PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Risk factors for new-onset atrial fibrillation on the general adult ICU: Protocol for a systematic review
AUTHORS	Bedford, Jonathan; Harford, Mirae; Petrinic, Tatjana; Young, Duncan; Watkinson, Peter J

VERSION 1 – REVIEW

REVIEWER	Tomoko Fujii Kyoto University, Japan
REVIEW RETURNED	15-Jun-2018

GENERAL COMMENTS	1. Please clarify which platform of the databases you are going to use. 2. For the search strategy for Medline, I would suggest peer review of the search strategy. I know the author team involves a librarian, but I could not find some MeSH terms in the MEDLINE; #8, #21-23. In addition, there are duplicates in #12 and 13, and #25 and 27. 3. Please show the definition of "new-onset AF" for this review. 4. For data extraction, authors mentioned to the incidence of AF, Please be aware that it is only available in a properly conducted cohort study, as authors will include case-control studies as well. 5. What are the expected risk factors? There are many possible risk factors for AF, but could authors list them up? 6. How authors collect and synthesise the data if the risk factors are assessed using continuous variables and the effect estimates are not shown in odds ratio? What if a variable is dichotomized with different cut-off? i.g. K<3.5 and K<4.0. 7. Please mention to the way the authors assess the heterogeneity of the synthesized data. Cardiac patients may often have a right heart cath. 8. If an eligible study assessed several models or conducted several analysis, i.e. uni- and multivariable, which odds ratio do the authors will adopt? 9. If a study dropped some variables of the interest in this review during a variable selection process, then how authors assess the effect of the variables? Are those missing data? 10. Odds ratios change along with the selected covariates in the model. Please explain why it is legitimate to synthesize odds ratios from different studies and different models.

REVIEWER	Prashant Bhave Wake Forest University USA
REVIEW RETURNED	20-Jun-2018

GENERAL COMMENTS	Bedford et al present a protocol for a systematic review examining risk factors for new-onset AF in the adult ICU. It is noted that risk

	factors for the development of AF in a variety of settings, including the ICU, are already fairly well described in the literature. The methods outlined appear appropriate. I would reinforce the idea that identifying truly “new-onset” AF from administrative datasets is quite challenging. The authors state that their rationale for undertaking this project is to try to create a clinically useful risk-prediction model for new-onset AF in the ICU and to promote an evidence based approach towards AF prevention at the bedside. While I think that creating a risk-prediction model is within the scope of this project, there is little chance that this work will develop an approach to AF prevention at the bedside. Creating realistic expectations in the protocol design is important.

REVIEWER	Takuo Yoshida Intensive Care Unit, Department of Anesthesiology, Jikei University School of Medicine, Tokyo, Japan
REVIEW RETURNED	26-Jun-2018

GENERAL COMMENTS	The general purpose of this systematic review is to provide a protocol concerning the determination of risk factors for new-onset AF. New-onset AF in critically ill patients is common and reported to be associated with poor outcomes. Thus, to identify the modifiable risk factors for new-onset AF is very important. However, the following are some considerations： 1. In the section of the exclusion criteria, the authors presented that they will exclude patients with narrow group of procedures. However, in the section of the inclusion criteria, the authors presented that they will include surgical and mixed ICU. If a study conducted in mixed ICU or surgical ICU are included, the study may include patients that underwent specific procedures, such as esophageal surgery or thoracic surgery without cardiac surgery (which are known as high-risk populations for new-onset AF). Are the authors going to exclude those studies? How do the authors exclude these population? 2. In the Appendix 2 with the search strategy for Medline, the authors include “supraventricular tachycardia”. However, “supraventricular tachycardia” may include the benign arrythmia other than atrial fibrillation and atrial flatter, such as AVNRT or AVRT called paroxysmal supra ventricular tachycardia. There is a difference in the degree of risk for developing ischemic events between benign and malignant arrythmias. Will the authors address the difference between the arrythmias?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

1. Please clarify which platform of the databases you are going to use.

We will use the Ovid platform. We have added this information to page 4, lines 4-5.

