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Nitrate Medications, Fractures and Change in Bone Mineral Density in Postmenopausal Women: Results from the Women's Health Initiative

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Abstract

Nitrate medications may increase bone mineral density (BMD), although information on fracture outcomes is sparse. We examined the association of nitrate medications with fractures (hip, wrist/arm and total fractures) and changes in BMD (hip, spine and whole body) in the Women's Health Initiative (WHI) Clinical Trials and Observational Study. A total of 139,211 postmenopausal women 50 to 79 years old without history of hip fracture were included in this prospective study. Medication use was ascertained directly from drug containers at baseline during in-person interviews in 1993-1998. Exposure measures included any use (use/non-use), type of nitrate (as-needed, maintenance) and duration of use (≤ 5 years, > 5 years). We used separate multivariable Cox proportional hazard models to analyze associations between each exposure and fracture outcome, with results presented as hazard ratios (HRs) and 95% confidence intervals (CI). Multivariable linear regression models were used to examine 3 and 6-year changes in BMD. At baseline, 1.2% (n=1647) women were using a nitrate. During the mean (SD) follow-up of 7.7 (1.5) years through 2005, women experienced 1582 hip fractures, 5156 wrist or arm fractures, and 22,589 total fractures. After adjustment for confounders, nitrate use was not statistically associated with risk for hip (HR, 0.81; 95% CI, 0.56–1.18), wrist/arm (HR, 0.95; 95% CI, 0.74–1.23) or total fractures (HR, 0.96; 95% CI, 0.85–1.08). As-needed nitrate use, but not maintenance therapy, was associated with a lower risk of total fractures (HR, 0.77; 95% CI, 0.62–0.95) and wrist/arm fractures (HR, 0.57; 95% CI, 0.34–0.98). Nitrate use was not associated with 3 or 6-year changes in BMD at any site. We conclude that any nitrate use was not significantly associated with lower risk of fractures or higher BMD, however as-needed nitrates were associated with lower risks of total and wrist/arm fractures.

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Keywords

osteoporosis; fracture prevention; therapeutics; aging; epidemiology

INTRODUCTION

Osteoporosis is characterized by reduced bone mineral density (BMD) which can lead to increased fracture risk. Osteoporotic fractures are associated with significant morbidity and mortality, and may leave individuals with poor quality of life and long-term disability.^(1,2) Bisphosphonates remain first-line treatment for osteoporosis, however these medications have safety concerns which limit long-term use.⁽³⁾

Organic nitrates (e.g. isosorbide mononitrate, isosorbide dinitrate, nitroglycerin) are medications used to treat angina that have been proposed as potential novel therapeutic options for osteoporosis.^(4,5) Serving as nitric oxide donors, these medications uncouple bone resorption and formation resulting in beneficial effects on bone metabolism.⁽¹⁾ *In vitro* and animal studies suggest that nitric oxide donors decrease bone resorption by reducing osteoclastic activity and to a lesser extent may enhance osteoblast activity (e.g. leading to enhanced bone formation).⁽¹⁾ Nitroglycerin prevented bone loss in ovariectomized and corticosteroid-treated rats.^(6,7) Epidemiological studies have suggested higher BMD and lower rates of bone turnover in people using nitrates.^(8,9) However, two randomized controlled trials (RCT) that examined the effects of nitroglycerin ointment on BMD yielded conflicting results.^(10,11) The RCT demonstrating that nitroglycerin ointment led to increased BMD at several sites, which was the impetus for the current analysis,⁽¹¹⁾ has since been retracted.⁽¹²⁾ Limited evidence suggests that nitrate use may also be associated with a slightly lower risk for fracture.^(13,14)

