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Zoledronic Acid in Reducing Clinical Fracture and Mortality after Hip Fracture

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Abstract

BACKGROUND—Mortality is increased after a hip fracture, and strategies that improve outcomes are needed.

METHODS—In this randomized, double-blind, placebo-controlled trial, 1065 patients were assigned to receive yearly intravenous zoledronic acid (at a dose of 5 mg), and 1062 patients were assigned to receive placebo. The infusions were first administered within 90 days after surgical repair of a hip fracture. All patients received supplemental vitamin D and calcium. The median follow-up was 1.9 years. The primary end point was a new clinical fracture.

RESULTS—The rates of any new clinical fracture were 8.6% in the zoledronic acid group and 13.9% in the placebo group, a 35% risk reduction (P = 0.001); the respective rates of a new clinical vertebral fracture were 1.7% and 3.8% (P = 0.02), and the respective rates of new nonvertebral fractures were 7.6% and 10.7% (P = 0.03). In the safety analysis, 101 of 1054 patients in the zoledronic acid group (9.6%) and 141 of 1057 patients in the placebo group (13.3%) died, a reduction of 28% in deaths from any cause in the zoledronic-acid group (P = 0.01). The most frequent adverse events in patients receiving zoledronic acid were pyrexia, myalgia, and bone and musculoskeletal pain. No cases of osteonecrosis of the jaw were reported, and no adverse effects on the healing of fractures were noted. The rates of renal and

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cardiovascular adverse events, including atrial fibrillation and stroke, were similar in the two groups.

CONCLUSIONS—An annual infusion of zoledronic acid within 90 days after repair of a low-trauma hip fracture was associated with a reduction in the rate of new clinical fractures and improved survival. (ClinicalTrials.gov number, NCT00046254.)

Hip fractures are associated with increased morbidity, functional decline, and death in older adults, as well as increased use of health care services.1,2 Mortality is increased in the year after hip fracture, with reported rates of 15 to 25% and an estimated 9 excess deaths per 100 patients among women 70 years of age or older.2–10

One source of the excess morbidity and cost incurred by patients with hip fractures is new osteoporotic fractures. Such fractures occur at a rate of 10.4 per 100 patients per year, which is 2.5 times as high as the rate in age-matched persons without previous hip fracture.10 However, data suggest that few patients with hip fracture actually receive pharmacologic therapy for osteoporosis.11–13

Zoledronic acid is a potent bisphosphonate that can be administered intravenously once yearly. The drug has been associated with a significant reduction of the risk of vertebral, hip, and nonvertebral fractures in women with postmenopausal osteoporosis.14,15 We present the results of a randomized trial that tested the efficacy and safety of zoledronic acid (at a dose of 5 mg) administered intravenously once yearly for the prevention of new clinical fractures in women and men who had undergone recent surgical repair of a hip fracture.

METHODS

STUDY DESIGN

The Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) Recurrent Fracture Trial was an international, multicenter, randomized, double-blind, placebo-controlled trial involving patients with recent hip fracture.16 Patients were randomly assigned to receive either zoledronic acid by intravenous infusion or placebo infusion during a 15-minute period. Study drugs were infused within 90 days after the surgical repair of a hip fracture and every 12 months thereafter for the duration of the study. If the serum 25-hydroxyvitamin D level was 15 ng per milliliter or less or if the level was not available, patients received a loading dose of either vitamin D_3 or D_2 (at a dose of 50,000 to 125,000 IU given orally or intramuscularly) 14 days before first infusion of a study drug. Thereafter, all patients received daily supplementation with oral calcium (1000 to 1500 mg) and vitamin D (800 to 1200 IU).

Patients were monitored for up to 5 years with quarterly telephone interviews and yearly clinic visits. All study procedures were approved by the local institutional review board at each participating site.

The academic investigators initiated the concept of the study, which was jointly designed with the sponsor. An independent data and safety monitoring board met semiannually to oversee the conduct and safety of the study. In November 2006, after requesting an

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additional unplanned interim analysis after 185 events had accrued, the data and safety monitoring board recommended that the trial be stopped on the basis of having surpassed the prespecified efficacy boundaries. Data analysis was performed by the sponsor and confirmed by independent statisticians at the Coordinating Center at the University of California at San Francisco, San Francisco.

