Age-Specific Impact of Atrial Fibrillation on Cardiovascular Mortality Among Japanese Men and Women (The Ibaraki Prefectural Health Study [IPHS])

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The age-specific impact of atrial fibrillation (AF) on cardiovascular diseases remains unclear. A total of 90,629 participants who were from 40 to 79 years of age in 1993 were followed up until 2013 as part of the Ibaraki Prefectural Health Study. Hazard ratios for mortality stratified by gender and age groups were calculated using Cox's proportional hazards regression models. A total of 22,794 patients (11,329 men and 11,465 women) died during the follow-up period, including 6,684 patients who died of cardiovascular causes (2,951 men and 3,733 women). On multivariable analysis, participants with AF had an increased risk of cardiovascular-related mortality compared with those without AF. Among participants aged 40 to 64 years, the adjusted hazard ratios were 3.2 (95% confidence interval [CI] 2.0 to 5.3) for men and 7.1 (95% CI 3.2 to 16.0) for women; the corresponding adjusted hazard ratios among participants aged 65 to 79 years were 3.0 (95% CI 2.2 to 4.0) for men and 3.7 (95% CI 2.5 to 5.4) for women. No significant difference in hazard ratios between age groups was found for either gender. AF was significantly associated with all-cause mortality in each age and gender group; again, no significant difference in hazard ratios between the age groups was found in terms of AF. AF may be an independent risk factor for cardiovascular and all-cause mortalities regardless of age. **(Am J Cardiol 2019;124:1413−1419)**

Cardiovascular diseases (CVDs) are a major contributor to the loss of healthy years worldwide.[1] Aging along with certain systemic vascular risk factors can cause an abnormal atrial tissue substrate, or atrial cardiopathy, that can result in atrial fibrillation (AF) and thromboembolism.[2] AF is a major risk factor for CVDs,[3−8] and its prevalence increases with age. In Japan, for example, the estimated number of patients with AF will increase in the near future because of its rapidly aging population.[9,10] For this reason, managing AF ought to be a high public health priority to avoid CVDs and early death, especially in countries with aging populations. At the same time, several studies showed that the impact of hypertension (a major risk factor for CVDs) on the total CVD mortality and all-cause mortality decreases with age.[11,12] Conversely, the impact of AF on the total CVD mortality might be greater in the elderly population than among the middle-aged patients because deaths due to cerebral infarction, which is strongly associated with AF, constitute a larger proportion of total cerebrovascular disease-related mortalities in elderly patients than in middle-aged patients.[13] It remains uncertain whether the impact of AF on CVD-related mortality and on all-cause mortality varies by age; such information would be useful for devising anti-AF measures to prevent CVD and early death. However, to the best of our knowledge, the age-specific health impacts of AF have not been examined in prospective cohort studies in the general population. Therefore, we examined the age-specific association of AF with the risk of mortality from all causes as well as specifically from CVD.

Methods

The protocol of our population-based cohort study, the Ibaraki Prefectural Health Study, has been described

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See page 1418 for disclosure information.

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Table 1
Gender-specific baseline characteristics according to the absence or presence of atrial fibrillation, stratified by age group

