Assessment of **RE**mote **HEA**rt **R**hythm **S**ampling using the AliveCor heart monitor to scr**E**en for **A**trial **F**ibrillation: The REHEARSE-AF Study

Short title. The REHEARSE-AF Study

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ABSTRACT

Background:

Asymptomatic Atrial fibrillation (AF) is increasingly common in the ageing population and implicated in many ischaemic strokes. Earlier identification of AF with appropriate anticoagulation may decrease stroke morbidity and mortality.

Methods:

We conducted a randomized controlled trial (DOI 10.1186/ISRCTN10709813) of AF screening using an AliveCor Kardia monitor attached to a Wifi enabled iPod to obtain electrocardiograms (iECG) in ambulatory patients. Patients ≥65y with CHADS-VASc ≥2 free from AF were randomized to iECG arm or routine care (RC). iECG participants acquired iECGs twice-weekly over 12-months (+ additional iECGs if symptomatic) onto a secure study server with over-read by an automated AF detection algorithm and also by cardiac physiologist +/- consultant cardiologist. Time to diagnosis of AF was the primary outcome measure. The overall cost of the devices, ECG interpretation and patient management was captured and utilized to generate the cost per AF diagnosis in iECG patients. Clinical events and patient attitudes/experience were also evaluated.

Results:

We studied 1001 patients (500 iECG, 501 RC) aged 72.6+/-5.4y, 534 female. Mean CHADS-VASc score was 3.0 (heart failure = 1.4%; hypertension = 54%; diabetes mellitus = 30%; prior stroke/TIA = 6.5%; arterial disease = 15.9%. All CHADS-VASc risk factors were evenly distributed between groups).

Nineteen patients in the iECG group were diagnosed with AF over the 12 month study period vs 5 in the RC arm (Hazard Ratio 3.9, 95%CI = 1.4-10.4, p = 0.007) at a cost per AF diagnosis of $10,780 (£8,255). There were a similar number of stroke/TIA/systemic embolic events (6 vs 10 iECG vs RC HR=0.61, 95%CI = 0.22-1.69, p=0.34)
The majority of iECG patients were satisfied with the device, finding it easy to use, without restricting activities or causing anxiety.

Conclusions:

Screening using twice-weekly single lead iECG with remote interpretation in ambulatory patients ≥65y at increased risk of stroke is significantly more likely to identify incident AF than RC over a 12-month period. This approach is also highly acceptable to this group of patients, supporting further evaluation in an appropriately-powered, event-driven clinical trial.

Clinical Trial Registration:

ISRCTN10709813 DOI 10.1186/ISRCTN10709813

https://www.isrctn.com/ISRCTN10709813?q=Assessment%20of%20REmote%20HEArt%20Rhythm%20Sampling%20using%20the%20AliveCor%20heart%20monitor%20to%20scrEen%20for%20Atrial%20Fibrillation&filters=&sort=&offset=1&totalResults=1&page=1&pageSize=10&searchType=basic-search

Clinical Perspective

What is new?

- This is the first prospective randomized trial evaluating the ability of remote ECG acquisition and transmission using a handheld device with remote interpretation to screen for atrial fibrillation (AF) in at risk people over 65y over an extended period of time (1y).
- This approach is at least 3 times more likely to identify incident AF than routine care at a cost of just over $10,000 per case identified and is a highly acceptable approach in this group of patients. A CHADS-VASc score of ≥4 was the strongest predictor of incident AF.

What are the clinical implications?

- Our findings suggest that this approach could be considered for AF screening in routine practice, particularly in the highest risk patients.
- Although strokes and TIAs were numerically fewer in monitored patients, the study was not statistically powered to evaluate hard clinical outcomes and this difference was not statistically significant.
- These results support consideration of evaluation in an appropriately-powered, event-driven randomised trial to confirm clinical and cost-effectiveness of such an approach to stroke prevention in AF.