2. For the search strategy for Medline, I would suggest peer review of the search strategy. I know the author team involves a librarian, but I could not find some MeSH terms in the MEDLINE; #8, #21-23. In addition, there are duplicates in #12 and 13, and #25 and 27.

Thank you for these observations. In summer 2017 Medline was undertaking amalgamation of two MeSH terms: “INTENSIVE CARE/” and “CRITICAL CARE/”. Since writing the protocol, “INTENSIVE CARE/” has been removed as a MeSH term. We have replaced this term in the search strategy accordingly with “CRITICAL CARE/”.

MeSH terms 21-23 are indeed MeSH terms available when using the Ovid platform. However, we are aware that this platform may not be available to all readers. We have therefore consolidated these terms and replaced them with “BIOMARKERS/”, which is accepted on other platforms such as PubMed. As suggested the updated search strategy has been reviewed by the research team including our subject specialist librarian and checked for duplication and term accuracy.

3. Please show the definition of "new-onset AF" for this review.

We have included our definition on page 3, lines 2-3: “AF occurring after admission to ICU in a patient with no known history of chronic or paroxysmal AF”.

4. For data extraction, authors mentioned to the incidence of AF, Please be aware that it is only available in a properly conducted cohort study, as authors will include case-control studies as well.

We have re-written part of the data extraction section on page 5, lines 19-22 to reflect the reviewer’s important comment. Thissection now reads “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”.

5. What are the expected risk factors? There are many possible risk factors for AF, but could authors list them up?

A list of suggested risk factors may be of interest to some readers. However the purpose of this proposed systematic review will be to identify these risk factors systematically and evaluate the evidence for each one. With respect, we feel that a list of potential candidate risk factors, drawn unsystematically prior to the research being conducted, would add little to this protocol for a systematic review.

6. How authors collect and synthesise the data if the risk factors are assessed using continuous variables and the effect estimates are not shown in odds ratio? What if a variable is dichotomized with different cut-off? i.g. K<3.5 and K<4.0.

This is an important point and one we gave much thought to prior to developing the protocol. Fortunately the proposed semi-quantitative data synthesis methodology as outlined in the original protocol (page 5, lines 34-41) allows for grouping by risk factor e.g. “hypokalaemia”, and permits an evidence synthesis even where associations may have been demonstrated using different statistical methods or using different cut-offs.

7. Please mention to the way the authors assess the heterogeneity of the synthesized data. Cardiac patients may often have a right heart cath.

We are expecting the data to be heterogeneous and for this reason we have decided that a meta-analysis would be inappropriate, and have adopted the semi-quantitative analysis described in the protocol (page 5, lines 34-41). The reviewer’s point is an important one regarding patients with cardiac conditions, and we will exclude studies based on service-specific ICUs e.g. cardiac surgical ICUs or neurological ICUs, as detailed in the original inclusion and exclusion criteria.

8. If an eligible study assessed several models or conducted several analysis, i.e. uni- and multivariable, which odds ratio dothe authors will adopt?

Thank you for this important point. We will extract odds / risk ratios identified through both uni- and multivariate analysis. If a study identifies and reports a risk factor to have a significant association through any accepted, robust statistical technique, then it will be included in our analysis. Our synthesis methodology is based on the number of studies in which a risk factor has been reported, along with the methodological quality of those studies. One aspect of methodological quality is adjustment for confounding. Use of multivariate analysis is therefore taken into account in our synthesis. All extracted odds/risk ratios will be reported in the supplementary material. We have clarified the above by adding an additional sentence on page 5, lines 22-23.

9. If a study dropped some variables of the interest in this review during a variable selection process, then how authors assess the effect of the variables? Are those missing data?

We will extract all reported risk factors from identified studies. This will include any risk factors identified through univariate analysis prior to a variable selection process. If a study does not report a certain variable then this variable will not be included in our analysis.

We are aware that a different range of variables will be reported between studies. Out synthesis methodology is therefore 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 risk of bias assessment tool.

10. Odds ratios change along with the selected covariates in the model. Please explain why it is legitimate to synthesize odds ratios from different studies and different models.

Thank you for this comment and you raise an important point. As you suggest, a meta-analysis of odds/risk ratios drawn from studies using different analytical technique and models would be inappropriate. We have opted to undertake a semi-quantitative analysis based on a well-established and published technique as outlined in the data synthesis and analysis section. This was felt to be a more clinically useful method rather than a solely narrative review.