The optimal dosing regimen to maximize bone effects remains unclear.⁽⁴⁾ The action of nitrates on bone appears to be dose-dependent and continuous exposure may cause tachyphylaxis in bone as it does with angina symptom control. In ovariectomized rats, once daily administration of nitroglycerin ointment increased BMD, whereas more frequent application did not have beneficial effects.⁽¹⁵⁾ Based on this potential for tachyphylaxis, randomized controlled trials that have examined nitroglycerin effects on BMD have used once daily dosing of nitroglycerin ointment, which is a short-acting formulation.^(4,11,16) In contrast, this same medication would be dosed several times a day for management of angina symptoms (e.g. maintenance therapy), which is hypothesized not to have beneficial bone effects. The difficulty in capturing the nitrate regimen that optimizes benefits to bone from data available in observational studies where frequency of as-needed use is rarely captured makes it challenging to examine the relationship between nitrates and bone outcomes. Observational studies have attempted to differentiate intermittent dosing—which may have beneficial effects on bone—from maintenance therapy by focusing on short acting preparations that are used for as-needed therapy for an angina attack.^(8,13) Definitions of intermittent use or as-needed therapy have varied,^(9,14) which may explain the conflicting results that have been observed.

To our knowledge, no study has examined the association of nitrate medications with fracture and BMD in the same cohort. Therefore, we used data from the Women's Health Initiative (WHI) studies to examine the association of nitrate medications with fractures (hip, wrist/arm and total fractures) and changes in BMD (hip, spine and whole body). We hypothesized that as-needed use of nitrate medications would be associated with lower fracture risk.

MATERIALS AND METHODS

Study setting and participants

We analyzed prospectively collected data in postmenopausal women 50 to 79 years old enrolled in the WHI Clinical Trials (CT) and Observational Study (OS). Women were enrolled from 40 clinical sites throughout the United States from 1993–1998. Details of scientific rationale, eligibility, implementation and other aspects of the study design have been extensively described elsewhere.^(17,18) Women were eligible for this analysis if they had no prior hip fracture and provided a medication inventory at study entry (n=160, 972). We excluded those with missing covariates for a sample of 139 211. Participants were followed through 2005. Protocols were approved by institutional review boards at participating institutions and all women gave written informed consent.

Outcome Ascertainment

Fracture Outcomes—Total fractures were defined as all reported clinical fractures other than those of the ribs, sternum, skull or face, fingers, toes, and cervical vertebrae. Incident fractures were ascertained prospectively using annual (OS) or semiannual (CT) self-report questionnaires. All fracture outcomes were verified by central review of radiology reports in CT whereas only hip fractures were centrally adjudicated for women in OS. When self-reported fractures were confirmed by physician review, self-report was reasonably accurate for wrist/arm (81%) and overall fractures (71%) and less so for vertebral fractures (51%).⁽¹⁹⁾ Primary outcomes were hip fracture, wrist/arm, and total fractures. We used adjudicated fractures when available, otherwise fractures were self-reported.

Measurement of BMD—The BMD at the total hip, posterior-anterior spine, and total body was measured at baseline at 3 of the 40 clinical centers among 10 833 women (97% of participants enrolled in Pittsburgh, Pennsylvania; Birmingham, Alabama; and Phoenix and Phoenix and Tucson, Arizona) with dual-energy x-ray absorptiometry using a Hologic QDR densitometer (Hologic Inc, Waltham, Massachusetts). BMD was also assessed at year 3 and year 6. Standard protocols for positioning and analysis were used by trained technicians and ongoing quality assurance program was conducted.

Definition of Nitrate exposure

Current medication use was ascertained by having women bring all containers for medications taken for the 2 weeks prior to the baseline visit. Clinic interviewers entered each medication name directly from the containers into the WHI database, the Medispan (First DataBank Inc, San Bruno, California) Master Drug Data Base. Women reported duration of use for current medications, but information about dose or frequency was not

collected. Women were categorized as users or nonusers of nitrates based on use at study entry. Duration was categorized as ≤ 5 years or > 5 years. We categorized nitrate medications according to indication for use as either as-needed (sublingual nitroglycerin, nitroglycerin spray and sublingual and chewable formulations of isosorbide dinitrate) or maintenance therapy (transdermal or topical nitroglycerin, any regular or extended release formulations of nitroglycerin, isosorbide mononitrate, other isosorbide dinitrate). Women using both maintenance and as-needed nitrates were categorized as using maintenance therapy. As-needed nitrates are short acting and indicated for use at the onset of angina symptoms, whereas other products are used as maintenance therapy.

