Relative and absolute risks of all-cause and cause-specific deaths attributable to atrial fibrillation in middle-aged and elderly community dwellers

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ABSTRACT

Background: The relative and absolute risks of outcomes other than all-cause death (ACD) attributable to atrial fibrillation (AF) stratified age have not been sufficiently investigated.
Methods: A prospective study of 23,634 community dwellers aged 40 years or older without organic cardiovascular disease (AF = 335, non-AF = 23,299) was conducted. Multivariate-adjusted rates, rate ratios (RRs) and excess deaths (EDs) for ACD, cardiovascular death (CVD) and non-cardiovascular death (non-CVD), and sex- and age-adjusted RR and ED in middle-aged (40 to 69) and elderly (70 years or older) for ACD, CVD, non-CVD, sudden cardiac death (SCD), stroke-related death (Str-D), neoplasm-related death (NPD), and infection-related death (IFD) attributable to AF were estimated using Poisson regression.
Results: Multivariate-adjusted analysis revealed that AF significantly increased the risk of ACD (RR [95% confidence interval]:1.70 [1.23–2.95]) and CVD (3.86 [2.38–6.27]), but not non-CVD. Age-stratified analysis revealed that AF increased the risk of Str-D in middle-aged (14.5 [4.77–44.3]) and elderly individuals (4.92 [1.91–12.7]), SCD in elderly individuals (3.21 [1.37–7.51]), and might increase the risk of IFD in elderly individuals (2.02 [0.80–4.65], $p = 0.098$). The RR of CVD was higher in middle-aged versus elderly individuals (RRs, 6.19 vs. 3.57) but the absolute risk difference was larger in elderly individuals (EDs: 7.6 vs. 3.0 per 1000 person-years).
Conclusions: Larger absolute risk differences for ACD and CVD attributable to AF among elderly people indicate that the absolute burden of AF is higher in elderly versus middle-aged people despite the relatively small RR.
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1. Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia and contributes to increased socioeconomic [1,2] and direct medical burden [3]. AF is associated with a 4 to 5-fold increased risk of stroke and thromboembolism, even in individuals with non-valvular AF [4].

AF also contributes to a 2-fold higher risk of all-cause death [5–12]. Since most studies were conducted in North America and Europe, whether AF is associated with the risk of all-cause death and stroke-related burden should also be investigated in other nations and ethnicities.

The prevalence of AF greatly increases with age both in Western countries [2,13] as well as regions outside North America and Europe [14]. If the relative risk (RR) of all-cause death and cardiovascular morbidity and mortality are similar between middle-aged and elderly individuals, absolute risk differences of outcomes

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attributable to AF would be markedly higher in elderly individuals because of their much higher prevalence of AF. Burdens due to AF should also be investigated separately in middle-aged and elderly populations.

Whether AF contributes to a higher risk for outcomes other than all-cause death or stroke-related burden has also not been sufficiently examined to date. If AF contributes to an increased risk of non-cardiovascular death, it is unclear which causes of death are increased by the presence of AF and whether the absolute risk difference for non-cardiovascular death is larger than the absolute risk difference of cardiovascular death due to AF.

Therefore, we attempted to determine the RR and absolute risk difference (expressed as the number of excessive deaths) of both cardiovascular and non-cardiovascular deaths attributable to AF among community dwellers without apparent cardiovascular disease separately in middle-aged and elderly groups.

2. Methods

2.1. Subjects

The study subjects were participants of the Iwate-Kenpoku Cohort Study (The Iwate-KENCO Study). The study region consists of the northern part of Iwate Prefecture (Fig. 1). The methodology of the Iwate-KENCO study has been described elsewhere [15,16]. The original cohort study sample consisted of 26,469 participants. We excluded subjects that were less than 40 years of age (n = 1100), participants with a history of myocardial infarction or stroke (n = 976), and those who lacked data for at least one explanatory variable in the analysis (n = 759). We analyzed data from participants (AF = 335, non-AF = 23,299) without organic cardiovascular disease to estimate the relative and absolute risks for all-cause and cause-specific deaths attributable to AF (Fig. 2). The study was approved by the Medical Ethics Committee of Iwate Medical University and conducted in accordance with the Declaration of Helsinki [15]. The authors of this manuscript certify that they have complied with the Principal of Ethical Publishing in the International Journal of Cardiology.

