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Risk factors for new-onset atrial fibrillation on the general adult ICU: Protocol for a systematic review

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Word count: 1658

Keywords: Atrial fibrillation, risk factors, critical illness, intensive care units, intensive care

ABSTRACT

Introduction

Atrial fibrillation (AF) is a common arrhythmia in the critical care environment. New-onset AF is associated with increased mortality and intensive care unit (ICU) length of stay. Observational studies have identified several epidemiologic and disease severity-related factors associated with developing new-onset AF on the ICU. However, there is limited data on the modifiable risk-factors in the general adult ICU population.

We describe a protocol for a systematic review of modifiable and non-modifiable risk factors for new-onset AF in the general adult ICU population.

Methods and analysis

MEDLINE, EMBASE and the Cochrane Library, including Cochrane Database of Systematic Reviews and the Cochrane Central Register of Controlled Trials (CENTRAL) will be searched for studies that assess the association of patient variables, investigation results, interventions and diagnoses associated with subsequent new-onset atrial fibrillation on the ICU.

Only studies involving adult patients admitted to non-service-specific ICUs will be included. We will extract data relating to the statistical association between reversible and non-reversible factors and AF, the quality of the studies and the generalisability of the results. This systematic review will be reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA).

Ethics and dissemination

This proposed systematic review will be based on published data, and therefore ethical approval is not required. The results of this review will aid the development of future risk prediction tools along with informing current bedside practice in the prevention of new-onset atrial fibrillation on the ICU. The findings of this study will be disseminated through publication in a peer reviewed journal and will be presented at conferences.

Trial registration number

CRD42017074221.

ARTICLE SUMMARY

Strengths and limitations of this study

- New-onset atrial fibrillation in intensive care is a common and important condition
- This protocol will ensure a targeted and comprehensive analysis of this poorly-understood phenomenon
- This protocol addresses issues with previous reviews in this area
- This protocol will guide an unbiased systematic review based on agreed best practice principles
- The results of this review will inform current practice and aid the development of risk prediction tools

INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia in critically ill patients[1,2]. AF is particularly common after cardiac surgery, with a prevalence ranging from 10-65% depending on the nature of the surgery[3]. Data regarding new-onset atrial fibrillation in non-service-specific intensive care units (ICUs) is more limited. Observational data suggest new-onset AF occurs in 4.5-15% of patients in this setting[4-9] and up to 46% of patients with septic shock[10].

New onset atrial fibrillation in critically ill patients is associated with increased mortality and length of stay[1 8 11]. It is unclear whether AF itself is an independent contributor to poor outcome, or rather a marker of disease severity[7]. However, given the detrimental effects of AF on cardiac output and filling pressures, it is feasible that the arrhythmia itself contributes to increased mortality[12]. Furthermore, atrial fibrillation in critically ill patients is associated with thromboembolic complications and these may contribute to poorer outcomes[13].

Risk factors for developing AF on the ICU include patient factors such as increasing age or presence of comorbidities, and ICU interventions including renal replacement therapy, vasopressor use and the use of pulmonary artery catheters[7 9 13]. The risk of developing new-onset AF also increases with increasing disease severity e.g. APACHE score[7]. Whilst a systematic review of AF risk factors in sepsis has been undertaken[14], this included studies that did not exclude patients with potential prior or paroxysmal AF[15-17]. A systematic review has also been undertaken in the general adult ICU population[18]. However, this again did not focus on true new-onset AF, and did not provide an evidence synthesis.

There is a paucity of data around reversible / modifiable antecedents in this context. Current practice of preventing atrial fibrillation in critically ill patients is variable and not based on robust evidence. Given the potential morbidity and mortality associated with new-onset AF on the ICU, a better understanding of modifiable and non-modifiable risk factors may improve patient care and outcomes.

OBJECTIVE

We will conduct a systematic review to identify studies of factors that are associated with an increased risk of new-onset atrial fibrillation in adult patients on non-service specific intensive care units.

METHODS

This protocol will adhere to the requirements of Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol (PRISMA-P)[19] (Appendix 1). The protocol is registered, PROSPERO: CRD42017074221.

Patient and public involvement

We have involved the Oxford ICU patient forum. This is a cohort participants previously managed on Oxford ICUs and their relatives. They are recruited from the ICU follow-up clinic. Within this group are members who experienced atrial fibrillation during their stay. They stressed the importance of producing evidence to guide the prevention and management strategies for new-onset AF on the ICU. They felt the phenomenon was poorly understood, including investigations and management after discharge.

Search strategy

Papers will be identified by searching Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica database (EMBASE), the Cochrane Database of Systematic Reviews and the Cochrane Central Register of Controlled Trials (CENTRAL). We will include additional papers from other sources including the references of reviews articles or studies identified during screening. A full description of the search strategy is outlined in Appendix 2.

Study selection

Two reviewers will independently undertake initial relevance screening of titles and abstracts. The researchers will not be blinded to the journal titles or to the study authors or institutions. If there is disagreement or uncertainty regarding eligibility, the article will be included in the next stage of screening for further analysis for inclusion/exclusion. The full text will be retrieved for all articles not excluded by the initial screening. These papers will be assessed against the inclusion and exclusion criteria. Disagreements about eligibility will be resolved by discussion between the screening researchers or a third party.

Data management

We will use Covidence (Veritas Health Innovation Ltd., Melbourne, Australia) software to identify duplicate records and for relevance screening. We will use a reference manager program (EndNoteX8, Clarivate Analytics, Philadelphia, USA) to store identified citations and their electronic text.

Inclusion criteria

Types of studies

Quantitative studies published in peer reviewed journals assessing adults will be eligible for inclusion in this review. Studies are likely to be prospective or retrospective cohort or case-control studies.

Study characteristics

Eligible studies must include both a cohort of patients who developed new-onset atrial-fibrillation and a cohort who did not. They must include at least one risk factor that was investigated. The studies must be based in non-service-specific ICUs. These will include general medical, surgical or mixed ICUs. Studies of cohorts defined by a single disease or narrow group of diseases (e.g. myocardial infarction or sepsis) will be included. Identified studies published from January 1970 until the day of search completion will be included.

