The official journal of the Japan Atherosclerosis Society and
the Asian Pacific Society of Atherosclerosis and Vascular Diseases

Original Article

J Atheroscler Thromb, 2021; 28: 241-248. http://doi.org/10.5551/jat.53629

Atrial Fibrillation With and Without Cardiovascular Risk Factors and Stroke Mortality

Toshimi Sairenchi[1, 2, 3], Kazumasa Yamagishi[2, 3, 4], Hiroyasu Iso[5], Fujiko Irie[6], Ai Koba[4, 6], Masanori Nagao[2, 7], Mitsumasa Umesawa[1, 2], Yasuo Haruyama[1], Nobuko Takaoka[1, 2], Hiroshi Watanabe[3], Gen Kobashi[1] and Hitoshi Ota[2, 3]

[1]Department of Public Health, Dokkyo Medical University School of Medicine, Tochigi, Japan
[2]Ibaraki Health Plaza, Ibaraki, Japan
[3]Ibaraki Health Service Association, Ibaraki, Japan
[4]Department of Public Health Medicine, Faculty of Medicine, and Health Services Research and Development Center, University of Tsukuba, Tsukuba, Japan
[5]Public Health, Department of Social Medicine, Osaka University Graduate School of Medicine, Osaka, Japan
[6]Department of Health and Welfare, Ibaraki Prefectural Office, Ibarali, Japan
[7]Office of Epidemiology, Radiation Medical Science Center for the Fukushima Health Management Survey, Fukushima Medical University, Fukushima, Japan

Aim: The association between atrial fibrillation (AF) and risk of stroke mortality among men and women without traditional cerebrocardiovascular risk factors (TCVRFs) is unclear. This study aimed to determine whether AF was a risk factor for stroke and total cardiovascular disease mortality among individuals without TCVRFs.

Methods: A total of 90,629 Japanese subjects from the Ibaraki Prefectural Health Study aged 40–79 years, with and without TCVRFs, were studied from 1993 to 2013. Hazard ratios (HRs) were calculated using the Cox proportional hazard regression model stratified by sex and the presence of TCVRFs. Covariates were age, systolic blood pressure, anti-hypertensive medication use, and serum total cholesterol levels. A standard 12-lead electrocardiogram at rest was used to screen AF. Cause-specific mortality was classified according to the International Classification of Disease code.

Results: Compared with participants without AF, multivariable-adjusted hazard ratios (with 95% confidence intervals) for stroke mortality among participants without TCVRFs were 4.3 (1.1–17.8) and 15.0 (5.5–40.8) for men and women with AF, respectively. HRs for total cardiovascular disease mortality were 6.2 (2.8–14.2) for men and 10.7 (4.8–24.1) for women. For participants with TCVRFs, multivariable-adjusted HRs for stroke mortality were 3.1 (2.2–4.6) and 4.3 (2.6–7.3), whereas HRs for total cardiovascular disease mortality were 2.9 (2.2–3.8) and 3.5 (2.4–5.1) for men and women, respectively.

Conclusions: AF was found to be an independent risk factor for stroke and total cardiovascular mortality even in individuals without other TCVRFs.

See editorial vol. 28: 225-226

Key words: Atrial fibrillation, Stroke, Cardiovascular disease, Cohort studies

Introduction

In 2012, non-communicable diseases were responsible for 68% of all deaths worldwide[1)]. In the same year, >75% of deaths among those younger than 70 years were caused by cardiovascular diseases, cancer, diabetes, and chronic respiratory disease. In 2015, cardiovascular diseases were also a major global contributor to the loss of healthy years[1)]. Cardiovascular disease, including stroke, is therefore a major pub-

Address for correspondence: Toshimi Sairenchi, Department of Public Health, Dokkyo Medical University School of Medicine, 880 Mibu, Tochigi 321-0293, Japan
E-mail: tossair@dokkyomed.ac.jp

Received: November 13, 2019 Accepted for publication: April 29, 2020

lic health issue worldwide.

