PRELIMINARY COMMUNICATION

Effect of Nitroglycerin Ointment on Bone Density and Strength in Postmenopausal Women

A Randomized Trial

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Context Nitroglycerin stimulates bone formation and inhibits bone resorption, is inexpensive, and is widely available. Its effects on bone density, bone structure, and bone strength are unknown.

Objectives To determine if nitroglycerin increases lumbar spine bone mineral density (BMD) and to evaluate changes in hip BMD, bone geometry, and density at the radius and tibia, and markers of bone turnover.

Design, Setting, and Participants A single-center, double-blind, placebo-controlled randomized trial conducted in Toronto, Ontario, Canada, for 24 months starting in November 2005 and completed in March 2010, of 243 postmenopausal women with lumbar spine T scores of between 0 and –2.0 who completed a 1-week run-in period taking nitroglycerin ointment.

Intervention Nitroglycerin ointment (15 mg/d) or placebo applied at bedtime for 24 months.

Main Outcome Measures Areal BMD at the lumbar spine, femoral neck, and total hip. Secondary outcomes included indices of bone geometry and strength at the distal radius and tibia, and biomarkers of bone formation (bone-specific alkaline phosphatase) and bone resorption (urine *N*-telopeptide).

Results At 2 years, women randomized to the nitroglycerin group had significant increases in areal BMD at the lumbar spine (from 1.05 to 1.14 g/cm^2 vs placebo from 1.06 to 1.08 g/cm^2; percentage change, 6.7%; 95% confidence interval [CI], 5.2%-8.2%; $P<.001$); total hip (from 0.92 to 0.97 g/cm^2 vs placebo from 0.93 to 0.92 g/cm^2; 6.2%; 95% CI, 5.6%-7.0%; $P<.001$); and femoral neck (from 0.88 to 0.93 g/cm^2 vs placebo from 0.87 to 0.86 g/cm^2; 7.0%; 95% CI, 5.5%-8.5%; $P<.001$). At 2 years, nitroglycerin also increased volumetric trabecular BMD (11.9% and 8.5%), cortical thickness (13.9% and 24.6%), periosteal circumference (7.4% and 2.9%), polar section modulus (10.7% and 9.8%), and polar moment of inertia (7.3% and 14.5%) at the radius and tibia, respectively (all $P<.001$); and increased bone-specific alkaline phosphatase by 34.8% and decreased urine *N*-telopeptide by 54.0% ($P<.001$). Incidence of serious adverse events did not differ between nitroglycerin (5 [4.2%]) and placebo (5 [4.3%]) groups. Among those women who continued treatment for 24 months, headaches were reported by 40 (35%) in nitroglycerin and 6 (5.4%) in placebo groups during the first month, decreasing substantially after 12 months.

Conclusion Among postmenopausal women, nitroglycerin ointment modestly increased BMD and decreased bone resorption.

Trial Registration isrctn.org Identifier: ISRCTN94484747

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THE NUMBER OF OSTEOPOROTIC fractures is increasing worldwide as populations age.[1,2] An inexpensive and widely available treatment may help limit this increase. Nitric oxide can inhibit osteoclast activity and acts as a signaling molecule in osteoblasts and osteocytes.[3-8] Nitric oxide donors, such as nitroglycerin, isosorbide mononitrate, and isosorbide dinitrate, can prevent bone loss associated with estrogen deficiency and glucocorticoid administration in rodents.[9,10] Continuous administration of nitrates induces tachyphylaxis to the effects,[11] and observational studies indicate that older women taking nitrates intermittently for angina have higher bone mineral density (BMD) at the hip compared with nonusers and women taking it continuously.[12] An observational study[13] suggested that women taking nitrates have a lower risk of all fractures, including hip fractures. A short-term randomized controlled trial (RCT)[14] showed that isosorbide mononitrate taken once at bedtime decreased a marker of bone resorption and increased a marker of bone formation. An RCT of nitroglycerin ointment (Nitro-Bid 22.5 mg/d) did not find increased BMD at the lumbar spine, femoral neck, or total hip; how-

For editorial comment see p 826.