PATIENTS

All patients who were enrolled in the trial had undergone a hip fracture and were unable or unwilling to take an oral bisphosphonate. All patients signed an informed consent form that stated, “If you or your physician decides that you should take alendronate (Fosamax), risedronate (Actonel), etidronate (Didronel), or teriparatide (Forteo), you should not participate in this study.” Men and women 50 years of age or older were eligible for inclusion within 90 days after surgical repair of a hip fracture sustained with minimal trauma (i.e., a fall from standing height or a lower height). Additional enrollment criteria included being ambulatory before the hip fracture and having both legs.

Concomitant therapy with nasal calcitonin, selective estrogen-receptor modulators, hormone replacement, tibolone, and external hip protectors was allowed at the discretion of the investigator. Previous use of bisphosphonates or parathyroid hormone was allowed after a washout period that varied according to the drug and the duration of its use. Previous use of strontium or sodium fluoride was not allowed. Patients with delirium or dementia were included only after consent had been obtained from both the patient and the legal surrogate.

Exclusion criteria were previous hypersensitivity to a bisphosphonate, a potential for pregnancy, a calculated creatinine clearance of less than 30 ml per minute, a corrected serum calcium level of more than 11.0 mg per deciliter (2.8 mmol per liter) or less than 8.0 mg per deciliter (2.0 mmol per liter), active cancer, metabolic bone disease other than osteoporosis, and a life expectancy of less than 6 months in the investigator’s judgment.

Bone mineral density at the hip and femoral neck and the calculated creatinine clearance were determined at baseline and annually. If patients had a clinical fracture or if measures of bone mineral density at the total hip declined by more than 8% from baseline to month 12 or by more than 10% from baseline to month 24, patients were given the options of continuing in the study, adding an approved medication (calcitonin, hormone-replacement therapy, tibolone, or raloxifene) and continuing in the study, beginning treatment with a prohibited medication (teriparatide or an oral bisphosphonate) and stopping infusions of the study drug but continuing follow-up, or discontinuing active participation in the trial. The study drug was withheld for those patients whose creatinine clearance fell below 30 ml per minute; however, their follow-up continued.

RANDOMIZATION AND BLINDING

Patients were randomly assigned to study groups at a central location through an interactive voice-response system that created randomized permuted blocks according to site. Because the infusion of zoledronic acid sometimes caused an influenza-like syndrome in previous studies,15 patients were given acetaminophen at the time of the study-drug infusion and then as needed for the next 72 hours. Study patients, investigators, steering committee members,

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the study sponsor, and faculty who adjudicated the clinical and safety end points remained unaware of study-group assignments throughout the trial.

END POINTS

The primary end point was a new clinical fracture, excluding facial and digital fractures and fractures in bone containing metastases. Although the final statistical analysis plan indicated that the mean time to the first fracture would be reported as the primary outcome, because the overall rate of fractures was low, the hazard ratio for fracture was calculated with the use of a Cox proportional-hazards model; these rates were reported as the primary outcome. (For details, see the Supplementary Appendix, available with the full text of this article at www.nejm.org.) Secondary end points included the change in bone mineral density in the nonfractured hip, as measured annually with dual-energy x-ray absorptiometry; new vertebral, nonvertebral, and hip fractures; and prespecified safety end points, including death.

ASSESSMENT OF OUTCOMES

At baseline, most patients underwent lateral radiography of the chest and lumbar spine. A nonvertebral fracture (defined as a skeletal fracture that was not a vertebral, facial, digital, or skull fracture) was confirmed when a radiograph, a radiographic report, or a medical record documented a new fracture. A possible vertebral fracture required blinded review of both baseline and recent radiographs with the use of a semiquantitative technique.17 A new clinical vertebral fracture was defined as new or worsening back pain with a reduction in vertebral body height of 20% (grade 1) or more, as compared with baseline radiographs, or a reduction in vertebral body height of 25% (grade 2) or more if no baseline radiograph was available.