Atrial fibrillation (AF) is a major risk factor for cardiovascular disease[2-7] and stroke[8-14]. During atrial fibrillation, the upper chambers of the heart (atria) do not beat effectively, resulting in the formation of blood clots. If a clot breaks loose, it may travel to and obstruct a brain artery, causing a stroke[15]. Therefore, AF promotes thrombus formation and cerebral embolism[16]. Aging and systemic vascular risk factors lead to an abnormal atrial tissue substrate, or atrial cardiopathy, that may cause AF and thromboembolism[17]. The health and economic burden of AF is increasing considerably and has already become an epidemic[18].

In Japan, the prevalence of AF has been predicted to increase within the next few decades[19]. Congenital heart disease is associated with the risk of AF[20]. Although AF is commonly caused by hypertension, diabetes, obesity, and heart failure, it may occur in the absence of these factors[21]. For white Americans at the age of 55 years, the lifetime risk of AF in adults with no risk factors was previously found to be 23.4%[22]. However, the relationship between AF and the risk of cardiovascular diseases among individuals without traditional cerebrocardiovascular risk factors (TCVRFs), such as hypertension, dyslipidemia, diabetes mellitus, habitual smoking, and heavy drinking, remains unclear. Therefore, in this study, we aimed to investigate the association between AF and the risk of death from cardiovascular diseases and stroke in Japan among individuals without TCVRFs.

Methods

Participants

The protocol of the Ibaraki Prefectural Health Study is described elsewhere[23]. In summary, the cohort comprised participants aged 40–79 years who completed a health check-up in 1993. Those with incomplete health check-up data or self-reported history of stroke and/or heart disease or those lost to follow-up were excluded.

Baseline Measurements

A standard 12-lead electrocardiogram (ECG) at rest for ~15 min was obtained by a trained medical technologist by using an ECG-8300 device (Nihon Kohden, Tokyo, Japan). Trained physicians evaluated the ECG for the absence or presence of AF. A single physician evaluated each ECG. AF was diagnosed by ECG findings of irregular RR intervals and f waves. Blood pressure was measured on the right arm of seated subjects by trained nurses by using standard mercury sphygmomanometers.

Participants were classified into two groups: the group with risk factors, comprising participants who had TCVRFs, and the group without risk factors, comprising those without any TCVRFs. In this study, the TCVRFs were hypertension, dyslipidemia, diabetes mellitus, habitual smoking, and heavy drinking. Therefore, the group without TCVRFs included individuals with impaired glucose tolerance and/or elevated blood pressure. Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, and/or use of a hypertensive medication. Dyslipidemia was defined as serum levels of total cholesterol ≥ 220 mg/dL, serum high-density lipoprotein cholesterol < 40 mg/dL, and/or use of an anti-dyslipidemic medication. Diabetes mellitus was defined as fasting blood glucose ≥ 126 mg/dL, non-fasting blood glucose ≥ 200 mg/dL, and/or use of an anti-diabetic medication. For non-diabetic participants, prediabetes was defined as fasting blood glucose ≥ 110 mg/dL and/or non-fasting blood glucose ≥ 140 mg/dL. A questionnaire was administered to obtain information on smoking status, number of cigarettes smoked per day, and usual intake of alcohol. A current smoker was defined as either occasional or regular smoker. Heavy drinking was defined as a daily alcohol intake ≥ 66 g/day.

Follow-Up Surveillance

To ascertain deaths in the cohort, investigators conducted a detailed review of death certificates. Data of the date of death or relocation were obtained from the local government records. The underlying causes of death of this cohort were obtained from the Ministry of Health and Welfare. Cause-specific mortality was classified according to the International Classification of Disease (ICD) code of the underlying cause of death. Deaths due to stroke were identified as codes 430–438 and I60–I69 in ICD-9 and -10, respectively. Total cardiovascular disease deaths were identified as codes 393–459 and I00–I99 in ICD-9 and -10, respectively.

Statistical Analysis

Baseline characteristics were compared on the basis of the presence of AF by using an analysis of variance for age, body mass index, systolic blood pressure, diastolic blood pressure, serum total cholesterol level, and serum high-density lipoprotein cholesterol level and by using the χ^2 test for anti-hypertensive medication use, smoking status, alcohol intake, anti-dyslipidemic medication use, glucose metabolism, and anti-diabetic medication use.

