ORIGINAL ARTICLE

Fracture Prevention with Infrequent Zoledronate in Women 50 to 60 Years of Age

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ABSTRACT

BACKGROUND

Zoledronate prevents fractures in older women when administered every 12 to 18 months, but its effects on bone density and bone turnover persist beyond 5 years. Whether infrequent zoledronate administration would prevent vertebral fractures in early postmenopausal women is unknown.

METHODS

We conducted a 10-year, prospective, double-blind, randomized, placebo-controlled trial involving early postmenopausal women (50 to 60 years of age) with bone mineral density T scores lower than 0 and higher than –2.5 (scores of –1 or higher typically indicate normal bone mineral density) at the lumbar spine, femoral neck, or hip. Participants were randomly assigned to receive an infusion of zoledronate at a dose of 5 mg at baseline and at 5 years (zoledronate–zoledronate group), zoledronate at a dose of 5 mg at baseline and placebo at 5 years (zoledronate–placebo group), or placebo at both baseline and 5 years (placebo–placebo group). Spinal radiographs were obtained at baseline, 5 years, and 10 years. The primary end point was morphometric vertebral fracture, which was assessed semiquantitatively and defined as at least a 20% change in vertebral height from that seen on the baseline radiograph. Secondary end points were fragility fracture, any fracture, and major osteoporotic fracture.

RESULTS

Of 1054 women with a mean age of 56.0 years at baseline, 1003 (95.2%) completed 10 years of follow-up. A new morphometric fracture occurred in 22 women (6.3%) in the zoledronate–zoledronate group, in 23 women (6.6%) in the zoledronate–placebo group, and in 39 women (11.1%) in the placebo–placebo group (relative risk, zoledronate–zoledronate vs. placebo–placebo, 0.56 [95% confidence interval {CI}, 0.34 to 0.92; P=0.04]; and zoledronate–placebo vs. placebo–placebo, 0.59 [95% CI, 0.36 to 0.97; P=0.08]). The relative risk of fragility fracture, any fracture, and major osteoporotic fracture was 0.72 (95% CI, 0.55 to 0.93), 0.70 (95% CI, 0.56 to 0.88), and 0.60 (95% CI, 0.42 to 0.86), respectively, when zoledronate–zoledronate was compared with placebo–placebo and 0.79 (95% CI, 0.61 to 1.02), 0.77 (95% CI, 0.62 to 0.97), and 0.71 (95% CI, 0.51 to 0.99), respectively, when zoledronate–placebo was compared with placebo–placebo.

CONCLUSIONS

Ten years after trial initiation, zoledronate administered at baseline and 5 years was effective in preventing morphometric vertebral fracture in early postmenopausal women. (Funded by the Health Research Council of New Zealand; Australian New Zealand Clinical Trials Registry number, ACTRN12612000270819.)

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At menopause, women have a remaining lifetime risk of fracture of more than 50%. In addition, fracture risk is inversely related to bone mineral density.[1,2] Decreases in bone mineral density, which are almost universal among postmenopausal women, start before menopause, with an average loss of bone density of 0.5 to 1% per year thereafter.[1,2] Currently, most fracture-prevention strategies focus on persons at highest risk for fracture: elderly persons and persons with low bone mineral density or with previous fractures. However, this focus is severely limited because only 20% of fractures occur in women with a bone mineral density that indicates osteoporosis.[3,4] Another possibility for the primary prevention of fractures would be to prevent bone loss in early postmenopausal women and maintain bone mineral density near the peak level of a young person. Because low bone mineral density was found to be a strong predictor of fracture risk in epidemiologic studies,[5] preventing postmenopausal bone loss might reduce the risk of fractures later in life.

Zoledronate has features that might be suitable for the prevention of primary fractures. When administered as an intravenous infusion annually or every 18 months, zoledronate reduces the incidence of fracture among osteopenic and osteoporotic populations,[6-8] and it has an excellent safety profile for up to 9 years with annual treatment.[6-10] It also has a prolonged duration of action — the effects of a single 5-mg dose on bone mineral density and bone turnover are stable and persist well beyond 5 years.[11-13] Fracture risk remains reduced for several years after treatment discontinuation,[14] and in one post hoc analysis, reductions in the incidence of total and vertebral fractures after 3 years were similar among patients who received a single 5-mg dose of zoledronate and among those who received an annual dose.[15] Therefore, we investigated whether very infrequent infusions of zoledronate would prevent vertebral fractures and maintain bone mineral density in early postmenopausal women.

