



Effect of Atrial Fibrillation on the Incidence and Outcome of Osteoporotic Fracture

— A Nationwide Population-Based Study —

Daehoon Kim, MD; Pil-Sung Yang, MD; Tae-Hoon Kim, MD;
Jae-Sun Uhm, MD, PhD; Junbeom Park, MD, PhD; Hui-Nam Pak, MD, PhD;
Moon-Hyoung Lee, MD, PhD; Boyoung Joung, MD, PhD

Background: Both atrial fibrillation (AF) and osteoporosis are common in older adults. The purpose of this study was to investigate whether comorbid AF in patients with osteoporosis is associated with fracture incidence, or death after fracture.

Methods and Results: From the National Health Insurance Service database of Korea, we selected 31,778 patients with osteoporosis. During a median follow-up of 48 months, the incidence of bone fractures was higher in AF patients than in non-AF patients (3.20 vs. 2.18 per 100 person-years), respectively. In the multivariate Cox regression analysis, AF was associated with fracture independently of other risk factors with an adjusted hazard ratio (HR) of 1.21 (95% confidence interval [CI], 1.02–1.41; $P=0.031$). The mortality rate after fracture was significantly higher in AF patients than it was in non-AF patients (adjusted HR, 1.92; 95% CI, 1.35–3.27; $P=0.016$). After propensity score-matching, AF was consistently associated with a higher risk of osteoporotic fracture and subsequent death after fracture. In AF patients, older age, female sex, being underweight (body mass index <18.5 kg/m²), decreased physical activity (exercise <3 times/week), history of stroke or transient ischemic attack, thiazide use, sedative use, and higher CHA₂DS₂-VASc (≥ 2 points) scores were associated with the incidence of fractures.

Conclusions: Comorbid AF in patients with osteoporosis was associated with an increased risk of bone fracture and death after fracture.

Key Words: Atrial fibrillation; Death; Fractures; General population; Osteoporosis

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in the elderly and it is associated with an increased risk of stroke, heart failure (HF), dementia, and death.^{1,2} Osteoporosis is another common medical issue in the elderly. The 2 conditions share common etiological factors, including age, hypertension (HTN), diabetes mellitus (DM), and HF.^{3,4} Bone fractures are a frequent and important cause of disability and medical costs worldwide.^{5,6} Prior studies have found that cardiovascular diseases, such as ischemic heart disease, stroke, HF, and peripheral vascular disease, increase a patient's risk of hip and other bone fractures.^{7–9}

AF is a potential risk factor for fractures, because it not only causes structural and functional alterations in the cardiovascular system, but also exerts thromboembolic effects on the nervous system, and disturbs postural steadiness. Therefore, AF is now recognized as an independent

risk factor for non-accidental falls.¹⁰ Vitamin K antagonists, which are used to prevent stroke in AF, might be associated with reduced bone mineral density (BMD) and increased risk of osteoporotic fracture.^{11–13} With respect to bone strength, the thromboembolic effects of AF may reduce bone mass through reduction in the osseous blood supply.¹⁴ We thus hypothesized that comorbid AF would be associated with incidental bone fractures. However, there is controversy regarding the association between AF and fracture risk.^{15–17} We also hypothesized that AF would be related to increased mortality after fracture events. We aimed to investigate whether comorbid AF was associated with fracture occurrence or death in patients with osteoporosis using a large-scale database maintained by the Korean National Health Insurance Service (NHIS).

Received October 23, 2017; revised manuscript received April 4, 2018; accepted April 11, 2018; released online May 24, 2018
Time for primary review: 63 days

Division of Cardiology, Yonsei University College of Medicine, Seoul (D.K., P.-S.Y., T.-H.K., J.-S.U., H.-N.P., M.-H.L., B.J.); Department of Cardiology, CHA Bundang Medical Center, CHA University, Seongnam (P.-S.Y.); and Department of Cardiology, School of Medicine, Ewha Womans University, Seoul (J.P.), Republic of Korea

The first two authors contributed equally to this work (D.K., P.-S.Y.).

Mailing address: Boyoung Joung, MD, PhD, Professor of Medicine, Cardiology Division, Yonsei University College of Medicine, 50 Yonsei-ro, Seodaemun-gu, Seoul 03722, Republic of Korea. E-mail: cby6908@yuhs.ac

ISSN-1346-9843 All rights are reserved to the Japanese Circulation Society. For permissions, please e-mail: cj@j-circ.or.jp

