Atrial fibrillation prevalence, incidence and risk of stroke and all-cause death among Chinese☆

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Abstract

Background: We investigated atrial fibrillation (AF) prevalence, incidence and the risk of stroke and all-cause death because little is known about AF risk among ethnic Chinese.

Methods: We conducted a community-based prospective cohort study among 3560 participants. Prevalent and incident AF was documented by using the 12-lead ECG in baseline and serial follow-ups, and the stroke and all-cause death events were ascertained.

Results: Overall prevalence rates of AF in the cohort were 1.4% in men and 0.7% in women. Incidence rates of AF were 1.68 per 1000 person-years for men and 0.76 per 1000 person-years for women. During a median 13.8 years′ follow-up, we documented 208 cases of stroke and 776 deaths. As compared with those without AF, participants with AF had nearly 4 times the age, gender-adjusted risk of stroke (relative risk [RR], 3.87, 95% confidence interval [CI], 2.12–7.15), and twice the risk of death associated with all causes (RR, 2.23, 95% CI, 1.52–3.27). Further adjustment for body mass index, lifestyle factors, socioeconomic status and clinical diseases slightly attenuated these risks. In addition, after adjusting for echocardiographic measures, the following risks remained significant: the multivariate RRs were 2.90 (95% CI, 1.28–6.59) for risk of stroke and 2.05 (95% CI, 1.27–3.32) for risk of all-cause death among participants with AF.

Conclusion: Our data demonstrate that AF is a significant risk factor for stroke and all-cause death for the Chinese. © 2008 Elsevier Ireland Ltd. All rights reserved.

Keywords: Atrial fibrillation; Community-based cohort; Chinese

1. Introduction

Atrial fibrillation (AF) is associated with congestive heart failure and thromboembolic mortality and morbidity, and is highly prevalent among the elderly population [1–3]. The substantial clinical impact and potential curable disease of AF have made it mandatory for health professionals to understand the prevalence, incidence and associated factors of AF risk [1,4]. Although AF data on the Caucasian and African-American populations are available [5,6], less is known about Asians and other ethnicities, especially from the community-based general population [7,8]. In addition, various risk factors associated with AF are also related to cardiovascular events and all-cause death in the general population and in specific clinical settings [9], such as older age, poor left ventricular function and hypertension [2,10]. Previous studies, based on cohort follow-ups in the general population or hospital setting [11,12], have demonstrated

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that AF was a significant predictor for stroke and all-cause death. In addition, AF as a predictor for stroke and all-cause death in the Chinese general population is still unknown. Therefore, we investigated the AF risk based on the Chin-Shan Community Cardiovascular Cohort (CCC) study, which provided a unique opportunity to explore the new-onset AF using its serial follow-up and complete biochemical and anthropometric measurements of the adult participants living in the community.

2. Methods

2.1. Study design and study participants

Full details of the CCC study can be found in other publications [13–16]. Briefly, the CCC Study began in 1990 by recruiting 1703 men and 1899 women ≥35 years old, homogeneous in Chinese ethnicity, and living in the Chin-Shan township 30 km north of metropolitan Taipei, Taiwan. Information about anthropometry, lifestyle, and medical conditions was assessed by interview questionnaires in two-year cycles, and the validity and reproducibility of the collected data and measurements have been reported in detail [16]. The National Taiwan University College of Public Health Committee Review Board approved the study protocol.

2.2. Clinical measurements and echocardiographic measurements

In the survey, all of the study participants were individually interviewed from a structured questionnaire. Information was collected on their socio-demographic characteristics, physical activity, smoking, alcohol drinking habits, dietary characteristics, personal and family histories of diseases, and hospitalizations. Their body mass index was recorded and calculated as weight (in kilograms)/height (in meters) in baseline and serial measurements. Blood pressure was taken after 10 min of rest and measured by a mercury sphygmomanometer with the subject seated comfortably, with arms supported and positioned at the level of the heart. Two blood pressure readings were taken in both arms. The cuff bladder was inflated quickly and then deflated 2 mm Hg every second. If the readings varied by more than 10 mm Hg, an additional reading was taken. The disappearance of Korotkoff phase V sound was recorded as diastolic pressure. The medication rates of antihypertensive drugs were 11% in the study participants.