Investigators performed assessments for delayed union of the qualifying hip fracture at each study visit during the first 12 months. Delayed union was defined as persistent pain or an inability to bear weight plus radiographic evidence of any one of the following: a lack of bridging callus over at least two cortices, a persistent fracture line, the appearance of a new fracture line if it had been previously unapparent, or displacement of a previously aligned fracture.

Dual-energy x-ray absorptiometry of the contralateral hip or spine was performed at baseline and annually thereafter. Bone mineral density and T scores were adjusted to correct for site and brand variations of the imaging equipment.18,19

Baseline serum levels of 25-hydroxyvitamin D were measured centrally (by Covance) in a subgroup of 385 patients. Serum calcium and creatinine levels were measured with an autoanalyzer at baseline and subsequently within 4 weeks before each annual infusion of the study drug.

ADVERSE EVENTS AND LABORATORY MEASURES

The site investigator reported adverse events and serious adverse events at each study visit. Such events were categorized with the use of the *Medical Dictionary for Regulatory*

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Activities.20 Independent expert committees whose members were unaware of the study-group assignment adjudicated laboratory criteria and targeted adverse events, including ocular events, osteonecrosis of the jaw, avascular necrosis at other skeletal sites, cardiac arrhythmias reported as serious adverse events, deteriorating renal function, hypocalcemia, delayed fracture healing, and primary cause of death.

STATISTICAL ANALYSIS

The trial was event driven and required 211 clinical fractures to have a power of 90%. A two-sided level of significance of 0.05, with two interim analyses performed with the use of an O'Brien–Fleming spending function,21 was needed to detect a 35% reduction in the rate of clinical fracture in the zoledronic acid group, as compared with the placebo group. The trial planned two interim analyses with prespecified stopping rules using O'Brien–Fleming superiority and futility boundaries. After the second interim analysis, the data and safety monitoring board requested a third interim analysis and concluded that the trial had met its efficacy objectives when 185 patients had a confirmed clinical fracture. Between-group differences for the time to the first clinical fracture were determined by the log-rank test in the intention-to-treat population (all randomized patients), with hazard ratios reported on the basis of a proportional-hazards model that included treatment as a variable and were confirmed by the per protocol analysis (which excluded patients with protocol deviations). 22 Data were censored for patients without an event on the date when they withdrew consent or died or the date of the last follow-up visit, whichever came first.

Because the protocol called for three annual infusions and because the number of patients who were followed for more than 3 years was small, survival curves were truncated at 36 months. Changes in bone mineral density at the total hip and femoral neck were compared in the two study groups with the use of an analysis-of-variance model adjusted for treatment and region. Four prespecified secondary analyses were performed with the use of the same proportional-hazards methods to assess the time until the first nonvertebral fracture, hip fracture, clinical vertebral fracture, or death. Rates of adverse events were compared with the use of Fisher's exact test.

Summary statistics for baseline clinical and demographic variables are presented according to the study group. Differences in baseline characteristics between the study groups were evaluated with the use of the chi-square test for discrete variables and t-tests for continuous variables.

RESULTS

BASELINE CHARACTERISTICS AND FOLLOW-UP

Of a total of 2127 patients, 1065 patients were randomly assigned to receive zoledronic acid, and 1062 patients were assigned to receive placebo; 71.3% of the patients completed the trial (Fig. 1). The median follow-up time was 1.9 years. A total of 3.0% of patients were lost to follow-up, and rate of loss was similar in the two groups. All patients received their intravenous study medication (zoledronic acid or placebo) unless it was withheld because of a decrease in the calculated creatinine clearance to a level below 30 ml per minute.

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Baseline demographic and clinical characteristics were similar in the two groups (Table 1), with 41.8% of patients having a T score of less than −2.5 SD at the femoral neck.23 The most common coexisting medical conditions in this population at baseline were hypertension, coronary artery disease, osteoarthritis, previous stroke, depression, and diabetes mellitus. Active tachyarrhythmia was present in 5.8% of patients in the zoledronic acid group and in 7.5% of patients in the placebo group.