INTRODUCTION

Atrial fibrillation (AF) is a common cardiac arrhythmia, affecting an estimated 33.5 million individuals worldwide.[1] AF is an important risk factor for stroke, being implicated in up to 1 in 3 cases[2-4] and often not diagnosed beforehand.[5] AF-related strokes commonly result in greater disability than ischemic stroke secondary to arterial disease.[6]

The annual stroke risk conferred by AF increases with age and other common risk factors and can be estimated using the CHADS-VASc score in those without rheumatic mitral valve disease or metallic valvular prosthesis.[7] Stroke risk can be reduced by around two thirds by the use of oral anticoagulant (OAC) therapy (including nonvitamin-K antagonists (N)OACs). [8,9]

Presentation with AF may be atypical or asymptomatic, especially in older subjects.[10] Data from a range of sources (including the retrospective MOST study and the TRENDS study), have shown that asymptomatic AF may potentially pose a greater thromboembolic risk than where symptoms are typical.[10-14] AF may also occur on an intermittent basis ("paroxysmal" [PAF]), with an increased stroke risk[15, 16] and identical recommendations for antithrombotic management as permanent AF.

AF incidence varies according to the population characteristics and diagnostic strategy.[17] Single-timepoint ECG recording in a general population ≥65 years of age identified AF in 1.4%.[18] Furthermore, twice-daily intermittent single lead ECG recording over two weeks using a handheld device identified AF in 3.0% of 75-76 year olds,

including 7.4% of those screened who had ≥1 additional stroke risk factor.[19, 20] A recent expert consensus paper has confirmed that AF identified at screening is not benign and justifies consideration of anticoagulation in those with stroke risk factors.[21] Whilst validated handheld electrocardiogram (ECG) recording devices are already considered appropriate technologies for AF screening, expert groups recognize that large prospective trials are required to strengthen the evidence base and refine population screening strategies.[21]

We therefore undertook a 1-year randomized controlled trial of twice weekly monitoring with the AliveCor Kardia device (a smartphone/tablet-based single lead ECG capture system) versus routine clinical care in patients over the age of 65 with ≥1 additional stroke risk factor.[22] The Primary outcome was incidence and time to diagnosis of AF.

METHODS *(Full methods: Supplement 1)*

Study Population

Individuals over 65y with a CHADS-VASc score ≥2 without a known diagnosis of AF, currently in receipt of OAC therapy, a known contraindication to anticoagulation or permanent cardiac pacing implant were recruited. Participants were required to have access to the internet via Wifi and be able to operate the AliveCor Kardia system (AliveCor inc. Mountain View, CA) attached to an iPod (Apple inc. Cupertino CA) after simple instruction. Eligibility was confirmed by a brief history, physical examination and single lead ECG recorded with the AliveCor device (iECG). Written consent was obtained and eligible participants were randomised (1:1) to an "intervention" (iECG)

group or routine care (RC) group. Ethical approval was obtained from the Wales Research Ethics Committee 6 (REC Reference 14/WA/1227).

Participants in the "intervention" iECG arm were instructed to undertake twice weekly recording and transmission of a 30 second single lead iECG trace to a secure server (Monday and Wednesday recommended, plus additional submissions if symptomatic), over a 12 month period. iECG traces were analyzed by an automated analysis software algorithm (AliveCor version 2.2.0 [build 21]) and also sent for offline analysis by a physiologist-led ECG reading service (Technomed Ltd UK). Abnormal ECGs were over read by a cardiologist with clinical review and appropriate care arranged for those with AF or other clinically significant arrhythmia. Patients in the RC arm were followed up as normal by their general practitioner. All patients were contacted by a member of the study team at 12, 32 and 52 weeks to assess progress. Clinical events were followed up and confirmed by clinical chart review.

Patients with Identified AF

AF was defined as a 30-second iECG recording with irregular rhythm without p waves.[23] All new AF diagnoses were confirmed and reviewed by a senior study cardiologist who made arrangements for OAC initiation and clinical management according to current UK (NICE) guidance.[24] RC participants with AF were diagnosed and managed by local clinicians, with all AF diagnoses validated by a study cardiologist.

Clinical Event Monitoring

Adverse events (AEs) were reported either at the time of event or identified by telephone at 12, 32 and 52 weeks, with confirmation from source clinical records.

Participant Experience Survey

All study participants were invited to participate in a survey at the end of the study. They were asked if they were more anxious about and more aware of heart rhythm problems, whether they were more likely to visit their doctor or if they would prefer to switch study group (Responses reported via 10-point visual analog scale). iECG patients were also asked about ease of use, restriction of activities, anxiety, concern regarding data security and their general satisfaction with the device (Responses reported via 5-point Likert scale).

