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Clinical Research Article

Antifracture Efficacy of 5- or 10-Yearly Zoledronate in Women Aged 50 to 60 Years: Secondary Analyses of a Randomized Trial

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Abstract

Context: We recently reported that zoledronate (zol) given once at baseline or twice (every 5 years) reduced fracture risk over 10 years.

Objective: We assessed whether the effects of zol differ over time or across important baseline variables, and how they relate to changes in bone mineral density (BMD) over time.

Methods: A 10-year, prospective, randomized, double-blind, placebo-controlled trial, was conducted at a clinical research center from 2012 to 2023. Participants included 1054 postmenopausal women, aged 50 to 60 years, with BMD T-score at the lumbar spine, femoral neck, or total hip between 0 and −2.5. Intervention included either 5-yearly 5-mg zol (zol-zol), 5-mg zol infusion at baseline and placebo at 5 years (zol-placebo), or 5-yearly placebo (placebo-placebo). Main outcome measures included morphometric vertebral fractures, major osteoporotic, and any fractures.

Results: Morphometric vertebral fractures were not reduced in the years 0 to 5 following zol but were reduced in years 5 to 10 by 58% (95% CI, 21%-77%) (zol-zol) and 57% (21%-77%) (zol-placebo). For any fracture and major osteoporotic fracture, similar temporal patterns were observed. There were no interactions between treatment effect and baseline variables (including age, body mass index, BMD, falls or fracture history, and estimated fracture risk) or between treatment effect and changes in BMD with zol.

Conclusion: Fracture reductions with single-dose or 5-yearly zol appear greater during years 5 to 10 than years 0 to 5. The risk reductions are broadly consistent across this cohort and independent of baseline or change in BMD. This suggests that routine BMD monitoring may not be necessary for low-risk women considering the option of less frequent zol for long-term fracture risk reduction.

Key Words: zoledronate, fracture, postmenopausal women, bone mineral density

Abbreviations: BMD, bone mineral density; HR, hazard ratio; MOF, major osteoporotic fracture; RR, relative risk.

Currently, most fracture-prevention strategies target people at high risk of fracture: older individuals, and those with low bone mineral density (BMD) or previous fractures. We recently reported that zoledronate (zol) given either as a single infusion at baseline or every 5 years reduced fracture risk and prevented BMD loss over 10 years in a randomized, placebo-controlled trial of 1054 women aged 50 to 60 years at baseline (1). Less frequent zol could therefore be offered to people at low risk of fracture and then continued lifelong. This might be attractive for people concerned about their long-term fracture risk who want to prevent fractures and BMD loss.

Given the implications of offering infrequent zol to a much broader range of the population, it is important to determine whether the benefits of zol were consistent throughout the 10 years of the study, and whether there were particular subgroups who did not appear to benefit from treatment. Therefore, we have assessed the effects of zol on fractures in years 0 to 5 and 5 to 10 of the study, whether the effects differ across important baseline variables such as age, BMD, and fracture risk, and how they relate to changes in BMD over time.

Materials and Methods

The study protocol and design have previously been published (1). Briefly, this was a 10-year, prospective, randomized, double-blind, placebo-controlled trial in women aged 50 to 60 years. A total of 1054 women were randomly assigned (1:1:1) to 1 of 3 groups to receive either zol 5 mg at baseline and 5 years (zol-zol), or zol 5 mg at baseline and placebo at 5 years (zol-placebo), or placebo at baseline and 5 years (placebo-placebo). No other interventions (such as vitamin D or calcium supplements) were provided as part of the study. The trial was registered with the Australian

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Table 1. Characteristics of study participants at baseline

	Zoledronate/Zoledronate (n = 352)	Zoledronate/Placebo (n = 351)	Placebo/Placebo (n = 351)
Age, y	56 (3.0)	56 (3.0)	56 (2.9)
European ethnicity	295 (84%)	305 (87%)	295 (84%)
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	15 (4.3%)	16 (4.6%)	20 (5.7%)
Dietary calcium intake, mg/d	740 (350)	762 (391)	736 (366)
Nonvertebral fracture after age 45 y	62 (18%)	39 (11%)	57 (16%)
Estimated 10-y fracture risk, %	9.2 (3.8)	8.6 (3.1)	9.0 (3.5)
Bone density			
Lumbar spine T-score	−0.45 (1.16)	−0.36 (1.14)	−0.44 (1.11)
Total hip T-score	−0.51 (0.74)	−0.46 (0.77)	−0.55 (0.74)

Data are mean (SD), or n (%). Fracture risk was estimated for fragility fracture using the Garvan fracture risk calculator: https://fractureriskcalculator.com.au/calculator/.

New Zealand Clinical Trials Registry with number ACTRN12612000270819.

