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Incident Atrial Fibrillation and the Risk of Fracture in the Cardiovascular Health Study

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Abstract

In this prospective cohort of 4462 older adults, incident atrial fibrillation (AF) was not statistically significantly associated with subsequent risk of incident fracture.

Purpose—AF is associated with stroke, heart failure, dementia, and death, but its association with fracture is unknown. Therefore, we examined the association of incident AF with the risk of subsequent fracture in the Cardiovascular Health Study (CHS) cohort.

Methods—4462 CHS participants aged ≥65 years were followed between 1991 and 2009, mean follow up 8.8 years. Incident AF was identified by annual study ECG, hospital discharge diagnosis codes, or Medicare claims. Fractures of the hip, distal forearm, humerus, or pelvis were identified using hospital discharge diagnosis codes or Medicare claims. We used Cox proportional hazards models to estimate hazard ratios (HR) and 95% confidence intervals (CI) for the association between incident AF (time-varying) and the risk of subsequent fracture. We also evaluated whether AF was associated with risk of sustaining a fall.

Results—Crude incident fracture rate was 22.9 per 1,000 person-years in participants with AF and 17.7 per 1,000 person-years in participants without AF. Individuals with incident AF were not at significantly higher risk of hip fracture (adjusted HR=1.09, 95% CI 0.83, 1.42) or fracture at any selected site (adjusted HR=0.97, 95% CI 0.77, 1.22) or risk of sustaining a fall (adjusted HR=1.00, 95% CI=0.87-1.16) compared with those without AF.

Conclusion—In this cohort of older, community-dwelling adults, incident AF was not shown to be associated with falls or hip or other fractures.

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Keywords

Atrial fibrillation; arrhythmia; fracture; hip fracture

INTRODUCTION

More than 1.5 million osteoporotic fractures occur annually in the U.S and contribute to significant morbidity and mortality in the elderly [1, 2]. As the number of U.S. adults aged 65 years and older is expected to double over the next 25 years, there is a need to identify modifiable risk factors that influence fracture risk in older adults.

Atrial fibrillation (AF) is one potential risk factor for fractures. Stroke and heart failure, two conditions strongly associated with AF, have been associated with a higher risk of hip or other osteoporotic fractures [3]. Symptoms and complications of AF, such as weakness, dizziness, and decreased brain perfusion may increase the likelihood of falls [4]. Compared to individuals without AF, those with AF experience accelerated rates of cognitive decline and have a higher burden of covert brain infarctions and white matter abnormalities, which have been linked to impaired gait, and increased risk of falls and hip fractures [5-7]. In addition, warfarin, an anticoagulant used to prevent stroke, has been associated with reduced bone mineral density [8]. Warfarin use has been associated with a higher risk of fracture in some [9], but not all [10], observational studies.

One previous study in Taiwanese adults observed that incident AF was associated with a nearly two-fold increased risk of fracture[11]. However, the association between incident AF and fracture has not been assessed in a population generalizable to older U.S. adults. Therefore, the goal of this study was to examine the association of incident AF with the risk of hip and other fractures in older men and women using data from the Cardiovascular Health Study.

METHODS

The Cardiovascular Health Study (CHS) is a population-based longitudinal cohort study of coronary heart disease and stroke risk factors in individuals aged 65 years and older. Details about CHS have been published elsewhere [12]. Briefly, participants (N=5,888) were recruited from a random sample of Medicare beneficiary lists from four U.S. communities. The original CHS cohort (N=5201) was enrolled in 1989-1990, and 687 additional participants, predominantly African Americans, were enrolled in 1992-1993. Participants completed in-clinic examinations alternating with phone interviews every 6 months for the first ten years of the study, and phone interviews every 6 months thereafter. Clinic visits included ascertainment of medication use, laboratory tests, and electrocardiograms (ECGs), and participants were asked about hospitalizations at every contact. CHS obtained and reviewed medical records and discharge summaries for all hospitalizations. Additional surveillance for incident AF and fracture events was conducted via a linkage to Medicare claims for inpatient stays and outpatient visits, and physician claims for services covered under Medicare Part B. The institutional review boards for each study site approved the study, and all participants provided written informed consent.

Administrative claims data used to identify incident AF and fractures were available from 1991 onward and were available only for participants enrolled in fee-for-service Medicare (FFS). Therefore, participants not enrolled in FFS (n=737) were excluded from this analysis. Individuals entered the analytic cohort at the start of Medicare claims data availability and were censored if they disenrolled from FFS. For most participants, the start of Medicare claims data availability was approximately 1.5 years after CHS enrollment. Follow-up for this analysis extended through June 30, 2009. Individuals with prevalent AF (N=171) or a history of stroke or heart failure (N=436) at baseline were excluded from the analysis.