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ever, adherence to treatment in the study was poor.[15] No other RCT has examined the effect of nitrates on BMD and no trial to our knowledge has tested their effect on bone geometry and strength.

We tested the efficacy of once-daily nitroglycerin ointment to increase BMD at the lumbar spine over 24 months. Secondary end points included the effects of the ointment on BMD at the hip, indices of bone geometry and strength at the radius and tibia, and markers of bone formation and bone resorption.

METHODS

Protocol

Our trial was a single-center, double-blind, placebo-controlled RCT. Participants received nitroglycerin ointment (15 mg/d) applied at bedtime during a 1-week run-in period. Participants were instructed to measure out 1 inch of 2% nitroglycerin ointment (15 mg of nitroglycerin) onto a premarked piece of onion skin and then tape this, ointment side down, to their upper outer arm. Those participants who took all doses of nitroglycerin were randomly assigned to continue treatment with daily nitroglycerin ointment applied at bedtime or matched placebo control for 2 years. The study started in November 2005 and was completed in March 2010.

We estimated participants' calcium and vitamin D intakes from a food frequency questionnaire[16] and provided supplements, if needed, to achieve a calcium intake of 1200 to 1500 mg/d and vitamin D intake of 800 IU/d.[17] Change in lumbar spine BMD was the primary end point.

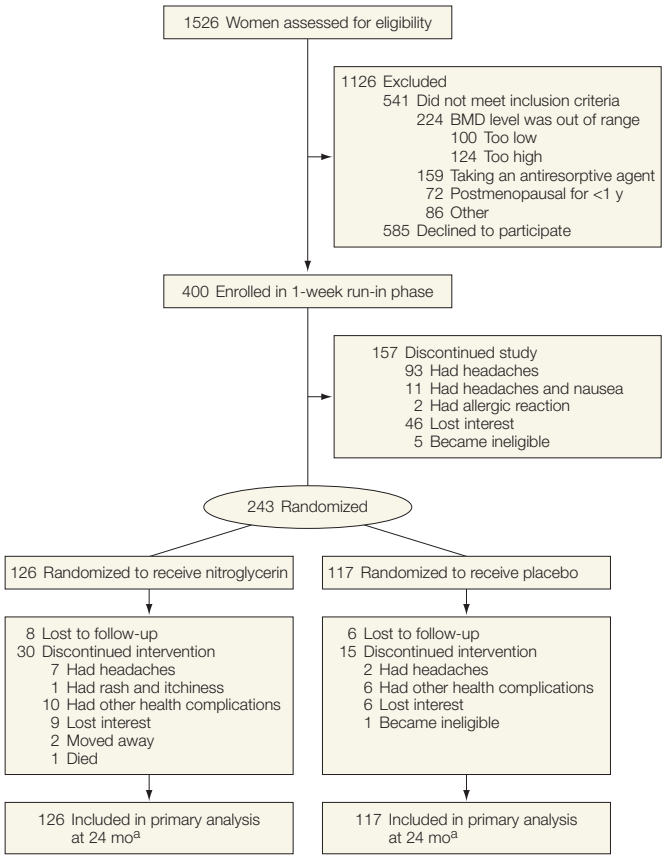
Study Conduct

The trial was approved by the University of Toronto's institutional review boards and unblinded data were monitored by a data and safety monitoring board. Study medication was stopped if a participant's BMD at any site decreased to or below a T score of –2.5; if a clinical spine, proximal forearm, or hip fracture occurred; or if she began medical treatment with a nitrate. All participants gave written informed consent. Participants were not financially compensated for participation in the trial.

