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Bisphosphonate Use Is Associated With Reduced Risk of Myocardial Infarction in Patients With Rheumatoid Arthritis

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Abstract

Bisphosphonates have been shown to reduce mortality in patients with osteoporotic fractures, but the mechanism is unclear. Bisphosphonates have immunomodulatory effects that may influence the development of vascular disease. We sought to determine if bisphosphonate use is associated with a reduced risk of myocardial infarction (MI) in a rheumatoid arthritis (RA) population with high prevalence of bisphosphonate use and vascular disease. Adult patients with RA enrolled in the National Data Bank for Rheumatic Diseases, a longitudinal study of RA patients enrolled continuously from U.S. rheumatology practices between 2003 and 2011, were included in the analysis (n = 19,281). Patients completed questionnaires every 6 months. including questions on medication use, demographic information, clinical information, and health status. MIs were confirmed by a central adjudicator. Among the 5689 patients who were treated with bisphosphonates at some time during the study period, the risk of MI while on bisphosphonate compared to when not on bisphosphonate was 0.56 (95% confidence interval [CI], 0.37–0.86; p < 0.01) after adjustment for multiple confounders. In models including all 19,281 treated and untreated patients, the adjusted risk of first MI was 0.72 (95% CI, 0.54–0.96; p = 0.02) and of all MIs it was 0.72 (95% CI, 0.53–0.97; p = 0.03) in bisphosphonate users compared to nonusers. This finding suggests a potential mechanism for the mortality reduction observed with bisphosphonate medications.

Keywords

Bisphosphonate; Myocardial Infarction; Rheumatoid Arthritis

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Introduction

Osteoporosis and the resulting skeletal fractures are a significant worldwide health problem, causing pain, disability, and an increased risk of mortality.[1,2] In addition to the well-recognized excess mortality following vertebral and hip fractures, there are now studies demonstrating that increased mortality occurs with other major and minor fractures.[1,3–6] The causes for the increased mortality are still being debated, and the impact is greater for men than women, and in patients at older ages.[3] Despite these negative consequences of osteoporosis and fractures, most patients who sustain fractures are not offered therapy.[7–9]

A randomized, controlled trial treating patients within 90 days of a hip fracture with an annual intravenous dose of the bisphosphonate, zoledronic acid, or placebo demonstrated a 28% reduction in mortality in the treated group.[10] A post hoc analysis of these data showed that after controlling for baseline risk factors, only 8% of the reduction in mortality could be explained by the reduction in subsequent fracture risk; therefore, 20% of the mortality reduction was due to other factors.[11] Post hoc analyses of two additional trials have since shown that the oral bisphosphonates alendronate and risedronate are associated with similar reductions in mortality when given to patients with hip fractures,[12,13] and a meta-analysis of osteoporosis treatment trials (including bisphosphonates and other medication classes) showed a 10% to 11% relative reduction in mortality.[14] A prospective cohort study found that oral bisphosphonates are associated with reduced mortality in both women and men irrespective of their initial bone mineral density.[15] Although all of these studies support that bisphosphonates reduce mortality in both women and men with osteoporosis, it is not clear which pathways are involved in their mechanism of action.

Rheumatoid arthritis (RA) causes bone loss and osteoporosis due to reduced physical activity, inflammation from the underlying disease, and medications used for treatment.[16–18] RA is also associated with an increased risk of myocardial infarction (MI), thought to be caused at least in part by increased circulating levels of inflammatory cytokines.[19–21] Based on previous epidemiologic studies and known immunologic effects of bisphosphonates, we hypothesized that one mechanism by which bisphosphonates could reduce mortality was by decreasing the risk of MI. In the current study we examined the effect of bisphosphonates on the risk of MI in patients with RA. We selected an RA population because MI occurs with higher frequency in patients with that illness, as does the use of bisphosphonates prescribed for osteoporosis.