All echocardiographic studies were made with commercially available echocardiographs (HP2500) each equipped with a 2.5/2.0-MHZ phase-array transducer and a VHS videotape recorder as described in another study [17]. In brief, a two-dimensional parasternal long-axis view of left ventricle was obtained to adjust M-mode cursor position perpendicular to the interventricular septum and posterior wall of LV at the mitral valve chordal level. The left ventricular dimensions at end-diastole and at end-systole were measured and used to calculate left ventricular ejection fraction quantitatively. The ejection fraction was assessed by the area-length method in the apical four chamber view if regional wall motion abnormality was noted. Left ventricular mass was calculated from the Penn convention, according to the equation of Devereux and Reichek [18]. The intraclass correlation reliability was calculated by a simple replication one-way analysis of variance test. The values of correlation reliability were between 0.70 and 0.85 [17].

2.3. Identification of AF prevalence and incidence

Participants were examined at baseline and in the biennial follow-ups. Among the 3560 participants who had the available ECG data at baseline, 38 cases (1.07%) showed AF. For serial ECG tracking, 3116 undertook the first follow-up ECG in 1992–93, 2988 participants had their second visit in 1994–1995, 2645 had their fifth ECG in 1999–2000. Hospital records were obtained for hospitalization, with
adjudication of cardiovascular events by research committee [19]. Participants who were free from AF at baseline were defined as new-onset AF if AF was present on an electrocardiogram obtained from the serial follow ups. The electrocardiographic interpretation of AF was confirmed by one of three cardiologists (KC, TS, or WC).

Table 2

<table>
<thead>
<tr>
<th>Variable</th>
<th>No AF</th>
<th>AF</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean ± SD</td>
<td>N</td>
</tr>
<tr>
<td>Age, years</td>
<td>5322</td>
<td>54.8 ± 12.3</td>
<td>38</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>3501</td>
<td>23.5 ± 3.4</td>
<td>38</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>3505</td>
<td>125.5 ± 20.5</td>
<td>38</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>3500</td>
<td>198.1 ± 45.4</td>
<td>38</td>
</tr>
<tr>
<td>Triglyceride, mg/dL</td>
<td>3498</td>
<td>125.9 ± 95.9</td>
<td>38</td>
</tr>
<tr>
<td>HDL-cholesterol, mg/dL</td>
<td>3406</td>
<td>47.6 ± 12.7</td>
<td>37</td>
</tr>
<tr>
<td>LDL-cholesterol, mg/dL</td>
<td>3393</td>
<td>137.9 ± 44.1</td>
<td>37</td>
</tr>
</tbody>
</table>

Echocardiographic measures

| Left atrium, mm                | 2652       | 33.0 ± 5.7  | 27      | 45.5 ± 10.1  | <.0001  |
| IVS dimension, mm              | 2622       | 10.4 ± 2.4  | 27      | 11.6 ± 3.2   | 0.06    |
| LV posterior wall, mm          | 2622       | 10.0 ± 1.9  | 27      | 11.5 ± 1.9   | <.0001  |
| LVDD, mm                       | 2622       | 46.0 ± 5.6  | 27      | 48.7 ± 6.5   | 0.012   |
| LVDS, mm                       | 2621       | 28.2 ± 5.3  | 27      | 32.1 ± 8.7   | 0.029   |
| LV mass, g                     | 2622       | 193.9 ± 67.5| 27      | 259.6 ± 106.3| 0.004   |
| End-diastolic volume, mm³      | 2622       | 99.3 ± 27.9 | 27      | 114.0 ± 35.2 | 0.007   |
| End-systolic volume, mm³       | 2553       | 32.4 ± 14.7 | 27      | 46.0 ± 32.4  | 0.039   |
| LV ejection fraction           | 2621       | 0.68 ± 0.10 | 27      | 0.62 ± 0.16  | 0.05    |

Abbreviation: SD, standard deviation; IVS, interventricular septum; LV, left ventricular; LVDD, LV end-diastolic internal dimension; LVDS, LV end-systolic internal dimension.

