Incident atrial fibrillation and adverse clinical outcomes during extended follow-up of participants recruited to the Remote Heart Rhythm Sampling Using the AliveCor Heart Monitor to Screen for Atrial Fibrillation The REHEARSE-AF Study

Running title: REHEARSE-AF extended follow-up evaluation

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The original study was funded by a joint grant from the Welsh Government Health Technology and Telehealth Fund and AliveCor.

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Word count:2767

Abstract

Aims: Atrial fibrillation (AF) is an important risk factor for stroke, which is commonly asymptomatic, particularly in older patients, and often undetected until cardiovascular events occur. Development of novel technology has helped to improve detection of AF. However, the longer-term benefit of systematic ECG screening on cardiovascular outcomes is unclear.

Methods: In the original REHEARSE-AF study, patients were randomised to twice-weekly portable electrocardiogram (iECG) assessment or routine care (RC). After discontinuing the trial portable iECG assessment, electronic health record data sources provided longer-term follow-up analysis. Cox regression was used to provide unadjusted and adjusted hazard ratios (95% confidence interval) for clinical diagnosis, events and anticoagulant prescriptions during the follow-up period.

Results: Over the median 4.2 years follow-up, although a greater number of patients were diagnosed with AF in the original iECG group (43 vs 31), this was not significant (HR1.37 95%CI 0.86-2.19). No differences were seen in the number of strokes/systemic embolisms or deaths between the two groups (HR0.92 95%CI 0.54-1.54 & 1.07 95%CI 0.66-1.73). Findings were similar when restricted to those with a CHADS-VASc ≥4.

Conclusion: A 1-year period of home based, twice-weekly screening for AF, increased diagnosis of AF for the sceening period, but did not lead to increased diagnoses of AF or reduction in cardiovascular related events or all-cause death over a median of 4.2 years, even in those at highest risk of AF. These results suggest that benefits of regular ECG screening over a 1-year period are not maintained after cessation of the screening protocol.

Keywords: atrial fibrillation; electrocardiography; mass screening; preventive medicine; stroke

Lay summary:

A follow-up of patients who had undergone a 1-year screening programme to detect atrial fibrillation (a heart rhythm problem) was carried out using electronic health records to see if there were differences in atrial fibrillation diagnoses, strokes or deaths between those who had the screening device and those who had routine care.

- Extended follow-up of the patients showed no overall increase in the diagnosis of atrial fibrillation in the screened population, despite a higher detection rate during the screening period.
- Numbers of stroke/systemic embolism and deaths were similar in the screened and routine care groups over the extended period of follow-up (including the year of screening).

Introduction

Atrial fibrillation (AF) is an important risk factor for stroke, which is commonly asymptomatic, particularly in older patients, and therefore often undetected until diagnosis at the time of an associated cardiovascular event[1,2]. However, identification of AF and subsequent treatment with oral anticoagulants reduces the risk of stroke and other cardiovascular events[3,4]. Development of novel devices and technology allowing easy and accurate electrocardiographic rhythm assessment has facilitated screening of patients, improving identification of those with AF. Indeed, a study (REHEARSE-AF) by our group in patients identified as being at high risk of AF, demonstrated that twice-weekly ECG screening with a WiFi-enabled iPod ECG device (iECG), identified significantly more incident AF over a 1-year period than those patients who received normal care[5]. Other studies have also shown detection of AF can be increased using alternative screening strategies[6,7].

However, the limited follow-up period of these studies has not allowed a fuller evaluation of the effectiveness of a 1-year screening intervention for preventing cardiovascular events over the longer-term, beyond the screening period. Two recent studies, the STROKESTOP and LOOP studies have looked at the effects of screening on the risk of stroke and other cardiovascular outcomes but with conflicting findings[8,9].

Linking data from the REHEARSE-AF study to routinely held clinical data for the trial participants this analysis aimed to explore potential differences in AF diagnoses, stroke and death rates during longer-term, routine clinical follow-up in patients who received routine care versus those who underwent the twice weekly iECG monitoring regime for the first year of the extended evaluation period[5].