METHODS

STUDY DESIGN

We conducted a 10-year, prospective, double-blind, randomized, placebo-controlled trial designed to determine whether very infrequent zoledronate infusions prevent vertebral fractures in early postmenopausal women. The participants were randomly assigned in a 1:1:1 ratio to receive infusions of zoledronate at a dose of 5 mg at baseline and again at 5 years (zoledronate–zoledronate group), an infusion of zoledronate at a dose of 5 mg at baseline and an infusion of normal saline (placebo) at 5 years (zoledronate–placebo group), or infusions of normal saline at baseline and at 5 years (placebo–placebo group). Participants were followed for 10 years. The infusion volume was 100 ml and was given over at least 15 minutes, and the infusion containers used for zoledronate and placebo were identical and were prepared by staff members who had no contact with participants. The participants and all trial staff were unaware of trial-group assignments for the duration of the trial. No other interventions were provided as part of the trial (such as routine vitamin D or calcium supplements). Consecutive participants were assigned to trial groups on the basis of a randomization list with computer-generated numbers with a variable block size, which was prepared by the trial statistician. The trial took place at the Clinical Research Centre, University of Auckland, and was approved by the Northern X Regional Health and Disability Ethics Committee, registered with the Australian New Zealand Clinical Trials Registry, and funded by the Health Research Council of New Zealand (HRC). All participants provided written informed consent. Recruitment took place from May 2012 through August 2013. The final trial visit occurred in October 2023.

The trial was designed by the first author and the last four authors; data were gathered by the first six authors and by research assistants; analyses were performed by the first author and the second-to-last author, who also vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol (available with the full text of this article at NEJM.org); and the first author wrote the first draft of the manuscript. All the authors participated in the decision to submit the manuscript for publication. None of the authors had any data confidentiality agreements. The authors are independent of the HRC. The HRC had no role in the design or conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or

the decision to submit the manuscript for publication.

PARTICIPANTS

Postmenopausal women 50 to 60 years of age were randomly selected from the electoral roll in Auckland, New Zealand, and invited by letter to participate in the trial. Women were eligible if their bone mineral density T score at the lumbar spine, femoral neck, or total hip was lower than 0 (scores of –1 or higher typically indicate normal bone density). Exclusion criteria were a T score of –2.5 or less at any of these sites, any major systemic illness or metabolic bone disease, a previous clinical spine or hip fracture, use of any bisphosphonates or hormone-replacement therapy within 12 months before randomization, any previous use of zoledronate, or use of oral glucocorticoid drugs equivalent to an average dose of prednisone of 2.5 mg per day or more during the preceding 6 months.

END POINTS

The primary end point was a new morphometric vertebral fracture, which was determined with the use of spinal radiographs. Secondary end points were fragility fracture, any fracture, and major osteoporotic fracture. Fragility fractures were defined as any fracture, including radiographic vertebral fractures, but excluding fractures involving toes, metatarsals, fingers, metacarpals, the skull, or the face.[8] Major osteoporotic fractures were defined as fractures of the wrist, spine, shoulder, hip, or pelvis. Fractures were not excluded on the basis of trauma severity but pathologic fractures were excluded from all end points.[8] Other secondary end points included changes in bone mineral density at the proximal femur and lumbar spine and changes in markers of bone turnover.

ASSESSMENTS

Participants reported fractures, adverse events, and changes in medications in a questionnaire every 6 months. They underwent clinical assessments at baseline, 5 years, and 10 years, during which height and weight were measured. Lateral radiographs of the spine were obtained at baseline, 5 years, and 10 years. Digital images were assessed semiquantitatively by one of the authors (a radiologist), who used a scale that was described previously by Genant et al.[16] According to this scale, a normal vertebra is scored 0, a borderline deformity is scored 0.5, and a fracture is scored 1 to 3, with a higher score indicating a more severe fracture. An incident vertebral fracture was defined as a change in score of at least 0.5, a change in a vertebral height of at least 20% from that seen on the baseline radiograph, and a final score of at least 1. Fractures reported by participants were confirmed by radiology reports. The bone mineral density of the lumbar spine (L1 through L4) and both proximal femora was measured at baseline, 5 years, and 10 years in all participants with the use of a dual-energy x-ray absorptiometer (Prodigy, GE Lunar). The mean bone mineral density of both hips is reported. The coefficients of variation used in our laboratory are 1.4% for the lumbar spine and 1.1% for the total hip.

