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Protocol for Home-Based Solution for Remote Atrial Fibrillation Screening to Prevent Recurrence Stroke (HUA-TUO AF Trial): a randomised controlled trial

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ABSTRACT

Introduction Current international guidelines recommend ECG monitoring after an ischaemic stroke to detect atrial fibrillation (AF) in order to prevent stroke recurrence. However, optimal strategies to detect AF and the downstream management to prevent stroke recurrence remain to be established. The objective of the study was to explore the use of long-term home-based ECG monitoring for AF detection and stroke prevention in patients with a history of stroke.

Methods and analysis This prospective, randomised, open-label trial with blinded endpoint adjudication aimed to evaluate the efficacy of long-term home-based ECG monitoring for AF detection and stroke prevention in a 24-month period. Patients aged >18 years with a history of ischaemic stroke will be stratified according to the time from the index ischaemic stroke: <1, 1–3 and >3 years and then randomised in 1:1 to (1) home-based AF screening and (2) control. The home-based AF screening system comprises (1) a handheld single-lead ECG recorder (Comfit Healthcare Devices, Hong Kong SAR, China) and (2) a patient-facing smartphone application specially designed for the study. Patients randomised to the home-based AF group will record a 30 s single-lead ECG using a specially designed handheld ECG device every morning or when symptomatic. All remotely obtained data will be automatically transmitted in real-time through the study smartphone application to a secured cloud hosting and analysed using an artificial intelligence-based diagnostic system. When a diagnosis of AF is made with the system, the patients will be called back for a formal cardiology consultation within 1 week. The primary endpoint is the time to first detection of AF at 24 months of follow-up. Secondary endpoints include recurrent stroke or transient ischaemic attack, initiation of long-term anticoagulation therapy, hospitalisation for heart failure, cardiovascular death and all-cause death.

Ethics and dissemination The study protocol has been approved by the institutional review board of The University of Hong Kong, and Hong Kong West Cluster, Hospital Authority, Hong Kong SAR, China. Results will be published in peer-reviewed journals.

Trial registration number NCT04523649.

Strengths and limitations of this study

- ⇒ This is the first randomised clinical trial to evaluate the efficacy of long-term home-based ECG monitoring for atrial fibrillation (AF) detection and stroke prevention.
- ⇒ Contrary to other clinical trials investigating long term AF using Holter devices, low cost single-lead handheld ECG devices will be used as a novel strategy.
- ⇒ All physiological parameters and electrocardiograms collected will be transferred through a specifically designed smartphone application to server and a remote monitoring centre for centralised analysis to improve efficiency.
- ⇒ The home-based AF screening strategy require active participation and overall efficacy may be limited by degree of protocol adherence by recruited subjects.
- ⇒ As the clinical trial will be conducted mainly in Hong Kong SAR, Macau SAR and Mainland China, it is expected that most recruited subjects will be of Chinese ethnicity, which may limit generalisability of the trial results.

INTRODUCTION

Stroke is the leading cause of mortality and morbidity worldwide. Patients surviving the first-ever stroke remain at high risk of stroke recurrence. In a meta-analysis involving 13 studies with 9115 stroke survivors, the pooled cumulative risks of stroke recurrence were 3.1%, 11.1%, 26.4%, and 39.2% at 30 days and

1, 5 and 10 years, respectively.[1] While the cause of stroke recurrence is multifactorial, atrial fibrillation (AF) has been recognised as one of the most important factors for stroke recurrence.[2] Despite the fact that AF-related stroke is highly preventable with long-term oral anticoagulation therapy particularly non-vitamin K oral anticoagulants (NOACs),[3–14] arrhythmia is often not diagnosed until stroke recurrence due to its paroxysmal and asymptomatic nature. In a study involving 5575 patients hospitalised with ischaemic stroke in Northern California, patients with newly diagnosed AF after hospital discharge have an annual risk of stroke recurrence of 18.9% compared with 4.9% in those without newly diagnosed AF. More importantly, among patients with both newly diagnosed AF and recurrent stroke, more than 50% of AF was diagnosed at the time of stroke recurrence, precluding any meaningful preventive measure.