Covariates

We considered demographic characteristics, health characteristics and health conditions that could be potential confounders.^(8,9,13) Baseline questionnaires ascertained information on age, race or ethnicity, level of education, self-rated health, alcohol intake, current and past smoking, history of fracture, and parental history of hip fracture. Ten-year risk of major osteoporotic fracture was calculated for each participant by the WHO Collaborating Centre for Metabolic Bone Disease, using the Fracture Risk Assessment Tool (FRAX) without BMD.^(20,21) Self-reported physical activity was measured as metabolic equivalent tasks (METs) in hours per week.⁽²²⁾ Rand-36 physical function was measured by using the 10-item Medical Outcomes Study scale (a score >90 defines high function).⁽²³⁾ Body mass index was calculated as weight in kilograms divided by height in meters squared. Information was collected on self-report of physician-diagnosed heart failure and ischemic heart disease (e.g. myocardial infarction, angina, and/or coronary artery bypass graft or percutaneous coronary angioplasty). Other health conditions ascertained included treated hypertension (e.g. taking a medication for high blood pressure or having a blood pressure of $\geq 140/90$ mmHg) and treated diabetes mellitus. Medications included hormone therapy, thiazides, corticosteroids, proton pump inhibitors, bisphosphonates, and total number of psychoactive medications (e.g. anxiolytics, hypnotics, antidepressants, antipsychotics, and antiepileptic agents). Dietary intake of calcium and vitamin D was calculated by using a semiquantitative food-frequency questionnaire. Total calcium or vitamin D intake was described as the total amount from supplements and diet.

Statistical Analysis

We used multivariable Cox proportional hazard survival modeling to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) to examine associations between nitrate use variables and risks for fractures. The time scale was time since study entry. Women contributed follow-up time until the occurrence of fracture, death, or end of follow-up, whichever came first. All models were stratified by 5-year age intervals, study component (CT vs. OS) and current hormone therapy use. We examined two models. A minimally adjusted model included linear age at screening, race/ethnicity, study component (OS versus CT) and randomization arm. We then further adjusted for self-rated health, smoking status, history of fracture, physical activity, physical function score, body mass index, treated hypertension, treated diabetes, heart failure, ischemic heart disease, use of several medications (hormone therapy, corticosteroids, proton pump inhibitors, number of psychoactive medications), and calcium.

We developed interaction models to evaluate effect modification of the fracture outcomes by hormone therapy use, body mass index (<30, 30) and FRAX score (median, >median). In addition, we restricted the analyses to those participants with ischemic heart disease, heart failure or hypertension to reduce the potential for confounding by indication. A sensitivity analysis was conducted using updated exposure information at year 3.

The mean BMDs according to nitrate use were presented with standard errors. A complete case analysis was performed with samples of 6856 for hip, 6710 for spine and 6818 for total body. Multivariable linear regression methods were used to assess the association of any nitrate use with baseline BMD, as well as 3-year changes in BMD. To further evaluate the differences in BMD according to nitrate use, changes in BMD from baseline to years 3 and 6 were examined using repeated measures models adjusted for the same variables included in the fracture models.

All analyses were conducted using SAS statistical software (version 9.3; SAS Institute Inc, Cary, North Carolina).