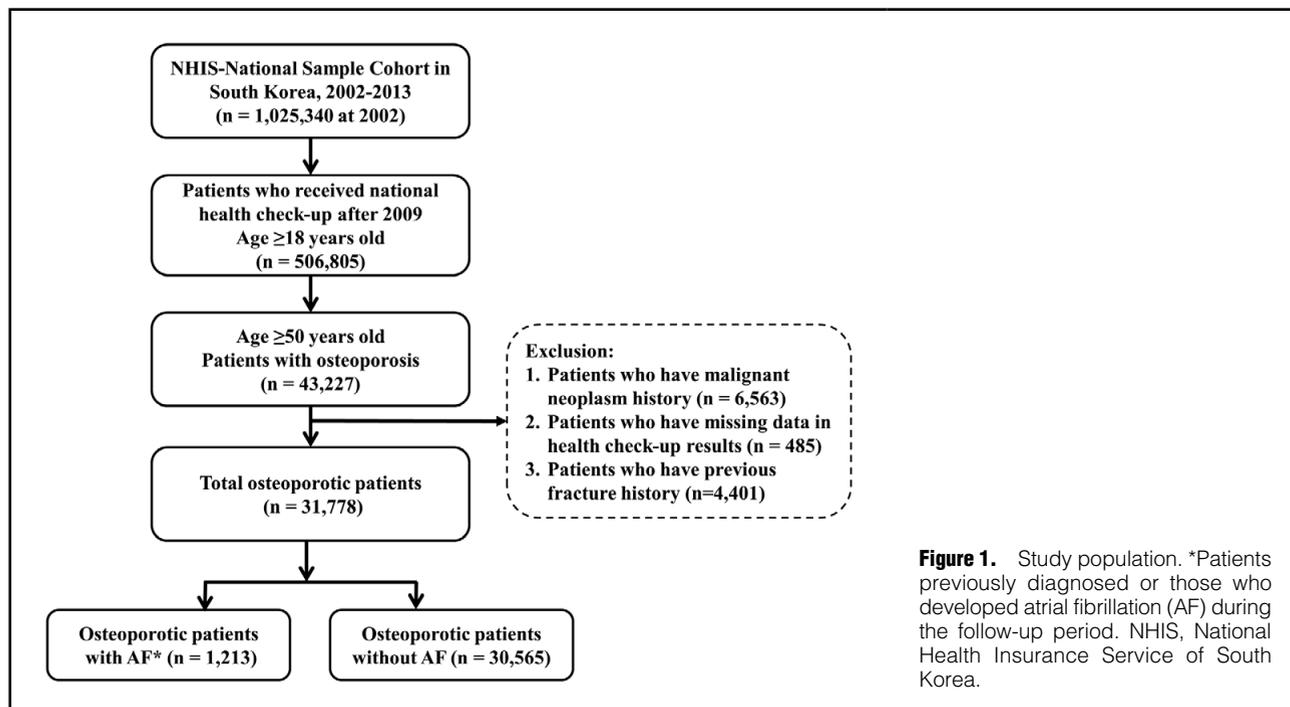


Figure 1. Study population. *Patients previously diagnosed or those who developed atrial fibrillation (AF) during the follow-up period. NHIS, National Health Insurance Service of South Korea.

Methods

Data Source

We used the National Sample Cohort (NSC) of the NHIS database, which was released by the Korean NHIS in 2015 for research purposes. The Korean NHIS was founded in 1963 as the single insurer managed by the Korean government. Most (97.1%) South Koreans are mandatory subscribers, with the remaining 3% of the population being medical aid subjects, so every South Korean is enrolled in the NHIS database. The NHIS-NSC database consists of detailed healthcare data from 1,025,340 enrollees, representing approximately 2.2% of Korea's population in 2002 (46,604,433). These patients were followed for 11 years (up to 2013). The database contains the following medical information: sociodemographic information, use of inpatient and outpatient services, pharmacy dispensing claims, and mortality data. Because all enrollees are required to undergo at least biennial national health examinations, the database also provides baseline laboratory data and health-related risk factors, which were updated periodically during the 5-year follow-up period (January 2009–December 2013).¹⁸

This study was approved by the Institutional Review Board of Yonsei University Hospital. Informed consent was waived. Data were fully de-identified prior to analysis.

Study Population and Data Collection

Among 506,805 subjects (aged ≥ 18 years) who underwent national health examinations between 2009 and 2013, a total of 43,227 patients aged ≥ 50 years with a diagnosis of osteoporosis during the screening period from January 2002 to December 2008 were identified. Patients with malignant neoplasms ($n=6,563$) were excluded in order to avoid pathologic fractures related to underlying malignancies. A total of 485 patients were excluded because of missing health examination data. Patients with a history of bone

fracture ($n=4,401$) were excluded. Finally, 31,778 patients were included (**Figure 1**).

Baseline comorbidities were evaluated during the 7-year screening period (January 2002–December 2008), and identified from the medical claims according to the codes of the International Classification of Disease 10th Revision (ICD-10). Osteoporosis was diagnosed using ICD-10 codes M80-, M81-, and M82- (excluding M82.0; osteoporosis in multiple myelomatosis). AF was diagnosed using ICD-10 code I48, which includes both AF and atrial flutter. We excluded patients with a record of either mitral stenosis (I05.0, I05.2, and I34.2) or prosthetic heart valves (Z95.2–Z95.4), resulting in a typical “non-valvular” AF population. In order to ensure diagnostic accuracy, we defined patients with osteoporosis, AF, and other comorbidities (including HF, HTN, DM, chronic obstructive pulmonary disease [COPD], chronic kidney disease [CKD], peripheral arterial disease [PAD], a history of myocardial infarction [MI], and a history of stroke and/or transient ischemic attack [TIA]) when it was a discharge diagnosis or was confirmed at least twice in an outpatient setting, which was similar to previous studies using the NHIS-NSC.^{19–21} The definitions of comorbidities are presented in **Table S1**. The CHADS₂ and CHA₂DS₂-VASc scores for each subject were estimated at the end of the screening period. Prescription medication use was ascertained by identifying NHIS database claims. To avoid underestimation of aspirin utilization because of over-the-counter (OTC) purchases in the study population, we included this source in our analysis.

Outcomes and Follow-up

The primary clinical outcome was a bone fracture requiring hospitalization during the 5-year follow-up period (January 2009–December 2013). Bone fracture was based on the principal diagnosis of hospital admission according to the ICD-10 codes (**Table S1**). To exclude fractures caused by trauma, any fractures that accompanied a record of motor

