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ORIGINAL ARTICLE

Myocardial Infarction Risk Among Patients With Fractures Receiving Bisphosphonates

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Abstract

Objective: To determine if bisphosphonates are associated with reduced risk of acute myocardial infarction (AMI).

Patients and Methods: A cohort of 14,256 veterans 65 years or older with femoral or vertebral fractures was selected from national administrative databases operated by the US Department of Veterans Affairs and was derived from encounters at Veterans Affairs facilities between October 1, 1998, and September 30, 2006. The time to first AMI was assessed in relationship to bisphosphonate exposure as determined by records from the Pharmacy Benefits Management Database. Time to event analysis was performed using multivariate Cox proportional hazards regression. An adjusted survival analysis curve and a Kaplan-Meier survival curve were analyzed.

Results: After controlling for atherosclerotic cardiovascular disease risk factors and medications, bisphosphonate use was associated with an increased risk of incident AMI (hazard ratio, 1.38; 95% CI, 1.08-1.77; P=.01). The timing of AMI correlated closely with the timing of bisphosphonate therapy initiation.

Conclusion: Our observations in this study conflict with our hypothesis that bisphosphonates have antiatherogenic effects. These findings may alter the risk-benefit ratio of bisphosphonate use for treatment of osteoporosis, especially in elderly men. However, further analysis and confirmation of these findings by prospective clinical trials is required.

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Atherosclerotic cardiovascular disease and osteoporosis are 2 major health burdens in the aging United States population. Cardiovascular disease is the nation's number one killer and is estimated to result in 17.3 million deaths annually.[1] In the United States between 2007 and 2011, the prevalence of coronary heart disease among those 65 years or older was 19.1%.[2]

Although osteoporosis is most common among postmenopausal women, it is also highly prevalent in aging men. Nearly 20% of men at least 50 years of age have osteoporosis of the hip, spine, or wrist. Men in this age group have a 13% lifetime risk of osteoporotic fracture.[3,4] Osteoporosis and cardiovascular disease are linked by common risk factors and biochemical pathways. Examples of common risk factors include age, smoking, menopause, decreased physical activity, dyslipidemia, oxidative stress, inflammation, hyperhomocysteinemia, hypertension, and diabetes.[5-14] Accumulating evidence indicates that arterial calcification is associated with low bone mineral density (BMD), even after adjustment for age.[10,15-17] The Multi-Ethnic Study of Atherosclerosis (MESA) Abdominal Aortic Calcium Study found a correlation between lower lumbar volumetric BMD and greater coronary artery calcium score in women and higher abdominal aortic calcium score among women and men.[18]

Bisphosphonates, which are used to treat and prevent osteoporosis, have been shown to have inhibitory effects on arterial calcification[19] and antiatherogenic effects[20,21] in animal models. Additionally, bisphosphonates have been associated with decreased prevalence of cardiovascular calcification in older women.[16]

This theoretical association between bisphosphonates and inhibition of atherosclerosis

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prompted us to examine the association between bisphosphonates and acute myocardial infarction (AMI) in a large national cohort, controlling for conditions associated with AMI. We hypothesized that in a cohort of elderly patients with prior hip or vertebral fractures, the risk of incident AMI would be lower in patients exposed to bisphosphonates than in those who are bisphosphonate naive. In addition, given the recent association of oral calcium supplement use with myocardial infarction,[22] we hypothesized that the risk of incident AMI is greater for patients exposed to oral calcium supplements than for those who are not.

PATIENTS AND METHODS

Study Population

This study was a retrospective administrative database study of patients 65 years or older who visited a US Department of Veterans Affairs (VA) facility between October 1, 1998, and September 30, 2006, and who had a known fracture. *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) codes, inpatient and outpatient encounter data, and demographic data used in this study were obtained from the VA Corporate Franchise Data Center. The source of all inpatient and outpatient pharmacy data in this study was the Pharmacy Benefits Management Database, a national repository of pharmacy data for all VA patients. Data from the Pharmacy Benefits Management Database included product, dosage, quantity dispensed, prescription instructions, and refills. A unique patient identifier was used to link the clinical and pharmacy data. Additional information regarding VA data can be found at the VA Information Resource Center website.[23] This study was approved by the human studies committees of the St. Louis, Missouri, and Hines, Illinois, VA medical centers.

