Title

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Journal

CHEST Journal, 149(5)

ISSN

0012-3692

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Publication Date

2016-05-01

DOI

10.1016/j.chest.2015.11.022

Peer reviewed

CHEST

Relationship of Bisphosphonate Therapy and Atrial Fibrillation/Flutter

Outcomes of Sleep Disorders in Older Men (MrOS Sleep) Study

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BACKGROUND: Prior studies suggested an association between bisphosphonates and atrial fibrillation/flutter (AF) in women. This relationship in men, including those with sleep-disordered breathing (SDB), remains unclear. This study evaluated the relationship between bisphosphonate use and prevalent (nocturnal) and incident (clinically relevant) AF in a population of community-dwelling older men.

METHODS: A total of 2,911 male participants (mean age, 76 years) of the prospective observational Osteoporotic Fractures in Men Study sleep cohort with overnight in-home polysomnography (PSG) constituted the analytic cohort. Nocturnal AF from ECGs during PSG and incident AF events were centrally adjudicated. The association of bisphosphonate use and AF was examined using multivariable-adjusted logistic regression for prevalent AF and Cox proportional hazards regression for incident AF.

RESULTS: A total of 123 (4.2%) men were current bisphosphonate users. Prevalent nocturnal AF was present in 138 participants (4.6%). After multivariable adjustment, there was a significant association between current bisphosphonate use and prevalent AF (OR, 2.33; 95% CI, 1.13-4.79). In the subset of men with moderate to severe SDB, this association was even more pronounced (OR, 3.22; 95% CI, 1.29-8.03). However, the multivariable-adjusted relationship between bisphosphonate use and incident AF did not reach statistical significance (adjusted hazard ratio, 1.53; 95% CI, 0.96-2.45).

CONCLUSIONS: These results support an association between bisphosphonate use and prevalent nocturnal AF in community-dwelling older men. The data further suggest that those with moderate to severe SDB may be a particularly vulnerable group susceptible to bisphosphonate-related AF. Similar associations were not seen for bisphosphonate use and clinically relevant incident AF. CHEST 2016; 149(5):1173-1180

KEY WORDS: atrial fibrillation; bisphosphonates; sleep-disordered breathing

ABBREVIATIONS: AF = atrial fibrillation/flutter; AHI = apnea-hypopnea index; BMD = bone mineral density; HR = hazard ratio; MrOS = Osteoporotic Fractures in Men Study; PASE = Physical Activity Scale for the Elderly; PSG = polysomnography; SDB = sleep-disordered breathing

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This work was previously presented at the American College of Cardiology conference in April 2011 in New Orleans, LA.

FUNDING/SUPPORT: The Osteoporotic Fractures in Men Study (MrOS) is supported by National Institutes of Health funding: the

Bisphosphonates, commonly used to treat osteoporosis, have been shown to increase bone mineral density (BMD) and decrease the risk of osteoporotic fractures.[1-6] However, several randomized trials and observational studies have shown an association between bisphosphonate use and development of atrial fibrillation/flutter (AF).

These trials and the meta-analyses of these trials have relied on adverse event reporting, with follow-up from approximately 2 to 4 years.[7-12] Bisphosphonate use was not related to the occurrence of any AF event but was, however, related to the occurrence of serious AF events in some[7,12] but not all[8,10,11] studies.

The results from observational studies are inconsistent.[13-19] Most studies have been retrospective case-control studies using registry or health-care claims data. Some prior studies have been criticized because the populations were older or had increased comorbid burden, which can predispose people to developing AF. Many studies had few AF events. Most studies have been of women.[7,9,10,13,15,18,19] Of those with male participants,[8,11,14,16] only one reported results by sex.[14] These studies lacked a standardized methodology to assess AF, which could result in clinically unrecognized AF and misclassification.

Although the relationship between sleep-disordered breathing (SDB) and AF has been previously described,[20,21] the role of bisphosphonates in modulating this relationship has not been evaluated. We hypothesized that in a community-dwelling population of older men, bisphosphonate use would be associated with both increased prevalence of nocturnal AF observed during overnight polysomnography (PSG) and increased incidence of symptom-based or clinically relevant AF.