Postmenopausal women aged 50 to 60 years randomly selected from the electoral roll were invited to participate and were eligible if their BMD T-score at the lumbar spine, femoral neck, or total hip was less than 0 and greater than −2.5. Other exclusion criteria were 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, or zol ever, or use of oral glucocorticoid drugs equivalent to an average dose of prednisone greater than or equal to 2.5 mg/day during the preceding 6 months. The primary end point was the proportion of women with new vertebral fracture, as determined using spinal radiographs. Secondary end points were incidence of fragility, any, and major osteoporotic fractures (MOFs). For the purpose of the present analyses, we have used vertebral fracture, any, and MOFs as end points. MOFs were defined as fractures of the wrist, spine, shoulder, hip, or pelvis. Fractures were not excluded based on trauma severity but pathological fractures were excluded from all end points (2).

Lateral spine radiographs were obtained at baseline, 5, and 10 years. Digital images were assessed semi-quantitatively by a single radiologist (S.B.) following the method of Genant (3). An incident morphometric vertebral fracture was defined as a change in grade of at least 0.5 and a change in a vertebral height of at least 20% from the previous radiograph, and a final grade of at least 1. Clinical fractures were reported by participants in a 6-monthly questionnaire, and then confirmed from radiology reports. BMD of the lumbar spine (L1-L4) and dual total hip was measured at baseline, 5, and 10 years in all participants using a Prodigy dual-energy x-ray absorptiometer (GE-Lunar).

Statistical Analysis

We included all participants who had a baseline spinal x-ray and at least one follow-up x-ray in the analyses for vertebral fractures, and all participants in the analyses for any fractures in an intention-to-treat approach.

First, we assessed the time course of fractures during the study, separating out fractures between 0 and 5 years and those between 5 and 10 years. Because the two zol groups received identical treatment for the first 5 years, we pooled the zol-zol and zol-placebo group for the 0 to 5 years analyses but treated them separately for the 5 to 10 years analyses.

The relative risk (RR) of a new vertebral fracture was assessed at 0 to 5 years in women in the pooled zol groups compared to the placebo group using a chi-square test. For the 5 to 10 years' analysis, the zol groups were kept separate. For the analysis of any fracture and MOFs, we followed the same approach. To aid visual presentation, we have presented time-to-first-fracture analyses modeled using a Cox proportional hazards approach, with the 2 zol groups pooled for 0 to 5 years, and this graph combined with the 5 to 10 years' section of the 0 to 10 years' analysis for the 3 treatment groups analyzed separately.

Next, we compared the relationship between baseline variables and fracture outcomes over 10 years. We used a Cox proportional hazards model to compare the incidence of any fracture in each zol group with placebo restricted to each tertile of characteristic at the baseline visit for continuous variables or each level for categorical variables. We plotted the individual hazard ratios (HRs) on a forest plot for each variable. To assess the interaction between the treatment group and the baseline variable, we repeated the analyses for the entire cohort including treatment, tertile/level of baseline variable, and the interaction term in the model, and report the *P*-value for the tertile/level × treatment interaction.

For the continuous variables of age, estimated fracture risk, and BMD, we assessed for an interaction between treatment effect and the continuous variable. For each variable, we plotted separately for each treatment group the predicted probability of any fracture from a logistic regression model including treatment and the baseline variable across the range of the variable, and the *P* value is for the interaction between the variable and treatment.

Finally, we assessed whether change in BMD was associated with fracture risk reduction. We plotted histograms of the change in total hip BMD at 5 and 10 years for each treatment group. We then treated change in BMD as a time-varying covariate and incorporated the tertile of changes in BMD from 0 to 5 years and 5 to 10 years separately into a Cox proportional hazards model that included the baseline total hip BMD and adjusted for individual clustering of changes in BMD. Results are presented for the HR relative to the lowest tertile of BMD change, and the *P* value is for the tertile of change in BMD.

