Preventing Recurrent Cardioembolic Stroke

Right Approach, Right Patient (PRECISE) Study Protocol

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Published in:
Cerebrovascular Diseases

DOI (link to publication from Publisher):
10.1159/000525918

Publication date:
2023

Document Version
Publisher's PDF, also known as Version of record

Cerebrovascular Diseases

Protocols

Cerebrovasc Dis
DOI: 10.1159/000525918

Received: February 8, 2022
Accepted: June 23, 2022
Published online: August 29, 2022

Preventing Recurrent Cardioembolic Stroke: Right Approach, Right Patient (PRECISE) Study Protocol

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Keywords
Atrial fibrillation · Ischaemic stroke · Cardiac rhythm monitoring · Biomarker

Abstract
Cardiac rhythm monitoring is performed to search for atrial fibrillation (AF) after ischaemic stroke or transient ischaemic attack (TIA). Prolonged cardiac rhythm monitoring increases AF detection but is challenging to implement in many healthcare settings and is not needed for all people after ischaemic stroke/TIA. We aimed to develop and validate a model that includes clinical, electrocardiogram (ECG), blood-based, and genetic biomarkers to identify people with a low probability of AF detection after ischaemic stroke or TIA. We will recruit 675 consenting participants who are aged over 18 years, who were admitted with ischaemic stroke or TIA in the 5 days prior, who are not known to have AF, and who would be suitable for anticoagulation if AF is found. We will collect baseline demographic and clinical data, a 12-lead ECG, and a venous blood sample for blood biomarkers (including midregional pro-atrial natriuretic peptide, MRproANP) and genetic data. We will perform up to 28 days of cardiac rhythm monitoring using an R-test or patch device to search for AF in all participants. The sample size of 675 participants is based on true sensitivity of 92.5%, null hypothesis sensitivity of 80%, 80% power, and 5% significance. The primary outcome is AF detection ≥30 s duration during 28 days of cardiac rhythm monitoring. Secondary outcomes are AF detection at 1-year, recurrent cardiovascular events, and mortality and will be identified by electronic linkage and telephone follow-up. The results will guide the development of a more personalized care pathway to search for AF after ischaemic stroke or TIA. This could help to reduce cardiac rhythm monitoring for people with a low probability of AF detection and allow more intensive cardiac monitoring to be focused on people who are more likely to have AF and benefit. Participants will be consented for their data to be used in future research studies, providing a rich resource for stroke and cardiovascular research communities.

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Introduction

Cardiac thromboembolism, typically due to atrial fibrillation (AF), accounts for 25% of ischaemic strokes and results in strokes that are more severe and with societal costs that are around double those of minor strokes [1]. One-third of strokes are recurrent, and anticoagulant drugs are highly effective at preventing recurrent strokes in people who are found to have AF [2]. People are screened for AF after ischaemic stroke or transient ischaemic attack (TIA) with a cardiac rhythm monitor. Standard practice is to perform a 3-day cardiac Holter monitor that detects AF in approximately 4% of people [3]. However, there are delays in obtaining cardiac monitoring in many healthcare systems [4], which leave patients at risk of stroke recurrence, and the yield of investigation is low.

Longer periods of cardiac-rhythm monitoring can detect many more people with AF after stroke [5, 6]. An external loop recorder that is worn for up to 30 days can detect AF in 16% of people after ischaemic stroke where no other cause has been found [5]. An implantable loop recorder for 1 year can identify AF in 24% of such people [6]. However, these approaches are costly and are not widely available in many healthcare systems, and implementing them would require substantial investment given the problems with providing even 3-day cardiac rhythm monitors [4]. Furthermore, while the yield is higher with longer durations of monitoring, the majority of people investigated do not have AF [5, 6].

This could be tackled by better selection of people for cardiac monitoring after stroke. A solution could be to identify people with a low probability of having AF, which would allow more intensive cardiac monitoring approaches to be focused on people who are more likely to have AF and benefit. While scores exist to predict incident AF in people after stroke, these scores focus mainly on identifying higher risk people and are limited by modest predictive value, and some perform less well in external validation [7–9].