Reviewer: 2

Bedford et al present a protocol for a systematic review examining risk factors for new-onset AF in the adult ICU. It is noted that risk factors for the development of AF in a variety of settings, including the ICU, are already fairly well described in the literature.

The methods outlined appear appropriate.

I would reinforce the idea that identifying truly "new-onset" AF from administrative datasets is quite challenging.
The authors state that their rationale for undertaking this project is to try to create a clinically useful risk-prediction model for new-onset AF in the ICU and to promote an evidence based approach towards AF prevention at the bedside.
While I think that creating a risk-prediction model is within the scope of this project, there is little chance that this work will develop an approach to AF prevention at the bedside. Creating realistic expectations in the protocol design is important.

Thank you for your comments. We agree that that identifying truly "new-onset" AF from administrative datasets is challenging. Should studies of this kind be identified in our review, they will be excluded if they do not make robust efforts to exclude patients with a background of AF or those with AF on admission to ICU. We have added a sentence to reinforce this fact on page 5, lines 11-12. Furthermore we have adapted the penultimate sentence in the discussion to reflect the reviewer's comments about realistic expectations, focussing more on informing future research (page 6, line 21). The sentence now reads "It may lead to a clinically useful risk-prediction model and inform future research into AF prevention on the ICU". We have also updated the related comment in the abstract (page 2, lines 9-10)

Reviewer: 3

1.
In the section of the exclusion criteria, the authors presented that they will exclude patients with narrow group of procedures. However, in the section of the inclusion criteria, the authors presented that they will include surgical and mixed ICU. If a study conducted in mixed ICU or surgical ICU are included, the study may include patients that underwent specific procedures, such as esophageal surgery or thoracic surgery without cardiac surgery (which are known as high-risk populations for new-onset AF). Are the authors going to exclude those studies? How do the authors exclude these population?

Thank you for your comment and for the opportunity to explain. We have not stated that we will exclude *patients* with a narrow group of procedures, but rather *studies* that define their cohort by a narrow group of procedures e.g. AF risk factors in patients undergoing surgery x. There may be patients who underwent oesophageal surgery on a mixed or surgical ICU, however providing the study defines its cohort based on location, rather than procedure, this study would be included in the analysis.

2.
In the Appendix 2 with the search strategy for Medline, the authors include "supraventricular tachycardia". However, "supraventricular tachycardia" may include the benign arrythmia other than atrial fibrillation and atrial flatter, such as AVNRT or AVRT called paroxysmal supra ventricular tachycardia. There is a difference in the degree of risk for developing ischemic events between benign and malignant arrythmias. Will the authors address the difference between the arrythmias?

We include "supraventricular tachycardia" in our search strategy because an initial scoping search revealed that some relevant papers did contain this MeSH term. We understand that this umbrella term contains other rhythms not of interest, and have accounted for this in our original inclusion criteria: "we will include studies investigating new-onset supraventricular arrhythmias, providing atrial fibrillation constituted at least 70% of arrhythmia episodes".

VERSION 2 – REVIEW

REVIEWER	Tomoko Fujii Kyoto University, Japan
REVIEW RETURNED	23-Jul-2018

GENERAL COMMENTS	1. The approach to "semi-quantitatively synthesize" reported risk factors does not address cut-off values or the levels of deranged values. This will UNFORTUNATELY drop valuable information that would be useful to interpret or utilize the result in future studies. Please refer to the limitation of this method in the discussion. 2. The heterogeneity in the type of variables in original studies, i.e. continuous or binary, could affect the results of regression analysis 3. Authors mentioned to odds ratio and risk ratio in the data synthesis section. (In previous manuscript they did not mention to risk ratio in this section. Please track it once you make changes.) However, they mentioned only to risk ratios in the data extraction section. Please be careful and consistent throughout the manuscript. 4. Authors did not mention the beta coefficient. If authors are going to include all the identified risk factors in statistical models, some variables would be reported with a beta coefficient for their effect estimates. Please be aware that the protocol should be clearly and comprehensively written. 5. The heterogeneity in the ICU population is not solely about the location. Cardiac surgery patients or GI surgery patients can be included in studies from mixed ICUs. It is not easy to manage heterogeneity of the study population in critical care research;

	therefore, this should be mentioned in the discussion as a limitation. 6. It is still unclear how this review handles the effect estimates from uni- and multivariable analysis in one study. Authors replied that they will identify "both." Does it mean they count it as two when the risk factor was identified both in univariable analysis and in multivariable analysis, or do they prioritize multivariable analysis? Please make it clear in the manuscript how they handle the unit of analysis issue.