The first 225 participants to provide consent also took part in a substudy in which bone mineral density and markers of bone turnover were measured every 2.5 years. At baseline, 2.5 years, 5 years, 7.5 years, and 10 years, fasting blood samples were obtained from the substudy participants, and the serum was stored at −80°C until analyzed. The markers of bone turnover — β-isomer of C-terminal telopeptide of type I collagen (CTx) and procollagen type I N-terminal propeptide (P1NP) — were measured in batches at study completion with the use of the Roche Elecsys 2010 platform (Roche Diagnostics). Coefficients of variation were 5.1% for CTx and 1.9% for P1NP.

STATISTICAL ANALYSIS

Assuming an average age of 55 years, we expected a vertebral fracture incidence of approximately 10 per 1000 patient-years in the placebo–placebo group.[17] Thus, we calculated that a total sample size of 1050 participants (350 in each group) would give the trial at least 80% power (alpha level of 0.05) to detect a 60% decrease in the risk of a new vertebral fracture in the two groups who received zoledronate as compared with the placebo group, allowing for 20% of participants to be lost to follow-up or to withdraw because of nonprotocol treatment with other antiosteoporotic therapies.

Because of the long duration between protocol finalization and trial completion, a statistical analysis plan was developed to supersede and expand on the relevant sections in the protocol.

The statistical analysis plan underwent development starting in July 2021, was submitted for ethical approval in March 2022, and was approved on April 6, 2022. The final document was approved by the statistician and the principal investigator in October 2023, before the trial was completed and any analyses were performed. No interim analyses were conducted.

All analyses were performed in accordance with the intention-to-treat (ITT) principle. In the preplanned primary analysis, the risk of a new vertebral fracture at 10 years among women with a baseline spinal radiograph and at least one follow-up radiograph (modified ITT population) in the zoledronate–zoledronate group and in the zoledronate–placebo group was compared with the risk among those in the placebo–placebo group with the use of Fisher's exact test, and the results are presented as relative risks with 95% confidence intervals. The two primary aims were the comparison of the effect of a single 5-mg dose of zoledronate with the effect of placebo on vertebral fractures and the comparison of the effect of two 5-mg doses of zoledronate, separated by 5 years, with the effect of placebo on vertebral fractures. To conform to *Journal* policy, which requires adjustment for multiplicity and analysis of the full ITT population, we used multiple imputation accounting for missing data (63 women [6%] did not have any follow-up spinal radiographs) for the primary analysis (see the Supplementary Methods section of the Supplementary Appendix, available at NEJM.org) with Bonferroni-adjusted P values (i.e., unadjusted P value times 2). The widths of the confidence intervals for the primary analysis and the secondary analysis (described below) have not been adjusted for multiplicity and may not be used in place of hypothesis testing The results of the prespecified analysis, which considered the two primary aims as separate experiments (and therefore included no adjustment for multiple statistical comparisons), are reported in Table S1 in the Supplementary Appendix.

The same approach was used for other fracture types in all participants who underwent randomization. Time-to-first-fracture analyses were modeled with the use of a Cox proportional-hazards approach, the log-rank statistic was estimated, and Kaplan–Meier curves were drawn. The proportional-hazards assumption was tested through inspection of the Kaplan–Meier and Schoenfeld residual plots and through testing the hypothesis of proportionality by fitting time-dependent covariates in the model. In all cases, the assumption was met. In a secondary analysis, the two zoledronate groups were simply pooled and the analyses for fractures repeated. A mixed-models approach to repeated measures was used to compare the zoledronate–zoledronate group and the zoledronate–placebo group with the placebo–placebo group with respect to bone mineral density and bone-turnover markers.

Analyses were conducted with the use of SAS, version 9.4 (SAS Institute). All tests were two-tailed, and P values less than 0.05 were considered to indicate statistical significance.