Health Economic Evaluation

The costs associated with screening for AF using AliveCor device were estimated from the perspective of the UK NHS and personal social services,[25] utilising data from study activity and relevant costs.[26-28]

Statistical Methods

The study sample size of 500 participants per study arm was estimated to provide 92% power to detect a significant difference (α =5%) in the time to AF diagnosis between groups (PS: Power and Sample Size Calculation version 3.1.2, 2014).[29]

Baseline characteristics were compared using either a Chi-square test (for groups), Fisher's Exact tests, or t-test. Compliance with ECG submission was evaluated using one-way ANOVA. The primary outcome of time to AF diagnosis and relationships between baseline characteristics and AF outcome were evaluated using Cox regression. Major adverse outcomes were also compared between groups using Cox regression. Comparison of the distribution of questionnaire responses was made using the

Wilcoxon rank-sum test. All analyses were performed using SPSS version 22.0 (IBM Corp. Released 2013. IBM SPSS Statistics for Macintosh, Armonk, NY: IBM Corp).

RESULTS

Participants

We invited 5846 individuals to participate (5726 identified via GP records, 120 in person during attendance at clinical research facility for other study-related visit). Of these, 3305 did not reply and 1269 declined participation. The 1272 volunteers were reviewed further by telephone/verbal screening, of whom 240 did not meet criteria for inclusion (24 with AF not identified on initial notes review, 22 taking warfarin, 4 with permanent pacemaker 127 with no internet access and 63 miscellaneous) and were not invited to attend for further screening. A further 28 of the 1032 who attended for a screening visit were excluded, 18 due to a new AF diagnosis on screening iECG ; 10 for other reasons (including inability to obtain interpretable iECG traces or to use the device properly [N=5], lack of access to the internet [N=2] or previously unidentified exclusion criteria [N=3]).

We randomized 1004 participants, of whom 3 were excluded immediately after enrolment for protocol violations: one who was noted to have been in AF on their baseline iECG trace (missed at the time of screening) one with an uninterpretable iECG at baseline and one who was found to have had prior hemorrhagic stroke on further review of their medical notes (Figure 1).

Age, sex and clinical characteristics of study participants were similar in iECG and RC groups (Table 1). All risk factors were well represented except for heart failure (N=14).

Baseline medication prescription was similar in both study groups (Supplement 2 Table). All randomized participants were in sinus rhythm at baseline.

We were able to access the NHS records of all patients to establish mortality and cardiovascular admissions during the study period. Three participants in the iECG arm withdrew (1 after completing 12 week and 2 after 12 and 32 week follow-up calls) and 2 were lost to follow up (1 after participation in 12 week and 1 after 12 and 32 week follow-up). All other patients completing the study participated fully in all telephone interviews at 12, 32 and 52 week except for 1 follow-up call missed at 32 weeks by an iECG participant. All practices responded to our requests regarding whether or not AF had been diagnosed in their respective patients

iECG recording and transmission

The participants in the iECG arm recorded 60,440 ECGs over the 12-month follow-up period. 74% of participants completed the trial without missing a single week of ECG submission. Recommended twice-weekly ECGs were submitted successfully on average by the iECG participants in 39 of the 52 weeks and at least one weekly ECG was submitted in 48 out of the 52 weeks of the trial. Approximately 4 out of 5 of participants submitted at least 1 weekly iECG during ≥90% and at least 2 iECGs during ≥75% of the study weeks (Figure 2). Increasing participant age did not affect compliance; mean number of study weeks with iECG transmitted on 2 (or more) separate days was similar in those aged 65-75y, 75-79y and 80y+ (77%, 73% and 74% respectively, p = 0.143). Of the 76% of iECGs that were reported normal by the automated algorithm, none were finally confirmed to be AF; only 6 iECGs of the 21% reported as undetermined were finally confirmed to be AF; only 5% of the approximately 1% iECGs reported as AF by

the device were finally confirmed to be in AF and 2.2% of iECGs were reported as unreadable.