RESULTS

Among the 139,211 women in the cohort, 1647 (1.2%) were using a nitrate medication at baseline. Of those using a nitrate, 1201 (72.9%) had used for more than 5 years, and 446 (27.1%) for 5 years or less. A total of 1132 women were using maintenance nitrate therapy, whereas 515 (31.3%) were using only as needed. Compared with nonusers, nitrate users were more likely to be older, obese, have lower physical functioning, report fair/poor self-rated health and have several health conditions (e.g. ischemic heart disease, diabetes, hypertension and heart failure) (Table 1). Nitrate users were more likely to take thiazides, psychoactive medications and proton pump inhibitors but less likely to take hormone therapy.

Fractures

During 1,074,649 person-years of follow-up, women experienced 1582 hip fractures, 5156 wrist or arm fractures and 22,589 total fractures. The annualized rates of hip fractures per 10,000 were 14.6 and 28.6, wrist or arm fractures were 48.7 and 60.5, and total fractures were 226.7 and 319.0 for nitrates nonusers and users, respectively (Table 2). In the multivariable adjusted models, nitrate use was not related to risk for hip (HR, 0.81; 95% CI, 0.56–1.18), wrist or arm (HR, 0.95; 95% CI, 0.74–1.23) or total fractures (HR, 0.96; 95% CI, 0.85–1.08). When examining the results according to type of nitrate, maintenance use was not associated with any fracture outcome, but as-needed nitrate use was associated with a lower risk for wrist or arm fractures (HR, 0.57; 95% CI, 0.34–0.98) and total fractures (HR, 0.77; 95% CI, 0.62–0.95) compared with non-use. As-needed nitrate use was not associated with hip fractures. Duration of nitrate use was not related to any fracture outcome.

Sensitivity analyses—We did not find evidence of effect modification in the subgroups examined (body mass index, hormone treatment or FRAX score). When we repeated the analyses restricted to women who had ischemic heart disease, heart failure or hypertension

(n=50487), our results were appreciably unchanged. When using a time-dependent exposure, as needed therapy continued to be associated with lower risk for wrist or arm (HR 0.66; 0.38 to 1.14) and total fractures (HR 0.83; 0.66 to 1.04), however the results were no longer significant.

Bone Mineral Density

At baseline, women using nitrates had similar BMD at the hip (adjusted mean, 0.87 vs 0.87 g/cm²), spine (adjusted mean, 0.97 vs 0.99 g/cm²), and total body (adjusted mean, 1.01 vs 1.02 g/cm²) compared with nonusers (Table 3). We did not find significant differences in the 3-year change in BMD at the hip ($P=0.528$), spine ($P=0.604$) or total body ($P=0.907$). Using a repeated measures model to examine changes of BMD from baseline at years 3 and 6, we found no differences in rates of change at the hip ($P=0.297$), spine ($P=0.931$) or total body ($P=0.673$) in users of nitrates compared to non-users (Figure 1). It should be noted that the small increase in BMD over time is a result of some participants receiving active treatment in the CT studies involving hormone therapy and/or calcium and Vitamin D supplementation.

DISCUSSION

In this large population-based study of postmenopausal women without history of hip fracture, there were no significant associations between overall nitrate use and risks of hip, wrist/arm or total fractures. We found a small association between as-needed use of nitrates and lower risk for wrist/arm and total fractures, but not with hip fractures. In contrast, maintenance use of nitrates was not associated with lower fracture risk. Nitrate use was not associated with changes in BMD over 6 years.