Materials and Methods

Participants

Participants were from the Osteoporotic Fractures in Men Study (MrOS), a prospective cohort study of 5,994 community-dwelling men 65 years or older enrolled between 2000 and 2002 at six clinical centers in the United States. Participants needed to be able to walk without assistance and must not have had a bilateral hip replacement.[22,23]

The MrOS Sleep Study, an ancillary study of the MrOS cohort, was conducted between December 2003 and March 2005 and recruited 3,135 MrOS participants for a comprehensive sleep assessment. Men undergoing sleep apnea treatment (eg, positive airway pressure therapy) or receiving nocturnal oxygen therapy were excluded. Of the 2,859 men who did not participate, 349 died before the visit, 39 had terminated the study, 324 were not asked because recruitment goals were met, 150 were ineligible, and 1,997 refused. The 2,859 men who did not participate were similar in age, race, and BMI compared with the 3,135 MrOS Sleep Study participants. Of the 3,135 men, PSG recordings were available for 2,911. Incident AF was adjudicated in 2,861.

All men provided written informed consent. The study was approved by the institutional review board at each site. The committee names and approval numbers are as follows: University of Alabama at Birmingham Institutional Review Board for Human Use, F030725004; Human Research Protection Program at the University of Minnesota, 0307M50161; Stanford University, Protocol ID, 13647; University of Pittsburgh Institutional Review Board, IRB980305; Oregon Health & Science University, Institutional Review Board IRB00001296, CR00020385; University of California, San Diego Human Research Protections Program, 071795; and Sutter Health Institutional Review Board, 348922-9.

Prevalent Nocturnal AF

In-home overnight PSG was completed using unattended, portable units (Safiro; Compumedics Ltd). The data collection method has been previously described.[20] Data quality was excellent, with a failure rate of $< 4\%$ and $> 70\%$ of studies graded as being of excellent or outstanding quality.

ECG-specific software was used to analyze the ECG data collected during PSG (Somté; Compumedics Ltd). Data were scored as supraventricular (including AF as a subcategory), ventricular ectopic, or normal sinus beats. The data were manually reviewed by a polysomnologist with ECG training, with arbitration by a board-certified critical care physician (R.M.) for any uncertainty in event categorization. The intraclass correlation coefficients for this reviewer and the physician for coding arrhythmia in a random sample of 20 PSGs were 0.98 to 0.99.[21] All PSG recordings demonstrating nocturnal AF were confirmed by the physician. Any questionable categorization of arrhythmias was referred to a cardiologist for further arbitration. Prevalent nocturnal AF was considered the presence of any duration of AF during sleep observed during the course of the overnight sleep study (mean $\pm$ SD, 5.9 $\pm$ 1.2 hours).

National Institute on Aging, the National Institute of Arthritis and Musculoskeletal and Skin Diseases, the National Center for Advancing Translational Sciences, and National Institutes of Health Roadmap for Medical Research under the following grant numbers: U01 AG027810, U01 AG042124, U01 AG042139, U01 AG042140, U01 AG042143, U01 AG042145, U01 AG042168, U01 AR066160, and UL1 TR000128. The National Heart, Lung, and Blood Institute provides funding for the MrOS Sleep ancillary study "Outcomes of Sleep Disorders in Older Men" under the following grant numbers: R01 HL071194, R01 HL070848, R01 HL070847, R01 HL070842, R01 HL070841, R01 HL070837, R01 HL070838, and R01 HL070839.

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DOI: http://dx.doi.org/10.1016/j.chest.2015.11.022

Incident AF

Participants were surveyed for potential incident cardiovascular events by postcard and/or phone contact every 4 months, with a 99% response rate. Medical records and supporting documentation from any potential event, including death certificates, were obtained and used in centralized adjudication. When no medical records were available for out-of-hospital deaths, proxy interviews with next of kin were obtained. All documents were adjudicated by a board-certified cardiologist using a prespecified protocol developed using methods that had been successfully used for randomized trials and epidemiologic studies (e-Appendix 1).

Clinically relevant arrhythmia events were defined as those that resulted in symptoms (fatigue, palpitations, light-headedness, presyncope, syncope, chest pain, or dyspnea) or an ED visit, hospitalization and/or prolongation of hospitalization, or invasive procedure directly attributable to the potential arrhythmia in question. Documentation required for adjudication of an event included one or more of the following: emergency medical services notes and/or rhythm strips, ECG (including stress testing), in-hospital telemetry, ambulatory ECG (Holter monitor and/or event monitor), pacemaker or defibrillator telemetry (for patients with a device already implanted), or invasive cardiac electrophysiology testing results.

