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Incremental yield of ECG screening repeated annually over 4 years in an adult Japanese population without prior atrial fibrillation: a retrospective cohort study

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ABSTRACT

Objectives International guidelines recommend opportunistic screening for atrial fibrillation (AF); however, there is no current data to inform how often to repeat screening. We aimed to investigate the incremental annual yield and stroke risk of new AF cases in individuals screened annually over 4 years.
Design A retrospective cohort study.
Setting Hokuriku Health Service Association, Toyama prefecture, Japan.
Participants Employees and their families receiving annual health examinations from Hokuriku Health Service Association.
Intervention Each subject received an annual health examination (including 12-lead ECG) from 2014 to 2017. Only subjects with baseline ECGs in 2012 and/or 2013 were included.
Main outcome measures Rates (cases/100 person-years) of new AF identified each year for 4 consecutive years of screening (stratified according to gender and age groups). Calculated stroke risk of new AF cases using modified CHA_2DS_2-VASc scores (without heart failure data) (CHA_2DS_2VASc = C: congestive heart failure [1 point]; H: hypertension [1 point]; A2: age 65-74 years [1 point] or age ≥75 years [2 points]; D: diabetes mellitus [1 point]; S: prior stroke or transientischemic attack [2points]; VA: vascular disease [1 point]; and Sc: sex category [female] [1 point])
Results In 2014, 88 218 subjects had an ECG (46.8±12.5 years; 64% men): identifying 346 (0.39%) known AF and 69 (0.08%) new AF. The incidence rate of new AF increased with age from 0.01% (<50 years) to 0.98% (≥75 years) and was higher in men (0.1%) than women (0.05%). Repeated annual screening over 4 years identified a consistent new AF yield 0.06%–0.10% per year (0.33%–0.55% ≥65 years). Forty-two per cent of all new AF cases, and 76% of cases aged ≥65 years, had a class-1 oral anticoagulation (OAC) recommendation (modified CHA_2DS_2-VASc score ≥2 men, ≥3 women).
Conclusions Repeated annual ECG screening of the same population provides a consistent yield of new AF each year. The majority of new AF (≥65 years) are eligible for anticoagulation for stroke prevention. Although

Strengths and limitations of this study

► This is the first study to investigate the effect on the annual yield of new atrial fibrillation by repeating screening each year in the same population.
► This study uses a large database of more than 140 000 individuals attending annual health examinations in Japan.
► The analysis includes more than 57 500 people who were screened annually with an ECG for four consecutive years.
► Although the age distribution of the database was skewed towards a younger demographic, the analysis included ~6600 individuals aged 65 years and over.

AF prevalence and incidence are lower in Japan than Western countries, 2318 new cases would be identified in Toyama prefecture each year with annual screening, of whom ~927 would have a high stroke risk with a recommendation for OAC therapy.

INTRODUCTION

Atrial fibrillation (AF) is a global health-care problem with evidence suggesting an increasing prevalence and incidence world-wide.[1] As stroke registries indicate that a third of all ischaemic strokes are AF related, early identification is essential.[2 3] Screening people ≥65 years in Western countries, with a single screen, is likely to yield 1.44% with new AF.[4] In Japan, screening is likely to identify a lower incidence of AF; however, those identified have a high relative risk of stroke (1.61; 95% CI 0.50 to 5.16) and all-cause mortality (1.71; 95% CI 1.20 to 2.43).[5]

International guidelines recommend opportunistic screening for AF in the clinic by pulse palpation in people aged ≥65 years to reduce AF-related strokes.[6 7] The Wilson

Health examination 2014
n=141,441

Exclude n=53,223
• Without ECG 2014 (n=30,649)
• Without prior ECG 2012 +/1 2013 (n=22,443)
• Under 20 years (n=1,331)

