

ORIGINAL RESEARCH ARTICLE



Screening-Detected Atrial Fibrillation and Cardiovascular Outcomes in Working-Age Adults

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BACKGROUND: Early detection of atrial fibrillation (AF) is essential for preventing ischemic stroke and other cardiovascular complications. However, the incidence and prognosis of AF in the general middle-aged population remain unclear. In Japan, annual health screenings for employees include mandatory ECGs, offering a unique opportunity to fill this evidence gap.

METHODS: This retrospective cohort study aimed to evaluate the incidence and subsequent cardiovascular outcomes of screening-detected AF in the general working population in Japan, using the Japan Health Insurance Association database, which covers one-quarter of the working-age population of the country. From individuals 35 to 59 years of age who underwent annual health screenings between April 2015 and March 2020, excluding those with a history of cardiovascular disease, those with initial AF detection upon screening ECGs were identified. The primary outcome was hospitalization for ischemic stroke. The secondary outcomes were all-cause death and hospitalization for heart failure. The association between screening-detected AF and outcomes was evaluated using adjusted subdistribution hazard models compared with matched controls.

RESULTS: Among 9.5 million individuals included in our study, 11 790 initial AF cases (42.4 of 100 000 person-years [95% CI, 41.6–43.1]) were detected. Individuals with AF were older (mean age, 50.9 versus 46.3 years) and more likely to be men (91.6% versus 63.6%) compared with non-AF cases. Among these individuals with screening-detected AF, the 3-year incidences of ischemic stroke, all-cause death, and heart failure were 1.83% (95% CI, 1.57–2.09), 0.78% (95% CI, 0.61–0.95), and 3.87% (95% CI, 3.50–4.24), respectively. Compared with age- and sex-matched controls, individuals with AF had a higher risk of incident ischemic stroke (hazard ratio, 5.38 [95% CI, 4.51–6.42]), all-cause death (hazard ratio, 1.98 [95% CI, 1.66–2.36]), and heart failure (hazard ratio, 18.35 [95% CI, 15.10–22.31]).

CONCLUSIONS: AF was detected in 1 of every 2400 screening ECGs among the middle-aged population in Japan, with higher relative risks of ischemic stroke and heart failure, compared with those without AF. These findings highlight the association of screening-detected AF with stroke and heart failure, warranting further study into AF as an early sign of heart failure and optimal cardiovascular risk reduction strategies after AF detection in the general middle-aged population.

Key Words: atrial fibrillation ■ heart failure ■ middle age ■ screening ■ stroke

Atrial fibrillation (AF) significantly increases the risk of stroke and other cardiovascular complications, leading to substantial morbidity and mortality.¹ Although symptomatic AF typically prompts patients to seek clinical evaluation and diag-

nosis, individuals with milder or no symptoms often remain undetected. Undetected AF is estimated to contribute to 10% to 20% of ischemic stroke cases² and also increases the risk for other cardiovascular complications.³

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Clinical Perspective

What Is New?

- Among adults 35 to 59 years of age, 11 790 cases of atrial fibrillation (AF) were newly detected among 27.8 million screening ECGs (1 of every 2400 ECGs).
- Screening-detected AF was associated with a 5-fold higher risk of incident stroke (1.83% in 3 years) and an 18-fold higher risk of heart failure (3.87% in 3 years).

What Are the Clinical Implications?

- Although individuals with screening-detected AF have a lower absolute risk compared with older cohorts, they face a significantly higher risk of ischemic stroke and heart failure compared with their peers without AF.
- Early identification of AF may allow for timely intervention and closer monitoring to prevent adverse cardiovascular outcomes, including heart failure.

Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
aHR	adjusted hazard ratio
BNP	B-type natriuretic peptide
BP	blood pressure
ICD-10	<i>International Classification of Diseases, Tenth Revision</i>
JHIA	Japan Health Insurance Association
LDL-C	low-density lipoprotein cholesterol

The latest US Preventive Services Task Force recommendation⁴ does not support ECG screening for AF in the general population, primarily because of insufficient evidence to support its adoption or rejection. Moreover, although recent advancements in arrhythmia detection technologies, such as wearable devices, have made detection more accessible compared with previous eras, existing evidence is primarily derived from older populations.^{5–8} This highlights the paucity of large-scale studies on AF incidence in younger, working-age populations, in which undetected cases may result in significant clinical and societal consequences.

The Japanese health screening program offers a unique opportunity to address this knowledge gap. All public health insurers in Japan are required to provide annual health screenings to all working-age individuals,⁹ including a 12-lead ECG for middle-aged and older adults. The Japan Health Insurance Association (JHIA), the largest public health insurer covering >30 million working adults, representing more than a quarter of the working-age population, provides annual ECGs for adults ≥35 years of age as part of their health screenings.¹⁰ The JHIA annual health screening database, integrated with

claims records, enables the study of ECG abnormalities, particularly the incident detection of AF cases and their clinical outcomes.

Accordingly, leveraging the JHIA data from 2015 to 2023, we aimed to: (1) estimate the incidence of screening-detected AF in the general working-age population of Japan, (2) evaluate the 3-year incidence of cardiovascular outcomes after AF detection, and (3) compare the risk of these outcomes with age- and sex-matched individuals without AF.

