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Risk-Based Community Screening for the Evaluation of Atrial Fibrillation Trial (R-BEAT): a randomised controlled crossover trial protocol

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ABSTRACT

Background:
Undiagnosed atrial fibrillation is a major care-gap in stroke prevention. We describe a protocol for a randomised cross-over controlled trial evaluating a community-based approach to detecting covert atrial fibrillation, comparing routine external loop recorder monitoring with routine pulse screening, in a primary care population.

Methods:
We are undertaking a randomised controlled, cross-over multi-center trial in general practice comparing routine external loop recorder (ELR) cardiac monitoring (R-Test) for 1 week with usual care (pulse screening and completion of cardiac rhythm assessment if pulse is irregular). The target population is patients aged ≥55 years with $CHA_2DS_2VASc > 2$ who do not have a contraindication for oral anticoagulation, as determined by the General Practitioner. The trial is being conducted in 10 general practice sites in the West of Ireland. Participants are randomly assigned by computer generated block randomisation with variable block size to the immediate or delayed external loop recorder group assigning individual participants in a 1:1 ratio. The trial is conducted in an open-label fashion, with blinded outcome assessment. The trial also evaluates the role of serial participant self-pulse screening for detection/exclusion of atrial fibrillation. The primary outcome measure is newly
detected, and centrally confirmed cases of atrial fibrillation/flutter greater than two minutes in duration. Recruitment is ongoing.

Discussion:
The R-BEAT study will determine whether a 1-week ELR is associated with a greater detection rate of atrial fibrillation versus pulse screening in patients attending General Practice with a CHA_2DS_2VASc score of greater than 2.

Trial Registration:
ClinicalTrials.gov Register: NCT03911986, registered on April 11th, 2019

Background

1 Stroke is a leading cause of death and disability (1). Undiagnosed atrial fibrillation is a major care-gap in stroke prevention, given that about 40% of patients with acute ischemic stroke have atrial fibrillation identified at the time of acute presentation (2,3). Once identified, oral anticoagulation therapy significantly reduces the risk of ischemic stroke in those with atrial fibrillation, associated with up to 80% risk reduction in those adherent with treatment, therefore identifying cases is of utmost importance (4,5).

There is insufficient evidence at present to recommend population wide screening for atrial fibrillation, with conflicting results across a variety of different screening approaches (6). It is accepted that screening will identify more cases of atrial fibrillation but whether screening with cardiac monitoring

offers an incremental benefit over standard of care with pulse screening depends in part on the intensity of cardiac monitoring and also upon adherence to pulse screening as a standard of care (6). Pulse palpation for atrial fibrillation is considered part of usual care when screening for atrial fibrillation in general practice but the yield can differ depending on the frequency of pulse checks and whether pulse screening is applied to different patient populations opportunistically or systematically (7). Pulse check is a cheap initial tool but there is varying sensitivity and specificity reported depending on the context of its use (8). Sensitivity may be improved with repeated pulse checks over time (9).

An alternative to pulse screening is systematic population screening with cardiac monitoring devices such as external loop recorders, which demonstrates improvements in yield over single point in time assessments (8). Cross sectional studies have demonstrated that patient initiated intermittent electrocardiogram monitoring offers improved diagnostic yield over pulse screening (9). In high-risk populations, such as in post-stroke patients, targeted screening for atrial fibrillation with extended cardiac monitoring has been a successful strategy (10,11). Screening an inflated population of older adults with a $CHA_2DS_2VASc > 2$ may offer improved diagnostic accuracy.

External loop recorder monitoring is a non-invasive approach to screening with cardiac monitors which is favored by patients (12), and atrial fibrillation detected on an external loop recorder is likely to be of a clinically relevant burden. In contrast, AF detected by continuous monitoring with implantable loop recorders may be subject to dilution of effect by detecting higher frequency of low-burden AF (8). The type of device used for screening is important too and there are concerns that direct to participants screening devices such as wearable technologies or patches that patients self-apply may introduce a potential selection bias, preferentially including patients who are technologically attuned (13,14).

