Pharmacological and non-pharmacological treatments and outcomes for new-onset atrial fibrillation in ICU patients: the CAFE scoping review and database analyses

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Scientific summary

The CAFE scoping review and database analyses

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Scientific summary

Background

Of the 170,000 adults treated on UK intensive care units (ICUs) annually, 10,000–20,000 develop new-onset atrial fibrillation (NOAF) and are clustered in subgroups, such as patients with sepsis. NOAF in patients on ICUs can cause cardiovascular instability and thromboembolism. It is independently associated with increases in length of hospital stay, mortality and health-care costs. It may also be associated with increased long-term morbidity and mortality in patients who survive until hospital discharge.

The current atrial fibrillation (AF) treatment guidelines are based on patients outside ICUs. NOAF in patients in an ICU differs in the causes of rhythm disturbance, and the risks and clinical effectiveness of treatments. There is little evidence to guide NOAF treatment on ICUs; consequently, practice varies. It is unclear whether or not NOAF developed in an ICU results in future episodes of AF, heart failure or stroke. Optimal management strategies in ICUs and post ICU discharge are unknown.

Objectives

Scoping review

- To evaluate the evidence for the clinical effectiveness and safety of pharmacological and non-pharmacological NOAF treatments.
- To provide guidance for the database analysis on:
    - NOAF definitions used for patients in an ICU
    - patient subgroups who develop NOAF in an ICU
    - inclusion/exclusion of specific treatments and potential confounders
    - determining barriers to future research.

Database analysis: RISK-II

- To determine how common NOAF is in critical care.
- To determine the typical characteristics of patients with NOAF in critical care and how they compare with those of other patients in critical care.
- To increase the understanding of the outcomes of patients with NOAF in critical care and how they compare with those of other patients in critical care.
- To investigate how much of the difference in outcomes is explained by differences in patient characteristics and comorbidities.

Database analysis: MIMIC-III and PICRAM

- To compare the use and clinical effectiveness of pharmacological and non-pharmacological NOAF treatments.
- To determine the incidence of short- and long-term NOAF complications.

Methods

Scoping review

In March 2019, we searched 13 electronic databases and trial registries, including MEDLINE, EMBASE™ (Elsevier, Amsterdam, the Netherlands) and Cumulative Index to Nursing and Allied Health Literature (CINAHL), without date and language restrictions to identify published and unpublished studies.

Adults aged ≥ 16 years in general medical, surgical or mixed ICUs were eligible. We excluded studies of cohorts defined by a single disease or a narrow disease group that are not normally admitted to a general ICU, and studies based on service-specific ICUs. Pharmacological, electrical and other non-pharmacological treatment strategies for treatment or prevention of NOAF and the use of short- or long-term anticoagulation were eligible. Any eligible intervention could be a comparator, as could no treatment, standard care and placebo. Outcomes were rhythm and rate control, length of ICU and hospital stay, mortality (ICU, hospital, 30 days and long term), arterial thromboembolism and adverse treatment effects. Quantitative studies (randomised and non-randomised trials, cohort studies, case series with five or more patients reported, and trial protocols) were eligible. We included reviews, practitioner surveys and opinion pieces.

Two reviewers independently screened titles, abstracts and full-text articles. Discrepancies were resolved through discussion or via a third reviewer. Study details and findings were presented in structured tables and described and summarised narratively.

Included studies were quality assessed using version 2 of the Cochrane risk-of-bias tool for randomised trials and the Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) tool for larger non-randomised comparative studies.

Expert panel

We identified a list of variables from our scoping review that may affect the treatment choice for NOAF. We then circulated this list among our expert panel, who added to and refined the list. We collated a final list of these confounding variables, which was ratified by our expert panel. We repeated this process with definitions of NOAF, interventions of interest and outcomes of interest.

Database analysis: RISK-II

To investigate the long-term outcomes associated with NOAF, we analysed patient records from the RISK-II database. RISK-II combines anonymised, linked, routinely collected data from the Case Mix Programme national clinical audit of adult intensive care, Hospital Episode Statistics (HES) for England and the Office for National Statistics (ONS) mortality databases. It includes patients admitted to ICUs in England between 1 April 2009 and 31 March 2016. We categorised admissions as involving NOAF, possible NOAF, pre-existing AF or no AF, in accordance with evidence available from the linked HES records.

To compare characteristics and outcomes, we selected a cohort of comparator patients who did not develop NOAF and who were matched on hospital and month/year of admission to an ICU. We identified comorbidities using the *International Classification of Diseases and Related Health Problems*, Tenth Revision, codes from linked HES records. We identified the date and cause of death from linked ONS records. We identified subsequent hospital admissions using linked HES records and classified these as involving AF, stroke or heart failure. We estimated associations between NOAF and outcomes before and after adjustment for patient characteristics and comorbidities using multivariable regression models adjusting for age, sex and comorbidities.