FRACTURES

A total of 424 new clinical fractures occurred in 231 patients during the follow-up period. Zoledronic acid was associated with a rate of new clinical fractures of 8.6%, as compared with 13.9% in the placebo group, an absolute risk reduction of 5.3% and a relative reduction of 35% (Table 2 and Fig. 2). Among patients who had a fracture, the mean time to clinical fracture was 39.8 months in the zoledronic acid group and 36.4 months in the placebo group. The risk reduction was very similar in the intention-to-treat and per-protocol populations. The rates of a new clinical vertebral fracture were 1.7% in the zoledronic-acid group and 3.8% in the placebo group (P = 0.02); the rates of a new clinical nonvertebral fracture were 7.6% and 10.7%, respectively (P = 0.03). New hip fractures occurred in 27% of patients in the zoledronic acid group and in 3.5% of those in the placebo group, a nonsignificant reduction in relative risk of 30%. In a post hoc analysis, significant divergence in the fracture-free survival curves between the two groups for all clinical fractures was seen as early as 12 months (P=0.02 by the log-rank test) (Fig. 2).

BONE MINERAL DENSITY

Bone mineral density at the total hip increased in the zoledronic acid group by 2.6% at 12 months, 4.7% at 24 months, and 5.5% at 36 months and declined in the placebo group by 1.0%, 0.7%, and 0.9%, respectively. Bone mineral density at the femoral neck increased in the zoledronic acid group by 0.8% at 12 months, 2.2% at 24 months, and 3.6% at 36 months and declined in the placebo group by 1.0%, 0.7%, and 0.9%, respectively. The differences in bone mineral density at the total hip and femoral neck between the zoledronic acid group and the placebo group were significant (P<0.001 for all comparisons). On the basis of prespecified bone safety measures, 26 patients in the zoledronic acid group had a clinically important loss of bone mineral density, of whom 4 patients were withdrawn from the trial (15.4%), and 126 patients in the placebo group had a clinically important loss of bone mineral density, of whom 21 patients were withdrawn from the trial (16.7%).

DEATH

In the safety analysis, a total of 242 of 2111 patients (11.5%) died during the study, of whom 101 of 1054 (9.6%) were in the zoledronic acid group and 141 of 1057 (13.3%) were in the placebo group (hazard ratio for the zoledronic acid group, 0.72; 95% CI, 0.56 to 0.93; P = 0.01). One patient in each study group died without having received the assigned study drug. The adjudication committee determined that 11 deaths (1.0%) were from cardiovascular disease and 7 deaths (0.7%) were from cerebrovascular disease in the zoledronic acid group, as compared with 18 deaths (1.7%) and 7 deaths (0.7%), respectively, in the placebo group.

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ADVERSE EVENTS

Adverse events were reported in 867 patients (82.3%) in the zoledronic acid group and in 852 patients (80.6%) in the placebo group (Table 3). Serious adverse events occurred with similar frequency in the two groups (38.3% in the zoledronic acid group and 41.2% in the placebo group). More patients in the zoledronic acid group than in the placebo group reported pyrexia (8.7% vs. 3.1%), myalgia (4.9% vs. 2.7%), bone pain (3.2% vs. 1.0%), or musculoskeletal pain (3.1% vs. 1.2%). More patients in the placebo group (11.4%) reported having fallen than in the zoledronic-acid group (9.7%).

The incidence of cardiovascular events was similar in the two groups. A total of 24 patients in the zoledronic acid group (2.3%) and 39 patients in the placebo group (3.7%) had a serious adverse event of arrhythmia; these events were confirmed by adjudication in 19 patients in the zoledronic acid group (1.8%) and 28 patients in the placebo group (2.6%). Atrial fibrillation occurred in 12 patients in the zoledronic acid group (1.1%) and in 14 patients in the placebo group (1.3%) (Table 3). The incidence of renal adverse events was similar in the two study groups, including events among patients with a baseline creatinine clearance of 30 to 60 ml per minute.

Although no specific case-finding effort was made, no cases of osteonecrosis of the jaw were reported or confirmed by the central adjudication committee after a search of the database. The incidence of delayed union of the qualifying hip fracture was 34 (3.2%) in the zoledronic acid group and 29 (2.7%) in the placebo group (risk ratio for the zoledronic acid group, 1.17; 95% CI, 0.72 to 1.90; P = 0.61).