Hazard ratios (HRs) and 95% confidence intervals (CIs) for stroke and total cardiovascular mortality for AF versus no AF were calculated using the Cox

proportional hazards regression model. Covariates in the group with risk factors included age, systolic blood pressure, anti-hypertensive medication use (yes or no), serum total cholesterol levels, serum high-density lipoprotein cholesterol levels, and anti-dyslipidemic medication use (yes or no). In addition, blood glucose levels (normal, pre-, and diabetes), anti-diabetic medication use (yes or no), smoking status (never smoker, ex-smoker, current smoker smoking < 20 cigarettes/day, and current smoker smoking ≥ 20 cigarettes/day), and alcohol intake (never, sometimes, < 66 g/day almost every day, and ≥ 66 g/day almost every day) were included.

Covariates in the group without risk factors included age, systolic blood pressure, serum total cholesterol levels, serum high-density lipoprotein cholesterol levels, blood glucose levels (normal and prediabetes), smoking status (never smoker and ex-smoker), and alcohol intake (never, sometimes, and < 66 g/day almost every day). Furthermore, the differences in HRs between participants with and without TCVRFs were analyzed with interaction terms (AF * TCVRFs). Covariates were age, systolic blood pressure, anti-hypertensive medication use, serum total cholesterol levels, serum high-density lipoprotein cholesterol levels, anti-dyslipidemic medication use, blood glucose levels, anti-diabetic medication use, smoking status, and alcohol intake.

All statistical tests were two-sided, and a *P* value of < 0.05 was considered statistically significant. All statistical analyses were performed using the SAS, version 9.4 (SAS Institute, Inc, Cary, NC), software.

Ethics

Informed consent was obtained from community representatives to conduct an epidemiological study. The study was approved by the Ethics Committee of Ibaraki Prefecture (H25-1) and the Bioethics Committee of the Dokkyo Medical University (Daigaku28005). Furthermore, information and opportunity of opting-out from the study are published on our homepage (http://www.hsc-i.jp/05_chousa/iphs1_2.htm; last visit date: April 20, 2020).

Results

Of the 97,078 participants, 6,449 were excluded for lack of complete health check-up data (n = 1,093), self-reported history of stroke and/or heart disease (n = 5,323), and loss to follow-up (n = 33). Finally, 90,629 individuals (men, 30,706; women, 59,923) were enrolled into the study and were followed up until December 31, 2013 using the Basic Resident Register and death certificates. The median (interquartile range) of the follow-up time was 20.1 (14.8–20.3) years for men and 20.2 (19.8–20.4) years for women.

Sex-specific baseline characteristics according to the absence or presence of AF, and stratified by the absence or presence of TCVRFs, are presented in **Table 1**. In the group without TCVRFs, significant differences were found between individuals with and without AF in terms of age in both genders and glucose metabolism in men.

A total of 22,794 total deaths (men, 11,329; women, 11,465), 6,684 total cardiovascular deaths (men, 2,951; women, 3,733), and 2,914 total stroke-related deaths (men, 1,298; women, 1,616) occurred within the follow-up period. A total of 357 total stroke-related deaths (men, 110; women, 247) were noted in participants without TCVRFs.

The sex-specific HRs (with 95% CIs) for stroke-related mortality for AF versus no AF, stratified by the absence or presence of TCVRFs, are presented in **Table 2**. In the group without TCVRFs, multivariable-adjusted HRs for stroke were significantly higher in men and women with AF. Moreover, the HR among women without TCVRFs was higher than the HR among both, women with TCVRFs (*P* for interaction = 0.020) and both genders (*P* for interaction = 0.041).

The sex-specific HRs (with 95% CIs) for total cardiovascular disease mortality for AF versus no AF, stratified by the absence or presence of TCVRFs, are presented in **Table 3**. In both the absence and presence of TCVRFs, multivariable-adjusted HRs for total cardiovascular disease mortality were significantly higher in men and women with AF. Moreover, the HR among women without TCVRFs was higher than that among both, women with TCVRFs (*P* for interaction = 0.012) and both genders (*P* for interaction = 0.003).

Discussion

This study demonstrates an association of AF with the risk of stroke and total cardiovascular disease mortality in men and women, irrespective of the presence or absence of TCVRFs. Furthermore, the results reveal that the added risk associated with AF is considerably higher among women without TCVRFs than among women with TCVRFs. Many previous studies involving participants with TCVRFs have shown an association between AF and the risk of cardiovascular diseases[2-7], particularly stroke[8-14], with a relative risk of ≥ 2-fold. Moreover, our results are consistent with those of several previous studies, which demonstrated that the excess risk is higher in women than in men[24].

