Multivariable prediction models for atrial fibrillation after cardiac surgery: a systematic review protocol

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ABSTRACT

Introduction
Dozens of multivariable prediction models for atrial fibrillation after cardiac surgery (AFACS) have been published, but none have been incorporated into regular clinical practice. One of the reasons for this lack of adoption is poor model performance due to methodological weaknesses in model development. In addition, there has been little external validation of these existing models to evaluate their reproducibility and transportability. The aim of this systematic review is to critically appraise the methodology and risk of bias of papers presenting the development and/or validation of models for AFACS.

Methods
We will identify studies that present the development and/or validation of a multivariable prediction model for AFACS through searches of PubMed, Embase and Web of Science from inception to 31 December 2021. Pairs of reviewers will independently extract model performance measures, assess methodological quality and assess risk of bias of included studies using extraction forms adapted from a combination of the Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies checklist and the Prediction Model Risk of Bias Assessment Tool. Extracted information will be reported by narrative synthesis and descriptive statistics.

Ethics and dissemination
This systematic review will only include published aggregate data, so no protected health information will be used. Study findings will be disseminated through peer-reviewed publications and scientific conference presentations. Further, this review will identify weaknesses in past AFACS prediction model development and validation methodology so that subsequent studies can improve upon prior practices and produce a clinically useful risk estimation tool.

PROSPERO registration number CRD42019127329.

BACKGROUND
Atrial fibrillation after cardiac surgery (AFACS) is the most common adverse event following cardiac surgery, occurring in 30%–50% of cases.1–4 Prophylactic treatments decrease the length of hospital stay and, therefore, costs, but these treatments are not risk-free.5 Several evidence-based recommendations to prevent AFACS have been released from leading cardiovascular societies in recent years.5–7 Many of these recommendations require stratifying patients into ‘normal’ and ‘elevated’ risk groups for AFACS, but stratification criteria have not been clearly defined. A robust prediction model to identify high-risk patients has the potential to facilitate targeted prophylaxis and improve patient outcomes. While many AFACS risk prediction models have been published, there has been little systematic appraisal of their development and validation strategies. A systematic review of AFACS risk prediction models was recently published.8 However, investigators solely screened articles that could be retrieved as full text directly from bibliographic databases (Ovid MEDLINE and PubMed Central) and the publication provided only limited details on the methodology of included primary studies. Therefore, a systematic review of AFACS risk prediction model literature with a comprehensive bibliographic database search and in-depth critical appraisal of primary study methodology is warranted.

The aim of this study is to perform a systematic review and critical appraisal of

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The review will be the most comprehensive appraisal of multivariable prediction models for atrial fibrillation after cardiac surgery to date.
⇒ The review will rigorously assess methodology and risk of bias for included studies, identifying areas of improvement for future model development and validation.
⇒ The review will not incorporate individual participant data, so evaluation must rely on investigator report of all information (eg, model performance metrics).
multivariable prediction models developed or validated for predicting the absolute risk of AFACS for individual patients.

METHODS
This systematic review protocol is registered under PROSPERO number CRD42019127329 and follows the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols 2015 statement.9

Selection criteria
This study will include manuscripts that meet the inclusion and exclusion criteria described in table 1.

In order to achieve our goal, we will follow the PICOTS items described in table 2.

Search strategy
Studies from PubMed, Embase and Web of Science will be searched from inception to 31 December 2021. Article references of included studies will be reviewed to identify any additional eligible studies. Searches will be guided by a critical care information specialist. Study authors will be contacted if key article information is not available within the article. Online supplemental appendix A shows the full search strategy for all databases.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Eligibility criteria</th>
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<tr>
<td>Criteria</td>
<td>Type of studies</td>
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<tr>
<td>Inclusion</td>
<td>Clinical studies that present the development, adjustment, updating or external validation of multivariable models containing preoperative, intraoperative and early postoperative factors for predicting the absolute risk of atrial fibrillation (including or excluding atrial flutter) within 30 days after cardiac surgery for individual patients. Minimum required follow-up time for atrial fibrillation will be 72 hours after surgery.</td>
</tr>
<tr>
<td>Exclusion</td>
<td>Studies presenting the development or validation of models for predicting the following outcomes: ► Tachyarrhythmias not limited to atrial fibrillation and atrial flutter ► Silent atrial fibrillation only (pending review of outcome definition on case-by-case basis) ► Permanent atrial fibrillation only (pending review of outcome definition on case-by-case basis) ► Studies solely assessing genetic predictors If the same model is validated multiple times using an extension of the same cohort, only the validation using the largest cohort will be included in the systematic review.</td>
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<tr>
<td>Type of reports:</td>
<td>Conference abstracts</td>
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<td></td>
<td>Case studies</td>
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<td></td>
<td>Narrative reviews, systematic reviews or meta-analyses</td>
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<td></td>
<td>Editorials, comments, responses or letters to the editor</td>
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Disagreements between reviewers will be resolved by consensus or, if necessary, adjudicated by a third reviewer. The number of records retrieved from the database search, identified through other sources (eg, snowballing), and included or excluded at each screening step will be documented using a flow diagram as suggested in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.