Methods

Transparency and openness promotion

The data used in this evaluation are openly available in the SAIL Databank at Swansea University, Swansea, UK. Due to the sensitive nature of these data, all proposals to use SAIL data are subject to review by an independent Information Governance Review Panel (IGRP). SAIL has an established application process for all projects and users who want to access data via SAIL https://www.saildatabank.com/application-process. This project was approved by the IGRP at Swansea University (SAIL project number 0982).

Original study

The method of the original study is reported in Halcox et al. [5]. Briefly, in 2015, 1,001 patients (53.3% female) over 65 years (mean age 72.6 ±5.4 years), with a CHADs-VASc score ≥2, without a known diagnosis of AF, known contraindication to anticoagulation or permanent cardiac pacing implantation were recruited and allocated to either routine care (RC, n=501) or the intervention arm (iECG, n=500). Participants in the intervention arm undertook twice-weekly recording of a 30-second single-lead iECG trace for 12-months (AliveCor Kardia Mobile system, AliveCor Inc, Mountain View, CA) attached to an iPod (Apple Inc, Cupertino, CA) which were transmitted via an encrypted process to a secure server. Additional traces could be submitted if participants were symptomatic. iECG traces were analysed by an automated analysis software algorithm (AliveCor version 2.2.0 [build 21]) and transmitted over a secure server for analysis by a physiologist-led electrocardiographic reading service (Technomed Ltd UK). Abnormal and 10% of normal ECGs were overread by a cardiologist. Clinical review and appropriate care were arranged for those with clinically significant arrhythmia. Patients in the RC arm were followed up as normal by their general practitioner (GP). Ethics approval was obtained from the Wales Research Ethics Committee 6

(REC reference 14/WA/1227), and the clinical trial was registered at URL: https://www.isrctn.com. Unique identifier: ISRCTN10709813.

Follow-up

The original study data set was imported into the SAIL Databank, a world-leading privacy-protecting trusted research environment (TRE) that holds anonymised individual-level, population-scale data, through which access to and linkage of the data was enabled[10,11]. The randomisation date into the trial was taken as time zero, and participants were followed-up until 31st December 2019. Both the primary care (Welsh Longitudinal General Practice [WLGP]) data and population-scale national secondary care data (Patient Episode Database for Wales [PEDW]) were used to identify any diagnosis of atrial fibrillation, stroke (haemorrhagic or ischaemic), transient ischaemic attacks (TIA), systemic embolism (SE), acute coronary syndrome, deep vein thrombosis, pulmonary embolism and hospitalisation for bleeds[12,13]. Prescription of anticoagulation medication was also identified from WLGP data. Death was identified from the Office for National Statistics (ONS) mortality data (Annual District Death Extract [ADDE])[14].

Statistical analysis

The primary outcome for this study was AF diagnosis, secondary outcome measures were stroke/TIA/SE (SSE) and death. Hospital admissions for acute coronary syndrome, venous thromboembolism and bleeding were also assessed. Cox regression was used to provide both unadjusted and adjusted hazard ratios and 95% confidence intervals for clinical events and prescribing of anticoagulation therapy during the follow-up period. Variables included in the adjusted model were age ≥75, sex, hypertension, diabetes, previous stroke, peripheral artery disease and CHADS-VASc score ≥4. Kaplan-Meier plots were used to estimate event rates

for AF diagnosis, SSE and death between the groups. The CHADS-VASc score had been calculated for all patients in the main study and the analysis was repeated in those with a CHADS-VASc ≥4, as in the original analysis, this variable was a significant predictor of AF. SPSS (version 28, IBM Corp, Armonk, NY) and R (version 4.1.3) were used for analysis.

Results

Successful linkage between study data and EHR data sources within the SAIL Databank was achieved for 99.6% (997 of the original 1,001 participants) in the study. The median period of follow-up was 4.2 years (1547 days IQR 159), including the year of screening. Table 1 shows the baseline characteristics of those participants included in this analysis by treatment group. There were no differences in the age and sex or medical history of the two groups with linked data, as observed in the original trial.