SI conversion factor: To convert triglycerides to mmol/L, multiply values by 0.01134. To convert total, HDL, and LDL cholesterol to mmol/L, multiply values by 0.0259.

Fig. 1. Histograms of the prevalence rates in the baseline (upper, 1990–1991) and the incidence rates of atrial fibrillation during a median of 9.0 years’ follow-up period (lower, 1990–2000) of the study population. The 95% confidence intervals were estimated according to the exact binomial test.
2.4. Outcome ascertainment and definition

Incident CHD cases were defined by nonfatal myocardial infarction, fatal coronary heart disease and hospitalization due to percutaneous coronary intervention and coronary bypass surgery [13]. Fatal CHD was considered to have occurred if fatal myocardial infarction was confirmed by hospital records or if CHD was listed as the cause of death on the death certificate as the underlying and most plausible cause of death, or if evidence of previous CHD was available. Incident stroke cases were ascertained according to the following criteria: a sudden neurological symptom of vascular origin that lasted longer than 24 h, with supporting evidence from the image study [19]. Transient ischemic attacks were not included in this study. The cases were confirmed by internists. Deaths were identified from official certificate documents, further verified by house-to-house visits.

2.5. Statistical analysis

The gender and age specific prevalence and incidence rates of AF were plotted and 95% confidence intervals were presented and estimated according to the exact binomial test. The distributions of demographics, lifestyle factors, socioeconomic status, clinical measures and echocardiographic measures were presented according to prevalent AF status. Incidence rates of stroke and all-cause death events were calculated as the number of events per 1000 person-years at risk. Kaplan–Meier estimated event-free survival functions were plotted and the log-rank test was applied. The Cox proportional-hazards regression model was used to estimate the relative risk (RR) and 95% confidence interval (CI) associated with AF and the risk of stroke and all-cause death. We calculated the RR after adjusting confounding variables: Model 1 was adjusted for age groups (35–44, 45–54, 55–64, 65–74, >75 years old) and gender only. Model 2 included additional confounding factors: body mass index (<18, 18 to 20.9, 21 to 22.9, 23 to 24.9, or >=25 kg/m²), smoking (yes/no or abstinence), current alcohol drinking (regular/no), marital status (single, married and living with spouse, or divorced and separated), education level (less than 9 years, at least 9 years), occupation (no work, labor, office, or business), regular exercise habit (yes/no). Model 3 included more clinical covariates such as baseline hypertension (yes/no, defined by blood pressure at least 140/90 mm Hg or on medication), diabetes mellitus (yes/no, defined by fasting plasma glucose at least 126 mg/dL or on medication), and history of stroke and coronary heart disease. Model 4 included additional electrocardiographic left ventricular hypertrophy, and echocardiographic measures as left atrium, left ventricular mass and left ventricular ejection fraction in the model among the participants with available echocardiographic measures. We developed the scoring system (defined as LVEF<40%), hypertension, age 75 years or older, and diabetes mellitus and assigning 2 points for history of stroke or transient ischemic attack in applying to the subcohort who underwent echocardiographic data (n=2648).

We used the area under the curve of receiver operator characteristics (ROC curve) to compare the discriminative ability of various risk factors [21]. The area under the ROC curve was considered as a global performance indicator for a prognostic factor [22]. We calculated several performance measures to check the predictive power of AF for outcomes, including a reclassification table [23], Hosmer–Lemeshow statistics, net reclassification improvement (NRI) and integrated discrimination improvement (IDI), which provided new insight on model comparison and prediction [24]. Briefly, the NRI was a sum of differences between the ‘upward’ movement in categories for event subjects and the ‘downward’ movement in those for nonevent subjects [24]. We assumed the a priori risk categories according to quartiles and evaluated the NRI values in different risk settings. The IDI was viewed as a difference between improvement in average sensitivity and any potential