Table 1. Baseline characteristics by sex and atrial fibrillation status, stratified by traditional cardiovascular risk factors

	Traditional cardiovascular risk factors					
	Absent			Present		
	Atrial fibrillation			Atrial fibrillation		
	No	Yes	*P* for difference	No	Yes	*P* for difference
Men						
Participants, *n*	3,714	19		26,787	186	
Age, years	58.8 ± 10.6	67.3 ± 5.2	0.001	60.4 ± 9.9	66.1 ± 7.5	< 0.001
Body mass index, kg/m^2	22.6 ± 2.7	22.8 ± 3.0	0.728	23.4 ± 3.0	23.6 ± 3.3	0.450
Systolic blood pressure, mmHg	122.2 ± 10.3	124.0 ± 9.8	0.457	138.3 ± 17.3	139.7 ± 18.5	0.280
Diastolic blood pressure, mmHg	74.3 ± 7.8	75.6 ± 6.2	0.481	81.9 ± 10.7	84.5 ± 10.8	0.001
Antihypertensive medication use, %	0.0	0.0	-	22.4	30.1	0.012
Smoking status, %			0.533			0.001
Non-smoker	49.3	42.1		18.4	15.1	
Ex-smoker	50.7	57.9		23.1	26.3	
Current smoking < 20 cigarettes/day	0.0	0.0		17.6	27.4	
Current smoking ≥ 20 cigarettes/day	0.0	0.0		40.8	31.2	
Alcohol intake, %			0.689			0.206
Never drinker	39.0	36.8		33.5	31.7	
Ex-drinker	18.7	26.3		13	11.3	
Sometimes	42.4	36.8		45.3	44.6	
Almost everyday	0.0	0.0		8.2	12.4	
Serum total cholesterol level, mg/dL	182.8 ± 22.3	183.4 ± 28.2	0.914	194.3 ± 34.9	186.7 ± 33.0	0.003
Serum high-density lipoprotein cholesterol level, mg/dL	56.2 ± 12.2	53.0 ± 14.4	0.267	51.9 ± 15.1	53.5 ± 14.9	0.153
Anti-dyslipidemic medication use, %	0.0	0.0	-	1.4	0.0	0.108
Glucose metabolism, %			0.007			0.148
Normal	88.5	68.4		77.9	73.7	
Prediabetes	11.5	31.6		15.8	21	
Diabetes mellitus	0.0	0.0		6.3	5.4	
Anti-diabetic medication use, %	0.0	0.0	-	4.2	2.7	0.296
Women						
Participants, *n*	19,501	12		40,342	68	
Age, years	52.8 ± 9.9	60.8 ± 12.5	0.005	60.0 ± 9.5	68.4 ± 7.0	< 0.001
Body mass index, kg/m^2	22.6 ± 2.9	24.1 ± 4.7	0.082	24.1 ± 3.3	24.6 ± 3.3	0.140
Systolic blood pressure, mmHg	119.4 ± 11.3	119.0 ± 12.6	0.907	137.8 ± 17.4	139.1 ± 18.1	0.548
Diastolic blood pressure, mmHg	72.1 ± 8.1	69.8 ± 10.0	0.330	80.5 ± 10.5	83.3 ± 10.6	0.030
Antihypertensive medication use, %	0.0	0.0	-	28.8	36.8	0.145
Smoking status, %			0.757			0.826
Non-smoker	99.2	100		92.1	92.6	
Ex-smoker	0.8	0.0		0.7	1.5	
Current smoking < 20 cigarettes/day	0.0	0.0		4.7	4.4	
Current smoking ≥ 20 cigarettes/day	0.0	0.0		2.5	1.5	
Alcohol intake, %			0.411			0.172
Never drinker	89.5	91.7		90.8	98.5	
Ex-drinker	7.2	0.0		5.6	1.5	
Sometimes	3.3	8.3		3.4	0.0	
Almost everyday	0.0	0.0		0.2	0.0	
Serum total cholesterol level, mg/dL	186.1 ± 21.3	184.8 ± 26.8	0.818	218.1 ± 35.3	204.1 ± 35.4	0.001
Serum high-density lipoprotein cholesterol level, mg/dL	59.1 ± 12.1	55.9 ± 8.4	0.368	55.7 ± 14.7	54.9 ± 15.6	0.650
Anti-dyslipidemic medication use, %	0.0	0.0	-	4.7	1.5	0.210
Glucose metabolism, %			0.796			0.353
Normal	93.5	91.7		85.6	79.4	
Prediabetes	6.5	8.3		10.5	14.7	
Diabetes mellitus	0.0	0.0		4.0	5.9	
Anti-diabetic medication use, %	0.0	0.0	-	3.2	5.9	0.211