Characteristics	All patients with osteoporosis (n=31,778)		
	AF (n=1,213)	Non-AF (n=30,565)	P value
Age, years	69.9±8.4	65.3±8.7	<0.001
Female	1,031 (85.0)	28,086 (91.9)	<0.001
BMI, kg/m ²	24.4±3.6	24.1±3.2	0.003
Ex-/current smoker	137 (11.3)	2,463 (8.1)	<0.001
Alcohol use, glasses/week	1.5±6.4	1.8±8.3	0.167
Physical activity, times of exercising/week*	2.6±2.6	2.8±2.6	0.009
CHADS ₂ score	2.1±1.4	1.1±1.2	<0.001
CHA ₂ DS ₂ -VASc score	3.9±1.7	2.7±1.6	<0.001
Medical history			
HF	404 (33.3)	2,289 (7.5)	<0.001
HTN	983 (81.0)	16,440 (53.8)	<0.001
DM	271 (22.3)	4,379 (14.3)	<0.001
History of stroke/TIA	291 (24.0)	3,689 (12.1)	<0.001
History of MI	100 (8.2)	599 (2.0)	<0.001
PAD	394 (32.5)	7,259 (23.7)	<0.001
COPD	335 (27.6)	4,878 (16.0)	<0.001
CKD	351 (28.9)	4,360 (14.3)	<0.001
Cardiac medications			
Antiplatelet drugs	677 (55.8)	8,462 (27.7)	<0.001
Vitamin K antagonists	288 (23.7)	97 (0.3)	<0.001
β-blockers	538 (44.4)	6,030 (19.7)	<0.001
Calcium-channel blockers	618 (50.9)	10,363 (33.9)	<0.001
Digoxin	210 (17.3)	261 (0.9)	<0.001
Antiarrhythmic drugs*	100 (8.2)	47 (0.2)	<0.001
ACEI or ARB	597 (49.2)	7,801 (25.5)	<0.001
Loop diuretics	210 (17.3)	943 (3.1)	<0.001
Thiazide diuretics	427 (35.2)	6,084 (19.9)	<0.001
Spirolactone	161 (13.3)	856 (2.8)	<0.001
HMG-CoA reductase inhibitors	457 (37.7)	7,877 (25.8)	<0.001
Noncardiac medications			
Proton pump inhibitors	169 (13.9)	2,948 (9.6)	<0.001
Corticosteroids	149 (12.3)	3,615 (11.8)	0.630
Osteoporosis medications [†]	182 (15.0)	5,561 (18.2)	0.005
Thyroid replacement	66 (5.4)	1,272 (4.2)	0.030
Anticonvulsants	146 (12.0)	2,491 (8.1)	<0.001
Sedatives [‡]	618 (50.9)	11,170 (36.5)	<0.001
Selective serotonin reuptake inhibitors	41 (3.4)	571 (1.9)	<0.001

Data are expressed mean ± standard deviation or number (%). *Antiarrhythmic drugs included class Ic and class III drugs. †Osteoporosis medications included bisphosphonates, calcitonin, estrogen preparations, hormone replacement therapy, selective estrogen-receptor modulators, ipriflavone, and recombinant parathyroid hormone. ‡Sedatives included benzodiazepines, chloral hydrate, buspirone, and zopiclone. ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin-receptor blocker; BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HF, heart failure; HTN, hypertension; MI, myocardial infarction; PAD, peripheral artery disease; TIA, transient ischemic attack.

vehicle accident on the same date, open fractures, skull/facial bone fractures, finger fractures, and toe fractures were excluded. Major fracture events were defined as hip fractures, vertebral fractures, and fractures of the pelvis and acetabulum. All remaining bony fractures were considered as minor. The follow-up period was from the index date to the date of either the first fracture, detection of a malignancy, withdrawal from the NHIS-NSC (including death), motor vehicle accident, or the end of data collection (31 December 2013), whichever occurred first. To evaluate deaths after fracture, patients were followed from the time of the first fracture until death during any subsequent

inpatient course.

Diagnosis Validation

In order to evaluate the accuracy of our definition of osteoporosis, we conducted a validation study using medical records between 2009 and 2013. After excluding patients with M82.0 (as described), we identified 5,314 patients using the ICD-10 codes M80-, M81-, and M82-. Osteoporosis diagnosis was based on the patient's BMD, measured using central dual X-ray absorptiometry according to the World Health Organization criteria.²² The positive predictive value (PPV) was 96% (5,101 of 5,314 patients).

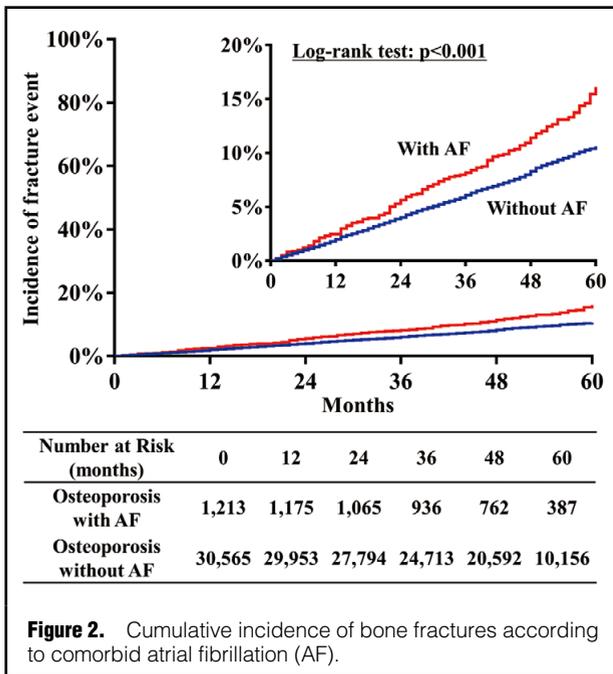


Figure 2. Cumulative incidence of bone fractures according to comorbid atrial fibrillation (AF).

In order to validate our diagnosis of bone fracture, 498 patients were randomly chosen based on their inpatient principal diagnoses using ICD-10 codes from a single tertiary medical center. Their radiographic findings, including x-rays and CT scans, were reviewed. The PPV was 98% (494 of 504 patients).