We conducted a systematic review and meta-analysis that highlights clinical, electrocardiogram (ECG), and blood-based biomarkers that are associated with increased or reduced odds of AF detection in the year after ischaemic stroke or TIA [10]. The natriuretic peptides have strong potential to help stratify probability of AF detection after stroke. In particular, midregional pro-atrial natriuretic peptide (MRproANP) is highly specific and independently associated with newly detected AF in people after ischaemic stroke [11, 12]. Our review identified many predictive ECG parameters [10], and a machine learning/artificial intelligence approach to ECG analysis can identify people who are known to have AF from their resting sinus rhythm ECG with high accuracy (area under the receiver operating characteristic [AUROC] curve 0.87, 95% CI 0.86–0.88) [13]. AF has a substantial genetic basis, and AF genetic risk scores may also help to stratify risk of AF detection [14–16]. Indeed, AF genetic risk scores are associated with incident AF in non-stroke populations [15, 16], while AF genetic risk is associated with cardioembolic stroke [14].

Study Aims

The "Preventing Recurrent Cardioembolic Stroke – Right Approach, Right Patient" (PRECISE) study aims to develop and validate a prognostic model that includes clinical, ECG, blood, and genetic biomarkers to identify people with a low probability of AF detection after ischaemic stroke or TIA.

Methods

Design

The PRECISE study is a prospective cohort study that aims to recruit 675 near-consecutive people admitted with ischaemic stroke or TIA in the 5 days prior to enrolment, who are not known to have AF, and who would be suitable for anticoagulant therapy if AF is detected. Recruitment started in August 2021; by January 18, 2022, 78 participants had been recruited, 64 people had completed cardiac rhythm monitoring, and AF has been detected in 10 people (16%). Recruitment will continue until August 2023 or until 675 participants have been recruited. Participants are currently recruited from the Queen Elizabeth University Hospital Glasgow and Glasgow Royal Infirmary, although the study may be extended to additional sites.

Patient Population

Inclusion Criteria

- Admitted with ischaemic stroke or TIA in the 5 days prior to enrolment
- Age >18 years
- No known AF
- Suitable for venous blood sampling
- Able to provide informed consent

Exclusion Criteria

- Contraindication to anticoagulant therapy

Study Assessments and Intervention

Baseline Assessment

Participants undergo routine clinical assessment for ischaemic stroke or TIA. This includes review by a stroke specialist; assessment of demographic and clinical data; an ECG; and neurovascular imaging, with standard practice being used to perform magnetic resonance imaging to exclude stroke or TIA mimics if the diagnosis is uncertain, as it is recommended by national guidelines (Fig. 1) [17].