Table 3

| Incident cases, person-years, rates, relative risks, and 95% confidence intervals of stroke and all-cause death rates during a median of 13.8 years’ period according to prevalent AF status in the CCCC study participants |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Stroke          | AF(−)           | AF(+)           |                 |                 |
| Cases           | 196             | 12              |                 |                 |
| Person-year     | 44010.0         | 318.6           |                 |                 |
| Rates (/1000)   | 4.5             | 37.7            |                 |                 |
| Relative risk   | 95% CI          | P               |                 |                 |
| Model 1         | 1               | 3.87 (2.12–7.05) | <.0001         |                 |
| Model 2         | 1               | 3.85 (2.11–7.05) | <.0001         |                 |
| Model 3         | 1               | 3.58 (1.92–6.66) | <.0001         |                 |
| Model 4         | 1               | 2.90 (1.28–6.59) | 0.011          |                 |
| All-cause death |                 |                 |                 |                 |
| Cases           | 748             | 28              |                 |                 |
| Person-year     | 44661           | 340.0           |                 |                 |
| Rates (/1000)   | 16.7            | 82.3            |                 |                 |
| Relative risk   | 95% CI          | P               |                 |                 |
| Model 1         | 1               | 2.23 (1.52–3.27) | <.0001         |                 |
| Model 2         | 1               | 2.03 (1.38–2.98) | 0.0003         |                 |
| Model 3         | 1               | 1.96 (1.33–2.89) | 0.001          |                 |
| Model 4         | 1               | 2.05 (1.27–3.32) | 0.003          |                 |

Model 1 was adjusted for age groups (35–44, 45–54, 55–64, 65–74, >75 years old) and gender only. Model 2 included additional confounding factors: body mass index (<18, 18 to 20.9, 21 to 22.9, 23 to 24.9, or >=25 kg/m²), smoking (yes/no or abstinence), current alcohol drinking (regular/no), marital status (single, married and living with spouse, or divorced and separated), education level (less than 9 years, at least 9 years), occupation (no work, labor, office, or business), regular exercise habit (yes/no). Model 3 included more clinical covariates such as baseline hypertension (yes/no, defined by blood pressure at least 140/90 mm Hg or on medication), diabetes mellitus (yes/no, defined by fasting plasma glucose at least 126 mg/dL or on medication), and history of stroke and coronary heart disease. Model 4 included additional electrocardiographic left ventricular hypertrophy, and echocardiographic measures as left atrium, left ventricular mass and left ventricular ejection fraction in the model among the participants with available echocardiographic measures (n=2679).
increase in average ‘one minus specificity’ [24], and the statistic was a difference in Yates discrimination slopes between the new and old models [25,26].

All statistical tests were two-tailed and probability values less than 0.05 were considered statistically significant. Analyses were performed with SAS version 9.1 (SAS Institute, Cary, NC) and Stata version 9.1 (Stata Corporation, College Station, Texas).

3. Results

Of the 3560 participants with available electrographic data at baseline, 38 had established AF rhythm. Table 1 shows the baseline characteristics of study participants specified by prevalent AF status. Participants with prevalent AF were more likely to be male, of older age, white collar or no job status, and smokers, and more likely to have hypertension, diabetes and poor left ventricular ejection fraction than those without prevalent AF. The lifestyle factors, including alcohol intake and exercise habits, and socioeconomic status, including marital status, education level, and history of stroke and coronary heart disease were similar between participants with and without AF. Participants with AF were more likely to have a high age systolic blood pressure, and lower cholesterol levels than those without AF (Table 2). With regards to echocardiographic measures, participants with AF had higher measures of left atrium, left ventricular septum, posterior wall, dimensions, and left ventricular mass, yet had a lower left ventricular ejection fraction than those without AF. Overall, the incidence rates of AF were 1.68 per 1000 person-years for men and 0.76 per 1000 person-years for women (Fig. 1). The incidence of AF increased appreciably with increasing age, and the highest incidence rates were 4.3 per 1000 person-years for men in the 65–74 year group and 1.7 per 1000 person-years for women in 75 years or older (Fig. 1, lower).