**Data extraction**

Pairs of reviewers will independently extract data and assess methodological quality for each multivariable prediction model with respect to data source, study participants, candidate and final model predictors, model outcomes and analytical approach into piloted REDCap forms. Disagreements between reviewers will be resolved by consensus or, if necessary, adjudicated by a third reviewer. Each included study will be independent assessed by two reviewers using PROBAST. The tool comprises 23 signaling questions within four domains (participant selection, predictors, outcome and analysis). Articles will be classified as low, high or unclear risk of for each domain. Articles will be classified as having overall low risk of bias if all domains are rated at low risk of bias.

**Study selection**

Pairs of authors will use Covidence to independently screen records for eligibility first by title and abstract, then by full text review. Disagreements between reviewers will be resolved by consensus or, if necessary, adjudicated by a third reviewer. The number of records retrieved from the database search, identified through other sources (eg, snowballing), and included or excluded at each screening step will be documented using a flow diagram as suggested in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.

**Table 2** PICOTS

| Population | Human patients 18 years of age or older undergoing cardiac surgery that present to surgery in sinus rhythm |
| Intervention (Model) | Multivariable models developed or validated for predicting the absolute risk of atrial fibrillation (including or excluding atrial flutter) after cardiac surgery in individual patients |
| Comparator | Not applicable |
| Outcomes | Atrial fibrillation and atrial flutter by any definition |
| Timing | Within 30 days after cardiac surgery (minimum 72-hour follow-up required) |
| Setting | Hospital inpatient |

**Risk of bias assessment**

Each included study will be independent assessed by two reviewers using PROBAST. The tool comprises 23 signaling questions within four domains (participant selection, predictors, outcome and analysis). Articles will be classified as low, high or unclear risk of for each domain. Articles will be classified as having overall low risk of bias if all domains are rated at low risk of bias.
Evidence synthesis

Results will be summarised using descriptive statistics, graphical plots and a narrative synthesis. If three or more studies with similar methodology, reporting of key performance measures and low risk of bias evaluate the same prediction model, we will consider summarising their performance using a random-effects meta-analysis.

Patient and public involvement

Patient and public involvement is integral to the PARA-DISE project. Representatives will be involved in model development, will take part in meetings considering the importance and identification of risk factors and are key to our publicity strategy. Two patient advocacy groups, StopAfib.org and the Arrhythmia Alliance/AF Association will help with model development and will help publicise our findings.

Ethics and dissemination

Ethics approval is not required for this study because it will only use published aggregate data. Results will be disseminated through peer-reviewed publications and conference presentations. Further, this review will identify weaknesses in past AFACS prediction model development and validation methodology so that future AFACS prediction model development and validation can improve on prior approaches and produce a clinically useful risk estimation tool.

DISCUSSION

Although many AFACS prediction models have been published, none are routinely used in clinical practice. Existing models are not employed largely due to insufficient predictive performance. Additional reasons include practitioners’ belief that AFACS is a transient phenomenon without significant sequelae, as well as concerns regarding effectiveness and side effects of AFACS prophylaxis and treatments. However, a well-performing risk model could be used to avoid the potential for harmful side effects from prophylactic strategies (eg, amiodarone toxicity) in low-risk patients. Additionally, it could be used to optimise the surgical procedure (eg, left atrial appendage ligation, concomitant AF ablation, posterior left pericardiotomy) to prevent AFACS and be used as an early detection tool to prevent AFACS-related morbidity. This systematic review and critical appraisal will identify weaknesses in past AFACS prediction model development and validation methodology, which may have contributed to suboptimal performance that precluded incorporation into clinical practice.

The strengths of this study will include the comprehensive search of three bibliographic databases and a robust appraisal of study methodology. A study limitation is that this review will not include models containing ‘cutting-edge’ variables, such as inflammatory biomarkers, genomic predictors, real-time waveform data or atrial single-cell sequencing data. While these predictors may prove extremely valuable and likely add substantially to an existing clinical-only model, they have not been sufficiently validated to incorporate into a routine prediction model. An additional limitation will be the inclusion of only English language publications, leading to the under-representation of studies in other languages. Despite these limitations, this systematic review will identify flaws in prior AFACS prediction model development and validation studies. This will inform methodological improvements in subsequent research that will hopefully produce a clinically applicable risk tool.

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Contributors All authors helped develop the protocol and approved the final protocol manuscript. TP provided guidance on the database search strategy. AR, HA, JM and KGF will screen records under the guidance of GSC and JDM. AE, AR, HA, JM and KGF will extract data under the guidance of GSC, JDM and MH. AE, AR, HA, JM and KGF will perform the critical appraisal under the guidance of BO’B, DAC, GSC, GYHl, JPB, JDM, MH, OCR, PJW and RP.

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Disclaimer The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the HTA Programme, NIHR, NHS or the Department of Health.

Competing interests None declared.

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