Three patients in the zoledronic acid group (0.3%) and no patient in the placebo group had adjudicated hypocalcemia. Four patients in the zoledronic acid group (0.4%) and one patient in the placebo group (0.1%) had ocular events that were considered possibly or probably related to a study drug according to an expert review.

DISCUSSION

Patients with hip fracture represent an important population to target for the prevention of secondary fractures. Data have been needed to show that available osteoporosis therapies are effective in such patients. Because the patients in our study were older and had more coexisting conditions and a higher risk of falls than patients in many clinical trials of treatment for osteoporosis, our findings contain helpful information for clinicians and for patients who have had a hip fracture.

Poor adherence to oral bisphosphonate therapy has been shown to compromise the efficacy of this treatment for fracture reduction and to increase medical costs24,25; such findings have been particularly notable in frail older adults.26 The once-yearly intravenous regimen that we used offers another option for affected patients.

Vitamin D deficiency is frequently observed in older patients and is associated with an increased risk of hypocalemia when bisphosphonates are administered before a normal vitamin D level has been achieved.27 Within 2 months after the initiation of our study (after

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one patient had been randomly assigned), a loading dose of vitamin D was administered to any patient with a vitamin D deficiency 2 weeks before the administration of a study drug. Since very high rates of vitamin D deficiency were observed in the first 385 patients who underwent randomization, a subsequent protocol amendment provided for a loading dose of vitamin D in all patients, regardless of the level of serum 25-hydroxyvitamin D. This approach might explain the low rate of hypocalcemia (in three patients) seen in our study.

Although some observers have questioned the appropriateness of a placebo-controlled trial involving patients at high risk for fracture, patients who were enrolled in our trial could not tolerate or would not take an oral bisphosphonate. In addition, the trial allowed for open-label concomitant use of several approved osteoporosis therapies. Furthermore, few data are available to guide treatment in frail older patients with osteoporosis; a previous risedronate trial was not successful in reducing hip fracture in patients over the age of 80 years.28 Finally, many studies show that patients with osteoporotic fractures are frequently not given therapy to prevent further fractures.29,30 We therefore believed that clinical equipoise existed and that a positive result would probably improve the care provided to patients after hip fracture.

Increased rates of death after hip fracture are well described. Indeed, mortality in our study was about three times as high as that reported in the recently completed study of zoledronic acid in postmenopausal women.15 We observed a reduction of 28% in the risk of death in the zoledronic acid group. The reduction in the risk of death observed in the zoledronic acid group may have been related in part to a reduction in new fractures after the initial hip fracture. However, further investigation is needed to understand more fully the reason for the reduction in the risk of death, which is probably multifactorial.

The safety profile for zoledronic acid indicated few areas of concern. There were transient post-infusion symptoms, as previously reported in patients receiving intravenous bisphosphonates,15 which may have been attenuated by the routine administration of acetaminophen. We did not find an increased incidence of renal adverse events, despite high baseline rates of mild-to-moderate chronic kidney disease. Although an increased risk of atrial fibrillation was unexpectedly observed in one zoledronic acid study involving postmenopausal women,15 we found no increased incidence of atrial fibrillation. One concern related to bisphosphonate treatment of patients with peripheral fractures has been a possible adverse effect on fracture healing. We observed no significant difference in delayed union of fractured bone between the two study groups.

Our study had several limitations. The study patients were, on average, slightly younger and healthier than are patients with hip fracture in the general population, as suggested by data regarding 1-year mortality. However, patients in our study ranged widely in age (up to 98 years), and some had cognitive impairment. Because we did not evaluate spinal radiographs unless symptoms of a possible vertebral fracture developed, we probably underestimated the prevalence of new vertebral fractures.

In conclusion, our findings indicate that treatment with zoledronic acid after a hip fracture is associated with reduced rates of new clinical factures and death from all causes.

