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Atrial fibrillation and risk of hip fracture: A population-based analysis of 113,600 individuals

Christopher X. Wong *[,1], Siang Wei Gan [1], Sarah W. Lee [1], Celine Gallagher [1], Ned J. Kinnear [1], Dennis H. Lau [1], Rajiv Mahajan [1], Kurt C. Roberts-Thomson [1], Prashanthan Sanders [1]

Centre for Heart Rhythm Disorders (CHRD), South Australian Health and Medical Research Institute (SAHMRI), University of Adelaide, Royal Adelaide Hospital, Adelaide, Australia

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ABSTRACT

Background: A number of cardiovascular diseases have been linked with bone health and an increased risk of osteoporotic fracture. Whether atrial fibrillation (AF) is associated with subsequent fracture risk is not known.
Methods: Administrative, clinical and hospitalisation information were linked over a 14-year period. From this longitudinal, population-based dataset of 113,600 individuals, time-dependent exposures using multivariate Cox proportional hazards regression models were employed to determine incidence rates and hazard ratios (HR) for hip fracture according to a history of AF.
Results: The annualised incidence rate for hip fracture was 7.4 per 1000 person-years (95% CI 7.1–7.7) in those without AF and 17.5 per 1000 person-years (95% CI 16.8–18.1) in those with AF. Compared to individuals without AF, those with AF were more likely to develop incident hip fracture in both men (unadjusted HR 2.39 [95% CI 1.96–2.91]) and women (unadjusted HR 2.91 [95% CI 2.55–3.34]). After adjusting for potential confounders, these associations were attenuated but remained statistically significant (adjusted HR 1.97 [95% CI 1.61–2.42] in men; adjusted HR 2.08 [95% CI 1.80–2.39] in women).
Conclusions: A history of AF was associated with an increased risk of hip fracture in this large, population-based analysis. This association appeared to remain significant even after adjusting for potential confounders such as age, comorbidities and medication use. Patients with a history of AF may represent a clinical population in whom screening for and treatment of osteoporosis may be warranted to reduce the risk of subsequent fracture.

1. Introduction

Atrial fibrillation (AF) is the most common, sustained heart rhythm disorder. Although the appropriate focus of clinicians and researchers is stroke-related morbidity and mortality, there is a growing appreciation that AF may have broader implications for patients. Recent data has demonstrated that AF is associated not only with an increased risk of stroke, heart failure and death, but also with outcomes not traditionally connected with AF, including ischaemic heart disease, sudden cardiac death, peripheral vascular disease and chronic kidney disease [1,2]. A further sequela of AF and these complications is significant healthcare utilisation that is likely to rise as the AF epidemic continues [3,4,19].

In the context of the ageing populations seen in developed countries, cardiovascular disease and osteoporosis are highly prevalent. A number of previous studies have highlighted the role that many cardiovascular diseases may have in increasing the risk of osteoporotic fractures. Ischaemic heart disease, peripheral vascular disease, stroke and heart failure have all been associated with fracture risk [5–7]. Like these other cardiovascular conditions, AF shares a number of risk factors with osteoporosis, including age, hypertension, diabetes and heart failure [8,9]. There is also evidence that mutual pathophysiologic mechanisms, potentially underpinned by common genetic pathways, may lead to both AF and osteoporotic fracture [9]. Moreover, the presence of AF itself may predispose to hip fracture, for example via an increased risk of falls that could be further exacerbated with medication use. To the best of our knowledge, however, the potential association between AF and fracture risk has not been previously examined in the literature. We thus used a large, longitudinal, population-based cohort to explore the risk of hip fracture in men and women associated with AF.

Abbreviations: AF, atrial fibrillation; ICD-10-AM, International Classification of Diseases, 10th Rev, Australian Modification; HR, hazard ratio; CI, confidence interval.

* Corresponding author at: Centre for Heart Rhythm Disorders, Department of Cardiology, Royal Adelaide Hospital, Adelaide, SA 5000, Australia.
E-mail address: c.wong@adelaide.edu.au (C.X. Wong).

