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Myocardial Infarction Risk Among Fracture Patients 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 (VA), and were derived from encounters at VA facilities between October 1, 1998, and September 30, 2006. The time-to-first AMI was assessed in relation to bisphosphonate exposure as determined by records from the Pharmacy Benefits Management Database (PBM). Time-to-event analysis was performed using multivariable 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 (HR 1.38;

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95% CI, 1.08–1.77; $P=0.012$). The timing of AMI correlated closely with the timing of bisphosphonate therapy initiation.

Conclusion—These observations conflict with our hypothesis that bisphosphonates have anti-atherogenic effects, and 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.

Keywords

Bisphosphonates (MeSH heading = Diphosphonates); Osteoporosis; Myocardial infarction

INTRODUCTION

Atherosclerotic cardiovascular disease and osteoporosis are two 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 2005–2010, the prevalence of coronary heart disease among those greater than 65 years of age was 21.7%.²

While osteoporosis is most common among postmenopausal women, it is also highly prevalent amongst aging males. 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.^{5,6,7,8,9,10,11,12,13,14} Accumulating evidence indicates that arterial calcification is associated with low bone mineral density (BMD), even after adjustment for age.^{15,16,10,17} The Multi-Ethnic Study of Atherosclerosis (MESA) Abdominal Aortic Calcium Study demonstrated a correlation between lower lumbar volumetric BMD with greater coronary artery calcium score in women, and with greater abdominal aortic calcium score among women and men¹⁸.

Bisphosphonates, which are used to treat and prevent osteoporosis, have been shown to have inhibitory effects on arterial calcification¹⁹ and anti-atherogenic effects^{20,21} in animal models. Additionally, bisphosphonates have been associated with decreased prevalence of cardiovascular calcification in older women.¹⁶

Due to this theoretical association between bisphosphonates and inhibition of atherosclerosis, we examined 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 for those who are bisphosphonate naïve. In addition, given the recent association of oral calcium supplement use with myocardial infarction²², we hypothesized that the risk of incident AMI is greater for patients exposed to oral calcium supplements than for those who are not.

MATERIALS AND METHODS

This study was a retrospective administrative database study of patients 65 years or older attending 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 Pharmacy Benefits Management 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 Web site.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 who were 65 years or older with a femoral or vertebral fracture ICD-9-CM codes 805.2–805.5, 806.2–806.5, 820.X, and 821.X) and who had a documented VA prescription for a non-bisphosphonate medication for at least 12 months before cohort entry (12 month bisphosphonate wash-out period). This was done to ensure that individuals captured were more likely to be a first-time bisphosphonate user. 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 410.x) within 24 months following their initial medication prescription from the VA (24 month AMI washout). See Figure 1 for assembly of the cohort and eFigure 1 for a visual representation of the time periods described.

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 on 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 since the shortest trial duration in the Bolland et al. meta-analysis was 2 years (range 2 to 5 years, mean 3.7 years).²²

Other variables included in the analysis were: age; gender; race (Caucasian, 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, cigarette use, congestive heart failure, atrial fibrillation, depression, vitamin D deficiency); and medication use (anti-platelet/anti-claudication/anti-anginal, warfarin, anti-hypertensives and diuretics, lipid-lowering medications, diabetic medications, bisphosphonate use, other osteoporosis drug, hormone therapy, calcium, vitamin D). Comorbid medical conditions were defined using accepted definitions where possible, using combinations of ICD-9-CM codes and medication prescriptions (see eAppendix 1^{24, 25, 26, 27, 28, 29}). Over the counter medications such as aspirin and fish oil were not included as these are not supplied by the VA pharmacy.

The primary outcome, incident AMI, was defined by ICD-9-CM codes 410.0–410.9.^{30, 31, 32, 33} The primary outcome was considered present if the patient had 1 inpatient ICD-9 diagnostic code or 2 outpatient ICD-9 diagnostic codes for AMI during the study period.

