ORIGINAL ARTICLE

Fracture Prevention with Zoledronate in Older Women with Osteopenia

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ABSTRACT

BACKGROUND

Bisphosphonates prevent fractures in patients with osteoporosis, but their efficacy in women with osteopenia is unknown. Most fractures in postmenopausal women occur in those with osteopenia, so therapies that are effective in women with osteopenia are needed.

METHODS

We conducted a 6-year, double-blind trial involving 2000 women with osteopenia (defined by a T score of –1.0 to –2.5 at either the total hip or the femoral neck on either side) who were 65 years of age or older. Participants were randomly assigned to receive four infusions of either zoledronate at a dose of 5 mg (zoledronate group) or normal saline (placebo group) at 18-month intervals. A dietary calcium intake of 1 g per day was advised, but calcium supplements were not provided. Participants who were not already taking vitamin D supplements received cholecalciferol before the trial began (a single dose of 2.5 mg) and during the trial (1.25 mg per month). The primary end point was the time to first occurrence of a nonvertebral or vertebral fragility fracture.

RESULTS

At baseline, the mean (±SD) age was 71±5 years, the T score at the femoral neck was –1.6±0.5, and the median 10-year risk of hip fracture was 2.3%. A fragility fracture occurred in 190 women in the placebo group and in 122 women in the zoledronate group (hazard ratio with zoledronate, 0.63; 95% confidence interval, 0.50 to 0.79; P<0.001). The number of women that would need to be treated to prevent the occurrence of a fracture in 1 woman was 15. As compared with the placebo group, women who received zoledronate had a lower risk of nonvertebral fragility fractures (hazard ratio, 0.66; P=0.001), symptomatic fractures (hazard ratio, 0.73; P=0.003), vertebral fractures (odds ratio, 0.45; P=0.002), and height loss (P<0.001).

CONCLUSIONS

The risk of nonvertebral or vertebral fragility fractures was significantly lower in women with osteopenia who received zoledronate than in women who received placebo. (Funded by the Health Research Council of New Zealand; Australian New Zealand Clinical Trials Registry number, ACTRN12609000593235.)

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Bisphosphonates are the principal class of medications used in the management of postmenopausal osteoporosis and have been shown to prevent fractures.[1] Prevention of fractures with bisphosphonates has been shown most clearly in patients with osteoporosis, which is defined either by a bone-density T score of less than –2.5 or by the presence of prevalent vertebral fractures; whether bisphosphonates are efficacious in patients with osteopenia alone is uncertain. However, treating only patients who have osteoporosis has only a limited capacity to decrease total numbers of fractures, since fractures tend to occur in the much larger group of women whose bone mineral density is in the osteopenic range.[2] If interventions are to achieve a substantial decrease in the total numbers of fractures, therapies shown to be effective in women with osteopenia are needed.

Consistent evidence to show that fracture prevention is possible in patients with osteopenia is lacking. The results of a trial reported by Cummings et al. did not show a significantly lower risk of clinical fractures with alendronate than with placebo among women with osteopenia, although prevention of fractures among women with osteoporosis was observed.[3] In contrast, pooled results from trials of risedronate suggested fracture prevention among patients who had osteopenia,[4] and treatment with clodronate was found to reduce the incidence of total fractures among community-dwelling women older than 75 years of age whose participation in the trial was not based on the presence or absence of osteoporosis.[5] The need to establish treatment efficacy in osteopenia has become more pressing, given the clinical trend to base intervention decisions on absolute fracture risk.[6] Many patients at high risk for fracture do not have T scores of less than –2.5 but rather have osteopenia in combination with other risk factors, such as age. Intervention in such patients currently lacks an adequate evidence base.

Zoledronate (also known as zoledronic acid) has characteristics that make it attractive for use in women who have osteopenia. It is administered by intravenous injection at intervals of 1 year or longer, it is preferred over oral bisphosphonates by a majority of patients,[7] and it has had a satisfactory safety profile.[8,9] The current trial assesses the effects of zoledronate on fracture in postmenopausal women with hip bone mineral density that is characterized as osteopenia.