Variables	Age (years)								
	Total			40−64			65−79		
	Atrial fibrillation			Atrial fibrillation			Atrial fibrillation		
	No	Yes	p value	No	Yes	p value*	No	Yes	p value
Men									
Participants, n	30,501	205		18,556	76		11,945	129	
Age (years)	60.2 ± 10.0	66.2 ± 7.3	<0.001	54.0 ± 7.6	58.8 ± 5.2	<0.001	69.9 ± 3.8	70.6 ± 4.1	0.048
Body mass index (kg/m^2)	23.3 ± 3.0	23.5 ± 3.2	0.350	23.7 ± 2.9	23.9 ± 3.0	0.562	22.7 ± 3.0	23.3 ± 3.4	0.033
Systolic blood pressure (mm Hg)	136.4 ± 17.4	138.2 ± 18.4	0.124	133.8 ± 17.1	137.1 ± 17.2	0.093	140.4 ± 17.2	138.9 ± 19.1	0.339
Diastolic blood pressure (mm Hg)	81.0 ± 10.7	83.7 ± 10.8	<0.001	81.4 ± 11.0	84.6 ± 10.8	0.010	80.3 ± 10.2	83.1 ± 10.8	0.002
Antihypertensive medication use	19.7%	27.3%	0.006	13.7%	23.7%	0.011	28.9%	29.5%	0.896
Smoking status			0.001			0.004			0.064
Non-smoker	22.2%	17.6%		22.6%	14.5%		21.6%	19.4%	
Ex-smoker	26.5%	29.3%		23.1%	14.5%		31.7%	38.0%	
Current smoking <20 cigarettes/day	15.5%	24.9%		12.1%	23.7%		20.7%	25.6%	
Current smoking ≥20 cigarettes/day	35.9%	28.3%		42.2%	47.4%		26.0%	17.1%	
Alcohol intake			0.169			0.006			0.612
Never	34.2 %	32.2%		29.1%	23.7%		42.1%	37.2%	
Ex-drinker	13.7%	12.7%		15.4%	13.2%		11.1%	12.4%	
Sometimes	44.9%	43.9%		46.2%	42.1%		42.9%	45.0%	
Almost everyday	7.2%	11.2%		9.3%	21.1%		3.9%	5.4%	
Serum total cholesterol level (mg/dl)	192.9 ± 33.8	186.4 ± 32.5	0.006	194.9 ± 34.4	191.7 ± 33.6	0.426	189.9 ± 32.6	183.3 ± 31.6	0.023
Serum high-density lipoprotein cholesterol level (mg/dl)	52.5 ± 14.8	53.5 ± 14.9	0.323	52.0 ± 14.6	54.8 ± 16.3	0.098	53.2 ± 15.1	52.7 ± 13.9	0.744
Anti-dyslipidemia medication use	1.2%	0.0%	0.114	1.0%	0.0%	0.372	1.5%	0.0%	0.166
Glucose metabolism			0.030			0.154			0.269
Normal	79.2%	73.2%		79.8%	72.4%		78.2%	73.6%	
Prediabetes	15.3%	22.0%		14.5%	22.4%		16.4%	21.7%	
Diabetes mellitus	5.5%	4.9%		5.6%	0.0%		5.4%	4.7%	
Antidiabetic medication use	3.7%	2.4%	0.334	3.0%	1.3%	0.390	4.8%	3.1%	0.361
Women									
Participants, n	59,843	80		42,043	25		17,800	55	
Age (years)	57.7 ± 10.2	67.2 ± 8.4	<0.001	52.6 ± 7.4	57.9 ± 7.6	<0.001	69.7 ± 3.7	71.5 ± 4.3	0.001
Body mass index (kg/m^2)	23.6 ± 3.2	24.6 ± 3.5	0.007	23.6 ± 3.2	24.4 ± 4.1	0.214	23.6 ± 3.3	24.6 ± 3.3	0.024
	131.8 ± 17.9	136.1 ± 18.8	0.033	128.8 ± 17.4	132.0 ± 17.5	0.353	139.1 ± 17.0	138.0 ± 19.2	0.630

(*continued on next page*)

Table 1 (***Continued***)

Variables	Age (years)								
	Total			40−64			65−79		
	Atrial fibrillation			Atrial fibrillation			Atrial fibrillation		
	No	Yes	p value	No	Yes	p value*	No	Yes	p value
Systolic blood pressure (mm Hg)	77.8 ± 10.5	81.3 ± 11.5	0.003	77.4 ± 10.7	79.7 ± 10.8	0.295	78.6 ± 10.1	82.0 ± 11.8	0.013
Diastolic blood pressure (mm Hg)	19.4%	31.3%	0.007	13.1%	0.0%	0.176	34.1%	43.6%	0.138
Antihypertensive medication use						0.504			0.626
Smoking status	94.4%	93.8%	0.924	93.8%	88.0%		95.7%	96.4%	
Non-smoker	0.7%	1.3%		0.7%	0.0%		0.7%	1.8%	
Ex-smoker	3.2%	3.8%		3.4%	8.0%		2.8%	1.8%	
Current smoking <20 cigarettes/day	1.7%	1.3%		2.0%	0.0%		0.8%	0.0%	
Current smoking ≥20 cigarettes/day			0.193			0.570			0.566
Alcohol intake	90.4	97.5		88.9	96.0		93.8	98.2	
Never	6.1	1.3		7.3	0.0		3.4	1.8	
Ex-drinker	3.4	0.0		3.7	4.0		2.8	0.0	
Sometimes	0.1	0.0		0.2	0.0		0.0	0.0	
Almost everyday	207.7 ± 34.8	201.2 ± 34.8	0.098	205.7 ± 35.0	200.5 ± 39.9	0.456	212.4 ± 33.8	201.6 ± 32.7	0.018
Serum total cholesterol level (mg/dl)	56.8 ± 14.0	55.1 ± 14.7	0.263	57.5 ± 14.0	57.9 ± 17.9	0.882	55.2 ± 13.9	53.8 ± 12.9	0.436
Serum high-density lipoprotein cholesterol level (mg/dl)	3.2%	1.3%	0.329	2.5%	0.0%	0.421	4.7%	1.8%	0.317
Antidyslipidemia medication use			0.145			0.126			0.372
Glucose metabolism	88.1%	81.3%		89.7%	88.0%		84.4%	78.2%	
Normal	9.2%	13.8%		8.0%	0.0%		12.0%	18.2%	
Prediabetes	2.7%	5.0%		2.3%	0.0%		3.6%	3.6%	
Diabetes mellitus	2.2%	5.0%	0.081	1.6%	0.0%	0.009	3.6%	3.6%	0.987
Antidiabetic medication use									