RESULTS

PARTICIPANTS

The flow of participants through the trial is shown in Figure S1. A total of 1054 participants were randomly assigned to the zoledronate–zoledronate group (352 participants), the zoledronate–placebo group (351 participants), or the placebo–placebo group (351 participants); of these, 1003 (95.2%) completed 10 years of follow-up. Of the 703 participants who received zoledronate at baseline, 581 (82.6%) had a second infusion of either zoledronate or placebo; in comparison, of the 351 participants who received placebo at baseline, 315 (89.7%) received a second infusion of placebo. Selected baseline characteristics of participants were similar in the three trial groups (Table 1). Additional information about participant representativeness with respect to age, sex, and race or ethnic group is provided in Table S2. The trial participants were women 50 to 60 years of age (mean age at baseline, 56.0 years), who were mainly of European descent; thus, the results are generalizable to that population.

VERTEBRAL FRACTURES

A total of 991 women (94.0%) had at least two evaluable spinal radiographs. A new morphometric vertebral fracture (the primary end point) occurred in 6.3% of the participants in the zoledronate–zoledronate group, 6.6% in the zoledronate–placebo group, and 11.1% in the placebo–placebo group (Table 2 and Fig. 1A). After multiple imputation of missing data on vertebral fractures, the relative risk as compared with the placebo–placebo group was 0.56 (95% confidence interval

Table 1. Demographic and Clinical Characteristics of Trial Participants at Baseline.*

Characteristic	Zoledronate–Zoledronate (N=352)	Zoledronate–Placebo (N=351)	Placebo–Placebo (N=351)
Age — yr	56.1±3.0	55.8±3.0	56.0±2.9
European ancestry — no. (%)†	295 (83.8)	305 (86.9)	295 (84.0)
Height — cm	162.7±6.0	162.8±7.3	162.9±6.3
Weight — kg	70.8±14.6	72.5±13.9	70.4±13.8
Current smoker — no. (%)	15 (4.3)	16 (4.6)	20 (5.7)
Dietary calcium intake — mg/day	740±350	762±391	736±366
Physical activity — h/wk	35.5±9.1	35.9±10.7	35.5±9.6
Nonvertebral fracture after age 45 yr — no. (%)	62 (17.6)	39 (11.1)	57 (16.2)
Estimated 10-year fracture risk — %‡	9.2±3.8	8.6±3.1	9.0±3.5
Lumbar spine bone density — g/cm^2	1.13±0.14	1.14±0.14	1.13±0.13
T score§	–0.45±1.16	–0.36±1.14	–0.44±1.11
Total hip bone density — g/cm^2	0.94±0.09	0.95±0.10	0.94±0.09
T-score§	–0.51±0.74	–0.46±0.77	–0.55±0.74
P1NP — μg/liter	56.1±21.2	61.6±20.0	63.2±24.5
β-CTx — μg/liter	0.50±0.20	0.53±0.18	0.51±0.19

* Plus–minus values are means ±SD. β-CTx denotes β-isomer of C-terminal telopeptide of type I collagen, placebo–placebo administration of placebo at baseline and 5 years, P1NP procollagen type I N-terminal propeptide, zoledronate–placebo administration of zoledronate at baseline and placebo at 5 years, and zoledronate–zoledronate administration of zoledronate at baseline and 5 years.
† Ancestry was reported by the participants.
‡ Fracture risk was estimated for fragility fracture with the use of the Garvan Institute of Medical Research fracture risk calculator (https://fracturerisk calculator.com.au/calculator/).
§ T scores of –1 or higher typically indicate normal bone density.

[CI], 0.34 to 0.92; P=0.04) in the zoledronate–zoledronate group and 0.59 (95% CI, 0.36 to 0.97; P=0.08) in the zoledronate–placebo group. When the two zoledronate groups were pooled, the relative risk as compared with the placebo–placebo group was 0.58 (95% CI, 0.38 to 0.87). The number needed to treat to prevent one woman from having a new morphometric vertebral fracture during the 10-year period was 21 in the zoledronate–zoledronate group and 22 in the zoledronate–placebo group. As compared with the zoledronate–placebo group, the relative risk of a new morphometric vertebral fracture in the zoledronate–zoledronate group was 0.94 (95% CI, 0.54 to 1.66).

OTHER FRACTURES

As compared with the placebo–placebo group, the relative risk of any fracture was 0.70 (95% CI, 0.56 to 0.88) in the zoledronate–zoledronate group and 0.77 (95% CI, 0.62 to 0.97) in the zoledronate–placebo group (Table 2 and Fig. 1). The results for fragility fracture and for major osteoporotic fracture were similar to the results for any fracture. For all fracture categories, the relative risks tended to be slightly lower in the zoledronate–zoledronate group than in the zoledronate–placebo group (the relative risk of fracture in the zoledronate–zoledronate group as compared with the zoledronate–placebo group ranged from 0.83 to 0.94), but the confidence intervals around these relative risks were wide.