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APPENDIX

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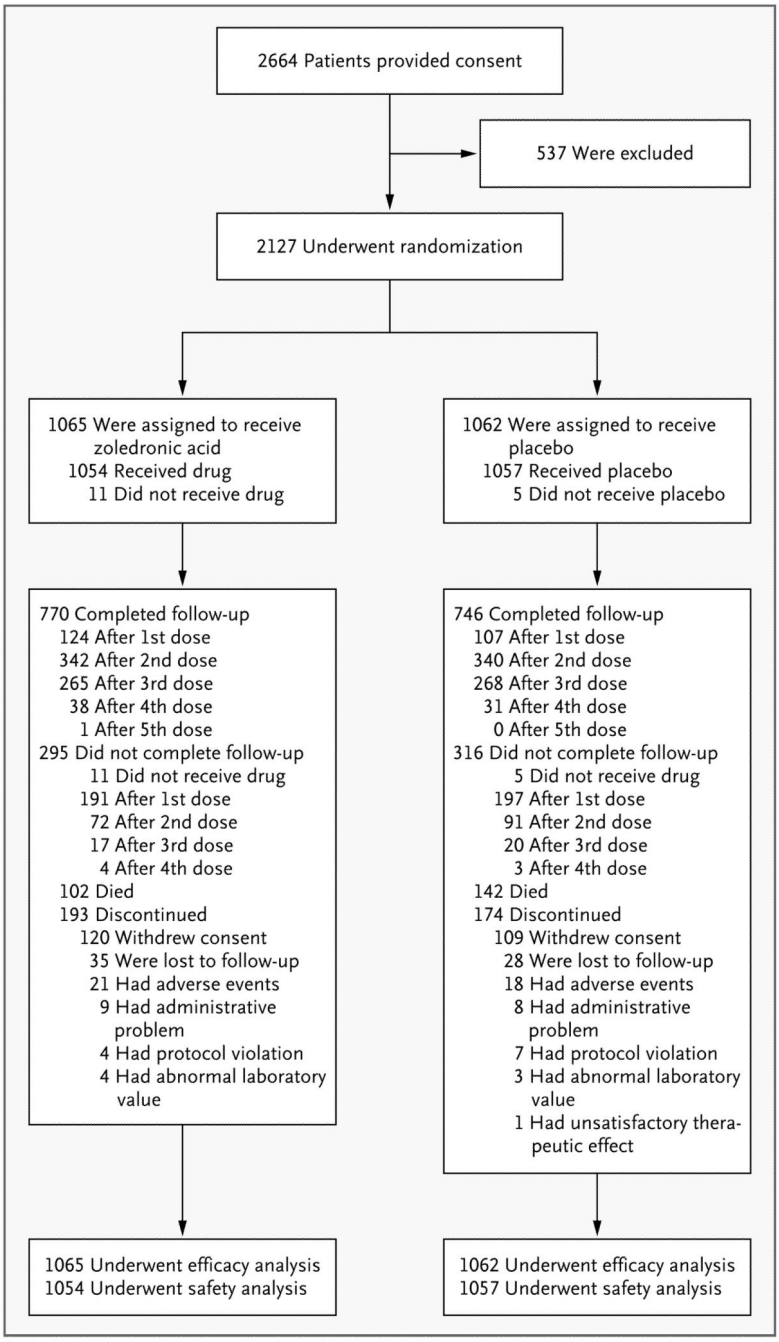

Figure 1.
Enrollment and Outcomes.