Phenomenon of interest

Studies must describe a statistical relationship between a patient-derived variable (e.g. age, blood pressure or serum potassium level) and the development of new-onset atrial fibrillation. 'Diagnosis' may be included as a variable. We will include studies that group atrial fibrillation with atrial flutter, providing no other arrhythmia types were included. We will include studies investigating new-onset supraventricular arrhythmias, providing atrial fibrillation constituted at least 70% of arrhythmia episodes.

Population

Studies that sample adult patients admitted to the ICU types specified above will be considered for inclusion.

For the purpose of this review, an adult is defined as ≥16 years of age. There will be no other restrictions.

Exclusion criteria

Types of studies

Qualitative studies, case studies, editorials, letters, practice guidelines and abstract-only reports will be excluded.

Study characteristics

Studies of cohorts defined by a single procedure or narrow group of procedures (e.g. appendicectomy or hepatobiliary surgery) will be excluded. Studies based on service-specific (e.g. cardiac, cardiothoracic surgical or neurosurgical) ICUs will also be excluded. Studies published in a language other than English will be excluded.

Phenomenon of interest

Studies will be excluded if no risk factors are analysed. Studies that do not specify arrhythmia type will also be excluded.

Population

Studies of participants under 16 years old will be excluded.

Data extraction

Data will be extracted from identified full text articles and supplementary material. One researcher (JB) will be responsible for data extraction. All uncertainties regarding data extraction will be resolved by discussion amongst the study team. Extracted data will include study design, study setting, incidence of AF, AF detection method(s) and risk factor estimates including odds ratios, confidence intervals and p-values for statistical significance. We will populate pre-specified data extraction tables. Where insufficient data is presented we will request additional data from the authors.

Risk of bias assessment

We will assess risk of bias using an adapted Newcastle-Ottawa Scale (NOS)[20]. The NOS is a scoring system designed to assess the quality of non-randomised studies in meta-analyses. Scores are attributed to each paper after assessing domains including the selection of study groups, the comparability of the groups and the ascertainment of the outcome of interest. We have incorporated adaptations from a previous systematic review of risk factors[21]. We have further modified this with the intention of best evaluating our phenomenon of interest. The scoring system used in this systematic review will allocate scores from zero to nine and is outlined in Appendix 3.

Data synthesis and analysis

We will extract summary comparison data as odds ratios (95% confidence intervals) where possible. Where sufficient original data is presented we will calculate odds ratios. We will then conduct a semi-quantitative synthesis of results from included studies using a method previously described by Zaal, et al. [22] and adapted by Dettmer, et al. [23]. Identified variables with associated p-values of ≤0.05 or 95% confidence intervals that do not cross 1 will be allocated a relative strength. This will be based on a composite of the number of articles in which an association is identified, and the methodological quality of those articles as defined by our adapted NOS. Criteria for strength of evidence is outlined in table 1.

Table 1 - Level of evidence for risk factors for new-onset atrial fibrillation

Level of evidence	Criteria
Strong evidence	Consistent findings in ≥ 2 high quality studies (adapted NOS score 8-9)

	AND no conflicting studies
Moderate evidence	Consistent findings in 1 high quality study AND ≥1 acceptable quality study (adapted NOS score 6-7) AND no conflicting studies
Weak evidence	Consistent findings in ≥ 3 low quality studies (adapted NOS score ≤5 OR ≥ 2 acceptable quality studies OR 1 high quality study in isolation

DISCUSSION

Several epidemiological and disease severity-related factors have been associated with new-onset atrial fibrillation on the ICU in observational studies. These have not yet been investigated in the general adult ICU population in a systematic review with an evidence synthesis. Data is also limited regarding modifiable or reversible risk factors; available evidence is scarce regarding specific patient vital signs, laboratory results or ICU procedures that may increase the risk of AF. Current clinical practice is therefore variable and not evidence-based.

The findings from this review will contribute towards an improved understanding of the modifiable and non-modifiable antecedents of new-onset AF on the ICU. It may lead to a clinically useful risk-prediction model and promote an evidence-based approach towards AF prevention at the bedside. Given the high prevalence and significant associated morbidity and mortality of new-onset AF on the ICU, optimal prevention strategies may result in improved patient outcomes.

DECLARATIONS

Abbreviations

AF: atrial fibrillation; CENTRAL: The Cochrane Database of Systematic Reviews and the Cochrane Central Register of Controlled Trials; EMBASE: Excerpta Medica database; ICU: Intensive care unit; MEDLINE: Medical Literature Analysis and Retrieval System Online; PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocol.

Funding

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Availability of data and materials

Not applicable.

Author contributions

JB, DY and PW have substantially contributed to the design of the systematic review. TP has developed the search strategy. JB, DY and PW wrote this manuscript. MH will contribute toward study selection. All authors read and approved the final manuscript. The funders have not been involved in the study design or reporting. PW is guarantor of this review. The authors would like to thank the patients involved in the development of this protocol.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

Not applicable.

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APPENDIX 1

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section topic	Item	Checklist item	Present in review Y/N	Page and line
		ADMINISTRATIVE INFORMATION		
Title:				
Identification	1a	Identify the report as a protocol of a systematic review	Yes	Page 1 Line 2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	No	-
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Yes	Page 3 Line 30-31
Authors:				
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Yes	Page 1 Lines 4-6
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Yes	Page 6 Lines 21-24
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	No	-
Support:				
Sources	5a	Indicate sources of financial or other support for the review	Yes	Page 6 Lines 15-17
Sponsor	5b	Provide name for the review funder and/or sponsor	Yes	Page 6 Lines 15-17
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	Yes	Page 6 Line 15-17
		INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known	Yes	Page 3 Lines 2-24

Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Yes	Page 3 Lines 26-27
		METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Yes	Page 4 Lines 10-39 Page 5 Lines 1-5
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Yes	Page 3 Lines 33-37
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Yes	Page 10 Lines 2-34
Study records:				
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Yes	Page 4 Lines 5-7
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Yes	Page 3 Lines 39-42 Page 4 Lines 1-3
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Yes	Page 5 Lines 7-12
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Yes	Page 5 Lines 9-11
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Yes	Page 4 Line 20-25
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Yes	Page 5 Lines 14-18
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Yes	Page 5 Lines 20-27