Materials and Methods

Design overview

This work was a post hoc analysis of a prospective cohort study using the National Data Bank for Rheumatic Diseases (NDB) longitudinal study of RA outcomes.[22] The NDB utilizes an open cohort design in which patients were enrolled continuously beginning in 1998 and followed until death or study withdrawal. The study database characteristics, including drug assessment methods and validity, completeness of follow-up, and validity of self-reported data has been reported previously.[22–26]

Setting and participants

We included all 19,281 adult patients with a rheumatologist-confirmed diagnosis of RA who participated in the NDB and completed at least two 6-month questionnaires. Participants were volunteers, recruited from the practices of U.S. rheumatologists, who complete extensive mailed or Internet questionnaires about their health at 6-month intervals. Participants were recruited in all 50 states, and were not compensated for their participation.

The study was carried out in compliance with the Helsinki Declaration, and was approved by the Institutional Review Boards of the St. Francis Regional Medical Center, Wichita, KS, the Medical University of South Carolina, and Duke University Medical Center. All patients signed an informed consent.

Interventions

Patients were assessed on a semiannual basis between July 2003 and June 2011. At each assessment we inquired about treatment and events that occurred in the previous 6 months. Treatment data included nonprescription medications, dose, and treatment start and end dates.[22]

Outcomes and follow-up

Case definition of MI—Only MIs that were confirmed by a central adjudication committee were included in this study. As described,[23] possible MIs were identified from study questionnaires, hospitalization records, physician reports, and death records. If primary source documents were not available to adjudicate a potential MI, we contacted the patient's physician and/or interviewed the patient or family with a structured, preplanned interview designed to address the reported condition. Comparison of patient self-reports with medical records indicates agreement in more than 94% of cases. Review of potential cases was performed by two trained, experienced NDB staff reviewers. This review was followed by an independent physician review. Death records in which MI was recorded as the underlying cause of death must have referred to deaths that occurred within 6 months of the last questionnaire to be included as an MI.

Selection of covariates—To identify possible covariates associated with bisphosphonate prescription, we analyzed potential variables in a multivariable generalized estimating equation (GEE) logistic model that included all study observations. We included sex, age, education categories, household income, body mass index (BMI) categories,[27] prior clinical fractures, the presence of a bone density test, and marital status. In addition, we examined variables present in the last 6 months potentially related to MI risk, including recent MI, hypertension, diabetes, BMI, and smoking. Finally, to assess for long-term risk factors we included "lagged variables" reported to be present prior to the most recent semiannual questionnaire. Lagged variables included Health Assessment Questionnaire (HAQ) score,[28] use of statins, antihypertensives, calcium, and prednisone, and all clinical fractures within the last 5 years. Because statin use was not found to distinguish between bisphosphonate users and non-users in multivariable models, and antihypertensive use was not different between groups, other specific cardiovascular agents were not included in the models.

Statistical analysis

Three models were constructed using different inclusion criteria and modeling strategies in order to assess the sensitivity of the results to different underlying assumptions. Because bisphosphonate treatment is not random and likely relates to underlying MI risk through unmeasured factors such as health behaviors and contact with the healthcare system, our primary model included only patients who had been treated with bisphosphonates at some time during the follow-up period in order to minimize selection bias. Two additional sensitivity models allowed us to examine the effect in ever-treated versus never-treated patients, and to include multiple MI events. In all models, subjects were censored at death or loss to follow-up, and all covariates significantly different at the $p < 0.05$ level were included.

Model I: treated patients only—Using Cox regression with start time at the first subject observation and bisphosphonate use as a time varying covariate, we estimated the hazard ratio (HR) of a first MI during treatment compared to off treatment, after adjustment for covariates. Thus, subjects contributed "on treatment" follow-up time while taking bisphosphonates, and "off treatment" follow-up time before and/or after their bisphosphonate exposure. The use of a treated-patient model decreases patient heterogeneity, because only patients who receive therapy are evaluated.

Model II: treated patients and untreated patients—We performed Cox regression in all treated and untreated patients beginning with the first study observation, and estimated the effect of bisphosphonates on the risk of the first MI, after adjustment for covariates. The all-patients model allows comparison between treated patients and those who never received treatment.