METHODS

Data Availability, Study Design, and Setting

The institutional review board of Kyoto University approved all study procedures and waived informed consent from individuals because all data used in this study were anonymized by JHIA. A minimum subset of the data necessary for replicating statistical analysis can be shared upon reasonable request to the corresponding author and approval of the data provider. Statistical code is available from the corresponding author upon reasonable request. The present study was conducted in accordance with the Declaration of Helsinki¹¹ and followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines¹² (Table S1).

The insurance system in Japan operates as a universal, mandatory framework that guarantees equitable, affordable, and comprehensive health care access to all residents, regardless of their income level, employment status, or social background. Established in 1961, it is characterized by a combination of public and private insurance system, primarily divided into employee health insurance, which covers employed working-age individuals, and National Health Insurance, which covers the self-employed and elderly population.¹³ JHIA is a pivotal entity within the Employee Health Insurance framework. Established in 2008 after revisions to the Health Insurance Act, JHIA took over the government-managed health insurance system, enhancing efficiency and responsiveness to the needs of insured individuals.¹⁴ JHIA is the largest public health insurer in the country, covering more than a quarter of the working-age population.

This retrospective cohort study used insurance claims, death certificates, and health screening records from the JHIA between April 1, 2015, and March 31, 2023. In JHIA, health screenings were provided with full subsidization to insured members, and the screening included physical examination, laboratory testing, and 12-lead ECGs. The list of the *International Classification of Diseases, Tenth Revision (ICD-10)* codes used to define each variable is presented in Table S2.

Study Population

In this study, we collected data from all health screening records of the insured members of JHIA 35 to 59 years of age that occurred between April 1, 2015, and March 31, 2020. We defined the lookback period for past medical histories from the date of insurance enrollment up to the health screening date. The *ICD-10* codes to ascertain past medical histories were available from insurance enrollment, even before April 1, 2015. For each annual cycle (from April 1 to March 31), we applied the following exclusion criteria to ensure a sufficient lookback

period and restrict participants to individuals without previous cardiovascular comorbidities:

1. Insured through JHIA for <365 days at the time of index ECG screening.
2. Evidence of AF before the ECG screening date, indicated either through insurance claims (*ICD-10*: I48) or health screening record (Minnesota code 8-3-1 or 8-3-3).
3. History of cardiac disease (*ICD-10*: B332, I01, I020, I05-I09, I20-I52, or Q24), cerebrovascular disease (*ICD-10*: I60-69), or peripheral vascular disease (*ICD-10*: K551, K558, K559, I70, I71, I731, I738, I739, I771, I790, I792, Z958, or Z959).
4. Previous insurance claims of dialysis.

Among eligible individuals, those with screening-detected AF were identified based on the annual health screening records. As a comparator group, individuals without AF, defined as those with no record of screening-detected AF throughout the inclusion period, were randomly selected in a chronological order without replacement for each individual with screening-detected AF at a 1:5 ratio using exact matching on sex and single-year age within the same screening year. The matching ratio was determined to maintain statistical precision¹⁵ and computational efficiency. Matching variables were simplified to basic demographic characteristics to understand what the outcomes are after AF detection compared with the general population.

ECG Analysis in the Annual Health Screening

A resting 12-lead ECG was performed at each health screening site using a regulatory-approved ECG machine. Initial interpretation was automatically conducted by the ECG machine based on the Minnesota Code Classification (AF: Minnesota code 8-3-1 or 8-3-3) and subsequently verified by at least one physician¹⁰ in accordance with the Japanese guideline.¹⁶

Outcomes and Follow-Up

The primary outcome of interest was fatal or nonfatal hospitalizations for ischemic stroke (*ICD-10*: I63),¹⁷ with secondary outcomes including all-cause death, and fatal or nonfatal hospitalizations for heart failure (*ICD-10*: I50, I110, I130, or I132).¹⁷ Participants were followed until March 31, 2023, the occurrence of an outcome event, or discontinuation of JHIA coverage, whichever came first (ie, retirement or change of employment).

Covariates

Baseline characteristics for age, sex at birth, body mass index, systolic blood pressure (BP), diastolic BP, directly measured serum LDL-C (low-density lipoprotein cholesterol), serum creatinine, and current smoking status were collected from the health screening records. Blood pressure (BP) measurements took place during a single health screening visit. A health technician used a validated oscillometric device to take 2 consecutive BP measurements, and the mean of these measurements was recorded as the participant's BP.¹⁸ Blood samples were immediately centrifuged at each health screening site and analyzed within 24 hours of collection. Smoking status was self-reported, with current smoking defined as having smoked within the past month, having a smoking duration of >6 months, and having consumed >100 cigarettes in their lifetime.¹⁹ The

Japanese estimated glomerular filtration rate estimation formula²⁰ was used to calculate estimated glomerular filtration rate following the local society guideline.²¹ In addition, the CHA₂DS₂-VASc and CHADS₂ scores were calculated for each participant. Further, information on a history of hypertension (*ICD-10*: I11-I15),²² diabetes (*ICD-10*: E10-E14),²² and dyslipidemia (*ICD-10*: E780-E785)²³ was collected from the JHIA database.