	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	Yes	Page 5 Lines 20-27
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	No	
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Yes	Page 5 Lines 20-27
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	No	-
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Yes	Page 5 Lines 20-27

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

APPENDIX 2

Draft search strategy for Medline

1.	ATRIAL FIBRILLATION/
2.	ATRIAL FLUTTER/
3.	SUPRAVENTRICULAR TACHYCARDIA/
4.	"atrial fibrillation* ".ab,ti.
5.	"atrial flutter* ".ab,ti.
6.	"supraventricular tachycardia* ".ab,ti.
7.	1 or 2 or 3 or 4 or 5 or 6
8.	INTENSIVE CARE/
9.	INTENSIVE CARE UNIT/
10.	CRITICAL CARE/
11.	"intensive care".ab,ia,in,ti.
12.	"critical care".ab,ia,in,ti.
13.	"critical*".ab,ia,in,ti.
14.	(ITU or ICU or AICU).ab,ia,in,ti.
15.	8 or 9 or 10 or 11 or 12 or 13 or 14
16.	RISK FACTORS/
17.	EPIDEMIOLOGY/
18.	"risk factor*".ab,ti.
19.	"epidemiology".ab,ti.
20.	"*etiology".ab,ti.
21.	BIOCHEMICAL MARKER/
22.	BIOLOGIC MARKER/
23.	CLINICAL MARKER/
24.	"determinant*".ab,ti.
25.	"precursor*".ab,ti.
26.	"antecedent*".ab,ti.
27.	"precursor*".ab,ti.
28.	"predict*".ab,ti.
29.	"trigger*".ab,ti.
30.	"marker*".ab,ti.
31.	16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
32.	7 and 15 and 31

APPENDIX 3

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1. Representativeness of the study population
    a. Truly representative of the general adult ICU population ★
    b. Somewhat representative of the general adult ICU population ★
    c. Poorly representative of the general adult ICU population
    d. No description of the derivation of the cohort
2. Demonstration that outcome of interest was not present at start of study
    a. Exclusion of AF (current and historic) described ★
    b. AF (current and historic) excluded but no description
3. Ascertainment of presence of risk factor
    a. Medical record or investigation result ★
    b. Structured interview ★
    c. Written self-report
    d. No description or none of the above
4. Study size
    a. ≥100 participants in each group ★
    b. <100 participants in each group

Comparability

1. Comparability of cohorts on the basis of the design or analysis
    a. Study design controls for confounding factors ★
    b. Study controls for confounding factors in data analysis ★

Outcome

1. Study design
    a. Prospective ★
    b. Retrospective
2. Assessment of outcome
    a. Independent assessment of heart rhythm from primary source (e.g. monitor / ECG) ★
    b. Non-independent assessment or heart rhythm identified from secondary source (e.g. patient records)
    c. Other identification of heart rhythm
    d. No description
3. Adequacy of follow up of cohorts
    a. complete follow up - all subjects accounted for ★
    b. subjects lost to follow up unlikely to introduce bias - small number lost - ≥90% follow up, or description provided of those lost) ★
    c. follow up rate < 90% and no description of those lost
    d. no statement

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	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	No	
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Yes	Page 5 Lines 20-27
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Risk factors for new-onset atrial fibrillation on the general adult ICU: Protocol for a systematic review

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Word count: 1740

Keywords: Atrial fibrillation, risk factors, critical illness, intensive care units, intensive care

ABSTRACT

Introduction

Atrial fibrillation (AF) is a common arrhythmia in the critical care environment. New-onset AF is associated with increased mortality and intensive care unit (ICU) length of stay. Observational studies have identified several epidemiologic and disease severity-related factors associated with developing new-onset AF on the ICU. However, there is limited data on the modifiable risk-factors in the general adult ICU population.

We describe a protocol for a systematic review of modifiable and non-modifiable risk factors for new-onset AF in the general adult ICU population. The results of this review will aid the development of risk prediction tools and inform future research into AF prevention on the ICU.

Methods and analysis

MEDLINE, EMBASE and the Cochrane Library, including Cochrane Database of Systematic Reviews and the Cochrane Central Register of Controlled Trials (CENTRAL) will be searched for studies that assess the association of patient variables, investigation results, interventions and diagnoses associated with subsequent new-onset atrial fibrillation on the ICU.

Only studies involving adult patients admitted to non-service-specific ICUs will be included. We will extract data relating to the statistical association between reversible and non-reversible factors and AF, the quality of the studies and the generalisability of the results. This systematic review will be reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA).

Ethics and dissemination

This proposed systematic review will be based on published data, and therefore ethical approval is not required. The findings of this study will be disseminated through publication in a peer reviewed journal and will be presented at conferences.

Trial registration number

CRD42017074221.

ARTICLE SUMMARY

Strengths and limitations of this study

- New-onset atrial fibrillation in intensive care is a common and important condition
- This protocol will ensure a targeted and comprehensive analysis of this poorly-understood phenomenon
- This protocol addresses issues with previous reviews in this area
- This protocol will guide an unbiased systematic review based on agreed best practice principles
- The results of this review will inform current practice and aid the development of risk prediction tools

INTRODUCTION

New-onset atrial fibrillation (AF) in intensive care is defined for the purposes of this protocol as AF occurring after admission to ICU in a patient with no known history of chronic or paroxysmal AF. It is the most common arrhythmia in critically ill patients[1,2]. It is particularly common after cardiac surgery, with a prevalence ranging from 10-65% depending on the nature of the surgery[3]. Data regarding new-onset AF in non-service-specific intensive care units (ICUs) is more limited. Observational data suggest new-onset AF occurs in 4.5-15% of patients in this setting[4-9] and up to 46% of patients with septic shock[10].

New-onset AF in critically ill patients is associated with increased mortality and length of stay[1 8 11]. It is unclear whether AF itself is an independent contributor to poor outcome, or rather a marker of disease severity[7]. However, given the detrimental effects of AF on cardiac output and filling pressures, it is feasible that the arrhythmia itself contributes to increased mortality[12]. Furthermore, atrial fibrillation in critically ill patients is associated with thromboembolic complications and these may contribute to poorer outcomes[13].

