over the 5 years posthospital discharge in those who developed NOAF.⁹ Notably, the relative increase in mortality risk reduced over time, with no evident increase in adjusted risk after 1 year. We show that after comprehensively accounting for comorbidities and illness severity at ICU admission, ICU-acquired NOAF is not independently associated with mortality after hospital discharge. While persistent or recurrent AF after an ICU admission may result in stroke and heart failure, deaths from these conditions were rare (see Supplementary material online, Table S3). Our study may therefore have been underpowered to detect excess deaths directly resulting from sequalae of ICU-acquired NOAF. Elevated post-discharge mortality in previous studies is unlikely to be accounted for by these segualae and may instead reflect residual confounding from the higher illness severity that often coexists with NOAF, but which was accounted for in our study.

Conclusions

Patients who develop NOAF during an ICU admission are at considerably higher risk of future hospital admissions with AF, heart failure, and stroke than those who did not develop AF. These differences remain after accounting for differences in demographics and comorbid status. Patients with NOAF have higher mortality inhospital and after hospital discharge, though post-discharge mortality is explained by differences in demographics, comorbidities, and ICU admission factors. Future studies to identify patients most at risk of AF recurrence and stroke are required to inform postdischarge management of this common problem. Patients who develop NOAF during an ICU admission are likely to benefit from cardiological surveillance and follow-up after hospital discharge.

Supplementary material

Supplementary material is available at European Heart Journal: Acute Cardiovascular Care online.

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Data availability

Information about accessing the anonymized data underlying this article can be found at https://www.icnarc.org/Our-Audit/Audits/Cmp/ Reports/Access-Our-Data.

References

- Wetterslev M, Haase N, Hassager C, Belley-Cote EP, McIntyre WF, An Y, Shen J, Cavalcanti AB, Zampieri FG, Guimaraes HP, Granholm A, Perner A, Møller MH. New-onset atrial fibrillation in adult critically ill patients: a scoping review. *Intensive Care Med* 2019;45:928–938. https://doi.org/10.1007/s00134-019-05633-x
- Klouwenberg PMK, Frencken JF, Kuipers S, Ong DS, Peelen LM, van Vught LA, Schultz MJ, van der Poll T, Bonten MJ, Cremer OL. Incidence, predictors, and outcomes of new-onset atrial fibrillation in critically ill patients with sepsis: a cohort study. Am J Respir Crit Care Med 2017;195:205–211. https://doi.org/10.1164/rccm. 201603-0618OC
- Bedford JP, Gerry S, Hatch RA, Rechner I, Young JD, Watkinson PJ. Hospital outcomes associated with new-onset atrial fibrillation during ICU admission: a multicentre competing risks analysis. J Crit Care 2020;60:72–78. https://doi.org/10.1016/j.jcrc. 2020.07.009
- Bedford JP, Ede J, Watkinson PJ. Triggers for new-onset atrial fibrillation in critically ill patients. *Intensive Crit Care Nurs* 2021;67:103114. https://doi.org/10.1016/j.iccn.2021. 103114
- Bosch NA, Cimini J, Walkey AJ. Atrial fibrillation in the ICU. Chest 2018;154: 1424–1434. https://doi.org/10.1016/j.chest.2018.03.040
- Meierhenrich R, Steinhilber E, Eggermann C, Weiss M, Voglic S, Bogelein D, Gauss A, Georgieff M, Stahl W. Incidence and prognostic impact of new-onset atrial fibrillation in patients with septic shock: a prospective observational study. *Crit Care* 2010;**14**: R108. https://doi.org/10.1186/cc9057
- Liu WC, Lin WY, Lin CS, Huang HB, Lin TC, Cheng SM, Yang SP, Lin JC, Lin WS. Prognostic impact of restored sinus rhythm in patients with sepsis and new-onset atrial fibrillation. *Crit Care* 2016;20:373. https://doi.org/10.1186/s13054-016-1548-2
- Frost L, Engholm G, Johnsen S, Moller H, Husted S. Incident stroke after discharge from the hospital with a diagnosis of atrial fibrillation. *Am J Med* 2000;**108**:36–40. https://doi.org/10.1016/s0002-9343(99)00415-5
- Walkey AJ, Hammill BG, Curtis LH, Benjamin EJ. Long-term outcomes following development of new-onset atrial fibrillation during sepsis. *Chest* 2014;**146**:1187–1195. https://doi.org/10.1378/chest.14-0003
- 10. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P, Agewall S, Camm J, Baron Esquivias G, Budts W, Carerj S, Casselman F, Coca A, De Caterina R, Deftereos S, Dobrev D, Ferro JM, Filippatos G, Fitzsimons D, Gorenek B, Guenoun M, Hohnloser SH, Kolh P, Lip GYH, Manolis A, McMurray J, Ponikowski P, Rosenhek R, Ruschitzka F, Savelieva I, Sharma S, Suwalski P, Tamargo JL, Taylor CJ, Van Gelder IC, Voors AA, Windecker S, Zamorano JL, Zeppenfeld K. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016;**37**: 2893–2962. https://doi.org/10.1093/eurhearti/ehw210
- 11. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. *Circulation* 2014;**130**:2071–2104. https://doi.org/10.1161/ CIR.0000000000000040
- National Institute for Health and Care Excellence. Atrial fibrillation: diagnosis and management. nice.org.uk/guidance/ng196 (1 September 2021).
- Chean CS, McAuley D, Gordon A, Welters ID. Current practice in the management of new-onset atrial fibrillation in critically ill patients: a UK-wide survey. PeerJ 2017;5: e3716. https://doi.org/10.7717/peerj.3716
- Watkinson PJ, Mouncey P, Rowan K, Corbett M, Johnson A, Harrison D, Rajappan K, Young JD. Critical care atrial fibrillation evaluation (CAFE): a scoping review and database analysis. National Institute for Health and Care Research; 2019. https://njladmin.nihr.ac.uk/document/download/2028570 (19 February 2022).
- Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement. *PLoS Med* 2015;**12**: e1001885. https://doi.org/10.1371/journal.pmed.1001885
- 16. Harrison DA, Brady AR, Rowan K. Case mix, outcome and length of stay for admissions to adult, general critical care units in England, Wales and Northern Ireland: the Intensive Care National Audit & Research Centre Case Mix Programme Database. Crit Care 2004;8:R99–R111. https://doi.org/10.1186/cc2834