Diagnosing AF before stroke recurrence has been recognised as one of the most important objectives for stroke management. Strategies to detection of AF in stroke survivors have been recommended including Holter monitoring of 7 or 14 days at the early poststroke period. Recently, in the Cryptogenic Stroke and Underlying Atrial Fibrillation (CRYSTAL AF) trial exploring the clinical application of insertable cardiac monitor to detect AF in patients with recent cryptogenic stroke, AF was detected in 12.4% of patients implanted with insertable cardiac monitor at 12 months compared with only 2.0% patients in conventional care. While conceptually attractive, such strategy has not been routinely implemented in real clinical practice because of its invasive nature and associated cost. Other than patients with cryptogenic stroke, patients with ischaemic stroke due to other cardiovascular comorbidities such as hypertension and diabetes are likewise at high risk of AF. In the past decade, advance in ECG technology has made it possible to record ECG using handheld smartphone accessory devices in the household setting. Together with the rapidly developing artificial intelligence-based ECG diagnosis and mobile communication, it is possible to remotely monitor hundreds of thousand ECGs from patients at risk of AF. Few randomised trials have assessed the effectiveness of handheld ECG recording device for AF detection in patients with history of stroke. Here we test the hypothesis that long-term home-based ECG monitoring will be more sensitive than standard care in detecting AF in patients with history of stroke but not documented AF for 24 months. Secondarily, we will investigate whether early detection of AF might confer a benefit on longer-term clinical outcomes.

METHODS AND ANALYSIS

This clinical trial protocol follows the Standard Protocol Items: Recommendations for Interventional Trials.[15 16] The underlying protocol follows the Consolidated Standards of Reporting Trials.[17 18] The study is registered with the www.ClinicalTrials.gov.

Study design

This is a prospective, multicentred, randomised controlled, parallel-group study to compare the time to detect AF with portable handheld single-lead ECG recorder versus conventional care in patients with history of ischaemic stroke without documented AF. Patients will be randomly assigned in a 1:1 ratio to a home-based AF screening group and a control group (figure 1). The trial will primarily be conducted in Hong Kong SAR, Macau SAR and Mainland China. The start date of the randomised controlled trial is intended to be 1 March 2022.

Study participants

Box 1 summarises inclusion and exclusion criteria for the study. Briefly, adult patients with a history of ischaemic stroke will be recruited. The diagnosis of stroke is defined as a neurological deficit of sudden onset that persists for more than 24 hours and corresponds to a vascular

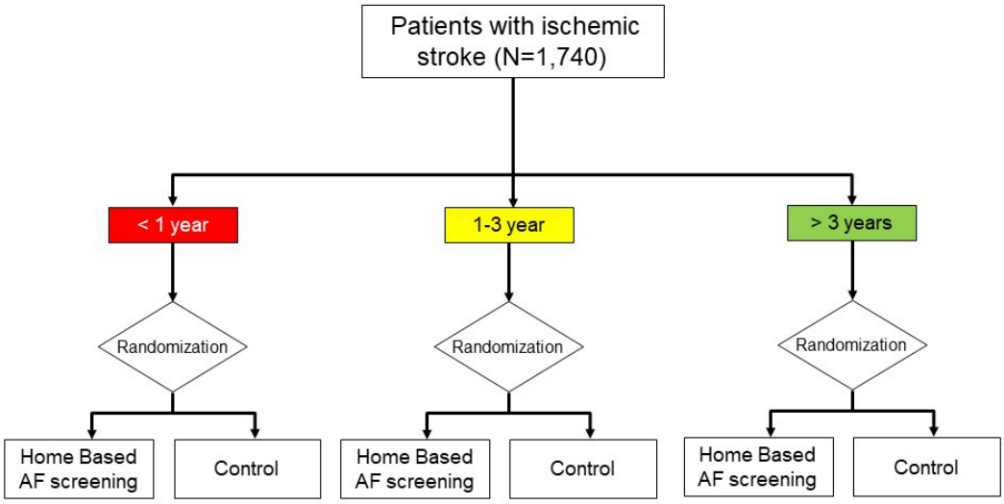

Figure 1 Study overview. AF, atrial fibrillation.

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Box 1 Inclusion and exclusion criteria

Inclusion criteria
⇒ Age ≥18 years.
⇒ History of ischaemic stroke within 5 years.
⇒ Voluntarily agrees to participate by providing written informed consent.