Risk factors for developing AF on the ICU include patient factors such as increasing age or presence of comorbidities, and ICU interventions including renal replacement therapy, vasopressor use and the use of pulmonary artery catheters[7 9 13]. The risk of developing new-onset AF also increases with increasing disease severity e.g. APACHE score[7]. Whilst a systematic review of AF risk factors in sepsis has been undertaken[14], this included studies that did not exclude patients with potential prior or paroxysmal AF[15-17]. A systematic review has also been undertaken in the general adult ICU population[18]. However, this again did not focus on true new-onset AF, and did not provide an evidence synthesis.

There is a paucity of data around reversible / modifiable antecedents in this context. Current practice of preventing atrial fibrillation in critically ill patients is variable and not based on robust evidence. Given the potential morbidity and mortality associated with new-onset AF on the ICU, a better understanding of modifiable and non-modifiable risk factors may improve patient care and outcomes.

OBJECTIVE

We will conduct a systematic review to identify studies of factors that are associated with an increased risk of new-onset atrial fibrillation in adult patients on non-service specific intensive care units.

METHODS

This protocol will adhere to the requirements of Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol (PRISMA-P)[19] (Appendix 1). The protocol is registered, PROSPERO: CRD42017074221.

Patient and public involvement

We have involved the Oxford ICU patient forum. This is a cohort participants previously managed on Oxford ICUs and their relatives. They are recruited from the ICU follow-up clinic. Within this group are members who experienced atrial fibrillation during their stay. They stressed the importance of producing evidence to guide the prevention and management strategies for new-onset AF on the ICU. They felt the phenomenon was poorly understood, including investigations and management after discharge.

Search strategy

Papers will be identified by searching Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica database (EMBASE), the Cochrane Database of Systematic Reviews and the Cochrane Central Register of Controlled Trials (CENTRAL). MEDLINE and EMBASE will be accessed via the Ovid platform. We will include additional papers from other sources including the references of reviews articles or studies identified during screening. A full description of the search strategy is outlined in Appendix 2.

Study selection

Two reviewers will independently undertake initial relevance screening of titles and abstracts. The researchers will not be blinded to the journal titles or to the study authors or institutions. If there is disagreement or uncertainty regarding eligibility, the article will be included in the next stage of screening for further analysis for inclusion/exclusion. The full text will be retrieved for all articles not excluded by the initial screening. These papers will be assessed against the inclusion and exclusion criteria. Disagreements about eligibility will be resolved by discussion between the screening researchers or a third party.

Data management

We will use Covidence (Veritas Health Innovation Ltd., Melbourne, Australia) software to identify duplicate records and for relevance screening. We will use a reference manager program (EndNoteX8, Clarivate Analytics, Philadelphia, USA) to store identified citations and their electronic text.

Inclusion criteria

Types of studies

Quantitative studies published in peer reviewed journals assessing adults will be eligible for inclusion in this review. Studies are likely to be prospective or retrospective cohort or case-control studies.

Study characteristics

Eligible studies must include both a cohort of patients who developed new-onset atrial-fibrillation and a cohort who did not. They must include at least one risk factor that was investigated. The studies must be based in non-service-specific ICUs. These will include general medical, surgical or mixed ICUs. Studies of cohorts defined by a single disease or narrow group of diseases (e.g. myocardial infarction or sepsis) will be included. Identified studies published from January 1970 until the day of search completion will be included.

Phenomenon of interest

Studies must describe a statistical relationship between a patient-derived variable (e.g. age, blood pressure or serum potassium level) and the development of new-onset atrial fibrillation. ‘Diagnosis’ may be included as a variable. We will include studies that group atrial fibrillation with atrial flutter, and we will include studies investigating new-onset supraventricular arrhythmias, providing atrial fibrillation constituted at least 70% of arrhythmia episodes.

Population

Studies that sample adult patients admitted to the ICU types specified above will be considered for inclusion.

For the purpose of this review, an adult is defined as ≥16 years of age. There will be no other restrictions.

Exclusion criteria

Types of studies

Qualitative studies, case studies, editorials, letters, practice guidelines and abstract-only reports will be excluded.

Study characteristics

Studies of cohorts defined by a single procedure or narrow group of procedures (e.g. appendicectomy or hepatobiliary surgery) will be excluded. Studies based on service-specific (e.g. cardiac, cardiothoracic surgical or neurosurgical) ICUs will also be excluded. Studies published in a language other than English will be excluded.

Phenomenon of interest

Studies will be excluded if no risk factors are analysed. Studies that do not explicitly exclude or separate patients with a history of chronic or paroxysmal AF will be excluded. Studies that do not specify arrhythmia type will also be excluded.

Population

Studies of participants under 16 years old will be excluded.

Data extraction

Data will be extracted from identified full text articles and supplementary material. One researcher (JB) will be responsible for data extraction. All uncertainties regarding data extraction will be resolved by discussion amongst the study team. Extracted data will include: 1) characteristics of study setting and patient population; 2) study methodology (including ascertainment of risk factors, definition and assessment of outcome, and control of confounding variables); 3) risk factor estimates including measures quantifying risk, confidence intervals and p-values for statistical significance. We will extract risk ratios identified through both univariate and multivariate analysis and record the analysis method. We will populate pre-specified data extraction tables. Where insufficient data is presented we will request additional data from the authors.

Risk of bias assessment

We will assess risk of bias using an adapted Newcastle-Ottawa Scale (NOS)[20]. The NOS is a scoring system designed to assess the quality of non-randomised studies in meta-analyses. Scores are attributed to each paper after assessing domains including the selection of study groups, the comparability of the groups and the ascertainment of the outcome of interest. We have incorporated adaptations from a previous systematic review of risk factors[21]. We have further modified this with the intention of best evaluating our phenomenon of interest. The scoring system used in this systematic review will allocate scores from zero to nine and is outlined in Appendix 3.

Data synthesis and analysis

We will extract summary comparison data as odds ratios (95% confidence intervals) where possible. Where sufficient original data is presented we will calculate risk ratios. We will then conduct a semi-quantitative synthesis of results from included studies using a method previously described by Zaal, et al. [22] and adapted by Dettmer, et al. [23]. Identified variables with associated p-values of ≤0.05 or 95% confidence intervals that do not cross 1 will be allocated a relative strength. This will be based on a composite of the number of articles in which an association is identified, and the methodological quality of those articles as defined by our adapted NOS. Criteria for strength of evidence is outlined in table 1.