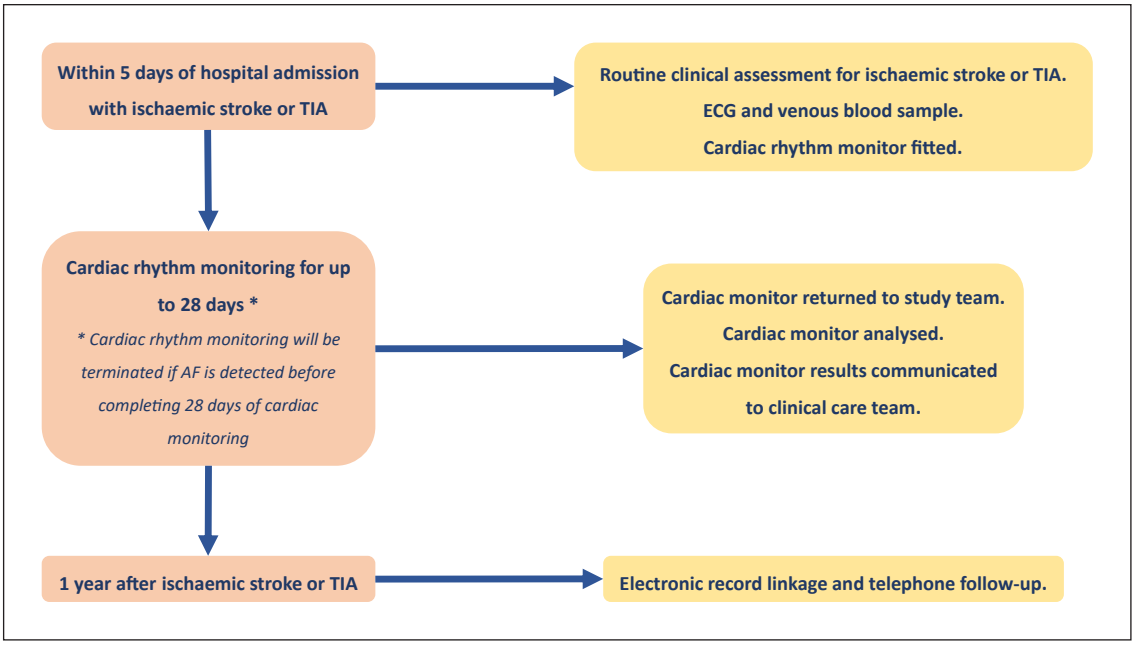

Fig. 1. Flowchart of recruitment and study protocol.

Blood Sampling and Analysis

Participants provide a 5-mL sample of venous blood into an EDTA tube as soon as possible after enrolment and within 5 days of the admission with ischaemic stroke or TIA. Venous blood samples are separated by centrifugation at 1,500 *g* for 15 min and stored at −80 °C. Plasma samples will be analysed for MRproANP levels via immunofluorescence (B R A H M S KRYPTOR analyser, Thermo Fisher Scientific), and DNA extraction/genotyping will be performed in the Glasgow Biomarker Laboratory. Plasma will also be analysed for other cardiovascular biomarkers, including high sensitivity troponin-T and N-terminal pro-B-type natriuretic peptide. However, our focus is on MRproANP as we believe that MRproANP has the strongest validation data for the identification of newly detected AF in people after stroke [12].

Electrocardiograms

A 12-lead ECG is performed for each participant, and an anonymized PDF copy is recorded electronically.

Neurovascular Imaging

All participants will have neurovascular imaging performed as part of routine clinical practice [17]. This will include a head computerized tomography and/or magnetic resonance imaging scan and carotid imaging, in the form of Doppler ultrasonography or computerized tomography/MR angiography. Neurovascular imaging information will be assessed as part of clinical data when developing the prognostic model.

Cardiac Monitoring

Participants are fitted with a cardiac-rhythm monitor that is worn for up to 28 days as soon as possible after study enrolment. Two cardiac-rhythm monitors may currently be used in the study: (1) a Novacor R-test or (2) a Bardy Carnation Ambulatory Monitor patch, which are both CE-marked devices that can accurately identify rhythm disorders and have been used to identify AF in previous studies [18–20]. The Novacor R-test is the main device that is currently used, although approval is in place for Carnation Ambulatory Monitor patches if needed. Other validated systems could be used dependent on costs and availability.

Follow-Up

Participants will be followed up by electronic record linkage and telephone review, 12 months after the index event.

Outcome Measures

Primary Outcome

The primary outcome is AF detection ≥30 s duration during 28 days of cardiac rhythm monitoring. The AF definition is based on international guidelines that define clinical AF as an episode lasting ≥30 s [3], which is recommended as an indication for anticoagulation [21].

Secondary Outcomes

Secondary outcomes are AF detection at 1 year; recurrent stroke; systemic embolism; cardiovascular death; major adverse cardiovascular events; myocardial infarction; heart failure; anticoagulant prescriptions; and all-cause mortality within 1 year after index ischaemic stroke or TIA. Secondary outcomes will be identified through electronic record linkage and telephone follow-up.