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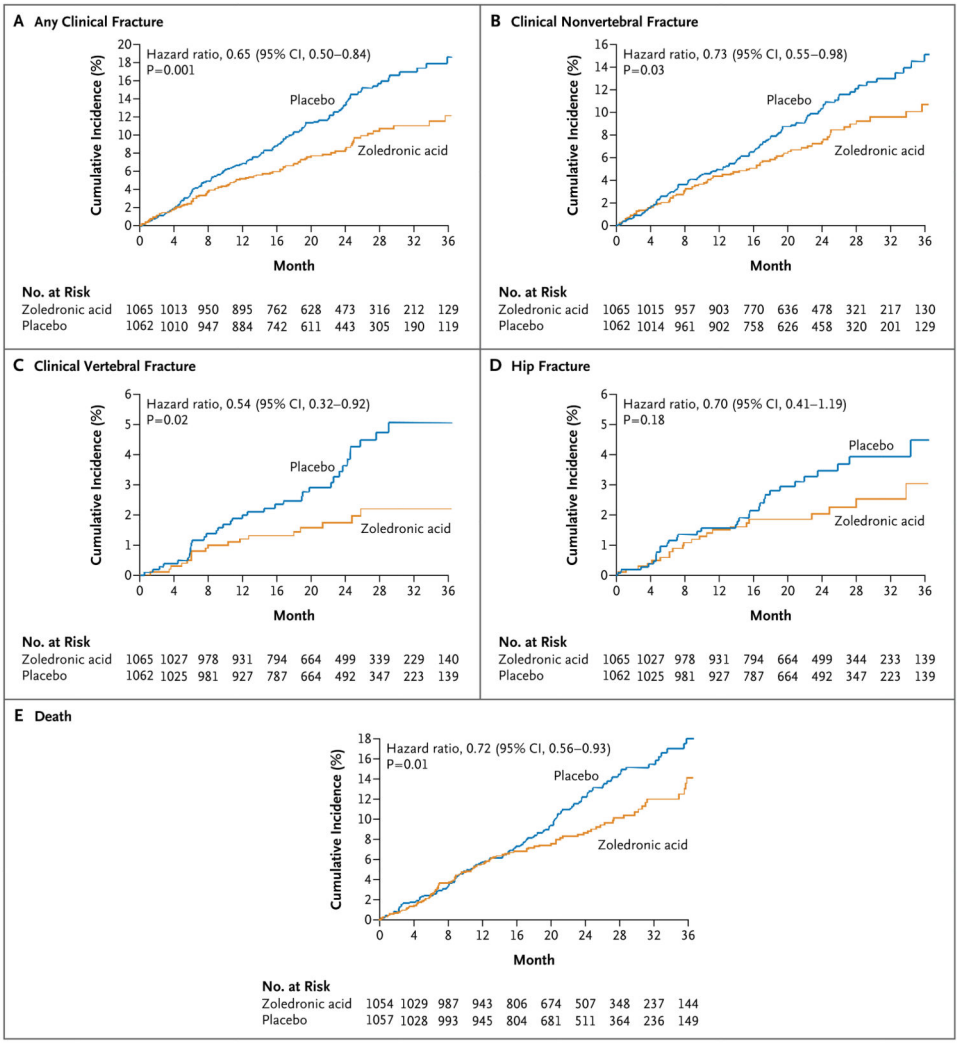

Figure 2.
Time to Primary or Secondary End Point.

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Table 1

Baseline Characteristics of the Patients.*

Variable	Placebo (N = 1062)	Zoledronic Acid (N = 1065)	P Value†
Race or ethnic group — no. (%)‡			0.67
White	965 (90.9)	973 (91.4)	
Hispanic	70 (6.6)	70 (6.6)	
Black	12 (1.1)	6 (0.6)	
Other	15 (1.4)	16 (1.5)	
Sex — no. (%)			0.52
Female	802 (75.5)	817 (76.7)	
Male	260 (24.5)	248 (23.3)	
Age			
Mean — yr	74.6±9.86	74.4±9.48	0.68
Range — no. (%)			
<65 yr	192 (18.1)	172 (16.2)	
65–74 yr	269 (25.3)	307 (28.8)	
75–84 yr	449 (42.3)	446 (41.9)	
≥85 yr	152 (14.3)	140 (13.1)	
Body-mass index	24.8±4.5	24.7±4.4	0.55
Region — no. (%)			0.92
Western Europe	353 (33.2)	359 (33.7)	
North America	318 (29.9)	305 (28.6)	
Eastern Europe	260 (24.5)	269 (25.3)	
Latin America	131 (12.3)	132 (12.4)	
Bone mineral density — g/cm^2			
Femoral neck	0.65±0.122	0.65±0.127	0.25
Total hip	0.70±0.152	0.70±0.153	0.84
T score at femoral neck — no. (%)			0.91
−2.5 or less	437 (41.1)	451 (42.3)	
More than −2.5 to −1.5	375 (35.3)	360 (33.8)	
More than −1.5	121 (11.4)	123 (11.5)	
Missing data	129 (12.1)	131 (12.3)	
Patients who received concomitant osteoporosis therapy — no. (%)	125 (11.8)	99 (9.3)	0.07

*Plus–minus values are means ±SD. The body-mass index is the weight in kilograms divided by the square of the height in meters. Percentages may not total 100 because of rounding.