AF = atrial fibrillation.

previously.[14] Briefly, the cohort comprised of participants aged 40 to 79 years who completed a health check-up in 1993. Among 97,078 participants, 6,449 were excluded owing to incomplete health check-up data (n = 1,093), most of which included "no stature" due to presence of kyphosis, or "no blood sample" due to difficulties in vascular access. Patients with a self-reported history of stroke and/or heart disease (n = 5,323) were excluded to avoid relapsing contamination. In addition, the data of those lost to follow-up (n = 33), most of which included unregistered community dwellers at baseline, were excluded. Thus, 90,629 patients (30,706 men and 59,923 women) were included in the present study and were followed until December 31, 2013 using the Basic Resident Register as well as death certificates. A standard 12-lead resting electrocardiogram (ECG) was obtained by a trained medical technologist using an ECG-8300 device (Nihon Kohden, Tokyo, Japan) at baseline. Trained physicians evaluated the ECG for the absence or presence of AF.

Informed consent was obtained from community representatives to conduct an epidemiological investigation. Informed consent was not obtained from patients since the data collected was anonymous. The Ethical Guidelines for Epidemiological Research were enforced by the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labor and Welfare on June 17, 2002. These were the first Japanese guidelines for epidemiological research. Since this study was ongoing at the time, the Ethics Committee of Ibaraki Prefecture approved this study in February 2004, according to the guidelines. The study complied with the Declaration of Helsinki and was approved by the ethics committee of Ibaraki Prefecture (H25-1) and the Bioethics Committee of Dokkyo Medical University (Daigaku 28005).

The cause of deaths in the cohort was ascertained by reviewing the death certificates systematically. Cause-specific mortality was classified according to the International Classification of Disease (ICD) code of the underlying cause of death. The total CVD-related deaths were identified as codes 393−459 in the ICD ninth edition and as codes I00−I99 in the ICD tenth edition.

Participants were divided into 2 groups according to age: 40 to 64 and 65 to 79 years. Baseline characteristics were

Table 2
Gender-specific hazard ratios of cardiovascular mortality in all participants with versus without atrial fibrillation stratified by age group

Variables	Age (years)						P-value for interaction
	Total		40−64		65−79		
	Atrial fibrillation		Atrial fibrillation		Atrial fibrillation		
	No	Yes	No	Yes	No	Yes	
Men							
Number of participants	30,501	205	18,556	76	11,945	129	
Person-years	517,918.2	2,764.1	341,502.3	1,296.0	176,415.9	1,468.1	
Number of deaths from cardiovascular disease	2,887	64	842	16	2,045	48	
Age−adjusted hazard ratio (95% CI)	1 (ref.)	3.0 (2.4−3.9)	1 (ref.)	3.6 (2.2−5.8)	1 (ref.)	2.9 (2.2−3.9)	0.489
Multivariable−adjusted hazard ratio (95% CI)*	1 (ref.)	3.0 (2.4−3.9)	1 (ref.)	3.2 (2.0−5.3)	1 (ref.)	3.0 (2.2−4.0)	0.754
Women							
Number of participants	59,843	80	42,043	25	17,800	55	
Person-years	1,093,207.2	1,139.4	795,287.1	442.4	297,920.1	697.0	
Number of deaths from cardiovascular disease	3,699	34	851	6	2,848	28	
Age-adjusted hazard ratio (95% CI)	1 (ref.)	4.2 (3.0−5.9)	1 (ref.)	7.6 (3.4−16.9)	1 (ref.)	3.9 (2.7−5.6)	0.138
Multivariable−adjusted hazard ratio (95% CI)*	1 (ref.)	4.0 (2.9−5.6)	1 (ref.)	7.1 (3.2−16.0)	1 (ref.)	3.7 (2.5−5.4)	0.138
Men and women							
Number of participants	90,344	285	60,599	101	29,745	184	
Person-years	1,611,125.4	3,903.5	1,136,789.4	1,738.4	474,336.0	2,165.1	
Number of deaths from cardiovascular disease	6,586	98	1,693	22	4,893	76	
Age-adjusted hazard ratio (95% CI)	1 (ref.)	3.3 (2.7−4.1)	1 (ref.)	4.1 (2.7−6.3)	1 (ref.)	3.2 (2.6−4.0)	0.089
Multivariable-adjusted hazard ratio (95% CI)†	1 (ref.)	3.3 (2.7−4.0)	1 (ref.)	3.8 (2.5−5.7)	1 (ref.)	3.2 (2.5−4.0)	0.209

