Feasibility and cost-effectiveness of stroke prevention through community screening for atrial fibrillation using iPhone ECG in pharmacies

The SEARCH-AF study

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Summary

Atrial fibrillation (AF) causes a third of all strokes, but often goes undetected before stroke. Identification of unknown AF in the community and subsequent anti-thrombotic treatment could reduce stroke burden. We investigated community screening for unknown AF using an iPhone electrocardiogram (iECG) in pharmacies, and determined the cost-effectiveness of this strategy. Pharmacists performed pulse palpation and iECG recordings, with cardiologist iECG over-reading. General practitioner review/12-lead ECG was facilitated for suspected new AF. An automated AF algorithm was retrospectively applied to collected iECGs. Cost-effectiveness analysis incorporated costs of iECG screening, and treatment/outcome data from a United Kingdom cohort of 5,555 patients with incidentally detected asymptomatic AF. A total of 1,000 pharmacy customers aged ≥65 years (mean 76 ± 7 years; 44% male) were screened. Newly identified AF was found in 1.5% (95% CI, 0.8–2.5%); mean age 79 ± 6 years; all had CHA_2DS_2-VASc score ≥2. AF prevalence was 6.7% (67/1,000). The automated iECG algorithm showed 98.5% (CI, 92–100%) sensitivity for AF detection and 91.4% (CI, 89–93%) specificity. The incremental cost-effectiveness ratio of extending iECG screening into the community, based on 55% warfarin prescription adherence, would be $AUD5,988 (€3,142; $USD4,066) per Quality Adjusted Life Year gained and $AUD30,481 (€15,993; $USD20,695) for preventing one stroke. Sensitivity analysis indicated cost-effectiveness improved with increased treatment adherence. Screening with iECG in pharmacies with an automated algorithm is both feasible and cost-effective. The high and largely preventable stroke/thromboembolism risk of those with newly identified AF highlights the likely benefits of community AF screening. Guideline recommendation of community iECG AF screening should be considered.

Keywords

Atrial fibrillation, screening, stroke prevention, cost-effectiveness, anticoagulation

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Previous Presentation: This study was presented in part as an oral presentation at the Cardiac Society of Australia and New Zealand Conference; 9 August 2013; Sydney, Australia, abstract published in Heart Lung Circulation 2013;22:S223.
Trial registration: Australian New Zealand clinical trials registry: ACTRN12612000406808.

Financial support:
The screening study was supported by an investigator-initiated grant from Bristol-Myers Squibb/Pfizer, and a small investigator-initiated project award from Boehringer Ingelheim. Cost-effectiveness analysis was supported by an investigator-initiated grant from Bayer. AliveCor provided ECG Heart Monitors for study purposes. The investigators are not affiliated with, nor have any financial or other interest in AliveCor. Dr Redfern is funded by a Career Development and Future Leader Fellowship co-funded by the NHMRC and National Heart Foundation (APP1061793). Dr Neubeck is an NHMRC early career fellow (APP1036763). Ms Lowres is funded by a National Heart Foundation Postgraduate Scholarship (PP12S6990).

Received: March 13, 2014
Accepted after minor revision: March 18, 2014
Prepublished online: April 1, 2014

http://dx.doi.org/10.1160/TH14-03-0231
Thromb Haemost 2014; 112: 1167–1176

Introduction

Atrial fibrillation (AF) is an increasingly important risk factor for stroke. Recent data suggest almost one third of all strokes are due to AF (1, 2), and in the Adelaide stroke incidence study (1) 11.6% of all strokes were due to unknown AF. Early identification of AF can significantly impact stroke and thromboembolism prevention, as treatment with oral anticoagulants (OAC) reduces stroke by 64% (3). Because asymptomatic AF is common (4) and those with undiagnosed asymptomatic AF are at increased risk of sustaining a stroke prior to AF detection (5, 6), practical approaches are required for widespread early detection. An additional motivation is that AF related strokes are more severe and produce greater disability than non-AF strokes (7–9).

Opportunistic screening is advocated for people aged ≥65 years in European AF management guidelines (10, 11), and the National Institute for Health and Clinical Excellence (NICE) recommend pulse palpation and electrocardiography (ECG) confirmation if AF is suspected, regardless of symptoms, especially in high-risk groups (12), while American (ACCF/AHA/HRS) AF guidelines do not mention screening (13). However, if screening is limited to general practice many with asymptomatic AF may go undetected, unless advice is sought for another condition and the practitioner checks the pulse. Single time-point screening, in both community or general practice settings, can identify 1.4% with unknown AF in people aged ≥65 years as determined by a systematic review of screening for AF (14), with an increased yield for repeat ECG recordings over several days (15). The combination of community-based screening and more systematic general-practice screening, has the potential to detect additional numbers of previously undiagnosed AF and could be implemented if shown cost-effective in prevention of stroke and systemic thromboembolism.