Our results should be considered within the context of 2 large nationwide case-control studies using administrative data that reported a small reduced risk for hip fracture^(13,14) and overall fractures with any nitrate use.⁽¹⁴⁾ Rejnmark et al. used nationwide computerized registers to examine nitrate use and fracture outcomes in Denmark. People who had sustained a fracture (n=124,655) between January 1, 2000 and December 31, 2000 were matched to 373,962 age- and sex-matched controls. Nitrate use over a 5 year period was associated with a lower risk for any fracture [OR=0.89, 95% CI= 0.86–0.92] and hip fracture [OR=0.85, 95% CI=0.79–0.92] but not fractures at other locations (e.g. spine or forearm).⁽¹⁴⁾ When further examining the risk according to type of nitrate (e.g. as-needed or maintenance use), these authors did not find that the magnitude of risk varied considerably according to type, however, the results remained statistically significant for only those using as-needed therapy (e.g. rapid acting nitrates). For example, the adjusted OR for hip fracture was 0.88 (95% CI 0.81–0.95) for people using as-needed nitrates and 0.90 (95% CI, 0.82–1.00) for maintenance nitrates. In a case-control study using the Dutch PHARMO Record Linkage System (1991–2002) 6,763 hip fracture cases and 26,341 controls were identified. Pouwels et al reported a lower risk for hip fracture with any nitrate use (OR 0.92, 95% CI 0.85–0.99), with use of combined maintenance and as-needed nitrates (0.89; 0.79–0.99), with as-needed nitrates alone (0.87; 0.78–0.99), but not with maintenance therapy alone (OR 1.06; 0.91–1.23).⁽¹³⁾ The authors also looked at associations according to current use, recent

use and past use, however, these results were difficult to interpret because of low numbers of nitrate users for some of the exposure subgroups.⁽¹³⁾ Both studies found reduced fracture with any use of nitrates (combined as-needed and maintenance) and did not find that the reduced risk was only with as-needed therapy.

Although we examined a large cohort of women, the number of fractures in our study was considerably lower than the two previously described studies.^(13,14) We are unable to rule out that any nitrate use may be associated with a modestly lower risk for hip fracture as we were underpowered for that outcome (i.e. only 34 hip fractures among nitrate users) as reflected in the wide confidence interval. The hazard ratio for hip fracture found in our study was 0.81 and the CI indicates that the true HR may be as low as 0.56 or as high as 1.18. This finding is of similar magnitude, if not lower, than the associations reported in the Danish (OR.85) and the Dutch (0.90) studies that were statistically significant, .

We did not find an association between nitrate use and BMD changes at the hip, spine or total body after 3 and 6 years. Our results are in line with the results of a 3-year randomized control trial⁽¹⁰⁾.^(8,9) in which nitroglycerin ointment 22.5 mg/day did not result in changes in BMD at any site. The authors suggested that low adherence to treatment may explain why they did not find a beneficial effect on bone.⁽¹⁰⁾ In contrast, a few observational studies have reported slightly higher BMD with nitrate use.^(8,9) The low prevalence of as-needed nitrate use in our study precluded us from investigating the association between type of nitrate and changes in BMD. Other observational studies have reported mixed results when examining BMD according to type, with one study reporting that intermittent use (and less so with maintenance treatment) was related to higher hip BMD⁽⁹⁾ and another study finding increased BMD only with daily therapy (i.e. maintenance therapy).⁽⁸⁾

The strengths of the current study are the population-based setting, the large sample size, the diversity of women, the large number of fracture events and the adjudication of hip fractures. We had information on several potential confounding factors (e.g., body mass index, physical function, physical activity, FRAX score, calcium and vitamin D intake) that were not available in the two studies that have examined fracture outcomes that have relied on administrative data.^(13,14) To our knowledge, we are the only cohort study with both BMD measures and fracture outcomes on a large number of women. A few limitations should be noted. The prevalence of nitrate use in our study cohort was low which precluded us from examining BMD according to type of nitrate use. We did not have information of nitrate dose and frequency of use. We had to rely on the indication of use for nitrate products to attempt to capture intermittent use, however, the frequency of use among as-needed use likely varies considerably. Women using nitrates had more chronic health conditions and risk factors for fractures. We did our best to adjust for these baseline differences, but, like all observational studies, residual confounding may have made it more difficult to observe small differences in risk of fractures among groups.

In conclusion, we found no association between overall nitrate use and fractures but did find a lower risk of wrist or arm and total fracture among using as-needed nitrates. We also found no association between nitrate use and BMD. The effectiveness of nitrates in reducing

fracture risk needs to be examined in a randomized control trial before therapy can be recommended for management of osteoporosis.