During a median 13.8 years’ follow up (interquartile range, 13.5–14.6 years, total 45,001 person-years), we documented 208 cases of stroke, 122 cases of CHD and 776 deaths among the 3560 participants. The estimated cumulative event-free rate of stroke for participants with AF was 50%, as compared with 90% for those without AF, and the
cumulative event-free rate of all-cause death was similar (both the log-rank test, \( P<0.0001 \), Fig. 2). Incidence rates for stroke and all-cause death were significantly higher for participants with AF (Table 3); as compared with those without AF, participants with AF had nearly 4 times the age, gender-adjusted risk of stroke (RR, 3.87, 95% CI, 2.12–7.15), and twice the risk of death associated with all causes (RR, 2.23, 95% CI, 1.52–3.27). Further adjustments for body mass index, lifestyle factors, socioeconomic status and clinical diseases slightly attenuate the risks. In addition, after adjusting for echocardiographic measures including left atrium, left ventricular mass and ejection fraction status that are closely related with AF, the following risks remained significant: the multivariate RRs were 2.90 (95% CI, 1.28–6.59) for risk of stroke and 2.05 (95% CI, 1.27–3.32) for risk of all-cause death among participants with AF. However, we did not find significant association between AF and CHD risk (data not shown).

The mean (standard deviation) of CHADS2 score was 0.52 (0.75), and the distribution range was 0–4 in the study participants. Although the CHADS2 score was significantly associated with stroke risk (RR, 2.45, 95% CI, 2.11–2.90, \( P<0.001 \)) in the univariate model, the risk diminished appreciably after adjusting for other covariates. However, prevalent AF were still related to stroke risk in the same model (multivariate RR, 2.90, 95% CI, 1.28–6.59, \( P=0.011 \)). We concluded that CHADS2 risk score didn’t provide additional information for stroke prediction.

Table 4 shows the areas under the ROC curves, their Hosmer–Lemeshow goodness-of-fit statistics, integrated discrimination improvement, and net reclassification improvement between the extensive multivariate models with and without AF. The Hosmer–Lemeshow test did not reject the goodness of fit for any of the models. For stroke and all-cause death, the multivariate model with AF outperformed the model without AF in predicting the outcomes — that is, the areas under their ROC curves are in each case larger than the areas under the ROC curves for their counterpart without AF. Although IDI and NRI values increased somewhat, they did not reach any significant difference (all \( P>0.05 \)). The NRI values for stroke and all-cause death remained stable irrespective of risk category.

4. Discussion

In this prospective cohort of middle-aged to older ethnic Chinese, we clearly demonstrated AF as a significant predictor for stroke and all-cause death, after extensive adjustments. AF was also highly prevalent and incident among elderly Chinese adults.

Our findings are consistent with other population-based studies on the prevalence and incidence of AF risk [7,27]. With regards to the prevalence rates, our data were consistent with a cross-sectional survey data in the US [5] wherein the AF prevalence ranged widely from 0.1% among adults younger than 55 years to 9% among octogenarians. Age was an important determinant for AF risk. A survey on the Asian population reported relatively low rates for AF prevalence. A study on young healthy residents in northern India showed only 0.1% prevalence of AF [28]. Zhou and colleagues found that the age-standardized AF prevalence rate was only 0.61% among a representative Chinese sample of 2000 adults who were recruited randomly [29]. The Japanese survey showed a prevalence rate of 0.64% [30]. Our findings were also compatible with the European-based serial survey on participants of 50- to 89-year-olds, which showed AF incidence rates of 1.4–3.3% in men and 1.0–1.5% in women [31]. However, our findings showed an unexpectedly low incidence pattern of AF among ethnic Chinese. In the Framingham Heart Study that covered a 38-year follow-up period, Kannel and colleagues estimated the incidence of 2–3 cases per 1000 person-years of AF among participants of 55–64 years old [2]. A European-based cohort composed of participants of 55 years and older showed an overall incidence AF rate of up to 9.9 per 1000 person-years. According to this European data, the lowest rate was 1.1 per 1000 person-years among 55–59 years old and their results were similar to our data in the corresponding age groups. Furthermore, Psaty and colleagues have demonstrated that African-American ethnicity was associated with a lower risk of AF than whites in an elderly population composed of 5201 participants older than 65 years [6]. The high incidence rates (12.0 per 1000 person-years among African-Americans and 19.5 per 1000 person-years) were explained by the advanced age in the study population. Another study among the longitudinal community-based older cohort of Olmsted County, Minnesota was composed of 4618 adults with an average of 73 years. The adjusted incidence rates were much lower, ranging from 3.04 to 3.68 per 1000 person-years [32], which was comparable to our data in a similar age group. The relatively lower AF incidence rate in our data may be