Selection of Participants

We recruited participants from newspaper advertisements, posters placed in community centers, fitness centers, and osteoporosis clinics in the greater Toronto area. We collected data on race/ethnicity (by self-report), because these might contribute to differences in BMD. We included women aged 50 years or older who were at least 1 year postmenopausal with BMD T scores between 0 and –2.0 at the lumbar spine and higher than –2.0 at the total hip. Women were excluded if they had medical conditions that influenced bone metabolism; used androgen, calcitonin, estrogen, progesterone, fluoride in a tablet form, raloxifene, tamoxifen, etidronate, prednisone, or equivalent at 5 mg/d for 12 months or more; used lithium or anticonvulsants for 6 months before study entry; or reported use of alendronate or risedronate for at least 4 weeks, within the last 3 years. We also excluded women who were prescribed nitrates for cardiac conditions; had a systolic blood pressure of 100 mm Hg or less or a diastolic blood pressure of 110 mm Hg or more at the baseline screening examination; an abnormal

Figure 1. Participant Flow Diagram



BMD indicates bone mineral density.
[a] Missing data for 8 participants in nitroglycerin group and 6 participants in placebo group at 24 months were analyzed using last observation carried forward.

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electrocardiogram at the baseline screening examination; a history of myocardial infarction, angina, valvular, or congenital heart disease; had migraine headaches; or reported a hypersensitivity to nitrates (FIGURE 1).

Assignment

Treatment was assigned by simple randomization using computer generated codes. Each tube (placebo or active nitroglycerin) was packaged identically and labeled with a nonrepeating allocation number that could be revealed only for safety concerns. The research pharmacist who generated the allocation schedule did not communicate with the research assistant (C.J.H.) who enrolled participants and assigned the study drug.

Table 1. Baseline Characteristics of Study Participants by Treatment Allocation[a]

Characteristics	Nitroglycerin (n = 126)	Placebo (n = 117)
Age, y	61.3 (6.6)	61.9 (7.3)
Weight, kg	70.3 (11.9)	70.9 (13.3)
White race, No. (%)	118 (94)	107 (91)
Years since menopause	11.8 (8.2)	11.8 (8.3)
Walks ≥2 h per wk, No. (%)	104 (89)	109 (87)
Nonsmoker, No. (%)	124 (98)	113 (97)
Intake		
Vitamin D, IU/d	783.2 (251.2)	753.2 (237.2)
Calcium, mg/d	1548.8 (317.2)	1565.6 (373.6)
T score		
Lumbar spine	−0.9 (0.6)	−1.1 (0.6)
Femoral neck	−0.9 (0.6)	−0.8 (0.7)
Total hip	−0.6 (0.7)	−0.6 (0.7)

[a] Data presented as mean (SD) unless otherwise specified.

End Points

Areal BMD was measured by dual-energy x-ray absorptiometry at the lumbar spine, femoral neck, and total hip at baseline, 12 months, and 24 months. Measurements were performed by International Society of Clinical Densitometry certified technicians blinded to treatment assignment using a densitometer (GE Lunar Prodigy, Madison, Wisconsin). The reproducibility measurements in our study were 1.2% at the spine, 1.5% at the femoral neck, and 0.9% at the total hip.

At baseline, 12 months, and 24 months, volumetric BMD and bone geometry were measured at the radius and tibia using peripheral quantitative computed tomography (pQCT; Norland/Stratec XCT 2000; Stratec Medizintechnik GmbH, Pforzheim, Germany) and indices of bone strength were calculated using the manufacturer's software (version 6.00). All scans were performed by a technician and a phantom was scanned each day before performing scans on study participants. In vivo precision in our laboratory for all parameters was less than 3% coefficient of variation for all pQCT measurements.

We measured urine *N*-telopeptide of type 1 collagen (Osteomark, Seattle, Washington), a marker of bone resorption, on a second morning urine sample (intra-assay variability was 7.6% and interassay variability was 4.0%).[18] We measured serum bone-specific alkaline phosphatase, a marker of bone formation, on a fasting serum sample using a monoclonal antibody technique (Metra Biosystems, San Diego, California) (intra-assay variability was 5.8% and interassay variability was 5.2%).[19]

Adverse Events

Participants were contacted daily by telephone during the 1-week run-in phase, 1 week after randomization, and monthly for the remainder of the trial. We inquired generally about adverse events, serious adverse events[20] (defined as emergency department visits, hospitalizations, and visits to walk-in clinics), and specifically about the occurrence of fractures, headache, nausea, and dizziness.[21] We did not measure blood pressure during the trial. We confirmed fractures by review of radiologic reports.