We validated our definitions of fracture and AMI on a sample of patients from our primary site. This was completed through review of VA medical records by a physician (JRM) who

is American Board of Internal Medicine certified in Internal Medicine, and who has extensive experience in data abstraction. Fracture was validated for all patients meeting our fracture definition at the primary study site (n=41). Fracture was considered present when report of a radiologic study from before or at any time during the observation period diagnosed fracture of vertebra, hip, femoral neck, or intertrochanteric region of the femur as probable, likely, or present. Alternatively, a progress note from a physician or mid-level provider stating the diagnosis of fracture (probable, likely, or present) was accepted. AMI was validated on a random convenience sample of patients (n=25) who met our AMI definition at the primary study site. For validation purposes, AMI was considered present if, within 45 days before or after the first occurrence of an ICD-9 code for AMI, a physician or mid-level provider stated a diagnosis of AMI and a biochemical marker of AMI (troponin or creatine kinase-MB) was elevated (either in lab records or in provider notes). Standardized searches of text elements within notes using preestablished text strings were used to facilitate identification of text strings of interest.

Patient-time for a single patient may be attributed toward both the bisphosphonate exposed (during receipt of bisphosphonates) and the bisphosphonate naïve (prior to first bisphosphonate prescription) groups (see eFigure 1 for a visual representation). In fact, most of the bisphosphonate exposed patients (2183 of 2197) were bisphosphonate naïve at cohort entry, and were subsequently exposed to bisphosphonates (see Fig 1). Patients were censored at the earliest of the following events: a) the date of first AMI occurrence, b) the date of the last bisphosphonate prescription (or the date of the last prescription for any drug if the patient is bisphosphonate naïve) plus the number of days' supply of drug plus 365 days, or c) 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 through September 30, 2006.

Statistical methods

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 naïve were not compared using a T-test Chi-square 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 Chi-square tests is independence, so that we cannot compare the bisphosphonate naïve 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 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 naïve even when patients switch groups over time.

Variables that were significantly under-coded were excluded. Cox proportional-hazards regression was used to model time-to-AMI. Time-dependent variables, including comorbid diagnoses and medication exposures, were used in the analysis to more accurately model the effect of bisphosphonate exposure and covariates on AMI. A p-value of <0.05 was considered statistically significant. SAS software version 9.2 (SAS Institute, Cary, North Carolina) 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.

RESULTS

The study cohort was assembled as illustrated in the flow diagram (see Figure 1). Our final cohort included 14,256 patients, with 51,558 patient-years of observation. On average, subjects were followed for 3.6 (1.9 std) years. Subjects who were never exposed to bisphosphonates ($n=12,059$) had an average of 3.5 (2.0 std) years of follow up. Subjects exposed to bisphosphonates contributed an average of 2.4 (1.5 std) of non-exposed years and 2.0 (1.4 std) of bisphosphonate exposed years to the total follow-up time. Bisphosphonates were received by 2,197 patients (15.3% of the cohort), accounting for 8.6% of patient-time. Baseline patient demographics and medical conditions are shown in Table 1. The majority of study patients were white males. The majority of the fractures experienced by the cohort were femoral (77.4%), followed by vertebral (24.5%) and multiple (22.7%). There was a high burden of co-morbid medical conditions, the most common being essential hypertension (71% of the cohort), hyperlipidemia (27% of the cohort), depression (24% of the cohort), and diabetes mellitus (21% of the cohort). A total of 692 AMIs occurred during the study period (82 bisphosphonate exposed, 610 bisphosphonate naïve). The rate of AMI was 0.018 per patient-year in the bisphosphonate –exposed group and 0.013 per patient year in the bisphosphonate-naïve group (see 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 97.6% of bisphosphonate exposures, with risedronate accounting for the majority of the remaining exposures. No patients used ibandronate, and very few used zoledronate, pamidronate, or etidronate. While 22.9% of bisphosphonate-exposed patients were considered calcium supplement users by our definition, only 4.5% of bisphosphonate naïve patients used calcium supplements.

Validation of our fracture definition was performed on all 41 patients meeting our fracture definition at the primary study site. 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 on a random convenience sample of 25 patients meeting our AMI definition at the primary study site. Of those, 23 were confirmed to have AMI, for a positive predictive value of 0.92.