Exclusion criteria
⇒ Previously documented atrial fibrillation and/or atrial flutter.
⇒ Long-term anticoagulation therapy.
⇒ Short life expectancy (<1 year) due to concomitant medical condition(s).
⇒ Cardiac implantable electronic device.
⇒ Inability or refusal to provide informed consent.
⇒ Lack of skills in operating simple electronic devices.
⇒ Unavailability of a mobile network service in the place of residence.

territory in the absence of primary haemorrhage and that cannot be explained by other causes (trauma, infection and vasculitis), and is confirmed by computerised axial tomography or MRI of the brain. Ischaemic stroke will be further classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification of subtypes of acute ischaemic stroke into (1) large artery atherosclerosis, (2) cardioembolism, (3) small vessel occlusion, (4) stroke of other determined aetiology and (5) stroke of undetermined aetiology.[19] Patients will be excluded if they have previously documented AF and/or atrial flutter, have cardiac implantable electronic device implantation, receive long-term anticoagulation therapy, have a short life expectance (<1 year) due to concomitant medical condition, are unable to operate simple electronic devices, are unable or refuse to provide informed consent, or if a mobile network service is unavailable in the place of residence.

Home-based remote cardiovascular risk factor management system

Written informed consents from all study participants will be obtained by research staff responsible for recruitment after detailed discussion (online supplemental appendix 1). Subsequently, hardware and software required for the clinical trial will be allocated to each study participant. Education regarding trial protocol will be provided at the recruitment session. Compensation will be paid for trial participation. A patient-facing smartphone application specifically designed for the study will be installed to all participants' smartphone. Study participants will be asked to record their blood pressure measured using standard blood pressure monitor with CE mark two times per day (early morning and evening), body weight every week, daily cigarette and alcohol consumption to the study smartphone application. All remotely obtained data will be automatically transmitted in real-time through the study smartphone application to a secured cloud hosting and displayed on a web-based dashboard at the clinicians' offices for review. The population-attributable risk of stroke caused by hypertension is up to 50% in some racial and ethnic groups.[20] To ensure optimal blood pressure control, antihypertensive medication(s) will be adjusted daily based on the blood pressure results according to the prespecific blood pressure algorithm with reference to American Heart Association/American Stroke Association guidelines.[20] Medication adjustment will be confirmed by trial centre cardiologists using a web-based dashboard. The patients will receive instructions on drug regimen from their smartphone application. Drug will be dispensed through trial centre if additional drugs are required. Trial participants are allowed to contact remote monitoring centre staff should they require other forms of assistance. In addition, serum cholesterol and serum creatinine concentration will be checked every 6 months, and glycosylated haemoglobin will be checked every 3 months for those with diabetes mellitus and every 12 months for those without diabetes mellitus. Medications will then be adjusted according to current guidelines.[21 22] Table 1 summarises the targets for cardiovascular risk factors.

Table 1 Targets for cardiovascular risk factors[21 22]

Risk factors	Targets
Resting SBP (mm Hg)	<140
Resting DBP (mm Hg)	<90
LDL-C	► <1.8 mmol/L. ► ≥50% LDL-C reduction from baseline.
Glycosylated haemoglobin	<7%
Cigarette consumption	0 cigarette per day
Alcohol consumption	≤2 units per day

DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

Home-based AF screening

The home-based AF screening system comprises (1) a handheld single-lead ECG recorder (Comfit Healthcare Devices) and (2) a patient-facing smartphone application specially designed for the study (figure 2A,B). The home-based AF screening procedure is shown in figure 3. Precisely, patients randomised to the home-based AF group will be instructed to record a 30 s single-lead ECG using the handheld ECG device every morning or when symptomatic. All ECG data will be automatically transmitted daily through the study smartphone application to a secured cloud hosting and displayed on a web-based dashboard at the remote monitoring centre for centralised review by cardiologists. All ECG recordings will be analysed and stratified using an artificial intelligence-based diagnosis system. All electrocardiograms will be reviewed by remote monitoring centre cardiologists daily. When a diagnosis of AF is made with the system, participants will be called back using a phone by research staff for a standard 12-lead ECG to confirm the diagnosis within 1