Table 1 - Level of evidence for risk factors for new-onset atrial fibrillation

Level of evidence	Criteria
Strong evidence	Consistent findings in ≥ 2 high quality studies (adapted NOS score 8-9) AND no conflicting studies
Moderate evidence	Consistent findings in 1 high quality study AND ≥1 acceptable quality study (adapted NOS score 6-7) AND no conflicting studies
Weak evidence	Consistent findings in ≥ 3 low quality studies (adapted NOS score ≤5 OR ≥ 2 acceptable quality studies OR 1 high quality study in isolation

DISCUSSION

Several epidemiological and disease severity-related factors have been associated with new-onset atrial fibrillation on the ICU in observational studies. These have not yet been investigated in the general adult ICU population in a systematic review with an evidence synthesis. Data is also limited regarding modifiable or reversible risk factors; available evidence is scarce regarding specific patient vital signs, laboratory results or ICU procedures that may increase the risk of AF. Current clinical practice is therefore variable and not evidence-based.

The findings from this review will contribute towards an improved understanding of the modifiable and non-modifiable antecedents of new-onset AF on the ICU. It may lead to a clinically useful risk-prediction model and inform future research into AF prevention on the ICU. Given the high prevalence and significant associated morbidity and mortality of new-onset AF on the ICU, optimal prevention strategies may result in improved patient outcomes.

DECLARATIONS

Abbreviations

AF: atrial fibrillation; CENTRAL: The Cochrane Database of Systematic Reviews and the Cochrane Central Register of Controlled Trials; EMBASE: Excerpta Medica database; ICU: Intensive care unit; MEDLINE: Medical Literature Analysis and Retrieval System Online; PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocol.

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Availability of data and materials

Not applicable.

Author contributions

JB, MH, DY and PW have substantially contributed to the design of the systematic review protocol. TP has developed the search strategy. JB, DY and PW wrote this manuscript. All authors read and approved the final manuscript. The funders have not been involved in the study design or reporting. PW is guarantor of this review. The authors would like to thank the patients involved in the development of this protocol.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

Not applicable.

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APPENDIX 1

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section topic	Item	Checklist item	Present in review Y/N	Page and line
		ADMINISTRATIVE INFORMATION		
Title:				
Identification	1a	Identify the report as a protocol of a systematic review	Yes	Page 1 Line 2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	No	-
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Yes	Page 3 Line 32-33
Authors:				
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Yes	Page 1 Lines 4-6
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Yes	Page 6 Lines 28-32
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	No	-
Support:				
Sources	5a	Indicate sources of financial or other support for the review	Yes	Page 6 Lines 22-24
Sponsor	5b	Provide name for the review funder and/or sponsor	Yes	Page 6 Lines 22-24
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	Yes	Page 6 Lines 22-24
		INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known	Yes	Page 3 Lines 2-26

Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Yes	Page 3 Lines 28-29
		METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Yes	Page 4 Lines 21-41 Page 5 Lines 2-15
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Yes	Page 4 Lines 2-7
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Yes	Appendices Page 4 Lines 1-32
Study records:				
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Yes	Page 4 Lines 17-19
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Yes	Page 4 Lines 9-13
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Yes	Page 5 Lines 17-25
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Yes	Page 5 Lines 19-23
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Yes	Page 4 Line 32-36
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Yes	Page 5 Lines 27-33
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Yes	Page 5 Lines 35-42
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of	Yes	Page 5 Lines 35-42

		combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)		
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	No	
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Yes	Page 5 Lines 35-42
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	No	-
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Yes	Page 5 Lines 35-42

APPENDIX 2

Draft search strategy for Medline

1	ATRIAL FIBRILLATION/
2	ATRIAL FLUTTER/
3	SUPRAVENTRICULAR TACHYCARDIA/
4	"atrial fibrillation* ".ab,ti.
5	"atrial flutter* ".ab,ti.
6	"supraventricular tachycardia* ".ab,ti.
7	1 or 2 or 3 or 4 or 5 or 6
8	CRITICAL CARE/
9	INTENSIVE CARE UNIT/
10	"intensive care".ab,ia,in,ti.
11	"critical care".ab,ia,in,ti.
12	"acute physiology".ab,ti.
13	"critical* ill* ".ab,ia,in,ti.
14	(ITU or ICU or AICU).ab,ia,in,ti.
15	8 or 9 or 10 or 11 or 12 or 13 or 14
16	RISK FACTORS/
17	"risk factor* ".ab,ti.
18	EPIDEMIOLOGY/
19	"epidemiolog*".ab,ti.
20	"*etiolog*".ab,ti.
21	"determinant*".ab,ti.
22	"precursor*".ab,ti.
23	"predict*".ab,ti.
24	"trigger*".ab,ti.
25	"marker*".ab,ti.
26	"antecedent*".ab,ti.
27	BIOMARKERS/
28	"new onset".ab,ti.
29	16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
30	7 and 15 and 29

APPENDIX 3

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1. Representativeness of the study population
    a. Truly representative of the general adult ICU population ★
    b. Somewhat representative of the general adult ICU population ★
    c. Poorly representative of the general adult ICU population
    d. No description of the derivation of the cohort
2. Demonstration that outcome of interest was not present at start of study
    a. Exclusion of AF (current and historic) described ★
    b. AF (current and historic) excluded but no description
3. Ascertainment of presence of risk factor
    a. Medical record or investigation result ★
    b. Structured interview ★
    c. Written self-report
    d. No description or none of the above
4. Study size
    a. ≥100 participants in each group ★
    b. <100 participants in each group

Comparability

1. Comparability of cohorts on the basis of the design or analysis
    a. Study design controls for confounding factors ★
    b. Study controls for confounding factors in data analysis ★