METHODS

TRIAL DESIGN

We conducted a randomized, double-blind, placebo-controlled trial to determine the efficacy of zoledronate, as compared with placebo, in the prevention of fractures in postmenopausal women 65 years of age or older. A total of 2000 women were recruited with the use of electoral registers from the Auckland region of New Zealand and were randomly assigned, in a 1:1 ratio, to receive four infusions of either zoledronate at a dose of 5 mg (zoledronate group) or normal saline (placebo group), packaged in identical containers, at 18-month intervals. Consecutive eligible participants were assigned to one of the two trial groups on the basis of a randomization list with variable block size that was prepared by the trial statistician. Infusion bottles were labeled by staff members who had no contact with trial participants. All the trial personnel were unaware of the initial trial-group assignments. Each participant was followed for 6 years. Women who were not already taking vitamin D supplements were given a single oral dose of cholecalciferol (2.5 mg [100,000 IU]) at least 1 week before their first infusion and subsequently received cholecalciferol at a dose of 1.25 mg per month for the duration of the trial. A dietary calcium intake of 1 g per day was advised, but calcium supplements were not supplied. Trial procedures took place at the Clinical Research Center, University of Auckland, which participants visited every 18 months. The trial protocol, available with the full text of this article at NEJM.org, was approved by the regional Health and Disability Ethics Committee. All the participants provided written informed consent. The statistical analysis was performed by the last author at the University of Auckland. All the authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

Funding for the trial was provided by the Health Research Council of New Zealand. The trial medication was supplied by Novartis. Neither entity had any other role in the trial.

PARTICIPANTS

Eligible participants were ambulatory postmenopausal women 65 years of age or older, with a T score of –1.0 to –2.5 at either the total hip or the femoral neck on either side; both hips were

assessed in all patients. A T score of less than –2.5 at one hip site (total hip or femoral neck on either side) did not preclude participation in the trial, as long as another hip site met the criteria, so patients at the interface of osteopenia and osteoporosis were included. The presence of spinal osteoporosis was not an exclusion criterion as long as the T score was above –3.0. Other exclusion criteria were an estimated glomerular filtration rate of less than 30 ml per minute per 1.73 m^2 of body-surface area, major systemic disease, cancer in the previous 2 years, metabolic bone disease, or regular use of bone-active drugs in the previous year (including bisphosphonates, estrogen, antiestrogens, and prednisone at a dose of 2.5 mg or greater per day or equivalent).

END POINTS

The primary end point was the time to first occurrence of a fragility fracture. Fragility fractures were defined as any nonvertebral fractures (excluding fractures of the toes, metatarsal bones, fingers, metacarpal bones, skull, facial bones, and mandible) and vertebral fractures as confirmed by radiographic evidence. The severity of the trauma that led to the fracture was not part of the definition of a fragility fracture. Secondary end points were the occurrence of a symptomatic (clinical) fracture, the occurrence of a vertebral fracture, change in height, and mortality. Both the time to the first occurrence of fracture and the incidence of fracture were assessed for all end points, with the exception of vertebral fracture. The occurrence of nonvertebral fragility fracture, symptomatic vertebral fracture, hip fracture, and forearm or wrist fracture were prespecified exploratory end points. Pathological fractures were excluded from all trial end points. In light of previous findings with zoledronate, the following adverse events were prespecified for analysis: death, sudden death, myocardial infarction, coronary-artery revascularization, stroke, transient ischemic attack, cancer, osteonecrosis of the jaw, atrial fibrillation, and any component of the composite of vascular events: sudden death, myocardial infarction, coronary-artery revascularization, or stroke.

PROCEDURES

Participants recorded fractures, adverse events, and changes in medications in a quarterly questionnaire and were also asked to report fractures immediately. In cases in which a participant was hospitalized, an investigator confirmed diagnoses directly from the participant's medical records and reviewed this information with another investigator if in doubt. At the conclusion of the trial, the vital status of all the participants was confirmed with the use of a national database of death records.