Bisphosphonate Use

Participants were asked to bring all medications used within 30 days. If a participant forgot to bring medications, clinic staff obtained this information over the telephone or at a return visit. Medications were entered into an electronic database and were matched to their ingredient(s) on the basis of the Iowa Drug Information Service Drug Vocabulary (College of Pharmacy, University of Iowa).[24] Bisphosphonate use occurring after the sleep visit was gathered at four subsequent visits 1.2 ± 0.3, 3.4 ± 0.5, 5.5 ± 0.5, and 6.5 ± 0.7 years later. Men were considered previous users of bisphosphonates if they had not taken a bisphosphonate within 30 days of the sleep visit but had been classified as a bisphosphonate user in the past.

Other Measurements

At the time of the visit, participants completed questionnaires with items about demographics, medical history, self-reported health status, physical activity, smoking, and caffeine and alcohol intake. Physical activity level was assessed using the Physical Activity Scale for the Elderly (PASE).[25] Caffeine intake was calculated based on intake of caffeinated coffee, tea, and soda.[26]

An examination included measurements of blood pressure, body weight, and height. BMI was calculated as weight in kilograms divided by height in meters squared. Femoral neck BMD was obtained from dual x-ray absorptiometry scans (Hologic). SDB was measured by means of PSG by using the apnea-hypopnea index (AHI), with hypopneas defined as reduction in breathing amplitude at least 30% lower than baseline breathing lasting > 10 seconds and associated with a $\geq 3\%$ oxygen desaturation.[27]

Statistical Analysis

Participant characteristics were compared between current users and nonusers of bisphosphonates by using χ^2 tests for categorical variables, Student t tests for normally distributed continuous variables, and Wilcoxon rank-sum tests for skewed continuous variables. The association between current bisphosphonate use and prevalent nocturnal AF was examined using logistic regression, with results presented as ORs and 95% CIs.

The association between current bisphosphonate use and incident AF was examined using Cox proportional hazards regression with results presented as hazard ratios (HRs) and 95% CIs. Because the follow-up for incident AF extended across multiple time points at which medication data were gathered, bisphosphonate use was also examined as a time-dependent covariate in secondary analyses, with use updated at each subsequent examination.[28,29]

Models were unadjusted and then multivariable adjusted. Covariates included age, race, and clinic site plus those covariates thought to be clinically relevant (history of cardiovascular disease) or related to bisphosphonate use at $P < .10$: BMI, femoral neck BMD, hypertension, diabetes mellitus, fracture history, use of angiotensin-converting enzyme inhibitors, and calcium supplementation. Digoxin use, a common treatment for AF, was not included because it may be a marker for the outcome. Because SDB was associated with prevalence of AF in a prior study, we examined the possible interaction between bisphosphonate use and AHI in secondary analyses.[20] Results were stratified by AHI (< 15, ≥ 15) where the interaction was significant. Sensitivity analyses were performed removing previous bisphosphonate users from the nonuser category, removing digoxin users, and removing those with a history of AF from the incident AF models.

Significance levels reported were two-sided. Analyses were conducted using SAS version 9.4 (SAS Institute Inc).

Results

Overall

Of the 2,911 men in our analysis, 123 (4.2%) were current bisphosphonate users, and 2,788 (95.8%) were nonusers. Bisphosphonates used included alendronate (n = 93), risedronate (n = 25), etidronate (n = 3), and zoledronate (n = 3). Compared with nonusers, bisphosphonate users had lower BMI and BMD, were less likely to have a history of diabetes mellitus, and were more likely to have a history of fracture or to have used calcium supplements (Table 1). Rates of SDB and prior history of AF were similar in both groups ($P \geq .19$). Digoxin use was related to baseline AF ($P < .001$), with 57% of users self-reporting a history of AF.