Model III: treated patients and untreated patients—We used all observations in a GEE analysis with a logit link and robust standard errors to determine the population averaged risk for any MI associated with bisphosphonate therapy, after adjustment for covariates. The GEE model allows evaluation of multiple MIs in an individual patient.

All Cox models satisfied the proportional hazards assumption. The relationship between age and risk of MI was nonlinear. To better analyze the data, age was modeled using a restricted cubic spline with four knots. Data were analyzed using Stata 12.0 (Stata Corporation, College Station, TX, USA). Because the study aims were exploratory, no adjustment for multiple comparison was made.

Covariates were missing in 4% to 6% of observations. Because the data were longitudinal, prior values of fixed characteristics were often available; ie, diabetes reported in a previous observation. In the case of such variables, we replaced the current missing values with the most recent present value. This left between 0.6% and 1.8% of observations with missing covariates. In this instance we used a randomly selected hot-decked replacement or a mean substitution by sex. Because the rate of missingness was very low, we did not use multiple imputation.

Results

Characteristics of patients treated and not treated with bisphosphonates

Eighty-one percent of NDB participants provided at least 6 months of follow-up data and were included in the analysis (n = 19,281). Of these, 5689 used bisphosphonates at some time during the study period: 61.2% used alendronate; 26.2% used risedronate; 12.2% used ibandronate; and 1.4% used etidronate, pamidronate, or zoledronic acid. We combined users of any of the above bisphosphonates into a single "bisphosphonate" user variable. The mean starting year of bisphosphonate therapy was the second half of 2006, and the mean ± SD duration of therapy was 2.5 ± 2.1 (range, 0.5–8.0) years. The mean ± SD duration of follow-up in the study was 4.19 ± 3.0 (range, 0.50–9.0) years. The average dose of bisphosphonate was very similar to the recommended osteoporosis treatment dose for each agent.

As measured at a random observation, patients treated with bisphosphonates differed from those not treated in all demographic and clinical characteristics studied, although some of the differences were small (Table 1). Treated patients were older (67.6 versus 59.5 years of age), had lower household income ($35,000 versus $45,000), were more likely to be female (86.8% versus 75.2%), had a lower BMI (26.5 kg/m^2 versus 28.9 kg/m^2), had more fractures over the course of the study (26.9% versus 11.7%), and were more likely to be receiving prednisone therapy (43.1% versus 28.5%). With respect to cardiovascular risk factors,

diabetes was more prevalent (12.5% versus 10.1%) and statin use more common (21.9% versus 18.3%) in never-users, whereas hypertension (38.2% versus 35.8%) was more common in ever-users. Patients treated with bisphosphonates had more severe RA as evidenced by increased use of prednisone and opioids (26.8% versus 23.8%), and worse functional status as measured by HAQ score (1.2 versus 1.0) and 36-item Short Form Health Survey Physical Component Summary (SF-36 PCS) score (35.3 versus 36.8).

Reduction in the risk of MI with bisphosphonate therapy

During follow-up, approximately 1.8% of the cohort experienced a first MI, with 340 events in 19,281 patients. The 5689 patients starting on bisphosphonates at some time during the study period (Model I: treated patients; Table 2) were analyzed in unadjusted and adjusted Cox regressions. The relative hazard of first MI while on bisphosphonates compared to when not on bisphosphonate was 0.53 (95% confidence interval [CI], 0.35–0.81) in the unadjusted model and 0.56 (95% CI, 0.37–0.86) in the adjusted model, with an absolute decrease in the rate of MI from 6.0 MI per 1000 person-years to 2.6 MI per 1000 person years. When all 19,281 treated and untreated patients were considered (Model II; Table 2), the unadjusted relative risk was 0.69 (95% CI, 0.52–0.92) and the adjusted relative risk was 0.72 (95% CI, 0.54–0.96), with an absolute decrease in the rate of MI from 4.3 MI per 1000 person-years to 3.5 MI per 1000 person years. Finally, we used a population averaged GEE model that allowed inclusion of multiple MIs per patient (Model III). As with the other models, bisphosphonate therapy was associated with a protective effect, odds ratio 0.71 (95% CI, 0.53–0.95) for the unadjusted model and odds ratio 0.72 (95% CI, 0.53–0.97) for the adjusted model.