Over the full period of follow-up, although detection of AF was 38.7% greater in the iECG group compared with routine care, this difference was not statistically significant (Table 2). There was no difference in the number of deaths, strokes or TIA's between the two groups.

Although more participants in the iECG group were prescribed anticoagulant therapy, this difference did not reach statistical significance (Table 2). Of the 74 patients who developed AF, 66 were treated with anticoagulants (89%), and 8 were not (11%). The SAIL data governance protocol does not permit us to present absolute numbers due to the small number of patients (<5) not being prescribed anticoagulants in one or both groups. However, the proportion of participants who developed AF and were treated with anticoagulants was similar in the two groups (p=0.71). 21 participants received anticoagulant treatment for another indication.

Participants in the iECG care group were less likely to have an acute coronary syndrome event during the follow-up period than in the routine care group (10 vs 21 p=0.044, Table 2).

There were no differences between the groups with regard to time to diagnosis of AF, stroke and systemic embolism or death (Kaplan Meier plots; Figure 1).

A sub-group analysis was undertaken in those with a CHADS-VASc score ≥4 at baseline, as this was an independent predictor for increased detection of AF with iECG screening. Similar numbers of diagnoses of AF, stroke/TIA/SE and deaths were seen in both groups, with fewer acute coronary syndromes occurring in the iECG group (Table 3), as observed in the overall study.

Discussion

Although a 1-year period of iECG monitoring with the AliveCor Kardia Mobile device increased the detection of AF compared with routine care during the screening period, there was no overall reduction in the number of strokes, TIAs, systemic emboli or deaths over a mean follow-up period of 4.2 years from enrolment into the study. In addition, whilst the number of patients diagnosed with AF over the entire follow-up period, including the year of screening, was greater in the screening group, the difference between the groups no longer remained statistically significant over the longer-term follow-up. Hence the initial advantage in detection of AF was gradually eroded beyond the screening period. Interestingly, patients in the iECG group were less likely to have an acute coronary syndrome during follow-up. These findings were replicated when the analyses were restricted to only those with a higher likelihood of an AF diagnosis in the original screening study, who would also be expected to be at greater risk of events (CHADS-VASc score ≥4).

The original REHEARSE-AF study showed an increased detection of AF (19 iECG vs 5 RC p=0.007) and a trend towards fewer associated stroke/transient ischaemic attack/systemic embolism (6 iECG vs 10 RC p=0.34) events in the iECG group during 1 year of monitoring, suggesting that this might be a promising approach to reducing the risk of major complications of AF[5]. These early trends seen during the first year, did not translate into a measurable reduction of hard clinical events in a cohort of this size. We note that the original study was not powered to evaluate clinical outcomes. The power of this follow-up is considerably improved with the four-fold increase in the follow up time, and hence expected event count, but there is still considerable uncertainty in the estimates for clinical event differences, as reflected in the 95% confidence intervals for the hazard ratios. Thus we cannot exclude small effects on clinical events. We note that the hazard ratio point estimate for stroke is centred very close to 1, but with a 95% confidence interval from 0.54 to 1.54. However, as the regular iECG screening approach was discontinued after 1 year, the benefits of screening are only likely to have been realised by those patients in whom AF was diagnosed during the screening period. As such, this analysis cannot determine whether extending the period of screening beyond 1 year would result in further differential increases in AF diagnoses and fewer clinical events in the iECG compared with the routine care groups. Nonetheless, these findings suggest that the benefit of this screening approach may not be as marked as initially hoped for, if discontinued after 1 year. However, whether the initial promise of this approach to increase AF detection and reduce hard clinical events could be realised by an ongoing screening strategy beyond 1 year, would require further study in larger and or longer clinical trials. Ongoing screening would also agree with the WHO principles of early disease detection, specifically that case finding should be a continuing process and not a 'once and for all project'[15]. However, the clinical and cost effectiveness of such a strategy would need to be formally evaluated before being recommended.