Statistical Analysis

The incidence rate of screening-detected AF was calculated by dividing the number of screening-detected AF cases by the total number of health screening records (cases per person-years). The 95% CI was estimated using the Clopper-Pearson exact method.²⁴ The 1-year and 3-year cumulative incidence of each outcomes after AF detection were estimated using the Aalen-Johansen estimator,²⁵ accounting for competing risk of death, or the Kaplan-Meier method for all-cause death events. Unadjusted cumulative incidence curves accounting for competing risk of death were described for those with screening-detected AF and matched non-AF individuals. Adjusted hazard ratios (aHRs) between these groups were estimated by fitting Fine-Gray subdistribution hazard models, which also accounted for competing risk of death (or Cox proportional hazard model for all-cause death events). These models adjusted for age, sex, body mass index, LDL-C, estimated glomerular filtration rate, smoking status, and histories of hypertension, diabetes, and dyslipidemia at baseline. Unadjusted hazard ratios were also estimated for comparison. Missing covariate data were imputed using a random forest imputation method²⁶ based on the same set of covariates. Subgroup analyses were conducted for age (<50 years versus ≥50 years), body mass index (<25 kg/m² versus ≥25 kg/m²), systolic BP (<140 versus ≥140 mm Hg), LDL-C levels (<100 mg/dL versus ≥100 mg/dL), estimated glomerular filtration rate (<60 mL versus ≥60·min⁻¹·1.73 m⁻²), and CHA₂DS₂-VASc score (lowest [0 for men versus 1 for women] or above). These cutoffs were determined based on clinical relevance. As a sensitivity analysis, we evaluated the aHRs using a complete-case approach, excluding individuals with missing covariates.

All tests were 2-tailed, and *P*<0.05 was considered statistically significant. All statistical analyses were conducted using R, version 4.3.1 (R Project for Statistical Computing). Survival analyses accounting for competing risk were conducted using the package "cmprsk."²⁷

RESULTS

Among 20969945 unique individuals aged 35 to 59 during the study period, 11 679 560 (55.7%) individuals attended at least one annual health screening between April 2015 and March 2020, contributing to a total of 33 928 053 person-years of health screening records. Of these, 27 832 305 screening records from 9 482 225 individuals remained after applying our selection criteria, and screening-detected AF was found among 11 790 individuals or 42.4 cases per 100 000 person-years (95% CI, 41.6–43.1; Figure 1). The incidence rate was higher in men (60.9 cases per 100 000 person-years [95% CI, 59.8–62.1]) than in women (9.8

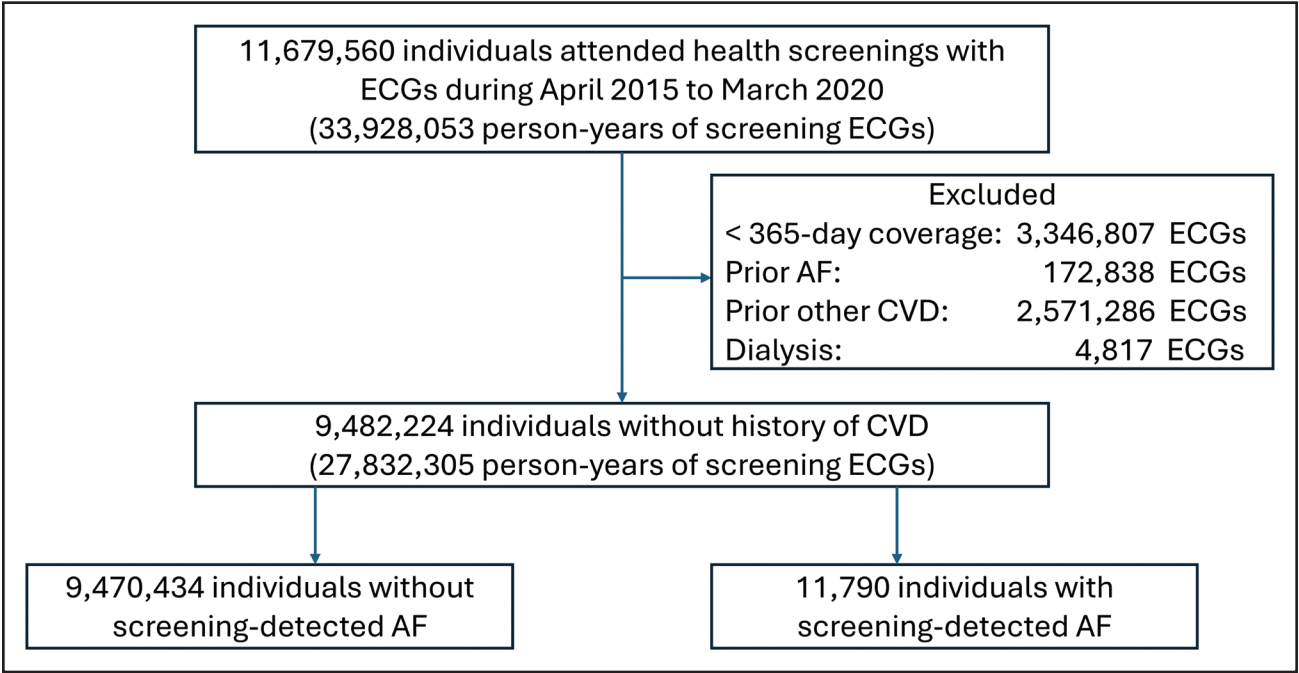


Figure 1. Patient selection.
AF indicates atrial fibrillation; and CVD, cardiovascular disease.

cases per 100 000 person-years [95% CI, 9.2–10.4]) and increased with older age. (Figure 2). Further, the 11 790 individuals with AF were matched to 58 950 individuals without AF to compare the incidences of the 3 outcomes of interest. Of these 70 740 individuals, 99 individuals (0.14%) had missing covariate data (Table S3).