[1] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

2. Methods

2.1. Study population

Administrative, clinical and hospitalisation databases from the Royal Adelaide Hospital, a tertiary referral centre and teaching hospital of the Universities of Adelaide and South

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Australia, were linked to aggregate data on patients managed at this institution over a 14-year period from 1999 through to 2012 inclusive. Patients with at least two hospital encounters and no history of hip fracture at baseline were included in analyses. Diagnoses of prevalent and incident hip fracture, AF and other comorbidities were ascertained from a comprehensive review of aggregated data. The accuracy of these linked databases has been previously demonstrated [10,11]. The *International Classification of Diseases, 10th Rev., Australian Modification* (ICD-10-AM) was used for coding diagnoses. Patients with prevalent and incident AF were identified using ICD-10-AM diagnosis code I48 that includes both AF and atrial flutter. A history of hip fracture was identified from ICD-10-AM diagnosis code S72. Other comorbidities we considered as covariates in our models included age, gender, ethnicity, smoking history, hypertension, diabetes, chronic obstructive pulmonary disease, ischaemic heart disease, heart failure, stroke, osteoporosis, hyperthyroidism, hypothyroidism, alcoholism and medication use (angiotensin converting enzyme inhibitors, angiotensin-receptor blockers, beta blockers, calcium channel blockers, diuretics, corticosteroids, calcium supplementation and hormone replacement therapy).

2.2. Statistical analysis

Summary statistics at baseline were computed for all participants and according to a history of AF. Continuous variables are reported as means with standard deviations and categorical variables reported as counts and percentages. Study sample characteristics according to subgroups were compared using an independent samples *t*-test for mean values and chi-squared tests for percentages.

To model time to incident hip fracture during study follow-up, multivariate Cox proportional hazards models were employed with survival time calculated from date of first contact as time origin to date of incident event. Age and gender were fitted as time invariant covariates, while comorbidities and medication use were fitted as time varying covariates. Participants diagnosed with incident AF contributed exposure time at risk for hip fractures to the non-AF subgroup before their AF diagnosis, and to the AF subgroup after their AF diagnosis. Once a participant was diagnosed with incident AF, they could not be later categorised as not having a history of AF. Each participant's observation time ended at the time of incident hip fracture, or loss to/end of follow-up, whichever occurred first. Baseline covariates were used as predictors. All models were stratified by sex given well-recognised differences in hip fracture incidence. Statistical tests were performed using Stata 13.0 (Stata Corporation, Texas, USA) and two-tailed *p*-value of $p < 0.05$ was considered statistically significant.

3. Results

3.1. Patient characteristics

A total of 115,401 individuals were identified for inclusion in these analyses. Of these, 113,600 individuals did not have a history of hip fracture at baseline. The mean age of study individuals was 55.8 years and 46.6% were female. A total of 5563 (4.9%) individuals had a history of AF. Compared to those without a history of AF, those with a history of AF were older, had significantly more comorbid conditions, and were more likely to be using prescription medications (Table 1).

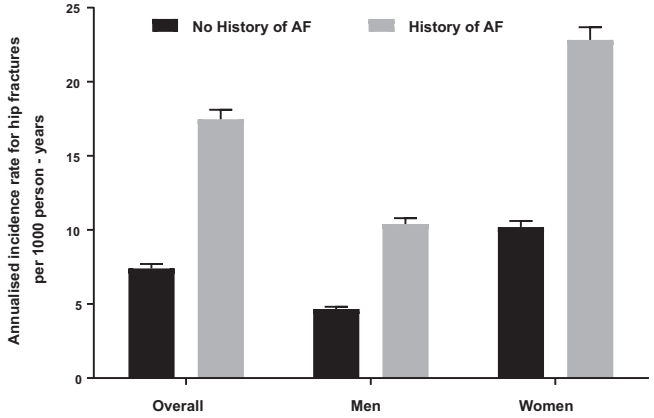

Fig. 1. Annualised incidence rates of hip fracture by gender and history of atrial fibrillation (AF).