From the eligible pool of patients, we selected individuals 65 years or older who had a femoral or vertebral fracture (*ICD-9-CM* codes 805.2-805.5, 806.2-806.5, 820.0-820.3, 820.8, 820.9, and 821.0-821.3) and a documented VA prescription for a nonbisphosphonate medication for at least 12 months before cohort entry (12-month bisphosphonate washout period). This was done to ensure that individuals selected were most likely first-time bisphosphonate users. To ensure that patients had consistent health care during the study period, patients were excluded if they did not have at least 2 separate outpatient or inpatient clinical encounters during the study period. Additionally, in order to avoid any potential bias introduced by differential prescribing of bisphosphonates to those with or without recent AMI, we further excluded individuals if they had a diagnostic code for AMI (*ICD-9-CM* codes 410.0-410.9) within 24 months after their initial medication prescription from the VA (24-month AMI washout). Figure 1 shows assembly of the cohort, and a visual representation of the time periods is presented in Supplemental Figure 1 (available online at http://www.mayoclinicproceedings.org).

Study Variables

Patients were considered exposed to bisphosphonates if they received at least one dispensation of a bisphosphonate after satisfying the 12-month bisphosphonate washout and the 24-month AMI washout criteria. Patients were considered to be receiving bisphosphonates from the date of first prescription until the date that the supply of medication from the last prescription would have been exhausted, provided the patient took the medication as prescribed. Calcium receipt was defined as prescription for at least 1000 mg of elemental calcium daily for 2 years (not necessarily consecutive), equaling a cumulative dose of 730,000 mg. Two years was chosen because the shortest trial duration in the meta-analysis by Bolland et al[22] was 2 years (range, 2-5 years; mean, 3.7 years).

Other variables included in the analysis were age, sex, race (white, African American, other, or unknown), proximity to the VA (within 20 miles of a VA hospital, yes/no), number of visits per month to the VA clinic/hospital, comorbid medical conditions (obesity, essential hypertension, hyperlipidemia, diabetes mellitus, chronic kidney disease, rheumatoid arthritis, congestive heart failure, atrial fibrillation, depression, vitamin D deficiency), cigarette smoking status, and medication use (antiplatelet/anticlaudication/antianginal agents, warfarin, antihypertensives and diuretics, lipid-lowering medications, diabetic medications, bisphosphonates, other osteoporosis drugs, hormone therapy, calcium,

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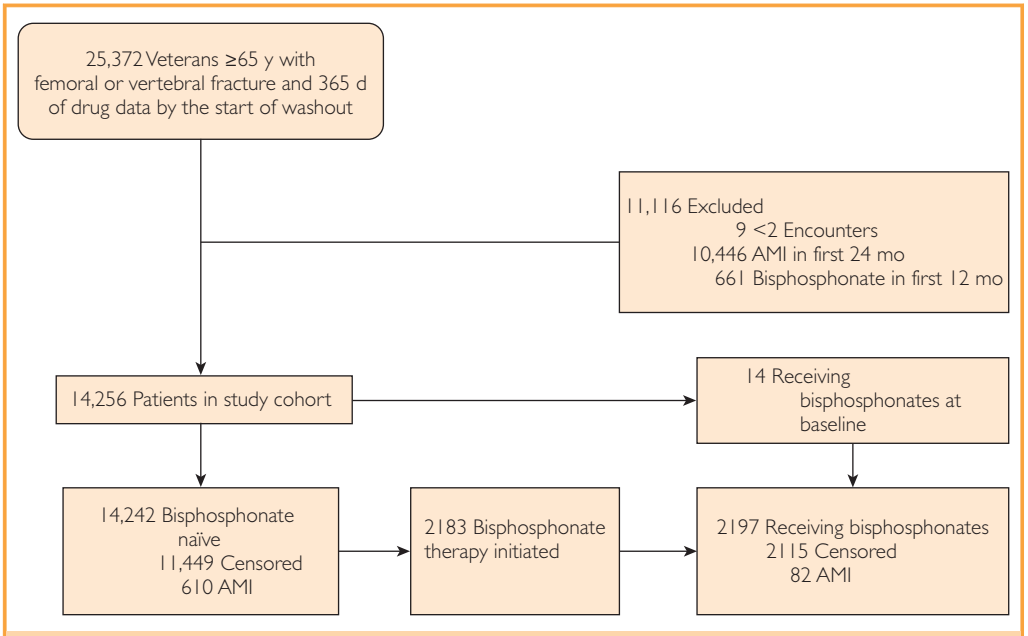