2014 ECG
(with prior ECG 2012 +/- 2013)
n=88,218

Known AF (on ECG 2012 +/- 2013)
n=346

New AF n= 69

Loss follow up n= 13,826

2015 ECG n= 73,977

New AF n= 76

Loss follow up n= 9,074

2016 ECG n= 64,827

New AF n= 49

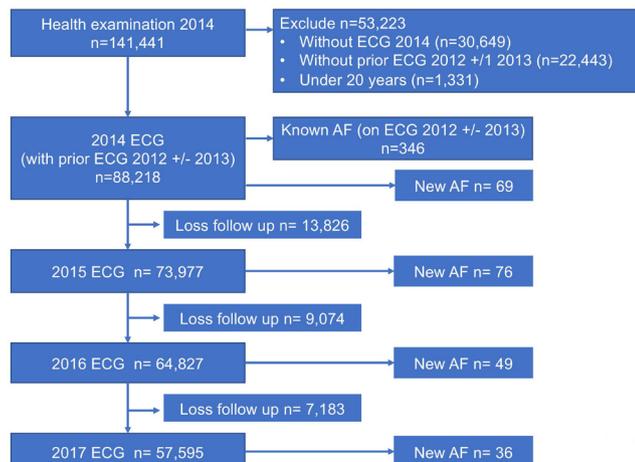Loss follow up n= 7,183

2017 ECG n= 57,595

New AF n= 36

Figure 1 Study flowchart. AF, atrial fibrillation.

and Jungner, WHO, criteria for a screening test requires that any screening intervention must have a defined timeframe for when screening should be repeated and that it is not a once-off process.[8] However, there is no clear recommendation in the AF guidelines regarding if screening should be once only or repeated, and what the frequency for repetition of screening should be.[6 7] To date, there are no published data regarding the incremental yield that would be found by repeating opportunistic or systematic screening each year in people without AF, and it is uncertain whether there would be diminishing returns from screening with each subsequent year. In order to determine the incremental yield of repeated screening, physicians need to repeat screening in an AF-negative population on a regular basis.

In Japan, employers have a legal obligation to provide annual health examinations for the employees and their families. For non-employed or retired residents, the government provides access to annual health examinations, although attendance is optional. The annual health examination screen is comprehensive, including screening for respiratory, metabolic, cardiovascular, ophthalmology, hearing, gynaecology and lifestyle disorders, with many companies, including a 12-lead ECG. We had the unique opportunity to investigate the effect of repeating screening each year on the yield of new AF, by assessing a large database of annual ECGs taken during health examinations in Toyama prefecture, Japan. Therefore, this study aimed to: (1) investigate the incremental yield of new AF identified through annual screening repeated over a 4-year period; (2) determine the stroke risk of new AF cases identified through screening and (3) determine the estimated prevalence of AF in Toyama prefecture, Japan.

METHODS

This retrospective cohort study examined data from annual health examinations performed in Toyama prefecture by the Hokuriku Health Service Association between 2012 and 2017.

Annual health examination

Hokuriku Health Service Association in Toyama prefecture performs annual health examinations on approximately 150 000 workers and their families each year. The annual health examination includes a 12-lead ECG, chest X-ray, blood pressure measurement, body mass index, blood sugar, HbA1c (hemoglobin A1c), cholesterol (total cholesterol, low density lipoprotein, triglyceride, high density lipoprotein), uric acid, liver enzyme (aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transpeptidase), renal function (blood urea nitrogen, creatinine), urinalysis and testing for blood cell count and blood chemistry. The examination also comprises a self-reported health questionnaire which includes information on the previous history of stroke, diabetes mellitus, hypertension, myocardial infarction, angina pectoris and arrhythmia.