Two other randomised controlled trials have evaluated the impact of screening for AF on clinical outcomes, with differing results. In the LOOP study, a similar number of strokes and systemic embolisms were seen in patients aged 70 to 90 years without known AF, but one risk factor for stroke undergoing monitoring with an implantable loop recorder (n=1420) compared with controls (n=4,503) over a median follow up period of 5.4 years[9]. However, in the recent STROKESTOP study, which followed 7,165 patients who used a single lead hand-held device twice daily for 2-weeks and 14,381 controls for a median of 6.9 years, a reduction in the composite end point of any stroke/bleed/death (p=0.045) was observed in the screening group but with no difference in the incidence of ischaemic stroke[8]. Notably, the difference in the composite endpoint emerged between the groups during the later period of follow-up (years 5-6), which was greater than in the current study. Furthermore, the patients in the STOKESTOP study were on average older (all aged 75-76 years on recruitment) than those in the REHEARSE- AF (mean [SD] 72.6 [55] years) but also included those who already had a diagnosis of AF.

The VITAL -AF study evaluated 30,715 patients aged 65 years and over who attended primary care clinics over a period of 12 months[16]. Practices were randomised to offer iECG assessment with the AliveCor device during patient appointments versus usual care. Although there were a similar number of diagnoses of AF and major adverse clinical outcomes in both study groups, this was effectively a study of opportunistic single lead ECG testing in those attending primary care for usual reasons, rather than a trial of systematic screening for AF.

Considered together with the inconsistent results from these outcome studies, the evidence from our study suggests that the ultimate clinical impact of systematic screening for AF using single lead ECG in at-risk populations remains uncertain and may not be as substantial as initially thought, at least with screening protocols of limited duration. However, we note that

a number of larger outcome studies using different approaches in different target populations are ongoing, the results of which are eagerly awaited[17,18].

Although these studies considered together, do not currently support a role for systematic AF screening at present, they do not diminish the value of point of care single lead ECG assessment as a clinical tool, especially in settings where a 12 lead ECG is not readily and/or rapidly available such as primary and community care settings or where they may be used as an alternative to ambulatory monitoring in appropriately selected patients with intermittent symptoms. Indeed, recent UK-based National Institute for Health and Care Excellence (NICE) guidelines have recently recommended the AliveCor for use in patients with suspected paroxysmal AF presenting with symptoms such as palpitations and have been referred for ambulatory ECG monitoring by their clinician[19].

The finding of fewer acute coronary syndromes in the iECG group was somewhat unexpected. It is possible that the nature of the monitoring process in this group led to increased interaction with their clinicians and better general preventive advice and treatment. However, a formal evaluation of these issues is outside the scope of this study and can only be speculative. Alternatively, it may also be due to a type 1 error as this was not a primary outcome, given the relatively small number of events.

Limitations

The patients were predominantly of White European ethnicity and from a single UK regional health authority, which may limit the generalisability of the findings to other populations. Although the follow-up period is greater than 4-years and a longer period may be required to fully evaluate the benefit of this screening approach and tease out potential clinical effects further, the fact that the gap in the proportion of patients with stroke or systemic embolism

observed during the initial year of study (albeit non-significant), narrowed over the longer-term period of follow up suggests this would be unlikely to be the case.

The current guidelines do not discriminate between screen-detected versus clinically detected AF regarding the recommended approach to management, including antithrombotic strategy. However, there are fewer data available with regard to thromboembolic risk and net clinical benefit of anticoagulation in screen-detected AF. Nonetheless, several studies have shown a greater risk of adverse outcomes in asymptomatic/screen-detected AF patients at increased cardiovascular disease risk[20-22]. Studies of patients with implanted devices have shown an increased risk of adverse events in patients with atrial high-rate episodes consistent with AF/ atrial tachyarrhythmia, but these patients are not necessarily representative of the general population. Further randomised controlled trials are needed to determine the impact on outcome measures.