Prevalent Nocturnal AF

On nocturnal ECG recordings from PSG, 10 (8.1%) bisphosphonate users had a prevalent nocturnal AF event compared with 128 (4.6%) in the nonuser group ($P = .071$). Although the unadjusted model examining the association of current bisphosphonate use and prevalence of nocturnal AF was not significant (OR, 1.84; 95% CI, 0.94-3.60), the multivariable-adjusted model demonstrated a significant relationship (OR, 2.33; 95% CI, 1.13-4.79) (Table 2). Results were similar after removing prior bisphosphonate users (OR, 2.34; 95% CI, 1.13-4.82). Because prevalent nocturnal AF was seen in 33% of digoxin users, results were attenuated after excluding digoxin users (OR, 2.05; 95% CI, 0.82-5.11).

TABLE 1] Baseline Characteristics by Current Bisphosphonate Use

Characteristic	Nonusers (n = 2,788)	Users (n = 123)	*P* Value[a]
Age, y	76.36 ± 5.56	76.80 ± 4.77	.32
Race, %			.82
White	90.8	90.2	
Black	3.4	2.4	
Asian	2.9	3.3	
Other	2.9	4.1	
BMI, kg/m^2	27.25 ± 3.80	25.36 ± 3.32	<.001
Femoral neck BMD, g/cm^2	0.785 ± 0.129	0.683 ± 0.104	<.001
Systolic blood pressure, mm Hg	126.90 ± 16.37	125.61 ± 15.19	.39
Diastolic blood pressure, mm Hg	67.70 ± 9.39	67.54 ± 10.87	.88
Apnea-hypopnea index ≥ 15, %	43.4	43.9	.91
Medical history, %			
Atrial fibrillation/flutter	11.3	15.3	.19
Hypertension	50.3	41.5	.055
Diabetes mellitus	13.6	6.5	.02
Congestive heart failure	6.1	4.1	.36
Cardiovascular disease[b]	32.1	33.6	.73
Stroke or TIA	11.0	12.2	.67
Myocardial infarction	17.5	16.3	.72
Angina	14.9	20.3	.099
Pacemaker placement	4.1	4.1	.99
COPD	5.1	6.5	.50
Nonspine fracture after age 50 years	24.6	44.7	<.001
Self-reported health good or excellent, %	87.0	82.1	.12
Current use of medications, %			
ACE inhibitors	25.6	17.9	.055
Nitrates	4.4	4.1	.85
Statins	41.8	43.9	.65
Warfarin	8.6	12.2	.16
Aspirin	58.6	52.0	.15
Beta-blockers	27.8	26	.66
Calcium channel blockers	15.2	10.6	.16
Digoxin	5.0	8.9	.055
Amiodarone	1.1	1.6	.39
Calcium supplements	29.6	70.7	<.001
Current smoker, %	2.0	1.6	.79
Alcohol use per week, %			.81
0-2 drinks	59.5	60.2	
3-13 drinks	35.1	33.3	
14+ drinks	5.3	6.5	
Caffeine intake, mg/day	236.55 ± 246.20	212.39 ± 251.44	.11
PASE physical activity score	145.94 ± 71.49	140.01 ± 67.79	.37

Data are presented as mean ± SD unless indicated otherwise. ACE = angiotensin-converting enzyme; BMD = bone mineral density; PASE = Physical Activity Scale for the Elderly; TIA = transient ischemic attack.

[a]*P* values for normally distributed continuous variables are from a Student *t* test, *P* values for skewed data are from a Wilcoxon rank-sum test, and *P* values for categorical data are from a χ^2 test.

[b]Cardiovascular diseases included myocardial infarction, angina, congestive heart failure, bypass surgery, or percutaneous coronary intervention.

TABLE 2] Association of Current Bisphosphonate Use and Prevalent Nocturnal AF at the Sleep Visit

Model	Total No. of Users	Prevalent Nocturnal AF Events, No. (%)	OR (95% CI)
Unadjusted			
Current bisphosphonate nonusers	2,788	128 (4.6)	1 (reference)
Current bisphosphonate users	123	10 (8.1)	1.84 (0.94-3.60)
Multivariable adjusted[a]			
Current bisphosphonate nonusers	2,756	127 (4.6)	1 (reference)
Current bisphosphonate users	121	10 (8.3)	2.33 (1.13-4.79)
Multivariable adjusted removing previous users[b]			
Current bisphosphonate nonusers	2,739	126 (4.6)	1 (reference)
Current bisphosphonate users	121	10 (8.3)	2.34 (1.13-4.82)

AF = atrial fibrillation/flutter.
[a]Adjusted for age, race or ethnicity, clinic site, history of cardiovascular disease (myocardial infarction, angina, congestive heart failure, bypass surgery, and percutaneous coronary intervention), BMI, femoral neck bone mineral density, history of hypertension, history of diabetes mellitus, history of a nonspine fracture after age 50 years, use of angiotensin-converting enzyme inhibitors, and use of calcium supplements.
[b]Removing 17 prior users from the nonuser category.