Blinding

Collection and review of data were blinded to treatment assignment. Results of bone densitometry during follow-up were not available to study participants. Treatment assignments were kept in a locked file by the pharmacist who generated the random allocation sequence.

Table 2. Absolute Changes in BMD at the Lumbar Spine, Total Hip, and Femoral Neck at Baseline, 12 Months, and 24 Months

	BMD, Absolute Change (95% CI), g/cm^2		
Site and Group	Baseline	12 Months	24 Months
Lumbar spine			
Placebo	1.06 (1.05-1.08)	1.06 (1.05-1.08)	1.08 (1.06-1.09)
Nitroglycerin	1.05 (1.04-1.07)	1.11 (1.10-1.13)	1.14 (1.12-1.15)
Total hip			
Placebo	0.93 (0.91-0.94)	0.92 (0.91-0.94)	0.92 (0.90-0.94)
Nitroglycerin	0.92 (0.91-0.94)	0.96 (0.94-0.98)	0.97 (0.96-0.99)
Femoral neck			
Placebo	0.87 (0.86-0.89)	0.87 (0.85-0.88)	0.86 (0.85-0.88)
Nitroglycerin	0.88 (0.86-0.90)	0.91 (0.89-0.92)	0.93 (0.92-0.95)

Abbreviations: BMD, bone mineral density; CI, confidence interval.

Statistical Analyses

We estimated that 107 participants per group were needed to provide 90% power with 2-sided α=.05 to detect a 2% difference between the nitroglycerin and placebo groups for change in lumbar spine BMD since baseline. We chose a 2% difference in lumbar spine density because all other osteoporosis treatments that reduced vertebral fracture risk had 2-year increases in BMD of at least

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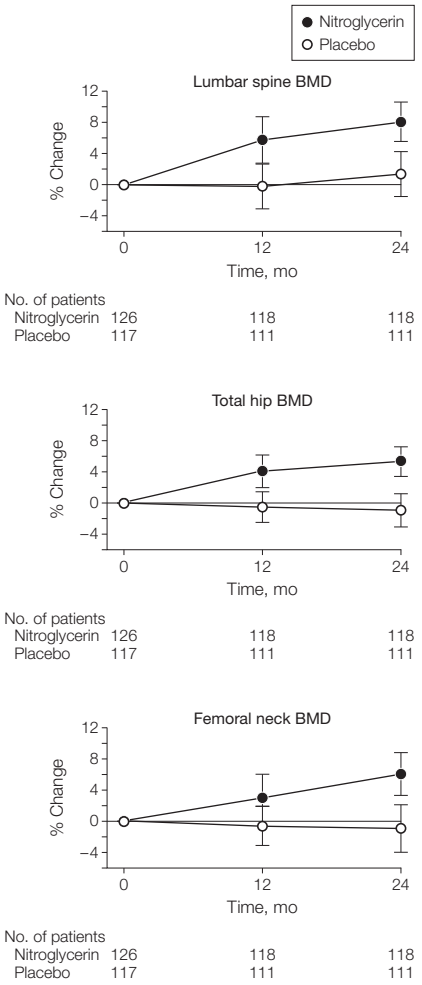
3%.[22-26] For all main outcome measures, we compared differences at 24 months between both groups. We used *t* test for statistical significance of differences in changes of BMD and measurements and indices from pQCT. For BMD and all bone geometry measures, we calculated the percentage change from baseline to year 2 for each participant and each measurement using [(absolute measure at year 2 – absolute measure at baseline)/(absolute measure at baseline)] × 100. The relative percentage change was calculated as percentage change in nitroglycerin group – percentage change in placebo group. For bone turnover markers, we calculated the percentage of baseline for the level of each marker at 3, 12, and 24 months. Data were log transformed; means and confidence intervals (CIs) were calculated for the log transformed data. The means were back-transformed to provide a geometric mean and 95% CIs as percentages of the baseline values. We performed an independent samples *t* test to compare the change at 24 months between both groups for each marker. We used an intention-to-treat analysis using the last observation carried forward to account for missing data and conducted our analyses using STATA version 11 (Stata Corp, College Station, Texas) for BMD and pQCT data, and used PASW Statistics version 18 (SPSS Inc, Chicago, Illinois) for the analysis of bone marker levels. $P<.05$ was considered to be statistically significant.