Exposure

The primary exposure was incident AF (defined as either atrial fibrillation or atrial flutter), ascertained from any of three sources: (1) ECGs from annual study examinations, (2) hospital discharge diagnoses indicating AF (from CHS follow-up or Medicare data), or (3) diagnoses of AF from outpatient or physician visits (from Medicare data). Study ECGs were read and interpreted by the CHS Electrocardiography Reading Center using standard methods. For AF identified using hospital discharge or Medicare data, a diagnosis of AF was based on a single inpatient claim or hospital discharge diagnosis or 2 outpatient or physician claims within 365 days (ICD-9-CM code 427.31 or 427.32) [13]. The date of AF diagnosis was based on the earlier of: (1) the date of ECG indicating AF, (2) the admission date of the hospitalization associated with the qualifying discharge diagnosis or qualifying inpatient claim, or (3) the service date of the second qualifying outpatient or physician claim. Once an AF diagnosis was made, participants were classified thereafter as having AF.

Outcomes

Fracture of the hip, distal forearm, humerus, and pelvis were ascertained using hospital discharge diagnoses, outpatient visit claims, and physician claims. Fractures at these sites are considered classic osteoporotic fractures because they are associated with low bone mineral density [14]. To minimize misclassification from rule-out diagnoses, diagnosis claims for fractures were required to have concomitant procedure codes consistent with treatment of a fracture, as defined by previously validated algorithms [15, 16]. The date of fracture was based on the admission date of the hospitalization associated with the qualifying discharge diagnosis or the service date of the outpatient or physician claim. Fractures may have occurred at more than one skeletal site.

Covariates

Participant age, sex, race, education, physical activity levels, alcohol use and smoking history were self-reported, at CHS study baseline. Body mass index (BMI, kg/m^2) was calculated from weight and height at CHS study baseline. Physical activity levels, alcohol use, smoking history, and BMI were updated at some clinic visits and the measurements closest to entry into FFS were used for the analysis. Antihypertensive medication use and use of warfarin or bisphosphonates were assessed and updated at each clinic visit using a medication inventory [17]. Diabetes (either prevalent or newly recognized) and hypertension were assessed and updated at each clinic visit (through 1999) and at each phone contact. Baseline and incident coronary heart disease, incident stroke, and incident heart failure were identified by the semi-annual contacts (telephone or clinic visit) or through linkage with

Medicare hospitalization data, and were confirmed by physician adjudication using medical and hospital records. AF-associated stroke risk was estimated using $CHADS_2$ (i.e. Congestive heart failure, Hypertension, Age, Diabetes, Stroke) scores. Individuals with $CHADS_2$ scores of 2 or higher are generally advised to receive oral anticoagulants as they are considered at high risk of stroke [18] For this analysis, $CHADS_2$ score was dichotomized (<2 points, ≥ 2 points).

Statistical Analysis

Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for the association between incident AF, modeled as a time-varying exposure, and the risk of fracture at any of the selected sites (hip, distal forearm, humerus, and pelvis) and the risk of incident hip fracture alone. All estimates were adjusted for age (continuous, in years), sex, race (white, non-white), clinic, education (beyond 12^{th} grade, yes/no), and baseline BMI (continuous, in kg/m^2), smoking (never, former, current), alcohol use (mean number of drinks per week), physical activity (continuous, in kcal/week), and the following time-varying binary covariates: hypertension, bisphosphonate use, coronary heart disease, diabetes. Analyses were repeated separately for men and women. Wald tests were used to assess effect modification by sex. Because stroke and heart failure may mediate the association between AF and fracture risk, analyses were repeated after adjustment for incident stroke or heart failure during follow-up (yes/no, modeled as a time-varying covariate). Secondary analyses were conducted to assess whether the association between incident AF and the risk of fracture differed by race, warfarin use (yes/no, time-varying), or $CHADS_2$ score (<2 points/≥2 points, time-varying), and tests for interaction conducted using the Wald test.

Because one of the mechanisms through which AF may influence the risk of fracture is through a fall, a secondary analysis was conducted to examine whether AF was associated with a higher risk of falling. Data on self-reported falls were only available through 1999, corresponding to the end of clinic visits. Because falls were self-reported over the entire past year, we could not be certain when a fall occurred. Therefore, we assigned the date of the first reported fall as the midpoint between clinic visits. We used Cox proportional hazards models to estimate the association between incident AF and the risk of a subsequent fall and adjusted for all covariates included in the primary analysis of incident AF and fracture risk.