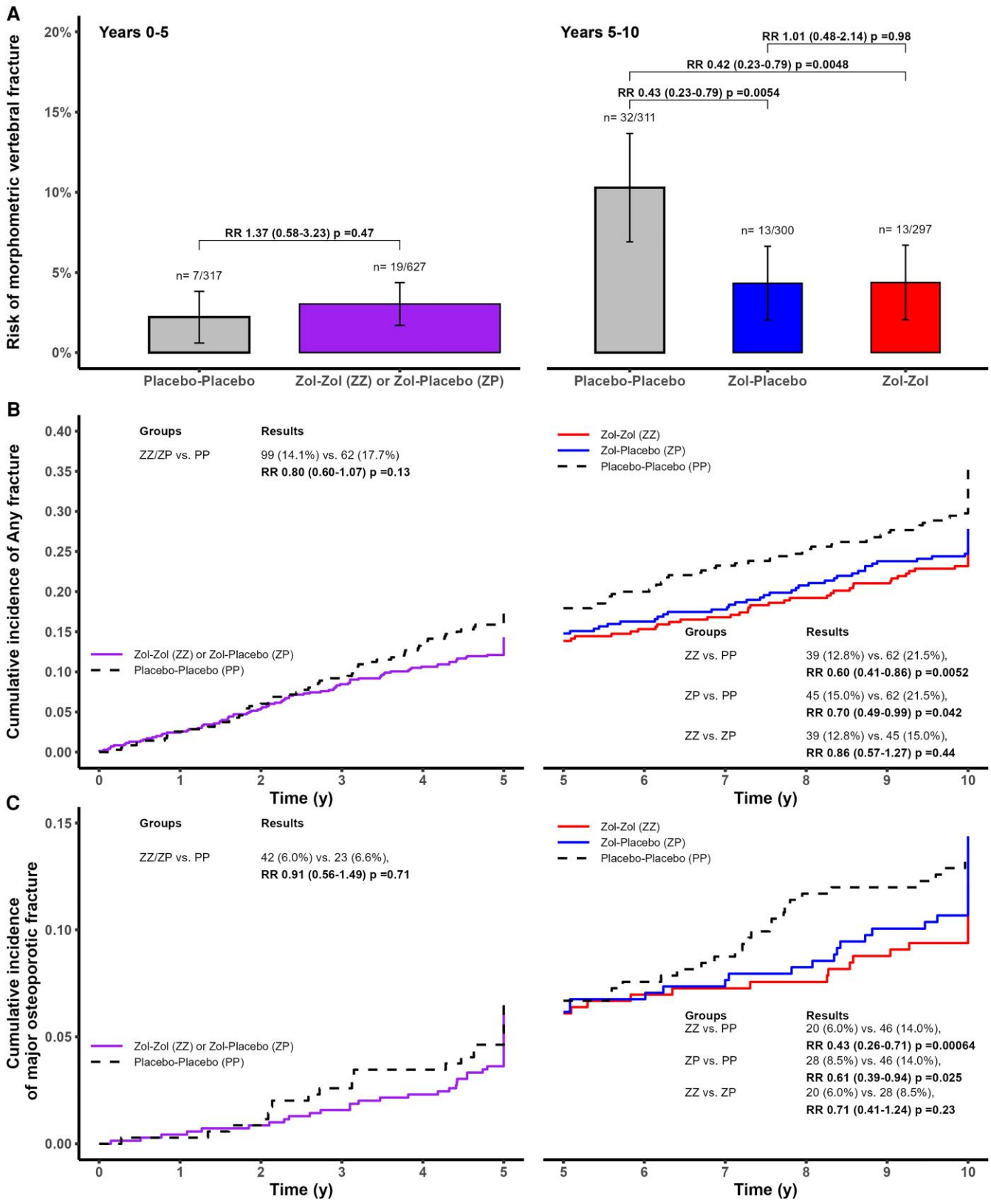

Figure 1. The time course of fractures between 0 to 5 years and 5 to 10 years. A shows the number, risk, and relative risk of morphometric vertebral fractures. B and C show the number, relative risk, and cumulative incidence of any or major osteoporotic fractures. In all the left panels, the two zoledronate groups were pooled because the treatment was identical for that time period. BMD, bone mineral density; BMI, body mass index; PP, placebo-placebo group; RR, relative risk; Zol-Placebo/ZP, zoledronate-placebo group; Zol-Zol/ZZ, zoledronate-zoledronate group.