Outcome

1. Study design
    a. Prospective ★
    b. Retrospective
2. Assessment of outcome
    a. Independent assessment of heart rhythm from primary source (e.g. monitor / ECG) ★
    b. Non-independent assessment or heart rhythm identified from secondary source (e.g. patient records)
    c. Other identification of heart rhythm
    d. No description
3. Adequacy of follow up of cohorts
    a. complete follow up - all subjects accounted for ★
    b. subjects lost to follow up unlikely to introduce bias - small number lost - ≥90% follow up, or description provided of those lost) ★
    c. follow up rate < 90% and no description of those lost
    d. no statement

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	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Yes	Page 5 Lines 35-42
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BMJ Open

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Complete List of Authors:	Bedford, Jonathan; University of Oxford, Nuffield Department of Clinical Neurosciences Harford, Mirae; University of Oxford, Nuffield Department of Clinical Neurosciences Petrinic, Tatjana; University of Oxford, Bodleian Health Care Libraries Young, Duncan; University of Oxford, Nuffield Department of Clinical Neurosciences Watkinson, Peter; University of Oxford, Nuffield Department of Clinical Neurosciences
Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Cardiovascular medicine, Epidemiology, Anaesthesia, Evidence based practice
Keywords:	INTENSIVE & CRITICAL CARE, Adult cardiology < CARDIOLOGY, EPIDEMIOLOGY

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[2]Bodleian Health Care Libraries, University of Oxford, Oxford, UK.

Word count: 1864

Keywords: Atrial fibrillation, risk factors, critical illness, intensive care units, intensive care

ABSTRACT

Introduction

Atrial fibrillation (AF) is a common arrhythmia in the critical care environment. New-onset AF is associated with increased mortality and intensive care unit (ICU) length of stay. Observational studies have identified several epidemiologic and disease severity-related factors associated with developing new-onset AF on the ICU. However, there is limited data on the modifiable risk-factors in the general adult ICU population.

We describe a protocol for a systematic review of modifiable and non-modifiable risk factors for new-onset AF in the general adult ICU population. The results of this review will aid the development of risk prediction tools and inform future research into AF prevention on the ICU.

Methods and analysis

MEDLINE, EMBASE and the Cochrane Library, including Cochrane Database of Systematic Reviews and the Cochrane Central Register of Controlled Trials (CENTRAL) will be searched for studies that assess the association of patient variables, investigation results, interventions and diagnoses associated with subsequent new-onset atrial fibrillation on the ICU.

Only studies involving adult patients admitted to non-service-specific ICUs will be included. We will extract data relating to the statistical association between reversible and non-reversible factors and AF, the quality of the studies and the generalisability of the results. This systematic review will be reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA).

Ethics and dissemination

This proposed systematic review will be based on published data, and therefore ethical approval is not required. The findings of this study will be disseminated through publication in a peer reviewed journal and will be presented at conferences.

Trial registration number

CRD42017074221.

ARTICLE SUMMARY

Strengths and limitations of this study

- New-onset atrial fibrillation in intensive care is a common and important condition
- This protocol will ensure a targeted and comprehensive analysis of this poorly-understood phenomenon
- This protocol addresses issues with previous reviews in this area
- This protocol will guide an unbiased systematic review based on agreed best practice principles
- The results of this review will inform current practice and aid the development of risk prediction tools

INTRODUCTION

New-onset atrial fibrillation (AF) in intensive care is defined for the purposes of this protocol as AF occurring after admission to ICU in a patient with no known history of chronic or paroxysmal AF. It is the most common arrhythmia in critically ill patients[1,2]. It is particularly common after cardiac surgery, with a prevalence ranging from 10-65% depending on the nature of the surgery[3]. Data regarding new-onset AF in non-service-specific intensive care units (ICUs) is more limited. Observational data suggest new-onset AF occurs in 4.5-15% of patients in this setting[4-9] and up to 46% of patients with septic shock[10].

New-onset AF in critically ill patients is associated with increased mortality and length of stay[1 8 11]. It is unclear whether AF itself is an independent contributor to poor outcome, or rather a marker of disease severity[7]. However, given the detrimental effects of AF on cardiac output and filling pressures, it is feasible that the arrhythmia itself contributes to increased mortality[12]. Furthermore, atrial fibrillation in critically ill patients is associated with thromboembolic complications and these may contribute to poorer outcomes[13].

Risk factors for developing AF on the ICU include patient factors such as increasing age or presence of comorbidities, and ICU interventions including renal replacement therapy, vasopressor use and the use of pulmonary artery catheters[7 9 13]. The risk of developing new-onset AF also increases with increasing disease severity e.g. APACHE score[7]. Whilst a systematic review of AF risk factors in sepsis has been undertaken[14], this included studies that did not exclude patients with potential prior or paroxysmal AF[15-17]. A systematic review has also been undertaken in the general adult ICU population[18]. However, this again did not focus on true new-onset AF, and did not provide an evidence synthesis.

There is a paucity of data around reversible / modifiable antecedents in this context. Current practice of preventing atrial fibrillation in critically ill patients is variable and not based on robust evidence. Given the potential morbidity and mortality associated with new-onset AF on the ICU, a better understanding of modifiable and non-modifiable risk factors may improve patient care and outcomes.

OBJECTIVE

We will conduct a systematic review to identify studies of factors that are associated with an increased risk of new-onset atrial fibrillation in adult patients on non-service specific intensive care units.

METHODS

This protocol will adhere to the requirements of Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol (PRISMA-P)[19] (Appendix 1). The protocol is registered, PROSPERO: CRD42017074221.

Patient and public involvement

We have involved the Oxford ICU patient forum. This is a cohort participants previously managed on Oxford ICUs and their relatives. They are recruited from the ICU follow-up clinic. Within this group are members who experienced atrial fibrillation during their stay. They stressed the importance of producing evidence to guide the prevention and management strategies for new-onset AF on the ICU. They felt the phenomenon was poorly understood, including investigations and management after discharge.

Search strategy

Papers will be identified by searching Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica database (EMBASE), the Cochrane Database of Systematic Reviews and the Cochrane Central Register of Controlled Trials (CENTRAL). MEDLINE and EMBASE will be accessed via the Ovid platform. We will include additional papers from other sources including the references of reviews articles or studies identified during screening. A full description of the search strategy is outlined in Appendix 2.