There was a significant interaction of current bisphosphonate use and SDB (P-interaction = .046). Among men with AHI ≥ 15, there was a significant association of current bisphosphonate use and prevalent AF (OR, 3.22; 95% CI, 1.29-8.03) (Fig 1). There was no significant association seen among men with AHI < 15.

Incident AF

Incident AF events occurred in 368 men during 8.2 ± 2.4 years of follow-up, with 20 (16.3%) in the bisphosphonate group and 348 (12.5%) in the nonuser group (P = .20). No significant relationship was seen between current bisphosphonate use and incident AF (Table 3). Results were similar after removing previous bisphosphonate users or those with a history of AF and when bisphosphonate use was analyzed as a time-dependent variable. No significant interaction of bisphosphonate use and SDB was seen (P-interaction = .75).

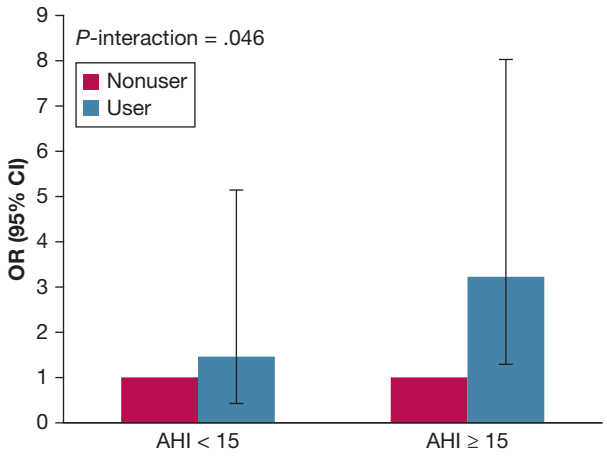

Figure 1 – *Multivariable-adjusted association of current bisphosphonate use and prevalent nocturnal atrial fibrillation/flutter at the sleep visit stratified by sleep-disordered breathing status. The adjustment is for age, race or ethnicity, clinic site, history of cardiovascular disease (myocardial infarction, angina, congestive heart failure, bypass surgery, and percutaneous coronary intervention), BMI, femoral neck bone mineral density, history of hypertension, history of diabetes mellitus, history of a nonspine fracture after age 50 years, use of angiotensin-converting enzyme inhibitors, and use of calcium supplements. AHI = apnea-hypopnea index.*

Discussion

In a large, community-dwelling population of older men, bisphosphonate use, after adjusting for potential confounding variables, was associated with a more than twofold increase in the likelihood of prevalent nocturnal AF. This relationship was even stronger in men with significant SDB. However, there was no association between bisphosphonate use and the incidence of clinically relevant AF.

The Food and Drug Administration investigated the association between bisphosphonates and AF and determined that results were inconclusive and that health-care professionals should not change their prescribing patterns.[30] In the HORIZON Pivotal Fracture Trial, serious AF occurred more often in the group that received zoledronic acid once yearly.[7] Most events occurred 30 days after infusion, when serum levels of zoledronic acid are undetectable. Although the association of bisphosphonate use and clinically relevant incident AF was not statistically significant in our study (HR, 1.53; 95% CI, 0.96-2.45; P = .07), the effect size was similar to the association of bisphosphonate use and serious AF events in women found in two meta-analyses using data from randomized controlled trials of

TABLE 3] Association of Current Bisphosphonate Use at the Sleep Visit and Clinically Relevant Incident AF