Results of the multivariable Cox proportional hazards regression are reported in Table 3. Obesity was excluded from our analysis due to undercoding. Though smoking was also undercoded, we included it in the analysis due to 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; $P=0.012$). Other predictors of AMI included age, residence within 20 miles of a VA hospital, increased visits to the VA, 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 to the referent population, Caucasians. 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; $P=0.59$). A survival analysis plot adjusted for the variables in Table 3 is shown in Figure 2. The rates of AMI-free survival remain comparable between the bisphosphonate exposed and naïve groups until approximately 29 months, at which point the lines diverge, with the bisphosphonate exposed AMI-free survival plot falling below the bisphosphonate naïve survival plot. Interestingly, 29 months is also the mean time at which patients initiated bisphosphonate treatment. A cohort effect was not seen. A Kaplan-Meier survival curve (see eFigure 2), which is not adjusted, likewise

illustrates a lower AMI-free survival in the bisphosphonate exposed compared with the bisphosphonate naïve 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 sub-analysis of incident AMI in patients treated with other osteoporosis drugs (calcitonin or teriparatide) vs. bisphosphonates, while underpowered due to small sample size (HR 1.26; 95% CI 0.78–2.02; $P=0.35$), suggested an association of AMI with bisphosphonate treatment..

DISCUSSION

In a cohort of largely elderly male patients with a fracture history and without recent AMI, we found a higher incidence of AMI among patients prescribed bisphosphonates compared to 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 showed an increased risk of incident AMI in patients who received calcium supplements and had a dietary calcium intake exceeding the median of 805 mg/day.²²

Nitrogen-containing bisphosphonates (NCBP) act on the cholesterol biosynthesis pathway and inhibit farnesyl-pyrophosphate synthetase, the enzyme downstream from 3-hydroxy-3-methyl-glutaryl-CoA reductase, the site of statin action.³⁵ NCBP have several pharmacological effects in common with the statins, including increasing serum high-density lipoprotein cholesterol, decreasing LDL cholesterol^{36,37}, and inhibiting the secretion of several inflammatory cytokines.^{38,39} NCBP also inhibit hydroxyapatite crystal aggregation in vitro.⁴⁰ Considering the mechanisms of action of bisphosphonates, it is reasonable to hypothesize that these compounds might be expected to decrease vascular calcification, which is a predictor of cardiovascular disease.^{12,41,42} Animal and human studies of etidronate^{43,44,45} suggest that bisphosphonates have anti-atherogenic properties. Etidronate has been found to reduce carotid intima-medial thickness⁴⁴ and reduce arterial calcification in the coronary arteries and the aorta of hemodialysis patients.^{46,47} Other NCBP 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 regards to myocardial infarction, human studies present conflicting data. In a large database study ($n>47,000$) Bunch et al.⁴⁸ compared patients who received bisphosphonates with those who did not, with the endpoints being atrial fibrillation, AMI, and death. The authors were unable to find a statistical difference in rates for AMI, AF, or mortality. To the contrary, another population-based retrospective cohort study which used Taiwan's National Health Insurance database showed an increased risk of myocardial infarction when bisphosphonates were compared to 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. As alendronate was compared to 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 database⁵⁰ that showed that patients treated with alendronate 70 mg per week 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 endpoint that mixed electrophysiologic and cardiovascular outcomes.

Our study has several limitations. While administrative data provides 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, since as previously discussed, arterial calcification is associated with low bone mineral density (BMD). Therefore, patients who receive bisphosphonates due to 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 with the Bolland et al study with regard to calcium use and AMI, echoing the potential flaws of a retrospective analysis. As our cohort consisted primarily of men, our results may not necessarily apply to women with osteoporosis. We observed our cohort for one year past the last prescription for a bisphosphonate. Given this study design, it is possible that we are not capturing 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 healthcare 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 providers, thus being counted as bisphosphonate naïve when in fact they are exposed. However, we believe this is unlikely as most veterans elect to have their prescriptions filled at VA pharmacies to utilize generous VA pharmacy benefits.