We were unable to measure the exact time bisphosphonate use was initiated or stopped within a 6-month period, only whether it was used during that period or not. To examine the effect of duration of therapy we assumed that usage within a 6-month period was for the entire 6 months. Under that assumption, using GEE analyses in the fully adjusted model, we found a trend for an association between time on bisphosphonate and MI, OR 0.92 (95% CI, 0.84–1.0; $p = 0.053$).

In our adjusted Cox analysis for all subjects who had ever received bisphosphonate, we tested for the interaction between previous MI and bisphosphonate effect. Although the test for interaction was not significant ($p = 0.12$), the hazard ratios (HRs) suggested a possibly greater MI reduction effect in those without a prior MI (HR 0.58) than in those with a prior MI (HR 1.66). There was no significant bisphosphonate by gender interaction ($p = 0.93$). In sensitivity analyses completed with and without fracture patients included, results were unchanged.

Because calcium and vitamin D have been reported to impact the risk of cardiovascular events,[29,30] we also evaluated bisphosphonate therapy in combination with calcium and vitamin D treatment. The combination of bisphosphonates, calcium, and vitamin D was significantly superior to no treatment, and the effect was consistent across all models. Figure 1 shows the effect of different combinations of bisphosphonate, calcium, and vitamin D therapies on the risk of MI for the Cox model including all patients. Figure 2 displays the proportion of the sample surviving without first MI over time in subjects on bisphosphonates with and without calcium and vitamin D.

Discussion

Recent work has demonstrated that treating patients with osteoporotic fractures with bisphosphonates results in both a reduced risk for subsequent fracture and a reduced mortality rate. The reduction in mortality appears after 18 months to 2 years of treatment,[10]

and is only partially attributable to a reduction in subsequent fracture.[11] Because previous work suggested a possible impact of bisphosphonates on cardiovascular outcomes,[11,31] we investigated whether the use of bisphosphonates could be protective against MI in a high-risk RA population.

In this study, the risk of MI was substantially reduced among patients with RA who were taking bisphosphonates after adjustment for multiple known cardiovascular risk factors, disease severity indicators, and functional status. The data were consistent in several different sensitivity models, and suggest that a portion of the bisphosphonate effect on decreasing mortality following a hip fracture may be due to a reduction in the rate of MI. Although the absolute risk difference in our study was small given the relatively low incidence of MI in the sample, because cardiovascular disease is one of the most common chronic illnesses in older adults,[32] this is a potentially important finding that, if confirmed in other studies, may have important public health ramifications.

Prior epidemiologic studies and secondary data analyses support a link between bisphosphonate use and reduced cardiovascular disease. A meta-analysis of subjects enrolled in the clinical trials testing risedronate showed a trend toward a lower cardiovascular mortality, driven mainly by a reduction in strokes.[31] Exploratory analyses of a large clinical trial of zoledronic acid suggested a similar incidence, but a lower risk, of death from cardiac arrhythmias in those receiving zoledronic acid, perhaps driven by changes in cardiac ischemia.[11] Nitrogen-containing bisphosphonates were associated with decreased prevalence of cardiovascular calcification in older subjects enrolled in the Multi-Ethnic Study of Atherosclerosis, but more prevalent cardiovascular calcification in younger subjects.[33] More recently, a large case-control study of bisphosphonate users in Denmark reported an inverse dose–response relationship between alendronate use and MI, with a 50% higher increased risk of MI in those with low adherence and a nonsignificant 20% decreased risk in those who were adherent to the drug, with a significant test for trend.[34] A healthy user effect was postulated as one explanation for these findings.