FIGURE 1. Patient flowchart: assembly of the study cohort. AMI = acute myocardial infarction.

vitamin D). Comorbid medical conditions were defined using accepted definitions when possible, using combinations of *ICD-9-CM* codes and medication prescriptions[24-29] (Supplemental Table, available online at http://www.mayoclinicproceedings.org). Over-the-counter medications such as aspirin and fish oil were not included because they are not supplied by the VA pharmacy.

Primary Outcome and Validation

The primary outcome, incident AMI, was defined by *ICD-9-CM* codes 410.0-410.9.[30-33] The primary outcome was considered present if the patient had 1 inpatient *ICD-9-CM* diagnostic code or 2 outpatient *ICD-9-CM* diagnostic codes for AMI during the study period.

We validated our definitions of fracture and AMI in a sample of patients from our primary site. The validation was completed through review of VA medical records by a physician (J.R.M.) who is certified in internal medicine by the American Board of Internal Medicine and who has extensive experience in data abstraction. Fracture was validated for all 41 patients from the primary study site who met our fracture definition. Fracture was considered present when results of a radiologic study undertaken before or at any time during the observation period indicated that a fracture of a vertebra, the hip, the femoral neck, or the intertrochanteric region of the femur was probable, likely, or present. Alternatively, a progress note from a physician or midlevel health care professional stating the diagnosis of fracture (probable, likely, or present) was accepted. Acute myocardial infarction was validated in a random convenience sample of 25 patients from the primary study site who met our AMI definition. For validation purposes, AMI was considered present if, within 45 days before or after the first occurrence of an *ICD-9-CM* code for AMI, a physician or midlevel health care professional reported a diagnosis of AMI and a biochemical marker of AMI (troponin or creatine kinase-MB) was elevated (reported in laboratory records or in clinical notes). Standardized searches of text elements within notes using preestablished text strings were used to facilitate identification of text strings of interest.

Study Timeline

Patient-time for a single patient was attributed to both the bisphosphonate-exposed (during receipt of bisphosphonates) and the bisphosphonate-naive (before first bisphosphonate prescription) groups (Supplemental Figure 1). In fact, most of

TABLE 1. Demographic and Medical Characteristics of Study Patients, Categorized by Bisphosphonate Exposure[a,b]