Model	Total No. of Users	Incident AF Events, No. (%)	Age-Adjusted Rate per 1,000 Person-Years (95% CI)	Hazard Ratio (95% CI)
Unadjusted				
Current bisphosphonate nonusers	2,741	348 (12.7)	16.1 (14.4-17.8)	1 (reference)
Current bisphosphonate users	120	20 (16.7)	26.4 (9.9-42.9)	1.34 (0.86-2.12)
Multivariable adjusted[a]				
Current bisphosphonate nonusers	2,709	344 (12.7)	16.1 (14.4-17.8)	1 (reference)
Current bisphosphonate users	118	20 (17.0)	26.5 (9.9-43.1)	1.53 (0.96-2.45)
Multivariable adjusted removing previous users[b]				
Current bisphosphonate nonusers	2,692	341 (12.7)	16.1 (14.4-17.8)	1 (reference)
Current bisphosphonate users	118	20 (17.0)	26.5 (9.8-43.2)	1.52 (0.95-2.44)
Multivariable adjusted removing those with a self-reported history of AF[c]				
Current bisphosphonate nonusers	2,185	230 (10.5)	13.1 (11.4-14.8)	1 (reference)
Current bisphosphonate users	91	14 (15.4)	21.5 (4.5-38.6)	1.65 (0.94-2.91)

See Table 2 legend for expansion of abbreviation.
[a]Adjusted for age, race or ethnicity, clinic site, history of cardiovascular disease (myocardial infarction, angina, congestive heart failure, bypass surgery, and percutaneous coronary intervention), BMI, femoral neck bone mineral density, history of hypertension, history of diabetes mellitus, history of a nonspine fracture after age 50 years, use of angiotensin-converting enzyme inhibitors, and use of calcium supplements.
[b]Removing 17 prior users from the nonuser category.
[c]Removing 292 with a self-report of AF and 259 missing data on self-reported AF.

bisphosphonates vs placebo (relative risk, 1.53; 95% CI, 1.17-2.00; OR, 1.47; 95% CI, 1.01-2.14),[12,31] as well as results from the Fracture Intervention Trial of alendronate vs placebo (HR, 1.51; 95% CI, 0.97-2.40; $P = .07$).[9] One cohort study found a significant association of bisphosphonate use and incident AF in men (HR, 1.39; 95% CI, 1.04-1.86).[14] Although prior studies have been mixed about the association of bisphosphonate use and AF in women, to our knowledge, our study is the first to demonstrate an association between bisphosphonate use and prevalent nocturnal AF in men.

There are several possible explanations for the biological mechanisms by which bisphosphonates may increase AF risk. Increased inflammation is a known risk factor for AF.[32] A prior study showed an increase in inflammatory markers after use of parenteral bisphosphonates.[33] Another possible mechanism is alterations in cardiac conduction through ion channels and electrolyte shifts.

Our study showed an association between bisphosphonate use and prevalent nocturnal AF but not incident clinically relevant AF. Although prevalent AF was ascertained in a rigorous and uniform fashion from nocturnal PSG recordings, incident clinically relevant arrhythmia events represented the subset of events that were severe enough to result in or contribute to the prolongation of a hospitalization, an ED visit, a medical or surgical procedure, or death. Up to 50% of patients with AF are asymptomatic, and there are 12 times as many asymptomatic episodes as symptomatic episodes.[34] Therefore, incident AF can be occult because patients often have no symptoms and ECGs may not capture paroxysmal AF. By contrast, prevalent AF did not rely on the presence of symptoms.

The significant interaction of bisphosphonate use and SDB and the stronger association of bisphosphonate use and prevalent AF in those with moderate to severe SDB compared with those with AHI < 15 suggest that SDB-related physiologic influences such as intermittent hypoxia may be modulating this relationship. Biologic plausibility is supported by data identifying hypoxia as an influential factor in myocyte intracellular calcium handling,[35] lending credence to the possibility of hypoxia and bisphosphonate intake adversely affecting calcium metabolism and increasing cardiac arrhythmogenicity. The clinical implications are important because these data suggest that those with moderate to severe SDB may be a particularly vulnerable group susceptible to bisphosphonate-related AF.

The strengths of our study include its prospective design, large community-based population, standardized data collection, adjudicated events, several hours of

continuous nocturnal ECG monitoring, length of follow-up, and centralized scoring of arrhythmias. Our study also has limitations. It is difficult to generalize the findings to a specific bisphosphonate. Alendronate is a widely prescribed bisphosphonate, but power was limited in this study to examine the association of its use and AF. Bisphosphonate users might differ from nonusers in several ways. They are taking a medication presumably because of high risk of fracture, which may be accompanied by comorbid disease. However, bisphosphonate use in men is fairly rare and may be influenced by greater access to care. We adjusted our results for coexisting medical conditions; however, we also note that there may be unresolved confounding. Finally, this study may have been underpowered with an 80% power to detect an adjusted HR of 2.2 for the incident AF outcome.