At present, a mechanism for the effect of bisphosphonates on the risk for MI is unknown. Although avidly taken up by bone after administration, bisphosphonates are also deposited in other tissues, including the myocardium and arterial tissue.[35] Therefore, bisphosphonates may have a direct effect on the pathogenesis of MI, rather than indirectly through their impact on bone turnover. In addition, bisphosphonates have systemic effects outside of bone, which may impact both the development of cardiovascular disease and bone turnover. Common pathophysiologic mechanisms linking osteoporosis and cardiovascular disease include suppression of monocyte-macrophage differentiation and function, alterations in serum cytokine levels, and vascular calcium deposition[36–39]; bisphosphonates impact several of these areas directly or indirectly. Intravenous, but not oral, bisphosphonates significantly reduce serum low-density lipoprotein in postmenopausal women.[39] Bisphosphonates have an immunomodulatory effect on gamma-delta T cells, which have been shown to mediate cardiac apoptosis.[40] In animal models, bisphosphonates accumulate in arterial tissue and may inhibit macrophage migration and plaque inflammation,[41] although zoledronic acid given immediately before coronary artery ligation in a rat model did not impact macrophage migration or other measures of infarct severity.[42]. Finally, bisphosphonates have complex effects on levels of circulating inflammatory cytokines,[43–46], which have been associated with risk of vascular events.

Recent reports suggest a possible association between vitamin D supplements and lower risk of vascular events,[30] and between calcium supplements and a higher risk of vascular events.[29] Because these supplements are frequently but not universally prescribed with bisphosphonates, we performed an exploratory subgroup analysis looking at risk of MI in

patients on different combinations of bisphosphonate, calcium, and vitamin D therapy. Overall, the direction of the HRs for most bisphosphonate-treated subgroups favored a protective effect, although the strongest effect in all three models was consistently observed in patients taking bisphosphonate plus both calcium and vitamin D (Table 3, Fig. 1). One possible explanation for our findings is that those taking all three therapies may represent a unique subgroup of highly compliant patients with lower MI risk; however, other recognized markers of compliance including income level and marital status were not associated with MI risk in our models. Alternatively, the limitations in our assessment of calcium and vitamin D supplementation use may have resulted in the pattern observed. To explore the validity of the calcium and vitamin D use self-report, we contacted 109 current bisphosphonate users and noted that, similar to the rate reported in our sample, 60% also used calcium and vitamin D.

Limitations of this cohort study should be noted. The aim of this exploratory study was to examine a potential mechanism of the bisphosphonate mortality benefit, and the findings require confirmation with prospective studies or meta-analysis of randomized trials. Selection bias, in which patients who are prescribed and agree to take bisphosphonates have a different underlying MI risk due to health status, lifestyle, compliance, or other factors, is likely. We attempted to minimize the impact of selection bias in our models by including only bisphosphonatetreated subjects in our main model, and adjusting for the risk of bisphosphonate prescription in our sensitivity models. However, the possibility of unmeasured confounding remains. We chose to study RA patients because the population is enriched for both bisphosphonate prescription and MI, but the generalizability of our findings is uncertain and should be confirmed in other populations. We combined all bisphosphonates together and are unable to distinguish different effects based on route of administration or type, although more than 98% were taking oral agents, primarily alendronate. We did not have measures of bisphosphonate adherence available in the study, although the duration of use was accounted for in our Cox proportional hazards model. Finally, we are not able to determine the time-to-benefit in our population.

Our study also has several strengths. We used three different modeling strategies with different underlying assumptions in different patient groups, and our findings were robust and consistent. Clinical events were adjudicated centrally by study personnel blinded to the study hypothesis. In patients with RA, functional status is a powerful predictor of mortality,[47] and our investigation accounted for this with use of the HAQ score as well as with other variables including use of prednisone and opioid medications. A common bias in observational studies is confounding by indication, which occurs where patients at higher risk for the outcome (MI) are more likely to receive treatment (bisphosphonate) because of a suspected beneficial impact of treatment on MI risk. During the study time period there was no indication in the medical literature that bisphosphonates might reduce the risk of MI, and in fact, some concerns that it might increase risk.[48] Thus, the probability of confounding by indication is low for this study.