BONE MINERAL DENSITY

The effect of each of the two zoledronate regimens on bone mineral density is shown in Figure 2. At 5 years, the differences in the percent change in bone mineral density at the total hip and at the spine between each of the zoledronate groups and the placebo–placebo group ranged from 4.9 to 6.6 percentage points. At 10 years, the differences in the percent change in bone mineral density at these sites between the zoledronate–zoledronate group and the placebo–placebo group ranged

Table 2. The Effect of Zoledronate on Fracture Outcomes.*

End Point	Zol–Zol (N=352)	Zol–Placebo (N=351)	Placebo–Placebo (N=351)	Zol–Zol and Zol–Placebo (N=703)	Zol–Zol vs. Placebo–Placebo	Zol–Placebo vs. Placebo–Placebo	Zol–Zol vs. Zol–Placebo	Zol–Zol and Zol–Placebo vs. Placebo–Placebo
	no. of women with ≥1 new fracture (%)				*relative risk (95% CI)*			
Primary end point								
Morphometric vertebral fracture†	22 (6.3)	23 (6.6)	39 (11.1)	45 (6.4)	0.56 (0.34–0.92)‡	0.59 (0.36–0.97)‡	0.94 (0.54–1.66)	0.58 (0.38–0.87)
Secondary end points								
Fragility fracture	71 (20.2)	78 (22.2)	99 (28.2)	149 (21.2)	0.72 (0.55–0.93)	0.79 (0.61–1.02)	0.91 (0.68–1.21)	0.75 (0.60–0.94)
Any fracture	87 (24.7)	96 (27.4)	124 (35.3)	183 (26.0)	0.70 (0.56–0.88)	0.77 (0.62–0.97)	0.90 (0.70–1.16)	0.74 (0.61–0.89)
Major osteoporotic fracture	41 (11.6)	49 (14.0)	69 (19.7)	90 (12.8)	0.60 (0.42–0.86)	0.71 (0.51–0.99)	0.83 (0.57–1.23)	0.65 (0.49–0.87)

* Confidence interval widths have not been adjusted for multiplicity and may not be used in place of hypothesis testing. Zol denotes zoledronate.
† Post hoc multiple imputation analyses were performed to account for missing data in the intention-to-treat population; see the Supplementary Methods section of the Supplementary Appendix for details.
‡ P=0.04 for zol–zol as compared with placebo–placebo and P=0.08 for zol–placebo as compared with placebo–placebo. P values were adjusted for multiple statistical tests with the use of the conservative Bonferroni method (i.e., unadjusted P value times 2).

from 7.4 to 8.8 percentage points, between the zoledronate–placebo group and the placebo–placebo group ranged from 5.0 to 6.3 percentage points, and between the zoledronate–zoledronate group and the zoledronate–placebo group ranged from 2.4 to 2.5 percentage points.

BONE-TURNOVER MARKERS

At 5 years, markers of bone turnover had remained stable or had increased in the placebo–placebo group but had decreased by approximately 30 to 40% in each of the zoledronate groups (Fig. 2). Thereafter, markers of bone turnover slowly increased in the zoledronate–placebo group but remained below baseline levels at 10 years, whereas levels were similar at 5 years and 10 years in the zoledronate–zoledronate group.

ADVERSE EVENTS AND OTHER RESULTS

In general, there were few adverse events (Table S3). A total of 8 participants (1.1%) had uveitis and 1 participant (0.1%) had episcleritis after the baseline infusion of zoledronate, whereas no participants in the placebo group had either condition.[18] No participants had uveitis or episcleritis after the second infusion. No cases of osteonecrosis of the jaw and no atypical femoral fractures occurred during the trial. A total of 11 participants died during the trial, 8 had a myocardial infarction, 7 had a stroke, and 49 had cancer, 22 of whom had breast cancer. For each type of adverse event, the incidence was similar in the three groups.