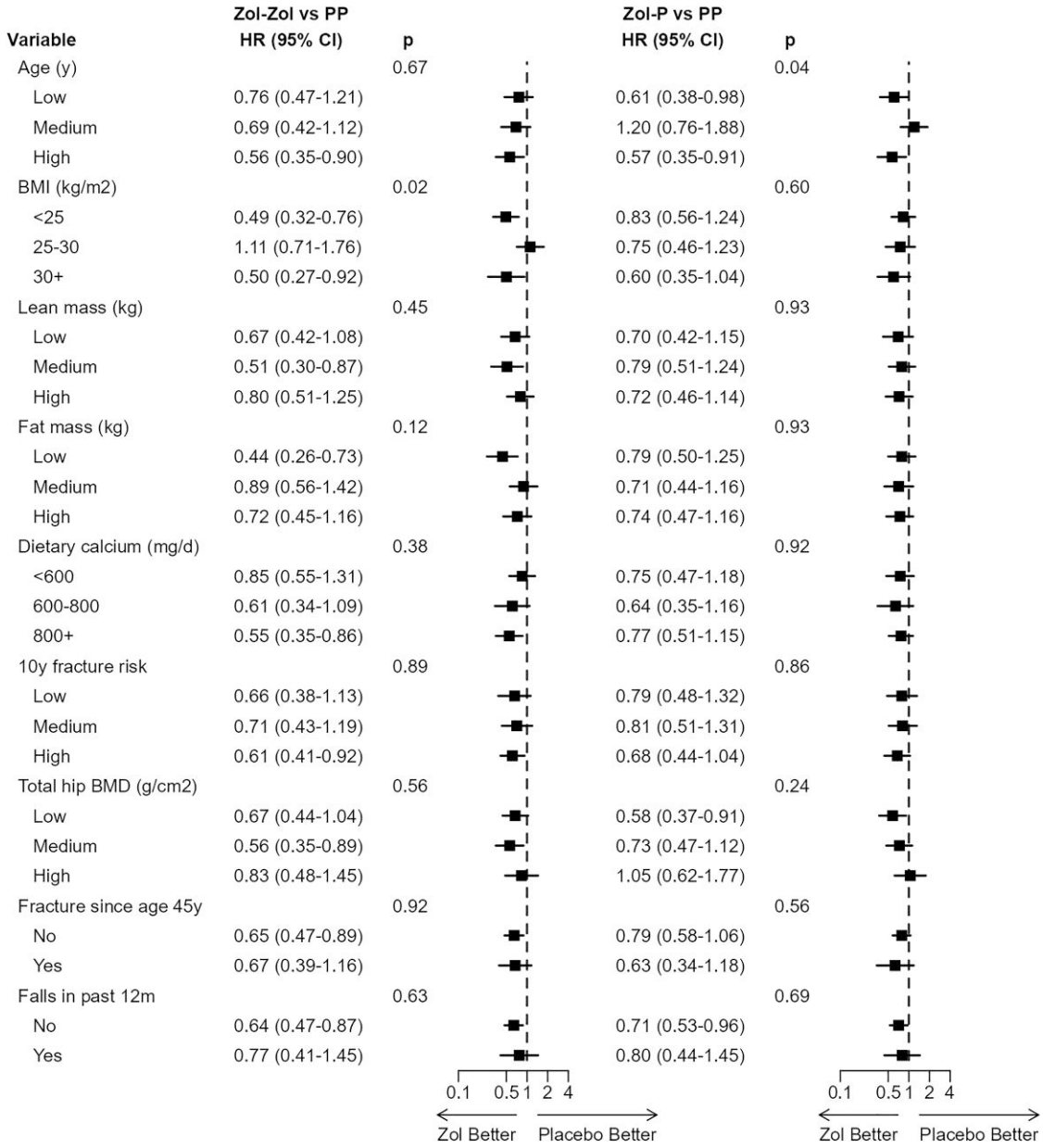

Figure 2. The effects of zoledronate on risk of any fracture in subgroups defined by tertile of baseline characteristics. The hazard ratio (HR) comes from a Cox proportional hazards model restricted to the subgroup of interest, while the *P* value comes from a model assessing the interaction between the baseline characteristics by tertile and the treatment group. Lean and fat mass were assessed on the dual-energy x-ray absorptiometry scan.

Abbreviations: PP, placebo-placebo group; Zol-Placebo, zoledronate-placebo group; Zol-Zol, zoledronate-zoledronate group.

Analyses were conducted using R software Packages (R Core Team [2024], R Foundation for Statistical Computing). All tests were 2-tailed, and *P* values less than .05 were considered statistically significant. Because all the tests were secondary tests and exploratory in nature, we did not adjust *P* values for multiple statistical testing.

Results

Full details of the baseline characteristics and fracture outcomes have been published previously (1). Selected baseline characteristics of the participants are shown in Table 1. The mean age was 56 years, and the majority of women (85%) were of European ethnicity.

Fig. 1 shows the time course of fractures during the study. For morphometric vertebral fractures for 0 to 5 years, there were few fractures, and risk was not reduced in the zol groups. However, from 5 to 10 years, the risk of a fracture was reduced by 58% in the zol-zol and 57% in the zol-placebo compared with the placebo-placebo group, leading to an overall reduction from 0 to 10 years of 44% and 41%, respectively (1). For any fracture and MOF, the patterns were similar. The zol groups had small, statistically nonsignificant reductions in risk for years 0 to 5 (20% any fracture, 9% MOF) that then increased in magnitude and were statistically significant during years 5 to 10: any fracture 40% and 30%; MOF 57% and 39%, for zol-zol and zol-placebo, respectively. Overall, the respective risk reductions between 0 and 10 years were 30% and 23% for any fracture, and 40% and 29% for MOF, for zol-zol and zol-placebo, respectively (1).