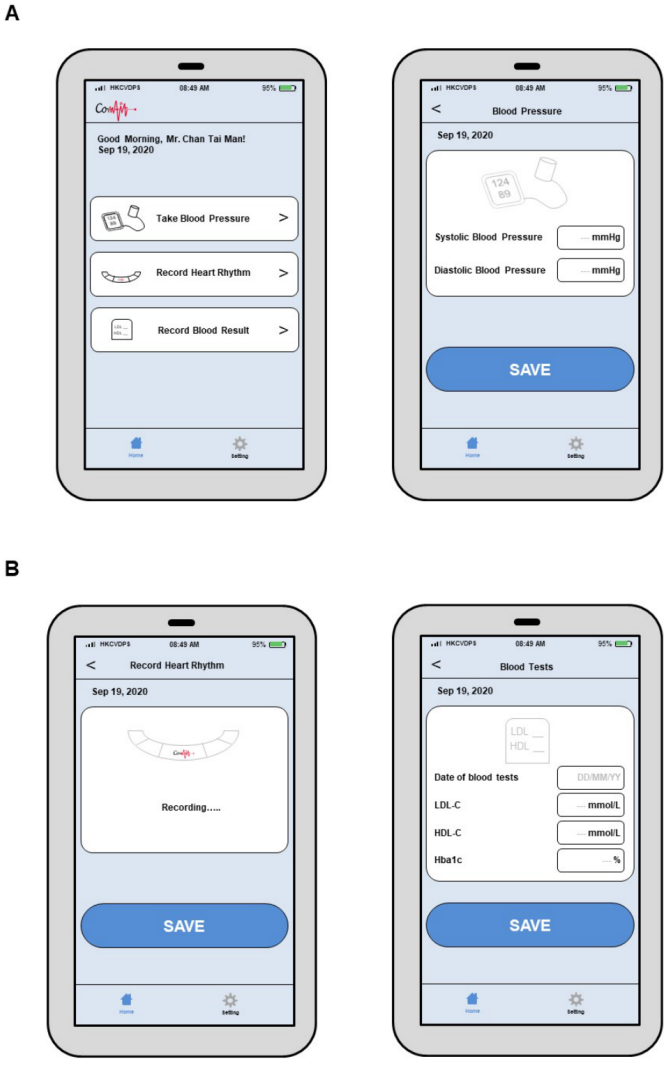

Figure 2 Patient facing smartphone application.

week. This will be followed by echocardiogram and blood tests to determine the possible options of long-term anticoagulation therapy. All participants with ECG-confirmed AF will be seen by a cardiologist for formal consultation. Malignant rhythm identified by the cardiologist at the remote monitoring centre will be further managed by liaising with corresponding trial centre cardiologists responsible for the patient in concern to arrange further management.

Study endpoints

The primary endpoint is the time to first detection of AF at 2 years of follow-up. Secondary endpoints include recurrent stroke or transient ischaemic attack, initiation of long-term anticoagulation therapy, hospitalisation of heart failure, target achievement of various cardiovascular risk factors, cardiovascular death and all-cause death. AF is defined as an episode of irregular heart rhythm, without detectable P waves, lasting more than 30 s. Two independent cardiologists who are blinded to random assignment will review all the ECG tracings recorded to provide a reference diagnosis using standard criteria.[23] All endpoints will be adjudicated by an adjudication committee, blind to the random assignment.

Sample size calculation

The primary analysis is to test whether home-based AF screening is superior to conventional care to detect new-onset AF. A total sample size of 1740 patients who had stroke is expected to achieve 90% power to detect a statistically significant difference ($p<0.05$) in time to first documented AF episode at 24 months. The sample size calculation is based on cumulative AF detection of 4% (2% per year) in the control group and 8% (4% per year) in the home-based AF screening group at 2 years. An attrition rate of 15% is accounted for in this sample size.

Statistical analysis

Data normality of continuous variables will be assessed using skewness statistics. Baseline characteristics of the two groups will be compared using analysis of variance, χ^2 test or Fisher's exact test, as appropriate. Analysis of the primary and secondary outcomes will conform to the intention-to-treat principle, with all patients who undergo randomisation included in the analysis. Clinical events that occur after randomisation and until the end of the study (at 2 years or mortality) will be included in the primary analysis of clinical outcomes. A p value of <0.05 is considered as significant. Calculations will be performed using SPSS software V.12.0.