RESULTS

Of 400 women who entered the run-in trial, 243 were randomized (n=126 in nitroglycerin ointment group and n=117 in placebo group). Of the 157 women who were not randomized, 104 discontinued the study due to headaches, 46 lost interest, 5 became ineligible, and 2 had an allergic reaction. Thirty participants (23.8%) assigned to the nitroglycerin group and 15 (12.8%) assigned to placebo discontinued treatment—the rest of the participants reported continued use of the ointment on a daily basis during monthly telephone calls—and data were missing at 24 months for 8 participants in nitroglycerin group and 6 participants in placebo group (Figure 1). The mean (SD) age of the participants was 61.6 (6.9) years, none of the participants had osteoporosis based on T scores at the spine or hip, and there were no statistical differences in the distribution of baseline characteristics by treatment assignment (TABLE 1). During the 24 months, none of the participants initiated medications that are known to influence bone metabolism.

Compared with placebo, women randomized to nitroglycerin group had significant increases in areal BMD at the lumbar spine (6.7%; 95% CI, 5.2%-8.2%; $P<.001$), total hip (6.2%; 95% CI, 5.6%-7.0%; $P<.001$), and femoral neck (7.0%; 95% CI, 5.5%-8.5%; $P<.001$) at 24 months (TABLE 2 and FIGURE 2). During the 24 months of treatment, nitroglycerin users had increases in volumetric trabecular BMD (11.9% [95% CI, 8.1%-15.7%] at the radius and 8.5% [95% CI, 4.3%-12.7%] at the tibia), cortical BMD (2.2% [95% CI, 0.6%-3.7%] at the radius and 1.5% [95% CI, 0.8%-2.3%] at the tibia), cortical thickness (13.9% [95% CI, 6.0%-21.7%] at the radius and 24.6% [95% CI, 18.9%-30.4%] at the tibia), and periosteal circumference (7.4% [95% CI, 4.3%-10.4%] at the radius and 2.9% [95% CI, 1.0%-6.8%] at the tibia) compared with placebo users (TABLE 3). Treatment with nitroglycerin ointment was also associated with increases in indices of bone strength (10.7% and 9.8% increases in polar section modulus and 7.3% and 14.5% increases in polar moment of inertia at the radius and tibia, respectively) (Table 3 and eTable; available at http://www.jama.com). Compared with placebo at 3, 12, and 24 months, treatment with nitroglycerin was significantly associated with a 14.4%, 20.7%, and 34.8% increase ($P<.001$) in bone-specific alkaline phosphatase, a marker of bone formation; and a 20.1%, 32.8%, and 54.0% decrease ($P<.001$) in urine *N*-telopeptide, a marker of bone resorption (FIGURE 3).

Figure 2. Percentage Change in Lumbar Spine, Total Hip, and Femoral Neck BMD in the Nitroglycerin and Placebo Groups Over 24 Months



BMD indicates bone mineral density. Error bars represent 95% confidence intervals.