Hypertension was diagnosed if peripheral blood pressure was ≥140/90 mm Hg,[9] or if the health questionnaire indicated current treatment for hypertension. Diabetes was diagnosed using HbA1c ≥6.5% (National Glycohemoglobin Standardization Program), a fasting blood glucose concentration of ≥126 mg/dL, or a random blood glucose concentration of ≥200 mg/dL,[10] or if the health questionnaire indicated current treatment for diabetes. AF was diagnosed from the 12-lead ECG by a trained cardiology doctor in Hokuriku Health Service Association: AF (Minnesota Codes 8-3-1 and 8-3-3) or atrial flutter (Minnesota Codes 8-3-2 and 8-3-4). AF symptoms were determined from information contained in the health questionnaire. AF symptoms were classified into typical symptoms (palpitations or erratic pulse), atypical symptoms (dizziness, orthostatic dizziness, dyspnoea and chest pain) or asymptomatic (ie, no symptoms).

Study subjects

Data were retrieved from electronic records for all 141 441 people who attended for a health examination in 2014: a 12-lead ECG was performed in 110 792 of the examinations. Only people aged ≥20 years, and with a prior ECG recorded in 2012 or 2013, were deemed eligible; therefore, the baseline sample consisted of 88 218 subjects (figure 1). Study subjects with AF diagnosed on ECG in either 2012 or 2013 were considered to have 'known AF', which is likely to be mainly permanent and persistent forms of AF. All subjects without known AF were followed up over 4 years, from 2014 until 2017, with consecutive health examinations, including an annual ECG. The annual incidence (cases per 100 person-years) of new-onset AF was calculated for each year (2014–2017) and stratified according to gender and age groups.

Modified CHA$_2$DS$_2$-VASc score

An estimation of stroke risk (ie, modified CHA$_2$DS$_2$-VASc score) was calculated without points for heart failure or peripheral artery disease, as health examination data were not available for the presence of either of these co-morbidities (CHA$_2$DS$_2$VASc = C: congestive heart
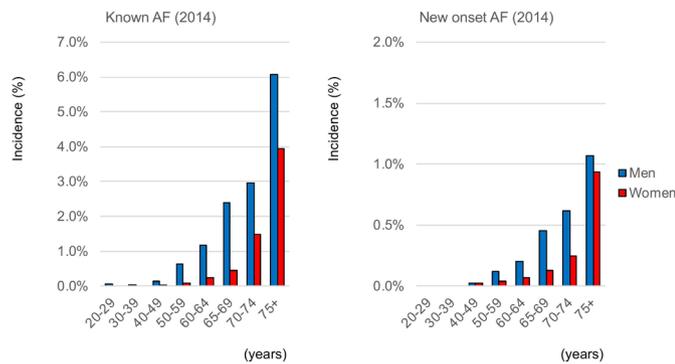
Figure 2 Yield of known and new-onset AF stratified by age and gender. AF, atrial fibrillation.

Table 1	Characteristics of eligible cohort in 2014
Characteristics	**Cohort (n=88 218)**
Age, years, mean±SD	46.8±12.5
Age 65–74 years, n (%)	5874 (6.7)
Age 75 and over years, n (%)	814 (0.9)
Gender, men, n (%)	56 781 (64)
Co-morbidities	
Hypertension	10 771 (12)
Diabetes mellitus	3597 (4.1)
Previous cerebrovascular disease	1029 (1.2)
Myocardial infarction	335 (0.4)
Angina pectoris	541 (0.6)

failure [1 point]; H: hypertension [1 point]; A2: age 65-74 years [1 point] or age ≥75 years [2 points]; D: diabetes mellitus [1 point]; S: prior stroke or transientischemic attack [2points]; VA: vascular disease [1 point]; and Sc: sex category [female] [1 point]). The modified CHA_2DS_2-VASc score was calculated for known AF using 2014 data and for new AF using data from the year of detection. Subjects were categorised according to guideline recommendations for oral anticoagulation (OAC): 'no OAC recommendation' (modified CHA_2DS_2-VASc score: 0 men, 1 women); 'consider OAC' (modified CHA_2DS_2-VASc score: 1 men, 2 women) or 'class-1 OAC recommendation' (modified CHA_2DS_2-VASc score: ≥2 men, ≥3 women).[6]