Newly Diagnosed AF

Nineteen patients in the iECG group were diagnosed with AF during the 12-month study period vs 5 in the RC arm (Hazard Ratio 3.9, 95%CI = 1.4-10.4, p = 0.007)(Figure 3). Ten iECG patients had a ventricular rate >100/min at the time of diagnosis and the other 9 between 60-100/min. There were no significant differences in compliance between those diagnosed with AF (iECG group n = 19) and those not diagnosed with AF (mean study weeks with iECG submitted on 2 separate days in those diagnosed vs not diagnosed with AF=69% vs 76% respectively, one way ANOVA p = 0.11).

The iECG patients diagnosed with AF had CHADS-VASc scores of 2(N=3), 3(N=5), 4(N=7, 5(N=2) and 6(N=1); RC AF patients had CHADS-VASc scores of 2 (N=1), 3(N=2) and 4(N=2). Twelve (63%) of the iECG patients diagnosed with AF had paroxysmal AF at the time of diagnosis and 7 (37%) were in persistent AF, compared with 0 (0%) and 5 (100%) respectively in the RC arm.

Eight (42%) of the iECG patients were asymptomatic at the time of diagnosis, with only 4 (21%) experiencing palpitations and 7 (37%) aware of other symptoms. In the RC arm, two (40%) were diagnosed with AF during palpitations and the other 3 (60%) during other symptoms.

Trends for the relationship between baseline variables and development of AF were as expected, although only age (>75), CHADS-VASc (≥4) and arterial disease were statistically significantly associated with an increased likelihood AF diagnosis (Table 2).

Including all variables in a regression model (excluding HF which was rare) only CHADS-VASc ≥4 remained a significant predictor of AF (adjusted hazard ratio=4.0, 95% CI 1.1 to 15.2, p = 0.04). Similar findings were noted when only significant variables were included in a single model (less susceptible to over-fitting given the relatively small event rate). The hazard ratio, and significance, for the difference between treatment groups also remained unchanged in a model adjusting for baseline variables (in any combination). For example, adjusting for CHADS-VASc ≥4, the hazard ratio between study groups was 3.9 (95% CI 1.5-10.4) p = 0.007. CHADS-VASc ≥4 also remained significant in the mutually adjusted model. Study arm (iECG) also remained significantly associated with an increased likelihood of AF diagnosis after adjustment for CHADS-VASc in a further model.

Patients diagnosed with AF in the iECG arm were all treated promptly with anticoagulation (9 with warfarin and 10 with a non-coumadin OAC [NOAC]). In the RC arm, 3 were treated with warfarin, 1 with NOAC and 1 with clopidogrel.

Clinical Events

There were no significant differences in the number of serious adverse clinical events occurring in each arm. Although numerically fewer, there was no statistically significant difference in the numbers of strokes or TIAs (6 vs 10 in iECG and RC arms respectively, hazard ratio = 0.61, 95%CI = 0.22-1.69, p=0.34). Table 3, Supplement 3 Figure). There were no peripheral arterial embolic events. In the iECG arm, one participant suffered a hemorrhagic stroke (not previously found to be in AF/anticoagulated) and one suffered an ischemic stroke during a complicated post-operative course following aortic valve replacement surgery. The other 4 events in the iECG group were of undetermined

aetiology. In the RC arm, two of these events were embolic due to AF diagnosed following presentation with stroke, 6 stroke/TIA were of undetermined aetiology and 2 were due to carotid disease. Thus 4 ischemic strokes or TIAs were due to an uncertain cause in the iECG group and 8 due to AF or uncertain cause in the RC group (hazard ratio = 0.51, 95%CI (0.15, 1.7) p = 0.27).

We noted 2 clinically significant bleeds (both lower GI) in the iECG arm and 1 (ocular) in the RC arm. None of these bleeds occurred in patients who had been anticoagulated following AF diagnosis. There were no differences between the study groups in the incidence of all cause mortality or significant adverse clinical events due to other causes (Table 3).

Participant Experience Surveys

Participants' experience (reported using a 1-10 visual analogue scale), showed small increases in the iECG arm in the reported awareness of the risk (mean score 6.8 vs 6.1, p = 0.001) but slightly less anxiety about the risk of heart rhythm abnormalities and stroke (mean score 2.2 vs 2.5, p = 0.003) as well as slightly lower reported likelihood of intending to visit their physician regarding concerns about their heart rhythm (mean score 7.1 vs 7.5, p = 0.04). Notably, RC participants reported a considerably greater preference to have been able to switch to the other study arm (mean score 1.9 vs 6.2, p < 0.0001).