Randomisation

Randomisation will be stratified according to the time from the index ischaemic stroke into (1) <1 year, (2) 1–3 years and (3) >3 years, and each study site for variations in patient demographics and diagnosis. At each site, patients will be randomised to 'permuted blocks of four' (two of each study arm) to assist in equality of numbers in each arm. An independent research officer who is blinded to this study will generate the random-number table. Study staff responsible for enrolment will be informed of randomisation assignment by phone. Subjects and clinicians will not be blinded to the randomisation assignment. Data staff responsible for data entry will be blinded from randomisation assignment.

Data collection and management

After enrolment, each subject will be assigned a unique identifier to be used in a database. Data will be entered by study staff, and data accuracy will be verified by the study principal investigator. Data quality control measures include queries to identify missing data, outliers and discrepancies. The database will be password protected and encrypted. Only study staff will have access to the database. All paper records will be deidentified and stored securely in a locked cabinet for 5 years. Subjects who withdraw from the study will have continuous monitoring stopped, usual care continued and final outcome collected for analysis.

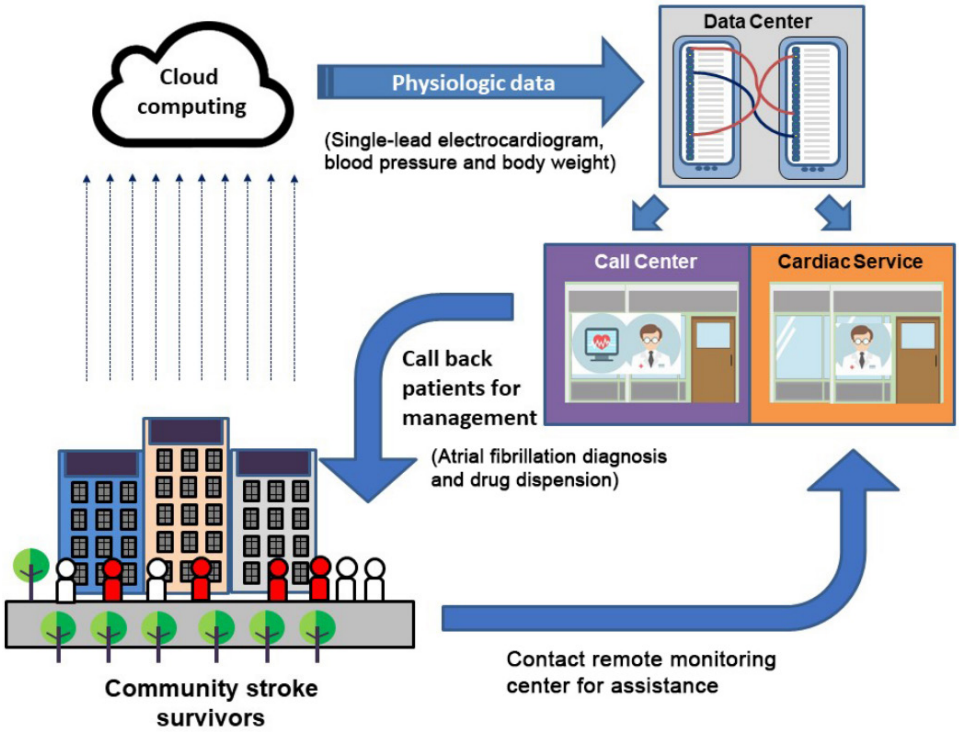

Figure 3 Data flow (online supplemental appendix 1).

Data monitoring and safety

An independent safety committee will be established comprising an emergency clinician, a clinical pharmacologist and a toxicologist. The safety committee is led by Professor Bernard Cheung from the Clinical Pharmacology, Faculty of Medicine, the University of Hong Kong, Hong Kong SAR, China. For patient safety, discontinuation of the study is at the discretion of the cardiology clinician to enable informed decisions to be made regarding subsequent management and alternative medication use. Any medication or therapy, intervention or procedure thought to be necessary for the safe management of the patient may be administered at the discretion of the managing clinician.

Data sharing plan

Dataset used during the study will be available from the corresponding author on reasonable request from the date of publication for 2 years. Collaboration with other investigators will be welcomed. The results of the trial will be published in peer-reviewed journals and will be presented in conferences.