Pharmacists are well placed to undertake screening as they are actively involved in community triage of health problems (16), and have a large flow-through of customers especially those aged ≥65 years (17). Moreover, screening programs for various chronic health problems have been shown feasible and effective when delivered through pharmacies (18, 19). This cross-sectional study aimed to determine the feasibility, impact and cost-effectiveness of community pharmacy-based screening, using innovative iPhone ECG technology (20) to identify previously undiagnosed AF, with onward referral to the general practitioner (GP) for review and management, with the ultimate aim of reducing the burden of stroke and thromboembolism.

Figure 1: AliveCor Heart Monitor (AliveCor Inc.).

Methods

Study design

A cross-sectional study of community-based screening to identify unknown AF in Sydney, Australia was conducted between June 2012 to January 2013 (ACTRN12612000406808). The study was approved by the Sydney Local Health District Human Research Ethics Committee – Concord Repatriation General Hospital zone (HREC/11/CRGH/274). The study protocol has been described elsewhere (21). In brief, 10 pharmacies were recruited and pharmacists received training to implement the screening protocol. To ensure a feasible and maximum variation sample, pharmacies were selected from different demographic regions of Sydney. All people aged ≥65 years entering the pharmacy were eligible to participate, with the exception of those with a severe coexisting medical condition preventing participation (e.g. severe dementia or terminal illness). Screening was opportunistic. Availability of screening in participating pharmacies was advertised through flyers displayed within each pharmacy, and pharmacists and staff also directly approached potentially eligible clients.

Screening procedure

Participants provided written informed consent. Each screen entailed a brief medical history (i.e. symptoms, co-morbidities and medications), pulse palpation and a handheld iPhone-based lead-I ECG (iECG) using the AliveCor Heart Monitor (AliveCor Inc., San Francisco, CA, USA) (►Figure 1). We have previously validated this device using an automated algorithm showing 98% sensitivity and 97% specificity for detection of AF (20). Participants were also taught to take their own pulse. The pulse was measured for 30 seconds (sec) and iECG recorded for 30–60 sec, with the whole screening episode taking less than 5 minutes. Each iECG was read and interpreted by the pharmacist, transmitted to a secure server, and over-read by a cardiologist as the automated algorithm was not available for use at the commencement of this study, but became available as an instantaneous online feature after conclusion of the study. When AF was suspected from the screen, the participant's general practitioner (GP) was advised and asked to confirm any known AF history, with the participant referred back to their GP for review and management.

Cost-effectiveness analysis

A modelled cost-effectiveness analysis from an Australian health funder perspective was performed comparing the cost of iECG population-based screening for AF, to diagnosed AF in an unscreened population of Australian men and women aged 65 to 84 years. The model assumes a base rate of known and unknown AF in the population and follows a prevalent cohort of men and women aged 65 to 84 years over a period of 10 years with annual incident stroke events and death from any cause.

An initial round of AF screening is based on the assumption that the prevalence of AF in the population aged ≥65 years is 4.4% and the rate of newly identified AF is 1.4% (14), and test sensitivity

and specificity of iECG screening using the automated algorithm is 98.5% and 91.4% respectively. Calculated costs for those identified with AF (outlined in Suppl. Material Appendix 1, available online at www.thrombosis-online.com) include:

- The cost per iECG screen $AUD 20 (€10.5; $USD13.5) (22);
- Diagnostic assessment of AF: $AUD 252 (€132; $USD171), i.e. initial GP consultation, initial specialist consultation and 12-lead ECG;
- Anticoagulation and monitoring: $AUD 803.80 (€422; $USD546) per annum, i.e treatment with warfarin, INR monitoring, three annual GP consultations and an annual specialist consultation.

The benefits of detecting AF and subsequent treatment with warfarin are based on data obtained from the UK Clinical Practice Research Datalink (CPRD) using a subset of 5,555 patients with asymptomatic AF detected incidentally and a non-AF cohort of 24,772 patients matched on birth year, gender, and date of incident AF (23). These data showed a significant reduction in the incidence of stroke and all-cause mortality in patients treated with warfarin (Suppl. Material Appendix 2, available online at www.thrombosis-online.com). In this subset, incidence rates of stroke and all-cause deaths are calculated by the number of incident outcome events during the study period divided by total person-years at risk in the asymptomatic AF and non-AF cohorts, respectively. The prognosis of the cohort with asymptomatic AF is comparable to that of a large Canadian population study with recently diagnosed AF (24). The rates are estimated for men and women aged 65 to 84 years and are projected out to 10 years following the initial screen, for a non-AF cohort, treated AF and untreated AF. When the rates are not constant over time, then annual rates are provided.

For each stroke prevented by screening, a present value of 5.09 Quality Adjusted Life Years (QALYs) gained over a lifetime for an ischaemic stroke was taken from Cadillac et al. (25), as was the cost of hospital treatment following stroke (inflated to 2011 prices using a health price deflator) $AUD 64,872 (€34,036; $USD44,045). All future costs were discounted at a rate of 5%. The results are expressed as an incremental cost-effectiveness ratio (ICER) per stroke avoided and per QALY gained.