Table 2. Hazard ratios (95% CIs) for stroke mortality stratified by traditional cardiovascular risk factors

	Traditional cardiovascular risk factors				*P* for interaction
	Absent		Present		
	Atrial fibrillation		Atrial fibrillation		
	No	Yes	No	Yes	
Men					
Number of subjects	3,714	19	26,787	186	
Person-years	66,309.0	249.2	451,609.2	2,514.9	
Number of deaths from stroke	108	2	1,160	28	
Age-adjusted hazard ratio	1 (ref.)	3.8 (0.9–15.5)	1 (ref.)	3.1 (2.1–4.5)	0.829
Multivariable-adjusted hazard ratio[§]	1 (ref.)	4.3 (1.1–17.8)	1 (ref.)	3.1 (2.2–4.6)	0.781
Women					
Number of subjects	19,501	12	40,342	68	
Person-years	364,984.8	178.5	728,222.4	960.9	
Number of deaths from stroke	243	4	1,354	15	
Age-adjusted hazard ratio	1 (ref.)	14.9 (5.5–40.3)	1 (ref.)	4.5 (2.7–7.5)	0.030
Multivariable-adjusted hazard ratio[§]	1 (ref.)	15.0 (5.5–40.8)	1 (ref.)	4.3 (2.6–7.3)	0.020
Men and women					
Number of subjects	23,215	31	67,129	254	
Person-years	431,293.8	427.7	1,179,831.6	3,475.8	
Number of deaths from stroke	351	6	2,514	43	
Age-adjusted hazard ratio (95% CI)	1 (ref.)	7.7 (3.4–17.4)	1 (ref.)	3.5 (2.6–4.7)	0.078
Multivariable-adjusted hazard ratio (95% CI)[‡]	1 (ref.)	8.1 (3.6–18.3)	1 (ref.)	3.5 (2.6–4.7)	0.041

Abbreviations: CI: confidence interval.
[§]Adjusted for age, systolic blood pressure, anti-hypertensive medication use, serum total cholesterol level, serum high-density lipoprotein cholesterol level, anti-dyslipidemic medication use, blood glucose level, anti-diabetic medication use, smoking status, and alcohol intake in the risk factors present group and for age, systolic blood pressure, serum total cholesterol level, serum high-density lipoprotein cholesterol level, blood glucose level, smoking status, and alcohol intake in the risk factors absent group. [‡]Adjusted for sex in addition to the items described above.

According to the CHA_2DS_2-VASc score, female sex is a risk factor for stroke among subjects with AF[25]. However, they did not investigate the association among individuals without TCVRFs.

The mechanisms for the association between AF and the risk of stroke are well known. AF is associated with abnormal blood stasis that involves atrial hypocontractility and the loss of atrial kick, atrial structural remodeling, and activation of platelets and the coagulation cascade, which promote thrombus formation and ischemic stroke[16]. Our study indicated that the existence of AF without TCVRFs was associated with an increased risk of stroke-related mortality. The possible mechanism for the difference in the impact of AF between persons with and without TCVRFs is uncertain. Anticoagulant therapy for AF might have been more frequently provided for patients with TCVRFs than those without TCVRFs[25]; this may have reduced the risk of stroke from AF more conspicuously in patients with TCVRFs than in patients without TCVRFs. Another possibility is that, when TCVRFs are absent, AF may be more likely to be causal for stroke mortality.