Participants in the iECG group were further asked about their experience using the AliveCor device during the study (measured on a 5 point Likert scale). The vast majority of iECG participants were "Not at all" or "slightly anxious", "Not at all restricted" by,

"Extremely" or "Very" confident in using the device, "Extremely" or "Very" comfortable with the process of sharing clinical, iECG and personal information with the study team and were generally "Extremely" or "Very" satisfied with use of the device. (Figure 4)

Health Economic Analysis

The overall cost of the intervention was $204,830 (£156,837). This consisted of device costs of $28,698 (£21,974), patient training costs of $3,750 (£2,871) and defective technology costs of $2,194 (£1,680). A total of 60,440 ECGs were recorded, which amounted to a cost of $116,823 (£89,451) in commercial ECG over-reads. The cost of ECG pathway co-ordination was $37,793 (£28,938) and 704 ECGs were identified as 'AF' by AliveCor, producing a cost of $7,972 (£6,104) for cardiologist over-read. In addition, 74 review appointments were made; 44 were nurse reviews and 30 cardiologist reviews. Overall, 19 cases of AF were detected thus the intervention cost was $10,780 (£8,255) per AF diagnosis.

DISCUSSION

In this study we found that regular twice-weekly iECG recording and submission is logistically feasible over a 1 year period and highly acceptable to people over 65 with increased risk of AF and stroke. This approach results in an almost four-fold increase in the likelihood of a diagnosis of AF being made over the course of a year at a cost of $10,780 (£8,255) per additional AF diagnosis. The overall incidence of stroke+TIA was similar in both groups, however, this study was not statistically powered to detect a difference in clinical events in this population.

Outcome of Screening Strategy

To be worthwhile, screening tests should employ a low-risk, accurate methodology with acceptable cost effectiveness. The success of such a strategy depends on the incidence/prevalence of the condition in the screened population and the accuracy of the testing strategy. As age is the strongest predictor of AF,[1] a screening cutoff ≥65y is recommended based on expert consensus, [30] as the clinical- and cost-effectiveness of different screening strategies remains to be confirmed in randomized control trials (RCT) powered to evaluate outcomes.[21]

We found 19 (1.84%) of the 1033 individuals to be in AF at the time of screening, despite careful pre-assessment to identify and exclude those with known AF. This compares favourably with new AF diagnosis in an iECG screening study of patients ≥65y visiting community pharmacy (1.5%).[31] These findings contrast with the 0.5% diagnosed with AF at initial ECG screening in a community study of 75-76 year old patients.[19, 31] However, in that study, new AF was diagnosed in a further 218 patients (3.0% 95%CI 2.7-3.5%) during 2 weeks of twice daily ECG recording.

Studies evaluating incidence of AF with continuous monitoring/implantable devices have shown that atrial "high rate events" (usually AF) are generally associated with strokes or systemic thromboembolism, although there is frequently temporal discordance noted between the "AF" and thromboembolic event suggesting other contributing risk factors in these individuals.[21] The RATE registry shows that short (15-20s) episodes of AF/AT were not associated with an increased risk of stroke in device patients, whereas prolonged episodes were independently associated as were episodes lasting over 5min in the MOde Selection Trial and at least 6 minutes in the ASSERT study.[12, 32,14] In contrast, other studies have found that only device-detected AF duration of several hours was associated with increased risk,[13, 33, 34] A pooled analysis of 3 studies suggested at least an hour's duration of device-detected AT/AF was the best predictor of risk.[35] We found that 63% of newly diagnosed AF was paroxysmal vs 37% persistent/permanent in the iECG arm; we have not further subdivided the latter as accurate classification would have required longer term follow-up of their subsequent care and should not affect consideration of stroke risk and indication for anticoagulation. It is unclear how the risk associated with increasing duration of AF identified with an implantable device compares with the risk associated with asymptomatic PAF of uncertain frequency and duration diagnosed during routine/screening evaluation. Nonetheless, recurrent episodes of PAF are common and as CHADS-VASc scores were high in iECG patients (all ≥2; most ≥3), we made the decision to anticoagulate all patients identified with (P)AF according to ESC and local guidance.[24, 30]