Symptomatic fractures were confirmed by radiology reports or by review of radiographs if reports were equivocal. Symptomatic vertebral fractures were confirmed by vertebral morphometric assessment. Radiographs of the lateral spine were obtained at baseline and at 3 years and 6 years for vertebral morphometry. Digital images were assessed semiquantitatively by a radiologist according to the method described by Genant et al.[10] In cases in which such an assessment suggested an incident fracture, the vertebral body height was measured. A decrease in height of 20% or greater and 4 mm or greater indicated an incident fracture. Height was measured in triplicate with a Harpenden stadiometer at baseline and at 3 years and 6 years, and the mean of the three measurements was used. All femoral fractures excluding those of the hip were reviewed to determine whether they met the criteria for "atypical femoral fractures."[11]

Bone mineral density (which was measured on a single GE Prodigy densitometer) and markers of bone turnover (carboxy-terminal collagen crosslinks and procollagen type 1 N-propeptide) were assessed as described previously.[12]

STATISTICAL ANALYSIS

We planned to recruit two groups of 921 women each (which was increased to 1000 women in each group to allow for loss to follow-up) to enable us to detect a hazard ratio for fragility fracture of 0.7 favoring zoledronate over placebo, assuming an event rate of 16% and a standard deviation of the predictor variable of 0.65.[13] Analyses were based on the intention-to-treat principle, and missing data were not imputed. The prespecified primary analysis was the time to first occurrence of a fragility fracture, which was modeled with the use of the Cox proportional-hazards approach. The proportional-hazards assumption was tested. The number of participants in each trial group who had at least one vertebral fracture or at least one adverse event were compared with the use of the mid-P exact test, and data are reported as odds ratios with 95% confidence intervals. Events per woman-year were tabulated.

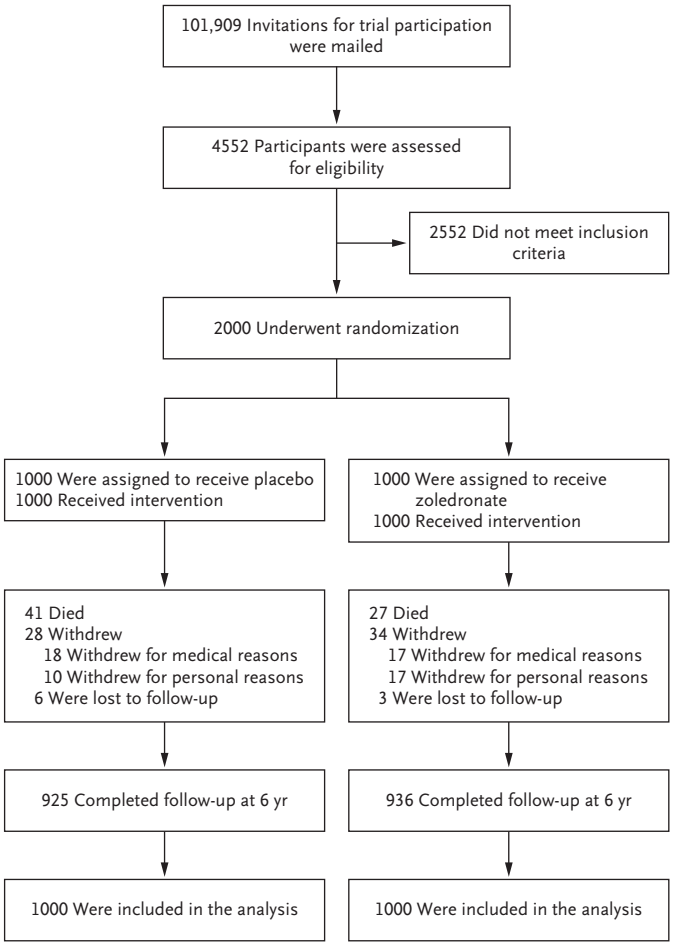

Figure 1. Enrollment, Randomization, and Follow-up of Trial Participants.
In the placebo group, 825 women received four doses of the trial regimen, 80 received three doses, 53 received two doses, and 42 received one dose. In the zoledronate group, 806 women received four doses of the trial regimen, 58 received three doses, 50 received two doses, and 86 received one dose. "Completed follow-up" indicates that the participant either attended the final visit at 6 years or had a telephone consultation that permitted ascertainment of fractures and adverse events.

All other analyses were performed with SAS software, version 9.4 (SAS Institute). Comparisons between the zoledronate group and the placebo group for normally distributed continuous variables were performed with the use of a mixed-models approach to repeated measures. An unstructured covariance was assumed. We evaluated significant main effects (time and trial-group assignment) and interaction effects (time by trial-group assignment) using the Tukey test. All tests were two-tailed. For the primary end point, a P value of less than 0.05 was considered to indicate statistical significance. Secondary analyses and sensitivity analyses were not adjusted for multiplicity.