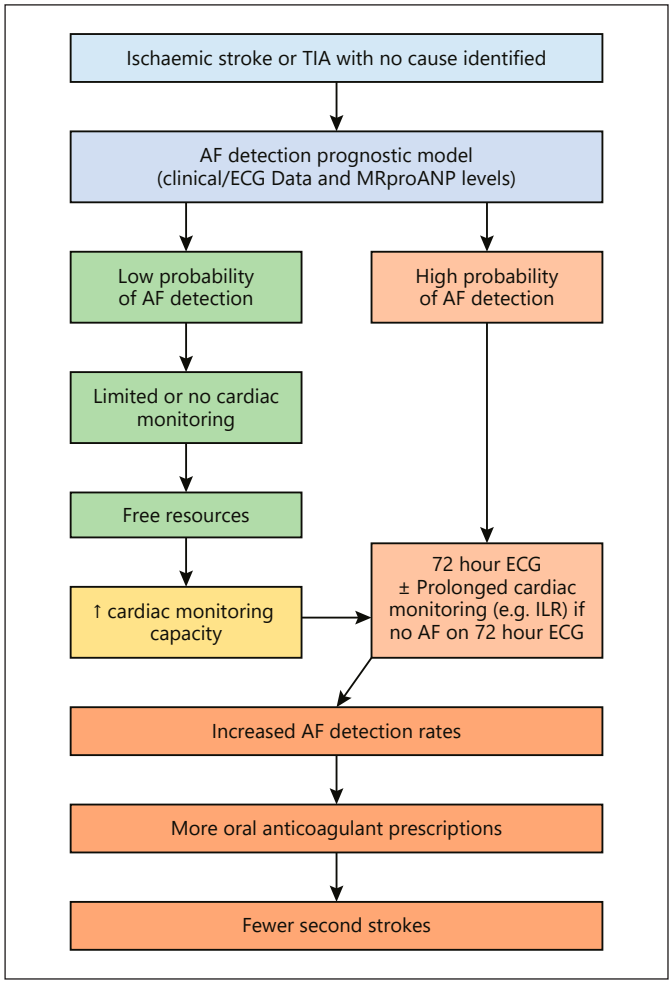

Fig. 2. Illustration of a more personalized care pathway to search for AF after stroke that could be designed based on the prognostic model from the study.

Effects to Minimize Bias

Three study investigators (J.D., A.C.C., and A.H.A.-R.) report cardiac rhythm monitors and are experienced in this technique. All cases of AF detected on cardiac rhythm monitoring are confirmed by at least two investigators (J.D., A.C.C., or A.H.A.-R.) and a cardiologist (R.T.C. or K.D.). Systems are in place to consult with cardiology colleagues if necessary.

Data Management

Data Capture and Management

All data are captured on a case report form (CRF) and entered into a secure, password-protected electronic database. All participant data are anonymized, and participants are only identified by their study identification number. Cardiac monitor reports are uploaded to the hospital record for review by the clinical team.

Record Retention and Archiving

Anonymized CRFs and study samples will be stored for 10 years after completion of the study.

Sample Size Estimates

The power calculation is based on minimizing the false negative rate to achieve high sensitivity. Our aim is to establish whether the model is potentially useful to identify people who are unlikely to have AF. Assuming a true sensitivity of 92.5% and an absolute margin of error of 0.05 (as recommended by Riley, BMJ 2020) [22], 108 patients with AF are needed. Since the prevalence of AF is estimated to be 16%, this means that 675 participants will be needed in total. It also ensures that the sensitivity can be measured with an absolute margin of error of at most 0.042.

Statistical Analyses

We will develop a predictive model for the absence of AF detection on cardiac-rhythm monitoring. Variables will be chosen by penalized logistic regression [23]. AF genetic risk scores will be calculated using a previously described 12-SNP AF genetic risk score that is determined for each participant based on the weighted combination of 12 genetic risk loci [16]. We will assess sensitivity, specificity, negative predictive value, and AUROC curves to develop a model that highlights people with a low probability of AF detection. Calibration and discrimination analyses will be performed by χ^2 analysis and assessment of AUROC with c-statistics. We will assess discrimination of the model incorporating clinical data ± ECG analysis ± MRproANP levels ± genetic risk scores. This will define the potential benefit of including ECG analysis, MRproANP levels, and genetic risk in a model to identify people with a low probability of AF detection after ischaemic stroke/TIA.