Adverse Events

During the run-in phase, 104 of 157 women who discontinued treatment did so because of headaches, nausea, or both. During the first year, 7 women (5.6%) in the nitroglycerin group and 2 women (1.7%) in the

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placebo group discontinued treatment due to headaches; no one discontinued treatment due to headaches after 12 months. Although the incidence of serious adverse events was not different between the nitroglycerin (5 [4.2%]) and placebo (5 [4.3%]) groups, among those women who continued treatment for 24 months, headaches were reported by 40 (35%) in the nitroglycerin group and 6 (5.4%) in the placebo group during the first month, 11 (9.6%) and 2 (1.8%), respectively, during the first 6 months, 6 (5.3%) and 1 (0.9%), respectively, during the next 6 months, and 2 (2%) in the nitroglycerin group during the last 12 months. There were 2 fractures each in the nitroglycerin and placebo groups, and 1 death due to stroke in the nitroglycerin group.

COMMENT

Treatment with 15 mg/d of nitroglycerin for 24 months increased bone formation and decreased bone resorption, resulting in an increased areal BMD at the spine and proximal femur and increased volumetric trabecular BMD in the distal radius and tibia. Furthermore, nitroglycerin increased cortical thickness and cortical area in the radius and tibia along with statistically significant increases in periosteal diameter. This combination of changes in bone density and structure led to significant increases in polar section modulus and polar moment of inertia in the radius and tibia, indicating increases in bone bending and twisting strength. Together, these findings suggest that nitroglycerin may significantly decrease the risk of fractures, including fractures in long bones, such as the hip, legs, and upper arm, which are largely composed of cortical bone.

Bone resorption by osteoclasts is generally coupled with subsequent formation of bone by osteoblasts. Consequently, treatments that substantially decrease bone resorption, such as bisphosphonates, denosumab, estrogen, and raloxifene, also substantially decrease bone formation.[25,27-31] Teriparatide increases bone formation but also increases bone resorption.[32] The results of our trial indicate that nitroglycerin uncouples bone forma-

Table 3. Percentage Changes in Bone Geometry, Density, and Strength by pQCT at the Radius and Tibia

	% Change					
	Radius			Tibia		
Measurements[a]	Baseline to Year 1	Year 1 to Year 2	Total 2 Years	Baseline to Year 1	Year 1 to Year 2	Total 2 Years
Trabecular BMD, mg/cm^3						
Placebo	–1.1	0.2	–0.9	0	–0.7	–0.7
Nitroglycerin	5.3	5.7	11.0	6.5	1.3	7.8
Difference (95% CI)	6.4	5.5	11.9 (8.1-15.7)	6.5	2.0	8.5 (4.3-12.7)
Cortical BMD, mg/cm^3						
Placebo	0.2	–0.4	–0.2	0	–0.4	–0.4
Nitroglycerin	1.4	0.4	1.8	0.8	0.3	1.1
Difference (95% CI)	1.3	0.9	2.2 (0.6-3.7)	0.8	0.7	1.5 (0.8-2.3)
Cortical area, mm^2						
Placebo	–1.0	–1.2	–2.2	–0.2	–0.1	–0.3
Nitroglycerin	5.8	2.7	8.5	8.0	1.7	9.7
Difference (95% CI)	6.7	3.9	10.6 (6.9-14.3)	8.2	1.8	10.0 (5.2-15.0)
Cortical thickness, mm						
Placebo	–0.2	–1.2	–1.4	–0.6	–1.5	–2.1
Nitroglycerin	7.7	4.8	12.5	19.2	3.3	22.5
Difference (95% CI)	7.9	6.0	13.9 (6.0-21.7)	19.8	1.8	24.6 (18.9-30.4)
Periosteal circumference, mm						
Placebo	–0.4	0.1	–0.3	0.5	0.6	1.1
Nitroglycerin	3.6	3.5	7.1	3.2	0.8	4.0
Difference (95% CI)	4.0	3.4	7.4 (4.3-10.4)	2.7	0.2	2.9 (1.0-6.8)
Polar moment of inertia, mm^4						
Placebo	–0.7	–1.2	–1.9	0.4	0.6	1.0
Nitroglycerin	4.2	1.2	5.4	11.5	4.1	15.6
Difference (95% CI)	4.9	2.4	7.3 (4.6-10.1)	11.0	3.5	14.5 (3.2-25.8)
Polar section modulus, mm^3						
Placebo	–0.3	–1.1	–1.4	–0.1	0.7	0.6
Nitroglycerin	8.2	1.1	9.3	5.5	4.8	10.3
Difference (95% CI)	8.5	2.2	10.7 (7.5-13.8)	5.6	4.2	9.8 (0.2-19.4)