The diagnostic accuracy of AF (with a PPV of 94.1%), MI (with a PPV of 86.5%), ischemic stroke (with a PPV of 88–95%), and intracranial hemorrhage (with a PPV of 78–92%) in the Korean NHIS has been validated previously.^{19–21,23}

Propensity Score-Matching Analysis

We performed propensity score-matching to reduce the potential selection bias associated with an observational study. Propensity scores were estimated using a non-parsimonious multiple logistic regression model. The following 16 variables were entered: age, sex, BMI (body mass index), HF, HTN, DM, previous stroke/TIA, previous MI, PAD, COPD, CKD, CHADS₂ score, CHA₂DS₂-VASc score, smoking history, alcohol (glasses per week), and physical activity (exercise sessions/week). The cases were then matched (without replacement) with controls 1:1 based on the closest possible value of the propensity score (nearest neighbor matching). The caliper size was set at 0.10-fold the standard deviation of the logit of the propensity scores.²⁴ Based on this propensity score-matching, we assembled a cohort of patients with AF (n=1,209) and matched patients without AF (n=1,209). The balance between the 2 groups was checked by paired comparison tests and standardized differences of the 16 baseline covariates.²⁵

Statistical Analysis

Continuous variables are expressed as mean±standard deviation. Normally distributed continuous data in both cohorts were compared using unpaired Student's t-test. Categorical variables were compared with χ^2 -analysis with Fischer's exact correction. Kaplan-Meier survival curves for

bone fractures and deaths after fractures were constructed. They were compared in-between using the log-rank test. In order to investigate the association between the presence of AF and the risk of fracture in patients with osteoporosis, we used Cox proportional hazards regression models. We also conducted a sensitivity analysis: to control for possible confounding by instability caused by stroke, the regression models were reevaluated with exclusion of patients who had a stroke history at the time of entry into the cohort.

P<0.05 were considered statistically significant. All analyses were performed using SPSS software version 23.0 (SPSS, Chicago, IL, USA).

Results

Patients' Characteristics

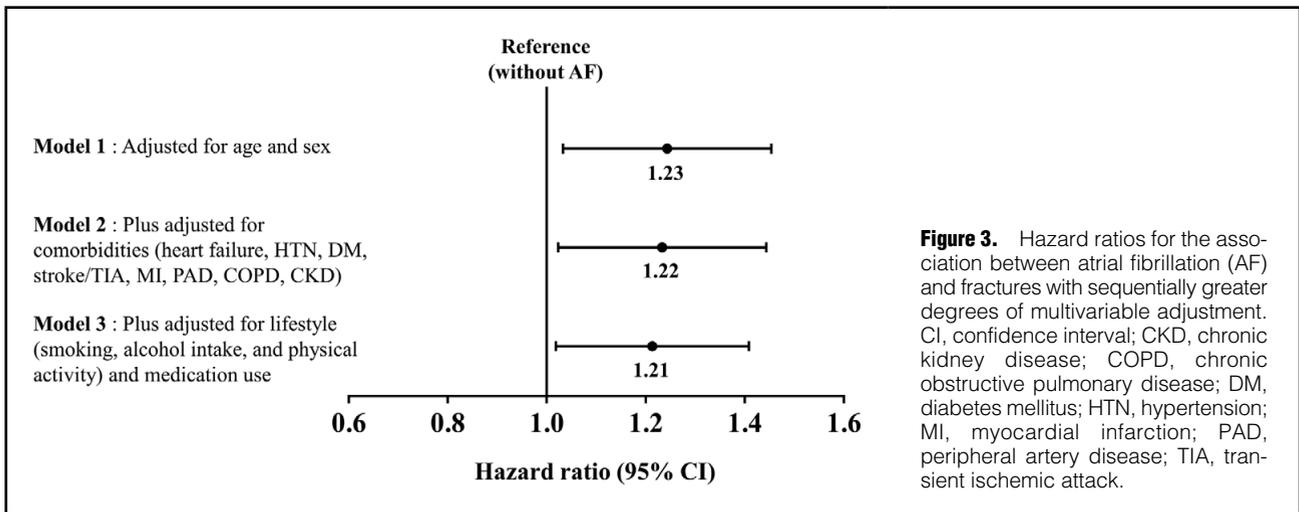
The patients' clinical characteristics are presented in **Table 1**. In general, the AF group was older (69.9 ± 8.4 vs. 65.3 ± 8.7 , P<0.001) and included fewer females (85.0% vs. 91.9%, P<0.001) than the non-AF group. The proportions of comorbidities, including HF, HTN, DM, stroke/TIA, MI, PAD, COPD, and CKD, were higher in the AF group than in the non-AF group (all P<0.001). The CHADS₂ and CHA₂DS₂-VASc scores were higher in the AF group (both P<0.001). The patients in the AF group had higher BMI (P<0.001) and were less physically active (P=0.009).

Risk of Osteoporotic Fracture by the Presence of AF

During a median 48 months of follow-up (interquartile range, 36–60 months), the incidence rates of fracture were higher in the AF group than in the non-AF group (total fracture: 3.20 vs. 2.18 per 100 person-years; major fracture: 1.92 vs. 1.13 per 100 person-years; **Table S2**). The test for subgroup difference indicated consistent higher fracture risk of the AF group across prespecified subgroups according to age (<65 years; 65–74 years; ≥ 75 years) and sex (P for interaction, age: 0.206; sex: 0.624). The cumulative incidence of fracture events according to the presence of AF is presented in **Figure 2**. The cumulative incidence of fractures was significantly higher in the AF group than in the non-AF group (log-rank P<0.001).