Sensitivity analyses were performed varying the base assumptions of a guideline-adherence rate for anticoagulant prescription between 40% through to 80%. Sensitivity analyses also included increasing the cost of treatment to a level indicative of the novel oral anticoagulants (NOAC), using a price of $AUD 1,508 (€791; $USD1,024) per annum, including price of medication, two GP visits, a specialist visit and single pathology assessment, and assuming 10% of patients will still be prescribed warfarin. To obtain 95% confidence intervals (CIs) for all ICERs we performed a multifactorial Monte Carlo simulation (26) based on the precision of all age- and gender-specific stroke and death incidence rate estimates derived from our CPRD cohort described above. We generated 100,000 sets of pseudorandom incidence rates based on the asymptotic lognormal distribution of the respective incidence rate estimates and calculated the corresponding ICERs. The 2.5th and 97.5th percentile of these 100,000 ICERs were taken as the 95% CI borders. This procedure was performed for all different combinations of other model input factors, e.g. different treatment adherence rates. The complete list of assumptions is provided in Suppl. Material Appendices 1 and 2 (available online at www.thrombosis-online.com).

Outcomes

Co-primary outcomes

- Determination of the proportion of participants with newly identified AF, from the cardiologists' interpretation of the iECG (in combination with the noise-reduced iECG and a 12-lead ECG which was advised for all participants with suspected unknown AF).
- A cost-effectiveness analysis of the ICER per QALY gained and stroke avoided for screening vs a non-screened population of men and women aged 65 to 84 years.

Secondary outcomes

- Estimated stroke risk of participants (calculated using CHA_2DS_2-VASc score [10])
- Level of agreement between the pharmacist and cardiologist interpretation of the iECG (calculated using weighted Cohen's Kappa)
- Level of agreement for identification of AF between pulse palpation by the pharmacist and the cardiologist interpretation of the iECG (calculated using Cohen's Kappa)
- Sensitivity and specificity of screening tests for AF identification using: pharmacist interpretation of pulse palpation; pharmacist interpretation of iECG; and computer-generated algorithm retrospectively applied to the iECGs (compared to the cardiologists' interpretation of the iECG in combination with the noise-reduced iECG and a 12-lead ECG where performed). The computer algorithm was not available at the time of writing the protocol and was not originally included as a secondary endpoint.

Impact measures

Pharmacist knowledge of AF was assessed prior to training and at completion of the screening study. Knowledge was assessed with a purpose-designed questionnaire comprising eight questions with free-text responses (Suppl. Material Appendix 3, available online at www.thrombosis-online.com). The questionnaire sought information about general AF knowledge, associated health risks, symptoms, risk factors, stroke risk, screening modes, and medications, and was evaluated by number of correct answers out of a total score of 23 points (Suppl. Material Appendix 3, available online at www.thrombosis-online.com).

Statistical methods

Primary analyses were conducted using SPSS for Windows (Version 21.0) and Monte Carlo simulations using STATA MP Version 13.1 (StataCorp LP). New episodes of AF are expressed as true positives divided by total number screened with accompanying 95% binomial CIs. Continuous variables are reported as means ± standard deviations (SD), and categorical variables as numbers and percentages. A sample size of n=1,000 was chosen to provide a confidence interval of ± 0.8%, based on previous research which suggests an incidence of 1.4% (14). Two-tailed p-values of <0.05 were considered significant.

Results

Participants

A total of 1,051 pharmacy customers were recruited but 51 were not eligible for inclusion (►Figure 2): two withdrew consent, three were recruited twice, 42 were under 65 years, and screening was unable to be completed in four cases due to excessive movement artefact resulting in non-diagnostic traces. Of the 1,000 eligible screened participants, 436 (44%) were male and mean (± SD) age was 76 ± 7 years.

Newly identified AF

Newly identified AF was found in 15 participants (1.5%; 95% CI, 0.8–2.5%). Of these, 10 participants (1.0%; CI, 0.5–1.8%) had no prior history of AF. The additional five participants (0.5%; CI, 0.2–1.2%) had an unknown recurrence of AF ≥3 years after cardioversion (mean 10 ± 3 years), and were not receiving OAC as their practitioner deemed them to be in stable sinus rhythm.

The mean age of those with newly identified AF (n=15) was 79 ± 6 years. Only 2/15 reported palpitations, similar to the proportion of participants with no history of AF reporting palpitations (p=0.28) (►Table 1). Resting mean heart rates for those with newly identified AF were not elevated when compared to the other