Prevalence of AF in Toyama prefecture

The estimated prevalence of AF, in the Toyama prefecture, was calculated using the rates of known and new AF detected in our study in 2014 and assuming that the rate is constant. These rates were extrapolated to the 2014 Toyama population data sourced from the Toyama prefectural government.[11] The data were stratified according to age and gender-specific prevalence, using age-stratified and gender-stratified results from our study (online supplementary 1) and the 2014 Toyama population data.[11]

Statistical analysis

Continuous variables are presented as mean±SD and categorical variables as numbers and percentages. The yield of known AF and new AF detected through screening are presented as rates (ie, cases per 100 person-years) with accompanying binomial 95% CI calculated using Clopper-Pearson methodology. AF detection rates were stratified according to age groups and gender. Estimated AF prevalence rates are also presented as rates (cases per 100 person-years). Logistic regression, linear regression and Pearsons χ^2 test were used to assess time trends for the yield of new AF detected each year. Data were collected and analysed by the Statistical Package for Social Sciences software (IBM SPSS Statistics V.25).

Patient and public involvement

There were no funds or time allocated for patient and public inolvement so we were unable to involve patients. We have invited patients to help us develop our dissemination strategy.

RESULTS

The eligible cohort included 88 218 people, ranging in age from 20 to 109 years (mean age 46.8±12.5 years), of which 92% were <65 years old and 64% were male (table 1, online supplementary 2). Table 1 outlines the characteristics of the eligible cohort. In 2014, the rate of known AF was 0.39% (95% CI 0.35% to 0.44%) (n=346), mean age 62.9±11.4 years (range 22–103 years) (figure 2, online supplementary 1). The sex-specific rate of known AF was 0.52% (95% CI 0.46% to 0.58%) in men and 0.16% (95% CI 0.12% to 0.21%) in women. From the 2014 ECG, new-onset AF was identified in 0.08% (95% CI 0.06% to 0.10%) (n=69), mean age 64.0±12.6 years (range 43–109 years) (figure 2, online supplementary 1). The sex-specific incidence rate of new-onset AF was 0.10% (95% CI 0.07% to 0.12%) in men and 0.05% (95% CI 0.03% to 0.08%) in women. The rate of both known and new onset AF increased with age and was higher in men than women. From the 6688 subjects aged 65 years and over in 2014, there were 149 known AF cases (2.23%, 95% CI 1.89% to 2.61%) and 30 new-onset AF cases (0.45%, 95% CI 0.30% to 0.64%).

For the 2014 cohort with known AF, 51% (175/346 cases) had hypertension for which 77% were on medication and 22% (77/346 cases) had diabetes for which 56% were on medication. In those with new-onset AF in 2014, hypertension was present in 45% (31/69 cases) with 77% on medication and diabetes was present in 16% (11/69 cases) for which 45% were taking medication.

Incremental yield of annual screening

The incremental yield of new-onset AF identified through repeat annual ECG screening of the same cohort with no prior history of AF is outlined in figure 1. Of the 88 218 people screened in 2014, 73 977 were screened again in
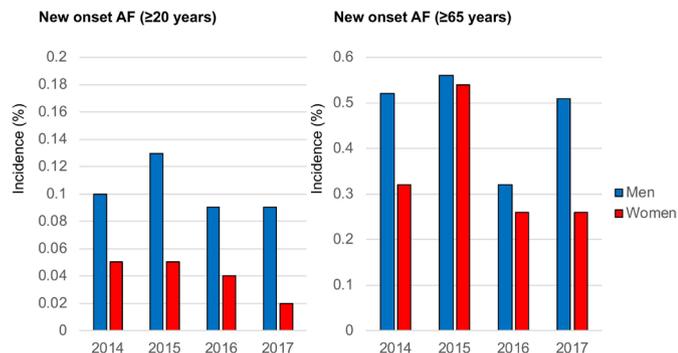
Figure 3 Incidence of new-onset AF detected each year from 2014 to 2017. AF, atrial fibrillation.