A major strength of the present study was the inclusion of a large population-based cohort, in which sex-stratified and TCVRF-specific analyses were possible. All resting ECGs were acquired using the same device and were evaluated by registered trained physicians. Furthermore, all blood samples were analyzed using the same device, reagents, and quality control protocol at a single laboratory.

However, our study has several limitations. First, the small number of participants with AF and single ECG AF determination could be limitations. However, these would likely lead to underestimation rather than overestimation. This study reveals the association between AF and stroke and cardiovascular mortality among participants without TCVRFs despite the above limitations and potential underestimation. Second, the cause of death was defined based on only the death certificates. However, previous studies have indicated that in Japan, death certificates provide valid

Table 3. Hazard ratios (95% CIs) for total cardiovascular disease mortality stratified by traditional cardiovascular risk factors

	Traditional cardiovascular risk factors				*P* for interaction
	Absent		Present		
	Atrial fibrillation		Atrial fibrillation		
	No	Yes	No	Yes	
Men					
Number of subjects	3,714	19	26,787	186	
Person–years	66,309.0	249.2	451,609.2	2,514.9	
Number of deaths from cardiovascular disease	227	6	2,660	58	
Age–adjusted hazard ratio	1 (ref.)	5.6 (2.5–12.5)	1 (ref.)	2.9 (2.2–3.7)	0.169
Multivariable–adjusted hazard ratio[§]	1 (ref.)	6.2 (2.8–14.2)	1 (ref.)	2.9 (2.2–3.8)	0.150
Women					
Number of subjects	19,501	12	40,342	68	
Person–years	364,984.8	178.5	728,222.4	960.9	
Number of deaths from cardiovascular disease	573	6	3,126	28	
Age–adjusted hazard ratio	1 (ref.)	10.1 (4.5–22.7)	1 (ref.)	3.7 (2.5–5.3)	0.021
Multivariable–adjusted hazard ratio[§]	1 (ref.)	10.7 (4.8–24.1)	1 (ref.)	3.5 (2.4–5.1)	0.012
Men and women					
Number of subjects	23,215	31	67,129	254	
Person–years	431,293.8	427.7	1,179,831.6	3,475.8	
Number of deaths from cardiovascular disease	800	12	5,786	86	
Age–adjusted hazard ratio (95% CI)	1 (ref.)	7.3 (4.1–13.0)	1 (ref.)	3.1 (2.5–3.8)	0.010
Multivariable–adjusted hazard ratio (95% CI)[‡]	1 (ref.)	7.7 (4.3–13.7)	1 (ref.)	3.1 (2.5–3.8)	0.003

Abbreviations: CI, confidence interval.
[§]Adjusted for age, systolic blood pressure, anti-hypertensive medication use, serum total cholesterol level, serum high-density lipoprotein cholesterol level, anti-dyslipidemic medication use, blood glucose level, anti-diabetic medication use, smoking status, and alcohol intake in the group with risk factors, and for age, systolic blood pressure, serum total cholesterol level, serum high-density lipoprotein cholesterol level, blood glucose level, smoking status, and alcohol intake in the group without risk factors. [‡]Adjusted for sex in addition to the items described above.fig

data for stroke-related deaths, because of the high prevalence of computed tomography scans or magnetic resonance imaging in Japanese hospitals[26, 27]. Third, the ECGs were generally acquired for short periods, which may have led to a higher false-negative rate for paroxysmal AF. However, because strong associations were found despite potential underestimation from false-negative results for paroxysmal AF, the influence on the results of the present study is likely to be small. Fourth, each ECG was evaluated by a single physician and not verified by another physician. Therefore, a certain degree of misclassification of EGC could not be excluded. Fifth, in the present study, the deaths from non-cardiovascular disease after the onset of some cardiovascular diseases could not be included in the cardiovascular mortality. This may have led to underestimation as these were treated as withdrawal cases. However, the influence is likely to be small because the positive associations were found despite the situation of the potential underestimation. Last, the subjects in this study were participants in a health check-up for residents; the response rate was approximately 40%. Therefore, a "healthy participant" effect cannot be ruled out. However, for the association between AF and risk of cardiovascular mortality, the influence of the potential effect on our results is likely to be small. In view of the aging population, the burden of AF is increasing in developed countries[18, 19].