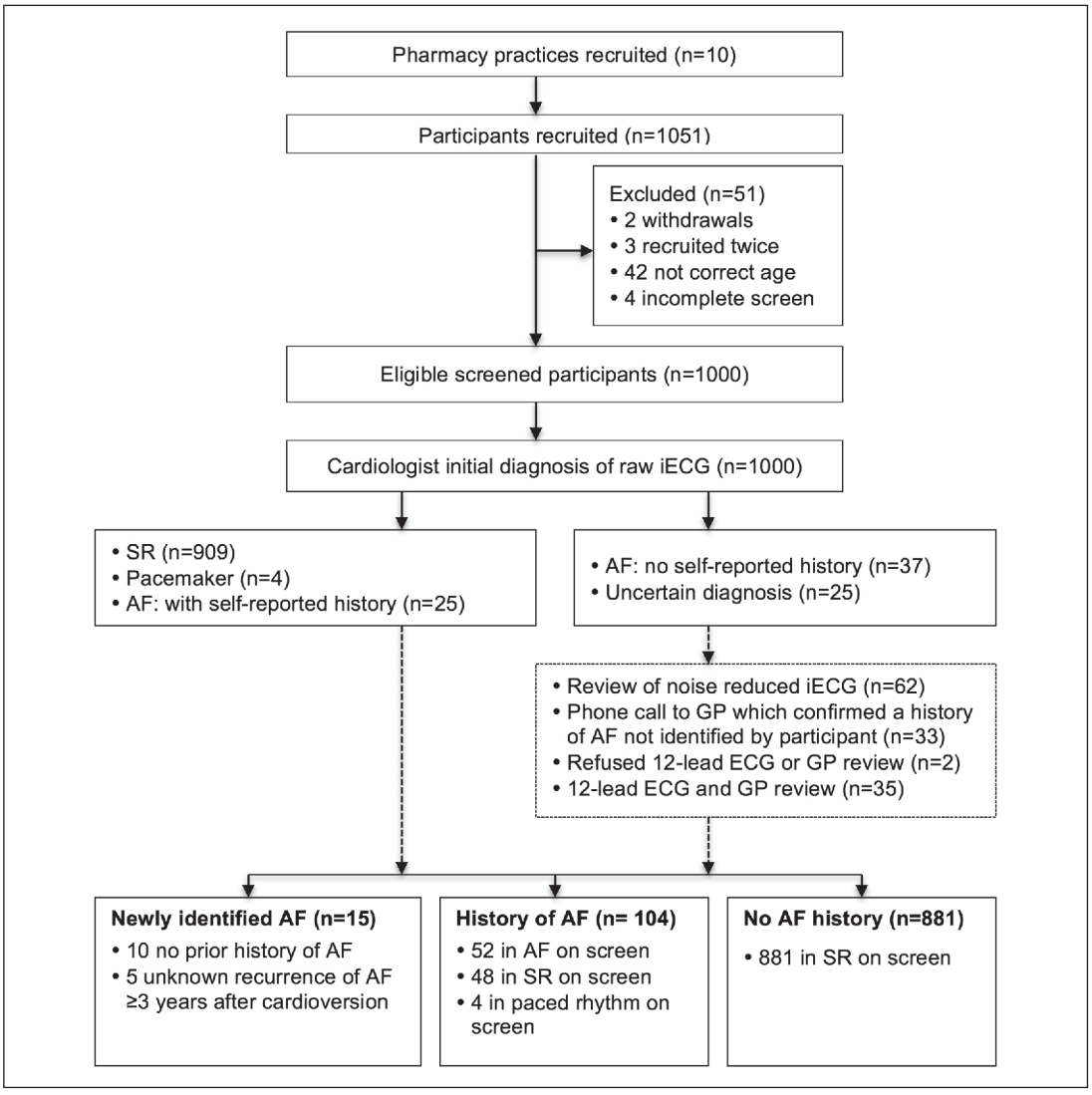

Figure 2: Study flow. iECG = iPhone single-lead ECG; AF = atrial fibrillation; SR = sinus rhythm; GP = general practitioner.

groups (►Table 1). All 15 were guideline-eligible for consideration of OAC (10), with a CHA_2DS_2-VASc score ≥2 and mean score of 3.7 ± 1.1 (►Table 1). The incidence of newly identified AF was higher for men aged 75 to 84 years (p=0.04) (►Table 2).

Review by the GP occurred in 14 of the 15 newly identified AF cases with a mean time between screening and 12-lead ECG of 16.6 ± 14.3 days. Of the 10 participants with no prior history of AF, two had paroxysmal AF that reverted to sinus rhythm prior to their 12-lead ECG, with one referred to a cardiologist but neither were prescribed OAC. Seven of ten had AF still present on 12-lead ECG, and six were referred for further cardiology review. One participant declined both GP review and 12-lead ECG. OAC was prescribed in 6/10. For the five participants with unknown recurrence of AF, all were reviewed by a cardiologist, and three participants were subsequently prescribed OAC.

Prevalence of AF

The prevalence of AF identified by screening was 6.7% (67/1,000) (95% CI, 5.2–8.4%); comprising 15 with unknown AF, and 52 with a history of AF and in AF when screened. Of the 52 participants with known AF, only 38% reported palpitations (►Table 1). AF knowledge in this group was poor: all 52 participants were known to their GP as having a diagnosis of AF, but 23 (44%) were unaware of this diagnosis despite 18 of them taking OAC.

An additional 52 (5.2%) participants reported a history of AF, but were either in sinus or paced rhythm at the time of screening, making a total of 109 participants with a history of AF (►Figure 2). Of those, 105 (96%) participants had a CHA_2DS_2-VASc score ≥2. Sixty-two participants had a $CHADS_2$ score ≥2, but only 36 (58%) of these participants were being prescribed OAC.