Next, we assessed whether differences in baseline characteristics altered the observed risk reductions for any fracture by treatment group. Fig. 2 shows the HRs in the 2 zol groups

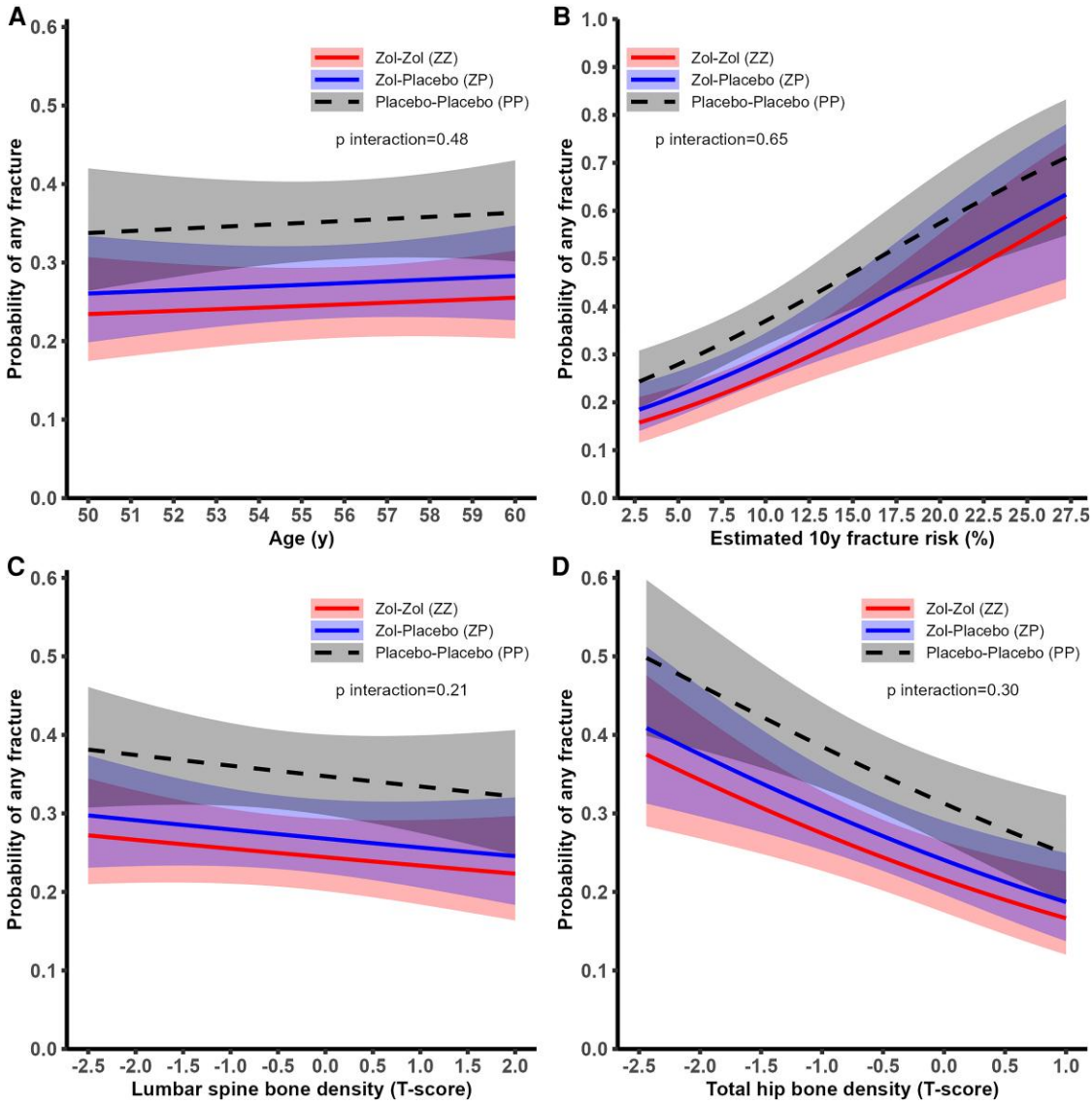

Figure 3. The probability of A, any fracture vs age; B, estimated 10 years' fracture risk (%); C, lumbar spine; and D, total hip bone density T-score. The solid lines are the estimated probability, and the shaded areas the 95% CI.

Abbreviations: PP, placebo-placebo group; Zol-placebo, zoledronate-placebo group; Zol-Zol, zoledronate-zoledronate group.

either by tertile of the baseline variable or by relevant clinical categories. There were no consistent interactions between the tertile or level of the baseline variables and the treatment. One result was statistically significant, which is consistent with the number of results with *P* less than .05 expected by chance. There were also no statistically significant interactions between treatment and tertiles of baseline weight, height, physical activity, or lumbar spine BMD, or smoking status (data not shown).