Variable	Total cohort (N=14,256)	Bisphosphonates	
		Exposed (n=2197)	Naive (n=14,242)
Male	13,671 (95.9)	1973 (89.8)	13,660 (95.9)
Age (y)	75.6 (6.7)	77.2 (6.5)	75.6 (6.7)
Race			
African American	1491 (10.5)	130 (5.9)	1490 (10.5)
White	11,733 (82.3)	1887 (85.9)	11,722 (82.3)
Other	139 (1.0)	30 (1.4)	139 (1.0)
Unknown	893 (6.3)	150 (6.8)	891 (6.3)
Lives within 20 miles of VA hospital	7475 (52.4)	1200 (54.6)	7467 (52.4)
No. of visits/mo to VA facility	1.5 (1.9)	1.6 (1.2)	1.5 (1.9)
Type of fracture			
Vertebral	3486 (24.5)	1024 (46.6)	3484 (24.5)
Femoral	11,033 (77.4)	1267 (57.7)	11,020 (77.4)
Multiple	3234 (22.7)	644 (29.3)	3230 (22.7)
Comorbid condition			
Essential hypertension	10,141 (71.1)	1583 (72.1)	9962 (70.0)
Hyperlipidemia	3795 (26.6)	697 (31.7)	3612 (25.4)
Diabetes mellitus	2974 (20.9)	352 (16.0)	2929 (20.6)
Chronic kidney disease	957 (6.7)	131 (6.0)	913 (6.4)
Rheumatoid arthritis	216 (1.5)	97 (4.4)	209 (1.5)
Congestive heart failure	1413 (9.9)	244 (11.1)	1318 (9.3)
Atrial fibrillation	2592 (18.2)	419 (19.1)	2467 (17.3)
Depression	3346 (23.5)	613 (27.9)	3180 (22.3)
Vitamin D deficiency	198 (1.4)	94 (4.3)	152 (1.1)
Cigarette smoking	2573 (18.0)	476 (21.7)	2572 (18.1)
Time in cohort, patient-years	51,558	4451	47,107
Outcomes			
AMI	692 (4.9)	82 (3.7)	610 (4.3)
Rate of AMI, events/patient-year	0.013	0.018	0.013

[a]AMI = acute myocardial infarction; VA = Veterans Affairs.

[b]Data are presented as No. (percentage) of patients or mean (SD). Numbers in subgroups do not equal number for the total cohort because some patients switched groups: 2183 of the 2197 bisphosphonate-exposed patients were bisphosphonate naive at cohort entry and were subsequently exposed to bisphosphonates.

the bisphosphonate-exposed patients (2183 of 2197) were bisphosphonate naive at cohort entry and were subsequently exposed to bisphosphonates (Figure 1). Patients were censored at the earliest of the following events: (1) the date of the first AMI occurrence, (2) the date of the last bisphosphonate prescription (or the date of the last prescription for any drug if the patient was bisphosphonate naive) plus the number of days' supply of drug plus 365 days, or (3) the date of the last episode of VA care. Censoring indicates that data following the event were not included in the analysis, and thus, recurrent AMI was not included in the analysis. Uncensored patients were followed up through September 30, 2006.

Statistical Analyses

A time-dependent survival model was used to eliminate immortal time bias, which can be an issue in cohort studies that use a flawed approach to design and data analysis.[34] Patient characteristics for those receiving a bisphosphonate and those who were bisphosphonate naive were not compared using a *t* test or χ^2 test because patients could contribute time to both cohorts. Therefore, Table 1 does not contain *P* values. One of the assumptions of both the *t* test and the χ^2 test is independence, so we could not compare the bisphosphonate-naive with the bisphosphonate-exposed group because of the overlap between groups. The time-dependent survival model defines independence differently. It assumes no overlap between groups at the same point in time. At each point in time, the model computes a rate for each group, and the hazard ratio (HR) is a summary of these rates across time. As long as each rate at each point in time is independent, then the assumption holds. Essentially, this is a person-time analysis, allowing us to compare the rates of bisphosphonate-exposed to bisphosphonate-naive groups even when patients switch groups over time.

Variables that were significantly undercoded were excluded. Cox proportional hazards regression was used to model time to AMI. Time-dependent variables, including comorbid conditions and medication exposures, were used in the analysis to more accurately model the effect of bisphosphonate exposure and covariates on AMI. $P<.05$ was considered statistically significant. SAS software version 9.2 (SAS Institute Inc) was used to perform all analyses. An adjusted survival analysis curve and a Kaplan-Meier survival curve were generated using R software version 2.13 (The R Project for Statistical Computing).