RESULTS

PARTICIPANTS

Participants were enrolled in the trial from September 2009 through October 2011. The last trial visit was in January 2018. Information on the enrollment, randomization, and follow-up of the participants is shown in Figure 1. Final follow-up results (either to trial completion at 6 years or to death) were available in 97% of the participants in the placebo group and in 96% of the participants in the zoledronate group. Analyses were based on 5899 woman-years of follow-up in the placebo group and on 5940 woman-years of follow-up in the zoledronate group. The number of participants who received only one infusion of zoledronate or placebo was greater in the zoledronate group than in the placebo group (86 vs. 42, P<0.001). In the zoledronate group, 56 women declined to receive the second infusion owing to an acute phase response after the first infusion, and an additional 6 women did not receive the second infusion owing to iritis. In the placebo group, a second infusion was declined by 5 women because of an acute phase response after the first infusion; there were no cases of iritis. During the trial, treatment with bisphosphonates was initiated in 115 women in the placebo group (13, 29, 42, and 31 women in the first to fourth quarters of the trial, respectively), and in 33 women in the zoledronate group (6, 8, 5, and 14 women in the respective quarters). Subsequent infusions were withheld from these participants, but they continued to be followed in accordance with the intention-to-treat principle. Demographic and clinical characteristics of the participants were similar in the two groups at baseline (Table 1).

FRACTURES AND CHANGES IN HEIGHT

A fragility fracture occurred in 190 women in the placebo group (227 fractures) and in 122 women in the zoledronate group (131 fractures) (hazard ratio with zoledronate, 0.63; 95% confidence interval [CI], 0.50 to 0.79; P<0.001) (Fig. 2 and Table 2). The number of women that would need to be treated for 6 years to prevent the occurrence of a fragility fracture in 1 woman was 15, and the number that would need to be treated

Table 1. Characteristics of the Trial Participants at Baseline.*

Characteristic	Placebo (N=1000)	Zoledronate (N=1000)
Age — yr	71±5.1	71±5.0
Ethnic group — no. (%)†		
European	940 (94.0)	954 (95.0)
Maori	14 (1.4)	17 (1.7)
Pacific Islander	15 (1.5)	7 (0.7)
East Asian	24 (2.4)	15 (1.5)
Indian	5 (0.5)	5 (0.5)
Other	2 (0.2)	2 (0.2)
Height — cm	160.4±5.8	160.7±5.8
Weight — kg	69.2±12.2	69.1±12.5
Body-mass index‡	26.9±4.7	26.8±4.6
Dietary calcium intake — mg per day	882±388	871±360
History of nonvertebral fracture after 45 yr of age — no. (%)§	238 (23.8)	237 (23.7)
Prevalent vertebral fracture — no. (%)¶	126 (12.6)	137 (13.7)
Median 10-year risk of osteoporotic fracture (IQR) — %	12 (9–15)	12 (9–16)
Median 10-year risk of hip fracture (IQR) — %	2.3 (1.5–3.8)	2.4 (1.5–3.9)
Bone mineral density — g/cm^2		
Lumbar spine	1.08±0.14	1.07±0.13
Total hip	0.85±0.08	0.85±0.08
Femoral neck	0.81±0.07	0.81±0.07
Total body	1.06±0.07	1.06±0.07
Bone density T score		
Lumbar spine	–0.87±1.16	–0.91±1.12
Total hip	–1.24±0.60	–1.27±0.59
Femoral neck	–1.63±0.47	–1.64±0.47
Total body	–0.80±0.90	–0.81±0.86
Current smoker — no. (%)	33 (3.3)	23 (2.3)

* Plus–minus values are means ±SD. There were no significant differences between the trial groups in any of the characteristics evaluated at baseline. Percentages may not sum to 100 because of rounding. IQR denotes interquartile range.
† Ethnic group was reported by the participant.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ Nonvertebral fracture excludes fractures of the skull, face, mandible, hands, and feet.
¶ The fracture was assessed by radiography as grade 2 or 3 on the Genant grading scale (grades range from 0 to 3, with higher grades indicating greater severity).

