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

Kara G Fields ,[1] Jie Ma ,[2] Tatjana Petrinic,[3] Hassan Alhassan ,[4] Anthony Eze ,[5] Ankith Reddy ,[6] Mona Hedayat ,[1] Rui Providencia ,[7,8] Gregory Y H Lip ,[9,10] Jonathan P Bedford ,[11] David A Clifton ,[12] Oliver C Redfern ,[11] Benjamin O'Brien ,[13,14,15] Peter J Watkinson ,[11,16,17] Gary S Collins ,[2] Jochen D Muehlschlegel [1]

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For numbered affiliations see end of article.

Correspondence to
Dr Jochen D Muehlschlegel; jmuehlschlegel@bwh.harvard.edu

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 systemic 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.

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).

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.[6 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

Table 1 Eligibility criteria

Criteria	Type of studies	Target population
Inclusion	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.	Human patients 18 years of age or older who present to cardiac surgery in sinus rhythm. Cardiac surgeries of interest include: ► Coronary artery bypass graft ► Aortic valve repair or replacement (including for bacterial endocarditis) ► Mitral valve repair or replacement (including for bacterial endocarditis) ► Any combination of the above ► Any of the above with the following concomitant procedures: left atrial appendage resection, left ventricular aneurysm repair, subaortic stenosis resection, ascending aorta or aortic arch repair or replacement (without deep hypothermic circulatory arrest)
	Type of report: ► Articles published through 31 December 2021 in the English language	
Exclusion	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.	Studies including only patients undergoing the following cardiac surgery types: ► Congenital (eg, ventricular septal defect repair) ► Cardiac tumour (eg, left atrial myxoma surgery) ► Cardiac trauma ► Surgical ventricular restoration Studies including any patients undergoing the following cardiac surgery types: ► Transcatheter ► Percutaneous ► Mitral balloon valvuloplasty ► Pulmonary thromboendarterectomy ► Implantation of left ventricular assist devices ► Ascending aorta or aortic arch repair or replacement without concomitant included procedure (coronary artery bypass graft, aortic valve repair or replacement and/or mitral valve repair or replacement) ► Cardiac transplant ► Surgical ventricular septal myectomy ► Transaortic myectomy ► Fontan procedure ► Maze ► Cardiac ablation (eg, atrial ablation, pulmonary vein isolation) ► Closed valvotomy
	Type of reports: ► Conference abstracts ► Case studies ► Narrative reviews, systematic reviews or meta-analyses ► Editorials, comments, responses or letters to the editor	

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 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

Study selection

Pairs of authors will use Covidence[10] 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.[11] 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.[12]

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.[13 14] Extraction forms will be adapted from a combination of the Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies[15] checklist and the Prediction Model Risk of Bias Assessment Tool (PROBAST).[16] Disagreements between reviewers will be resolved by consensus or, if necessary, adjudicated by a third reviewer.[11] Study authors will be contacted by email 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, randomised 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 (including or excluding 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 predictors, use of penalisation/shrinkage techniques, assessment of interactions, handling of continuous predictors (eg, inclusion of original vs categorised measurement).
  - 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 (eg, nomogram).
- External model validation: Total number of observations, total number of outcome events, target population, setting, data source, predictor distribution (compared with model development sample), amount and handling of missing data. Whether and how model was adjusted or updated (eg, 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 SEs or CIs 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 SEs or CIs and p values where provided: area under the receiver operating characteristic curve, D-statistic and log-rank test. Other reported performance measures (eg, decision curve analysis) will be recorded as present versus absent.
  - Simplified models: Performance measures will also be extracted for any simplified model (eg, integer scoring system) presented.[17]

Risk of bias assessment

Each included study will be independent assessed by two reviewers using PROBAST.[16] 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 PARADISE 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,[18] concomitant AF ablation,[19] posterior left pericardiotomy[20]) 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 underrepresentation 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.

Author affiliations
[1]Department of Anesthesiology, Perioperative and Pain Medicine, Harvard Medical School, Boston, Massachusetts, USA
[2]Centre for Statistics in Medicine, Nuffield Department of Orthopedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, UK
[3]Bodleian Health Care Libraries, University of Oxford, Oxford, UK
[4]Department of Medicine, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA
[5]Department of Surgery, Duke University Medical Center, Durham, North Carolina, USA
[6]University of Texas Medical Branch, School of Medicine, Galveston, Texas, USA
[7]Institute of Health Informatics Research, University College London, London, UK
[8]Department of Cardiac Electrophysiology, Barts Heart Centre, St. Bartholomew's Hospital, Barts Health NHS Trust, London, UK
[9]Liverpool Centre for Cardiovascular Science at University of Liverpool, Liverpool John Moores University and Liverpool Heart and Chest Hospital, Liverpool, UK
[10]Department of Clinical Medicine, Aalborg University, Aalborg, Denmark
[11]Kadoorie Centre for Critical Care Research and Education, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK
[12]Department of Engineering Science, University of Oxford, Oxford, UK
[13]Department of Cardiac Anesthesiology and Intensive Care Medicine, Deutsches Herzzentrum Berlin, Charité Universitätsmedizin Berlin, Berlin, Germany
[14]Department of Perioperative Medicine, St. Bartholomew's Hospital and Barts Heart Centre, Barts Health NHS Trust, London, UK
[15]Outcomes Research Consortium, Cleveland, Ohio, USA
[16]Oxford University Hospitals NHS Trust, Oxford, UK
[17]NIHR Biomedical Research Centre, Oxford University Hospitals NHS Foundation Trust, Oxford, UK

Twitter Hassan Alhassan @adam_dr_, Jonathan P Bedford @JonBedford, Gary S Collins @GSCollins and Jochen D Muehlschlegel @DannyMuehlschMD

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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ORCID iDs
Kara G Fields http://orcid.org/0000-0002-8910-4863
Jie Ma http://orcid.org/0000-0002-3900-1903
Hassan Alhassan http://orcid.org/0000-0003-1663-1045
Anthony Eze http://orcid.org/0000-0003-2534-4515
Ankith Reddy http://orcid.org/0000-0001-7979-7611
Mona Hedayat http://orcid.org/0009-0005-8125-5914
Rui Providencia http://orcid.org/0000-0001-9141-9883
Gregory Y H Lip http://orcid.org/0000-0002-7566-1626
Jonathan P Bedford http://orcid.org/0000-0001-9455-022X
David A Clifton http://orcid.org/0000-0002-9848-8555
Oliver C Redfern http://orcid.org/0000-0002-3596-3806
Benjamin O'Brien http://orcid.org/0000-0001-7024-2337
Peter J Watkinson http://orcid.org/0000-0003-1023-3927
Gary S Collins http://orcid.org/0000-0002-2772-2316
Jochen D Muehlschlegel http://orcid.org/0000-0002-6209-7253

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