The R-BEAT trial is enveloped within usual care in General Practice and answers the primary research question of whether extended cardiac rhythm monitoring with external loop recorder for 1-week, compared to standard care, in patients pre-identified to be at high-risk of atrial fibrillation (defined by CHA_2DS_2VASc score > 2) increases the detection of atrial fibrillation, in a manner that is efficient, acceptable to patients, and cost-effective. The secondary research question is to examine if self-screening with regular pulse checking identifies patients with high-risk of atrial fibrillation.

Methods

2 **Design**

We are undertaking a randomised controlled, cross-over multi-center trial in general practice comparing opportunistic pulse screening with external loop recorder cardiac monitoring (R-Test) for 1 week in patients aged ≥55 years with $CHA_2DS_2VASc > 2$. Patients are deemed not to have a contraindication for oral anticoagulation by their General Practitioner. We determine the yield of each method individually and in comparison, with each patient acting as their own control.

3 **Setting: practices and patients**

Patients are recruited from 10 general practices that participate in the Irish primary care research network (iPCRN). In stage 1 we undertake pre-trial identification of an eligible population. The Irish primary care research network has developed software which integrates with the GP's electronic software (SOCRATES) which allows a list of patients to be identified with a cut off $CHADS_2$ score of greater than two. This list is autogenerated in each practice and patients with atrial fibrillation on this list are excluded at this stage. In each practice this standardised electronic search is undertaken and

supplemented with a manual review and cross-check to confirm the CHA_2DS_2VASc score of those identified with $CHADS_2$ score of greater than two and to review key eligibility criteria.

The inclusion criteria for selection of the cohort includes patients 55 years or older, with a CHA_2DS_2VASc score of greater than two, and attendance at minimum one GP appointment within the last 12 months. Exclusion criteria includes a pre-specified contra-indication to oral anticoagulation, known atrial fibrillation/flutter, current prescription of oral anticoagulation therapy at treatment doses for prevention of stroke in atrial fibrillation, unsuitable for anticoagulation therapy or cardiac monitoring in the opinion of the general practitioner, allergies to plasters or adhesives, or cardiac monitoring for greater than 48 hours within the last 12 months. After applying the inclusion and exclusion criteria the list of patients is reviewed by the practice GP to additionally identify whether patients are considered unsuitable for oral
anticoagulation therapy or extended cardiac monitoring.

In stage 2, written invitations are sent from the General Practice to invite potentially eligible participants to take part in the R-BEAT clinical trial. This invitation contains a description of the research study, educational information on atrial fibrillation and explains the practicalities of the screening procedure. The screening invitation explains to participants that their GP has reviewed their medical notes and considers them suitable for the study. A contact number is provided, and the participant is subsequently called by a member of the research team to follow-up on this screening invitation.

In stage 3, patients are enrolled and randomized, to early or delayed external loop recorder measurement for 1 week. For those agreeable to participate written informed consent is completed and all participants undergo initial pulse screening and a clinical and physical assessment. Participants are randomly assigned by computer generated block randomisation with variable block size to the immediate or delayed external loop recorder group assigning individual participants in a 1:1 ratio. A web-based randomisation
software programme (Sealed Envelope) is used.

The trial is conducted in an open-label fashion, with blinded outcome assessment and blinding of statistical analysis. Participants, and their GP, are not made aware of the results of the external loop recorder until the 2-week clinical trial period has been completed. Baseline characteristics and all data are entered into a secured trial management system iDatafax). The system also gathers all other data during the study. Investigators enter data directly into the system using electronic case record forms (eCRF). Patients are followed up at 3 months, 1 year by telephone from the date of randomisation (Table 1).

4 Usual Care Period

In the usual care period of the study, opportunistic pulse screening is undertaken at baseline, 1 week and 2 week follow up and consists of 2 minutes pulse measurement by a trained research healthcare professional. In patients who have an irregular pulse identified a pulse-check at baseline, an ECG or measurement with AliveCor Kardia Mobile Device is completed, depending on local practice in General Practice, to rule-out or diagnose atrial fibrillation. To best represent usual care, the baseline pulse assessment (with cardiac rhythm assessment) is used as the primary outcome for detection of atrial fibrillation in the control period. While pulse measurement occurs at other time-points, a cardiac rhythm measurement is not completed, to avoid contamination of the ELR intervention. All cardiac rhythm measurements are reviewed by a Consultant Cardiologist.