AF was associated with osteoporotic fracture with an unadjusted hazard ratio (HR) of 1.47 (95% confidence interval [CI], 1.24–1.74; P<0.001). HRs for the association between AF and fracture with sequentially greater degrees of multivariable adjustment are shown in **Figure 3**. After adjusting for age and sex (model 1), the risk of fracture in patients with AF was 23% higher than in patients without AF (95% CI, 4–46%; P=0.018). With progressive sequential adjustment by comorbidities including HF, HTN, DM, previous stroke/TIA, previous MI, PAD, COPD, and CKD, AF was independently correlated with fracture incidence with a HR of 1.22 (95% CI, 1.03–1.45; P=0.021) (model 2). In the final fully adjusted model (model 3), adjusted for lifestyle including smoking, alcohol intake, and physical activity, and medication use in addition to model 2, the association remained statistically significant, with a HR of 1.21 (95% CI, 1.02–1.41; P=0.031).

The following variables were found to be associated with fractures using multivariate Cox regression analysis of demographic and comorbid variables: older age, female sex, decreased physical activity, DM, stroke/TIA, MI, PAD, loop diuretics use, corticosteroid use, and sedative use (**Table S3**). In subgroup analyses stratified by sex (**Table S4**), the association between AF and fracture was



consistently significant in both sexes. In females, increasing alcohol use, smoking, and anticonvulsant use were additionally found to be independently correlated to fracture.

In a sensitivity analysis that excluded patients with stroke history at the time of entry into the cohort (n=28,944), the adjusted risk of fracture had a similar magnitude and was statistically significant (HR, 1.20; 95% CI, 1.01–1.42; P=0.040) in the final fully adjusted model.

Death After Fracture Event According to the Presence of AF

The Kaplan-Meier survival curves of patients after fracture according to the presence of AF are presented in **Figure 4**. During the follow-up after fracture event, 18 (12.7%) patients with AF and 95 (3.8%) patients without AF died (mortality rate, with AF: 6.82 vs. without AF: 1.85 per 100 person-years; log-rank P<0.001). The clinical characteristics of the patients with fracture events are presented in **Table S5**.

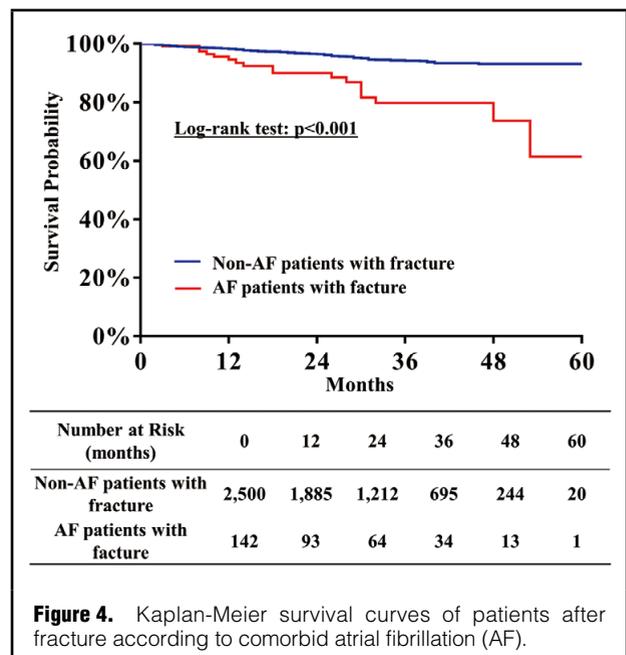
Among patients with bone fractures, those with AF had a higher mortality rate than those without AF (adjusted HR, 1.92; 95% CI, 1.35–3.27; P=0.016). Other factors independently associated with death were older age, being underweight (BMI <18.5kg/m²), smoking, decreased physical activity, DM, and CKD (**Table S6**). In the subgroup analyses stratified by sex (**Table S7**), the association between AF and death was consistently significant in both sexes.

Predictors for Osteoporotic Fracture in Patients With AF

In patients with AF and osteoporosis, the following variables were identified as predictors of bone fracture using multivariate Cox regression analysis: older age, female sex, being underweight, decreased physical activity (exercising <3 times/week), history of stroke/TIA, thiazide use, and sedative use (**Table 2**, model 1). Cox regression analysis also demonstrated that higher CHADS₂ (≥2 points) and CHA₂DS₂-VASc (≥2 points) scores independently correlated with the incidence of bone fractures (HR 2.46, 95% CI 1.62–3.72; P<0.001; and HR 1.61, 95% CI 1.14–2.82; P=0.007), compared with those with scores of 0–1 point (**Table 2**, models 2 and 3).

Propensity Score-Matching Analysis

Baseline characteristics after propensity score-matching



are shown in **Table S8**. There were no significant differences between the AF and non-AF groups with regard to demographic characteristics and comorbidities.

Similar to the results of the non-matched cohort, the incidence rates of fracture were higher in the AF group than in the non-AF group (total fracture: 3.18 vs. 2.68 per 100 person-years; major fracture: 1.90 vs. 1.54 per 100 person-years; **Table S9**). AF was associated with a higher risk of fracture in comparison with patients without AF (HR 1.18, 95% CI 1.02–1.35; P=0.033). Among the patients with bone fractures (n=259), those with AF had a higher mortality rate after the fracture event than did those without AF (6.85 vs. 4.73 per 100 person-years). AF was associated with a higher risk of death after a fracture event (HR 1.44, 95% CI 1.24–1.69, P<0.001).