RESULTS

The study cohort was assembled as illustrated in Figure 1. Our final cohort included 14,256 patients with 51,558 patient-years of observation. The patients were followed up for a mean (SD) of 3.6 (1.9) years. Those who were never exposed to bisphosphonates (n=12,059) had a mean (SD) of 3.5 (2.0) years of follow-up. Patients who were exposed to bisphosphonates contributed a mean (SD) of 2.4 (1.5) nonexposed years

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and 2.0 (1.4) bisphosphonate-exposed years to the total follow-up time. Bisphosphonates were received by 2197 patients (15.4% of the cohort), accounting for 8.6% of patient-time. Baseline patient demographic characteristics, medical conditions, and smoking status are shown in Table 1. The study patients were primarily white men. Most of the fractures experienced by the cohort were femoral (11,033 patients [77.4%]), followed by vertebral (3486 patients [24.5%]) and multiple (3234 patients [22.7%]) fractures. There was a high burden of comorbid medical conditions, the most common being essential hypertension (10,141 patients [71.1%]), hyperlipidemia (3795 patients [26.6%]), depression (3346 patients [23.5%]), and diabetes mellitus (2974 patients [20.9%]). A total of 692 AMIs occurred during the study period (82 in bisphosphonate-exposed patients and 610 in bisphosphonate-naive patients). The rate of AMI was 0.018 per patient-year in the bisphosphonate-exposed group and 0.013 per patient-year in the bisphosphonate-naive group (Table 1).

Bisphosphonate use in the cohort is presented in Table 2, along with other medications relevant to the diagnoses of osteoporosis and atherosclerotic cardiovascular disease. Alendronate was the most commonly used bisphosphonate, accounting for 97.0% (2128 of 2197 patients) of bisphosphonate exposures, with risedronate accounting for most of the remaining exposures (153 of 2197 patients [7.0%]). No patients used ibandronate, and very few used zoledronate (5 patients [0.2%]), pamidronate (5 patients [0.2%]), or etidronate (13 patients [0.6%]). Of the 2197 bisphosphonate-exposed patients, 504 (22.9%) were considered calcium supplement users by our definition, whereas only 641 of the 14,242 bisphosphonate-naive patients (4.5%) used calcium supplements.

Validation of our fracture definition was performed in all 41 patients at the primary study site who met our fracture definition. Of those, 38 were confirmed to have hip or vertebral fracture, for a positive predictive value of 0.93. Validation of our AMI definition was performed in a random convenience sample of 25 patients at the primary study site who met our AMI definition. Of those, 23 were confirmed to have AMI, for a positive predictive value of 0.92.

Results of the multivariate Cox proportional hazards regression are reported in Table 3. Obesity was excluded from our analysis because of undercoding. Although smoking was also undercoded, we included it in the analysis because of its strong association with AMI. After controlling for atherosclerotic cardiovascular disease risk factors and medications, bisphosphonate use was associated with an increased risk of incident AMI (HR, 1.38; 95% CI, 1.08-1.77; P=.01). Other predictors of AMI included age, residence within 20 miles of a VA hospital, increased number of visits to a VA facility, essential hypertension, diabetes mellitus, chronic kidney disease, congestive heart failure, and atrial fibrillation. African American and unknown race had a decreased risk of AMI when compared with the referent population, whites. Calcium supplement use was not a predictor of incident AMI nor protective of AMI in this cohort (HR, 0.90; 95% CI, 0.62-1.31; P=.59). A survival analysis plot adjusted for the variables in Table 3 is

TABLE 2. VA Medication Prescriptions for the Study Patients, Categorized by Bisphosphonate Exposure[a,b]