In conclusion, 1-year of home-based, twice-weekly screening for AF did not lead to a reduction in cardiovascular related events or all-cause death after a median 4.2-year follow-up compared with patients who had routine care, even in those at highest risk of AF. Further research is required to identify a patient population and ECG testing strategy that may obtain improved outcomes from a targeted screening programme for AF.

Acknowledgements

This study makes use of anonymised data held in the Secure Anonymised Information Linkage (SAIL) Databank. We would like to acknowledge all the data providers who make anonymised data available for research.

Sources of funding

The original study was funded by a joint grant from the Welsh Government Health Technology and Telehealth Fund and AliveCor.

Conflicts of interest

The original study was funded predominantly by the Welsh Government but in part by a project grant from AliveCor. The study data were analysed and reported independently without involvement of the company. JH had full access to all the study data and takes responsibility for its integrity and data analysis. None of the authors have received personal financial support for speaking or consulting on behalf of AliveCor Inc. There are no other disclosures to report.

Authors contributions

JPH and EAE contributed to the conception of the work. EAE, DH, MBG and JPH contributed to the analysis and interpretation of data for the work. EAE drafted the manuscript. KW, MH, MG, JPB, CJP, MBG and JPH were responsible for delivering the REHEARSE-AF clinical trial. KW, DH, AA, MH, MG, JPB, CJP, MBG and JPH critically revised the manuscript. All authors gave final approval and agreed to be accountable for all aspects of the work ensuring integrity and accuracy.

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Figure legend

Figure 1. Kaplan-Meier plots describing time to event curves for diagnosis of atrial fibrillation (A), stroke/TIA/SE (B) and death (C). Shaded areas represent 95% confidence regions. Log-rank P= 0.28, 0.83 & 0.87 (Mantel-Cox) respectively. Day 0 on the x axis is point of randomisation in the study.

1 Table 1. Baseline Characteristics of the Study Participants with Data Linkage

	iECG (n=499)	**Routine care (n=498)**
Age (SD) y	72.60 (5.5)	72.55 (5.4)
Female, n (%)	260 (52.1)	273 (54.8)
Heart failure, n (%)	5 (1.0)	9 (1.8)
Hypertension, n (%)	267 (53.7)	271 (55.0)
Diabetes Mellitus, n (%)	128 (25.7)	140 (28.2)
Stroke, n (%)	35 (7.1)	28 (5.7)
Vascular disease, n (%)	71 (14.4)	78 (15.8)
CHADS-VASc score (SD)	2.97 (1.0)	3.01 (1.0)
Mean follow-up period (SD)	1,534 (214)	1,530 (222)

2 Vascular disease; ischaemic heart disease or peripheral vascular disease

Table 2. Number of Clinical Events and Anticoagulation Therapy Prescription

Outcome n(%)	iECG	Routine care	Unadjusted	Adjusted
Death	35 (7.0)	33 (6.6)	1.05 (0.65-1.69)	1.07 (0.66-1.73)
Atrial fibrillation	43 (8.6)	31 (6.2)	1.41 (0.89-2.24)	1.37 (0.86-2.19)
Stroke/TIA/SE	28 (5.6)	32 (6.4)	0.87 (0.52-1.44)	0.92 (0.54-1.54)
Ischaemic stroke	23 (4.6)	27 (5.4)	0.84 (0.48-1.47)	0.90 (0.51-1.60)
Transient ischaemic attack	13 (2.6)	16 (3.2)	0.81 (0.39-1.68)	0.86 (0.41 -1.82)
Acute coronary syndrome	10 (2.0)	21 (4.2)	0.47 (0.22-1.00)	0.45 (0.21-0.97)
Bleed	34 (6.8)	38 (7.6)	0.88 (0.56-1.40)	0.85 (0.53-1.35)
Anticoagulant therapy	50 (10.0)	37 (7.4)	1.38 (0.90-2.11)	1.28 (0.83-1.96)

*Governance restrictions within SAIL prohibit the reporting of numbers <5 due to privacy protection and disclosure control.