2015; 64827 had repeat screens in both 2015 and 2016 and 57595 had repeat screens in 2015, 2016 and 2017. Therefore, the follow-up rate for all 4 years was 65% of the baseline population.

Yield of new AF did not appear to decline with each consecutive year of screening from 2014 to 2017 (0.08% (95% CI 0.06% to 0.10%), 0.10% (95% CI 0.08% to 0.13%), 0.08% (95% CI 0.06% to 0.10%) and 0.06% (95% CI 0.04% to 0.09%) in each year, respectively) (online supplementary 3). The incremental yield was notably and consistently higher in men than women (figure 3). The mean incidence rates of new-onset AF over the 4 years were 0.10% in men and 0.04% in women.

When focusing the results to subjects aged 65 years and over, in line with guideline recommendations for AF screening, the screening yield was higher than that for the general population. The incidence rate remained relatively constant over the four consecutive years of screening and was 0.45% (95% CI 0.30% to 0.64%), 0.55% (95% CI 0.36% to 0.80%), 0.33% (95% CI 0.18% to 0.57%) and 0.42% (95% CI 0.22% to 0.71%), respectively, with no noticeable decline over time (online supplementary 3). Overall, there was a higher yield for men than women despite a reduction in the incidence rate for men in the
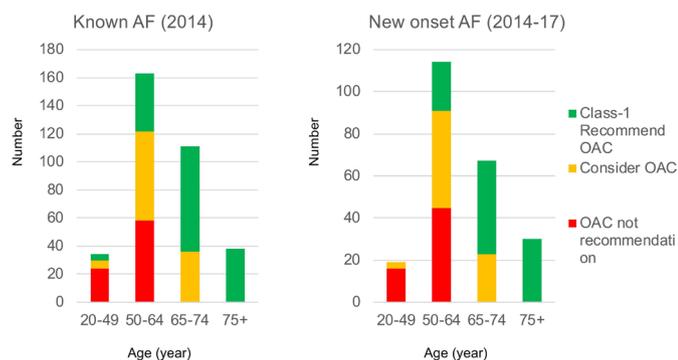

Figure 4 Oral-anticoagulation recommendations. AF, atrial fibrillation; OAC, oral-anticoagulation therapy. Note. Modified CHA_2DS_2-VASc scores are likely an underestimation as scores were calculated from health examination data, which did not include information on heart failure or peripheral artery disease.

third year of screening (figure 3). The mean incidence rates were 0.48% in men and 0.37% in women.

In total, 230 cases of new-onset AF were identified over the 4 years. Most of these cases were asymptomatic 73% (n=167). Typical symptoms were reported by only 20% (n=45) and atypical symptoms were reported by 8% (n=18).

Stroke risk and oral anticoagulation eligibility
As anticipated, mean modified CHA_2DS_2-VASc scores increased with age, reaching 4.1±1.5 for known AF and 3.7±1.2 for new AF in those aged ≥75 years (online supplementary 4). Almost half (n=255, 44%) of all AF cases had a class-1 recommendation for OAC: 46% (n=158) of known AF and 42% (n=97) of new-onset AF (figure 4). When considering only subjects ≥65 years (n=246), the number with a class-1 OAC recommendation rose significantly to 76% (n=187) of the population: 76% (113/149) of known AF and 76% (74/97) of new-onset AF (figure 4).

Estimated AF prevalence in Toyama prefecture
The number of people with known AF in Toyama prefecture in 2014 was estimated to be 11212 (6351 men, 4861 women), based on the age-specific and sex-specific rates of known and new AF in the study cohort in 2014, and assuming that the rate is constant (online supplementary 5). This equates to an overall AF prevalence of 1.53% for adults ≥20 years old in the Toyama prefecture: 1.79% prevalence for men and 1.30% prevalence for women. As expected, numbers of known AF increase with increasing age in both men and women. Each year, there is likely to be an additional 2318 new cases of AF (1165 men, 1154 women). Due to the large population of women over 75 years in Toyama prefecture, almost half of all new AF cases are likely to be women aged ≥75 years, who all have a class-1 OAC recommendation.