Economic analysis

For population-based AF screening for men and women aged 65 to 84 years, assuming a 50% screening participation rate, 55% treatment adherence, and test sensitivity 98.5% and specificity 91.4%, the ICER per QALY gained was $AUD 5,988 (€3,142; $USD4,066) (95% CI, $AUD 1,613 – 13,435) and the ICER per stroke avoided was $AUD 30,481 (€15,993; $USD20,695) (CI, $AUD 8,210 – 68,384). Increasing the cost per screen to $AUD30 (€15.7; $USD20.4) lowers the cost-effectiveness to $AUD 8,223 (€4,315; $USD5,632) (CI, $AUD 3,263 – 16,723) per QALY gained. The results are sensitive to treatment adherence rate (►Table 3): e.g. at 80% adherence and $AUD 20 per screen the ICER per QALY gained was $AUD 3,888 (€2,040; $USD2,640) (CI, $AUD 58 – 10,341). Cost-effectiveness was independent of screening participation rate.

Substituting the cost of NOAC treatment $AUD 1,508 (€791; $USD1,024) for warfarin $AUD 803.80 (€422; $USD546) and assuming NOAC treatment is at least clinically non-inferior to warfarin and 10% of the total would still be placed on warfarin, the ICER per QALY gained is $AUD 11,944 (€6,267; $USD8,109) (CI, $AUD 5,960 – 21,864), and the ICER per stroke prevented by

Table 1: Stroke risk and symptom presentation.

	Newly identified AF (n=15) [a]	AF History (In AF) (n=52)	AF History (Sinus or paced rhythm) (n=52)	No AF history (n=881)	All participants (n=1000)
Age, mean ± SD, years	79 ± 6	79 ± 7 [b]	76 ± 6	76 ± 7 [b]	76 ± 7
$CHADS_2$, mean ± SD	1.9 ± 1.1	1.8 ± 1.0	1.8 ± 1.3	1.5 ± 1.0	1.5 ± 1.0
CHA_2DS_2-VASc, mean ± SD	3.7 ± 1.1	3.5 ± 1.2	3.4 ± 1.4	3.2 ± 1.1	3.3 ± 1.2
ECG rate, mean ± SD, bpm	75 ± 16	80 ± 16 [c,d]	72 ± 13 [c]	74 ± 12 [d]	74 ± 13
Palpitations, n (%)	2 (13) [e]	20 (38) [f]	26 (50) [e,g]	211 (24) [f,g]	259 (26)
Other symptoms [h], n (%)	4 (27)	13 (25)	13 (25)	229 (26)	259 (26)
Congestive heart failure / left ventricular dysfunction, n (%)	1 (7)	4 (8)	7 (13)	15 (2)	27 (3)
Hypertension, n (%)	11 (73)	34 (65)	29 (56)	545 (62)	619 (62)
Diabetes, n (%)	1 (7)	13 (25)	10 (19)	205 (23)	229 (23)
Prior stroke / TIA / thromboembolism, n (%)	2 (13)	4 (8)	8 (15)	59 (7)	73 (7)
Vascular disease, n (%)	7 (47)	16 (31)	16 (31)	123 (14)	162 (16)

SD = standard deviation; AF = atrial fibrillation; ECG = electrocardiogram; bpm = beats per minute; $CHADS_2$ = (C for congestive heart failure, H for high blood pressure, A for age, D for diabetes and S_2 for stroke/transient ischaemic attack); CHA_2DS_2-VASc = (C for congestive heart failure/left ventricular dysfunction, H for high blood pressure, A_2 for age >75 years, D for diabetes, S_2 for stroke/transient ischaemic attack/thromboembolism, V for vascular disease [coronary artery disease, myocardial infarction, peripheral artery disease, aortic plaque], A for age 65 – 74 years, Sc for sex category female); TIA = transient ischaemic attack; a = Consists of 10 with no prior AF history and 5 with unknown AF recurrence ≥3 years after cardioversion; b = Between group difference (p=0.009); c = Between group difference (p=0.02); d = Between group difference (p=0.04); e = Between group difference (p=0.01); f = Between group difference (p=0.01); g = Between group difference (p<0.001); h = Reported light-headedness or dyspnoea only.

screening is $AUD 60,795 (€31,897; $USD41,277) (CI, $AUD 30,336 – 111,287) with 80% adherence with treatment. The results are sensitive to the cost of NOAC (▶Table 3).

iECG (Cardiologist)

The raw iECG provided a clear diagnosis in 97.5% of those screened. In 2.5% of cases (25/1,000) the cardiologist determined the rhythm diagnosis from the raw iECG was unclear. After viewing a noise-reduced iECG trace, and where available a 12-lead ECG, 8/25 were diagnosed as probable AF, and 17 as probable sinus rhythm (13 with multiple atrial ectopics and/or sinus arrhythmia and low voltage p waves in lead-I).