Table 2. Independent Correlates of Fracture Incidence: Multivariable Cox Proportional Hazards Model in AF Patients With Osteoporosis (n=1,213)

Variables	Level	Osteoporotic fracture	
		Adjusted HR (95% CI)	P value
Model 1^a			
Age	Per year increase	1.07 (1.05–1.10)	<0.001
Female		2.69 (1.33–5.43)	0.006
Underweight	BMI <18.5 kg/m ²	2.27 (1.16–4.47)	0.017
Decreased physical activity	<3 times/week of exercise	1.08 (1.01–1.14)	0.020
Ischemic stroke/TIA		1.46 (1.02–2.09)	0.040
Thiazide use		1.35 (1.01–1.81)	0.042
Sedative use*		1.53 (1.14–2.05)	0.020
Model 2^b			
CHADS ₂ score	≥2	2.46 (1.62–3.72)	<0.001
Female		2.52 (1.18–5.36)	0.017
Underweight	BMI <18.5 kg/m ²	2.91 (1.49–5.68)	0.002
Sedative use*		1.46 (1.04–2.07)	0.031
Model 3^c			
CHA ₂ DS ₂ -VASc score	≥2	1.61 (1.14–2.82)	0.007
Underweight	BMI <18.5 kg/m ²	2.91 (1.49–5.69)	0.002
Decreased physical activity	<3 times/week of exercise	1.51 (1.07–2.14)	0.020
Thiazide use		1.52 (1.08–2.13)	0.017
Sedative use*		1.57 (1.12–2.22)	0.010

^aAdjusted for all patient characteristics and medications shown in Table 1. ^bAdjusted for sex, CHADS₂ score, BMI-group, lifestyle (smoking, alcohol use, and physical activity), and all medications shown in Table 1. ^cAdjusted for CHA₂DS₂-VASc score, BMI-group, lifestyle (smoking, alcohol use, and physical activity), and all medications shown in Table 1. *Sedatives included benzodiazepines, chloral hydrate, buspirone, and zopiclone. CI, confidence interval; HR, hazard ratio. Other abbreviations as in Table 1.

Discussion

Main Findings

Using a nationwide cohort of Korean patients with osteoporosis, we found that the incidence of bone fractures was significantly higher in patients with AF than in those without AF. In addition, AF was associated with a 21% increase in the risk of fractures during a median 4 years of follow-up. This association appeared to remain significant after adjusting for potential confounders such as age, sex, comorbidities, lifestyle, and medication use. The mortality rate after fracture was significantly higher in patients with AF than in those without. After propensity score-matching, AF was consistently associated with a higher risk of osteoporotic fracture and subsequent death after fracture. In AF patients, the risk of fracture was significantly increased in those who were older, female, underweight, and less physically active, with a history of stroke/TIA, thiazide/sedative use, and higher CHADS₂ or CHA₂DS₂-VASc score.

Risk of Osteoporotic Fracture and Death After Fracture Event by the Presence of AF

Our data supported the hypothesis that AF is an independent risk factor for bone fractures. There are several probable explanations for this association. Previous studies have indicated that bone fracture is associated with multiple exogenous and endogenous factors that increase fall risk and weaken bony structures.^{26–28} Sanders et al found that AF is independently associated with increased falls.¹⁰ Possible explanations for this association include hemodynamic alterations with regard to decreased cardiac output

from loss of the atrial kick and irregular ventricular response; these changes can impair brain perfusion, causing a loss of postural tone, which in turn, can result in falls.²⁹ Patients with AF often have sinus node diseases,³⁰ which can result in bradycardia, and even asystole post-AF termination. With regard to bone strength, AF might affect the microvasculature in bones through thromboembolism, thus affecting bone formation.³¹

Recent studies from Taiwan and Australia showed that individuals with AF have a 2-fold increase in risk of fracture,^{15,17} but Wallace et al found no significant association between AF and fracture risk.¹⁶ In our study, the association was modest but remained statistically significant, with a 21% increase in risk. The strength of this study over previous studies is the use of extensive data to adjust for potential confounders that would not have been available in the other studies, including more varied comorbidities, BMI, lifestyle factors, and cardiac/noncardiac medications. It is a novel finding that AF was associated with a 1.92-fold increase in death among patients after fracture events. Our findings on higher fracture incidence and mortality rates suggested that individuals with AF may potentially benefit from close screening by clinical history and BMD testing and should be at least carefully monitored after fracture.

Predictors for Osteoporotic Fracture in Patients With AF

In the general population, older age, low BMI, and decreased physical activity are important risk factors for both osteoporosis and fractures.^{32,33} We demonstrated that older age, low BMI, and decreased physical activity are independent risk factors for osteoporosis-related fractures

in AF patients. In our study, although sedative use was associated with increased fracture risk in both the general osteoporosis group and the AF subgroup, thiazide use correlated with fracture only in the AF subgroup. Those medications might be related to increased risk of fall, and the finding implies that thiazide diuretics should be prescribed more carefully in AF patients with osteoporosis. The CHADS₂ and CHA₂DS₂-VASc scores, which are validated tools that predict stroke and systemic embolism in patients with AF,^{34,35} share common etiological factors with osteoporosis including older age, HF, HTN, and DM. We found that in AF patients, the risk of bone fracture increases with higher CHADS₂ or CHA₂DS₂-VASc score. That finding suggested that among patients diagnosed with AF, the risk of fracture can be detected using a well-known stroke risk score and its cutoff. In doing so, we can identify patients who need to be screened with BMD testing. Furthermore, we can properly counsel these patients with regard to calcium and vitamin D supplementation, regular exercise, smoking cessation, and identification of unnecessary medications.

Antithrombotic Therapy and the Risk of Bone Fractures in Patients With AF

There is controversy regarding warfarin's deleterious effects on bone density and subsequent increased fracture risk. Several studies have reported that warfarin therapy might be associated with reduced BMD,^{12,13} but this observation is inconsistent across the literature.³⁶ Prior groups have investigated whether warfarin exposure is associated with fracture, and have found conflicting results. Gage et al found that long-term (≥ 1 year) warfarin use was associated with osteoporotic fractures in men with AF.¹¹ In contrast, a more recent Taiwanese national cohort study found that warfarin users had significantly lower risk of bone fractures than did non-warfarin users among AF patients with CHA₂DS₂-VASc score ≥ 1 point.¹⁷ In our study, warfarin use did not independently correlate with the incidence of fracture in the entire osteoporosis population or in the AF subgroup. Further understanding of the mechanisms and randomized prospective studies are needed to resolve the ongoing controversy.

