

What is the fracture rate in post-menopausal women, with or without osteoporosis, who took Zoledronic Acid vs women who took Placebo?

Case: A 57-year-old postmenopausal woman has been prescribed zoledronic acid (Zometa) and wants to know how her risk of bone fracture compares when taking the medication versus not taking it.

Summary of studies:

Study 1: Bolland et al. 2025 - Early Postmenopausal Women

Population: Early postmenopausal women aged 50-60 years

Treatment Duration: 10 years

Dosing Strategy: Infrequent dosing (zoledronate infusions at baseline and/or year 5)

Treatment Group	N Participants	Fractures (N)	Fracture Rate	Follow-up
Zoledronic acid year 1 then repeat dose at 5 years	350	22	6.3%	10 years
Zoledronic acid year 1 then give Placebo at 5 years	352	23	6.6%	10 years
Placebo only	352	39	11.1%	10 years

Key Findings: Infrequent zoledronate dosing (every 5 years) reduced morphometric vertebral fractures by 41-44% compared to placebo. Even a single dose at baseline showed protective effects over 10 years[1].

Study Link: <https://pubmed.ncbi.nlm.nih.gov/39813642/>

Study 2: HORIZON-Pivotal Fracture Trial

Population: Postmenopausal women with osteoporosis, aged 65-89 years

Treatment Duration: 3 years

Dosing Strategy: Annual intravenous infusions of zoledronic acid 5 mg

Treatment Group	N Participants	Fractures (N)	Fracture Rate	Follow-up
Vertebral Fractures				
Zoledronic acid 5mg yearly	3,875	147	3.8%	3 years
Placebo	3,861	494	12.8%	3 years
Hip Fractures				
Zoledronic acid 5mg yearly	3,875	54	1.4%	3 years
Placebo	3,861	97	2.5%	3 years

Key Findings: Once-yearly zoledronic acid 5 mg achieved highly significant reductions in vertebral fractures (70% relative risk reduction), hip fractures (41% relative risk reduction),

Study Link: <https://pmc.ncbi.nlm.nih.gov/articles/PMC5101059/>

Study 3: HORIZON-PFT Extension - 6 Years

Population: Women from the core HORIZON-PFT study who received 3 years of zoledronic acid

Treatment Duration: 3 additional years (extension phase)

Dosing Strategy: Continued annual zoledronic acid vs placebo after initial 3 years

Treatment Group	N Participants	Fractures (N)	Fracture Rate	Follow-up
Continued Zoledronic acid (6 years total)	466	14 vertebral	3.0%	6 years

Stopped Zoledronic acid at 3 years then given placebo	484	30 vertebral	6.2%	6 years
---	-----	--------------	------	---------

Key Findings: Continuing zoledronic acid for 6 years total reduced morphometric vertebral fractures by 49% compared to stopping after 3 years. However, women who stopped treatment after 3 years maintained residual anti-fracture benefits compared to never-treated patients

Study Link: <https://pmc.ncbi.nlm.nih.gov/articles/PMC3427916/>

Study 4: Ma Chao et al. 2013 - Chinese Population Study

Population: Postmenopausal women with osteoporosis in China, mean age 54-55 years

Treatment Duration: 3 years

Dosing Strategy: Zoledronic acid 5 mg IV at baseline and 12 months

Treatment Group	N Participants	Fractures (N)	Fracture Rate	Follow-up
Zoledronic acid 5mg (baseline and every 18 months)	327	28 non-vertebral	8.7%	3 years
Placebo	333	46 non-vertebral	14.3%	3 years

Table 4: Non-vertebral fracture outcomes in Chinese postmenopausal women

Key Findings: Zoledronic acid significantly reduced non-vertebral fracture incidence by approximately 39% and increased bone mineral density at multiple sites compared to placebo in a Chinese population[5].

Study Link: <https://pmc.ncbi.nlm.nih.gov/articles/PMC3905367/>

Study 5: Reid et al. 2018 (NEJM) – Older Women with Osteopenia

Population: Community-dwelling postmenopausal women aged 65 years or older with osteopenia and no prior vertebral fracture.

Treatment Duration: 6 years.

Dosing Strategy: Intravenous zoledronate 5 mg given every 18 months (four infusions over 6 years) versus placebo infusions on the same schedule.

Treatment Group	N Participants	Fractures (N)	Approx. Fracture Rate*	Follow-up
Zoledronate (every 18 months)	1000	122	12.2%	6 years
Placebo	1000	190	19.0%	6 years

Study Link: <https://www.nejm.org/doi/10.1056/NEJMoa1808082>

NOTE: A 10-year follow-up study to the above Reid Study found that zoledronate's fracture-prevention benefit in older women with osteopenia persists for a few years after treatment stops, then gradually wears off so fracture risk returns to about the same as untreated women.

- Women had already received four intravenous doses of zoledronate over 6 years in the original trial. During years 6–10 there was no trial-mandated treatment; further osteoporosis care was left to each woman's usual doctor, and researchers simply observed outcomes.
- Fracture rates (per 1000 woman-years) increased over time: about 15 in years 4–6 (end of the original trial), 24 in years 6–8, and 42 in years 8–10, with the 8–10 year rate very similar to the placebo group from the original trial.
- Interpretation: fracture protection stayed strong for roughly 1.5–3.5 years after the last zoledronate dose, then faded so that by 8–10 years after starting treatment, risk was back to “untreated” levels.
- **Study Link;**
<https://www.sciencedirect.com/science/article/abs/pii/S2213858724000032>