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Figure 1. Nitrate Use and Bone Mineral Density at Hip, Spine, and Total Body A, Total hip; B, Total spine; and C, Total body.

Table 1.Baseline Characteristics According to Nitrate Use^a

Characteristic	Nitrate Non-users N= 137564		Nitrate Users N= 1647		P Value
	N	%	N	%	
Demographic Characteristics					
Age, mean (SD)	63.1	7.2	67.9	6.6	< .001
Ethnicity					< .001
White	115265	83.8	1284	78.0	
Black	11333	8.2	249	15.1	
Other	10966	7.9	127	7.0	
Some college	93385	68.5	858	52.5	< .001
Health Characteristics					
Fair/poor self-rated health	11190	8.1	660	40.1	< .001
>7 drinks/week					< .001
Non drinker	14328	10.4	234	14.2	
No	35988	26.2	286	17.4	
Yes	16652	12.1	116	7.1	
Smoking status					< .001
Never	69920	50.8	765	46.4	
Past	58311	42.4	744	45.2	
Current	9333	6.8	138	8.4	
History of fracture	52888	38.4	699	42.4	<.001
Parental history of hip fracture	3616	11.1	44	13.0	0.287
FRAX score, mean (SD)	10.21	6.8	12.1	7.5	< .001
Physical activity (METS, h/week)					< .001
Inactive	21297	15.5	321	19.5	
<5	28671	20.8	413	25.1	
5-12	32831	23.9	442	26.8	
12	54765	39.8	471	28.6	
Physical function score >90	52038	37.8	115	7.0	< .001
Body Mass Index					< .001
Underweight (< 18.5)	1199	0.9	13	0.8	
Normal (18.5 - 24.9)	47977	34.9	330	20	
Overweight (25.0 - 29.9)	47653	34.6	563	34.2	
Obese (≥ 30)	40735	29.6	741	45.0	
Comorbidity and Medications					
Treated hypertension	34378	25.0	989	60.0	< .001
Treated diabetes	5619	4.1	326	19.8	< .001
Heart failure	880	0.6	205	12.4	< .001
Ischemic heart disease	7974	5.8	1436	87.2	< .001
Hormone therapy	65743	47.8	615	37.3	< .001

Characteristic	Nitrate Non-users N= 137564		Nitrate Users N= 1647		P Value
	N	%	N	%	
Thiazide use	7588	5.5	122	7.4	< .001
Corticosteroid use	1141	0.8	28	1.7	< .001
Proton pump inhibitor use	2808	2	133	8.1	< .001
Bisphosphonate use	2728	2	29	1.8	.520
No. of psychoactive medications					< .001
0	123453	89.7	1302	79.1	
1	11694	8.5	264	16.0	
2+	2417	1.8	81	4.9	
Calcium intake, mg					< .001
<600	26648	19.4	441	26.8	
600-1200	52842	38.4	643	39.0	
>1200	58074	42.2	563	34.2	
Vitamin D intake, IU					.018
<400	76057	55.3	960	58.3	
400-600	34404	25.0	404	24.5	
>600	27103	19.7	283	17.2	

Table 2:

Adjusted Hazards Ratio Relating Nitrate Use to Incident Fractures

Fracture Type	Number	Annualized, Rate per 10,000	Minimally Adjusted ^a HR (95% CI)	Adjusted ^b HR (95% CI)
Hip Fracture				
Any nitrate use				
Nonuser	1548	14.6	1 (Reference)	1 (Reference)
User	34	28.6	1.22 (0.87-1.72)	0.81 (0.56-1.18)
Duration of use (years)				
Nonuser	1548	14.6	1 (Reference)	1 (Reference)
5	9	27.9	1.27 (0.66-2.47)	0.89 (0.46-1.76)
>5	25	28.9	1.20 (0.81-1.79)	0.79 (0.52-1.20)
Type of use				
Nonuser	1548	14.6	1 (Reference)	1 (Reference)
As-needed	11	29.0	1.33 (0.73-2.41)	0.93 (0.50-1.71)
Maintenance	23	28.4	1.17 (0.77-1.78)	0.77 (0.50-1.19)
Wrist or Arm				
Any nitrate use				
Nonuser	5085	48.7	1 (Reference)	1 (Reference)
User	71	60.5	1.10 (0.87-1.40)	0.95 (0.74-1.23)
Duration of use (years)				
Nonuser	5085	48.7	1 (Reference)	1 (Reference)
5	20	62.6	1.20 (0.77-1.86)	1.02 (0.65-1.60)
>5	51	59.7	1.07 (0.81-1.41)	0.93 (0.69-1.24)
Type of use				
Nonuser	5085	48.7	1 (Reference)	1 (Reference)
As-needed	14	37.1	0.66 (0.39-1.12)	0.57 (0.34-0.98)
Maintenance	57	71.5	1.32 (1.01-1.71)	1.14 (0.86-1.50)
Total Fracture				
Any nitrate use				
No	22244	226.7	1 (Reference)	1 (Reference)
Yes	345	319.0	1.26 (1.13-1.40)	0.96 (0.85-1.08)
Duration of use (years)				
Nonuser	22244	226.7	1 (Reference)	1 (Reference)
5	81	272.7	1.10 (0.89-1.37)	0.86 (0.69-1.08)
>5	264	336.6	1.32 (1.16-1.49)	.99 (0.87-1.13)
Type of use				
Nonuser	22244	226.7	1 (Reference)	1 (Reference)
As-needed	89	252.5	0.99 (0.81-1.22)	0.77 (0.62-0.95)
Maintenance	256	351.2	1.39 (1.23-1.57)	1.05 (0.92-1.20)

^aAdjusted for age, race/ ethnicity, study component, randomization arm^bAdjusted for age, race/ ethnicity, study component, randomization arm, self-rated health, smoking status, history of fracture, physical activity, physical function score, body mass index, treated hypertension, treated diabetes, heart failure, ischemic heart disease, hormone therapy,

corticosteroid use, proton pump inhibitor use, number of psychoactive medications (including antipsychotic, antiepileptic, anxiolytic, hypnotic and antidepressant drug use), and calcium.

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Table 3.

Three-Year Changes in Mean Bone Mineral Density (BMD) According to Nitrate Use

	Nitrate User		Nitrate Non-user		<i>P</i> Value ^a	Adjusted <i>P</i> Value ^b
	N	Mean* (SE)	N	Mean* (SE)		
Total hip						
Initial, g/cm ²	115	0.87 (0.02)	8239	0.87 (0.01)	.751	.628
Final, g/cm ²	94	0.86 (0.02)	6823	0.88 (0.01)	.221	.257
Change, %	94	0.53 (0.52)	6762	0.34 (0.31)	.652	.528
Total spine						
Initial, g/cm ²	113	0.97 (0.02)	8025	0.99 (0.01)	.122	.095
Final, g/cm ²	94	0.98 (0.02)	6653	1.02 (0.01)	.071	.050
Change, %	94	2.97 (0.69)	6616	2.68 (0.42)	.602	.604
Total body						
Initial, g/cm ²	113	1.01 (0.01)	8237	1.02 (0.01)	.302	.208
Final, g/cm ²	94	1.01 (0.01)	6782	1.03 (0.01)	.221	.174
Change, %	93	1.17 (0.44)	6725	1.18 (0.27)	.980	.907

^a Adjusted for age, race/ ethnicity and study component, randomization arm^b Adjusted for age, race/ ethnicity, study component, randomization arm, self-rated health, smoking status, history of fracture, physical activity, physical function score, body mass index, treated hypertension, treated diabetes, heart failure, ischemic heart disease, hormone therapy, corticosteroid use, number of psychoactive medications (including antipsychotic, antiepileptic, anxiolytic, hypnotic and antidepressant drug use), proton pump inhibitor use, and calcium