Individuals with screening-detected AF showed a mean (SD) age of 50.9 (6.4) years, of whom 990 (8.4%) were women, 2271 (19.3%) had hypertension, and 222 (1.9%) had diabetes at the time of AF detection. The mean (SD) CHA₂DS₂-VASc score was 0.30 (0.51) points, with 0 points in 8593 (72.9%), 1 point in 2917 (24.7%), 2 points in

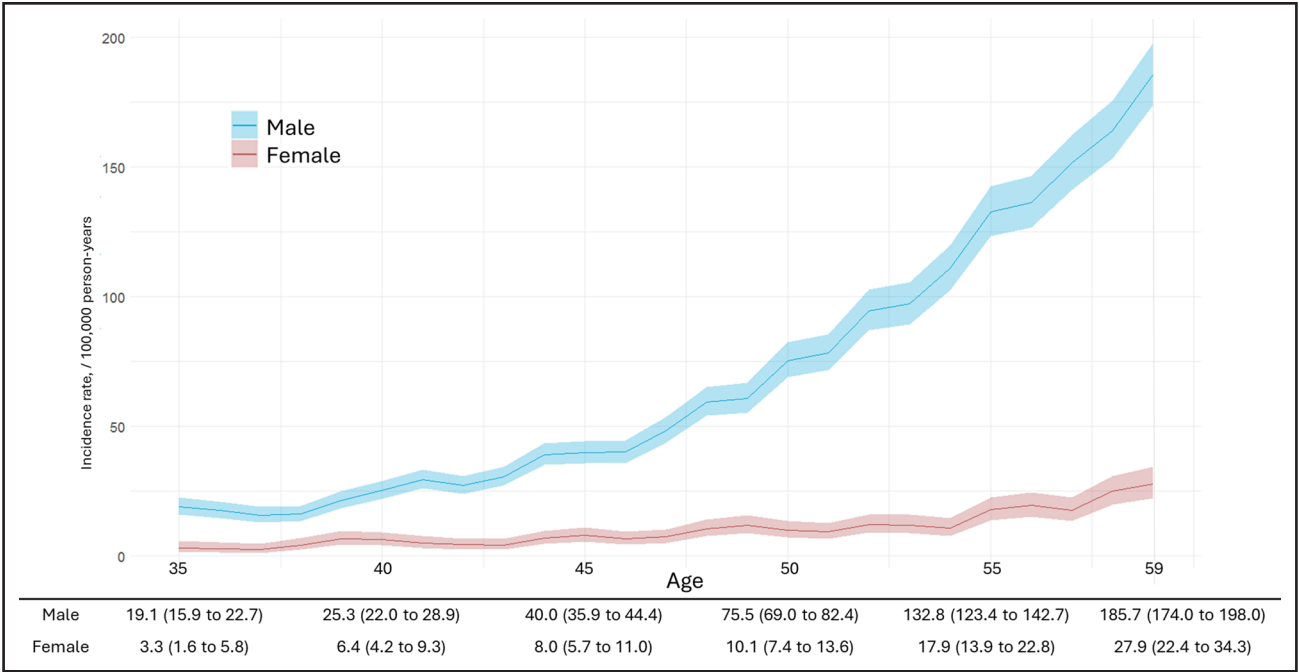


Figure 2. Incidence rate of screening-detected AF by age and sex.
In each age and sex stratum, the incidence rate of screening-detected atrial fibrillation per 100 000 person-years was separately estimated by dividing the number of screening-detected AF cases by the total number of health screening records. The 95% CI (indicated in the parentheses) was estimated using the Clopper-Pearson exact method. AF indicates atrial fibrillation.