DISCUSSION

Intravenous zoledronate administered once every 5 years reduced the incidence of morphometric vertebral fractures during a 10-year period. As compared with the placebo–placebo group, the relative risk of any fracture was 0.70 (95% CI, 0.56 to 0.88) in the zoledronate–zoledronate group and 0.77 (95% CI, 0.62 to 0.97) in the zoledronate–placebo group. The differences in the percent change in bone mineral density between each of the zoledronate groups and the placebo–placebo group were approximately 5 to 9 percentage points at 10 years. Bone mineral density at 10 years had not increased after a second dose of zoledronate in the zoledronate–zoledronate group, but the difference in the percent change between the zoledronate–zoledronate group and

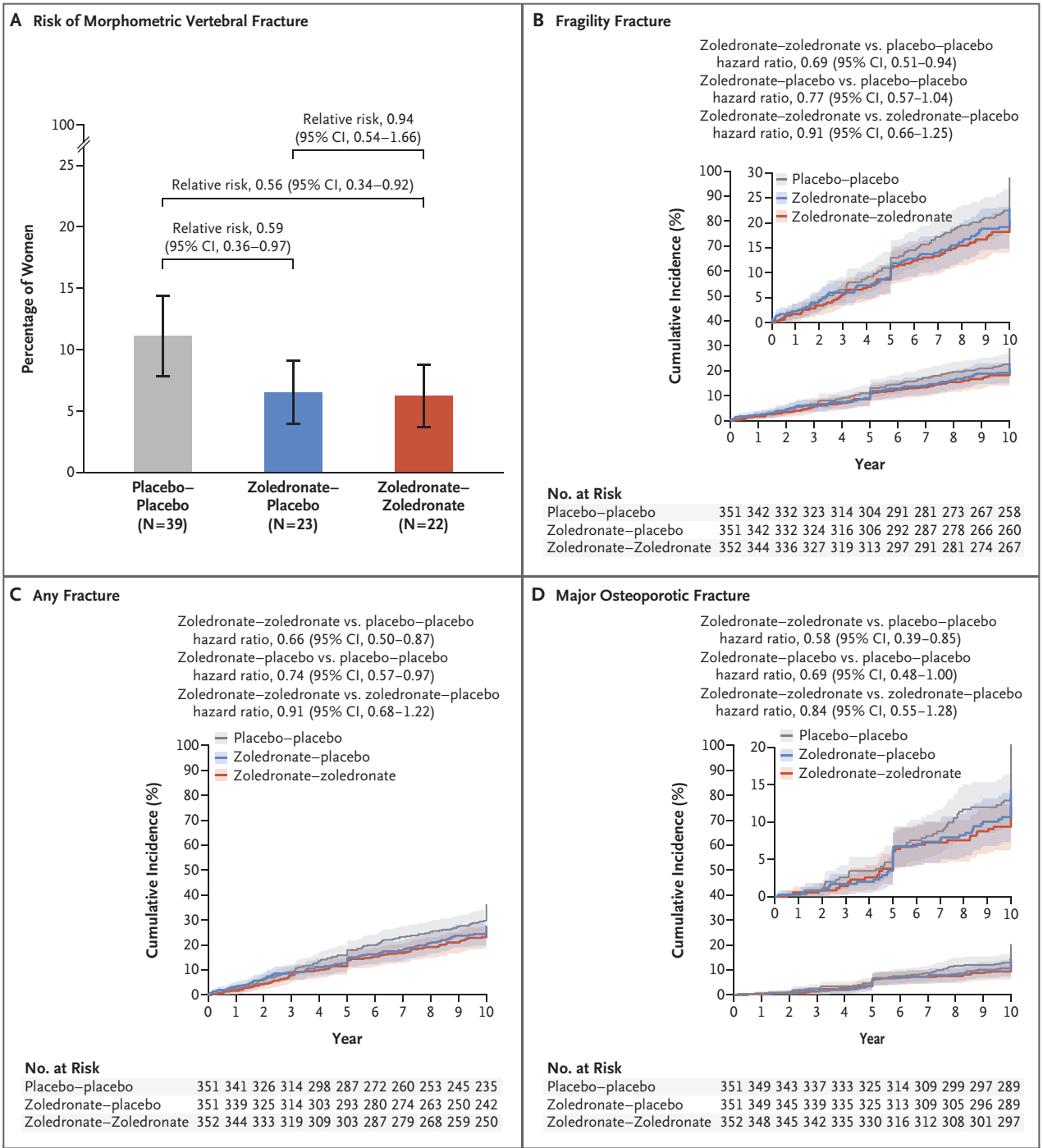

Figure 1. Incidence of Fracture.