Our study has several strengths. This is the first study of AMI risk in bisphosphonate users to include a large cohort of primarily male osteoporosis patients. We utilized a large dataset, 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

In conclusion, we found that bisphosphonate use was associated with an increased risk of acute myocardial infarction. Our findings may significantly alter the risk-benefit ratio of bisphosphonate medications, particularly in elderly men with osteoporosis. While 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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LIST OF ABBREVIATIONS

AMI	acute myocardial infarction
BMD	bone mineral density
CI	confidence interval
HR	hazard ratio
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
NCBP	Nitrogen-containing bisphosphonates
VA	US Department of Veterans Affairs

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Figure 1.
Assembly of the study cohort.
Legend: AMI= acute myocardial infarction

*p-value = 0.012

Figure 2. Survival curve, adjusted for all variables in Table 3, showing the percentage of bisphosphonate users and bisphosphonate naïve who have not experienced AMI over six years of monitoring.

Table 1

Demographics and medical characteristics of 14,256 VA patients 65 years old with a documented femoral or vertebral fracture, categorized by bisphosphonate exposure

Variable	Cohort n ^c =14,256	Bisphos. ^a Exposed n ^c =2,197	Bisphos. ^a Naïve n ^c =14,242
Male gender, n (%)	13,671 (95.9)	1,973 (89.8)	13,660 (95.9)
Age, mean (SD)	75.6 (6.7)	77.2 (6.5)	75.6 (6.7)
Race, n (%)			
African American	1,491 (10.5)	130 (5.9)	1,490 (10.5)
Caucasian	11,733 (82.3)	1,887 (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, n (%)	7,475 (52.4)	1,200 (54.6)	7,467 (52.4)
Number of visits/month to VA facility	1.5 (1.9)	1.6 (1.2)	1.5 (1.9)
Type of fracture, n (%)			
Vertebral	3,486 (24.5)	1,024 (46.6)	3,484 (24.5)
Femoral	11,033 (77.4)	1,267 (57.7)	11,020 (77.4)
Multiple	3,234 (22.7)	644 (29.3)	3,230 (22.7)
Comorbid diagnoses, n (%)			
Essential Hypertension	10,141 (71.1)	1,583 (72.1)	9,962 (70)
Hyperlipidemia	3,795 (26.7)	697 (31.7)	3,612 (25.4)
Diabetes mellitus	2,974 (20.9)	352 (16.0)	2,929 (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)
Cigarette smoking	2,573 (17.3)	476 (21.7)	2,572 (18.1)
Congestive heart failure	1,413 (9.9)	244 (11.1)	1,318 (9.3)
Atrial fibrillation	2,592 (18.2)	419 (19.1)	2,467 (17.3)
Depression	3,346 (23.5)	613 (27.9)	3,180 (22.3)
Vitamin D deficiency	198 (1.4)	94 (4.3)	152 (1.1)
Time in cohort, patient-years	51558	4451	47107
Outcomes			
AMI ^b , n (%)	692 (4.9)	82 (3.7)	610 (4.3)
Rate of AMI, events/patient-year	0.013	0.018	0.013

^a Bisphos. = bisphosphonate;

^b AMI = Acute Myocardial Infarction;

^c n for the subgroups do not add up to n for the total cohort because some patients switch groups: 2183 of the 2197 bisphos exposed patients were bisphos naïve at cohort entry, and were subsequently exposed to bisphosphonates

Table 2

VA Medication prescriptions for patients in the bisphosphonate exposed and naïve groups

