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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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