DISCUSSION
To our knowledge, this is the first study to report the incremental yield of new AF identified from repeating screening each year in a population without prior AF. Our study in Toyama prefecture, Japan, identified that the yield of new AF ranged between 0.06% and 0.1% each year (for the cohort ≥20 years), and did not appear to decline over time during the 4-year follow-up period. When limiting the results to subjects aged 65 years and over, as per guideline recommendations for AF screening, the annual yield of new AF ranged between 0.33% and 0.55% each year, and again, did not appear to decline over the 4-year period. Across all age groups, the incremental yield of new AF was greater in men than in women, in keeping with the higher prevalence in men than women. It is important to note that 80% of the new AF cases aged 65 years and over had a sufficient stroke risk to receive a class-1 recommendation for OAC. This is likely an underestimation of the actual number eligible for OAC as we were unable to assign points to the CHA_2DS_2-VASc scores

for heart failure or peripheral artery disease due to the absence of these data. The high proportion of treatable AF indicates that the annual screen-detected AF is of great clinical relevance and, with appropriate antithrombotic therapy, would be expected to reduce cardioembolic stroke due to unknown AF.

It is well established that significant racial differences exist, and rates of AF in Japan are much lower across all age groups, compared with representative data reported from Western countries.[12 13] It is therefore not surprising that the incidence rate of new AF for people aged ≥65 years is also lower in our study (~0.45%/year) than the rate of 1.4% in Western Countries, identified in a systematic review of screening.[14] It is thought that lower AF rates in Japan may be related to overall lower incidences of cardio-metabolic and other risk factors for AF, but over the next few decades, AF prevalence may increase with a gradual increase in lifestyle-related cardio-metabolic risk factors.[12 13] Therefore, the incidence of new AF in Japan may escalate in the future and will benefit from early detection. However, it is likely that many cases would not be detected without annual screening, as the majority (~73%) of our new AF cases were asymptomatic. This high rate of asymptomatic AF is well documented across many countries, supporting the need to screen.[15] An American study interrogating pacemaker data has shown that palpitations occur in only 30% of all AF episodes, and a study using data from the Fushimi AF registry, Japan, has also reported that 50.3% patients with AF were asymptomtic.[16]

As annual health checks, including an ECG, are available to all residents, early detection of new-onset AF should be possible on a population-wide level in Japan. Annual health checks are comparable in some ways to systematic screening due to their organised nature; however, it also differs from systematic AF screening as it is not targeted at the desired age-group ≥65 years, testing is not focused on detecting AF, and it lacks a clear and established treatment/management pathway should AF be detected. Nonetheless, as detection rates are known to be the same for both opportunistic and systematic screening,[17] it is likely that our results could be valid for both methods.

The constant yield identified each year through screening is important in terms of guiding screening recommendations and indicates repeating screening on an annual basis may be viable, at least over 4 years. Data from our study can be used to inform and model cost-effectiveness analyses of repeating single-timepoint ECG screening annually. However, the likely costs and potential benefits of repeating screening each year will need to be individually assessed for each setting in relation to the prevalence of AF in the local population and the method of screening, especially in countries where annual health checks (including 12-lead ECG) are not an established practice. Many studies have demonstrated the cost-effectiveness of AF single-timepoint screening in various settings, including general practice and community in Western countries.[17–21] In Japan, both annual ECG screening and annual pulse palpation screening programmes have been deemed to be cost-effective for stroke prevention, when calculated using a Markov modelling programme, regardless of the lower incidence of new AF in Japanese people.[22]