External Validation

External validation of the model including MRproANP levels will be performed using data from people admitted with ischaemic stroke at collaborators' sites in Switzerland. This will include people admitted with ischaemic stroke who have MRproANP measured to screen for eligibility to participate in a clinical trial of anticoagulation in people with ischaemic stroke, elevated MRproANP levels, and no known AF (the MOSES study) and people who had MRproANP measured in a cohort study that demonstrated associations between MRproANP and newly detected AF after ischaemic stroke (the BIOSIGNAL study). Model discrimination and calibration analyses will be performed by assessment of AUROC curves with c-statistics.

Ethics and Regulatory Approval

The study is approved by the West of Scotland Research Ethics Committee 3, and all participants provide written, informed consent prior to study enrolment.

Study Organization and Funding

The PRECISE study is coordinated from the Queen Elizabeth University Hospital Glasgow by the Study Management Committee (SMC), which constitutes coinvestigators and the study manager. The SMC meets six-monthly to review study progress and is consulted ad hoc as necessary. The study is funded by the Heart Research UK (Scotland) Award (RG2700/21/24), the Royal College of Physicians and Surgeons of Glasgow Ritchie Trust Research Award, and the Mason Medical Research Trust Award.

Data Access

After study completion, anonymized data will be available for secondary uses that are approved by an appropriate Research Ethics Committee if participants agree to this at enrolment.

Discussion

PRECISE is a prospective cohort study that aims to develop and externally validate a model to identify people with a low probability of AF detection after ischaemic stroke or TIA. Identifying predictors of poststroke AF to help develop more tailored approaches to cardiac-rhythm monitoring to search for AF after stroke is a key knowledge gap that is highlighted by the AF Screen International Collaboration White Paper [21]. Moreover, it has been suggested that predictors of poststroke AF may be better used to rule out, rather than rule in, in relation to decision-making around investigation and management after stroke [24]. The PRECISE study is designed to address these issues and will identify multimodal biomarkers that can be included in a prognostic model to highlight people with a low probability of AF detection on detailed cardiac rhythm monitoring after stroke. We acknowledge the need for robust AF case ascertainment to develop a "rule out" model, and we believe that up to 28 days of cardiac-rhythm monitoring provides a balance between detailed cardiac investigation to rule out AF and feasibility within a large prospective cohort study.

Outcomes will be assessed 1 year after the index stroke or TIA by telephone follow-up and electronic record linkage via Information Services Division (ISD) Scotland datasets within the NHS GG&C Safe Haven environment. Electronic record linkage using routinely collected healthcare data in Scotland has a robust track record and utilizes some of the best health service data worldwide [25].

We will use the prognostic model that we develop to guide the design of a more personalized care pathway to search for AF in people after stroke that can be implemented in healthcare systems. This could involve performing limited cardiac monitoring for people with a low probability of AF detection and focussing prolonged cardiac monitoring on people who are more likely to have AF and benefit through increased AF detection and anticoagulation to prevent second strokes (Fig. 2).

The PRECISE study will provide a rich cohort of people affected by ischaemic stroke and TIA who are well phenotyped with respect to demographic and clinical data, ECG and blood-based cardiovascular biomarkers, and genetic information. Moreover, participants are consented for their data to be used in future research studies. This is particularly important given the difficulties that can be encountered in recruiting people affected by stroke into clinical studies and the challenges that can be encountered in securing funding to support clinical research following the COVID-19 pandemic.

We have not planned to include echocardiographic features in the prognostic model as clinical guidelines do not recommend routinely performing echocardiography in all people after stroke, and this test is only performed in selected patients [17, 26, 27]. We therefore believe that only a small proportion of our cohort will have an echocardiogram performed. We also wished to avoid developing a prognostic model that requires information from an additional cardiac test that would place further resource strain on cardiac departments, increase the burden of tests for stroke survivors, and delay the time to when information for the prognostic model calculation would be available when applied in a real-world setting. However, we will perform exploratory analyses including echocardiogram features in people who have this test performed.

We will include people with stroke due to pathologies such as small-vessel disease, large-artery disease, and other pathologies. The STROKE-AF study demonstrates a high rate of AF detection (12.1%) during long-term cardiac monitoring in people with stroke attributed to large- or small-vessel disease [28], and we therefore believe it is important to include such people. We will not include people who would not be suitable for anticoagulation to avoid exposure to a burden of investigation and study involvement that is unlikely to alter their management. We believe it is unlikely that stroke clinicians would pursue intensive cardiac monitoring to search for AF in someone who is not suitable for anticoagulation after stroke. We therefore believe it is unlikely that this aspect of our inclusion criteria will impact the application of the prognostic model in clinical practice.