REVIEWER	Prashant Bhave Wake Forest University USA
REVIEW RETURNED	23-Jul-2018

GENERAL COMMENTS	The authors have adequately addressed my concerns.

REVIEWER	Takuo Yoshida Intensive Care Unit, Department of Anesthesiology, Jikei University School of Medicine, Tokyo, Japan
REVIEW RETURNED	25-Jul-2018

GENERAL COMMENTS	The authors have adequately answered my remarks.

VERSION 2 – AUTHOR RESPONSE

Reviewer:1

1. The approach to "semi-quantitatively synthesize" reported risk factors does not address cut-off values or the levels of deranged values. This will UNFORTUNATELY drop valuable information that would be useful to interpret or utilize the result in future studies. Please refer to the limitation of this method in the discussion.

We agree, and accept the limitations of this method. The analytical technique that we will employ has been used with success in previous ICU studies and provides a useful synthesis where other methods e.g. narrative synthesis would not, at the expense of certain study-level data. We have emphasised the requirement to group variables in the data synthesis section (page 5, lines 39-41), and referred to its limitations in a new section of the discussion (page 6, lines 14-17).

2. The heterogeneity in the type of variables in original studies, i.e. continuous or binary, could affect the results of regression analysis.

Thank you, this is a good point. We will include this point in the limitations section of the systematic review depending on the variables identified.

3. Authors mentioned to odds ratio and risk ratio in the data synthesis section. However, they mentioned only to risk ratios in the data extraction section. Please be careful and consistent throughout the manuscript.

Thank you. Studies may report measures quantifying risk in different ways, including risk ratios and odds ratios. We have adapted the wording to include "risk estimates" and "measures of risk" to avoid confusion (page 5, lines 24, 36 & 37).

4. Authors did not mention the beta coefficient. If authors are going to include all the identified risk factors in statistical models, some variables would be reported with a beta coefficient for their effect estimates. Please be aware that the protocol should be clearly and comprehensively written.

Thank you. We had considered this to be a measure of effect magnitude and thus included within the "measures quantifying risk". However in order to clarify, we have added a line on page 5, lines 22-23 explaining that we will extract β coefficients where available.

5. The heterogeneity in the ICU population is not solely about the location. Cardiac surgery patients or GI surgery patients can be included in studies from mixed ICUs. It is not easy to manage heterogeneity of the study population in critical care research; therefore, this should be mentioned in the discussion as a limitation.

This review will include studies based in non-service-specific ICUs across a range of healthcare systems. Study populations are likely to be heterogeneous however this is not possible to quantify this prior to undertaking the research. We will certainly discuss the heterogeneity of identified populations in the manuscript of the systematic review once it is completed.

6. It is still unclear how this review handles the effect estimates from uni- and multivariable analysis in one study. Authors replied that they will identify "both." Does it mean they count it as two when the risk factor was identified both in univariable analysis and in multivariable analysis, or do they prioritize multivariable analysis? Please make it clear in the manuscript how they handle the unit of analysis issue.

Thank you for this comment and for highlighting a lack of clarity. We have added the following sentence to the data synthesis section: "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."

Risk factors will only be counted once per study, as suggested by page 5, line 42-43: "[the strength of evidence] 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".

Reviewer: 2

The authors have adequately addressed my concerns

Reviewer: 3

The authors have adequately answered my remarks.

VERSION 3 – REVIEW

REVIEWER	Tomoko Fujii Kyoto University, Japan
REVIEW RETURNED	04-Aug-2018

GENERAL COMMENTS	The authors have largely responded to my comments.