Study selection

Two reviewers will independently undertake initial relevance screening of titles and abstracts. The researchers will not be blinded to the journal titles or to the study authors or institutions. If there is disagreement or uncertainty regarding eligibility, the article will be included in the next stage of screening for further analysis for inclusion/exclusion. The full text will be retrieved for all articles not excluded by the initial screening. These papers will be assessed against the inclusion and exclusion criteria. Disagreements about eligibility will be resolved by discussion between the screening researchers or a third party.

Data management

We will use Covidence (Veritas Health Innovation Ltd., Melbourne, Australia) software to identify duplicate records and for relevance screening. We will use a reference manager program (EndNoteX8, Clarivate Analytics, Philadelphia, USA) to store identified citations and their electronic text.

Inclusion criteria

Types of studies

Quantitative studies published in peer reviewed journals assessing adults will be eligible for inclusion in this review. Studies are likely to be prospective or retrospective cohort or case-control studies.

Study characteristics

Eligible studies must include both a cohort of patients who developed new-onset atrial-fibrillation and a cohort who did not. They must include at least one risk factor that was investigated. The studies must be based in non-service-specific ICUs. These will include general medical, surgical or mixed ICUs. Studies of cohorts defined by a single disease or narrow group of diseases (e.g. myocardial infarction or sepsis) will be included. Identified studies published from January 1970 until the day of search completion will be included.

Phenomenon of interest

Studies must describe a statistical relationship between a patient-derived variable (e.g. age, blood pressure or serum potassium level) and the development of new-onset atrial fibrillation. ‘Diagnosis’ may be included as a variable. We will include studies that group atrial fibrillation with atrial flutter, and we will include studies investigating new-onset supraventricular arrhythmias, providing atrial fibrillation constituted at least 70% of arrhythmia episodes.

Population

Studies that sample adult patients admitted to the ICU types specified above will be considered for inclusion.

For the purpose of this review, an adult is defined as ≥16 years of age. There will be no other restrictions.

Exclusion criteria

Types of studies

Qualitative studies, case studies, editorials, letters, practice guidelines and abstract-only reports will be excluded.

Study characteristics

Studies of cohorts defined by a single procedure or narrow group of procedures (e.g. appendicectomy or hepatobiliary surgery) will be excluded. Studies based on service-specific (e.g. cardiac, cardiothoracic surgical or neurosurgical) ICUs will also be excluded. Studies published in a language other than English will be excluded.

Phenomenon of interest

Studies will be excluded if no risk factors are analysed. Studies that do not explicitly exclude or separate patients with a history of chronic or paroxysmal AF will be excluded. Studies that do not specify arrhythmia type will also be excluded.

Population

Studies of participants under 16 years old will be excluded.

Data extraction

Data will be extracted from identified full text articles and supplementary material. One researcher (JB) will be responsible for data extraction. All uncertainties regarding data extraction will be resolved by discussion amongst the study team. Extracted data will include: 1) characteristics of study setting and patient population; 2) study methodology (including ascertainment of risk factors, definition and assessment of outcome, and control of confounding variables); 3) risk factor estimates including measures quantifying risk, confidence intervals and p-values for statistical significance. Where available we will extract β coefficients and the units of measurement to which they refer. We will extract risk estimates identified through both univariate and multivariate analysis and record the analysis method. We will populate pre-specified data extraction tables. Where insufficient data is presented we will request additional data from the authors.

Risk of bias assessment

We will assess risk of bias using an adapted Newcastle-Ottawa Scale (NOS)[20]. The NOS is a scoring system designed to assess the quality of non-randomised studies in meta-analyses. Scores are attributed to each paper after assessing domains including the selection of study groups, the comparability of the groups and the ascertainment of the outcome of interest. We have incorporated adaptations from a previous systematic review of risk factors[21]. We have further modified this with the intention of best evaluating our phenomenon of interest. The scoring system used in this systematic review will allocate scores from zero to nine and is outlined in Appendix 3.

Data synthesis and analysis

We will extract summary comparison data as measures of risk (e.g. odds ratios or risk ratios) where possible. Where sufficient original data is presented we will calculate these measures if required. We will then conduct a semi-quantitative synthesis of results from included studies using a method previously described by Zaal, et al. [22] and adapted by Dettmer, et al. [23]. This method requires grouping of risk factors across studies. Grouped risk factors may be heterogeneous in terms of variable type (e.g. continuous or categorical) or cut-off value. Identified variables with associated p-values of ≤0.05 or 95% confidence intervals that do not cross 1 will be allocated a relative strength. This will be based on a composite of the number of articles in which an association is identified, and

the methodological quality of those articles as defined by our adapted NOS. Adjustment for confounding variables contributes to a study's risk of bias score. Risk factors identified through multivariate analysis will therefore be prioritised in the data synthesis. Criteria for strength of evidence is outlined in table 1.

Table 1 - Level of evidence for risk factors for new-onset atrial fibrillation

Level of evidence	Criteria
Strong evidence	Consistent findings in ≥ 2 high quality studies (adapted NOS score 8-9) AND no conflicting studies
Moderate evidence	Consistent findings in 1 high quality study AND ≥1 acceptable quality study (adapted NOS score 6-7) AND no conflicting studies
Weak evidence	Consistent findings in ≥ 3 low quality studies (adapted NOS score ≤5 OR ≥ 2 acceptable quality studies OR 1 high quality study in isolation

DISCUSSION

Several epidemiological and disease severity-related factors have been associated with new-onset atrial fibrillation on the ICU in observational studies. These have not yet been investigated in the general adult ICU population in a systematic review with an evidence synthesis. Data is also limited regarding modifiable or reversible risk factors; available evidence is scarce regarding specific patient vital signs, laboratory results or ICU procedures that may increase the risk of AF. Current clinical practice is therefore variable and not evidence-based.

We will synthesise the weight of evidence behind identified risk factors using a semi-quantitative analytical technique. This method will not provide a synthesis of strength of association for each risk factor. However this information, along with study-level data such as cut-off values, will be provided in the supplementary material.

The findings from this review will contribute towards an improved understanding of the modifiable and non-modifiable antecedents of new-onset AF on the ICU. It may lead to a clinically useful risk-prediction model and inform future research into AF prevention on the ICU. Given the high prevalence and significant associated morbidity and mortality of new-onset AF on the ICU, optimal prevention strategies may result in improved patient outcomes.