In summary, this cohort study in a high-risk population for both osteoporosis and cardiovascular disease found a reduced risk for MI in patients taking bisphosphonates, particularly in combination with calcium and vitamin D supplements. Because both cardiovascular disease and osteoporosis are highly prevalent in older persons, this finding has important clinical implications if confirmed. Further study is warranted to help delineate the mechanism by which bisphosphonates may mitigate cardiovascular risk.

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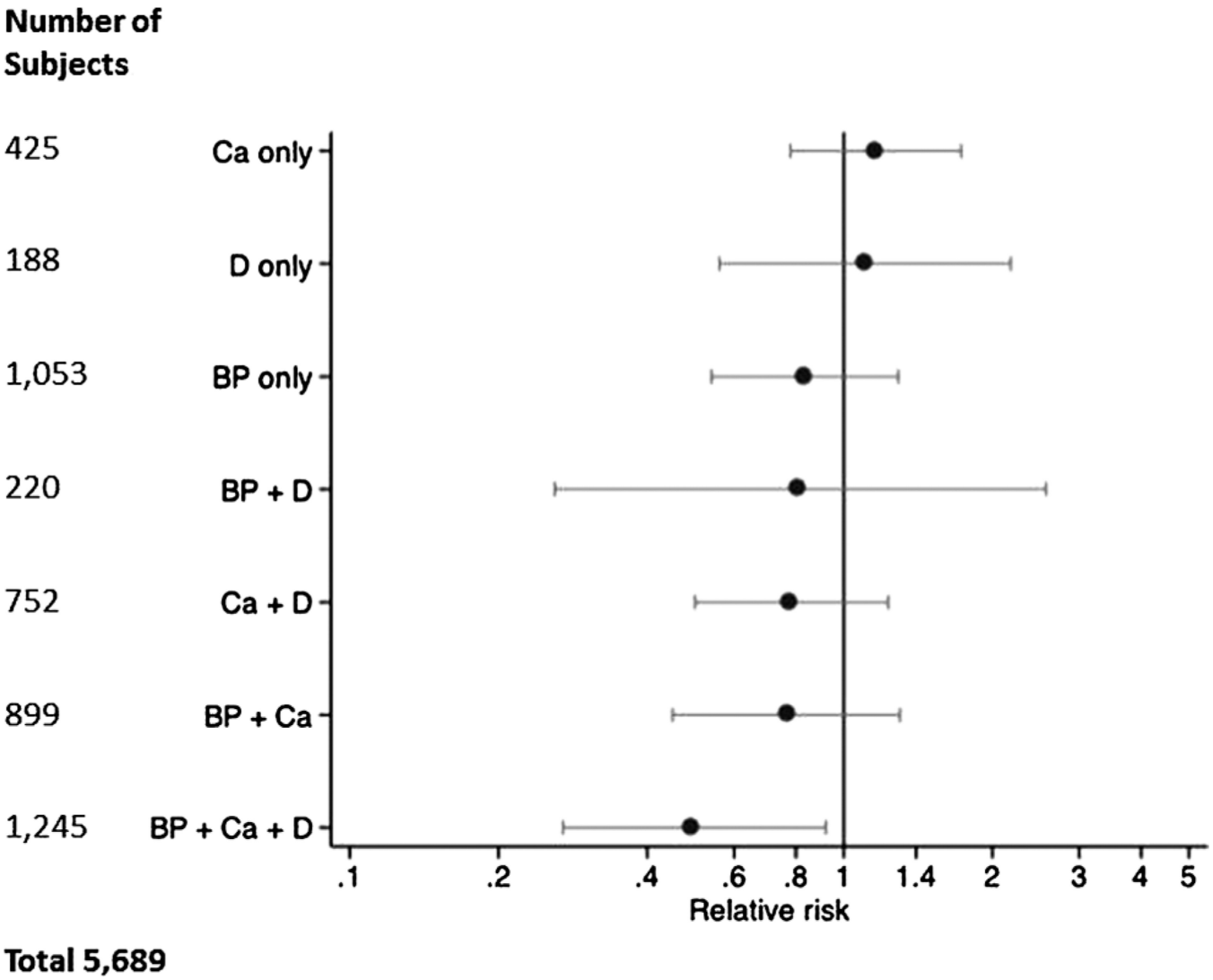