Table 1. Baseline Characteristics before and after Age and Sex Matching

	Before matching		ASMD	After matching		ASMD
	Non-AF	AF		Non-AF	AF	
Variable	n=27 808 117	n=11 790		n=58 950	n=11 790	
Age, y	46.33 (6.83)	50.94 (6.38)	0.698	50.94 (6.38)	50.94 (6.38)	<0.001
35–39	5 411 392 (19.5)	729 (6.2)		3645 (6.2)	729 (6.2)	
40–49	12 923 822 (46.5)	3621 (30.7)		18 105 (30.7)	3621 (30.7)	
50–59	9 472 903 (34.1)	7440 (63.1)		37 200 (63.1)	7440 (63.1)	
Women	10 106 100 (36.3)	990 (8.4)	0.712	4950 (8.4)	990 (8.4)	<0.001
BMI, kg/m ²	23.44 (3.96)	25.07 (4.59)	0.382	23.86 (3.60)	25.07 (4.59)	0.294
Missing	1934 (0.0)	1 (0.0)		7 (0.0)	1 (0.0)	
SBP, mm Hg	121.27 (16.87)	123.55 (17.53)	0.132	125.82 (17.33)	123.55 (17.53)	0.130
Missing	931 (0.0)	1 (0.0)		2 (0.0)	1 (0.0)	
DBP, mm Hg	75.78 (12.42)	80.50 (13.65)	0.362	79.39 (12.19)	80.50 (13.65)	0.086
Missing	1062 (0.0)	1 (0.0)		3 (0.0)	1 (0.0)	
LDL-C, mg/dL	124.01 (32.19)	121.56 (34.08)	0.074	126.51 (32.28)	121.56 (34.08)	0.149
Missing	11 966 (0.0)	7 (0.1)		22 (0.0)	7 (0.1)	
eGFR, mL·min ⁻¹ ·1.73 m ⁻²	80.66 (14.07)	76.46 (18.21)	0.556	78.14 (13.70)	76.46 (18.21)	0.104
Missing	30 492 (0.1)	13 (0.1)		70 (0.1)	13 (0.1)	
Current smoking	9 967 523 (35.8)	5079 (43.1)	0.149	25 182 (42.7)	5079 (43.1)	0.007
Missing	670 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Hypertension	3 014 104 (10.8)	2271 (19.3)	0.237	10 151 (17.2)	2271 (19.3)	0.053
Diabetes	345 215 (1.2)	222 (1.9)	0.052	1077 (1.8)	222 (1.9)	0.004
Dyslipidemia	3 582 548 (12.9)	1697 (14.4)	0.044	9857 (16.7)	1697 (14.4)	0.064
CHA ₂ DS ₂ VASc score	0.48 (0.57)	0.30 (0.51)	0.369	0.26 (0.49)	0.30 (0.51)	0.043
0	15 424 952 (55.5)	8593 (72.9)		43 938 (74.5)	8593 (72.9)	
1	11 332 519 (40.8)	2917 (24.7)		13 865 (23.5)	2917 (24.7)	
2	1 019 038 (3.7)	274 (2.3)		1 128 (1.9)	274 (2.3)	
3	31 608 (0.1)	6 (0.1)		19 (0.0)	6 (0.1)	
CHADS ₂ score	0.12 (0.34)	0.21 (0.43)	0.236	0.19 (0.42)	0.21 (0.43)	0.050
0	24 608 467 (88.5)	9429 (80.0)		48 280 (81.9)	9429 (80.0)	
1	3 039 981 (10.9)	2229 (18.9)		10 112 (17.2)	2229 (18.9)	
2	159 669 (0.6)	132 (1.1)		558 (0.9)	132 (1.1)	

Values were presented in mean (SD) or n (%). The maximum values of the CHA₂DS₂VASc score and CHADS₂ score in our study cohort were 3 and 2 (theoretically, 9 and 6), respectively, because of the eligibility criteria of the study that restricted the study cohort to middle-aged individuals without cardiovascular comorbidities. The non-AF cases in “before matching” includes the records of same individuals in different screening cycles, and n indicates the total number of screening records. AF indicates atrial fibrillation; ASMD, absolute standardized mean difference; BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; LDL-C, low density lipoprotein cholesterol; and SBP, systolic blood pressure.

274 (2.3%), and 3 points in 6 (0.1%) individuals. Compared with age-, sex-, and year-matched individuals without AF, those with AF had a higher body mass index, lower systolic BP, and lower LDL-C (absolute standardized mean difference >0.1 for all). Other baseline characteristics were comparable between groups (Table 1). When stratified by sex, women with screening-detected AF presented a higher proportion of current smokers compared with women without AF (Table S4). Baseline characteristics before and after imputation were almost similar (Table S5). Of note, during the first year after initial AF detection, AF-related outpatient visits (health care encounters associated with ICD-10

code I48) occurred in 5738 (48.7%) individuals, anticoagulants (warfarin and direct oral anticoagulants) were prescribed in 4321 (36.7%) individuals, antiarrhythmic agents (agents available in Japan with the Vaughan Williams classifications Ia, Ic, and III: procainamide, quinidine, disopyramide, cibenzoline, pirmenol, pilsicainide, flecainide, propafenone, amiodarone, nifekalant, and sotalol) were prescribed in 1537 (13.0%) individuals, and catheter ablations were performed in 1421 (12.1%) individuals.

The median follow-up duration was 1680 days (interquartile range, 1125–2368 days), with a follow-up rate of 91.0% at 1 year and 76.1% at 3 years after the day

of health screening that led to AF detection. The estimated incidence of ischemic stroke hospitalization after AF detection was 0.74% (95% CI, 0.58%–0.90%) at 1 year and 1.83% (95% CI, 1.57%–2.09%) at 3 years. Over the 3-year follow-up period, the absolute numbers of ischemic stroke hospitalizations were 190 of 11 790 (1.58%) and 163 of 58 950 (0.28%) in individuals with and without screening-detected AF, respectively. On these ischemic stroke hospitalizations, patients with screening-detected AF, compared with those without, exhibited higher proportions of tPA (tissue plasminogen activator) administration (15.8% [30 of 190] versus 4.9% [8 of 163]) and mechanical thrombectomy (11.6% [22 of 190] versus 1.2% [2 of 163]), and a higher 30-day crude mortality rate after the day of stroke admission (3.7% [7 of 190] versus 0.0% [0 of 163]).