Panel A shows the percentage of women who had a new morphometric vertebral fracture during 10 years of follow-up, stratified according to trial group. Panels B, C, and D show the cumulative incidence of fragility fracture, any fracture, and major osteoporotic fracture over time, respectively, stratified according to trial group; the insets show the same data on an expanded y axis. Shaded areas represent 95% confidence intervals. Confidence interval widths have not been adjusted for multiplicity and may not be used in place of hypothesis testing. Placebo–placebo denotes administration of placebo at baseline and 5 years, zoledronate–placebo administration of zoledronate at baseline and placebo at 5 years, and zoledronate–zoledronate administration of zoledronate at baseline and 5 years.

the zoledronate–placebo group was approximately 2.5 percentage points. Markers of bone turnover remained low in the zoledronate–zoledronate group at 10 years; these markers increased after 5 years in the zoledronate–placebo group but were still below baseline levels after 10 years.

The results show that prevention of vertebral fractures in early postmenopausal women is possible with very infrequent infusions of zoledronate. The relative risks for any fracture observed in the current trial are similar to those observed in trials of zoledronate in older women and in persons at higher risk of fracture.[6-8] Early postmenopausal women who wish to reduce their risk of fracture could consider a strategy involving the administration of zoledronate either every 5 years or every 10 years. The cost of the