In our study, the rate of known AF (0.39%) was lower than the rates reported in earlier studies in Japan, whose cohorts had very different characteristics. Our study subjects were younger (age ≥20 years; mean 47 years) than other studies; and the majority of subjects were healthy workers and their families. A study of registry data in 2009 identified a higher AF prevalence rate of 0.56% using health examinations from a mixture of company clinics, health centres and local governments in Japan, in adults aged ≥40 years, with the majority (73%) of the cohort aged 50 years and over.[23] In a second study using annual health examination data of non-employee residents in local government, the AF prevalence rate was higher again at 1.6% for adults aged ≥40 years (mean age ~72±10 years).[24] As local governments provide annual health examinations for retired workers (retirement occurs at ~60–65 years of age) and those unable to work, studies using local government health examinations are likely to have a more elderly or unwell population than our study. However, when considering just the population over 65 years, our data suggest an overall AF prevalence (known plus new AF) of ~2.7% which is in line with rates from other Japanese studies reporting a prevalence of 1.0%–1.5% for ages 60–69 years; 2.9% for age 70+ years and 3.2% for age 80+ years.[23–25]

Our data indicate that there will be 2318 new cases of AF in Toyama prefecture each year, and 40% will have a high risk of stroke and a guideline recommendation for OAC. In current practice, OAC prescription is low: the reported OAC prescription rate from the Fushimi AF Registry was 55% despite a mean CHA_2DS_2-VASc score of 3.4,[26] and the Shinken Database reported OAC prescription rates of 46%.[5] Furthermore, analysis of the J-Rhythm registry, Fushimi AF registry, and the Shinken database identified a high rate of stroke (18.4 per 1000 person-years) in AF patients with a CHA_2DS_2-VASc score ≥2 not receiving OAC.[27] In a retrospective study of Danish patients with AF, 39% received antiplatelet therapy alone, and 25% patients with AF did not receive any antithrombotic therapy before the stroke.[28] It is, therefore, vital that guideline-based OAC prescription is improved. To compound this issue, there is no current defined pathway for medical review if new AF is identified through annual health checks in Japan. Therefore, there is a need to establish viable treatment pathways for those identified with new AF, to ensure appropriate access to medical review and evidence-based OAC treatment to prevent stroke.

Limitations

Although our analysis was based on 88 218 people screened, the distribution of the sample was skewed towards a younger demographic with a mean age of 47 years, and the primary age of interest in AF screening is

generally ≥65 years. However, it is important to note that our data contains ~6600 people over 65 years, and there are few other screening studies who have managed to screen more than 4000 people over the age of 65 years.[4] As a single ECG screen was performed each year, it is likely that some people with paroxysmal AF may not have been identified, and those who were identified most likely had permanent and persistent forms of AF. Consequently, our baseline sample may contain some people with undetected paroxysmal AF, and it is possible that our results may underestimate the prevalence of AF in the Toyama prefecture. Furthermore, as we did not have data on heart failure and peripheral artery disease in the study dataset, we presented a modified CHA_2DS_2-VASc score. The modified score will likely underestimate the overall stroke risk to a small degree, meaning our results should be considered a conservative estimate of stroke risk. Our data were collected from one site in the Toyama prefecture, Japan, and therefore may not be generalisable to other prefectures in Japan or other countries.

CONCLUSION

Repeating screening on an annual basis seems likely to yield a relatively consistent rate of AF each year, at least over 4 years of follow-up in Japan. Incidence of new AF, and overall AF prevalence, is lower in Japan than Western countries, but the majority of new AF cases identified (aged 65 years and over) have a guideline OAC recommendation for stroke prevention. Annual ECG screening in this population is likely to identify an incremental yield of ~0.08% with unknown AF, equating to 2318 new cases annually in Toyama prefecture, Japan. It is important to have a viable treatment pathway in place for these newly identified AF cases, to ensure appropriate access to medical review and evidence-based OAC treatment to prevent stroke. The potential application of annual AF screening to other countries where systematic annual health screening, including an ECG, is not established practice would need careful examination in relation to likely cost and potential benefit.

Data availability statement Data may be obtained from a third party and are not publicly available.

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