The 1- and 3-year incidences of heart failure hospitalization after AF detection were 2.23% (95% CI, 1.96%–2.50%) and 3.87% (95% CI, 3.50%–4.24%), respectively; and the incidences of all-cause death were 0.24% (95% CI, 0.15%–0.33%) and 0.78% (95% CI, 0.61%–0.95%), respectively. In comparison, the 3-year incidences of ischemic stroke, heart failure hospitalization, and all-cause death among individuals without AF were 0.31% (95% CI, 0.26%–0.36%), 0.15% (95% CI, 0.12%–0.19%), and 0.40% (95% CI, 0.35%–0.46%), respectively (Figure 3). Individuals with AF and a low CHA₂DS₂-VASc score (0 for men and 1 for women) experienced fewer ischemic stroke events than those with higher scores (Figure S1).

Detection of AF was associated with a higher risk of incident ischemic stroke (aHR, 5.38; 95% CI, 4.51–6.42; $P<0.001$), all-cause deaths (aHR, 1.98; 95% CI, 1.66–2.36; $P<0.001$), and heart failure (aHR, 18.35; 95% CI, 15.10–22.31; $P<0.001$) compared with those without AF. These associations were consistent in the unadjusted models (Table S6). Subgroup analyses found largely consistent associations (Table 2; Table S7). The sensitivity analysis using a complete-case approach yielded similar results (aHR for ischemic stroke, 5.41; 95% CI, 4.53–6.45; $P<0.001$; aHR for all-cause death, 1.98; 95% CI, 1.66–2.36; $P<0.001$; and aHR for heart failure hospitalization, 18.45; 95% CI, 15.17–22.44; $P<0.001$).

DISCUSSION

In this retrospective cohort study leveraging a representative nationwide public health insurance database in Japan covering more than a quarter of the working-age individuals, screening-detected AF was identified in 1 of every 2400 annual screening ECGs. Approximately 2% of those with screening-detected AF experienced ischemic stroke within 3 years after detection, representing a 5-fold increased risk relative to age- and sex-matched individuals without AF. In addition, those with AF had a 2-fold increased risk of all-cause death and an 18-fold increased risk of hospitalization for heart failure. Our findings suggest that, although the absolute incidence of AF in this young population is low, the downstream

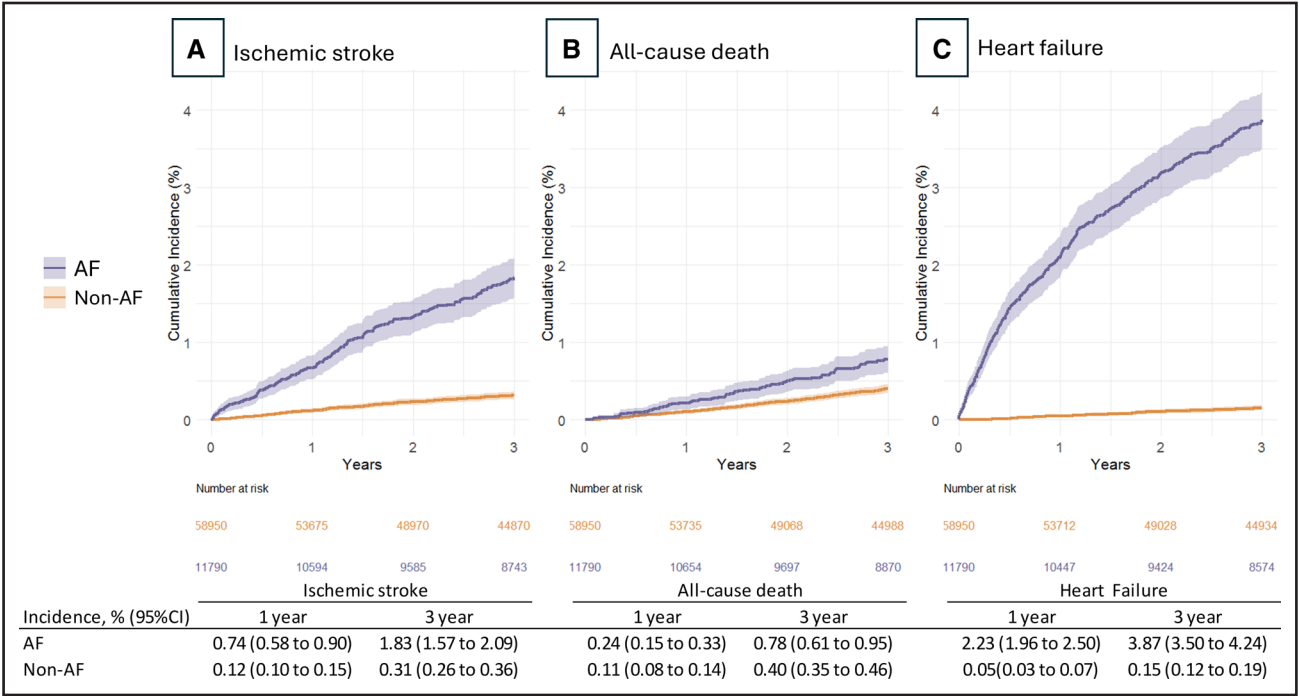


Figure 3. Cumulative incidence of cardiovascular disease events among those with and without screening-detected AF. Unadjusted cumulative incidence curves and 95% CIs for ischemic stroke (A) and heart failure events (C) were estimated based on the Aalen-Johansen estimator, accounting for competing risk of death. The curve for all-cause death (B) was based on the Kaplan-Meier method. AF indicates atrial fibrillation.