Agreement, sensitivity and specificity of AF diagnosis

The four iECGs with paced rhythm are not included in the agreement, sensitivity, or specificity analyses; therefore analyses are based on 996/1,000 iECGs.

iECG (Pharmacist)

Data for the pharmacist's interpretation of the iECG was missing for 5/996 cases. Pharmacists identified 51 of the 67 AF cases using the iECG, and only 9/15 cases of newly identified AF. The pharmacist had the option of choosing a diagnosis of AF, sinus rhythm or uncertain. In 87 cases an "uncertain" diagnosis was chosen, and for the purpose of this analysis these were classified as the incorrect interpretation. For the pharmacist iECG interpretation, weighted Kappa agreement with the cardiologist diagnosis was moderate κ=0.4 (SE of kappa = 0.043). Sensitivity and specificity for diagnosing AF were 77% (95% CI, 65–87%) and 87% (CI, 85–89%), respectively.

iECG (Algorithm)

When the previously validated algorithm (20) was retrospectively applied to the 996 unprocessed iECGs, it showed 98.5% (CI, 92–100%) sensitivity and 91.4% (CI, 89–93%) specificity for AF diagnosis. Importantly, the algorithm identified all 15 cases of newly identified AF.

Table 2: Demographic distribution and history of AF.

Age range, years	Newly identified AF, n		AF history, n		No AF history, n	
	Male	Female	Male	Female	Male	Female
65–74 years (n=481)	2	2	25	15	175	262
75–84 years (n=405)	8	1	33	17	141	205
≥85 years (n=114)	0	2	11	3	41	57
All (n=1000)	10	5	69	35	357	524

AF = atrial fibrillation

Pulse palpation (Pharmacist)

Pharmacist pulse interpretation data was missing for 24/996 cases. Using pulse palpation, pharmacists identified 51/67 AF cases, and 11/15 cases of newly identified AF. For the pharmacist interpretation of the pulse, kappa agreement with the cardiologist diagnosis was moderate κ=0.52 (SE of kappa = 0.046). Sensitivity and specificity were 77% (CI, 65–87%) and 93% (CI, 91–95%), respectively. In 48/66 cases with a false positive pulse diagnosis, there were multiple atrial or ventricular ectopic beats or sinus arrhythmia noted on the iECG.

Pharmacist knowledge

As a result of participation in the study, assessed pharmacist AF knowledge significantly improved from a mean (± SD) test score of 49 ± 25% at baseline, to 86 ± 8% post-study (p<0.001). While only a minority of pharmacists were able to outline symptoms, health risks, risk factors, and screening methods for AF prior to participation in the study, at completion the majority accurately answered these questions.

Discussion

Statement of findings

Newly identified AF was found in 1.5% of participants screened, all with high stroke risk, and all guideline-eligible for consideration of oral anticoagulants. This finding is consistent with the predicted 1.4% of new AF shown in a systematic review (14). The mean CHA_2DS_2-VASc score of participants with new AF was 3.7, and all had a score of ≥2, indicating that an individual screened in this way and identified with new AF is a likely candidate for oral anticoagulants due to elevated stroke risk. Furthermore, as the majority of these participants were asymptomatic, it is unlikely they would present to their GP for medical review and therefore may have remained undetected if not for community screening. If iECG screening was extended into the community the ICER would be $AUD 5,988 (€3,142; $USD4,066) (CI, $AUD 1,613 – 13,435) per QALY gained and $AUD 30,481 (€15,993; $USD20,695) (CI, $AUD 8,210 – 68,384) for prevention of one stroke, figures well within the usual willingness to pay thresholds for third party funders.

Strengths and weaknesses

Our study design utilised a cardiologist to over-read each iECG and provide a provisional diagnosis. This was necessary as the automated algorithm (20) was not available for use during the recruitment period of our study, and the device did not have regulatory approval at study initiation. Although pharmacist interpretation of both pulse palpation and iECG had moderate agreement

Table 3: Two-way cost-effectiveness sensitivity analysis.

ASSUMPTIONS	ICER per QALY gained (95% confidence intervals)					
	40% treatment adherence	50% treatment adherence	BASE CASE 55% treatment adherence	60% treatment adherence	70% treatment adherence	80% treatment adherence
BASE CASE						
• $AUD 20 per screen • Warfarin cost $AUD 803.80pa • 5.09 QALYs gained per stroke avoided • 98.5% sensitivity and 91.4% specificity for screening	$8,509 ($3,473–17,086)	$6,660 ($2,103–14,355)	$5,988 ($1,613–13,435)	$5,428 ($1,203–12,615)	$4,548 ($557–11,330)	$3,888 ($58–10,341)
DEVIATIONS FROM BASE CASE						
• $AUD 30 per screen	$11,582 ($5,737–21,478)	$9,119 ($3,883–17,882)	$8,223 ($3,263–16,723)	$7,477 ($2,728–15,578)	$6,304 ($1,837–13,895)	$5,425 ($1,184–12,609)
• Treatment = 90% NOAC @ $AUD 1,508pa and 10% Warfarin @$AUD 803.80pa	$16,564 ($9,351–28,821)	$14,716 ($7,989–26,102)	$14,044 ($7,517–25,087)	$13,484 ($7,119–24,216)	$12,604 ($6,448–23,070)	$11,944 ($5,960–21,864)
• Treatment = 90% NOAC @ $AUD 1,174pa and 10% Warfarin @$AUD 803.80pa	$12,747 ($6,568–23,264)	$10,899 ($5,182–20,547)	$10,227 ($4,742–19,412)	$9,667 ($4,318–18,776)	$8,787 ($3,649–17,479)	$8,127 ($3,195–16,529)
• 4.275 QALYs gained per stroke avoided (Pink et al 2011 – over 75 sub group)(41)	$10,131 ($4,129–20,307)	$7,930 ($2,524–17,104)	$7,130 ($1,895–16,017)	$6,463 ($1,421–14,983)	$5,415 ($643–13,452)	$4,629 ($78–12,375)
• 6.39 QALYs gained per stroke avoided (using Pink et al 2011)(41)	$6,778 ($2,746–13,640)	$5,305 ($1,664–11,440)	$4,770 ($1,306–10,715)	$4,324 ($960–9,997)	$3,623 ($413–9,017)	$3,097 ($58 – 8,274)