All statistical analyses were conducted using STATA version 13.0 (Stata Corp, College Station, Texas).

RESULTS

Of 5,888 CHS enrollees, 4462 were included in the final analysis cohort (see Supplementary Figure 1). Compared to participants excluded from final analyses due to lack of enrollment in fee-for-service Medicare, those in the analysis cohort were less likely to be male (41% vs. 44%), more likely to be white (86% vs. 76%), and less likely to have hypertension (56% vs. 61%). Over a mean follow-up of 8.8 years, 1007 (23%) of participants in the analysis cohort developed AF and 717 (16%) sustained a fracture, 421 at the hip. Of participants diagnosed with AF during follow-up, 9% had AF initially identified by study ECG, 66% from an

inpatient claim or hospitalization, and 25% from an outpatient or physician claim. Incident AF was more common in men, and participants who developed incident AF were more likely to have hypertension, diabetes, and coronary heart disease at baseline (Table 1).

The crude incidence rate of composite fracture (hip, distal radius, humerus, pelvis) was 22.9 per 1,000 person-years in participants with AF and 17.7 per 1,000 person-years in participants without AF. In multivariable-adjusted models, participants with incident AF were not at statistically significantly higher risk of fracture (adjusted composite fracture HR=0.97; 95%CI=0.77-1.21; adjusted hip fracture HR=1.09; 95%CI=0.84-1.43) compared with those without AF (Table 2). The crude AF incidence rates suggested a higher risk of composite fracture in participants with AF than in those without, but the adjusted HR indicated no association. Confounding by sex was the primary reason for this difference in associations, as men were at higher risk for AF, but at lower risk for fracture. Estimates for the association between incident AF and hip or composite fractures were higher in women than men, but confidence intervals were wide and tests for effect modification were not statistically significant ($p>0.05$ for both fracture types). Additional adjustment for incident stroke and heart failure did not materially change these estimates.

There was marginal evidence that the association between incident AF and the risk of hip fracture may differ by oral anticoagulant use. Among participants who used warfarin, those with AF were at a statistically significantly higher risk of hip but not composite fractures compared with those without AF, whereas among individuals not using warfarin, incident AF was not associated with a statistically significantly higher risk of either type of fracture (Supplementary Table 1). There was no evidence that the relationship between incident AF and fracture risk differed by race, or $CHADS_2$ score ($p>0.05$ for interaction for each comparison).

The secondary analysis of incident AF and the risk of a subsequent self-reported fall included 4258 participants with data on falls. Over a mean follow-up of 6.3 years, 590 (14%) of participants developed AF, and 1815 (43%) reported a fall. Participants with incident AF were not shown to be at higher risk of sustaining a fall than those without incident AF (Crude rates = 117.2 and 61.7 per 1,000 person-years, respectively; adjusted HR=1.00, 95% CI=0.87-1.16).

DISCUSSION

We observed no statistically significant association between incident AF and risk of subsequent fracture in this large cohort of community-dwelling older men and women. Results were consistent for multiple types of fractures and unchanged after adjustment for multiple potentially confounding variables, including demographics, medical history, medication use, and stroke risk. These findings countered our hypothesis that AF would independently increase risk of fractures.

These findings are in contrast to those by Lai et al., who observed that individuals with AF were at higher fracture risk than those without AF in a Taiwanese population [11]. Our study differed from the study by Lai and colleagues in several ways beyond the differing

populations studied. Lai et al. included individuals with prevalent heart failure or a history of stroke. We excluded such individuals to study the AF-fracture association independent of stroke and heart failure. The risk estimates for the AF-fracture association in Lai et al. were adjusted for the individual's total number of comorbidities (up to 7) rather than directly adjusted for specific comorbidities known to be linked to both AF and fracture, and thus may be partly due to residual confounding. Finally, we had extensive information about other confounding factors that would not have been available from administrative claims data used by Lai et al., including lifestyle factors, medications, and indicators of socioeconomic status.

One of the primary mechanisms through which we hypothesized that AF would influence the risk of fracture was through an increased risk of falling. However, we did not observe an association between incident AF and the risk of falls. Possibly our inability to determine the exact date of falls obscured any relationship between incident AF and the risk of falls. Since warfarin inhibits the carboxylation of osteocalcin, an important factor in bone metabolism and the maintenance of bone mineral density, we thought a positive association between AF and fractures may be attributable to warfarin use among patients with AF [19]. However, individuals with AF judged by their physicians to be at high risk of falling are less likely to be prescribed warfarin [20]. This complexity is reflected in these analyses, as we observed that among participants with AF, the crude fracture rate was higher in warfarin non-users than in users.