3.2. History of AF and incidence of hip fracture

In the total study population, a total of 2560 cases of incident hip fracture (899 in men and 1661 in women) occurred over 345,480 person-years (193,222 person-years in men and 162,811 person-years in women). The annualised incidence rate for hip fracture in those with no history of AF over 345,480 person-years was 7.4 per 1000 person-years (95% CI 7.1–7.7); 4.7 per 1000 person-years (95% CI 4.5–4.8) in men and 10.2 per 1000 person-years (95% CI 9.8–10.6) in women (Fig. 1). In those individuals with a history of AF, including men and women, a total of 361 cases of incident hip fracture (113 in men and 223 in women) occurred over 20,678 person-years (10,909 person-years in men and 9769 person-years in women). The annualised incidence rate for hip fracture in those with a history of AF over 20,678 person-years was 17.5 per 1000 person-years (95% CI 16.8–18.1); 10.4 per 1000-person years (95% CI 10.0–10.8) in men and 22.8 per 1000-person years (95% CI 22.0–23.7) in women (Fig. 1).

3.3. Risk of hip fracture by history of AF status

Compared to individuals without a history of AF, those with a history of AF were more likely to develop incident hip fracture over the follow-

Table 1
Baseline patient characteristics.

	All patients ($n = 113,600$)	No history of AF ($n = 108,037$)	History of AF ($n = 5563$)	*P* Value
Age, mean (SD), y	55.8 (19.7)	55.0 (19.6)	71.9 (13.4)	<0.001
Female, n (%)	52,963 (46.6)	50,424 (46.7)	2539 (45.6)	0.13
Hypertension, n (%)	16,342 (53.4)	14,271 (13.2)	2071 (37.2)	<0.001
Diabetes, n (%)	13,868 (12.2)	12,493 (11.6)	1375 (24.7)	<0.001
IHD, n (%)	12,781 (11.3)	11,227 (10.4)	1554 (27.9)	<0.001
Heart failure, n (%)	4247 (3,7)	2888 (2.7)	1359 (24.4)	<0.001
Stroke, n (%)	2718 (2.4)	2289 (2.1)	429 (7.7)	<0.001
COPD, n (%)	3548 (3.1)	3038 (2.8)	510 (9.2)	<0.001
Osteoporosis, n (%)	1460 (1.3)	1331 (1.2)	129 (2.3)	<0.001
Hyperthyroidism, n (%)	178 (0.2)	153 (0.1)	25 (0.5)	<0.001
Hypothyroidism, n (%)	1468 (1.3)	1278 (1.2)	190 (3.4)	<0.001
Smoking history, n (%)	7580 (6.7)	7322 (6.8)	258 (4.6)	<0.001
Alcohol abuse, n (%)	3704 (3.3)	3580 (3.3)	124 (2.2)	<0.001
ACEI use, n (%)	12,434 (11.0)	10,595 (9.8)	1839 (33.1)	<0.001
ARB use, n (%)	3923 (3.5)	3504 (3.2)	419 (7.5)	<0.001
CCB use, n (%)	7569 (6.7)	6588 (6.1)	981 (17.6)	<0.001
BB use, n (%)	9.782 (8.6)	8080 (7.5)	1792 (30.6)	<0.001
Diuretic use, n (%)	9754 (8.6)	8025 (7.4)	1728 (31.1)	<0.001
Steroid use, n (%)	4103 (3.6)	3828 (3.5)	275 (4.9)	<0.001
Calcium supplement use, n (%)	2618 (2.3)	2348 (2.2)	270 (4.9)	<0.001
HRT use, n (%)	1004 (0.9)	952 (0.9)	52 (0.9)	0.68

AF indicates atrial fibrillation; SD, standard deviation; y, years; n, number; IHD, ischemic heart disease; COPD, chronic obstructive pulmonary disease; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; BB, beta blocker; and HRT, hormone replacement therapy.

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