2.2. Initial investigation

The initial examination consisted of a questionnaire, measurement of blood pressure and anthropometric data, blood tests, and an electrocardiogram (ECG). The methods for determining serum lipid profiles, serum high-sensitivity C-reactive protein levels (hsCRPs), plasma glucose levels, plasma glycosylated hemoglobin (HbA$_{1c}$) levels, and urinary albumin to creatinine ratios (UACRs) were previously described [15,17,18]. A resting 12-lead ECG was performed in each participant after 5 min of rest. A trained clinical technician and a medical doctor in Iwate Health Service Association independently evaluated ECG findings according to the original coding system developed by the Iwate Health Service Association [15]. A past history of stroke or myocardial infarction was identified by self-administered questionnaires and review of data from the Iwate Prefecture Stroke Registration program and Northern Iwate Heart Disease Registry Consortium [19]. Details of the stroke registry [16,20–23] and heart disease registry [18,24] have been described previously.

Hypertension (HT) was defined as systolic blood pressure (SBP) of 140 mm Hg or higher, diastolic blood pressure (DBP) of 90 mm Hg or higher, use of antihypertensive agents, or a combination thereof. Diabetes mellitus (DM) was defined as plasma glucose level of 200 mg/dL or higher, plasma HbA$_{1c}$ level (National Glycohemoglobin Standardization Program (NGSP) equivalent value) of 6.5% or higher, use of anti-diabetes agents or a combination thereof. Dyslipidemia was defined as serum total cholesterol (TC) of 220 mg/dL or higher, serum high-density lipoprotein cholesterol (HDLC) level less than 40 mg/dL, use of anti-hyperlipidemia agents, or a combination thereof. Regular alcohol drinking was defined as consuming alcohol on 5 days or more per week. Regular exercise was defined as engaging in exercise for at least 60 min on at least 8 days per month. Metabolic syndrome (METS) was defined as having at least three of the following factors: overweight (body mass index (BMI) $\geq$25 kg/m^2), low HDLC (<40 mg/dL in men, <50 mg/dL in women), elevated blood pressure (SBP $\geq$ 130 mm Hg or DBP $\geq$ 85 mm Hg), or DM diagnosed based on criteria in the joint interim statement by NHLBI with some modifications [25]. Serum glucose and triglyceride levels were not used as inclusion criteria because non-fasting blood samples were collected.
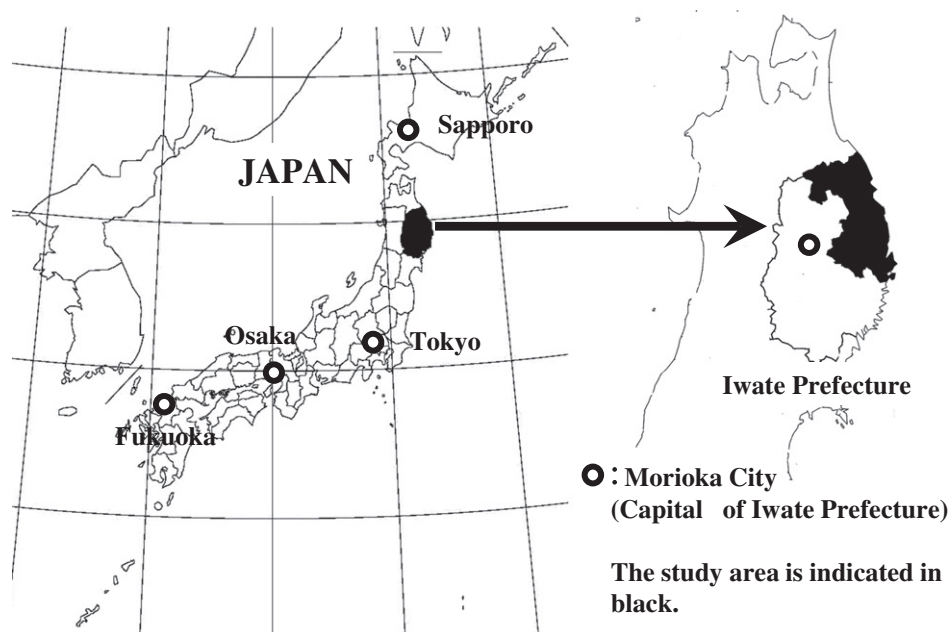

Fig. 1. The study area. This figure shows a map of Japan and a map of Iwate Prefecture. Iwate Prefecture is located in the northeastern part of the main island (Honshu Island) of Japan. The black area within Iwate Prefecture indicates the study area.