Study Limitations

First, although we adjusted for many potential risk factors of osteoporotic fracture, we did not measure others, including falls, frailty, BMD, calcium/vitamin D status (supplements are available without prescription), and non-vitamin K antagonist oral anticoagulant prescription. These unmeasured variables may confound the observed association between AF and fracture. Second, studies using administrative databases are potentially susceptible to errors arising from coding inaccuracies, although we applied the definition that we had already validated in previous studies using a Korean NHIS sample cohort.^{19-21,23} Third, we could not distinguish the types of AF (paroxysmal or nonparoxysmal) and patients with atrial flutter were included without being distinguished. A fourth limitation is that we did not include minor bone fractures not requiring hospitalization. Fifth, we analyzed only all-cause death data and it is unclear whether the increased mortality rate observed was directly related to AF. Sixth, our study only enrolled Asian patients, potentially making it difficult to generalize our results to other populations. Finally, because of the observational nature of this study, we could not

establish causality, only correlation.

Conclusions

Patients with AF were at a higher risk of osteoporotic fracture and subsequent death after fracture than were patients without AF in this study. Older age, female sex, being underweight, decreased physical activity, history of stroke or TIA, usage of thiazides or sedatives, and higher CHADS₂ or CHA₂DS₂-VASc score were associated with fractures in patients with AF. We suggest that a diagnosis of AF portends a substantially increased risk of fractures and thus such patients require close screening, as well as counseling regarding preventive strategies.

Sources of Funding

This study was supported by a CMB-Yuhan research grant of Yonsei University College of Medicine (6-2015-0173), research grants from the Basic Science Research Program through the National Research Foundation of Korea funded by the Ministry of Education, Science and Technology (NRF-2012R1A2A2A02045367), and a grant from the Korean Healthcare Technology R&D project funded by the Ministry of Health & Welfare (H116C0058, H115C1200).

Disclosures

The authors have no conflicts of interest to disclose.

References

- Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, et al. Prevalence of diagnosed atrial fibrillation in adults: National implications for rhythm management and stroke prevention: The AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA* 2001; **285**: 2370–2375.
- Wattigney WA, Mensah GA, Croft JB. Increasing trends in hospitalization for atrial fibrillation in the United States, 1985 through 1999: Implications for primary prevention. *Circulation* 2003; **108**: 711–716.
- McFarlane SI, Muniyappa R, Shin JJ, Bahtiyar G, Sowers JR. Osteoporosis and cardiovascular disease: Brittle bones and boned arteries, is there a link? *Endocrine* 2004; **23**: 1–10.
- Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. *JAMA* 1994; **271**: 840–844.
- Adib Hajbaghery M, Abbasinia M. Quality of life of the elderly after hip fracture surgery: A case-control study. *J Caring Sci* 2013; **2**: 53–59.
- De Laet CE, van Hout BA, Burger H, Weel AE, Hofman A, Pols HA. Incremental cost of medical care after hip fracture and first vertebral fracture: The Rotterdam study. *Osteoporos Int* 1999; **10**: 66–72.
- Aluoch AO, Jessee R, Habal H, Garcia-Rosell M, Shah R, Reed G, et al. Heart failure as a risk factor for osteoporosis and fractures. *Curr Osteoporos Rep* 2012; **10**: 258–269.
- Benzinger P, Rapp K, Konig HH, Bleibler F, Globas C, Beyersmann J, et al. Risk of osteoporotic fractures following stroke in older persons. *Osteoporos Int* 2015; **26**: 1341–1349.
- Sennerby U, Melhus H, Gedeberg R, Byberg L, Garmo H, Ahlbom A, et al. Cardiovascular diseases and risk of hip fracture. *JAMA* 2009; **302**: 1666–1673.
- Sanders NA, Ganguly JA, Jetter TL, Daccarett M, Wasmund SL, Brignole M, et al. Atrial fibrillation: An independent risk factor for nonaccidental falls in older patients. *Pacing Clin Electrophysiol* 2012; **35**: 973–979.
- Gage BF, Birman-Deych E, Radford MJ, Nilasena DS, Binder EF. Risk of osteoporotic fracture in elderly patients taking warfarin: Results from the National Registry of Atrial Fibrillation 2. *Arch Intern Med* 2006; **166**: 241–246.
- Myers KE, Nakamura JM. Maternal and fetal sequelae of anticoagulation during pregnancy. *Am J Cardiol* 1990; **65**: 1410.
- Caraballo PJ, Gabriel SE, Castro MR, Atkinson EJ, Melton LJ 3rd. Changes in bone density after exposure to oral anticoagulants: A meta-analysis. *Osteoporos Int* 1999; **9**: 441–448.
- Thompson B, Towler DA. Arterial calcification and bone