Medication	Total cohort (N=14,256)	Bisphosphonates	
		Exposed (n=2197)	Naive (n=14,242)
Warfarin	2313 (16.2)	405 (18.4)	2203 (15.5)
Bisphosphonates (any)	2197 (15.4)	NA	NA
Alendronate	2128 (14.9)	2128 (97.0)	NA
Risedronate	153 (1.1)	153 (7.0)	NA
Ibandronate	0 (0.0)	0 (0.0)	NA
Zoledronate	5 (0.04)	5 (0.2)	NA
Pamidronate	5 (0.04)	5 (0.2)	NA
Etidronate	13 (0.1)	13 (0.6)	NA
Other osteoporosis drug[c]	938 (6.6)	386 (17.6)	790 (5.5)
Teriparatide	13 (0.1)	8 (0.4)	5 (0.04)
Calcitonin	932 (6.5)	384 (17.5)	786 (5.5)
Hormone therapy	537 (3.8)	215 (9.8)	479 (3.4)
Tamoxifen	28 (0.2)	9 (0.4)	27 (0.2)
Raloxifene	16 (0.1)	7 (0.3)	13 (0.1)
Estrogen	226 (1.6)	96 (4.4)	218 (1.5)
Progesterone	1 (0.01)	0 (0.0)	1 (0.01)
Conjugated estrogen	0 (0.0)	0 (0.0)	0 (0.0)
Conjugated estrogen/MDPA	18 (0.1)	10 (0.5)	18 (0.1)
Testosterone	278 (2.0)	108 (4.9)	228 (1.6)
Calcium[d]	1027 (7.2)	504 (22.9)	641 (4.5)

[a]MDPA = medroxyprogesterone acetate; NA = not applicable; VA = Veterans Affairs.
[b]Data presented as No. (percentage) of patients. Numbers for the subgroups do not equal the number for the total cohort because some patients switched groups: 2183 of the 2197 bisphosphonate-exposed patients were bisphosphonate naive at cohort entry and were subsequently exposed to bisphosphonates.
[c]Aspirin and fish oil are not included because they are not supplied by the VA pharmacy.
[d]Calcium receipt was defined as prescription for at least 1000 mg of elemental calcium daily for 2 years (not necessarily consecutive), equaling a cumulative dose of 730,000 mg.

TABLE 3. Results of Multivariate Cox Proportional Hazards Regression for Time to AMI[a,b]

Variable	AMI	No AMI	HR (95% CI)	*P* value
Bisphosphonate use	82	2115	1.38 (1.08-1.77)	.01
Age (y), mean	76.1	75.6	1.03 (1.02-1.04)	<.001
Male sex	667	13,004	1.42 (0.91-2.21)	.13
Race				
African American	56	1435	0.63 (0.48-0.84)	.001
White	615	11,118	Reference	NA
Other	6	133	0.72 (0.32-1.61)	.43
Unknown	15	878	0.46 (0.28-0.78)	.003
Lives within 20 miles of VA hospital	431	7044	1.31 (1.12-1.54)	<.001
No. of visits/mo to VA facility, mean	2.0	1.5	1.12 (1.08-1.17)	<.001
Comorbid condition				
Essential hypertension	521	9620	1.27 (1.06-1.53)	.009
Hyperlipidemia	161	3634	0.89 (0.74-1.07)	.21
Diabetes mellitus	193	2781	1.55 (1.30-1.85)	<.001
Chronic kidney disease	62	895	1.59 (1.21-2.09)	<.001
Rheumatoid arthritis	16	200	1.30 (0.78-2.14)	.31
Congestive heart failure	93	1320	1.63 (1.29-2.05)	<.001
Atrial fibrillation	135	2457	1.41 (1.12-1.78)	.004
Depression	144	3202	0.99 (0.82-1.20)	.95
Vitamin D deficiency	9	189	1.20 (0.61-2.34)	.60
Cigarette smoking	121	2452	0.94 (0.77-1.15)	.54
Medication[c]				
Warfarin	114	2199	0.90 (0.71-1.16)	.42
Calcium	38	989	0.90 (0.62-1.31)	.59
Other osteoporosis drug	42	896	1.22 (0.88-1.69)	.24
Hormone therapy	26	511	1.07 (0.69-1.65)	.77

[a]AMI = acute myocardial infarction; HR = hazard ratio; NA = not applicable; VA = Veterans Affairs.

[b]Data are presented as No. of patients unless indicated otherwise. This adjusted model treated the majority of covariates as time varying.