to prevent the occurrence of a single fragility fracture was 10. The treatment effect was independent of baseline vertebral fracture status (P=0.27 for the interaction), and the hazard ratio with zoledronate was 0.65 (95% CI, 0.50 to 0.83) among participants who did not have prevalent vertebral fracture. A total of 163 women had a baseline T score (at the spine, total hip, or femoral neck) of less than –2.5, so they could be considered to have had osteoporosis; when the data from these participants were excluded from the analysis of the primary end point, the hazard ratio with zoledronate was 0.63 (95% CI, 0.49 to 0.80). A total of 707 women had either a baseline risk of hip fracture of more than 3% or a baseline risk of osteoporotic fracture of more than 20%, which were determined with the use of the fracture risk calculator; when the data from

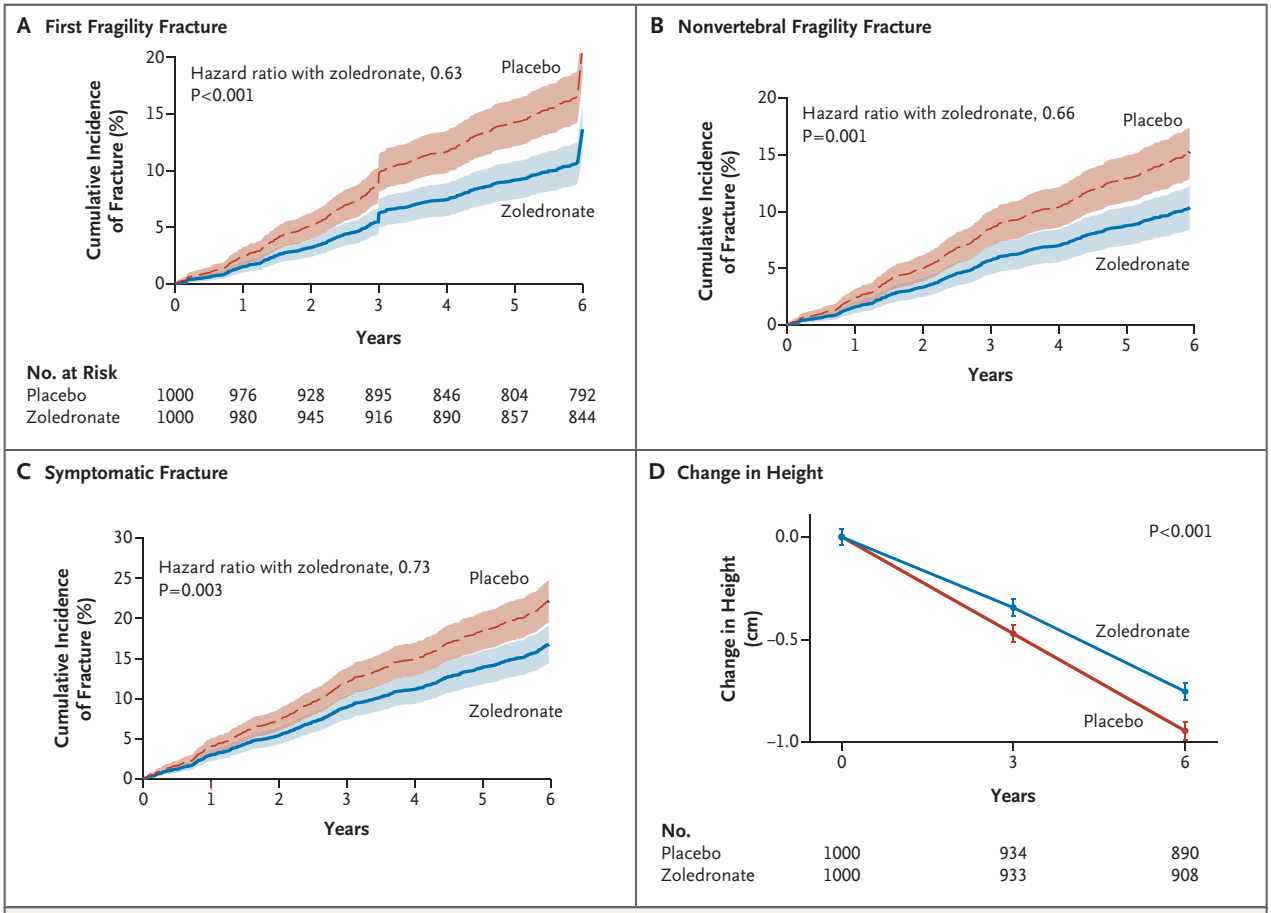

Figure 2. Cumulative Incidence of Fractures and Change in Height.