We found that age, arterial disease and CHADS-VASc scores were associated with an increased likelihood of AF diagnosis, but only a CHADS-VASc score ≥4 independently predicted AF . In the STROKESTOP study increasing CHADS-VASc score increased the likelihood of AF diagnosis, as did heart failure, which was relatively underrepresented in our study.[19]

iECG Device and Monitoring Strategy

We used the AliveCor device to record and upload iECGs in this study. This handheld technology involves use of a pair of electrodes linked to a mobile device to provide a single-lead rhythm strip comparable to Lead 1 of standard ECG. It employs an FDA-cleared automatic algorithm with 98% sensitivity and 97% specificity reported for AF diagnosis.[22] AliveCor technology is already widely used for remote detection of AF and common arrhythmias in routine clinical practice, having several attractive features including the quality of the trace, a validated AF reporting algorithm, remote access for clinicians over a secure server, and HIPAA compliance. However, other validated technologies are available, [36-40] suggesting a need for comparative studies evaluating their relative effectiveness and acceptability.

Mondays and Wednesdays were selected for ECG recording and transmission. As the small study team was only routinely available Monday to Friday this approach would allow the study coordinator to review the ECG reports the following day and arrange clinical evaluation within 24-48 hours of an abnormal ECG being uploaded . This approach could be varied in routine practice according to size and availability of the clinical team.

Clinical Events

There were no significant differences in the number of serious adverse clinical events occurring in each arm. Although numerically fewer, there was no statistically significant difference in the numbers of strokes or TIAs. Of note, two patients presenting with strokes in the RC arm were found to have asymptomatic AF, one diagnosed at the time of and one shortly after presentation with stroke, whereas none of these events in iECG patients were due to previously undetected/untreated AF. Indeed, numerically fewer ischemic stroke/TIA in iECG participants were of uncertain aetiology (N=4) than in the RC arm of which 8 were due to definite AF or uncertain aetiology, although not statistically significantly different. Up to 30% of strokes of undetermined aetiology may be a consequence of previously undetected/untreated AF, with incidence varying according to the population characteristics and monitoring strategy.[41] It is therefore possible that 1 in 3 or 4 of these events in our higher-risk population could have been due to undetected AF. Thus, our findings raise the possibility that remote iECG monitoring may not only increase detection of AF, but could also reduce the incidence of ischaemic stroke. This would clearly require a large RCT, appropriately powered to evaluate major clinical outcomes.

Health Economic Evaluation

We found the cost per diagnosis of AF to be £8,255 ($10,750) according to current UK National Health Service tariffs. Further detailed health economic analyses will permit modelling of the potential cost effectiveness of this approach to stroke prevention in the community. This will require imputation of multiple detailed assumptions including the accuracy of the detection rate, the estimated net risk reduction in those identified and treated and the specific costs of the systems required to implement the ongoing ECG

surveillance programme, which are beyond the remit of this clinical manuscript. Previous studies have suggested that point of care screening for AF in over 65s in primary care, community pharmacy or at influenza immunization could be cost effective[31, 42, 43] as could the 2 week, twice daily period of ECG recording in the STROKESTOP study.[19] Our preliminary health economic findings are aligned with the conclusions from these and other studies[19, 31] including a systematic review with cost-effectiveness analysis.[44] These indicated that both systematic opportunistic screening and systematic population screening followed by NOAC therapy, when indicated, are likely to be cost-effective compared with no screening (current practice). The costs per AF diagnosis in our study (where the mean age was 72.6) are lower than the costs derived by the economic model, but given that the aim of the study was to assess the costs of identifying AF, we have not yet factored the management of such patients into the overall costs and the longer-term benefits. It is unlikely that the additional costs of NOAC therapy will inflate the costs to such a degree that it would not represent value for money. Indeed, given the proportion of iECG AF patients provided with NOAC in our study (53%), we estimate that this approach is likely to result in an incremental net benefit (based on a cost/QALY of $26,118 (£20,000) with an incremental cost-QALY ratio of <$13,058 (<£10,000). Evidence from screening study cost-effectiveness modelling and systematic review highlights that at ages lower than 65 years and over 80 years, screening strategies are less cost-effective but nevertheless remain within acceptable limits.[19, 31, 44] Nonetheless, the full morbidity and mortality benefits and consequent health economic outcome, including specifically the impact of variation in uptake and effectiveness of anticoagulation in practice, can only be realistically determined by prospective randomized controlled outcome trials.