In summary, in a population of geriatric, community-dwelling men, there is an association between bisphosphonate use and prevalent nocturnal AF, which is even stronger in those with moderate to severe SDB. No significant association was seen with incident, clinically relevant AF. Prospective studies are needed to characterize further the biological basis of the relationship between nocturnal AF and bisphosphonate use.

Acknowledgments

Author contributions: T.B. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. S.R.T. contributed to analysis and interpretation of data and preparation of the manuscript. B.R. and G.M.M. contributed to interpretation of data and critical review of the manuscript. T.B. contributed to analysis and interpretation of data and preparation of the manuscript. R.M., K.L.S., P.D.V., S.R.C., and P.M.C. contributed to study concept and design, acquisition of data, interpretation of data, and critical review of the manuscript.

Financial/nonfinancial disclosures: The authors have reported to *CHEST* the following: R. M. has received funding from the National Institutes of Health for Research (National Institutes of Health, National Heart, Lung, and Blood Institute 1R01HL109493 and R21HL108226), her institution has received positive airway devices from Philips Respironics for research for which she is the principal investigator, and she has received honoraria from the American Academy of Sleep Medicine. K. L. S. is a consultant for Merck. G. M. M. received research support from Medtronic and SentreHeart, Inc and is a consultant and equity holder of InCarda Therapeutics. None declared (S. R. T., B. R., T. B., P. D. V., S. R. C., P. M. C.).

Role of sponsors: The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or the decision to submit the manuscript for publication.

Additional information: The e-Appendix can be found in the Supplemental Materials section of the online article.

References

1. Chesnut CH 3rd, McClung MR, Ensrud KE, et al. Alendronate treatment of the postmenopausal osteoporotic woman: effect of multiple dosages on bone mass and bone remodeling. *Am J Med*. 1995;99(2):144-152.
2. Liberman UA, Weiss SR, Broll J, et al. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis: the Alendronate Phase III Osteoporosis Treatment Study Group. *N Engl J Med*. 1995;333(22):1437-1443.
3. Tucci JR, Tonino RP, Emkey RD, et al. Effect of three years of oral alendronate treatment in postmenopausal women with osteoporosis. *Am J Med*. 1996;101(5):488-501.
4. Cummings SR, Black DM, Thompson DE, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. *JAMA*. 1998;280(24):2077-2082.
5. Orwoll E, Ettinger M, Weiss S, et al. Alendronate for the treatment of osteoporosis in men. *N Engl J Med*. 2000;343(9):604-610.
6. Bone HG, Hosking D, Devogelaer JP, et al. Ten years' experience with alendronate for osteoporosis in postmenopausal women. *N Engl J Med*. 2004;350(12):1189-1199.
7. Black DM, Delmas PD, Eastell R, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med*. 2007;356(18):1809-1822.
8. Lyles KW, Colón-Emeric CS, Magaziner JS, et al. Zoledronic acid and clinical fractures and mortality after hip fracture. *N Engl J Med*. 2007;357(18):1799-1809.
9. Cummings SR, Schwartz AV, Black DM. Alendronate and atrial fibrillation. *N Engl J Med*. 2007;356(18):1895-1896.
10. Lewiecki EM, Cooper C, Thompson E, et al. Ibandronate does not increase risk of atrial fibrillation in analysis of pivotal clinical trials. *Int J Clin Pract*. 2010;64(6):821-826.
11. Barrett-Connor E, Swern AS, Hustad CM, et al. Alendronate and atrial fibrillation: a meta-analysis of randomized placebo-controlled clinical trials. *Osteoporos Int*. 2012;23(1):233-245.
12. Loke YK, Jeevanantham V, Singh S. Bisphosphonates and atrial fibrillation: systematic review and meta-analysis. *Drug Saf*. 2009;32(3):219-228.
13. Sorensen HT, Christensen S, Mehnert F, et al. Use of bisphosphonates among women and risk of atrial fibrillation and flutter: population based case-control study. *BMJ*. 2008;336(7648):813-816.
14. Abrahamsen B, Eiken P, Brixen K. Atrial fibrillation in fracture patients treated with oral bisphosphonates. *J Intern Med*. 2009;265(5):581-592.
15. Huang WF, Tsai YW, Wen YW, et al. Osteoporosis treatment and atrial fibrillation: alendronate versus raloxifene. *Menopause*. 2010;17(1):57-63.
16. Wilkinson GS, Baillargeon J, Kuo YF, Freeman JL, Goodwin JS. Atrial fibrillation and stroke associated with intravenous bisphosphonate therapy in older patients with cancer. *J Clin Oncol*. 2010;28(33):4898-4905.
17. Bunch TJ, Anderson JL, May HT, et al. Relation of bisphosphonate therapies and risk of developing atrial fibrillation. *Am J Cardiol*. 2009;103(6):824-828.
18. Pazianas M, Compston J, Huang CL. Atrial fibrillation and bisphosphonate therapy. *J Bone Miner Res*. 2010;25(1):2-10.
19. Heckbert SR, Li G, Cummings SR, Smith NL, Psaty BM. Use of alendronate and risk of incident atrial fibrillation in women. *Arch Intern Med*. 2008;168(8):826-831.
20. Mehra R, Stone KL, Varosy PD, et al. Nocturnal arrhythmias across a spectrum of obstructive and central sleep-disordered breathing in older men: outcomes of sleep disorders in older men (MrOS sleep) study. *Arch Intern Med*. 2009;169(12):1147-1155.
21. Mehra R, Benjamin EJ, Shahar E, et al. Association of nocturnal arrhythmias with sleep-disordered breathing: the Sleep Heart Health Study. *Am J Respir Crit Care Med*. 2006;173(8):910-916.
22. Blank JB, Cawthon PM, Carrion-Petersen ML, et al. Overview of recruitment for the osteoporotic fractures in men study (MrOS). *Contemp Clin Trials*. 2005;26(5):557-568.