The results from the PRECISE study have the potential to improve care for people affected by stroke. First, it could help to avoid unnecessary tests and additional burdens for people with a low probability of AF. While tests to identify the cause of stroke are important, we must ensure these are directed to the correct people to avoid unnecessary additional burdens during what can be a challenging time for people affected by stroke. If we can safely identify people with a low probability of AF who require no, or only a brief period of, cardiac monitoring, then this would substantially reduce the burden of investigation. Second, it will free resources to allow more intensive approaches to cardiac rhythm monitoring to be focused on people who are more likely to have AF and benefit. Overall, it is likely that this will increase AF detection rates, allow more people to benefit from anticoagulant drugs, and prevent more recurrent strokes, which has the potential to save substantial amounts in healthcare and societal costs.

Conclusions

The PRECISE study will guide the development of more personalized approaches to cardiac-rhythm monitoring to search for AF in people after stroke. This could help to reduce testing for people with a low probability of AF detection and allow more intensive cardiac-rhythm monitoring to be focused on people who are more likely to have AF and benefit.

Acknowledgements

We would like to thank members of the study research team for their support, including the Research Nurses Elizabeth Colquhoun, Wendy Jackson, and Lesley McDonald, and the Study Manager Ozzy Dincarslan.

Statement of Ethics

The study protocol was reviewed and is approved by the West of Scotland Research Ethics Committee 3 (NHS Health Research Authority; REC Reference 21/WS/0064). The study is conducted according to the Declaration of Helsinki, and all study participants give written, informed consent.

Conflict of Interest Statement

Gregory Y.H. Lip is a consultant and speaker for BMS/Pfizer, Boehringer Ingelheim, and Daiichi-Sankyo and is an Associate Editor of *Cerebrovascular Diseases*. No fees are received personally. Jesse Dawson has received research grants from Pfizer and honoraria from Medtronic, Bayer, Boeringher Ingelheim, BMS, Pfizer, and Daiichi-Sankyo. Alan C. Cameron has received research grants from Pfizer and honoraria from BMS, Pfizer, AstraZeneca, and Boeringher Ingelheim. Mira Katan has received grants from the Swiss National Science Foundation (182267), the Swiss Heart Foundation, and the Baasch Medicus Foundation; nonfinancial support (in kind contributions) from B R A H M S Thermo Fisher Scientific; and honoraria from Bayer and AstraZeneca. Mira Katan has been serving on the Advisory Board of Medtronic, outside the submitted work.

Funding Sources

The study is supported by the Heart Research UK Scotland Award (RG2700/21/24), the Royal College of Physicians and Surgeons of Glasgow Ritchie Trust Research Award, and the Mason Medical Research Trust Award.

Author Contributions

Alan C. Cameron, Gregory Y.H. Lip, Azmil H. Abdul-Rahim, and Jesse Dawson researched the literature and conceived the study design. Alan C. Cameron, Jesse Dawson, Gregory Y.H. Lip, and Mira Katan contributed to securing funding. Alan C. Cameron, Georgios Katsas, Markus Arnold, Kieran Docherty, Ross Campbell, John D. McClure, Mira Katan, Gregory Y.H. Lip, Azmil H. Abdul-Rahim, and Jesse Dawson contributed to protocol development. Alan C. Cameron, Georgios Katsas, Azmil H. Abdul-Rahim, and Jesse Dawson contributed to gaining ethical approval. Alan C. Cameron wrote the first draft of the manuscript. Alan C. Cameron, Georgios Katsas, Markus Arnold, Kieran Docherty, Ross Campbell, David Murdoch, John D. McClure, Mira Katan, Gregory Y.H. Lip, Azmil H. Abdul-Rahim, and Jesse Dawson reviewed and edited the manuscript and approved the final version of the manuscript.

Data Availability Statement

The data from the study are not currently available as the study is ongoing.

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