5 **Intervention Period: External Loop Recorder**

All participants are fitted with the R-Test external loop recorder device with two electrodes placed on the thorax. This is a re-usable, battery-powered, lightweight ECG monitor (weight 42g), which records events triggered by cardiac arrhythmias. At study initiation patients wore the R-Test for 14 days but this was revised down to 7 days after analysis of an initial vanguard phase was supplemented with observational analysis of an existing cohort of patients who had completed 14 day external loop recorder monitoring (15). Cardiac monitoring is triggered by tachycardia or detection of irregular pulses. Participants may trigger a recording if the participant experience symptoms (e.g. palpitations).

The R-Test device is directly attached to an ECG electrode and a chest lead extends from the base of the R-Test onto another ECG electrode which is placed in the left fifth intercostal space. The R-Test 4 is CE marked and uses an FDA-approved algorithm for automatic detection of atrial fibrillation. It permits 5 minutes of pre-event recording and 5 minutes of post-event recording. An educational session is completed to review maintenance of device, trouble-shooting problems, and practical issues (e.g., changing electrodes if displaced, showering etc.).

All participants wear the external loop recorder for a 1-week period and return to the General Practice, or where more convenient to the Clinical Research Facility (Galway University Hospital, Galway, Ireland) at the end of the monitoring period. At the end of the two-week trial duration, the results are reviewed by a Cardiologist to assess the presence of atrial fibrillation/flutter and duration of atrial fibrillation (greater than 2 minutes duration on the ELR). The R-Test records time of measurement to allow a measure of adherence with cardiac monitoring. Patients who are diagnosed with atrial fibrillation at the end of the study are scheduled for a review with a cardiologist in the hospital where further assessment is conducted. Patients are reviewed to assess if oral anticoagulation should be commenced and if any additional management is warranted.

6 **Self-Pulse Screening Protocol**

Participants receive a standardized education session on self-pulse screening and are trained on how to recognize a normal pulse rhythm, and how to recognize an irregular pulse rhythm. All participants are asked to complete 3 measurements each day, completing each pulse measurement for at least 2 minutes. Participants are asked to keep a diary of episodes of abnormal pulse and episodes of palpitations for the two-week period the participant is enrolled in the study.

Study Outcomes

7 **Primary Outcome Measures:**

1) New detected (and centrally confirmed) cases of atrial fibrillation/flutter > 2 minutes in duration on R-test, or detected on ECG/Rhythm strip following baseline pulse screen.

8 **Secondary Outcome Measures:**

1) New detected cases of atrial fibrillation/flutter > 2 minutes in duration resulting in introduction of oral anticoagulant therapy.
2) All new detected cases of atrial fibrillation/flutter.
3) New detected cases of cardiac arrhythmia that result in change in clinical management (e.g., pacemaker
insertion, anti-arrhythmic, ablation).

4) All new detected cases of cardiac arrhythmia.
5) Stroke.
6) Major bleeding.
7) Sensitivity, specificity, positive predictive value, and negative predictive value of difference pulse screening strategies compared with R-Test device.
8) Patient adherence with the screening strategies including pulse check and R-Test device.
9) Patient satisfaction with the screening strategies, and tolerability of the ECG monitor (defined as the incidence of adverse skin reactions related).
10) Cost-effectiveness and cost-utility of atrial fibrillation screening.

Statistical Considerations

9 Data will be analysed on an intention-to-screen basis. Descriptive statistics will be used to describe the baseline characteristics of the study population, the flow of trial participants and the level of missing data. Loss to follow up and withdrawal of consent will be accounted, and reasons documented.
The primary outcome measure is newly detected, and centrally confirmed cases of atrial fibrillation/flutter, required to be greater than two minutes in duration for external loop recorder (R-test measurement). The difference in yield of new atrial fibrillation between intervention and usual care will be estimated calculating the difference in detection rate of new atrial fibrillation during the control period and the intervention period, with each participant acting as their own control, using the McNemar test for statistical significance (primary analysis). We will explore whether there is an order-effect, i.e. whether detection differed by early versus delayed ELR groups (P-interaction). We will compare participant characteristics among those with atrial fibrillation versus without atrial fibrillation detected. We will compare patient characteristics among
those with atrial fibrillation greater than two minutes and sub-diagnostic atrial fibrillation (< 2 minutes). Logistic regression analysis will be used to determine the influence of important covariates on the rate of newly detected atrial fibrillation. Pre-specified sensitivity analyses will include subgroup analyses by age categories, gender, BMI, history of hypertension, prior palpitations, prior completion of pulse check, and the range of CHA_2DS_2VASc scores.