Variable	Cohort n ^d =14256	Bisphos. ^a Exposed n ^d =2,197	Bisphos. ^a Naïve n ^d =14,242
Warfarin, n(%)	2,313 (16.2)	405 (18.4)	2,203 (15.5)
Bisphosphonates (any), n(%)	2,197 (15.3)		
Alendronate, n(%)	2,128 (14.9)	2,128 (97.6)	n/a
Risedronate, n(%)	153 (1.1)	153 (7.0)	n/a
Ibandronate, n(%)	0 (0.0)	0 (0.0)	n/a
Zoledronate, n(%)	5 (0.04)	5 (0.2)	n/a
Pamidronate, n(%)	5 (0.04)	5(0.2)	n/a
Etidronate, n(%)	13 (0.1)	13 (0.6)	n/a
Other osteoporosis drug, n(%)	938 (6.6)	386 (17.6)	790 (5.5)
Teriparatide, n(%)	13 (0.1)	8 (0.4)	5 (0.04)
Calcitonin, n(%)	932 (6.5)	384 (17.6)	786 (5.5)
Hormonal therapy, n(%)	537 (3.8)	215 (9.8)	479 (3.4)
Tamoxifen, n(%)	28 (0.2)	9 (0.4)	27 (0.2)
Raloxifene, n(%)	16 (0.1)	7 (0.3)	13 (0.1)
Estrogen, n(%)	226 (1.6)	96 (4.4)	218 (1.5)
Progesterone, n(%)	1 (0.0)	0 (0.0)	1 (0.0)
Conj. ^b estrogens, n(%)	0 (0.0)	0 (0.0)	0 (0.0)
Conj. ^b estrogens/ medroxyprog. ^c , n(%)	18 (0.1)	10 (0.5)	18 (0.1)
Testosterone, n(%)	278 (2.0)	108 (4.9)	228 (1.6)
Calcium (by our definition), n(%)	1,027 (7.2)	504 (22.9)	641 (4.5)

^a Bisphos= bisphosphonate;^b Conj. = conjugated;^c medroxyprog = medroxyprogesterone acetate;^d n for the subgroups do not add up to n for the total cohort because some patients switch groups: 2183 of the 2197 bisphos exposed patients were bisphos naïve at cohort entry, and were subsequently exposed to bisphosphonates.^e Aspirin and fish oil not included because these are not supplied by VA pharmacy.

Table 3

Results of multivariable Cox proportional hazards regression for time to acute myocardial infarction

Variable	AMI ^a , n	No AMI ^a , n	HR ^b (95% CI ^c)	p-value
Bisphosphonate use	82	2,115	1.38 (1.08–1.77)	0.01
Age	76.1	75.6	1.03 (1.02–1.04)	<0.0001
Male gender	667	13,004	1.42 (0.91–2.21)	0.13
Race				
African American	56	1,435	0.63 (0.48–0.84)	0.001
Caucasian	615	11,118	Ref	
Other	6	133	0.72 (0.32–1.61)	0.43
Unknown	15	878	0.46 (0.28–0.78)	0.003
Lives within 20 miles of VA Hospital	431	7,044	1.31 (1.12–1.54)	<0.001
Number of visits/month to VA facility	2.0	1.5	1.12 (1.08–1.17)	<0.0001
Comorbid diagnoses				
Essential Hypertension	521	9,620	1.27 (1.06–1.53)	0.009
Hyperlipidemia	161	3,634	0.89 (0.74–1.07)	0.21
Diabetes mellitus	193	2,781	1.55 (1.30–1.85)	<0.0001
Chronic kidney disease	62	895	1.59 (1.21–2.09)	<0.001
Rheumatoid arthritis	16	200	1.30 (0.78–2.14)	0.31
Cigarette smoking	121	2,452	0.94 (0.77–1.15)	0.54
Congestive heart failure	93	1,320	1.63 (1.29–2.05)	<0.0001
Atrial fibrillation	135	2,457	1.41 (1.12–1.78)	0.004
Depression	144	3,202	0.99 (0.82–1.20)	0.95
Vitamin D deficiency	9	189	1.20 (0.61–2.34)	0.60
Medications				
Warfarin	114	2,199	0.90 (0.71–1.16)	0.42
Calcium	38	989	0.90 (0.62–1.31)	0.59
Other osteoporosis drug	42	896	1.22 (0.88–1.69)	0.24
Hormone therapy	26	511	1.07 (0.69–1.65)	0.77

^a AMI= acute myocardial infarction;^b HR= hazard ratio;^c CI= confidence interval.^d Other prescription drugs were included in the model indirectly because they were used to define medical comorbid diagnoses (see eAppendix1).^e This adjusted model treated the majority of covariates as time varying.