Unadjusted and adjusted hazard ratios with routine care as the reference. iECG, iPod ECG; SE, systemic embolism; TIA, transient ischaemic attack.

Table 3. Number of Clinical Events and Anticoagulation Therapy Prescription During Follow-up period in participants with a CHADS-VASc score ≥4

Outcome n(%)	iECG (n=135)	Routine care (n=136)	Unadjusted	Adjusted
Death	14 (10.4)	13 (9.6)	1.10 (0.52-2.33)	1.16 (0.53-2.53)
Atrial fibrillation	15 (11.1)	10 (7.4)	1.57 (0.71-3.50)	1.46 (0.65-3.27)
Stroke/TIA/SE	15 (11.1)	11 (8.1)	1.42 (0.65-3.10)	1.37 (0.61-3.09)
Ischaemic stroke	13 (9.6)	10 (7.4)	1.35 (0.59-3.07)	1.28 (0.54-3.04)
Transient ischaemic attack	6 (4.4)	<5*	2.08 (0.52-8.33)	2.15 (0.53-8.67)
Acute coronary syndrome	<5*	10 (7.4)	0.30 (0.08-1.10)	0.23 (0.06-0.83)
Bleed	13 (9.6)	11 (8.1)	1.21 (0.54-2.69)	1.10 (0.49-2.47)
Anticoagulant therapy	18 (13.3)	11 (8.1)	1.75 (0.82-3.70)	1.64 (0.77-3.48)

*Governance restrictions within SAIL prohibit the reporting of numbers <5 due to privacy protection and disclosure control.

Unadjusted and adjusted hazard ratios with routine care as the reference.