Secondary outcome measures will include new detected cases of atrial fibrillation/flutter greater than two minutes in duration resulting in oral anticoagulation therapy.

The diagnostic test characteristics of different pulse screening approaches using the 1-week external loop recorder as reference standard will be reported. Sensitivity and specificity, positive predictive value and
negative predictive value will be reported. Different pulse screening strategies will explore the yield of pulse screen by trained study staff, pulse screen by study participants, and a combined approach incorporating results of pulse screen by both study staff and study participants.

We will use descriptive statistics to describe the outcomes of quality of life (EQ-5D-5L) and symptom diary in patients with incident atrial fibrillation and those without. Categorical data will be presented by number of patients (%) and numerical data by mean (SD) or median (interquartilerange, IQR), where appropriate. Follow up data at 3 months and 1 year will be reported. P-value of <0.05 or 95% confidence intervals that do not include 1.0 will be considered statistically significant. Statistical analysis will be performed using R statistical software (Version 4.3.0).

10 **Sample Size Calculation**

The primary outcome is new detected cases of atrial fibrillation greater than 2 minutes in duration or detected on ECG/Rhythm strip following baseline pulse screen (assume duration longer than 2 minutes in usual care). We estimate that opportunistic screening is expected to detect approximately an additional 0.8% over the time period of the trial (16). Based on similar screening studies using external loop recorder screening approaches we would expect the intervention arm to detect atrial fibrillation in approximately 4% over the time period (13). Accordingly, we require a per period sample size of 695 participants, increased to a total sample size of 755 participants, to account for a maximum of 8% non-completion rate.

Discussion

11 The R-BEAT randomised controlled trial is a large-scale screening trial which compares an external-loop recorder screening approach with a pulse screening approach. We describe a study protocol which addresses the initial steps in the screening chain, including the post-diagnostic care pathway and not just the ECG detection component of screening.

We use a cross-over design to increase the proportion of patients undergoing external loop recorder screening, which increases event rates, and improves the ability to complete analyses of predictors of atrial
fibrillation. Each participant serves as their own control and this design reduces the potential for baseline imbalances that may result in confounding. All participants receive the intervention while maintaining the randomisation comparison. Offering all participants the opportunity of external loop recorder will increase participation in the trial. We will reduce the risk of contamination, which may occur if patients were randomised to no external loop recorder, and then sought this out in clinical practice. This is an advantage
over other screening studies without an active comparator (17,18).

Other atrial fibrillation screening studies have compared external loop recorder monitors with internal loop recorder implantation (19), smart watches and ECG patches (14,18), or the use of home ECG machines (20). These approaches are invasive or require participants to be actively involved in using the technology along the screening steps, and this may exacerbate disparities that already exist in traditional cardiovascular care (21). In contrast the R-BEAT study recruits from a GP setting and targets an intervention that is readily accessible to all participants. The sampling strategy of identifying patients from an electronic healthcare record uses a contemporary approach to standardized risk factor profiling which is embedded within routine clinical practice. This approach has external validity and can be transferred to future clinical practice. It is not dependent on individual-level wealth, literacy, or ability to use smartphone technology, such as in operating handheld ECG screening applications, or managing the logistics of using direct to consumer products such as putting on and returning wearable ECG patches (Zios patch). In addition, this approach lends itself to ultimately embedding point-of-care diagnosis in General Practice, limiting false positive results, excessive costs, and patient anxiety.

This study also evaluates the utility of regular pulse screening (self-administered at least 3 times a day for 1 week) as a screening step for excluding paroxysmal atrial fibrillation. Participants are instructed to keep a diary of episodes of irregular pulse and episodes of palpitations and initiate R-Test recording if these occur. This trial will evaluate if home self-pulse screening is a useful adjunct to improve the ability to detect atrial fibrillation through refinement of high-risk groups. Pulse screening could potentially be a step in the screening algorithm to identify high-risk patients for whom external loop recorder cardiac monitoring could be carried out. However long term adherence to pulse checking is known to be

suboptimal (22) and this study will highlight if it practical to recommend self-administered pulse screening.