CI = confidence interval.

* Adjusted for age, systolic blood pressure, antihypertensive medication use (yes or no), serum total cholesterol level, serum high-density lipoprotein cholesterol level, antidyslipidemia medication use (yes or no), plasma glucose level (normal, prediabetes, and diabetes), antidiabetes medication use (yes or no), smoking status (never smoker, ex-smoker, currently <20 cigarettes/day, and currently ≥20 cigarettes/day), and alcohol intake (never, sometimes, <66 g/day almost every day, and ≥66 g/day almost every day).

† Adjusted for gender in addition to the items described above.

Table 3
Gender-specific hazard ratios of all-cause mortality in all participants with versus without atrial fibrillation stratified by age group

Variables	Age (years)						p value for interaction
	Total		40–64		65–79		
	Atrial fibrillation		Atrial fibrillation		Atrial fibrillation		
No	Yes		No	Yes	No	Yes	
Men							
Number of participants	30,501	205	18,556	76	11,945	129	
Person-years	517,918.2	2,764.1	341,502.3	1,296.0	176,415.9	1,468.1	
Number of deaths from all-cause	11,195	134	3,790	33	7,405	101	
Age-adjusted hazard ratio (95% CI)	1 (ref.)	1.7 (1.4–2.0)	1 (ref.)	1.7 (1.2–2.4)	1 (ref.)	1.7 (1.4–2.1)	0.489
Multivariable-adjusted hazard ratio (95% CI)*	1 (ref.)	1.7 (1.4–2.0)	1 (ref.)	1.5 (1.0–2.1)	1 (ref.)	1.7 (1.4–2.1)	0.754
Women							
Number of participants	59,843	80	42,043	25	17,800	55	
Person-years	1,093,207.2	1,139.4	795,287.1	442.4	297,920.1	697.0	
Number of deaths from all-cause	11,412	53	3,565	8	7,847	45	
Age-adjusted hazard ratio (95% CI)	1 (ref.)	2.4 (1.8–3.1)	1 (ref.)	2.7 (1.4–5.4)	1 (ref.)	2.3 (1.7–3.1)	0.138
Multivariable-adjusted hazard ratio (95% CI)*	1 (ref.)	2.2 (1.7–2.9)	1 (ref.)	2.5 (1.3–5.0)	1 (ref.)	2.2 (1.6–2.9)	0.138
Men and women							
Number of participants	90,344	285	60,599	101	29,745	184	
Person-years	1,611,125.4	3,903.5	1,136,789.4	1,738.4	474,336.0	2,165.1	
Number of deaths from all-cause	22,607	187	7,355	41	15,252	146	
Age-adjusted hazard ratio (95% CI)	1 (ref.)	1.8 (1.6–2.1)	1 (ref.)	1.8 (1.3–2.5)	1 (ref.)	1.9 (1.6–2.2)	0.089
Multivariable-adjusted hazard ratio (95% CI)†	1 (ref.)	1.8 (1.5–2.1)	1 (ref.)	1.6 (1.2–2.2)	1 (ref.)	1.8 (1.6–2.2)	0.209

AF = atrial fibrillation; CI = confidence interval.

* Adjusted for age, systolic blood pressure, antihypertensive medication use (yes or no), serum total cholesterol level, serum high-density lipoprotein cholesterol level, antidyslipidemia medication use (yes or no), plasma glucose level (normal, prediabetes, and diabetes), antidiabetes medication use (yes or no), smoking status (never smoker, ex-smoker, currently <20 cigarettes/day, and currently ≥20 cigarettes/day), and alcohol intake (never, sometimes, <66 g/day almost every day, and ≥66 g/day almost every day).