Conclusions

The present study revealed that AF was an independent risk factor for stroke and total cardiovascular mortality, even among individuals who did not have other TCVRFs. We also found that the impact of AF was greater among women without TCVRFs than among women with TCVRFs.

Acknowledgments

This work was supported by a Grant-in-Aid from the Ministry of Health, Labor and Welfare, Health

and Labor Sciences Research Grants, Japan (Research on Health Services: H17-Kenkou-007, Comprehensive Research on Cardiovascular and Life-Style Related Diseases: H18-Junkankitou[Seishuu]-Ippan-012, Comprehensive Research on Cardiovascular and Life-Style Related Diseases: H20-Junkankitou[Seishuu]-Ippan-013, Intractable Diseases Conquest Research: H21-Nanchi-Ippan-059, Comprehensive Research on Cardiovascular and Life-Style Related Diseases: H23-Junkankitou[Seishuu]-Ippan-005, an Intramural Research Fund (22-4-5) for Cardiovascular Diseases of National Cerebral and Cardiovascular Center; and Comprehensive Research on Cardiovascular and Life-Style-Related Diseases: H26-Junkankitou [Seisaku]-Ippan-001 and H29-Junkankitou [Seishuu]-Ippan-003), and a Grant-in-Aid from the Japan Agency for Medical Research and Development (AMED) (Grant Number: JP18ek0210082).

The funders were not involved in the study design; collection, analysis, and interpretation of data; preparation of the report; and the decision to submit the article for publication.

Conflict of Interest Statement

The authors declare that they have no competing interests.

References

1) World Health Organization: World health statistics 2016: monitoring health for the SDGs, sustainable development goals, WHO Press, Geneva, 2016
2) Conen D, Chae CU, Glynn RJ, Tedrow UB, Everett BM, Buring JE and Albert CM: Risk of death and cardiovascular events in initially healthy women with new-onset atrial fibrillation. JAMA, 2011; 305: 2080-2087
3) Krahn AD, Manfreda J, Tate RB, Mathewson FA and Cuddy TE: The natural history of atrial fibrillation: incidence, risk factors, and prognosis in the Manitoba Follow-Up Study. Am J Med, 1995; 98: 476-484
4) Ohsawa M, Okamura T, Ogasawara K, Ogawa A, Fujioka T, Tanno K, Yonekura Y, Omama S, Turin TC, Itai K, Ishibashi Y, Morino Y, Itoh T, Miyamatsu N, Onoda T, Kuribayashi T, Makita S, Yoshida Y, Nakamura M, Tanaka F, Ohta M, Sakata K and Okayama A: Relative and absolute risks of all-cause and cause-specific deaths attributable to atrial fibrillation in middle-aged and elderly community dwellers. Int J Cardiol, 2015; 184: 692-698
5) Ohsawa M, Okayama A, Okamura T, Itai K, Nakamura M, Tanno K, Kato K, Yaegashi Y, Onoda T, Sakata K and Ueshima H: Mortality risk attributable to atrial fibrillation in middle-aged and elderly people in the Japanese general population: nineteen-year follow-up in NIPPON DATA80. Circ J, 2007; 71: 814-819
6) Ruff CT, Bhatt DL, Steg PG, Gersh BJ, Alberts MJ, Hoffman EB, Ohman EM, Eagle KA, Lip GY, Goto S and Investigators RR: Long-term cardiovascular outcomes in patients with atrial fibrillation and atherothrombosis in the REACH Registry. Int J Cardiol, 2014; 170: 413-418
7) Stewart S, Hart CL, Hole DJ and McMurray JJ: A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. Am J Med, 2002; 113: 359-364
8) Flegel KM, Shipley MJ and Rose G: Risk of stroke in non-rheumatic atrial fibrillation. Lancet, 1987; 1: 526-529
9) Kannel WB, Abbott RD, Savage DD and McNamara PM: Epidemiologic features of chronic atrial fibrillation: the Framingham study. N Engl J Med, 1982; 306: 1018-1022
10) Ohsawa M, Okamura T, Tanno K, Ogasawara K, Itai K, Yonekura Y, Konishi K, Omama S, Miyamatsu N, Turin TC, Morino Y, Itoh T, Onoda T, Sakata K, Ishibashi Y, Makita S, Nakamura M, Tanaka F, Kuribayashi T, Ohta M and Okayama A: Risk of stroke and heart failure attributable to atrial fibrillation in middle-aged and elderly people: Results from a five-year prospective cohort study of Japanese community dwellers. J Epidemiol, 2017; 27: 360-367
11) Tanizaki Y, Kiyohara Y, Kato I, Iwamoto H, Nakayama K, Shinohara N, Arima H, Tanaka K, Ibayashi S and Fujishima M: Incidence and risk factors for subtypes of cerebral infarction in a general population: the Hisayama study. Stroke, 2000; 31: 2616-2622
12) Wolf PA, Abbott RD and Kannel WB: Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke, 1991; 22: 983-988
13) Wolf PA, Dawber TR, Thomas HE, Jr. and Kannel WB: Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: the Framingham study. Neurology, 1978; 28: 973-977
14) Chien KL, Su TC, Hsu HC, Chang WT, Chen PC, Chen MF and Lee YT: Atrial fibrillation prevalence, incidence and risk of stroke and all-cause death among Chinese. Int J Cardiol, 2010; 139: 173-180
15) Mayo Clinic: Mayo Clinic Healthy Heart for Life!, Time Home Entertainment Inc., New York, 2012
16) Kim YH and Roh SY: The Mechanism of and Preventive Therapy for Stroke in Patients with Atrial Fibrillation. J Stroke, 2016; 18: 129-137
17) Kamel H, Okin PM, Elkind MS and Iadecola C: Atrial Fibrillation and Mechanisms of Stroke: Time for a New Model. Stroke, 2016; 47: 895-900
18) Ball J, Carrington MJ, McMurray JJ and Stewart S: Atrial fibrillation: profile and burden of an evolving epidemic in the 21st century. Int J Cardiol, 2013; 167: 1807-1824
19) Ohsawa M, Okayama A, Sakata K, Kato K, Itai K, Onoda T and Ueshima H: Rapid increase in estimated number of persons with atrial fibrillation in Japan: an analysis from national surveys on cardiovascular diseases in 1980, 1990 and 2000. J Epidemiol, 2005; 15: 194-196
20) Hu WS and Lin CL: Risk of Atrial Fibrillation in Patients with Congenital Heart Disease: Results of a Propensity Score-Matched, Nationwide Cohort Study. J Atheroscler Thromb, 2019; 26: 670-677
21) Evans W and Swann P: Lone auricular fibrillation. Br Heart J, 1954; 16: 189-194