Uptake of Anticoagulation

All of the patients diagnosed with AF in the iECG arm were started promptly on anticoagulation (53% with NOAC). We did not routinely collect data on medication concordance, nor time in therapeutic range on warfarin, as that was outside the scope of this screening study. These issues will influence the clinical effectiveness of a screening programme and require evaluation in a prospective outcome study.

Limitations

Our study is the first randomized, prospective study to examine the effectiveness of longer-term intermittent ECG recording to diagnose AF in an at risk population. Patients who did not have access to the Internet or could not use the device were excluded from participation in the study, excluding those who could not comply with the monitoring protocol which likely include a proportion of those at the highest risk. This introduces a potential selection bias towards our findings being representative of this approach in the more independent, educated elderly who would likely still benefit considerably from lower AF-related stroke risk. Nonetheless, we were still able to recruit a large number of older patients who were no less compliant than the younger patients in our population. All study patients required internet access and documentation of proficiency with the device at screening, excluding additional bias between groups. The majority of iECG patients submitted traces on two occasions per week. Despite their generally very good concordance with the monitoring protocol and higher AF diagnosis rate, it is likely that asymptomatic paroxysmal AF has been missed in some participants, albeit unlikely that persistent/permanent AF was missed. Increasing the frequency of iECG acquisition should increase AF detection rate, but would increase logistical and financial demand on clinical services as well as further burden participants. Although

longer-term continuous external monitoring or use of implantable devices to identify incident AF would be expected to increase the capture of clinically relevant AF episodes, such approaches would not be without an adverse effect on patients in terms of convenience, discomfort, risk and acceptability. We were interested to note that participants were generally very satisfied with the AliveCor device and study protocol, with most finding it easy and acceptable to use, without increasing anxiety regarding their heart or likelihood of consulting with their physician. It was particularly noteworthy that RC participants expressed a far greater preference to have been allocated to the iECG arm. These findings provide reassurance that if such a programme is considered clinically and economically viable in the future, it will also be highly acceptable to the target population.

Only the iECG patients were contacted and brought back for clinical review +/- further testing where clinically indicated by their iECG results. There was no specific instruction regarding how to manage RC patients and data on nature and frequency of these visits for comparison have not been formally evaluated. Although we did not undertake a full face to face clinical evaluation and chart review of all patients at the completion of the study, all patients underwent detailed questioning at 12, 32 and 52 weeks with specific reference to heart rhythm abnormalities and major clinical events with only one missed call accounting for those dying, withdrawing or being lost to follow-up. Furthermore, patients and practitioners tended to notify us at the time of most relevant clinical events during follow up, with deaths and cardiovascular admissions confirmed through the NHS Wales clinical IT system. Whilst it is possible that events were underreported because patients did not remember or chose not to report them, participants were on the whole very engaged with the study and happy to volunteer relevant clinical

information. It is possible that the closer contact between the study team and iECG participants would make it more likely that relevant events would have been missed in RC patients.

We have not yet completed a full assessment of the diagnostic performance of the device and the reporting service. This is an extensive undertaking and beyond the scope of this manuscript. Our initial analysis of the diagnostics shows that a normal automated iECG report provides excellent negative predictive ability to exclude AF, but there appears to be a relatively high false positive rate in the small proportion of those reported as AF by the device, with these data and patients requiring careful review. A full, detailed evaluation of agreement between the automated alogorithm and overreading physiologist and cardiologist has not been completed and will be the subject of a further manuscript. Patients often submitted multiple ECGs when the automated report suggested AF or undetermined and clinical review with confirmatory testing required in several cases. These factors have been considered in the health economic evaluation.