† Adjusted for gender in addition to the items described above.

compared according to the presence of AF 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. Moreover, the chi-square test was used to compare antihypertensive medication use, smoking status, alcohol intake, antidyslipidemia medication use, glucose metabolism, and antidiabetes medication use.

Hazard ratios (HRs) and 95% confidence intervals of total CVD mortality and all-cause mortality of patients with versus without AF were calculated using Cox's proportional hazards regression models. Furthermore, the differences in HRs between participants in each age group were analyzed using the interaction terms (AF × age groups).

The data were retrospectively analyzed. All statistical tests were 2-sided, and $p < 0.05$ was considered statistically significant. All statistical analyses were conducted using the SAS software, version 9.4 (SAS Institute, Inc., Cary, North Carolina).

Results

Gender-specific baseline participant characteristics according to the absence or presence of AF and stratified by age groups are shown in Table 1. Among men of all ages, patients with versus without AF had significant differences in age, diastolic blood pressure, antihypertensive medication use, smoking status, serum total cholesterol level, and glucose metabolism. Among women of all ages, those with versus without AF had significantly different ages, body mass indices, systolic and diastolic blood pressures, and antihypertensive medication use.

Using the Kaplan-Meier method, the survival rates at 5, 10, 15, and 20 years were 0.991, 0.9745, 0.9481, and 0.9152, respectively. Table 2 shows the gender-specific analysis of total CVD mortality comparing all patients with versus without AF as well as the patients in each age group. The risk of total CVD mortality was significantly higher in men, women, and patients of both genders who had AF in each age group as well as both age groups combined. No significant differences in risk ratios were found in men, women, or patients of both genders between age groups.

Table 3 shows the results of all-cause mortality analysis in patients with versus without AF in each age group and in both combined. Multivariable-adjusted HRs of all-cause mortality were significantly higher in patients with AF among men, women, and patients of both genders in each age groups as well as in both groups together. Again, no significant differences were found for men, women, and both genders combined between age groups.

Discussion

To our knowledge, ours is the first study to show an association between AF and risk of CVD and all-cause mortality in men and women across all ages. Previous studies revealed an association between AF and the risk of CVD,[3–8] particularly stroke (in which the relative risk scores were 2.0 or

more);[15–22] however, they did not investigate such associations in patients stratified by age group.

The mechanisms linking AF to the risk of stroke are well known. AF is associated with the activation of platelets and the coagulation cascade, which promote thrombus formation and, ultimately, cerebral infarction.[23] Among all those who died of cerebrovascular disease, the proportion of elderly people (65 to 79 years) who died owing to cerebral infarction, which is strongly associated with AF, was larger than that of middle-aged participants (40 to 64 years) who died of the same cause (44.1% vs 13.7%).[13] Meanwhile, death owing to intracranial hemorrhage, which is weakly associated with AF, was a more common cause of cerebrovascular disease-related death in middle-aged patients than in elderly people (83.7% vs 53.2%). The administration of anticoagulation therapy to patients with AF is linked to an increased risk of intracranial hemorrhage[24] although nonvitamin K antagonist-type oral anticoagulants can reduce the risk[25] and have been widely used in Japan since 2011.[26] Therefore, in terms of comparing the impact of AF on CVD-related deaths in elderly versus middle-aged populations, the age-related increase in the incidences of cerebral infarction in elderly patients may be counterbalanced by the anticoagulation therapy-linked increase in the occurrence of intracranial hemorrhage among middle-aged people.

The strength of our study is that we used a large population-based cohort in which gender-stratified and age-specific analyses were possible. All resting ECGs were measured using the same device and were evaluated by trained and registered physicians.

Conversely, the study had several limitations. First, the ECG measuring time was generally short, which may have resulted in a higher number of false negative paroxysmal AF diagnoses. However, the influence of any such false diagnoses on the results of the study is likely to be small because strong associations were found despite the underestimation of potential false negative (paroxysmal AF-related) results. Second, the causes of death were derived only from death certificates; however, previous studies indicated that death certificate designations of stroke, which is a major cause of CVD mortality in Japan, are reliable owing to the high prevalence of computed tomography and magnetic resonance imaging use at Japanese hospitals.[27,28] Lastly, the study cohort comprised health check-up participants, the community participation rate was approximately 40%; thus, a "healthy" participant effect, which could underestimate the prevalence of AF, cannot be ruled out. Nevertheless, the sample size for our study was large.

In conclusion, our data suggest that AF is an independent risk factor for CVD and all-cause mortalities regardless of age.

Disclosures

The authors have no conflicts of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.07.047.

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