- physiology: Role of the bone-vascular axis. *Nat Rev Endocrinol* 2012; **8**: 529–543.
15. Wong CX, Gan SW, Lee SW, Gallagher C, Kinnear NJ, Lau DH, et al. Atrial fibrillation and risk of hip fracture: A population-based analysis of 113,600 individuals. *Int J Cardiol* 2017; **243**: 229–232.
 16. Wallace ER, Siscovick DS, Sitlani CM, Dublin S, Mitchell P, Robbins JA, et al. Incident atrial fibrillation and the risk of fracture in the cardiovascular health study. *Osteoporos Int* 2017; **28**: 719–725.
 17. Lai HC, Chien WC, Chung CH, Lee WL, Wu TJ, Wang KY, et al. Atrial fibrillation, CHA2DS2-VASc score, antithrombotics and risk of non-traffic-, non-cancer-related bone fractures: A population-based cohort study. *Eur J Intern Med* 2015; **26**: 798–806.
 18. Lee J, Lee JS, Park SH, Shin SA, Kim K. Cohort profile: The National Health Insurance Service-National Sample Cohort (NHIS-NSC), South Korea. *Int J Epidemiol* 2017; **46**: e15.
 19. Kim TH, Yang PS, Kim D, Yu HT, Uhm JS, Kim JY, et al. CHA2DS2-VASc score for identifying truly low-risk atrial fibrillation for stroke: A Korean nationwide cohort study. *Stroke* 2017; **48**: 2984–2990.
 20. Lee HY, Yang PS, Kim TH, Uhm JS, Pak HN, Lee MH, et al. Atrial fibrillation and the risk of myocardial infarction: A nationwide propensity-matched study. *Sci Rep* 2017; **7**: 12716.
 21. Lee SS, Ae Kong K, Kim D, Lim YM, Yang PS, Yi JE, et al. Clinical implication of an impaired fasting glucose and prehypertension related to new onset atrial fibrillation in a healthy Asian population without underlying disease: A nationwide cohort study in Korea. *Eur Heart J* 2017; **38**: 2599–2607.
 22. Kanis JA, Melton LJ 3rd, Christiansen C, Johnston CC, Khaltaev N. The diagnosis of osteoporosis. *J Bone Miner Res* 1994; **9**: 1137–1141.
 23. Park TH, Choi JC. Validation of stroke and thrombolytic therapy in Korean National Health Insurance claim data. *J Clin Neurol* 2016; **12**: 42–48.
 24. Austin PC. The use of propensity score methods with survival or time-to-event outcomes: Reporting measures of effect similar to those used in randomized experiments. *Stat Med* 2014; **33**: 1242–1258.
 25. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med* 2009; **28**: 3083–3107.
 26. Watts NB, Lewiecki EM, Miller PD, Baim S. National Osteoporosis Foundation 2008 Clinician's Guide to Prevention and Treatment of Osteoporosis and the World Health Organization Fracture Risk Assessment Tool (FRAX): What they mean to the bone densitometrist and bone technologist. *J Clin Densitom* 2008; **11**: 473–477.
 27. Kaminska MS, Brodowski J, Karakiewicz B. Fall risk factors in community-dwelling elderly depending on their physical function, cognitive status and symptoms of depression. *Int J Environ Res Public Health* 2015; **12**: 3406–3416.
 28. Rice LA, Ousley C, Sosnoff JJ. A systematic review of risk factors associated with accidental falls, outcome measures and interventions to manage fall risk in non-ambulatory adults. *Disabil Rehabil* 2015; **37**: 1697–1705.
 29. Naito M, David D, Michelson EL, Schaffenburg M, Dreifus LS. The hemodynamic consequences of cardiac arrhythmias: Evaluation of the relative roles of abnormal atrioventricular sequencing, irregularity of ventricular rhythm and atrial fibrillation in a canine model. *Am Heart J* 1983; **106**: 284–291.
 30. Andersen HR, Nielsen JC, Thomsen PE, Thuesen L, Mortensen PT, Vesterlund T, et al. Long-term follow-up of patients from a randomised trial of atrial versus ventricular pacing for sick-sinus syndrome. *Lancet* 1997; **350**: 1210–1216.
 31. Towler DA. Arteriosclerosis, bone biology, and calciotropic hormone signaling: Learning the ABCs of disease in the bone-vascular axis. *J Am Soc Nephrol* 2015; **26**: 243–245.
 32. Roy DK, O'Neill TW, Finn JD, Lunt M, Silman AJ, Felsenberg D, et al. Determinants of incident vertebral fracture in men and women: Results from the European Prospective Osteoporosis Study (EPOS). *Osteoporos Int* 2003; **14**: 19–26.
 33. Cummings SR, Nevitt MC, Browner WS, Stone K, Fox KM, Ensrud KE, et al. Risk factors for hip fracture in white women: Study of Osteoporotic Fractures Research Group. *N Engl J Med* 1995; **332**: 767–773.
 34. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: Results from the National Registry of Atrial Fibrillation. *JAMA* 2001; **285**: 2864–2870.
 35. Olesen JB, Lip GY, Hansen ML, Hansen PR, Tolstrup JS, Lindhardsen J, et al. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: Nationwide cohort study. *BMJ* 2011; **342**: d124.
 36. Jamal SA, Browner WS, Bauer DC, Cummings SR. Warfarin use and risk for osteoporosis in elderly women: Study of Osteoporotic Fractures Research Group. *Ann Intern Med* 1998; **128**: 829–832.

Supplementary Files

Supplementary File 1

Table S1. ICD-10 codes of comorbidities

Table S2. Risk of fracture according to comorbid AF in patients with osteoporosis (n=31,778)

Table S3. Cox regression analysis of the predictive factors for fractures in patients with osteoporosis (n=31,778)

Table S4. Independent correlates of fracture incidence: multivariable Cox proportional hazards model in subgroups of patients with osteoporosis according to sex

Table S5. Characteristics of patients with fracture event (n=2,642)

Table S6. Independent correlates of death after fracture event: multivariable Cox proportional hazards model in patients with fracture event (n=2,642)

Table S7. Independent correlates of death after fracture event: multivariable Cox proportional hazards model in subgroups of patients with fracture event according to sex (n=2,642)

Table S8. Baseline patient characteristics before and after propensity score-matching

Table S9. Risk of fracture according to comorbid AF in patients with osteoporosis after propensity-matching (n=2,418)

Please find supplementary file(s);
<http://dx.doi.org/10.1253/circj.CJ-17-1179>