We are utilizing a seven day external loop recorder screening period. Seven days was chosen as a pragmatic duration of monitoring after internal auditing in our institution demonstrated that atrial fibrillation was identified in 94% of patients within one week when wearing prolonged cardiac monitoring (15). A week was chosen to balance patient adherence with a long enough duration of screening to detect a burden of atrial fibrillation. Prolonged application of continuous forms of atrial fibrillation monitoring increases the likelihood of detecting short episodes of atrial fibrillation which may be of uncertain clinical significance and this duration of screening is intended to balance sensitivity and the risk of false positive diagnoses (23). While not all episodes of atrial fibrillation appear to be associated with a significant increase in stroke risk (24) there is increasing evidence that atrial fibrillation burden is related to stroke risk and the atrial fibrillation identified on a one week external loop recorder check is likely to be of a clinically relevant
burden to merit oral anticoagulation (25).

Our target population are patients aged 55 and older with a high CHA_2DS_2VASc score. CHA_2DS_2VASc is able to predict patients with a risk of atrial fibrillation (26). By including a CHA_2DS_2VASc cut off score of greater than two we are identifying patients at higher risk of stroke, and those who are likely to derive greatest benefit from anticoagulant therapy. An additional advantage is that established computer search strategies in general practice can be used to pre-identify patients with increased CHA_2DS_2VASc scores, and also identify those that have a clear contra-indication to oral anticoagulant therapy.

A systematic screening approach will also yield important information from a future planning point of view to guide efforts for future national screening strategies. The advantage of using externally worn loop recorders is that they can be re-used, while other methods of monitoring such as internal loop recorders or wearable patches are expensive and for single use only. Accordingly, external loop recorders represent an opportunity for detection of paroxysmal atrial fibrillation in high-risk individuals, which appears sustainable
and can be replicated across healthcare settings.

We will provide evidence about whether the intervention or control measures could be realistically implemented into general practice. This study is being embedded in GP which means we will be able to reach and include marginalised older adults who have frailty, cognitive impairment and come from a lower socioeconomic strata, who have not been represented to date in current studies. It is accepted that more research is needed on implementation strategies to determine how to integrate optimal diagnostic methods in daily work routines for atrial fibrillation (27). While recommended as standard of care pulse check does not actually take place in a standardised fashion (28) . There is evidence that exposure to screening initiatives can change practice when it involves a quick, non-invasive intervention and embedding a sequential screening approach within GP such as in this study will likely have a legacy effect (29).

In conclusion atrial fibrillation is an important risk factor for stroke, and early detection is desirable to enable prevention of serious complications. The R-BEAT study will provide valuable evidence of the efficacy of a systematic screening approach and on the optimal method for detecting atrial fibrillation.

Trial Status

12 The trial has started in 2019 and was temporarily paused during the COVID-19 pandemic. We are

currently completing the recruitment of patients from the final GP practices.

Ethical Considerations

13 The study is being conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. The protocol has been approved by a recognised research ethics committee (REC) before initiation.

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Table 1: Table of Study Visits

15

A	B	C	D	E	F
Timing Window	Baseline	Randomisation Week 0 (+/- 1 week)	Week 1 (+/- 1 week)	Week 2 (+/- 1 week)	Month 3, Year 1 (+/- 1 month)
Informed Consent	X				
Demographics	X				
Medical History	X				
Blood Pressure	X				
Physical Measurements	X				
CHADS2VASc Score	X				
Eligibility Criteria	X				
Randomisation		X			
Education on Pulse Screening		X			
Education on Pulse Diary Completion		X			
R Test Fitting		X1	X2		
R Test Training		X1	X2		
R Test Return			X1	X2	
Pulse Check		X	X	X	

	A	B	C	D	E	F
	EQ-5D-5L	X				
	Telephone Follow Up					X
	ECG/AliveCor Kardia Mobile Device Test	X				

1 Only for patients randomised to: (A) Immediate Heart Monitoring (R Test will be fitted at randomisation visit for 1 week) + pulse screening
2 Only for patients randomised to: (B) Delayed Heart Monitoring (R Test will be fitted 1 week after randomisation visit) + pulse screening
Completion of the Pulse Diary occurs for the duration of the 2 weeks that the participants are in the study.