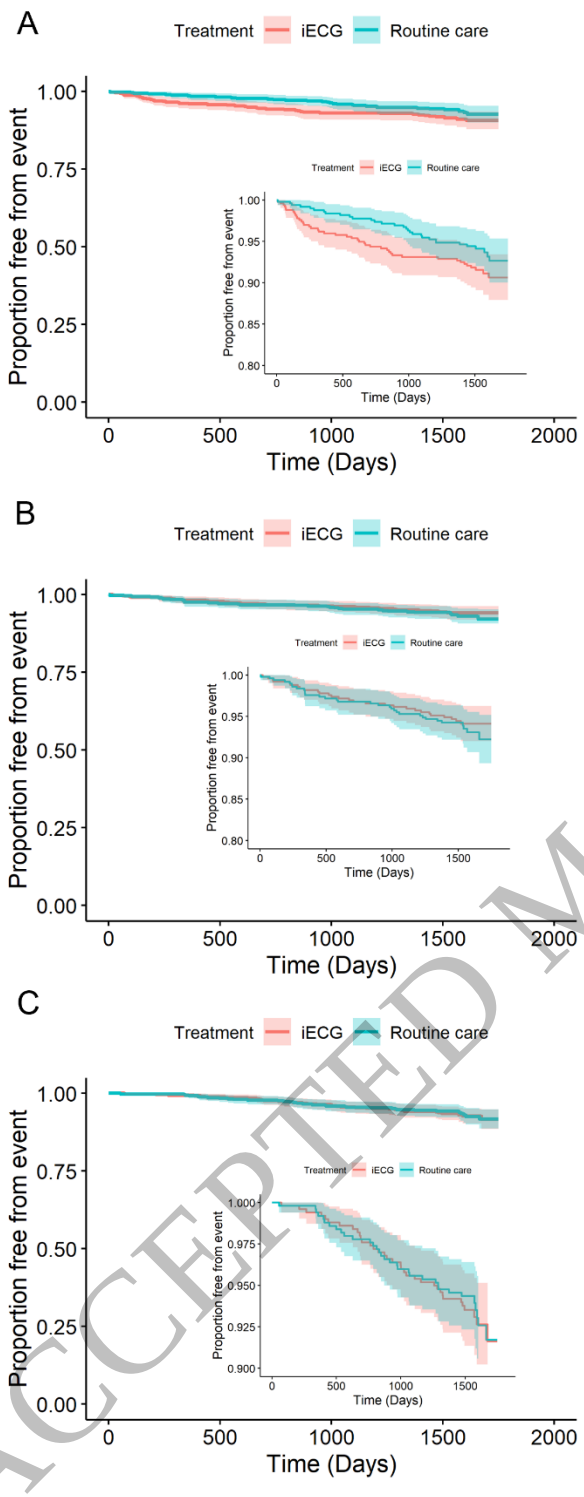
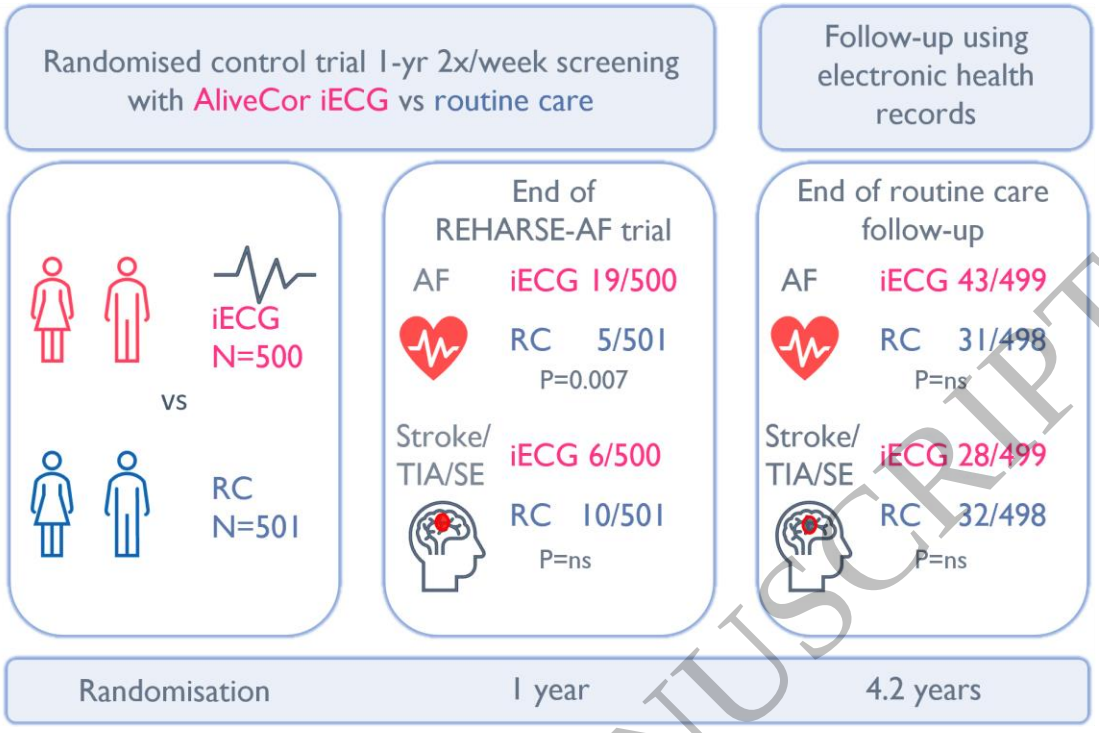


Figure 1. Kaplan-Meier plots describing time to event curves for diagnosis of atrial fibrillation (A), stroke/TIA/SE (B) and death (C). Shaded areas represent 95% confidence regions. Log-rank P= 0.28, 0.83 & 0.87 (Mantel-Cox) respectively. Day 0 on the x axis is point of randomisation in the study.

Libby Ellins is a senior research officer based at Swansea University with an interest in cardiovascular disease prevention. She started her career as a vascular technologist specialising in non-invasive measures to assess vascular structure and function at the Institute of Child Health, University College London. She continued this at Cardiff University from where she obtained her PhD. Now at Swansea University her interests have diversified into data science, using electronic health records to investigate cardiovascular disease prevention with a particular interest in mental and women's health.



Graphical Abstract