ICER = Incremental cost-effectiveness ratio; QALY = Quality Adjusted Life Year; NOAC = novel oral anticoagulant; $=$AUD (To calculate Purchasing Power Parity use: $AUD1 = €0.5247 = $USD0.6789)(22); pa = per annum.

with the cardiologist iECG interpretation, pulse palpation was relatively insensitive. The computer-generated iECG algorithm provided high sensitivity and specificity, and is almost instantaneously available when an iECG is taken. Therefore for widespread screening, pharmacists would use the device with the validated predictive algorithm (20) providing an immediate diagnosis, and improving work flow for subsequent referral.

It is probable that some participants with paroxysmal AF were not identified in our study as we used only a single-time point iECG screen. In fact two patients with AF identified at screening had reverted to sinus rhythm by the time a 12-lead ECG was recorded. Allowing people to be screened on repeated visits to their pharmacy may identify those with paroxysmal AF in sinus rhythm on initial screen. Additionally, our study was not large-scale and recruited only 1,000 participants, limited to Sydney, Australia. As this was a real-world trial testing the potential for using community pharmacy as a setting for conducting screening, strategies for recruitment differed slightly between sites and was dependent on the pharmacist's availability/workload at different times of the day; hence, it is not possible to infer which was the more effective recruitment strategy. It is also likely that the screening program captured individuals with a greater interest in or concern about their health, and could thereby underestimate prevalence of undiagnosed AF in people attending a community pharmacy. However, given the consistency of results with other larger screening studies (14), the comparability of the proportion of the study population reporting palpitations to that of other studies (4), and our wide demographic coverage, it is likely our results are generalisable to other populations and settings.

Our cost-effectiveness analysis assumed non-inferiority for NOACs vs warfarin, which may be clinically conservative (27, 28), and therefore may be an underestimate of the possible net clinical benefit for stroke and major bleeds from use of NOACs (29). Additionally it is possible that NOAC price may reduce with additional market competition (30) which would further improve cost-effectiveness.

Implications for health professionals and policymakers

The 2013 Cochrane review of systematic screening for AF (31), primarily based on the SAFE study (32), concluded both systematic and opportunistic screening increased the detection rate of AF, and identified the need to examine the effectiveness of alternative

screening strategies for AF. Our study has explored the effectiveness of screening for AF in community pharmacies and demonstrates this is a plausible option for identification of unknown AF, the cause of at least 11.6% of all strokes (1). Unlike other community screening studies organised around designated events (33, 34), our study offered opportunistic screening of an ongoing nature. Pharmacists were confidently able to screen for AF, with cardiologist iECG over-reading, and facilitate a GP review for those with suspected AF.

Past research conducted in the UK concluded systematic screening in general practice using 12-lead ECG was not cost-effective (32). In contrast, our study identified that community screening using iECG is cost-effective. The estimated ICER of screening to prevent one stroke or to increase one QALY is well within the range that would be fundable on a population basis (35), using either warfarin or NOAC. The sensitivity analysis indicates cost-effectiveness improves with increased adherence to guideline recommendations for anticoagulation prescription, as has also been shown in other cost-effectiveness analyses (36), and NOACs are likely to be associated with greater adherence rates (37). Greater detection of AF, as implied in this study, would have a significantly larger impact for stroke prevention with the use of NOACs, given the improved net clinical benefit incurred by increasing the use of oral anticoagulation (38). Of course patient preference for stroke prevention and tolerance of risk of haemorrhage will be important factors to consider in determining how many will decide to take oral anticoagulants (39, 40).

These results have important ramifications for health policy and for funding of pharmacy risk assessments, or assessments provided in alternative primary care settings. This is particularly significant given the high risk of stroke and premature death identified in people with asymptomatic AF detected incidentally, the salutary effect of OACs in reducing these adverse outcomes (23), and the published cost-effectiveness of NOACs in prevention of stroke and thromboembolism (41, 42). If the findings from our study were extrapolated to the current population of Australia aged 65–84 years (approx. 2.9 million people), this would translate to identification of unknown AF in 20,156 people, and the prevention of 1,228 strokes, assuming that 55% (i.e. 11,086) of those identified were treated with appropriate OAC. Furthermore, if we assume 80% compliance with guidelines using NOACs, 1,787 strokes would be prevented assuming non-inferiority to warfarin, and larger numbers if greater efficacy in stroke prevention is assumed for some NOACs.