[c]Other prescription drugs were included in the model indirectly because they were used to define comorbid conditions (see Supplemental Table, available online at http://www.mayoclinicproceedings.org).

shown in Figure 2. The rates of AMI-free survival remained comparable between the bisphosphonate-exposed and bisphosphonate-naive groups until approximately 29 months, at which point the lines diverge, with the bisphosphonate-exposed AMI-free survival falling below the bisphosphonate-naive survival. Interestingly, 29 months is also the mean time at which patients started bisphosphonate treatment. A cohort effect was not seen. A Kaplan-Meier survival curve (Supplemental Figure 2, available online at http://www.mayoclinicproceedings.org), which is not adjusted, likewise illustrates a lower AMI-free survival in the bisphosphonate-exposed compared with the bisphosphonate-naive group.

As a subanalysis, we wished to investigate whether the increased incidence of AMI in bisphosphonate-treated patients may have been an artifact of the epidemiological association between osteoporosis and atherosclerotic cardiovascular disease or whether there was a true association between bisphosphonate usage and AMI. A subanalysis of incident AMI in patients treated with other osteoporosis drugs (calcitonin or teriparatide) vs bisphosphonates, while underpowered because of small sample size (HR, 1.26; 95% CI, 0.78-2.02; *P*=.35), suggested an association of AMI with bisphosphonate treatment.

DISCUSSION

In a cohort composed primarily of elderly men with a fracture history and without recent AMI, we found a higher incidence of AMI among patients prescribed bisphosphonates compared with those not prescribed bisphosphonates, controlling for atherosclerotic cardiovascular disease risk factors and medications. This is a novel finding and conflicts with our original hypothesis. Additionally, in our cohort, calcium supplementation was not associated with increased risk of AMI. This contradicts the findings of a meta-analysis by Bolland et al,[22] which revealed an increased risk of incident AMI in patients who received calcium supplements and had a dietary calcium intake exceeding the median of 805 mg/d.

Nitrogen-containing bisphosphonates (NCBPs) act on the cholesterol biosynthesis pathway and inhibit farnesyl pyrophosphate synthetase, the enzyme downstream from 3-hydroxy-3-methylglutaryl-coenzyme A reductase, the site of statin action.[35] The NCBPs have several pharmacological effects in common with the statins, including increasing serum high-density lipoprotein cholesterol, decreasing low-density lipoprotein cholesterol,[36,37] and inhibiting the secretion of several inflammatory cytokines.[38,39] The NCBPs also inhibit hydroxyapatite crystal aggregation in vitro.[40] Considering the mechanisms of action of bisphosphonates, it is reasonable to hypothesize that these compounds might decrease vascular calcification, which is a predictor of cardiovascular disease.[12,41,42] Animal and human studies of etidronate[43-45] suggest that bisphosphonates have antiatherogenic properties. Etidronate has been found to reduce carotid intima-media thickness[44] and reduce arterial calcification in the coronary arteries

and aorta of patients undergoing hemodialysis.[46,47] Other NCBPs including ibandronate, alendronate, risedronate, and zoledronate, which are more potent inhibitors of bone resorption, have also been found to inhibit vascular calcification. Alendronate and ibandronate inhibited arterial calcification in rats treated with warfarin and vitamin D, drugs that are known to induce vascular calcification.[19]

With regard to myocardial infarction, human studies present conflicting data. In a large database study that included more than 47,000 patients, Bunch et al[48] compared patients who received bisphosphonates with those who did not, with the end points being atrial fibrillation, AMI, and death. The investigators were unable to find a statistical difference in rates for AMI, atrial fibrillation, or mortality. To the contrary, another population-based retrospective cohort study that used Taiwan's National Health Insurance database found an increased risk of myocardial infarction when bisphosphonates were compared with raloxifene.[49] In this study, only those patients who received alendronate for more than 1 year and had a history of prior cardiac events were at increased risk of myocardial infarction. Because alendronate was compared with raloxifene rather than placebo, the apparent increased risk of AMI in the alendronate group may actually represent a reduction of cardiovascular events in the raloxifene group, with no increase in the alendronate group. Complicating these findings, however, is another study using the same Taiwanese database[50] that revealed that patients treated with alendronate, 70 mg/wk, were at a *lower* risk of atrial fibrillation, stroke, or AMI compared with the raloxifene group. However, this second study may have obscured the true cardiovascular disease effects by relying on a combined end point that mixed electrophysiologic and cardiovascular outcomes.

