Atrial Fibrillation With and Without Cardiovascular Risk Factors and Stroke Mortality

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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.

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

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Introduction

In 2012, non-communicable diseases were responsible for 68% of all deaths worldwide1). 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 years1). Cardiovascular disease, including stroke, is therefore a major pub-
lic health issue worldwide.

Atrial fibrillation (AF) is a major risk factor for cardiovascular disease and stroke. 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. Therefore, AF promotes thrombus formation and cerebral embolism. Aging and systemic vascular risk factors lead to an abnormal atrial tissue substrate, or atrial cardiopathy, that may cause AF and thromboembolism. The health and economic burden of AF is increasing considerably and has already become an epidemic.

In Japan, the prevalence of AF has been predicted to increase within the next few decades. Congenital heart disease is associated with the risk of AF. Although AF is commonly caused by hypertension, diabetes, obesity, and heart failure, it may occur in the absence of these factors. 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%. 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. 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 100–199 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 χ² 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
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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/iph1_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 (inter-quartile 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 diseases2-7, particularly stroke6-14, 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 men20.
Table 1. Baseline characteristics by sex and atrial fibrillation status, stratified by traditional cardiovascular risk factors

|                      | Traditional cardiovascular risk factors | Atrial fibrillation | Atrial fibrillation | P for difference |
|----------------------|----------------------------------------|--------------------|--------------------|------------------|
|                      | Absent (No) | Yes | Present (No) | Yes | 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/m² | 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 | 0.533 | 22.4 | 30.1 | 0.012 |
| Smoking status, %    |             |     |             |     |           |
| Non-smoker           | 49.3        | 42.1 | 18.4       | 15.1 |           |
| Systolic blood pressure, mmHg | 0.0 | 0.0 | 17.6       | 27.4 |           |
| Ex-smoker            | 50.7        | 57.9 | 23.1       | 26.3 |           |
| Current smoking < 20 cigarettes/day | 0.0 | 0.0 | 40.8       | 31.2 |           |
| Current smoking ≥ 20 cigarettes/day | 0.0 | 0.0 |           |     |           |
| Alcohol intake, %    |             |     |             |     |           |
| 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/m² | 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, %    |             |     |             |     |           |
| 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, %    |             |     |             |     |           |
| Normal               | 89.5        | 91.7 | 90.8       | 98.5 |           |
| Prediabetes          | 7.2         | 0.0  | 5.6        | 1.5  |           |
| Diabetes mellitus    | 3.3         | 8.3  | 3.4        | 0.0  |           |
| Anti-diabetic medication use, % | 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, % | 93.0        | 91.7 | 85.6       | 79.4 |           |
| 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 |
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 2. Hazard ratios (95% CIs) for stroke mortality stratified by traditional cardiovascular risk factors |
|---------------------------------------------------------------|
| **Traditional cardiovascular risk factors**                  | **Absent** | **Present** | **P for interaction** |
| **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 CHA²DS2-VASc score, female sex is a risk factor for stroke among subjects with AF. 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 hypokinesis and the loss of atrial kick, atrial structural remodeling, and activation of platelets and the coagulation cascade, which promote thrombus formation and ischemic stroke. 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; 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...
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 countries18, 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.

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**Conflict of Interest Statement**

The authors declare that they have no competing interests.

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