- Herbert A, Wijlaars L, Zylbersztejn A, Cromwell D, Hardelid P. Data resource profile: hospital episode statistics admitted patient care (HES APC). *Int J Epidemiol* 2017; 46:1093–1093i. https://doi.org/10.1093/ije/dyx015
- Coviello V, Boggess M. Cumulative incidence estimation in the presence of competing risks. Stata J 2004;4:103–112. https://doi.org/10.1177/1536867(0400400201
- Lau B, Cole SR, Gange SJ. Competing risk regression models for epidemiologic data. Am J Epidemiol 2009;**170**:244–256. https://doi.org/10.1093/aje/kwp107
- Harrison DA, Parry GJ, Carpenter JR, Short A, Rowan K. A new risk prediction model for critical care: the Intensive Care National Audit & Research Centre (ICNARC) model. Crit Care Med 2007;35:1091–1098. https://doi.org/10.1097/01.CCM. 0000259468.24532.44
- Harrell J Jr. Regression Modeling Strategies: With Applications to Linear Models, Logistic Regression, and Survival Analysis. New York: Springer; 2001.
- Kim K, Yang PS, Jang E, Yu HT, Kim TH, Uhm JS, Kim JY, Sung JH, Pak HN, Lee MH, Lip GYH, Joung B. Long-term impact of newly diagnosed atrial fibrillation during critical care: a south Korean nationwide cohort study. *Chest* 2019;**156**:518–528. https://doi. org/10.1016/j.chest.2019.04.011
- 23. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2014;64:e1–e76. https://doi.org/10.1016/j.jacc. 2014.03.022
- 24. Fuster V, Ryden LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, Halperin JL, Le Heuzey JY, Kay GN, Lowe JE, Olsson SBI, Prystowsky EN, Tamargo JL, Wann S, Smith

- SC, Jacobs AK, Adams CD, Anderson JL, Antman EM, Halperin JL, Hunt SA, Nishimura R, Ornato JP, Page RL, Riegel B, Priori SG, Blanc JJ, Budaj A, Camm AJ, Dean V, Deckers JW, Despres C, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Tamargo JL, Zamorano JL. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (writing committee to revise the 2001 guidelines for the management of patients with atrial fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Circulation*;2006: e257–e354. https://doi.org/10.1161/CIRCULATIONAHA.106.177292
- Labbe V, Bagate F, Cohen A, Voiriot G, Fartoukh M, Mekontso-Dessap A. A survey on the management of new onset atrial fibrillation in critically ill patients with septic shock. J Crit Care 2021;61:18–20. https://doi.org/10.1016/j.jcrc.2020.09.025
- Bedford JP, Johnson A, Redfern O, Gerry S, Doidge J, Harrison D, Rajappan K, Rowan K, Young JD, Mouncey P, Watkinson P. Comparative effectiveness of common treatments for new-onset atrial fibrillation within the ICU: accounting for physiological status. *J Crit Care* 2022;67:149–156. https://doi.org/10.1016/j.jcrc.2021.11.005
- Kanji S, Williamson DR, Yaghchi BM, Albert M, McIntyre L. Epidemiology and management of atrial fibrillation in medical and noncardiac surgical adult intensive care unit patients. J Crit Care 2012;27:326.e1–326.e8. https://doi.org/10.1016/j.jcrc.2011. 10.011
- Champion S, Lefort Y, Gauzere BA, Drouet D, Bouchet BJ, Bossard G, Djouhri S, Vandroux D, Mayaram K, Mégarbane B. CHADS2 and CHA2DS2-VASc scores can predict thromboembolic events after supraventricular arrhythmia in the critically ill patients. J Crit Care 2014;29:854–858. https://doi.org/10.1016/j.jcrc.2014.05.010