Figure 1.
Forest plot of the relative risk of myocardial infarction associated with combinations of calcium, vitamin D, and bisphosphonate therapy (subgroup analyses).

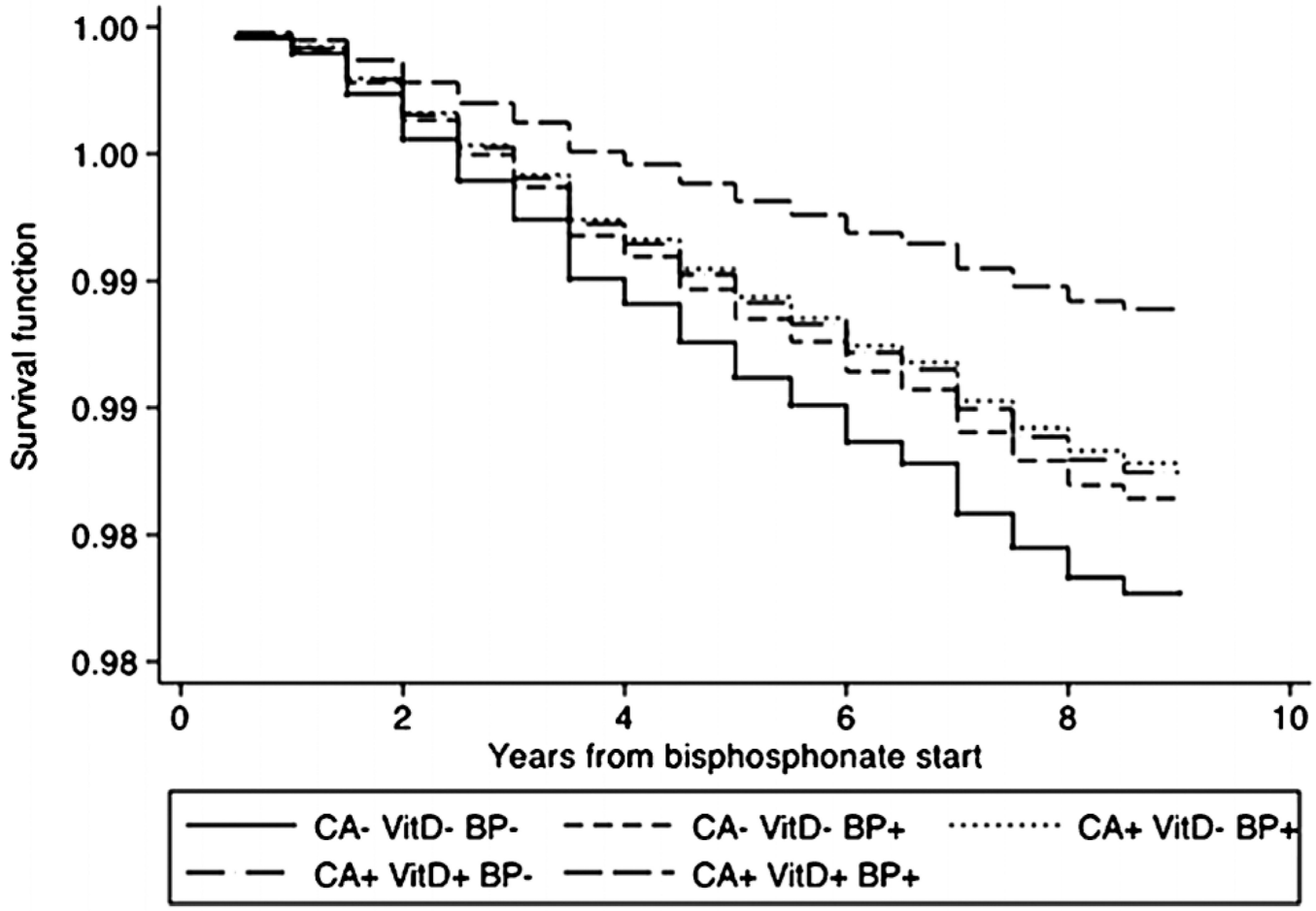

Figure 2.
Survival function for risk of myocardial infarction among groups not treated and variously treated with bisphosphonates.

Table 1

Characteristics of Bisphosphonate Users and Non-Users

Variable	Patients who ever used bisphosphonates (*n* = 5891)	Patients who never used bisphosphonates (*n* = 13,390)
Age (years), mean ± SD	67.6 ± 11.1	59.5 ± 13.4
Male sex (%)	13.2	24.8
Education (years)		
0–8 (%)	2.6	2.5
8–11 (%)	7.8	6.7
12 (%)	37.7	32.7
13–15 (%)	25.5	28.8
≥16 (%)	26.5	29.3
Median household income ($1000 s)	35.0	45.0
Smoking category		
Never (%)	57.2	52.4
Past (%)	32.0	33.1
Current (%)	10.8	14.5
BMI (kg/m^2), mean ± SD	26.5 ± 5.6	28.9 ± 6.5
Hospitalized (%)	14.2	11.2
Fracture during study (%)	26.9	11.7
Comorbidity index (0–9), mean ± SD	1.9 ± 1.6	1.8 ± 1.6
Diabetic (%)	10.1	12.5
Hypertension now (%)	38.2	35.8
Physical component score (SF-36), mean ± SD[a]	35.3 ± 10.9	36.8 ± 11.3
Mean HAQ (0–3)[b]	1.2 ± 0.7	1.0 ± 0.7
Prednisone (%)	43.1	28.5
Opioids (%)	26.8	23.8
Ever on vitamin D during observation (%)	63.4	32.6
Ever on calcium during observation (%)	78.8	42.4
Statins (%)	18.3	23.9
Antihypertensives (%)	48.7	42.6

Comparison is at a random observation. All variables are significantly different (<0.001) between groups.