For the important continuous variables of age, estimated 10 years' fracture risk, and BMD T-score at the hip or spine, we plotted the predicted probability of any fracture against the range of the variable for each of the treatment groups. Fig. 3 shows that for all 4 variables, the predicted probability of fracture varied as expected across the range of the variable. The curves for the 3 treatment groups were approximately parallel, indicating that there was no interaction between the variable and treatment, so that the risk reductions remained similar for each treatment across the range of the variable.

Finally, we assessed the relationship between change in BMD during the study with the antifracture efficacy of treatment. Fig. 4 shows the distribution of changes in BMD at the total hip at 5 and 10 years. At each time point, the zol-zol group had the highest proportion of participants whose BMD had increased. At the total hip site, 56% of the zol-zol group had increased bone density from baseline at 10 years compared with 32% in the zol-placebo and 5% in the placebo-placebo groups. The comparable proportion of participants with an increase at the lumbar spine were 65% (zol-zol), 52% (zol-placebo), and 17% (placebo-placebo, data not shown).

Fig. 5 shows the incidence of any fracture by treatment group stratified by the tertile of change in total hip BMD over 10 years, which was treated as a time-varying covariate with changes from 0 to 5 years and 5 to 10 years separately incorporated in the model. There were no consistent differences in fracture risk between people with the highest tertile of BMD change and those in the middle or lowest tertile of BMD

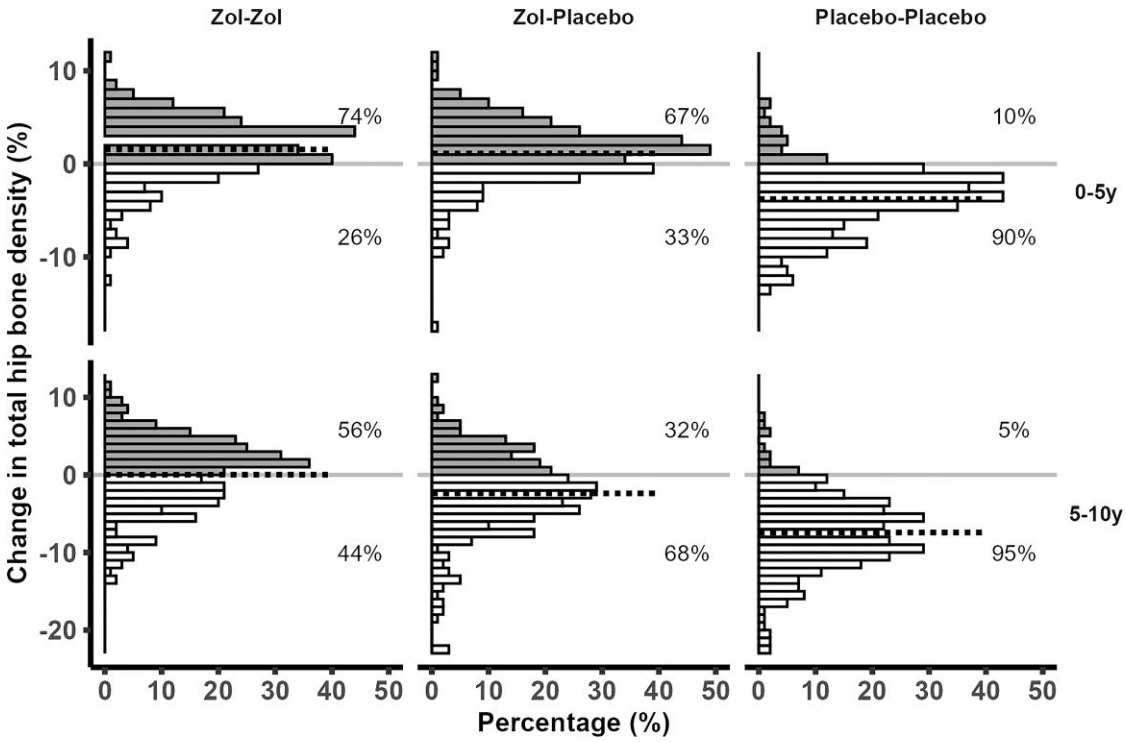

Figure 4. The distribution of change in bone mineral density (BMD) at the total hip at 5 and 10 years by treatment group. The gray-shaded bars are the percentages with increases in BMD from baseline and the white bars are percentages with decreases from baseline. The dotted line represents the mean change in BMD from baseline for the treatment group and the percentages indicate the proportion whose bone density had increased or decreased at each time point.