Cumulative incidence was calculated with the use of the Cox proportional-hazards model for the risk of first fragility fracture (i.e., nonvertebral fragility fractures plus vertebral fractures) (Panel A), the risk of nonvertebral fragility fracture (excluding fractures of the toes, metatarsal bones, fingers, metacarpal bones, skull, facial bones, and mandible) (Panel B), and the risk of symptomatic fracture (i.e., symptomatic vertebral fracture plus any nonvertebral fracture) (Panel C). Shaded areas indicate 95% confidence intervals. Asymptomatic vertebral fractures detected on radiographs at 3 years or 6 years were considered to have occurred at the time of the radiographs, which accounts for the abrupt increases in fracture numbers at those time points (Panel A). The apparent attrition of participants at risk (shown in Panel A) is substantially accounted for by participants who had a fracture during the trial so are no longer at risk for their first fracture. Changes from baseline in height (Panel D) were measured with the use of a stadiometer; values are shown as means, and I bars denote 95% confidence intervals. P values in all four panels are for between-group comparisons.

these participants were excluded, the hazard ratio with zoledronate was 0.60 (95% CI, 0.44 to 0.81). When we excluded the data from all these women plus those with a history of nonvertebral fracture after 45 years of age, the risk of total fragility fractures and nonvertebral fragility fractures was still lower with zoledronate than with placebo (hazard ratio with zoledronate for total fragility fractures, 0.60 [95% CI, 0.39 to 0.91]; hazard ratio with zoledronate for nonvertebral fragility fractures, 0.57 [95% CI, 0.37 to 0.86]).

For the secondary end point of symptomatic fracture, the hazard ratio with zoledronate was 0.73 (P=0.003), and the number of women that would need to be treated to prevent the occurrence of a symptomatic fracture in 1 woman was 20. The risk of a vertebral fracture was also lower in the zoledronate group than in the placebo group (odds ratio, 0.45; P=0.002), as was the risk of height loss (Fig. 2). In the placebo group, 368 of 890 women lost at least 1 cm in height as compared with 292 of 908 women in the zoledronate group (odds ratio with zoledronate, 0.67; 95% CI, 0.55 to 0.82). The analyses of the explor-

Table 2. Overview of Fracture Data at 6 Years.

Fracture Category	Placebo (N=1000)			Zoledronate (N=1000)			Hazard Ratio with Zoledronate (95% CI)
	Fractures	Fractures per 1000 Woman-Yr (95% CI)	Women with Fracture	Fractures	Fractures per 1000 Woman-Yr (95% CI)	Women with Fracture	
	no.		*no.*	*no.*		*no.*	
Fragility*	227	38.5 (33.8–43.8)	190	131	22.1 (18.5–26.1)	122	0.63 (0.50–0.79)
Symptomatic†	276	46.9 (41.6–52.6)	214	185	31.2 (26.9–35.9)	163	0.73 (0.60–0.90)
Vertebral							
Total	64	10.9 (8.4–13.8)	49	25	4.2 (2.8–6.1)	23	0.45 (0.27–0.73)§
Symptomatic	39	6.6 (4.8–9.0)	34	14	2.4 (1.3–3.9)	14	0.41 (0.22–0.75)
Nonvertebral							
Fragility‡	178	30.2 (26.0–34.9)	148	108	18.2 (15.0–21.9)	101	0.66 (0.51–0.85)
Hip	12	2.0 (1.1–3.5)	12	8	1.3 (0.6–2.6)	8	0.66 (0.27–1.16)
Forearm or wrist	68	11.6 (9.0–14.6)	63	38	6.4 (4.6–8.7)	36	0.56 (0.37–0.85)

* This category included nonvertebral fragility fractures (excluding fractures of the toes, metatarsal bones, fingers, metacarpal bones, skull, facial bones, and mandible) and morphometric vertebral fractures.
† This category included symptomatic vertebral fractures and all nonvertebral fractures.
‡ This category excluded fractures of the toes, metatarsal bones, fingers, metacarpal bones, skull, facial bones, and mandible.
§ These data are the odds ratio and 95% CI.

