

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

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**Amendments:** This protocol represents an amendment to the previously registered  
PROSPERO protocol CRD42019127329. Changes include the following:

1. The systematic review has been absorbed by the PARADISE project, a study funded by the National Institute of Health Research, Health Technology Assessment Programme.
2. Study and target population inclusion and exclusion criteria have been clarified.
3. The original protocol included only multivariable prediction models with preoperative predictors of atrial fibrillation after cardiac surgery. The review will now also include multivariable prediction models that contain intraoperative and/or postoperative predictors.
4. External validation of identified prediction models will no longer be coupled with the systematic review. The external validation will be undertaken at a later stage of the PARADISE project.
5. An updated database search strategy. Updates include minor changes to search terms to ensure uniform strategies across databases and to explicitly incorporate atrial flutter, extension of search through 8/31/21 (previously 3/16/2019), and automatic exclusion of conference abstracts, case studies, reviews, editorials, comments, responses, and letters to the editor.



## **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 using a comprehensive bibliographic database search. 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 (CHARMS) checklist and the Prediction model Risk Of Bias ASsessment Tool (PROBAST). Extracted information will be reported by narrative synthesis and descriptive statistics.

### **Ethics and dissemination**

This systemic review will only include published aggregate data, so no protected health information will be utilized. This review will identify weaknesses in past AFACS prediction model development and validation methodology so that subsequent AFACS prediction model development and validation can improve upon prior methodology and produce a clinically useful risk estimation tool.

**PROSPERO registration number:** CRD42019127329.

**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 upon investigator report of all information (e.g., model performance metrics).

## **BACKGROUND**

Atrial fibrillation after cardiac surgery (AFACS) is the most common adverse event after cardiac surgery, occurring in 30-50% of cases. Prophylactic treatments decrease length of hospital stay and therefore costs, but these treatments are not risk-free. Several evidence-based recommendations to prevent AFACS have been released from leading cardiovascular societies in recent years. Many of these recommendations require stratifying patients into 'normal' and 'elevated' risk groups for AFACS<sup>1, 2</sup>, although stratification criteria have not been clearly defined. A robust risk 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<sup>3</sup>. 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 multivariable prediction models developed or validated for predicting the absolute risk of atrial fibrillation after cardiac surgery for individual patients.

## **METHODS**

This systematic review is registered under PROSPERO number CRD42019127329 and follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) 2015 statement.

### **Selection criteria**

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

Criteria	Type of studies	Target Population
<b>Inclusion</b>	Clinical studies that present the development, adjustment, updating, or external validation of multivariable models containing pre-, intra-, and early post-operative factors for predicting the absolute risk of atrial fibrillation within 30 days after cardiac surgery for individual patients. Minimum required follow-up time for atrial fibrillation will be 72 hours after surgery.	Human patients 18 years of age or older who present to cardiac surgery in sinus rhythm. Cardiac surgeries of interest include: <ul style="list-style-type: none"> <li>• Coronary artery bypass graft</li> <li>• Aortic valve repair or replacement (including for bacterial endocarditis)</li> <li>• Mitral valve repair or replacement (including for bacterial endocarditis)</li> <li>• Any combination of the above</li> <li>• Any of the above with the following concomitant procedures: left atrial appendage resection, left ventricular aneurysm repair, sub-aortic stenosis resection</li> </ul>
	<b>Type of report:</b> <ul style="list-style-type: none"> <li>- Articles published through 8/31/2021</li> </ul>	
<b>Exclusion</b>	Studies presenting the development or validation of models for predicting the following outcomes: <ul style="list-style-type: none"> <li>• Tachyarrhythmias not limited to atrial fibrillation and flutter</li> </ul>	Studies including only patients undergoing the following cardiac surgery types <ul style="list-style-type: none"> <li>• Congenital (e.g., ventricular septal defect repair)</li> </ul>

	<ul style="list-style-type: none"> <li>• Silent atrial fibrillation only (pending review of outcome definition on case-by-case basis)</li> <li>• Permanent atrial fibrillation only (pending review of outcome definition on case-by-case basis)</li> <li>• Studies solely assessing genetic predictors</li> </ul>	<ul style="list-style-type: none"> <li>• Cardiac tumor (e.g., left atrial myxoma surgery)</li> <li>• Cardiac trauma</li> <li>• Surgical ventricular restoration</li> </ul> <p>Studies including any patients undergoing the following cardiac surgery types</p> <ul style="list-style-type: none"> <li>• Transcatheter</li> <li>• Percutaneous</li> <li>• Mitral balloon valvuloplasty</li> <li>• Pulmonary thromboendarterectomy</li> <li>• Implantation of left ventricular assist devices</li> <li>• Ascending aorta or aortic arch repair or replacement without concomitant atrial valve repair or replacement</li> <li>• Cardiac transplant</li> <li>• Surgical ventricular septal myectomy</li> <li>• Transaortic myectomy</li> <li>• Fontan procedure</li> <li>• Maze</li> <li>• Cardiac ablation (e.g., atrial ablation, pulmonary vein isolation)</li> </ul>
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		<ul style="list-style-type: none"> <li>• Closed valvotomy</li> </ul>
	<b>Type of reports:</b> <ul style="list-style-type: none"> <li>• Conference abstracts</li> <li>• Case studies</li> <li>• Narrative reviews, systematic reviews, or meta-analyses</li> <li>• Editorials, comments, responses, or letters to the editor</li> </ul>	

**Table 1.** Eligibility Criteria

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

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

**Table 2.** PICOTS

### Search Strategy

Studies from MEDLINE, Embase, and Web of Science will be searched from inception through 8/31/2021. 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. Supplementary appendix A shows the full search strategy for all the databases.