Abbreviations: PP, placebo-placebo group; Zol-placebo, zoledronate-placebo group; Zol-Zol, zoledronate-zoledronate group.

change within each treatment group. We repeated the analyses using change in lumbar spine BMD and increases or decreases in BMD at the 10-year visit for both sites, and the results were similar with no consistent between-subgroups differences for the treatment groups (data not shown).

Discussion

The results of these more detailed analyses about the effects of very infrequent zol on fracture incidence show that the reduction in risk tended to be greater during years 5 to 10 than in years 0 to 5, particularly for morphometric vertebral fractures. In fact, at 5 years, there were few morphometric vertebral fractures in all 3 treatment groups, and the risks were similar (2%-3%) in the placebo and pooled zol groups. By contrast, during years 5 to 10, there were nearly 60% reductions in risk in the 2 zol groups. For any fracture and MOF, the pattern was similar with larger risk reductions in years 5 to 10 compared to years 0 to 5. The reductions in fracture risk with zol were consistent across all baseline variables, including those variables most strongly associated with fracture risk such as age and BMD. A total of 56% of women in the zol-zol group had increased total hip BMD at 10 years, compared with 32% in the zol-placebo group and 5% in the placebo-placebo group. However, the effects of zoledronate on fracture incidence did not differ by tertile of change in BMD over the 10 years within each treatment group, nor by whether BMD increased or decreased from baseline.

Previous large randomized, controlled trials of bisphosphonates with fracture as the primary end point have similar patterns in risk reductions during the trial to what we observed, although none have been powered to draw definitive conclusions. Trials of alendronate (4, 5) and risedronate (6) show fracture incidence curves running almost parallel for the first 6 to 18 months between the placebo and treatment groups and thereafter separating, implying an increasing risk reduction throughout the trial. Likewise, in trials of zol, the reductions in risk for vertebral fracture (7) and nonvertebral and hip fracture (2, 7, 8) tended to follow a similar pattern. However, all of these trials have been conducted in older people at higher fracture risk. There have been few trials with fracture as an outcome in women aged 50 to 60 years. Hosking and colleagues (9) reported the effect of alendronate 2.5 mg or 5 mg daily compared with placebo in 1499 postmenopausal women aged 45 to 59 years (mean age, 53 years) who mostly did not have low BMD. After 2 years, 3% of the placebo group had any fracture compared with 4% in both alendronate groups (RR 1.58; 95% CI, 0.82%-3.06% for both alendronate groups) (9). However, after 6 years, the percentages with fracture were 11.5% in the placebo group, 10.0% in the alendronate 2.5 mg group (RR 0.90; 95% CI, 0.51%-1.58%), and 8.9% in the alendronate 5 mg group (RR 0.78; 95% CI, 0.43%-1.40%) (10). The results of all these studies, together with the present study, suggest there might be an increase in treatment efficacy over time with bisphosphonates.

It would be of interest to assess the fracture risk beyond 10 years, and to that end we have started an extension study in which we will compare the effects of 5-yearly and 10-yearly zol for up to 20 years, as well as the effects of 5-yearly zol in treatment-naive women between ages 60 and 70 years.

The design of this study focused on fracture prevention in low-risk women. Therefore, it is important to assess whether the benefits of treatment apply broadly across the cohort recruited. There were no apparent differences in treatment