Abbreviations: BMD, bone mineral density; CI, confidence interval; pQCT, peripheral quantitative computed tomography.
[a] Trabecular BMD was measured at the distal radius and tibia (4%); remainder of the measurements were obtained at the midshaft radius (20%) and midshaft tibia (38%). Absolute changes in bone geometry, density, and strength can be found in the eTable (available at http://www.jama.com).

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tion from bone resorption, allowing significant formation of bone despite substantial decreases in the rate of bone resorption. Our findings are consistent with those of a previous RCT finding that isosorbide mononitrate (20 mg/d) decreased urine *N*-telopeptide by 45% and increased bone-specific alkaline phosphatase by 23% over 3 months.[14] Furthermore, we found that the differential effects of nitroglycerin on formation and resorption appear to widen with time, suggesting that its efficacy continues or even increases during 24 months of use. In contrast, the effects of other antiresorptives and teriparatide either plateau or wane with time. The mechanisms by which nitroglycerin stimulates formation but decreases resorption are not known; however, adding nitric oxide to bone cell cultures decreases osteoclast maturation and bone resorbing activity.[4,8,33,34] Some, but not all, studies have found that low concentrations of nitric oxide also stimulate the proliferation and differentiation of osteoblasts.[35] Our results are consistent with the concept that in vivo nitric oxide has independent effects on osteoclasts and osteoblasts.

We found that nitroglycerin increased areal BMD by 6% to 7% at all sites over 24 months; the changes in 3-dimensional, volumetric BMD of trabecular bone were larger. Although the magnitude of change in BMD cannot be directly compared between studies, these increases at the spine and total hip are similar to those observed with other therapies; and the increase in femoral neck density (7%) that we observed by 24 months with nitroglycerin is greater than what has been reported with all currently available therapies, including teriparatide.[25,27-32]

Our findings are different than another RCT of nitroglycerin ointment (Nitro-Bid 22.5 mg/d), which did not find increased BMD at the lumbar spine, femoral neck, or total hip.[15] Although the reasons for the difference in results is not certain, adherence in that study was poor.

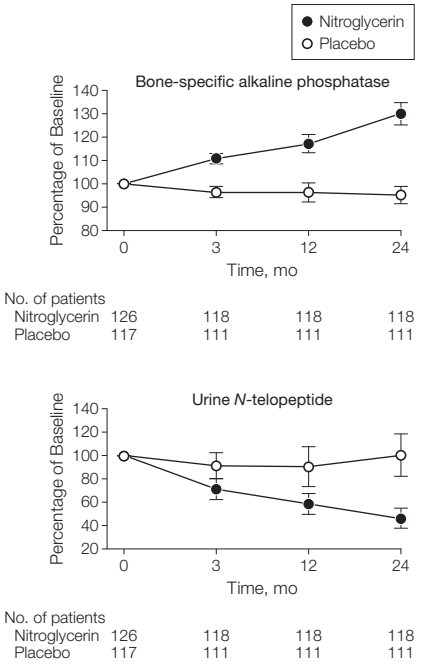
To our knowledge our trial is the first study to report on the effects of nitroglycerin on bone geometry by pQCT. Observational studies have reported that cortical and trabecular parameters from pQCT are associated with fracture risk independent of BMD.[36-38] The substantial increase in cortical thickness and area along with an increased periosteal circumference at the radius and tibia suggests that nitroglycerin may be stimulating the periosteal apposition of bone. The increased cortical thickness might also reflect decreased bone resorption with decreased loss of endosteal bone.