Database analysis: PICRAM and MIMIC-III

We carried out a retrospective cohort study of two large within-ICU databases from the USA and the UK. We excluded patients with known pre-existing AF or an arrhythmia within 3 hours of ICU admission. We identified the occurrence of AF from observation chart data.

We compared patients who developed NOAF with patients who did not. We analysed the mortality associated with NOAF before and after adjusting for confounding variables. We then identified a cohort of patients who received treatment for their NOAF. We analysed the characteristics of treated NOAF, including time to onset and duration. We also analysed the changes in haemodynamic parameters and vasoactive medication use associated with NOAF onset.

We balanced treatment groups using propensity score weighting. We then investigated the efficacy of different NOAF treatments for rate control, rhythm control and mortality.

Results

Scoping review

We screened 3651 articles by title and abstract, identifying 198 articles of potential interest. After full-text screening, we included 25 group studies, 12 reviews, one survey and four opinion pieces.

A limited evidence base was available. Of 25 primary studies included in the review, two were randomised controlled trials (RCTs). Of 11 non-randomised comparative studies, three attempted to control for confounding factors. Where studies attempted to control for confounding, quality assessment still identified concerns that bias might affect results. Most studies were single-group studies lacking a comparator group. Studies used different treatment doses, administration methods and time points to assess the success of conversion to sinus rhythm. Six studies were available as conference abstracts only. Limited evidence from four studies suggested that beta-blockers might be more effective than amiodarone for conversion to sinus rhythm and in reducing mortality. It is unclear whether or not anticoagulant therapy results in a reduction in stroke risk and whether or not the potential benefits outweigh the increased risk of bleeding in ICU patients. No conclusive findings have been reported owing to the low quality of the reviewed evidence and the methodological differences between the included studies. Most studies and reviews concluded that further research is needed urgently.

Expert panel

The expert panel ratified a list of treatments of interest and confounding variables. The scoping review highlighted that definitions of NOAF in patients on ICUs and definitions of treatment success varied. In the absence of any consensus definition of NOAF, we adopted the agreed definition of AF in patients outside an ICU, namely any AF lasting $\geq$ 30 seconds. We defined time to cardioversion as the time to first reversion of sinus rhythm, and time to rate control as the time to a heart rate of $<$ 110 beats per minute (b.p.m.).

Database analysis: RISK-II

The analysis included 841,005 ICU admissions for 733,038 patients. We identified 4615 (0.6%) admissions as involving NOAF and a further 3548 (0.4%) as involving possible NOAF. Each admission involving NOAF was matched to six comparator admissions with no AF from the same month/year and ICU. Patients with NOAF were older (mean age 71.5 years vs. 59.1 years) and had higher levels of comorbidity, especially hypertension (66.1% vs. 47.2%), heart failure (24.8% vs. 10.1%) and valvular heart disease (12.5% vs. 6.2%), than the comparator patients. After controlling for these differences, patients with NOAF had substantially higher mortality in hospital and during the first 90 days after discharge than patients who did not [adjusted odds ratio (aOR) 2.32, 95% confidence interval (CI) 2.16 to 2.48; adjusted hazard ratio (aHR) 1.46, 95% CI 1.26 to 1.70, respectively], and higher rates of subsequent hospitalisation with AF, stroke and heart failure [adjusted cause-specific hazard ratio (CHR) 5.86, 95% CI 5.33 to 6.44; adjusted CHR 1.47, 95% CI 1.12 to 1.93; and adjusted CHR 1.28, 95% CI 1.14 to 1.44, respectively) than patients who did not.

Database analysis: MIMIC-III and PICRAM

New-onset atrial fibrillation was common in ICU patients, occurring in 1065 out of 18,559 (5.7%) eligible patients in US data and 952 out of 8367 (11.4%) eligible patients in UK data. In the study cohort (patients treated for NOAF), the median time to onset of NOAF was 40 hours, with a median duration of 14.4 hours.

In the combined database analysis, NOAF was associated with a significant increase in heart rate of 18 b.p.m., a reduction in systolic blood pressure of 5 mmHg and an increase in vasoactive-inotropic score of 2.3 (all $p < 0.001$). NOAF was associated with a significantly increased risk of hospital mortality after adjusting for confounding factors (CHR 1.84, 95% CI 1.69 to 2.00; adjusted CHR 1.58, 95% CI 1.45 to 1.71).