atory end points also showed a risk of fracture that was lower with zoledronate than with placebo for nonvertebral fragility fractures (hazard ratio with zoledronate, 0.66; P=0.001), symptomatic vertebral fractures (hazard ratio with zoledronate, 0.41; P=0.004), and forearm or wrist fractures (hazard ratio with zoledronate, 0.56; P=0.001); however, the risk of hip fractures was not significantly lower with zoledronate than with placebo (hazard ratio, 0.66; 95% CI, 0.27 to 1.16).

BONE MINERAL DENSITY AND MARKERS OF BONE TURNOVER

Marked between-group differences in bone mineral density were observed by year 3 (Fig. S1 in the Supplementary Appendix, available at NEJM.org), with some further separation between the groups in the second 3 years of the trial. In the placebo group, serum concentrations of bone-turnover markers did not change significantly during the course of the trial. By the end of the trial, the median concentration of procollagen type 1 N-propeptide was 37% lower in the zoledronate group than in the placebo group, and the median concentration of carboxy-terminal collagen crosslinks was 50% lower (P<0.001).

ADVERSE EVENTS

A total of 1017 serious adverse events were reported in 443 participants in the placebo group, and 820 serious adverse events were reported in 400 participants in the zoledronate group (odds ratio with zoledronate, 0.84; 95% CI, 0.70 to 1.00). These events included fractures that resulted in hospitalization. When the serious adverse events were grouped according to high-level *Medical Dictionary for Regulatory Activities* (MedDRA) terms (data not shown), only neoplasms and injuries (including fractures) had confidence intervals that did not overlap 1.

Prespecified adverse events of interest are shown in Table 3. The odds ratio for death was 0.65 (95% CI, 0.40 to 1.05) with zoledronate, and the odds ratio for cancer was 0.67 (95% CI, 0.50 to 0.89). Among the 68 deaths that occurred between randomization and year 6 of the trial, 41 were from neoplasms (25 in the placebo group and 16 in the zoledronate group), 8 were from strokes (7 in the placebo group and 1 in the zoledronate group [odds ratio with zoledronate, 0.14; 95% CI, 0.01 to 0.92]), and 7 were from cardiac events (3 in the placebo group and 4 in the zoledronate group). No atypical femoral frac-

Table 3. Prespecified Adverse Events of Interest.

Adverse Event	Placebo (N=1000)			Zoledronate (N=1000)			Odds Ratio with Zoledronate (95% CI)
	Events	Events per 1000 Woman-Yr (95% CI)	Women with at Least One Event	Events	Events per 1000 Woman-Yr (95% CI)	Women with at Least One Event	
	no.		*no.*	*no.*		*no.*	
Death	41	7.0 (5.4–9.4)	41	27	4.5 (3.0–6.6)	27	0.65 (0.40–1.05)
Sudden death	1	0.2 (0.002–0.9)	1	3	0.5 (0.1–14.8)	3	3.01 (0.3–28.9)
Myocardial infarction	43	7.3 (5.3–9.8)	39	25	4.2 (2.7–6.2)	24	0.61 (0.36–1.02)
Coronary-artery revascularization	32	5.4 (3.7–7.7)	30	23	3.9 (2.5–5.8)	21	0.72 (0.41–1.27)
Stroke	22	3.7 (2.3–5.7)	20	20	3.4 (2.1–5.2)	17	0.85 (0.44–1.63)
Composite of vascular events*	98	16.6 (13.5–20.3)	69	71	12.0 (9.3–15.1)	53	0.76 (0.52–1.09)
Transient ischemic attack	15	2.5 (1.4–4.2)	14	24	4.0 (2.6–6.0)	23	1.66 (0.85–3.24)
Cancer†	127	21.5 (18.0–18.1)	121	87	14.7 (11.7–18.1)	84	0.67 (0.50–0.89)
Osteonecrosis of the jaw	0	0	0	0	0	0	Not applicable
Atrial fibrillation	92	15.6 (12.6–19.1)	55	88	14.8 (11.9–18.3)	54	0.98 (0.67–1.44)

* This category included any of the following events: sudden death, myocardial infarction, coronary-artery revascularization, or stroke.
† This category excluded nonmelanoma skin cancers.

tures or cases of osteonecrosis of the jaw were reported in either group.