Table 2. Subgroup Analysis on the Adjusted Hazard Ratio of Ischemic Stroke Events After AF Detection

Subgroup	n	HR (95% CI)	P value	P for interaction
Overall	70 740	5.38 (4.51–6.42)	<0.001	NA
Age, y				
<50	26 100	7.62 (5.20–11.16)	<0.001	0.066
≥50	44 640	4.90 (4.01–5.98)	<0.001	
Sex				
Men	64 800	5.18 (4.32–6.21)	<0.001	0.080
Women	5940	12.61 (4.94–32.20)	<0.001	
BMI, kg/m ²				
<25	46 265	6.25 (4.94–7.90)	<0.001	0.081
≥25	24 475	4.88 (3.79–6.29)	<0.001	
SBP, mmHg				
<140	57 760	6.25 (5.01–7.70)	<0.001	0.025
≥140	12 980	3.87 (2.87–5.21)	<0.001	
LDL-C, mg/dL				
<100	14 832	6.93 (4.68–10.25)	<0.001	0.150
≥100	55 908	4.91 (4.02–6.01)	<0.001	
eGFR, mL·min ⁻¹ ·1.73 m ⁻²				
<60	5566	4.78 (2.94–7.77)	<0.001	0.660
≥60	65 174	5.40 (4.48–6.52)	<0.001	
CHA ₂ DS ₂ VASc score				
Low	57 709	5.57 (4.55–6.81)	<0.001	0.078
Intermediate to High	13 031	4.86 (3.37–7.02)	<0.001	

HRs were estimated based on the Fine-Gray subdistribution hazard model accounting for competing risk of death, adjusting for age, BMI, SBP, diastolic blood pressure, LDL-C, eGFR, smoking history, and histories of hypertension, diabetes, and dyslipidemia. Individuals with missing values in adjusted variables (99 of 70 740) were excluded in these analyses. *P* for interaction was based on a model incorporated a categorical variable to define the subgroup, instead of treating the variable continuously, and an interaction term of AF and the categorical variable. Category of CHA₂DS₂VASc score was defined as follows: low (0 for men and 1 for women) or intermediate to high (≥1 for men and ≥2 for women). BMI indicates body mass index; eGFR, estimated glomerular filtration rate; HR, hazard ratio; LDL-C, low density lipoprotein cholesterol; NA, not applicable; and SBP, systolic blood pressure.

consequences are significant compared with similarly aged counterparts without AF. Further, strong associations between AF and incident ischemic stroke and heart failure hospitalizations highlight opportunities for early intervention and management to prevent adverse outcomes.

The 2022 US Preventive Services Task Force recommendation statement⁴ concluded that there is insufficient evidence to assess the benefits and harms of screening for AF among asymptomatic adults without a history of transient ischemic attack or stroke, emphasizing the need for further research on the risk of stroke associated with screening-detected AF. Our study contributes to filling this evidence gap by examining a nationwide cohort representing the general working-age population, leveraging 27 million annual routine screening ECGs to identify AF, and further following these individuals through the

public health insurance database. This distinction in the study population characteristics compared with previous investigations remains significant regardless of screening modalities including 12-lead ECG, single-lead ECG,²⁸ continuous ECG monitor,⁸ or newer technologies such as wearable devices²⁹ or implantable cardiac monitors.³⁰ Leveraging this unique opportunity, we investigated the incidence of screening-detected AF among the working-age general population, estimated the incidence of cardiovascular disease events after AF detection, and compared these events with individuals without AF.

Screening-detected AF in the study population carried a 5-fold higher ischemic stroke risk compared with those without AF. It is important to note that approximately 80% of the study population had the lowest CHA₂DS₂-VASc score (ie, 0 points in men or 1 point in women), for which current guidelines do not routinely recommend anticoagulation therapy.³¹ Although the absolute risk of approximately 2% in 3 years among these individuals with screening-detected AF may not be high in absolute terms, this indicates a potentially preventable stroke burden. These findings highlight the need for further research to refine risk stratification tools, particularly to identify low-risk individuals who may still benefit from established interventions.

An 18-fold increased risk of heart failure hospitalization was observed among those with screening-detected AF compared with those without. This association may reflect the relationship between AF and pre-heart failure (ie, stage B heart failure),³² a relationship that has garnered increasing interest over the past decade. Although we excluded individuals with pre-existing cardiovascular diagnoses through administrative codes, subclinical cardiac dysfunction may have been present at the time of AF detection as pre-heart failure status is generally asymptomatic. Given that AF is considered to be both a cause and consequence of adverse cardiac remodeling,³³ these findings emphasize the importance of cardiac function assessment upon AF detection, even among apparently healthy individuals, to identify those at pre-heart failure and implement appropriate preventive strategies including medical therapies that have been shown to improve HF outcomes.