22) Staerk L, Wang B, Preis SR, Larson MG, Lubitz SA, Ellinor PT, McManus DD, Ko D, Weng LC, Lunetta KL, Frost L, Benjamin EJ and Trinquart L: Lifetime risk of atrial fibrillation according to optimal, borderline, or elevated levels of risk factors: cohort study based on longitudinal data from the Framingham Heart Study. BMJ, 2018; 361: k1453
23) Sairenchi T, Iso H, Yamagishi K, Irie F, Okubo Y, Gunji J, Muto T and Ota H: Mild retinopathy is a risk factor for cardiovascular mortality in Japanese with and without hypertension: the Ibaraki Prefectural Health Study. Circulation, 2011; 124: 2502-2511
24) Emdin CA, Wong CX, Hsiao AJ, Altman DG, Peters SA, Woodward M and Odutayo AA: Atrial fibrillation as risk factor for cardiovascular disease and death in women compared with men: systematic review and meta-analysis of cohort studies. BMJ, 2016; 532: h7013
25) January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC, Jr., Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM and Yancy CW: 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol, 2014; 64: e1-76
26) Kita Y, Okayama A, Ueshima H, Wada M, Nozaki A, Choudhury SR, Bonita R, Inamoto Y and Kasamatsu T: Stroke incidence and case fatality in Shiga, Japan 1989-1993. Int J Epidemiol, 1999; 28: 1059-1065
27) Sankai T, Miyagaki T, Iso H, Shimamoto T, Iida M, Tanigaki M, Naito Y, Sato S, Kiyama M, Kitamura A, Konishi M, Terao A, Doi M and Komachi Y: A population-based study of the proportion by type of stroke determined by computed tomography scan (in Japanese). Nippon Koshu Eisei Zasshi, 1991; 38: 901-909