In the combined database analysis, we found no differences between beta-blockers and amiodarone in rates of achieving rate control (aHR 1.14, 95% CI 0.91 to 1.44) or rhythm control (aHR 0.86, 95% CI 0.67 to 1.11). We found that digoxin therapy was associated with a lower rate of achieving rate control than amiodarone (aHR 0.52, 95% CI 0.32 to 0.86). We found that calcium channel blocker therapy was associated with a lower rate of achieving rhythm control than amiodarone (aHR 0.56, 95% CI 0.39 to 0.79). These findings were consistent with analyses of individual databases.

Discussion

Our scoping review revealed marked differences in the definitions of NOAF and the definitions of treatment success between studies. Limited evidence suggested that beta-blockers might be more effective than amiodarone for conversion to sinus rhythm and mortality outcomes. However, residual bias may explain these assertions. The available literature suggests that it is unclear whether or not the benefits of administering anticoagulants in critically ill patients with NOAF for stroke prevention outweigh the increased risk of bleeding. Reluctance to initiate anticoagulation demonstrated in surveys may be owing to the uncertainty of this risk–benefit balance.

The scoping review was performed using systematic, transparent and robust methods. The bibliographic database searches were comprehensive, maximising identification of relevant studies, while also minimising the possibility of publication or language biases affecting the review. The main limitation of the scoping review was the methodological shortcomings of the studies identified, preventing conclusive findings.

The scoping review allowed definitions of NOAF and treatment success for the database analyses to be agreed following the expert panel meeting, along with a long list of interventions and potential confounders.

Analysis of the RISK-II database identified a group of patients who develop NOAF in critical care who have substantially worse short- and long-term outcomes, including readmission with heart failure and thromboembolism, than similar patients without any record of AF during or prior to ICU admission. However, the group identified by hospital coding is much smaller than that found by analysis of ICU data. Whether or not the findings would be replicated in this larger group is unclear. The increased incidence of stroke suggests that there may be a role for anticoagulation in some patients who develop NOAF during an ICU stay; however, the appropriate patient group, timing and duration of anticoagulation are unknown.

Our within-ICU database analysis found that the treatment of NOAF with digoxin or calcium channel blockers as first-line therapy, compared with amiodarone, is associated with poorer rate control and rhythm control, respectively. Previous studies have suggested that beta-blocker therapy may be associated with better outcomes than amiodarone therapy. Our findings revealed that patients who received beta-blockers were less unwell at admission and more stable around AF onset. After comprehensive adjustment of these factors, there were no identifiable differences in outcomes

between these two treatments. To the best of our knowledge, our ICU database analysis provides the first comparative study of NOAF treatments, where differences between treatment groups around AF onset are adjusted for. The use of routine data provided a sample size large enough to detect differences between these treatment groups. However, it is limited by its retrospective nature and residual unmeasured confounding may contribute to any identified effects.

Applicability

Our RISK II database analysis included national data and our results are, therefore, meaningful for most general adult ICUs in the UK. Our within-ICU database analysis included data from tertiary centres and district general hospitals in the UK, alongside data from the USA, suggesting that our findings are applicable elsewhere.

Conclusions

Our scoping review highlighted the need for standardised definitions in future research into NOAF.

We found that NOAF during an ICU stay is common and is associated with substantially increased mortality, after correction for associated risk factors. Identifying optimal treatment strategies is a research priority, with the potential to improve patient outcomes. Both amiodarone and beta-blockers are commonly used but have significant side effects. Whether or not one is superior to the other is unknown. A RCT of amiodarone compared with beta-blockers for the management of NOAF in critically ill patients should be undertaken. Current evidence does not support the use of calcium channel blockers or digoxin as first-line therapy for undifferentiated patients who develop NOAF during an ICU stay.

There is little evidence for or against anticoagulation for patients who develop NOAF in an ICU. The risk of thromboembolism is increased compared with those who do not develop NOAF, even when corrected for known risk factors. However, current risk stratification tools have not been validated in the 'new-onset atrial fibrillation during intensive care unit population' and do not take account of within-ICU factors that may affect future outcome. Whether or not subgroups of patients who develop NOAF while in an ICU may benefit from long-term anticoagulation is unknown. Studies should be undertaken to create risk stratification tools or investigate whether or not current tools are applicable to the 'new-onset atrial fibrillation during intensive care unit population' to identify patients sufficiently at risk of future thromboembolism to merit consideration of anticoagulation.

Readmission with heart failure and thromboembolism increases over the 5 years following an episode of NOAF while in an ICU, particularly in the first year. Whether or not these events are driven by persistent left ventricular dysfunction and/or AF is unknown. A prospective cohort study to demonstrate the incidence of AF and/or left ventricular dysfunction at hospital discharge and at 3 months following development of NOAF should be undertaken.

Trial registration

This trial is registered as ISRCTN13252515.

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This report

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