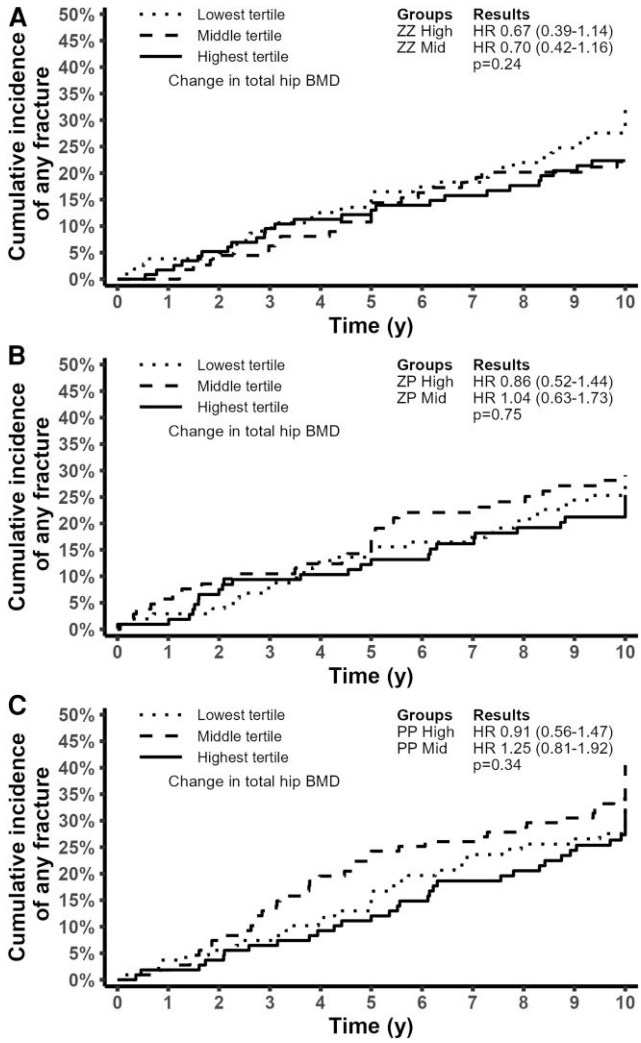

Figure 5. The cumulative incidence of any fracture over time stratified by tertile of total hip bone mineral density (BMD) change by treatment group: A, zoledronate-zoledronate (ZZ); B zoledronate-placebo (ZP); and C placebo-placebo (PP). Changes in BMD are time-varying with changes from 0 to 5 years and 5 to 10 years incorporated separately in the model. Data are hazard ratio (HR) (95% CI) compared to the reference group (lowest tertile of BMD change). The *P* value is from a separate model for each treatment group of time to first fracture vs tertile of change in total hip BMD adjusted for baseline total hip BMD and individual clustering of changes in BMD.

effects across the baseline ranges of variables that have an important relationship with fracture risk, including age, body mass index, BMD, and falls. Similarly, treatment effects appeared consistent across the range of baseline estimated fracture risk. This suggests that the results do apply broadly to the population recruited. It is important to note that this does not mean the results would necessarily be generalizable to men, older women, other ethnic groups, or individuals with very high estimated fracture risk. A possible explanation for the lack of the relationship between change in BMD and fracture risk is that there were too few fractures to detect a relationship, which has been consistently seen in other bisphosphonate studies (11).

Although prevention of fractures is the primary goal of bisphosphonate treatment, many patients and clinicians find value in BMD as a surrogate measure of bone health and fracture risk. Both treatment regimens studied prevented BMD loss over 10 years, with the zol-zol regimen more effective than the zol-placebo regimen. At 10 years, more than half the zol-zol group and one-third of the zol-placebo had an increased total hip BMD from baseline compared with 5% of the placebo-placebo group. Thus, where maintenance of BMD or prevention of BMD loss is the treatment goal, 5-yearly zol is a reasonable option. Fig. 4 shows that zol treatment largely shifts the whole distribution of changes in total hip BMD in the positive direction. However, despite average BMD for the zol-treated groups remaining stable over 10 years, there was still a tail of individuals whose BMD decreased by more than 1%/year. This is a familiar problem in clinical practice where individuals continue to lose BMD despite prolonged, regular treatment with oral and/or intravenous bisphosphonates. The reasons for this BMD loss, and the appropriate clinical response to BMD loss despite treatment, warrants further research.

The changes in BMD over time, and whether BMD increased or decreased from baseline, did not appear to influence the treatment effects of zol on fracture incidence. This calls into question the value of BMD in the management of fracture prevention and treatment in a low-risk population. Fracture risk can be estimated without BMD using online calculators. If fracture prevention occurs regardless of baseline BMD, it could be argued that, if the aim of the treatment is to prevent fractures (and maintain BMD or slow BMD loss) in a low-risk individual, knowledge of BMD would not influence management and therefore a dual-energy x-ray absorptiometry scan prior to treatment is unnecessary. In a similar vein, if changes in BMD with treatment are not associated with fracture risk, measuring BMD while receiving infrequent zol would also not alter management and could be avoided. A counterview is that the lifetime risk of fracture is very low when BMD is well above average in women aged 50 to 60 years, suggesting that prevention of fractures in such women would not be cost-effective. Likewise, if "nonresponders" to zol (ie, those whose BMD declined steadily despite zol) have increased fracture rates, BMD measurement would be required to identify this group.

In summary, very infrequent zol prevents fractures in low-risk women aged 50 to 60 years, and the treatment benefits seem to be greater between 5 and 10 years compared with 0 to 5 years. The benefits were observed in all important population subgroups. The benefits of treatment appear independent of baseline BMD and changes in BMD, raising the question of the role of BMD measurement in low-risk populations. Overall, very infrequent zol appears to be an attractive option for individuals concerned about their long-term fracture risk.

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Disclosures

I.R.R. has received speaking fees from Amgen, Abbott, and Medison Pharma. A.G. is a shareholder in Auckland Bone Density, a private company that provides bone densitometry services. None of the other authors has a conflict of interest to declare.

Data Availability

All datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request including the provision of a methodologically sound research protocol.

Clinical Trial Information

Australian New Zealand Clinical Trials Registry number ACTRN12612000270819 (registered March 6, 2012).

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