23. Orwoll E, Blank JB, Barrett-Connor E, et al. Design and baseline characteristics of the osteoporotic fractures in men (MrOS) study: a large observational study of the determinants of fracture in older men. *Contemp Clin Trials*. 2005;26(5):569-585.

24. Pahor M, Chrischilles EA, Guralnik JM, et al. Drug data coding and analysis in epidemiologic studies. *Eur J Epidemiol*. 1994;10(4):405-411.

25. Washburn RA, Smith KW, Jette AM, Janney CA. The Physical Activity Scale for the Elderly (PASE): development and evaluation. *J Clin Epidemiol*. 1993;46(2):153-162.

26. Barone JJ, Roberts HR. Caffeine consumption. *Food Chem Toxicol*. 1996;34(1):119-129.

27. Quan SF, Howard BV, Iber C, et al. The Sleep Heart Health Study: design, rationale, and methods. *Sleep*. 1997;20(2):1077-1085.

28. Collett D. *Modelling Survival Data in Medical Research*. 1st ed. New York, NY: Chapman & Hall; 1994.

29. Allison PD. *Survival Analysis Using SAS: A Practical Guide*. Cary, NC: SAS Institute; 1995.

30. US Food and Drug Administration. Update of safety review follow-up to the October 1, 2007 early communication about the ongoing safety review of bisphosphonates. US Department of Health & Human Services Website. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm136201.htm. Accessed March 13, 2012.

31. Bhuriya R, Singh M, Molnar J, et al. Bisphosphonate use in women and the risk of atrial fibrillation: a systematic review and meta-analysis. *Int J Cardiol*. 2010;142(3):213-217.

32. Aviles RJ, Martin DO, Apperson-Hansen C, et al. Inflammation as a risk factor for atrial fibrillation. *Circulation*. 2003;108(24):3006-3010.

33. Hewitt RE, Lissina A, Green AE, et al. The bisphosphonate acute phase response: rapid and copious production of proinflammatory cytokines by peripheral blood gd T cells in response to aminobisphosphonates is inhibited by statins. *Clin Exp Immunol*. 2005;139(1):101-111.

34. Savelieva I, Camm AJ. Clinical relevance of silent atrial fibrillation: prevalence, prognosis, quality of life, and management. *J Interv Card Electrophysiol*. 2000;4(2):369-382.

35. Silverman HS, Wei S, Haigney MC, Ocampo CJ, Stern MD. Myocyte adaptation to chronic hypoxia and development of tolerance to subsequent acute severe hypoxia. *Circ Res*. 1997;80(5):699-707.