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attributed to the rather young age of the cohort participants and having only electrocardiographic evidence as outcome measurements. Another possible explanation for the low AF rate was the lower rate of congestive heart failure risk in our participants, compared with the Caucasian population [9].

Our findings support the notion that AF is a significant predictor for stroke and all-cause death. Ohkawa and colleagues collected single electrocardiographic AF data from a randomly selected sample of 9483 Japanese adults (older than 30 years) and examined the mortality causes nearly 20 years later [30]. AF was associated with stroke and all-cause mortality. Among 6417 older adult residents (mean 73 years old) who were diagnosed as having first-time atrial fibrillation in Olmsted County, Minnesota, and followed up for 5 years, an appreciably high risk of death developed in the early months, indicating a comorbidity status of new developed AF [33]. For the risk of stroke, AF was a predictive factor for stroke among 7547 Swedish middle-aged men during a 28-year follow-up period [34].

Our investigation cannot prove that an elevated body mass index is related to the prevalence and incidence of AF, although obesity was identified as an important risk factor [35–39]. The nonsignificant association might be attributable to the relatively low body mass index among our study participants, compared with Caucasians so that inconclusive result was found. We also demonstrated that blood pressure, hypertension, diabetes and left ventricular hypertrophy were associated with AF prevalence, consistent with other population-based studies [5,8,40].

In our study, advanced age and male gender were significant risks for AF incidence, which was consistent with other studies. This is clearly an issue that deserves further attention as the elderly population continues to grow rapidly and public health burdens steadily increase. Regardless, elderly women also have high risks of developing AF and should be treated optimally for AF control [41,42]. The unmodifiable risk factors still have an important impact on AF incidence. Besides being male and having advanced age, lifestyle risk factors, including modest fish intake and moderate alcohol drinking, were associated with AF [43,44].

Our data showed that in addition to lifestyle factors and socioeconomic status, clinical hypertension, diabetes, and poor left ventricular ejection fraction were significantly associated with prevalent AF; these findings are consistent with previous studies [8,40]. Furthermore, various echocardiographic parameters, such as left atrium, left ventricular mass and ejection fraction, were appreciably associated with AF status [45]. Our data supported the additional information that echocardiography was a significant factor for further stroke and death events. Echocardiographic measurement for evaluating left ventricular function and structure could provide additional information for prognosis, which has become a gold standard for clinical practice.

To our knowledge, this is the first extensive investigation of the prevalence, incidence and effect on risk of stroke and all-cause death for AF among ethnic Chinese. Because of the prospective cohort design, the baseline measurements of all cohort members were unlikely to be affected by exposure factors and laboratory issues. The use of a community-based population could reduce the possibility of selection bias. We also included important socioeconomic status, lifestyle factors, clinical measures and echocardiographic parameters in the models to control the potential confounding factors.

Our study had several potential limitations. First, the incident cases of AF events were relatively so small that the power to detect the risk of AF might have been reduced. Second, we did not specify AF cases into paroxysmal vs. chronic AF separately, similar to the limitation of the Framingham cohort [40]. Third, we did not investigate the anti-arrhythmic medication or other treatment modality histories among the study subjects. For newly diagnosed AF, there exist efficient and useful treatment modalities for controlling the rhythm or rates [46]. We have no detailed treatment data for subjects who developed new-onset AF. Finally, with regards to the low antihypertensive medication rate in baseline, poor health service accessibility and low socioeconomic status of these participants may be the probable reasons. We didn’t clarify the detailed list of medication.

In conclusion, our data provided prevalent AF data among ethnic Chinese and we have demonstrated that AF was appreciably associated with the risk of stroke and all-cause death. Further research on AF prevention and treatment is warranted.

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References