DISCUSSION

The current trial showed that administration of zoledronate every 18 months for 6 years reduced the risk of fragility fractures (both vertebral and nonvertebral) in older women with hip bone mineral density indicating osteopenia. The reduction in the risk of nonvertebral fracture was similar to that reported previously in patients with osteoporosis who were treated with zoledronate.[8,9] Our findings were also consistent with those of trials of clodronate[5] and estrogen[14] that showed similar fracture prevention in women who did not necessarily have osteoporotic bone mineral density. Our results address an important knowledge gap identified in the recently published American College of Physicians guidelines on osteoporosis, which stated that "current evidence is limited for a treatment benefit for women aged 65 years or older with osteopenia." Consequently, those guidelines were equivocal in endorsing pharmaceutical treatment in this patient group.[15] In contrast, the National Osteoporosis Foundation guidelines of 2014 did endorse pharmaceutical intervention in women with osteopenia who had a 10-year risk of hip fracture greater than 3%, although the guideline noted that "there are relatively few data confirming fracture risk reductions with pharmacotherapy in this group of patients."[6] Our trial addressed this knowledge gap.

The current trial differs from the two phase 3 trials of zoledronate[8,9] in that dosing in our trial was at 18-month intervals, and the use of calcium supplementation was very low (approximately 2%). Zoledronate has a sustained duration of action, with bone-turnover markers still suppressed by almost half 5 years after a single infusion.[16] McClung et al. found that annual administration of zoledronate for 2 years had effects on bone mineral density and bone-turnover markers that were almost equal to the effect of a single baseline dose.[17] The reduction in the risk of fractures observed in the current trial suggests that annual administration may be unnecessary for maximal efficacy in the prevention of fractures and that even longer intervals between doses should be considered. Calcium supplements act as weak antiresorptive agents in the management

of osteoporosis, and this effect is likely to be trivial when combined with zoledronate, which exhibits effects that are much more potent.

The adverse-event data from the current trial are not completely consistent with data from other trials, and confirmation of our results is warranted. Imbalances between the groups in the incidence of cancer, coronary heart disease, and death were observed in our trial. Previously, a meta-analysis of bisphosphonate trials showed that treatment with bisphosphonate reduced the risk of mortality,[18] and similar results were also observed in one of the phase 3 trials of zoledronate.[9,19] The reason that the other phase 3 trial of zoledronate[8] did not reproduce that finding remains unclear, although the women who were enrolled in the trial had lower bone mineral density and were geographically more diverse than those who participated in the trial by Lyles et al.[9] or in the current trial. The results of some[20] but not all[21] trials of breast cancer suggest that bisphosphonates have antitumor effects. There is also evidence from trials that suggests that bisphosphonates reduce the risk of vascular disease,[18,22-25] and observational studies of myocardial infarction support this possibility.[26-28] The possible vascular and cancer benefits in the current trial justify additional trials of zoledronate in which these conditions are the primary end points. The current findings may appear to be reassuring with respect to atypical femoral fractures and osteonecrosis of the jaw, but the trial is underpowered to definitively assess such rare events.

The strengths of the current trial are that it was well powered for the primary end point, it was of long duration, and the rate of participant retention was high. In the placebo group, treatment with bisphosphonates was initiated in 11.5% of participants (as compared with 3.3% of participants in the zoledronate group), so the estimates of benefit are conservative. The duration of the trial indicated that the intervention can be sustained on a long-term basis in clinical practice. We did not formally adjust for the number of secondary and exploratory end points, so some positive findings should be considered in that light. Of the 22 prespecified secondary and exploratory end points in the trial, approximately 1 might be expected on the basis of chance alone. Our trial involved only women who were 65 years of age or older and had hip bone mineral density that was characterized as osteopenia, so our findings should not be extrapolated to younger women, men, or persons who have normal bone mineral density.

The current trial showed that treatment with zoledronate every 18 months, with minimal use of calcium supplements, reduced the risk of fragility fractures (vertebral and nonvertebral) over the course of 6 years in older women with hip bone mineral density characterized as osteopenia.

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