Longitudinal data on bone geometry in response to osteoporosis therapies are limited to 3 studies that report on alendronate, denosumab, and teriparatide.[39-41] Although we used a different technique to assess bone geometry, we found that nitroglycerin led to substantially greater increases in cortical thickness at the tibia (a 22.5% increase from baseline over 2 years) compared with alendronate (a 3% increase over 2 years), denosumab (a 5% increase over 1 year), and teriparatide (a 1.5% increase over 1 year). Furthermore, we found that nitrates increased periosteal circumference or bone size at both the radius and the tibia, which has not been reported with any other agent. Biomechanical principles dictate that increased bone size allows for greater resistance to applied forces, particularly in bending and torsion. Moreover, several studies have shown that, independent of BMD, increased bone size either at the femur or wrist protects against fractures.[42,43]

The changes in cortical bone geometry that we observed with nitroglycerin may translate into a clinically important reduction in fractures—nonvertebral fractures in particular. Nonvertebral fractures account for most of the disability and costs due to fractures.[44] Even the most potent antiresorptive drugs reduce the risk of nonvertebral fractures by less than one-third[25,27-31] and although teriparatide may decrease the risk of a subset of very "low trauma fractures" by 40%, the use of the agent is limited by the fact that it is very expensive, requires daily injections, and cannot be used for more than 24 months.[32]

Our study has limitations. Headaches were common, accounting for more than half of the dropouts during the run-in phase and approximately 25% of the dropouts among those women randomized to nitroglycerin. However, among women who continued treatment in the main trial, headaches were common during the first year, decreased over time, and led to discontinuation in fewer than 5% over 2 years. The possibility that different preparations, doses, or schedules of administration would reduce the frequency of headaches without diminishing effects on bone should be

Figure 3. Percentage of Baseline in Bone-Specific Alkaline Phosphatase and Urine *N*-telopeptide in the Nitroglycerin and Placebo Groups Over 24 Months



Error bars represent 95% confidence intervals. Bone-specific alkaline phosphatase is a marker of bone formation and urine *N*-telopeptide is a marker of bone resorption.

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explored in future studies. Nevertheless, headaches may limit the use of nitroglycerin in clinical practice. We excluded women with osteoporosis; it is possible that the effects might differ somewhat in those women with lower BMD. We measured 1 marker of bone formation (bone-specific alkaline phosphatase) and 1 marker of bone resorption (urine *N*-telopeptide); further studies may test the effects of nitroglycerin on additional markers of formation and resorption. Although the incidence of adverse events was low and similar in both groups, longer and larger studies would better clarify the adverse effects of nitroglycerin use in healthy women. In addition, our study was too small to determine the effects of nitroglycerin on fracture risk.

In conclusion, daily administration of nitroglycerin ointment increases bone formation and decreases bone resorption; thereby, substantially improving BMD, bone structure, and indices of bone strength at least as much as existing treatments. Together, these findings suggest that daily nitroglycerin may reduce the risk of vertebral and nonvertebral fractures. Furthermore, nitrates have a potential advantage of easy administration as an ointment, patch, or pill and wide availability of generic preparations. The efficacy of nitrates for reducing risk of fracture should be tested in a larger RCT.

Author Contributions: Dr Jamal had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Jamal, Cummings.
Acquisition of data: Jamal, Hamilton.
Analysis and interpretation of data: Jamal, Hamilton, Eastell, Cummings.
Drafting of the manuscript: Jamal, Hamilton, Cummings.
Critical revision of the manuscript for important intellectual content: Jamal, Hamilton, Eastell, Cummings.
Statistical analysis: Jamal, Eastell.
Obtained funding: Jamal.
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Study supervision: Jamal, Cummings.
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> Life was meant to be lived. . . . One must never, for whatever reason, turn his back on life.
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> —Eleanor Roosevelt (1884-1962)

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