†Continuous variables were compared with the use of a two-sample t-test. Categorical variables were compared with the use of a chi-square test.

‡Race or ethnic group was reported by the patients.

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Table 2

Rates of Fracture and Death in the Study Groups.*

Variable	Placebo (N = 1062)	Zoledronic Acid (N = 1065)	Hazard Ratio (95% CI)	P Value
	no. (cumulative rate or %)			
Fracture				
Any	139 (13.9)	92 (8.6)	0.65 (0.50–0.84)	0.001
Nonvertebral	107 (10.7)	79 (7.6)	0.73 (0.55–0.98)	0.03
Hip	33 (3.5)	23 (2.0)	0.70 (0.41–1.19)	0.18
Vertebral	39 (3.8)	21 (1.7)	0.54 (0.32–0.92)	0.02
Death	141 (13.3)	101 (9.6)	0.72 (0.56–0.93)	0.01

*Rates of clinical fracture were calculated by Kaplan–Meier methods at 24 months and therefore are not simple percentages. Because of variable follow-up, the number and percentage of patients who died are provided on the basis of 1057 patients in the placebo group and 1054 patients in the zoledronic acid group in the safety population.

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Table 3

Adverse Events in the Safety Population.*

Event	Placebo (N = 1057)	Zoledronic Acid (N = 1054)	P Value†
General — no. (%)			
Any adverse event	852 (80.6)	867 (82.3)	0.34
Any serious adverse event	436 (41.2)	404 (38.3)	0.18
Death‡	141 (13.3)	101 (9.6)	0.01
Discontinuation of follow-up owing to adverse event	18 (1.7)	21 (2.0)	0.63
Renal event — no./total no. (%)			
Increase in serum creatinine >0.5 mg/dl	50/900 (5.6)	55/886 (6.2)	0.62
Calculated creatinine clearance <30 ml/min	65/891 (7.3)	72/882 (8.2)	0.53
Five typical symptoms ≤3 days after infusion — no. (%)§			
Myalgia	9 (0.9)	33 (3.1)	<0.001
Influenza-like symptoms	3 (0.3)	6 (0.6)	0.34
Headache	9 (0.9)	16 (1.5)	0.17
Arthralgia	23 (2.2)	33 (3.1)	0.18
Pyrexia¶			
Any event	9 (0.9)	73 (6.9)	<0.001
After first infusion	7 (0.7)	72 (6.8)	<0.001
After second infusion	2 (0.3)	3 (0.4)	0.68
After third infusion	0	3 (0.9)	0.25
Cardiovascular or cerebrovascular event — no. (%)			
Atrial fibrillation			
Any event	27 (2.6)	29 (2.8)	0.79
Serious adverse event	14 (1.3)	12 (1.1)	0.84
Stroke			
Serious adverse event	38 (3.6)	46 (4.4)	0.37
Fatal event	6 (0.6)	9 (0.9)	0.45
Myocardial infarction	17 (1.6)	13 (1.2)	0.58
Death from cardiovascular causes	52 (4.9)	36 (3.4)	0.10

*All adverse events were reported before adjudication.

†P values for all comparisons except death were calculated with the use of Fisher's exact test. P values for death were computed with the use of the log-rank test.

‡Two patients (one in the zoledronic acid group and one in the placebo group) died without having received the study drug and were excluded from the safety population.

§The five symptoms listed were the most frequently cited in Black et al.15 and other studies.

¶Patients could report more than one event. A total of 753 in the placebo group and 739 in the zoledronic acid group underwent a second infusion, and 322 in the placebo group and 325 in the zoledronic acid group underwent a third infusion.