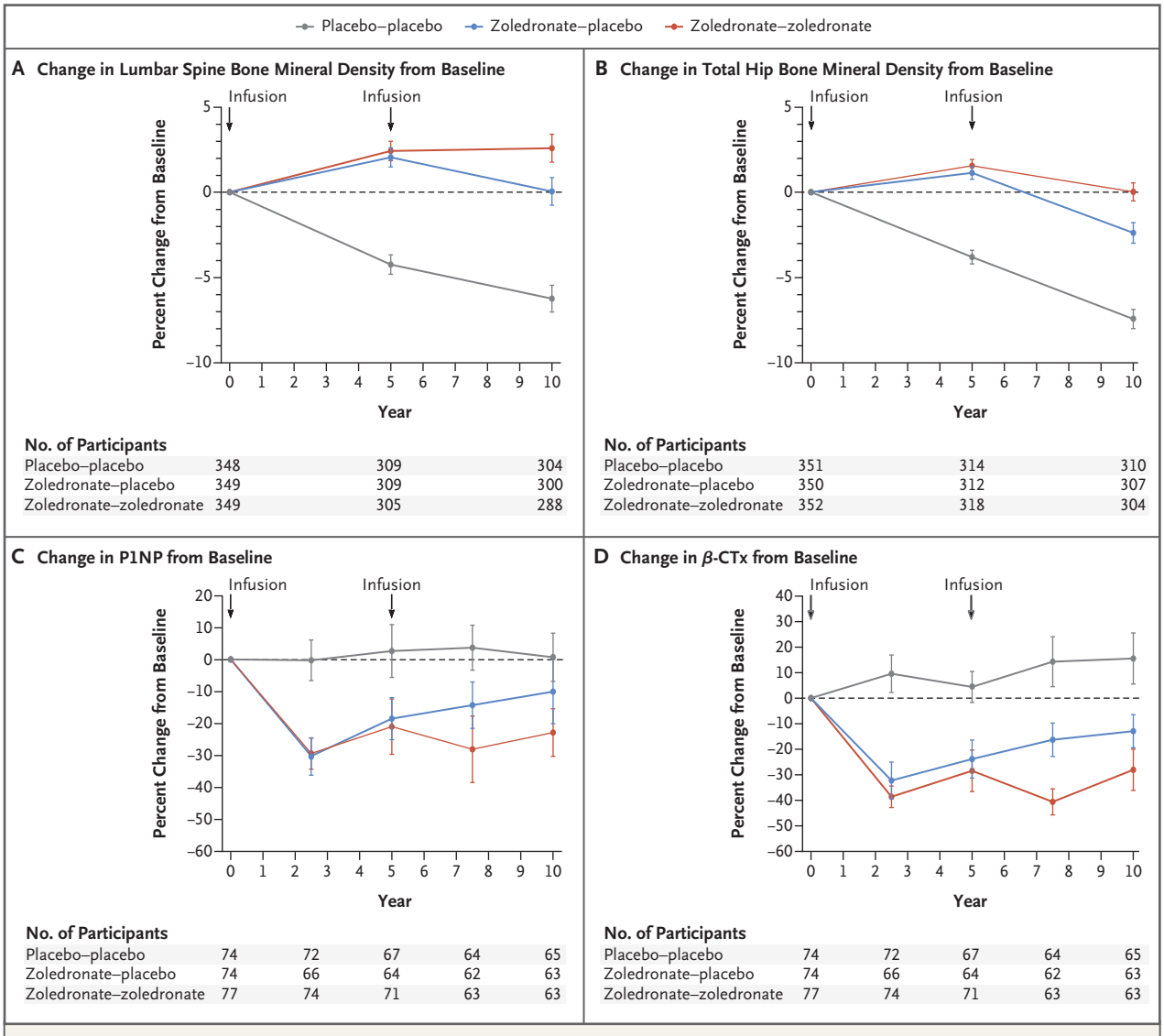

Figure 2. Effect of Zoledronate on Bone Mineral Density and Bone-Turnover Markers.

Panels A and B show the percent change from baseline in bone mineral density at the lumbar spine and total hip, respectively, and Panels C and D show the percent change from baseline in the bone-turnover markers procollagen type I N-terminal propeptide (P1NP) and β-isomer of C-terminal telopeptide of type I collagen (β-CTx), respectively, in the first 225 consenting participants. Results are stratified according to trial group. Circles indicate the mean, and I bars indicate 95% confidence intervals. The number of measurements per time point are listed. The arrows indicate infusion times (baseline and 5 years). Confidence interval widths have not been adjusted for multiplicity and may not be used in place of hypothesis testing.

treatment, either to individual patients or to health systems, is likely to be low because the drug is generic and the frequency of administration low. Previously, a small, 9-year trial of estrogen therapy in women with a mean age of 48 years at baseline who had surgically induced menopause also showed the prevention of vertebral fractures.[19] Fractures in postmenopausal women younger than 65 years are relatively common; approximately 1 in 10 of these women will have a fracture during a 10-year period,[20] and fractures in adults 50 to 65 years of age account for approximately one fourth of all fractures in adults over 50 years of age.[21] Collectively, these data suggest that fracture-prevention strategies for early postmenopausal women can be effective, and although the benefit for individual persons at low risk for fracture is small, such strategies, including infrequent infusions of zoledronate, could substantially reduce the number of fractures that occur in the population. Thus, the very infrequent infusions of zoledronate to prevent vertebral fractures and bone loss in early postmenopausal women offers a clinically realistic therapeutic option for women who are concerned about bone loss or their future risk of fracture.

Clinical-trial evidence of fracture outcomes in older adults is limited to dosing intervals of 12 to 18 months, but the effects of zoledronate on surrogate markers of bone health, such as bone mineral density and bone-turnover markers, persist for 5 to 10 years after one or two annual zoledronate infusions.[11-13,22] Persistent effects of zoledronate of similar duration with respect to bone mineral density and bone-turnover markers were also seen in the current trial. However, the most effective dosing interval for zoledronate remains unknown. It is possible that more-frequent dosing intervals for zoledronate as used in previous studies, such as annual[6,7] or every 18 months,[8] might be more effective than the intervals used in our trial, particularly in persons with a higher risk of fracture.

Interestingly, in our trial, bone mineral density did not increase after a second dose of zoledronate at 5 years when markers of bone turnover were still low, a finding also seen in a previous trial.[23] In contrast, another trial showed that 5 years after the administration of zoledronate doses of 1 mg and 2.5 mg, bone turnover had nearly returned to baseline levels, and bone mineral density then increased after a further dose of zoledronate was administered.[13]

The strengths of this trial are its long duration of double-blind, randomized follow-up; retention of a high number of participants; and the high number of participants who adhered to the trial interventions. Limitations include the fact that the trial cohort comprised early postmenopausal women without osteoporosis, so the results may not apply to older women, men, or persons with osteoporosis. In the analyses of secondary end points, we did not statistically adjust for multiple testing, so the secondary end-point results should be interpreted cautiously.

Ten years after trial initiation, zoledronate administered at baseline and 5 years was effective in preventing morphometric vertebral fracture in early postmenopausal women.

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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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