Because screening for AF entails potential harms associated with downstream diagnostic procedures, excessive treatment, and financial burden at both the individual and societal levels,⁴ risk-based cost-effective approaches may be necessary to detect AF to improve health outcomes in this younger, productive population. Previous randomized controlled trials^{5,8} in older populations demonstrated limited effectiveness of universal AF screening in reducing embolism events. The STROKESTOP trial (Clinical Outcomes in Systematic Screening for Atrial Fibrillation)⁵ reported minimal benefit in reducing ischemic stroke among adults 75 or 76 years of age with a 14-day intermittent ECG intervention during a median follow-up of 6.9 years with cost-effectiveness reported at €27 000/quality-adjusted life-year.³⁴ Further, the GUARD-AF trial (Reducing Stroke

by Screening for Undiagnosed Atrial Fibrillation in Elderly Individuals)⁸ found no significant reduction in ischemic stroke among adults aged 70 or older with 14-day continuous ECG monitoring during a median follow-up of 15.3 months. Given the results of these clinical trials, universal ECG screening for AF in a younger middle-aged population may not reach the same extent of risk reduction or cost-effectiveness observed in previous studies. On tailored approaches, the STROKESTOP II trial (Randomized Invitation to Systematic NT-proBNP and ECG Screening in 75-Year-Olds to Detect Atrial Fibrillation)²⁸ found that AF screenings combined with BNP (brain natriuretic peptide)-level-based screening frequency determination did not reduce embolism events, whereas the secondary analysis of the LOOP study³⁵ found that individuals with NT-proBNP (N-terminal pro-B-type natriuretic peptide) levels ≥ 125 pg/mL benefited from AF screenings using implantable loop recorders in reducing embolism events during a median follow-up of 5.4 years. These results indicate the need for additional risk stratification tools to establish targeted strategies and subsequent management for AF among the working-age population.

The present study has limitations. First, despite physician verification, Minnesota code-based AF ascertainment may be subject to misclassification bias. In addition, despite previous validation studies on the universal health insurance system of Japan, we cannot exclude the possibility of underestimating outcome events because of reliance on administrative codes from hospitalization records. Nonetheless, the JHIA database is the largest insurance claims database that allows researchers to investigate the incidence of unique ECG features and outcomes after health screenings. Second, although the detection in screening settings implies AF without severe symptoms, our data set lacks detailed clinical information on AF duration (paroxysmal, persistent, or permanent), and symptoms captured through patient interviews or patient-reported outcome measures. In addition, the true incidence of AF may be higher when applying screening tools that allow longer observation time (eg, wearable devices). However, such tools are often less affordable and therefore not scalable to the broader population, making them prone to selection bias. Third, minor methodological variations for blood sample analysis may exist across screening sites, although all laboratory tests were performed at accredited facilities for clinical practice in Japan. Fourth, the absence of cause-specific mortality data in our database constrains the interpretation of all-cause deaths. Fifth, although our outcome definition only included ischemic stroke events that required hospitalizations, the detailed information on disease severity was unknown. Future research using databases with detailed clinical information (eg, electronic health records) would be valuable to further investigate the clinical relevance of incidentally detected AF. Sixth, potential self-selection bias may exist because of the study population being restricted to health screen-

ing attendees (11.7 million of 21.0 million eligible insured members during the study period), possibly excluding less health-conscious individuals who may be at higher risk for AF and tend to be older adults and have a lower education attainment level.³⁶ Seventh, although the aHR models did incorporate various covariates as potential confounders, we were not able to include factors such as socioeconomic status, family history, and echocardiographic findings that were not collected in our database. Eighth, the relatively low proportion of women in the JHIA data set before matching (36%) may restrict the representativeness of our data for Japanese working-age women. Last, the study population comprised all Japanese citizens, and the findings may not be generalizable to other regions, as AF-related thromboembolic risk could vary by race, ethnicity, region, and socioeconomic settings.³⁷ It is important to note that outcomes may differ by the degree of health care access influencing the frequency of health care use and interventions after AF detection. In addition, the risks and benefits of detecting AF by screening 12-lead ECGs and early treatment to reduce cardiovascular outcomes warrant further study, particularly on tailored approaches, cost-effectiveness, and quality-of-life improvements.

Conclusions

Among working-age adults without known cardiovascular disease in Japan, AF was detected in 1 of every 2400 ECGs through annual screenings. Despite low thromboembolic risk profiles, individuals with screening-detected AF presented a higher relative risk for cardiovascular disease events compared with those without AF. These findings highlight an important opportunity of cardiovascular risk reduction through early management after AF detection. Further research is needed for optimal detection and management strategies for AF in the working-age population.

ARTICLE INFORMATION

Received February 24, 2025; accepted August 25, 2025.

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Author Contributions

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Sources of Funding

The study was funded by the Japan Health Insurance Association (22JHIA04).

Disclosures

All authors have completed the International Committee of Medical Journal Editors uniform disclosure format (available on request from the corresponding author). Dr Mori has received research grants from the Kyoto University Medical Innovation Program and Health Care Science Institute for other work not related to this study. Dr Sawano has been partially supported by research funding from Polybio, Pfizer, and Novartis through Yale University; he has also received lecture honoraria from Boehringer Ingelheim. Dr Tsugawa receives funding from the National Institutes of Health and GRoW@Annenberg for other work not related to this study, and serves on the board of directors of M3, Inc. Dr Yanagita has received research grants from Mitsubishi Tanabe Pharma and Boehringer Ingelheim for other work not related to this study. Dr Fukuma receives funding from Japan Agency for Medical Research and Development (AMED), Health and Labour Sciences Research Grant from the Ministry of Health, Labour and Welfare of Japan (MHLW), and Cancer Scan.

Supplemental Material

Tables S1–S7

Figure S1

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