Patient and public involvement

We received input from clinicians and patients which guided the design of the current study and choice of research questions. No patients were directly involved in the design of the study and choice of outcome measures. No patients will be involved in recruitment or conduct of the study. Results of the study will be disseminated to subjects, the public and the scientific community.

Ethics and dissemination

This research protocol complies with the Declaration of Helsinki and the International Conference on Harmonisation–Good Clinical Practice. The study protocol has been approved by the institutional review board of The University of Hong Kong and Hong Kong West Cluster, Hospital Authority, Hong Kong (UW 21–587). Written informed consent will be obtained from all study participants by study staff responsible for recruitment. Important protocol modifications will be conveyed to investigators, institutional review boards, trial registries, regulators, journals and trial participants. After enrolment, each subject will be assigned a unique identifier to be used in the database. The personal identity of subjects will not be used for any public purpose or publication, or transmitted outside of the study team.

Dataset used during the study will be available from the corresponding author on reasonable request from date of publication for 2 years. Collaboration with other investigators will be welcomed. The results of the trial will be published in peer-reviewed journals and will be presented in conferences.

DISCUSSION

Patients surviving their first ever stroke are at high risk of stroke recurrence. AF has been recognised as one of the most modified risk factors for stroke recurrence, given the superiority efficacy and overall safety of NOAC over antiplatelet agent and vitamin K antagonist anticoagulant.

However, early detection of the arrhythmia remains challenging in real clinical practice.

Current guidelines recommend prolonged ECG monitoring to detect AF (up to 30 days) for patients with an acute ischaemic stroke or transient ischaemic stroke within 6 months of the index event. Nonetheless, optimal timing and duration of ECG monitoring in patients who had stroke remain to be determined. For instance, in the CRYSTAL AF study, the cumulative AF detection rates among patients with recent cryptogenic stroke randomised to implantable cardiac monitor were 3.7%, 8.9%, 12.4% and 30.0% at 1, 6, 12 and 36 months, respectively. While it would not be possible to substantiate the causal relationship between the index stroke and the subsequently detected AF, the continuously increasing incidence of AF represents a potentially important modifiable factor to prevent stroke recurrence. Of note, 81% of these newly detected AF were asymptomatic, necessitating active clinical surveillance for its early detection. While implantable cardiac monitoring devices can continuously monitor cardiac rhythm and promptly detect AF, the invasive nature and the associated cost hamper widespread clinical implementation. In the present study, the use of non-invasive handheld ECG devices circumvents the need of device implantation, thereby increasing patients' acceptance. Inevitably, the intermittent nature (once per day) of handheld ECG monitoring will undermine the sensitivity to detect AF episodes, particularly those of shorter duration compared with implantable cardiac monitor. However, the clinical relevance of device-detected AF, particularly those of short duration, remains to be determined. Of note, in a meta-analysis including seven studies using cardiac implantable electronic devices to detect AF with a total of 18 943 patients, only patients with atrial high rate episode burden over 24 hours had an increased risk of stroke, while those with atrial high-rate episode burden less than 24 hours did not.[24] Arguably, the intermittent ECG monitoring tends to detect AF with longer duration and might have the advantage over the continuous monitoring counterpart to minimise the false positivity without affecting specificity to detect clinically relevant episodes of AF in order to prevent stroke. While AF detection is the essential first step to prevent stroke recurrence, the downstream management pathway after the detection of the arrhythmia is of equal importance to realise the potential to reduce stroke recurrence. In the present study, after AF detection with the system, patients will be informed together with a structural assessment within 1 week in order to promptly implement appropriate stroke preventive measure.

Limitation

First, the home-based AF screening strategy requires active participation, and overall efficacy may be limited by the degree of protocol adherence by recruited subjects. Post hoc analysis on protocol adherence will be performed. Second, cost-effectiveness analysis, which may provide important insight regarding real-world applicability of the home-based AF screening system, is not incorporated into the primary and secondary outcomes of the clinical trial. Post hoc cost-effectiveness analysis may be performed instead. Third, as the clinical trial will be conducted mainly in Hong Kong SAR, Macau SAR and Mainland China, it is expected that most recruited subjects will be of Chinese ethnicity, which may limit generalisability of the trial results.

The study is designed to provide clinicians with information regarding strategy to prevent recurrence of stroke in stroke survivors. The results will have immediate and long-term impacts on the management of these very high-risk patients with AF.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

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