This study has several strengths. We used data from a population-based longitudinal cohort study with extensive information on potential confounders. Multiple data sources were used to identify incident AF and fractures, including capturing clinically unrecognized AF and fractures diagnosed and treated outside of the hospital.

There are also several limitations to this study. AF can occur transiently and in the absence of symptoms. Episodes of AF that did not rise to clinical attention and were not detected on ECG during the annual exams through 1999 would have been missed and would have resulted in under-ascertainment of incident AF. Assuming that errors in measuring AF are non-differential, this may have attenuated any associations between incident AF and the risk of fracture. Administrative claims data were used to identify both incident AF and fracture. Administrative claims data may include both random and potentially systematic errors in coding diagnoses and procedures. We attempted to reduce the bias from coding inaccuracies in fracture ascertainment by utilizing previously validated algorithms. We required two outpatient or physician claims for AF to minimize rule-out diagnoses [13]. Finally, we were not able to distinguish between paroxysmal or persistent AF, and the risk of fracture may differ by AF type.

In summary, we found that in a large cohort of older adults, incident AF was not independently associated with an increased risk of falls or with subsequent hip or other fractures. The results of this study suggest that prevention of AF alone will not reduce the burden of fracture in older adults. Additional studies are needed to identify preventable risk factors for fractures in the elderly.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Baseline characteristics of participants

Characteristic	All N=4462	No AF during follow-up N=3455	Incident AF during follow-up N=1007
Age, mean (SD)	74 (5)	73 (5)	74 (5)
Male, %	40.6	38.2	48.5
White, %	85.9	84.8	89.9
Education beyond 12th grade, %	43.8	43	46.3
Smoking, %			
Current	12.4	13.1	9.9
Former	41	40.2	43.6
Alcohol use, %	50.3	50.1	51.2
Mean number of drinks per week (SD)	5.2 (16.3)	5.3 (18.0)	5.2 (8.6)
Physical activity (kcal) per week, mean (SD)	1791 (2075)	1802 (2094)	1756 (2012)
Body mass index (kg/m2), mean (SD)	26.6 (4.7)	26.6 (4.7)	26.8 (4.7)
Diabetes, %	14.6	14.1	16.2
Coronary heart disease, %	18	16.2	24.3
Chronic kidney disease, %	37.1	36.1	40.8
Hypertension, %	56.1	54.9	60.6
Antihypertensive medication use, %	45.2	43.4	51.2
Bisphosphonate use, %	2.8	2.7	3.1
Gait speed (m/s), mean (SD)	0.87 (0.21)	0.87 (0.21)	0.87 (0.20)

Table 2

Incident AF and the risk of fracture, overall and by sex

	No AF			Incident AF			Hazard Ratio (95% Confidence Interval)[a]		
Outcome	**Number of events**	**Person-years**	**Rate per 1,000 person-years**	**Number of events**	**Person-years**	**Rate per 1,000 person-years**	**Minimally adjusted[b]**	**Fully adjusted[c,d]**	**Further adjusted for incident stroke and heart failure**
Any fracture									
All	620	35044	17.7	97	4228	22.9	1.01 (0.81, 1.26)	0.97 (0.77, 1.21)	0.97 (0.77, 1.22)
Men	130	13037	10.0	25	2063	12.1	0.70 (0.45, 1.09)	0.66 (0.42, 1.04)	0.66 (0.41, 1.04)
Women	490	22008	22.3	72	2165	33.3	1.12 (0.87, 1.45)	1.07 (0.82, 1.38)	1.08 (0.83, 1.42)
Hip fracture									
All	351	36716	9.6	70	4476	15.6	1.15 (0.89, 1.50)	1.09 (0.83, 1.43)	1.06 (0.80, 1.40)
Men	82	13306	6.2	19	2107	9.0	0.80 (0.48, 1.34)	0.75 (0.44, 1.28)	0.75 (0.44, 1.29)
Women	269	23410	11.5	51	2369	21.5	1.31 (0.96, 1.78)	1.22 (0.89, 1.67)	1.17 (0.84, 1.62)

[a] Referent category is No AF

[b] Adjusted for age, sex, race and clinic

[c] Adjusted for age, sex, race, clinic, education, BMI, smoking, alcohol use, physical activity, hypertension (time-varying), coronary heart disease (time-varying), diabetes (time-varying), and use of bisphosphonates (time-varying)

[d] Estimates by sex represent stratified analyses. Wald p-values for effect modification by sex, p=0.28 and p=0.27 for any fracture and hip fracture, respectively; a single model with an interaction term between AF and sex was used to assess effect modification.