DECLARATIONS

Abbreviations

AF: atrial fibrillation; CENTRAL: The Cochrane Database of Systematic Reviews and the Cochrane Central Register of Controlled Trials; EMBASE: Excerpta Medica database; ICU: Intensive care unit; MEDLINE: Medical Literature Analysis and Retrieval System Online; PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocol.

Funding

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Availability of data and materials

Not applicable.

Author contributions

JB, MH, DY and PW have substantially contributed to the design of the systematic review protocol. TP has developed the search strategy. JB, DY and PW wrote this manuscript. All authors read and approved the final manuscript. The funders have not been involved in the study design or reporting. PW is guarantor of this review. The authors would like to thank the patients involved in the development of this protocol.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

Not applicable.

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APPENDIX 1

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section topic	Item	Checklist item	Present in review Y/N	Page and line
		ADMINISTRATIVE INFORMATION		
Title:				
Identification	1a	Identify the report as a protocol of a systematic review	Yes	Page 1 Line 2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	No	-
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Yes	Page 3 Line 32-33
Authors:				
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Yes	Page 1 Lines 4-6
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Yes	Page 6 Lines 28-32
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	No	-
Support:				
Sources	5a	Indicate sources of financial or other support for the review	Yes	Page 6 Lines 22-24
Sponsor	5b	Provide name for the review funder and/or sponsor	Yes	Page 6 Lines 22-24
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	Yes	Page 6 Lines 22-24
		INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known	Yes	Page 3 Lines 2-26

Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Yes	Page 3 Lines 28-29
		METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Yes	Page 4 Lines 21-41 Page 5 Lines 2-15
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Yes	Page 4 Lines 2-7
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Yes	Appendices Page 4 Lines 1-32
Study records:				
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Yes	Page 4 Lines 17-19
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Yes	Page 4 Lines 9-13
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Yes	Page 5 Lines 17-25
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Yes	Page 5 Lines 19-23
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Yes	Page 4 Line 32-36
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Yes	Page 5 Lines 27-33
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Yes	Page 5 Lines 35-42
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of	Yes	Page 5 Lines 35-42

		combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)		
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	No	
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Yes	Page 5 Lines 35-42
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	No	-
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Yes	Page 5 Lines 35-42

APPENDIX 2

Draft search strategy for Medline

1	ATRIAL FIBRILLATION/
2	ATRIAL FLUTTER/
3	SUPRAVENTRICULAR TACHYCARDIA/
4	"atrial fibrillation* ".ab,ti.
5	"atrial flutter* ".ab,ti.
6	"supraventricular tachycardia* ".ab,ti.
7	1 or 2 or 3 or 4 or 5 or 6
8	CRITICAL CARE/
9	INTENSIVE CARE UNIT/
10	"intensive care".ab,ia,in,ti.
11	"critical care".ab,ia,in,ti.
12	"acute physiology".ab,ti.
13	"critical* ill* ".ab,ia,in,ti.
14	(ITU or ICU or AICU).ab,ia,in,ti.
15	8 or 9 or 10 or 11 or 12 or 13 or 14
16	RISK FACTORS/
17	"risk factor* ".ab,ti.
18	EPIDEMIOLOGY/
19	"epidemiolog*".ab,ti.
20	"*etiolog*".ab,ti.
21	"determinant*".ab,ti.
22	"precursor*".ab,ti.
23	"predict*".ab,ti.
24	"trigger*".ab,ti.
25	"marker*".ab,ti.
26	"antecedent*".ab,ti.
27	BIOMARKERS/
28	"new onset".ab,ti.
29	16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
30	7 and 15 and 29

APPENDIX 3

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1. Representativeness of the study population
    a. Truly representative of the general adult ICU population ★
    b. Somewhat representative of the general adult ICU population ★
    c. Poorly representative of the general adult ICU population
    d. No description of the derivation of the cohort
2. Demonstration that outcome of interest was not present at start of study
    a. Exclusion of AF (current and historic) described ★
    b. AF (current and historic) excluded but no description
3. Ascertainment of presence of risk factor
    a. Medical record or investigation result ★
    b. Structured interview ★
    c. Written self-report
    d. No description or none of the above
4. Study size
    a. ≥100 participants in each group ★
    b. <100 participants in each group

Comparability

1. Comparability of cohorts on the basis of the design or analysis
    a. Study design controls for confounding factors ★
    b. Study controls for confounding factors in data analysis ★

Outcome

1. Study design
    a. Prospective ★
    b. Retrospective
2. Assessment of outcome
    a. Independent assessment of heart rhythm from primary source (e.g. monitor / ECG) ★
    b. Non-independent assessment or heart rhythm identified from secondary source (e.g. patient records)
    c. Other identification of heart rhythm
    d. No description
3. Adequacy of follow up of cohorts
    a. complete follow up - all subjects accounted for ★
    b. subjects lost to follow up unlikely to introduce bias - small number lost - ≥90% follow up, or description provided of those lost) ★
    c. follow up rate < 90% and no description of those lost
    d. no statement

APPENDIX 1

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Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Yes	Page 3 Line 32-33
Authors:				
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Yes	Page 1 Lines 4-6
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Yes	Page 7 Lines 3-7
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	No	-
Support:				
Sources	5a	Indicate sources of financial or other support for the review	Yes	Page 6 Lines 30-32
Sponsor	5b	Provide name for the review funder and/or sponsor	Yes	Page 6 Lines 30-32
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	Yes	Page 6 Lines 30-32
		INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known	Yes	Page 3 Lines 2-26
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Yes	Page 3 Lines 28-29

		METHODS		
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Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Yes	Page 5 Lines 19-26
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Yes	Page 4 Line 32-36
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Yes	Page 5 Lines 28-34
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Yes	Page 5 Lines 36-43
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	Yes	Page 5 Lines 36-43 Page 6 lines 1-4
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	No	

	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Yes	Page 5 Lines 36-43 Page 6 lines 1-4
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	No	-
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Yes	Page 5 Lines 36-43 Page 6 lines 1-4