Our study has several limitations. Although administrative data provide a large cohort for study, the quality of data is imperfect and is subject to the limitations of a retrospective administrative data study, including the inability to adjust for all baseline risk for AMI. Selection bias may be present because, as previously discussed, arterial calcification is associated with low BMD. Therefore, patients who receive bisphosphonates because of low BMD may have a higher baseline risk of AMI than those who do not. Our study design tried to eliminate this bias by requiring a fracture for cohort entry, and therefore, all patients had osteoporosis, a medical indication to receive bisphosphonates. It is difficult to explain the contradiction of our study findings with those from the study by Bolland et al[22] with regard to calcium use and AMI, echoing the potential flaws of a retrospective analysis. Because our cohort consisted primarily of men, our results may not necessarily apply to women with osteoporosis. We observed our cohort for 1 year past the last prescription for a bisphosphonate. Given this study design, it is possible that we did not capture late outcomes from bisphosphonate usage. Obesity was relatively undercoded and thus was excluded from our analysis. Smoking is often not reliably coded in the VA medical record system, and thus our data were incomplete. Additionally, our study was unable to estimate dietary calcium intake or use of over-the-counter preparations of calcium, aspirin, or fish oil. Some veterans who receive VA health care also seek care outside the VA. We attempted to capture this with the variable indicating the patients' proximity to the VA facility. We also considered the possibility that patients might receive bisphosphonate prescriptions from non-VA physicians, thus being counted as bisphosphonate naive when in fact they were exposed. However, we believe this is unlikely because most veterans elect to have their prescriptions filled at VA pharmacies to utilize generous VA pharmacy benefits.

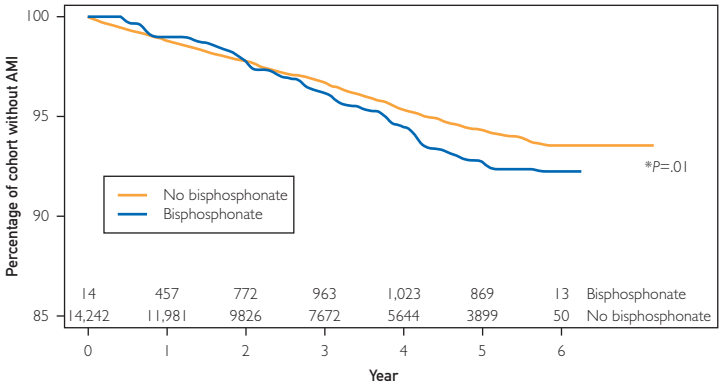

FIGURE 2. Survival curve, adjusted for all variables in Table 3, showing the percentage of bisphosphonate-exposed and bisphosphonate-naive patients who did not experience acute myocardial infarction (AMI) during 6 years of monitoring.

Our study has several strengths as well. To our knowledge, this is the first study of AMI risk in bisphosphonate users to include a large cohort of primarily male patients with osteoporosis. We utilized a large data set, which excluded those with recent prior AMI and was designed to capture new bisphosphonate users, and the positive predictive value of our definitions of myocardial infarction and fracture was excellent.

CONCLUSION

We found that bisphosphonate use was associated with an increased risk of AMI. Our findings may significantly alter the risk-benefit ratio of bisphosphonate medications, particularly in elderly men with osteoporosis. Although our findings are biologically plausible, other animal and human studies addressing the potential cardiovascular effects of bisphosphonates have produced conflicting results. Given the broad use of bisphosphonates for the treatment of osteoporosis, our conclusions should be examined by future studies, including studies with larger populations of women.

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SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org.

Abbreviations and Acronyms: **AMI** = acute myocardial infarction; **BMD** = bone mineral density; **HR** = hazard ratio; ***ICD-9-CM*** = *International Classification of Diseases, Ninth Revision, Clinical Modification*; **NCBP** = nitrogen-containing bisphosphonate; **VA** = Veterans Affairs

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