The study was not blinded, with ECG over reads, diagnosis of AF and determination of clinical outcomes undertaken by the senior physician investigators. Although ECG and clinical diagnoses were validated, an element of observer bias cannot be excluded. The study was conducted in a single centre, based in a UK University Hospital with the majority of participants of white European ethnicity and thus the findings may not be generalizable to different patient populations or healthcare systems. We could not be certain that patients were truly free from (paroxysmal) AF prior to enrolment, but we excluded anyone with a prior record of AF in their primary care record or reported a

prior diagnosis of AF as well as the 19 who were found to be in (asymptomatic) AF on their initial iECG (including one who was inappropriately randomised and excluded due to protocol violation). We excluded cardiac pacing subjects as we felt that identification of asymptomatic high atrial rate episodes during routine pacing checks could potentially bias the results of the study. We acknowledge that this could have been a useful control, but as the numbers would have been small, any question of diagnostic superiority of internal vs intermittent external monitoring could not be answered definitively in this study.

The study data were analysed and reported independently and without involvement of the company. The investigators do not have any fiduciary involvement with the company.

Summary and Conclusions

Regular twice-weekly iECG screening is highly acceptable to people over 65 at increased risk of AF and stroke and results in an almost four-fold increase in the diagnosis of AF over the course of a year. This impact on AF detection and lower incidence of ischemic stroke/TIA due to AF or undetermined cause with this monitoring strategy, suggests a potential clinical benefit warranting further evaluation in a larger outcome trial.

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Figure legends

Figure 1: *Recruitment of local participants over 65 years of age with CHADS-VASc≥2.*

Figure 2: *Compliance in the iECG arm can be measured as the proportion of weeks in which a participant submits the recommended number of iECG. Here we show proportion of patients who submitted iECGs at least once per week (left panel) or at least twice per week vs the % of study weeks when this was achieved (fewer than 50%, 50-75%, 75-90%, or over 90% of the study weeks).*

Figure 3: *Kaplan-Meier plot showing the estimated detection probabilities for AF in each arm of the study over the 52 weeks of the trial. Shaded areas represent 95% confidence regions. Log-rank p = 0.004 (Mantel-Cox).*

Figure 4: *Pie charts showing iECF participant experience questionnaire responses to regarding use of AliveCor device in the study*

Tables

	iECG (N=500)	Routine Care (N=501)	p-value
Sex M/F	241/259 (48%/52%)	225/275 (45%/55%)	0.30
Mean age (SD)	72.6 y (5.4)	72.6 y (5.4)	0.98
Age 65-74 y	328	330	0.93
Age >= 75 y*	172	171	0.93
Heart Failure	5 (1%)	9 (2%)	0.28
Hypertension	268 (54%)	272 (55%)	0.75
Diabetes Mellitus	129 (26%)	140 (28%)	0.43
Stroke or TIA	35 (7%)	28 (6%)	0.37
Vascular Disease	71 (14%)	79 (16%)	0.50
CHADS-VASc (SD)	3.0 (1.0)	3.0 (1.0)	0.57

Table 1: *Baseline characteristics of study participants. TIA=transient ischaemic attack.*

**65 patients in the iECG and 56 in the RC arm were at least 80 years of age.*

	Hazard Ratio (95% CI)	p-value
Gender M/F	1.9 (0.9, 4.5)	0.11
Age >= 75	2.3 (1.0, 5.1)	0.04
Hypertension	0.91 (0.6, 1.4)	0.68
Diabetes Mellitus	1.1 (0.7, 1.6)	0.79
Stroke or TIA	1.2 (0.6, 2.5)	0.64
Arterial Disease	1.5 (1.0, 2.4)	0.05
CHADS-VASc Score ≥4	2.3 (1.0, 5.1)	0.04

Table 2: *Baseline variables as predictors of AF. The table shows results from separate Cox regression models. When variables were combined in a multivariable model, only CHADS-VASc score of ≥4 was independently associated with an increased risk of being diagnosed with AF.*

Adverse event	iECG (N)	RC (N)	p-value
Death	3	5	0.51
Stroke/TIA/SE	6	10	0.34
Clinically Significant Bleeds	2	1	0.56
DVT/PE	3	1	0.31
Other cardiovascular	8	13	0.27
Respiratory	7	3	0.20
Neurological	3	2	0.65
Orthopaedic/Musculoskeletal/Fall	14	14	0.99
Gastroenterological	10	10	0.99
Renal / Urological	2	5	0.26
Other	7	6	0.78

Table 3: *Adverse clinical events. Raw numbers of events in each arm of the study. Comparison between groups (p-values) were calculated using Cox regression.*