BMI = body mass index; HAQ = Health Assessment Questionnaire.

[a] 36-Item Short Form Health Survey.(49)

[b] Health Assessment Questionnaire Disability Index.(50)

Table 2

MI Risk Reduction Associated With Bisphosphonate Therapy

Analyses	Subjects	MIs	Model	RR/OR (95% CI)	*p*
Adjusted for age and sex	5689	101	I: Cox regression (treated patients)	RR 0.53 (0.35–0.81)	0.004
Full model[a]	5689	101	I: Cox regression (treated patients)	RR 0.56 (0.37–0.86)	0.009
Adjusted for age and sex	19,281	330	II: Cox regression (all patients)	RR 0.69 (0.52–0.92)	0.011
Full model[a]	19,281	330	II: Cox regression (all patients)	RR 0.72 (0.54–0.96)	0.025
Adjusted for age and sex	19,281	340	III: GEE analysis (all patients)	OR 0.71 (0.53–0.95)	0.020
Full model[a]	19,281	340	III: GEE analysis (all patients)	OR 0.72 (0.53–0.97)	0.030

[a]Adjusted for age, sex, education, smoking status, household income, marital status, body mass index, diabetes, hypertension, fracture in the last 6 months, lagged fracture in the last 6 months, fracture in the last 5 years, prior MI, bone density determination in last year. Lagged Health Assessment Questionnaire (HAQ), lagged statin, calcium, and prednisone use.

MI = myocardial infarction; RR = relative risk; OR = odds ratio; CI = confidence interval; GEE = generalized estimating equation.

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