## **Study Selection**

Pairs of authors will use Covidence<sup>4</sup> to independently screen records for eligibility first by title and abstract, then by full text review. Disagreements between reviewers will be resolved consensus or, if necessary, adjudicated by a third reviewer<sup>5</sup>. The number of records retrieved from the database search, identified through other sources (e.g., 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 (PRISMA) statement<sup>6</sup>

## **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 analytic approach into a piloted Research Electronic Data Capture (REDCap) forms/instruments<sup>7, 8</sup>. Extraction forms will be adapted from a combination of the Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling studies (CHARMS)<sup>9</sup> checklist. Disagreements between reviewers will be resolved consensus or, if necessary, adjudicated by a third reviewer<sup>5</sup>. Study authors will be contacted by e-mail where additional information is required. We will extract the following information from included studies and models:

- Citation information: Authors, title, journal, publication date.
- Study design and data source: Prospective cohort, retrospective cohort, randomized trial participants, nested case-control, non-nested case-control, case-cohort, registry data.
- Participant information: Inclusion and exclusion criteria, recruitment method, study dates, cardiac surgery types

- Outcome: Atrial fibrillation and/or atrial flutter diagnosed within 30 days after cardiac surgery (with minimum 72-hours postoperative follow-up).
- Candidate predictors: Names and number examined for predicting the outcome
- Final model: Type of model, predictor selection method, list of predictors in the final model
- Missing data: Number of patients with any missing data, data missing on predictors / outcome / both, method for handling missing data
- Model development: Total number of observations, total number of outcome events, model name (where applicable), model building approach, model assumptions evaluated, method for selecting candidate and final model predicts, use of penalization/shrinkage techniques, assessment of interactions, handling of continuous predictors
  - Internal model validation: apparent validation (no split-sample, bootstrap, or cross-validation), internal validation (split-sample, bootstrap, cross-validation)
- Model reporting: whether multivariable models are presented with weights, intercepts, baseline survival (for survival models), and alternative model presentations (e.g., nomogram)
- External model validation: Total number of observations, total number of outcome events, target population, setting, data source, predictor distribution (compared to model development sample), amount and handling of missing data. Whether and how model was adjusted or updated (e.g., recalibrated) based on observed predictive performance.
- Model performance measures: We will extract performance measures from apparent, internal, and external validation (where available). We will record whether each of the following calibration measures was presented, and extract the corresponding point estimates with standard errors or confidence intervals and p values where provided: calibration plots, calibration slope, calibration intercept (calibration-in-the-large), Hosmer-Lemeshow goodness of fit test, and observed to expected outcome ratio. We will record

whether each of the following discrimination measures was presented, and extract the corresponding point estimates with standard errors or confidence intervals and p values where provided: area under the receiver operating characteristic (ROC) curve (AUC), D-statistic, and log-rank test. Other reported performance measures (e.g., decision curve analysis) will be recorded as present vs. absent.

- Simplified models: Performance measures will also be extracted for any simplified model (e.g., integer scoring system) presented<sup>10</sup>.

### **Risk of bias assessment**

Each included study will be independently assessed by two reviewers using the Prediction model Risk Of Bias ASsessment Tool (PROBAST)<sup>11</sup>. The tool comprises 23 signalling 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 summarized using descriptive statistics, graphical plots and a narrative synthesis. We do not plan to perform a quantitative synthesis.

### **Patient and Public Involvement**

Patient and public involvement is integral to our work. Representatives will be involved in this 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.

## **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. This systematic review and critical appraisal will identify weaknesses in past AFACS prediction model development and validation methodology which may have contributed to sub-optimal performance. Once these flaws are identified, subsequent AFACS prediction model development and validation can improve upon prior methodology and hopefully produce a clinically applicable risk tool.

**Conflicts of interest:** None

**Author Contributions:**

- **J Daniel Muehlschlegel:** This author helped in the protocol development and guidance on record screening, data extraction and critical appraisal.
- **Kara G. Fields:** This author helped in the protocol development, record screening, data extraction and critical appraisal.
- **Gary S Collins:** This author helped in the protocol development and guidance on record screening, data extraction and critical appraisal.
- **Peter J Watkinson:** This author helped in the protocol development and critical appraisal.
- **Rui Providencia:** This author helped in the protocol development and critical appraisal.
- **Gregory Y.H. Lip:** This author helped in the protocol development and critical appraisal.
- **Benjamin O'Brien:** This author helped in the protocol development and critical appraisal.
- **Jonathan Bedford:** This author helped in the protocol development and critical appraisal.
- **David Clifton:** This author helped in the protocol development and critical appraisal.
- **Oliver Redfern:** This author helped in the protocol development and critical appraisal.
- **Jie Ma:** This author helped in the protocol development, record screening, data extraction and critical appraisal.
- **Tatjana Petrinic:** This author helped in the database search guidance.
- **Hassan Alhassan:** This author helped in the protocol development, record screening, data extraction and critical appraisal.
- **Anthony Eze:** This author helped in the record data extraction and critical appraisal.

- **Ankith Reddy:** This author helped in the record data extraction and critical appraisal.
- **Mona Hedayat:** This author helped in the record data extraction and critical appraisal.

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