Through participation in our study the pharmacist's knowledge of AF increased significantly, suggesting pharmacists could provide an improved educative role to the public in regards to AF. The need for this educative role is highlighted in the low recall and recognition of AF diagnosis by participants in this study, even in those prescribed OAC treatment. This lack of patient knowledge is reflected in other studies (43–47), where 50–60% of those surveyed had minimal knowledge of AF or warfarin therapy, perceived their condition as not serious, and/or were unaware or not concerned about their increased stroke risk. In the "SPEAK about AF Survey" (43), 26% of participants indicated they would first consult their local pharmacist for additional information about AF. Therefore there is potential for pharmacies to provide ongoing community screening for AF and act as an educational resource. As understanding the risks and consequences of AF is paramount to compliance with appropriate medication and treatment, this identified lack of knowledge is concerning, and coupled with the widely known treatment gap highlighted in this study, brings attention to areas of need for future interventions.

What is known about this topic?

- Atrial fibrillation (AF) is responsible for one third of all strokes.
- The majority of AF episodes in people with unknown AF are asymptomatic.
- Screening at a single time-point can identify previously unknown AF in 1.4% of those screened aged ≥65 years.

What does this paper add?

- Community-based screening by trained pharmacists using iPhone ECG is a feasible strategy to identify significant numbers with unknown AF.
- If iECG screening was extended to the general community, the incremental cost-effectiveness ratio would be $AUD 5,988 (€3,142; $USD4,066) (95% CI, $AUD 1,613 – 13,435) per Quality Adjusted Life Year gained and $AUD 30,481 (€15,993; $USD20,695) (CI, $AUD 8,210 – 68,384) for prevention of one stroke.
- The validated automated AF algorithm provides high accuracy for diagnosis of AF when used in a community setting.

Unanswered questions and future research

Identification of unknown AF through screening is the first of three steps towards stroke prevention. However, the additional well-known gaps of adherence to guidelines, and poor patient knowledge and awareness of AF are also highlighted in our study. Addressing all of these additional gaps for AF is required to achieve effective stroke prevention and should be incorporated in policy statements on stroke prevention, but discussion of the role of AF is currently lacking from the recent American Heart Association/American Stroke Association policy statement on predicting the future of stroke (48, 49). Research investigating feasible and cost-effective ways to close these gaps is required.

Conclusion

Community screening in pharmacies is a feasible and cost-effective strategy to identify a sizeable cohort with newly identified AF, at sufficient risk to require OACs for stroke prevention. High overall stroke risk, relatively low oral anticoagulant prescription, and poor knowledge of diagnosed AF sufferers highlight the need for community-based screening and education. This study demonstrates that iECG screening in pharmacies is a cost-effective mechanism to address these gaps, and could potentially reduce the high

Data sharing

Patient level data and technical appendix are available from the corresponding author.

cost and societal burden of stroke and systemic thromboembolism associated with AF.

Acknowledgements

We thank the staff of the participating community pharmacies for their invaluable time conducting the screening; Jennifer K Peat, consultant statistician, Concord Repatriation General Hospital, for assistance with statistical analysis; Aileen Siney, RN, Concord Repatriation General Hospital, and Vineta Sahai, RN, Concord Repatriation General Hospital, for assistance with clinical support to the pharmacies; Julie Rhodes, Administration Officer, Concord Repatriation General Hospital, for administrative support; and members of our stakeholder group for their contribution refining the study protocol.

Conflicts of interest

Prof Freedman reports grants, personal fees and non-financial support from Bayer Pharma AG outside the submitted work, grants and non-financial support from Boehringer Ingelheim outside the submitted work, grants and personal fees from BMS/Pfizer outside the submitted work, personal fees from Servier outside the submitted work, personal fees from Astra-Zeneca outside the submitted work; Prof McLachlan has research support from GlaxoSmithKline (postgraduate student scholarship), IMgateway (research support for a drug interaction database), Pharmaceutical Society of Australia (travel support), and Australian Antidoping Research Panel (Board Member); Dr Martinez reports grants, personal fees and non-financial support from Bayer Pharma AG, personal fees from Boehringer Ingelheim, grants and personal fees from CSL Behring, outside the submitted work; Dr Bennett reports personal fees from Pharmacy Guild of Australia (PGA) outside the submitted work; Prof Salkeld reports personal fees from Anzac Research Institute, during the conduct of the study; Prof Brieger reports unrestricted research grants from Astra Zeneca, personal fees for invited lectures from Astra Zeneca, outside the submitted work; Ms Lowres, Dr Neubeck, Prof Krass, Dr Redfern, A/Prof Briffa, Prof Bauman, Dr Lau, Dr Sy and Mr Wallenhorst have nothing to disclose.

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